UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Celltrion, Inc.

Petitioner,

v.

Genentech, Inc.

Patent Owner

Patent No. 6,407,213

Inter Partes Review No. IPR2017-01374

**EXPERT DECLARATION OF LUTZ RIECHMANN, PH.D.
IN SUPPORT OF PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE**

I, Lutz Riechmann, Ph.D. declare as follows:

I. Introduction

1. I am the same Lutz Riechmann who submitted a declaration in support of Celltrion's Petition for Inter Partes Review of U.S. Patent 6,407,213 (the '213 patent) in May 2017. A detailed description of my background and qualifications may be found in that declaration, which I refer to as my "first declaration." In addition to the materials listed in Exhibit 1003B to my first declaration, I have also considered the materials set forth in the Addendum to this declaration.

2. I am being compensated at my standard rate for my time spent preparing this declaration, and my compensation is not contingent on the outcome of any matter or on any of the opinions provided below. I have no financial interest in the outcome of this proceeding.

3. I provided my understanding of legal concepts as they relate to this proceeding in my first declaration. My understanding of those concepts has not changed since I submitted my first declaration.

II. Opinions

A. A Person of Ordinary Skill In the Art Would Understand that The Disclosure of the Patent Is Limited

4. A person of ordinary skill would understand that the patent does not teach that all of the claimed back mutations and possible combinations of back

mutations will improve the binding of all antibodies that could be covered by the claims, or that any specific back mutation will work for a specific antibody other than those in the examples that were tested for binding. A person of ordinary skill would have understood from the prior art disclosing the specific structures of humanized antibodies, as well as the examples in the patent, that the back mutations that will increase binding will vary from antibody to antibody. The patent requires a person of ordinary skill to construct models to determine which of the described back mutations might possibly improve binding in a given project, and then use mutagenesis, which is the making of antibodies with different back mutations and then testing them, to confirm which precise combination of mutations works best to increase binding. A person of ordinary skill would have understood that there is no significant difference between this method and the methods in Queen 1989 and 1990 and the other prior art I have cited.

B. A Person of Ordinary Skill in the Art Would Have Been Motivated to Combine Queen 1989 and/or Queen 1990 with the PDB

5. Dr. Wilson argues that a person of ordinary skill in the art would not have combined the PDB with either of Queen 1989 or Queen 1990 in the manner I described in my first declaration. (Ex. 2041 (Wilson Decl. for IPR2017-01373) at ¶¶ 177-84.) I do not agree with Dr. Wilson's criticisms. As I explained in my first declaration, a person of ordinary skill would have used the publically available x-ray crystallographic studies of antibodies in the PDB during the humanization

process, because the PDB database provided a collection of the available antibody structures at that time. In fact, a person of ordinary skill in the art would have known it would not have been possible to create an accurate molecular model without using the information put forth in the PDB (or similar database). As I discussed, a person of ordinary skill could have processed the information either using one of a number of commercially available software packages such as CONTAX, PAIRS, or MIDAS, or could have done the calculations using a spreadsheet program such as Microsoft Excel. Regardless of the mechanism used to do these calculations, the results would have been the same.

6. Further, Dr. Wilson's assertion that Queen 1989 and Queen 1990 would have taught a POSA to model structure of the parent murine antibody and not the human framework is immaterial to my analysis. Regardless of whether the starting point was the murine structure or a humanized structure, a person of ordinary skill in the art would have used the data from the three-dimensional model to locate the framework residues that could, because of their positions within the heavy and light chains of the variable domain, either alter the structure of the CDRs or interact directly with the antigen during binding. A person of ordinary skill also would have regarded the Queen methodology as a reliable means of identifying framework substitutions that could be used to improve binding affinity. Dr. Wilson has not explained any reason why the outcome of the identification of

possible framework residues for substitution would be different if the person of ordinary skill modeled the human framework with the murine CDRs inserted within it, and I am not aware of any reason.

7. Also, Queen 1989 considered "other antibody V domains with known crystal structure" when constructing the antibody models used in Queen's method, (Ex. 1034 (Queen 1989) at 3), and Queen 1990 disclosed using "known structures" of the mAbs in the PDB as rough models that could be used to help construct the antibody models used in Queen's method. (Ex. 1050 (Queen 1990) at 16, 14:32-36.)

C. Dr. Wilson Ignores the Impact of Interspecies Homology

8. Dr. Wilson suggests that my analysis is flawed because the references on which I rely disclose additional potential residue back mutations that I did not specifically address and asserts that a person of ordinary skill in the art would not have been able to select the relevant back-mutations for a given humanized antibody from this larger group. (Ex. 2041 (Wilson Decl.) at ¶¶ 227-34.) I disagree.

9. As the '213 patent acknowledges, while the number of potential back mutations in any humanization project can be relatively large, the process of identifying which residues from this set of potential back mutations are more likely than others to improve the binding of a given humanized antibody would have

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