Appendix 2 Statement of Material Facts Relied Upon in Motion.

Appendix 3 Claim chart comparing Adair claim 24 presented in 2005 and Adair involved claim 24.

Appendix 2

STATEMENT OF MATERIAL FACTS RELIED UPON IN MOTION

1. On December 21, 1989, Adair filed Great Britain Application GB 8928874.0 ("the UK Application"). (Ex. 2036).

2. On December 21, 1990, Adair filed PCT Application PCT/GB90/02017 ("the PCT Application"). (Ex. 2005).

3. Exhibit 2037 is a computer generated comparison (using Workshare™ Professional 5.2 SR2 software) of the typewritten text of the UK Application to the typewritten text of the PCT Application. The last page of Exhibit 2037 contains a color-coded legend for identifying deletions, additions, and movement of text.

4. On September 17, 1991, Adair entered the U.S. national stage by filing U.S. Patent Application No. 07/743,329 ("the '329 application"). (Ex. 2006).

5. Adair's '329 application contained claims 1-23, which are identical to claims 1-23 as originally filed with Adair's PCT application. (Ex. 2005, pp. 67-70 and Ex. 2006, pp. 67-70).

6. Original claim 1 of the Adair '329 application reads as follows:

> 1. A CDR-grafted antibody heavy chain having a variable region domain comprising acceptor framework and donor antigen binding regions wherein the framework comprises donor residues at at least one of positions 6, 23 and/or 24, 48 and/or 49, 71 and/or 73, 75 and/or 76 and/or 78 and 88 and/or 91. [Ex. 2006, p. 67].

7. At pages 4-6 of the specification, Adair provides a discussion of "recent" disclosures by Queen *et al*. relating to CDR-grafted antibodies and the substitution of acceptor framework residues with donor residues. (Ex. 2002, pp. 4-6).

8. At page 6, lines 22-28, the Adair specification states:

This has enabled us to establish a protocol for obtaining satisfactory CDR-grafted products which may be applied very widely irrespective of the level of homology between the donor immunoglobulin and acceptor framework. The set of residues which we have identified as being of critical importance does not coincide with the residues identified by Queen…." [Ex. 2002, p. 6, lns. 22-28].

9. The Abstract of Adair's involved specification reads, in part, as follows:

CDR-grafted antibody heavy and light chains comprise acceptor framework and donor antigen binding regions, the heavy chains comprising donor residues at at least one of positions (6, 23) and/or (24, 48) and/or (49, 71) and/or (73, 75) and/or (76) and/or (78) and (88) and/or (91). [Ex. 2002, Abstract].

10. At page 6, lines 31-37, the Adair specification reads as follows:

Accordingly, in a first aspect the invention provides a CDR-grafted antibody heavy chain having a variable region domain comprising acceptor framework and donor antigen binding regions wherein the framework comprises donor residues at at least one of positions 6, 23 and/or 24, 48 and/or 49, 71 and/or 73, 75 and/or 76 and/or 78 and 88 and/or 91. [Ex. 2002, p. 6, lns. 31-37].

11. At page 7, lines 1-5, the Adair specification reads as follows:

In preferred embodiments, the heavy chain framework comprises donor residues at positions 23, 24, 49, 71, 73 and 78 or at positions 23, 24 and 49. The residues at positions 71, 73 and 78 of the heavy chain framework are preferably either all acceptor or all donor residues. [Ex. 2002, p. 7, lns. 1-5].

12. At page 16, line 30 to page 19, line 9, Adair describes its "preferred protocol" for obtaining CDR-grated antibodies. (Ex. 2002, p. 16, ln. 30 to p. 19, ln. 9).

13. At page 17, lines 27-30, the involved Adair specification reads as follows under a section titled "Protocol":

2. Heavy Chain
2.1 Choose donor residues at <u>all</u> of positions 23, 24, 49, 71, 73 and 78 of the heavy chain or <u>all</u> of positions 23, 24 and 49 (71, 73 and 78 are <u>always</u> either <u>all</u> donor or <u>all</u> acceptor). [Ex. 2002, p. 17, lns. 25-30; Emphasis added].

14. At page 17, lines 32-35, the involved Adair specification states:

2.2. Check that the following have the same amino acid in donor and acceptor sequences, and if not preferably choose the donor: 2, 4, 6, 25, 36, 37, 39, 47, 48, 93, 94, 103, 104, 106 and 107. [Ex. 2002, p. 17, lns. 32-35].

15. At pages 19-23 of its involved specification, Adair offers a "rationale" for its protocol. (Ex. 2002, pp. 19-23).

16. At page 20, line 27, the involved Adair specification states "Heavy Chain - Key residues are 23, 71 and 73." (Ex. 2002, p. 20, ln. 27).

17. At page 21, line 9, for the "packing residues near the CDRs," the involved Adair specification states "Heavy Chain - Key residues are 24, 49 and 78." (Ex. 2002, p. 21, ln. 9).

18. At page 48, lines 25-27, the involved Adair specification explains: "the presence of the 6, 23 and 24 changes are important to maintain a binding affinity similar to that of the murine antibody." (Ex. 2002, p. 48, lns. 25-27).

19. At page 52, lines 25-29, the Adair involved specification states:

> These and other results lead us to the conclusion that of the 11 mouse framework residues used in the gH341A (JA185) construct, it is important to retain mouse residues at all of positions 6, 23, 24, 48 and 49, and possibly for maximum binding affinity at 71, 73 and 78. [Ex. 2002, p. 52, lns. 25-29].

20. On November 18, 1992, the U.S. Patent and Trademark Office entered a non-final office action rejecting Adair's original claims 1-23 on various grounds. (Ex. 2038).

21. At page 5 of the November 1992 office action, the Examiner rejected claims 1-5 under 35 U.S.C. § 112, first paragraph as not being enabled. In particular, the Examiner stated that practicing the invention as claimed would require undue experimentation relative to the teachings of the Adair specification. (Ex. 2038, p. 5).

22. At page 6 of the November 1992 office action, the Examiner rejected claims 1-5 under 35 U.S.C. § 112, second paragraph, as being indefinite in their recitation of "at least one of positions 6, 23 and/or 24, 48 and/or 49, 71 and/or 73, 75 and/or 76 and/or 78 and 88 and/or 91" because it was unclear whether the heavy chain,

a. had at least one of 6, 23, 24, 48, 49, 71, 73, 75, 76, 78, 88, or 91, or alternatively,

b. had at least one of (6) or (23 and/or 24) or (48 and/or 49) or (71 and/or 73) or (75 and/or 76 and/or 78 and 88 and/or 91), or alternatively,

c. had at least one of (6, 23) and/or (24, 48) and/or (49, 71) and/or (73, 75) and 76 and/or (78 and 88) and/or (91). (Ex. 2038, p. 6).

23. At pages 7-12 of the November 1992 office action, the Examiner rejected Adair's claims under 102/103 in view of Riechmann *et al*., *Nature*, Vol. 332, pp. 323-327 (March 1988) and Queen *et al*., *Proc. Natl. Acad. Sci. USA*, Vol. 86, pp. 10029-10033 (December 1989) . (Ex. 2038, pp. 7-12; Ex. 2011, and Ex. 2023).

24. On January 19, 1993, Adair responded to the November 1992 Office action. (Ex. 2007).

25. In the January 1993 amendment, Adair responded to the rejection of claims under 35 U.S.C. § 112, second paragraph, by cancelling claims 1-12. (Ex. 2007, pp. 29-32).

26. In the January 19, 1993, amendment, Adair responded to the rejection of claims under 35 U.S.C. § 102(b) in view of Riechmann *et al.* as follows:

> In Part A of this rejection, claims 1, 5, 6-8, and 12-22 were rejected as anticipated by Riechmann et al. The Examiner stated that claim 1 and claim 6 were interpreted to mean that the framework has donor residues in at least one of any of positions 6, 23, 24, 48, 49, 71, 73, 75, 76, 78, 88, or 91 in the heavy chain and (1, 3, 46, or 47) or 46, 48, 58, or 71) in the light chain, and thus, the teachings of Riechmann et al. anticipate the invention as claimed.
>
> The Examiner contends that the original claims lacked novelty over Riechmann et al. Claims 1, 5, 6-8, 12 and 22 have been cancelled without prejudice and submitted as new claims that more distinctly point out certain aspects of the present invention.

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