UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS, INC., and
MERCK SHARP & DOHME CORP.,
Petitioners

v.

GENENTECH, INC. AND CITY OF HOPE
Patent Owners

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IPR No. 2016-0710[1]

U.S. PATENT NO. 6,331,415

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DECLARATION OF MARC J. SHULMAN IN SUPPORT OF PETITIONER'S REPLY

[1] Case IPR2017-00047 has been joined with this proceeding.

DECLARATION OF MARC J. SHULMAN

I, Marc J. Shulman, hereby declare and state as follows:

I. INTRODUCTION

1. This declaration is submitted on behalf of Merck Sharp & Dohme Corp. ("Merck") in IPR No. 2016-00170, regarding U.S. Patent No. 6,331,415, "Methods of Producing Immunoglobulins, Vectors and Transformed Host Cells for Use Therein," owned by Genentech, Inc. and City of Hope (collectively, "Patent Owners").

2. In response to statements made in Patent Owners' Response (Paper 31) and the opinions expressed by Patent Owners' expert Dr. John Fiddes (Ex. 2019), I have been asked to provide information on my scientific work related to recombinant expression of immunoglobulin heavy and light chains in mammalian cells, which took place in the early 1980s. Specifically, I have been asked to explain how the work that my colleagues and I performed prior to April 1983 refutes Patent Owners' and Dr. Fiddes' arguments regarding the alleged uncertainties surrounding recombinant expression of antibodies in April 1983 and their arguments that the "prevailing mindset" in April 1983 was to express only one exogenous protein per host cell.

II. BACKGROUND AND EXPERIENCE

3. I am currently Professor Emeritus in the Department of Immunology and the Department of Molecular and Medical Genetics, in the Faculty of Medicine

of the University of Toronto in Toronto, Canada. My *curriculum vitae* is attached hereto as Appendix A.

4. I received a B.A. in Physics from Harvard University in 1962, and a Ph.D. in Biology from Massachusetts Institute of Technology in 1969.

5. In 1969-1970, after receiving my Ph.D., I was a postdoctoral fellow at Massachusetts Institute of Technology and the National Institutes of Health. During the summers of 1971-1972, I was an investigator at the Marine Biological Laboratory, Woods Hole, Massachusetts.

6. In 1972 until 1973, I was a National Science Foundation Fellow at the Institut de Biologie Moleculaire, L'Universite de Paris, in Paris, France. From 1970-1976, I was also a Staff Fellow, Lab of Molecular Biology at the National Cancer Institute, National Institutes of Health, in Bethesda, Maryland.

7. In 1976, I became a Member of the Basel Institute for Immunology, in Basel, Switzerland, where I remained until 1979.

8. In 1979, I became Assistant Professor in the Department of Medical Biophysics at the University of Toronto, in Toronto, Canada. In 1985, I became a faculty member in the Immunology Department and Medical Genetics (now Molecular and Medical Genetics) Department and subsequently promoted to Associate Professor. In 1990, I was promoted to Professor, and in 2007, I retired as Professor Emeritus.

9. During my scientific career, I have been awarded over 35 research grants, and I have published nearly 100 peer-reviewed articles, most of which pertain to immunoglobulin production and structure/function. (*c.f.*, Appendix A.)

III. COMPENSATION

10. I am being compensated for my work on this case at my standard consulting rate of $600/hour. My compensation is not contingent upon the results of my analysis or the substance of my testimony. I have no stake in the outcome of this proceeding or any related litigation or administrative proceedings. I have no financial interest in Merck, and similarly have no financial interest in the patent at issue, U.S. Patent 6,331,415 ("the '415 patent") or its owners.

IV. MY INITIAL WORK ON IMMUNOGLOBULINS

11. I began conducting research in the immunoglobulin (Ig) field in 1976 at the Basel Institute for Immunology, in Basel, Switzerland, where I worked closely with future Nobel Laureate Dr. Georges Köhler. We published several papers together including a paper describing our development of a cell line called Sp2/0. Ex. 1117 (Shulman, et al., 1978).

12. The Sp2/0 cell line makes no immunoglobulin chains, neither the heavy chain, e.g., μ, nor light chain, e.g., κ. However, this cell line is capable of serving as a fusion partner for making hybridomas. *Id.* Importantly, the Sp2/0 cell line is also an advantageous recipient cell for expressing vectors encoding

recombinant immunoglobulin genes, as it provides all the specialized cellular machinery for transcribing immunoglobulin genes, and for assembling and processing the immunoglobulin heavy and light chains into functional immunoglobulin.

13. To elaborate briefly on the preceding point – before the advent of recombinant DNA and gene transfer technology, cell hybrids were sometimes used to gain insight into the cellular requirement for expressing tissue-specific genes. In particular, it had been shown that a hybrid cell could be formed by fusing an Ig-expressing myeloma cell line with a fibroblast cell line making no Ig. The interesting result was that this hybrid cell did not produce immunoglobulin. Ex. 1139 (Coffino et al., 1971). This result was a strong indication that immunoglobulin gene expression required cellular factors that were present in myeloma cell lines and absent (and presumably suppressed by factors) in fibroblasts. Accordingly, this result indicated that vectors bearing cloned versions of the natural genomic immunoglobulin DNA segments would not be expressed in fibroblast cell lines but would likely be expressed in lymphoid, *e.g.*, hybridoma, cell lines.

14. Dr. Köhler and I also developed a method of isolating mutant hybridoma cell lines that were defective in the normal production of either their immunoglobulin light or heavy chain. Ex. 1118 (Köhler & Shulman 1980). Our

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