UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

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ASSOCIATION FOR MOLECULAR PATHOLOGY; AMERICAN COLLEGE OF MEDICAL GENETICS; AMERICAN SOCIETY FOR CLINICAL PATHOLOGY; COLLEGE OF AMERICAN PATHOLOGISTS; HAIG KAZAZIAN, MD; ARUPA GANGULY, PhD; WENDY CHUNG, MD, PhD; HARRY OSTRER, MD; DAVID LEDBETTER, PhD; STEPHEN WARREN, PhD; ELLEN MATLOFF, M.S.; ELSA REICH, M.S.; BREAST CANCER ACTION; BOSTON WOMEN'S HEALTH BOOK COLLECTIVE; LISBETH CERIANI; RUNI LIMARY; GENAE GIRARD; PATRICE FORTUNE; VICKY THOMASON; KATHLEEN RAKER,

Plaintiff,

-against-

UNITED STATES PATENT AND TRADEMARK OFFICE; MYRIAD GENETICS; LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, and MICHAEL K. YOUNG, in their official capacity as Directors of the University of Utah Research Foundation,

Defendant.

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No. Civil Action No. 09-4515 (RWS)

ECF Case

DECLARATION OF JOSEPH SCHLESSINGER. PH.D.

I, Joseph Schlessinger hereby declare that:

1. I am the Chairman of the Department of Pharmacology at Yale University School of Medicine and William H. Prusoff Professor since 2001. Prior to my appointment at Yale, I was the Director of the Skirball Institute for Biomolecular Medicine at New York University (NYU) Medical Center from 1998–2001 and the Milton and Helen Kimmelman Professor and Chairman of the Department of Pharmacology at NYU Medical School from 1990–2001. I was also a member of the faculty of the Weizmann Institute from 1978–1991 and the Ruth and Leonard Simon Professor of Cancer Research in the Department of Immunology from 1985–1991. My qualifications, experience and list of my publications are set forth in my curriculum vitae attached hereto as Exhibit 1. (Ex. 1)

2. I received a B.Sc. degree in Chemistry and Physics in 1968 (magna cum laude), and a M.Sc. degree in chemistry (magna cum laude) in 1970 from the Hebrew University in Jerusalem. I obtained my Ph.D. degree in biophysics from the Weizmann Institute of Science in 1974. From 1974–1976, I was a postdoctoral fellow in the Departments of Chemistry and Applied Physics at Cornell University, and from 1977–1978, I was a visiting fellow in the immunology branch of the National Cancer Institute of NIH.

3. In addition to my academic appointments, I was a Research Director at Meloy laboratory in Rockville, Maryland and later on in Rorer Biotechnology in King of Prussia, Pennsylvania from 1985–1990. Thereafter, I co-founded Sugen, Inc. in 1991. One of the pipeline products developed at Sugen (SU11248) was ultimately approved by the FDA (Sutent or Sunitinib) for treating gastrointestinal stromal tumors, renal cell carcinoma and endocrine pancreatic cancer . In 2001, I co-founded Plexxikon, a company that uses a pioneering

structural biology-based platform for drug discovery. I am currently the Chairman of the Board and a member of the Scientific Advisory Board of Plexxikon. In 2008 I founded Kolltan, a company that uses a novel approach for developing a new generation of therapeutic antibodies that block the activity of oncogenic receptor tyrosine kinases

4. I received the following awards: Michael Landau Prize (1973), Sara Leady Prize (1980), Hestrin Prize (1983), Levinson Prize (1984), Ciba-Drew Award (1995), Antoine Lacassagne Prize (1995), The Distinguished Service Award of Miami Biotechnology in (1999), Honorary Membership of the Japanese Biochemical Society (1999), Taylor Prize (2000), Honorary Doctor of Philosophy from the University of Haifa (2002) and the Dan David Prize (2006).

5. I was elected to the National Academy of Sciences in 2000, to the American Academy of Arts and Sciences in 2001, and as Member of the Institute of Medicine of the National Academies in 2005. I am a member of the European Molecular Biology Organization (EMBO) (1982), a fellow of the Neuroscience Research Program (2000) and a member of the European Academy of Sciences (2004).

6. I serve on the editorial boards of numerous journals, including Cell, Molecular Cell., the Journal of Cell Biology, and the Science magazine 'Science Signaling' journal. I have authored over 450 scientific original and review articles in the area of molecular biology, biochemistry, structural biology and drug discovery, mostly in the area of tyrosine kinase signaling.

7. I have delivered many named lectures including The Fourth Kroc Lecture, Harvard Medical School (1988); E.J. Cohn Lecture, Harvard Medical School (1993); E. Fisher

Lecture, University of Geneva (1993); Lamport Lecture, University of Seattle (1993); Harvey Lecture, Rockefeller University (1994); Deans Lecture, Mount Sinai Medical School (1994); Feigen Lecture, Stanford University (1994); Randall Lecture, University of Pennsylvania (1994); Sigma Tau Lecture, Rome, Italy (1995); Lindner Lecture, Weizmann Institute (1996); Burroughs Wellcome Lectures, University of Indiana (1997); Juan March Lecture, Madrid, Spain (1998); Bayer Lecture, Berkeley (1999); Sixth Kroc Lecture, University of Massachusetts (1999); NIH Director Lecture (2000); K.F. Naidorf Lecture, Columbia University (2000); Distinguished Speaker, University of Texas, San Antonio (2000); Severo Ochoa Lecture, Madrid, Spain (2000); First Alton Meister Lecture, Cornell University (2001); Fritz Lipmann Lecture, German Society for Biochemistry and Molecular Biology (2001); Karl Beyer Lectures, University of Wisconsin, Madison (2003); Asher Rothstein Lecture, The Hospital for Sick Children Research Institute, Toronto, Canada (2003); and the Distinguished Lecture on Molecular Targets for Cancer Prevention, AACR, Baltimore, Maryland (2005).

8. My area of research has focused on signaling through tyrosine phosphorylation, which is important in many areas of cellular regulation, especially growth control and cancer. My studies have led to an understanding of the mechanism of transmembrane signaling by receptor tyrosine kinases and how the resulting signals are transmitted within the cell to regulate gene expression, control cell growth and differentiation. Tyrosine kinase signaling plays a critical role in the control of many cellular processes including gene expression, cell proliferation, differentiation, metabolism, as well as cell survival and migration. Tyrosine kinases play a particularly important role in cancer, and several agents that block their activity are now used as anti-cancer drugs, such as Gleevec, Sutent and many others.

9. I reviewed the following documents: Plaintiffs' Memorandum of Law in Support of Motion for Summary Judgment ("Memo"); Plaintiffs' Rule 56.1 Statement of Material Facts ("SMF"); Declaration of Sir John Sulston, Ph.D. of August 17, 2009 ("Sulston"); Declaration of Christopher E. Mason of August 20, 2009 ("Mason"); and Declaration of Myles W. Jackson of August 18, 2009 ("Jackson").

10. As a scientist practicing in both the academic and industrial biotechnology/pharmaceutical arenas, I have experience with patents. I am a named inventor on a number of patents relating to screening methods and therapeutics. I have been asked to share my observations on the impact that patents have on research and development in the biotechnology field, and the role that patents have in bringing diagnostic and therapeutic products to the market making them available to patients. I am not a lawyer and express no legal opinion.

BACKGROUND

11. By way of background, genes are hereditary units contained within chromosomes – threadlike parts of the nucleus of cells in the body. The body does not have a mechanism for isolating genes, contrary to what I read in the Memo at p. 25 citing Jackson, ¶¶ 26-31 and Mason ¶¶ 11-12. A gene is part of a chromosome and is always surrounded by proteins.

12. Chromosomes are composed of DNA (**d**eoxyribo**n**ucleic **a**cid) and proteins. DNA is a chemical composition -- a polymer of building blocks called "nucleotides". Each nucleotide is composed of a deoxyribose sugar, a phosphate and one of four nitrogenous bases: adenine (A), guanine (G), thymine (T), and cytosine (C). DNA is double stranded and the

strands are crosslinked via the bases – A always links with T and G always links with C. A DNA molecule can be characterized by the sequence of the bases in the DNA polymer.

13. A gene on its own cannot do anything – other parts of the cell are required for a gene to have its biological effect. In general, this is to make one or more proteins vital to the structure and function of cells in the body. To do this, the gene's DNA is first copied or "transcribed" into RNA (ribonucleic acid) – a polymer of nucleotides that differ from DNA, each unit composed of a ribose sugar, a phosphate and one of four bases: adenine (A), guanine (G), uracil (U), and cytosine (C). For transcription, the DNA "unzips" and one of the DNA strands serves as the template for RNA assembly – A always links to U; G always links to C. The RNA transcript is then processed to form messenger RNA (mRNA) that is "translated" into a polypeptide (another biopolymer composed of building blocks called amino acids) which is a component of proteins responsible for the functions vital to the cell.

14. The RNA transcribed from a gene is processed into one or more messenger RNAs ("mRNAs") through a process called splicing in which portions of the RNA transcript that are not required for protein production are removed. Alternative splicing is a process in which different portions of the RNA transcript are reconnected in multiple ways. These different mRNAs resulting from transcription of one gene may then be translated into different polypeptides. Thus, a single gene may code for multiple mRNAs and protein products.

15. Using enzymatic reactions, a DNA molecule can be synthesized that is complementary to an mRNA (cDNA). But this DNA molecule would capture only one splice variant expressed from the gene. Thus, contrary to statements made by the plaintiffs, a cDNA is not necessarily informationally identical to the gene in the body. The plaintiffs' basis for this --

the old dogma of "one gene, one enzyme" -- is dead. SMF, ¶¶ 59, 61, 62; Mason, ¶¶ 9, 28-29, 32-33.

DECIPHERING THE STRUCTURE OF A GENE AND FUNCTION OF ITS PRODUCTS

16. Deciphering the structure of a gene and the function of its products is very relevant for diagnostics and drug development. If you do not know the sequence of a gene and the function of its products, you cannot design diagnostics and therapies to treat patients. The genome has been sequenced and published. But the raw sequence data does not tell you where a particular gene is exactly located and most importantly, the structure and function of the protein or proteins expressed from the gene.

17. I am puzzled by Dr. Sulston's view that an isolated DNA molecule cannot be an invention. He seems to rationalize his conclusion by simplifying DNA to an arrangement of letters that carries biological information dictated by nature that is identical to the information of its genomic counterpart. *See* Sulston, ¶¶ 10-19. Categorizing isolated genes as natural products/information that should be relegated to the public domain seems to me a bit superficial.

18. If you look hard enough, all things have natural origins. There are many examples of "natural products" that have been patented. Some examples of patented, small molecule "natural products" are antibiotics (*e.g.*, penicillin), chemotherapeutics (*e.g.*, taxol, mitomycin C) and statins (*e.g.*, lovastatin). Larger biomolecular "natural products," *i.e.*, proteins, have been patented as well, such as antibodies, erythropoietin, interferon and proteins that control blood clotting such as tissue plasminogen activator (TPA), streptokinase, and urokinase. DNA molecules whose biological function has been revealed by research should be treated in the

same manner. There is no difference between discovering the function of a gene and developing a diagnostic, and discovering a new natural chemical product and developing a new drug.

19. I disagree with Dr. Sulston's assessment that DNA is only information. *See* Sulston, ¶ 13-17. DNA is not merely a linear digital code consisting of a sequence of letters. DNA is a chemical composition – a polymer of building blocks called nucleotides. Each nucleotide is composed of a deoxyribose sugar, a phosphate and one of four nitrogenous bases: adenine, guanine, thymine and cytosine. Those bases are represented by the letters A, G, T, and C, respectively. The letters are just designations assigned to the nucleotides so that we can easily depict a DNA molecule. This system is analogous to the chemical formulas we use for describing other chemical compounds. For example, the chemical formula for water is H_2O, where "H" represents a hydrogen atom, "2" represents the number of hydrogen atoms present in the compound, and "O" represents an oxygen atom.

20. Sequencing the genome yields information that is fantastically important, *but* it does not tell you the exact location of the gene and most importantly what function is specified by the gene or by a mutated disease causing gene. I can understand why one should not be allowed to patent DNA without having any knowledge about its function, but an isolated DNA where the function of its products has been determined is a different story - here, an invention has been made. Moreover, if you figure out a direct link or an association between a gene sequence and a cause for or if you figure out the correlations or associations between a gene sequence and an increased risk for a specific disease, this discovery can be used to develop diagnostics and drugs that help people. I do not see any reason why a patent should not be awarded for such inventions.

21. To decipher the function of the proteins expressed from a gene takes a lot of work, ingenuity and luck. We have only 20,000 genes (humans have fewer genes than rice!). To manage all of the traits manifested by a human being, strategies evolved to use the limited supply of genes to provide all the functions needed by the body. For example, alternative splicing of RNA transcribed from a gene is a mechanism the cell uses to generate multiple mRNAs and their encoded protein products from each gene to provide the functions necessary for survival. Alternative splicing greatly increases the diversity of proteins that can be encoded by the genome.

22. In my field, there are approximately 518 genes that encode for protein kinases. On average, five alternatively spliced products result from the expression of each protein kinase gene, and this does not take into account the post-translational modifications of the resulting polypeptides and proteins which lead to regulation. Thus, there are at least 2,500 forms of protein product(s) that result from the expression of over 518 genes that encode the protein kinases.

23. In other situations, fully functional proteins are encoded by two or more genes. For example, antibodies, receptors, ion channels and many other proteins are composed of multiple polypeptides each encoded by different genes, *e.g.*, mammalian cytochrome c oxidase has 13 different polypeptide subunits with 3 being coded by a mitochondrial and nuclear genes and 10 by a nuclear gene. Tomitake Tsukihara, *et al.*, 1995, "Structures of Metal Sites of Oxidized Bovine Heart Cytochrome *c* Oxidase at 2.8 Å" *Science* 269:1069-1074 (Exhibit 2).

24. One approach to deciphering the function of a protein is to isolate or synthesize the DNA containing the gene and use it to produce protein product(s) to study their biochemical

functions. This requires first deciphering the sequence of the gene responsible for expression of the protein.

25. In another approach, you can use genetics to eliminate the gene from the genome of a cell or laboratory animal (sometimes referred to as "knocking out" the gene). If you are lucky and the gene is not redundant, you can figure out what the gene product does by observing the loss or gain of biochemical or physiological function in the cell or animal. For example, for tumor suppressor genes, like the BRCA genes, the elimination of the gene in these experiments should result in a loss of the protective function and increase the animal's risk for developing cancer.

26. In my view, a scientist who, using his ingenuity and aided by a little luck, spends a great deal of time and effort to investigate and discover what a gene product does and how to use it, has made an invention.

27. Once the scientist has deciphered the function of the gene's products, synthetic DNAs can be designed for diagnostics, cells can be engineered for drug screening, and therapeutics can be developed. The isolated DNA acquires functions it did not have as a gene in the body. Unlike genes in the body which are chemically bound in the chromosomes, isolated DNA molecules or their fragments can be used as a probe or primer for diagnostics, to synthesize proteins for therapeutic use, and/or for drug screening.

28. A probe or a primer can be used to detect target DNAs or RNAs based on its ability to bind, *i.e.*, hybridize, to its complementary nucleotide strand. A nucleotide strand is complementary to another when the bases of one strand are properly paired with the bases of the

other, *i.e.*, A always pairs with T (U in RNA) and G always pairs with C. For example, the complementary strand to a DNA molecule represented by ATCG will be depicted as TAGC.

29. An isolated DNA molecule can be used as a probe to identify target DNAs or RNAs in sample that are complementary to the arrangement of the probe's bases. In this application, the DNA probe is tagged with a molecular marker, *e.g.*, a radioactive isotope, and contacted with the sample under appropriate conditions to allow for hybridization. After washing away unbound material, the detection of the radioactive isotope in the sample indicates hybridization of the DNA probe to a complementary target.

30. An isolated DNA can also be used as a primer to amplify a specific region of a DNA strand (the DNA target) by a process called **p**olymerase **c**hain **r**eaction ("PCR"). In this approach, primers complementary to the target region along with an enzyme called DNA polymerase are added to a sample under appropriate reaction conditions. The primer serves as a starting point for synthesis of a new DNA strand complementary to the target DNA which serves as a template. The reaction is repeated to allow for amplification of the synthesized fragments. A gene in the body cannot be used as a probe or primer.

PATENTS ARE CRITICAL FOR RESEARCH AND DEVELOPMENT

31. In my experience in the biotechnology industry, companies would not be able to raise money to do the research needed to develop diagnostic and therapeutic products without patent protection. Scientists involved in the Human Genome Project have been very fortunate to have the financial backing of organizations such as the Wellcome Trust. Ironically, the income used to establish the Wellcome Trust was derived from Burroughs Wellcome, a pharmaceutical company that amassed a fortune selling patented drugs. Most institutions do not have the luxury

of a trust fund, and need patent protection to obtain investments and funding. If these institutions cannot raise the capital to start companies or invest in research and development, promising new diagnostics and therapeutics will not be developed.

32. Moreover, without patent protection, large pharmaceutical and diagnostic companies would not take a drug or diagnostic test through clinical trials and to market. As a result, discoveries that would otherwise help patients, would remain a mere laboratory curiosity. The exclusivity that patents afford is the incentive for the large pharmaceutical companies to take the risk of investing large quantities of money to take a candidate drug or diagnostic through expensive clinical trials.

33. Pursuant to 28 U.S.C. § 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on December 21, 2009

Joseph Schlessinger, Ph.D.

APPENDIX 1

LIST OF EXHIBITS

Exhibit No.	Title
Exhibit 1	*Curriculum Vitae*
Exhibit 2	Tsukihara, T. *et al.*, 1995, "Structures of Metal Sites of Oxidized Bovine Heart Cytochrome *c* Oxidase at 2.8 Å" *Science* 269:1069-1074

CERTIFICATE OF SERVICE

This is to certify that on December 23, 2009, a true and correct copy of the foregoing document has been served on all counsel of record via the court's ECF system.

/s/ Brian M. Poissant
Brian M. Poissant