UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BLUEBIRD BIO, INC.,
Petitioner,

v.

SLOAN KETTERING INSTITUTE FOR CANCER RESEARCH,
Patent Owner.

Case No. IPR2023-00074
Patent No. 8,058,061

DECLARATION OF DR. LUCIO LUZZATTO
IN SUPPORT OF PATENT OWNER'S PRELIMINARY RESPONSE

I, Lucio Luzzatto, declare as follows:

1. I am over the age of 21 years and am fully competent to make this Declaration. I make the following statements based on personal knowledge and, if called to testify to them, could and would do so.

2. I earned a Maturita Classica from Liceo D'Oria in Genova, Italy in 1953. In 1959, I received my M.D. from the University of Genova Medical School, Genova, Italy. In 1968, I received my Ph.D. in Biochemistry from the Ministry of Education, Italy. I am certified in Hematology in Italy and in UK (FRCPath). I received my medical license from the State of New York in 1995. I have been also licensed in Italy, Nigeria, the U.K., and Tanzania.

3. After obtaining my M.D., I became a resident in infectious diseases in Genova, Italy. In 1963, I became a fellow in Haematology at Columbia Presbyterian Hospital's Department of Medicine. In the period from 1964 to 1994 I was a lecturer and then professor of hematology first in Ibadan and later in London, and I directed a Genetics Research Institute in Naples.

4. From 1994 to 2000, I served as the Chairman of the Department of Human Genetics and as Attending Physician in Genetics and Hematology at Memorial Sloan Kettering Cancer Center. Thereafter, I served as the Scientific Director for the National Institute for Cancer Research in Genova, Italy from 2000 to 2004. I also served as a Professor of Haematology at the University of Genova from 2002 to 2006.

5. From 2005 to 2015, I was the Scientific Director at the *Istituto Toscano Tumori* in Florence Italy. I was also a Professor of Haematology (Honorary since 2008) at the University of Florence in Italy.

6. Until December 31, 2022, I have been a Professor of Haematology at Muhimbili University College of Health and Allied Sciences in Dar-es-Salaam, Tanzania.

7. Attached as Appendix A is my current CV.

8. As Chairman of the Department of Human Genetics at Memorial Sloan-Kettering Cancer Center (MSKCC), I oversaw various research labs. One of those labs was run by Dr. Michel Sadelain, whom I had recruited. I was aware of the research that Dr. Sadelain and his team were conducting in the mid to late 1990s. Specifically, they were pursuing the idea of gene therapy, based on gene transfer into hematopoietic stem cells, to treat hemoglobinopathies. Several individuals worked in his lab, including Stefano Rivella and Chad May; and there was collaboration with Joseph Bertino, who was chairman of the Department of Pharmacology at MSKCC.

9. Throughout the 1990s, there were several other labs working on finding a vector capable of integrating into hematopoietic stem cells, that would also result in adequate expression of the beta globin gene *in vivo*. One might say there was a sort of race as to who would first find a solution.

10. I remember Dr. Sadelain's team was working on finding a solution over my entire tenure at MSKCC, i.e., from 1994 to 2000. In fact, I had multiple conversations with Dr. Sadelain over the years about his research, the challenges he was facing, the progress his team had made, etc.

11. In or around the 1996-1998 timeframe, Dr. Sadelain and his team tested many vectors, and with a. vector they termed TNS9 they had a breakthrough. They believed this vector was capable of successfully transferring a globin gene into hematopoietic stem cells, and achieving a level of expression that would be therapeutically-relevant.

12. In or around 1999, the team initiated *in vivo* studies in mice. The results of those studies were very encouraging. Not only was the beta-globin of the TNS9 vector being expressed, but it was being expressed at therapeutic levels that could be sustained over a period. I remember Dr Sadelan and all in his lab being, understandably, very excited; and so was I by reflection.

13. The TNS9 vector and accompanying research became the subject of U.S. Patent No. 7,541,179 ("the '179 Patent") and U.S. Patent No. 8,058,061 ("the '061 Patent"). I am familiar with these patent applications.

14. I understand the TNS9 vector is one embodiment of the vector claimed in the '179 and '061 Patents. It utilized a lentiviral virus as the backbone of the vector. It also included a human beta-globin gene, plus a 3.2 kb nucleotide portion, which was taken from the human β-globin locus control region (LCR).

The 3.2 kb nucleotide portion consisted of three fragments, each of which encompassed one of the hypersensitive sites (HS) known to exist within the LCR. I understand these fragments were created using restriction enzymes to cut the DNA but other approaches would have been known and were regularly used, including the polymerase chain reaction (PCR). The LCR was known to regulate physiologically the expression of the globin genes, including the beta-globin gene and the gamma-globin genes, It was and is my understanding that the different globin genes share common characteristics and structures, making it possible for their expression to come under the control of the same LCR.

15. While the TNS9 vector initially was tested for expression of a human beta-globin gene, I remember recognizing that the vector design could be used with other globin genes. This could be done by substituting the human beta-globin gene with the nucleotide sequence of a different functional globin on the TNS9 vector. I remember I had discussion with Dr. Sadelain and his team about this.

16. On July 6, 2000, an article reporting some of Dr. Sadelain and his team's work was published in Nature (referred to as "the Nature Article"). I understand this article is Exhibit 1005 in the IPR proceedings and is being asserted by the Petitioner against the '179 and '061 Patents. This article was entitled, "Therapeutic Haemoglobin Synthesis in β-Thalassaemic Mice Expressing Lentivirus-Encoded Human β-globin." Chad May is one of the

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