Human immunoglobulin expression in these genetically engineered animals may also be affected by B-cell development of the non-human B-cells carrying the human or humanized immunoglobulin loci. The influence of the B-cell receptor (BCR) on B-cell development has been studied extensively in mice. However, it has been unclear how a human or partially human antibody combines to form a functional BCR, and whether such a BCR would efficiently influence the development and survival of non-human B-cells expressing human(ized) Ig, in transgenic animals, which, in turn, would affect antibody yields.

Brief Description of Drawings

Figure 1 shows an amino acid alignment of the human Igα polypeptide sequence (SEQ ID NO: 1) with other non-human Igα sequences (SEQ ID NOs: 2-6).

Figure 2 shows an amino acid alignment of the human Igβ polypeptide sequence (SEQ ID NO: 7) with other non-human Igβ sequences (SEQ ID NOs: 8-12).

Summary ~~of the Invention~~

~~In one aspect, t~~The ~~invention~~disclosure provides a transgene construct encoding a chimeric Igα subunit of the BCR, wherein the chimeric Igα subunit comprises an intracellular domain sequence and a transmembrane domain sequence of a non-human, Igα polypeptide sequence; and further, a polypeptide having at least 85% sequence identity to the extracellular domain of human Igα of SEQ ID NO.: 1.

~~In a second aspect, t~~The ~~invention~~disclosure provides a transgene construct encoding a chimeric Igβ subunit of the BCR, wherein the chimeric Igβ subunit comprises an intracellular domain sequence and a transmembrane domain sequence of a non-human, Igβ polypeptide sequence, and further, a polypeptide having at least 85% sequence identity to the extracellular domain of the human Igβ of SEQ ID NO.:7.

In a certain embodiment of the ~~invention,~~disclosure the type of non-human Igα polypeptide sequence includes, but is not limited to, the bovine (SEQ ID NO: 2); murine (SEQ ID NO: 3); canine (SEQ ID NO: 4); primate ((SEQ ID NO: 5); rabbit (SEQ ID NO: 6) or other non-human sequences. In another embodiment of the ~~invention~~disclosure, the type of non-human Igβ polypeptide sequence includes, but is not

limited to, the canine (SEQ ID NO: 8); rat (SEQ ID NO: 9); bovine (SEQ ID NO: 10); murine (SEQ ID NO: 11); chicken (SEQ ID NO: 12) or other non-human sequences.

~~In a third aspect~~Disclosed herein is, the non-human transgenic animal comprises (a) a transgene construct encoding either a full-length, human Igα subunit of SEQ ID NO.: 1, or the chimeric Igα subunit as defined above, and/or, (b) a transgene construct encoding either a full-length, human Igβ subunit of SEQ ID NO.: 7, or the chimeric Igβ subunit, as defined above, and, (c) a transgene construct encoding a human(ized) immunoglobulin locus, wherein the resultant transgene products combine to form a human(ized) B-cell receptor complex. In one aspect, there is provided a non-human transgenic animal comprising:

(a) a transgene construct encoding a full-length, human Igα subunit of SEQ ID NO.: 1; and,

(b) a transgene construct encoding a full-length, human Igβ subunit of SEQ ID NO.: 7; and,

(c) a transgene construct encoding a human(ized) immunoglobulin locus;

wherein the resultant transgene products combine to form a human(ized) B-cell receptor complex.

In one embodiment ~~of this aspect~~, the expression of any endogenous Ig production, and/or, endogenous Igα and/or endogenous Igβ subunit expression, of the non-human transgenic animal is substantially reduced.

In another embodiment, the non-human transgenic animal is selected from a group consisting of rabbit, mouse, rat, pig, sheep, goat, bird, horse, donkey and cow. In a preferred embodiment, the non-human transgenic animal is a rabbit.

~~In a fourth aspect~~, ~~t~~The ~~invention~~disclosure also provides an isolated human(ized) immunoglobulin from the non-human transgenic animal defined above, which is either an antibody or an antibody fragment. In a certain embodiment of this ~~aspect~~disclosure the isolated human(ized) immunoglobulin is either a polyclonal or a monoclonal antibody, or alternately, is an antibody fragment. The antibody fragment can be either from a polyclonal or a monoclonal antibody. Further, the antibody or the antibody fragment can be labeled, or fused to a toxin to form an immunotoxin, or coupled to a

therapeutic agent, or fused to any heterologous amino acid sequence well-defined and used in the art. In some embodiments, the antibody fragment is a Fc, Fv, Fab, Fab' or $F(ab')_2$ fragment.

~~In a fifth aspect~~, ~~t~~The ~~invention~~disclosure provides an isolated B-cell from the non-human transgenic animal defined above, where the B-cell expresses either the native human Igα subunit or a chimeric Igα subunit and/or either the native human Igβ subunit or

the chimeric Igβ subunit, and further, also expresses the human(ized) immunoglobulin locus. In certain embodiments, this B-cell is immortalized and in a preferred embodiment, is derived from a rabbit. In another aspect, there is provided an isolated B-cell from said non-human transgenic animal as defined above, wherein said B-cell expresses the native Igα subunit and the native human Igβ subunit, and the human(ized) immunoglobulin locus.

~~In a sixth aspect, t~~The ~~invention~~disclosure provides an antibody preparation comprising an antibody or an antibody fragment, as described above.

~~In a seventh aspect, t~~The ~~invention~~disclosure provides a pharmaceutical composition comprising an antibody or antibody fragment, as described above, in a mixture with a pharmaceutically acceptable ingredient. The pharmaceutical composition can comprise either a monoclonal antibody or a fragment thereof, or, one or a plurality of polyclonal antibodies or fragments thereof.

~~In an eighth aspect~~, tThe ~~invention~~disclosure provides a method for producing human(ized) antibodies in a non-human animal comprising: (a) introducing and expressing a transgene construct encoding either a native human Igα subunit or a chimeric Igα subunit, and/or a transgene construct encoding either a native human Igβ subunit or a chimeric Igβ subunit into the non-human animal; and, (b) introducing and expressing a transgene construct encoding a human(ized) immunoglobulin locus into the non-human animal; (c) subjecting the animal to an antigenic stimulus; and (d) isolating human(ized) antibodies from the animal. In a certain embodiment of this ~~aspect~~disclosure, the antibody is either a polyclonal or a monoclonal antibody, or is a fragment of a polyclonal or a monoclonal antibody. Further, the antibody or antibody fragment can either be labeled, or can be fused to a toxin to form an immunotoxin, or coupled to a therapeutic agent, or can be fused to any heterologous amino acid sequence.

~~In a ninth aspect, t~~The ~~invention~~disclosure provides a method for producing a non-human animal expressing human(ized) antibodies comprising: (a) introducing and expressing a transgene construct encoding either a native human Igα subunit or a chimeric Igα subunit and/or a transgene construct encoding either a native human Igβ subunit or a chimeric Igβ subunit into the B-cell of the non-human animal; and, (b) introducing and expressing a transgene construct encoding a human(ized) immunoglobulin locus into the non-human animal; wherein the resultant transgene products combine to form