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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-02032
Patent 6,407,213 B1

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

INTRODUCTION

Boehringer Ingelheim Pharmaceuticals, Inc. ("Petitioner") filed a Petition for an *inter partes* review of claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71–73, 75–78, 80, and 81 of U.S. Patent No. 6,407,213 B1 ("the '213 patent," Ex. 1001). Paper 1 ("Pet."). Genentech, Inc. ("Patent Owner") timely filed a Preliminary Response. Paper 9 ("Prelim. Resp."). We review the Petition, Preliminary Response, and accompanying evidence under 35 U.S.C. § 314.

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). Because Petitioner has established a reasonable likelihood that it would prevail in showing the unpatentability of at least one challenged claim, we institute an *inter partes* review of claims 1, 2, 4, 25, 29, 62–64, 66, 67, 69, 71, 73, 75–78, 80, and 81.

Related Proceedings

According to the parties, the '213 patent is at issue in several district court cases, including *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01407 (D. Del.); *Amgen Inc. v. Genentech, Inc.*, No. 2-17-cv-07349 (C.D. Cal.); *Genentech, Inc. v. Amgen Inc.*, No. 1-17-cv-01471 (D. Del.); *Genentech, Inc. et al. v. Pfizer, Inc*. 1-17-cv-01672 (D. Del.); *Celltrion, Inc. v. Genentech, Inc.*, No. 18-cv-00274 (N.D. Cal.); and *Genentech, Inc. v. Celltrion, Inc.*, No. 18-cv-00095 (D. Del.). Paper 7, 5; Paper 8, 3; Paper 16, 2.

Petitioner has concurrently filed IPR2017-02031, challenging the same claims of the '213 patent based on different prior art references. Paper 1, 2.

The ’213 patent is the subject of IPR2016-01693 and IPR2016-01694, filed by Mylan Pharmaceuticals Inc. Paper 1, 2. We terminated those two proceedings before issuing an institution decision because the parties settled. *Mylan Pharm. Inc. v. Genentech, Inc.*, IPR2016-01693 (PTAB March 10, 2017) (Paper 24); IPR2016-01694 (PTAB March 10, 2017) (Paper 23).

The ’213 patent is also the subject of the following pending matters: IPR2017-01373 and IPR2017-01374 brought by Celltrion, Inc.; and IPR2017-01488 and IPR2017-01489 brought by Pfizer, Inc. We previously instituted *inter partes* reviews in those cases, and joined IPR2017-02139 and IPR2017-02140, brought by Samsung Bioepis Co., Ltd., to IPR2017-01488 and IPR2017-01489, respectively.

The ’213 Patent and Relevant Background

The ’213 patent relates to “methods for the preparation and use of variant antibodies and finds application particularly in the fields of immunology and cancer diagnosis and therapy.” Ex. 1001, 1:12–14.

A naturally occurring antibody (immunoglobulin) comprises two heavy chains and two light chains. *Id.* at 1:18–20. Each heavy chain has a variable domain (V_H) and a number of constant domains. *Id.* at 1:21–23. Each light chain has a variable domain (V_L) and a constant domain. *Id.* at 1:23–24.

The variable domains are involved directly in binding the antibody to the antigen. *Id.* at 1:36–38. Each variable domain “comprises four framework (FR) regions, whose sequences are somewhat conserved, connected by three hyper-variable or complementarity determining regions (CDRs).” *Id.* at 1:40–43. The constant domains are not involved directly in

binding the antibody to an antigen, but are involved in various effector functions. *Id.* at 1:33–34.

Before the '213 patent, monoclonal antibodies targeting a specific antigen, obtained from animals, such as mice, had been shown to be antigenic in human clinical use. *Id.* at 1:51–53. The '213 patent recognizes efforts to construct chimeric antibodies and humanized antibodies in the prior art. *Id.* at 1:59–2:52. According to the '213 patent, chimeric antibodies are "antibodies in which an animal antigen-binding variable domain is coupled to a human constant domain" (*id.* at 1:60–62), whereas "humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies" (*id.* at 2:32–35).

The '213 patent also acknowledges the following as known in the prior art:

1. In certain cases, in order to transfer high antigen binding affinity, it is necessary to not only substitute CDRs, but also replace one or several FR residues from rodent antibodies for the human CDRs in human frameworks. *Id.* at 2:53–61.

2. "For a given antibody[,] a small number of FR residues are anticipated to be important for antigen binding" because they either directly contact antigen or "critically affect[] the conformation of particular CDRs and thus their contribution to antigen binding." *Id.* at 2:62–3:8.

3. In a few instances, a variable domain "may contain glycosylation sites, and that this glycosylation may improve or abolish antigen binding." *Id.* at 3:9–12.

4. The function of an antibody is dependent on its three-dimensional structure, and amino acid substitutions can change the three-dimensional structure of an antibody. *Id.* at 3:40–43.

5. The antigen binding affinity of a humanized antibody can be increased by mutagenesis based upon molecular modelling. *Id.* at 3:44–46.

Despite such knowledge in the field, according to the '213 patent, at the time of its invention, humanizing an antibody with retention of high affinity for antigen and other desired biological activities was difficult to achieve using then available procedures. *Id.* at 3:50–52. The '213 patent purportedly provides methods for rationalizing the selection of sites for substitution in preparing humanized antibodies and, thereby, increasing the efficiency of antibody humanization. *Id.* at 3:53–55. This involves:

> a. obtaining the amino acid sequences of at least a portion of an import antibody variable domain and of a consensus variable domain;
>
> b. identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human variable domain sequences;
>
> c. substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
>
> d. aligning the amino acid sequences o(a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
>
> e. identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
>
> f. determining if the non-homologous import amino acid residue is reasonably expected to have at least one of the following effects:
>
> 1. non-covalently binds antigen directly,

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