UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner

v.

GENENTECH, INC. AND CITY OF HOPE
Patent Owner

Case IPR2016-00710
Patent 6,331,415

DECLARATION OF REINER GENTZ, PH.D.

Mylan v. Genentech

I, Reiner Gentz, do hereby declare and state:

1. I am a citizen of Germany and reside in Belo Horizonte, Minas Gerais, Brazil.

2. From approximately the end of 2003 to the present, I have acted as a biotechnology consultant. I am currently the President of Gentz & Gentz Biotechnology Consultants, which I founded around 2012, and which is based in Belo Horizonte, Minas Gerais, Brazil.

3. My career in the biotechnology industry has spanned over thirty years. It formally began in 1984 when, upon completion of my Ph.D., I was hired by Hoffman La Roche AG in Basel, Switzerland. I worked there as a Senior Scientist until 1987. I then took sabbatical leave and served as a visiting scientist at Roche Institute of Molecular Biology in Nutley, New Jersey until 1989. I then returned to Hoffman La Roche AG, where I worked for another 4 years.

4. In 1993, I joined Human Genome Sciences in Rockville, Maryland, where I worked for the next 10 years in various executive positions.

5. Before joining Hoffman La Roche AG in 1984, I studied at the University of Heidelberg in Germany, from which I received my Master's degree in biology/biological sciences in 1981 and my Ph.D. in biology in 1984.

6. From 1980-1984, I was a student in the laboratory of Dr. Hermann Bujard, first in pursuit of my Master's degree and then in pursuit of my Ph.D.

7. I have been asked by Genentech and City of Hope to describe research relating to T5 promoters that I was a part of in the Bujard laboratory while I was a Master's and Ph.D. student.

8. I have also been asked to give my views on how a scientist, with a Ph.D. in molecular biology or a related discipline as of April 8, 1983, would have interpreted the work done by my group at the Bujard lab, as disclosed in the publication Gentz *et al.*, Cloning and analysis of strong promoters is made possible by the downstream placement of a

RNA termination signal," *Proc. Natl. Acad. Sci. USA* 78(8):4936-4940 (1981) (Ex. 2060) ("the Gentz publication"), and in U.S. Patent No. 4,495,280 (Ex. 1002) ("the Bujard patent").

9. Promoters are the regulatory elements that drive transcription of DNA into mRNA, the first general step in gene expression. Translation, the second general step in gene expression, is the process by which mRNA is translated into protein. By 1980, it was known that some T5 promoters were particularly strong, *i.e.*, they exhibited higher transcription levels than other promoters, but as a result, it was difficult to stably introduce them into plasmids in a controlled fashion.

10. In 1980, when I began working in the Bujard lab, the group had already been trying to clone some of the T5 promoters into plasmids, but had not yet been successful in doing so.

11. During the 1980-1981 timeframe, I collaborated with other members of the Bujard lab (including Dr. Bujard and Annette Langner) as well as several scientists from Stanford (Dr. Stanley Cohen and Annie Chang), to develop a way to stably introduce T5 promoters into plasmids to facilitate further characterization of the promoters.

12. We ultimately did this by introducing T5 promoters into a plasmid, designated pLBU3, that includes a strong terminator located downstream of the cloning site for the promoter. The pLBU3 plasmid also includes a gene that confers tetracycline resistance located downstream of the terminator signal.

13. Transformation of *E. coli* with pLBU3 provides only nominal resistance to tetracycline due to the presence of the strong terminator, but we theorized that the insertion of strong T5 promoters should result in an increase in tetracycline resistance, because more RNA polymerases would read through the terminator and transcribe the gene conferring tetracycline resistance.

14. Additionally, we theorized that expression levels of a gene placed between the T5 promoter and terminator should be high relative to the expression levels of the gene conferring tetracycline resistance,

due the strength of the T5 promoter and the placement of the additional gene upstream of the terminator. In our experiments, we inserted a small fragment of the β-galactosidase gene that encodes a peptide of approximately 71 amino acids in between the T5 promoter and the terminator signal. The β-galactosidase gene fragment complements enzyme activity in a bacterial strain and the resulting enzyme cleaves the substrate, which results in a deep blue color of the colonies.

15. Finally, we theorized that the presence of a strong terminator might be sufficient to balance the T5 promoter and allow for it to be cloned into the expression plasmid.

16. Our experiments confirmed that the presence of the strong terminator does in fact balance strong T5 promoters and allow for them to be cloned into the expression plasmid.

17. We also demonstrated that the presence of a balanced T5 promoter increased expression levels of both the β-galactosidase gene fragment and the gene conferring tetracycline resistance located downstream of the terminator signal, with much higher expression levels of the β-galactosidase gene fragment being demonstrated by the presence of a dark blue color of the colonies on the plates.

18. Our work was published in 1981 in Gentz *et al.*, Cloning and analysis of strong promoters is made possible by the downstream placement of a RNA termination signal. *Proc. Natl. Acad. Sci. USA*, 78(8): 4936-4940 (1981) (Ex. 2060).

19. After completing the work described above, during 1981-1983, when I was working on my Ph.D. thesis, I continued to characterize various T5 promoters, but also did work demonstrating that by using the strong promoter/terminator system in a modified plasmid, one could express large amounts of eukaryotic protein in *E. coli*, such that it constitutes 50% of the total protein in the bacteria.

20. In my work, I used a murine dihydrofolate reductase ("DHFR") gene as the eukaryotic gene to be expressed. This gene was chosen for further study of the strong promoter/terminator system, because it

encodes a relatively simple monomeric enzyme. The murine DHFR gene was inserted between strong T5 promoters (which included ribosomal binding sites) and strong terminator in the plasmid.

21. In these experiments, a chloramphenicol acetyltransferase ("CAT") gene that confers resistance to the antibiotic chloramphenicol was located downstream of the terminator instead of a gene conferring tetracycline resistance, which we had used previously.

22. High expression levels of DHFR were obtained, while the CAT resistance gene was expressed at much lower levels, but at sufficient levels to identify and select colonies that exhibited CAT resistance.

23. While I was working in the Bujard lab, the lab's research was not focused on methods of protein production. Rather, the lab was pursuing exploratory research directed to characterizing various promoters and understanding why some are more efficient than others. Dr. Bujard's publications from this timeframe, all of which report research relating to studies of promoters and transcription, reflect this focus. *See*, *e.g.*, Kammerer, *et al.*, Functional dissection of Escherichia coli promoters: information in the transcribed region is involved in late steps of the overall process. *EMBO J.* 5(11):2995-3000 (1986) (Ex. 2074); Deuschle, *et al.*, Promoters of Escherichia coli: a hierarchy of in vivo strength indicates alternate structures. *EMBO J.* 5(11):2987-94 (1986) (Ex. 2075); Deuschle, *et al.*, lac Repressor blocks transcribing RNA polymerase and terminates transcription. *Proc. Natl. Acad. Sci. USA* 83(12):4134-37 (1986) (Ex. 2076); Peschke, *et al.*, Efficient utilization of Escherichia coli transcriptional signals in Bacillus subtilis. *J. Mol. Biol.* 186(3):547-55 (1985) (Ex. 2077); Gentz & Bujard, Promoters recognized by Escherichia coli RNA polymerase selected by function: highly efficient promoters from bacteriophage T5. *J. Bacteriol.* 164(1):70-77 (1985) (Ex. 2078); Bujard, *et al.*, Insertion of transcriptional elements outside the replication region can interfere with replication, maintenance, and stability of Co1E1-derived plasmids. *Basic Life Sci.* 30:45-52 (1985) (Ex. 2079).

24. During this timeframe, I did not contemplate using the strong promoter/terminator system we had created to express two different

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