EXHIBIT 6

PART ONE OF TWO

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

ARIAD PHARMACEUTICALS, INC., MASSACHUSETTS INSTITUTE OF TECHNOLOGY, THE WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH, and THE PRESIDENT AND FELLOWS OF HARVARD COLLEGE Plaintiffs, v. ELI LILLY AND CO., Defendants.	Civil Action No. 02 CV 11280 RWZ U.S. District Judge Rya W. Zobel

RULE 26(A)(2) REBUTTAL REPORT OF THOMAS R. KADESCH, Ph.D.

I, Thomas R. Kadesch, Ph.D., submit the following report on behalf of ARIAD Pharmaceuticals, Inc., Massachusetts Institute of Technology, The Whitehead Institute for Biomedical Research, and The President and Fellows of Harvard College (collectively "Ariad") Plaintiffs in this action.

I. Introduction

1. I have been asked to prepare a report on certain issues related to the validity of U.S. Patents No. 6,410,516 ("the '516 patent"), including a rebuttal to certain opinions expressed in the reports of Drs. David Latchman (hereinafter "Latchman") and Peter Barnes (hereinafter "Barnes"), served on behalf of defendant Eli Lilly & Co. ("Lilly") on September 9, 2005.

2. I anticipate testifying as an expert at trial based on the opinions expressed herein. These opinions are based upon the information I have received so far. They may be supplemented or modified if I receive additional information. They may also be supplemented to

reply to additional information or opinions provided by Lilly (or by witnesses retained by Lilly), and issues that may arise at trial.

3. If requested to do so, I expect to testify at trial or court hearings regarding my opinions and as to the pertinent underlying facts and information. I may provide to the Court and jury a tutorial on relevant technology implicated by the asserted claims and expect that I may use visual aides, such as graphics, charts, pictures, diagrams, animations and physical objects to help illustrate, demonstrate, and explain the technology, my testimony, and any opinions asserted in this or any other report I may submit.

II. Qualifications

4. My qualifications for providing this report are based on my experience in the field of molecular biology and academia. I have been working independently in the field of molecular biology for over 20 years. My curriculum vitae is attached hereto as Exhibit A, and includes a list of all publications authored or co-authored by me during the past ten years.

5. I am currently Professor of Genetics at the University of Pennsylvania School of Medicine in Philadelphia, Pennsylvania. I received my B.S. in Biochemistry in 1975 from the University of California at Santa Barbara and my Ph.D. in Biochemistry in 1980 from the University of California at Berkeley, working with Dr. Michael Chamberlin on the enzymology of transcription in bacterial cells. I carried out 3 years of postdoctoral training in the Department of Biochemistry at Stanford University, working with Dr. Paul Berg, Nobel Laureate, on transcriptional regulation in mammalian cells. I have been on the faculty at Penn since 1984.

6. My research focuses on the regulation of transcription in mammalian cells. Notably, from the mid-1980's to mid-1990's my laboratory carried out the initial cloning and characterization of several novel DNA binding proteins (transcription factors) so I am well-qualified to judge the state of the field at the time of the '516 patent. The impact of my work has

been recognized through its publication in high-impact scientific journals and through invitations to speak both nationally and internationally. I have also taught, for the past 20 years, the advanced graduate student seminar on gene expression and the section on transcriptional control in the introductory survey course required of all first year students in our graduate program. Thus, I have a broad knowledge and appreciation of the transcription literature, including those papers on NF-κB, which led to in the '516 patent.

7. From 1992-1996 I served as Editor of the scientific journal Molecular and Cellular Biology. This is a top-tier journal from the American Society of Microbiology that publishes papers of extremely high quality. My responsibility as Editor was to handle those submitted papers in the area of transcriptional regulation.

III. Compensation & Prior Testimony

8. My rate of compensation for my work in this civil action is $ 500 per hour. My compensation is not dependent upon the outcome of this case.

9. I have not testified as an expert at trial or by deposition in the past four years.

IV. Materials Reviewed

10. In preparing this report, I reviewed the claims, specifications, and prosecution file histories of the '516 patent, especially the file of Application Serial No 08/464,364 (the '364 application) and Application Serial No. 07/341,436 ("the '436 application"). I have also reviewed relevant legal documents, including among others, the Claim Construction Order of March 3, 2004 and deposition transcripts of the named inventors of the '516 patent (Baltimore Inventors). In forming my opinions, I have also relied upon the publicly available scientific literature on issues relevant to this report, my professional experience, and specifically the articles and other materials cited within this report and listed in Exhibit B.

V. My Understanding of the Legal Principles Involved

11. I understand that Ariad is asserting claims 14, 69, 71, 72, 80, 84, 85, 93 - 96, 144 - 146 of the '516 patent (the asserted claims) against Lilly. The language of these claims is included in Section X below. I understand that the sufficiency of a patent disclosure is measured from the perspective of a hypothetical person "of ordinary skill in the art" as of the patent filing date; and that person is charged with knowledge of the entire body of prior art in the field.

12. I understand that the specification of a patent must teach one of ordinary skill in the art to make and use the full scope of a claimed invention without undue experimentation in order to meet the enablement requirement set forth in 35 U.S.C. § 112. I understand that several factors are relevant to whether or not the amount of experimentation is undue, including: (a) the quantity of experimentation necessary to practice the claimed invention; (b) the amount of direction or guidance provided in the specification; (c) the presence or absence of working examples in the specification; (d) the nature of the invention; (e) the state of the prior art at the time the application was filed; (f) the relative skill of those in the art at the time the application was filed; (g) the predictability/unpredictability of the art; and (h) the breadth of the patent claims.

13. I understand that the enablement inquiry is generally based on the state of the art at the time of filing but that post-filing developments can be considered to the extent they may support or refute the existence of an enabling disclosure at the time the application was filed. I understand that the enablement requirement does not require that the specification describe all possible applications of the claimed inventions, but rather asks whether one of skill in the art could use the disclosure of the specification to practice the claimed invention without undue experimentation.

14. I also understand that the written description requirement of 35 U.S.C. §112, paragraph 1, requires that the patent specification describe the claimed invention in sufficient detail that an ordinarily skilled scientist can reasonably conclude that the inventor had possession of the claimed invention. I further understand that compliance with the written description inquiry is determined by comparing the disclosure of the specification with the invention as set forth in the patent claims.

15. I understand that disclosure of any relevant identifying characteristics, i.e., structure or other physical and/or chemical properties, or functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of such identifying characteristics, may be sufficient to satisfy the written description requirement. I further understand that a claimed genus is adequately described when one of ordinary skill can recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. I have also been advised that information which is known in the art need not be described in detail in the specification. It is my understanding that the specification need not describe future technological developments.

16. I understand that 35 U.S.C. §112, paragraph 2, requires that the specification of a patent conclude with claims that particularly point out and distinctly claim the subject matter of the invention. I understand that the requirement is objective and looks to whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art rather than considering the views of the applicant.

17. I understand that the Court's claim construction sets forth the controlling definition of many of the terms used in the asserted claims of the patent-in-suit and that the remaining terms are defined according to the parties' agreed upon construction or given ordinary meaning.

VI. Overview of the Patents and Technology At Issue

18. I expect to testify on the general concepts of cellular and molecular biology, as such concepts are described in standard biology textbooks, as well as the specific technology described and taught by the Baltimore Inventors.

A. Cells From All Organisms Contain Molecules Which Carry Out Critical Functions.

19. Cells can be classified as either prokaryotic or eukaryotic. Eukaryotic cells have a nucleus which is an internal compartment of the cell where DNA is stored. A membrane separates the nucleus from the rest of the cell's cytoplasm. The cytoplasm is separated from its surrounding environment by an outer membrane. Each living cell is composed of numerous molecules and chemicals that direct the functions of the cell. Among the most critical cellular building blocks are molecules known as DNA, RNA and proteins.

B. Life's Master Molecules: DNA, RNA and Protein and the Central Dogma

a. DNA: Master Blueprint

20. Deoxyribonucleic acid ("DNA") molecules carry key hereditary information and serve as the cell's source of genetic information. DNA is formed by two strands of nucleotides joined together by hydrogen bonds and twisted into a double helical structure. There are four different nucleotides that present on strands of DNA - adenine ("A"), guanine ("G"), cytosine ("C"), and thymine ("T"). Each nucleotide pairs with a single other nucleotide on the opposite nucleotide strand of the DNA double helix, i.e. A always pairs with T, and G always pairs with C. The two nucleotide strands of DNA are therefore said to be complementary. DNA is often depicted simplistically as a linear structure read from left to right. By convention, the left end is referred to as the 5' end and the right end is called the 3' end.

21. The nucleotide sequences of DNA direct the production of proteins by the cell, such that the correct protein is produced in the proper amount and at the proper time to support necessary functions of the cell. Certain regions of nucleotides in the cell's DNA regulate the expression of proteins while other regions direct the structure of the resulting protein. The particular nucleotide sequence comprising the regulatory regions and that encoding a specific protein is commonly referred to as a "gene."

b. RNA: the Information Carrier

22. Ribonucleic acid ("RNA") molecules also exist in the cellular environment and function to carry genetic information from DNA to other cellular molecules. Like DNA, RNA is made of a sequence of connected nucleotides; however, RNA consists of only a single nucleotide strand, unlike DNA which has two strands. RNA also has four nucleotide bases - the nucleotides adenine, guanine and cytosine (used in DNA) and uracil ("U") in place of thymine in DNA. "U" and "T" convey the same genetic information and, by convention, "T" is often used to indicate both DNA and RNA sequences.

23. The single RNA nucleotide strand can pair with complementary RNA and DNA molecules, A pairing with T and G pairing with C. Some RNA molecules act as "messengers" that transfer the genetic information encoded by DNA molecules to the cellular molecules that make proteins. This type of RNA is therefore called messenger RNA ("mRNA").

c. Protein: Structural Building Blocks and Functional Enzymes.

24. The proteins produced by cells are essential to all living things. All cellular proteins are built of connected strings of twenty possible amino acids combined in various orders. This chain of amino acids is often called a polypeptide. Polypeptide lengths range from a few amino acids to thousands of amino acids. The amino acid chain of a polypeptide assumes a three

dimensional structure determined by its sequence, length and environment. The determined structures are flexible, which allows a protein to have more than one stated conformation.

25. Amino acids are specified by groups of three nucleotides known as "codons". Each codon, with the exception of stop codons, corresponds to one of the twenty possible amino acids that form a protein. The relationship between the nucleotide building blocks of DNA and RNA and the amino acids that form polypeptides is called "the genetic code." The three nucleotides of a codon are read together during the process of translation, which converts nucleic acid sequence to amino acid sequence.

26. Cells use the information conveyed by the genetic code to regulate cellular functions by expressing proteins. The nucleotide sequence "ATG" is the most common "initiation codon" and signals the "starting place" for synthesis of a protein. The "stop codons" that terminate translation and expression are TAG, TAA and TGA. The nucleotide sequence that falls between the initiation codon and the stop codon defines the "structural gene" that is translated into a protein according to the specific relationships defined by the genetic code.

27. The four possible nucleotides (A, C, G and T) can form 64 possible three nucleotide codon sequences; however, there are only 20 possible amino acids that can be made. Therefore, the genetic code is called "degenerative" because most amino acids can be specified by more than one three nucleotide codon. For example, four different codons (TTA, TTC, TTG and TTT) code for the amino acid serine. However, the reverse is not true - each codon specifies only a single amino acid.

d. The Central Dogma: DNA→ RNA→ protein

28. The "central dogma" refers to the universal process for the flow of genetic information from DNA to RNA to protein to which all living organisms share. Prior to 1989, it

had been established that organisms as different as bacteria and mammals share the same genetic code.

29. All living cells therefore follow the same process for "gene expression," which refers to the cellular mechanisms that read the genetic information encoded by a nucleotide sequence to produce the specified protein. This commonly shared mechanism follows a two step process: (1) transcription, and (2) translation.

a. Transcription

30. In the first step of gene expression, the nucleotide sequence of DNA is "transcribed" (or copied) into an intermediate mRNA molecule by a cellular component called RNA polymerase. RNA polymerase functions by binding to certain specific nucleotides in the DNA sequence known as promoters. The promoter is a start signal at the beginning of a gene which, by binding RNA polymerase, directs the RNA polymerase to initiate synthesis of mRNA at a specific position and on a specific strand of the DNA template. The resulting mRNA copy carries the genetic information encoded by the DNA molecule to the molecular machinery of the cell responsible for protein synthesis.

31. Nucleotide sequences within the promoter (and sometimes elsewhere in a gene) that direct the activity and function of RNA polymerase are part of the regulatory system which functions to regulate gene expression by acting as “on” and “off” switches, and are collectively known as the "control regions." The different parts of the control regions are referred to as “regulatory elements.” When a DNA sequence is depicted linearly, the sequences comprising the control regions are usually, but not always, found adjacent to the side of the coding region of the gene. By the early 1980’s, a number of studies had established the nucleotide sequences that were necessary for the initiation of transcription.

32. Transcriptional regulatory elements or DNA work in conjunction with proteins known as "transcription factors". The association and dissociation of transcription factors to regulatory elements of a gene controls, or regulates the expression of the gene. Many genes require the binding of a number of different, very specific factors to initiate transcription. Other genes are more promiscuous and transcription can be initiated by a number of different types of factors. Proper arrangement of transcription factors on the regulatory elements is necessary for transcription but not sufficient. The DNA - transcription factor complex must be able to recruit and activate RNA polymerase or else transcription will not occur. The Baltimore Inventors explained how a certain transcription factor, the nuclear transcription factor kappa B (NF-κB) regulates the expression of genes that have a κB element in their control region (discussed below).

b. Translation

33. The second step in gene expression is translation. During translation, complex cellular molecules composed of proteins and RNA molecules, called "ribosomes," translate the information carried by mRNA. Ribosomes function to "read" the nucleotide sequences of the mRNA codons to assemble the corresponding amino acids into a polypeptide chain. Just as with the preceding step of transcription, translation requires an element of the control region, known as the ribosome binding site, which functions as an "on switch." The most common "start" signal in the mRNA codon sequence is AUG (encoded in DNA as "ATG") which corresponds to the amino acid methionine. Virtually all polypeptide sequences therefore begin with an N-terminal methionine residue (N-Met).

C. The Tools of Molecular Biology in 1989

a. DNA Technology

34. Recombinant DNA research was made possible in the early 1970's by molecular biologists who developed a wide variety of molecular "tools" to manipulate DNA. These included specialized proteins called enzymes which had a variety of useful functions: for example, cutting DNA at specific nucleotides, ligating cut DNA molecules together, or making DNA or RNA by enzymatic means. These tools allowed the practice of "cloning," which is defined as the process of making numerous, identical copies of a nucleotide sequence of DNA. By 1989, foreign DNA could be introduced into host cells using standard techniques known in the art. Therefore, once the DNA fragment to be cloned had been obtained it could be inserted into a cloning vehicle, such as a plasmid.

35. Plasmids are small, circular pieces of DNA that are naturally found inside bacteria, and which can be removed from their natural bacterial hosts, molecularly modified (for example by the insertion of a fragment of DNA to be cloned), and introduced into other bacteria. The biochemical machinery of the bacterial host cell can then be exploited to replicate the plasmid (including the introduced DNA fragment), thus producing many copies of the cloned DNA fragment.

36. By using a control region endogenous to and recognized by a host cell, those skilled in the art could further modify plasmids and use them to express cloned foreign genes. By utilizing the host's own machinery, foreign genes could be expressed in human cells.

37. By at least 1989, one of skill would have had available various techniques for manipulating recombinant DNA, which could have been used to construct plasmids. For example, such methodology included techniques for inserting DNA into plasmids and methods for introducing those "recombinant" plasmids into human host cells. The techniques which were routine to molecular biologists in the 1980s that I have discussed and others are described in

detail in laboratory manuals such as Maniatis et al. (1989) Molecular Cloning; A Laboratory Manual, Cold Springs Harbor Laboratory Press, N.Y., Vol. 1-3; and earlier published editions. (The editor is a named inventor on the '516 patent).

b. Synthetic Gene Construction

38. The methodology of synthetic gene construction is well known in the art. See Brown, et al. (1979) Methods in Enzymology, Academic Press, N.Y., Vol. 68, pgs. 109-151. DNA sequences that encode particular protein molecules may be designed based on the amino acid sequences of the desired proteins. Once designed, the sequence itself may be generated using conventional DNA synthesizing apparatus. See U.S. Patent Nos. 5,500,365, 5,625,136 for examples of the construction of synthetic genes.

39. It was also well known in the art prior to 1989 that to effect the expression of protein molecules in a cell, one inserts the engineered synthetic DNA sequence in any one of many appropriate recombinant DNA expression vectors through the use of appropriate restriction endonucleases, which are enzymes that cut DNA. Restriction endonuclease cleavage sites are engineered into either end of the DNA to facilitate isolation from, and integration into, known amplification and expression vectors. The particular endonucleases employed will be dictated by the restriction endonuclease cleavage pattern of the parent expression vector to be employed. The choice of restriction sites is chosen so as to properly orient the coding sequence with control sequences to achieve proper expression of the protein of interest. The coding sequence must be positioned so as to be in proper reading frame with the promoter and ribosome binding site of the expression vector, both of which are functional in the host cell in which the protein is to be expressed. So as to achieve efficient transcription of the synthetic gene, said gene must be operably associated with a promoter region/control region. Therefore, the promoter

region/control region of the synthetic gene is placed in the same sequential orientation with respect to the ATG start codon of the synthetic gene.

40. A variety of expression vectors derived from viruses and plasmids useful for transforming prokaryotic and eukaryotic cells are well known in the art. A number of useful vectors were identified to the USTPO during the prosecution of the '516 patent. ('364 application Response and Amendment, September 1999, p.7, ADL 0000702)

c. Screening & Assays

41. Use of high throughput assays to screen binding interactions was routinely performed in the art in 1989. Following the '516 specification, it would have been a routine matter to identify reagents that block binding of NF-κB to NF-κB recognition sites. A large number of candidate molecules were available for screening at the filing date of the invention. See e.g. (Horuk 1989; Scott 1990). Such molecules include peptides and peptide mimetics, members of combinatorial libraries, as well as large numbers of small organic molecules and natural products, including fermentation broths, all of which were available for drug screening.

42. Combinatorial approaches for generating large libraries including phage display methods were also known. (Scott 1990; *see also* WO/9002809).

43. Another mass screening procedure that could be applicable to both peptides and other molecules is disclosed in WO/9015070.

44. Screening of libraries of peptides or other compounds can typically identify library members that have specific affinity for a given target without any prior knowledge of the molecular structure needed for binding.

D. The Baltimore et al. Invention

45. I expect to testify about the discovery of NF-κB, the invention of the '516 patent and the contributions to the field made by the Baltimore Inventors, including how NF-κB works in

cells to regulate gene expression and how drugs can be used to intervene in the NF-κB signaling pathway to reduce gene expression. I may explain and summarize the written description of the '516 patent from the perspective of one of ordinary skill in the art, and the prosecution history of the applications giving rise to the United States Patent and Trademark Office (USPTO) granting of the '516 patent.

46. The Baltimore Inventors described the mechanism by which NF-κB regulates the expression of genes. In resting cells NF-κB resides in the cytoplasm bound to another protein inhibitor of NF-κB, called IκB by the Baltimore Inventors. Stimulation of cells by agents acting on the outside surface of the cell membrane induces a cascade of intracellular kinases that phosphorylate IκB. A kinase is an enzyme that adds a phosphate group to a protein that can alter the conformation/structure of the modified protein. Once phosphorylated, IκB is disassociated from NF-κB and degraded. The unbound NF-κB is then free to translocate to the nucleus of the cell, where it can interact with the cell's DNA. In the nucleus NF-κB recognizes the κB elements on genes where it binds and promotes transcription.

47. Having explained this remarkable mechanism of how gene expression in the nucleus is induced by external influences, the Baltimore Inventors were able to describe methods by which one of skill in the art could affect NF-κB mediated gene expression. They state:

> As a result of this finding, it is now possible to alter or modify the activity of NF-κB as an intracellular messenger and, as a result, to alter or modify the effect of a variety of external influences, referred to as inducing substances, whose messages are transduced within cells through NF-κB activity. Alteration or modification, whether to enhance or reduce NF-κB activity or to change its binding activity (e.g., affinity, specificity), is referred to herein as regulation of NF-κB activity. The present invention relates to a method of regulating or influencing transduction, by NF-κB, of extracellular signals into specific patterns of gene expression and, thus, of regulating NF-κB-mediated gene expression in the cells and systems in which it occurs.

> In particular, the present invention relates to a method of regulating (enhancing or diminishing) the activity of NF-κB in cells in which it is present and capable of acting as an intracellular messenger, as well as to substances or composition useful in such a method. Such methods and compositions are designed to make use of the role of NF-κB as a mediator in the expression of genes in a variety of cell types. The expression of a gene having a NF-κB binding recognition sequence can be regulated, either positively or negatively, to provide for increased or decreased production of the protein whose expression is mediated by NF-κB. NF-κB-mediated gene expression can also be selectively regulated by altering the binding domain of NF-κB in such a manner that binding specificity and/or affinity are modified. . . . As a result of the present invention, cellular interactions between NF-κB and a gene or genes whose expression is mediated by NF-κB activity and which have, for example, medical implications (e.g., NF-κB/cytokine interactions; NF-κB/HTLV-I tax gene product interactions) can be altered or modified.

('516 patent, col. 3, line 59 - col. 4, line 28). One of skill in the art would recognize that the '516 patent describes methods to modify and alter the normal signaling pathways that the Baltimore Inventors discovered.

48. There are specific disclosures of the claimed methods which support my opinion on written description and enablement. For example the column 35 line 39 through column 38 line 24 provides information that one of ordinary skill in that art would recognize and understand to be an invention.

> Methods and compositions of the present invention are based on use of the role of NF-κB as a second messenger, or mediator, in the expression of genes in a wide variety of cell types. The expression of a gene having an NF-κB binding recognition sequence can be positively or negatively regulated to provide, respectively, for increased or decreased production of the protein whose expression is mediated by NF-κB. Furthermore, genes which do not, in their wild type form, have NF-κB, recognition sequences can be placed under the control of NF-κB by inserting NF-κB binding site in an appropriate position, using techniques known to those skilled in the art.

('516 patent, col. 35, lines 42-53).

49. It is expressly stated that the invention is related to "agents or drugs which enhance or block the activity of NF-κB or of the NF-κB inhibitor (e.g. IκB)". ('516 patent col. 3, lines 23-26).

50. There is not only a single means of reducing NF-κB activity described in the '516 patent. From reading the specification of the '516 patent one of skill in the art understands that there is more than one place to intervene in the multistep mechanism described by the '516 patent.

51. I disagree with some of the statements made by Dr. Barnes in his "NF-κB Tutorial" (Barnes § III). First, there is at least one well-publicized example of an effective drug has been rationally designed to work on reducing NF-κB activity based on the teachings of the '516 paper. The drug, molecule PS-341, inhibits NF-κB mediated gene expression by a mechanism which includes inhibition of proteins that mediate IκB degradation. (Palombella 1998). Second, his analogy to cancer cells misses the point. To illustrate, we can imagine at least three classes of drug that could inhibit overall NF-κB activity. The first of these would include PS-341 and comprise those compounds that sustain IκB activity. The second would include those that specifically inhibit binding of NF-κB once it enters the nucleus (e.g. decoys and dominant negative NF-κBs). The third, not specifically illustrated in the patent, would be drugs that inhibit NF-κB activity, even when it's bound to DNA (e.g. "squelching" proteins). (Gill and Ptashne 1988).

52. In further response to Dr. Barnes I may explain that the asserted claims are directed to reducing NF-κB activity that is induced from external influences such as LPS. The methods are not directed to completely blocking all levels of NF-κB activity in all cells. To imply that drugs that work by intervening in a function necessary to normal cells as well as diseased cells are

useless is misleading. Many modern cancer chemotherapeutic drugs work by inhibiting cell division, a necessary function of both normal and cancerous cells. Drugs that work by this mechanism can be administered at a dose so as to effectively prevent cancer cells from multiplying and spreading throughout the body, without killing all the cells. Side effects from these drugs include hair loss and gastrointestinal irritation because the normal cells in those systems require frequent cell division. By analogy, inhibitors of NF-κB can be given at doses that would be clinically effective.

VII. Person of Ordinary Skill in the Art

53. As discussed above, the '516 patent relates to a field of molecular biology which is often referred to as gene regulation. People working on gene regulation in the late 1980s and early 1990s most often held advanced doctorate level degrees in biology, chemistry or related fields and most would have had three or more years of post-doctoral training. A person at this level of experience does not need a great deal of guidance in performing molecular biology experiments and would not expect detailed explanations of existing technology to be included in scientific publications. A person of skill in the art would be able to isolate native proteins from cells, clone genes, synthesize genes, and express foreign genes in mammalian cells. Furthermore a person of skill in the art would have had expertise to measure activity of transcription factors with artificial reporter constructs.

54. In reaching an opinion on the level of skill in the art I have considered the education and experience of the Baltimore Inventors in the late 1980s time frame. I have also taken into consideration the level of skill of people I knew to be working in the molecular biology field between 1985 and 1995. The USPTO examiner noted, "the relative skill of those in the art of gene regulation is high". ('364 application, Office Action, July 1998, pp. 7, 17, ADL 0000548, ADL 0000558).

55. I note that Dr. Barnes states, without explanation or further specificity, that he is "prepared to respond to questions about what was generally known in the art by persons of ordinary skill as of the relevant dates about one particular transcription factor, NF-κB, its natural inhibitor, IκB and address inaccuracies that may be raised by Plaintiffs in their tutorial." (Barnes p.3). If in the future, Dr. Barnes were to disclose his specific opinions regarding persons of ordinary skill in the art then I may supplement this rebuttal report to address his opinions directly.

VIII. Enablement

A. The Asserted Claims Are Enabled Because the Specification Provides the Skilled Practitioner with Sufficient Guidance to Make and Use the Claimed Methods Without Undue Experimentation.

56. Given the state of the art at the time the '516 patent was filed, the skilled practitioner would have a number feasible alternatives for practicing the methods of the asserted claims. (*See, e.g.* '364 application, Office Action, March 17, 1999, p.8, ADL 0000618).

a. Small Molecules Were Available for Use in the Claims

57. One of ordinary skill in the art following the teachings of the patent can find substances that may be useful in therapy of diseases associated with overactivity of a transcriptional regulatory factor ('516 patent col. 34, line 66 - col. 35, line 12). It was understood from the specification that NF-κB – dependent gene expression can be inhibited in vitro. (*See* Ray 1995).

58. By at least 1989 screening and assay techniques were available for identification of compounds with specific biological activities. I expect to testify that those skilled in the art would be able to carry out a variety of different drug screening assays based on the disclosure and experience developed in the art, including for example, detecting inhibitors of protein phosphorylation, detecting inhibitors of protein degradation, detecting inhibitors of

protein:protein interactions, detecting inhibitors of protein localization in a cell, detecting inhibitors of protein:DNA interactions. As the attorneys for the Baltimore Inventors explained to the USPTO, formats for these types of screens were recognized in the art. ('364 application, Amendment and Response, January 27, 1999, p.13, ADL 0000582).

59. For example, a microtiter assay has been used to examine the effect of a series of structurally diverse histamine type II (H2) receptor antagonists on histamine-mediated immune suppression. Human peripheral blood lymphocytes were placed in 96 well microtiter plates, and pytohaemagglutinin M was added. Cells were incubated with test drugs for 72 hours, and pulsed with [3H]-thymidine for the last 16 hours. Cells were harvested on an automated multiple sample harvester and cell-associated radioactivity was determined by scintillation counting. (Badger 1984). With the information disclosed in the '516 patent a screen of this type could be adapted for the purpose of identifying NF-κB inhibitors.

60. In the prosecution of the '516 patent, a review article that describes the general state of combinatorial protein libraries throughout the late 1980's was brought to the attention of USPTO. (Gallop 1994; '364 application, Amendment and Response June 11, 1998, ADL 0000517-0000540).

61. Screens based on the '516 patent have been employed to identify inhibitors of NF-κB. (Gehrt 1998; Fiedler 1998; '364 application Amendment and Response January 27, 1999, ADL 0000579-0000608). Following the disclosed teachings of the '516 patent on the mechanism of NF-κB activation, which included the phosphorylation of IκB and the subsequent proteolytic degradation of the modified IκB, those skilled in the art are able to identify a number of other substances capable of reducing NF-κB activity.

62. In addition to PS-341 noted above, emodin, when properly administered, is capable of inhibiting NF-κB mediated gene expression by a mechanism which includes inhibition of degradation of IκB proteins. (Kumar 1998; *see also* Meng 1999 and Fenteany 1995 for other proteosome inhibitors).

63. The compound helenalin, of the sesquiterpene lactone class of compounds has been reported to inhibit NF-κB mediated gene expression in certain circumstances by a process which includes irreversible alkylation of NF-κB in order to inhibit the DNA binding activity of NF-κB. (Lyss 1998).

64. These and/or other small molecules like these compounds could have entered a drug development pipeline and, if not eliminated for other reasons, been developed into drugs which work through the methods claimed in the patent. By 1989 the steps taken to develop a drug were well defined and routinely applied.

65. The USPTO examiner "agreed that the experimental techniques disclosed in the specification that were used to elucidate the mechanism of NF-κB regulation could be readily adapted by the skilled artisan to screen for agents which alter NF-κB and IκB activity." The USPTO examiner "further agreed that the specification does suggest that agents which regulate these two proteins could be screened for." ('364 application, Office Action March 17 1999, p.5, ADL 0000615). I concur with these statements.

b. The Disclosure of IκB Supports the Enablement of the Claims

66. The specification of the '516 patent discloses that the mechanism of NF-κB activation is due to IκB being phosphorylated and subsequently degraded by proteolysis. A number of references recognize the Baltimore Inventors for describing this mechanism. (See references cited in paragraph 10 of Baltimore Declaration signed September 14, 1999, ADL 0000627). The patent suggests that the one of the kinases responsible for phosphorylation is Protein Kinase

C, a specific kinase activated by phorbol esters that also activate NF-κB. The '516 patent references Protein Kinase C at several points. (See '516 patent, col. 27, lines 1-8; col. 30, lines 60-65; col. 31, lines 7-10; col. 31, lines 15-23; col. 31, lines 30-34; col. 33, lines 52-56; col. 71, lines 42-50; col. 72, lines 12-18; col. 72, lines 24-29; col. 76, lines 17-21; col. 76, lines 54-57; col. 76, line 58 – col. 77, line 3.)

67. Reading the '516 patent as a whole, with particular focus on the references to Protein Kinase C, provides a clear direction to screen for kinase inhibitors as a way to identify compounds that could inhibit NF-κB activity and be used in the asserted claims.

68. I expect to testify that

> the art taught a number of assays for detecting changes in phosphorylation of intracellular proteins upon treatment of a cell with a small organic molecule, protein, or other agent likely to be tested in a drug screening assay. See, for example, Auberger et al. *Regulation of protein phosphorylation by polyamines in hepatocytes. Studies using two effectors: amiloride and natural aliphatic polyamines* Biochimie (1985) 67:1125-32; Malkinson et al., *Decrease in the protein kinase C-catalyzed phosphorylation of an endogenous lung protein* (Mr 36,00) *following treatment of mice with the tumor-modulatory agent butylated hydroxytoluene* Cancer Res (1985) 45:5751-6; and Robinson and Dunkley, *Altered protein phosphorylation in intact rat cortical synaptosomes after in vivo administration of fluphenazine* Biochem Pharmacol (1987) 36:2203-8. One skilled in the art would recognize that these and other prior art techniques for detecting protein phosphorylation could be adapted for use in the present invention as assays for identifying agents which inhibit or potentiate IκB phosphorylation

('346 application, Amendment and Response, June 1998, ADL 0000517-0000540).

69. Following the disclosure of the '516 patent and the scientific articles cited throughout the specification, one of skill in the art would be able to obtain a clone of IκB using well-established routine techniques. The patent teaches that IκB is a protein; therefore, one of skill in the art would know that there is necessarily a gene which encodes it. ('516 patent, Examples 10 - 14). Obtaining the gene would only require technology taught by the '516 patent or already

known in the art in 1989. (*See* '516 patent col. 32, lines 28-40). Indeed, Bose and coworkers identified a protein, designated pp40, based on its stable interaction with v-Rel and c-Rel. (Tung 1988). Using standard biochemical and molecular biological techniques they purified pp40, generated an antiserum, and cloned its cDNA. (Davis 1991). It tuned out to be the chicken homologue of MAD-3. One skilled in the art could have easily looked for proteins that stably interacted with mammalian c-Rel and cloned their corresponding cDNAs using methods analogous to those employed by Bose. Their function as IκB proteins could have been confirmed using the teachings of the '516 patent. (*see* Haskill 1991; Davis 1991).

70. As directed by the patent, an "IκB gene can be incorporated into an appropriate vector … and introduced into cells in which NF-κB activity is to be inhibited (partially or totally)." One of ordinary skill could accomplish this with only routine experimentation. It has been shown that overexpression of IκB can inhibit NF-κB-dependent gene transcription both *in vitro* and *in vivo*. (Cai 1997; Esslinger 1997).

71. I expect to testify that protein defined in Figure 43 is an IκB-like molecule. (Davis 1991; Haskill 1991). If the gene described in Figure 43 were over expressed in a human cell NF-κB activity could be reduced.

72. Techniques for domain mapping of proteins were available in the art. Given the functional description of IκB, those skilled in the art were able to identify the domains or fragments of IκB that are responsible for NF-κB binding and NF-κB release. A number of references describing combinatorial techniques for generating and processing large library variants of a protein were brought to the attention of the USPTO. ('364 application, Amendment and Response, June 11, 1998, ADL 0000517-0000540). For example, Cunningham 1989;

McKnight 1982; Meyers 1986; Leung 1989; Miller 1992; and Bass 1990 all describe technology that was routine in the art in 1989 that could be used to generate and identify variants of IκB.

73. One of skill in the art could make IκB-like molecules which are constitutively active for having a higher affinity for NF-κB or resistance to degradation in the cytoplasm. The protein domains involved in inducible and basal degradation of IκB in intact cells has been determined using routine experimentation. (Krappman 1996; '364 application Amendment and Response of June 11, 1998, ADL 0000517-0000540).

74. A successful strategy using an IκB variant to reduce NF-κB activity has been employed as a result of the disclosure in the '516 patent. (Brown 1995). To accomplish this, Brown et al. introduced deletions and point mutations into the DNA encoding IκB-α, and transfected the mutated DNA into cells. In one series of experiments, these authors used Ntera-2 cells, which do not express high levels of NF-κB or IκB. Co-transfection of the p65 subunit of NF-κB and either wild-type or mutant IκB-α resulted in inhibition of expression of a κB-sensitive reporter gene. Importantly, in cells stimulated with PMA and ionomycin, inhibition of NF-κB transactivation was relieved (i.e., disinhibited) by transfection of wild-type IκB-α, but not by transfection of IκB-α with mutations (i.e., Ser^{32} ---> and Ala or Ser^{36} ---> Ala) which prevented phosphorylation and proteolysis. Thus, mutated IκB can be used to reduce NF-κB activity. (*See also* McKinsey 1997).

c. Dominantly Interfering Molecules and Decoy Molecules Support Enablement of the Claims

75. The concepts of decoy molecules and dominantly interfering molecules as described in the '516 patent are closely related and well understood in the art. They stem conceptually from basic biochemistry and enzymology. Both types of molecule can be viewed as competitive inhibitors, but acting through slightly different mechanisms. The activation of transcription via

DNA binding proteins can be viewed most easily as an ordered, two-step process: binding of the protein to the regulatory element (DNA) of a gene target followed by the stimulation of transcription through the recruitment or activation of RNA polymerase. The process can be inhibited at either step. (Trepicchio 1993).

76. In teaching the use of decoy molecules the '516 patent exploits this concept. In a cell NF-κB binds to the regulatory region of a gene. Given that this occurs in the context of over 3 billion base pairs of DNA with a limited amount of NF-κB, the binding to one particular gene target must be highly specific. If, however, one introduces a sufficient number of copies of a small piece of DNA capable of binding NF-κB, but not linked to a gene, the cell's NF-κB will also bind to this "decoy," thus reducing the effective amount of NF-κB available for binding the normal gene target and reducing the apparent overall activity of NF-κB.

77. A number of papers describing the use of NF-κB decoys were brought to the attention of the USPTO during the examination of the '516 patent. ('364 application, Amendment and Response June 1998, p.21-22, ADL 0000537-0000538). The articles by Morishita et al. 1997 and Sawa et al. 1997 demonstrate the decoy concept described in the '516 patent. Decoy molecules that inhibit NF-κB, as taught in the '516 patent, have been demonstrated *in vitro* and *in vivo*. (Kawamura 2001; Cho Chung U.S. Patent No. 6,060,310). Modified oligonucleotides as a means of inhibiting NF-κB function have been described. (Khaled 1998; Tomita 1998). In fact, Lilly scientists have also published on the use of DNA decoy oligonucleotides against NF-κB to reduce induced NF-κB activity. (Du 2005).

78. The patent office examiner recognized that NF-κB decoy molecules were enabled by the specification, in view of the art. The examiner wrote on one of occasion (there were others) that

> The post-filing date art submitted by the applicants contains several teachings of the effective use of nucleic acid decoy molecules and expression of full length IκB in cultured cells to block NF-κB activation to inhibit the transcription of genes containing NF-κB binding site, including the HIV LTR, as was taught in the specification. This is deemed to substantiate the disclosure of the present application in terms of using full length IκB or a decoy nucleic acid to inhibit the expression of HIV DNA in isolated cells infected with HIV.

('364 application, Office Action July 1998, p.18-19, ADL 0000559-0000560; *see also* Office Action, August 2000, p.9, ADL 0000831).

79. Dominantly interfering molecules take advantage of the observation that most transcription factors have separable DNA binding domains (DBDs) and "transcriptional activation" domains (TADs). That is, one part of the protein is used for DNA binding, while the other instructs the RNA polymerase. If the DBD is disrupted the transcription factor cannot bind DNA and, hence, will not activate transcription. If the TAD is disrupted, the protein will bind DNA, but cannot instruct the RNA polymerase to initiate transcription. Such a version of the transcription factor c-Jun was shown to block the activity of a variety of cancer-causing genes, implicating a role for the normal c-Jun protein in these processes. (Lloyd 1991). The '516 patent exploits this latter concept and proposes the use of such "dominantly interfering" versions of NF-κB to block access by the cell's normal NF-κB to its target genes, thus reducing the level of target gene activation. Indeed, v-Rel, a naturally occurring oncogenic version of c-Rel encoded by an avian virus, lacks the corresponding c-Rel activation domain (which is distinct from the DBD) and can be used in appropriate methods to inhibit NF-κB-mediated gene activation. (Ballard 1990). This finding is conceptually identical to what is taught in the '516 patent.

80. Persons skilled in the art have also exploited the fact that the DNA binding domains are distinct from the activating domains, to make dominant negative mutants as taught by the

'516 patent. Specifically, they constructed p50 subunits with either deletions or point mutations which formed heterodimers with RelA, but interfered with DNA binding. These mutant proteins functioned as inhibitors of NF-κB activity. (Logeat 1991; Bressler 1993).

81. Cell permeable peptide inhibitors of NF-κB activity are known. (Fujihara 2000).

B. The Latchman and Barnes Reports Provide No Clear and Convincing Basis for Establishing the Asserted Claims of the'516 Patent Are Not Enabled

82. I have considered the arguments and the references included in the Latchman and Barnes reports. The reports do not provide a clear and convincing basis for concluding that one of ordinary skill in the art in 1989 would require more than routine experimentation to practice the claims. For example there is no basis to suggest that a person of skill in the art in 1989 could not reduce the level of expression of genes, such as cytokine genes, which are activated by extracellular influences, such as LPS, by reducing binding of NF-κB to NF-κB recognition sites.

83. Whether or not the sequence in Figure 43 of the '516 patent is IκB-α is unimportant to whether one of skill in the art could practice the claims. (See Latchman para. 26). As discussed above, given the structural and complete functional characterization of IκB as an inhibitor of NF-κB mediated gene expression those of skilled in the art would be able to obtain a clone, and over express an IκB and super IκB molecules in cells to practice the claimed method.

84. Techniques for introducing proteins and nucleic acids into cells were available prior to 1989. One of the more common techniques involves the use of liposomes. (Nicolau 1984; Boda 1987; Reisine 1985; *see also* Roozemond 1987; for other methods *see* Berns 1984 and Gesner 1988; for an example of administration of DNA in liposomes *see* Nabel 1996).

85. Gene therapy is not recited in the asserted claims. However, at the time the '516 patent was filed people of skill in the art thought that gene therapy would be possible in the near future. The first cell culture model of gene therapy was published by Mulligan and Berg in

1980. Much of the work since that time has involved the perfection of viral vectors, stable transgene expression and delivery protocols. Although work with humans has been restricted to clinical trials and has suffered some notable setbacks, work in dogs has been much more encouraging, leading, for example, to an effective therapy for hemophilia (Arruda 2005). Nevertheless, in my reading and understanding of the asserted claims there is no requirement to practice gene therapy. (Claim Construction Order).

86. I have seen patents from Lilly that purport to show that gene therapy is a practicable approach to deliver proteins. For example U.S. Patent 6,841,371 states

> Gene Therapy--A therapeutic regime which includes the administration of a vector containing DNA encoding a therapeutic protein, directly to affected cells where the therapeutic protein will be produced. Target tissue for gene delivery include, for example, skeletal muscle, vascular smooth muscle, and liver. Vectors include, for example, plasmid DNA, liposomes, protein-DNA conjugates, and vectors based on adenovirus or herpes virus. Gene therapy has been described, for example, by Kessler et al., PNAS, USA, 93:14082-87, 1996.

('371 patent col.6, lines 41-50)

87. That gene therapy was credible to a person of skill in that art in the mid 1980's is supported by the fact that the National Institutes of Health NIH adopted gene therapy guidelines in September 1985, "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy". (For a discussion of the guidelines *see* Roberts *The New York Times* September 29, 1985).

IX. Written Description

A. The Specification of the '516 Patent Contains and Adequate Written Description of the Asserted Claims Because It Demonstrates that the Baltimore Inventors Were in Possession of the Claimed Methods at the Time of Filing.

88. The '516 patent specification and earlier applications (see discussion below on earlier filed applications), describe methods of reducing induced NF-κB activity in cells to reduce the expression of NF-κB regulated genes. The description clearly allows one of ordinary skill in art to recognize that the Baltimore Inventors invented what is claimed. It allows one skilled in the art to visualize himself or herself practicing the claimed methods. In forming my opinion of have considered the specification of the '516 patent as a whole giving weight to all of the words, structures, figures, diagrams, and formulas.

89. For many of the same reasons that the specification enables one of skill in the art to practice the claims, the specification provides a written description. Therefore, the reader is referred to my discussion on enablement above for further support of my reasons. In particular one of ordinary skill in the art reading the specification finds a detailed description of:

- the mechanism of NF-κB activation, (see above ¶¶ 46-52);
- IκB as an inhibitor of NF-κB, (see above ¶¶ 66-74);
- assays for the analysis of protein DNA interactions, (see above ¶¶ 57-65);
- decoy molecules, (see above ¶¶ 75-78);
- dominantly interfering molecules, (see above ¶¶ 79-81).

90. In addition to being enabling to those of ordinary skill in the art the disclosure clearly sets forth the limitations of the asserted claims.

a. The specification describes that NF-κB mediated intracellular signaling is induced by external influences, including LPS.

91. The '516 patent explains that the transcription factor NF-κB is "inducible" ('516 patent col. 2, lines 28-31; col. 10, lines 30-56), that it acts as an "intracellular transducer of external influences" ('516 patent col. 2, lines 39-40), such as virus infection or the treatment of cells with double-stranded RNA ('516 patent col. 2, lines 42-43), and that stimulation can be from extra cellular influences such as lipopolysaccharide, extracellular polypeptides and from chemical agents such as phorbol esters, which stimulate intracellular kinases that, under appropriate circumstances, can activate NF-κB. ('516 patent col. 2, lines 54-59). Inducibility of NF-κB activity by external influences is demonstrated by least Example 8 ('516 patent col. 68, line 30 - col. 73, line 55), which shows experimentally that, among other things, cells which had been stimulated with PHA or PMA, under the conditions disclosed, contained detectable levels of NF-κB and that co-stimulation cells showed higher levels of the factor (*e.g.* '516 patent col. 73, lines 1-6). The combination of agents that can, under certain conditions, induce NF-κB activity is described. ('516 patent col. 33, lines 52 - 59) That NF-κB is inducible is further exemplified in Example 15 ('516 patent col. 78, line 43 - col. 82, line 4).

92. That NF-κB activity is induced by external influences is supported by the description of the role of NF-κB in cytokine gene regulation in the specification ('516 patent col. 12, line 56 - col. 14, line 54) and by the description that NF-κB acts as an intracellular messenger in inducible systems ('516 patent col. 15, line 54 - col. 17, line 52).

b. The specification describes genes that are activated through NF-κB mediated intracellular signaling.

93. The '516 patent teaches that certain genes are "transcriptionally regulated by NF-κB." For example it is shown that NF-κB "stimulates transcription of genes encoding kappa immunoglobulins in B lymphocytes" ('516 patent col. 2, lines 23-25) and that NF-κB positively regulates the human β-interferon (β-IFN) gene, ('516 patent col. 2, lines 34-35) and controls the

expression of HIV ('516 patent col. 2, lines 44-45; *see also* col. 10, lines 30-56; col. 17, line 53 through col. 18, line 51). MHC gene has an NF-κB recognition sequence. ('516 patent col. 13, line 54 – 65) Under appropriate conditions, human cells can be stimulated to produce IL-2 by the combined influence of PHA and PMA. ('516 patent col. 72, line 44 – 48; *see also* discussion below on LPS induced expression of cytokines in mammalian cells. ¶¶ 100-103.

c. The specification describes "reducing NF-KB activity"

94. The '516 patent discloses that the invention relates to NF-κB inhibitors. ('516 patent col. 3, lines 23-26; col. 37, line 43 through col. 38, line 23).

95. Decoy and dominantly interfering molecules are taught by the '516 patent as agents that could be used to reduce NF-κB activity. ('516 patent col. 4, line 29 - 52). As discussed above, those of skill in the art understood the concepts of competitive binding and therefore would recognize that decoy molecules and dominantly interfering molecules as described in the '516 patent can be useful for reducing NF-κB activity. ('516 patent col. 37, line 64 through col. 38, line 25).

96. The patent suggests that NF-κB activation depends on protein kinase C. ('516 patent col. 31, line 10 - 56; col. 72, lines 12-26). One of skill in the art would recognize that an appropriate inhibitor of PKC could be used to reduce phorbol ester induced NF-κB activity.

d. The specification describes diminished NF-KB mediated intracellular signaling, modified NF-KB mediated effects of external influences, and reduced expression of genes.

97. One of ordinary skill in the art would recognize that, as described in the '516 patent:

> the data are consistent with a molecular mechanism of inducible gene expression by which a cytoplasmic transcription factor-inhibitor complex is dissociated by the action of TPA, presumably through activation of protein kinase C. The dissociation event results in activation and apparent nuclear translocation of the transcription factor.

('516 patent col. 27, line 1 - 7).