EXHIBIT 6

PART TWO OF TWO

e. The specification describes "binding of NF-κB to NF-κB recognition sites"

98. The '516 patent describes "NF-κB recognition sites" as recited in the claims. ('516 patent col. 12, lines 18-20). Table 2 provides examples of specific nucleotide sequences from known genes that are "recognized" by NF-κB as well as a consensus sequence derived by the Baltimore Inventors which allows one of skill in the art to identify NF-κB binding sites in other genes ('516 patent col. 35, line 54 through col. 35, line 23; col. 37, lines 1 - 43).

99. There is also a description of a DNA binding assay which is useful to determine if a substance is capable of reducing binding of NF-κB to NF-κB recognition sites ('516 patent col. 18, line 52 through col. 20, line 25).

B. The Specification of the '516 Patent Contains an Adequate Written Description of the Asserted Claims Because It Describes the Induction of Cytokine Genes with Lipopolysaccharide.

100. A person of skill in the art reading the '516 patent understands that expression of a gene is dependent on a number of different processes, including but not limited to transcription factor activation of the gene. Within the realm of transcription regulators, in many instances more than the NF-κB transcription factor is required to allow gene expression; some genes require further release from a repressor factor. The "theme of multiple signals" is exemplified by the cytokine β-INF gene. ('516 patent col. 16, line 64). The '516 patent teaches that virus-induced expression of the β-INF gene involves the activation of NF-κB and that NF-κB is induced by LPS (see below). The fact that β-INF transcription depends on additional regulatory elements does not negate the necessary role that NF-κB has in regulating its transcription. It would be incorrect to conclude from the statements in the patent that LPS cannot induce expression of β-INF under any conditions. Certainly one expects from the teachings of the patent that in the presence of stimuli that operate to activate through PRDI and release repression

at NRDI that LPS would induce expression of β-INF. To one of skill in the art there is a clear teaching that the expression of β-INF can be induced by LPS under conditions that satisfy the other transcription regulatory requirements of that gene.

101. The '516 patent teaches that lipopolysaccharide (LPS) induces the disassociation of NF-κB from IκB and translocation of NF-κB into the nucleus. Once NF-κB is present in the nucleus it can function as a transcription factor at any available recognition site. Given functional NF-κB in the nucleus, whether or not the expression of an NF-κB regulated gene is expressed may depend on the availability of other factors and conditions. (Lenardo 1989).

102. With the benefit of the '516 patent one of skill in the art at the time would recognize that cytokine genes having a κB control element in the promoter may very well be expressed in response to LPS. Perhaps not under all conditions but certainly under the right conditions where all other necessary factors are present, LPS does induce the expression of cytokines. In fact, IL-2 expression is regulated by NF-κB as the Baltimore Inventors described in the '516 patent. (Hoyos 1989). Expression of other cytokines, such as IL-1 and TNF-α, are induced by LPS and that induction is augmented by other influences. (Shakhov 1990; Schindler 1990).

103. An important additional issue to recognize with respect to genes regulated by NF-κB concerns the distinction between necessary and sufficient. Although a gene, such as that encoding β-INF or those encoding other cytokines, may not be activated by treating cells with LPS alone (NF-κB is sufficient), inhibitors of NF-κB may very well block induction of the gene upon, for example, virus infection (NF-κB is necessary). Thus, the relevance of an NF-κB binding site in a promoter/control region of a gene does not require that the gene be induced by

LPS alone, but its expression may be inhibited by NF-κB inhibitors. This concept is exemplified by the β-INF promoter/control region and is taught in the '516 patent.

C. The USPTO Found Support in the Specification and the Art for the Asserted Claims.

104. Support for the claims was reviewed by the Patent Office during the prosecution of the '516 patent. For example the information provided to USPTO in June 1995 show where certain claim language is supported in the specification. ('364 application, Amendment and Response, June 10, 1998, pp.9-12, ADL 0000525-0000528). Also, attorneys for the Baltimore Inventors explained to the USPTO where support for use of assays can be found in the specification:

- at page 6, the specification states that the invention relates to "*drugs which enhance or block the activity of NF-κB or of the NF-κB inhibitor (e.g., IkB)*";
- at page 7, the specification states "*the subject invention further relates to methods of regulating (including or preventing) activation of NF-κB, controlling expression of the immunoglobulin kappa light chain gene and other genes whose expression is controlled by NF-κB*";
- at page 8, the specification states *"[a]lterations 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*";
- at page 9, the specification states *"the cloned genes permit development of assays to screen for agonists or antagonists of gene expression and/or of the factors themselves. Further, because the binding site for NF-κB in the kappa gene is clearly defined, an assay for blockers or inhibitors of binding is available, as is an assay to determine whether active NF-κB is present*";

> The examiner's attention is also directed to page 23:lines 2-29, page 55:lines 5-16, page 74:lines 1-14; page 87:line 1 - page 88:line 17 and claims 57-63 as originally filed. These and other teachings of the instant application provide ample guidance and sufficient written description for the pending claims.

('364 Application, Amendment and Response January 14, 1999, p.13, ADL 0000602).

105. In an April 1998 interview with the USPTO examiner the Applicants attorneys discussed the support in the application ('364 application, Examiner Interview Summary, April 7, 1998, ADL 0000495). The details of the discussion were memorialized in a subsequent paper. I expect to testify that the description of the specification and the state of the art were accurately represented to the USPTO. ('364 application Amendment and Response June 11, 1998, p.17-23, ADL 0000533-0000539). The examiner agreed that the cited references were sufficient to show that the use of full length IκB and decoy nucleic acids could be used to inhibit NF-κB activation in cells. ('364 application, Office Action, July 1998, p.14, ADL 0000530).

106. In a Response and Amendment in application number USSN 08/464,364 (the '364 application) sent to the USPTO on September 12, 2001, applicants made citations to the specification to show support for the amended claims. ('364 application Response and Amendment, September 12, 2001, p.5-6, ADL 0000878-0000879). The response to the September 12, 2001 Amendments by the USPTO Examiner was a "Notice of Allowability", in which the Examiner wrote:

> Examiner has reviewed the last response and accompanying references which provide substantiating examples of the claimed methods. The claims are deemed allowable in view of applicants' withdrawal of the remaining pending claims to expedite prosecution and their agreement to make several language changes of a formal nature.

('364 application, Examiner's Amendment, October 4, 2001, p.30, ADL 0000952).

107. In addition to parts of the specification which Applicants pointed to in the prosecution history, and the USPTO accepted, I have found several other passages in the

specification of the '516 patent arising from the '354 application and its predecessor applications to support my opinion that a person of ordinary skill in the art in the late 1980s timeframe would recognize that the Baltimore Inventors invented what is claimed in the '516 patent. Citations to the most relevant passages are included in a Table in Section V below.

D. Priority Applications

108. I have reviewed the file history of the '516 patent. I expect to testify that earlier filed ("priority") applications support the asserted claims of the '516 patent. The USPTO accorded an effective filing date of March 1, 1988. ('364 application, Office Action, January 1997, p.3, ADL 0000449). Below, I have summarized some of additions made to the specification at particular stages of the prosecution.

109. Application Serial No. 07/318,901 ("the '901 application") was filed on March 3, 1989. The application includes figures that characterize IκB as a 60 to 70 kD protein. The specification discloses that NF-κB exists as a heterodimer with a molecular weight of 120 to 130kD, composed of NF-κB, with a molecular weight of 55 to 62kD, and IκB, with a molecular weight of 60 to 70 kD. The specification further describes the reversibility and kinetics of the inactivation of NF-κB. The specification also discloses that NF-κB is activated by phosphorylation of the NF-κB-IκB complex resulting in NF-κB activity. ('901 application, pp. 7-8, 23-34). The specification demonstrates that NF-κB can be activated in a variety of cells including T cell lines (H9, Jurkat), fibroblasts, human kidney cells, and a variety of murine tissues. ('901 application, pp. 22-23).

110. Application Serial No. 07/341,436 ("the '436 application") was filed on April 21, 1989. The application discloses that NF-κB plays a role in cytokine regulation, which was studied by using β-IFN gene expression. In particular, the specification demonstrates that NF-κB interacts at the gene element PRDII. The inventors observed a correlation between NF-κB

binding and induction of β-IFN. Further, mutations to the PRDII binding site decrease β-IFN gene inducibility. The specification also discloses that NF-κB appears to play a prominent role in the interactions between cytokines IL-1 and TNF-α and NF-κB binding. By altering or modifying NF-κB activity one of skill in the art can produce medical effects, e.g., by affecting cytokine interactions. ('436 application, pp. 5-6, 10-23). The disclosure demonstrates that NF-κB activity can be affected by crude preparations of I-κB, which, under the circumstances disclosed, effectively inhibit binding of NF-κB. ('436 application, pp.10-23). The specification also discloses other methods of positively or negatively regulating expression of genes controlled by NF-κB, in particular, by increasing or decreasing the availability of NF-κB. The specification referenced Singh et al 1988, which discloses an assay that can be used to identify molecules that will bind to NF-κB binding sites. The application lists a consensus binding site for NF-κB derived from the examination of sequences of numerous genes regulated by NF-κB. Additionally, in a prophetic example, the specification teaches that IκB may be used to reduce NF-κB activity by introducing appropriate amounts of IκB into a cell. The specification also discloses the use of decoy molecules and dominantly interfering molecules to regulate NF-κB activity. ('436 application, pp. 23-30).

111. I expect to testify that '436 application has enough of the disclosure found in the '516 patent that the asserted claims are enabled and described by this application.

112. I may supplement this report in response to any contentions raised by the defendant on the issue of written description, enablement and priority. I may also supplement this report as new information becomes available to me. I may testify in rebuttal regarding issues addressed by the defendant's experts.

Date 10/21/05

Thomas Kadesch

X. Asserted Claims of the '516 Patent

No.	'516 Patent Claim
14.	A method for reducing bacterial lipopolysaccharide-induced expression of cytokines in mammalian cells, which method comprises reducing NF-κB activity in the cells so as to reduce bacterial lipopolysaccharide-induced expression of said cytokines in the cells.
69.	The method of claim 6 [for diminishing induced NF-κB-mediated intracellular signaling comprising reducing NF-κB activity in cells such that NF-κB-mediated intracellular signaling is diminished] wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes transcriptionally regulated by NF-κB.
71.	The method of claim 6 carried out on human cells
72.	The method of claim 70 or 71, carried out on immune cells.
80.	The method of claim 8 [for modifying effects of external influences on a eukaryotic cell, which external influences induce NF-κB-mediated intracellular signaling, the method comprising reducing NF-κB activity in the cells such that NF-κB-mediated effects of external influences are modified] wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.
84.	The method of claim 8, carried out on human cells.
85.	The method of any of claims 81-84, carried out on immune cells.
93.	The method of claim 9 [for reducing, in eukaryotic cells, the level of expression of genes which are activated by extracellular influences which induce NF-κB-mediated intracellular signaling, the method comprising reducing NF-κB activity in the cells such that expression of said genes is reduced] wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.
94.	The method of claim 9, carried out on mammalian cells.
95.	The method of claim 9, carried out on human cells.
96.	The method of claim 94 or 95, carried out on immune cells.
144.	The method of claim 14 wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.
145.	The method of claim 14, carried out on human cells.
146.	The method of claim 14 or 145, carried out on immune cells.

XI. Support in the Specification of of the '516 Patent for Asserted Claims

'516 Patent Claim No.	Support
14. A method for reducing bacterial lipopolysaccharide-induced expression of cytokines in mammalian cells, which method comprises reducing NF-κB activity in the cells so as to reduce bacterial lipopolysaccharide induced expression of said cytokines in the cells.	'516 specification col. 2, lines 27-43; col. 3. line 59-col. 4, line 19; col. 4, lines 23-28; col. 9, line 1-col.10, line 15; col. 12, line 36-col. 13, line 3; col. 13, line 13-col. 14, line 54; col. 15, lines 3-36; col. 15, line 54-col. 17, line 52; col. 35, lines 43-60; col. 36, lines 1-11; col. 36, lines 40-67; col. 37, lines 1-col. 38, line 22 (also discussed at col. 31, line 57-col. 32, line 28); col. 78, lines 43-col. 82, line 11; col. 6, lines 5-55; col. 7, line 1-col. 8, line 67; col. 17, line 53-col. 18, line 24; col. 22, line 9-col. 24, line 46; col. 24, line 57-col. 29, line 46; col. 29, line 57-col. 31, line 56; col. 35, lines 13-42; col. 73, line 57-col. 74, line 50; col. 76, line 11-col. 78, line 42; col. 18, line 52-col. 20, line 25; col. 49, line 63-col. 51, line 41, and generally col. 4, line 54-col. 5, line 44, and generally col. 5, line 59-col. 6, line 4; col. 31, line 57-col. 32, line 63; and all Figures specifically cited in these sections; incorporating disclosure from prior applications, specifically: '436 application: page 1, line 15-page 3, line 27; page 4, line 15 - page 6, line 8; page 6, lines 13-19; Figures 1 through 4, including "Brief Descriptions" page 6, line 20-page 9, line 24; "Detailed Description of the Invention", page 9, line 25-page 11, line 20; in particular, page 12, line 1-page 16, line 2; page 16, line 21-page 17, line 29; page 18, line 18-page 22, line 11; in particular, page 22, line 12-page 23, line 21; "Use of Methods and Compositions of the Present Invention", page 23, line 22-page 24, line 15, page 24, line 25-page 25, line 4, page 26, line 5-page 27, line 5; page 28 (Table I), page 29, line 1-page 30, line 23; in particular page 30, line 26-page 39, line 21; page 39, line 23-page 45, line 8; and all Figures specifically cited in these sections; '901 application: page 2, line 4-page 3, line 9; "Summary of the Invention" page 3, line 10-page 4, line 5; "Brief Description of the Drawings," page 4, line 6-page 5, line 31, page 6, line 13-page 10, line 24, "Detailed Description of the Drawings" page 10, line 25-page 12, line 27; page 13, line 1-page 18, line 15; page 18, line 27-page 29, line 32; page 30, line 12-page

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	34, line 32; page 35, line 1-page 36, line 8; page 38, line 5-page 39, line 5; page 39, line 9-page 40, line 7; page 43, line 7-page 48, line 15 and all Figures specifically cited in these sections; '173 application: page 12, line 6-page 16, line 5; page 53, line 10-page 57, line 18, and generally, page 24, line 1-page 34, line 14; and all Figures specifically cited in these sections; '680 application: page 1, line 29-page 3, line 4; "Summary of the Invention" page 3, lines 5-30; "Brief Description of the Drawings," page 4, line 1-page 5, line 25; Figs. 1-3; 5-9; page 6, line 6- page 12, line 29, page 13, line 22-page 19, line 8; page 21, line 5-page 24, line 8, page 25, line 7-page 27, line 6; and all Figures specifically cited in these sections. Additionally, disclosure relating to underlying science, as well as background to the invention, corresponding to prior applications incorporated by reference in the above applications, may be found in portions of the '516 specification (including Figures cited to) as follows: '516 specification, col. 4, lines 29-49; col. 4, line 55-col. 5, line 44, col. 5, line 58-col. 6, line 4; col. 10, line 57-col. 11, line 23; col. 20, line 26-col. 22, line 9; col. 33, line 60-col. 35, line 12; col. 38, line 28-col. 42, line 34; col. 46, line 35-col. 49, line 61; col. 52, line 64-col. 54, line 30; col. 56, line 22-col. 57, line 42; col. 68, line 30-col. 73, line 56; col. 74, line 52-col. 76, line 9.
69. The method of claim 6 [for diminishing induced NF-κB-mediated intracellular signaling comprising reducing NF-κB activity in cells such that NF-κB-mediated intracellular signaling is diminished] wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes transcriptionally regulated by NF-κB.	'516 specification col. 2, lines 27-43; col. 3. line 59-col. 4, line 19; col. 4, lines 23-28; col. 9, line 1-col.10, line 15; col. 12, line 36-col. 13, line 3; col. 13, line 13-col. 14, line 54; col. 15, lines 3-36; col. 15, line 54-col. 17, line 52; col. 35, lines 43-60; col. 36, lines 1-11; col. 36, lines 40-67; col. 37, lines 1-col. 38, line 22 (also discussed at col. 31, line 57-col. 32, line 28); col. 78, lines 43-col. 82, line 11; col. 6, lines 5-55; col. 7, line 1-col. 8, line 67; col. 17, line 53-col. 18, line 24; col. 22, line 9-col. 24, line 46; col. 24, line 57-col. 29, line 46; col. 29, line 57-col. 31, line 56; col. 35, lines 13-42;

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	col. 73, line 57-col. 74, line 50; col. 76, line 11-col. 78, line 42; col. 18, line 52-col. 20, line 25; col. 49, line 63-col. 51, line 41, and generally col. 4, line 54-col. 5, line 44, and generally col. 5, line 59-col. 6, line 4; col. 31, line 57-col. 32, line 63; and all Figures specifically cited in these sections; incorporating disclosure from prior applications, specifically: '436 application: page 1, line 15-page 3, line 27; page 4, line 15 - page 6, line 8; page 6, lines 13-19; Figures 1 through 4, including "Brief Descriptions" page 6, line 20-page 9, line 24; "Detailed Description of the Invention", page 9, line 25-page 11, line 20; page 12, line 1-page 16, line 2; page 16, line 21-page 17, line 29; page 18, line 18-page 23, line 21; "Use of Methods and Compositions of the Present Invention", page 23, line 22-page 24, line 15, page 24, line 25-page 25, line 4, page 26, line 5-page 27, line 5; page 28 (Table I), page 29, line 1-page 30, line 23; generally page 30, line 26-page 39, line 21; page 39, line 23-page 45, line 8; and all Figures specifically cited in these sections; '901 application: page 2, line 4-page 3, line 9; "Summary of the Invention" page 3, line 10-page 4, line 5; "Brief Description of the Drawings," page 4, line 6-page 5, line 31, page 6, line 13-page 10, line 24, "Detailed Description of the Drawings" page 10, line 25-page 12, line 27; page 13, line 1-page 18, line 15; page 18, line 27-page 29, line 32; page 30, line 12-page 34, line 32; page 35, line 1-page 36, line 8; page 38, line 5-page 39, line 5; page 39, line 9-page 40, line 7; page 43, line 7-page 48, line 15 and all Figures specifically cited in these sections; '173 application: page 12, line 6-page 16, line 5; page 53, line 10-page 57, line 18, and generally, page 24, line 1-page 34, line 14; and all Figures specifically cited in these sections; '680 application: page 1, line 29-page 3, line 4; "Summary of the Invention" page 3, lines 5-30; "Brief Description of the Drawings," page 4, line 1-page 5, line 25; Figs. 1-3; 5-9; page 6, line 6- page 12, line 29, page 13, line 22-page 19, line 8; page 21, line 5-page

'516 Patent Claim No.	Support
	24, line 8, page 25, line 7-page 27, line 6; and all Figures specifically cited in these sections. Additionally, disclosure relating to underlying science, as well as background to the invention, corresponding to prior applications incorporated by reference in the above applications, may be found in portions of the '516 specification (including Figures cited to) as follows: '516 specification, col. 4, lines 29-49; col. 4, line 55-col. 5, line 44, col. 5, line 58-col. 6, line 4; col. 10, line 57-col. 11, line 23; col. 20, line 26-col. 22, line 9; col. 33, line 60-col. 35, line 12; col. 38, line 28-col. 42, line 34; col. 46, line 35-col. 49, line 61; col. 52, line 64-col. 54, line 30; col. 56, line 22-col. 57, line 42; col. 68, line 30-col. 73, line 56; col. 74, line 52-col. 76, line 9.
71. The method of claim 6 carried out on human cells.	See response to claim 69, and in particular, '516 specification col. 27, lines 27-43; col. 12, lines 57-col. 13, line 3; col. 13, lines 13-29; col. 17, lines 19-52; col. 37, lines 1-42; col. 49, line 62-col. 51, line 40; col. 78, line 43-col. 79, line 10; col. 79, line 64-col. 80, line 19; col. 81, lines 9-45; (for example, see '436 application, page 4, line 15-page 5, line 6; page 11, lines 4-20;page 12, lines 1-19; page 22, line 12-page 23, line 21; page 28; page 31, line 1-page 32, line 2; page 34, line 5-page 35, line 2, page 37, line 8-page 38, line 20) (for example, see '901 application, page 3, line 10-page 4, line 5; Fig. 6, page 6, lines 16-18; Fig. 14, page 10, lines 5-24; page 20, line 17-page 23, line 12; page 35, line 1-page 36, line 8; page 38, line 5-page 39, line 5, Example 6) (for example, see '173 application, page 53, line 10-page 57, line 18) (for example, see '680 application, page 6, line 6-page 7, line 25; page 25, line 8-page 27, line 6).
72. The method of claim 70 or 71.	See response to claim 69, and in particular, '516

'516 Patent Claim No.	Support
carried out on immune cells.	specification col. 27, lines 27-43; col. 12, lines 57-col. 13, line 3; col. 13, lines 13-29; col. 13, line 66-col. 14, line 33; col. 17, lines 19-52; col. 37, lines 1-42; col. 78, line 43-col. 79, line 10; col. 79, line 64-col. 80, line 19; col. 81, line 9-col. 82, line 11; (for example, see '436 application, page 4, line 15-page 5, line 6; page 11, lines 4-20; page 12, lines 1-19; page 13, line 29-page 16, line 2; page 22, line 12-page 23, line 21; page 28; page 31, line 1-page 32, line 2; page 34, line 5-page 35, line 2, page 37, line 8-page 39, line 21) (for example, see '901 application, page 3, line 10-page 5, line 31; Figs. 1-3; Figs. 5-13, page 6, line 13-page 10, line 4; page 10, line 25-page 20, line 16; page 20, line 17-page 30, line 28; page 32, line 6-page 36, line 8; page 38, line 5-page 39, line 5, Examples 1, 3-5) (for example, see '173 application, page 53, line 10-page 57, line 18) (for example, see '680 application, page 6, line 6-page 7, line 25; page 18, line 1-page 19, line 8).
80. The method of claim 8 [for modifying effects of external influences on a eukaryotic cell, which external influences induce NF-κB-mediated intracellular signaling, the method comprising reducing NF-κB activity in the cells such that NF-κB-mediated effects of external influences are modified] wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.	'516 specification col. 2, lines 27-43; col. 3. line 59-col. 4, line 19; col. 4, lines 23-28; col. 9, line 1-col.10, line 15; col. 12, line 36-col. 13, line 3; col. 13, line 13-col. 14, line 54; col. 15, lines 3-36; col. 15, line 54-col. 17, line 52; col. 35, lines 43-60; col. 36, lines 1-11; col. 36, lines 40-67; col. 37, lines 1-col. 38, line 22 (also discussed at col. 31, line 57-col. 32, line 28); col. 78, lines 43-col. 82, line 11; col. 6, lines 5-55; col. 7, line 1-col. 8, line 67; col. 17, line 53-col. 18, line 24; col. 22, line 9-col. 24, line 46; col. 24, line 57-col. 29, line 46; col. 29, line 57-col. 31, line 56; col. 35, lines 13-42; col. 73, line 57-col. 74, line 50; col. 76, line 11-col. 78, line 42; col. 18, line 52-col. 20, line 25; col. 49, line 63-col. 51, line 41, and generally col. 4, line 54-col. 5, line 44, and generally col. 5, line 59-col. 6, line 4; col. 31, line 57-col. 32, line 63; and all Figures specifically cited in these sections; incorporating disclosure from prior applications, specifically:

'516 Patent Claim No.	Support
	'436 application: page 1, line 15-page 3, line 27; page 4, line 15 - page 6, line 8; page 6, lines 13-19; Figures 1 through 4, including "Brief Descriptions" page 6, line 20-page 9, line 24; "Detailed Description of the Invention", page 9, line 25-page 11, line 20; page 12, line 1-page 16, line 2; page 16, line 21-page 17, line 29; page 18, line 18-page 23, line 21; "Use of Methods and Compositions of the Present Invention", page 23, line 22-page 24, line 15, page 24, line 25-page 25, line 4, page 26, line 5-page 27, line 5; page 28 (Table I), page 29, line 1-page 30, line 23; generally page 30, line 26-page 39, line 21; page 39, line 23-page 45, line 8; and all Figures specifically cited in these sections; '901 application: page 2, line 4-page 3, line 9; "Summary of the Invention" page 3, line 10-page 4, line 5; "Brief Description of the Drawings," page 4, line 6-page 5, line 31, page 6, line 13-page 10, line 24, "Detailed Description of the Drawings" page 10, line 25-page 12, line 27; page 13, line 1-page 18, line 15; page 18, line 27-page 29, line 32; page 30, line 12-page 34, line 32; page 35, line 1-page 36, line 8; page 38, line 5-page 39, line 5; page 39, line 9-page 40, line 7; page 43, line 7-page 48, line 15 and all Figures specifically cited in these sections; '173 application: page 12, line 6-page 16, line 5; page 53, line 10-page 57, line 18, and generally, page 24, line 1-page 34, line 14; and all Figures specifically cited in these sections; '680 application: page 1, line 29-page 3, line 4; "Summary of the Invention" page 3, lines 5-30; "Brief Description of the Drawings," page 4, line 1-page 5, line 25; Figs. 1-3; 5-9; page 6, line 6- page 12, line 29, page 13, line 22-page 19, line 8; page 21, line 5-page 24, line 8, page 25, line 7-page 27, line 6; and all Figures specifically cited in these sections. Additionally, disclosure relating to underlying science, as well as background to the invention, corresponding to prior applications incorporated by reference in the above applications, may be found in portions of the

'516 Patent Claim No.	Support
	'516 specification (including Figures cited to) as follows: '516 specification, col. 4, lines 29-49; col. 4, line 55-col. 5, line 44, col. 5, line 58-col. 6, line 4; col. 10, line 57-col. 11, line 23; col. 20, line 26-col. 22, line 9; col. 33, line 60-col. 35, line 12; col. 38, line 28-col. 42, line 34; col. 46, line 35-col. 49, line 61; col. 52, line 64-col. 54, line 30; col. 56, line 22-col. 57, line 42; col. 68, line 30-col. 73, line 56; col. 74, line 52-col. 76, line 9.
84. The method of claim 8, carried out on human cells.	See response to claim 80, and in particular, '516 specification col. 27, lines 27-43; col. 12, lines 57-col. 13, line 3; col. 13, lines 13-29; col. 17, lines 19-52; col. 37, lines 1-42; col. 49, line 62-col. 51, line 40; col. 78, line 43-col. 79, line 10; col. 79, line 64-col. 80, line 19; col. 81, lines 9-45; (for example, see '436 application, page 4, line 15-page 5, line 6; page 11, lines 4-20;page 12, lines 1-19; page 22, line 12-page 23, line 21; page 28; page 31, line 1-page 32, line 2; page 34, line 5-page 35, line 2, page 37, line 8-page 38, line 20) (for example, see '901 application, page 3, line 10-page 4, line 5; Fig. 6, page 6, lines 16-18; Fig. 14, page 10, lines 5-24; page 20, line 17-page 23, line 12; page 35, line 1-page 36, line 8; page 38, line 5-page 39, line 5, Example 6) (for example, see '173 application, page 53, line 10-page 57, line 18) (for example, see '680 application, page 6, line 6-page 7, line 25; page 25, line 8-page 27, line 6).
85. The method of any of claims 81-84, carried out on immune cells.	See response to claim 80, in particular, '516 specification col. 27, lines 27-43; col. 12, lines 57-col. 13, line 3; col. 13, lines 13-29; col. 13, line 66-col. 14, line 33; col. 17, lines 19-52; col. 37, lines 1-42; col. 78, line 43-col. 79, line 10; col. 79, line 64-col. 80, line 19; col. 81, line 9-col. 82, line 11; (for example, see '436 application, page 4, line 15-page

'516 Patent Claim No.	Support
	5, line 6; page 11, lines 4-20;page 12, lines 1-19; page 13, line 29-page 16, line 2; page 22, line 12-page 23, line 21; page 28; page 31, line 1-page 32, line 2; page 34, line 5-page 35, line 2, page 37, line 8-page 39, line 21) (for example, see '901 application, page 3, line 10-page 5, line 31; Figs. 1-3; Figs. 5-13, page 6, line 13-page 10, line 4; page 10, line 25-page 20, line 16; page 20, line 17-page 30, line 28; page 32, line 6-page 36, line 8; page 38, line 5-page 39, line 5, Examples 1, 3-5) (for example, see '173 application, page 53, line 10-page 57, line 18) (for example, see '680 application, page 6, line 6-page 7, line 25; page 18, line 1-page 19, line 8).
93. The method of claim 9 [for reducing, in eukaryotic cells, the level of expression of genes which are activated by extracellular influences which induce NF-κB-mediated intracellular signaling, the method comprising reducing NF-κB activity in the cells such that expression of said genes is reduced] wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.	'516 specification col. 2, lines 27-43; col. 3. line 59-col. 4, line 19; col. 4, lines 23-28; col. 9, line 1-col.10, line 15; col. 12, line 36-col. 13, line 3; col. 13, line 13-col. 14, line 54; col. 15, lines 3-36; col. 15, line 54-col. 17, line 52; col. 35, lines 43-60; col. 36, lines 1-11; col. 36, lines 40-67; col. 37, lines 1-col. 38, line 22 (also discussed at col. 31, line 57-col. 32, line 28); col. 78, lines 43-col. 82, line 11; col. 6, lines 5-55; col. 7, line 1-col. 8, line 67; col. 17, line 53-col. 18, line 24; col. 22, line 9-col. 24, line 46; col. 24, line 57-col. 29, line 46; col. 29, line 57-col. 31, line 56; col. 35, lines 13-42; col. 73, line 57-col. 74, line 50; col. 76, line 11-col. 78, line 42; col. 18, line 52-col. 20, line 25; col. 49, line 63-col. 51, line 41, and generally col. 4, line 54-col. 5, line 44, and generally col. 5, line 59-col. 6, line 4; col. 31, line 57-col. 32, line 63; and all Figures specifically cited in these sections; incorporating disclosure from prior applications, specifically: '436 application: page 1, line 15-page 3, line 27; page 4, line 15 - page 6, line 8; page 6, lines 13-19; Figures 1 through 4, including "Brief Descriptions" page 6, line 20-page 9, line 24; "Detailed Description of the Invention", page 9, line 25-page 11, line 20; page 12, line 1-page 16, line 2; page 16, line 21-page 17, line

'516 Patent Claim No.	Support
	29; page 18, line 18-page 23, line 21; "Use of Methods and Compositions of the Present Invention", page 23, line 22-page 24, line 15, page 24, line 25-page 25, line 4, page 26, line 5-page 27, line 5; page 28 (Table I), page 29, line 1-page 30, line 23; generally page 30, line 26-page 39, line 21; page 39, line 23-page 45, line 8; and all Figures specifically cited in these sections; '901 application: page 2, line 4-page 3, line 9; "Summary of the Invention" page 3, line 10-page 4, line 5; "Brief Description of the Drawings," page 4, line 6-page 5, line 31, page 6, line 13-page 10, line 24, "Detailed Description of the Drawings" page 10, line 25-page 12, line 27; page 13, line 1-page 18, line 15; page 18, line 27-page 29, line 32; page 30, line 12-page 34, line 32; page 35, line 1-page 36, line 8; page 38, line 5-page 39, line 5; page 39, line 9-page 40, line 7; page 43, line 7-page 48, line 15 and all Figures specifically cited in these sections; '173 application: page 12, line 6-page 16, line 5; page 53, line 10-page 57, line 18, and generally, page 24, line 1-page 34, line 14; and all Figures specifically cited in these sections; '680 application: page 1, line 29-page 3, line 4; "Summary of the Invention" page 3, lines 5-30; "Brief Description of the Drawings," page 4, line 1-page 5, line 25; Figs. 1-3; 5-9; page 6, line 6- page 12, line 29, page 13, line 22-page 19, line 8; page 21, line 5-page 24, line 8, page 25, line 7-page 27, line 6; and all Figures specifically cited in these sections. Additionally, disclosure relating to underlying science, as well as background to the invention, corresponding to prior applications incorporated by reference in the above applications, may be found in portions of the '516 specification (including Figures cited to) as follows: '516 specification, col. 4, lines 29-49; col. 4, line 55-col. 5, line 44, col. 5, line 58-col. 6, line 4; col. 10, line 57-col. 11, line 23; col. 20, line 26-col. 22, line 9; col. 33, line 60-col. 35, line 12; col. 38, line 28-col. 42, line

'516 Patent Claim No.	Support
	34; col. 46, line 35-col. 49, line 61; col. 52, line 64-col. 54, line 30; col. 56, line 22-col. 57, line 42; col. 68, line 30-col. 73, line 56; col. 74, line 52-col. 76, line 9.
94 & 95. The method of claim 9, carried out on human cells.	See response to claim 93, and in particular, '516 specification col. 27, lines 27-43; col. 12, lines 57-col. 13, line 3; col. 13, lines 13-29; col. 17, lines 19-52; col. 37, lines 1-42; col. 49, line 62-col. 51, line 40; col. 78, line 43-col. 79, line 10; col. 79, line 64-col. 80, line 19; col. 81, lines 9-45; (for example, see '436 application, page 4, line 15-page 5, line 6; page 11, lines 4-20;page 12, lines 1-19; page 22, line 12-page 23, line 21; page 28; page 31, line 1-page 32, line 2; page 34, line 5-page 35, line 2, page 37, line 8-page 38, line 20) (for example, see '901 application, page 3, line 10-page 4, line 5; Fig. 6, page 6, lines 16-18; Fig. 14, page 10, lines 5-24; page 20, line 17-page 23, line 12; page 35, line 1-page 36, line 8; page 38, line 5-page 39, line 5, Example 6) (for example, see '173 application, page 53, line 10-page 57, line 18) (for example, see '680 application, page 6, line 6-page 7, line 25; page 25, line 8-page 27, line 6).
96. The method of claim 94 or 95, carried out on immune cells.	See response to claim 93, and in particular, '516 specification col. 27, lines 27-43; col. 12, lines 57-col. 13, line 3; col. 13, lines 13-29; col. 13, line 66-col. 14, line 33; col. 17, lines 19-52; col. 37, lines 1-42; col. 78, line 43-col. 79, line 10; col. 79, line 64-col. 80, line 19; col. 81, line 9-col. 82, line 11; (for example, see '436 application, page 4, line 15-page 5, line 6; page 11, lines 4-20;page 12, lines 1-19; page 13, line 29-page 16, line 2; page 22, line 12-page 23, line 21; page 28; page 31, line 1-page 32, line 2; page 34, line 5-page 35, line 2, page 37, line 8-page 39, line 21) (for example, see '901 application, page 3, line 10-page

'516 Patent Claim No.	Support
	5, line 31; Figs. 1-3; Figs. 5-13, page 6, line 13-page 10, line 4; page 10, line 25-page 20, line 16; page 20, line 17-page 30, line 28; page 32, line 6-page 36, line 8; page 38, line 5-page 39, line 5, Examples 1, 3-5) (for example, see '173 application, page 53, line 10-page 57, line 18) (for example, see '680 application, page 6, line 6-page 7, line 25; page 18, line 1-page 19, line 8).
144. The method of claim 14 wherein reducing NF-κB activity comprises reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB.	'516 specification col. 2, lines 27-43; col. 3. line 59-col. 4, line 19; col. 4, lines 23-28; col. 9, line 1-col.10, line 15; col. 12, line 36-col. 13, line 3; col. 13, line 13-col. 14, line 54; col. 15, lines 3-36; col. 15, line 54-col. 17, line 52; col. 35, lines 43-60; col. 36, lines 1-11; col. 36, lines 40-67; col. 37, lines 1-col. 38, line 22 (also discussed at col. 31, line 57-col. 32, line 28); col. 78, lines 43-col. 82, line 11; col. 6, lines 5-55; col. 7, line 1-col. 8, line 67; col. 17, line 53-col. 18, line 24; col. 22, line 9-col. 24, line 46; col. 24, line 57-col. 29, line 46; col. 29, line 57-col. 31, line 56; col. 35, lines 13-42; col. 73, line 57-col. 74, line 50; col. 76, line 11-col. 78, line 42; col. 18, line 52-col. 20, line 25; col. 49, line 63-col. 51, line 41, and generally col. 4, line 54-col. 5, line 44, and generally col. 5, line 59-col. 6, line 4; col. 31, line 57-col. 32, line 63; and all Figures specifically cited in these sections; incorporating disclosure from prior applications, specifically: '436 application: page 1, line 15-page 3, line 27; page 4, line 15 - page 6, line 8; page 6, lines 13-19; Figures 1 through 4, including "Brief Descriptions" page 6, line 20-page 9, line 24; "Detailed Description of the Invention", page 9, line 25-page 11, line 20; page 12, line 1-page 16, line 2; page 16, line 21-page 17, line 29; page 18, line 18-page 23, line 21; "Use of Methods and Compositions of the Present Invention", page 23, line 22-page 24, line 15, page 24, line 25-page 25, line 4, page 26, line 5-page 27, line 5; page 28 (Table I), page 29, line 1-page 30, line 23; generally page 30, line 26-page 39, line 21; page 39, line 23-page 45, line 8; and all Figures specifically cited in these sections;

'516 Patent Claim No.	Support
	'901 application: page 2, line 4-page 3, line 9; "Summary of the Invention" page 3, line 10-page 4, line 5; "Brief Description of the Drawings," page 4, line 6-page 5, line 31, page 6, line 13-page 10, line 24, "Detailed Description of the Drawings" page 10, line 25-page 12, line 27; page 13, line 1-page 18, line 15; page 18, line 27-page 29, line 32; page 30, line 12-page 34, line 32; page 35, line 1-page 36, line 8; page 38, line 5-page 39, line 5; page 39, line 9-page 40, line 7; page 43, line 7-page 48, line 15 and all Figures specifically cited in these sections; '173 application: page 12, line 6-page 16, line 5; page 53, line 10-page 57, line 18, and generally, page 24, line 1-page 34, line 14; and all Figures specifically cited in these sections; '680 application: page 1, line 29-page 3, line 4; "Summary of the Invention" page 3, lines 5-30; "Brief Description of the Drawings," page 4, line 1-page 5, line 25; Figs. 1-3; 5-9; page 6, line 6- page 12, line 29, page 13, line 22-page 19, line 8; page 21, line 5-page 24, line 8, page 25, line 7-page 27, line 6; and all Figures specifically cited in these sections. Additionally, disclosure relating to underlying science, as well as background to the invention, corresponding to prior applications incorporated by reference in the above applications, may be found in portions of the '516 specification (including Figures cited to) as follows: '516 specification, col. 4, lines 29-49; col. 4, line 55-col. 5, line 44, col. 5, line 58-col. 6, line 4; col. 10, line 57-col. 11, line 23; col. 20, line 26-col. 22, line 9; col. 33, line 60-col. 35, line 12; col. 38, line 28-col. 42, line 34; col. 46, line 35-col. 49, line 61; col. 52, line 64-col. 54, line 30; col. 56, line 22-col. 57, line 42; col. 68, line 30-col. 73, line 56; col. 74, line 52-col. 76, line 9.
145. The method of claim 14, carried out on human cells.	See response to claim 14, and in particular, '516 specification col. 27, lines 27-43; col. 12, lines 57-col. 13, line 3; col. 13, lines 13-29; col. 17, lines 19-52; col.

'516 Patent Claim No.	Support
	37, lines 1-42; col. 49, line 62-col. 51, line 40; col. 78, line 43-col. 79, line 10; col. 79, line 64-col. 80, line 19; col. 81, lines 9-45; (for example, see '436 application, page 4, line 15-page 5, line 6; page 11, lines 4-20;page 12, lines 1-19; page 22, line 12-page 23, line 21; page 28; page 31, line 1-page 32, line 2; page 34, line 5-page 35, line 2, page 37, line 8-page 38, line 20) (for example, see '901 application, page 3, line 10-page 4, line 5; Fig. 6, page 6, lines 16-18; Fig. 14, page 10, lines 5-24; page 20, line 17-page 23, line 12; page 35, line 1-page 36, line 8; page 38, line 5-page 39, line 5, Example 6) (for example, see '173 application, page 53, line 10-page 57, line 18) (for example, see '680 application, page 6, line 6-page 7, line 25; page 25, line 8-page 27, line 6).
146. The method of claim 14 or 145, carried out on immune cells.	See response to claim 14, and in particular, '516 specification col. 27, lines 27-43; col. 12, lines 57-col. 13, line 3; col. 13, lines 13-29; col. 13, line 66-col. 14, line 33; col. 17, lines 19-52; col. 37, lines 1-42; col. 78, line 43-col. 79, line 10; col. 79, line 64-col. 80, line 19; col. 81, line 9-col. 82, line 11; (for example, see '436 application, page 4, line 15-page 5, line 6; page 11, lines 4-20;page 12, lines 1-19; page 13, line 29-page 16, line 2; page 22, line 12-page 23, line 21; page 28; page 31, line 1-page 32, line 2; page 34, line 5-page 35, line 2, page 37, line 8-page 39, line 21) (for example, see '901 application, page 3, line 10-page 5, line 31; Figs. 1-3; Figs. 5-13, page 6, line 13-page 10, line 4; page 10, line 25-page 20, line 16; page 20, line 17-page 30, line 28; page 32, line 6-page 36, line 8; page 38, line 5-page 39, line 5, Examples 1, 3-5) (for example, see '173 application, page 53, line 10-

'516 Patent Claim No.	Support
	page 57, line 18) (for example, see '680 application, page 6, line 6-page 7, line 25; page 18, line 1-page 19, line 8).

XII. Materials Considered for Opinions

A. Depositions

Baeuerle, Patrick; December 1, 2004.

Baldwin, Albert S., Jr.; October 26, 2004.

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B. Case Documents

Answer

Complaint, June 25, 2002

Latchman Report

Barnes Report

Memorandum of Decision and Order, March 3, 2004 (Claim Construction)

Plaintiffs Ariad Pharmaceuticals, Inc et al. Third Supplemental Response to Eli Lilly & Co.'s First Set of Rule 33 Interrogatories (Nos. 1-5)

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U.S. Pat. No. 5,939,421

U.S. Pat. No. 6,060,310

U.S. Pat. No. 6,410,516

U.S. Pat. No. 6,841,371

U.S. Ser. No. 06/817,441, filed Jan. 9, 1986

U.S. Ser. No. 06/946,365, filed Dec. 24, 1986

U.S. Ser. No. 07/162,680, filed Mar. 1, 1988

U.S. Ser. No. 07/155,207, filed Feb. 12, 1988

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C. Publications and Patents

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CERTIFICATE OF SERVICE

I, Denise Lopez, hereby certify that on October 21, 2005, true and correct copies of the Rule 26(a)(2) Report of Bert Spilker, Ph.D., M.D. with attached CD, the Rule 26(a)(2) Rebuttal Report of George R. Stark, Ph.D. with attached CD, the Rule 26(a)(2) Rebuttal Report of Thomas R. Kadesch, Ph.D. with attached CD, the Expert Report of Jeffrey V. Ravetch, M.D., Ph.D. with attached CD, and the Expert Report of Dr. Stephen Prescott with Attached CD, were served by the indicated means to the persons at the addresses listed:

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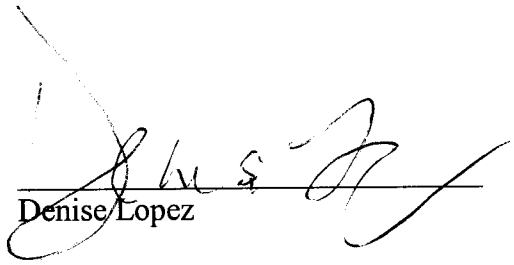

Denise Lopez