VARIANT NUCLEIC ACID LIBRARIES FOR CRTH2

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/904,595 filed on September 23, 2019; U.S. Provisional Patent Application No. 62/935,590 filed on November 14, 2019; and U.S. Provisional Patent Application No. 62/945,752 filed on December 9, 2019, each of which is incorporated by reference in its entirety.

BACKGROUND

[0002] G protein-coupled receptors (GPCRs) such as Prostaglandin D2 receptor 2 (DP2 or CRTH2R) are implicated in a wide variety of diseases. Raising antibodies to GPCRs has been difficult due to problems in obtaining suitable antigen because GPCRs are often expressed at low levels in cells and are very unstable when purified. Thus, there is a need for improved agents for therapeutic intervention which target GPCRs.

INCORPORATION BY REFERENCE

[0003] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF SUMMARY

[0004] In one aspect, p~~P~~rovided herein is a~~are~~ nucleic acid library~~ies~~: a plurality of nucleic acids, wherein each of the nucleic acids encodes for a sequence that when translated encodes for a CRTH2R binding immunoglobulin, wherein the CRTH2R binding immunoglobulin comprises a variant of a CRTH2R binding domain, wherein the CRTH2R binding domain is a ligand for the CRTH2R, and wherein the nucleic acid library comprises at least 10,000 variant immunoglobulin heavy chains and at least 10,000 variant immunoglobulin light chains. Further provided herein are nucleic acid libraries, wherein the nucleic acid library comprises at least 50,000 variant immunoglobulin heavy chains and at least 50,000 variant immunoglobulin light chains. Further provided herein are nucleic acid libraries, wherein the nucleic acid library comprises at least 100,000 variant immunoglobulin heavy chains and at least 100,000 variant immunoglobulin light chains. Further provided herein are nucleic acid libraries, wherein the nucleic acid library comprises at least 10^5 non-identical nucleic acids. Further provided herein are nucleic acid libraries, wherein a length of the immunoglobulin heavy chain when translated is about 90 to about 100 amino acids. Further provided herein are nucleic acid libraries, wherein a length of the

immunoglobulin heavy chain when translated is about 100 to about 400 amino acids. Further provided herein are nucleic acid libraries, wherein the variant immunoglobulin heavy chain when translated comprises at least 80% sequence identity to any one of SEQ ID NO: 2338-2360 or 2403-2405. Further provided herein are nucleic acid libraries, wherein the variant immunoglobulin light chain when translated comprises at least 80% sequence identity to any one of SEQ ID NO: 2361-2381 or 2406-2408.

[0005] In one aspect, p~~P~~rovided herein is a~~are~~ nucleic acid library~~ies~~ comprising a plurality of nucleic acids, wherein each nucleic acid of the plurality of nucleic acids encodes for a sequence that when translated encodes for an antibody or antibody fragment thereof, wherein the antibody or antibody fragment thereof comprises a variable region of a heavy chain (VH) that comprises a CRTH2R binding domain, wherein each nucleic acid of the plurality of nucleic acids comprises a sequence encoding for a sequence variant of the CRTH2R binding domain, and wherein the antibody or antibody fragment binds to its antigen with a K_D of less than 100 nM. Further provided herein are nucleic acid libraries, wherein a length of the VH is about 90 to about 100 amino acids. Further provided herein are nucleic acid libraries, wherein a length of the VH is about 100 to about 400 amino acids. Further provided herein are nucleic acid libraries, wherein a length of the VH is about 270 to about 300 base pairs. Further provided herein are nucleic acid libraries, wherein a length of the VH is about 300 to about 1200 base pairs. Further provided herein are nucleic acid libraries, wherein the library comprises at least 10^5 non-identical nucleic acids.

[0006] In one aspect, p~~P~~rovided herein is a~~are~~ nucleic acid library~~ies~~ comprising: a plurality of nucleic acids, wherein each of the nucleic acids encodes for a sequence that when translated encodes for a CRTH2R single domain antibody, wherein each sequence of the plurality of sequences comprises a variant sequence encoding for a CDR1, CDR2, or CDR3 on a variable region of a heavy chain (VH); wherein the library comprises at least 30,000 variant sequences; and wherein the CRTH2R single domain antibody binds to its antigen with a K_D of less than 100 nM. Further provided herein are nucleic acid libraries, wherein a length of the VH when translated is about 90 to about 100 amino acids. Further provided herein are nucleic acid libraries, wherein a length of the VH when translated is about 100 to about 400 amino acids. Further provided herein are nucleic acid libraries, wherein a length of the VH is about 270 to about 300 base pairs. Further provided herein are nucleic acid libraries, wherein a length of the VH is about 300 to about 1200 base pairs. Further provided herein are nucleic acid libraries, wherein the VH when translated comprises at least 80% sequence identity to any one of SEQ ID NO: 2338-2360 or 2403-2405.

[0007] In one aspect, p~~P~~rovided herein is an ~~are~~ antibody~~ies~~ or antibody fragment~~s~~ that binds CRTH2R, comprising an immunoglobulin heavy chain and an immunoglobulin light chain: a. wherein the immunoglobulin

thereof is chimeric or humanized. Further provided are antibodies or antibody fragments that bind CRTH2R, wherein the antibody has an EC50 less than about 25 nanomolar in a cAMP assay. Further provided are antibodies or antibody fragments that bind CRTH2R, wherein the antibody has an EC50 less than about 20 nanomolar in a cAMP assay. Further provided are antibodies or antibody fragments that bind CRTH2R, wherein the antibody has an EC50 less than about 10 nanomolar in a cAMP assay.

[0008] In one aspect, p~~P~~rovided herein is an~~are~~ antibody~~ies~~ or antibody fragment~~s~~, the antibody or antibody fragment comprises a complementarity determining region (CDR) comprising an amino acid sequence at least about 90% identical to that set forth in any one of SEQ ID NOs: 2382-2402.

[0009] In one aspect, p~~P~~rovided herein is an~~are~~ antibody~~ies~~ or antibody fragment~~s~~, wherein the antibody or antibody fragment comprises a sequence of any one of SEQ ID NOs: 2382-2402 and wherein the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a camelized antibody, a single-chain Fvs (scFv), a single chain antibody, a Fab fragment, a F(ab′)2 fragment, a Fd fragment, a Fv fragment, a single-domain antibody, an isolated complementarity determining region (CDR), a diabody, a fragment comprised of only a single monomeric variable domain, disulfide-linked Fvs (sdFv), an intrabody, an anti-idiotypic (anti-Id) antibody, or ab antigen-binding fragments thereof.

[0009a] In one aspect, provided herein is a use of an antibody or antibody fragment as described herein in the manufacture of a medicament for treating a disease or disorder of the central nervous system, kidney, intestine, lung, hair, skin, bone, or cartilage.

[0009b] In one aspect, provided herein is a use of an antibody or antibody fragment as described herein in the manufacture of a medicament for treating a disease or disorder characterized by an inflammatory response.

[0009c] In one aspect, provided herein is a use of an antibody or antibody fragment as described herein in the manufacture of a medicament for treating an allergic reaction.

[0009d] In one aspect, provided herein is a use of an antibody or antibody fragment as described herein in the manufacture of a medicament for treating asthma.

[0009e] In one aspect, provided herein is a use of an antibody or antibody fragment as described herein in the manufacture of a medicament for treating alopecia or baldness.

[0010] Provided herein are methods of treating a disease or disorder of the central nervous system, kidney, intestine, lung, hair, skin, bone, or cartilage, comprising administering the antibody or antibody fragment described herein.

[0011] Provided herein are methods of treating a disease or disorder characterized by an inflammatory response, comprising administering the antibody or antibody fragment described herein.

[0012] Provided herein are methods of treating an allergic reaction, comprising administering the antibody or antibody fragment described herein. Further provided herein are methods, wherein the allergic reaction is chronic idiopathic urticaria or allergic rhinitis.

[0013] Provided herein are methods of treating asthma, comprising administering the antibody or antibody fragment described herein.

[0014] Provided herein are methods of treating alopecia or baldness, comprising administering the antibody or antibody fragment described herein.

[0015] In one aspect, p~~P~~rovided herein is a ~~are~~ method~~s~~ for generating a nucleic acid library encoding for a CRTH2R antibody or antibody fragment thereof comprising: (a) providing predetermined sequences encoding for: i. a first plurality of polynucleotides, wherein each polynucleotide of the

first plurality of polynucleotides encodes for at least 1000 variant sequence encoding for CDR1 on a heavy chain; ii. a second plurality of polynucleotides, wherein each polynucleotide of the second plurality of polynucleotides encodes for at least 1000 variant sequence encoding for CDR2 on a heavy chain; iii. a third plurality of polynucleotides, wherein each polynucleotide of the third plurality of polynucleotides encodes for at least 1000 variant sequence encoding for CDR3 on a heavy chain; and (b) mixing the first plurality of polynucleotides, the second plurality of polynucleotides, and the third plurality of polynucleotides to form the nucleic acid library of variant nucleic acids encoding for the CRTH2R antibody or antibody fragment thereof, and wherein at least about 70% of the variant nucleic acids encode for an antibody or antibody fragment that binds to its antigen with a K_D of less than 100 nM. Further provided herein are methods for generating a nucleic acid library, wherein the CRTH2R antibody or antibody fragment thereof is a single domain antibody. Further provided herein are methods for generating a nucleic acid library, wherein the single domain antibody comprises one heavy chain variable domain. Further provided herein are methods for generating a nucleic acid library, wherein the single domain antibody is a VHH antibody. Further provided herein are methods for generating a nucleic acid library, wherein the nucleic acid library comprises at least 50,000 variant sequences. Further provided herein are methods for generating a nucleic acid library, wherein the nucleic acid library comprises at least 100,000 variant sequences. Further provided herein are methods for generating a nucleic acid library, wherein the nucleic acid library comprises at least 10^5 non-identical nucleic acids. Further provided herein are methods for generating a nucleic acid library, wherein the nucleic acid library comprises at least one sequence encoding for the CRTH2R antibody or antibody fragment that binds to CRTH2R with a K_D of less than 75 nM. Further provided herein are methods for generating a nucleic acid library, wherein the nucleic acid library comprises at least one sequence encoding for the CRTH2R antibody or antibody fragment that binds to CRTH2R with a K_D of less than 50 nM. Further provided herein are methods for generating a nucleic acid library, wherein the nucleic acid library comprises at least one sequence encoding for the CRTH2R antibody or antibody fragment that binds to CRTH2R with a K_D of less than 10 nM. Further provided herein are methods for generating a nucleic acid library, wherein the nucleic acid library comprises at least 500 variant sequences. Further provided herein are methods for generating a nucleic acid library, wherein the nucleic acid library comprises at least five sequences encoding for the CRTH2R antibody or antibody fragment that binds to CRTH2R with a K_D of less than 75 nM.

[0016] In one aspect, p~~P~~rovided herein is a~~are~~ protein library~~ies~~ encoded by the nucleic acid library as described herein, wherein the protein library comprises peptides. Further provided herein are protein libraries, wherein the protein library comprises immunoglobulins. Further provided herein are

protein libraries, wherein the protein library comprises antibodies. Further provided herein are protein libraries, wherein the protein library is a peptidomimetic library.

[0017] In one aspect, provided herein is a ~~Provided herein are~~ vector library~~ies~~ comprising the nucleic acid library as described herein.

[0018] In one aspect, provided herein is a ~~Provided herein are~~ cell library~~ies~~ comprising the nucleic acid library as described herein.

[0019] In one aspect, provided herein is a ~~Provided herein are~~ cell library~~ies~~ comprising the protein library as described herein.

[0019a] In one aspect, provided herein is an antibody or antibody fragment as described herein for use in therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] **Figure 1** depicts a schematic of G protein-coupled receptor (GPCR) ligand interaction surfaces.

[0021] **Figure 2A** depicts a first schematic of an immunoglobulin scaffold.

[0022] **Figure 2B** depicts a second schematic of an immunoglobulin scaffold.

[0023] **Figure 3** depicts a schematic of a motif for placement in a scaffold.

[0024] **Figure 4** depicts a schematic of a GPCR.

[0025] **Figure 5** depicts schematics of segments for assembly of clonal fragments and non-clonal fragments.

[0026] **Figure 6** depicts schematics of segments for assembly of clonal fragments and non-clonal fragments.

[0027] **Figure 7** presents a diagram of steps demonstrating an exemplary process workflow for gene synthesis as disclosed herein.

[0028] **Figure 8** illustrates an example of a computer system.

[0029] **Figure 9** is a block diagram illustrating an architecture of a computer system.

[0030] **Figure 10** is a diagram demonstrating a network configured to incorporate a plurality of computer systems, a plurality of cell phones and personal data assistants, and Network Attached Storage (NAS).

[0031] **Figure 11** is a block diagram of a multiprocessor computer system using a shared virtual address memory space.

[0032]

[0033] **Figure 12A** depicts a schematic of an immunoglobulin scaffold comprising a VH domain attached to a VL domain using a linker.

[0034] **Figure 12B** depicts a schematic of a full-domain architecture of an immunoglobulin scaffold comprising a VH domain attached to a VL domain using a linker, a leader sequence, and pIII sequence.

[0035] **Figure 12C** depicts a schematic of four framework elements (FW1, FW2, FW3, FW4) and the variable 3 CDR (L1, L2, L3) elements for a VL or VH domain.

CLAIMS

WHAT IS CLAIMED IS:

1. A nucleic acid library, comprising: a plurality of nucleic acids, wherein each of the nucleic acids encodes for a sequence that when translated encodes for a CRTH2R binding immunoglobulin, wherein the CRTH2R binding immunoglobulin comprises a variant of a CRTH2R binding domain, wherein the CRTH2R binding domain is a ligand for the CRTH2R, and wherein the nucleic acid library comprises at least 10,000 variant immunoglobulin heavy chains and at least 10,000 variant immunoglobulin light chains.

2. The nucleic acid library of claim 1, wherein the nucleic acid library comprises at least 50,000 variant immunoglobulin heavy chains and at least 50,000 variant immunoglobulin light chains.

3. The nucleic acid library of claim 1, wherein the nucleic acid library comprises at least 100,000 variant immunoglobulin heavy chains and at least 100,000 variant immunoglobulin light chains.

4. The nucleic acid library of claim 1, wherein the nucleic acid library comprises at least 10^5 non-identical nucleic acids.

5. The nucleic acid library of claim 1, wherein a length of the immunoglobulin heavy chain when translated is about 90 to about 100 amino acids.

6. The nucleic acid library of claim 1, wherein a length of the immunoglobulin heavy chain when translated is about 100 to about 400 amino acids.

7. The nucleic acid library of claim 1, wherein the variant immunoglobulin heavy chain when translated comprises at least 80% sequence identity to any one of SEQ ID NO: 2338-2360 or 2403-2405.

8. The nucleic acid library of claim 1, wherein the variant immunoglobulin light chain when translated comprises at least 80% sequence identity to any one of SEQ ID NO: 2361-2381 or 2406-2408.

9. A nucleic acid library comprising a plurality of nucleic acids, wherein each nucleic acid of the plurality of nucleic acids encodes for a sequence that when translated encodes for an antibody or antibody fragment thereof, wherein the antibody or antibody fragment thereof comprises a variable region of a heavy chain (VH) that comprises a CRTH2R binding domain, wherein each nucleic acid of the plurality of nucleic acids comprises a sequence encoding for a sequence variant of the CRTH2R binding domain, and wherein the antibody or antibody fragment binds to its antigen with a K_D of less than 100 nM.

10. The nucleic acid library of claim 9, wherein a length of the VH is about 90 to about 100 amino acids.

11. The nucleic acid library of claim 9, wherein a length of the VH is about 100 to about 400 amino acids.

12. The nucleic acid library of claim 9, wherein a length of the VH is about 270 to about 300 base pairs.

13. The nucleic acid library of claim 9, wherein a length of the VH is about 300 to about 1200 base pairs.

14. The nucleic acid library of claim 9, wherein the library comprises at least 10^5 non-identical nucleic acids.

15. A nucleic acid library comprising: a plurality of nucleic acids, wherein each of the nucleic acids encodes for a sequence that when translated encodes for a CRTH2R single domain antibody, wherein each sequence of the plurality of sequences comprises a variant sequence encoding for a CDR1, CDR2, or CDR3 on a variable region of a heavy chain (VH); wherein the library comprises at least 30,000 variant sequences; and wherein the CRTH2R single domain antibody binds to its antigen with a K_D of less than 100 nM.

16. The nucleic acid library of claim 15, wherein a length of the VH when translated is about 90 to about 100 amino acids.

17. The nucleic acid library of claim 15, wherein a length of the VH when translated is about 100 to about 400 amino acids.

18. The nucleic acid library of claim 15, wherein a length of the VH is about 270 to about 300 base pairs.

19. The nucleic acid library of claim 15, wherein a length of the VH is about 300 to about 1200 base pairs.

20. The nucleic acid library of claim 15, wherein the VH when translated comprises at least 80% sequence identity to any one of SEQ ID NO: 2338-2360 or 2403-2405.

21. An antibody or antibody fragment that binds CRTH2R, comprising an immunoglobulin heavy chain and an immunoglobulin light chain:

a. wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in any one of SEQ ID NO: 2338-2360 or 2403-2405; and

b. wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in any one of SEQ ID NO: 2361-2381 or 2406-2408.

22. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2338; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2361.

23. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2339; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2362.

24. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2340; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2363.

25. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2341; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2364.

26. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2342; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2365.

27. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2343; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2366.

28. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2344; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2367.

29. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2345; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2368.

30. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO:

2346; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2369.

31. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2347; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2370.

32. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2348; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2371.

33. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2349; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2372.

34. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2350; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2373.

35. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2351; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2374.

36. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2352; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2375.

37. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2353; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2376.

38. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2354; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2377.

39. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2355; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2378.

40. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2356; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2379.

41. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2357; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2380.

42. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2358; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2381.

43. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2403; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2406.

44. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2404; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2407.

45. The antibody or antibody fragment of claim 21, wherein the immunoglobulin heavy chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2405; and wherein the immunoglobulin light chain comprises an amino acid sequence at least about 90% identical to that set forth in SEQ ID NO: 2408.

46. The antibody or antibody fragment of claim 21, wherein the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a camelized antibody, a single-chain Fvs (scFv), a single chain antibody, a Fab fragment, a F(ab′)2 fragment, a Fd fragment, a Fv fragment, a single-domain antibody, an isolated complementarity determining region (CDR), a diabody, a fragment comprised of only a single monomeric variable

domain, disulfide-linked Fvs (sdFv), an intrabody, an anti-idiotypic (anti-Id) antibody, or ab antigen-binding fragments thereof.

47. The antibody or antibody fragment of claim 21, wherein the antibody or antibody fragment thereof is chimeric or humanized.

48. The antibody or antibody fragment of claim 21, wherein the antibody has an EC50 less than about 25 nanomolar in a cAMP assay.

49. The antibody or antibody fragment of claim 21, wherein the antibody has an EC50 less than about 20 nanomolar in a cAMP assay.

50. The antibody or antibody fragment of claim 21, wherein the antibody has an EC50 less than about 10 nanomolar in a cAMP assay.

51. An antibody or antibody fragment, wherein the antibody or antibody fragment comprises a complementarity determining region (CDR) comprising an amino acid sequence at least about 90% identical to that set forth in any one of SEQ ID NOs: 2382-2402.

52. An antibody or antibody fragment, wherein the antibody or antibody fragment comprises a sequence of any one of SEQ ID NOs: 2382-2402 and wherein the antibody is a monoclonal antibody, a polyclonal antibody, a bi-specific antibody, a multispecific antibody, a grafted antibody, a human antibody, a humanized antibody, a synthetic antibody, a chimeric antibody, a camelized antibody, a single-chain Fvs (scFv), a single chain antibody, a Fab fragment, a F(ab′)2 fragment, a Fd fragment, a Fv fragment, a single-domain antibody, an isolated complementarity determining region (CDR), a diabody, a fragment comprised of only a single monomeric variable domain, disulfide-linked Fvs (sdFv), an intrabody, an anti-idiotypic (anti-Id) antibody, or ab antigen-binding fragments thereof.

53. Use of an antibody or antibody fragment of any one of claims 21-52 in the manufacture of a medicament ~~A method~~for ~~of~~ treating a disease or disorder of the central nervous system, kidney, intestine, lung, hair, skin, bone, or cartilage.~~, comprising administering the antibody or antibody fragment of any one of claims 21-52.~~

54. Use of an antibody or antibody fragment of any one of claims 21-52 in the manufacture of a medicament for ~~A method of~~ treating a disease or disorder characterized by an inflammatory response.~~, comprising administering the antibody or antibody fragment of any one of claims 21-52.~~

55. Use of an antibody or antibody fragment of any one of claims 21-52 52 in the manufacture of a medicament for ~~A method of~~ treating an allergic reaction.~~, comprising administering the antibody or antibody fragment of any one of claims 21-52.~~

56. The use ~~method~~ of claim 55, wherein the allergic reaction is chronic idiopathic urticaria or allergic rhinitis.

57. Use of an antibody or antibody fragment of any one of claims 21-52 in the manufacture of a medicament for ~~A method of~~ treating asthma.~~, comprising administering the antibody or antibody fragment of any one of claims 21-52.~~

58. Use of an antibody or antibody fragment of any one of claims 21-52 in the manufacture of a medicament for~~A method of~~ treating alopecia or baldness.~~, comprising administering the antibody or antibody fragment of any one of claims 21-52.~~

59. A method for generating a nucleic acid library encoding for a CRTH2R antibody or antibody fragment thereof comprising:

(a) providing predetermined sequences encoding for:

i. a first plurality of polynucleotides, wherein each polynucleotide of the first plurality of polynucleotides encodes for at least 1000 variant sequence encoding for CDR1 on a heavy chain;

ii. a second plurality of polynucleotides, wherein each polynucleotide of the second plurality of polynucleotides encodes for at least 1000 variant sequence encoding for CDR2 on a heavy chain;

iii. a third plurality of polynucleotides, wherein each polynucleotide of the third plurality of polynucleotides encodes for at least 1000 variant sequence encoding for CDR3 on a heavy chain; and

(b) mixing the first plurality of polynucleotides, the second plurality of polynucleotides, and the third plurality of polynucleotides to form the nucleic acid library of variant nucleic acids encoding for the CRTH2R antibody or antibody fragment thereof, and wherein at least about 70% of the variant nucleic acids encode for an antibody or antibody fragment that binds to its antigen with a K_D of less than 100 nM.

60. The method of claim 59, wherein the CRTH2R antibody or antibody fragment thereof is a single domain antibody.

61. The method of claim 60, wherein the single domain antibody comprises one heavy chain variable domain.

62. The method of claim 60, wherein the single domain antibody is a VHH antibody.

63. The method of claim 59, wherein the nucleic acid library comprises at least 50,000 variant sequences.

64. The method of claim 59, wherein the nucleic acid library comprises at least 100,000 variant sequences.

65. The method of claim 59, wherein the nucleic acid library comprises at least 10^5 non-identical nucleic acids.

66. The method of claim 59, wherein the nucleic acid library comprises at least one sequence encoding for the CRTH2R antibody or antibody fragment that binds to CRTH2R with a K_D of less than 75 nM.

67. The method of claim 59, wherein the nucleic acid library comprises at least one sequence encoding for the CRTH2R antibody or antibody fragment that binds to CRTH2R with a K_D of less than 50 nM.

68. The method of claim 59, wherein the nucleic acid library comprises at least one sequence encoding for the CRTH2R antibody or antibody fragment that binds to CRTH2R with a K_D of less than 10 nM.

69. The method of claim 68, wherein the nucleic acid library comprises at least 500 variant sequences.

70. The method of claim 59, wherein the nucleic acid library comprises at least five sequences encoding for the CRTH2R antibody or antibody fragment that binds to CRTH2R with a K_D of less than 75 nM.

71. A protein library encoded by the nucleic acid library of any one of claims 1-20, wherein the protein library comprises peptides.

72. The protein library of claim 71, wherein the protein library comprises immunoglobulins.

73. The protein library of claim 71, wherein the protein library comprises antibodies.

74. The protein library of claim 71, wherein the protein library is a peptidomimetic library.

75. A vector library comprising the nucleic acid library of any one of claims 1-20.

76. A cell library comprising the nucleic acid library of any one of claims 1-20.

77. A cell library comprising the protein library of any one of 71-74.

78. An antibody or antibody fragment of any one of claims 21-52 for use in therapy.