LIGANDS THAT BIND IL-4 AND/OR IL-13

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/761,708, filed on January 24, 2006. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Interleukin-4 (IL-4) is a pleiotropic cytokine that has a broad spectrum of biological effects on B cells, T cells, and many non-lymphoid cells including monocytes, endothelial cells and fibroblasts. For example, IL-4 stimulates the proliferation of several IL-2- and IL-3-dependent cell lines, induces the expression of class II major histocompatability complex molecules on resting B cells, and enhances the secretion of IgG4 and IgE by human B cells. IL-4 is associated with a Th2-type immune response, and is produced by and promotes differentiation of Th2 cells. IL-4 has been implicated in a number of disorders, such as allergy and asthma.

Interleukin-13 (IL-13) is a pleiotropic cytokine that induces immunoglobulin isotype switching to IgG4 and IgE, CD23 up regulation, VCAM-1 expression, and directly activates eosinphils and mast cells, for example. IL-13 is mainly produced by Th2 cells and inhibits the production of inflammatory cytokines (IL-1, IL-6, TNF, IL-8) by LPS-stimulated monocytes. IL-13 is closely related to IL-4 with which it shares 20-25% sequence similarity at the amino acid level. (Minty *et. al.*, *Nature*, 363(6417):248-50 (1993)). Although many activities of IL-13 are similar to those of IL-4, IL-13 does not have growth promoting effects on activated T cells or T cells clones as IL-4 does. (Zurawski *et al.*, *EMBO J.* 12:2663 (1993)).

The cell surface receptors and receptor complexes bind IL-4 and/or IL-13 with different affinities. The principle components of receptors and receptor complexes that bind IL-4 and/or IL-13 are IL-4Rα, IL-13Rα1 and IL-13Rα2. These chains are expressed on the surface of cells as monomers or heterodimers of IL-4Rα/IL-13Rα1 or IL-4Rα/IL-13Rα2. IL-4rα monomer binds IL-4, but not IL-13.

IL-13Rα1 and IL-13Rα2 monomers bind IL-13, but do not bind IL-4. IL-4Rα/IL-13Rα1 and IL-4Rα/IL-13Rα2 heterodimers bind both IL-4 and IL-13.

Th2-type immune responses promote antibody production and humoral immunity, and are elaborated to fight off extracellular pathogens. Th2 cells are mediators of Ig production (humoral immunity) and produce IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13 (Tanaka, et. al., Cytokine Regulation of Humoral Immunity, 251-272, Snapper, ed., John Wiley and Sons, New York (1996)). Th2-type immune responses are characterized by the generation of certain cytokines (*e.g.*, IL-4, IL-13) and specific types of antibodies (IgE, IgG4) and are typical of allergic reactions, which may result in watery eyes and asthmatic symptoms, such as airway inflammation and contraction of airway muscle cells in the lungs.

Both IL-4 and IL-13 are therapeutically important proteins based on their biological functions. IL-4 has been shown to be able to inhibit autoimmune disease and IL-4 and IL-13 have both shown the potential to enhance anti-tumor immune responses. Since both cytokines are involved in the pathogenesis of allergic diseases, inhibitors of these cytokines could provide therapeutic benefits. However, inhibiting only IL-4 or IL-13 using conventional agents may not provide desired therapeutic results because many of the activities and functions of these cytokines are similar. Accordingly, a need exists for improved agents that inhibit IL-4, inhibit IL-13, and single agents that inhibit both IL-4 and IL-13

SUMMARY OF THE INVENTION

The invention relates to ligands that have binding specificity for IL-4 (*e.g.*, human IL-4), ligands that have binding specificity for IL-13 (*e.g.*, human IL-13), and to ligands that have binding specificity for IL-4 and IL-13 (*e.g.*, human IL-4 and human IL-13). For example, the ligand can comprise a polypeptide domain having a binding site with binding specificity for IL-4, a polypeptide domain having a binding site with binding specificity for IL-13, or comprise a polypeptide domain having a binding site with binding specificity for IL-4 and a polypeptide domain having a binding site with binding specificity for IL-13.

In one aspect, the invention relates to a ligand that has binding specificity for IL-4 and for IL-13. Such ligands comprise a protein moiety that has a binding site

with binding specificity for IL-4 and a protein moiety that has a binding site with binding specificity for IL-13. The protein moiety that has a binding site with binding specificity for IL-4 and the protein moiety that has a binding site with binding specificity for IL-13 can be any suitable binding moiety. The protein moieties can be a peptide moiety, polypeptide moiety or protein moiety. For example, the protein moieties can be provided by an antibody fragment that has a binding site with binding specificity for IL-4 or IL-13, such as an immunoglobulin single variable domain that has binding specificity for IL-4 or IL-13.

The ligand can comprise a protein moiety that has a binding site with binding specificity for IL-4 that competes for binding to IL-4 with IL-4Rα, an IL-4-binding portion of IL-4Rα or an anti-IL-4 domain antibody (dAb). In some embodiments, the ligand comprises a protein moiety that has a binding site with binding specificity for IL-4 (*e.g.*, an immunoglobulin single variable domain) that competes for binding to IL-4 with an anti-IL-4 dAb selected from the group consisting of the anti-IL-4 dAbs disclosed herein (*i.e.*, DOM9-15 (SEQ ID NO:175), DOM9-17(SEQ ID NO:176), DOM9-23 (SEQ ID NO:177), DOM9-24 (SEQ ID NO:178), DOM9-25 (SEQ ID NO:179), DOM9-27 (SEQ ID NO:180), DOM9-28 (SEQ ID NO:181), DOM9-29 (SEQ ID NO:182), DOM9-30 (SEQ ID NO:183), DOM9-31 (SEQ ID NO:184), DOM9-32 (SEQ ID NO:185), DOM9-33 (SEQ ID NO:186), DOM9-50 (SEQ ID NO:187) , DOM9-57 (SEQ ID NO:188), DOM9-59 (SEQ ID NO:189), DOM9-63 (SEQ ID NO:190), DOM9-67 (SEQ ID NO:191), DOM9-68 (SEQ ID NO:192), DOM9-70 (SEQ ID NO:193), DOM9-79 (SEQ ID NO:194), DOM9-82 (SEQ ID NO:195), DOM9-86 (SEQ ID NO:196) , DOM9-94 (SEQ ID NO:197), DOM9-108 (SEQ ID NO:198), DOM9-112 (SEQ ID NO:199), DOM9-112-1 (SEQ ID NO:200), DOM9-112-2 (SEQ ID NO:201), DOM9-112-3 (SEQ ID NO:202), DOM9-112-4 (SEQ ID NO:203), DOM9-112-5 (SEQ ID NO:204), DOM9-112-6 (SEQ ID NO:205), DOM9-112-7 (SEQ ID NO:206), DOM9-112-8 (SEQ ID NO:207), DOM9-112-9 (SEQ ID NO:208), DOM9-112-10 (SEQ ID NO:209), DOM9-112-11 (SEQ ID NO:210), DOM9-112-12 (SEQ ID NO:211), DOM9-112-13 (SEQ ID NO:212), DOM9-112-14 (SEQ ID NO:213), DOM9-112-15 (SEQ ID NO:214), DOM9-112-16 (SEQ ID NO:215), DOM9-112-17 (SEQ ID NO:216), DOM9-112-18 (SEQ ID NO:217), DOM9-112-19 (SEQ ID NO:218), DOM9-112-

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In further embodiments, the ligand comprises a protein moiety that has a binding site with binding specificity for IL-4 (*e.g.*, an immunoglobulin single variable domain) that competes for binding to IL-4 with an anti-IL-4 dAb selected from the group consisting of DOM9-15 (SEQ ID NO:175), DOM9-17(SEQ ID NO:176), DOM9-23 (SEQ ID NO:177), DOM9-24 (SEQ ID NO:178), DOM9-25 (SEQ ID NO:179), DOM9-27 (SEQ ID NO:180), DOM9-28 (SEQ ID NO:181), DOM9-29 (SEQ ID NO:182), DOM9-30 (SEQ ID NO:183), DOM9-31 (SEQ ID

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Additionally, or in other embodiments, the ligand can comprise a protein moiety that has a binding site with binding specificity for IL-13 that competes for binding to IL-13 with IL-13Rα1, an IL-13-binding portion of IL-13Rα1, IL-13Rα2, an IL-13-binding portion of IL-13Rα2 or an anti-IL-13 domain antibody (dAb). The ligand can comprise a protein moiety that has a binding site with binding specificity for IL-13 (*e.g.*, an immunoglobulin single variable domain) that competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the anti-IL-13 dAbs disclosed herein (*i.e.*, DOM10-53 (SEQ ID NO:967), DOM10-53-1 (SEQ ID NO:968), DOM10-53-2 (SEQ ID NO:969), DOM10-53-3 (SEQ ID NO:970), DOM10-53-4 (SEQ ID NO:971), DOM10-53-5 (SEQ ID NO:972), DOM10-53-6 (SEQ ID NO:973), DOM10-53-7 (SEQ ID NO:974), DOM10-53-8 (SEQ ID NO:975), DOM10-53-9 (SEQ ID NO:976), DOM10-53-10 (SEQ ID NO:977), DOM10-53-11 (SEQ ID NO:978), DOM10-53-12 (SEQ ID NO:979), DOM10-53-13 (SEQ ID NO:980), DOM10-53-14 (SEQ ID NO:981), DOM10-53-15 (SEQ ID NO:982), DOM10-53-16 (SEQ ID NO:983), DOM10-53-17 (SEQ ID NO:984), DOM10-53-18 (SEQ ID NO:985), DOM10-53-19 (SEQ ID NO:986), DOM10-53-20 (SEQ ID NO:987), DOM10-53-21 (SEQ ID NO:988), DOM10-53-122 (SEQ ID NO:989), DOM10-53-123 (SEQ ID NO:990), DOM10-53-24 (SEQ ID NO:991), DOM10-53-25 (SEQ ID NO:992), DOM10-53-26 (SEQ ID NO:993), DOM10-53-27 (SEQ ID NO:994), DOM10-53-28 (SEQ ID NO:995), DOM10-53-29 (SEQ ID NO:996) , DOM10-53-30 (SEQ ID NO:997), DOM10-53-31 (SEQ ID NO:998), DOM10-53-32 (SEQ ID NO:1999), DOM10-53-43 (SEQ ID NO:1000), DOM10-53-44 (SEQ ID NO:1001), DOM10-53-45 (SEQ ID NO:1002), DOM10-53-46 (SEQ ID NO:1003), DOM10-53-47 (SEQ ID NO:1004), DOM10-53-48 (SEQ ID NO:1005), DOM10-53-49 (SEQ ID NO:1006), DOM10-53-50 (SEQ ID

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The ligand can also comprise a protein moiety that has a binding site with binding specificity for IL-13 (*e.g.*, an immunoglobulin single variable domain) that competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the group consisting of DOM10-236 (SEQ ID NO:2129), DOM10-238 (SEQ ID NO:2130), DOM10-241 (SEQ ID NO:2131), DOM10-245 (SEQ ID NO:2132), DOM10-249 (SEQ ID NO:2133), DOM10-250 (SEQ ID NO:2134), DOM10-251 (SEQ ID NO:2135), DOM10-254 (SEQ ID NO:2136), DOM10-256 (SEQ ID NO:2137), DOM10-259 (SEQ ID NO:2138), DOM10-260 (SEQ ID NO:2139), DOM10-261 (SEQ ID NO:2140), DOM10-263 (SEQ ID NO:2141), DOM10-264 (SEQ ID NO:2142), DOM10-273 (SEQ ID NO:2143), DOM10-278 (SEQ ID

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NO:2291), DOM10-53-526 (SEQ ID NO:2292), DOM10-53-527 (SEQ ID NO:2293), DOM10-53-528 (SEQ ID NO:2294), DOM10-53-518 (SEQ ID NO:2295), DOM10-53-523 (SEQ ID NO:2296), DOM10-53-524 (SEQ ID NO:2297), DOM10-53-525 (SEQ ID NO:2298), DOM10-53-601 (SEQ ID NO:2299), DOM10-53-602 (SEQ ID NO:2300), DOM10-53-605 (SEQ ID NO:2301), DOM10-53-606 (SEQ ID NO:2302), DOM10-53-607 (SEQ ID NO:2303), DOM10-53-608 (SEQ ID NO:2304), DOM10-53-609 (SEQ ID NO:2305), DOM10-53-610 (SEQ ID NO:2306), DOM10-53-611 (SEQ ID NO:2307), DOM10-53-612 (SEQ ID NO:2308), DOM10-53-603 (SEQ ID NO:2309), DOM10-53-604 (SEQ ID NO:2310), DOM10-53-429 (SEQ ID NO:2311), DOM10-53-432 (SEQ ID NO:2312), DOM10-53-433 (SEQ ID NO:2313), DOM10-53-435 (SEQ ID NO:2314), DOM10-53-430 (SEQ ID NO:2315), DOM10-53-431 (SEQ ID NO:2316), DOM10-53-434 (SEQ ID NO:2317), DOM10-53-436 (SEQ ID NO:2318), DOM10-53-437 (SEQ ID NO:2319), DOM10-53-438 (SEQ ID NO:2320), DOM10-53-440 (SEQ ID NO:2321), DOM10-53-439 (SEQ ID NO:2322), DOM10-53-441 (SEQ ID NO:2323), DOM10-53-442 (SEQ ID NO:2324), DOM10-53-443 (SEQ ID NO:2325), DOM10-53-444 (SEQ ID NO:2326), DOM10-53-445 (SEQ ID NO:2327), DOM10-53-446 (SEQ ID NO:2328), DOM10-53-447 (SEQ ID NO:2329), DOM10-53-449 (SEQ ID NO:2330), DOM10-53-448 (SEQ ID NO:2331), DOM10-53-450 (SEQ ID NO:2332), DOM10-53-451 (SEQ ID NO:2333), DOM10-53-452 (SEQ ID NO:2334), DOM10-53-453 (SEQ ID NO:2335), DOM10-53-454 (SEQ ID NO:2336), DOM10-53-455 (SEQ ID NO:2337), DOM10-53-456 (SEQ ID NO:2338), DOM10-53-457 (SEQ ID NO:2339), DOM10-53-458 (SEQ ID NO:2340), DOM10-53-459 (SEQ ID NO:2341), DOM10-53-461 (SEQ ID NO:2342), DOM10-53-462 (SEQ ID NO:2343), DOM10-53-465 (SEQ ID NO:2344), DOM10-53-466 (SEQ ID NO:2345), DOM10-53-467 (SEQ ID NO:2346), DOM10-53-468 (SEQ ID NO:2347), DOM10-53-460 (SEQ ID NO:2348), DOM10-53-463 (SEQ ID NO:2349), DOM10-53-464 (SEQ ID NO:2350), DOM10-53-469 (SEQ ID NO:2351), DOM10-53-471 (SEQ ID NO:2352), DOM10-53-470 (SEQ ID NO:2353), DOM10-53-533 (SEQ ID NO:2354), DOM10-53-534 (SEQ ID

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In particular embodiments, the ligand that has binding specificity for IL-4 and for IL-13 comprises a protein moiety that has a binding site with binding specificity for IL-4 that competes for binding to IL-4 with an anti-IL-4 domain antibody (dAb) selected from the group consisting of DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-44-502 (SEQ ID NO:512) , DOM9-155-5 (SEQ ID NO:606), DOM9-155-25 (SEQ ID NO:617), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512), and further comprises a protein moiety that has a binding site with binding specificity for IL-13 that competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587),

DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

The ligand that has binding specificity for IL-4 and IL-13 can inhibit binding of IL-4 to IL-4R, inhibit the activity of IL-4, and/or inhibit the activity of IL-4 without substantially inhibiting binding of IL-4 to IL-4R.

Preferably, the ligand (*e.g.*, immunoglobulin single variable domain) that binds IL-4 inhibits binding of IL-4 to an IL-4 receptor (*e.g.*, IL-4Rα) with an inhibitory concentration 50 (IC50) that is ≤ 10 μM, ≤ 1 μM, ≤ 100 nM, ≤ 10 nM, ≤ 1 nM, ≤ 500 pM, ≤ 300 pM, ≤ 100 pM, or ≤ 10 pM. The *IC50* is preferably determined using an *in vitro* receptor binding assay, such as the assay described herein.

It is also preferred that the ligand (*e.g.*, immunoglobulin single variable domain) that binds an IL-4 receptor inhibits IL-4 induced functions in a suitable *in vitro* assay with a neutralizing dose 50 (ND50) that is ≤ 10 μM, ≤ 1 μM, ≤ 100 nM, ≤ 10 nM, ≤ 1 nM, ≤ 500 pM, ≤ 300 pM, ≤ 100 pM, or ≤ 10 pM. For example, the ligand that binds an IL-4 receptor can inhibit IL-4 induced proliferation of TF-1 cells (ATCC Accession No. CRL-2003) in an *in vitro* assay, such as the assay described herein.

It is also preferred that the ligand (*e.g.*, immunoglobulin single variable domain) that binds an IL-4 receptor inhibits house dust mite (HDM) induced proliferation of peripheral blood mononuclear cells (PBMC) by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% in a suitable *in vitro* assay, such as the assay described herein where 4 x 10^6 cells/ml are stimulated with 20-50 ug/ml HDM and 100 nM anti-IL-4 dAbs are added.

A ligand (*e.g.*, immunoglobulin single variable domain) that does not substantially inhibit binding of IL-4 to an IL-4 receptor (*e.g.*, IL-4Rα) does not significantly inhibit binding of IL-4 to an IL-4 receptor in the receptor binding assay described herein. For example, such a ligand might inhibit binding of IL-4 to an IL-4 receptor in the receptor binding assay described herein with an IC50 of about 1

mM or higher or inhibits binding by no more than about 20%, no more than about 15%, no more than about 10%, or no more than about 5%.

The ligand that has binding specificity for IL-4 and IL-13 can inhibit binding of IL-13 to IL-13Rα1 and/or IL-13Rα2, inhibit the activity of IL-13, and/or inhibit the activity of IL-13 without substantially inhibiting binding of IL-13 to IL-13Rα1 and/or IL-13Rα2.

Preferably, the ligand (*e.g.*, immunoglobulin single variable domain) that *binds IL-13* inhibits binding of IL-13 to an IL-13 receptor (*e.g.*, IL-13Rα1, IL-13Rα2) with an inhibitory concentration 50 (IC50) that is ≤ 10 μM, ≤ 1 μM, ≤ 100 nM, ≤ 10 nM, ≤ 1 nM, ≤ 500 pM, ≤ 300 pM, ≤ 100 pM, or ≤ 10 pM. The IC50 is preferably determined using an *in vitro* receptor binding assay, such as the assay described herein.

It is also preferred that the ligand (*e.g.*, immunoglobulin single variable domain) that binds an IL-13 receptor inhibits IL-13 induced functions in a suitable *in vitro* assay with a neutralizing dose 50 (ND50) that is ≤ 10 μM, ≤ 1 μM, ≤ 100 nM, ≤ 10 nM, ≤ 1 nM, ≤ 500 pM, ≤ 300 pM, ≤ 100 pM, ≤ 10 pM, ≤ 1 pM ≤ 500 fM, ≤ 300 fM, ≤ 100 fM, ≤ 10 fM. For example, the ligand that binds an IL-13 receptor can inhibit IL-13 induced proliferation of TF-1 cells (ATCC Accession No. CRL-2003) in an *in vitro* assay, such as the assay described herein wherein TF-1 cells were mixed with 5 ng/ml final concentration of IL-13.

It is also preferred that the ligand that binds an IL-13 receptor inhibits IL-13 induced B cell proliferation by at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% in an *in vitro* assay, such as the assay described herein where 1 x 10^5 B cells were incubated with 10 or 100nM anti-IL-13 dAbs.

A ligand (*e.g.*, immunoglobulin single variable domain) that does not substantially inhibit binding of IL-13 to an IL-13 receptor (*e.g.*, IL-13Rα1, IL-13Rα2) does not significantly inhibit binding of IL-13 to an IL-13 receptor in the receptor binding assay or sandwich ELISA described herein. For example, such a ligand might inhibit binding of IL-13 to an IL-13 receptor in the receptor binding assay described herein with an IC50 of about 1 mM or higher or inhibit binding by

no more than about 20%, no more than about 15%, no more than about 10%, or no more than about 5%.

In more particular embodiments, the ligand that has binding specificity for IL-4 and for IL-13 comprises an immunoglobulin single variable domain with binding specificity for IL-4 and an immunoglobulin single variable domain with binding specificity for IL-13, wherein an immunoglobulin single variable domain with binding specificity for IL-4 competes for binding to IL-4 with an anti-IL-4 domain antibody (dAb) selected from the group of anti-IL-4 dAbs disclosed herein.

In more particular embodiments, the ligand that has binding specificity for IL-4 and for IL-13 comprises an immunoglobulin single variable domain with binding specificity for IL-4 and an immunoglobulin single variable domain with binding specificity for IL-13, wherein an immunoglobulin single variable domain with binding specificity for IL-13 competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the group consisting of the anti-IL-13 dAbs disclosed herein.

The ligand that has binding specificity for IL-4 and IL-13 can contain a protein binding moiety (*e.g.*, immunoglobulin single variable domain) with binding specificity for IL-4 that binds IL-4 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

The ligand that has binding specificity for IL-4 and IL-13 can contain a protein binding moiety (*e.g.*, immunoglobulin single variable domain) with binding specificity for IL-13 that binds IL-13 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

The ligand that has binding specificity for IL-4 and IL-13 can bind IL-4 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

The ligand that has binding specificity for IL-4 and IL-13 can bind IL-13 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

The ligand that has binding specificity for IL-4 and IL-13 can comprise an immunoglobulin single variable domain with binding specificity for IL-4 and an immunoglobulin single variable domain with binding specificity for IL-13, wherein

the immunoglobulin single variable domains are selected from the group consisting of a human V_H and a human V_L.

In some embodiments, the ligand that has binding specificity for IL-4 and IL-13 can be an IgG-like format comprising two immunoglobulin single variable domains with binding specificity for IL-4, and two immunoglobulin single variable domains with binding specificity for IL-13.

In some embodiments, the ligand that has binding specificity for IL-4 and for IL-13 can comprise an antibody Fc region.

In some embodiments, the ligand that has binding specificity for IL-4 and IL-13 can comprise an IgG constant region.

The invention also relates to a ligand that has binding specificity for IL-4 comprising an immunoglobulin single variable domain with binding specificity for IL-4, wherein an immunoglobulin single variable domain with binding specificity for IL-4 competes for binding to IL-4 with an anti-IL-4 domain antibody (dAb) selected from the group consisting of the anti-IL-4 dAbs disclosed herein.

For example, an immunoglobulin single variable domain with binding specificity for IL-4 can comprise an amino acid sequence that has at least about 85% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of the anti-IL-4 dAbs disclosed herein.

The ligand that has binding specificity for IL-4 can inhibit binding of IL-4 to IL-4R, inhibit the activity of IL-4 and/or inhibit the activity of IL-4 without substantially inhibiting the binding of IL-4 to IL-4R.

Preferably, the ligand (*e.g.*, immunoglobulin single variable domain) that binds IL-4 inhibits binding of IL-4 to an IL-4 receptor (*e.g.*, IL-4Rα) with an inhibitory concentration 50 (IC50) that is ≤ 10 μM, ≤ 1 μM, ≤ 100 nM, ≤ 10 nM, ≤ 1 nM, ≤ 500 pM, ≤ 300 pM, ≤ 100 pM, or ≤ 10 pM. The IC50 is preferably determined using an *in vitro* receptor binding assay, such as the assay described herein.

It is also preferred that the ligand (*e.g.*, immunoglobulin single variable domain) that binds an IL-4 receptor inhibits IL-4 induced functions in a suitable *in vitro* assay with a neutralizing dose 50 (ND50) that is ≤ 10 μM, ≤ 1 μM, ≤ 100 nM, ≤ 10 nM, ≤ 1 nM, ≤ 500 pM, ≤ 300 pM, ≤ 100 pM, or ≤ 10 pM. For example, the

ligand that binds an IL-4 receptor can inhibit IL-4 induced proliferation of TF-1 cells (ATCC Accession No. CRL-2003) in an *in vitro* assay, such as the assay described herein.

It is also preferred that the ligand (*e.g.*, immunoglobulin single variable domain) that binds an IL-4 receptor inhibits house dust mite (HDM) induced proliferation of peripheral blood mononuclear cells (PBMC) by at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% in a suitable *in vitro* assay, such as the assay described herein where 4×10^6 cells/ml are stimulated with 20-50 ug/ml HDM and 100 nM anti-IL-4 dAbs are added.

A ligand (*e.g.*, immunoglobulin single variable domain) that does not substantially inhibit binding of IL-4 to an IL-4 receptor (*e.g.*, IL-4Rα) does not significantly inhibit binding of IL-4 to an IL-4 receptor in the receptor binding assay described herein. For example, such a ligand might inhibit binding of IL-4 to an IL-4 receptor in the receptor binding assay described herein with an IC50 of about 1 mM or higher or inhibits binding by no more than about 20%, no more than about 15%, no more than about 10%, or no more than about 5%.

The ligand that has binding specificity for IL-4 can contain an immunoglobulin single variable domain with binding specificity for IL-4 that binds IL-4 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

The ligand that has binding specificity for IL-4 can bind IL-4 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

The ligand that has binding specificity for IL-4 can comprise an immunoglobulin single variable domain with binding specificity for IL-4 that is selected from the group consisting of a human V_H and a human V_L.

In some embodiments, the ligand that has binding specificity for IL-4 is an IgG-like format comprising at least two immunoglobulin single variable domains with binding specificity for IL-4.

In some embodiments, the ligand that has binding specificity for IL-4 comprises an antibody Fc region.

In some embodiments, the ligand that has binding specificity for IL-4 comprises an IgG constant region.

The invention also relates to a ligand that has binding specificity for IL-13 comprising an immunoglobulin single variable domain with binding specificity for IL-13, wherein an immunoglobulin single variable domain with binding specificity for IL-13 competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the group consisting of the anti-IL-13 dAbs disclosed herein.

For example, the immunoglobulin single variable domain with binding specificity for IL-13 can comprise an amino acid sequence that has at least about 85% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of the anti-IL-13 dAbs disclosed herein.

The ligand that has binding specificity for IL-13 can inhibit binding of IL-13 to IL-13Rα1 and/or IL-13Rα2, inhibit the activity of IL-13, and/or inhibit the activity of IL-13 without substantially inhibiting binding of IL-13Rα1 and/or IL-13Rα2 to IL-13.

Preferably, the ligand (*e.g.*, immunoglobulin single variable domain) that binds IL-13 inhibits binding of IL-13 to an IL-13 receptor (*e.g.*, IL-13Rα1, IL-13Rα2) with an inhibitory concentration 50 (IC50) that is ≤ 10 μM, ≤ 1 μM, ≤ 100 nM, ≤ 10 nM, ≤ 1 nM, ≤ 500 pM, ≤ 300 pM, ≤ 100 pM, or ≤ 10 pM. The IC50 is preferably determined using an *in vitro* receptor binding assay, such as the assay described herein.

It is also preferred that the ligand (*e.g.*, immunoglobulin single variable domain) that binds an IL-13 receptor inhibits IL-13 induced functions in a suitable *in vitro* assay with a neutralizing dose 50 (ND50) that is ≤ 10 μM, ≤ 1 μM, ≤ 100 nM, ≤ 10 nM, ≤ 1 nM, ≤ 500 pM, ≤ 300 pM, ≤ 100 pM, ≤ 10 pM, ≤ 1 pM ≤ 500 fM, ≤ 300 fM, ≤ 100 fM, ≤ 10 fM. For example, the ligand that binds an IL-13 receptor can inhibit IL-13 induced proliferation of TF-1 cells (ATCC Accession No. CRL-2003) in an *in vitro* assay, such as the assay described herein wherein TF-1 cells were mixed with 5 ng/ml final concentration of IL-13.

It is also preferred that the ligand that binds an IL-13 receptor inhibits IL-13 induced B cell proliferation by at least at least about 70%, at least about 80%, or at

least about 90% in an *in vitro* assay, such as the assay described herein where 1 x 10^5 B cells were incubated with 10 or 100nM anti-IL-13 dAbs.

A ligand (*e.g.*, immunoglobulin single variable domain) that does not substantially inhibit binding of IL-13 to an IL-13 receptor (*e.g.*, IL-13Rα1, IL-13Rα2) does not significantly inhibit binding of IL-13 to an IL-13 receptor in the receptor binding assay or sandwich ELISA described herein. For example, such a ligand might inhibit binding of IL-13 to an IL-13 receptor in the receptor binding assay described herein with an IC50 of about 1 mM or higher or inhibit binding by no more than about 20%, no more than about 15%, no more than about 10%, or no more than about 5%.

The ligand that has binding specificity for IL-13 can contain an immunoglobulin single variable domain with binding specificity for IL-13 that binds IL-13 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

The ligand that has binding specificity for IL-13 can bind IL-13 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

The ligand that has binding specificity for IL-13 can comprise an immunoglobulin single variable domain with binding specificity for IL-13 that is selected from the group consisting of a human V_H and a human V_L.

In some embodiments, the ligand that has binding specificity for IL-13 is an IgG-like format comprising at least two immunoglobulin single variable domains with binding specificity for IL-13.

In some embodiments, the ligand that has binding specificity for IL-13 comprises an antibody Fc region.

In some embodiments, the ligand that has binding specificity for IL-13 comprises an IgG constant region.

The invention also relates to a ligand (*e.g.*, a fusion protein) that has binding specificity for IL-4 and IL-13, comprising an immunoglobulin single variable domain with binding specificity for IL-4, wherein an immunoglobulin single variable domain with binding specificity for IL-4 competes for binding to IL-4 with an anti-IL-4 domain antibody (dAb) selected from the group consisting of the anti-

IL-4 dAbs disclosed herein and comprising an immunoglobulin single variable domain with binding specificity for IL-13, wherein an immunoglobulin single variable domain with binding specificity for IL-13 competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the group consisting of the anti-IL-13 dAbs disclosed herein.

For example, the ligand (*e.g.*, fusion protein) comprising an immunoglobulin single variable domain with binding specificity for IL-4 can comprise an amino acid sequence that has at least 85% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of the anti-IL-4 dAbs disclosed herein.

In another example, the ligand (*e.g.*, fusion protein) comprising an immunoglobulin single variable domain with binding specificity for IL-13 can comprise an amino acid sequence that has at least 85% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of the anti-IL-13 dAbs disclosed herein.

In some embodiments, the ligand (*e.g.*, fusion protein) comprising an immunoglobulin single variable domain with binding specificity for IL-4 and an immunoglobulin single variable domain with binding specificity for IL-3 further comprises a linker moiety.

The invention also relates to a ligand comprising a protein moiety that has a binding site with binding specificity for IL-4, wherein said protein moiety comprises an amino acid sequence that is the same as the amino acid sequence of CDR3 of an anti-IL-4 dAb disclosed herein.

In some embodiments, the ligand comprising a protein moiety that has a binding site with binding specificity for IL-4, wherein the protein moiety has an amino acid sequence that is the same as the amino acid sequence of CDR3 of an anti-IL-4 dAb disclosed herein, and also comprises an amino acid sequence that is the same as the amino acid sequence of CDR1 and/or CDR2 of an anti-IL-4 dAb disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-4, wherein the immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of an anti-IL-4 dAb

disclosed herein at no more than 25 amino acid positions and has a CDR1 sequence that has at least 50% identity to the CDR1 sequence of the anti-IL-4 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of an anti-IL-4 dAb disclosed herein at no more than 25 amino acid positions and has a CDR2 sequence that has at least 50% identity to the CDR2 sequence of the anti-IL-4 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of an anti-IL-4 dAb disclosed herein at no more than 25 amino acid positions and has a CDR3 sequence that has at least 50% identity to the CDR3 sequence of the anti-IL-4 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of an anti-IL-4 dAb disclosed herein at no more than 25 amino acid positions and has a CDR1 sequence and a CDR2 sequence that has at least 50% identity to the CDR1 or CDR2 sequences, respectively, of the anti-IL-4 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of an anti-IL-4 dAb disclosed herein at no more than 25 amino acid positions and has a CDR2 sequence and a CDR3 sequence that has at least 50% identity to the CDR2 or CDR3 sequences, respectively, of the anti-IL-4 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-4 differs from the amino acid

sequence of an anti-IL-4 dAb disclosed herein at no more than 25 amino acid positions and has a CDR1 sequence and a CDR3 sequence that has at least 50% identity to the CDR1 or CDR3 sequences, respectively, of the anti-IL-4 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of an anti-IL-4 dAb disclosed herein at no more than 25 amino acid positions and has a CDR1 sequence, a CDR2 sequence and a CDR3 sequence that has at least 50% identity to the CDR1, CDR2 or CDR3 sequences, respectively, of the anti-IL-4 dAbs disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the immunoglobulin single variable domain that binds IL-4 has a CDR2 sequence that has at least 50% identity to the CDR2 sequences of an anti-IL-4 dAb disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the immunoglobulin single variable domain that binds IL-4 has a CDR3 sequence that has at least 50% identity to the CDR3 sequences of an anti-IL-4 dAb disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the immunoglobulin single variable domain that binds IL-4 has a CDR1 and a CDR2 sequence that has at least 50% identity to the CDR1 and CDR2 sequences, respectively, of an anti-IL-4 dAb disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the immunoglobulin single variable domain that binds IL-4 has a CDR2 and a CDR3 sequence that has at least 50% identity to the CDR2 and CDR3 sequences, respectively, of an anti-IL-4 dAb disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the immunoglobulin single variable domain that binds IL-4 has a CDR1 and a CDR3 sequence that has at least 50% identity to the CDR1 and CDR3 sequences, respectively, of an anti-IL-4 dAb disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the immunoglobulin single variable domain that binds IL-4 has a CDR1, CDR2, and a CDR3 sequence that has at least 50% identity to the CDR1, CDR2 and CDR3 sequences, respectively, of an anti-IL-4 dAb disclosed herein.

In some embodiments, the ligand comprises a protein moiety that has a binding site that binds IL-13 , wherein said protein moiety comprises an amino acid sequence that is the same as the amino acid sequence of CDR3 of an anti-IL-13 dAb disclosed herein.

In other embodiments, the ligand comprises a protein moiety that has a binding site that binds IL-13, wherein said protein moiety comprises an amino acid sequence that is the same as the amino acid sequence of CDR3 of an anti-IL-13 dAb disclosed herein and has an amino acid sequence that is the same as the amino acid sequence of CDR1 and/or CDR2 of an anti-IL-13 dAb disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of an anti-IL-13 dAb disclosed herein at no more than 25 amino acid positions and has a CDR1 sequence that has at least 50% identity to the CDR1 sequences of the anti-IL-13 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of an anti-IL-13 dAb disclosed herein at no more than 25 amino acid positions and has a CDR2 sequence that has at least 50% identity to the CDR2 sequences of the anti-IL-13 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of an anti-IL-13 dAb disclosed herein at no more than 25 amino acid positions and has a CDR3 sequence that has at least 50% identity to the CDR3 sequences of the anti-IL-13 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of an anti-IL-13 dAb disclosed herein at no more than 25 amino acid positions and has a CDR1 sequence and a CDR2 sequence that has at least 50% identity to the CDR1 and CDR2 sequences, respectively, of the anti-IL-13 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of an anti-IL-13 dAb disclosed herein at no more than 25 amino acid positions and has a CDR2 sequence and a CDR3 sequence that has at least 50% identity to the CDR2 and CDR3 sequences, respectively, of the anti-IL-13 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of an anti-IL-13 dAb disclosed herein at no more than 25 amino acid positions and has a CDR1 sequence and a CDR3 sequence that has at least 50% identity to the CDR1 and CDR3 sequences, respectively, of the anti-IL-13 dAbs disclosed herein.

In other embodiments, the ligand comprises an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of the immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of an anti-IL-13 dAb disclosed herein at no more than 25 amino acid positions and has a CDR1 sequence, CDR2 sequence and a CDR3 sequence that has

at least 50% identity to the CDR1, CDR2 and CDR3 sequences, respectively, of the anti-IL-13 dAbs disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the immunoglobulin single variable domain comprises a CDR2 sequence that has at least 50% identity to the CDR2 sequence of an anti-IL-13 dAb disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the immunoglobulin single variable domain comprises a CDR3 sequence that has at least 50% identity to the CDR3 sequence of an anti-IL-13 dAb disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the immunoglobulin single variable domain comprises a CDR1 and a CDR2 sequence that has at least 50% identity to the CDR1 and CDR2 sequences, respectively, of an anti-IL-13 dAb disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the immunoglobulin single variable domain comprises a CDR2 and a CDR3 sequence that has at least 50% identity to the CDR2 and CDR3 sequences, respectively, of an anti-IL-13 dAb disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the immunoglobulin single variable domain comprises a CDR1 and a CDR3 sequence that has at least 50% identity to the CDR1 and CDR3 sequences, respectively, of an anti-IL-13 dAb disclosed herein.

In another embodiment, the invention is a ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the immunoglobulin single variable domain comprises a CDR1, CDR2, and a CDR3 sequence that has at least 50% identity to the CDR1, CDR2, and CDR3 sequences, respectively, of an anti-IL-13 dAb disclosed herein.

In other embodiments, any of the ligands described herein further comprises a half-life extending moiety, such as a polyalkylene glycol moiety, serum albumin or

a fragment thereof, transferring receptor or a transferring-binding portion thereof, or a moiety comprising a binding site for a polypeptide that enhance half-life *in vivo*. In some embodiments, the half-life extending moiety is a moiety comprising a binding site for a polypeptide that enhances half-life *in vivo* selected from the group consisting of an affibody, a SpA domain, an LDL receptor class A domain, an EGF domain, and an avimer.

In other embodiments, the half-life extending moiety is a polyethylene glycol moiety.

In other embodiments, the half-life extending moiety is an antibody or antibody fragment (*e.g.*, an immunoglobulin single variable domain) comprising a binding site for serum albumin or neonatal Fc receptor.

The invention also relates to a ligand of the invention for use in therapy or diagnosis, and to the use of a ligand of the invention for the manufacture of a medicament for treatment, prevention or suppression of a disease described herein (*e.g.*, allergic disease, Th2-mediated disease, asthma, cancer).

The invention also relates to a ligand of the invention for use in treating, suppressing or preventing a Th2-type immune response.

The invention also relates to therapeutic methods that comprise administering a therapeutically effective amount of a ligand of the invention to a subject in need thereof. In one embodiment, the invention relates to a method for inhibiting a Th2-type immune response comprising administering to a subject in need thereof a therapeutically effective amount of a ligand of the invention.

In other embodiments, the invention relates to a method for treating asthma comprising administering to a subject in need thereof a therapeutically effective amount of a ligand of the invention.

In other embodiments, the invention relates to a method for treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a ligand of the invention.

The invention also relates to the use of any of the ligands of the invention for the manufacture of a medicament for simultaneous administration of an anti-IL-4 treatment and an anti-IL-13 treatment. In other embodiments, the invention relates to a method of administering to a subject anti-IL-4 treatment and anti-IL-13

treatment, comprising simultaneous administration of an anti-IL-4 treatment and an anti-IL-13 treatment by administering to the subject a therapeutically effective amount of a ligand that has binding specificity for IL-4 and IL-13.

The invention also relates to a composition (*e.g.*, pharmaceutical composition) comprising a ligand of the invention and a physiologically acceptable carrier. In some embodiments, the composition comprises a vehicle for intravenous, intramuscular, intraperitoneal, intraarterial, intrathecal, intraarticular, subcutaneous administration, pulmonary, intranasal, vaginal, or rectal administration.

The invention also relates to a drug delivery device comprising the composition (*e.g.*, pharmaceutical composition) of the invention. In some embodiments, the drug delivery device comprises a plurality of therapeutically effective doses of ligand.

In other embodiments, the drug delivery device is selected from the group consisting of parenteral delivery device, intravenous delivery device, intramuscular delivery device, intraperitoneal delivery device, transdermal delivery device, pulmonary delivery device, intraarterial delivery device, intrathecal delivery device, intraarticular delivery device, subcutaneous delivery device, intranasal delivery device, vaginal delivery device, rectal delivery device, syringe, a transdermal delivery device, a capsule, a tablet, a nebulizer, an inhaler, an atomizer, an aerosolizer, a mister, a dry powder inhaler, a metered dose inhaler, a metered dose sprayer, a metered dose mister, a metered dose atomizer, and a catheter.

The invention also relates to an isolated or recombinant nucleic acid encoding any of the ligands of the invention. In other embodiments, the invention relates to a vector comprising the recombinant nucleic acid of the invention.

The invention also relates to a host cell comprising the recombinant nucleic acid of the invention or the vector of the invention.

The invention also relates to a method for producing a ligand, comprising maintaining a host cell of the invention under conditions suitable for expression of a nucleic acid or vector of the invention, whereby a ligand is produced. In other embodiments, the method of producing a ligand further comprises isolating the ligand.

The invention also relates to a method of inhibiting proliferation of peripheral blood mononuclear cells (PBMC) in an allergen-sensitized subject, comprising administering to a subject a pharmaceutical composition comprising any of the ligands of the invention. In some embodiments, the allergen is selected from house dust mite, cat allergen, grass allergen, mold allergen, and pollen allergen.

The invention also relates to a method of inhibiting proliferation of B cells in a subject, comprising administering to the subject a pharmaceutical composition comprising a ligand of the invention.

The invention also relates to a pharmaceutical composition for treating preventing or suppressing a disease as described herein (*e.g.*, Th2-mediated disease, allergic disease, asthma, cancer), comprising as an active ingredient a ligand as described herein.

The invention also relates to a ligand that has binding specificity for IL-4 and IL-13 comprising a protein moiety that has a binding site with binding specificity for IL-4, and a protein moiety that has a binding site with binding specificity for IL-13, wherein the protein moiety that has binding specificity for IL-4 does not compete for binding with any of the anti-IL-4 dAbs disclosed herein.

The invention also relates to a ligand that has binding specificity for IL-4 and IL-13 comprising a protein moiety that has a binding site with binding specificity for IL-4, and a protein moiety that has a binding site with binding specificity for IL-13, wherein the protein moiety that has binding specificity for IL-13 does not compete for binding with any of the anti-IL-13 dAbs disclosed herein.

The invention also relates to a ligand that has binding specificity for IL-4 and IL-13, wherein the ligand is a fusion protein comprising an immunoglobulin single variable domain with binding specificity for IL-4 and an immunoglobulin single variable domain with binding specificity for IL-13, wherein the immunoglobulin single variable domain with binding specificity for IL-4 competes for binding to IL-4 with an anti-IL-4 domain antibody (dAb) selected from the group consisting of DOM9-112-210 and DOM9-155-78, and the immunoglobulin single variable domain with binding specificity for IL-13 competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the group consisting of DOM10-

208, DOM10-212, DOM10-213, DOM10-215, DOM10-224, DOM10-270, DOM10-416, DOM10-236, DOM10-273, DOM10-275, DOM10-276 and DOM10-277.

In some embodiments, the invention relates to a ligand that has binding specificity for IL-4, comprising an immunoglobulin single variable domain with binding specificity for human IL-4 and a non-human IL-4. In preferred embodiments, the non-human IL-4 is selected from rhesus IL-4 and cynomolgous IL-4. It is also preferred that the binding affinity of the immunoglobulin single variable domain for non-human IL-4 and the binding affinity for human IL-4 differ by no more than a factor of 10, 50, 100, 500 or 1000.

In some embodiments, the invention relates to a ligand that has binding specificity for IL-13, comprising an immunoglobulin single variable domain with binding specificity for human IL-13 and a non-human IL-13. In preferred embodiments, the non-human IL-13 is selected from rhesus IL-13 and cynomolgous IL-13. It is also preferred that the binding affinity of the immunoglobulin single variable domain for non-human IL-13 and the binding affinity for human IL-13 differ by no more than a factor of 10, 50, 100, 500 or 1000.

In other embodiments, the invention relates to a ligand that has binding specificity for IL-4 and IL-13, comprising an immunoglobulin single variable domain with binding specificity for IL-4 and an immunoglobulin single variable domain with binding specificity for IL-13, wherein the immunoglobulin single variable domain with binding specifity for IL-4 binds human IL-4 and a non-human IL-4 and the immunoglobulin single variable domain with binding specificity for IL-13 binds human IL-13 and a non-human IL-13. In preferred embodiments, the non-human IL-4 is selected from rhesus IL-4 and cynomolgous IL-4 and the non-human IL-13 is selected from rhesus IL-13 and cynomolgous IL-13. It is also preferred that the binding affinity of the immunoglobulin single variable domain for non-human IL-4 and the binding affinity for human IL-4 differ by no more than a factor of 10, 50, 100, 500 or 1000, and the binding affinity of the immunoglobulin single variable domain for non-human IL-13 and the binding affinity for human IL-13 differ by no more than a factor of 10, 50, 100, 500 or 1000.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A-1U illustrates several nucleotide sequences that encode human (*Homo sapiens)* V_H domain antibodies (dAbs) that specifically bind human IL-4. The nucleotide sequences presented are SEQ ID NOS:1-174.

FIG. 2A-2J illustrates the amino acid sequences of the dAbs encoded by the nucleic acid sequences shown in FIG. 1A-1U. The amino acid sequences presented are SEQ ID NOS:175-348.

FIG. 3A-3S illustrates several nucleotide sequences that encode human (*Homo sapiens*) V_κ domain antibodies (dAbs) that specifically bind human IL-4. The nucleotide sequences presented are SEQ ID NOS:349-499.

FIG. 4A-4H illustrates the amino acid sequences of the dAbs encoded by the nucleic acid sequences shown in FIG. 3A-3S. The amino acid sequences presented are SEQ ID NOS:500-650.

FIG. 5A-5Z, 5AA-5MM illustrates several nucleotide sequences that encode human (*Homo sapiens*) V_H domain antibodies (dAbs) that specifically bind human IL-13. The nucleotide sequences presented are SEQ ID NOS:651-966.

FIG. 6A-6Q illustrates the amino acid sequences of the dAbs encoded by the nucleic acid sequences shown in FIG. 5A-5Z, 5AA-5MM. The amino acid sequences presented are SEQ ID NOS:967-1282.

FIG. 7A-7Z, 7AA-7BB illustrates several nucleotide sequences that encode human (*Homo sapiens*) V_κ domain antibodies (dAbs) that specifically bind human IL-13. The nucleotide sequences presented are SEQ ID NOS:1283-1507.

FIG. 8A-8L illustrates the amino acid sequences of the dAbs encoded by the nucleic acid sequences shown in FIG.7A-7Z, 7AA, 7BB. The amino acid sequences presented are SEQ ID NOS:1508-1732.

FIG. 9A is an alignment of the amino acid sequences of six V_κs that bind rat serum albumin (RSA). The aligned amino acid sequences are from V_κs designated

DOM7r-1 (SEQ ID NO:1736), DOM7r-3 (SEQ ID NO:1737), DOM7r-4 (SEQ ID NO:1738), DOM7r-5 (SEQ ID NO:1739), DOM7r-7 (SEQ ID NO:1740), and DOM7r-8 (SEQ ID NO:1741).

FIG. 9B is an alignment of the amino acid sequences of six V_κs that bind human serum albumin (HSA). The aligned amino acid sequences are from V_κs designated DOM7h-2 (SEQ ID NO:1742), DOM7h-3 (SEQ ID NO:1743), DOM7h-4 (SEQ ID NO:1744), DOM7h-6 (SEQ ID NO:1745), DOM7h-1 (SEQ ID NO:1746), and DOM7h-7 (SEQ ID NO:1747).

FIG. 9C is an alignment of the amino acid sequences of seven V_Hs that bind human serum albumin and a consensus sequence (SEQ ID NO:1755). The aligned sequences are from V_Hs designated DOM7h-22 (SEQ ID NO:1748), DOM7h-23 (SEQ ID NO:1749), DOM7h-24 (SEQ ID NO:1750), DOM7h-25 (SEQ ID NO:1751), DOM7h-26 (SEQ ID NO:1752), DOM7h-21 (SEQ ID NO:1753), and DOM7h-27 (SEQ ID NO:1754).

FIG. 9D is an alignment of the amino acid sequences of three Vκs that bind human serum albumin and rat serum albumin. The aligned amino acid sequences are from Vκs designated DOM7h-8 (SEQ ID NO:1756), DOM7r-13 (SEQ ID NO:1757), and DOM7r-14 (SEQ ID NO:1758).

FIG. 10 is an illustration of the amino acid sequences of Vκs that bind rat serum albumin (RSA). The illustrated sequences are from Vκs designated DOM7r-15 (SEQ ID NO:1759), DOM7r-16 (SEQ ID NO:1760), DOM7r-17 (SEQ ID NO:1761), DOM7r-18 (SEQ ID NO:1762), DOM7r-19 (SEQ ID NO:1763).

FIG. 11A-11B is an illustration of the amino acid sequences of the amino acid sequences of V_Hs that bind rat serum albumin (RSA). The illustrated sequences are from V_Hs designated DOM7r-20 (SEQ ID NO:1764), DOM7r-21 (SEQ ID NO:1765), DOM7r-22 (SEQ ID NO:1766), DOM7r-23 (SEQ ID NO:1767), DOM7r-24 (SEQ ID NO:1768), DOM7r-25 (SEQ ID NO:1769), DOM7r-26 (SEQ ID NO:1770), DOM7r-27 (SEQ ID NO:1771), DOM7r-28 (SEQ ID NO:1772), DOM7r-29 (SEQ ID NO:1773), DOM7r-30 (SEQ ID NO:1774), DOM7r-31 (SEQ ID NO:1775), DOM7r-32 (SEQ ID NO:1776), and DOM7r-33 (SEQ ID NO:1777).

FIG. 12 illustrates the amino acid sequences of several *Camelid* V_{HH}s that bind mouse serum albumin that are disclosed in WO 2004/041862. Sequence A (SEQ ID NO:1778), Sequence B (SEQ ID NO:1779), Sequence C (SEQ ID NO:1780), Sequence D (SEQ ID NO:1781), Sequence E (SEQ ID NO:1782), Sequence F (SEQ ID NO:1783), Sequence G (SEQ ID NO:1784), Sequence H (SEQ ID NO:1785), Sequence I (SEQ ID NO:1786), Sequence J (SEQ ID NO:1787), Sequence K (SEQ ID NO:1788), Sequence L (SEQ ID NO:1789), Sequence M (SEQ ID NO:1790), Sequence N (SEQ ID NO:1791), Sequence O (SEQ ID NO:1792), Sequence P (SEQ ID NO:1793) and Sequence Q (SEQ ID NO:1794).

FIG. 13 is a sensogram showing that some dAbs that bind IL-4 (DOM9-112-22, DOM9-44, and DOM9-155-1) bind to different epitopes on IL-4. IL-4 was immobilized on a surface plasmon resonance chip and a first anti-IL4 dAb was flowed over the surface and then a second dAb was flowed over the surface. This figure shows that DOM9-155-1 did not bind to IL-4 after DOM9-44 was bound. Similarly, DOM9-44 did not bind after DOM9-155-1 was bound. However, the third and fourth peaks show that DOM9-112-22 did bind IL-4 after DOM9-44 was bound and also after DOM9-155-1 was bound, demonstrating that these dAbs bind to different epitopes on the IL-4 antigen.

FIG. 14A is a graph showing the effect of 100 nM anti-IL-4 dAb (DOM9-44-502) on house dust mite (HDM) induced proliferation of peripheral blood mononuclear cells (PBMC) from twelve individual donors in an *in vitro* assay. Cell proliferation was assessed by measuring 3[H] thymidine incorporation. The addition of the anti-IL-4 dAb inhibited allergen-induced proliferation of PBMC obtained from ten out of the twelve donors. The average inhibition was 38%.

FIG. 14B is a graph showing the effect of 100 nM anti-IL-4 dAb (DOM9-155-11) on house dust mite (HDM) induced proliferation of PBMC from twelve individual donors in an *in vitro* assay. Cell proliferation was assessed by measuring 3[H] thymidine incorporation. The addition of the anti-IL-4 dAb inhibitied allergen-induced proliferation of PBMC obtained from ten out of twelve donors. The average inhibition was 34%

FIG. 15 is a graph showing the effect of anti-IL-13 dAbs DOM10-53-338 and DOM10-176-535 on IL-13-induced B cell proliferation. Cell proliferation was

assessed by measuring 3[H] thymidine incorporation. Both dAbs showed an average inhibition of 80% at 10nM and an average inhibition of 100% at 100 nM concentration.

FIG. 16A is a graph showing the effect of an extended half-life format dual specific ligand that binds IL-4 and IL-13 (PEGylated DOM9-112 (AST) DOM10-53-343) on IL-4 binding in an IL-4 receptor binding assay. The potency of the anti-IL-4 arm of the dual specific ligand (PEGylated DOM9-112 (AST) DOM10-53-343) was 13 nM. The potency of the dAb DOM9-112 monomer was 3.5 nM. The graph shows that the potency of the dual specific ligand (PEGylated DOM9-112 (AST) DOM10-53-343) was only slightly reduced as compared to the dAb.

FIG. 16B is a graph showing the effect of an extended half-life format dual specific ligand that binds IL-4 and IL-13 (PEGylated DOM9-112 (AST) DOM10-53-343) on IL-13 binding in an IL-13 receptor binding assay. The potency of the anti-IL-13 arm of the dual specific ligand was 310 pM and the potency of the dAb DOM10-53-343 monomer was 230 pM. The graph shows that the potency of the dual specific ligand was about the same as the dAb monomer.

FIG. 17A is a graph showing the effect of dual specific ligand (DOM9-112 (ASTKGPS) DOM10-53-344) on IL-4 binding in the IL-4 receptor binding assay. The potency of the anti IL-4 arm of the dual specific ligand and of the dAb DOM9-112 monomer were approximately 1 nM. The graph shows potency of the dual specific ligand was about the same as the dAb monomer.

FIG. 17B is a graph showing the effect of dual specific ligand (DOM9-112 (ASTKGPS) DOM10-53-344) on IL-13 binding in the IL-13 receptor binding assay. The potency of the anti IL-13 arm of the dual specific ligand was 120 pM. The potency of the dAb DOM10-53-344 monomer was 40 pM. The graph shows potency of the dual specific ligand was only slightly reduced as compared to the dAb monomer.

FIG. 18A is a graph showing the effect of a dual specific IgG-like format that binds IL-4 and IL-13 (IgG:9-44-502 x 10-176-535) on IL-4 binding in the IL-4 receptor binding assay. The potency of the dAb DOM9-44-502 monomer was 4 nM and the potency of the dual specific IgG-like format was 13 nM. The graph shows

the potency of the anti-IL-4 dAb DOM9-44-502 monomer was reduced by 3-4 fold when formatted into the IgG-like format.

FIG. 18B is a graph showing the effect of a dual specific IgG-like format that binds IL-4 and IL-13 (IgG:9-44-502 x 10-176-535) on IL-13 binding in the IL-13 sandwich ELISA. The potency for both the dual specific IgG-like format and the dAb DOM10-176-535 monomer were 1 nM.

FIG. 19A-19Z, 19AA-19ZZ, 19AAA-19HHH illustrates several nucleotide sequences that encode human (*Homo sapiens*) domain antibodies (dAbs) that specifically bind human IL-13 and the nucleotide sequences of several primers. The nucleotide sequences presented are SEQ ID NOS:1804-2128.

FIG. 20A-20Z, 20AA-20CC illustrates the amino acid sequences of the dAbs encoded by the nucleic acid sequences shown in FIG. 19A-19Z, 19AA-19ZZ, 19AAA-19HHH. The amino acid sequences presented are SEQ ID NOS:2129-2392.

FIG. 21A-21E illustrates several nucleotide sequences that encode human (*Homo sapiens*) domain antibodies (dAbs) that specifically bind human IL-4. the nucleotide sequences presented are SEQ ID NOS:2393-2425.

FIG. 22A-22C illustrates the amino acid sequences of the dAbs encoded by the nucleic acid sequences shown in FIG. 21A-21E. The amino acid sequences presented are SEQ ID NOS:2426-2455 and SEQ ID NOS:1733-1735.

DETAILED DESCRIPTION OF THE INVENTION

Within this specification embodiments have been described in a way which enables a clear and concise specification to be written, but it is intended and will be appreciated that embodiments may be variously combined or separated without parting from the invention.

As used herein, the term "ligand" refers to a compound that comprises at least one peptide, polypeptide or protein moiety that has a binding site with binding specificity for a desired endogenous target compound (*e.g.*, IL-4, IL-13). The ligands according to the invention preferably comprise immunoglobulin variable domains which have different binding specificities, and do not contain variable domain pairs which together form a binding site for target compound (*i.e.*, do not

comprise an immunoglobulin heavy chain variable domain and an immunoglobulin light chain variable domain that together form a binding site for IL-4 or IL-13). Preferably each domain which has a binding site that has binding specificity for a target is an immunoglobulin single variable domain (*e.g.*, immunoglobulin single heavy chain variable domain (*e.g.*, V_H, V_{HH}), immunoglobulin single light chain variable domain (*e.g.*, V_L)) that has binding specificity for a desired target (*e.g.*, IL-4, IL-13). Each polypeptide domain which has a binding site that has binding specificity for a target (*e.g.*, IL-4, IL-13) can also comprise one or more complementarity determining regions (CDRs) of an antibody or antibody fragment (*e.g.*, an immunoglobulin single variable domain) that has binding specificity for a desired target (*e.g.*, IL-4, IL-13) in a suitable format, such that the binding domain has binding specificity for the target. For example, the CDRs can be grafted onto a suitable protein scaffold or skeleton, such as an affibody, a SpA scaffold, an LDL receptor class A domain, or an EGF domain. Further, the ligand can be bivalent (heterobivalent) or multivalent (heteromultivalent) as described herein. Thus, "ligands" include polypeptides that comprise two dAbs wherein each dAb binds to a different target (*e.g.*, IL-4, IL-13). Ligands also include polypeptides that comprise at least two dAbs that bind different targets (or the CDRs of dAbs) in a suitable format, such as an antibody format (*e.g.*, IgG-like format, scFv, Fab, Fab', $F(ab')_2$) or a suitable protein scaffold or skeleton, such as an affibody, a SpA scaffold, an LDL receptor class A domain, an EGF domain, avimer and multispecific ligands as described herein.

The polypeptide domain which has a binding site that has binding specificity for a target (*e.g.*, IL-4, IL-13) can also be a protein domain comprising a binding site for a desired target, *e.g.*, a protein domain is selected from an affibody, a SpA domain, an LDL receptor class A domain, an avimer (see, *e.g.*, U.S. Patent Application Publication Nos. 2005/0053973, 2005/0089932, 2005/0164301). If desired, a "ligand" can further comprise one or more additional moieties, that can each independently be a peptide, polypeptide or protein moiety or a non-peptidic moiety (*e.g.*, a polyalkylene glycol, a lipid, a carbohydrate). For example, the ligand can further comprise a half-life extending moiety as described herein (*e.g.*, a polyalkylene glycol moiety, a moiety comprising albumin, an albumin fragment or

albumin variant, a moiety comprising transferrin, a transferrin fragment or transferrin variant, a moiety that binds albumin, a moiety that binds neonatal Fc receptor).

As used herein, the phrase "target" refers to a biological molecule (*e.g.*, peptide, polypeptide, protein, lipid, carbohydrate) to which a polypeptide domain which has a binding site can bind. The target can be, for example, an intracellular target (*e.g.*, an intracellular protein target), a soluble target (*e.g.*, a secreted protein such as IL-4, IL-13), or a cell surface target (*e.g.*, a membrane protein, a receptor protein). Preferably, the target is IL-4 or IL-13.

The phrase "immunoglobulin single variable domain" refers to an antibody variable region (V_H, V_{HH}, V_L) that specifically binds a target, antigen or epitope independently of other V domains; however, as the term is used herein, an immunoglobulin single variable domain can be present in a format (*e.g.*, hetero-multimer) with other variable regions or variable domains where the other regions or domains are not required for antigen binding by the single immunoglobulin variable domain (*i.e.*, where the immunoglobulin single variable domain binds antigen independently of the additional variable domains). Each "immunoglobulin single variable domain" encompasses not only an isolated antibody single variable domain polypeptide, but also larger polypeptides that comprise one or more monomers of an antibody single variable domain polypeptide sequence. A "domain antibody" or "dAb" is the same as an "immunoglobulin single variable domain" polypeptide as the term is used herein. An immunoglobulin single variable domain polypeptide, is preferably a mammalian immunoglobulin single variable domain polypeptide, more preferably human, and includes rodent immunoglobulin single variable domains (for example, as disclosed in WO 00/29004, the contents of which are incorporated herein by reference in their entirety) and camelid V_{HH} dAbs. As used herein, camelid dAbs are immunoglobulin single variable domain polypeptides which are derived from species including camel, llama, alpaca, dromedary, and guanaco, and comprise heavy chain antibodies naturally devoid of light chain (V_{HH}). Similar dAbs, can be obtained from single chain antibodies from other species, such as nurse shark. Preferred ligands comprises at least two different immunoglobulin single variable domain polypeptides or at least two different dAbs.

The immunoglobulin single variable domains (dAbs) described herein contain complementarity determining regions (CDR1, CDR2 and CDR3). The locations of CDRs and frame work (FR) regions and a numbering system have been defined by Kabat *et al.* (Kabat, E.A. *et al.*, *Sequences of Proteins of Immunological Interest*, Fifth Edition, U.S. Department of Health and Human Services, U.S. Government Printing Office (1991)). The amino acid sequences of the CDRs (CDR1, CDR2, CDR3) of the V_H and V_K dAbs disclosed herein will be readily apparent to the person of skill in the art based on the well known Kabat amino acid numbering system and definition of the CDRs. According to the Kabat numbering system V_L (V_K or V_λ) CDR1 is from position 24-34, V_L CDR2 is from position 50-56, V_L CDR3 is from position 89-97, and V_H CDR1 is from position 31-35, V_H CDR2 is from position 50-65 and V_H CDR3 is from position 95-102. Heavy chain CDR-H3 have varying lengths, insertions are numbered between residue H100 and H101 with letters up to K (i.e. H100, H100A ... H100K, H101). Residue 103 which is the start of FR4 is almost always a W.

As used herein "interleukin-4" (IL-4) refers to naturally occurring or endogenous mammalian IL-4 proteins and to proteins having an amino acid sequence which is the same as that of a naturally occurring or endogenous corresponding mammalian IL-4 protein (*e.g.*, recombinant proteins, synthetic proteins (*i.e.*, produced using the methods of synthetic organic chemistry)). Accordingly, as defined herein, the term includes mature IL-4 protein, polymorphic or allelic variants, and other isoforms of an IL-4 and modified or unmodified forms of the foregoing (*e.g.*, lipidated, glycosylated). Naturally occurring or endogenous IL-4 includes wild type proteins such as mature IL-4, polymorphic or allelic variants and other isoforms and mutant forms which occur naturally in mammals (*e.g.*, humans, non-human primates). Such proteins can be recovered or isolated from a source which naturally produces IL-4, for example. These proteins and proteins having the same amino acid sequence as a naturally occurring or endogenous corresponding IL-4, are referred to by the name of the corresponding mammal. For example, where the corresponding mammal is a human, the protein is designated as

a human IL-4. Several mutant IL-4 proteins are known in the art, such as those disclosed in WO 03/038041.

As used herein "interleukin-13" (IL-13) refers to naturally occurring or endogenous mammalian IL-13 proteins and to proteins having an amino acid sequence which is the same as that of a naturally occurring or endogenous corresponding mammalian IL-13 protein (*e.g.*, recombinant proteins, synthetic proteins (*i.e.*, produced using the methods of synthetic organic chemistry)). Accordingly, as defined herein, the term includes mature IL-13 protein, polymorphic or allelic variants, and other isoforms of IL-13 (*e.g.*, produced by alternative splicing or other cellular processes), and modified or unmodified forms of the foregoing (*e.g.*, lipidated, glycosylated). Naturally occurring or endogenous IL-13 include wild type proteins such as mature IL-13, polymorphic or allelic variants and other isoforms and mutant forms which occur naturally in mammals (*e.g.*, humans, non-human primates). For example, as used herein IL-13 encompasses the human IL-13 variant in which Arg at position 110 of mature human IL-13 is replaced with Gln (position 110 of mature IL-13 corresponds to position 130 of the precursor protein) which is associed with asthma (atopic and nonatopic asthma) and other variants of IL-13. (Heinzmann *et al., Hum Mol Genet.* 9:549-559 (2000).) Such proteins can be recovered or isolated from a source which naturally produces IL-13, for example. These proteins and proteins having the same amino acid sequence as a naturally occurring or endogenous corresponding IL-13, are referred to by the name of the corresponding mammal. For example, where the corresponding mammal is a human, the protein is designated as a human IL-13. Several mutant IL-13 proteins are known in the art, such as those disclosed in WO 03/035847.

"Affinity" and "avidity" are terms of art that describe the strength of a binding interaction. With respect to the ligands of the invention, avidity refers to the overall strength of binding between the targets (*e.g.*, first cell surface target and second cell surface target) on the cell and the ligand. Avidity is more than the sum of the individual affinities for the individual targets.

As used herein, "toxin moiety" refers to a moiety that comprises a toxin. A toxin is an agent that has deleterious effects on or alters cellular physiology (*e.g.*, causes cellular necrosis, apoptosis or inhibits cellular division).

As used herein, the term "dose" refers to the quantity of ligand administered to a subject all at one time (unit dose), or in two or more administrations over a defined time interval. For example, dose can refer to the quantity of ligand (*e.g.*, ligand comprising an immunoglobulin single variable domain that binds IL-4 and an immunoglobulin single variable domain that binds IL-13) administered to a subject over the course of one day (24 hours) (daily dose), two days, one week, two weeks, three weeks or one or more months (*e.g.*, by a single administration, or by two or more administrations). The interval between doses can be any desired amount of time.

As used herein "complementary" refers to when two immunoglobulin domains belong to families of structures which form cognate pairs or groups or are derived from such families and retain this feature. For example, a V_H domain and a V_L domain of an antibody are complementary; two V_H domains are not complementary, and two V_L domains are not complementary. Complementary domains may be found in other members of the immunoglobulin superfamily, such as the V_α and V_β (or γ and δ) domains of the T-cell receptor. Domains which are artificial, such as domains based on protein scaffolds which do not bind epitopes unless engineered to do so, are non-complementary. Likewise, two domains based on (for example) an immunoglobulin domain and a fibronectin domain are not complementary.

As used herein, "immunoglobulin" refers to a family of polypeptides which retain the immunoglobulin fold characteristic of antibody molecules, which contains two β sheets and, usually, a conserved disulphide bond. Members of the immunoglobulin superfamily are involved in many aspects of cellular and non-cellular interactions *in vivo*, including widespread roles in the immune system (for example, antibodies, T-cell receptor molecules and the like), involvement in cell adhesion (for example the ICAM molecules) and intracellular signaling (for example, receptor molecules, such as the PDGF receptor). The present invention is applicable to all immunoglobulin superfamily molecules which possess binding domains. Preferably, the present invention relates to antibodies.

As used herein "domain" refers to a folded protein structure which retains its tertiary structure independently of the rest of the protein. Generally, domains are

responsible for discrete functional properties of proteins, and in many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the domain. By single antibody variable domain is meant a folded polypeptide domain comprising sequences characteristic of antibody variable domains. It therefore includes complete antibody variable domains and modified variable domains, for example in which one or more loops have been replaced by sequences which are not characteristic of antibody variable domains, or antibody variable domains which have been truncated or comprise N- or C-terminal extensions, as well as folded fragments of variable domains which retain at least in part the binding activity and specificity of the full-length domain. Thus, each ligand comprises at least two different domains.

"Repertoire" A collection of diverse variants, for example polypeptide variants which differ in their primary sequence. A library that encompasses a repertoire of polypeptides preferably comprises at least 1000 members.

"Library" The term library refers to a mixture of heterogeneous polypeptides or nucleic acids. The library is composed of members, each of which have a single polypeptide or nucleic acid sequence. To this extent, *library* is synonymous with *repertoire*. Sequence differences between library members are responsible for the diversity present in the library. The library may take the form of a simple mixture of polypeptides or nucleic acids, or may be in the form of organisms or cells, for example bacteria, viruses, animal or plant cells and the like, transformed with a library of nucleic acids. Preferably, each individual organism or cell contains only one or a limited number of library members. Advantageously, the nucleic acids are incorporated into expression vectors, in order to allow expression of the polypeptides encoded by the nucleic acids. In a preferred aspect, therefore, a library may take the form of a population of host organisms, each organism containing one or more copies of an expression vector containing a single member of the library in nucleic acid form which can be expressed to produce its corresponding polypeptide member. Thus, the population of host organisms has the potential to encode a large repertoire of genetically diverse polypeptide variants.

As used herein an antibody refers to IgG, IgM, IgA, IgD or IgE or a fragment (such as a Fab, $F(ab')_2$, Fv, disulphide linked Fv, scFv, closed conformation

multispecific antibody, disulphide-linked scFv, diabody) whether derived from any species naturally producing an antibody, or created by recombinant DNA technology; whether isolated from serum, B-cells, hybridomas, transfectomas, yeast or bacteria.

As described herein an "antigen' is a molecule that is bound by a binding domain according to the present invention. Typically, antigens are bound by antibody ligands and are capable of raising an antibody response *in vivo*. It may be a polypeptide, protein, nucleic acid or other molecule. Generally, the dual-specific ligands according to the invention are selected for target specificity against two particular targets (*e.g.*, antigens). In the case of conventional antibodies and fragments thereof, the antibody binding site defined by the variable loops (L1, L2, L3 and H1, H2, H3) is capable of binding to the antigen.

An "epitope" is a unit of structure conventionally bound by an immunoglobulin V_H/V_L pair. Epitopes define the minimum binding site for an antibody, and thus represent the target of specificity of an antibody. In the case of a single domain antibody, an epitope represents the unit of structure bound by a variable domain in isolation.

"Universal framework" refers to a single antibody framework sequence corresponding to the regions of an antibody conserved in sequence as defined by Kabat ("Sequences of Proteins of Immunological Interest", US Department of Health and Human Services) or corresponding to the human germline immunoglobulin repertoire or structure as defined by Chothia and Lesk, (1987) *J. Mol. Biol.* 196:910-917. The invention provides for the use of a single framework, or a set of such frameworks, which has been found to permit the derivation of virtually any binding specificity through variation in the hypervariable regions alone.

The phrase, "half-life," refers to the time taken for the serum concentration of the ligand to reduce by 50%, *in vivo*, for example due to degradation of the ligand and/or clearance or sequestration of the dual-specific ligand by natural mechanisms. The ligands of the invention are stabilized *in vivo* and their half-life increased by binding to molecules which resist degradation and/or clearance or sequestration. Typically, such molecules are naturally occurring proteins which themselves have a

long half-life *in vivo*. The half-life of a ligand is increased if its functional activity persists, *in vivo*, for a longer period than a similar ligand which is not specific for the half-life increasing molecule. Thus a ligand specific for HSA and two target molecules is compared with the same ligand wherein the specificity to HSA is not present, that is does not bind HSA but binds another molecule. For example, it may bind a third target on the cell.Typically, the half-life is increased by 10%, 20%, 30%, 40%, 50% or more. Increases in the range of 2x, 3x, 4x, 5x, 10x, 20x, 30x, 40x, 50x or more of the half-life are possible. Alternatively, or in addition, increases in the range of up to 30x, 40x, 50x, 60x, 70x, 80x, 90x, 100x, 150x of the half life are possible.

As referred to herein, the term "competes" means that the binding of a first target to its cognate target binding domain is inhibited when a second target is bound to its cognate target binding domain. For example, binding may be inhibited sterically, for example by physical blocking of a binding domain or by alteration of the structure or environment of a binding domain such that its affinity or avidity for a target is reduced.

As used herein, the terms "low stringency," "medium stringency," "high stringency," or "very high stringency conditions" describe conditions for nucleic acid hybridization and washing. Guidance for performing hybridization reactions can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6, which is incorporated herein by reference in its entirety. Aqueous and nonaqueous methods are described in that reference and either can be used. Specific hybridization conditions referred to herein are as follows: (1) low stringency hybridization conditions in 6X sodium chloride/sodium citrate (SSC) at about 45C, followed by two washes in 0.2X SSC, 0.1% SDS at least at 50C (the temperature of the washes can be increased to 55C for low stringency conditions); (2) medium stringency hybridization conditions in 6X SSC at about 45C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 60C; (3) high stringency hybridization conditions in 6X SSC at about 45C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 65C; and preferably (4) very high stringency hybridization conditions are 0.5M sodium phosphate, 7% SDS at 65C, followed by one or more washes at 0.2X SSC, 1% SDS at 65C. Very high stringency conditions

(4) are the preferred conditions and the ones that should be used unless otherwise specified.

Sequences similar or homologous (*e.g.*, at least about 70% sequence identity) to the sequences disclosed herein are also part of the invention. In some embodiments, the sequence identity at the amino acid level can be about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher. At the nucleic acid level, the sequence identity can be about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher. Alternatively, substantial identity exists when the nucleic acid segments will hybridize under selective hybridization conditions (*e.g.*, very high stringency hybridization conditions), to the complement of the strand. The nucleic acids may be present in whole cells, in a cell lysate, or in a partially purified or substantially pure form.

Calculations of "homology" or "sequence identity" or "similarity" between two sequences (the terms are used interchangeably herein) are performed as follows. The sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 80%, 90%, 100% of the length of the reference sequence. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid " homology" is equivalent to amino acid or nucleic acid "identity"). The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

Amino acid and nucleotide sequence alignments and homology, similarity or identity, as defined herein are preferably prepared and determined using the

algorithm BLAST 2 Sequences, using default parameters (Tatusova, T. A. *et al.*, FEMS Microbiol Lett, 174:187-188 (1999)). Alternatively, the BLAST algorithm (version 2.0) is employed for sequence alignment, with parameters set to default values. BLAST (Basic Local Alignment Search Tool) is the heuristic search algorithm employed by the programs blastp, blastn, blastx, tblastn, and tblastx; these programs ascribe significance to their findings using the statistical methods of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. USA 87(6):2264-8.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art (*e.g.*, in cell culture, molecular genetics, nucleic acid chemistry, hybridization techniques and biochemistry). Standard techniques are used for molecular, genetic and biochemical methods (see generally, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2d ed. (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. and Ausubel *et al.*, Short Protocols in Molecular Biology (1999) 4th Ed, John Wiley & Sons, Inc. which are incorporated herein by reference) and chemical methods.

The invention relates to ligands that have binding specificity for IL-4 (*e.g.*, human IL-4), ligands that have binding specificity for IL-13 (*e.g.*, human IL-13), and to ligands that have binding specificity for IL-4 and IL-13 (*e.g.*, human IL-4 and human IL-13). For example, the ligand can comprise a polypeptide domain having a binding site with binding specificity for IL-4, a polypeptide domain having a binding site with binding specificity IL-13, or comprise a polypeptide domain having a binding site with binding specificity for IL-4 and a polypeptide domain having a binding site with binding specificity for IL-13.

The invention also relates to ligands that have cross-reactivity with human IL-4 and a non-human IL-4 (*e.g.*, rhesus IL-4, cynomolgous IL-4), ligands that have cross-reactivity with human IL-13 and a non-human IL-13 (*e.g.*, rhesus IL-13, cynomolgous IL-13), and to ligands that have binding specificity for human IL-4, human IL-13, non-human IL-4 and non-human IL-13 (*e.g.*., rhesus IL-4, rhesus IL-13, cynomolgous IL-4 and cynomolgous IL-13).

The ligands of the invention provide several advantages. For example, as described herein, the ligand can be tailored to have a desired *in vivo* serum half-life. Domain antibodies are much smaller than conventional antibodies, and can be administered to achieve better tissue penetration than conventional antibodies. Thus, dAbs and ligands that comprise a dAb provide advantages over conventional antibodies when administered to treat disease, such as Th2-mediated disease, asthma, allergic diseases, cancer (*e.g.*, renal cell cancer). For example, asthma (*e.g.* allergic asthma) can be IgE-mediated or non-IgE-mediated, and ligands that have binding specificity for IL-4, IL-13 or IL-4 and IL-13 can be administered to treat both IgE-mediated and non-IgE-mediated asthma.

Similarly, due to the overlap and similarity in the biological activity of IL-4 and IL-13, therapy with agents that bind and inhibit only one of these cytokines may not produce the desired effects in all circumstances. Accordingly, ligands that have binding specificity for IL-4 and IL-13 can be administered to a patient (*e.g.*, a patient with allergic disease (*e.g.*, allergic asthma)) to provide superior therapy using a single therapeutic agent.

In some embodiments, the ligand has binding specificity for IL-4 and comprises an (at least one) immunoglobulin single variable domain with binding specificity for IL-4. In other embodiments, the ligand has binding specificity for IL-13 and comprises an (at least one) immunoglobulin single variable domain with binding specificity for IL-13. In certain embodiments, the ligand has binding specificity for IL-4 and IL-13, and comprises an (at least one) immunoglobulin single variable domain with binding specificity for IL-4 and an (at least one) immunoglobulin single variable domain with binding specificity for IL-13.

The ligand of the invention can be formatted as described herein. For example, the ligand of the invention can be formatted to tailor *in vivo* serum half-life. If desired, the ligand can further comprise a toxin or a toxin moiety as described herein. In some embodiments, the ligand comprises a surface active toxin, such as a free radical generator (*e.g.*, selenium containing toxin) or a radionuclide. In other embodiments, the toxin or toxin moiety is a polypeptide domain (*e.g.*, a dAb) having a binding site with binding specificity for an intracellular target. In

particular embodiments, the ligand is an IgG-like format that has binding specificity for IL-4 and IL-13 (*e.g.*, human IL-4 and human IL-13).

In one aspect, the invention relates to a ligand that has binding specificity for interleukin-4 (IL-4) and interleukin-13 (IL-13) comprising a protein moiety that has a binding site with binding specificity for IL-4; and a protein moiety that has a binding site with binding specificity for IL-13. The ligand that has binding specificity for IL-4 and IL-13 of this aspect of the invention, can be further characterized by any one or any combination of the following: (1) the proviso that said protein moiety that has a binding site with binding specificity for IL-4 is not an IL-4 receptor or IL-4-binding portion thereof, and said protein moiety that has a binding site with binding specificity for IL-13 is not an IL-13 receptor or IL-13-binding portion thereof; (2) the proviso that said binding site with binding specificity for IL-4 and said binding site with binding specificity for IL-13 each consist of a single amino acid chain; (3) the proviso that neither said binding site with binding specificity for IL-4 nor said binding site with binding specificity for IL-13 comprise an immunoglobulin heavy chain variable domain and an immunoglobulin light chain variable domain; and (4) the proviso that said protein moiety that has a binding site with binding specificity for IL-4 is not an antibody that binds IL-4 or an antigen-binding fragment thereof that comprises an immunoglobulin heavy chain variable domain and an immunoglobulin light chain variable domain that together form a binding site for IL-4, and said protein moiety that has a binding site with binding specificity for IL-13 is not an antibody that binds IL-13 or an antigen-binding fragment thereof that comprises an immunoglobulin heavy chain variable domain and an immunoglobulin light chain variable domain that together form a binding site for IL-13.

In one aspect, the invention relates to a ligand that has binding specificity for IL-4, comprising a protein moiety that has a binding site with binding specificity for IL-4. The ligand that has binding specificity for IL-4 of this aspect of the invention, can be further characterized by any one or any combination of the following: (1) the proviso that said protein moiety that has a binding site with binding specificity for IL-4 is not an antibody that binds IL-4 or an antigen-binding fragment thereof that comprises an immunoglobulin heavy chain variable domain and an immunoglobulin

light chain variable domain that together form a binding site for IL-4; (2) the proviso that said protein moiety that has a binding site with binding specificity for IL-4 is not an IL-4 receptor or IL-4-binding portion thereof; (3) the proviso that said binding site with binding specificity for IL-4 consists of a single amino acid chain; and (4) the proviso that said binding site with binding specificity for IL-4 does not consist of an immunoglobulin heavy chain variable domain and an immunoglobulin light chain variable domain.

In one aspect, the invention relates to a ligand that has binding specificity for IL-13, comprising a protein moiety that has a binding site with binding specificity for IL-13. The ligand that has binding specificity for IL-13 of this aspect of the invention, can be further characterized by any one or any combination of the following: (1) the proviso that said protein moiety that has a binding site with binding specificity for IL-13 is not an antibody that binds IL-13 or an antigen-binding fragment thereof that comprises an immunoglobulin heavy chain variable domain and an immunoglobulin light chain variable domain that together form a binding site for IL-13; (2) the proviso that said protein moiety that has a binding site with binding specificity for IL-13 is not an IL-13 receptor or IL-13-binding portion thereof; (3) the proviso that said binding site with binding specificity for IL-13 consists of a single amino acid chain; and (4) the proviso that said binding site with binding specificity for IL-13 does not consist of an immunoglobulin heavy chain variable domain and an immunoglobulin light chain variable domain.

Ligand Formats

The ligand of the invention can be formatted as a monospecific, dual specific or multispecific ligand as described herein. See, also WO 03/002609, the entire teachings of which are incorporated herein by reference, regarding ligand formatting. Such dual specific ligands comprise immunoglobulin single variable domains that have different binding specificities. Such dual specific ligands can comprise combinations of heavy and light chain domains. For example, the dual specific ligand may comprise a V_H domain and a V_L domain, which may be linked together in the form of an scFv (*e.g.*, using a suitable linker such as Gly_4Ser), or formatted into a bispecific antibody or antigen-binding fragment theref (*e.g.* $F(ab')_2$,

Fab', Fab fragment). The dual specific ligands do not comprise complementary V_H/V_L pairs which form a conventional two chain antibody antigen-binding site that binds antigen or epitope co-operatively. Instead, the dual format ligands can comprise a V_H/V_L complementary pair, wherein the V domains have different binding specificities.

The ligand (*e.g.*, monospecific, dual specific ligands) may comprise one or more C_H or C_L domains if desired. A hinge region domain may also be included if desired. Such combinations of domains may, for example, mimic natural antibodies, such as IgG or IgM, or fragments thereof, such as Fv, scFv, Fab or $F(ab')_2$ molecules. Other structures, such as a single arm of an IgG molecule comprising V_H, V_L, C_H1 and C_L domains, are envisaged. The ligand can comprise a heavy chain constant region of an immunoglobulin (*e.g.*, IgG (*e.g.*, IgG1, IgG2, IgG3, IgG4) IgM, IgA, IgD or IgE) or portion thereof (*e.g.*, Fc portion) and/or a light chain constant region (*e.g.*, C_λ, C_κ). For example, the ligand can comprise CH1 of IgG1 (*e.g.*, human IgG1), CH1 and CH2 of IgG1 (*e.g.*, human IgG1), CH1, CH2 and CH3 of IgG1 (*e.g.*, human IgG1), CH2 and CH3 of IgG1 (*e.g.*, human IgG1), or CH1 and CH3 of IgG1 (*e.g.*, human IgG1).

In one example, a dual specific ligand of the invention comprises only two variable domains although several such ligands may be incorporated together into the same protein, for example two such ligands can be incorporated into an IgG or a multimeric immunoglobulin, such as IgM. Alternatively, in another embodiment a plurality of dual specific ligands are combined to form a multimer. For example, two different dual specific ligands are combined to create a tetra-specific molecule. It will be appreciated by one skilled in the art that the light and heavy variable regions of a dual-specific ligand of the present invention may be on the same polypeptide chain, or alternatively, on different polypeptide chains. In the case that the variable regions are on different polypeptide chains, then they may be linked via a linker, generally a flexible linker (such as a polypeptide chain), a chemical linking group, or any other method known in the art.

Ligands can be formatted as bi- or multispecific antibodies or antibody fragments or into bi- or multispecific non-antibody structures. Suitable formats include, any suitable polypeptide structure in which an antibody variable domain or

one or more of the CDRs thereof can be incorporated so as to confer binding specificity for antigen on the structure. A variety of suitable antibody formats are known in the art, such as, bispecific IgG-like formats (*e.g.*, chimeric antibodies, humanized antibodies, human antibodies, single chain antibodies, heterodimers of antibody heavy chains and/or light chains, antigen-binding fragments of any of the foregoing (*e.g.*, a Fv fragment (*e.g.*, single chain Fv (scFv), a disulfide bonded Fv), a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment), a single variable domain (*e.g.*, V_H, V_L, V_{HH}), a dAb, and modified versions of any of the foregoing (*e.g.*, modified by the covalent attachment of polyalkylene glycol (*e.g.*, polyethylene glycol, polypropylene glycol, polybutylene glycol) or other suitable polymer). See, PCT/GB03/002804, filed June 30, 2003, which designated the United States, (WO 2004/081026) regarding PEGylated of single variable domains and dAbs, suitable methods for preparing same, increased *in vivo* half life of the PEGylated single variable domains and dAb monomers and multimers, suitable PEGs, preferred hydrodynamic sizes of PEGs, and preferred hydrodynamic sizes of PEGylated single variable domains and dAb monomers and multimers. The entire teaching of PCT/GB03/002804 (WO 2004/081026), including the portions referred to above, are incorporated herein by reference.

The ligand can be formatted using a suitable linker such as $(Gly_4Ser)_n$, where n = from 1 to 8, (*e.g.*, 1, 2, 3, 4, 5, 6 or 7). If desired, ligands, including dAb monomers, dimers and trimers, can be linked to an antibody Fc region, comprising one or both of C_H2 and C_H3 domains, and optionally a hinge region. For example, vectors encoding ligands linked as a single nucleotide sequence to an Fc region may be used to prepare such polypeptides.

Ligands and dAb monomers can also be combined and/or formatted into non-antibody multi-ligand structures to form multivalent complexes, which bind target molecules with the same antigen, thereby providing superior avidity. For example natural bacterial receptors such as SpA can been used as scaffolds for the grafting of CDRs to generate ligands which bind specifically to one or more epitopes. Details of this procedure are described in US 5,831,012. Other suitable scaffolds include those based on fibronectin and affibodies. Details of suitable procedures are described in WO 98/58965. Other suitable scaffolds include

lipocallin and CTLA4, as described in van den Beuken *et al.*, J. *Mol. Biol.* 310:591-601 (2001), and scaffolds such as those described in WO 00/69907 (Medical Research Council), which are based for example on the ring structure of bacterial GroEL or other chaperone polypeptides. Protein scaffolds may be combined; for example, CDRs may be grafted on to a CTLA4 scaffold and used together with immunoglobulin V_H or V_L domains to form a ligand. Likewise, fibronectin, lipocallin and other scaffolds may be combined

A variety of suitable methods for preparing any desired format are known in the art. For example, antibody chains and formats (*e.g.*, monospecific, bispecific, trispecific or tetraspecific IgG-like formats, chimeric antibodies, humanized antibodies, human antibodies, single chain antibodies, homodimers and heterodimers of antibody heavy chains and/or light chains) can be prepared by expression of suitable expression constructs and/or culture of suitable cells (*e.g.*, hybridomas, heterohybridomas, recombinant host cells containing recombinant constructs encoding the format). Further, formats such as antigen-binding fragments of antibodies or antibody chains (*e.g.*, bispecific binding fragments, such as a Fv fragment (*e.g.*, single chain Fv (scFv), a disulfide bonded Fv), a Fab fragment, a Fab' fragment, a $F(ab')_2$ fragment), can be prepared by expression of suitable expression constructs or by enzymatic digestion of antibodies, for example using papain or pepsin.

The ligand can be formatted as a multispecific ligand, for example as described in WO 03/002609, the entire teachings of which are incorporated herein by reference. Such multispecific ligand possesses more than one epitope binding specificity. Generally, the multi-specific ligand comprises two or more epitope binding domains, such dAbs or non-antibody protein domain comprising a binding site for an epitope, *e.g.*, an affibody, a SpA domain, an LDL receptor class A domain, an EGF domain, an avimer. Multispecific ligands can be formatted further as described herein.

In some embodiments, the ligand is an IgG-like format. Such formats have the conventional four chain structure of an IgG molecule (2 heavy chains and two light chains), in which one or more of the variable regions (V_H and or V_L) have been replaced with a dAb or immunoglobulin single variable domain of a desired

specificity. Preferably, each of the variable regions (2 V_H regions and 2 V_L regions) is replaced with a dAb or immunoglobulin single variable domain. The dAb(s) or immunoglobulin single variable domain(s) that are included in an IgG-like format can have the same specificity or different specificities. In some embodiments, the IgG-like format is tetravalent and can have one, two, three or four specificities. The IgG-like format can be bispecific and comprise, for example, a first and second dAb that have the same specificity, a third dAb with a different specificity and a fourth dAb with a different specificity from the first, second and third dAbs; or tetraspecific and comprise four dAbs that each have a different specificity.

The IgG-like format can be monospecific and comprise 4 dAbs that have the specificity for IL-4 or for IL-13. The IgG-like format can be bispecific and comprise, for example, 3 dAbs that have specificity for IL-4 and another dAb that has specificity for IL-13, or bispecific and comprise, for example two dAbs that have specificity for IL-4 and two dAbs that have specificity for IL-13. The IgG-like format can be bispecific and comprise, for example, 3 dAbs that have specificity for IL-13 and another dAb that has specificity for IL-14. When the IgG-like format contains two or more dAbs that bind IL-4, the dAbs can bind to the same or different epitopes. For example, the IgG-like format can comprise two, three or four dAbs that have binding specificity for IL-4 that bind the same or different epitopes on IL-4. Similarly, when the IgG-like format contains two or more dAbs that bind IL-13, the dAbs can bind to the same or different epitopes. For example, the IgG-like format can comprise two, three or four dAbs that have binding specificity for IL-13 that bind the same or different epitopes on IL-13.

In one example, the IgG-like format is a tetravalent IgG-like ligand that has binding specificity for IL-4 or IL-13 comprising two heavy chains and two light chains, wherein said heavy chains comprise the constant region of an immunoglobulin heavy chain and a single immunoglobulin variable domain that has binding specificity for IL-4 or IL-13; and said light chains comprise the constant region of an immunoglobulin light chain and a single immunoglobulin variable domain that has binding specificity for IL-4 or IL-13. The IgG-like format of this example can be further characterized by the proviso that when said heavy chains comprise a single immunoglobulin variable domain that has binding specificity for

IL-4, said light chains comprise a single immunoglobulin variable domain that has binding specificity for IL-13; and when said heavy chains comprise a single immunoglobulin variable domain that has binding specificity for IL-13, said light chains comprise a single immunoglobulin variable domain that has binding specificity for IL-4.

Antigen-binding fragments of IgG-like formats (*e.g.*, Fab, $F(ab')_2$, Fab', Fv, scF_V) can be prepared. In addition, a particular constant region or Fc portion (*e.g.*, constant region or Fc portion of an IgG, such as IgG1 (*e.g.*, CH1, CH2 and CH3; CH2 and CH3)), variant or portion thereof can be selected in order to tailor effector function. For example, if complement activation and/or antibody dependent cellular cytotoxicity (ADCC) function is desired, the ligand can be an IgG1-like format. If desired, the IgG-like format can comprise a mutated constant region (variant IgG heavy chain constant region) to minimize binding to Fc receptors and/or ability to fix complement. (see *e.g.* Winter *et al*, GB 2,209,757 B; Morrison *et al.*, WO 89/07142; Morgan *et al.*, WO 94/29351, December 22, 1994).

The ligands of the invention can be formatted as a fusion protein that contains a first immunoglobulin single variable domain that is fused directly (*e.g.*, through a peptide bond) or through a suitable linker (amino acid, peptide, polypeptide) to a second immunoglobulin single variable domain. If desired such a format can further comprise, for example, one or more immunoglobulin domains (*e.g.*, constant region , Fc portion) and/or a half life extending moiety as described herein. For example, the ligand can comprise a first immunoglobulin single variable domain that is fused directly to a second immunoglobulin single variable domain that is fused directly to an immunoglobulin single variable domain that binds serum albumin.

In one example, the ligand comprises a first single immunoglobulin single variable domain, a second immunoglobulin single variable domain and an Fc portion or an immunoglobulin constant region. The first and second immunoglobulin single variable domains can each have binding specificity for IL-4 or IL-13. Accordingly, this type of ligand can contain two binding sites (be bivalent) wherein each bindng site binds IL-4, each binding site binds IL-13 or wherein one binding site binds IL-4

and one binding site binds IL-13. For example, the ligands can have the structure V domain-V domain-IgG constant region or V domain-V domain-IgG Fc portion.

Generally the orientation of the polypeptide domains that have a binding site with binding specificity for a target and whether the ligand comprises a linker is a matter of design choice. However, some orientations, with or without linkers, may provide better binding characteristics than other orientations. All orientations (*e.g.*, dAb1-linker-dAb2; dAb2-linker-dAb1) are encompassed by the invention, and ligands that contain an orientation that provides desired binding characteristics can be easily identified by screening.

Half-life Extended Formats

The ligand, and dAb monomers disclosed herein, can be formatted to extend its *in vivo* serum half life. Increased *in vivo* half-life is useful in *in vivo* applications of immunoglobulins, especially antibodies and most especially antibody fragments of small size such as dAbs. Such fragments (Fvs, disulphide bonded Fvs, Fabs, scFvs, dAbs) are rapidly cleared from the body, which can limit clinical applications.

A ligand can be formatted as a larger antigen-binding fragment of an antibody or as an antibody (*e.g.*, formatted as a Fab, Fab', $F(ab)_2$, $F(ab')_2$, IgG, scFv) that has larger hydrodynamic size. Ligands can also be formatted to have a larger hydrodynamic size, for example, by attachment of a polyalkyleneglycol group (*e.g.* polyethyleneglycol (PEG) group, polypropylene glycol, polybutylene glycol), serum albumin, transferrin, transferrin receptor or at least the transferrin-binding portion thereof, an antibody Fc region, or by conjugation to an antibody domain. In some embodiments, the ligand (*e.g.*, dAb monomer) is PEGylated. Preferably the PEGylated ligand (*e.g.*, dAb monomer) binds IL-4 and/or IL-13 with substantially the same affinity or avidity as the same ligand that is not PEGylated. For example, the ligand can be a PEGylated ligand comprising a dAb that binds IL-4 or IL-13 with an affinity or avidity that differs from the avidity of ligand in unPEGylated form by no more than a factor of about 1000, preferably no more than a factor of about 100, more preferably no more than a factor of about 10, or with affinity or avidity substantially unchanged relative to the unPEGylated form. See,

PCT/GB03/002804, filed June 30, 2003, which designated the United States, (WO 2004/081026) regarding PEGylated single variable domains and dAbs, suitable methods for preparing same, increased *in vivo* half-life of the PEGylated single variable domains and dAb monomers and multimers, suitable PEGs, preferred hydrodynamic sizes of PEGs, and preferred hydrodynamic sizes of PEGylated single variable domains and dAb monomers and multimers. The entire teaching of PCT/GB03/002804 (WO 2004/081026), including the portions referred to above, are incorporated herein by reference.

Hydrodynamic size of the ligands (*e.g.*, dAb monomers and multimers) of the invention may be determined using methods which are well known in the art. For example, gel filtration chromatography may be used to determine the hydrodynamic size of a ligand. Suitable gel filtration matrices for determining the hydrodynamic sizes of ligands, such as cross-linked agarose matrices, are well known and readily available.

The size of a ligand format (*e.g.*, the size of a PEG moiety attached to a dAb monomer), can be varied depending on the desired application. For example, where a ligand is intended to leave the circulation and enter into peripheral tissues, it is desirable to keep the hydrodynamic size of the ligand low to facilitate diffusion from the blood stream. Alternatively, where it is desired to have the ligand remain in the systemic circulation for a longer period of time the size of the ligand can be increased, for example by formatting as an IgG-like protein or by addition of a 30 to 60 kDa PEG moiety (*e.g.*, linear or branched 30 kDa PEG to 40 kDa PEG, such as addition of two 20kDa PEG moieties.) The size of the ligand format can be tailored to achieve a desired *in vivo* serum half-life. For example, the size of the ligand format can be tailored to control exposure to a toxin and/or to reduce side effects of toxic agents.

The hydrodynamic size of a ligand (*e.g.*, dAb monomer) and its serum half-life can also be increased by conjugating or linking the ligand to a binding domain (*e.g.*, antibody or antibody fragment) that binds an antigen or epitope that increases half-life *in vivo*, as described herein. For example, the ligand (*e.g.*, dAb monomer) can be conjugated or linked to an anti-serum albumin or anti-neonatal Fc receptor

antibody or antibody fragment, (*e.g.*, an anti-SA or anti-neonatal Fc receptor dAb, Fab, Fab' or scFv), or to an anti-SA affibody or anti-neonatal Fc receptor affibody.

Examples of suitable albumin, albumin fragments or albumin variants for use in a ligand according to the invention are described in WO 2005/077042A2, which is incorporated herein by reference in its entirety. In particular, the following albumin, albumin fragments or albumin variants can be used in the present invention:

- SEQ ID NO:1 (as disclosed in WO 2005/077042A2, this sequence being explicitly incorporated into the present disclosure by reference);
- Albumin fragment or variant comprising or consisting of amino acids 1-387 of SEQ ID NO:1 in WO 2005/077042A2;
- Albumin, or fragment or variant thereof, comprising an amino acid sequence selected from the group consisting of: (a) amino acids 54 to 61 of SEQ ID NO:1 in WO 2005/077042A2; (b) amino acids 76 to 89 of SEQ ID NO:1 in WO 2005/077042A2; (c) amino acids 92 to 100 of SEQ ID NO:1 in WO 2005/077042A2; (d) amino acids 170 to 176 of SEQ ID NO:1 in WO 2005/077042A2; (e) amino acids 247 to 252 of SEQ ID NO:1 in WO 2005/077042A2; (f) amino acids 266 to 277 of SEQ ID NO:1 in WO 2005/077042A2; (g) amino acids 280 to 288 of SEQ ID NO:1 in WO 2005/077042A2; (h) amino acids 362 to 368 of SEQ ID NO:1 in WO 2005/077042A2; (i) amino acids 439 to 447 of SEQ ID NO:1 in WO 2005/077042A2 (j) amino acids 462 to 475 of SEQ ID NO:1 in WO 2005/077042A2; (k) amino acids 478 to 486 of SEQ ID NO:1 in WO 2005/077042A2; and (l) amino acids 560 to 566 of SEQ ID NO:1 in WO 2005/077042A2.

Further examples of suitable albumin, fragments and analogs for use in a ligand according to the invention are described in WO 03/076567A2, which is incorporated herein by reference in its entirety. In particular, the following albumin, fragments or variants can be used in the present invention:

- Human serum albumin as described in WO 03/076567A2, (*e.g.*, in figure 3) (this sequence information being explicitly incorporated into the present disclosure by reference);
- Human serum albumin (HA) consisting of a single non-glycosylated polypeptide chain of 585 amino acids with a formula molecular weight of 66,500 (See, Meloun, *et al.*, *FEBS Letters 58*:136 (1975); Behrens, *et al.*, *Fed. Proc. 34*:591 (1975); Lawn, *et al.*, *Nucleic Acids Research 9*:6102-6114 (1981); Minghetti, *et al.*, *J. Biol. Chem. 261*:6747 (1986));
- A polymorphic variant or analog or fragment of albumin as described in Weitkamp, *et al.*, *Ann. Hum. Genet. 37*:219 (1973);
- An albumin fragment or variant as described in EP 322094, (*e.g.*, HA(1-373), HA(1-388), HA(1-389), HA(1-369), and HA(1-419) and fragments between 1-369 and 1-419);
- An albumin fragment or variant as described in EP 399666, (*e.g.*, HA(1-177) and HA(1-200) and fragments between HA(1-X), where X is any number from 178 to 199).

Where a (one or more) half-life extending moiety (*e.g.*, albumin, transferrin and fragments and analogs thereof) is used in the ligands of the invention, it can be conjugated to the ligand using any suitable method, such as, by direct fusion to the target-binding moiety (*e.g.*, dAb or antibody fragment), for example by using a single nucleotide construct that encodes a fusion protein, wherein the fusion protein is encoded as a single polypeptide chain with the half-life extending moiety located N- or C-terminally to the cell surface target binding moieties. Alternatively, conjugation can be achieved by using a peptide linker between moieties, (*e.g.*, a peptide linker as described in WO 03/076567A2 or WO 2004/003019) (these linker disclosures being incorporated by reference in the present disclosure to provide examples for use in the present invention).

Typically, a polypeptide that enhances serum half-life *in vivo* is a polypeptide which occurs naturally *in vivo* and which resists degradation or removal by endogenous mechanisms which remove unwanted material from the organism (*e.g.*, human). For example, a polypeptide that enhances serum half-life *in vivo* can be selected from proteins from the extracellular matrix, proteins found in blood,

proteins found at the blood brain barrier or in neural tissue, proteins localized to the kidney, liver, lung, heart, skin or bone, stress proteins, disease-specific proteins, or proteins involved in Fc transport.

Suitable polypeptides that enhance serum half-life *in vivo* include, for example, transferrin receptor specific ligand-neuropharmaceutical agent fusion proteins (see U.S. Patent No. 5,977,307, the teachings of which are incorporated herein by reference), brain capillary endothelial cell receptor, transferrin, transferrin receptor (*e.g.*, soluble transferrin receptor), insulin, insulin-like growth factor 1 (IGF 1) receptor, insulin-like growth factor 2 (IGF 2) receptor, insulin receptor, blood coagulation factor X, αl-antitrypsin and HNF 1α. Suitable polypeptides that enhance serum half-life also include alpha-1 glycoprotein (orosomucoid; AAG), alpha-1 antichymotrypsin (ACT), alpha-1 microglobulin (protein HC; AIM), antithrombin III (AT III), apolipoprotein A-1 (Apo A-1), apolipoprotein B (Apo B), ceruloplasmin (Cp), complement component C3 (C3), complement component C4 (C4), C1 esterase inhibitor (C1 INH), C-reactive protein (CRP), ferritin (FER), hemopexin (HPX), lipoprotein(a) (Lp(a)), mannose-binding protein (MBP), myoglobin (Myo), prealbumin (transthyretin; PAL), retinol-binding protein (RBP), and rheumatoid factor (RF).

Suitable proteins from the extracellular matrix include, for example, collagens, laminins, integrins and fibronectin. Collagens are the major proteins of the extracellular matrix. About 15 types of collagen molecules are currently known, found in different parts of the body, *e.g.* type I collagen (accounting for 90% of body collagen) found in bone, skin, tendon, ligaments, cornea, internal organs or type II collagen found in cartilage, vertebral disc, notochord, and vitreous humor of the eye.

Suitable proteins from the blood include, for example, plasma proteins (*e.g.*, fibrin, α-2 macroglobulin, serum albumin, fibrinogen (*e.g.*, fibrinogen A, fibrinogen B), serum amyloid protein A, haptoglobin, profilin, ubiquitin, uteroglobulin and β-2-microglobulin), enzymes and enzyme inhibitors (*e.g.*, plasminogen, lysozyme, cystatin C, alpha-1-antitrypsin and pancreatic trypsin inhibitor), proteins of the immune system, such as immunoglobulin proteins (*e.g.*, IgA, IgD, IgE, IgG, IgM, immunoglobulin light chains (kappa/lambda)), transport proteins (*e.g.*, retinol

binding protein, α-1 microglobulin), defensins (*e.g.*, beta-defensin 1, neutrophil defensin 1, neutrophil defensin 2 and neutrophil defensin 3) and the like.

Suitable proteins found at the blood brain barrier or in neural tissue include, for example, melanocortin receptor, myelin, ascorbate transporter and the like.

Suitable polypeptides that enhance serum half-life *in vivo* also include proteins localized to the kidney (*e.g.*, polycystin, type IV collagen, organic anion transporter Kl, Heymann's antigen), proteins localized to the liver (*e.g.*, alcohol dehydrogenase, G250), proteins localized to the lung (*e.g.*, secretory component, which binds IgA), proteins localized to the heart (*e.g.*, HSP 27, which is associated with dilated cardiomyopathy), proteins localized to the skin (*e.g.*, keratin), bone specific proteins such as morphogenic proteins (BMPs), which are a subset of the transforming growth factor β superfamily of proteins that demonstrate osteogenic activity (*e.g.*, BMP-2, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8), tumor specific proteins (*e.g.*, trophoblast antigen, herceptin receptor, oestrogen receptor, cathepsins (*e.g.*, cathepsin B, which can be found in liver and spleen)).

Suitable disease-specific proteins include, for example, antigens expressed only on activated T-cells, including LAG-3 (lymphocyte activation gene), osteoprotegerin ligand (OPGL; see *Nature* 402, 304-309 (1999)), OX40 (a member of the TNF receptor family, expressed on activated T cells and specifically up-regulated in human T cell leukemia virus type-I (HTLV-I)-producing cells; see *Immunol.* 165 (1):263-70 (2000)). Suitable disease-specific proteins also include, for example, metalloproteases (associated with arthritis/cancers) including CG6512 Drosophila, human paraplegin, human FtsH, human AFG3L2, murine ftsH; and angiogenic growth factors, including acidic fibroblast growth factor (FGF-1), basic fibroblast growth factor (FGF-2), vascular endothelial growth factor/vascular permeability factor (VEGF/VPF), transforming growth factor-alpha (TGF-α), tumor necrosis factor-alpha (TNF-α), angiogenin, interleukin-3 (IL-3), interleukin-8 (IL-8), platelet-derived endothelial growth factor (PD-ECGF), placental growth factor (P1GF), midkine platelet-derived growth factor-BB (PDGF), and fractalkine.

Suitable polypeptides that enhance serum half-life *in vivo* also include stress proteins such as heat shock proteins (HSPs). HSPs are normally found intracellularly. When they are found extracellularly, it is an indicator that a cell has

died and spilled out its contents. This unprogrammed cell death (necrosis) occurs when as a result of trauma, disease or injury, extracellular HSPs trigger a response from the immune system. Binding to extracellular HSP can result in localizing the compositions of the invention to a disease site.

Suitable proteins involved in Fc transport include, for example, Brambell receptor (also known as FcRB). This Fc receptor has two functions, both of which are potentially useful for delivery. The functions are (1) transport of IgG from mother to child across the placenta (2) protection of IgG from degradation thereby prolonging its serum half-life. It is thought that the receptor recycles IgG from endosomes. (See, Holliger *et al, Nat Biotechnol* 15(7):632-6 (1997).)

Methods for pharmacokinetic analysis and determination of ligand half-life will be familiar to those skilled in the art. Details may be found in Kenneth, A. *et al:* Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists and in Peters *et al*, Pharmacokinetic Analysis: A Practical Approach (1996). Reference is also made to "Pharmacokinetics", M Gibaldi & D Perron, published by Marcel Dekker, 2nd Rev. ex edition (1982), which describes pharmacokinetic parameters such as t alpha and t beta half lives and area under the curve (AUC).

Ligands that Contain a Toxin Moiety or Toxin

The invention also relates to ligands that comprise a toxin moiety or toxin. Suitable toxin moieties comprise a toxin (*e.g.*, surface active toxin, cytotoxin). The toxin moiety or toxin can be linked or conjugated to the ligand using any suitable method. For example, the toxin moiety or toxin can be covalently bonded to the ligand directly or through a suitable linker. Suitable linkers can include noncleavable or cleavable linkers, for example, pH cleavable linkers that comprise a cleavage site for a cellular enzyme (*e.g.*, cellular esterases, cellular proteases such as cathepsin B). Such cleavable linkers can be used to prepare a ligand that can release a toxin moiety or toxin after the ligand is internalized.

A variety of methods for linking or conjugating a toxin moiety or toxin to a ligand can be used. The particular method selected will depend on the toxin moiety or toxin and ligand to be linked or conjugated. If desired, linkers that contain terminal functional groups can be used to link the ligand and toxin moiety or toxin.

Generally, conjugation is accomplished by reacting toxin moiety or toxin that contains a reactive functional group (or is modified to contain a reactive functional group) with a linker or directly with a ligand. Covalent bonds formed by reacting a toxin moiety or toxin that contains (or is modified to contain) a chemical moiety or functional group that can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond. If desired, a suitable reactive chemical group can be added to ligand or to a linker using any suitable method. (See, *e.g.*, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996).) Many suitable reactive chemical group combinations are known in the art, for example an amine group can react with an electrophilic group such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl ester (NHS), and the like. Thiols can react with maleimide, iodoacetyl, acrylolyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996)).

Suitable toxin moieties and toxins include, for example, a maytansinoid (*e.g.*, maytansinol, *e.g.*, DM1, DM4), a taxane, a calicheamicin, a duocarmycin, or derivatives thereof. The maytansinoid can be, for example, maytansinol or a maytansinol analogue. Examples of maytansinol analogs include those having a modified aromatic ring (*e.g.*, C-19-decloro, C-20-demethoxy, C-20-acyloxy) and those having modifications at other positions (*e.g.*, C-9-CH, C-14-alkoxymethyl, C-14-hydroxymethyl or aceloxymethyl, C-15-hydroxy/acyloxy, C-15-methoxy, C-18-N-demethyl, 4,5-deoxy). Maytansinol and maytansinol analogs are described, for example, in U.S. Patent Nos 5,208,020 and 6,333,410, the contents of which are incorporated herein by reference. Maytansinol can be coupled to antibodies and antibody fragmetns using, *e.g.*, an N-succinimidyl 3-(2-pyridyldithio)proprionate (also known as N-succinimidyl 4-(2-pyridyldithio)pentanoate (or SPP), 4-succinimidyl-oxycarbonyl-a-(2-pyridyldithio)-toluene (SMPT), N-succinimidyl-3-(2-pyridyldithio)butyrate (SDPB), 2 iminothiolane, or S-acetylsuccinic anhydride.

The taxane can be, for example, a taxol, taxotere, or novel taxane (see, *e.g.*, WO 01/38318). The calicheamicin can be, for example, a bromo-complex calicheamicin (*e.g.*, an alpha, beta or gamma bromo-complex), an iodo-complex calicheamicin (*e.g.*, an alpha, beta or gamma iodo-complex), or analogs and mimics thereof. Bromo-complex calicheamicins include I1-BR, I2-BR, I3-BR, I4-BR, J1-BR, J2-BR and K1-BR. Iodo-complex calicheamicins include I1-I, I2-I, I3-I, J1-I, J2-I, L1-I and K1-BR. Calicheamicin and mutants, analogs and mimics thereof are described, for example, in U.S. Patent Nos 4,970,198; 5,264,586; 5,550,246; 5,712,374, and 5,714,586, the contents of each of which are incorporated herein by reference. Duocarmycin analogs (*e.g.*, KW-2189, DC88, DC89 CBI-TMI, and derivatives thereof are described, for example, in U.S. Patent No. 5,070,092, U.S. Patent No. 5,187,186, U.S. Patent No. 5,641,780, U.S. Patent No. 5,641,780, U.S. Patent No. 4,923,990, and U.S. Patent No. 5,101,038, the contents of each of which are incorporated herein by reference.

Examples of other toxins include, but are not limited to antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, CC-1065 (see US Patent Nos. 5,475,092, 5,585,499, 5,846,545), melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, mitomycin, puromycin anthramycin (AMC)), duocarmycin and analogs or derivatives thereof, and anti-mitotic agents (*e.g.*, vincristine, vinblastine, taxol, auristatins (*e.g.*, auristatin E) and maytansinoids, and analogs or homologs thereof.

The toxin can also be a surface active toxin, such as a toxin that is a free radical generator (*e.g.* selenium containing toxin moieties), or radionuclide containing moiety. Suitable radionuclide containing moieties, include for example, moieties that contain radioactive iodine (^{131}I or ^{125}I), yttrium (^{90}Y), lutetium (^{177}Lu), actinium (^{225}Ac), praseodymium, astatine (^{211}At), rhenium (^{186}Re), bismuth (^{212}Bi or ^{213}Bi), indium (^{111}In), technetium (^{99}mTc), phosphorus (^{32}P), rhodium (^{188}Rh), sulfur

(^{35}S), carbon (^{14}C), tritium (^{3}H), chromium (^{51}Cr), chlorine (^{36}Cl), cobalt (^{57}Co or ^{58}Co), iron (^{59}Fe), selenium (^{75}Se), or gallium (^{67}Ga).

The toxin can be a protein, polypeptide or peptide, from bacterial sources, *e.g.*, diphtheria toxin, pseudomonas exotoxin (PE) and plant proteins, *e.g.*, the A chain of ricin (RTA), the ribosome inactivating proteins (RIPs) gelonin, pokeweed antiviral protein, saporin, and dodecandron are contemplated for use as toxins.

Antisense compounds of nucleic acids designed to bind, disable, promote degradation or prevent the production of the mRNA responsible for generating a particular target protein can also be used as a toxin. Antisense compounds include antisense RNA or DNA, single or double stranded, oligonucleotides, or their analogs, which can hybridize specifically to individual mRNA species and prevent transcription and/or RNA processing of the mRNA species and/or translation of the encoded polypeptide and thereby effect a reduction in the amount of the respective encoded polypeptide. Ching, *et al., Proc. Natl. Acad. Sci.* U.S.A. 86: 10006-10010 (1989); Broder, *et al., Ann. Int. Med.* 113: 604-618 (1990); Loreau, *et al., FEBS Letters* 274: 53-56 (1990); Useful antisense therapeutics include for example: Veglin ™ (VasGene) and OGX-011 (Oncogenix).

Toxins can also be photoactive agents. Suitable photoactive agents include porphyrin-based materials such as porfimer sodium, the green porphyrins, chlorin E6, hematoporphyrin derivative itself, phthalocyanines, etiopurpurins, texaphrin, and the like.

The toxin can be an antibody or antibody fragment that binds an intracellular target, such as a dAb that binds an intracellular target (an intrabody). Such antibodies or antibody fragments (dAbs) can be directed to defined subcellular compartments or targets. For example, the antibodies or antibody fragments (dAbs) can bind an intracellular target selected from erbB2, EGFR, BCR-ABL, p21Ras, Caspase3, Caspase7, Bcl-2, p53, Cyclin E, ATF-1/CREB, HPV16 E7, HP1, Type IV collagenases, cathepsin L as well as others described in Kontermann, R.E., *Methods*, 34:163-170 (2004), incorporated herein by reference in its entirety.

Polypeptide Domains that Bind IL-4

The invention provides polypeptide domains (*e.g.*, immunoglobulin single variable domains, dAb monomers) that have a binding site with binding specificity for IL-4. In preferred embodiments, the polypeptide domain (*e.g.*, dAb) binds to IL-4 with an affinity (KD; KD=K_{off}(kd)/K_{on} (ka)) of 300 nM to 1 pM (*i.e.*, 3 x 10^{-7} to 5 x 10^{-12}M), preferably 50 nM to 1 pM, more preferably 5 nM to 1 pM and most preferably 1 nM to 1 pM, for example a K_D of 1 x 10^{-7} M or less, preferably 1 x 10^{-8} M or less, more preferably 1 x 10^{-9} M or less, advantageously 1 x 10^{-10} M or less and most preferably 1 x 10^{-11} M or less; and/or a K_{off} rate constant of 5 x 10^{-1} s^{-1} to 1 x 10^{-7} s^{-1}, preferably 1 x 10^{-2} s^{-1} to 1 x 10^{-6} s^{-1}, more preferably 5 x 10^{-3} s^{-1} to 1 x 10^{-5} s^{-1}, for example 5 x 10^{-1} s^{-1} or less, preferably 1 x 10^{-2} s^{-1} or less, advantageously 1 x 10^{-3} s^{-1} or less, more preferably 1 x 10^{-4} s^{-1} or less, still more preferably 1 x 10^{-5} s^{-1} or less, and most preferably 1 x 10^{-6} s^{-1} or less as determined by surface plasmon resonance.

In some embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 competes for binding to IL-4 with a dAb selected from the group consisting of DOM9-15 (SEQ ID NO:175), DOM9-17(SEQ ID NO:176), DOM9-23 (SEQ ID NO:177), DOM9-24 (SEQ ID NO:178), DOM9-25 (SEQ ID NO:179), DOM9-27 (SEQ ID NO:180), DOM9-28 (SEQ ID NO:181), DOM9-29 (SEQ ID NO:182), DOM9-30 (SEQ ID NO:183), DOM9-31 (SEQ ID NO:184), DOM9-32 (SEQ ID NO:185), DOM9-33 (SEQ ID NO:186), DOM9-50 (SEQ ID NO:187), DOM9-57 (SEQ ID NO:188), DOM9-59 (SEQ ID NO:189), DOM9-63 (SEQ ID NO:190), DOM9-67 (SEQ ID NO:191), DOM9-68 (SEQ ID NO:192), DOM9-70 (SEQ ID NO:193), DOM9-79 (SEQ ID NO:194), DOM9-82 (SEQ ID NO:195), DOM9-86 (SEQ ID NO:196), DOM9-94 (SEQ ID NO:197), DOM9-108 (SEQ ID NO:198), DOM9-112 (SEQ ID NO:199), DOM9-112-1 (SEQ ID NO:200), DOM9-112-2 (SEQ ID NO:201), DOM9-112-3 (SEQ ID NO:202), DOM9-112-4 (SEQ ID NO:203), DOM9-112-5 (SEQ ID NO:204), DOM9-112-6 (SEQ ID NO:205), DOM9-112-7 (SEQ ID NO:206), DOM9-112-8 (SEQ ID NO:207), DOM9-112-9 (SEQ ID NO:208), DOM9-112-10 (SEQ ID NO:209), DOM9-112-11 (SEQ ID NO:210), DOM9-112-12 (SEQ ID NO:211), DOM9-112-13 (SEQ ID NO:212), DOM9-112-14 (SEQ ID NO:213), DOM9-112-15 (SEQ ID NO:214), DOM9-112-16 (SEQ ID NO:215), DOM9-112-17 (SEQ ID NO:216), DOM9-112-

18 (SEQ ID NO:217), DOM9-112-19 (SEQ ID NO:218), DOM9-112-20 (SEQ ID NO:219), DOM9-112-21 (SEQ ID NO:220), DOM9-112-22 (SEQ ID NO:221), DOM9-112-23 (SEQ ID NO:222), DOM9-112-25 (SEQ ID NO:223), DOM9-112-81 (SEQ ID NO:224), DOM9-112-82 (SEQ ID NO:225), DOM9-112-83 (SEQ ID NO:226), DOM9-112-84 (SEQ ID NO:227), DOM9-112-85 (SEQ ID NO:228), DOM9-112-86 (SEQ ID NO:229), DOM9-112-87 (SEQ ID NO:230), DOM9-112-88 (SEQ ID NO:231), DOM9-112-89 (SEQ ID NO:232), DOM9-112-90 (SEQ ID NO:233), DOM9-112-91 (SEQ ID NO:234), DOM9-112-92 (SEQ ID NO:235), DOM9-112-93 (SEQ ID NO:236), DOM9-112-94 (SEQ ID NO:237), DOM9-112-95 (SEQ ID NO:238), DOM9-112-96 (SEQ ID NO:239), DOM9-112-97 (SEQ ID NO:240), DOM9-112-98 (SEQ ID NO:241), DOM9-112-99 (SEQ ID NO:242), DOM9-112-100 (SEQ ID NO:243), DOM9-112-101 (SEQ ID NO:244), DOM9-1132-102 (SEQ ID NO:245), DOM9-112-103 (SEQ ID NO:246), DOM9-112-104 (SEQ ID NO:247), DOM9-112-105 (SEQ ID NO:248), DOM9-112-106 (SEQ ID NO:249), DOM9-112-107 (SEQ ID NO:250), DOM9-112-108 (SEQ ID NO:251), DOM9-112-109 (SEQ ID NO:252), DOM9-112-110 (SEQ ID NO:253), DOM9-112-111 (SEQ ID NO:254), DOM9-112-112 (SEQ ID NO:255), DOM9-112-113 (SEQ ID NO:256), DOM9-112-114 (SEQ ID NO:257), DOM9-112-115 (SEQ ID NO:258), DOM9-112-116 (SEQ ID NO:259), DOM9-112-117 (SEQ ID NO:260), DOM9-112-118 (SEQ ID NO:261), DOM9-112-119 (SEQ ID NO:262), DOM9-112-120 (SEQ ID NO:263), DOM9-112-121 (SEQ ID NO:264), DOM9-112-122 (SEQ ID NO:265), DOM9-112-123 (SEQ ID NO:266), DOM9-112-124 (SEQ ID NO:267), DOM9-112-125 (SEQ ID NO:268), DOM9-112-126 (SEQ ID NO:269), DOM9-112-127 (SEQ ID NO:270), DOM9-112-128 (SEQ ID NO:271), DOM9-112-134 (SEQ ID NO:272), DOM9-112-135 (SEQ ID NO:273), DOM9-112-136 (SEQ ID NO:274), DOM9-112-137 (SEQ ID NO:275), DOM9-112-138 (SEQ ID NO:276), DOM9-112-140 (SEQ ID NO:277), DOM9-112-141 (SEQ ID NO:278), DOM9-112-142 (SEQ ID NO:279), DOM9-112-143 (SEQ ID NO:280), DOM9-112-144 (SEQ ID NO:281), DOM9-112-145 (SEQ ID NO:282), DOM9-112-146 (SEQ ID NO:283), DOM9-112-147 (SEQ ID NO:284), DOM9-112-148 (SEQ ID NO:285), DOM9-112-149 (SEQ ID NO:286), DOM9-112-150 (SEQ ID NO:287), DOM9-112-151 (SEQ ID NO:288), DOM9-112-152 (SEQ ID NO:289), DOM9-

112-153 (SEQ ID NO:290), DOM9-112-154 (SEQ ID NO:291), DOM9-112-155 (SEQ ID NO:292), DOM9-112-156 (SEQ ID NO:293), DOM9-112-157 (SEQ ID NO:294), DOM9-112-158 (SEQ ID NO:295), DOM9-112-159 (SEQ ID NO:296), DOM9-112-160 (SEQ ID NO:297), DOM9-112-161 (SEQ ID NO:298), DOM9-112-162 (SEQ ID NO:299), DOM9-112-163 (SEQ ID NO:300), DOM9-112-164 (SEQ ID NO:301), DOM9-112-165 (SEQ ID NO:302), DOM9-112-166 (SEQ ID NO:303), DOM9-112-167 (SEQ ID NO:304), DOM9-112-168 (SEQ ID NO:305), DOM9-112-169 (SEQ ID NO:306), DOM9-112-170 (SEQ ID NO:307), DOM9-112-171 (SEQ ID NO:308), DOM9-112-172 (SEQ ID NO:309), DOM9-112-173 (SEQ ID NO:310), DOM9-112-174 (SEQ ID NO:311), DOM9-112-175 (SEQ ID NO:312), DOM9-112-176 (SEQ ID NO:313), DOM9-112-177 (SEQ ID NO:314), DOM9-112-178 (SEQ ID NO:315), DOM9-112-179 (SEQ ID NO:316), DOM9-112-180 (SEQ ID NO:317), DOM9-112-181 (SEQ ID NO:318), DOM9-112-182 (SEQ ID NO:319), DOM9-112-183 (SEQ ID NO:320), DOM9-112-184 (SEQ ID NO:321), DOM9-112-185 (SEQ ID NO:322), DOM9-112-186 (SEQ ID NO:323), DOM9-112-187 (SEQ ID NO:324), DOM9-112-188 (SEQ ID NO:325), DOM9-112-189 (SEQ ID NO:326), DOM9-112-190 (SEQ ID NO:327), DOM9-112-191 (SEQ ID NO:328), DOM9-112-192 (SEQ ID NO:329), DOM9-112-193 (SEQ ID NO:330), DOM9-112-194 (SEQ ID NO:331), DOM9-112-195 (SEQ ID NO:332), DOM9-112-196 (SEQ ID NO:333), DOM9-112-197 (SEQ ID NO:334), DOM9-112-198 (SEQ ID NO:335), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-112-201 (SEQ ID NO:338), DOM9-112-202 (SEQ ID NO:339), DOM9-120 (SEQ ID NO:340), DOM9-121 (SEQ ID NO:341), DOM9-122 (SEQ ID NO:342), DOM9-123 (SEQ ID NO:343), DOM9-124 (SEQ ID NO:344), DOM9-125 (SEQ ID NO:345), DOM9-128 (SEQ ID NO:346), DOM9-134 (SEQ ID NO:347), DOM9-136 (SEQ ID NO:348), DOM9-26 (SEQ ID NO:500), DOM9-35 (SEQ ID NO:501), DOM9-36 (SEQ ID NO:502), DOM9-37 (SEQ ID NO:503), DOM9-38 (SEQ ID NO:504), DOM9-39 (SEQ ID NO:505), DOM9-40 (SEQ ID NO:506), DOM9-41 (SEQ ID NO:507), DOM9-43 (SEQ ID NO:508), DOM9-44 (SEQ ID NO:509), DOM9-44-500 (SEQ ID NO:510), DOM9-44-501 (SEQ ID NO:511), DOM9-44-502 (SEQ ID NO:512), DOM9-44-503 (SEQ ID NO:513), DOM9-44-504 (SEQ ID NO:514), DOM9-44-505 (SEQ ID NO:515),

DOM9-44-506 (SEQ ID NO:516), DOM9-44-507 (SEQ ID NO:517), DOM9-44-509 (SEQ ID NO:518), DOM9-44-510 (SEQ ID NO:519), DOM9-44-511 (SEQ ID NO:520), DOM9-44-512 (SEQ ID NO:521), DOM9-44-513 (SEQ ID NO:522), DOM9-44-514 (SEQ ID NO:523), DOM9-44-515 (SEQ ID NO:524), DOM9-44-516 (SEQ ID NO:525), DOM9-44-517 (SEQ ID NO:526), DOM9-44-518 (SEQ ID NO:527), DOM9-44-519 (SEQ ID NO:528), DOM9-44-520 (SEQ ID NO:529), DOM9-44-521 (SEQ ID NO:530), DOM9-44-522 (SEQ ID NO:531), DOM9-44-523 (SEQ ID NO:532), DOM9-44-524 (SEQ ID NO:533), DOM9-44-525 (SEQ ID NO:534), DOM9-44-526 (SEQ ID NO:535), DOM9-44-527 (SEQ ID NO:536), DOM9-44-528 (SEQ ID NO:537), DOM9-44-529 (SEQ ID NO:538), DOM9-44-530 (SEQ ID NO:539), DOM9-44-531 (SEQ ID NO:540), DOM9-44-532 (SEQ ID NO:541), DOM9-44-533 (SEQ ID NO:542), DOM9-44-534 (SEQ ID NO:543), DOM9-44-535 (SEQ ID NO:544), DOM9-44-536 (SEQ ID NO:545), DOM9-44-537 (SEQ ID NO:546), DOM9-44-538 (SEQ ID NO:547), DOM9-44-539 (SEQ ID NO:548), DOM9-44-540 (SEQ ID NO:549), DOM9-44-541 (SEQ ID NO:550), DOM9-44-542 (SEQ ID NO:551), DOM9-44-543 (SEQ ID NO:552), DOM9-44-544 (SEQ ID NO:553), DOM9-44-545 (SEQ ID NO:554), DOM9-44-546 (SEQ ID NO:555), DOM9-44-547 (SEQ ID NO:556), DOM9-44-548 (SEQ ID NO:557), DOM9-44-549 (SEQ ID NO:558), DOM9-44-550 (SEQ ID NO:559), DOM9-44-551 (SEQ ID NO:560), DOM9-44-552 (SEQ ID NO:561), DOM9-44-553 (SEQ ID NO:562), DOM9-44-554 (SEQ ID NO:563), DOM9-44-555 (SEQ ID NO:564), DOM9-44-556 (SEQ ID NO:565), DOM9-44-557 (SEQ ID NO:566), DOM9-44-558 (SEQ ID NO:567), DOM9-44-559 (SEQ ID NO:568), DOM9-44-560 (SEQ ID NO:569), DOM9-44-561 (SEQ ID NO:570), DOM9-44-562 (SEQ ID NO:571), DOM9-44-563 (SEQ ID NO:572), DOM9-44-564 (SEQ ID NO:573), DOM9-44-565 (SEQ ID NO:574), DOM9-44-566 (SEQ ID NO:575), DOM9-44-625 (SEQ ID NO:576), DOM9-44-626 (SEQ ID NO:577), DOM9-44-627 (SEQ ID NO:578), DOM9-44-628 (SEQ ID NO:579), DOM9-44-629 (SEQ ID NO:580), DOM9-44-630 (SEQ ID NO:581), DOM9-44-631 (SEQ ID NO:582), DOM9-44-632 (SEQ ID NO:583), DOM9-44-633 (SEQ ID NO:584), DOM9-44-634 (SEQ ID NO:585), DOM9-44-636 (SEQ ID NO:586), DOM9-44-637 (SEQ ID NO:587), DOM9-44-639 (SEQ ID NO:588), DOM9-44-640 (SEQ ID NO:589), DOM9-44-641(SEQ ID

NO:590), DOM9-44-642 (SEQ ID NO:591), DOM9-44-643 (SEQ ID NO:592), DOM9-44-644 (SEQ ID NO:593), DOM9-45 (SEQ ID NO:594), DOM9-46 (SEQ ID NO:595), DOM9-47 (SEQ ID NO:596), DOM9-48 (SEQ ID NO:597), DOM9-143 (SEQ ID NO:598), DOM9-144 (SEQ ID NO:599), DOM9-146 (SEQ ID NO:600), DOM9-152 (SEQ ID NO:601), DOM9-155 (SEQ ID NO:602), DOM9-155-001 (SEQ ID NO:603), DOM9-155-3 (SEQ ID NO:604), DOM9-155-5 (SEQ ID NO:605), DOM9-155-8 (SEQ ID NO:606), DOM9-155-9 (SEQ ID NO:607), DOM9-155-11 (SEQ ID NO:608), DOM9-155-13 (SEQ ID NO:609), DOM9-155-14 (SEQ ID NO:610), DOM9-155-17 (SEQ ID NO:611), DOM9-155-19 (SEQ ID NO:612), DOM9-155-20 (SEQ ID NO:613), DOM9-155-22 (SEQ ID NO:614), DOM9-155-23 (SEQ ID NO:615), DOM9-155-24 (SEQ ID NO:616), DOM9-155-25 (SEQ ID NO:617), DOM9-155-26 (SEQ ID NO:618), DOM9-155-27 (SEQ ID NO:619), DOM9-155-28 (SEQ ID NO:620), DOM9-155-29 (SEQ ID NO:621), DOM9-155-30 (SEQ ID NO:622), DOM9-155-31 (SEQ ID NO:623), DOM9-155-32 (SEQ ID NO:624), DOM9-155-33 (SEQ ID NO:625), DOM9-155-34 (SEQ ID NO:626), DOM9-155-35 (SEQ ID NO:627), DOM9-155-36 (SEQ ID NO:628), DOM9-155-37 (SEQ ID NO:629), DOM9-155-38 (SEQ ID NO:630), DOM9-155-39 (SEQ ID NO:631), DOM9-155-41 (SEQ ID NO:632), DOM9-155-42 (SEQ ID NO:633), DOM9-155-43 (SEQ ID NO:634), DOM9-155-44 (SEQ ID NO:635), DOM9-155-45(SEQ ID NO:636), DOM9-155-46 (SEQ ID NO:637), DOM9-155-47 (SEQ ID NO:638), DOM9-155-48 (SEQ ID NO:639), DOM9-155-49 (SEQ ID NO:640), DOM9-155-50 (SEQ ID NO:641), DOM9-155-51 (SEQ ID NO:642), DOM9-155-52 (SEQ ID NO:643), DOM9-155-53 (SEQ ID NO:644), DOM9-158 (SEQ ID NO:645), DOM9-160 (SEQ ID NO:646), DOM9-161 (SEQ ID NO:647), DOM9-162 (SEQ ID NO:648), DOM9-163 (SEQ ID NO:649) and DOM9-164 (SEQ ID NO:650).

In some embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 competes for binding to IL-4 with a dAb selected from the group consisting of DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-204 (SEQ ID NO:2428), DOM9-112-205 (SEQ ID NO:2429), DOM9-112-206 (SEQ ID NO:2430), DOM9-112-207 (SEQ ID NO:2431), DOM9-112-208 (SEQ ID NO:2432), DOM9-112-209 (SEQ ID

NO:2433), DOM9-112-210 (SEQ ID NO:2434), DOM9-112-211 (SEQ ID NO:2435), DOM9-112-212 (SEQ ID NO:2436), DOM9-112-213 (SEQ ID NO:2437), DOM9-112-214 (SEQ ID NO:2438), DOM9-112-215 (SEQ ID NO:2439), DOM9-112-216 (SEQ ID NO:2440), DOM9-112-217 (SEQ ID NO:2441), DOM9-112-218 (SEQ ID NO:2442), DOM9-112-219 (SEQ ID NO:2443), DOM9-112-220 (SEQ ID NO:2444), DOM9-112-221 (SEQ ID NO:2445), DOM9-112-222 (SEQ ID NO:2446), DOM9-112-223 (SEQ ID NO:2447), DOM9-112-224 (SEQ ID NO:2448), DOM9-112-225 (SEQ ID NO:2449), DOM9-112-226 (SEQ ID NO:2450), DOM9-112-227 (SEQ ID NO:2451), DOM9-112-228 (SEQ ID NO:2452), DOM9-112-229 (SEQ ID NO:2453), DOM9-112-230 (SEQ ID NO:2454), DOM9-112-231 (SEQ ID NO:2455), DOM9-112-233 (SEQ ID NO:1734), DOM9-112-232 (SEQ ID NO:1733) and DOM9-112-234 (SEQ ID NO:1735).

In some embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 (*e.g.* a dAb) comprises an amino acid sequence that has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence or a dAb selected from the group consisting of DOM9-15 (SEQ ID NO:175), DOM9-17(SEQ ID NO:176), DOM9-23 (SEQ ID NO:177), DOM9-24 (SEQ ID NO:178), DOM9-25 (SEQ ID NO:179), DOM9-27 (SEQ ID NO:180), DOM9-28 (SEQ ID NO:181), DOM9-29 (SEQ ID NO:182), DOM9-30 (SEQ ID NO:183), DOM9-31 (SEQ ID NO:184), DOM9-32 (SEQ ID NO:185), DOM9-33 (SEQ ID NO:186), DOM9-50 (SEQ ID NO:187), DOM9-57 (SEQ ID NO:188), DOM9-59 (SEQ ID NO:189), DOM9-63 (SEQ ID NO:190), DOM9-67 (SEQ ID NO:191), DOM9-68 (SEQ ID NO:192), DOM9-70 (SEQ ID NO:193), DOM9-79 (SEQ ID NO:194), DOM9-82 (SEQ ID NO:195), DOM9-86 (SEQ ID NO:196), DOM9-94 (SEQ ID NO:197), DOM9-108 (SEQ ID NO:198), DOM9-112 (SEQ ID NO:199), DOM9-112-1 (SEQ ID NO:200), DOM9-112-2 (SEQ ID NO:201), DOM9-112-3 (SEQ ID NO:202), DOM9-112-4 (SEQ ID NO:203), DOM9-112-5 (SEQ ID NO:204), DOM9-112-6 (SEQ ID NO:205), DOM9-112-7 (SEQ ID NO:206), DOM9-112-8 (SEQ ID NO:207), DOM9-112-9

(SEQ ID NO:208), DOM9-112-10 (SEQ ID NO:209), DOM9-112-11 (SEQ ID NO:210), DOM9-112-12 (SEQ ID NO:211), DOM9-112-13 (SEQ ID NO:212), DOM9-112-14 (SEQ ID NO:213), DOM9-112-15 (SEQ ID NO:214), DOM9-112-16 (SEQ ID NO:215), DOM9-112-17 (SEQ ID NO:216), DOM9-112-18 (SEQ ID NO:217), DOM9-112-19 (SEQ ID NO:218), DOM9-112-20 (SEQ ID NO:219), DOM9-112-21 (SEQ ID NO:220), DOM9-112-22 (SEQ ID NO:221), DOM9-112-23 (SEQ ID NO:222), DOM9-112-25 (SEQ ID NO:223), DOM9-112-81 (SEQ ID NO:224), DOM9-112-82 (SEQ ID NO:225), DOM9-112-83 (SEQ ID NO:226), DOM9-112-84 (SEQ ID NO:227), DOM9-112-85 (SEQ ID NO:228), DOM9-112-86 (SEQ ID NO:229), DOM9-112-87 (SEQ ID NO:230), DOM9-112-88 (SEQ ID NO:231), DOM9-112-89 (SEQ ID NO:232), DOM9-112-90 (SEQ ID NO:233), DOM9-112-91 (SEQ ID NO:234), DOM9-112-92 (SEQ ID NO:235), DOM9-112-93 (SEQ ID NO:236), DOM9-112-94 (SEQ ID NO:237), DOM9-112-95 (SEQ ID NO:238), DOM9-112-96 (SEQ ID NO:239), DOM9-112-97 (SEQ ID NO:240), DOM9-112-98 (SEQ ID NO:241), DOM9-112-99 (SEQ ID NO:242), DOM9-112-100 (SEQ ID NO:243), DOM9-112-101 (SEQ ID NO:244), DOM9-1132-102 (SEQ ID NO:245), DOM9-112-103 (SEQ ID NO:246), DOM9-112-104 (SEQ ID NO:247), DOM9-112-105 (SEQ ID NO:248), DOM9-112-106 (SEQ ID NO:249), DOM9-112-107 (SEQ ID NO:250), DOM9-112-108 (SEQ ID NO:251), DOM9-112-109 (SEQ ID NO:252), DOM9-112-110 (SEQ ID NO:253), DOM9-112-111 (SEQ ID NO:254), DOM9-112-112 (SEQ ID NO:255), DOM9-112-113 (SEQ ID NO:256), DOM9-112-114 (SEQ ID NO:257), DOM9-112-115 (SEQ ID NO:258), DOM9-112-116 (SEQ ID NO:259), DOM9-112-117 (SEQ ID NO:260), DOM9-112-118 (SEQ ID NO:261), DOM9-112-119 (SEQ ID NO:262), DOM9-112-120 (SEQ ID NO:263), DOM9-112-121 (SEQ ID NO:264), DOM9-112-122 (SEQ ID NO:265), DOM9-112-123 (SEQ ID NO:266), DOM9-112-124 (SEQ ID NO:267), DOM9-112-125 (SEQ ID NO:268), DOM9-112-126 (SEQ ID NO:269), DOM9-112-127 (SEQ ID NO:270), DOM9-112-128 (SEQ ID NO:271), DOM9-112-134 (SEQ ID NO:272), DOM9-112-135 (SEQ ID NO:273), DOM9-112-136 (SEQ ID NO:274), DOM9-112-137 (SEQ ID NO:275), DOM9-112-138 (SEQ ID NO:276), DOM9-112-140 (SEQ ID NO:277), DOM9-112-141 (SEQ ID NO:278), DOM9-112-142 (SEQ ID NO:279), DOM9-112-143 (SEQ ID NO:280), DOM9-112-144

(SEQ ID NO:281), DOM9-112-145 (SEQ ID NO:282), DOM9-112-146 (SEQ ID NO:283), DOM9-112-147 (SEQ ID NO:284), DOM9-112-148 (SEQ ID NO:285), DOM9-112-149 (SEQ ID NO:286), DOM9-112-150 (SEQ ID NO:287), DOM9-112-151 (SEQ ID NO:288), DOM9-112-152 (SEQ ID NO:289), DOM9-112-153 (SEQ ID NO:290), DOM9-112-154 (SEQ ID NO:291), DOM9-112-155 (SEQ ID NO:292), DOM9-112-156 (SEQ ID NO:293), DOM9-112-157 (SEQ ID NO:294), DOM9-112-158 (SEQ ID NO:295), DOM9-112-159 (SEQ ID NO:296), DOM9-112-160 (SEQ ID NO:297), DOM9-112-161 (SEQ ID NO:298), DOM9-112-162 (SEQ ID NO:299), DOM9-112-163 (SEQ ID NO:300), DOM9-112-164 (SEQ ID NO:301), DOM9-112-165 (SEQ ID NO:302), DOM9-112-166 (SEQ ID NO:303), DOM9-112-167 (SEQ ID NO:304), DOM9-112-168 (SEQ ID NO:305), DOM9-112-169 (SEQ ID NO:306), DOM9-112-170 (SEQ ID NO:307), DOM9-112-171 (SEQ ID NO:308), DOM9-112-172 (SEQ ID NO:309), DOM9-112-173 (SEQ ID NO:310), DOM9-112-174 (SEQ ID NO:311), DOM9-112-175 (SEQ ID NO:312), DOM9-112-176 (SEQ ID NO:313), DOM9-112-177 (SEQ ID NO:314), DOM9-112-178 (SEQ ID NO:315), DOM9-112-179 (SEQ ID NO:316), DOM9-112-180 (SEQ ID NO:317), DOM9-112-181 (SEQ ID NO:318), DOM9-112-182 (SEQ ID NO:319), DOM9-112-183 (SEQ ID NO:320), DOM9-112-184 (SEQ ID NO:321), DOM9-112-185 (SEQ ID NO:322), DOM9-112-186 (SEQ ID NO:323), DOM9-112-187 (SEQ ID NO:324), DOM9-112-188 (SEQ ID NO:325), DOM9-112-189 (SEQ ID NO:326), DOM9-112-190 (SEQ ID NO:327), DOM9-112-191 (SEQ ID NO:328), DOM9-112-192 (SEQ ID NO:329), DOM9-112-193 (SEQ ID NO:330), DOM9-112-194 (SEQ ID NO:331), DOM9-112-195 (SEQ ID NO:332), DOM9-112-196 (SEQ ID NO:333), DOM9-112-197 (SEQ ID NO:334), DOM9-112-198 (SEQ ID NO:335), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-112-201 (SEQ ID NO:338), DOM9-112-202 (SEQ ID NO:339), DOM9-120 (SEQ ID NO:340), DOM9-121 (SEQ ID NO:341), DOM9-122 (SEQ ID NO:342), DOM9-123 (SEQ ID NO:343), DOM9-124 (SEQ ID NO:344), DOM9-125 (SEQ ID NO:345), DOM9-128 (SEQ ID NO:346), DOM9-134 (SEQ ID NO:347), DOM9-136 (SEQ ID NO:348), DOM9-26 (SEQ ID NO:500), DOM9-35 (SEQ ID NO:501), DOM9-36 (SEQ ID NO:502), DOM9-37 (SEQ ID NO:503), DOM9-38 (SEQ ID NO:504), DOM9-39 (SEQ ID NO:505), DOM9-40 (SEQ ID

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In some embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 (*e.g.* a dAb) comprises an amino acid sequence that has

at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence or a dAb selected from the group consisting of DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-204 (SEQ ID NO:2428), DOM9-112-205 (SEQ ID NO:2429), DOM9-112-206 (SEQ ID NO:2430), DOM9-112-207 (SEQ ID NO:2431), DOM9-112-208 (SEQ ID NO:2432), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434), DOM9-112-211 (SEQ ID NO:2435), DOM9-112-212 (SEQ ID NO:2436), DOM9-112-213 (SEQ ID NO:2437), DOM9-112-214 (SEQ ID NO:2438), DOM9-112-215 (SEQ ID NO:2439), DOM9-112-216 (SEQ ID NO:2440), DOM9-112-217 (SEQ ID NO:2441), DOM9-112-218 (SEQ ID NO:2442), DOM9-112-219 (SEQ ID NO:2443), DOM9-112-220 (SEQ ID NO:2444), DOM9-112-221 (SEQ ID NO:2445), DOM9-112-222 (SEQ ID NO:2446), DOM9-112-223 (SEQ ID NO:2447), DOM9-112-224 (SEQ ID NO:2448), DOM9-112-225 (SEQ ID NO:2449), DOM9-112-226 (SEQ ID NO:2450), DOM9-112-227 (SEQ ID NO:2451), DOM9-112-228 (SEQ ID NO:2452), DOM9-112-229 (SEQ ID NO:2453), DOM9-112-230 (SEQ ID NO:2454), DOM9-112-231 (SEQ ID NO:2455), DOM9-112-233 (SEQ ID NO:1734), DOM9-112-232 (SEQ ID NO:1733) and DOM9-112-234 (SEQ ID NO:1735).

In preferred embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 comprises an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence or a dAb selected from the group consisting of DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-

112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512). For example, the polypeptide domain that has a binding site with binding specificity for IL-4 can comprise DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605, DOM9-155-25 (SEQ ID NO:617), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

In some embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 competes with any of the dAbs disclosed herein for binding to IL-4.

Preferably the polypeptide domain that has a binding site with binding specificity for IL-4 is an immunoglobulin single variable domain. The polypeptide domain that has a binding site with binding specificity for IL-4 can comprise any suitable immunoglobulin variable domain, and preferably comprises a human variable domain or a variable domain that comprises human framework regions. In certain embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 comprises a universal framework, as described herein.

The universal framework can be a V_L framework (Vλ or Vκ) , such as a framework that comprises the framework amino acid sequences encoded by the human germline DPK1, DPK2, DPK3, DPK4, DPK5, DPK6, DPK7, DPK8, DPK9, DPK10, DPK12, DPK13, DPK15, DPK16, DPK18, DPK19, DPK20, DPK21, DPK22, DPK23, DPK24, DPK25, DPK26 or DPK 28 immunoglobulin gene segment. If desired, the V_L framework can further comprise the framework amino acid sequence encoded by the human germline J_K1, J_K2, J_K3, J_K4, or J_K5 immunoglobulin gene segment.

In other embodiments the universal framework can be a V_H framework, such as a framework that comprises the framework amino acid sequences encoded by the human germline DP4, DP7, DP8, DP9, DP10, DP31, DP33, DP38, DP45, DP46, DP47, DP49, DP50, DP51, DP53, DP54, DP65, DP66, DP67, DP68 or DP69 immunoglobulin gene segment. If desired, the V_H framework can further comprise

the framework amino acid sequence encoded by the human germline J_H1, J_H2, J_H3, J_H4, J_H4b, J_H5 and J_H6 immunoglobulin gene segment.

In certain embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 comprises one or more framework regions comprising an amino acid sequence that is the same as the amino acid sequence of a corresponding framework region encoded by a human germline antibody gene segment, or the amino acid sequences of one or more of said framework regions collectively comprise up to 5 amino acid differences relative to the amino acid sequence of said corresponding framework region encoded by a human germline antibody gene segment.

In other embodiments, the amino acid sequences of FW1, FW2, FW3 and FW4 of the polypeptide domain that have a binding site with binding specificity for IL-4 are the same as the amino acid sequences of corresponding framework regions encoded by a human germline antibody gene segment, or the amino acid sequences of FW1, FW2, FW3 and FW4 collectively contain up to 10 amino acid differences relative to the amino acid sequences of corresponding framework regions encoded by said human germline antibody gene segment.

In other embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 comprises FW1, FW2 and FW3 regions, and the amino acid sequence of said FW1, FW2 and FW3 regions are the same as the amino acid sequences of corresponding framework regions encoded by human germline antibody gene segments.

In particular embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 comprises the DPK9 V_L framework, or a V_H framework selected from the group consisting of DP47, DP45 and DP38. The polypeptide domain that has a binding site with binding specificity for IL-4 can comprise a binding site for a generic ligand, such as protein A, protein L and protein G.

The ligand of the invention (*e.g.*, ligand that has binding specificity for IL-4 and IL-13, ligand that has binding specificity for IL-4) can comprise a non-immunoglobulin binding moiety that has binding specificity for IL-4 and preferably inhibits a function of IL-4 (*e.g.*, binding to receptor), wherein the non-

immunoglobulin binding moiety comprises one, two or three of the CDRs of a V_H, V_L or V_{HH} that binds IL-4 and a suitable scaffold. In certain embodiments, the non-immunoglobulin binding moiety comprises CDR3 but not CDR1 or CDR2 of a V_H, V_L or V_{HH} that binds IL-4 and a suitable scaffold. In other embodiments, the non-immunoglobulin binding moiety comprises CDR1 and CDR2, but not CDR3 of a V_H, V_L or V_{HH} that binds IL-4 and a suitable scaffold. In other embodiments, the non-immunoglobulin binding moiety comprises CDR1, CDR2 and CDR3 of a V_H, V_L or V_{HH} that binds IL-4 and a suitable scaffold. Preferably, the CDR or CDRs of the ligand of these embodiments is a CDR or CDRs of an anti-IL-4 dAb described herein. Preferably, the non-immunoglobulin binding moiety comprises one, two, or three of the CDRs of one of the anti-IL-4 dAbs disclosed herein. In other embodiments, the ligand (*e.g.*, ligand that has binding specificity for IL-4 and IL-13, ligand that has binding specificity for IL-4) comprises only CDR3 of a V_H, V_L or V_{HH} that binds IL-4. The non-immunoglobulin domain can comprise an amino acid sequence that has one or more regions that have sequence identity to one, two or three of the CDRs of an anti-IL-4 dAb described herein. For example, the non-immunoglobulin domain can have an amino acid sequence that contains at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% sequence identity with CDR1, CDR2 and/or CDR3 of an anti-IL-4 dAb disclosed herein. Even more preferably, the non-immunoglobulin binding moiety comprises one, two, or three of the CDRs of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), and DOM9-112-200 (SEQ ID NO:337).

In certain embodiments, the polypeptide domain that has a binding site with binding specificity for IL-4 is substantially resistant to aggregation. For example, in some embodiments, less than about 10%, less than about 9%, less than about 8%, less than about 7%, less than about 6%, less than about 5%, less than about 4%, less than about 3%, less than about 2% or less than about 1% of the polypeptide domain that has a binding site with binding specificity for IL-4 aggregates when a 1-5 mg/ml, 5-10 mg/ml, 10-20 mg/ml, 20-50 mg/ml, 50-100 mg/ml, 100-200 mg/ml or

200-500 mg/ml solution of ligand or dAb in a solvent that is routinely used for drug formulation such as saline, buffered saline, citrate buffer saline, water, an emulsion, and, any of these solvents with an acceptable excipient such as those approved by the FDA, is maintained at about 22°C, 22-25°C, 25-30°C, 30-37°C, 37-40°C, 40-50°C, 50-60°C, 60-70°C, 70-80°C, 15-20°C, 10-15°C, 5-10°C, 2-5°C, 0-2°C, -10°C to 0°C, -20°C to -10°C, -40°C to -20°C, -60°C to -40°C, or -80°C to -60°C, for a period of about time, for example, 10 minutes, 1 hour, 8 hours, 24 hours, 2 days, 3 days, 4 days, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 6 months, 1 year, or 2 years.

Aggregation can be assessed using any suitable method, such as, by microscopy, assessing turbidity of a solution by visual inspection or spectroscopy or any other suitable method. Preferably, aggregation is assessed by dynamic light scattering. Polypeptide domains that have a binding site with binding specificity for IL-4 that are resistant to aggregation provide several advantages. For example, such polypeptide domains that have a binding site with binding specificity for IL-4 can readily be produced in high yield as soluble proteins by expression using a suitable biological production system, such as *E. coli*, and can be formulated and/or stored at higher concentrations than conventional polypeptides, and with less aggregation and loss of activity.

In addition, the polypeptide domain that has a binding site with binding specificity for IL-4 that is resistant to aggregation can be produced more economically than other antigen- or epitope-binding polypeptides (*e.g.*, conventional antibodies). For example, generally, preparation of antigen- or epitope-binding polypeptides intended for *in vivo* applications includes processes (*e.g.*, gel filtration) that remove aggregated polypeptides. Failure to remove such aggregates can result in a preparation that is not suitable for *in vivo* applications because, for example, aggregates of an antigen-binding polypeptide that is intended to act as an antagonist can function as an agonist by inducing cross-linking or clustering of the target antigen. Protein aggregates can also reduce the efficacy of therapeutic polypeptide by inducing an immune response in the subject to which they are administered.

In contrast, the aggregation resistant polypeptide domain that has a binding site with binding specificity for IL-4 of the invention can be prepared for *in vivo*

applications without the need to include process steps that remove aggregates, and can be used in *in vivo* applications without the aforementioned disadvantages caused by polypeptide aggregates.

In some embodiments, a polypeptide domain that has a binding site with binding specificity for IL-4 unfolds reversibly when heated to a temperature (Ts) and cooled to a temperature (Tc), wherein Ts is greater than the melting temperature (Tm) of the polypeptide domain that has a binding site with binding specificity for IL-4, and Tc is lower than the melting temperature of the polypeptide domain that has a binding site with binding specificity for IL-4. For example, a polypeptide domain that has a binding site with binding specificity for IL-4 can unfold reversibly when heated to 80°C and cooled to about room temperature. A polypeptide that unfolds reversibly loses function when unfolded but regains function upon refolding. Such polypeptides are distinguished from polypeptides that aggregate when unfolded or that improperly refold (misfolded polypeptides), *i.e.*, do not regain function.

Polypeptide unfolding and refolding can be assessed, for example, by directly or indirectly detecting polypeptide structure using any suitable method. For example, polypeptide structure can be detected by circular dichroism (CD) (*e.g.*, far-UV CD, near-UV CD), fluorescence (*e.g.*, fluorescence of tryptophan side chains), susceptibility to proteolysis, nuclear magnetic resonance (NMR), or by detecting or measuring a polypeptide function that is dependent upon proper folding (*e.g.*, binding to target ligand, binding to generic ligand). In one example, polypeptide unfolding is assessed using a functional assay in which loss of binding function (*e.g.*, binding a generic and/or target ligand, binding a substrate) indicates that the polypeptide is unfolded.

The extent of unfolding and refolding of a polypeptide domain that has a binding site with binding specificity for IL-4 can be determined using an unfolding or denaturation curve. An unfolding curve can be produced by plotting temperature as the ordinate and the relative concentration of folded polypeptide as the abscissa. The relative concentration of folded polypeptide domain that has a binding site with binding specificity for IL-4 can be determined directly or indirectly using any suitable method (*e.g.*, CD, fluorescence, binding assay). For example, a polypeptide

domain that has a binding site with binding specificity for IL-4 solution can be prepared and ellipticity of the solution determined by CD. The ellipticity value obtained represents a relative concentration of folded ligand or dAb monomer of 100%. The polypeptide domain that has a binding site with binding specificity for IL-4 in the solution is then unfolded by incrementally raising the temperature of the solution and ellipticity is determined at suitable increments (*e.g.*, after each increase of one degree in temperature). The polypeptide domain that has a binding site with binding specificity for IL-4 in solution is then refolded by incrementally reducing the temperature of the solution and ellipticity is determined at suitable increments. The data can be plotted to produce an unfolding curve and a refolding curve. The unfolding and refolding curves have a characteristic sigmoidal shape that includes a portion in which the polypeptide domain that has a binding site with binding specificity for IL-4 molecules is folded, an unfolding/refolding transition in which the polypeptide domain that has a binding site with binding specificity for IL-4 molecules is unfolded to various degrees, and a portion in which polypeptide domain that has a binding site with binding specificity for IL-4 is unfolded. The y-axis intercept of the refolding curve is the relative amount of refolded polypeptide domain that has a binding site with binding specificity for IL-4 recovered. A recovery of at least about 50%, or at least about 60%, or at least about 70%, or at least about 75%, or at least about 80%, or at least about 85%, or at least about 90%, or at least about 95% is indicative that the ligand or dAb monomer unfolds reversibly.

In a preferred embodiment, reversibility of unfolding of polypeptide domain that has a binding site with binding specificity for IL-4 is determined by preparing a polypeptide domain that has a binding site with binding specificity for IL-4 solution and plotting heat unfolding and refolding curves. The polypeptide domain that has a binding site with binding specificity for IL-4 solution can be prepared in any suitable solvent, such as an aqueous buffer that has a pH suitable to allow polypeptide domain that has a binding site with binding specificity for IL-4 to dissolve (*e.g.*, pH that is about 3 units above or below the isoelectric point (pI)). The polypeptide domain that has a binding site with binding specificity for IL-4 solution is concentrated enough to allow unfolding/folding to be detected. For example, the

ligand or dAb monomer solution can be about 0.1 μM to about 100 μM, or preferably about 1 μM to about 10 μM.

If the melting temperature (Tm) of the polypeptide domain that has a binding site with binding specificity for IL-4 is known, the solution can be heated to about ten degrees below the Tm (Tm-10) and folding assessed by ellipticity or fluorescence (*e.g.*, far-UV CD scan from 200 nm to 250 nm, fixed wavelength CD at 235 nm or 225 nm; tryptophan fluorescent emission spectra at 300 to 450 nm with excitation at 298 nm) to provide 100% relative folded ligand or dAb monomer. The solution is then heated to at least ten degrees above Tm (Tm+10) in predetermined increments (*e.g.*, increases of about 0.1 to about 1 degree), and ellipticity or fluorescence is determined at each increment. Then, the polypeptide domain that has a binding site with binding specificity for IL-4 is refolded by cooling to at least Tm-10 in predetermined increments and ellipticity or fluorescence determined at each increment. If the melting temperature of the polypeptide domain that has a binding site with binding specificity for IL-4 is not known, the solution can be unfolded by incrementally heating from about 25°C to about 100°C and then refolded by incrementally cooling to at least about 25°C, and ellipticity or fluorescence at each heating and cooling increment is determined. The data obtained can be plotted to produce an unfolding curve and a refolding curve, in which the y-axis intercept of the refolding curve is the relative amount of refolded protein recovered. In some embodiments, the polypeptide domain that has a binding site with binding specificity for VEGF does not comprise a *Camelid* immunoglobulin variable domain, or one or more framework amino acids that are unique to immunoglobulin variable domains encoded by *Camelid* germline antibody gene segments.

Preferably, the polypeptide domain that has a binding site with binding specificity for IL-4 is secreted in a quantity of at least about 0.5 mg/L when expressed in *E. coli* or in *Pichia* species (*e.g.*, *P. pastoris*). In other preferred embodiments, polypeptide domain that has a binding site with binding specificity for IL-4 is secreted in a quantity of at least about 0.75 mg/L, at least about 1 mg/L, at least about 4 mg/L, at least about 5 mg/L, at least about 10 mg/L, at least about 15 mg/L, at least about 20 mg/L, at least about 25 mg/L, at least about 30 mg/L, at least

about 35 mg/L, at least about 40 mg/L, at least about 45 mg/L, or at least about 50 mg/L, or at least about 100 mg/L, or at least about 200 mg/L, or at least about 300 mg/L, or at least about 400 mg/L, or at least about 500 mg/L, or at least about 600 mg/L, or at least about 700 mg/L, or at least about 800 mg/L, at least about 900 mg/L, or at least about 1g/L when expressed in *E. coli* or in *Pichia* species (*e.g.*, *P. pastoris*). In other preferred embodiments, a polypeptide domain that has a binding site with binding specificity for IL-4 is secreted in a quantity of at least about 1 mg/L to at least about 1g/L, at least about 1 mg/L to at least about 750 mg/L, at least about 100 mg/L to at least about 1 g/L, at least about 200 mg/L to at least about 1 g/L, at least about 300 mg/L to at least about 1 g/L, at least about 400 mg/L to at least about 1 g/L, at least about 500 mg/L to at least about 1g/L, at least about 600 mg/L to at least about 1 g/L, at least about 700 mg/L to at least about 1 g/L, at least about 800 mg/L to at least about 1g/L, or at least about 900 mg/L to at least about 1g/L when expressed in *E. coli* or in *Pichia* species (*e.g.*, *P. pastoris*). Although, polypeptide domain that has a binding site with binding specificity for IL-4 described herein can be secretable when expressed in *E. coli* or in *Pichia* species (*e.g.*, *P. pastoris*), they can be produced using any suitable method, such as synthetic chemical methods or biological production methods that do not employ *E. coli* or *Pichia* species.

Polypeptide Domains that Bind IL-13

The invention provides polypeptide domains (*e.g.*, dAb) that have a binding site with binding specificity for IL-13. In preferred embodiments, the polypeptide domain (*e.g.*, dAb) binds to IL-13 with an affinity (KD; KD=K_{off}(kd)/K_{on}(ka)) of 300 nM to 1 pM (*i.e.*, 3 x 10^{-7} to 5 x 10^{-12}M), preferably 100 nM to 1 pM, or 50 nM to 10 pM, more preferably 10 nM to 100 pM and most preferably about 1 nM, for example a K_D of 1 x 10^{-7} M or less, preferably 1 x 10^{-8} M or less, more preferably about 1 x 10^{-9} M or less, 1 x 10^{-10} M or less or 1 x 10^{-11} M or less; and/or a K_{off} rate constant of 5 x 10^{-1} s^{-1} to 1 x 10^{-7} s^{-1}, preferably 1 x 10^{-2} s^{-1} to 1 x 10^{-6} s^{-1}, more preferably 5 x 10^{-3} s^{-1} to 1 x 10^{-5} s^{-1}, for example 5 x 10^{-1} s^{-1} or less, preferably 1 x 10^{-2} s^{-1} or less, advantageously 1 x 10^{-3} s^{-1} or less, more preferably 1 x 10^{-4} s^{-1} or

less, still more preferably 1 x 10^{-5} s^{-1} or less, and most preferably 1 x 10^{-6} s^{-1} or less as determined by surface plasmon resonance.

In some embodiments, a polypeptide domain that has a binding site with binding specificity for IL-13 competes for binding to IL-13 with a dAb selected from the group consisting of DOM10-53 (SEQ ID NO:967), DOM10-53-1 (SEQ ID NO:968), DOM10-53-2 (SEQ ID NO:969), DOM10-53-3 (SEQ ID NO:970), DOM10-53-4 (SEQ ID NO:971), DOM10-53-5 (SEQ ID NO:972), DOM10-53-6 (SEQ ID NO:973), DOM10-53-7 (SEQ ID NO:974), DOM10-53-8 (SEQ ID NO:975), DOM10-53-9 (SEQ ID NO:976), DOM10-53-10 (SEQ ID NO:977), DOM10-53-11 (SEQ ID NO:978), DOM10-53-12 (SEQ ID NO:979), DOM10-53-13 (SEQ ID NO:980), DOM10-53-14 (SEQ ID NO:981), DOM10-53-15 (SEQ ID NO:982), DOM10-53-16 (SEQ ID NO:983), DOM10-53-17 (SEQ ID NO:984), DOM10-53-18 (SEQ ID NO:985), DOM10-53-19 (SEQ ID NO:986), DOM10-53-20 (SEQ ID NO:987), DOM10-53-21 (SEQ ID NO:988), DOM10-53-122 (SEQ ID NO:989), DOM10-53-123 (SEQ ID NO:990), DOM10-53-24 (SEQ ID NO:991), DOM10-53-25 (SEQ ID NO:992), DOM10-53-26 (SEQ ID NO:993), DOM10-53-27 (SEQ ID NO:994), DOM10-53-28 (SEQ ID NO:995), DOM10-53-29 (SEQ ID NO:996) , DOM10-53-30 (SEQ ID NO:997), DOM10-53-31 (SEQ ID NO:998), DOM10-53-32 (SEQ ID NO:1999), DOM10-53-43 (SEQ ID NO:1000), DOM10-53-44 (SEQ ID NO:1001), DOM10-53-45 (SEQ ID NO:1002), DOM10-53-46 (SEQ ID NO:1003), DOM10-53-47 (SEQ ID NO:1004), DOM10-53-48 (SEQ ID NO:1005), DOM10-53-49 (SEQ ID NO:1006), DOM10-53-50 (SEQ ID NO:1007), DOM10-53-51 (SEQ ID NO:1008), DOM10-53-52 (SEQ ID NO:1009) , DOM10-53-53 (SEQ ID NO:1010), DOM10-53-54 (SEQ ID NO:1011), DOM10-53-55 (SEQ ID NO:1012), DOM10-53-56 (SEQ ID NO:1013) , DOM10-53-57 (SEQ ID NO:1014), DOM10-53-59 (SEQ ID NO:1015), DOM10-53-60 (SEQ ID NO:1016), DOM10-53-61 (SEQ ID NO:1017), DOM10-53-62 (SEQ ID NO:1018), DOM10-53-63 (SEQ ID NO:1019), DOM10-53-64 (SEQ ID NO:1020), DOM10-53-65 (SEQ ID NO:1021), DOM10-53-66 (SEQ ID NO:1022), DOM10-53-67 (SEQ ID NO:1023), DOM10-53-68 (SEQ ID NO:1024), DOM10-53-69 (SEQ ID NO:1025), DOM10-53-70 (SEQ ID NO:1026), DOM10-53-71 (SEQ ID NO:1027), DOM10-53-72 (SEQ ID NO:1028), DOM10-53-73 (SEQ ID NO:1029), DOM10-53-74 (SEQ

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NO:1645), DOM10-176-594 (SEQ ID NO:1646), DOM10-176-595 (SEQ ID NO:1647), DOM10-176-596 (SEQ ID NO:1648), DOM10-176-597 (SEQ ID NO:1649), DOM10-176-598 (SEQ ID NO:1650), DOM10-176-599 (SEQ ID NO:1651), DOM10-176-600 (SEQ ID NO:1652), DOM10-176-601 (SEQ ID NO:1653), DOM10-176-602 (SEQ ID NO:1654), DOM10-176-603 (SEQ ID NO:1655), DOM10-176-604 (SEQ ID NO:1656), DOM10-176-605 (SEQ ID NO:1657), DOM10-176-606 (SEQ ID NO:1658), DOM10-176-607 (SEQ ID NO:1659), DOM10-176-608 (SEQ ID NO:1660), DOM10-176-609 (SEQ ID NO:1661), DOM10-176-610 (SEQ ID NO:1662), DOM10-176-611 (SEQ ID NO:1663), DOM10-176-612 (SEQ ID NO:1664), DOM10-176-613 (SEQ ID NO:1665), DOM10-176-614 (SEQ ID NO:1666), DOM10-176-615 (SEQ ID NO:1667), DOM10-176-616 (SEQ ID NO:1668), DOM10-176-617 (SEQ ID NO:1669), DOM10-176-618 (SEQ ID NO:1670), DOM10-176-619 (SEQ ID NO:1671), DOM10-176-620 (SEQ ID NO:1672), DOM10-176-621 (SEQ ID NO:1673), DOM10-176-622 (SEQ ID NO:1674), DOM10-176-623 (SEQ ID NO:1675), DOM10-176-624 (SEQ ID NO:1676), DOM10-176-625 (SEQ ID NO:1677), DOM10-176-626 (SEQ ID NO:1678), DOM10-176-627 (SEQ ID NO:1679), DOM10-176-628 (SEQ ID NO:1680), DOM10-176-629 (SEQ ID NO:1681), DOM10-176-630 (SEQ ID NO:1682), DOM10-176-631 (SEQ ID NO:1683), DOM10-176-632 (SEQ ID NO:1684), DOM10-176-633 (SEQ ID NO:1685), DOM10-176-634 (SEQ ID NO:1686), DOM10-176-635 (SEQ ID NO:1687), DOM10-176-636 (SEQ ID NO:1688), DOM10-176-637 (SEQ ID NO:1689), DOM10-176-638 (SEQ ID NO:1690), DOM10-176-639 (SEQ ID NO:1691), DOM10-176-640 (SEQ ID NO:1692), DOM10-176-641 (SEQ ID NO:1693), DOM10-176-643 (SEQ ID NO:1694), DOM10-176-644 (SEQ ID NO:1695), DOM10-176-645 (SEQ ID NO:1696), DOM10-176-646 (SEQ ID NO:1697), DOM10-176-647 (SEQ ID NO:1698), DOM10-176-648 (SEQ ID NO:1699), DOM10-176-649 (SEQ ID NO:1700), DOM10-176-650 (SEQ ID NO:1701), DOM10-176-651 (SEQ ID NO:1702), DOM10-176-652 (SEQ ID NO:1703), DOM10-176-653 (SEQ ID NO:1704), DOM10-176-654 (SEQ ID NO:1705), DOM10-176-655 (SEQ ID NO:1706), DOM10-176-656 (SEQ ID NO:1707), DOM10-176-657 (SEQ ID NO:1708), DOM10-176-658 (SEQ ID

NO:1709), DOM10-176-659 (SEQ ID NO:1710), DOM10-176-660 (SEQ ID NO:1711), DOM10-176-661 (SEQ ID NO:1712), DOM10-176-662 (SEQ ID NO:1713), DOM10-176-663 (SEQ ID NO:1714), DOM10-176-664 (SEQ ID NO:1715), DOM10-176-665 (SEQ ID NO:1716), DOM10-176-666 (SEQ ID NO:1717), DOM10-176-667 (SEQ ID NO:1718), DOM10-176-668 (SEQ ID NO:1719), DOM10-176-669 (SEQ ID NO:1720), DOM10-176-670 (SEQ ID NO:1721), DOM10-176-671 (SEQ ID NO:1722), DOM10-176-672 (SEQ ID NO:1723), DOM10-176-673 (SEQ ID NO:1724), DOM10-176-674 (SEQ ID NO:1725), DOM10-176-675 (SEQ ID NO:1726), DOM10-253 (SEQ ID NO:1727), DOM10-255 (SEQ ID NO:1728), DOM10-272 (SEQ ID NO:1729), DOM10-307 (SEQ ID NO:1730), DOM10-319 (SEQ ID NO:1731) and DOM10-319-1 (SEQ ID NO:1732).

In some embodiments, a polypeptide domain that has a binding site with binding specificity for IL-13 competes for binding to IL-13 with a dAb selected from the group consisting of DOM10-236 (SEQ ID NO:2129), DOM10-238 (SEQ ID NO:2130), DOM10-241 (SEQ ID NO:2131), DOM10-245 (SEQ ID NO:2132), DOM10-249 (SEQ ID NO:2133), DOM10-250 (SEQ ID NO:2134), DOM10-251 (SEQ ID NO:2135), DOM10-254 (SEQ ID NO:2136), DOM10-256 (SEQ ID NO:2137), DOM10-259 (SEQ ID NO:2138), DOM10-260 (SEQ ID NO:2139), DOM10-261 (SEQ ID NO:2140), DOM10-263 (SEQ ID NO:2141), DOM10-264 (SEQ ID NO:2142), DOM10-273 (SEQ ID NO:2143), DOM10-278 (SEQ ID NO:2144), DOM10-279 (SEQ ID NO:2145), DOM10-281 (SEQ ID NO:2146), DOM10-282 (SEQ ID NO:2147), DOM10-283 (SEQ ID NO:2148), DOM10-400 (SEQ ID NO:2149), DOM10-401 (SEQ ID NO:2150), DOM10-402 (SEQ ID NO:2151), DOM10-404 (SEQ ID NO:2152), DOM10-406 (SEQ ID NO:2153), DOM10-407 (SEQ ID NO:2154), DOM10-409 (SEQ ID NO:2155), DOM10-410 (SEQ ID NO:2156), DOM10-414 (SEQ ID NO:2157), DOM10-415 (SEQ ID NO:2158), DOM10-416 (SEQ ID NO:2159), DOM10-418 (SEQ ID NO:2160), DOM10-420 (SEQ ID NO:2161), DOM10-422 (SEQ ID NO:2162), DOM10-423 (SEQ ID NO:2163), DOM10-424 (SEQ ID NO:2164), DOM10-425 (SEQ ID NO:2165), DOM10-426 (SEQ ID NO:2166), DOM10-427 (SEQ ID NO:2167), DOM10-428 (SEQ ID NO:2168), DOM10-429 (SEQ ID NO:2169), DOM10-430

(SEQ ID NO:2170), DOM10-431 (SEQ ID NO:2171), DOM10-432 (SEQ ID NO:2172), DOM10-433 (SEQ ID NO:2173), DOM10-467 (SEQ ID NO:2174), DOM10-468 (SEQ ID NO:2175), DOM10-469 (SEQ ID NO:2176), DOM10-470 (SEQ ID NO:2177), DOM10-234 (SEQ ID NO:2178), DOM10-235 (SEQ ID NO:2179), DOM10-237 (SEQ ID NO:2180), DOM10-239 (SEQ ID NO:2181), DOM10-240 (SEQ ID NO:2182), DOM10-242 (SEQ ID NO:2183), DOM10-243 (SEQ ID NO:2184), DOM10-244 (SEQ ID NO:2185), DOM10-246 (SEQ ID NO:2186), DOM10-247 (SEQ ID NO:2187), DOM10-248 (SEQ ID NO:2188), DOM10-252 (SEQ ID NO:2189), DOM10-257 (SEQ ID NO:2190), DOM10-258 (SEQ ID NO:2191), DOM10-262 (SEQ ID NO:2192), DOM10-265 (SEQ ID NO:2193), DOM10-266 (SEQ ID NO:2194), DOM10-274 (SEQ ID NO:2195), DOM10-275 (SEQ ID NO:2196), DOM10-276 (SEQ ID NO:2197), DOM10-277 (SEQ ID NO:2198), DOM10-280 (SEQ ID NO:2199), DOM10-403 (SEQ ID NO:2200), DOM10-405 (SEQ ID NO:2201), DOM10-408 (SEQ ID NO:2202), DOM10-411 (SEQ ID NO:2203), DOM10-412 (SEQ ID NO:2204), DOM10-413 (SEQ ID NO:2205), DOM10-417 (SEQ ID NO:2206), DOM10-419 (SEQ ID NO:2207), DOM10-472 (SEQ ID NO:2208), DOM10-203 (SEQ ID NO:2209), DOM10-205 (SEQ ID NO:2210), DOM10-208 (SEQ ID NO:2211), DOM10-218 (SEQ ID NO:2212), DOM10-219 (SEQ ID NO:2213), DOM10-220 (SEQ ID NO:2214), DOM10-225 (SEQ ID NO:2215), DOM10-228 (SEQ ID NO:2216), DOM10-229 (SEQ ID NO:2217), DOM10-230 (SEQ ID NO:2218), DOM10-231 (SEQ ID NO:2219), DOM10-268 (SEQ ID NO:2220), DOM10-201 (SEQ ID NO:2221), DOM10-202 (SEQ ID NO:2222), DOM10-204 (SEQ ID NO:2223), DOM10-206 (SEQ ID NO:2224), DOM10-207 (SEQ ID NO:2225), DOM10-209 (SEQ ID NO:2226), DOM10-210 (SEQ ID NO:2227), DOM10-211 (SEQ ID NO:2228), DOM10-213 (SEQ ID NO:2229), DOM10-214 (SEQ ID NO:2230), DOM10-215 (SEQ ID NO:2231), DOM10-216 (SEQ ID NO:2232), DOM10-217 (SEQ ID NO:2233), DOM10-221 (SEQ ID NO:2234), DOM10-223 (SEQ ID NO:2235), DOM10-224 (SEQ ID NO:2236), DOM10-227 (SEQ ID NO:2237), DOM10-232 (SEQ ID NO:2238), DOM10-267 (SEQ ID NO:2239), DOM10-270 (SEQ ID NO:2240), DOM10-275-1 (SEQ ID NO:2241), DOM10-276-2 (SEQ ID NO:2242), DOM10-276-3 (SEQ ID NO:2243), DOM10-275-3 (SEQ ID NO:2244),

DOM10-277-2 (SEQ ID NO:2245), DOM10-277-3 (SEQ ID NO:2246), DOM10-273-1 (SEQ ID NO:2247), DOM10-273-2 (SEQ ID NO:2248), DOM10-275-2 (SEQ ID NO:2249), DOM10-275-4 (SEQ ID NO:2250), DOM10-276-1 (SEQ ID NO:2251), DOM10-276-4 (SEQ ID NO:2252), DOM10-277-1 (SEQ ID NO:2253), DOM10-275-13 (SEQ ID NO:2254), DOM10-275-15 (SEQ ID NO:2255), DOM10-275-20 (SEQ ID NO:2256), DOM10-275-8 (SEQ ID NO:2257), DOM10-276-13 (SEQ ID NO:2258), DOM10-276-14 (SEQ ID NO:2259), DOM10-276-15 (SEQ ID NO:2260), DOM10-276-17 (SEQ ID NO:2261), DOM10-276-7 (SEQ ID NO:2262), DOM10-276-8 (SEQ ID NO:2263), DOM10-275-11 (SEQ ID NO:2264), DOM10-275-12 (SEQ ID NO:2265), DOM10-275-14 (SEQ ID NO:2266), DOM10-275-16 (SEQ ID NO:2267), DOM10-275-17 (SEQ ID NO:2268), DOM10-275-5 (SEQ ID NO:2269), DOM10-275-6 (SEQ ID NO:2270), DOM10-275-7 (SEQ ID NO:2271), DOM10-275-9 (SEQ ID NO:2272), DOM10-276-10 (SEQ ID NO:2273), DOM10-276-11 (SEQ ID NO:2274), DOM10-276-12 (SEQ ID NO:2275), DOM10-276-16 (SEQ ID NO:2276), DOM10-276-5 (SEQ ID NO:2277), DOM10-276-6 (SEQ ID NO:2278), DOM10-276-9 (SEQ ID NO:2279), DOM10-212 (SEQ ID NO:2280), DOM10-53-424 (SEQ ID NO:2281), DOM10-53-425 (SEQ ID NO:2282), DOM10-53-426 (SEQ ID NO:2283), DOM10-53-422 (SEQ ID NO:2284), DOM10-53-423 (SEQ ID NO:2285), DOM10-53-613 (SEQ ID NO:2286), DOM10-53-517 (SEQ ID NO:2287), DOM10-53-519 (SEQ ID NO:2288), DOM10-53-520 (SEQ ID NO:2289), DOM10-53-521 (SEQ ID NO:2290), DOM10-53-522 (SEQ ID NO:2291), DOM10-53-526 (SEQ ID NO:2292), DOM10-53-527 (SEQ ID NO:2293), DOM10-53-528 (SEQ ID NO:2294), DOM10-53-518 (SEQ ID NO:2295), DOM10-53-523 (SEQ ID NO:2296), DOM10-53-524 (SEQ ID NO:2297), DOM10-53-525 (SEQ ID NO:2298), DOM10-53-601 (SEQ ID NO:2299), DOM10-53-602 (SEQ ID NO:2300), DOM10-53-605 (SEQ ID NO:2301), DOM10-53-606 (SEQ ID NO:2302), DOM10-53-607 (SEQ ID NO:2303), DOM10-53-608 (SEQ ID NO:2304), DOM10-53-609 (SEQ ID NO:2305), DOM10-53-610 (SEQ ID NO:2306), DOM10-53-611 (SEQ ID NO:2307), DOM10-53-612 (SEQ ID NO:2308), DOM10-53-603 (SEQ ID NO:2309), DOM10-53-604 (SEQ ID NO:2310), DOM10-53-429 (SEQ ID NO:2311), DOM10-53-432 (SEQ ID NO:2312), DOM10-53-433 (SEQ ID

NO:2313), DOM10-53-435 (SEQ ID NO:2314), DOM10-53-430 (SEQ ID NO:2315), DOM10-53-431 (SEQ ID NO:2316), DOM10-53-434 (SEQ ID NO:2317), DOM10-53-436 (SEQ ID NO:2318), DOM10-53-437 (SEQ ID NO:2319), DOM10-53-438 (SEQ ID NO:2320), DOM10-53-440 (SEQ ID NO:2321), DOM10-53-439 (SEQ ID NO:2322), DOM10-53-441 (SEQ ID NO:2323), DOM10-53-442 (SEQ ID NO:2324), DOM10-53-443 (SEQ ID NO:2325), DOM10-53-444 (SEQ ID NO:2326), DOM10-53-445 (SEQ ID NO:2327), DOM10-53-446 (SEQ ID NO:2328), DOM10-53-447 (SEQ ID NO:2329), DOM10-53-449 (SEQ ID NO:2330), DOM10-53-448 (SEQ ID NO:2331), DOM10-53-450 (SEQ ID NO:2332), DOM10-53-451 (SEQ ID NO:2333), DOM10-53-452 (SEQ ID NO:2334), DOM10-53-453 (SEQ ID NO:2335), DOM10-53-454 (SEQ ID NO:2336), DOM10-53-455 (SEQ ID NO:2337), DOM10-53-456 (SEQ ID NO:2338), DOM10-53-457 (SEQ ID NO:2339), DOM10-53-458 (SEQ ID NO:2340), DOM10-53-459 (SEQ ID NO:2341), DOM10-53-461 (SEQ ID NO:2342), DOM10-53-462 (SEQ ID NO:2343), DOM10-53-465 (SEQ ID NO:2344), DOM10-53-466 (SEQ ID NO:2345), DOM10-53-467 (SEQ ID NO:2346), DOM10-53-468 (SEQ ID NO:2347), DOM10-53-460 (SEQ ID NO:2348), DOM10-53-463 (SEQ ID NO:2349), DOM10-53-464 (SEQ ID NO:2350), DOM10-53-469 (SEQ ID NO:2351), DOM10-53-471 (SEQ ID NO:2352), DOM10-53-470 (SEQ ID NO:2353), DOM10-53-533 (SEQ ID NO:2354), DOM10-53-534 (SEQ ID NO:2355), DOM10-53-535 (SEQ ID NO:2356), DOM10-53-537 (SEQ ID NO:2357), DOM10-53-538 (SEQ ID NO:2358), DOM10-53-539 (SEQ ID NO:2359), DOM10-53-540 (SEQ ID NO:2360), DOM10-53-531 (SEQ ID NO:2361), DOM10-53-532 (SEQ ID NO:2362), DOM10-53-536 (SEQ ID NO:2363), DOM10-53-542 (SEQ ID NO:2364), DOM10-53-541 (SEQ ID NO:2365), DOM10-53-473 (SEQ ID NO:2366), DOM10-53-472 (SEQ ID NO:2367), DOM10-53-475 (SEQ ID NO:2368), DOM10-53-474 (SEQ ID NO:2369), DOM10-53-543 (SEQ ID NO:2370), DOM10-53-544 (SEQ ID NO: 2371), DOM10-53-545 (SEQ ID NO:2372), DOM10-53-548 (SEQ ID NO:2373), DOM10-53-546 (SEQ ID NO:2374), DOM10-53-549 (SEQ ID NO:2375), DOM10-53-547 (SEQ ID NO:2376), DOM10-53-550 (SEQ ID NO:2377), DOM10-53-551

(SEQ ID NO:2378), DOM10-53-560 (SEQ ID NO:2379), DOM10-53-565 (SEQ ID NO:2380), DOM10-53-559 (SEQ ID NO:2381), DOM10-53-561 (SEQ ID NO:2382), DOM10-53-562 (SEQ ID NO:2383), DOM10-53-563 (SEQ ID NO:2384), DOM10-53-564 (SEQ ID NO:2385), DOM10-53-566 (SEQ ID NO:2386), DOM10-53-554 (SEQ ID NO:2387), DOM10-53-552 (SEQ ID NO:2388), DOM10-53-553 (SEQ ID NO:2389), DOM10-53-558 (SEQ ID NO:2390), DOM10-53-556 (SEQ ID NO:2391) and DOM10-53-557 (SEQ ID NO:2392).

In some embodiments, the polypeptide domain that has a binding site with binding specificity for IL-13 (*e.g.*, a dAb) comprises an amino acid sequence that has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence or a dAb selected from the group consisting of DOM10-53 (SEQ ID NO:967), DOM10-53-1 (SEQ ID NO:968), DOM10-53-2 (SEQ ID NO:969), DOM10-53-3 (SEQ ID NO:970), DOM10-53-4 (SEQ ID NO:971), DOM10-53-5 (SEQ ID NO:972), DOM10-53-6 (SEQ ID NO:973), DOM10-53-7 (SEQ ID NO:974), DOM10-53-8 (SEQ ID NO:975), DOM10-53-9 (SEQ ID NO:976), DOM10-53-10 (SEQ ID NO:977), DOM10-53-11 (SEQ ID NO:978), DOM10-53-12 (SEQ ID NO:979), DOM10-53-13 (SEQ ID NO:980), DOM10-53-14 (SEQ ID NO:981), DOM10-53-15 (SEQ ID NO:982), DOM10-53-16 (SEQ ID NO:983), DOM10-53-17 (SEQ ID NO:984), DOM10-53-18 (SEQ ID NO:985), DOM10-53-19 (SEQ ID NO:986), DOM10-53-20 (SEQ ID NO:987), DOM10-53-21 (SEQ ID NO:988), DOM10-53-122 (SEQ ID NO:989), DOM10-53-123 (SEQ ID NO:990), DOM10-53-24 (SEQ ID NO:991), DOM10-53-25 (SEQ ID NO:992), DOM10-53-26 (SEQ ID NO:993), DOM10-53-27 (SEQ ID NO:994), DOM10-53-28 (SEQ ID NO:995), DOM10-53-29 (SEQ ID NO:996) , DOM10-53-30 (SEQ ID NO:997), DOM10-53-31 (SEQ ID NO:998), DOM10-53-32 (SEQ ID NO:1999), DOM10-53-43 (SEQ ID NO:1000), DOM10-53-44 (SEQ ID NO:1001), DOM10-53-45 (SEQ ID NO:1002), DOM10-53-46 (SEQ ID NO:1003), DOM10-53-47 (SEQ ID NO:1004), DOM10-53-48 (SEQ ID NO:1005), DOM10-53-49 (SEQ ID NO:1006), DOM10-53-50 (SEQ ID NO:1007), DOM10-53-51 (SEQ

ID NO:1008), DOM10-53-52 (SEQ ID NO:1009) , DOM10-53-53 (SEQ ID NO:1010), DOM10-53-54 (SEQ ID NO:1011), DOM10-53-55 (SEQ ID NO:1012), DOM10-53-56 (SEQ ID NO:1013) , DOM10-53-57 (SEQ ID NO:1014), DOM10-53-59 (SEQ ID NO:1015), DOM10-53-60 (SEQ ID NO:1016), DOM10-53-61 (SEQ ID NO:1017), DOM10-53-62 (SEQ ID NO:1018), DOM10-53-63 (SEQ ID NO:1019), DOM10-53-64 (SEQ ID NO:1020), DOM10-53-65 (SEQ ID NO:1021), DOM10-53-66 (SEQ ID NO:1022), DOM10-53-67 (SEQ ID NO:1023), DOM10-53-68 (SEQ ID NO:1024), DOM10-53-69 (SEQ ID NO:1025), DOM10-53-70 (SEQ ID NO:1026), DOM10-53-71 (SEQ ID NO:1027), DOM10-53-72 (SEQ ID NO:1028), DOM10-53-73 (SEQ ID NO:1029), DOM10-53-74 (SEQ ID NO:1030), DOM10-53-75 (SEQ ID NO:1031), DOM10-53-76 (SEQ ID NO:1032), DOM10-53-77 (SEQ ID NO:1033), DOM10-53-78 (SEQ ID NO:1034) , DOM10-53-79 (SEQ ID NO:1035), DOM10-53-80 (SEQ ID NO:1036), DOM10-53-81 (SEQ ID NO:1037), DOM10-53-82 (SEQ ID NO:1038), DOM10-53-83 (SEQ ID NO:1039), DOM10-53-84 (SEQ ID NO:1040), DOM10-53-85 (SEQ ID NO:1041), DOM10-53-86 (SEQ ID NO:1042) , DOM10-53-87 (SEQ ID NO:1043), DOM10-53-88 (SEQ ID NO:1044), DOM10-53-89 (SEQ ID NO:1045), DOM10-53-91 (SEQ ID NO:1046), DOM10-53-92 (SEQ ID NO:1047), DOM10-53-93 (SEQ ID NO:1048), DOM10-53-94 (SEQ ID NO:1049), DOM10-53-95 (SEQ ID NO:1050), DOM10-53-96 (SEQ ID NO:1051), DOM10-53-97 (SEQ ID NO:1052), DOM10-53-98 (SEQ ID NO:1053), DOM10-53-99 (SEQ ID NO:1054), DOM10-53-100 (SEQ ID NO:1055), DOM10-53-103 (SEQ ID NO:1056), DOM10-53-105 (SEQ ID NO:1057), DOM10-53-106 (SEQ ID NO:1058), DOM10-53-108 (SEQ ID NO:1059), DOM10-53-110 (SEQ ID NO:1060), DOM10-53-111 (SEQ ID NO:1061), DOM10-53-112 (SEQ ID NO:10632), DOM10-53-114 (SEQ ID NO:1063), DOM10-53-115 (SEQ ID NO:1064), DOM10-53-116 (SEQ ID NO:1065), DOM10-53-117 (SEQ ID NO:1066), DOM10-53-119 (SEQ ID NO:1067), DOM10-53-120 (SEQ ID NO:1068), DOM10-53-122 (SEQ ID NO:1069), DOM10-53-201 (SEQ ID NO:1070) , DOM10-53-203 (SEQ ID NO:1071), DOM10-53-204 (SEQ ID NO:1072), DOM10-53-205 (SEQ ID NO:1073), DOM10-53-206 (SEQ ID NO:1074), DOM10-53-207 (SEQ ID NO:1075), DOM10-53-208 (SEQ ID NO:1076), DOM10-53-209 (SEQ ID

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NO:1141), DOM10-53-275 (SEQ ID NO:1142), DOM10-53-276 (SEQ ID NO:1143), DOM10-53-277 (SEQ ID NO:1144), DOM10-53-278 (SEQ ID NO:1145), DOM10-53-279 (SEQ ID NO:1146), DOM10-53-280 (SEQ ID NO:1147), DOM10-53-281 (SEQ ID NO:1148), DOM10-53-282 (SEQ ID NO:1149), DOM10-53-283 (SEQ ID NO:1150), DOM10-53-284 (SEQ ID NO:1151), DOM10-53-285 (SEQ ID NO:1152), DOM10-53-286 (SEQ ID NO:1153), DOM10-53-287 (SEQ ID NO:1154), DOM10-53-288 (SEQ ID NO:1155), DOM10-53-289 (SEQ ID NO:1156) , DOM10-53-290 (SEQ ID NO:1157), DOM10-53-291 (SEQ ID NO:1158), DOM10-53-292 (SEQ ID NO:1159), DOM10-53-293 (SEQ ID NO:1160), DOM10-53-294 (SEQ ID NO:1161), DOM10-53-295 (SEQ ID NO:1162), DOM10-53-296 (SEQ ID NO:1163), DOM10-53-297 (SEQ ID NO:1164), DOM10-53-298 (SEQ ID NO:1165), DOM10-53-299 (SEQ ID NO:1166), DOM10-53-300 (SEQ ID NO:1167), DOM10-53-301 (SEQ ID NO:1168), DOM10-53-302 (SEQ ID NO:1169) , DOM10-53-303 (SEQ ID NO:1170), DOM10-53-304 (SEQ ID NO:1171), DOM10-53-305 (SEQ ID NO:1172), DOM10-53-306 (SEQ ID NO:1173), DOM10-53-307 (SEQ ID NO:1174), DOM10-53-308 (SEQ ID NO:1175), DOM10-53-309 (SEQ ID NO:1176), DOM10-53-310 (SEQ ID NO:11787), DOM10-53-311 (SEQ ID NO:1178), DOM10-53-312 (SEQ ID NO:1179), DOM10-53-314 (SEQ ID NO:1180), DOM10-53-315 (SEQ ID NO:1181), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-317 (SEQ ID NO:1183), DOM10-53-318 (SEQ ID NO:1184), DOM10-53-319 (SEQ ID NO:1185), DOM10-53-320 (SEQ ID NO:1186), DOM10-53-321 (SEQ ID NO:1187), DOM10-53-322 (SEQ ID NO:1188), DOM10-53-323 (SEQ ID NO:1189), DOM10-53-324 (SEQ ID NO:1190), DOM10-53-325 (SEQ ID NO:1191), DOM10-53-326 (SEQ ID NO:1192), DOM10-53-327 (SEQ ID NO:1193), DOM10-53-328 (SEQ ID NO:1194), DOM10-53-329 (SEQ ID NO:1195), DOM10-53-330 (SEQ ID NO:1196), DOM10-53-331 (SEQ ID NO:1197), DOM10-53-333 (SEQ ID NO:1198), DOM10-53-334 (SEQ ID NO:1199), DOM10-53-336 (SEQ ID NO:1200), DOM10-53-337 (SEQ ID NO:1201), DOM10-53-338 (SEQ ID NO:1202), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-340 (SEQ ID NO:1204), DOM10-53-341 (SEQ ID

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NO:1270), DOM10-53-410 (SEQ ID NO:1271), DOM10-53-411 (SEQ ID NO:1272), DOM10-53-412 (SEQ ID NO:1273), DOM10-53-413 (SEQ ID NO:1274), DOM10-53-414 (SEQ ID NO:1275), DOM10-53-415 (SEQ ID NO:1276), DOM10-53-416 (SEQ ID NO:1277), DOM10-53-417 (SEQ ID NO:1278), DOM10-53-418 (SEQ ID NO:1279), DOM10-53-419 (SEQ ID NO:1280), DOM10-53-420 (SEQ ID NO:1281), DOM10-53-421 (SEQ ID NO:1282), DOM10-168 (SEQ ID NO:1508), DOM10-169 (SEQ ID NO:1509), DOM10-176 (SEQ ID NO:1510), DOM10-176-1 (SEQ ID NO:1511), DOM10-176-2 (SEQ ID NO:1512), DOM10-173 (SEQ ID NO:1513), DOM10-176-4 (SEQ ID NO:1514), DOM10-176-5 (SEQ ID NO:1515), DOM10-176-6 (SEQ ID NO:1516), DOM10-176-23 (SEQ ID NO:1517), DOM10-176-24 (SEQ ID NO:1518), DOM10-176-25 (SEQ ID NO:1519), DOM10-176-26 (SEQ ID NO:1520), DOM10-176-27 (SEQ ID NO:1521), DOM10-176-28 (SEQ ID NO:1522), DOM10-176-29 (SEQ ID NO:1523), DOM10-176-30 (SEQ ID NO:1524), DOM10-176-31 (SEQ ID NO:1525), DOM10-176-32 (SEQ ID NO:1526), DOM10-176-33 (SEQ ID NO:1527), DOM10-176-34 (SEQ ID NO:1528), DOM10-176-35 (SEQ ID NO:1529), DOM10-176-36 (SEQ ID NO:1530), DOM10-176-37 (SEQ ID NO:1531), DOM10-176-38 (SEQ ID NO:1532), DOM10-176-39 (SEQ ID NO:1533), DOM10-176-40 (SEQ ID NO:1534), DOM10-176-101 (SEQ ID NO:1535), DOM10-176-102 (SEQ ID NO:1536), DOM10-176-103 (SEQ ID NO:1537), DOM10-176-104 (SEQ ID NO:1538), DOM10-176-105 (SEQ ID NO:1539), DOM10-176-106 (SEQ ID NO:1540), DOM10-176-107 (SEQ ID NO:1541), DOM10-176-108 (SEQ ID NO:1542), DOM10-176-109 (SEQ ID NO:1543), DOM10-176-110 (SEQ ID NO:1544), DOM10-176-111 (SEQ ID NO:1545), DOM10-176-112 (SEQ ID NO:1546), DOM10-176-113 (SEQ ID NO:1547), DOM10-176-114 (SEQ ID NO:1548), DOM10-176-115 (SEQ ID NO:1549), DOM10-176-116 (SEQ ID NO:1550), DOM10-176-117 (SEQ ID NO:1551), DOM10-176-500 (SEQ ID NO:1552), DOM10-176-501 (SEQ ID NO:1553), DOM10-176-502 (SEQ ID NO:1554), DOM10-176-503 (SEQ ID NO:1555), DOM10-176-504 (SEQ ID NO:1556), DOM10-176-505 (SEQ ID NO:1557), DOM10-176-506 (SEQ ID NO:1558), DOM10-176-507 (SEQ ID NO:1559), DOM10-176-508 (SEQ ID NO:1560), DOM10-176-509 (SEQ ID

NO:1561), DOM10-176-510 (SEQ ID NO:1562), DOM10-176-511 (SEQ ID NO:1563), DOM10-176-512 (SEQ ID NO:1564), DOM10-176-513 (SEQ ID NO:1565), DOM10-176-514 (SEQ ID NO:1566), DOM10-176-515 (SEQ ID NO:1567), DOM10-176-516 (SEQ ID NO:1568), DOM10-176-517 (SEQ ID NO:1569), DOM10-176-518 (SEQ ID NO:1570), DOM10-176-519 (SEQ ID NO:1571), DOM10-176-520 (SEQ ID NO:1572), DOM10-176-521 (SEQ ID NO:1573), DOM10-176-522 (SEQ ID NO:1574), DOM10-176-523 (SEQ ID NO:1575), DOM10-176-524 (SEQ ID NO:1576), DOM10-176-525 (SEQ ID NO:1577), DOM10-176-526 (SEQ ID NO:1578), DOM10-176-527 (SEQ ID NO:1579), DOM10-176-528 (SEQ ID NO:1580), DOM10-176-529 (SEQ ID NO:1581), DOM10-176-530 (SEQ ID NO:1582), DOM10-176-531 (SEQ ID NO:1583), DOM10-176-532 (SEQ ID NO:1584), DOM10-176-533 (SEQ ID NO:1585), DOM10-176-534 (SEQ ID NO:1586), DOM10-176-535 (SEQ ID NO:1587), DOM10-176-536 (SEQ ID NO:1588), DOM10-176-537 (SEQ ID NO:1589), DOM10-176-538 (SEQ ID NO:1590), DOM10-176-539 (SEQ ID NO:1591), DOM10-176-540 (SEQ ID NO:1592), DOM10-176-541 (SEQ ID NO:1593), DOM10-176-542 (SEQ ID NO:1594), DOM10-176-543 (SEQ ID NO:1595), DOM10-176-544 (SEQ ID NO:1596), DOM10-176-545 (SEQ ID NO:1597), DOM10-176-546 (SEQ ID NO:1598), DOM10-176-547 (SEQ ID NO:1599), DOM10-176-548 (SEQ ID NO:1600), DOM10-176-549 (SEQ ID NO:1601), DOM10-176-550 (SEQ ID NO:1602), DOM10-176-551 (SEQ ID NO:1603), DOM10-176-552 (SEQ ID NO:1604), DOM10-176-553 (SEQ ID NO:1605), DOM10-176-554 (SEQ ID NO:1606), DOM10-176-555 (SEQ ID NO:1607), DOM10-176-556 (SEQ ID NO:1608), DOM10-176-557 (SEQ ID NO:1609), DOM10-176-558 (SEQ ID NO:1610), DOM10-176-559 (SEQ ID NO:1611), DOM10-176-560 (SEQ ID NO:1612), DOM10-176-561 (SEQ ID NO:1613), DOM10-176-562 (SEQ ID NO:1614), DOM10-176-563 (SEQ ID NO:1615), DOM10-176-564 (SEQ ID NO:1616), DOM10-176-565 (SEQ ID NO:1617), DOM10-176-566 (SEQ ID NO:1618), DOM10-176-567 (SEQ ID NO:1619), DOM10-176-568 (SEQ ID NO:1620), DOM10-176-569 (SEQ ID NO:1621), DOM10-176-570 (SEQ ID NO:1622), DOM10-176-571 (SEQ ID NO:1623), DOM10-176-572 (SEQ ID NO:1624), DOM10-176-573 (SEQ ID

NO:1625), DOM10-176-574 (SEQ ID NO:1626), DOM10-176-575 (SEQ ID NO:1627), DOM10-176-576 (SEQ ID NO:1628), DOM10-176-577 (SEQ ID NO:1629), DOM10-176-578 (SEQ ID NO:1630), DOM10-176-579 (SEQ ID NO:1631), DOM10-176-580 (SEQ ID NO:1632), DOM10-176-581 (SEQ ID NO:1633), DOM10-176-582 (SEQ ID NO:1634), DOM10-176-583 (SEQ ID NO:1635), DOM10-176-584 (SEQ ID NO:1636), DOM10-176-585 (SEQ ID NO:1637), DOM10-176-586 (SEQ ID NO:1638), DOM10-176-587 (SEQ ID NO:1639), DOM10-176-588 (SEQ ID NO:1640), DOM10-176-589 (SEQ ID NO:1641), DOM10-176-590 (SEQ ID NO:1642), DOM10-176-591 (SEQ ID NO:1643), DOM10-176-592 (SEQ ID NO:1644), DOM10-176-593 (SEQ ID NO:1645), DOM10-176-594 (SEQ ID NO:1646), DOM10-176-595 (SEQ ID NO:1647), DOM10-176-596 (SEQ ID NO:1648), DOM10-176-597 (SEQ ID NO:1649), DOM10-176-598 (SEQ ID NO:1650), DOM10-176-599 (SEQ ID NO:1651), DOM10-176-600 (SEQ ID NO:1652), DOM10-176-601 (SEQ ID NO:1653), DOM10-176-602 (SEQ ID NO:1654), DOM10-176-603 (SEQ ID NO:1655), DOM10-176-604 (SEQ ID NO:1656), DOM10-176-605 (SEQ ID NO:1657), DOM10-176-606 (SEQ ID NO:1658), DOM10-176-607 (SEQ ID NO:1659), DOM10-176-608 (SEQ ID NO:1660), DOM10-176-609 (SEQ ID NO:1661), DOM10-176-610 (SEQ ID NO:1662), DOM10-176-611 (SEQ ID NO:1663), DOM10-176-612 (SEQ ID NO:1664), DOM10-176-613 (SEQ ID NO:1665), DOM10-176-614 (SEQ ID NO:1666), DOM10-176-615 (SEQ ID NO:1667), DOM10-176-616 (SEQ ID NO:1668), DOM10-176-617 (SEQ ID NO:1669), DOM10-176-618 (SEQ ID NO:1670), DOM10-176-619 (SEQ ID NO:1671), DOM10-176-620 (SEQ ID NO:1672), DOM10-176-621 (SEQ ID NO:1673), DOM10-176-622 (SEQ ID NO:1674), DOM10-176-623 (SEQ ID NO:1675), DOM10-176-624 (SEQ ID NO:1676), DOM10-176-625 (SEQ ID NO:1677), DOM10-176-626 (SEQ ID NO:1678), DOM10-176-627 (SEQ ID NO:1679), DOM10-176-628 (SEQ ID NO:1680), DOM10-176-629 (SEQ ID NO:1681), DOM10-176-630 (SEQ ID NO:1682), DOM10-176-631 (SEQ ID NO:1683), DOM10-176-632 (SEQ ID NO:1684), DOM10-176-633 (SEQ ID NO:1685), DOM10-176-634 (SEQ ID NO:1686), DOM10-176-635 (SEQ ID NO:1687), DOM10-176-636 (SEQ ID NO:1688), DOM10-176-637 (SEQ ID

NO:1689), DOM10-176-638 (SEQ ID NO:1690), DOM10-176-639 (SEQ ID NO:1691), DOM10-176-640 (SEQ ID NO:1692), DOM10-176-641 (SEQ ID NO:1693), DOM10-176-643 (SEQ ID NO:1694), DOM10-176-644 (SEQ ID NO:1695), DOM10-176-645 (SEQ ID NO:1696), DOM10-176-646 (SEQ ID NO:1697), DOM10-176-647 (SEQ ID NO:1698), DOM10-176-648 (SEQ ID NO:1699), DOM10-176-649 (SEQ ID NO:1700), DOM10-176-650 (SEQ ID NO:1701), DOM10-176-651 (SEQ ID NO:1702), DOM10-176-652 (SEQ ID NO:1703), DOM10-176-653 (SEQ ID NO:1704), DOM10-176-654 (SEQ ID NO:1705), DOM10-176-655 (SEQ ID NO:1706), DOM10-176-656 (SEQ ID NO:1707), DOM10-176-657 (SEQ ID NO:1708), DOM10-176-658 (SEQ ID NO:1709), DOM10-176-659 (SEQ ID NO:1710), DOM10-176-660 (SEQ ID NO:1711), DOM10-176-661 (SEQ ID NO:1712), DOM10-176-662 (SEQ ID NO:1713), DOM10-176-663 (SEQ ID NO:1714), DOM10-176-664 (SEQ ID NO:1715), DOM10-176-665 (SEQ ID NO:1716), DOM10-176-666 (SEQ ID NO:1717), DOM10-176-667 (SEQ ID NO:1718), DOM10-176-668 (SEQ ID NO:1719), DOM10-176-669 (SEQ ID NO:1720), DOM10-176-670 (SEQ ID NO:1721), DOM10-176-671 (SEQ ID NO:1722), DOM10-176-672 (SEQ ID NO:1723), DOM10-176-673 (SEQ ID NO:1724), DOM10-176-674 (SEQ ID NO:1725), DOM10-176-675 (SEQ ID NO:1726), DOM10-253 (SEQ ID NO:1727), DOM10-255 (SEQ ID NO:1728), DOM10-272 (SEQ ID NO:1729), DOM10-307 (SEQ ID NO:1730), DOM10-319 (SEQ ID NO:1731) and DOM10-319-1 (SEQ ID NO:1732).

In some embodiments, the polypeptide domain that has a binding site with binding specificity for IL-13 (*e.g.*, a dAb) comprises an amino acid sequence that has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence or a dAb selected from the group consisting of DOM10-236 (SEQ ID NO:2129), DOM10-238 (SEQ ID NO:2130), DOM10-241 (SEQ ID NO:2131), DOM10-245 (SEQ ID NO:2132), DOM10-249 (SEQ ID NO:2133), DOM10-250 (SEQ ID NO:2134), DOM10-251 (SEQ ID NO:2135), DOM10-254 (SEQ ID NO:2136), DOM10-256 (SEQ ID NO:2137),

DOM10-259 (SEQ ID NO:2138), DOM10-260 (SEQ ID NO:2139), DOM10-261 (SEQ ID NO:2140), DOM10-263 (SEQ ID NO:2141), DOM10-264 (SEQ ID NO:2142), DOM10-273 (SEQ ID NO:2143), DOM10-278 (SEQ ID NO:2144), DOM10-279 (SEQ ID NO:2145), DOM10-281 (SEQ ID NO:2146), DOM10-282 (SEQ ID NO:2147), DOM10-283 (SEQ ID NO:2148), DOM10-400 (SEQ ID NO:2149), DOM10-401 (SEQ ID NO:2150), DOM10-402 (SEQ ID NO:2151), DOM10-404 (SEQ ID NO:2152), DOM10-406 (SEQ ID NO:2153), DOM10-407 (SEQ ID NO:2154), DOM10-409 (SEQ ID NO:2155), DOM10-410 (SEQ ID NO:2156), DOM10-414 (SEQ ID NO:2157), DOM10-415 (SEQ ID NO:2158), DOM10-416 (SEQ ID NO:2159), DOM10-418 (SEQ ID NO:2160), DOM10-420 (SEQ ID NO:2161), DOM10-422 (SEQ ID NO:2162), DOM10-423 (SEQ ID NO:2163), DOM10-424 (SEQ ID NO:2164), DOM10-425 (SEQ ID NO:2165), DOM10-426 (SEQ ID NO:2166), DOM10-427 (SEQ ID NO:2167), DOM10-428 (SEQ ID NO:2168), DOM10-429 (SEQ ID NO:2169), DOM10-430 (SEQ ID NO:2170), DOM10-431 (SEQ ID NO:2171), DOM10-432 (SEQ ID NO:2172), DOM10-433 (SEQ ID NO:2173), DOM10-467 (SEQ ID NO:2174), DOM10-468 (SEQ ID NO:2175), DOM10-469 (SEQ ID NO:2176), DOM10-470 (SEQ ID NO:2177), DOM10-234 (SEQ ID NO:2178), DOM10-235 (SEQ ID NO:2179), DOM10-237 (SEQ ID NO:2180), DOM10-239 (SEQ ID NO:2181), DOM10-240 (SEQ ID NO:2182), DOM10-242 (SEQ ID NO:2183), DOM10-243 (SEQ ID NO:2184), DOM10-244 (SEQ ID NO:2185), DOM10-246 (SEQ ID NO:2186), DOM10-247 (SEQ ID NO:2187), DOM10-248 (SEQ ID NO:2188), DOM10-252 (SEQ ID NO:2189), DOM10-257 (SEQ ID NO:2190), DOM10-258 (SEQ ID NO:2191), DOM10-262 (SEQ ID NO:2192), DOM10-265 (SEQ ID NO:2193), DOM10-266 (SEQ ID NO:2194), DOM10-274 (SEQ ID NO:2195), DOM10-275 (SEQ ID NO:2196), DOM10-276 (SEQ ID NO:2197), DOM10-277 (SEQ ID NO:2198), DOM10-280 (SEQ ID NO:2199), DOM10-403 (SEQ ID NO:2200), DOM10-405 (SEQ ID NO:2201), DOM10-408 (SEQ ID NO:2202), DOM10-411 (SEQ ID NO:2203), DOM10-412 (SEQ ID NO:2204), DOM10-413 (SEQ ID NO:2205), DOM10-417 (SEQ ID NO:2206), DOM10-419 (SEQ ID NO:2207), DOM10-472 (SEQ ID NO:2208), DOM10-203 (SEQ ID NO:2209), DOM10-205 (SEQ ID NO:2210), DOM10-208 (SEQ ID NO:2211), DOM10-218 (SEQ ID

NO:2212), DOM10-219 (SEQ ID NO:2213), DOM10-220 (SEQ ID NO:2214), DOM10-225 (SEQ ID NO:2215), DOM10-228 (SEQ ID NO:2216), DOM10-229 (SEQ ID NO:2217), DOM10-230 (SEQ ID NO:2218), DOM10-231 (SEQ ID NO:2219), DOM10-268 (SEQ ID NO:2220), DOM10-201 (SEQ ID NO:2221), DOM10-202 (SEQ ID NO:2222), DOM10-204 (SEQ ID NO:2223), DOM10-206 (SEQ ID NO:2224), DOM10-207 (SEQ ID NO:2225), DOM10-209 (SEQ ID NO:2226), DOM10-210 (SEQ ID NO:2227), DOM10-211 (SEQ ID NO:2228), DOM10-213 (SEQ ID NO:2229), DOM10-214 (SEQ ID NO:2230), DOM10-215 (SEQ ID NO:2231), DOM10-216 (SEQ ID NO:2232), DOM10-217 (SEQ ID NO:2233), DOM10-221 (SEQ ID NO:2234), DOM10-223 (SEQ ID NO:2235), DOM10-224 (SEQ ID NO:2236), DOM10-227 (SEQ ID NO:2237), DOM10-232 (SEQ ID NO:2238), DOM10-267 (SEQ ID NO:2239), DOM10-270 (SEQ ID NO:2240), DOM10-275-1 (SEQ ID NO:2241), DOM10-276-2 (SEQ ID NO:2242), DOM10-276-3 (SEQ ID NO:2243), DOM10-275-3 (SEQ ID NO:2244), DOM10-277-2 (SEQ ID NO:2245), DOM10-277-3 (SEQ ID NO:2246), DOM10-273-1 (SEQ ID NO:2247), DOM10-273-2 (SEQ ID NO:2248), DOM10-275-2 (SEQ ID NO:2249), DOM10-275-4 (SEQ ID NO:2250), DOM10-276-1 (SEQ ID NO:2251), DOM10-276-4 (SEQ ID NO:2252), DOM10-277-1 (SEQ ID NO:2253), DOM10-275-13 (SEQ ID NO:2254), DOM10-275-15 (SEQ ID NO:2255), DOM10-275-20 (SEQ ID NO:2256), DOM10-275-8 (SEQ ID NO:2257), DOM10-276-13 (SEQ ID NO:2258), DOM10-276-14 (SEQ ID NO:2259), DOM10-276-15 (SEQ ID NO:2260), DOM10-276-17 (SEQ ID NO:2261), DOM10-276-7 (SEQ ID NO:2262), DOM10-276-8 (SEQ ID NO:2263), DOM10-275-11 (SEQ ID NO:2264), DOM10-275-12 (SEQ ID NO:2265), DOM10-275-14 (SEQ ID NO:2266), DOM10-275-16 (SEQ ID NO:2267), DOM10-275-17 (SEQ ID NO:2268), DOM10-275-5 (SEQ ID NO:2269), DOM10-275-6 (SEQ ID NO:2270), DOM10-275-7 (SEQ ID NO:2271), DOM10-275-9 (SEQ ID NO:2272), DOM10-276-10 (SEQ ID NO:2273), DOM10-276-11 (SEQ ID NO:2274), DOM10-276-12 (SEQ ID NO:2275), DOM10-276-16 (SEQ ID NO:2276), DOM10-276-5 (SEQ ID NO:2277), DOM10-276-6 (SEQ ID NO:2278), DOM10-276-9 (SEQ ID NO:2279), DOM10-212 (SEQ ID NO:2280), DOM10-53-424 (SEQ ID NO:2281), DOM10-53-425 (SEQ ID NO:2282), DOM10-53-426 (SEQ ID NO:2283), DOM10-53-422 (SEQ ID NO:2284), DOM10-53-423

(SEQ ID NO:2285), DOM10-53-613 (SEQ ID NO:2286), DOM10-53-517 (SEQ ID NO:2287), DOM10-53-519 (SEQ ID NO:2288), DOM10-53-520 (SEQ ID NO:2289), DOM10-53-521 (SEQ ID NO:2290), DOM10-53-522 (SEQ ID NO:2291), DOM10-53-526 (SEQ ID NO:2292), DOM10-53-527 (SEQ ID NO:2293), DOM10-53-528 (SEQ ID NO:2294), DOM10-53-518 (SEQ ID NO:2295), DOM10-53-523 (SEQ ID NO:2296), DOM10-53-524 (SEQ ID NO:2297), DOM10-53-525 (SEQ ID NO:2298), DOM10-53-601 (SEQ ID NO:2299), DOM10-53-602 (SEQ ID NO:2300), DOM10-53-605 (SEQ ID NO:2301), DOM10-53-606 (SEQ ID NO:2302), DOM10-53-607 (SEQ ID NO:2303), DOM10-53-608 (SEQ ID NO:2304), DOM10-53-609 (SEQ ID NO:2305), DOM10-53-610 (SEQ ID NO:2306), DOM10-53-611 (SEQ ID NO:2307), DOM10-53-612 (SEQ ID NO:2308), DOM10-53-603 (SEQ ID NO:2309), DOM10-53-604 (SEQ ID NO:2310), DOM10-53-429 (SEQ ID NO:2311), DOM10-53-432 (SEQ ID NO:2312), DOM10-53-433 (SEQ ID NO:2313), DOM10-53-435 (SEQ ID NO:2314), DOM10-53-430 (SEQ ID NO:2315), DOM10-53-431 (SEQ ID NO:2316), DOM10-53-434 (SEQ ID NO:2317), DOM10-53-436 (SEQ ID NO:2318), DOM10-53-437 (SEQ ID NO:2319), DOM10-53-438 (SEQ ID NO:2320), DOM10-53-440 (SEQ ID NO:2321), DOM10-53-439 (SEQ ID NO:2322), DOM10-53-441 (SEQ ID NO:2323), DOM10-53-442 (SEQ ID NO:2324), DOM10-53-443 (SEQ ID NO:2325), DOM10-53-444 (SEQ ID NO:2326), DOM10-53-445 (SEQ ID NO:2327), DOM10-53-446 (SEQ ID NO:2328), DOM10-53-447 (SEQ ID NO:2329), DOM10-53-449 (SEQ ID NO:2330), DOM10-53-448 (SEQ ID NO:2331), DOM10-53-450 (SEQ ID NO:2332), DOM10-53-451 (SEQ ID NO:2333), DOM10-53-452 (SEQ ID NO:2334), DOM10-53-453 (SEQ ID NO:2335), DOM10-53-454 (SEQ ID NO:2336), DOM10-53-455 (SEQ ID NO:2337), DOM10-53-456 (SEQ ID NO:2338), DOM10-53-457 (SEQ ID NO:2339), DOM10-53-458 (SEQ ID NO:2340), DOM10-53-459 (SEQ ID NO:2341), DOM10-53-461 (SEQ ID NO:2342), DOM10-53-462 (SEQ ID NO:2343), DOM10-53-465 (SEQ ID NO:2344), DOM10-53-466 (SEQ ID NO:2345), DOM10-53-467 (SEQ ID NO:2346), DOM10-53-468 (SEQ ID NO:2347), DOM10-53-460 (SEQ ID NO:2348), DOM10-53-463 (SEQ ID

NO:2349), DOM10-53-464 (SEQ ID NO:2350), DOM10-53-469 (SEQ ID NO:2351), DOM10-53-471 (SEQ ID NO:2352), DOM10-53-470 (SEQ ID NO:2353), DOM10-53-533 (SEQ ID NO:2354), DOM10-53-534 (SEQ ID NO:2355), DOM10-53-535 (SEQ ID NO:2356), DOM10-53-537 (SEQ ID NO:2357), DOM10-53-538 (SEQ ID NO:2358), DOM10-53-539 (SEQ ID NO:2359), DOM10-53-540 (SEQ ID NO:2360), DOM10-53-531 (SEQ ID NO:2361), DOM10-53-532 (SEQ ID NO:2362), DOM10-53-536 (SEQ ID NO:2363), DOM10-53-542 (SEQ ID NO:2364), DOM10-53-541 (SEQ ID NO:2365), DOM10-53-473 (SEQ ID NO:2366), DOM10-53-472 (SEQ ID NO:2367), DOM10-53-475 (SEQ ID NO:2368), DOM10-53-474 (SEQ ID NO:2369), DOM10-53-543 (SEQ ID NO:2370), DOM10-53-544 (SEQ ID NO: 2371), DOM10-53-545 (SEQ ID NO:2372), DOM10-53-548 (SEQ ID NO:2373), DOM10-53-546 (SEQ ID NO:2374), DOM10-53-549 (SEQ ID NO:2375), DOM10-53-547 (SEQ ID NO:2376), DOM10-53-550 (SEQ ID NO:2377), DOM10-53-551 (SEQ ID NO:2378), DOM10-53-560 (SEQ ID NO:2379), DOM10-53-565 (SEQ ID NO:2380), DOM10-53-559 (SEQ ID NO:2381), DOM10-53-561 (SEQ ID NO:2382), DOM10-53-562 (SEQ ID NO:2383), DOM10-53-563 (SEQ ID NO:2384), DOM10-53-564 (SEQ ID NO:2385), DOM10-53-566 (SEQ ID NO:2386), DOM10-53-554 (SEQ ID NO:2387), DOM10-53-552 (SEQ ID NO:2388), DOM10-53-553 (SEQ ID NO:2389), DOM10-53-558 (SEQ ID NO:2390), DOM10-53-556 (SEQ ID NO:2391) and DOM10-53-557 (SEQ ID NO:2392).

In preferred embodiments, the polypeptide domain that has a binding site with binding specificity for IL-13 (*e.g.*, a dAb) comprises an amino acid sequence that has at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence of DOM-10-53 (SEQ ID NO:967) or DOM10-176-535 (SEQ ID NO:1587). For example, the polypeptide domain that has a binding site with binding specificity for IL-13 can comprise the amino acid sequence of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID

NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

In some embodiments, the polypeptide domain that has a binding site with binding specificity for IL-13 competes with any of the dAbs disclosed herein for binding to IL-13.

Preferably the polypeptide domain that has a binding site with binding specificity for IL-13 is an immunoglobulin single variable domain. The polypeptide domain that has a binding site with binding specificity for IL-13 can comprise any suitable immunoglobulin variable domain, and preferably comprises a human variable domain or a variable domain that comprises human framework regions. In certain embodiments, the polypeptide domain that has a binding site with binding specificity for IL-13 comprises a universal framework, as described herein.

The ligand of the invention (*e.g.*, ligand that has binding specificity for IL-4 and IL-13, ligand that has binding specificity for IL-13) can comprise a non-immunoglobulin binding moiety that has binding specificity for IL-13 and inhibits a function of IL-13 (*e.g.*, binding to receptor), wherein the non-immunoglobulin binding moiety comprises one, two or three of the CDRs of a V_H, V_L or V_{HH} that binds IL-13 and a suitable scaffold. In certain embodiments, the non-immunoglobulin binding moiety comprises CDR3 but not CDR1 or CDR2 of a V_H, V_L or V_{HH} that binds IL-13 and a suitable scaffold. In other embodiments, the non-immunoglobulin binding moiety comprises CDR1 and CDR2, but not CDR3 of a V_H, V_L or V_{HH} that binds IL-13 and a suitable scaffold. In other embodiments, the non-immunoglobulin binding moiety comprises CDR1, CDR2 and CDR3 of a V_H, V_L or V_{HH} that binds IL-13 and a suitable scaffold. Preferably, the CDR or CDRs of the ligand of these embodiments is a CDR or CDRs of an anti-IL-13 dAb described herein. Preferably, the non-immunoglobulin binding moiety comprises one, two, or three of the CDRs of one ofthe anti-IL-13 dAbs disclosed herein. In other embodiments, the ligand (*e.g.*, ligand that has binding specificity for IL-4 and IL-13, ligand that has binding specificity for IL-13) comprises only CDR3 of a V_H, V_L or V_{HH} that binds IL-13. The non-immunoglobulin domain can comprise an amino acid sequence that has one or more regions that have sequence identity to one, two

or three of the CDRs of an anti-IL-13 dAb described herein. For example, the non-immunoglobulin domain can have an amino acid sequence that contains at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90% sequence identity with CDR1, CDR2 and/or CDR3 of an anti-IL13 dAb disclosed herein. Even more preferably, the non-immunoglobulin binding moiety comprises one, two, or three of the CDRs of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208) and DOM10-53-396 (SEQ ID NO:1260).

In certain embodiments, a polypeptide domain that has a binding site with binding specificity for IL-13 resists aggregation, unfolds reversibly, comprises a framework region and/or is secreted as described above for the polypeptide domain that has a binding site with binding specificity for IL-4

dAb Monomers that Bind Serum Albumin

The ligands of the invention can further comprise a dAb monomer that binds serum albumin (SA) with a K_d of 1nM to 500 μM (*i.e.*, x 10^{-9} to 5 x 10^{-4}), preferably 100 nM to 10 μ M. Preferably, for a ligand comprising an anti-SA dAb, the binding (*e.g.* K_d and/or K_{off} as measured by surface plasmon resonance, (*e.g.*, using BiaCore)) of the ligand its target(s) is from 1 to 100000 times (preferably 100 to 100000, more preferably 1000 to 100000, or 10000 to 100000 times) stronger than for SA. Preferably, the serum albumin is human serum albumin (HSA). In one embodiment, the first dAb (or a dAb monomer) binds SA (*e.g.*, HSA) with a K_d of approximately 50, preferably 70, and more preferably 100, 150 or 200 nM.

In certain embodiments, the dAb monomer that binds SA resists aggregation, unfolds reversibly and/or comprises a framework region as described above for dAb monomers that bind IL-4.

In particular embodiments, the antigen-binding fragment of an antibody that binds serum albumin is a dAb that binds human serum albumin. In certain embodiments, the dAb binds human serum albumin and competes for binding to albumin with a dAb selected from the group consisting of

DOM7r-1 (SEQ ID NO:1736), DOM7r-3 (SEQ ID NO:1737), DOM7r-4 (SEQ ID NO:1738), DOM7r-5 (SEQ ID NO:1739), DOM7r-7 (SEQ ID NO:1740), DOM7r-8 (SEQ ID NO:1741), DOM7h-2 (SEQ ID NO:1742), DOM7h-3 (SEQ ID NO:1743), DOM7h-4 (SEQ ID NO:1744), DOM7h-6 (SEQ ID NO:1745), DOM7h-1 (SEQ ID NO:1746), DOM7h-7 (SEQ ID NO:1747), DOM7h-22 (SEQ ID NO:1748), DOM7h-23 (SEQ ID NO:1749), DOM7h-24 (SEQ ID NO:1750), DOM7h-25 (SEQ ID NO:1751), DOM7h-26 (SEQ ID NO:1752), DOM7h-21 (SEQ ID NO:1753), DOM7h-27 (SEQ ID NO:1754), DOM7h-8 (SEQ ID NO:1756), DOM7r-13 (SEQ ID NO:1757), DOM7r-14 (SEQ ID NO:1758), DOM7r-15 (SEQ ID NO:1759), DOM7r-16 (SEQ ID NO:1760), DOM7r-17 (SEQ ID NO:1761), DOM7r-18 (SEQ ID NO:1762), DOM7r-19 (SEQ ID NO:1763), DOM7r-20 (SEQ ID NO:1764), DOM7r-21 (SEQ ID NO:1765), DOM7r-22 (SEQ ID NO:1766), DOM7r-23 (SEQ ID NO:1767), DOM7r-24 (SEQ ID NO:1768), DOM7r-25 (SEQ ID NO:1769), DOM7r-26 (SEQ ID NO:1770), DOM7r-27 (SEQ ID NO:1771), DOM7r-28 (SEQ ID NO:1772), DOM7r-29 (SEQ ID NO:1773), DOM7r-30 (SEQ ID NO:1774), DOM7r-31 (SEQ ID NO:1775), DOM7r-32 (SEQ ID NO:1776), and DOM7r-33 (SEQ ID NO:1777).

In certain embodiments, the dAb binds human serum albumin and comprises an amino acid sequence that has at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of DOM7r-1 (SEQ ID NO:1736), DOM7r-3 (SEQ ID NO:1737), DOM7r-4 (SEQ ID NO:1738), DOM7r-5 (SEQ ID NO:1739), DOM7r-7 (SEQ ID NO:1740), DOM7r-8 (SEQ ID NO:1741), DOM7h-2 (SEQ ID NO:1742), DOM7h-3 (SEQ ID NO:1743), DOM7h-4 (SEQ ID NO:1744), DOM7h-6 (SEQ ID NO:1745), DOM7h-1 (SEQ ID NO:1746), DOM7h-7 (SEQ ID NO:1747), DOM7h-22 (SEQ ID NO:1748), DOM7h-23 (SEQ ID NO:1749), DOM7h-24 (SEQ ID NO:1750), DOM7h-25 (SEQ ID NO:1751), DOM7h-26 (SEQ ID NO:1752), DOM7h-21 (SEQ ID NO:1753), DOM7h-27 (SEQ ID NO:1754), DOM7h-8 (SEQ ID NO:1756), DOM7r-13 (SEQ ID NO:1757), DOM7r-14 (SEQ ID NO:1758), DOM7r-15 (SEQ ID NO:1759),

DOM7r-16 (SEQ ID NO:1760), DOM7r-17 (SEQ ID NO:1761), DOM7r-18 (SEQ ID NO:1762), DOM7r-19 (SEQ ID NO:1763), DOM7r-20 (SEQ ID NO:1764), DOM7r-21 (SEQ ID NO:1765), DOM7r-22 (SEQ ID NO:1766), DOM7r-23 (SEQ ID NO:1767), DOM7r-24 (SEQ ID NO:1768), DOM7r-25 (SEQ ID NO:1769), DOM7r-26 (SEQ ID NO:1770), DOM7r-27 (SEQ ID NO:1771), DOM7r-28 (SEQ ID NO:1772), DOM7r-29 (SEQ ID NO:1773), DOM7r-30 (SEQ ID NO:1774), DOM7r-31 (SEQ ID NO:1775), DOM7r-32 (SEQ ID NO:1776), and DOM7r-33 (SEQ ID NO:1777).

For example, the dAb that binds human serum albumin can comprise an amino acid sequence that has at least about 90%, or at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% amino acid sequence identity with DOM7h-2 (SEQ ID NO:1742), DOM7h-3 (SEQ ID NO:1743), DOM7h-4 (SEQ ID NO:1744), DOM7h-6 (SEQ ID NO:1745), DOM7h-1 (SEQ ID NO:1746), DOM7h-7 (SEQ ID NO:1747), DOM7h-8 (SEQ ID NO:1756), DOM7r-13 (SEQ ID NO:1757), DOM7r-14 (SEQ ID NO:1758), DOM7h-22 (SEQ ID NO:1748), DOM7h-23 (SEQ ID NO:1749), DOM7h-24 (SEQ ID NO:1750), DOM7h-25 (SEQ ID NO:1751), DOM7h-26 (SEQ ID NO:1752), DOM7h-21 (SEQ ID NO:1753), and DOM7h-27 (SEQ ID NO:1754).

Amino acid sequence identity is preferably determined using a suitable sequence alignment algorithm and default parameters, such as BLAST P (Karlin and Altschul, *Proc. Natl. Acad. Sci. USA, 87*(6):2264-2268 (1990)).

In more particular embodiments, the dAb is a V_K dAb that binds human serum albumin and has an amino acid sequence selected from the group consisting of DOM7h-2 (SEQ ID NO:1742), DOM7h-3 (SEQ ID NO:1743), DOM7h-4 (SEQ ID NO:1744), DOM7h-6 (SEQ ID NO:1745), DOM7h-1 (SEQ ID NO:1746), DOM7h-7 (SEQ ID NO:1747), DOM7h-8 (SEQ ID NO:1756), DOM7r-13 (SEQ ID NO:1757), and DOM7r-14 (SEQ ID NO:1758), or a V_H dAb that has an amino acid sequence selected from the group consisting of: DOM7h-22 (SEQ ID NO:1748), DOM7h-23 (SEQ ID NO:1749), DOM7h-24 (SEQ ID NO:1750), DOM7h-25 (SEQ ID NO:1751), DOM7h-26 (SEQ ID NO:1752), DOM7h-21 (SEQ ID NO:1753), DOM7h-27 (SEQ ID NO:1754). In other embodiments, the antigen-binding

fragment of an antibody that binds serum albumin is a dAb that binds human serum albumin and comprises the CDRs of any of the foregoing amino acid sequences.

Suitable *Camelid* V_{HH} that bind serum albumin include those disclosed in WO 2004/041862 (Ablynx N.V.) and herein, such as Sequence A (SEQ ID NO:1778), Sequence B (SEQ ID NO:1779), Sequence C (SEQ ID NO:1780), Sequence D (SEQ ID NO:1781), Sequence E (SEQ ID NO:1782), Sequence F (SEQ ID NO:1783), Sequence G (SEQ ID NO:1784), Sequence H (SEQ ID NO:1785), Sequence I (SEQ ID NO:1786), Sequence J (SEQ ID NO:1787), Sequence K (SEQ ID NO:1788), Sequence L (SEQ ID NO:1789), Sequence M (SEQ ID NO:1790), Sequence N (SEQ ID NO:1791), Sequence O (SEQ ID NO:1792), Sequence P (SEQ ID NO:1793), Sequence Q (SEQ ID NO:1794). In certain embodiments, the *Camelid* V_{HH} binds human serum albumin and comprises an amino acid sequence that has at least about 80%, or at least about 85%, or at least about 90%, or at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% amino acid sequence identity with any one of SEQ ID NOS:1778-1794.

Amino acid sequence identity is preferably determined using a suitable sequence alignment algorithm and default parameters, such as BLAST P (Karlin and Altschul, *Proc. Natl. Acad. Sci. USA, 87*(6):2264-2268 (1990)).

In some embodiments, the ligand comprises an anti-serum albumin dAb that competes with any anti-serum albumin dAb disclosed herein for binding to serum albumin (*e.g.*, human serum albumin).

Nucleic Acid Molecules, Vectors and Host Cells

The invention also provides isolated and/or recombinant nucleic acid molecules encoding ligands, (dual-specific ligands and multispecific ligands) as described herein.

Nucleic acids referred to herein as "isolated" are nucleic acids which have been separated away from the nucleic acids of the genomic DNA or cellular RNA of their source of origin (*e.g.*, as it exists in cells or in a mixture of nucleic acids such as a library), and include nucleic acids obtained by methods described herein or other suitable methods, including essentially pure nucleic acids, nucleic acids produced by chemical

synthesis, by combinations of biological and chemical methods, and recombinant nucleic acids which are isolated (see *e.g.*, Daugherty, B.L. *et al.*, *Nucleic Acids Res.*, *19(9)*: 2471-2476 (1991); Lewis, A.P. and J.S. Crowe, *Gene, 101: 297-302* (1991)).

Nucleic acids referred to herein as "recombinant" are nucleic acids which have been produced by recombinant DNA methodology, including those nucleic acids that are generated by procedures which rely upon a method of artificial recombination, such as the polymerase chain reaction (PCR) and/or cloning into a vector using restriction enzymes.

In certain embodiments, the isolated and/or recombinant nucleic acid comprises a nucleotide sequence encoding a ligand, as described herein, wherein said ligand comprises an amino acid sequence that has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence of a dAb that binds IL-4 disclosed herein, or a dAb that binds IL-13 disclosed herein.

For example, in some embodiments, the isolated and/or recombinant nucleic acid comprises a nucleotide sequence encoding a ligand that has binding specificity for IL-4, as described herein, wherein said ligand comprises an amino acid sequence that has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of DOM9-15 (SEQ ID NO:175), DOM9-17(SEQ ID NO:176), DOM9-23 (SEQ ID NO:177), DOM9-24 (SEQ ID NO:178), DOM9-25 (SEQ ID NO:179), DOM9-27 (SEQ ID NO:180), DOM9-28 (SEQ ID NO:181), DOM9-29 (SEQ ID NO:182), DOM9-30 (SEQ ID NO:183), DOM9-31 (SEQ ID NO:184), DOM9-32 (SEQ ID NO:185), DOM9-33 (SEQ ID NO:186), DOM9-50 (SEQ ID NO:187), DOM9-57 (SEQ ID NO:188), DOM9-59 (SEQ ID NO:189), DOM9-63 (SEQ ID NO:190), DOM9-67 (SEQ ID NO:191), DOM9-68 (SEQ ID NO:192), DOM9-70 (SEQ ID NO:193), DOM9-79 (SEQ ID NO:194), DOM9-82 (SEQ ID

NO:195), DOM9-86 (SEQ ID NO:196), DOM9-94 (SEQ ID NO:197), DOM9-108 (SEQ ID NO:198), DOM9-112 (SEQ ID NO:199), DOM9-112-1 (SEQ ID NO:200), DOM9-112-2 (SEQ ID NO:201), DOM9-112-3 (SEQ ID NO:202), DOM9-112-4 (SEQ ID NO:203), DOM9-112-5 (SEQ ID NO:204), DOM9-112-6 (SEQ ID NO:205), DOM9-112-7 (SEQ ID NO:206), DOM9-112-8 (SEQ ID NO:207), DOM9-112-9 (SEQ ID NO:208), DOM9-112-10 (SEQ ID NO:209), DOM9-112-11 (SEQ ID NO:210), DOM9-112-12 (SEQ ID NO:211), DOM9-112-13 (SEQ ID NO:212), DOM9-112-14 (SEQ ID NO:213), DOM9-112-15 (SEQ ID NO:214), DOM9-112-16 (SEQ ID NO:215), DOM9-112-17 (SEQ ID NO:216), DOM9-112-18 (SEQ ID NO:217), DOM9-112-19 (SEQ ID NO:218), DOM9-112-20 (SEQ ID NO:219), DOM9-112-21 (SEQ ID NO:220), DOM9-112-22 (SEQ ID NO:221), DOM9-112-23 (SEQ ID NO:222), DOM9-112-25 (SEQ ID NO:223), DOM9-112-81 (SEQ ID NO:224), DOM9-112-82 (SEQ ID NO:225), DOM9-112-83 (SEQ ID NO:226), DOM9-112-84 (SEQ ID NO:227), DOM9-112-85 (SEQ ID NO:228), DOM9-112-86 (SEQ ID NO:229), DOM9-112-87 (SEQ ID NO:230), DOM9-112-88 (SEQ ID NO:231), DOM9-112-89 (SEQ ID NO:232), DOM9-112-90 (SEQ ID NO:233), DOM9-112-91 (SEQ ID NO:234), DOM9-112-92 (SEQ ID NO:235), DOM9-112-93 (SEQ ID NO:236), DOM9-112-94 (SEQ ID NO:237), DOM9-112-95 (SEQ ID NO:238), DOM9-112-96 (SEQ ID NO:239), DOM9-112-97 (SEQ ID NO:240), DOM9-112-98 (SEQ ID NO:241), DOM9-112-99 (SEQ ID NO:242), DOM9-112-100 (SEQ ID NO:243), DOM9-112-101 (SEQ ID NO:244), DOM9-1132-102 (SEQ ID NO:245), DOM9-112-103 (SEQ ID NO:246), DOM9-112-104 (SEQ ID NO:247), DOM9-112-105 (SEQ ID NO:248), DOM9-112-106 (SEQ ID NO:249), DOM9-112-107 (SEQ ID NO:250), DOM9-112-108 (SEQ ID NO:251), DOM9-112-109 (SEQ ID NO:252), DOM9-112-110 (SEQ ID NO:253), DOM9-112-111 (SEQ ID NO:254), DOM9-112-112 (SEQ ID NO:255), DOM9-112-113 (SEQ ID NO:256), DOM9-112-114 (SEQ ID NO:257), DOM9-112-115 (SEQ ID NO:258), DOM9-112-116 (SEQ ID NO:259), DOM9-112-117 (SEQ ID NO:260), DOM9-112-118 (SEQ ID NO:261), DOM9-112-119 (SEQ ID NO:262), DOM9-112-120 (SEQ ID NO:263), DOM9-112-121 (SEQ ID NO:264), DOM9-112-122 (SEQ ID NO:265), DOM9-112-123 (SEQ ID NO:266), DOM9-112-124 (SEQ ID NO:267), DOM9-112-125 (SEQ ID NO:268), DOM9-112-126 (SEQ ID NO:269),

DOM9-112-127 (SEQ ID NO:270), DOM9-112-128 (SEQ ID NO:271), DOM9-112-134 (SEQ ID NO:272), DOM9-112-135 (SEQ ID NO:273), DOM9-112-136 (SEQ ID NO:274), DOM9-112-137 (SEQ ID NO:275), DOM9-112-138 (SEQ ID NO:276), DOM9-112-140 (SEQ ID NO:277), DOM9-112-141 (SEQ ID NO:278), DOM9-112-142 (SEQ ID NO:279), DOM9-112-143 (SEQ ID NO:280), DOM9-112-144 (SEQ ID NO:281), DOM9-112-145 (SEQ ID NO:282), DOM9-112-146 (SEQ ID NO:283), DOM9-112-147 (SEQ ID NO:284), DOM9-112-148 (SEQ ID NO:285), DOM9-112-149 (SEQ ID NO:286), DOM9-112-150 (SEQ ID NO:287), DOM9-112-151 (SEQ ID NO:288), DOM9-112-152 (SEQ ID NO:289), DOM9-112-153 (SEQ ID NO:290), DOM9-112-154 (SEQ ID NO:291), DOM9-112-155 (SEQ ID NO:292), DOM9-112-156 (SEQ ID NO:293), DOM9-112-157 (SEQ ID NO:294), DOM9-112-158 (SEQ ID NO:295), DOM9-112-159 (SEQ ID NO:296), DOM9-112-160 (SEQ ID NO:297), DOM9-112-161 (SEQ ID NO:298), DOM9-112-162 (SEQ ID NO:299), DOM9-112-163 (SEQ ID NO:300), DOM9-112-164 (SEQ ID NO:301), DOM9-112-165 (SEQ ID NO:302), DOM9-112-166 (SEQ ID NO:303), DOM9-112-167 (SEQ ID NO:304), DOM9-112-168 (SEQ ID NO:305), DOM9-112-169 (SEQ ID NO:306), DOM9-112-170 (SEQ ID NO:307), DOM9-112-171 (SEQ ID NO:308), DOM9-112-172 (SEQ ID NO:309), DOM9-112-173 (SEQ ID NO:310), DOM9-112-174 (SEQ ID NO:311), DOM9-112-175 (SEQ ID NO:312), DOM9-112-176 (SEQ ID NO:313), DOM9-112-177 (SEQ ID NO:314), DOM9-112-178 (SEQ ID NO:315), DOM9-112-179 (SEQ ID NO:316), DOM9-112-180 (SEQ ID NO:317), DOM9-112-181 (SEQ ID NO:318), DOM9-112-182 (SEQ ID NO:319), DOM9-112-183 (SEQ ID NO:320), DOM9-112-184 (SEQ ID NO:321), DOM9-112-185 (SEQ ID NO:322), DOM9-112-186 (SEQ ID NO:323), DOM9-112-187 (SEQ ID NO:324), DOM9-112-188 (SEQ ID NO:325), DOM9-112-189 (SEQ ID NO:326), DOM9-112-190 (SEQ ID NO:327), DOM9-112-191 (SEQ ID NO:328), DOM9-112-192 (SEQ ID NO:329), DOM9-112-193 (SEQ ID NO:330), DOM9-112-194 (SEQ ID NO:331), DOM9-112-195 (SEQ ID NO:332), DOM9-112-196 (SEQ ID NO:333), DOM9-112-197 (SEQ ID NO:334), DOM9-112-198 (SEQ ID NO:335), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-112-201 (SEQ ID NO:338), DOM9-112-202 (SEQ ID NO:339), DOM9-120 (SEQ ID NO:340), DOM9-121 (SEQ ID NO:341), DOM9-

122 (SEQ ID NO:342), DOM9-123 (SEQ ID NO:343), DOM9-124 (SEQ ID NO:344), DOM9-125 (SEQ ID NO:345), DOM9-128 (SEQ ID NO:346), DOM9-134 (SEQ ID NO:347), DOM9-136 (SEQ ID NO:348), DOM9-26 (SEQ ID NO:500), DOM9-35 (SEQ ID NO:501), DOM9-36 (SEQ ID NO:502), DOM9-37 (SEQ ID NO:503), DOM9-38 (SEQ ID NO:504), DOM9-39 (SEQ ID NO:505), DOM9-40 (SEQ ID NO:506), DOM9-41 (SEQ ID NO:507), DOM9-43 (SEQ ID NO:508), DOM9-44 (SEQ ID NO:509), DOM9-44-500 (SEQ ID NO:510), DOM9-44-501 (SEQ ID NO:511), DOM9-44-502 (SEQ ID NO:512), DOM9-44-503 (SEQ ID NO:513), DOM9-44-504 (SEQ ID NO:514), DOM9-44-505 (SEQ ID NO:515), DOM9-44-506 (SEQ ID NO:516), DOM9-44-507 (SEQ ID NO:517), DOM9-44-509 (SEQ ID NO:518), DOM9-44-510 (SEQ ID NO:519), DOM9-44-511 (SEQ ID NO:520), DOM9-44-512 (SEQ ID NO:521), DOM9-44-513 (SEQ ID NO:522), DOM9-44-514 (SEQ ID NO:523), DOM9-44-515 (SEQ ID NO:524), DOM9-44-516 (SEQ ID NO:525), DOM9-44-517 (SEQ ID NO:526), DOM9-44-518 (SEQ ID NO:527), DOM9-44-519 (SEQ ID NO:528), DOM9-44-520 (SEQ ID NO:529), DOM9-44-521 (SEQ ID NO:530), DOM9-44-522 (SEQ ID NO:531), DOM9-44-523 (SEQ ID NO:532), DOM9-44-524 (SEQ ID NO:533), DOM9-44-525 (SEQ ID NO:534), DOM9-44-526 (SEQ ID NO:535), DOM9-44-527 (SEQ ID NO:536), DOM9-44-528 (SEQ ID NO:537), DOM9-44-529 (SEQ ID NO:538), DOM9-44-530 (SEQ ID NO:539), DOM9-44-531 (SEQ ID NO:540), DOM9-44-532 (SEQ ID NO:541), DOM9-44-533 (SEQ ID NO:542), DOM9-44-534 (SEQ ID NO:543), DOM9-44-535 (SEQ ID NO:544), DOM9-44-536 (SEQ ID NO:545), DOM9-44-537 (SEQ ID NO:546), DOM9-44-538 (SEQ ID NO:547), DOM9-44-539 (SEQ ID NO:548), DOM9-44-540 (SEQ ID NO:549), DOM9-44-541 (SEQ ID NO:550), DOM9-44-542 (SEQ ID NO:551), DOM9-44-543 (SEQ ID NO:552), DOM9-44-544 (SEQ ID NO:553), DOM9-44-545 (SEQ ID NO:554), DOM9-44-546 (SEQ ID NO:555), DOM9-44-547 (SEQ ID NO:556), DOM9-44-548 (SEQ ID NO:557), DOM9-44-549 (SEQ ID NO:558), DOM9-44-550 (SEQ ID NO:559), DOM9-44-551 (SEQ ID NO:560), DOM9-44-552 (SEQ ID NO:561), DOM9-44-553 (SEQ ID NO:562), DOM9-44-554 (SEQ ID NO:563), DOM9-44-555 (SEQ ID NO:564), DOM9-44-556 (SEQ ID NO:565), DOM9-44-557 (SEQ ID NO:566), DOM9-44-558 (SEQ ID NO:567), DOM9-44-559 (SEQ ID NO:568), DOM9-44-560 (SEQ ID

NO:569), DOM9-44-561 (SEQ ID NO:570), DOM9-44-562 (SEQ ID NO:571), DOM9-44-563 (SEQ ID NO:572), DOM9-44-564 (SEQ ID NO:573), DOM9-44-565 (SEQ ID NO:574), DOM9-44-566 (SEQ ID NO:575), DOM9-44-625 (SEQ ID NO:576), DOM9-44-626 (SEQ ID NO:577), DOM9-44-627 (SEQ ID NO:578), DOM9-44-628 (SEQ ID NO:579), DOM9-44-629 (SEQ ID NO:580), DOM9-44-630 (SEQ ID NO:581), DOM9-44-631 (SEQ ID NO:582), DOM9-44-632 (SEQ ID NO:583), DOM9-44-633 (SEQ ID NO:584), DOM9-44-634 (SEQ ID NO:585), DOM9-44-636 (SEQ ID NO:586), DOM9-44-637 (SEQ ID NO:587), DOM9-44-639 (SEQ ID NO:588), DOM9-44-640 (SEQ ID NO:589), DOM9-44-641(SEQ ID NO:590), DOM9-44-642 (SEQ ID NO:591), DOM9-44-643 (SEQ ID NO:592), DOM9-44-644 (SEQ ID NO:593), DOM9-45 (SEQ ID NO:594), DOM9-46 (SEQ ID NO:595), DOM9-47 (SEQ ID NO:596), DOM9-48 (SEQ ID NO:597), DOM9-143 (SEQ ID NO:598), DOM9-144 (SEQ ID NO:599), DOM9-146 (SEQ ID NO:600), DOM9-152 (SEQ ID NO:601), DOM9-155 (SEQ ID NO:602), DOM9-155-001 (SEQ ID NO:603), DOM9-155-3 (SEQ ID NO:604), DOM9-155-5 (SEQ ID NO:605), DOM9-155-8 (SEQ ID NO:606), DOM9-155-9 (SEQ ID NO:607), DOM9-155-11 (SEQ ID NO:608), DOM9-155-13 (SEQ ID NO:609), DOM9-155-14 (SEQ ID NO:610), DOM9-155-17 (SEQ ID NO:611), DOM9-155-19 (SEQ ID NO:612), DOM9-155-20 (SEQ ID NO:613), DOM9-155-22 (SEQ ID NO:614), DOM9-155-23 (SEQ ID NO:615), DOM9-155-24 (SEQ ID NO:616), DOM9-155-25 (SEQ ID NO:617), DOM9-155-26 (SEQ ID NO:618), DOM9-155-27 (SEQ ID NO:619), DOM9-155-28 (SEQ ID NO:620), DOM9-155-29 (SEQ ID NO:621), DOM9-155-30 (SEQ ID NO:622), DOM9-155-31 (SEQ ID NO:623), DOM9-155-32 (SEQ ID NO:624), DOM9-155-33 (SEQ ID NO:625), DOM9-155-34 (SEQ ID NO:626), DOM9-155-35 (SEQ ID NO:627), DOM9-155-36 (SEQ ID NO:628), DOM9-155-37 (SEQ ID NO:629), DOM9-155-38 (SEQ ID NO:630), DOM9-155-39 (SEQ ID NO:631), DOM9-155-41 (SEQ ID NO:632), DOM9-155-42 (SEQ ID NO:633), DOM9-155-43 (SEQ ID NO:634), DOM9-155-44 (SEQ ID NO:635), DOM9-155-45(SEQ ID NO:636), DOM9-155-46 (SEQ ID NO:637), DOM9-155-47 (SEQ ID NO:638), DOM9-155-48 (SEQ ID NO:639), DOM9-155-49 (SEQ ID NO:640), DOM9-155-50 (SEQ ID NO:641), DOM9-155-51 (SEQ ID NO:642), DOM9-155-52 (SEQ ID NO:643), DOM9-155-53 (SEQ ID NO:644), DOM9-158

(SEQ ID NO:645), DOM9-160 (SEQ ID NO:646), DOM9-161 (SEQ ID NO:647), DOM9-162 (SEQ ID NO:648), DOM9-163 (SEQ ID NO:649) and DOM9-164 (SEQ ID NO:650).

In some embodiments, the isolated and/or recombinant nucleic acid comprises a nucleotide sequence encoding a ligand that has binding specificity for IL-4, as described herein, wherein said ligand comprises an amino acid sequence that has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-204 (SEQ ID NO:2428), DOM9-112-205 (SEQ ID NO:2429), DOM9-112-206 (SEQ ID NO:2430), DOM9-112-207 (SEQ ID NO:2431), DOM9-112-208 (SEQ ID NO:2432), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434), DOM9-112-211 (SEQ ID NO:2435), DOM9-112-212 (SEQ ID NO:2436), DOM9-112-213 (SEQ ID NO:2437), DOM9-112-214 (SEQ ID NO:2438), DOM9-112-215 (SEQ ID NO:2439), DOM9-112-216 (SEQ ID NO:2440), DOM9-112-217 (SEQ ID NO:2441), DOM9-112-218 (SEQ ID NO:2442), DOM9-112-219 (SEQ ID NO:2443), DOM9-112-220 (SEQ ID NO:2444), DOM9-112-221 (SEQ ID NO:2445), DOM9-112-222 (SEQ ID NO:2446), DOM9-112-223 (SEQ ID NO:2447), DOM9-112-224 (SEQ ID NO:2448), DOM9-112-225 (SEQ ID NO:2449), DOM9-112-226 (SEQ ID NO:2450), DOM9-112-227 (SEQ ID NO:2451), DOM9-112-228 (SEQ ID NO:2452), DOM9-112-229 (SEQ ID NO:2453), DOM9-112-230 (SEQ ID NO:2454), DOM9-112-231 (SEQ ID NO:2455), DOM9-112-233 (SEQ ID NO:1734), DOM9-112-232 (SEQ ID NO:1733) and DOM9-112-234 (SEQ ID NO:1735).

In other embodiments, the isolated and/or recombinant nucleic acid comprises a nucleotide sequence encoding a ligand that has binding specificity for IL-13, as described herein, wherein said ligand comprises an amino acid sequence that has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%,

at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of DOM10-53 (SEQ ID NO:967), DOM10-53-1 (SEQ ID NO:968), DOM10-53-2 (SEQ ID NO:969), DOM10-53-3 (SEQ ID NO:970), DOM10-53-4 (SEQ ID NO:971), DOM10-53-5 (SEQ ID NO:972), DOM10-53-6 (SEQ ID NO:973), DOM10-53-7 (SEQ ID NO:974), DOM10-53-8 (SEQ ID NO:975), DOM10-53-9 (SEQ ID NO:976), DOM10-53-10 (SEQ ID NO:977), DOM10-53-11 (SEQ ID NO:978), DOM10-53-12 (SEQ ID NO:979), DOM10-53-13 (SEQ ID NO:980), DOM10-53-14 (SEQ ID NO:981), DOM10-53-15 (SEQ ID NO:982), DOM10-53-16 (SEQ ID NO:983), DOM10-53-17 (SEQ ID NO:984), DOM10-53-18 (SEQ ID NO:985), DOM10-53-19 (SEQ ID NO:986), DOM10-53-20 (SEQ ID NO:987), DOM10-53-21 (SEQ ID NO:988), DOM10-53-122 (SEQ ID NO:989), DOM10-53-123 (SEQ ID NO:990), DOM10-53-24 (SEQ ID NO:991), DOM10-53-25 (SEQ ID NO:992), DOM10-53-26 (SEQ ID NO:993), DOM10-53-27 (SEQ ID NO:994), DOM10-53-28 (SEQ ID NO:995), DOM10-53-29 (SEQ ID NO:996) , DOM10-53-30 (SEQ ID NO:997), DOM10-53-31 (SEQ ID NO:998), DOM10-53-32 (SEQ ID NO:1999), DOM10-53-43 (SEQ ID NO:1000), DOM10-53-44 (SEQ ID NO:1001), DOM10-53-45 (SEQ ID NO:1002), DOM10-53-46 (SEQ ID NO:1003), DOM10-53-47 (SEQ ID NO:1004), DOM10-53-48 (SEQ ID NO:1005), DOM10-53-49 (SEQ ID NO:1006), DOM10-53-50 (SEQ ID NO:1007), DOM10-53-51 (SEQ ID NO:1008), DOM10-53-52 (SEQ ID NO:1009) , DOM10-53-53 (SEQ ID NO:1010), DOM10-53-54 (SEQ ID NO:1011), DOM10-53-55 (SEQ ID NO:1012), DOM10-53-56 (SEQ ID NO:1013) , DOM10-53-57 (SEQ ID NO:1014), DOM10-53-59 (SEQ ID NO:1015), DOM10-53-60 (SEQ ID NO:1016), DOM10-53-61 (SEQ ID NO:1017), DOM10-53-62 (SEQ ID NO:1018), DOM10-53-63 (SEQ ID NO:1019), DOM10-53-64 (SEQ ID NO:1020), DOM10-53-65 (SEQ ID NO:1021), DOM10-53-66 (SEQ ID NO:1022), DOM10-53-67 (SEQ ID NO:1023), DOM10-53-68 (SEQ ID NO:1024), DOM10-53-69 (SEQ ID NO:1025), DOM10-53-70 (SEQ ID NO:1026), DOM10-53-71 (SEQ ID NO:1027), DOM10-53-72 (SEQ ID NO:1028), DOM10-53-73 (SEQ ID NO:1029), DOM10-53-74 (SEQ ID NO:1030), DOM10-53-75 (SEQ ID NO:1031), DOM10-53-76 (SEQ ID NO:1032), DOM10-53-77 (SEQ ID NO:1033), DOM10-53-78 (SEQ ID NO:1034) ,

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In other embodiments, the isolated and/or recombinant nucleic acid comprises a nucleotide sequence encoding a ligand that has binding specificity for IL-13, as described herein, wherein said ligand comprises an amino acid sequence that has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of DOM10-236 (SEQ ID NO:2129), DOM10-238 (SEQ ID NO:2130), DOM10-241 (SEQ ID NO:2131), DOM10-245 (SEQ ID NO:2132), DOM10-249 (SEQ ID NO:2133), DOM10-250 (SEQ ID NO:2134), DOM10-251 (SEQ ID NO:2135), DOM10-254 (SEQ ID NO:2136), DOM10-256 (SEQ ID NO:2137), DOM10-259 (SEQ ID NO:2138), DOM10-260 (SEQ ID NO:2139), DOM10-261 (SEQ ID NO:2140), DOM10-263 (SEQ ID NO:2141), DOM10-264 (SEQ ID NO:2142), DOM10-273 (SEQ ID NO:2143), DOM10-278 (SEQ ID NO:2144), DOM10-279 (SEQ ID NO:2145), DOM10-281 (SEQ ID NO:2146), DOM10-282 (SEQ ID NO:2147), DOM10-283 (SEQ ID NO:2148), DOM10-400 (SEQ ID NO:2149), DOM10-401 (SEQ ID NO:2150), DOM10-402 (SEQ ID NO:2151), DOM10-404 (SEQ ID NO:2152), DOM10-406 (SEQ ID NO:2153), DOM10-407 (SEQ ID NO:2154), DOM10-409 (SEQ ID NO:2155), DOM10-410 (SEQ ID NO:2156), DOM10-414 (SEQ ID NO:2157), DOM10-415 (SEQ ID NO:2158), DOM10-416 (SEQ ID NO:2159), DOM10-418 (SEQ ID NO:2160), DOM10-420 (SEQ ID NO:2161), DOM10-422 (SEQ ID NO:2162), DOM10-423

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NO:2307), DOM10-53-612 (SEQ ID NO:2308), DOM10-53-603 (SEQ ID NO:2309), DOM10-53-604 (SEQ ID NO:2310), DOM10-53-429 (SEQ ID NO:2311), DOM10-53-432 (SEQ ID NO:2312), DOM10-53-433 (SEQ ID NO:2313), DOM10-53-435 (SEQ ID NO:2314), DOM10-53-430 (SEQ ID NO:2315), DOM10-53-431 (SEQ ID NO:2316), DOM10-53-434 (SEQ ID NO:2317), DOM10-53-436 (SEQ ID NO:2318), DOM10-53-437 (SEQ ID NO:2319), DOM10-53-438 (SEQ ID NO:2320), DOM10-53-440 (SEQ ID NO:2321), DOM10-53-439 (SEQ ID NO:2322), DOM10-53-441 (SEQ ID NO:2323), DOM10-53-442 (SEQ ID NO:2324), DOM10-53-443 (SEQ ID NO:2325), DOM10-53-444 (SEQ ID NO:2326), DOM10-53-445 (SEQ ID NO:2327), DOM10-53-446 (SEQ ID NO:2328), DOM10-53-447 (SEQ ID NO:2329), DOM10-53-449 (SEQ ID NO:2330), DOM10-53-448 (SEQ ID NO:2331), DOM10-53-450 (SEQ ID NO:2332), DOM10-53-451 (SEQ ID NO:2333), DOM10-53-452 (SEQ ID NO:2334), DOM10-53-453 (SEQ ID NO:2335), DOM10-53-454 (SEQ ID NO:2336), DOM10-53-455 (SEQ ID NO:2337), DOM10-53-456 (SEQ ID NO:2338), DOM10-53-457 (SEQ ID NO:2339), DOM10-53-458 (SEQ ID NO:2340), DOM10-53-459 (SEQ ID NO:2341), DOM10-53-461 (SEQ ID NO:2342), DOM10-53-462 (SEQ ID NO:2343), DOM10-53-465 (SEQ ID NO:2344), DOM10-53-466 (SEQ ID NO:2345), DOM10-53-467 (SEQ ID NO:2346), DOM10-53-468 (SEQ ID NO:2347), DOM10-53-460 (SEQ ID NO:2348), DOM10-53-463 (SEQ ID NO:2349), DOM10-53-464 (SEQ ID NO:2350), DOM10-53-469 (SEQ ID NO:2351), DOM10-53-471 (SEQ ID NO:2352), DOM10-53-470 (SEQ ID NO:2353), DOM10-53-533 (SEQ ID NO:2354), DOM10-53-534 (SEQ ID NO:2355), DOM10-53-535 (SEQ ID NO:2356), DOM10-53-537 (SEQ ID NO:2357), DOM10-53-538 (SEQ ID NO:2358), DOM10-53-539 (SEQ ID NO:2359), DOM10-53-540 (SEQ ID NO:2360), DOM10-53-531 (SEQ ID NO:2361), DOM10-53-532 (SEQ ID NO:2362), DOM10-53-536 (SEQ ID NO:2363), DOM10-53-542 (SEQ ID NO:2364), DOM10-53-541 (SEQ ID NO:2365), DOM10-53-473 (SEQ ID NO:2366), DOM10-53-472 (SEQ ID NO:2367), DOM10-53-475 (SEQ ID NO:2368), DOM10-53-474 (SEQ ID NO:2369), DOM10-53-543 (SEQ ID NO:2370), DOM10-53-544 (SEQ ID NO:

2371), DOM10-53-545 (SEQ ID NO:2372), DOM10-53-548 (SEQ ID NO:2373), DOM10-53-546 (SEQ ID NO:2374), DOM10-53-549 (SEQ ID NO:2375), DOM10-53-547 (SEQ ID NO:2376), DOM10-53-550 (SEQ ID NO:2377), DOM10-53-551 (SEQ ID NO:2378), DOM10-53-560 (SEQ ID NO:2379), DOM10-53-565 (SEQ ID NO:2380), DOM10-53-559 (SEQ ID NO:2381), DOM10-53-561 (SEQ ID NO:2382), DOM10-53-562 (SEQ ID NO:2383), DOM10-53-563 (SEQ ID NO:2384), DOM10-53-564 (SEQ ID NO:2385), DOM10-53-566 (SEQ ID NO:2386), DOM10-53-554 (SEQ ID NO:2387), DOM10-53-552 (SEQ ID NO:2388), DOM10-53-553 (SEQ ID NO:2389), DOM10-53-558 (SEQ ID NO:2390), DOM10-53-556 (SEQ ID NO:2391) and DOM10-53-557 (SEQ ID NO:2392).

In other embodiments, the isolated and/or recombinant nucleic acid encoding a ligand that has binding specificity for IL-4, as described herein, wherein said nucleic acid comprises a nucleotide sequence that has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% nucleotide sequence identity with a nucleotide sequence encoding an anti-IL-4 dAb selected from the group consisting of DOM9-15 (SEQ ID NO:1), DOM9-17 (SEQ ID NO:2), DOM9-23 (SEQ ID NO:3), DOM9-24 (SEQ ID NO:4), DOM9-25 (SEQ ID NO:5), DOM9-27 (SEQ ID NO:6), DOM9-28 (SEQ ID NO:7), DOM9-29 (SEQ ID NO:8), DOM9-30 (SEQ ID NO:9), DOM9-31 (SEQ ID NO:10), DOM9-32 (SEQ ID NO:11), DOM9-33 (SEQ ID NO:12), DOM9-50 (SEQ ID NO:13), DOM9-57 (SEQ ID NO:14), DOM9-59 (SEQ ID NO:15), DOM9-63 (SEQ ID NO:16), DOM9-67 (SEQ ID NO:17), DOM9-68 (SEQ ID NO:18), DOM9-70 (SEQ ID NO:19), DOM9-79 (SEQ ID NO:20), DOM9-82 (SEQ ID NO:21), DOM9-86 (SEQ ID NO:22), DOM9-94 (SEQ ID NO:23), DOM9-108 (SEQ ID NO:24), DOM9-112 (SEQ ID NO:25), DOM9-112-1 (SEQ ID NO:26), DOM9-112-2 (SEQ ID NO:27), DOM9-112-3 (SEQ ID NO:28), DOM9-112-4 (SEQ ID NO:29), DOM9-112-5 (SEQ ID NO:30), DOM9-112-6 (SEQ ID NO:31), DOM9-112-7 (SEQ ID NO:32), DOM9-112-8 (SEQ ID NO:33), DOM9-112-9 (SEQ ID NO:34), DOM9-112-10 (SEQ ID NO:35), DOM9-112-11 (SEQ ID NO:36), DOM9-112-12 (SEQ ID NO:37), DOM9-112-13 (SEQ ID

NO:38), DOM9-112-14 (SEQ ID NO:39), DOM9-112-15 (SEQ ID NO:40), DOM9-112-16 (SEQ ID NO:41), DOM9-112-17 (SEQ ID NO:42), DOM9-112-18 (SEQ ID NO:43), DOM9-112-19 (SEQ ID NO;44), DOM9-112-20 (SEQ ID NO:45), DOM9-112-21 (SEQ ID NO:46), DOM9-112-22 (SEQ ID NO:47), DOM9-112-23 (SEQ ID NO:48), DOM9-112-25 (SEQ ID NO:49), DOM9-112-81 (SEQ ID NO:50), DOM9-112-82 (SEQ ID NO:51), DOM9-112-83 (SEQ ID NO:52), DOM9-112-84 (SEQ ID NO:53), DOM9-112-85 (SEQ ID NO:54), DOM9-112-86 (SEQ ID NO:55), DOM9-112-87 (SEQ ID NO:56), DOM9-112-88 (SEQ ID NO:57), DOM9-112-89 (SEQ ID NO:58), DOM9-112-90 (SEQ ID NO:59), DOM9-112-91 (SEQ ID NO:60), DOM9-112-92 (SEQ ID NO:61), DOM9-112-93 (SEQ ID NO:62), DOM9-112-94 (SEQ ID NO:63), DOM9-112-95 (SEQ ID NO:64), DOM9-112-96 (SEQ ID NO:65), DOM9-112-97 (SEQ ID NO:66), DOM9-112-98 (SEQ ID NO:67), DOM9-112-99 (SEQ ID NO:68), DOM9-112-100 (SEQ ID NO:69), DOM9-112-101 (SEQ ID NO:70), DOM9-112-102 (SEQ ID NO:71), DOM9-112-103 (SEQ ID NO:72), DOM9-112-104 (SEQ ID NO:73), DOM9-112-105 (SEQ ID NO:74), DOM9-112-106 (SEQ ID NO:75), DOM9-112-107 (SEQ ID NO:76), DOM9-112-108 (SEQ ID NO:77), DOM9-112-109 (SEQ ID NO:78), DOM9-112-110 (SEQ ID NO:79), DOM9-112-111 (SEQ ID NO:80), DOM9-112-112 (SEQ ID NO:81), DOM9-112-113 (SEQ ID NO:82), DOM9-112-114 (SEQ ID NO:83), DOM9-112-115 (SEQ ID NO:84), DOM9-112-116 (SEQ ID NO:85), DOM9-112-117 (SEQ ID NO:86), DOM9-112-118 (SEQ ID NO:87), DOM9-112-119 (SEQ ID NO:88), DOM9-112-120 (SEQ ID NO:89), DOM9-112-121 (SEQ ID NO:90), DOM9-112-122 (SEQ ID NO:91), DOM9-112-123 (SEQ ID NO:92), DOM9-112-124 (SEQ ID NO:93), DOM9-112-125 (SEQ ID NO:94), DOM9-112-126 (SEQ ID NO:95), DOM9-112-127 (SEQ ID NO:96), DOM9-112-128 (SEQ ID NO:97), DOM9-112-134 (SEQ ID NO:98), DOM9-112-135 (SEQ ID NO:99), DOM9-112-136 (SEQ ID NO:100), DOM9-112-137 (SEQ ID NO:101), DOM9-112-138 (SEQ ID NO:102), DOM9-112-140 (SEQ ID NO:103), DOM9-112-141 (SEQ ID NO:104), DOM9-112-142 (SEQ ID NO:105), DOM9-112-143 (SEQ ID NO:106), DOM9-112-144 (SEQ ID NO:107), DOM9-112-145 (SEQ ID NO:108), DOM9-112-146 (SEQ ID NO:109), DOM9-112-147 (SEQ ID NO:110), DOM9-112-148 (SEQ ID NO:111), DOM9-112-149 (SEQ ID NO:112), DOM9-112-150 (SEQ ID NO:113), DOM9-112-151 (SEQ ID

NO:114), DOM9-112-152 (SEQ ID NO:115), DOM9-112-153 (SEQ ID NO:116), DOM9-112-154 (SEQ ID NO:117), DOM9-112-155 (SEQ ID NO:118), DOM9-112-156 (SEQ ID NO:119), DOM9-112-157 (SEQ ID NO:120), DOM9-112-158 (SEQ ID NO:121), DOM9-112-159 (SEQ ID NO:122), DOM9-112-160 (SEQ ID NO:123), DOM9-112-161 (SEQ ID NO:124), DOM9-112-162 (SEQ ID NO:125), DOM9-112-163 (SEQ ID NO:126), DOM9-112-164 (SEQ ID NO:127), DOM9-112-165 (SEQ ID NO:128), DOM9-112-166 (SEQ ID NO:129), DOM9-112-167 (SEQ ID NO:130), DOM9-112-168 (SEQ ID NO:131), DOM9-112-169 (SEQ ID NO:132), DOM9-112-170 (SEQ ID NO:133), DOM9-112-171 (SEQ ID NO:134), DOM9-112-172 (SEQ ID NO:135), DOM9-112-173 (SEQ ID NO:136), DOM9-112-174 (SEQ ID NO:137), DOM9-112-175 (SEQ ID NO:138), DOM9-112-176 (SEQ ID NO:139), DOM9-112-177 (SEQ ID NO:140), DOM9-112-178 (SEQ ID NO:141), DOM9-112-179 (SEQ ID NO:142), DOM9-112-180 (SEQ ID NO:143), DOM9-112-181 (SEQ ID NO:144), DOM9-112-182 (SEQ ID NO:145), DOM9-112-183 (SEQ ID NO:146), DOM9-112-184 (SEQ ID NO:147), DOM9-112-185 (SEQ ID NO:148), DOM9-112-186 (SEQ ID NO:149), DOM9-112-187 (SEQ ID NO:150), DOM9-112-188 (SEQ ID NO:151), DOM9-112-189 (SEQ ID NO:152), DOM9-112-190 (SEQ ID NO:153), DOM9-112-191 (SEQ ID NO:154), DOM9-112-192 (SEQ ID NO:155), DOM9-112-193 (SEQ ID NO:156), DOM9-112-194 (SEQ ID NO:157), DOM9-112-195 (SEQ ID NO:158), DOM9-112-196 (SEQ ID NO:159), DOM9-112-197 (SEQ ID NO:160), DOM9-112-198 (SEQ ID NO:161), DOM9-112-199 (SEQ ID NO:162), DOM9-112-200 (SEQ ID NO:163), DOM9-112-201 (SEQ ID NO:164), DOM9-112-202 (SEQ ID NO:165) DOM9-120 (SEQ ID NO:166), DOM9-121 (SEQ ID NO:167), DOM9-122 (SEQ ID NO:168), DOM9-123 (SEQ ID NO:169), DOM9-124 (SEQ ID NO:170), DOM9-125 (SEQ ID NO:171), DOM9-128 (SEQ ID NO:172), DOM9-134 (SEQ ID NO:173), DOM9-136 (SEQ ID NO:174), DOM9-26 (SEQ ID NO:349), DOM9-35 (SEQ ID NO:350), DOM9-36 (SEQ ID NO:351), DOM9-37 (SEQ ID NO:352), DOM9-38 (SEQ ID NO:353), DOM9-39 (SEQ ID NO:354), DOM9-40 (SEQ ID NO:355), DOM9-41 (SEQ ID NO:356), DOM9-43 (SEQ ID NO:357), DOM9-44 (SEQ ID NO:358), DOM9-44-500 (SEQ ID NO:359), DOM9-44-501 (SEQ ID NO:360), DOM9-44-502 (SEQ ID NO:361), DOM9-44-503 (SEQ ID NO:362), DOM9-44-504 (SEQ ID

NO:363), DOM9-44-505 (SEQ ID NO:364), DOM9-44-506 (SEQ ID NO:365), DOM9-44-507 (SEQ ID NO:366), DOM9-44-509 (SEQ ID NO:367), DOM9-44-510 (SEQ ID NO:368), DOM9-44-511 (SEQ ID NO:369), DOM9-44-512 (SEQ ID NO:370), DOM9-44-513 (SEQ ID NO:371), DOM9-44-514 (SEQ ID NO:372), DOM9-44-515 (SEQ ID NO:373), DOM9-44-516 (SEQ ID NO:374), DOM9-44-517 (SEQ ID NO:375), DOM9-44-518 (SEQ ID NO:376), DOM9-44-519 (SEQ ID NO:377), DOM9-44-520 (SEQ ID NO:378), DOM9-44-521 (SEQ ID NO:379), DOM9-44-522 (SEQ ID NO:380), DOM9-44-523 (SEQ ID NO:381), DOM9-44-524 (SEQ ID NO:382), DOM9-44-525 (SEQ ID NO:383), DOM9-44-526 (SEQ ID NO:384), DOM9-44-527 (SEQ ID NO:385), DOM9-44-528 (SEQ ID NO:386), DOM9-44-529 (SEQ ID NO:387), DOM9-44-530 (SEQ ID NO:388), DOM9-44-531 (SEQ ID NO:389), DOM9-44-532 (SEQ ID NO:390), DOM9-44-533 (SEQ ID NO:391), DOM9-44-534 (SEQ ID NO:392), DOM9-44-535 (SEQ ID NO:393), DOM9-44-536 (SEQ ID NO:394), DOM9-44-537 (SEQ ID NO:395), DOM9-44-538 (SEQ ID NO:396), DOM9-44-539 (SEQ ID NO:397), DOM9-44-540 (SEQ ID NO:398), DOM9-44-541 (SEQ ID NO:399), DOM9-44-542 (SEQ ID NO:400), DOM9-44-543 (SEQ ID NO:401), DOM9-44-544 (SEQ ID NO:402), DOM9-44-545 (SEQ ID NO:403), DOM9-44-546 (SEQ ID NO:404), DOM9-44-547 (SEQ ID NO:405), DOM9-44-548 (SEQ ID NO:406), DOM9-44-549 (SEQ ID NO:407), DOM9-44-550 (SEQ ID NO:408), DOM9-44-551 (SEQ ID NO:409), DOM9-44-552 (SEQ ID NO:410), DOM9-44-553 (SEQ ID NO:411), DOM9-44-554 (SEQ ID NO:412), DOM9-44-555 (SEQ ID NO:413), DOM9-44-556 (SEQ ID NO:414), DOM9-44-557 (SEQ ID NO:415), DOM9-44-558 (SEQ ID NO:416), DOM9-44-559 (SEQ ID NO:417), DOM9-44-560 (SEQ ID NO:418), DOM9-44-561 (SEQ ID NO:419), DOM9-44-562 (SEQ ID NO:420), DOM9-44-563 (SEQ ID NO:421), DOM9-44-564 (SEQ ID NO:422), DOM9-44-565 (SEQ ID NO:423), DOM9-44-566 (SEQ ID NO:424), DOM9-44-625 (SEQ ID NO:425), DOM9-44-626 (SEQ ID NO:426), DOM9-44-627 (SEQ ID NO:427), DOM9-44-628 (SEQ ID NO:428), DOM9-44-629 (SEQ ID NO:429), DOM9-44-630 (SEQ ID NO:430), DOM9-44-631 (SEQ ID NO:431), DOM9-44-632 (SEQ ID NO:432), DOM9-44-633 (SEQ ID NO:433), DOM9-44-634 (SEQ ID NO:434), DOM9-44-636 (SEQ ID NO:435), DOM9-44-637 (SEQ ID NO:436), DOM9-44-639 (SEQ ID NO:437), DOM9-44-

640 (SEQ ID NO:438), DOM9-44-641 (SEQ ID NO:439), DOM9-44-642 (SEQ ID NO:440), DOM9-44-643 (SEQ ID NO:441), DOM9-44-644 (SEQ ID NO:442), DOM9-45 (SEQ ID NO:443), DOM9-46 (SEQ ID NO:444), DOM9-47 (SEQ ID NO:445), DOM9-48 (SEQ ID NO:446), DOM9-143 (SEQ ID NO:447), DOM9-144 (SEQ ID NO:448), DOM9-146 (SEQ ID NO:449), DOM9-152 (SEQ ID NO:450), DOM9-155 (SEQ ID NO:451), DOM9-155-001 (SEQ ID NO:452), DOM9-155-3 (SEQ ID NO:453), DOM9-155-5 (SEQ ID NO:454), DOM9-155-8 (SEQ ID NO:455), DOM9-155-9 (SEQ ID NO:456), DOM9-155-11 (SEQ ID NO:457), DOM9-155-13 (SEQ ID NO:458), DOM9-155-14 (SEQ ID NO:459), DOM9-155-17 (SEQ ID NO:460), DOM9-155-19 (SEQ ID NO:461), DOM9-155-20 (SEQ ID NO:462), DOM9-155-22 (SEQ ID NO:463), DOM9-155-23 (SEQ ID NO:464), DOM9-155-24 (SEQ ID NO:465), DOM9-155-25 (SEQ ID NO:466), DOM9-155-26 (SEQ ID NO:467), DOM9-155-27 (SEQ ID NO:468), DOM9-155-28 (SEQ ID NO:469), DOM9-155-29 (SEQ ID NO:470), DOM9-155-30 (SEQ ID NO:471), DOM9-155-31 (SEQ ID NO:472), DOM9-155-32 (SEQ ID NO:473), DOM9-155-33 (SEQ ID NO:474), DOM9-155-34 (SEQ ID NO:475), DOM9-155-35 (SEQ ID NO:476), DOM9-155-36 (SEQ ID NO:477), DOM9-155-37 (SEQ ID NO:478), DOM9-155-38 (SEQ ID NO:479), DOM9-155-39 (SEQ ID NO:480), DOM9-155-41 (SEQ ID NO:481), DOM9-155-42 (SEQ ID NO:482), DOM9-155-43 (SEQ ID NO:483), DOM9-155-44 (SEQ ID NO:484), DOM9-155-45 (SEQ ID NO:485), DOM9-155-46 (SEQ ID NO:486), DOM9-155-47 (SEQ ID NO:487), DOM9-155-48 (SEQ ID NO:488), DOM9-155-49 (SEQ ID NO:489), DOM9-155-50 (SEQ ID NO:490), DOM9-155-51 (SEQ ID NO:491), DOM9-155-52 (SEQ ID NO:492), DOM9-155-53 (SEQ ID NO:493), DOM9-158 (SEQ ID NO:494), DOM9-160 (SEQ ID NO:495), DOM9-161 (SEQ ID NO:496), DOM9-162 (SEQ ID NO:497), DOM9-163 (SEQ ID NO:498) and DOM9-164 (SEQ ID NO:499). Preferably, nucleotide sequence identity is determined over the whole length of the nucleotice sequence that encodes the selected anti-IL-4 dAb.

In other embodiments, the isolated and/or recombinant nucleic acid encoding a ligand that has binding specificity for IL-4, as described herein, wherein said nucleic acid comprises a nucleotide sequence that has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about

93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% nucleotide sequence identity with a nucleotide sequence encoding an anti-IL-4 dAb selected from the group consisting of DOM9-155-77 (SEQ ID NO:2393), DOM9-155-78 (SEQ ID NO:2394), DOM9-112-204 (SEQ ID NO:2395), DOM9-112-205 (SEQ ID NO:2396), DOM9-112-206 (SEQ ID NO:2397), DOM9-112-207 (SEQ ID NO:2398), DOM9-112-208 (SEQ ID NO:2399), DOM9-112-209 (SEQ ID NO:2400), DOM9-112-210 (SEQ ID NO:2401), DOM9-112-211 (SEQ ID NO:2402), DOM9-112-212 (SEQ ID NO:2403), DOM9-112-213 (SEQ ID NO:2404), DOM9-112-214 (SEQ ID NO:2405), DOM9-112-215 (SEQ ID NO:2406), DOM9-112-216 (SEQ ID NO:2407), DOM9-112-217 (SEQ ID NO:2408), DOM9-112-218 (SEQ ID NO:2409), DOM9-112-219 (SEQ ID NO:2410), DOM9-112-220 (SEQ ID NO:2411), DOM9-112-221 (SEQ ID NO:2412), DOM9-112-222 (SEQ ID NO:2413), DOM9-112-223 (SEQ ID NO:2414), DOM9-112-224 (SEQ ID NO:2415), DOM9-112-225 (SEQ ID NO:2416), DOM9-112-226 (SEQ ID NO:2417), DOM9-112-227 (SEQ ID NO:2418), DOM9-112-228 (SEQ ID NO:2419), DOM9-112-229 (SEQ ID NO:2420), DOM9-112-230 (SEQ ID NO:2421), DOM9-112-231 (SEQ ID NO:2422), DOM9-112-233 (SEQ ID NO:2423), DOM9-112-232 (SEQ ID NO:2424) and DOM9-112-234 (SEQ ID NO:2425).

In other embodiments, the isolated and/or recombinant nucleic acid encoding a ligand that has binding specificity for IL-13, as described herein, wherein said nucleic acid comprises a nucleotide sequence has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% nucleotide sequence identity with a nucleotide sequence encoding an anti-IL-13 dAb selected from the group consisting of DOM10-53 (SEQ ID NO:651), DOM10-53-1 (SEQ ID NO:652), DOM10-53-2 (SEQ ID NO:653), DOM10-53-3 (SEQ ID NO:654), DOM10-53-4 (SEQ ID NO:655), DOM10-53-5 (SEQ ID NO:656), DOM10-53-6 (SEQ ID NO:657), DOM10-53-7 (SEQ ID NO:658), DOM10-53-8 (SEQ ID NO:659), DOM10-53-9 (SEQ ID NO:660), DOM10-53-10 (SEQ ID NO:661), DOM10-53-11 (SEQ ID

NO:662), DOM10-53-12 (SEQ ID NO:663), DOM10-53-13 (SEQ ID NO:664), DOM10-53-14 (SEQ ID NO:665), DOM10-53-15 (SEQ ID NO:666), DOM10-53-16 (SEQ ID NO:667), DOM10-53-17 (SEQ ID NO:668), DOM10-53-18 (SEQ ID NO:669), DOM10-53-19 (SEQ ID NO:670), DOM10-53-20 (SEQ ID NO:671), DOM10-53-21 (SEQ ID NO:672), DOM10-53-122 (SEQ ID NO:673), DOM10-53-123 (SEQ ID NO:674), DOM10-53-24 (SEQ ID NO:675), DOM10-53-25 (SEQ ID NO:676), DOM10-53-26 (SEQ ID NO:677), DOM10-53-27 (SEQ ID NO:678), DOM10-53-28 (SEQ ID NO:679), DOM10-53-29 (SEQ ID NO:680), DOM10-53-30 (SEQ ID NO:681), DOM10-53-31 (SEQ ID NO:682), DOM10-53-32 (SEQ ID NO:683), DOM10-53-43 (SEQ ID NO:684), DOM10-53-44 (SEQ ID NO:685), DOM10-53-45 (SEQ ID NO:686), DOM10-53-46 (SEQ ID NO:687), DOM10-53-47 (SEQ ID NO:688), DOM10-53-48 (SEQ ID NO:689), DOM10-53-49 (SEQ ID NO:690), DOM10-53-50 (SEQ ID NO:691), DOM10-53-51 (SEQ ID NO:692), DOM10-53-52 (SEQ ID NO:693), DOM10-53-53 (SEQ ID NO:694), DOM10-53-54 (SEQ ID NO:695), DOM10-53-55 (SEQ ID NO:696), DOM10-53-56 (SEQ ID NO:697), DOM10-53-57 (SEQ ID NO:698), DOM10-53-59 (SEQ ID NO:699), DOM10-53-60 (SEQ ID NO:700), DOM10-53-61 (SEQ ID NO:701), DOM10-53-62 (SEQ ID NO:702), DOM10-53-63 (SEQ ID NO:703), DOM10-53-64 (SEQ ID NO:704), DOM10-53-65 (SEQ ID NO:705), DOM10-53-66 (SEQ ID NO:706), DOM10-53-67 (SEQ ID NO:707), DOM10-53-68 (SEQ ID NO:708), DOM10-53-69 (SEQ ID NO:709), DOM10-53-70 (SEQ ID NO:710), DOM10-53-71 (SEQ ID NO:711), DOM10-53-72 (SEQ ID NO:712), DOM10-53-73 (SEQ ID NO:713), DOM10-53-74 (SEQ ID NO:714), DOM10-53-75 (SEQ ID NO:715), DOM10-53-76 (SEQ ID NO:716), DOM10-53-77 (SEQ ID NO:717), DOM10-53-78 (SEQ ID NO:718), DOM10-53-79 (SEQ ID NO:719), DOM10-53-80 (SEQ ID NO:720), DOM10-53-81 (SEQ ID NO:721), DOM10-53-82 (SEQ ID NO:722), DOM10-53-83 (SEQ ID NO:723), DOM10-53-84 (SEQ ID NO:724), DOM10-53-85 (SEQ ID NO:725), DOM10-53-86 (SEQ ID NO:726), DOM10-53-87 (SEQ ID NO:727), DOM10-53-88 (SEQ ID NO:728), DOM10-53-89 (SEQ ID NO:729), DOM10-53-91 (SEQ ID NO:730), DOM10-53-92 (SEQ ID NO:731), DOM10-53-93 (SEQ ID NO:732), DOM10-53-94 (SEQ ID NO:733), DOM10-53-95 (SEQ ID NO:734), DOM10-53-96 (SEQ ID NO:735), DOM10-53-97 (SEQ ID NO:736), DOM10-53-

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In other embodiments, the isolated and/or recombinant nucleic acid encoding a ligand that has binding specificity for IL-13, as described herein, wherein said nucleic acid comprises a nucleotide sequence has at least about 80%, at least about 85%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% nucleotide sequence identity with a nucleotide sequence encoding an anti-IL-13 dAb selected from the group consisting of DOM10-236 (SEQ ID NO:1804), DOM10-238 (SEQ ID NO:1805), DOM10-241 (SEQ ID NO:1806), DOM10-245 (SEQ ID NO:1807), DOM10-249 (SEQ ID

NO:1808), DOM10-250 (SEQ ID NO:1809), DOM10-251 (SEQ ID NO:1810), DOM10-254 (SEQ ID NO:1811), DOM10-256 (SEQ ID NO:1812), DOM10-259 (SEQ ID NO:1813), DOM10-260 (SEQ ID NO:1814), DOM10-261 (SEQ ID NO:1815), DOM10-263 (SEQ ID NO:1816), DOM10-264 (SEQ ID NO:1817), DOM10-273 (SEQ ID NO:1818), DOM10-278 (SEQ ID NO:1819), DOM10-279 (SEQ ID NO:1820), DOM10-281 (SEQ ID NO:1821), DOM10-282 (SEQ ID NO:1822), DOM10-283 (SEQ ID NO:1823), DOM10-400 (SEQ ID NO:1824), DOM10-401 (SEQ ID NO:1825), DOM10-402 (SEQ ID NO:1826), DOM10-404 (SEQ ID NO:1827), DOM10-406 (SEQ ID NO:1828), DOM10-407 (SEQ ID NO:1829), DOM10-409 (SEQ ID NO:1830), DOM10-410 (SEQ ID NO:1831), DOM10-414 (SEQ ID NO:1832), DOM10-415 (SEQ ID NO:1833), DOM10-416 (SEQ ID NO:1834), DOM10-418 (SEQ ID NO:1835), DOM10-420 (SEQ ID NO:1836), DOM10-422 (SEQ ID NO:1837), DOM10-423 (SEQ ID NO:1838), DOM10-424 (SEQ ID NO:1839), DOM10-425 (SEQ ID NO:1840), DOM10-426 (SEQ ID NO:1841), DOM10-427 (SEQ ID NO:1842), DOM10-428 (SEQ ID NO:1843), DOM10-429 (SEQ ID NO:1844), DOM10-430 (SEQ ID NO:1845), DOM10-431 (SEQ ID NO:1846), DOM10-432 (SEQ ID NO:1847), DOM10-433 (SEQ ID NO:1848), DOM10-467 (SEQ ID NO:1849), DOM10-468 (SEQ ID NO:1850), DOM10-469 (SEQ ID NO:1851), DOM10-470 (SEQ ID NO:1852), DOM10-234 (SEQ ID NO:1853), DOM10-235 (SEQ ID NO:1854), DOM10-237 (SEQ ID NO:1855), DOM10-239 (SEQ ID NO:1856), DOM10-240 (SEQ ID NO:1857), DOM10-242 (SEQ ID NO:1858), DOM10-243 (SEQ ID NO:1859), DOM10-244 (SEQ ID NO:1860), DOM10-246 (SEQ ID NO:1861), DOM10-247 (SEQ ID NO:1862), DOM10-248 (SEQ ID NO:1863), DOM10-252 (SEQ ID NO:1864), DOM10-257 (SEQ ID NO:1865), DOM10-258 (SEQ ID NO:1866), DOM10-262 (SEQ ID NO:1867), DOM10-265 (SEQ ID NO:1868), DOM10-266 (SEQ ID NO:1869), DOM10-274 (SEQ ID NO:1870), DOM10-275 (SEQ ID NO:1871), DOM10-276 (SEQ ID NO:1872), DOM10-277 (SEQ ID NO:1873), DOM10-280 (SEQ ID NO:1874), DOM10-403 (SEQ ID NO:1875), DOM10-405 (SEQ ID NO:1876), DOM10-408 (SEQ ID NO:1877), DOM10-411 (SEQ ID NO:1878), DOM10-412 (SEQ ID NO:1879), DOM10-413 (SEQ ID NO:1880), DOM10-417 (SEQ ID NO:1881), DOM10-419 (SEQ ID NO:1882), DOM10-472

(SEQ ID NO:1883), DOM10-203 (SEQ ID NO:1884), DOM10-205 (SEQ ID NO:1885), DOM10-208 (SEQ ID NO:1886), DOM10-218 (SEQ ID NO:1887), DOM10-219 (SEQ ID NO:1888), DOM10-220 (SEQ ID NO:1889), DOM10-225 (SEQ ID NO:1890), DOM10-228 (SEQ ID NO:1891), DOM10-229 (SEQ ID NO:1892), DOM10-230 (SEQ ID NO:1893), DOM10-231 (SEQ ID NO:1894), DOM10-268 (SEQ ID NO:1895), DOM10-201 (SEQ ID NO:1896), DOM10-202 (SEQ ID NO:1897), DOM10-204 (SEQ ID NO:1898), DOM10-206 (SEQ ID NO:1899), DOM10-207 (SEQ ID NO:1900), DOM10-209 (SEQ ID NO:1901), DOM10-210 (SEQ ID NO:1902), DOM10-211 (SEQ ID NO:1903), DOM10-213 (SEQ ID NO:1904), DOM10-214 (SEQ ID NO:1905), DOM10-215 (SEQ ID NO:1906), DOM10-216 (SEQ ID NO:1907), DOM10-217 (SEQ ID NO:1908), DOM10-221 (SEQ ID NO:1909), DOM10-223 (SEQ ID NO:1910), DOM10-224 (SEQ ID NO:1911), DOM10-227 (SEQ ID NO:1912), DOM10-232 (SEQ ID NO:1913), DOM10-267 (SEQ ID NO:1914), DOM10-270 (SEQ ID NO:1915), DOM10-275-1 (SEQ ID NO:1918), DOM10-276-2 (SEQ ID NO:1919), DOM10-276-3 (SEQ ID NO:1920), DOM10-275-3 (SEQ ID NO:1979), DOM10-277-2 (SEQ ID NO:1980), DOM10-277-3 (SEQ ID NO:1981), DOM10-273-1 (SEQ ID NO:1982), DOM10-273-2 (SEQ ID NO:1983), DOM10-275-2 (SEQ ID NO:1984), DOM10-275-4 (SEQ ID NO:1985), DOM10-276-1 (SEQ ID NO:1986), DOM10-276-4 (SEQ ID NO:1987), DOM10-277-1 (SEQ ID NO:1988), DOM10-275-13 (SEQ ID NO:1989), DOM10-275-15 (SEQ ID NO:1990), DOM10-275-20 (SEQ ID NO:1991), DOM10-275-8 (SEQ ID NO:1992), DOM10-276-13 (SEQ ID NO:1993), DOM10-276-14 (SEQ ID NO:1994), DOM10-276-15 (SEQ ID NO:1995), DOM10-276-17 (SEQ ID NO:1996), DOM10-276-7 (SEQ ID NO:1997), DOM10-276-8 (SEQ ID NO:1998), DOM10-275-11 (SEQ ID NO:1999), DOM10-275-12 (SEQ ID NO:2000), DOM10-275-14 (SEQ ID NO:2001), DOM10-275-16 (SEQ ID NO:2002), DOM10-275-17 (SEQ ID NO:2003), DOM10-275-5 (SEQ ID NO:2004), DOM10-275-6 (SEQ ID NO:2005), DOM10-275-7 (SEQ ID NO:2006), DOM10-275-9 (SEQ ID NO:2007), DOM10-276-10 (SEQ ID NO:2008), DOM10-276-11 (SEQ ID NO:2009), DOM10-276-12 (SEQ ID NO:2010), DOM10-276-16 (SEQ ID NO:2011), DOM10-276-5 (SEQ ID NO:2012), DOM10-276-6 (SEQ ID NO:2013), DOM10-276-9 (SEQ ID NO:2014), DOM10-212 (SEQ ID NO:2016), DOM10-53-

424 (SEQ ID NO:2017), DOM10-53-425 (SEQ ID NO:2018), DOM10-53-426 (SEQ ID NO:2019), DOM10-53-422 (SEQ ID NO:2020), DOM10-53-423 (SEQ ID NO:2021), DOM10-53-613 (SEQ ID NO:2022), DOM10-53-517 (SEQ ID NO:2023), DOM10-53-519 (SEQ ID NO:2024), DOM10-53-520 (SEQ ID NO:2025), DOM10-53-521 (SEQ ID NO:2026), DOM10-53-522 (SEQ ID NO:2027), DOM10-53-526 (SEQ ID NO:2028), DOM10-53-527 (SEQ ID NO:2029), DOM10-53-528 (SEQ ID NO:2030), DOM10-53-518 (SEQ ID NO:2031), DOM10-53-523 (SEQ ID NO:2032), DOM10-53-524 (SEQ ID NO:2033), DOM10-53-525 (SEQ ID NO:2034), DOM10-53-601 (SEQ ID NO:2035), DOM10-53-602 (SEQ ID NO:2036), DOM10-53-605 (SEQ ID NO:2037), DOM10-53-606 (SEQ ID NO:2038), DOM10-53-607 (SEQ ID NO:2039), DOM10-53-608 (SEQ ID NO:2040), DOM10-53-609 (SEQ ID NO:2041), DOM10-53-610 (SEQ ID NO:2042), DOM10-53-611 (SEQ ID NO:2043), DOM10-53-612 (SEQ ID NO:2044), DOM10-53-603 (SEQ ID NO:2045), DOM10-53-604 (SEQ ID NO:2046), DOM10-53-429 (SEQ ID NO:2047), DOM10-53-432 (SEQ ID NO:2048), DOM10-53-433 (SEQ ID NO:2049), DOM10-53-435 (SEQ ID NO:2050), DOM10-53-430 (SEQ ID NO:2051), DOM10-53-431 (SEQ ID NO:2052), DOM10-53-434 (SEQ ID NO:2053), DOM10-53-436 (SEQ ID NO:2054), DOM10-53-437 (SEQ ID NO:2055), DOM10-53-438 (SEQ ID NO:2056), DOM10-53-440 (SEQ ID NO:2057), DOM10-53-439 (SEQ ID NO:2058), DOM10-53-441 (SEQ ID NO:2059), DOM10-53-442 (SEQ ID NO:2060), DOM10-53-443 (SEQ ID NO:2061), DOM10-53-444 (SEQ ID NO:2062), DOM10-53-445 (SEQ ID NO:2063), DOM10-53-446 (SEQ ID NO:2064), DOM10-53-447 (SEQ ID NO:2065), DOM10-53-449 (SEQ ID NO:2066), DOM10-53-448 (SEQ ID NO:2067), DOM10-53-450 (SEQ ID NO:2068), DOM10-53-451 (SEQ ID NO:2069), DOM10-53-452 (SEQ ID NO:2070), DOM10-53-453 (SEQ ID NO:2071), DOM10-53-454 (SEQ ID NO:2072), DOM10-53-455 (SEQ ID NO:2073), DOM10-53-456 (SEQ ID NO:2074), DOM10-53-457 (SEQ ID NO:2075), DOM10-53-458 (SEQ ID NO:2076), DOM10-53-459 (SEQ ID NO:2077), DOM10-53-461 (SEQ ID NO:2078), DOM10-53-462 (SEQ ID NO:2079), DOM10-53-465 (SEQ ID NO:2080), DOM10-53-466 (SEQ ID

NO:2081), DOM10-53-467 (SEQ ID NO:2082), DOM10-53-468 (SEQ ID NO:2083), DOM10-53-460 (SEQ ID NO:2084), DOM10-53-463 (SEQ ID NO:2085), DOM10-53-464 (SEQ ID NO:2086), DOM10-53-469 (SEQ ID NO:2087), DOM10-53-471 (SEQ ID NO:2088), DOM10-53-470 (SEQ ID NO:2089), DOM10-53-533 (SEQ ID NO:2090), DOM10-53-534 (SEQ ID NO:2091), DOM10-53-535 (SEQ ID NO:2092), DOM10-53-537 (SEQ ID NO:2093), DOM10-53-538 (SEQ ID NO:2094), DOM10-53-539 (SEQ ID NO:2095), DOM10-53-540 (SEQ ID NO:2096), DOM10-53-531 (SEQ ID NO:2097), DOM10-53-532 (SEQ ID NO:2098), DOM10-53-536 (SEQ ID NO:2099), DOM10-53-542 (SEQ ID NO:2100), DOM10-53-541 (SEQ ID NO:2101), DOM10-53-473 (SEQ ID NO:2102), DOM10-53-472 (SEQ ID NO:2103), DOM10-53-475 (SEQ ID NO:2104), DOM10-53-474 (SEQ ID NO:2105), DOM10-53-543 (SEQ ID NO:2106), DOM10-53-544 (SEQ ID NO: 107), DOM10-53-545 (SEQ ID NO:2108), DOM10-53-548 (SEQ ID NO:2109), DOM10-53-546 (SEQ ID NO:2110), DOM10-53-549 (SEQ ID NO:2111), DOM10-53-547 (SEQ ID NO:2112), DOM10-53-550 (SEQ ID NO:2113), DOM10-53-551 (SEQ ID NO:2114), DOM10-53-560 (SEQ ID NO:2115), DOM10-53-565 (SEQ ID NO:2116), DOM10-53-559 (SEQ ID NO:2117), DOM10-53-561 (SEQ ID NO:2118), DOM10-53-562 (SEQ ID NO:2119), DOM10-53-563 (SEQ ID NO:2120), DOM10-53-564 (SEQ ID NO:2121), DOM10-53-566 (SEQ ID NO:2122), DOM10-53-554 (SEQ ID NO:2123), DOM10-53-552 (SEQ ID NO:2124), DOM10-53-553 (SEQ ID NO:2125), DOM10-53-558 (SEQ ID NO:2126), DOM10-53-556 (SEQ ID NO:2127) and DOM10-53-557 (SEQ ID NO:2128).

The invention also provides a vector comprising a recombinant nucleic acid molecule of the invention. In certain embodiments, the vector is an expression vector comprising one or more expression control elements or sequences that are operably linked to the recombinant nucleic acid of the invention The invention also provides a recombinant host cell comprising a recombinant nucleic acid molecule or vector of the invention. Suitable vectors (*e.g.*, plasmids, phagmids), expression control elements, host cells and methods for producing recombinant host cells of the invention are well-known in the art, and examples are further described herein.

Suitable expression vectors can contain a number of components, for example, an origin of replication, a selectable marker gene, one or more expression control elements, such as a transcription control element (*e.g.*, promoter, enhancer, terminator) and/or one or more translation signals, a signal sequence or leader sequence, and the like. Expression control elements and a signal sequence, if present, can be provided by the vector or other source. For example, the transcriptional and/or translational control sequences of a cloned nucleic acid encoding an antibody chain can be used to direct expression.

A promoter can be provided for expression in a desired host cell. Promoters can be constitutive or inducible. For example, a promoter can be operably linked to a nucleic acid encoding an antibody, antibody chain or portion thereof, such that it directs transcription of the nucleic acid. A variety of suitable promoters for prokaryotic (*e.g.*, lac, tac, T3, T7 promoters for *E. coli*) and eukaryotic (*e.g.*, Simian Virus 40 early or late promoter, Rous sarcoma virus long terminal repeat promoter, cytomegalovirus promoter, adenovirus late promoter) hosts are available.

In addition, expression vectors typically comprise a selectable marker for selection of host cells carrying the vector, and, in the case of a replicable expression vector, an origin of replication. Genes encoding products which confer antibiotic or drug resistance are common selectable markers and may be used in prokaryotic (*e.g.* lactamase gene (ampicillin resistance), *Tet* gene for tetracycline resistance) and eukaryotic cells (*e.g.*, neomycin (G418 or geneticin), gpt (mycophenolic acid), ampicillin, or hygromycin resistance genes). Dihydrofolate reductase marker genes permit selection with methotrexate in a variety of hosts. Genes encoding the gene product of auxotrophic markers of the host (*e.g.*, *LEU2, URA3, HIS3*) are often used as selectable markers in yeast. Use of viral (*e.g.*, baculovirus) or phage vectors, and vectors which are capable of integrating into the genome of the host cell, such as retroviral vectors, are also contemplated. Suitable expression vectors for expression in mammalian cells and prokaryotic cells (*E. coli*), insect cells (Drosophila Schnieder S2 cells, Sf9) and yeast (*P. methanolica, P. pastoris, S. cerevisiae*) are well-known in the art.

Suitable host cells can be prokaryotic, including bacterial cells such as *E. coli, B. subtilis* and/or other suitable bacteria; eukaryotic cells, such as fungal or

yeast cells (*e.g.*, *Pichia pastoris*, *Aspergillus sp.*, *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Neurospora crassa*), or other lower eukaryotic cells, and cells of higher eukaryotes such as those from insects (*e.g.*, *Drosophila* Schnieder S2 cells, Sf9 insect cells (WO 94/26087 (O'Connor)), mammals (*e.g.*, COS cells, such as COS-1 (ATCC Accession No. CRL-1650) and COS-7 (ATCC Accession No. CRL-1651), CHO (*e.g.*, ATCC Accession No. CRL-9096, CHO DG44 (Urlaub, G. and Chasin, LA., *Proc. Natl. Acac. Sci. USA*, 77(7):4216-4220 (1980))), 293 (ATCC Accession No. CRL-1573), HeLa (ATCC Accession No. CCL-2), CV1 (ATCC Accession No. CCL-70), WOP (Dailey, L., *et al.*, *J. Virol.*, *54*:739-749 (1985), 3T3, 293T (Pear, W. S., *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, *90*:8392-8396 (1993)) NS0 cells, SP2/0, HuT 78 cells and the like, or plants (*e.g.*, tobacco). (See, for example, Ausubel, F.M. *et al.*, eds. *Current Protocols in Molecular Biology*, Greene Publishing Associates and John Wiley & Sons Inc. (1993).) In some embodiments, the host cell is an isolated host cell and is not part of a multicellular organism (*e.g.*, plant or animal). In preferred embodiments, the host cell is a non-human host cell.

The invention also provides a method for producing a ligand (*e.g.*, dual-specific ligand, multispecific ligand) of the invention, comprising maintaining a recombinant host cell comprising a recombinant nucleic acid of the invention under conditions suitable for expression of the recombinant nucleic acid, whereby the recombinant nucleic acid is expressed and a ligand is produced. In some embodiments, the method further comprises isolating the ligand.

Preparation of Immunoglobulin Based Ligands

Ligands (*e.g.*, dual specific ligands, multispecific) according to the invention can be prepared according to previously established techniques, used in the field of antibody engineering, for the preparation of scFv, "phage" antibodies and other engineered antibody molecules. Techniques for the preparation of antibodies are for example described in the following reviews and the references cited therein: Winter & Milstein, (1991) *Nature* 349:293-299; Pluckthun (1992) *Immunological Reviews* 130:151-188; Wright *et al.*, (1992) *Crit. Rev. Immunol.*12:125-168; Holliger, P. & Winter, G. (1993) *Curr. Op. Biotechn.* 4, 446-449; Carter, *et al.* (1995) *J. Hematother.* 4, 463-470; Chester, K.A. & Hawkins, R.E. (1995) *Trends Biotechn.*

13, 294-300; Hoogenboom, H.R. (1997) *Nature Biotechnol.* 15, 125-126; Fearon, D. (1997) *Nature Biotechnol.* 15, 618-619; Plückthun, A. & Pack, P. (1997) *Immunotechnology* 3, 83-105; Carter, P. & Merchant, A.M. (1997) *Curr. Opin. Biotechnol.* 8, 449-454; Holliger, P. & Winter, G. (1997) *Cancer Immunol.* Immunother. 45,128-130.

Suitable techniques employed for selection of antibody variable domains with a desired specificity employ libraries and selection procedures which are known in the art. Natural libraries (Marks *et al.* (1991) *J. Mol. Biol.*, 222: 581; Vaughan *et al.* (1996) *Nature Biotech.*, 14: 309) which use rearranged V genes harvested from human B cells are well known to those skilled in the art. Synthetic libraries (Hoogenboom & Winter (1992) *J. Mol. Biol.*, 227: 381; Barbas *et al.* (1992) *Proc. Natl. Acad. Sci. USA*, 89: 4457; Nissim *et al.* (1994) *EMBO J.*, 13: 692; Griffiths *et al.* (1994) *EMBO J.*, 13: 3245; De Kruif *et al.* (1995) *J. Mol. Biol.*, 248: 97) are prepared by cloning immunoglobulin V genes, usually using PCR. Errors in the PCR process can lead to a high degree of randomisation. V_H and/or V_L libraries may be selected against target antigens or epitopes separately, in which case single domain binding is directly selected for, or together.

Library vector systems

A variety of selection systems are known in the art which are suitable for use in the present invention. Examples of such systems are described below.

Bacteriophage lambda expression systems may be screened directly as bacteriophage plaques or as colonies of lysogens, both as previously described (Huse *et al.* (1989) *Science*, 246: 1275; Caton and Koprowski (1990) *Proc. Natl. Acad. Sci. U.S.A.*, 87; Mullinax *et al.* (1990) *Proc. Natl. Acad. Sci. U.S.A.*, 87: 8095; Persson *et al.* (1991) *Proc. Natl. Acad. Sci. U.S.A.*, 88: 2432) and are of use in the invention. Whilst such expression systems can be used to screen up to 10^6 different members of a library, they are not really suited to screening of larger numbers (greater than 10^6 members). Of particular use in the construction of libraries are selection display systems, which enable a nucleic acid to be linked to the polypeptide it expresses. As used herein, a selection display system is a system that

permits the selection, by suitable display means, of the individual members of the library by binding the generic and/or target.

Selection protocols for isolating desired members of large libraries are known in the art, as typified by phage display techniques. Such systems, in which diverse peptide sequences are displayed on the surface of filamentous bacteriophage (Scott and Smith (1990) *Science*, 249: 386), have proven useful for creating libraries of antibody fragments (and the nucleotide sequences encoding them) for the *in vitro* selection and amplification of specific antibody fragments that bind a target antigen (McCafferty *et al.*, WO 92/01047). The nucleotide sequences encoding the variable regions are linked to gene fragments which encode leader signals that direct them to the periplasmic space of *E. coli* and as a result the resultant antibody fragments are displayed on the surface of the bacteriophage, typically as fusions to bacteriophage coat proteins (*e.g.*, pIII or pVIII). Alternatively, antibody fragments are displayed externally on lambda phage capsids (phagebodies). An advantage of phage-based display systems is that, because they are biological systems, selected library members can be amplified simply by growing the phage containing the selected library member in bacterial cells. Furthermore, since the nucleotide sequence that encodes the polypeptide library member is contained on a phage or phagemid vector, sequencing, expression and subsequent genetic manipulation is relatively straightforward.

Methods for the construction of bacteriophage antibody display libraries and lambda phage expression libraries are well known in the art (McCafferty *et al.* (1990) *Nature*, 348: 552; Kang *et al.* (1991) *Proc. Natl. Acad. Sci. U.S.A.*, 88: 4363; Clackson *et al.* (1991) *Nature*, 352: 624; Lowman *et al.* (1991) *Biochemistry*, 30: 10832; Burton *et al.* (1991) *Proc. Natl. Acad. Sci U.S.A.*, 88: 10134; Hoogenboom *et al.* (1991) *Nucleic Acids Res.*, 19: 4133; Chang *et al.* (1991) *J. Immunol.*, 147: 3610; Breitling *et al.* (1991) *Gene*, 104: 147; Marks *et al.* (1991) supra; Barbas *et al.* (1992) supra; Hawkins and Winter (1992) *J. Immunol.*, 22: 867; Marks *et al.*, 1992, *J. Biol. Chem.*, 267: 16007; Lerner *et al.* (1992) *Science*, 258: 1313, incorporated herein by reference).

One particularly advantageous approach has been the use of scFv phage-libraries (Huston *et al.*, 1988, *Proc. Natl. Acad. Sci U.S.A.*, 85: 5879-5883;

Chaudhary *et al.* (1990) *Proc. Natl. Acad. Sci U.S.A.*, 87: 1066-1070; McCafferty *et al.* (1990) supra; Clackson *et al.* (1991) *Nature*, 352: 624; Marks *et al.* (1991) *J. Mol. Biol.*, 222: 581; Chiswell *et al.* (1992) Trends Biotech., 10: 80; Marks *et al.* (1992) *J. Biol. Chem.*, 267). Various embodiments of scFv libraries displayed on bacteriophage coat proteins have been described. Refinements of phage display approaches are also known, for example as described in WO96/06213 and WO92/01047 (Medical Research Council *et al.*) and WO97/08320 (Morphosys), which are incorporated herein by reference.

Other systems for generating libraries of polypeptides involve the use of cell-free enzymatic machinery for the *in vitro* synthesis of the library members. In one method, RNA molecules are selected by alternate rounds of selection against a target and PCR amplification (Tuerk and Gold (1990) *Science*, 249: 505; Ellington and Szostak (1990) *Nature*, 346: 818). A similar technique may be used to identify DNA sequences which bind a predetermined human transcription factor (Thiesen and Bach (1990) *Nucleic Acids Res.*, 18: 3203; Beaudry and Joyce (1992) *Science*, 257: 635; WO92/05258 and WO92/14843). In a similar way, *in vitro* translation can be used to synthesise polypeptides as a method for generating large libraries. These methods which generally comprise stabilised polysome complexes, are described further in WO88/08453, WO90/05785, WO90/07003, WO91/02076, WO91/05058, and WO92/02536. Alternative display systems which are not phage-based, such as those disclosed in WO95/22625 and WO95/11922 (Affymax) use the polysomes to display polypeptides for selection.

A still further category of techniques involves the selection of repertoires in artificial compartments, which allow the linkage of a gene with its gene product. For example, a selection system in which nucleic acids encoding desirable gene products may be selected in microcapsules formed by water-in-oil emulsions is described in WO99/02671, WO00/40712 and Tawfik & Griffiths (1998) *Nature Biotechnol* 16(7), 652-6. Genetic elements encoding a gene product having a desired activity are compartmentalised into microcapsules and then transcribed and/or translated to produce their respective gene products (RNA or protein) within the microcapsules. Genetic elements which produce gene product having desired

activity are subsequently sorted. This approach selects gene products of interest by detecting the desired activity by a variety of means.

Library Construction

Libraries intended for selection, may be constructed using techniques known in the art, for example as set forth above, or may be purchased from commercial sources. Libraries which are useful in the present invention are described, for example, in WO99/20749. Once a vector system is chosen and one or more nucleic acid sequences encoding polypeptides of interest are cloned into the library vector, one may generate diversity within the cloned molecules by undertaking mutagenesis prior to expression; alternatively, the encoded proteins may be expressed and selected, as described above, before mutagenesis and additional rounds of selection are performed. Mutagenesis of nucleic acid sequences encoding structurally optimized polypeptides is carried out by standard molecular methods. Of particular use is the polymerase chain reaction, or PCR, (Mullis and Faloona (1987) *Methods Enzymol.*, 155: 335, herein incorporated by reference). PCR, which uses multiple cycles of DNA replication catalyzed by a thermostable, DNA-dependent DNA polymerase to amplify the target sequence of interest, is well known in the art. The construction of various antibody libraries has been discussed in Winter *et al.* (1994) *Ann. Rev. Immunology* 12, 433-55, and references cited therein.

PCR is performed using template DNA (at least 1fg; more usefully, 1-1000 ng) and at least 25 pmol of oligonucleotide primers; it may be advantageous to use a larger amount of primer when the primer pool is heavily heterogeneous, as each sequence is represented by only a small fraction of the molecules of the pool, and amounts become limiting in the later amplification cycles. A typical reaction mixture includes: 2µl of DNA, 25 pmol of oligonucleotide primer, 2.5 µl of 10X PCR buffer 1 (Perkin-Elmer, Foster City, CA), 0.4 µl of 1.25 µM dNTP, 0.15 µl (or 2.5 units) of Taq DNA polymerase (Perkin Elmer, Foster City, CA) and deionized water to a total volume of 25 µl. Mineral oil is overlaid and the PCR is performed using a programmable thermal cycler. The length and temperature of each step of a PCR cycle, as well as the number of cycles, is adjusted in accordance to the stringency requirements in effect. Annealing temperature and timing are determined

both by the efficiency with which a primer is expected to anneal to a template and the degree of mismatch that is to be tolerated; obviously, when nucleic acid molecules are simultaneously amplified and mutagenised, mismatch is required, at least in the first round of synthesis. The ability to optimise the stringency of primer annealing conditions is well within the knowledge of one of moderate skill in the art. An annealing temperature of between 30 °C and 72 °C is used. Initial denaturation of the template molecules normally occurs at between 92°C and 99°C for 4 minutes, followed by 20-40 cycles consisting of denaturation (94-99°C for 15 seconds to 1 minute), annealing (temperature determined as discussed above; 1-2 minutes), and extension (72°C for 1-5 minutes, depending on the length of the amplified product). Final extension is generally for 4 minutes at 72°C, and may be followed by an indefinite (0-24 hour) step at 4°C.

Combining Single Variable Domains

Domains useful in the invention, once selected, may be combined by a variety of methods known in the art, including covalent and non-covalent methods. Preferred methods include the use of polypeptide linkers, as described, for example, in connection with scFv molecules (Bird *et al.*, (1988) Science 242:423-426). Discussion of suitable linkers is provided in Bird *et al. Science* 242, 423-426; Hudson *et al, Journal Immunol Methods* 231 (1999) 177-189; Hudson *et al, Proc. Nat. Acad. Sci. U.S.A.* 85, 5879-5883. Linkers are preferably flexible, allowing the two single domains to interact. One linker example is a $(Gly_4\ Ser)_n$ linker, where n=1 to 8, *e.g.*, 2, 3, 4, 5 or 7. The linkers used in diabodies, which are less flexible, may also be employed (Holliger *et al.*, (1993) *Proc. Nat. Acad. Sci. U.S.A.* 90:6444-6448). In one embodiment, the linker employed is not an immunoglobulin hinge region.

Variable domains may be combined using methods other than linkers. For example, the use of disulphide bridges, provided through naturally-occurring or engineered cysteine residues, may be exploited to stabilize V_H-V_H, V_L-V_L or V_H-V_L dimers (Reiter *et al.*, (1994) *Protein Eng.* 7:697-704) or by remodelling the interface between the variable domains to improve the "fit" and thus the stability of interaction (Ridgeway *et al.*, (1996) *Protein Eng.* 7:617-621; Zhu *et al.*, (1997)

Protein Science 6:781-788). Other techniques for joining or stabilizing variable domains of immunoglobulins, and in particular antibody V_H domains, may be employed as appropriate.

Characterisation of Ligands

The binding of a dual-specific ligand to the cell or the binding of each binding domain to each specific target can be tested by methods which will be familiar to those skilled in the art and include ELISA. In a preferred embodiment of the invention, binding is tested using monoclonal phage ELISA. Phage ELISA may be performed according to any suitable procedure: an exemplary protocol is set forth below.

Populations of phage produced at each round of selection can be screened for binding by ELISA to the selected antigen or epitope, to identify "polyclonal" phage antibodies. Phage from single infected bacterial colonies from these populations can then be screened by ELISA to identify "monoclonal" phage antibodies. It is also desirable to screen soluble antibody fragments for binding to antigen or epitope, and this can also be undertaken by ELISA using reagents, for example, against a C- or N-terminal tag (see for example Winter *et al.* (1994) *Ann. Rev. Immunology* 12, 433-55 and references cited therein.

The diversity of the selected phage monoclonal antibodies may also be assessed by gel electrophoresis of PCR products (Marks *et al.* 1991, *supra*; Nissim *et al.* 1994 *supra*), probing (Tomlinson *et al.*, 1992) *J. Mol. Biol.* 227, 776) or by sequencing of the vector DNA.

Structure of Ligands

In the case that each variable domain is selected from V-gene repertoires selected for instance using phage display technology as herein described, then these variable domains comprise a universal framework region, such that is they may be recognized by a generic ligand as herein defined. The use of universal frameworks, generic ligands and the like is described in WO99/20749.

Where V-gene repertoires are used, variation in polypeptide sequence is preferably located within the structural loops of the variable domains. The

polypeptide sequences of either variable domain may be altered by DNA shuffling or by mutation in order to enhance the interaction of each variable domain with its complementary pair. DNA shuffling is known in the art and taught, for example, by Stemmer, 1994, *Nature 370*: 389-391 and U.S. Patent No. 6,297,053, both of which are incorporated herein by reference. Other methods of mutagenesis are well known to those of skill in the art.

In general, nucleic acid molecules and vector constructs required for selection, preparation and formatting dual-specific ligands may be constructed and manipulated as set forth in standard laboratory manuals, such as Sambrook *et al.* (1989) *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor, USA.

The manipulation of nucleic acids useful in the present invention is typically carried out in recombinant vectors. As used herein, vector refers to a discrete element that is used to introduce heterologous DNA into cells for the expression and/or replication thereof. Methods by which to select or construct and, subsequently, use such vectors are well known to one of ordinary skill in the art. Numerous vectors are publicly available, including bacterial plasmids, bacteriophage, artificial chromosomes and episomal vectors. Such vectors may be used for simple cloning and mutagenesis; alternatively a gene expression vector is employed. A vector of use according to the invention may be selected to accommodate a polypeptide coding sequence of a desired size, typically from 0.25 kilobase (kb) to 40 kb or more in length. A suitable host cell is transformed with the vector after *in vitro* cloning manipulations. Each vector contains various functional components, which generally include a cloning (or "polylinker") site, an origin of replication and at least one selectable marker gene. If the given vector is an expression vector, it additionally possesses one or more of the following: an enhancer element, a promoter, transcription, termination and signal sequences, each positioned in the vicinity of the cloning site, such that they are operatively linked to the gene encoding a dual-specific ligand according to the invention.

Both cloning and expression vectors generally contain nucleic acid sequences that enable the vector to replicate in one or more selected host cells. Typically in cloning vectors, this sequence is one that enables the vector to replicate independently of the host chromosomal DNA and includes origins of replication or

autonomously replicating sequences. Such sequences are well known for a variety of bacteria, yeast and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 micron plasmid origin is suitable for yeast, and various viral origins (*e.g.* SV 40, adenovirus) are useful for cloning vectors in mammalian cells. Generally, the origin of replication is not needed for mammalian expression vectors unless these are used in mammalian cells able to replicate high levels of DNA, such as COS cells.

Advantageously, a cloning or expression vector may contain a selection gene also referred to as selectable marker. This gene encodes a protein necessary for the survival or growth of transformed host cells grown in a selective culture medium. Host cells not transformed with the vector containing the selection gene will therefore not survive in the culture medium. Typical selection genes encode proteins that confer resistance to antibiotics and other toxins, (*e.g.* ampicillin, neomycin, methotrexate or tetracycline), complement auxotrophic deficiencies, or supply critical nutrients not available in the growth media.

Since the replication of vectors encoding a dual-specific ligand according to the present invention is most conveniently performed in *E. coli*, an *E. coli*-selectable marker, for example, the β-lactamase gene that confers resistance to the antibiotic ampicillin, is of use. These can be obtained from *E. coli* plasmids, such as pBR322 or a pUC plasmid such as pUC18 or pUC19.

Expression vectors usually contain a promoter that is recognised by the host organism and is operably linked to the coding sequence of interest. Such a promoter may be inducible or constitutive. The term "operably linked" refers to a juxtaposition wherein the components described are in a relationship permitting them to function in their intended manner. A control sequence "operably linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences.

Promoters suitable for use with prokaryotic hosts include, for example, the β-lactamase and lactose promoter systems, alkaline phosphatase, the tryptophan (trp) promoter system and hybrid promoters such as the tac promoter. Promoters for use in bacterial systems will also generally contain a Shine-Delgarno sequence operably linked to the coding sequence.

The preferred vectors are expression vectors that enable the expression of a nucleotide sequence corresponding to a polypeptide library member. Thus, selection with the first and/or second antigen or epitope can be performed by separate propagation and expression of a single clone expressing the polypeptide library member or by use of any selection display system. As described above, the preferred selection display system is bacteriophage display. Thus, phage or phagemid vectors may be used, (*e.g.*, pIT1 or pIT2). Leader sequences useful in the invention include pelB, stII, ompA, phoA, bla and pelA. One example is phagemid vectors, which have an *E. coli.* origin of replication (for double stranded replication) and also a phage origin of replication (for production of single-stranded DNA). The manipulation and expression of such vectors is well known in the art (Hoogenboom and Winter (1992) supra; Nissim *et al.* (1994) supra). Briefly, the vector contains a β-lactamase gene to confer selectivity on the phagemid and a lac promoter upstream of an expression cassette that consists (N to C terminal) of a pelB leader sequence (which directs the expressed polypeptide to the periplasmic space), a multiple cloning site (for cloning the nucleotide version of the library member), optionally, one or more peptide tags (for detection), optionally, one or more TAG stop codon and the phage protein pIII. Thus, using various suppressor and non-suppressor strains of *E. coli* and with the addition of glucose, iso-propyl thio-β-D-galactoside (IPTG) or a helper phage, such as VCS M13, the vector is able to replicate as a plasmid with no expression, produce large quantities of the polypeptide library member only or produce phage, some of which contain at least one copy of the polypeptide-pIII fusion on their surface.

Construction of vectors encoding dual-specific ligands according to the invention employs conventional ligation techniques. Isolated vectors or DNA fragments are cleaved, tailored, and religated in the form desired to generate the required vector. If desired, analysis to confirm that the correct sequences are present in the constructed vector can be performed in a known fashion. Suitable methods for constructing expression vectors, preparing *in vitro* transcripts, introducing DNA into host cells, and performing analyses for assessing expression and function are known to those skilled in the art. The presence of a gene sequence in a sample is detected, or its amplification and/or expression quantified by conventional methods,

such as Southern or Northern analysis, Western blotting, dot blotting of DNA, RNA or protein, *in situ* hybridisation, immunocytochemistry or sequence analysis of nucleic acid or protein molecules. Those skilled in the art will readily envisage how these methods may be modified, if desired.

Skeletons

Skeletons may be based on immunoglobulin molecules or may be non-immunoglobulin in origin as set forth above. Each domain of a ligand (e.g, dual-specific ligand) may be a different skeleton. Preferred immunoglobulin skeletons as herein defined includes any one or more of those selected from the following: an immunoglobulin molecule comprising at least (i) the CL (kappa or lambda subclass) domain of an antibody; or (ii) the CH1 domain of an antibody heavy chain; an immunoglobulin molecule comprising the CH1 and CH2 domains of an antibody heavy chain; an immunoglobulin molecule comprising the CH1, CH2 and CH3 domains of an antibody heavy chain; or any of the subset (ii) in conjunction with the CL (kappa or lambda subclass) domain of an antibody. A hinge region domain may also be included. For example, the ligand can comprise a heavy chain constant region of an immunoglobulin (*e.g.*, IgG (*e.g.*, IgG1, IgG2, IgG3, IgG4) IgM, IgA, IgD or IgE) or portion thereof (*e.g.*, Fc portion) and/or a light chain constant region (*e.g.*, C_λ, C_κ). For example, the ligand can comprise CH1 of IgG1 (*e.g.*, human IgG1), CH1 and CH2 of IgG1 (*e.g.*, human IgG1), CH1, CH2 and CH3 of IgG1 (*e.g.*, human IgG1), CH2 and CH3 of IgG1 (*e.g.*, human IgG1), or CH1 and CH3 of IgG1 (*e.g.*, human IgG1). Such combinations of domains may, for example, mimic natural antibodies, such as IgG or IgM, or fragments thereof, such as Fv, scFv, Fab or $F(ab')_2$ molecules. Those skilled in the art will be aware that this list is not intended to be exhaustive.

Protein Scaffolds

Each binding domain can comprise a protein scaffold and one or more CDRs (*e.g.*, of the dAbs disclosed herein) which are involved in the specific interaction of the domain with one or more epitopes. Advantageously, an epitope binding domain according to the present invention comprises three CDRs. Suitable protein scaffolds

include any of those selected from the group consisting of the following: those based on immunoglobulin domains, those based on fibronectin, those based on affibodies, those based on CTLA4, those based on chaperones such as GroEL, those based on lipocallin and those based on the bacterial Fc receptors SpA and SpD. Those skilled in the art will appreciate that this list is not intended to be exhaustive. The binding domains can also comprise a protein scaffold that has a binding site that has binding specificity for a target (*e.g.*, IL-4, IL-13), but does not contain one or more CDRs (*e.g.*, of the dAbs disclosed herein). For example, the binding domain can be a protein scaffold that has a binding site that has binding specificity for a target selected from an affibody, an SpA domain, based on CTLA4, those based on chaperones such as GroEL, those based on lipocallin and those based on the bacterial Fc receptors SpA and SpD, an LDL receptor class A domain, an avimer (see, *e.g.*, U.S. Patent Application Publication Nos. 2005/0053973, 2005/0089932, 2005/0164301).

Scaffolds for Use in Constructing Ligands

Selection of the Main-chain Conformation

The members of the immunoglobulin superfamily all share a similar fold for their polypeptide chain. For example, although antibodies are highly diverse in terms of their primary sequence, comparison of sequences and crystallographic structures has revealed that, contrary to expectation, five of the six antigen binding loops of antibodies (H1, H2, L1, L2, L3) adopt a limited number of main-chain conformations, or canonical structures (Chothia and Lesk (1987) *J. Mol. Biol.*, 196: 901; Chothia *et al.* (1989) *Nature*, 342: 877). Analysis of loop lengths and key residues has therefore enabled prediction of the main-chain conformations of H1, H2, L1, L2 and L3 found in the majority of human antibodies (Chothia *et al.* (1992) *J. Mol. Biol.*, 227: 799; Tomlinson *et al.* (1995) *EMBO J.*, 14: 4628; Williams *et al.* (1996) *J. Mol. Biol.*, 264: 220). Although the H3 region is much more diverse in terms of sequence, length and structure (due to the use of D segments), it also forms a limited number of main-chain conformations for short loop lengths which depend on the length and the presence of particular residues, or types of residue, at key

positions in the loop and the antibody framework (Martin *et al.* (1996) *J. Mol. Biol.*, 263: 800; Shirai *et al.* (1996) *FEBS Letters*, 399: 1).

Libraries of ligands and/or binding domains can be designed in which certain loop lengths and key residues were chosen to ensure that the main-chain conformation of the members is known. Advantageously, these are real conformations of immunoglobulin superfamily molecules found in nature, to minimize the chances that they are non-functional, as discussed above. Germline V gene segments serve as one suitable basic framework for constructing antibody or T-cell receptor libraries; other sequences are also of use. Variations may occur at a low frequency, such that a small number of functional members may possess an altered main-chain conformation, which does not affect its function.

Canonical structure theory is also of use to assess the number of different main-chain conformations encoded by ligands, to predict the main-chain conformation based on dual-specific ligand sequences and to choose residues for diversification which do not affect the canonical structure. It is known that, in the human V_κ domain, the L1 loop can adopt one of four canonical structures, the L2 loop has a single canonical structure and that 90% of human V_κ domains adopt one of four or five canonical structures for the L3 loop (Tomlinson *et al.* (1995) supra); thus, in the V_κ domain alone, different canonical structures can combine to create a range of different main-chain conformations. Given that the V_λ domain encodes a different range of canonical structures for the L1, L2 and L3 loops and that V_κ and V_λ domains can pair with any V_H domain which can encode several canonical structures for the H1 and H2 loops, the number of canonical structure combinations observed for these five loops is very large. This implies that the generation of diversity in the main-chain conformation may be essential for the production of a wide range of binding specificities. However, by constructing an antibody library based on a single known main-chain conformation it has been found, contrary to expectation, that diversity in the main-chain conformation is not required to generate sufficient diversity to target substantially all antigens. Even more surprisingly, the single main-chain conformation need not be a consensus structure - a single naturally occurring conformation can be used as the basis for an entire library.

Thus, in a preferred aspect, the ligands of the invention possess a single known main-chain conformation.

The single main-chain conformation that is chosen is preferably commonplace among molecules of the immunoglobulin superfamily type in question. A conformation is commonplace when a significant number of naturally occurring molecules are observed to adopt it. Accordingly, in a preferred aspect of the invention, the natural occurrence of the different main-chain conformations for each binding loop of an immunoglobulin domain are considered separately and then a naturally occurring variable domain is chosen which possesses the desired combination of main-chain conformations for the different loops. If none is available, the nearest equivalent may be chosen. It is preferable that the desired combination of main-chain conformations for the different loops is created by selecting germline gene segments which encode the desired main-chain conformations. It is more preferable that the selected germline gene segments are frequently expressed in nature, and most preferable that they are the most frequently expressed of all natural germline gene segments.

In designing ligands (*e.g.*, ds-dAbs), or libraries thereof, the incidence of the different main-chain conformations for each of the six antigen binding loops may be considered separately. For H1, H2, L1, L2 and L3, a given conformation that is adopted by between 20% and 100% of the antigen binding loops of naturally occurring molecules is chosen. Typically, its observed incidence is above 35% (*i.e.* between 35% and 100%) and, ideally, above 50% or even above 65%. Since the vast majority of H3 loops do not have canonical structures, it is preferable to select a main-chain conformation which is commonplace among those loops which do display canonical structures. For each of the loops, the conformation which is observed most often in the natural repertoire is therefore selected. In human antibodies, the most popular canonical structures (CS) for each loop are as follows: H1 - CS 1 (79% of the expressed repertoire), H2 - CS 3 (46%), L1 - CS 2 of V_κ (39%), L2 - CS 1 (100%), L3 - CS 1 of V_κ (36%) (calculation assumes a κ:λ ratio of 70:30, Hood *et al.* (1967) *Cold Spring Harbor Symp. Quant. Biol.*, 48: 133). For H3 loops that have canonical structures, a CDR3 length (Kabat *et al.* (1991) *Sequences of proteins of immunological interest*, U.S. Department of Health and

Human Services) of seven residues with a salt-bridge from residue 94 to residue 101 appears to be the most common. There are at least 16 human antibody sequences in the EMBL data library with the required H3 length and key residues to form this conformation and at least two crystallographic structures in the protein data bank which can be used as a basis for antibody modelling (2cgr and 1tet). The most frequently expressed germline gene segments with this combination of canonical structures are the V_H segment 3-23 (DP-47), the J_H segment JH4b, the V_κ segment O2/O12 (DPK9) and the J_κ segment $J_\kappa 1$. V_H segments DP45 and DP38 are also suitable. These segments can therefore be used in combination as a basis to construct a library with the desired single main-chain conformation.

Alternatively, instead of choosing the single main-chain conformation based on the natural occurrence of the different main-chain conformations for each of the binding loops in isolation, the natural occurrence of combinations of main-chain conformations is used as the basis for choosing the single main-chain conformation. In the case of antibodies, for example, the natural occurrence of canonical structure combinations for any two, three, four, five or for all six of the antigen binding loops can be determined. Here, it is preferable that the chosen conformation is commonplace in naturally occurring antibodies and most preferable that it observed most frequently in the natural repertoire. Thus, in human antibodies, for example, when natural combinations of the five antigen binding loops, H1, H2, L1, L2 and L3, are considered, the most frequent combination of canonical structures is determined and then combined with the most popular conformation for the H3 loop, as a basis for choosing the single main-chain conformation.

Diversification of the Canonical Sequence

Having selected several known main-chain conformations or, preferably a single known main-chain conformation, dual-specific ligands (*e.g.*, ds-dAbs) or libraries for use in the invention can be constructed by varying each binding site of the molecule in order to generate a repertoire with structural and/or functional diversity. This means that variants are generated such that they possess sufficient diversity in their structure and/or in their function so that they are capable of providing a range of activities.

The desired diversity is typically generated by varying the selected molecule at one or more positions. The positions to be changed can be chosen at random or are preferably selected. The variation can then be achieved either by randomisation, during which the resident amino acid is replaced by any amino acid or analogue thereof, natural or synthetic, producing a very large number of variants or by replacing the resident amino acid with one or more of a defined subset of amino acids, producing a more limited number of variants.

Various methods have been reported for introducing such diversity. Error-prone PCR (Hawkins *et al.* (1992) *J. Mol. Biol.*, 226: 889), chemical mutagenesis (Deng *et al.* (1994) *J. Biol. Chem.*, 269: 9533) or bacterial mutator strains (Low *et al.* (1996) *J. Mol. Biol.*, 260: 359) can be used to introduce random mutations into the genes that encode the molecule. Methods for mutating selected positions are also well known in the art and include the use of mismatched oligonucleotides or degenerate oligonucleotides, with or without the use of PCR. For example, several synthetic antibody libraries have been created by targeting mutations to the antigen binding loops. The H3 region of a human tetanus toxoid-binding Fab has been randomised to create a range of new binding specificities (Barbas *et al.* (1992) *Proc. Natl. Acad. Sci. USA*, 89: 4457). Random or semi-random H3 and L3 regions have been appended to germline V gene segments to produce large libraries with unmutated framework regions (Hoogenboom & Winter (1992) *J. Mol. Biol.*, 227: 381; Barbas *et al.* (1992) *Proc. Natl. Acad. Sci. USA*, 89: 4457; Nissim *et al.* (1994) *EMBO J.*, 13: 692; Griffiths *et al.* (1994) *EMBO J.*, 13: 3245; De Kruif *et al.* (1995) *J. Mol. Biol.*, 248: 97). Such diversification has been extended to include some or all of the other antigen binding loops (Crameri *et al.* (1996) *Nature Med.*, 2: 100; Riechmann *et al.* (1995) *Bio/Technology*, 13: 475; Morphosys, WO97/08320, supra).

Since loop randomization has the potential to create approximately more than 10^{15} structures for H3 alone and a similarly large number of variants for the other five loops, it is not feasible using current transformation technology or even by using cell free systems to produce a library representing all possible combinations. For example, in one of the largest libraries constructed to date, 6×10^{10} different

antibodies, which is only a fraction of the potential diversity for a library of this design, were generated (Griffiths *et al.* (1994) supra).

Preferably, only the residues that are directly involved in creating or modifying the desired function of each domain of the dual-specific ligand molecule are diversified. For many molecules, the function of each domain will be to bind a target and therefore diversity should be concentrated in the target binding site, while avoiding changing residues which are crucial to the overall packing of the molecule or to maintaining the chosen main-chain conformation.

Diversification of the Canonical Sequence as it Applies to Antibody Domains

In the case of antibody based ligands (*e.g.*, ds-dAbs), the binding site for each target is most often the antigen binding site. Thus, preferably only those residues in the antigen binding site are varied. These residues are extremely diverse in the human antibody repertoire and are known to make contacts in high-resolution antibody/antigen complexes. For example, in L2 it is known that positions 50 and 53 are diverse in naturally occurring antibodies and are observed to make contact with the antigen. In contrast, the conventional approach would have been to diversify all the residues in the corresponding Complementarity Determining Region (CDR1) as defined by Kabat *et al.* (1991, supra), some seven residues compared to the two diversified in the library for use according to the invention. This represents a significant improvement in terms of the functional diversity required to create a range of antigen binding specificities.

In nature, antibody diversity is the result of two processes: somatic recombination of germline V, D and J gene segments to create a naive primary repertoire (so called germline and junctional diversity) and somatic hypermutation of the resulting rearranged V genes. Analysis of human antibody sequences has shown that diversity in the primary repertoire is focused at the centre of the antigen binding site whereas somatic hypermutation spreads diversity to regions at the periphery of the antigen binding site that are highly conserved in the primary repertoire (see Tomlinson *et al.* (1996) *J. Mol. Biol.*, 256: 813). This complementarity has probably evolved as an efficient strategy for searching sequence space and, although apparently unique to antibodies, it can easily be

applied to other polypeptide repertoires. The residues which are varied are a subset of those that form the binding site for the target. Different (including overlapping) subsets of residues in the target binding site are diversified at different stages during selection, if desired.

In the case of an antibody repertoire, an initial 'naive' repertoire can be created where some, but not all, of the residues in the antigen binding site are diversified. As used herein in this context, the term "naive" refers to antibody molecules that have no pre-determined target. These molecules resemble those which are encoded by the immunoglobulin genes of an individual who has not undergone immune diversification, as is the case with fetal and newborn individuals, whose immune systems have not yet been challenged by a wide variety of antigenic stimuli. This repertoire is then selected against a range of antigens or epitopes. If required, further diversity can then be introduced outside the region diversified in the initial repertoire. This matured repertoire can be selected for modified function, specificity or affinity.

Naive repertoires of binding domains for the construction of dual-specific ligands in which some or all of the residues in the antigen binding site are varied are known in the art. (See, WO 2004/058821, WO 2004/003019, and WO 03/002609). The "primary" library mimics the natural primary repertoire, with diversity restricted to residues at the center of the antigen binding site that are diverse in the germline V gene segments (germline diversity) or diversified during the recombination process (junctional diversity). Those residues which are diversified include, but are not limited to, H50, H52, H52a, H53, H55, H56, H58, H95, H96, H97, H98, L50, L53, L91, L92, L93, L94 and L96. In the "somatic" library, diversity is restricted to residues that are diversified during the recombination process (junctional diversity) or are highly somatically mutated. Those residues which are diversified include, but are not limited to: H31, H33, H35, H95, H96, H97, H98, L30, L31, L32, L34 and L96. All the residues listed above as suitable for diversification in these libraries are known to make contacts in one or more antibody-antigen complexes. Since in both libraries, not all of the residues in the antigen binding site are varied, additional diversity is incorporated during selection by varying the remaining residues, if it is desired to do so. It shall be apparent to one skilled in the art that any subset of any

of these residues (or additional residues which comprise the antigen binding site) can be used for the initial and/or subsequent diversification of the antigen binding site.

In the construction of libraries for use in the invention, diversification of chosen positions is typically achieved at the nucleic acid level, by altering the coding sequence which specifies the sequence of the polypeptide such that a number of possible amino acids (all 20 or a subset thereof) can be incorporated at that position. Using the IUPAC nomenclature, the most versatile codon is NNK, which encodes all amino acids as well as the TAG stop codon. The NNK codon is preferably used in order to introduce the required diversity. Other codons which achieve the same ends are also of use, including the NNN codon, which leads to the production of the additional stop codons TGA and TAA.

A feature of side-chain diversity in the antigen binding site of human antibodies is a pronounced bias which favors certain amino acid residues. If the amino acid composition of the ten most diverse positions in each of the V_H, V_κ and V_λ regions are summed, more than 76% of the side-chain diversity comes from only seven different residues, these being, serine (24%), tyrosine (14%), asparagine (11%), glycine (9%), alanine (7%), aspartate (6%) and threonine (6%). This bias towards hydrophilic residues and small residues which can provide main-chain flexibility probably reflects the evolution of surfaces which are predisposed to binding a wide range of antigens or epitopes and may help to explain the required promiscuity of antibodies in the primary repertoire.

Since it is preferable to mimic this distribution of amino acids, the distribution of amino acids at the positions to be varied preferably mimics that seen in the antigen binding site of antibodies. Such bias in the substitution of amino acids that permits selection of certain polypeptides (not just antibody polypeptides) against a range of target antigens is easily applied to any polypeptide repertoire. There are various methods for biasing the amino acid distribution at the position to be varied (including the use of tri-nucleotide mutagenesis, see WO97/08320), of which the preferred method, due to ease of synthesis, is the use of conventional degenerate codons. By comparing the amino acid profile encoded by all combinations of degenerate codons (with single, double, triple and quadruple

degeneracy in equal ratios at each position) with the natural amino acid used it is possible to calculate the most representative codon. The codons (AGT)(AGC)T, (AGT)(AGC)C and (AGT)(AGC)(CT) - that is, DVT, DVC and DVY, respectively using IUPAC nomenclature - are those closest to the desired amino acid profile: they encode 22% serine and 11% tyrosine, asparagine, glycine, alanine, aspartate, threonine and cysteine. Preferably, therefore, libraries are constructed using either the DVT, DVC or DVY codon at each of the diversified positions.

Therapeutic and diagnostic compositions and uses

The invention provides compositions comprising the ligands of the invention and a pharmaceutically acceptable carrier, diluent or excipient, and therapeutic and diagnostic methods that employ the ligands or compositions of the invention. The ligands according to the method of the present invention may be employed in *in vivo* therapeutic and prophylactic applications, *in vivo* diagnostic applications and the like.

Therapeutic and prophylactic uses of ligands of the invention involve the administration of ligands according to the invention to a recipient mammal, such as a human. The ligands bind to targets with high affinity and/or avidity. In some embodiments, such as IgG-like ligands, the ligands can allow recruitment of cytotoxic cells to mediate killing of cancer cells, for example by antibody dependent cellular cytoxicity.

Substantially pure ligands of at least 90 to 95% homogeneity are preferred for administration to a mammal, and 98 to 99% or more homogeneity is most preferred for pharmaceutical uses, especially when the mammal is a human. Once purified, partially or to homogeneity as desired, the ligands may be used diagnostically or therapeutically (including extracorporeally) or in developing and performing assay procedures, immunofluorescent stainings and the like (Lefkovite and Pernis, (1979 and 1981) Immunological Methods, Volumes I and II, Academic Press, NY).

In the instant application, the term "prevention" involves administration of the protective composition prior to the induction of the disease. "Suppression" refers to administration of the composition after an inductive event, but prior to the clinical appearance of the disease. "Treatment" involves administration of the protective

composition after disease symptoms become manifest. Treatment includes ameliorating symptoms associated with the disease, and also preventing or delaying the onset of the disease and also lessening the severity or frequency of symptoms of the disease.

For example, the ligands, of the present invention will typically find use in preventing, suppressing or treating disease states. For example, ligands can be administered to treat, suppress or prevent a chronic inflammatory disease, allergic hypersensitivity, cancer, bacterial or viral infection, autoimmune disorders (which include, but are not limited to, Type I diabetes, asthma, multiple sclerosis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, spondylarthropathy (*e.g.*, ankylosing spondylitis), systemic lupus erythematosus, inflammatory bowel disease (*e.g.*, Crohn's disease, ulcerative colitis), myasthenia gravis and Behcet's syndrome, psoriasis, endometriosis, and abdominal adhesions (*e.g.*, post abdominal surgery).

The ligands of the invention may be used to treat, suppress or prevent disease, such as an allergic disease, a Th2-mediated disease, IL-13-mediated disease, IL-4-mediated disease, and/or IL-4/IL-13-mediated disease. Examples of such diseases include, Hodgkin's disease, asthma, allergic asthma, atopic dermatitis, atopic allergy, ulcerative colitis, scleroderma, allergic rhinitis, COPD, idiopathic pulmonary fibrosis, chronic graft rejection, bleomycin-induced pulmonary fibrosis, radiation-induced pulmonary fibrosis, pulmonary granuloma, progressive systemic sclerosis, schistosomiasis, hepatic fibrosis, renal cancer, Burkitt lymphoma, Hodgkins disease, non-Hodgkins disease, Sezary syndrome, asthma, septic arthritis, dermatitis herpetiformis, chronic idiopathic urticaria, ulcerative colitis, scleroderma, hypertrophic scarring, Whipple's Disease, benign prostate hyperplasia, a lung disorder in which IL-4 receptor plays a role, condition in which IL-4 receptor-mediated epithelial barrier disruption plays a role, a disorder of the digestive system in which IL-4 receptor plays a role, an allergic reaction to a medication, Kawasaki disease, sickle cell disease, Churg-Strauss syndrome, Grave's disease, pre-eclampsia, Sjogren's syndrome, autoimmune lymphoproliferative syndrome, autoimmune hemolytic anemia, Barrett's esophagus, autoimmune uveitis, tuberculosis, cystic fibrosis, allergic bronchopulmonary mycosis, chronic obstructive pulmonary

disease, bleomycin-induced pneumopathy and fibrosis, pulmonary alveolar proteinosis, adult respiratory distress syndrome, sarcoidosis, hyper IgE syndrome, idiopathic hypereosinophil syndrome, an autoimmune blistering disease, pemphigus vulgaris, bullous pemphigoid, myasthenia gravis, chronic fatigue syndrome, nephrosis).

The term "allergic disease" refers to a pathological condition in which a patient is hypersensitized to and mounts an immunologic reaction against a substance that is normally nonimmunogenic. Allergic disease is generally characterized by activation of mast cells by IgE resulting in an inflammatory response (*e.g.*, local response, systemic response) that can result in symptoms as benign as a runny nose, to life-threatening anaphylactic shock and death. Examples of allergic disease include, but are not limited to, allergic rhinitis (*e.g.*, hay fever), asthma (*e.g.*, allergic asthma), allergic dermatitis (*e.g.*, eczema), contact dermatitis, food allergy and urticaria (hives).

As used herein "Th2-mediated disease" refers to a disease in which pathology is produced (in whole or in part) by an immune response (Th2-type immune response) that is regulated by $CD4^+$ Th2 T lymphocytes, which characteristically produce IL-4, IL-5, IL-10 and IL-13. A Th2-type immune response is associated with the production of certain cytokines (*e.g.*, IL-4, IL-13) and of certain classes of antibodies (*e.g.*, IgE), and is associate with humor immunity. Th2-meidated diseases are characterized by the presence of elevated levels of Th2 cytokines (*e.g.*, IL-4, IL-13) and/or certain classes of antibodies (*e.g.*, IgE) and include, for example, allergic disease (*e.g.*, allergic rhinitis, atopic dermatitis, asthma (*e.g.*, atopic asthma), allergic airways disease (AAD), anaphylactic shock, conjunctivitis), autoimmune disorders associated with elevated levels of IL-4 and/or IL-13 (*e.g.*, rheumatoid arthritis, host-versus-graft disease, renal disease (*e.g.*, nephritic syndrome, lupus nephritis)), and infections associated with elevated levels of IL-4 and/or IL-13 (*e.g.*, viral, parasitic, fungal (*e.g.*, *C. albicans*) infection).

Certain cancers are associated with elevated levels of IL-4 and/or IL-13 or associated with IL-4-induced and/or IL-13-induced cancer cell proliferation (*e.g.*, B cell lymphoma, T cell lymphoma, multiple myeloma, head and neck cancer, breast

cancer and ovarian cancer). These cancers can be treated, suppressed or prevented using the ligand of the invention.

Generally, the present ligands will be utilized in purified form together with pharmacologically appropriate carriers. Typically, these carriers include aqueous or alcoholic/aqueous solutions, emulsions or suspensions, and include saline and/or buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride and lactated Ringer's. Suitable physiologically-acceptable adjuvants, if necessary to keep a polypeptide complex in suspension, may be chosen from thickeners such as carboxymethylcellulose, polyvinylpyrrolidone, gelatin and alginates.

Intravenous vehicles include fluid and nutrient replenishers and electrolyte replenishers, such as those based on Ringer's dextrose. Preservatives and other additives, such as antimicrobials, antioxidants, chelating agents and inert gases, may also be present (Mack (1982) *Remington's Pharmaceutical Sciences*, 16th Edition). A variety of suitable formulations can be used, including extended release formulations.

The ligand of the present invention may be used as separately administered compositions or in conjunction with other agents. The ligands can be used in combination therapy with existing IL-13 therapeutics (*e.g.*, existing IL-13 agents (for example, anti-IL-13Rα1, IL-4/13 Trap, anti-IL-13) plus IL-4 dAb, and existing IL-4 agents (for example, anti-IL-4R, IL-4 Mutein, IL-4/13 Trap) plus IL-13 dAb) and IL-13 and IL-4 antibodies (for example, WO05/0076990 (CAT), WO03/092610 (Regeneron), WO00/64944 (Genetic Inst.) and WO2005/062967 (Tanox)). The ligands can be administered and or formulated together with one or more additional therapeutic or active agents. When a ligand is administered with an additional therapeutic agent, the ligand can be administered before, simultaneously with or subsequent to administration of the additional agent. Generally, the ligand and additional agent are administered in a manner that provides an overlap of therapeutic effect. Additional agents that can be administered or formulated with the ligand of the invention include, for example, various immunotherapeutic drugs, such as cylcosporine, methotrexate, adriamycin or cisplatinum, antibiotics, antimycotics, anti-viral agents and immunotoxins. For example, when the antagonist is

administered to prevent, suppress or treat lung inflammation or a respiratory disease (*e.g.*, asthma), it can be administered in conjuction with phosphodiesterase inhibitors (*e.g.*, inhibitors of phosphodiesterase 4), bronchodilators (*e.g.*, beta2-agonists, anticholinergerics, theophylline), short-acting beta-agonists (*e.g.*, albuterol, salbutamol, bambuterol, fenoterol, isoetherine, isoproterenol, levalbuterol, metaproterenol, pirbuterol, terbutaline and tornlate), long-acting beta-agonists (*e.g.*, formoterol and salmeterol), short acting anticholinergics (*e.g.*, ipratropium bromide and oxitropium bromide), long-acting anticholinergics (*e.g.*, tiotropium), theophylline (*e.g.* short acting formulation, long acting formulation), inhaled steroids (*e.g.*, beclomethasone, beclometasone, budesonide, flunisolide, fluticasone propionate and triamcinolone), oral steroids (*e.g.*, methylprednisolone, prednisolone, prednisolon and prednisone), combined short-acting beta-agonists with anticholinergics (*e.g.*, albuterol/salbutamol/ipratopium, and fenoterol/ipratopium), combined long-acting beta-agonists with inhaled steroids (*e.g.*, salmeterol/fluticasone, and formoterol/budesonide) and mucolytic agents (*e.g.*, erdosteine, acetylcysteine, bromheksin, carbocysteine, guiafenesin and iodinated glycerol.

Other suitable co-therapeutic agents that can be administed with a ligand of the invention to prevent, suppress or treat asthma (*e.g.*, allergic asthma), include a corticosteroid (*e.g.*, beclomethasone, budesonide, fluticasone), cromoglycate, nedocromil, beta-agonist (*e.g.*, salbutamol, terbutaline, bambuterol, fenoterol, reproterol, tolubuterol, salmeterol, fomtero), zafirlukast, salmeterol, prednisone, prednisolone, theophylline, zileutron, montelukast, and leukotriene modifiers.

The ligands of the invention can be coadministered with a variety of co-therapeutic agents suitable for treating diseases (*e.g.*, a Th-2 mediated disease, IL-4-mediated disease, IL-13-mediated disease, IL-4 and IL-13-mediated disease, cancer), including cytokines, analgesics/antipyretics, antiemetics, and chemotherapeutics.

Cytokines include, without limitation, a lymphokine, tumor necrosis factors, tumor necrosis factor-like cytokine, lymphotoxin, interferon, macrophage inflammatory protein, granulocyte monocyte colony stimulating factor, interleukin (including, without limitation, interleukin-1, interleukin-2, interleukin-6, interleukin-

12, interleukin-15, interleukin-18), growth factors, which include, without limitation, (*e.g.*, growth hormone, insulin-like growth factor 1 and 2 (IGF-1 and IGF-2), granulocyte colony stimulating factor (GCSF), platelet derived growth factor (PGDF), epidermal growth factor (EGF), and agents for erythropoiesis stimulation, *e.g.*, recombinant human erythropoietin (Epoetin alfa), EPO, a hormonal agonist, hormonal antagonists (*e.g.*, flutamide, tamoxifen, leuprolide acetate (LUPRON)), and steroids (*e.g.*, dexamethasone, retinoid, betamethasone, cortisol, cortisone, prednisone, dehydrotestosterone, glucocorticoid, mineralocorticoid, estrogen, testosterone, progestin).

Analgesics/antipyretics can include, without limitation, (*e.g.*, aspirin, acetaminophen, ibuprofen, naproxen sodium, buprenorphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate, meperidine hydrochloride, hydromorphone hydrochloride, morphine sulfate, oxycodone hydrochloride, codeine phosphate, dihydrocodeine bitartrate, pentazocine hydrochloride, hydrocodone bitartrate, levorphanol tartrate, diflunisal, trolamine salicylate, nalbuphine hydrochloride, mefenamic acid, butorphanol tartrate, choline salicylate, butalbital, phenyltoloxamine citrate, diphenhydramine citrate, methotrimeprazine, cinnamedrine hydrochloride, meprobamate, and the like).

Antiemetics can also be coadministered to prevent or treat nausea and vomiting, e,g., suitable antiemetics include meclizine hydrochloride, nabilone, prochlorperazine, dimenhydrinate, promethazine hydrochloride, thiethylperazine, scopolamine, and the like).

Chemotherapeutic agents, as that term is used herein, include, but are not limited to, for example antimicrotubule agents, (*e.g.*, taxol (paclitaxel)), taxotere (docetaxel); alkylating agents (*e.g.*, cyclophosphamide, carmustine, lomustine, and chlorambucil); cytotoxic antibiotics (*e.g.*, dactinomycin, doxorubicin, mitomycin-C, and bleomycin; antimetabolites (*e.g.*, cytarabine, gemcitatin, methotrexate, and 5-fluorouracil); antimiotics (*e.g.*, vincristine vinca alkaloids (*e.g.*, etoposide, vinblastine, and vincristine)); and others such as cisplatin, dacarbazine, procarbazine, and hydroxyurea; and combinations thereof.

Pharmaceutical compositions can include "cocktails" of various cytotoxic or other agents in conjunction with ligands of the present invention, or even

combinations of ligands according to the present invention having different specificities, such as ligands selected using different target antigens or epitopes, whether or not they are pooled prior to administration.

The route of administration of pharmaceutical compositions according to the invention may be any suitable route, such as any of those commonly known to those of ordinary skill in the art. For therapy, including without limitation immunotherapy, the ligands of the invention can be administered to any patient in accordance with standard techniques. The administration can be by any appropriate mode, including parenterally, intravenously, intramuscularly, intraperitoneally, transdermally, intrathecally, intraarticularly, *via* the pulmonary route, or also, appropriately, by direct infusion (*e.g.*, with a catheter). The dosage and frequency of administration will depend on the age, sex and condition of the patient, concurrent administration of other drugs, counterindications and other parameters to be taken into account by the clinician. Administration can be local (*e.g.*, local delivery to the lung by pulmonary administration,(*e.g.*, intranasal administration) or local injection directly into a tumor) or systemic as indicated.

The ligands of this invention can be lyophilised for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional immunoglobulins and art-known lyophilisation and reconstitution techniques can be employed. It will be appreciated by those skilled in the art that lyophilisation and reconstitution can lead to varying degrees of antibody activity loss (*e.g.* with conventional immunoglobulins, IgM antibodies tend to have greater activity loss than IgG antibodies) and that use levels may have to be adjusted upward to compensate.

The compositions containing the ligands can be administered for prophylactic and/or therapeutic treatments. In certain therapeutic applications, an adequate amount to accomplish at least partial inhibition, suppression, modulation, killing, or some other measurable parameter, of a population of selected cells is defined as a "therapeutically-effective dose". Amounts needed to achieve this dosage will depend upon the severity of the disease and the general state of the patient's health, but generally range from 0.005 to 5.0 mg of ligand *per* kilogram of body weight, with doses of 0.05 to 2.0 mg/kg/dose being more commonly used. For

prophylactic applications, compositions containing the present ligands or cocktails thereof may also be administered in similar or slightly lower dosages, to prevent, inhibit or delay onset of disease (*e.g.*, to sustain remission or quiescence, or to prevent acute phase). The skilled clinician will be able to determine the appropriate dosing interval to treat, suppress or prevent disease. When a ligand is administered to treat, suppress or prevent a disease, it can be administered up to four times per day, twice weekly, once weekly, once every two weeks, once a month, or once every two months, at a dose of, for example, about 10 μg/kg to about 80 mg/kg, about 100 μg/kg to about 80 mg/kg, about 1 mg/kg to about 80 mg/kg, about 1 mg/kg to about 70 mg/kg, about 1 mg/kg to about 60 mg/kg, about 1 mg/kg to about 50 mg/kg, about 1 mg/kg to about 40 mg/kg, about 1 mg/kg to about 30 mg/kg, about 1 mg/kg to about 20 mg/kg, about 1 mg/kg to about 10 mg/kg, about 10 μg/kg to about 10 mg/kg, about 10 μg/kg to about 5 mg/kg, about 10 μg/kg to about 2.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg or about 10 mg/kg. In particular embodiments, the ligand is administered to treat, suppress or prevent a chronic allergic disease once every two weeks or once a month at a dose of about 10 μg/kg to about 10 mg/kg (*e.g.*, about 10 μg/kg, about 100 μg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg or about 10 mg/kg.)

In particular embodiments, the ligand is administered to treat, suppress or prevent asthma each day, every two days, once a week, once every two weeks or once a month at a dose of about 10 μg/kg to about 10 mg/kg (*e.g.*, about 10 μg/kg, about 100 μg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg or about 10 mg/kg). The ligand can also be administered at a daily dose or unit dose (*e.g.*, to treat, suppress or prevent asthma) at a daily dose or unit dose of about 10 mg, about 9 mg, about 8 mg, about 7 mg, about 6 mg, about 5 mg, about 4 mg, about 3 mg, about 2 mg or about 1 mg.

In particular embodiments, the ligand of the invention is administered at a dose that provides saturation of IL-4 and/or IL-13 or a desired serum concentration *in vivo*. The skilled physician can determine appropriate dosing to achieve

saturation, for example by titrating ligand and monitoring the amount of free binding sites on IL-4 and/or IL-13 or the serum concentration of ligand. Therapeutic regiments that involve administering a therapeutic agent to achieve target saturation or a desired serum concentration of agent are common in the art.

Treatment or therapy performed using the compositions described herein is considered "effective" if one or more symptoms are reduced (*e.g.*, by at least 10% or at least one point on a clinical assessment scale), relative to such symptoms present before treatment, or relative to such symptoms in an individual (human or animal model) not treated with such composition or other suitable control. Symptoms will obviously vary depending upon the disease or disorder targeted, but can be measured by an ordinarily skilled clinician or technician. Such symptoms can be measured, for example, by monitoring the level of one or more biochemical indicators of the disease or disorder (*e.g.*, levels of an enzyme or metabolite correlated with the disease, affected cell numbers, etc.), by monitoring physical manifestations (*e.g.*, inflammation, tumor size, etc.), or by an accepted clinical assessment scale, for example, Juniper's Asthma Qualtiy of Life Questionnaire (American Thoracic Society's 32 item assessment evaluates the quality of life with respect to activity limitations, symptoms, emotional function and exposure to environmental stimuli; Juniper, *et. al.*, "Health-related Quality of Life in Moderate Asthma," Chest, 116:1297-1303 (1999).), the Expanded Disability Status Scale (for multiple sclerosis), the Irvine Inflammatory Bowel Disease Questionnaire (32 point assessment evaluates quality of life with respect to bowel function, systemic symptoms, social function and emotional status - score ranges from 32 to 224, with higher scores indicating a better quality of life), the Quality of Life Rheumatoid Arthritis Scale, or other accepted clinical assessment scale as known in the field. A sustained (*e.g.*, one day or more, preferably longer) reduction in disease or disorder symptoms by at least 10% or by one or more points on a given clinical scale is indicative of "effective" treatment. Similarly, prophylaxis performed using a composition as described herein is "effective" if the onset or severity of one or more symptoms is delayed, reduced or abolished relative to such symptoms in a similar individual (human or animal model) not treated with the composition.

A composition containing ligands according to the present invention may be utilized in prophylactic and therapeutic settings to aid in the alteration, inactivation, killing or removal of a select target cell population in a mammal. In addition, the ligands and selected repertoires of polypeptides described herein may be used extracorporeally or *in vitro* selectively to kill, deplete or otherwise effectively remove a target cell population from a heterogeneous collection of cells. Blood from a mammal may be combined extracorporeally with the ligands, *e.g.* antibodies, cell-surface receptors or binding proteins thereof whereby the undesired cells are killed or otherwise removed from the blood for return to the mammal in accordance with standard techniques.

EXAMPLES

EXAMPLE 1: GENERAL METHODS

For primary selections against human IL-13, libraries of VH dAbs and Vk dAbs were panned against biotinylated human IL-13 protein (R&D systems, Minneapolis, US). The IL-13 was biotinylated using a five fold molar excess of EZ-Link Sulfo-NHS-LC-Biotin reagent (Pierce, Rockford, USA). Round 1 was performed with streptavidin-coated magnetic beads (Dynal, Norway) and either 100 nM or 20 nM antigen; round 2 with neutravidin-coated beads and either 20 nM or 4 nM antigen (Henderikx *et al.*, 2002, Selection of antibodies against biotinylated antigens. Antibody Phage Display: Methods and protocols, Ed. O'Brien and Atkin, Humana Press).

In the second primary selection, the same VH and Vk dAb phage display libraries were panned while maintaining the antigen concentration at 100 nM, in the final volume of 1 ml PBS, containing 2% Marvel. In the first and third rounds, 4 mg of M280 Streptavidin Dynabeads (Dynal, Norway) were used to capture antigen-phage complexes. In the second round, 4 mg of Neutravidin-coated M270 Carboxy Dynabeads (Dynal, Norway) were used instead.

M270 Carboxy Dynabeads (Dynal, Norway) were coated with Neutravidin by standard cabodiimined chemistry as follows. 1 ml of Carboxy M-270 Dynabeads (30 mg/ml, $2x10^6$ beads/µl) were washed twice with 1 ml 0.01M NaOH allowing four minutes capture between washes. Sodium hydroxide was removed by two

washes with water, followed by activation of the carboxy groups with 1 ml of 40 mg/ml 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC) (Sigma, U.K) for 30 minutes at room temperature, with rotational mixing. EDC-activated beads were washed twice with water and 1 ml of 1 mg/ml Neutravidin (Pierce, U.S.A.) in 10 mM 2-Morpholinoethanesulfonic acid (MES, Sigma, U.K.) buffer pH5 was added to the activated beads. The coupling reaction was allowed to proceed with rotation for 30 minutes at room temperature. After coupling, the beads were captured, the unreacted Neutravidin was removed and the unreacted amine-reactive groups on the beads were quenched by incubation with 1 ml of 0.05 M tris(hydroxymethyl)aminomethane (Tris) buffer pH7.4 for fifteen minutes at room temperature. The coated and quenched beads were washed four times in PBS containing 0.1% BSA, resuspended in 1 ml of the same. Sodium azide (Sigma, U.K.) was added to 0.02% for preservation and the beads were stored at 4C until required.

The selection process for VH and Vk dAb phage libraries is described in the following tables (Table 1 and 2)

Table 1

Library	Round 1			Round 2			Round 3		
Ligand	Phage In	Phage out	Recovery %	Phage In	Phage out	Recovery %	Phage In	Phage out	Recovery %
Vk(G4+G6) with IL13	2.0E+12	2.0E+05	1.0E-05	1.0E+10	3.0E+04	3.0E-04	2.0E+10	6.2E+08	3.1
Vk(G4+G6) without IL13							2.0E+10	8.0E+06	0.04

Table 2

Library	Round 1			Round 2			Round 3		
Ligand	Phage In	Phage out	Recovery %	Phage In	Phage out	Recovery %	Phage In	Phage out	Recovery %
VH(G4+G6) +L	1.0E+12	3.0E+05	3.0E-05	1.0E+10	7.0E+04	7.0E-04	2.0E+10	8.0E+08	4

VH(G4+G6)-L							2.0E+10	5.0E+06	0.025

The selected VH (DOM10-236 (SEQ ID NO:1804), DOM10-238 (SEQ ID NO:1805), DOM10-241 (SEQ ID NO:1806), DOM10-245 (SEQ ID NO:1807), DOM10-249 (SEQ ID NO:1808), DOM10-250 (SEQ ID NO:1809), DOM10-251 (SEQ ID NO:1810), DOM10-254 (SEQ ID NO:1811), DOM10-256 (SEQ ID NO:1812), DOM10-259 (SEQ ID NO:1813), DOM10-260 (SEQ ID NO:1814), DOM10-261 (SEQ ID NO:1815), DOM10-263 (SEQ ID NO:1816), DOM10-264 (SEQ ID NO:1817), DOM10-273 (SEQ ID NO:1818), DOM10-278 (SEQ ID NO:1819), DOM10-279 (SEQ ID NO:1820), DOM10-281 (SEQ ID NO:1821), DOM10-282 (SEQ ID NO:1822), DOM10-283 (SEQ ID NO:1823), DOM10-400 (SEQ ID NO:1824), DOM10-401 (SEQ ID NO:1825), DOM10-402 (SEQ ID NO:1826), DOM10-404 (SEQ ID NO:1827), DOM10-406 (SEQ ID NO:1828), DOM10-407 (SEQ ID NO:1829), DOM10-409 (SEQ ID NO:1830), DOM10-410 (SEQ ID NO:1831), DOM10-414 (SEQ ID NO:1832), DOM10-415 (SEQ ID NO:1833), DOM10-416 (SEQ ID NO:1834), DOM10-418 (SEQ ID NO:1835), DOM10-420 (SEQ ID NO:1836), DOM10-422 (SEQ ID NO:1837), DOM10-423 (SEQ ID NO:1838), DOM10-424 (SEQ ID NO:1839), DOM10-425 (SEQ ID NO:1840), DOM10-426 (SEQ ID NO:1841), DOM10-427 (SEQ ID NO:1842), DOM10-428 (SEQ ID NO:1843), DOM10-429 (SEQ ID NO:1844), DOM10-430 (SEQ ID NO:1845), DOM10-431 (SEQ ID NO:1846), DOM10-432 (SEQ ID NO:1847), DOM10-433 (SEQ ID NO:1848), DOM10-467 (SEQ ID NO:1849), DOM10-468 (SEQ ID NO:1850), DOM10-469 (SEQ ID NO:1851), DOM10-470 (SEQ ID NO:1852), DOM10-234 (SEQ ID NO:1853), DOM10-235 (SEQ ID NO:1854), DOM10-237 (SEQ ID NO:1855), DOM10-239 (SEQ ID NO:1856), DOM10-240 (SEQ ID NO:1857), DOM10-242 (SEQ ID NO:1858), DOM10-243 (SEQ ID NO:1859), DOM10-244 (SEQ ID NO:1860), DOM10-246 (SEQ ID NO:1861), DOM10-247 (SEQ ID NO:1862), DOM10-248 (SEQ ID NO:1863), DOM10-252 (SEQ ID NO:1864), DOM10-257 (SEQ ID NO:1865), DOM10-258 (SEQ ID NO:1866), DOM10-262 (SEQ ID NO:1867), DOM10-265 (SEQ ID NO:1868), DOM10-266 (SEQ ID NO:1869), DOM10-274 (SEQ ID NO:1870),

DOM10-275 (SEQ ID NO:1871), DOM10-276 (SEQ ID NO:1872), DOM10-277 (SEQ ID NO:1873), DOM10-280 (SEQ ID NO:1874), DOM10-403 (SEQ ID NO:1875), DOM10-405 (SEQ ID NO:1876), DOM10-408 (SEQ ID NO:1877), DOM10-411 (SEQ ID NO:1878), DOM10-412 (SEQ ID NO:1879), DOM10-413 (SEQ ID NO:1880), DOM10-417 (SEQ ID NO:1881), DOM10-419 (SEQ ID NO:1882), DOM10-472 (SEQ ID NO:1883)) and Vk (DOM10-203 (SEQ ID NO:1884), DOM10-205 (SEQ ID NO:1885), DOM10-208 (SEQ ID NO:1886), DOM10-218 (SEQ ID NO:1887), DOM10-219 (SEQ ID NO:1888), DOM10-220 (SEQ ID NO:1889), DOM10-225 (SEQ ID NO:1890), DOM10-228 (SEQ ID NO:1891), DOM10-229 (SEQ ID NO:1892), DOM10-230 (SEQ ID NO:1893), DOM10-231 (SEQ ID NO:1894), DOM10-268 (SEQ ID NO:1895), DOM10-201 (SEQ ID NO:1896), DOM10-202 (SEQ ID NO:1897), DOM10-204 (SEQ ID NO:1898), DOM10-206 (SEQ ID NO:1899), DOM10-207 (SEQ ID NO:1900), DOM10-209 (SEQ ID NO:1901), DOM10-210 (SEQ ID NO:1902), DOM10-211 (SEQ ID NO:1903), DOM10-213 (SEQ ID NO:1904), DOM10-214 (SEQ ID NO:1905), DOM10-215 (SEQ ID NO:1906), DOM10-216 (SEQ ID NO:1907), DOM10-217 (SEQ ID NO:1908), DOM10-221 (SEQ ID NO:1909), DOM10-223 (SEQ ID NO:1910), DOM10-224 (SEQ ID NO:1911), DOM10-227 (SEQ ID NO:1912), DOM10-232 (SEQ ID NO:1913), DOM10-53-425 (SEQ ID NO:2018)) domain antibodies were cloned into pDOM5 expression vector for screening by ELISA or BIAcore off-rate analysis.

For primary selections against human IL-4, libraries of VH dAbs and libraries of Vk dAbs were panned against biotinylated human IL-4 protein (Peprotech, Rocky Hill, USA). The IL-4 was biotinylated as described above. Round 1 was performed with neutravidin-coated magnetic beads (Dynal, Norway) and 100 nM antigen; round 2 with streptavidin-coated beads and 20 nM antigen. Neutravidin-coated beads were prepared by incubating tosylactivated Dyna beads (Dynal, Norway) in 5 mg/ml Immunopure neutravidin biotin-binding protein/ 0.1 M borate buffer pH9.5 for 16 hours at 37°C, followed by incubation in 0.1 % (w/v) BSA/PBS for 5 minutes at 4°C, followed by incubation in 0.1 % (w/v) BSA/0.2 M Tris pH 8.5 for 16 hours at 4°C. Elution at each stage was with 1 mg/ml trypsin-PBS.

For affinity maturation selections, the above method was used but with the following modifications: two to four rounds of selection were performed using streptavidin-coated beads and decreasing concentrations of antigen (in the range of 1 nM to 50 pM). Phage vector from selection outputs (rounds 2 and 3) was isolated by plasmid prep (Qiagen) and dAb insert released by restriction digest with *Sal* I and *Not* I. This insert was ligated into *Sal* I/*Not* I cut pDOM5 and used to transform *E. coli* strain HB2151 for soluble expression and screening of dAbs.

pDOM5 is a pUC119-based expression vector under control of the *LacZ* promoter. Expression of dAbs into the supernatant was ensured by fusion to the universal GAS leader signal peptide at the N-terminal end. In addition, a myc-tag was appended at the C-terminal end of the dAbs. After transformation of *E. coli* HB2151 cells, colonies were used to inoculate 50 to 500 mL of Terrific Broth medium supplemented with carbenicillin (100 µg per mL). Induction was performed with the OVERNIGHT EXPRESS™ SYSTEM 1 (high-level protein expression system, Novagen) according to the manufacturer's instructions. The cultures were incubated at 30°C for 24-48 hours with shaking at 250 rpm. After cell pelleting by centrifugation (4,000 rpm for 20 min), the supernatants were filtered using a 0.45 µm filter and incubated overnight at 4°C with Streamline-protein A beads (Amersham Biosciences, binding capacity: 5 mg of dAb per mL of beads) for the V_H dAbs, or Protein L-sepharose beads (Affitech, binding capacity: 2 mg of dAb per mL of beads) for the V_L dAbs. The beads were then packed into drip columns, washed with 10 column volumes of PBS, and bound dAbs were eluted in 0.1 M glycine-HCl, pH 2.0 or 3.0 for the V_H and V_L dAbs, respectively. After neutralisation with 1 M Tris-HCl, pH 8.0, the protein samples were dialyzed in PBS and concentrated on Vivaspin 5-kDa concentrators (Vivascience) before storage at 4°C. Protein purity was estimated by visual analysis after SDS-PAGE on 12% acrylamide Tris-glycine gel (Invitrogen). Protein concentrations and yields (in mg per L of bacterial culture) were measured at 280 nm, using extinction coefficients calculated from the amino acid compositions.

Affinity maturation using phage libraries

Maturation was performed using error prone mutagenesis, site-directed mutagenesis of multiple residues and single residue screening technologies. For error-prone maturation libraries, plasmid DNA encoding the dAb to be matured was amplified by PCR, using the GENEMORPH® II RANDOM MUTAGENESIS KIT (random, unique mutagenesis kit, Stratagene). The product was digested with *Sal* I and *Not* I and used in a ligation reaction with cut phage vector pDOM4. For the site-directed mutagenesis and single residue libraries, PCR reactions were performed using degenerate oligonucleotides containing NNK or NNS codons to diversify the required positions in the dAb to be affinity matured. Assembly PCR was then used to generate a full length diversified insert. The insert was digested with *Sal* I and *Not* I and used in a ligation reaction with pDOM4 for mutagenesis of multiple residues and pDOM5 for mutagenesis of single residues. The ligation produced by either method was then used to transform *E. coli* strain TB1 by electroporation and the transformed cells plated on 2xTY agar containing 15 μg/ml tetracycline, yielding library sizes of $>1\times10^7$ clones.

pDOM4, is a derivative of the Fd phage vector in which the *gene III* signal peptide sequence is replaced with the yeast glycolipid anchored surface protein (GAS) signal peptide. It also contains a *c-myc* tag between the leader sequence and *gene III*, which puts the *gene III* back in frame. This leader sequence functions well both in phage display vectors but also in other prokaryotic expression vectors and can be universally used.

Affinity maturation using emulsification

Library construction.

One pg of template DNA of either DOM10-176 (SEQ ID NO:1285), DOM9-155 (SEQ ID NO:451), or DOM9-44 (SEQ ID NO:358) Vk dAb was PCR amplified using GENEMORPH II for 35 cycles with the primer set OA16 (ATACCATGGGGTCGACGGACATCCAG; SEQ ID NO:1797) and OA17n (TTCTTTTGCGGCCGCCCGTTTGATTTCCACC; SEQ ID NO:1798), followed by a restriction digest with SalI and NotI. The clean DOM10-176 (SEQ ID NO:1285), DOM9-155 (SEQ ID NO:451), and DOM9-44 (SEQ ID NO:358) fragments were ligated in either of the vectors pIE2aA or pIE7t3T using T4 DNA

ligase in 20 µl volume. All vectors are derived from the pIVEX2.2b Nde vector from Roche. 0.5 µl aliquots of the ligation product were amplified in the presence of competitor DNA or real-time PCR on BioRad Mini-Opticon thermal cycler to establish that the number of ligation events exceeded 10^9 per reaction. The libraries were PCR amplified from the ligation reaction using either SuperTaq and primers AS11 (TTCGCTATTACGCCAGCTGG; SEQ ID NO:1799) and AS17 (CAGTCAGGCACCGTGTATG; SEQ ID NO:1800)(scArc libraries) or Platinum pfx and primers AS12 (AAAGGGGGATGTGCTGCAAG; SEQ ID NO:1801) and AS18 (AACAATGCGCTCATCGTCATC; SEQ ID NO:1802) (Tus libraries). For targeted diversification libraries, oligonucleotides containing NNS codons at the indicated positions were used and the dAb was assembled by overlap PCR. The assembly reaction was PCR amplified with OA16/17n oligonucleotides using PfuUltra DNA polymerase and cloned SalI/NotI in the scArc or Tus *in vitro* translation (IVT) vectors.

Ten pg of template DNA of either DOM10-416 (SEQ ID NO:1834), DOM10-273 (SEQ ID NO:1818), DOM10-275 (SEQ ID NO:1871) or DOM10-276 (1872) VH dAb was PCR amplified using GenemorphII for 35 cycles with the primer set AS9 (SEQ ID NO:1916) and AS65 (SEQ ID NO:1917), followed by a restriction digest with SalI and NotI. The clean DOM10-416 (SEQ ID NO:1834), *DOM10-273 (DOM10-273), DOM10-275 (SEQ ID NO:1871)* or DOM10-276 (SEQ ID NO:1872) fragments were ligated into pIE2a^{2}A vector (SEQ ID:2015), a derivative of pIE2aA with twoArc operators per gene and potentially tetravalent display capability, using T4 DNA ligase in 20 µl volume. 0.5 µl aliquots of the ligation product were amplified using real-time PCR on BioRad Mini-Opticon *thermal cycler to establish that the number of ligation events exceeded 10^9* per reaction.

In vitro expression and emulsification.

The following reaction mixture was used for *in vitro* transcription/translation *of the library of PCR fragments: 1.5 µl 100 mM oxidized glutathione, 2 µl 5 mM* Methionine, 0.5 µl DNA (5.0 x 10^8 molecules), 10 µl H_2O, 0.25 µl of 50 mg/ml anti-HA mAb 3F10 (used only with scArc), biotinylated antigen at varying

concentrations, and 35 µl of EcoPro T7 coupled transcription-translation extract. Immediately after mixing, the extract was added to 0.7 ml of light white mineral oil containing 4.5% (v/v) Span-80 and 0.5% (v/v) Triton X-100. Emulsification was carried out by spinning a magnetic stirrer for 5 min at 2000 rpm in a 5 ml glass vial. Microscopic analysis of droplet formation confirmed that droplets were ~ 2 µm in diameter. The emulsion was incubated for 60 (Tus) to 180 (scArc) min at 25°C to allow expression and formation of the protein-DNA complex to take place. Breaking of the emulsion was performed by adding 0.25 ml of PBS/1% BSA/biotinylated antigen and 0.5 ml hexane/ 20% (v/v) mineral oil, followed by brief vortexing and centrifugation for 1 min at 13,000 rpm. After removal of the oil phase, 1 ml of hexane/mineral oil was added and the procedure repeated three times. The last extraction was performed using only hexane.

Selection and amplification.

Selection for binders was performed by incubating the extracted aqueous phase for 30 min in the presence 50 - 5 nM of biotinylated antigen (See below for exact conditions used per round). If off-rate selections were performed, this incubation was followed by addition of an excess of unbiotinylated antigen, or the parent VH dAb at 1 µM concentration, and incubation in the 5 – 100 min range. Each emulsion reaction was then divided over 5 wells of a streptavidin coated PCR plate (50 µl/well), incubated for 15 min at 25°C, and washed 4 times with PBS/BSA. Fifty µl of PCR mix containing either OA16/17n primers, PfuUltra buffer, dNTPs, 2.5 u PfuUltra DNA polymerase (Tus) or successive pairs of nested primers, dNTPs, KOD polymerase buffer and 2.5u KOD polymerase (scArc) was added to each well. PCR was performed for 25 (scArc) or 30 (Tus) cycles. For Tus selections, the PCR product was cleaned and digested with SalI/NotI. The fragment was then ligated in pIE7t^3T vector and amplified as described in library construction. For scArc, the PCR product was gel purified and used directly for a next round of selection.

PEGylation using aldehyde and NHS activated PEGs

Under appropriate conditions, proteins can be specifically PEGylated via the N-terminus using PEG-aldehyde (PEG-ALD). This has the advantage in that the

protein does not require any further engineering to introduce a specific amino acid for modification such as cysteine when using PEG-maleimide. Under non-optimized buffer conditions it is still possible for some of the protein to become modified via lysine residues when using PEG-ALD. An alternative method is to use NHS or SPA activated PEGs which react specifically with surface lysine residues.

EXAMPLE 2: ligands that bind IL-4

IL-4 receptor binding assay (RBA)

A MAXISORP™ plate (high protein binding ELISA plate, Nunc, Denmark) was coated overnight with 0.5 µg/ml recombinant human IL-4R/Fc (R&D Systems, Minneapolis, USA). The wells were washed three times with 0.1% (v/v) Tween 20 in PBS, followed by three washes with PBS, before blocking with 2% (w/v) BSA in PBS. The plates were washed again before the addition of 10 ng/ml biotinylated-IL-4 (R&D Systems) mixed with a dilution series of anti-IL-4 dAbs or IL-4. IL-4 binding was detected with peroxidase labelled anti-biotin antibody (Stratech, Soham, UK) and then developed with TBM substrate (KPL, Gaithersburg, USA). The reaction was stopped by the addition of HCl and the absorbance read at 450 nm. Anti-IL-4 dAb activity caused a decrease in IL-4 binding to the receptor and therefore a decrease in absorbance compared with the IL-4 only control.

IL-4 Cell Assay

Isolated dAbs were tested for their ability to inhibit IL-4 induced proliferation in cultured TF-1 cells (ATCC® catalogue no. CRL-2003). Briefly, 40000 TF-1 cells in phenol red free RPMI media (Gibco, Invitrogen Ltd, Paisley, UK) were placed in the well of a tissue culture microtitre plate and mixed with 1 ng/ml final concentration IL-4 (R&D Systems, Minneapolis, USA) and a dilution of the dAb to be tested. The mixture was incubated for 72 hours at 37°C 5% CO_2. CELLTITER 96® reagent (colorometric reagent for determining viability, Promega, Madison, USA) was then added and the number of cells per well was quantified by measuring the absorbance at 490 nm. Anti-IL-4 dAb activity caused a decrease in cell proliferation and a corresponding lower A_{490} than IL-4 alone.

Competition BIACORE® with anti IL-4 dAbs

These experiments were performed on a BIACORE® 3000 instrument, using a streptavidin coated SA chip (surface plasmon resonance system, Biacore) coupled with ~400 RU of biotinylated IL-4 (R&D Systems). Analytes were passed over the antigen-coated flow-cell, with in-line referencing against a blank flow-cell, at a flow rate of 30 µl/min in HBS-EP running buffer (Biacore). The first dAb was injected, followed immediately by injection of the second dAb using the Biacore's co-inject function. For this experiment dAbs DOM9-44 (SEQ ID NO:358), DOM9-155-1 (SEQ ID NO:452) and DOM9-112-22 (SEQ ID NO:47)were used. This competition protocol can generally be used to assess competition of a test antibody or fragment with a known dAb (or other antibody polypeptide) for binding to IL-4.

Allergen induced cell proliferation.

Blood was collected from donors allergic to house dust mite (HDM). Peripheral blood mononuclear cells (PBMC) were then isolated using a Ficoll gradient. Cells were seeded at $4x10^6$/ml in a 96 well plate and stimulated with HDM at 20-50ug/ml. Anti-IL-4 dAbs were added at 100 nM at the start of the culture (1.4 ug/ml). Cells were incubated for 5 days, with the addition of 3[H] thymidine for the final 18 hours. Cells were then harvested and proliferation was assessed by determining the amount of 3H incorporated into the cellular DNA.

Primary selection and screening for anti-IL-4 dAbs

Primary phage selections were performed using the VH and Vk dAb libraries and outputs sub-cloned into the soluble expression vector pDOM5. dAb clones that inhibit binding of IL-4 to IL-4 R were identified by supernatant receptor binding assay (RBA). Clones were then expressed, purified by protein A or protein L and tested as a dose-response in the RBA to estimate the potency with which the clones inhibited the binding of IL-4 to IL-4R. Table 3 shows the results for anti-IL-4 dAbs DOM9-44 (SEQ ID NO:358), DOM9-112 (SEQ ID NO:25), and DOM9-155 (SEQ ID NO:451) in such an RBA assay.

TABLE 3

IL-4 receptor binding assay	
dAb	IC50 (nM)
DOM9-44	122
DOM9-155	100
DOM9-112	3

Affinity Maturation of anti-IL-4 dAbs

DOM9-44 lineage

The DOM9-44 lineage was affinity matured using *in vitro* expression and emulsification. Libraries diversifying CDR2 and CDR3 residues were constructed and used in selections against biotinylated IL-4. Output clones were expressed, purified and screened in the IL-4 receptor binding assay (RBA). The most potent dAb from this lineage was DOM9-44-502 (SEQ ID NO:361), which had a potency of 5.5 nM in the IL-4 RBA (Table 4) and 4.5 nM in the IL-4 cell assay (Table 5).

TABLE 4

IL-4 receptor binding assay	
dAb	IC50 (nM)
DOM9-155-25	
Expt. 1	0.73
Expt. 2	1
average	0.86
DOM9-44-502	
Expt. 1	4.1
Expt. 2	3.6
Expt. 3	5.5
Expt. 4	8.6
average	5.5
DOM9-112-168	
Expt. 1	1.22
Expt. 2	0.64
average	0.9
DOM9-112-210	
Expt n=8	144 pM

TABLE 5

IL-4 Induced TF-1 Cell Proliferation	
dAb	ND50 (nM)
DOM9-155-25	
Expt. 1	0.55
Expt. 2	1.1
average	0.83
DOM9-44-502	
Expt. 1	4.5
DOM9-112-210	
Expt n=8	270 pM

DOM9-155 lineage

The DOM9-155 lineage was affinity matured using *in vitro* expression and emulsification. The DOM9-155 dAb (SEQ ID NO:451) was PCR amplified under error-prone conditions and ligated into the Tus vector, followed by a second PCR to amplify the IVT cassette. The libraries were then subjected to sequential rounds of selection against biotinylated IL-4. Ten rounds of selection were performed followed by cloning into the expression vector and overnight supernatant expression. Improved clones were identified by screening on the Biacore and were subsequently used as a template for libraries diversifying residues of the CDR1 by NNS mutagenesis. Output clones were expressed, purified and tested in the IL-4 receptor binding assay and the IL-4 cell assay. The most potent dAbs from the DOM9-155 lineage identified using these methods was DOM9-155-25 (SEQ ID NO:466) with an IC50 of 0.86 nM in the RBA (Table 4) and 0.83 nM in the cell assay (Table 5). Further screening of this output identified two additional dAbs with sub nanomolar potencies: DOM9-155-77 (SEQ ID NO: 2393) and DOM9-155-78 (SEQ ID NO: 2394).

DOM9-112 lineage

The DOM9-112 lineage was affinity matured by phage display using an error-prone maturation library, libraries diversifying multiple residues of CDR 1 and 2 libraries diversifying individual residues of the CDR1 and 2. The resulting phage libraries were used in selections against biotinylated IL-4. Outputs were cloned into

vector pDOM5 and expression supernatants were screened for improved off-rates compared to the parent. dAbs with improved off-rates were expressed, purified and tested in the IL-4 receptor binding assay (RBA) and cell assay. The most potent dAbs identified using these methods were DOM9-112-155 (SEQ ID NO:118), DOM9-112-168 (SEQ ID NO:131), DOM9-112-174 (SEQ ID NO:137), DOM9-112-199 (SEQ ID NO:162), DOM9-112-200 (SEQ ID NO:163), DOM9-112-202 (SEQ ID NO:165) and DOM9-112-210 (SEQ ID NO:2401) with IC50 values in the range of 0.9 to 3 nM, as measured in the IL-4 RBA (Table 4).

Epitope mapping of anti IL-4 dAbs

To determine the epitope specificity of the anti-IL-4 dAbs, BIACORE® (surface plasmon resonance, Biacore) competition experiments were performed. DOM9-44 (SEQ ID NO:358) dAb was injected over an IL-4 coupled chip, followed by injection of DOM9-155-1 (SEQ ID NO:452) dAb which could not bind to IL-4 after DOM9-44 (SEQ ID NO:358) was bound (FIG. 13). Similarly, DOM9-44 (SEQ ID NO:358) could not bind after DOM9-155-1 (SEQ ID NO:452) was bound. However dAb DOM9-112-22 (SEQ ID NO:47) could bind IL-4 after dAb DOM9-44 (SEQ ID NO:358) was bound and also after dAb 9-155-1 (SEQ ID NO:452) was bound. The results indicated that dAbs DOM9-44 (SEQ ID NO:358) and DOM9-155-1 (SEQ ID NO:452) bound to the same epitope and that DOM9-112-22 (SEQ ID NO:47) bound to a different epitope from DOM9-44 (SEQ ID NO:358) and DOM9-155-1 (SEQ ID NO:452). This competition protocol can generally be used to assess competition (and epitope mapping) of a test antibody or fragment with a known dAb (or other antibody polypeptide) for binding to IL-4.

Allergen induced cell proliferation.

PBMC from all allergic donors showed a dose-dependent proliferation when incubated with HDM (house dust mite). The addition of anti-IL-4 dAbs resulted in an inhibition of allergen induced proliferation in the majority of donors. dAb DOM9-44-502 (SEQ ID NO:361) inhibited proliferation of PBMC from 10 out of 12 donors (FIG. 14A), DOM9-155-11 (SEQ ID NO:457) inhibited proliferation of PBMC from 10 out of 12 donors (FIG. 14B) and DOM9-112-22 (SEQ ID NO:47)

inhibited proliferation of PBMC from 2 out of 2 donors. The average inhibition in all responding donors was 38%, 34% and 23% inhibition for dAb DOM9-44-502 (SEQ ID NO:361), DOM9-155-11 (SEQ ID NO:457) and DOM9-112-22 (SEQ ID NO:47), respectively. The reason that maximal responses of only 30-40% are observed is most likely because this allergen induced response is not only dependent on IL-4, but is also dependent on other interleukins such as IL-2.

IL-4 induced B cell proliferation

Blood was collected from normal blood donors. PBMC were isolated using Ficoll gradient. B cells were then isolated using a negative B cell isolation kit (EasySep Negative isolation kit, Stem Cell Technologies Inc). Purity was in excess of 98% as determined by flow cytometry and staining with CD3, CD4, CD8, CD14, CD14, CD19 and CD23. B cells were then plated at 1 $x10^5$ cells/well in the presence of IL-4 (10 ng/ml) in plates coated with irradiated $CD40L^+$ L cells. Cultures were incubated for 5 days with the addition of 3[H]thymidine for the final 18 hours. Anti-IL-4 dAbs were added at the start of the culture at 10nM or 100nM.

Cross-reactivity with rhesus and cynomolgous IL-4.

A desired requirement of these dAbs would be cross-reactivity with rhesus and cynomolgous IL-4. To that end, DOM9-112-210 (SEQ ID NO:2401), DOM9-155-5 (SEQ ID NO:454), DOM9-155-25 (SEQ ID NO:466), DOM9-155-77 (SEQ ID NO:2393) and DOM9-155-78 (SEQ ID NO:2394) were tested in the TF-1 cell proliferation assay (see above for description in more detail) in which cells are stimulated with human IL-4 (0.5 ng/ml, Peprotech), rhesus IL-4 (0.5 ng/ml, R&D systems) or cynomolgous IL-4 (1:25000 dilution of supernatant containing in-house expressed cynomolgous IL-4). A dose-response of the dAb will determine the ND50 in this set up. A summary of the values obtained is given in the table below (Table 6) and demonstrates cross-reactivity.

Table 6

dAb	Human IL-4 (nM)	Rhesus IL-4 (nM)	Cyno IL-4 (nM)
DOM9-155-5	0.3 – 0.5	1.8 - 2.7	
DOM9-155-77	1.1 – 1.7	3.6 – 5.4	
DOM9-155-78	0.5 – 0.7	1.3 – 2.0	
DOM9-155-25	0.75 – 1.1	2.7 – 4.1	2.6 – 3.8
DOM9-112-210	0.27	0.4	0.6

EXAMPLE 3: Ligands that bind IL-13

IL-13 Sandwich ELISA

A MAXISORP™ plate (high protein binding ELISA plate, Nunc, Denmark) was coated overnight with 2.5 µg/ml coating antibody (Module Set, Bender MedSystems, Vienna, Austria), then washed once with 0.05% (v/v) Tween 20 in PBS before blocking with 0.5% (w/v) BSA 0.05% (v/v) Tween 20 in PBS. The plates were washed again before the addition of 25 pg/ml IL-13 (Bender MedSystems) mixed with a dilution series of DOM10 dAb (*i.e.*, an anti-IL-13 dAb) or IL-13. The plates were washed again before binding of IL-13 to the capture antibody was detected using biotin conjugated detection antibody (Module Set, Bender Medsystems), followed by peroxidase labelled Streptavidin (Module Set, Bender MedSystems). The plate was then incubated with TMB substrate (KPL, Gaithersburg, USA), and the reaction was stopped by the addition of HCl and the absorbance read at 450 nm. Anti-IL-13 dAb activity caused a decrease in IL-13 binding and therefore a decrease in absorbance compared with the IL-13 only control.

IL-13 receptor binding assay (RBA) using the 8200 cellular detection system

SPHERO™ goat anti-human IgG (H&L) polystyrene particles (0.5% w/v) (goat-anti-human particles, Spherotech, Libertyville, USA) were coated overnight with 20 µg IL-13R alpha 1/Fc chimera or IL-13R alpha 2/Fc chimera (R&D Systems, Minneapolis, USA). The following reagents were then combined in a 384-well black sided clear bottomed FMAT plate (Applied Biosystems, Foster City, USA): dilution series of DOM-10 dAb or 0.1% (w/v) BSA in PBS; 0.5 µg/ml

biotinylated anti-IL-13 antibody (R&D Systems); 0.25 µg/ml STREPTAVIDIN ALEXA FLUOR® 647 conjugate (fluorescent probe, Molecular Probes, Invitrogen Ltd, Paisley, UK); 10 ng/ml recombinant human IL-13 (R&D Systems); and 1:10 dilution of IL-13R2/Fc coated particles. The plate was incubated for seven hours before being read in the 8200 cellular detection system (Applied Biosystems). Binding of IL-13 to the receptor coated particle causes a complex to form which is detected as a fluorescent event by the 8200. Anti-IL-13 dAb activity causes a decrease in IL-13 binding and thus a decrease in fluorescent events compared with the IL-13 only control.

IL-13 Cell Assay

Isolated dAbs were tested for their ability to inhibit IL-13 induced proliferation in cultured TF-1 cells (ATCC® catalogue no. CRL-2003). Briefly, 40000 TF-1 cells in phenol red free RPMI media (Gibco, Invitrogen Ltd, Paisley, UK) were placed in the well of a tissue culture microtitre plate and mixed with 5 ng/ml final concentration IL-13 (R&D Systems, Minneapolis, USA) and a dilution of the dAb to be tested. The mixture was incubated for 72 hours at 37°C 5% CO_2. CELLTITER 96® reagent (colorometric reagent for determining viability, Promega, Madison, USA) was then added and the number of cells per well was quantified by measuring the absorbance at 490 nm. Anti-IL-13 dAb activity caused a decrease in cell proliferation and a corresponding lower A_{490} than IL-13 alone.

BIACORE® Off-rate screening

A streptavidin coated SA chip (Biacore) was coated with approximately 500 RU of biotinylated IL-13 (R&D Systems, Minneapolis, USA). Supernatant containing soluble dAb was diluted 1:5 in running buffer. 50 to 100 ul of the diluted supernatant was injected (kininject) at 50 ul/min flow rate, followed by a 5 minute dissociation phase. Clones with improved off-rates compared to parent were identified by eye, or by measurement using BIAevaluation software v4.1 (Biacore).

Competition BIACORE® with anti IL-13 dAbs

These experiments were performed on a BIACORE® 3000 instrument (surface plasmon resonance instrument, Biacore), using a streptavidin coated SA chip (Biacore) coupled with ~400 RU of biotinylated IL-13 (R&D Systems). Analytes were passed over the antigen-coated flow-cell, with in-line referencing against a blank flow-cell, at a flow rate of 30 µl/min in HBS-EP running buffer (Biacore). The first dAb DOM10-176-535 (SEQ ID NO:1362) was injected, followed immediately by injection of dAb DOM 10-53-99 (SEQ ID NO:738), using the Biacore's co-inject function. This competition protocol can generally be used to assess competition of a test antibody or fragment with a known dAb (or other antibody polypeptide) for binding to IL-13.

Competition and epitope mapping

Epitope mapping of anti IL-13 dAbs

To determine the epitope specificity of the anti-IL-13 dAbs, Biacore competition experiments were performed. dAb DOM10-176-535 (SEQ ID NO:1362) was injected, followed immediately by injection of dAb DOM10-53-99 (SEQ ID NO:738). dAb DOM10-53-99 (SEQ ID NO:738) did not bind to IL-13 to which dAb DOM10-176-535 (SEQ ID NO:1362) has already bound. This indicates that these dAbs bound to the same epitope. This competition protocol can generally be used to assess competition (and epitope mapping) of a test antibody or fragment with a known dAb (or other antibody polypeptide) for binding to IL-13. The epitopes for a second set of dAbs was determined using a slightly modified BIAcore protocol in which first dAbs were injected over an IL-13 surface, then a high affinity binding dAb (DOM10-53-386 (SEQ ID NO:934)) was injected at high concentration (5 µM) saturating the IL-13 surface and finally the dAbs were again injected. If there is a difference between binding prior and post saturation with DOM10-53-386 (SEQ ID NO:934), the epitopes are at least partially overlapping. Using this experimental setup, it was determined that the Vk dAbs DOM10-212 (SEQ ID NO:2016), DOM10-270 (SEQ ID NO:1915), DOM10-213 (SEQ ID NO:1904) and DOM10-215 (SEQ ID NO:1906) share the same epitope as DOM10-53-386 (SEQ

ID NO:934), whereas DOM10-208 (SEQ ID NO1886): and DOM10-224 (SEQ ID NO:1911) have a different epitope. The same BIAcore setup was used for the injection of the Vh dAbs DOM10-416 (SEQ ID NO:1834), DOM10-236 (SEQ ID NO:1804), DOM10-273 (SEQ ID NO:1818), DOM10-275 (SEQ ID NO:1871), DOM10-276 (SEQ ID NO:1872) and DOM10-277 (SEQ ID NO:1873). All these dAbs were shown to have at least partially overlapping epitopes with DOM10-53-386 (SEQ ID NO:934). This demonstrates that less dAb binds once DOM10-53-386 (SEQ ID NO:934) has been injected.

IL-13 induced B cell proliferation

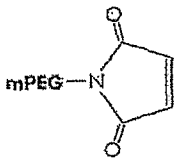
Blood was collected from normal blood donors. PBMC were isolated using Ficoll gradient. B cells were then isolated using a negative B cell isolation kit (EasySep Negative isolation kit, Stem Cell Technologies Inc). Purity was in excess of 98% as determined by flowcytometry and staining with CD3, CD4, CD8, CD14, CD19 and CD23. B cells were then plated at 1 $x10^5$ cells/well in the presence of IL-13 (10 ng/ml) in plates coated with irradiated $CD40L^+$ L cells. Cultures were incubated for 5 days with the addition of 3[H]thymidine for the final 18 hours. Anti-IL-13 dAbs were added at the start of the culture at 10 or 100nM.

Formatting:

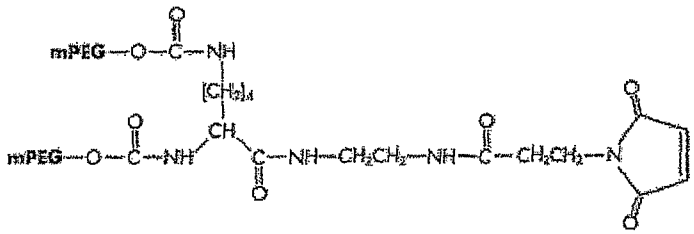
Site specific PEGylation of DOM10-53-343 using PEG-Maleimide

The anti-IL13 dAb DOM10-53-343 (SEQ ID NO:891) was engineered with a cysteine at the C-terminus of the protein. Expression and purification of the dAbs was performed as described above. The cysteine engineered dAb was specifically modified with a branched 40K PEG2-MAL to give monomeric modified protein. Other PEG formats are available such as linear PEG-MAL which may also be used to give PEGylated monomers, *e.g.* 30K or 40K linear PEG.

mPEG-MAL



mPEG2-MAL



mPEG-MAL formats may be used to PEGylate a monomeric dAb. The PEGs may be of MW from 500 to 60,000 (*e.g.*, from 2,000 to 40,000) in size and either linear or branched in nature

1 ml of 160 μM DOM10-53-343cys was reduced with 5 mM dithiothreitol and left at room temperature for 20 minutes. The sample was then buffer exchanged using a PD-10 column (Amersham Pharmacia), to remove the reducing agent. The column had been pre-equilibrated with 5 mM EDTA, 20 mM BIS-TRIS pH 6.5, 10% glycerol, and the sample applied and eluted following the manufacturer's guidelines. The sample (3.5 ml of ~50 μM dAb) was then mixed directly with a three fold molar excess of 40K PEG-MAL (~20mg). The reaction was left to proceed at room temperature for 3 hours.

Purification of PEGylated DOM10-53-343 cys monomer by anion exchange

The sample was further purified using anion exchange chromatography (1ml Resource Q column), to remove any unreacted PEG and protein. The sample was diluted 3-fold into equilibration buffer (50mM TRIS pH 8.0), before being applied on to the column which had also been equilibrated in the same buffer. The PEGylated material was separated from the unmodified dAb by running a linear sodium chloride gradient from 0 to 500 mM, in 50mM TRIS buffer over 20 column volumes. Fractions containing PEGylated dAb only were identified using SDS-PAGE and then pooled.

N-terminal PEGylation using 30K PEG-ALD

The anti-IL13 dAb DOM10-53-338 (SEQ ID NO:886) was PEGylated via the N-terminus (α-amino group) using a 30K PEG-ALD. The dAb was buffer exchanged into 20 mM phosphate buffer pH6.0 to give a final protein concentration of 2mg/ml (~166 μM). A 5-fold molar excess of PEG-ALD (830 μM polymer) was added directly to the dAb solution followed by the addition of 2 mM sodium cyanoborohydride to reduce the transient imine linkage to an amine which is stable to hydrolysis. The reaction was then allowed to proceed overnight at room temperature. The sample was further purified using anion exchange chromatography as described above.

PEGylation of surface lysine residues using 40K PEG2-NHS

The anti-IL13 dAb DOM10-53-338 (SEQ ID NO:886) was PEGylated via surface lysine residues using 40K PEG2-NHS. The dAb was buffer exchanged into 20 mM phosphate buffer pH8.0 to give a final protein concentration of 2mg/ml (~166 μM). A 5-fold molar excess of PEG-NHS (830 μM polymer) was added directly to the dAb solution and the reaction was allowed to proceed at room temperature overnight. The sample was further purified using anion exchange chromatography as described above.

Primary selection and screening for anti-IL-13 dAbs

Primary phage selections were performed using VH and Vk dAb libraries and outputs sub-cloned into soluble expression vector pDOM5. dAb clones that inhibit binding of IL-13 to IL-13RI were identified by supernatant RBA. Clones were then expressed, purified by protein A or protein L and tested as a dose-response in the RBA to determine the potency with which the clones inhibited the binding of IL-13 to IL-13RI. Table 7 shows the results for anti-IL-13 dAbs DOM10-53 (SEQ ID NO:651) and DOM10-176 (SEQ ID NO:1285) in such an RBA assay, where their IC_{50} values are 150 and 100 nM, respectively, while the rest have IC50 values in micromolar range.

TABLE 7

IL-13 receptor I binding assay	
dAb	IC50 (nM)
DOM10-53	150
DOM10-176	100
DOM10-416	6000
DOM10-273	600
DOM10-275	1000
DOM10-276	3000

Affinity Maturation of anti-IL-13 dAbs

DOM10-176 lineage

The nucleic acid encoding dAb DOM10-176-535 (SEQ ID NO:1362) was PCR amplified under error-prone conditions and ligated *in the scArc vector*, followed by a second PCR to amplify the IVT cassette. The libraries were then subjected to sequential rounds of selection, with antigen concentrations being stepwise decreased from 50 to 5 nM.

A separate library diversifying positions 52-54 in CDR2 of DOM10-176 (SEQ ID NO:1285) was constructed and used in further selections. The output clones were expressed as supernatants and screened for improved off-rates compared to the parent. dAbs with improved off-rates were expressed, purified and tested in the IL-13 sandwich ELISA and cell assay. The mutations from the best dAbs identified from both of these selections were combined, creating DOM10-176-535 (SEQ ID NO:1362). This was the most potent dAb of the DOM10-176 lineage, with an IC50 value in the RBA in the range of 0.5 nM and a value of 0.77 nM in the IL-13 cell assay (Tables 8 and 9).

TABLE 8

IL-13 assays	
IL-13 receptor I binding assay	
DOM10-176-535	
	IC50 (nM)
Expt. 1	0.56
Expt. 2	0.76
Expt. 3	0.63
Expt. 4	0.41

average	0.59
IL-13 sandwich ELISA	
	IC50 (pM)
DOM10-53-234	
Expt. 1	87
Expt. 2	81
Expt. 3	87
Expt. 4	40
average	73
DOM10-53-396	
Expt. 1	55
Expt. 2	30
average	42

TABLE 9

IL-13 Induced TF-1 Cell Proliferation	
	ND50 (nM)
DOM10-176-535	0.77
DOM10-53 lineage	
	ND50 (pM)
10-53-234	43
10-53-344	100 (n=2)

DOM10-53 lineage

The DOM10-53 lineage was affinity matured by phage display using an error-prone maturation library, libraries diversifying multiple residues of CDR 1, 2 and 3 and libraries diversifying individual residues of the CDR1, 2 and 3. The resulting phage libraries were used in selections against biotinylated IL-13. Outputs were cloned into vector pDOM5 and expression supernatants were screened for improved off-rates compared to the parent. dAbs with improved off-rates were expressed, purified and tested in the IL-13 sandwich ELISA and cell assay. The most potent dAbs identified using these methods were DOM10-53-223 (SEQ ID NO:774), DOM10-53-234 (SEQ ID NO:785), DOM10-53-316 (SEQ ID NO:866), DOM10-53-339 (SEQ ID NO:887), DOM10-53-344 (SEQ ID NO:892) and DOM10-53-396 (SEQ ID NO:944), with potency values as estimated in the IL-13

sandwich ELISA and IL-13 cell assay in the range of 100 pM to 40 pM (Table 8 and 9).

Inhibition of IL-13 binding to IL-13Rα2

Anti-IL-13 dAbs were tested for their ability to inhibit binding of IL-13 to IL13Rα2 in a competition assay. Table 10 shows that both DOM10-53-316 (SEQ ID NO:866) and DOM10-176-535 (SEQ ID NO:1362) were able to inhibit the binding of IL-13 to IL13Rα2 with IC50 values of 2nM and 8 nM respectively.

TABLE 10

IL-13 receptor α2 binding assay	
dAb	IC50 (nM)
DOM10-53-316	1.2
DOM10-176-535	7.9

Binding to variant IL-13 (R130Q)

Genetic variants of IL-13 have been associated with an increased risk for asthma (Heinzmann *et al. Hum Mol Genet.* (2000) 9549-59) and bronchial hyperresponsiveness (Howard *et al., Am. J. Resp. Cell Molec. Biol.* (2001) 377-384). Therefore it was determined whether the anti-IL-13 dAbs are able bind variant IL-13 (R130Q), the TF-1 proliferation assay was performed with variant IL-13 (R130Q), and increasing amounts of dAb. Table 11 shows that both DOM10-53-316 (SEQ ID NO:866) and DOM10-176-535 (SEQ ID NO:1362) were able to inhibit variant IL-13 induced TF-1 proliferation with ND50 values of approximately 0.5nM and 8nM respectively.

TABLE 11

Variant and human IL-13	
	IC50 (nM)
DOM10-53-316	1
Human IL-13	0.39
Variant IL-13	0.52
DOM10-176-535	
Human IL-13	6
Variant IL-13	7.8

Cross-reactivity with rhesus and cynomolgous IL-13.

A desired requirement of these dAbs would be cross-reactivity with rhesus and cynomolgous IL-13. To that end, DOM10-53-344 (SEQ ID NO:892) and DOM10-53-434 (SEQ ID NO:2053) were tested in the TF-1 cell proliferation assay (see above for description in more detail) in which cells are stimulated with human IL-13 (5 ng/ml, Peprotech), rhesus IL-13 (5 ng/ml, R&D systems) or cynomolgous IL-13 (1:4000 dilution of supernatant containing in-house expressed cynomolgous IL-13). A dose-response of the dAb will determine the ND50 in this set up. A summary of the values obtained are given in the table below (Table 12) and demonstrate cross-reactivity.

Table 12

dAb	Human IL-4	Rhesus IL-4	Cyno IL-4
DOM10-53-344	100 pM	n.d.	980 pM
DOM10-53-434	600 pM	2.8 nM	5.6 nM

DOM10-416, DOM10-273 DOM10-275 and DOM10-276 lineages.

The error-prone PCR libraries of VH dAbs DOM10-416 (SEQ ID NO:1834), DOM10-236 (SEQ ID NO:1804), DOM10-273 (SEQ ID NO:1818), DOM10-275 (SEQ ID NO:1871), DOM10-276 (SEQ ID NO:1872) and DOM10-277 (SEQ ID NO:1873) were prepared and quantified as described above. The rest of the ligation mix was used as a template for the second, regular Taq polymerase (SuperTaq, HT Biotechnology Ltd, Cambridge, UK) catalysed PCR reaction with primers AS11 and AS17 to amplify the IVT cassette. DOM10-275 (SEQ ID NO:1871) and DOM10-276 (SEQ ID NO:1872) were kept separate during the affinity maturation reaction, DOM 10-273 (SEQ ID NO:1818) and DOM10-416 (SEQ ID NO:1834) were pooled. The libraries were then subjected to ten rounds of selection. In the first four rounds of selection the antigen concentration was 75 nM, in the next two rounds 60 mM, followed by two rounds at 45 nM and the final two rounds at 30 nM.

The selection output was cloned into pDOM5 expression vector and the culture supernatants were screened by surface plasmon resonance on BIAcore 1000.

A number of clones with improved properties were identified. Surprisingly, the improved clones were mostly characterized not by point mutations from error-prone PCR, but by recombination events between the clones. DOM10-275-1 (SEQ ID NO:1918) comprises the CDR1 and CDR2 of DOM10-275 (SEQ ID NO:1871) and CDR3 of DOM10-273 (SEQ ID NO:1818). DOM10-276-2 (SEQ ID NO:1919) comprises of the CDR1 and CDR3 of DOM10-276 (SEQ ID NO:1872) and CDR2 of DOM10-416 (SEQ ID NO:1834). DOM10-276-2 (SEQ ID NO:1919) comprises of the CDR1 and CDR2 of DOM10-416 (SEQ ID NO:1834) and CDR3 of DOM10-276 (SEQ ID NO:1872). Clones from the error-prone PCR library selection are listed as DOM10-275-1 (SEQ ID NO:1918), DOM10-276-2 (SEQ ID NO:1919), *DOM10-276-3 (SEQ ID NO:1920)*, DOM10-275-3 (SEQ ID NO:1979), DOM10-277-2 (SEQ ID NO:1980), DOM10-277-3 (SEQ ID NO:1981), DOM10-273-1 (SEQ ID NO:1982), DOM10-273-2 (SEQ ID NO:1983), DOM10-275-2 (SEQ ID NO:1984), DOM10-275-4 (SEQ ID NO:1985), DOM10-276-1 (SEQ ID NO:1986), DOM10-276-4 (SEQ ID NO:1987) and DOM10-277-1 (SEQ ID NO:1988)

TABLE 13

IL-13 assays	
IL-13 BIAcore binding assay	
DOM10-275-1	
	Kd (nM)
Expt. 1	25
Expt. 2	28
average	27
IL-13 receptor I binding assay	
DOM10-275-1	
	IC50 (nM)
Expt. 1	13
Expt. 2	128
average	70
IL-13 sandwich ELISA	
	IC50 (nM)
DOM10-275-1	
Expt. 1	38

IL-13 cell binding assay	
	IC50 (nM)
Expt. 1	37

Targeted diversification libraries of DOM10-273, DOM10-275 and DOM10-276 VH dAbs.

VH domain antibodies DOM10-273 (SEQ ID NO:1818), DOM10-275 (SEQ ID NO:1871) or DOM10-276 (1872) were also affinity matured by diversification at positions 52, 54, 55, 57 and 59 of CDR2 and at positions 101, 102 and 104 of CDR3. At both CDRs two targeted positions at a time were randomized in all possible combinations. The libraries targeting the same CDR in the respective parent clones were pooled and recombined in framework three by SOE PCR, giving rise to a recombined library with four randomized residues per gene, two in CDR2 and two in CDR3, in all possible combinations surrounding their respective CDR1 regions (calculated diversity at nucleotide level $3x10^7$ different clones), *i.e.* three libraries in total. The same was repeated by pooling the 5' and 3' PCR fragments of all parent clones before the SOE PCR step, creating a library of about 10^8 theoretical diversity. Finally, the 5' fragment of DOM10-275 set of libraries encoding CDR1 and CDR2 was recombined with the 3' set of CDR3 libraries of DOM10-273.

Targeted diversification library 1.

The CDR2 region of DOM10-273 VH dAb (SEQ ID NO:1818) in pDOM5 vector was diversified in ten PCR reactions using 10 pg of template and SuperTaq DNA polymerase. The following forward primers: AS818 (SEQ ID NO:1921), AS819 (SEQ ID NO:1922), AS820 (SEQ ID NO:1923), AS821 (SEQ ID NO:1924), AS822 (SEQ ID NO:1925), AS823 (SEQ ID NO:1926), AS824 (SEQ ID NO:1927), AS825 (SEQ ID NO:1928), AS826 (SEQ ID NO:1929), AS827 (SEQ ID NO:1930) AS828 (SEQ ID NO:1931) were all used to run PCR amplification reactions using AS339 (SEQ ID NO:1951) as the reverese primer. The reaction products were pooled and gel purified on 2% E-Gel (Invitrogen, USA), forming Fragment Set 1. Fragment Set 1 was thereafter SOE PCR extended with the PCR reaction product formed from the amplification of the same vector construct with AS9 forward primer (SEQ ID NO:1916) and AS829 reverse primer (SEQ ID NO:1932). The

SOE PCR comprised of 15 cycles of amplification with SuperTaq DNA polymerase at 50°C annealing step. The formation of SOE product was verified by gel electrophoresis and a 5 µl aliquot of the reaction was further amplified with primers AS639 (SEQ ID NO:1952) and AS65 (TTGTAAAACGACGGCCAGTG; SEQ ID NO:1917). The CDR3 region of DOM10-273 VH dAb in pDOM5 vector was diversified in three PCR reactions using 10 pg of template and SuperTaq DNA polymerase. The following forward primers: AS830 (SEQ ID NO:1933), AS831 (SEQ ID NO:1934) and AS832 (SEQ ID NO:1935) were each combined with AS339 (CAGGAAACAGCTATGACCATG; SEQ ID NO:1951). The reaction products were pooled and gel purified on 2% E-Gel (Invitrogen, USA), forming Fragment Set 2. Fragment Set 2 was thereafter SOE PCR extended with the PCR reaction product formed from the amplification of the same vector construct with AS9 forward primer (SEQ ID NO:1916) and AS833 reverse primer (SEQ ID NO:1936). The SOE PCR comprised of 15 cycles of amplification with SuperTaq DNA polymerase at 50°C annealing step. The formation of SOE product was verified by gel electrophoresis and a 5 µl aliquot of the reaction was further amplified with primers AS339 (SEQ ID NO:1951) and AS65 (SEQ ID NO:1917).

The recombination reaction of CDR2 and CDR3-focused libraries of DOM10-273 (SEQ ID NO:1818), based on Fragment Sets 1 and 2, was performed in framework 3 region. The CDR2-library carrying fragments were generated by PCR amplification of Fragment Set 1 with primers AS639 (SEQ ID NO:1952) and AS660 (SEQ ID NO:1976). The CDR3-library carrying fragment was generated by PCR amplification of Fragment set 2 with primers AS659 (SEQ ID NO:1975) and AS65 (SEQ ID NO:1917). The SOE reaction was carried out as before, except that the extended product was reamplified with primers AS297 (SEQ ID NO:1977) and AS298 (SEQ ID NO:1978). The amplification reaction product was gel purified, cut with Sal I and Not I enzymes, re-purified on 2% E-Gels and then ligated into Sal I/Not I-cut pIE2a^{2}A vector.

Targeted diversification library 2.

The CDR2 region of DOM10-275 VH dAb in pDOM5 vector was diversified in ten PCR reactions using 10 pg of template and SuperTaq DNA

polymerase. The following forward primers: AS836 (SEQ ID NO:1939), AS837 (SEQ ID NO:1940), AS838 (SEQ ID NO:1941), AS839 (SEQ ID NO:1942), AS840 (SEQ ID NO:1943), AS841 (SEQ ID NO:1944), AS842 (SEQ ID NO:1945), AS843 (SEQ ID NO:1946), AS844 (SEQ ID NO:1947), AS845 (SEQ ID NO:1948) AS846 (SEQ ID NO:1949) were all used to run PCR amplification reactions using AS339 (SEQ ID NO:1951) as the reverese primer. The reaction products were pooled and gel purified on 2% E-Gel (Invitrogen, USA), forming Fragment Set 3. Fragment Set 3 was thereafter SOE PCR extended, as described above, with the PCR reaction product formed from the amplification of the same vector construct with AS9 forward primer (SEQ ID NO:1916) and AS847 reverse primer (SEQ ID NO:1950). The formation of SOE product was verified by gel electrophoresis and a 5 µl aliquot of the reaction was further amplified with primers AS65 (SEQ ID NO:1917) and AS639 (SEQ ID NO:1952). The CDR3 region of DOM10-273 VH dAb in pDOM5 vector was diversified in three PCR reactions using 10 pg of template and SuperTaq DNA polymerase. The following forward primers: AS848 (SEQ ID NO:1953), AS849 (SEQ ID NO:1954) and AS850 (SEQ ID NO:1955) were each combined with AS339 (SEQ ID NO:1951). The reaction products were pooled and gel purified on 2% E-Gel (Invitrogen, USA), forming Fragment Set 4. Fragment Set 4 was thereafter SOE PCR extended with the PCR reaction product formed from the amplification of the same vector construct with AS9 forward primer (SEQ ID NO:1916) and AS851 reverse primer (ATAAGCTTTCGCACAGTAATATAC; SEQ ID NO:1956). The formation of SOE product was verified by gel electrophoresis and a 5 µl aliquot of the reaction was further amplified with primers AS339 (SEQ ID NO:1951) and AS65 (SEQ ID NO:1917).

The recombination reaction of CDR2 and CDR3-focused libraries of DOM10-275, based on Fragment Sets 3 and 4, was performed in framework 3 of the dAb molecule. The CDR2-library carrying fragments were generated by PCR amplification of Fragment Set 3 with primers AS639 (SEQ ID NO:1952) and AS660 (SEQ ID NO:1976). The CDR3-library carrying fragment was generated by PCR amplification of Fragment set 4 with primers AS659 (SEQ ID NO:1975) and AS65 (SEQ ID NO:1917). The SOE reaction was carried out as above, except that the extended product was reamplified with primers AS297 (SEQ ID NO:1977) and

AS298 (SEQ ID NO:1978). The amplification reaction product was gel purified, cut with Sal I and Not I enzymes, re-purified on 2% E-Gels and then ligated into Sal I/Not I-cut pIE2a^{2}A vector.

Targeted diversification library 3.

The CDR2 region of DOM10-276 VH dAb in pDOM5 vector was diversified in ten PCR reactions using 10 pg of template and SuperTaq DNA polymerase. The following forward primers: AS854 (SEQ ID NO:1959), AS855 (SEQ ID NO:1960), AS856 (SEQ ID NO:1961), AS857 (SEQ ID NO:1962), AS858 (SEQ ID NO:1963), AS859 (SEQ ID NO:1964), AS860 (SEQ ID NO:1965), AS861 (SEQ ID NO:1966), AS862 (SEQ ID NO:1967), AS863 (SEQ ID NO:1968) AS864 (SEQ ID NO:1969) were all used to run PCR amplification reactions using AS339 (SEQ ID NO:1951) as the reverese primer. The reaction products were pooled and gel purified on 2% E-Gel (Invitrogen, USA), forming Fragment Set 5. Fragment Set 5 was thereafter SOE PCR extended, as described above, with the PCR reaction product formed from the amplification of the same vector construct with AS9 forward primer (SEQ ID NO:1916) and AS865 reverse primer (SEQ ID NO:1970). The formation of SOE product was verified by gel electrophoresis and a 5 µl aliquot of the reaction was further amplified with primers AS65 (SEQ ID NO:1917) and AS639 (SEQ ID NO:1952). The CDR3 region of DOM10-273 VH dAb in pDOM5 vector was diversified in three PCR reactions using 10 pg of template and SuperTaq DNA polymerase. The following forward primers: AS866 (SEQ ID NO:1971), AS867 (SEQ ID NO:1972) and AS868 (SEQ ID NO:1973) were each combined with AS339 (SEQ ID NO:1951). The reaction products were pooled and gel purified on 2% E-Gel (Invitrogen, USA), forming Fragment Set 6. Fragment Set 6 was thereafter SOE PCR extended with the PCR reaction product formed from the amplification of the same vector construct with AS9 forward primer (SEQ ID NO:1916) and AS869 reverse primer (ATAAGCTTTCGCACAGTAATATAC; SEQ ID NO:1974). The formation of SOE product was verified by gel electrophoresis and a 5 µl aliquot of the reaction was further amplified with primers AS339 (SEQ ID NO:1951) and AS65 (SEQ ID NO:1917).

The recombination reaction of CDR2 and CDR3-focused libraries of DOM10-276, based on Fragment Sets 5 and 6, was performed in framework 3 of the dAb molecule. The CDR2-library carrying fragments were generated by PCR amplification of Fragment Set 3 with primers AS639 (SEQ ID NO:1952) and AS660 (SEQ ID NO:1976). The CDR3-library carrying fragment was generated by PCR amplification of Fragment set 4 with primers AS659 (SEQ ID NO:1975) and AS65 (SEQ ID NO:1917). The SOE reaction was carried out as above, except that the extended product was reamplified with primers AS297 (SEQ ID NO:1977) and AS298 (SEQ ID NO:1978). The amplification reaction product was gel purified, cut with Sal I and Not I enzymes, re-purified on 2% E-Gels and then ligated into Sal I/Not I-cut pIE2a^{2}A vector.

Targeted diversification library 4.

The recombination reaction of all CDR2 and CDR3-focussed libraries across all three VH dAbs DOM10-273 (SEQ ID NO:1818), DOM10-275 (SEQ ID NO:1871) and DOM10-276 (SEQ ID NO:1872) was performed in framework 3 of the dAb molecule. The CDR2-library carrying fragments were generated by PCR amplification of libraries made from Fragment Sets 1, 3 and 5 with primers AS639 (SEQ ID NO:1952) and AS660 (SEQ ID NO:1976). The CDR3-library carrying fragment was generated by PCR amplification of libraries made from Fragment Sets 2, 4 and 6 with primers AS659 (SEQ ID NO:1975) and AS65 (SEQ ID NO:1917). The SOE reaction was carried out as before, except that the extended product was reamplified with primers AS297 (SEQ ID NO:1977) and AS298 (SEQ ID NO:1978). The amplification reaction product was gel purified, cut with Sal I and Not I enzymes, re-purified on 2% E-Gels and then ligated into Sal I/Not I-cut pIE2a^{2}A vector.

Targeted diversification library 5.

The recombination reaction of all CDR2-focused library of DOM10-273 (SEQ ID NO:1818) with the CDR3-focused library of DOM10-273 was performed in framework 3 of the dAb molecule. The CDR2-library carrying fragments were generated by PCR amplification of library made from Fragment Set 3 using primers

AS639 (SEQ ID NO:1952) and AS660 (SEQ ID NO:1976). The CDR3-library carrying fragment was generated by PCR amplification of libraries made from Fragment Sets 2 using primers AS659 (SEQ ID NO:1975) and AS65 (SEQ ID NO:1917). The SOE reaction was carried out as above, except that the extended product was reamplified with primers AS297 (SEQ ID NO:1977) and AS298 (SEQ ID NO:1978). The amplification reaction product was gel purified, cut with Sal I and Not I enzymes, re-purified on 2% E-Gel and then ligated into Sal I/Not I-cut pIE2a^{2}A vector.

Selections from targeted diversification libraries of DOM10-273 DOM10-275 and DOM10-276 lineages.

Targeted diversification libraries of DOM10-273 (SEQ ID NO:1818), DOM10-275 (SEQ ID NO:1871) and DOM10-276 (SEQ ID NO:1872) lineages were ligated and quantified as described above for the error-prone PCR libraries. The libraries were then subjected to ten rounds of selection. In the first round of selection the antigen concentration was 40 nM, in the second round 20 nM, followed by eight rounds at 10 nM. The competitor dAb DOM10-275-1 (SEQ ID NO:1918) was applied at 1 μM concentration starting from the fourth round of selection for 10, 20, 20, 30, 50, 90 and 90 minutes, after 15-minute equilibration with the antigen. The selection output was cloned into pDOM5 expression vector and the culture supernatants were screened by surface plasmon resonance on BIAcore 1000. A number of clones were identified (for example, DOM10-275-13 (SEQ ID NO:1989), DOM10-275-15 (SEQ ID NO:1990), DOM10-275-20 (SEQ ID NO:1991), DOM10-275-8 (SEQ ID NO:1992), DOM10-276-13 (SEQ ID NO:1993), DOM10-276-14 (SEQ ID NO:1994), DOM10-276-15 (SEQ ID NO:1995), DOM10-276-17 (SEQ ID NO:1996), DOM10-276-7 (SEQ ID NO:1997), DOM10-276-8 (SEQ ID NO:1998), DOM10-275-11 (SEQ ID NO:1999), DOM10-275-12 (SEQ ID NO:2000), DOM10-275-14 (SEQ ID NO:2001), DOM10-275-16 (SEQ ID NO:2002), DOM10-275-17 (SEQ ID NO:2003), DOM10-275-5 (SEQ ID NO:2004), DOM10-275-6 (SEQ ID NO:2005), DOM10-275-7 (SEQ ID NO:2006), DOM10-275-9 (SEQ ID NO:2007), DOM10-276-10 (SEQ ID NO:2008), DOM10-276-11 (SEQ ID NO:2009), DOM10-276-12 (SEQ ID NO:2010), DOM10-276-16 (SEQ ID NO:2011), DOM10-276-5

(SEQ ID NO:2012), DOM10-276-6 (SEQ ID NO:2013), DOM10-276-9 (SEQ ID NO:2014)).

TABLE 14

IL-13 assays	
IL-13 BIAcore binding assay	
DOM10-276-15	
	Kd (nM)
Expt. 1	1.5
IL-13 sandwich ELISA	
	IC50 (nM)
DOM10-276-15	
Expt. 1	100
IL-13 cell binding assay	
	IC50 (nM)
Expt. 1	90

Epitope mapping of anti-IL-13 dAbs

To determine the epitope specificity of the anti-IL-13 dAbs, Biacore competition experiments were performed. dAb DOM10-176-535 (SEQ ID NO:1362) was injected, followed immediately by injection of dAb *DOM10-53-99* (SEQ ID NO:738). *dAb DOM10-53-99 (SEQ ID NO:738)* did not bind to IL-13 to which dAb DOM10-176-535 (SEQ ID NO:1362) has already bound. This indicates that these dAbs bound to the same epitope. This competition protocol can generally be used to assess competition (and epitope mapping) of a test antibody or fragment with a known dAb (or other antibody polypeptide) for binding to IL-13.

B cell proliferation assay

It has been shown previously that CD40L is able to activate cells to be responsive to IL-13. Indeed all donors tested in this study showed a dose-dependent proliferation when their B cells were incubated with irradiated $CD40L^+$ L cells and increasing concentrations of IL-13. As negative controls B cells alone or CD40L transfected L cells alone were used. The addition of anti-IL-13 dAbs DOM10-53-338 (SEQ ID NO:886) and DOM10-176-535 (SEQ ID NO:1362) resulted in an

inhibition of IL-13 induced proliferation of B cells from all donors (FIG. 15). With both dAbs DOM10-53-338 (SEQ ID NO:886) and DOM10-176-535 (SEQ ID NO:1362) the average inhibition was 80% and 100% at concentrations of 10 nM and 100 nM respectively. Complete inhibition of the B cell proliferation was also observed with 3 μg/ml of positive control anti-IL 13 mAb (R&D). Control dAbs that did not bind IL-13 failed to inhibit this B cell proliferation.

PEGylated monomer

The anti-IL13 dAb DOM10-53-338 (SEQ ID NO:886) was PEGylated via the N-terminus using a 30K aldehyde PEG moiety or via surface lysines using the 40K PEG2-NHS activated moiety. The anti-IL13 dAbs DOM10-53-343 (SEQ ID NO:891) was also cloned with a cysteine at the C-terminus of the protein. This molecule was PEGylated via the C terminus using using PEG-Maleimide with a branched 40K PEG2-MAL moiety. To determine the effect of PEGylation the PEGylated DOM10-53-338 dAbs were tested for their ability to inhibit IL-13 binding in the IL-13 receptor binding assay and to inhibit IL-13 induced TF-1 cell proliferation. The potency of both the 30K PEGylated DOM10-53-338 dAb and the 40K PEGylated DOM10-53-338 dAb was maintained in the IL-13 receptor binding assay (Table 15) and in the IL-13 induced TF-1 cell proliferation assay (Table 15). To determine the effect of C-terminal PEGylation, the PEGylated (40K PEG2-MAL) DOM10-53-343 dAbs were tested for their ability to inhibit IL-13 binding in the IL-13 receptor binding assay (Table 15). The potency of the C-terminal PEGylated DOM10-53-343 dAb was slightly improved compared to the native DOM10-53-343 dAb in the IL-13 receptor binding assay.

TABLE 15

PEGylated anti IL-13 dAbs	
	IC50 (pM)
IL-13 receptor I binding assay	
DOM10-53-338	387
DOM10-53-338 30K PEG ALD	169
DOM10-53-338 40K PEG2 NHS	226
IL-13 induced TF-1 proliferation	
DOM10-53-338	423
DOM10-53-338 30K PEG ALD	181

DOM10-53-338 40K PEG2 NHS	231
IL-13 receptor I binding assay	
DOM10-53-343	136
DOM10-53-343 40K PEG2 MAL	33

Biophysical properties of anti-IL-13 dAbs

In order to develop a product for pulmonary delivery it is desired that the molecule has good biophysical properties. Poor chemical stability and physical stability may reduce the biological activity. Pulmonary delivered proteins may be exposed to additional stress e.g shearing forces and increased temperatures in the nebulising device. The lungs can metabolise some of the delivered dose and in some disease indications high levels of proteases can be present that can affect the biological activity. To this end we investigated the solution state by Multi Angle Light Scattering (MALS) and the melting temperature as determined by differential scanning calorimetry (DSC) of the DOM10-53 lineage molecules.

SEC-MALLS (*multi angle LASER light scattering*)

The in-solution properties of dAb proteins were determined by an initial separation on SEC (size exclusion chromatography; TSKgel G2000/3000SWXL, Tosoh Biosciences, Germany; BioSep-SEC-S2000/3000, Phenomenex, CA, USA) and subsequent on-line detection of eluting proteinaceous material by UV (Abs280nm), RI (refractive index) and light scattering (laser at 685nm). The proteins were at an initial concentration of 0.5-1mg/mL, as determined by absorbance at 280nm, and visually inspected for impurities by SDS-PAGE. The homogeneity of samples to be injected was usually >90%. 100uL were injected onto the SEC column. The protein separation on SEC was performed at 0.5mL/min for 45minutes. PBS (phosphate buffered saline ±10% EtOH) was used as mobile phase. The ASTRA software (Wyatt Inc; CA; USA) integrated the signals of all three detectors and allowed for the determination of the molar masses in kDa of proteins from 'first physical principles'. Self-association of proteins could reliably be determined as shown by orthogonal methods (i.e. AUC) for some characteristic dAbs. Inter-run variations and data quality was assessed by running a positive control of known in-solution state with every sample batch. For some DOM10-53 clones no reliable solution state could be assigned because the molecules bound

aspecifically to the column matrix or could not be resolved using the size exclusion column. For those cases when the solution state was reliable (*i.e.* DOM10-53 (SEQ ID NO: 651), DOM10-53-531 (SEQ ID NO:2097), and DOM10-53-612 (SEQ ID NO:2044)) it was shown that the DOM10-53 (SEQ ID NO:651) molecule is mostly a monomer in solution.

DSC (*differential scanning calorimetry*)

Proteins were dialysed overnight into PBS buffer (phosphate buffered saline), diluted and filtered to yield a concentration of 0.5 mg/ml in PBS, as determined by absorbance at 280nm. PBS buffer was used as a reference for all samples. DSC was performed using capillary cell microcalorimeter VP-DSC (Microcal, MA, USA), at a heating rate of 180°C/hour. A typical scan usually was from 25-90°C for both the reference buffer and the protein sample. After each reference buffer and sample pair, the capillary cell was cleaned with a solution of 1% Decon in water followed by PBS. Resulting data traces were analysed using Origin 7 Microcal software. The DSC trace obtained from the reference buffer was subtracted from the sample trace. The precise molar concentration of the sample was entered into the data analysis routine to yield values for appTm, enthalpy (ΔH) and van't Hoff enthalpy (ΔHv) values. Data usually were fitted to a non-2-state model. The DSC experiments showed that some DOM10-53 molecules (*e.g.* 10-53-472 (SEQ ID NO:2103) and 10-53-474 (SEQ ID NO:2105)) have higher melting temperatures compared to others (*e.g.* 10-53-344 and 10-53-434), whilst they maintain their potency. Such properties are indicative of increased stability and are useful for pulmonary delivery.

Table 16

Molecule	Tm (°C)	Mw	SEC MALLS	Potency IC50(pM)
10-53-344	52.6/54.2	-	n.d.	100
10-53-434	53.4	17kDa/27kDa	Monomer/dimer	290
10-53-531	62.7	15,5 kDa	Monomer	340
10-53	62.7		Monomer	100 nM
10-53-612	63.6		Monomer	20 nM

10-53-472	57.4		n.d.	54
10-53-474	57.5		n.d.	n.d.
10-53-475	55.3		n.d.	46

Determination of the Pharmacokinetics of an Anti-IL-13 dAb delivered via the pulmonary route of administration.

Test Substance

DOM10-53-613 (SEQ ID NO: 2022) binds human IL-13, but not murine IL-13. DOM10-53-613 (at 1.2 mg/ml) with an HA tag for detection was diluted in 20mM sodium citrate pH6.0, 100mM NaCl. It was warmed from its storage temperature to 37°C prior to administration. DOM10-53-613 (at 1.2 mg/ml) was administered to 8 week old male BALB/c mice. Animals were lightly anaesthetised and 50µl of the relevant dAb solution or vehicle dropped gently onto the nares. The animals were held in an upright position for a few seconds while spontaneously breathing in the solution before being allowed to recover and returned to their home cage. Thereafter mice were killed at the following time points at 10 minutes, 1 hour, 2 hours, 4 hours, 8 hours and 16 hours. Serum, lung gavage and lung homogenate were collected from each mouse at each time point. Three mice were sampled at each time point

ELISA to detect HA tagged dAbs

A 96-well Maxisorp (Nunc) assay plate was coated overnight at 4°C with 100µl per well of goat polyclonal anti HA tag antibody (Abcam) at 2µg/ml in carbonate buffer. Wells were washed 3 times with 0.05% tween/PBS and 3 times with PBS. 200µl per well of 2% BSA in PBS was added to block the plate. Wells were washed and then 100µl of HA tagged dAb standard or sample was added. Wells were washed and then 100µl Protein A – HRP (1:5000 dilution; Amersham) was added to each well. Plates were developed with 100µl of SureBlue 1-Component TMB MicroWell Peroxidase (KPL, Gaithersburg, USA) solution added to each well, and the plate was left at room temperature until a suitable signal had developed. The reaction was stopped by the addition of HCl and the absorbance was

read at 450 nm. Data was plotted in GraphPad and then fitted in WinNonLin using a non-compartmental model.

Results

The DOM10-53-613 (SEQ ID NO:2022) levels in the BAL show that the dAbs were delivered efficiently into the lung lumen. A maximum level of 19 μg/ml (~7 μg in 0.4 ml) can be detected in the BAL at 1 hr. This means that at least 12% (7 μg of 60μg total delivered) of the delivered dose was delivered in the lung lumen. It is likely that not all material can be recovered using the lavage procedure and this value is an underestimate. The levels in the BAL are maximal at 1 hour and dAbs are cleared with $t_{1/2}$ of 4.4 hrs, resulting in greater than 10-fold reduced concentrations at 16 hours.

DOM10-53-613 (SEQ ID NO:2022) levels in the lung show maximum levels at 2 hours of 3.4 μg/ml. This means that approximately 5- 6% of the delivered dose was present in the lung tissue. The decline of levels in the lung shows a similar pattern as for the BAL. There was a maximum level at 10 minutes followed by a clearance rate with $t_{1/2}$ of approximately 4.7 hours, resulting in greater than 10-fold reduced concentrations at 16 hours.

DOM10-53-613 (SEQ ID NO:2022) serum levels were detected. Serum levels were at a maximum at 4 hours. At 4 hours a maximum level of 0.73 μg/ml was detected in the serum. This means that ~1% (0.7 μg of 60 μg delivered) of the delivered material can be detected in the serum.

Table 17

	BAL	LUNG	SERUM
T ½ (hr)	4.4	4.7	3.5
AUC0 - ∞ (μg*hr/mL)	103.2	29.7	6.6
Clearance (mL/hr/kg)	29.1	101.1	455.5
C Max (μg/mL)	19.0	3.4	0.7

T Max (hr)	1	0.167	4

EXAMPLE 4: Ligands that bind IL-4 and IL-13

A. Fusion Proteins

Cloning and production of anti-IL-4 and anti-IL-13 dual specificity dimer

Nucleic acids encoding the anti-IL-4 dAb DOM9-112 and anti-IL-13 dAb DOM10-53-343 (SEQ ID NO:891) were cloned into a construct that encoded an in-line fusion protein with a C-terminal cysteine. The amino acid sequence AST was present between the two dAbs, this sequence is the natural CH sequence present in natural antibodies. The construct was cloned in the *Pichia pastoris* vector pPICZα (Invitrogen). Electrocompetent cells (X-33 or KM71H) were transformed with the construct and transformants were selected on 100 μg/ml Zeocin. 500ml cultures were grown on BMGY media at 30° C, 250 rpm for 24 hrs until the OD_{600} had reached ~15-20. The cells were then spun down and resuspended in BMMY media (containing 0.5% (v/v) methanol) to induce protein expression. The cultures were maintained at 30°C with shaking at 250 rpm. At 24 hour intervals the cultures were fed with the following incremental increase in the methanol concentration; 1%, 1.5% and 2% (v/v) using a 50% methanol solution. The cultures were then harvested by centrifugation and the supernatant containing the expressed protein stored at 4°C until required. The protein was purified from the supernatant using PrA streamline using the standard purification protocol.

The PrA purified protein was found to contain both dimer and monomer species. Therefore chromatofocusing was used to separate the two proteins. A Mono P 5/20 column was used (GE Healthcare) for the separation, using a pH gradient of 6 to 4. The poly-buffers used were as described by the manufacturer to make the 6 to 4 pH range. The sample was applied at pH6 and the pH gradient generated by using 100% buffer B over 35 column volumes run at 1ml/min. Dimer containing fractions were identified using SDS-PAGE and pooled for PEGylation.

The protein was then PEGylated using 40K PEG2-MAL using the method outlined above. This material was purified using anion exchange chromatography

up to a purity >95%. The potency of the resulting dual specific ligand (PEGylated DOM9-112 (AST) DOM10-53-344) was determined in an IL-4 RBA (FIG. 16A) and an IL-13 RBA (FIG. 16B). The potency of the anti-IL-4 arm of the dual specific ligand (13 nM) was slightly reduced compared with the potency of the dAb DOM9-112 monomer (3.5 nM), whereas the potency of the anti-IL-13 arm was maintained (310 pM for the dual specific ligand vs 230pM for the dAb monomer).

The anti-IL-4 and anti-IL-13 dAbs DOM9-112 (SEQ ID NO:25) and DOM10-53-344 (SEQ ID NO:892) were also cloned as an in-line fusion with the amino acid sequence ASTKGPS (SEQ ID NO:1803) present between the two dAbs, this sequence is the start of the CH sequence present in natural antibodies. The potency of the resulting purified dual specific ligand (DOM9-112 (ASTKGPS) DOM10-53-344) was determined in an IL-4 RBA (FIG. 17A) and an IL-13 sandwich ELISA (FIG. 17B). The potency of the anti-IL-4 arm was maintained (~1 nM) whereas the potency of the anti-IL-13 arm was only slightly reduced compared with the dAb monomer (40pM for the dAb monomer vs 120 pM for the dual specific ligand).

Additional dual targeting in-line fusions for IL-4 and IL-13.

To further understand the behaviour of dual targeting in-line fusions of IL4 and IL13 binding dAbs, a series of new in-line fusions and in-line fusion libraries were constructed. The DOM10-53 lineage was affinity matured using phage display using libraries diversifying triplet residues of FR1, CDR1, CDR2 and CDR3. The libraries were cloned in a phage vector and displayed as fusion potein to the gene3 protein as an (dAb1 linker dAb2) in-line fusion with dAb1 being DOM9-112-210 (SEQ ID NO: 2401), the linker being amino acid residues ASTKGPS (SEQ ID NO:1803) and dAb2 being the DOM10-53 library. The selection method, subcloning and expression in E coli and screening method were essentially performed as described above, except that in-line fusion constructs were used instead of single dAbs. Outputs were cloned into vector pDOM5 and expression supernatants were screened for improved expression by binding to a protein A coated Biacore chip.

In-line fusions with improved expression levels were expressed, purified and tested in a IL-13 sandwich ELISA and cell assay. A number of variants were selected (including DOM9-112-210 – ASTKGPS – DOM10-53-566). The most potent clones were DOM10-53-531 (SEQ ID NO:2097) and DOM10-53-546 (SEQ ID NO:2110) (see Table 18). Different protein preparations were made from these clones and these were tested in the IL-4 RBA and IL-13 sandwich assay as described above.

Table 18

Clone name	Expression level (mg/l)	IL-13 Sanwich ELISA (EC50 nM)	IL-4 RBA (IC50 nM)
DOM9-112-210-DOM10-53-531			
Prep 1	9.3	1.1/1.9	3.5/4.8
Prep 2	11.5	4.9	n.d.
Prep 3	4.5	2/2.8	13.9
Prep 4	10	1	5.4
DOM9-112-210-DOM10-53-546			
Prep 1	2.2	0.62/0.77	4.3
Prep 2	7.7	1	6

Further in-line fusions were constructed by SOE PCR of the DNA fragments encoding a dAb linker which is either ASTKGPS (SEQ ID NO:1803), if the first dAb was a Vh, or TVAAPS (SEQ ID NO:2459) if the first dAb was a Vk. This PCR product was digested with SalI/NotI and ligated in the *E. coli* expression vector pDOM5. After transformation to MACH1 (Invitrogen) cells, the clones were sequence verified and the in-line fusions were expressed. Expression was done by growing *E. coli* in 2TY supplemented with Onex media (Novagen) for 2 nights at 30°C, the cells were centrifuged and the supernatant was incubated with either Protein-L or Protein-A resin. After elution from the resin, the quality and quantity of produced in-line fusion product was verified on SDS-PAGE. The vast majority of product formed had the molecular mass of an in-line fusion with only limited free monomer. Therefore, no additional purification steps were required and the material could be tested directly.

Using the above described method the following IL-4/IL-13 in-line fusions were expressed, purified and characterised:

DOM9-112-210 – ASTKGPS – DOM10-208
DOM9-112-210 – ASTKGPS – DOM10-212
DOM9-112-210 – ASTKGPS – DOM10-213
DOM9-112-210 – ASTKGPS – DOM10-215
DOM9-112-210 – ASTKGPS – DOM10-224
DOM9-112-210 – ASTKGPS – DOM10-270
DOM9-112-210 – ASTKGPS – DOM10-416
DOM9-112-210 – ASTKGPS – DOM10-236
DOM9-112-210 – ASTKGPS – DOM10-273
DOM9-112-210 – ASTKGPS – DOM10-275
DOM9-112-210 – ASTKGPS – DOM10-276
DOM9-112-210 – ASTKGPS – DOM10-277
DOM10-208 – TVAAPS - DOM9-155-78
DOM10-212 - TVAAPS - DOM9-155-78
DOM10-213 - TVAAPS - DOM9-155-78
DOM10-215 - TVAAPS - DOM9-155-78
DOM10-224 - TVAAPS - DOM9-155-78
DOM10-270 - TVAAPS - DOM9-155-78
DOM10-416 - ASTKGPS - DOM9-155-78
DOM10-236 - ASTKGPS - DOM9-155-78
DOM10-273 - ASTKGPS - DOM9-155-78
DOM10-275 - ASTKGPS - DOM9-155-78
DOM10-276 - ASTKGPS - DOM9-155-78
DOM10-277 - ASTKGPS - DOM9-155-78

Once purified, the expression levels were determined (mg/l) and the activities were tested in an RBA for IL-4 binding and in a sandwich ELISA for IL-13 binding. The table below (Table 19) summarises the data for these in-line fusions:

Table 19

clone name	Expression mg/ml			IL-13 Biacore	Dom10 RBA (EC50 nM)	DOM9 RBA (IC50 nM)
DOM9-112-210-DOM10-208	0.3	19.2	37.4	√	-	2.48
DOM9-112-210-DOM10-212	3.7		6.3	√	999.9	3.21
DOM9-112-210-DOM10-213	5.6	0.2	4.9	√	1152	4.29
DOM9-112-210-DOM10-215	0.1	8.8	2.2	√	-	14.19
DOM9-112-210-DOM10-224	4.6		13.4	√	4575	2.75
DOM9-112-210-DOM10-270	3.7		2.7	√	397.5	2.79
DOM9-112-210-DOM10-416	6.9		0.0	√	34420	7.27
DOM9-112-210-DOM10-236	0.2	0.1	2.2	√	-	>20
DOM9-112-210-DOM10-273	1.2		0.3	√	4553	10.51
DOM9-112-210-DOM10-275	4.9	0.2	0.0	√	-	10.89
DOM9-112-210-DOM10-276	6.9		0.1	√	-	10.20
DOM9-112-210-DOM10-277	1.3	3.7	0.2	√	4385	11.74
DOM10-208-DOM9-155-78			41.0	√	4243	8.18
DOM10-212-DOM9-155-78			0.5	√	-	>20
DOM10-213-DOM9-155-78			16.9	√	62.04	6.91
DOM10-215-DOM9-155-78			22.6	√	10.82	6.65
DOM10-224-DOM9-155-78			3.6	√	-	12.49
DOM10-270-DOM9-155-78			2.9	√	37.23	8.60
DOM10-416-DOM9-155-78		1.1	26.3	√	443.7	5.88
DOM10-236-DOM9-155-78		3.6	10.8	√	372	2.54
DOM10-273-DOM9-155-78		6.4	16.2	√	185.2	2.25
DOM10-275-DOM9-155-78		0.2	0.0	-	-	-
DOM10-276-DOM9-155-78		0.2	20.0	√	-	5.02
DOM10-277-DOM9-155-78		1.1	1.3	√	648	9.45
					DOM9-112	3.60
					DOM9-155-78	0.41

Furthermore, an affinity matured variant of DOM10-275 (SEQ ID NO:2196), *i.e.* DOM10-275-1 (SEQ ID NO:2241), was specifically chosen to be paired with both DOM9-112-210 (SEQ ID NO:2434) and DOM9-155-78 (SEQ ID NO:2427). These in-line fusions were constructed and expressed as described above. In addition to testing in the mentioned IL-4 RBA and IL-13 sandwich ELISA, these in-line fusions were also tested for functionality in a TF-1 cell proliferation assay. In these assays the dAb was preincubated with a fixed amount of either IL-4 or IL-13, this mixture was added to the TF-1 cells and the cells were incubated for 72 hours.

After this incubation, the level of cell proliferation was determined. The results of this assay are summarised below (Table 20) and demonstrate that both arms of the in-line fusion were active in the cell assay.

Table 20

Sample	DOM9 RBA IC50 (nM)	DOM10 RBA IC50 (nM)	Il-4 cell assay IC50 (nM)	IL-13 cell assay IC50 (nM)
DOM9-112-210	0.391	-		
DOM9-155-78	0.456	-		
DOM10-275-1-DOM9-155-78	6.238	39.17	5.1 - 7.6	31 - 46
DOM9-112-210-DOM10-275-1	4.189	44.88	6.8 - 10.2	27 - 40
DOM10-275-1	-	31.30		

B. IgG-Like formats

Cloning, expression as dual specific IgG

IgG-like formats that bound IL-4 and IL-13 were expressed using the vector pDOM30. This vector is based on the Invitrogen pBudCE4.1 backbone and has been modified to comprise a codon-optimised heavy chain cassette under control of the CMV promoter and a codon-optimised light chain cassette under control of the EF1-alpha promoter. dAbs were cloned into the heavy chain cassette using the BamHI and XhoI restriction sites, and into the light chain cassette using SalI and BsiWI restriction sites. This strategy resulted in native heavy and light chain N-termini and the following variable-constant domain junctions. IgG expression constructs were transformed into chemically competent MachI cells (Invitrogen) grown on low salt LB agar supplemented with 250μg/L zeocin. For each construct, plasmid DNA was prepared from 3 or 4 randomly picked colonies and dAb sequences were verified using the primers CMV-F (CGCAAATGGGCGGTAGGCGTG) (SEQ ID NO:1795) and pIG(EF1-alpha) (TGAGTGGGTGGAGACTG) (SEQ ID NO:1796). Endotoxin-free plasmid DNA was prepared from 500mL overnight cultures using the Qiagen endo-free Megaprep kit for verified clones.

The specificity of the anti-IL-4 and anti-IL-13 specific IgG-like format was assessed in IL-4 receptor RBA, and the IL-13 sandwich ELISA. FIG. 18 shows that the potency of the anti-IL-4 dAb monomer DOM9-44-502 (SEQ ID NO:361) was 3-4 fold reduced when formatted in the IgG-like format (4nM for the dAb monomer vs. 13nM for the IgG-like format), whereas the potency of the anti-IL-13 dAb DOM10-176-535 (SEQ IDNO:1362) was 1nM for both the dAb monomer and the IgG-like format.

Determination of the Pharmacokinetics of [^{3}H]-PEGylated Anti-IL13 dAbs and anti-IL-4 and anti-IL13 in-line fusions

Radiolabelling of PEGylated Anti-IL13 dAbs and anti-IL-4 and anti-IL13 in-line fusions.

Anti-IL13 dAbs and anti-IL-4 and anti-IL13 in-line fusions were expressed and PEGylated using the N-terminus (α-amino group) or C-terminus using a 40K branched PEG as described above. The protein was radiolabelled with tritium using N-Succinimidyl[2,3-^{3}H]propionate (NSP) in hexane:ethyl acetate (9:1). 400µL of NSP was dispensed into a vial and the solvent was removed under a gentle stream of nitrogen at ≤30°C. The residue was then re-suspended in 100µL of DMSO. 2.5mL of DOM0910 40K branched PEG was then added to the NSP/DMSO and the mixture was incubated for 60 minutes at room temperature. Following incubation, the solution was loaded onto a PD10 column that was pre-equilibrated with 25mL of phosphate buffered saline (PBS) and the eluate was discarded. Radiolabelled protein was then eluted off the PD10 column using 3.5mL of PBS and the eluate was collected. The specific activity of the material was determined (assuming a 100% labelling efficiency and recovery of protein from the PD10 column) and the solution was used immediately or stored at approximately 4°C until required.

Animal Work.

For each molecule, 3 female Spargue-Dawley rats received a single intravenous dose at 1mg/kg. Serial blood samples were then collected from the tail vein after 2 minutes, 2 hours, 8 hours, 24 hours, 48 hours, 72 hours and 96 hours.

The final blood sample was collected after 120 hours immediately prior to sacrifice by cardiac puncture under anaesthetic.

To obtain serum, blood samples were collected and allowed to clot. Once clotted, samples were centrifuged at 3000rpm for 10mins. Serum was then harvested and stored at -20°C until analysis.

Determination of Radioactivity.

The radioactive content of each sample was determined by liquid scintillation counting with automatic quench correction. Serum samples were mixed with PBS prior to addition of scintillation fluid. Disintegration rates from appropriate blank sample vials were subtracted from sample disintegration rates to give net dpm for each sample. Gross radioactivity below twice background level was considered to be below the limit of reliable measurement.

Additional weighed aliquots of serum obtained after 2 minutes and 48 and 120 hours post dose were lyophilised prior to determination of radioactivity concentration to determine any contribution to total counts from free tritium.

Data have been fitted using Winonlin fitting software and terminal half life values are determined and described in Table 21. DOM9-112-210 ASTKGPS DOM10-53-612 with N-terminal 40K Branched PEG has a terminal half life of 41 hrs. whereas DOM9-112-210 ASTKGPS DOM10-53-612 with C-terminal 40K Branched PEG has an half life of 32 hrs.

Table 21

Molecule	Animal #1	Animal #2	Animal #3	Mean (hrs)
DOM9-112-210 ASTKGPS DOM10-53-612 C-term 40K Branched PEG	32.25	32.51	32.01	32.26
DOM9-112-210 ASTKGPS DOM10-53-612 N-term 40K Branched PEG	38.37	44.32	41.38	41.36
DOM10-53-612 N-term 40K Branched PEG	46.06	31.39	54.35	43.93
DOM10-53-612 C-term 40K Branched PEG	46.58	46.57	41.45	44.87

The teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A ligand that has binding specificity for interleukin-4 (IL-4) and interleukin-13 (IL-13) comprising

a protein moiety that has a binding site with binding specificity for IL-4; and

a protein moiety that has a binding site with binding specificity for IL-13,

with the proviso that said protein moiety that has a binding site with binding specificity for IL-4 is not an IL-4 receptor or IL-4-binding portion thereof, and said protein moiety that has a binding site with binding specificity for IL-13 is not an IL-13 receptor or IL-13-binding portion thereof.

2. The ligand of claim 1, wherein said protein moiety that has a binding site with binding specificity for IL-4 competes for binding to IL-4 with IL-4Rα, an IL-4-binding portion of IL-4Rα or an anti-IL-4 domain antibody (dAb) selected from the group consisting of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

3. The ligand of claim 1, wherein said protein moiety that has a binding site with binding specificity for IL-13 competes for binding to IL-13 with IL-13Rα1, an IL-13-binding portion of IL-13Rα1, IL-13Rα2, an IL-13-binding portion of IL-13Rα2, or an anti-IL-13 domain antibody (dAb) selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396

(SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO: 2369) and DOM10-275-1 (SEQ ID NO:2241).

4. The ligand of claim 1, wherein said protein moiety that has a binding site with binding specificity for IL-4 competes for binding to IL-4 with IL-4Rα, an IL-4-binding portion of IL-4Rα or an anti-IL-4 domain antibody (dAb) selected from the group consisting of DOM9-44-502(SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512); and said protein moiety that has a binding site with binding specificity for IL-13 competes for binding to IL-13 with IL-13Rα1, an IL-13-binding portion of IL-13Rα1, IL-13Rα2, and IL-13-binding portion of IL-13Rα2, or an anti-IL-13 domain antibody (dAb) selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

5. The ligand of any one of claims 1-4, wherein said protein moiety that has a binding site with binding specificity for IL-4 is provided by an antibody fragment, and said protein moiety that has a binding site with binding specificity for IL-13 is provided by an antibody fragment.

6. The ligand of claim 5, wherein the antibody fragments are each an immunoglobulin single variable domain.

7. The ligand of any one of claims 1-6, wherein said ligand inhibits binding of IL-4 to IL-4R.

8. The ligand of any one of claims 1-6, wherein said ligand inhibits the activity of IL-4.

9. The ligand of any one of claims 1-6, wherein said ligand inhibits the activity of IL-4 without substantially inhibiting binding of IL-4 to IL-4R.

10. The ligand of any one of claims 1-9, wherein said ligand inhibits binding of IL-13 to IL-13Rα1 and/or IL-13Rα2.

11. The ligand of any one of claims 1-9, wherein said ligand inhibits the activity of IL-13.

12. The ligand of any one of claims 1-9, wherein said ligand inhibits the activity of IL-13 without substantially inhibiting binding of IL-13 to IL-13Rα1 and/or IL-13Rα2.

13. A ligand that has binding specificity for IL-4 and IL-13, comprising an immunoglobulin single variable domain with binding specificity for IL-4 and an immunoglobulin single variable domain with binding specificity for IL-13, wherein

said immunoglobulin single variable domain with binding specificity for IL-4 competes for binding to IL-4 with an anti-IL-4 domain antibody (dAb) selected from the group consisting of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512); and

said immunoglobulin single variable domain with binding specificity for IL-13 competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223

(SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

14. The ligand of claim 13, wherein said ligand inhibits binding of IL-4 to IL-4R.

15. The ligand of claim 13, wherein said ligand inhibits the activity of IL-4.

16. The ligand of claim 13, wherein said ligand inhibits the activity of IL-4 without substantially inhibiting binding of IL-4 to IL-4R.

17. The ligand of any one of claims 13-16, wherein said ligand inhibits binding of IL-13 to IL-13Rα1 and/or IL-13Rα2.

18. The ligand of any one of claims 13-16, wherein said ligand inhibits the activity of IL-13.

19. The ligand of any one of claims 13-16, wherein said ligand inhibits the activity of IL-13 without substantially inhibiting binding of IL-13 to IL-13Rα1 and/or IL-13Rα2.

20. The ligand of any one of claims 13-19 wherein each said immunoglobulin single variable domain with binding specificity for IL-4 binds IL-4 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

21. The ligand of any one of claims 13-20 wherein each said immunoglobulin single variable domain with binding specificity for IL-13 binds IL-13 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

22. The ligand of any one of claims 13-19 wherein said ligand binds IL-4 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

23. The ligand of any one of claims 13-19 and 22 wherein said ligand binds IL-13 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

24. The ligand of any one of claims 13-23, wherein said immunoglobulin single variable domain with binding specificity for IL-4 and said immunoglobulin single variable domain with binding specificity for IL-13 are independently selected from the group consisting of a human V_H and a human V_L.

25. The ligand of any one of claims 13-24, wherein said ligand is an IgG-like format comprising two immunoglobulin single variable domains with binding specificity for IL-4, and two immunoglobulin single variable domains with binding specificity for IL-13.

26. The ligand of any one of claims 1-25, wherein said ligand comprises an antibody Fc region.

27. The ligand of any one of claims 1-25, wherein said ligand comprises an IgG constant region.

28. A ligand that has binding specificity for IL-4, comprising an immunoglobulin single variable domain with binding specificity for IL-4, wherein said immunoglobulin single variable domain with binding specificity for IL-4 competes for binding to IL-4 with an anti-IL-4 domain antibody (dAb) selected from the group consisting of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77

(SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

29. The ligand of claim 28, wherein said immunoglobulin single variable domain with binding specificity for IL-4 comprises an amino acid sequence that has at least about 85% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

30. The ligand of claim 28 or 29, wherein said ligand inhibits binding of IL-4 to IL-4Rα.

31. The ligand of claim 28 or 29, wherein said ligand inhibits the activity of IL-4.

32. The ligand of claim 28 or 29, wherein said ligand inhibits the activity of IL-4 without substantially inhibiting binding of IL-4 to IL-4Rα.

33. The ligand of any one of claims 28-32, wherein said immunoglobulin single variable domain with binding specificity for IL-4 binds IL-4 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

34. The ligand of any one of claims 28-32, wherein said ligand binds IL-4 with an affinity (KD) that is between 100 nM and about 1 pM, as determined by surface plasmon resonance.

35. The ligand of any one of claims 28-34, wherein said immunoglobulin single variable domain with binding specificity for IL-4 is selected from the group consisting of a human V_H and a human V_L.

36. The ligand of any one of claims 1-35, wherein said ligand is an IgG-like format.

37. The ligand of any one of claims 28-35, wherein said ligand comprises an antibody Fc region.

38. The ligand of any one of claims 28-35, wherein said ligand comprises an IgG constant region.

39. A ligand that has binding specificity for IL-13, comprising an immunoglobulin single variable domain with binding specificity for IL-13, wherein said immunoglobulin single variable domain with binding specificity for IL-13 competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

40. The ligand of claim 28, wherein said immunoglobulin single variable domain with binding specificity for IL-13 comprises an amino acid sequence that has at least about 85% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

41. The ligand of claim 39 or 40, wherein said ligand inhibits binding of IL-13 to IL-13Rα1 and/or IL-13Rα2.

42. The ligand of claim 39 or 40, wherein said ligand inhibits the activity of IL-13.

43. The ligand of claim 39 or 40, wherein said ligand inhibits the activity of IL-13 without substantially inhibiting binding of IL-13 to IL-13Rα1 and/or IL-13Rα2.

44. The ligand of any one of claims 39-43, wherein said immunoglobulin single variable domain with binding specificity for IL-13 binds IL-13 with an affinity (KD) that is between about 100 nM and about 1 pM, as determined by surface plasmon resonance.

45. The ligand of any one of claims 39-43, wherein said ligand binds IL-13 with an affinity (KD) that is between 100 nM and about 1 pM, as determined by surface plasmon resonance.

46. The ligand of any one of claims 39-45, wherein said immunoglobulin single variable domain with binding specificity for IL-13 is independently selected from the group consisting of a human V_H and a human V_L.

47. The ligand of any one of claims 39-46, wherein said ligand is an IgG-like format.

48. The ligand of any one of claims 39-46, wherein said ligand comprises an antibody Fc region.

49. The ligand of any one of claims 39-46, wherein said ligand comprises an IgG constant region.

50. A ligand that has binding specificity for IL-4 and IL-13, wherein said ligand is a fusion protein comprising an immunoglobulin single variable domain with

binding specificity for IL-4 and an immunoglobulin single variable domain with binding specificity for IL-13, wherein

said immunoglobulin single variable domain with binding specificity for IL-4 competes for binding to IL-4 with an anti-IL-4 domain antibody (dAb) selected from the group consisting of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512); and

said immunoglobulin single variable domain with binding specificity for IL-13 competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

51. The ligand of claim 50, wherein said immunoglobulin single variable domain with binding specificity for IL-4 comprises an amino acid sequence that has at least about 85% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

52. The ligand of claim 50 or 51, wherein said immunoglobulin single variable domain with binding specificity for IL-13 comprises an amino acid sequence that

has at least about 85% amino acid sequence identity with the amino acid sequence of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

53. The ligand of any one of claims 50-52, wherein said fusion protein further comprises a linker moiety.

54. A ligand that has binding specificity for IL-4 comprising a protein moiety that has a binding site with binding specificity for IL-4, wherein said protein moiety comprises an amino acid sequence that is the same as the amino acid sequence of CDR3 of a dAb selected from the group consisting of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

55. The ligand of claim 54, wherein said protein moiety further comprises an amino acid sequence that is the same as the amino acid sequence of CDR1 and/or CDR2 of a dAb selected from the group consisting of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

56. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) or DOM9-44-502 (SEQ ID NO:512) at no more than 25 amino acid positions and has a CDR1 sequence that has at least 50% identity to the CDR1 sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

57. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) or DOM9-44-502 (SEQ ID NO:512) at no more than 25 amino acid positions and has a CDR2 sequence that has at least 50% identity to the CDR2 sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID

NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

58. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512) at no more than 25 amino acid positions and has a CDR3 sequence that has at least 50% identity to the CDR3 sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

59. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO;337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512) at no more than 25 amino acid positions and has a CDR1 sequence and a

CDR2 sequence that have at least 50% identity to the CDR1 or CDR2 sequences, respectively, of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

60. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:605), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512) at no more than 25 amino acid positions and has a CDR2 sequence and a CDR3 sequence that have at least 50% identity to the CDR2 or CDR3 sequences, respectively, of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:605), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

61. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID

NO:617), DOM9-112-155 (SEQ ID NO:605), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512) at no more than 25 amino acid positions and has a CDR1 sequence and a CDR3 sequence that have at least 50% identity to the CDR1 or CDR3 sequences, respectively, of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

62. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-4 differs from the amino acid sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512) at no more than 25 amino acid positions and has a CDR1 seqequence, a CDR2 sequence and a CDR3 sequence that have at least 50% identity to the CDR1, CDR2 or CDR3 sequences, respectively, of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427),

DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

63. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein said immunoglobulin single variable domain that binds IL-4 comprises a CDR2 sequence that has at least 50% identity to the CDR2 sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

64. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein said immunoglobulin single variable domain that binds IL-4 comprises a CDR3 sequence that has at least 50% identity to the CDR3 sequence of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

65. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein said immunoglobulin single variable domain that binds IL-4 comprises a CDR1 and a CDR2 sequence that has at least 50% identity to the CDR1 and CDR2 sequences, respectively, of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337),

DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

66. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein said immunoglobulin single variable domain that binds IL-4 comprises a CDR2 and a CDR3 sequence that has at least 50% identity to the CDR2 and CDR3 sequences, respectively, of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

67. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein said immunoglobulin single variable domain that binds IL-4 comprises a CDR1 and a CDR3 sequence that has at least 50% identity to the CDR1 and CDR3 sequences, respectively, of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

68. A ligand comprising an immunoglobulin single variable domain that binds IL-4, wherein said immunoglobulin single variable domain that binds IL-4 comprises a CDR1, a CDR2 and a CDR3 sequence that has at least 50% identity to the CDR1, CDR2 and CDR3 sequences, respectively, of DOM9-44-502 (SEQ ID NO:512), DOM9-155-5 (SEQ ID NO:605), DOM9-155-25 (SEQ ID NO:617), DOM9-112-155 (SEQ ID NO:292), DOM9-112-168 (SEQ ID NO:305), DOM9-

112-174 (SEQ ID NO:311), DOM9-112-199 (SEQ ID NO:336), DOM9-112-200 (SEQ ID NO:337), DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-202 (SEQ ID NO:339), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434) and DOM9-44-502 (SEQ ID NO:512).

69. A ligand that has binding specificity for IL-13 comprising a protein moiety that has a binding site with binding specificity for IL-13, wherein said protein moiety comprises an amino acid sequence that is the same as the amino acid sequence of CDR3 of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

70. The ligand of claim 69, wherein said protein moiety further comprises an amino acid sequence that is the same as the amino acid sequence of CDR1 and/or CDR2 of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

71. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

at no more than 25 amino acid positions and has a CDR1 sequence that has at least 50% identity to the CDR1 sequence of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

72. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241) at no more than 25 amino acid positions and has a CDR2 sequence that has at least 50% identity to the CDR2 sequence of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

73. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241) at no more than 25 amino acid positions and has a CDR3 sequence that has at least 50% identity to the CDR3 sequence of a dAb selected from the group

consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

74. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241) at no more than 25 amino acid positions and has a CDR1 sequence and a CDR2 sequence that have at least 50% identity to the CDR1 or CDR2 sequences, respectively, of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

75. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241) at no more than 25 amino acid positions and has a CDR2 sequence and a CDR3 sequence that have at least 50% identity to the CDR2 or CDR3 sequences, respectively, of a dAb selected from the group consisting of DOM10-176-535 (SEQ

ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

76. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241) at no more than 25 amino acid positions and has a CDR1 sequence and a CDR3 sequence that have at least 50% identity to the CDR1 or CDR3 sequences, respectively, of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

77. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein the amino acid sequence of said immunoglobulin single variable domain that binds IL-13 differs from the amino acid sequence of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241) at no more than 25 amino acid positions and has a CDR1 seqequence, a CDR2 sequence and a CDR3 sequence that have at least 50% identity to the CDR1, CDR2 or CDR3 sequences, respectively, a dAb selected from the group consisting

of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

78. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein said immunoglobulin single variable domain that binds IL-13 comprises a CDR2 sequence that has at least 50% identity to the CDR2 sequence of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

79. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein said immunoglobulin single variable domain that binds IL-13 comprises a CDR3 sequence that has at least 50% identity to the CDR3 sequence of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

80. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein said immunoglobulin single variable domain that binds IL-4 comprises a CDR1 and a CDR2 sequence that has at least 50% identity to the CDR1 and CDR2 sequences, respectively, of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396

(SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

81. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein said immunoglobulin single variable domain that binds IL-13 comprises a CDR2 and a CDR3 sequence that has at least 50% identity to the CDR2 and CDR3 sequences, respectively, of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

82. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein said immunoglobulin single variable domain that binds IL-13 comprises a CDR1 and a CDR3 sequence that has at least 50% identity to the CDR1 and CDR3 sequences, respectively, of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

83. A ligand comprising an immunoglobulin single variable domain that binds IL-13, wherein said immunoglobulin single variable domain that binds IL-13 comprises a CDR1, a CDR2 and a CDR3 sequence that has at least 50% identity to the CDR1, CDR2 and CDR3 sequences, respectively, of a dAb selected from the group consisting of DOM10-176-535 (SEQ ID NO:1587), DOM10-53-223 (SEQ ID NO:1090), DOM10-53-234 (SEQ ID NO:1101), DOM10-53-316 (SEQ ID NO:1182), DOM10-53-339 (SEQ ID NO:1203), DOM10-53-344 (SEQ ID NO:1208), DOM10-53-396 (SEQ ID NO:1260), DOM10-53-474 (SEQ ID NO:2369) and DOM10-275-1 (SEQ ID NO:2241).

84. The ligand of any one of claims 1-83, wherein said ligand further comprises a half-life extending moiety.

85. The ligand of claim 84, wherein said half-life extending moiety is a polyalkylene glycol moiety, serum albumin or a fragment thereof, transferring receptor or a transferring-binding portion thereof, or a moiety comprising a binding site for a polypeptide that enhances half-life *in vivo*.

86. The ligand of claim 85, wherein said half-life extending moiety is a moiety comprising a binding site for a polypeptide that enhances half-life in vivo selected from the group consisting of an affibody, a SpA domain, an LDL receptor class A domain, an EGF domain, and an avimer.

87. The ligand of claim 85, wherein said half-life extending moiety is a polyethylene glycol moiety.

88. The ligand of claim 85, wherein said half-life extending moiety is an antibody or antibody fragment comprising a binding site for serum albumin or neonatal Fc receptor.

89. The ligand of claim 85, wherein said antibody or antibody fragment comprising a binding site for serum albumin or neonatal Fc receptor is an antibody fragment, and said antibody fragment is an immunoglobulin single variable domain comprising a binding site for serum albumin.

90. A ligand of any one of Claims 1-89 for use in therapy or diagnosis.

91. A ligand of any one of Claims 1-89 for use in treating, suppressing or preventing an allergic disease.

92. Use of the ligand of any one of Claims 1-89 for the manufacture of a medicament for in treating, suppressing or preventing an allergic disease.

93. A ligand of any one of claims 1-89 for use in treating, suppressing or preventing a Th2-type immune response.

94. Use of the ligand of any one of Claims 1-89 for the manufacture of a medicament for in treating, suppressing or preventing a Th2-type immune response.

95. A ligand of any one of claims 1-89 for use in treating, suppressing or preventing asthma.

96. Use of the ligand of any one of Claims 1-89 for the manufacture of a medicament for in treating, suppressing or preventing asthma.

97. A ligand of any one of claims 1-89 for use in treating, suppressing or preventing cancer.

98. Use of the ligand of any one of Claims 1-89 for the manufacture of a medicament for in treating, suppressing or preventing cancer.

99. A method for treating an allergic disease comprising administering to a subject in need thereof a therapeutically effective amount of ligand of any one of claims 1-89.

100. A method for inhibiting a Th2-type immune response comprising administering to a subject in need thereof a therapeutically effective amount of ligand of any one of claims 1-89.

101. A method for treating asthma comprising administering to a subject in need thereof a therapeutically effective amount of ligand of any one of claims 1-89.

102. A method for treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of ligand of any one of claims 1-89.

103. Use of a ligand of any one of claims 1-89 for the manufacture of a medicament for simultaneous administration of an anti-IL-4 treatment and an anti-IL-13 treatment.

104. A method of administering to a subject anti-IL-4 treatment and anti-IL-13 treatment, the method comprising simultaneous administration of an anti-IL-4 treatment and an anti-IL-13 treatment by administering to said subject a therapeutically effective amount of a ligand of any one of claims 1-27.

105. A pharmaceutical composition comprising a ligand of any one of Claims 1-89 and a physiologically acceptable carrier.

106. The pharmaceutical composition of claim 105, wherein said composition comprises a vehicle for intravenous, intramuscular, intraperitoneal, intraarterial, intrathecal, intraarticular, or subcutaneous administration.

107. The pharmaceutical composition of claim 105, wherein said composition comprises a vehicle for pulmonary, intranasal, vaginal, or rectal administration.

108. A drug delivery device comprising the pharmaceutical composition of claim 105.

109. The drug delivery device of claim 108, wherein said device comprises a plurality of therapeutically effective doses of ligand.

110. The drug delivery device of claim 108 or 109, wherein said drug delivery device is selected from the group consisting of a parenteral delivery device, intravenous delivery device, intramuscular delivery device, intraperitoneal delivery device, transdermal delivery device, pulmonary delivery device, intraarterial delivery device, intrathecal delivery device, intraarticular delivery device, subcutaneous delivery device, intranasal delivery device, vaginal delivery device, and rectal delivery device.

111. The drug delivery device of claim 110, wherein said device is selected from the group consisting of a syringe, a transdermal delivery device, a capsule, a tablet, a nebulizer, an inhaler, an atomizer, an aerosolizer, a mister, a dry powder inhaler, a metered dose inhaler, a metered dose sprayer, a metered dose mister, a metered dose atomizer, and a catheter.

112. An isolated or recombinant nucleic acid encoding a ligand of any one of claims 1-89.

113. A vector comprising the recombinant nucleic acid of claim 112.

114. A host cell comprising the recombinant nucleic acid of claim 112 or the vector of claim 113.

115. A method for producing a ligand comprising maintaining a host cell of claim 114 under conditions suitable for expression of said nucleic acid or vector, whereby a ligand is produced.

116. The method of claim 115, further comprising isolating the ligand.

117. A method of inhibiting proliferation of peripheral blood mononuclear cells (PBMC) in an allergen-sensitized subject, comprising administering to the subject a pharmaceutical composition comprising a ligand of any one of claims 1-89.

118. The method of Claim 117, wherein said allergen is selected from house dust mite, cat allergen, grass allergen, mold allergen, and pollen allergen.

119. A method of inhibiting proliferation of B cells in a subject, comprising administering to the subject a pharmaceutical composition comprising a ligand of any one of claims 1-89.

120. A ligand that has binding specificity for IL-4 and IL-13 comprising a protein moiety that has a binding site with binding specificity for IL-4; and a protein moiety that has a binding site with binding specificity for IL-13, wherein the protein moiety that has binding specificity for IL-4 does not compete for binding with DOM9-15 (SEQ ID NO:175), DOM9-17(SEQ ID NO:176), DOM9-23 (SEQ ID NO:177), DOM9-24 (SEQ ID NO:178), DOM9-25 (SEQ ID NO:179), DOM9-27 (SEQ ID NO:180), DOM9-28 (SEQ ID NO:181), DOM9-29 (SEQ ID NO:182), DOM9-30 (SEQ ID NO:183), DOM9-31 (SEQ ID NO:184), DOM9-32 (SEQ ID NO:185), DOM9-33 (SEQ ID NO:186), DOM9-50 (SEQ ID NO:187) , DOM9-57 (SEQ ID NO:188), DOM9-59 (SEQ ID NO:189), DOM9-63 (SEQ ID NO:190), DOM9-67 (SEQ ID NO:191), DOM9-68 (SEQ ID NO:192), DOM9-70 (SEQ ID NO:193), DOM9-79 (SEQ ID NO:194), DOM9-82 (SEQ ID NO:195), DOM9-86 (SEQ ID NO:196) , DOM9-94 (SEQ ID NO:197), DOM9-108 (SEQ ID NO:198), DOM9-112 (SEQ ID NO:199), DOM9-112-1 (SEQ ID NO:200), DOM9-112-2 (SEQ ID NO:201), DOM9-112-3 (SEQ ID NO:202), DOM9-112-4 (SEQ ID NO:203), DOM9-112-5 (SEQ ID NO:204), DOM9-112-6 (SEQ ID NO:205), DOM9-112-7 (SEQ ID NO:206), DOM9-112-8 (SEQ ID NO:207), DOM9-112-9 (SEQ ID NO:208), DOM9-112-10 (SEQ ID NO:209), DOM9-112-11 (SEQ ID NO:210), DOM9-112-12 (SEQ ID NO:211), DOM9-112-13 (SEQ ID NO:212), DOM9-112-14 (SEQ ID NO:213), DOM9-112-15 (SEQ ID NO:214), DOM9-112-16 (SEQ ID NO:215), DOM9-112-17 (SEQ ID NO:216), DOM9-112-18 (SEQ ID NO:217), DOM9-112-19 (SEQ ID NO:218), DOM9-112-20 (SEQ ID NO:219) , DOM9-112-21 (SEQ ID NO:220), DOM9-112-22 (SEQ ID NO:221), DOM9-112-23 (SEQ ID NO:222), DOM9-112-25 (SEQ ID NO:223), DOM9-112-81 (SEQ ID NO:224), DOM9-112-82 (SEQ ID NO:225), DOM9-112-83 (SEQ ID NO:226), DOM9-112-84 (SEQ ID NO:227), DOM9-112-85 (SEQ ID NO:228), DOM9-112-86 (SEQ ID NO:229), DOM9-112-87 (SEQ ID NO:230), DOM9-112-88 (SEQ ID NO:231), DOM9-112-89 (SEQ ID NO:232), DOM9-112-90 (SEQ ID NO:233), DOM9-112-91 (SEQ ID NO:234), DOM9-112-92 (SEQ ID NO:235), DOM9-112-93 (SEQ ID NO:236), DOM9-112-94 (SEQ ID NO:237), DOM9-112-95 (SEQ ID NO:238), DOM9-112-96 (SEQ ID NO:239), DOM9-112-97 (SEQ ID NO:240), DOM9-112-98 (SEQ ID NO:241), DOM9-112-99 (SEQ ID NO:242), DOM9-112-100 (SEQ ID

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121. A ligand that has binding specificity for IL-4 and IL-13 comprising a protein moiety that has a binding site with binding specificity for IL-4, and a protein moiety that has a binding site with binding specificity for IL-13, wherein the protein moiety that has binding specificity for IL-13 does not compete for binding with DOM10-53 (SEQ ID NO:967), DOM10-53-1 (SEQ ID NO:968), DOM10-53-2 (SEQ ID NO:969), DOM10-53-3 (SEQ ID NO:970), DOM10-53-4 (SEQ ID NO:971), DOM10-53-5 (SEQ ID NO:972), DOM10-53-6 (SEQ ID NO:973), DOM10-53-7 (SEQ ID NO:974), DOM10-53-8 (SEQ ID NO:975), DOM10-53-9 (SEQ ID NO:976), DOM10-53-10 (SEQ ID NO:977), DOM10-53-11 (SEQ ID NO:978), DOM10-53-12 (SEQ ID NO:979), DOM10-53-13 (SEQ ID NO:980), DOM10-53-14 (SEQ ID NO:981), DOM10-53-15 (SEQ ID NO:982), DOM10-53-16 (SEQ ID NO:983), DOM10-53-17 (SEQ ID NO:984), DOM10-53-18 (SEQ ID NO:985), DOM10-53-19 (SEQ ID NO:986), DOM10-53-20 (SEQ ID NO:987), DOM10-53-21 (SEQ ID NO:988), DOM10-53-122 (SEQ ID NO:989), DOM10-53-123 (SEQ ID NO:990), DOM10-53-24 (SEQ ID NO:991), DOM10-53-25 (SEQ ID NO:992), DOM10-53-26 (SEQ ID NO:993), DOM10-53-27 (SEQ ID NO:994), DOM10-53-28 (SEQ ID NO:995), DOM10-53-29 (SEQ ID NO:996) , DOM10-53-30 (SEQ ID

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122. The ligand of claim 120 or 121, with the proviso that the ligand does not comprise an IL-4 trap or an IL-13 trap.

123. A ligand that has binding specificity for IL-4 and IL-13 comprising a protein moiety that has a binding site with binding specificity for IL-4; and a protein moiety that has a binding site with binding specificity for IL-13, wherein the protein moiety that has binding specificity for IL-4 does not compete for binding with DOM9-155-77 (SEQ ID NO:2426), DOM9-155-78 (SEQ ID NO:2427), DOM9-112-204 (SEQ ID NO:2428), DOM9-112-205 (SEQ ID NO:2429), DOM9-112-206 (SEQ ID NO:2430), DOM9-112-207 (SEQ ID NO:2431), DOM9-112-208 (SEQ ID NO:2432), DOM9-112-209 (SEQ ID NO:2433), DOM9-112-210 (SEQ ID NO:2434), DOM9-112-211 (SEQ ID NO:2435), DOM9-112-212 (SEQ ID NO:2436), DOM9-112-213 (SEQ ID NO:2437), DOM9-112-214 (SEQ ID NO:2438), DOM9-112-215 (SEQ ID NO:2439), DOM9-112-216 (SEQ ID NO:2440), DOM9-112-217 (SEQ ID NO:2441), DOM9-112-218 (SEQ ID NO:2442), DOM9-112-219 (SEQ ID NO:2443), DOM9-112-220 (SEQ ID NO:2444), DOM9-112-221 (SEQ ID NO:2445), DOM9-112-222 (SEQ ID NO:2446), DOM9-112-223 (SEQ ID NO:2447), DOM9-112-224 (SEQ ID NO:2448), DOM9-112-225 (SEQ ID NO:2449), DOM9-112-226 (SEQ ID NO:2450), DOM9-112-227 (SEQ ID NO:2451), DOM9-112-228 (SEQ ID NO:2452), DOM9-112-229 (SEQ ID NO:2453), DOM9-112-230 (SEQ ID NO:2454), DOM9-112-231 (SEQ ID NO:2455), DOM9-112-233 (SEQ ID NO:1734), DOM9-112-232 (SEQ ID NO:1733) and DOM9-112-234 (SEQ ID NO:1735).

124. A ligand that has binding specificity for IL-4 and IL-13 comprising a protein moiety that has a binding site with binding specificity for IL-4; and a protein moiety that has a binding site with binding specificity for IL-13, wherein the protein moiety that has binding specificity for IL-13 does not compete for binding with DOM10-236 (SEQ ID NO:2129), DOM10-238 (SEQ ID NO:2130), DOM10-241 (SEQ ID NO:2131), DOM10-245 (SEQ ID NO:2132), DOM10-249 (SEQ ID NO:2133), DOM10-250 (SEQ ID NO:2134), DOM10-251 (SEQ ID NO:2135), DOM10-254 (SEQ ID NO:2136), DOM10-256 (SEQ ID NO:2137), DOM10-259 (SEQ ID NO:2138), DOM10-260 (SEQ ID NO:2139), DOM10-261 (SEQ ID NO:2140), DOM10-263 (SEQ ID NO:2141), DOM10-264 (SEQ ID NO:2142), DOM10-273

(SEQ ID NO:2143), DOM10-278 (SEQ ID NO:2144), DOM10-279 (SEQ ID NO:2145), DOM10-281 (SEQ ID NO:2146), DOM10-282 (SEQ ID NO:2147), DOM10-283 (SEQ ID NO:2148), DOM10-400 (SEQ ID NO:2149), DOM10-401 (SEQ ID NO:2150), DOM10-402 (SEQ ID NO:2151), DOM10-404 (SEQ ID NO:2152), DOM10-406 (SEQ ID NO:2153), DOM10-407 (SEQ ID NO:2154), DOM10-409 (SEQ ID NO:2155), DOM10-410 (SEQ ID NO:2156), DOM10-414 (SEQ ID NO:2157), DOM10-415 (SEQ ID NO:2158), DOM10-416 (SEQ ID NO:2159), DOM10-418 (SEQ ID NO:2160), DOM10-420 (SEQ ID NO:2161), DOM10-422 (SEQ ID NO:2162), DOM10-423 (SEQ ID NO:2163), DOM10-424 (SEQ ID NO:2164), DOM10-425 (SEQ ID NO:2165), DOM10-426 (SEQ ID NO:2166), DOM10-427 (SEQ ID NO:2167), DOM10-428 (SEQ ID NO:2168), DOM10-429 (SEQ ID NO:2169), DOM10-430 (SEQ ID NO:2170), DOM10-431 (SEQ ID NO:2171), DOM10-432 (SEQ ID NO:2172), DOM10-433 (SEQ ID NO:2173), DOM10-467 (SEQ ID NO:2174), DOM10-468 (SEQ ID NO:2175), DOM10-469 (SEQ ID NO:2176), DOM10-470 (SEQ ID NO:2177), DOM10-234 (SEQ ID NO:2178), DOM10-235 (SEQ ID NO:2179), DOM10-237 (SEQ ID NO:2180), DOM10-239 (SEQ ID NO:2181), DOM10-240 (SEQ ID NO:2182), DOM10-242 (SEQ ID NO:2183), DOM10-243 (SEQ ID NO:2184), DOM10-244 (SEQ ID NO:2185), DOM10-246 (SEQ ID NO:2186), DOM10-247 (SEQ ID NO:2187), DOM10-248 (SEQ ID NO:2188), DOM10-252 (SEQ ID NO:2189), DOM10-257 (SEQ ID NO:2190), DOM10-258 (SEQ ID NO:2191), DOM10-262 (SEQ ID NO:2192), DOM10-265 (SEQ ID NO:2193), DOM10-266 (SEQ ID NO:2194), DOM10-274 (SEQ ID NO:2195), DOM10-275 (SEQ ID NO:2196), DOM10-276 (SEQ ID NO:2197), DOM10-277 (SEQ ID NO:2198), DOM10-280 (SEQ ID NO:2199), DOM10-403 (SEQ ID NO:2200), DOM10-405 (SEQ ID NO:2201), DOM10-408 (SEQ ID NO:2202), DOM10-411 (SEQ ID NO:2203), DOM10-412 (SEQ ID NO:2204), DOM10-413 (SEQ ID NO:2205), DOM10-417 (SEQ ID NO:2206), DOM10-419 (SEQ ID NO:2207), DOM10-472 (SEQ ID NO:2208), DOM10-203 (SEQ ID NO:2209), DOM10-205 (SEQ ID NO:2210), DOM10-208 (SEQ ID NO:2211), DOM10-218 (SEQ ID NO:2212), DOM10-219 (SEQ ID NO:2213), DOM10-220 (SEQ ID NO:2214), DOM10-225 (SEQ ID NO:2215), DOM10-228 (SEQ ID NO:2216), DOM10-229 (SEQ ID NO:2217),

DOM10-230 (SEQ ID NO:2218), DOM10-231 (SEQ ID NO:2219), DOM10-268 (SEQ ID NO:2220), DOM10-201 (SEQ ID NO:2221), DOM10-202 (SEQ ID NO:2222), DOM10-204 (SEQ ID NO:2223), DOM10-206 (SEQ ID NO:2224), DOM10-207 (SEQ ID NO:2225), DOM10-209 (SEQ ID NO:2226), DOM10-210 (SEQ ID NO:2227), DOM10-211 (SEQ ID NO:2228), DOM10-213 (SEQ ID NO:2229), DOM10-214 (SEQ ID NO:2230), DOM10-215 (SEQ ID NO:2231), DOM10-216 (SEQ ID NO:2232), DOM10-217 (SEQ ID NO:2233), DOM10-221 (SEQ ID NO:2234), DOM10-223 (SEQ ID NO:2235), DOM10-224 (SEQ ID NO:2236), DOM10-227 (SEQ ID NO:2237), DOM10-232 (SEQ ID NO:2238), DOM10-267 (SEQ ID NO:2239), DOM10-270 (SEQ ID NO:2240), DOM10-275-1 (SEQ ID NO:2241), DOM10-276-2 (SEQ ID NO:2242), DOM10-276-3 (SEQ ID NO:2243), DOM10-275-3 (SEQ ID NO:2244), DOM10-277-2 (SEQ ID NO:2245), DOM10-277-3 (SEQ ID NO:2246), DOM10-273-1 (SEQ ID NO:2247), DOM10-273-2 (SEQ ID NO:2248), DOM10-275-2 (SEQ ID NO:2249), DOM10-275-4 (SEQ ID NO:2250), DOM10-276-1 (SEQ ID NO:2251), DOM10-276-4 (SEQ ID NO:2252), DOM10-277-1 (SEQ ID NO:2253), DOM10-275-13 (SEQ ID NO:2254), DOM10-275-15 (SEQ ID NO:2255), DOM10-275-20 (SEQ ID NO:2256), DOM10-275-8 (SEQ ID NO:2257), DOM10-276-13 (SEQ ID NO:2258), DOM10-276-14 (SEQ ID NO:2259), DOM10-276-15 (SEQ ID NO:2260), DOM10-276-17 (SEQ ID NO:2261), DOM10-276-7 (SEQ ID NO:2262), DOM10-276-8 (SEQ ID NO:2263), DOM10-275-11 (SEQ ID NO:2264), DOM10-275-12 (SEQ ID NO:2265), DOM10-275-14 (SEQ ID NO:2266), DOM10-275-16 (SEQ ID NO:2267), DOM10-275-17 (SEQ ID NO:2268), DOM10-275-5 (SEQ ID NO:2269), DOM10-275-6 (SEQ ID NO:2270), DOM10-275-7 (SEQ ID NO:2271), DOM10-275-9 (SEQ ID NO:2272), DOM10-276-10 (SEQ ID NO:2273), DOM10-276-11 (SEQ ID NO:2274), DOM10-276-12 (SEQ ID NO:2275), DOM10-276-16 (SEQ ID NO:2276), DOM10-276-5 (SEQ ID NO:2277), DOM10-276-6 (SEQ ID NO:2278), DOM10-276-9 (SEQ ID NO:2279), DOM10-212 (SEQ ID NO:2280), DOM10-53-424 (SEQ ID NO:2281), DOM10-53-425 (SEQ ID NO:2282), DOM10-53-426 (SEQ ID NO:2283), DOM10-53-422 (SEQ ID NO:2284), DOM10-53-423 (SEQ ID NO:2285), DOM10-53-613 (SEQ ID NO:2286), DOM10-53-517 (SEQ ID NO:2287), DOM10-53-519 (SEQ ID NO:2288), DOM10-53-520 (SEQ ID NO:2289), DOM10-53-521 (SEQ ID

NO:2290), DOM10-53-522 (SEQ ID NO:2291), DOM10-53-526 (SEQ ID NO:2292), DOM10-53-527 (SEQ ID NO:2293), DOM10-53-528 (SEQ ID NO:2294), DOM10-53-518 (SEQ ID NO:2295), DOM10-53-523 (SEQ ID NO:2296), DOM10-53-524 (SEQ ID NO:2297), DOM10-53-525 (SEQ ID NO:2298), DOM10-53-601 (SEQ ID NO:2299), DOM10-53-602 (SEQ ID NO:2300), DOM10-53-605 (SEQ ID NO:2301), DOM10-53-606 (SEQ ID NO:2302), DOM10-53-607 (SEQ ID NO:2303), DOM10-53-608 (SEQ ID NO:2304), DOM10-53-609 (SEQ ID NO:2305), DOM10-53-610 (SEQ ID NO:2306), DOM10-53-611 (SEQ ID NO:2307), DOM10-53-612 (SEQ ID NO:2308), DOM10-53-603 (SEQ ID NO:2309), DOM10-53-604 (SEQ ID NO:2310), DOM10-53-429 (SEQ ID NO:2311), DOM10-53-432 (SEQ ID NO:2312), DOM10-53-433 (SEQ ID NO:2313), DOM10-53-435 (SEQ ID NO:2314), DOM10-53-430 (SEQ ID NO:2315), DOM10-53-431 (SEQ ID NO:2316), DOM10-53-434 (SEQ ID NO:2317), DOM10-53-436 (SEQ ID NO:2318), DOM10-53-437 (SEQ ID NO:2319), DOM10-53-438 (SEQ ID NO:2320), DOM10-53-440 (SEQ ID NO:2321), DOM10-53-439 (SEQ ID NO:2322), DOM10-53-441 (SEQ ID NO:2323), DOM10-53-442 (SEQ ID NO:2324), DOM10-53-443 (SEQ ID NO:2325), DOM10-53-444 (SEQ ID NO:2326), DOM10-53-445 (SEQ ID NO:2327), DOM10-53-446 (SEQ ID NO:2328), DOM10-53-447 (SEQ ID NO:2329), DOM10-53-449 (SEQ ID NO:2330), DOM10-53-448 (SEQ ID NO:2331), DOM10-53-450 (SEQ ID NO:2332), DOM10-53-451 (SEQ ID NO:2333), DOM10-53-452 (SEQ ID NO:2334), DOM10-53-453 (SEQ ID NO:2335), DOM10-53-454 (SEQ ID NO:2336), DOM10-53-455 (SEQ ID NO:2337), DOM10-53-456 (SEQ ID NO:2338), DOM10-53-457 (SEQ ID NO:2339), DOM10-53-458 (SEQ ID NO:2340), DOM10-53-459 (SEQ ID NO:2341), DOM10-53-461 (SEQ ID NO:2342), DOM10-53-462 (SEQ ID NO:2343), DOM10-53-465 (SEQ ID NO:2344), DOM10-53-466 (SEQ ID NO:2345), DOM10-53-467 (SEQ ID NO:2346), DOM10-53-468 (SEQ ID NO:2347), DOM10-53-460 (SEQ ID NO:2348), DOM10-53-463 (SEQ ID NO:2349), DOM10-53-464 (SEQ ID NO:2350), DOM10-53-469 (SEQ ID NO:2351), DOM10-53-471 (SEQ ID NO:2352), DOM10-53-470 (SEQ ID NO:2353), DOM10-53-533 (SEQ ID

NO:2354), DOM10-53-534 (SEQ ID NO:2355), DOM10-53-535 (SEQ ID NO:2356), DOM10-53-537 (SEQ ID NO:2357), DOM10-53-538 (SEQ ID NO:2358), DOM10-53-539 (SEQ ID NO:2359), DOM10-53-540 (SEQ ID NO:2360), DOM10-53-531 (SEQ ID NO:2361), DOM10-53-532 (SEQ ID NO:2362), DOM10-53-536 (SEQ ID NO:2363), DOM10-53-542 (SEQ ID NO:2364), DOM10-53-541 (SEQ ID NO:2365), DOM10-53-473 (SEQ ID NO:2366), DOM10-53-472 (SEQ ID NO:2367), DOM10-53-475 (SEQ ID NO:2368), DOM10-53-474 (SEQ ID NO:2369), DOM10-53-543 (SEQ ID NO:2370), DOM10-53-544 (SEQ ID NO: 2371), DOM10-53-545 (SEQ ID NO:2372), DOM10-53-548 (SEQ ID NO:2373), DOM10-53-546 (SEQ ID NO:2374), DOM10-53-549 (SEQ ID NO:2375), DOM10-53-547 (SEQ ID NO:2376), DOM10-53-550 (SEQ ID NO:2377), DOM10-53-551 (SEQ ID NO:2378), DOM10-53-560 (SEQ ID NO:2379), DOM10-53-565 (SEQ ID NO:2380), DOM10-53-559 (SEQ ID NO:2381), DOM10-53-561 (SEQ ID NO:2382), DOM10-53-562 (SEQ ID NO:2383), DOM10-53-563 (SEQ ID NO:2384), DOM10-53-564 (SEQ ID NO:2385), DOM10-53-566 (SEQ ID NO:2386), DOM10-53-554 (SEQ ID NO:2387), DOM10-53-552 (SEQ ID NO:2388), DOM10-53-553 (SEQ ID NO:2389), DOM10-53-558 (SEQ ID NO:2390), DOM10-53-556 (SEQ ID NO:2391) and DOM10-53-557 (SEQ ID NO:2392).

125. A ligand that has binding specificity for IL-4 and IL-13, wherein said ligand is a fusion protein comprising an immunoglobulin single variable domain with binding specificity for IL-4 and an immunoglobulin single variable domain with binding specificity for IL-13, wherein

said immunoglobulin single variable domain with binding specificity for IL-4 competes for binding to IL-4 with an anti-IL-4 domain antibody (dAb) selected from the group consisting of DOM9-112-210 and DOM9-155-78; and

said immunoglobulin single variable domain with binding specificity for IL-13 competes for binding to IL-13 with an anti-IL-13 domain antibody (dAb) selected from the group consisting of DOM10-208, DOM10-212, DOM10-213, DOM10-

215, DOM10-224, DOM10-270, DOM10-416, DOM10-236, DOM10-273, DOM10-275, DOM10-276 and DOM10-277.

126. A ligand that has binding specificity for IL-4, comprising an immunoglobulin single variable domain with binding specificity for human IL-4 and a non-human IL-4.

127. The ligand of claim 126, wherein said non-human IL-4 is selected from the group consisting of rhesus IL-4 and cynomolgous IL-4.

128. The ligand of claim 126 or 127, wherein the binding affinity of said immunoglobulin single variable domain for non-human IL-4 and the binding affinity for human IL-4 differ by no more than a factor of 10.

129. A ligand that has binding specificity for IL-13, comprising an immunoglobulin single variable domain with binding specificity for human IL-13 and a non-human IL-13.

130. The ligand of claim 129, wherein said non-human IL-13 is selected from the group consisting of rhesus IL-13 and cynomolgous IL-13.

131. The ligand of claim 129 or 130, wherein the binding affinity of said immunoglobulin single variable domain for non-human IL-13 and the binding affinity for human IL-13 differ by no more than a factor of 10.

132. A ligand that has binding specificity for IL-4 and IL-13, comprising the immunoglobulin single variable domain of any one of claims 126-128; and an immunoglobulin single variable domain with binding specificty for human IL-13.

133. A ligand that has binding specificity for IL-4 and IL-13, comprising an immunoglobulin single variable domain with binding specificity for human IL-4; and the immunoglobulin single variable domain of any one of claims 129-131.

134. A ligand that has binding specificity for IL-4 and IL-13, comprising the immunoglobulin single variable domain of any one of claims 126-128; and the immunoglobulin single variable domain of any one of claims 129-131.