UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MERCK SHARP & DOHME CORP.
Petitioner

v.

GENENTECH, INC. AND CITY OF HOPE
Patent Owners

U.S. Patent No. 6,331,415

"Methods of Producing Immunoglobulins, Vectors and Transformed Host Cells for Use Therein"

Inter Partes Review No. 2016-01373

DECLARATION OF MICHAEL H. WIGLER IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,331,415

I. INTRODUCTION

I, Michael H. Wigler, hereby declare and state as follows:

1. I have been asked by counsel for Merck Sharp & Dohme Corp. ("Merck") to submit this declaration in connection with Merck's petition for *inter partes* review of U.S. Patent No. 6,331,415 ("the '415 patent"), which I am informed is being filed concurrently with this declaration.

2. I have no stake in the outcome of this proceeding or any related litigation or administrative proceedings. I have no financial interest in the Petitioner, and similarly have no financial interest in the '415 patent or its owner.

3. I am one of the named inventors on U.S. Patent No. 4,399,216 ("the Axel patent"). The method described in the Axel patent is sometimes referred to as the "Wigler method" because I was the lead author on several scientific papers that form the basis of the work described in the Axel patent. I have been asked to explain the technology and the invention embodied in the Axel patent.

II. BACKGROUND

4. I received a Bachelor of Arts degree in Mathematics from Princeton University in 1970, a Master of Medical Science degree in Medicine from Rutgers University in 1972, and a Doctor of Philosophy (Ph.D.) degree in Microbiology from Columbia University in 1978. I conducted my doctoral research in the Department of Microbiology at Columbia University.

5. After my studies, in 1978, I became a Professor of Mammalian Cell Genetics and Interim Chair of Quantitative Biology at Cold Spring Harbor Laboratory. In 1988, I became an Adjunct Professor in the Department of Genetics, College of Physicians and Surgeons at Columbia University. From 2008 to 2014, I was a Foreign Adjunct Professor of Tumor Biology in the Department of Oncology-Pathology at Karolinska Institutet in Stockholm, Sweden. I still presently hold my position at Cold Spring Harbor Laboratory.

6. I have over 35 years of experience in recombinant DNA technology. In the 1970s and 1980s, my research focused on developing methods for manipulating mammalian cells for the production of proteins, including pioneering recombinant gene co-expression and gene transfer techniques.

7. In addition to the research described below, my research group was the first to isolate a vertebrate gene using gene transfer techniques and the first to isolate a human oncogene by this means. Additionally, my laboratory discovered the involvement of three members of the *RAS* family in human cancer; pioneered the use of yeast as a model to explore more complex organisms; co-invented encoded combinatorial synthesis, which has accelerated the discovery of new drug candidates; co-invented RDA, a method for comparative genome analysis; and developed representational genomic approaches that are used widely in genotyping. I have published my research as an author or co-author of over 180

referred journal articles, including scientific literature directed to the transformation and expression of eukaryotic genes in mammalian host cells. I am also a named inventor on over 30 U.S. patents.

8. I have received several awards and honors for my work, including the American Business for Cancer Research Award in 1982, the Pfizer Biomedical Award in 1985, the NIH Outstanding Investigator Award in 1985, the American Cancer Society Lifetime Research Professorship Award in 1986, and the Double Helix Medal in 2007. I have also been elected into the National Academy of Sciences, the American Academy of Microbiology, and the American Academy of Arts & Sciences.

III. DEVELOPMENT OF MY CO-TRANSFORMATION TECHNIQUE

9. In 1976, I began the research that would ultimately lead to the Axel patent.

10. My initial research involved transfecting mouse L cells that were deficient in thymidine kinase ("tk") with DNA derived from the herpes simplex virus-l ("HSV-1") that encodes for tk. My co-authors and I were able to demonstrate that transformation with the HSV-1 tk gene restores tk activity in tk-deficient cells. This allowed us to use tk as a selectable marker, whereby we could select for host cells that had been successfully transformed by growing them in a medium containing hypoxanthine, aminopterin and thymidine ("HAT"). This is

because cells that do not express tk are unable to grow in the presence of HAT. The results of this research were published in the journal *Cell* in 1977: Wigler, M. et al., *Transfer of Purified Herpes Virus Thymidine Kinase Gene to Cultured Mouse Cells*, Cell 11:223-232 (1977) (Ex. 1029).

11. In 1978, I, along with my co-authors published a second paper in *Cell*: Wigler, M. et al., *Biochemical Transfer of Single-Copy Eucaryotic Genes Using Total Cellular DNA as Donor*, Cell 14:725-731 (1978) (Ex. 1030). My second *Cell* paper expanded upon my earlier work and demonstrated that DNA derived from sources other than HSV-1 could be used to transfer tk activity to tk deficient host cells. Among the species that were successfully used as sources of tk DNA were mice, hamsters, chickens, calves, and humans. Based upon our results, we concluded "[t]he method which we have used to transfer the thymidine kinase gene can, in principle, be applied to any gene for which conditional selection criteria are available." Ex. 1030, at 730.

12. In 1979, I extended my earlier work by demonstrating that a different gene, the gene for adenine phosphoribosyltransferase ("aprt"), could be transformed into eukaryotic host cells. This research was published in the *Proceedings of the National Academy of Sciences*: Wigler, M. et al., *DNA-Mediated Transfer of the Adenine Phosphoribosyltransferase Locus into Mammalian Cells*, Proc. Natl. Acad. Sci. USA, 76:1373-1376 (March 1979) (Ex.

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