

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the *Inter Partes* Review of:

Trial Number: To Be Assigned

U.S. Patent No. 6,407,213

Filed: November 17, 1993

Issued: June 18, 2002

Inventor(s): Paul J. Carter, Leonard G. Presta

Assignee: Genentech, Inc.

Title: Method for making humanized antibodies Panel: To Be Assigned

Mail Stop *Inter Partes* Review
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF TIMOTHY BUSS

TABLE OF CONTENTS

I.	QUALIFICATIONS AND BACKGROUND.....	1
A.	Education and Experience.....	1
B.	Bases for Opinions and Materials Considered.....	5
C.	Scope of Work.....	5
II.	SUMMARY OF OPINIONS.....	6
III.	LEGAL STANDARDS.....	9
IV.	PERSON OF ORDINARY SKILL IN THE ART.....	11
V.	THE '213 PATENT (EX. 1001).....	14
VI.	STATE OF THE ART OF MONOCLONAL ANTIBODY THERAPIES AND CANCER.....	14
A.	Early Antibody Therapy.....	14
B.	Efforts to Reduce Immunogenicity—Chimerization and Humanization.....	18
C.	Breast Cancer and HER-2.....	24
D.	Identification and Characterization of 4D5, a Potential Therapeutic Mouse Monoclonal Antibody to HER-2/ <i>neu</i>	30
E.	Humanization of 4D5 to Enable Therapeutic Use.....	37

1. My name is Timothy Buss I have been retained by counsel for Pfizer, Inc. (“Pfizer”). I understand that Pfizer intends to file petitions for *inter partes* review of U.S. Patent No. 6,407,213 (“the ’213 patent”) (Ex. 1001), which is assigned to Genentech, Inc. I also understand that Pfizer will request that the United States Patent and Trademark Office cancel certain claims of the ’213 patent as unpatentable in their petitions. I submit this expert declaration in support of Pfizer’s petitions.

I. QUALIFICATIONS AND BACKGROUND

A. Education and Experience

2. I am currently an independent consultant in the antibody engineering field. As a consultant, I help clients with a variety antibody discovery and development issues. In particular, I advise clients on choosing the best methods to immunize and screen monoclonal antibodies, humanize antibodies by CDR grafting onto human frameworks and develop methods for expression and purification of recombinant proteins. At the present time, I am working with two nonprofit research organizations and a gene therapy company on issues relating to antibody generation, engineering, affinity maturation and phage display.

3. In all, I have more than 25 years of practical and research experience specializing in antibody design, humanization, and expression. My *curriculum vitae* is attached hereto as Exhibit A.

4. I received my Higher National Certificate (“HNC”) in applied biology from Cambridgeshire College of Arts and Technology (now part of Anglia Ruskin University) in the UK where I attended from 1981–86. While attending Cambridgeshire College of Arts and Technology, I worked as an Assistant Scientific Officer in the Director’s Group, Agricultural and Food Research Council Institute of Animal Physiology and Genetics Research (1981–87).

5. In 1987, I became a Scientific Officer at the Medical Research Council (“MRC”) Group, Department of Neuroendocrinology at the AFRC Institute of Animal Physiology and Genetics Research. My work at the MRC included cloning, expression, and purification of proteins for polyclonal antibody production as well as associated animal work.

6. In 1991, I became a Higher Scientific Officer at the Cambridge Centre for Protein Engineering, Laboratory of Molecular Biology. There, I worked under Dr. Sir Gregory Winter and focused on, among other things, expression and purification of monoclonal and recombinant humanized antibodies and generation of vectors for antibody phage display. In 1993, I moved to the Fred Hutchinson Cancer Research Center in Seattle, WA. My work there included cloning, expression, and purification of humanized antibodies as well as the development of protocols for the expression and purification of recombinant proteins.

7. In 2002, I moved to the Sidney Kimmel Cancer Center, where my work involved the cloning and expression of monoclonal antibodies; the design, construction, and expression of murine, chimeric, and humanized antibodies for tumor targeting projects; and the generation of phage antibody libraries from immunized mice to generate novel binders to targets on vascular endothelial cells.

8. In 2008, I became a Senior Scientist at Ambrx, Inc. In that position, I was responsible for antibody generation and development, including the design and generation of recombinant proteins and chimeric and humanized antibodies. I also supervised development from initial antigen design through preclinical testing of the humanized antibody lead candidate, generated monoclonal antibodies for internal projects, designed and produced bispecific and multifunctional antibodies and antibody-based proteins, and made Fc modifications to alter effector functions. I was also project leader on several collaborations with large pharmaceutical companies. I remained at Ambrx, Inc. until 2015.

9. In addition to my full time experience described above, I have also been involved with a number of consulting projects. From August 2015 to March 2016, I worked as a Research Scientist and Consultant at the California Institute for Biomedical Research. In this position, I worked to troubleshoot antibody related projects and advise on antibody research, humanization, design, expression,

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.