Hot topics in pharma patenting

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Palau Pharma SA

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Hot topics in pharma patenting – Summary

• Basic facts that every medicinal chemist should know about patents
• Brief review of classical types of inventions in pharma patents
• New patenting trends
• Review of recent litigation
• Rights conferred by a patent. Experimental use exemption
• Patent term extensions for pharmaceuticals
Basic facts about patenting that every Med Chemist should know

• Patentability requirements:
  ✓ Novelty – absolute requirement (no prior publication in any form, place or language !)
  ✓ Inventive step/Non-obviousness
  ✓ Industrial applicability/utility

• Additional requirements:
  ✓ Sufficiency of disclosure
  ✓ Clarity

• Parts of a patent:
  ✓ Claims: the most important part of a patent → they define the scope of protection obtained
  ✓ Description: used to interpret the claims
  ✓ Abstract & title: only have informative purposes, no legal value
Basic facts about patenting that every Med Chemist should know

- Duration: 20 years from filing date

- Territorial nature: patents are national rights (no worldwide or international patent). Patents must be filed in every country where protection is desired

- Routes available for obtaining patents:
  - National offices
  - Regional treaties: European Patent Office (EPO) BUT an EP patent is not a Community patent
  - Patent Cooperation Treaty (PCT)

- Publication of applications at 18 months from earliest priority date

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Usual types of inventions in pharma patents

- New chemical entities:
  - Chemical class (Markush claims)
  - Individual compounds
- Salts
- Solvates/Hydrates
- Polymorphs
- New synthesis & intermediates
- Pharmaceutical formulations
- Combinations with other drugs
- New therapeutical uses
New trends in pharma patenting

• In addition to usual drug-related inventions, more and more basic research is being protected through patents

• Around 20% of human genes have been patented (Jensen & Murray, Science 2005, 310, 239-240)

• Patents are being filed both by universities and private companies

• Ongoing debate as to the benefits and risks of such patenting practices
New trends in pharma patenting

- The term research tool has been coined to refer to this type of inventions
- **Research tools** have been defined by the NIH as:

  “the full range of resources that scientists use in the laboratory including cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry libraries, drugs and drug targets, clones and cloning tools, methods, laboratory equipment and machines, databases and computer software”
New trends in pharma patenting

We will now focus on patents dealing with:

• Biological targets
• Screening assays
• “Mechanism” claims: claims attempting to obtain protection for a biological pathway
• Reach-through claims: claims aiming at obtaining protection for downstream products discovered using the research tool
• Protein crystals, \textit{in silico} screening methods & pharmacophores

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Assuming a new receptor X with biological function is found, the following types of claims can be found in patent applications:

1) A gene encoding receptor X
2) Receptor X
3) A transformed cell expressing the receptor
4) A method for screening modulators of receptor X
5) A receptor X modulator identified by the screening method
6) Use of a receptor X modulator in the manufacture of a medicament for the treatment of disease D
7) A method for treating disease D by modulating receptor X
8) A method for treating disease D by administering a receptor X modulator
**Biological targets – Some examples**

- WO 97/32019 Euroscreen

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<td>96870021.1 1 March 1996 (01.03.96) EP</td>
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<td>96870102.9 6 August 1996 (06.08.96) EP</td>
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<th>(71) Applicant (for all designated States except US):</th>
</tr>
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<tr>
<td>EUROSCREEN S.A. [BE/BE]; Avenue des Becassines 7, B-1160 Brussels (BE).</td>
</tr>
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| (74) Agents: VAN MALDEREN, Eric et al.; Office Van Malderen, Place Reine-Pabla 6/1, B-1083 Brussels (BE). |


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<td>Without international search report and to be republished upon receipt of that report. With an indication in relation to a deposited microorganism furnished under Rule 13bis separately from the description. Date of receipt by the International Bureau: 17 March 1997 (17.03.97)</td>
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<td>C-C CKR-5, CC-CHEMIKINES RECEPTOR, DERIVATIVES THEREOF AND THEIR USES</td>
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**Biological targets – Some examples**

1. **Peptide** having at least an amino acid sequence which presents more than 80% homology with the amino acid sequence as represented in SEQ ID NO. 1 shown in figures 1.

20. **Nucleic acid molecule** encoding a peptide according to any of the claims 1 to 17.

22. **Vector** comprising the nucleic acid molecule according to any of the claims 18 to 21.

28. **Cell**, preferably a human cell, comprising the vector according to any of the claims 22 to 27.

54. **Method for determining** whether a ligand can specifically bind to a peptide according to any of the claims 1 to 17, which comprises contacting a cell transfected with a vector expressing the nucleic acid molecule encoding said peptide with the ligand under conditions permitting binding of ligand to such peptide and detecting the presence of any such ligand bound specifically to said peptide, thereby determining whether the ligand binds specifically to said peptide.
63. Ligand detected by the method according to any of the claims 54 to 62.

65. Method of screening drugs to identify drugs which specifically bind to the peptide according to any of the claims 1 to 17 on the surface of the cell, which comprises contacting a cell transfected with a vector expressing the nucleic acid molecule encoding said peptide with a plurality of drugs under conditions permitting binding of said drugs to the peptide, and determining those drugs which specifically bind to the transfected cell, thereby identifying drugs which specifically bind to the peptide.

72. Drug detected by any of the methods according to claims 65 to 71.
Biological targets – Some examples

• EP 724637 Neurocrine Biosciences

NEW EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the opposition decision: 05.06.2002 Bulletin 2002/23


(21) Application number: 95925271.9

(22) Date of filing: 14.06.1995

(54) CORTICOTROPIN-RELEASING FACTOR 2 RECEPTORS
Claims

1. An isolated nucleic acid molecule encoding a CRF$_2$ receptor, wherein said CRF$_2$ receptor is encoded by:

   (a) a nucleic acid sequence having the coding region of any one of Sequence I.D. Nos. 1, 3, or 7, or a derivative thereof having greater than 80% homology with said coding region
   (b) a nucleic acid sequence which is capable of hybridization under conditions of high stringency to a nucleic acid sequence complementary to a nucleic acid sequence having the coding region of any one of sequence ID Nos 1, 3 or 7, or
   (c) nucleic acid sequences which are degenerate as a result of the genetic code to CRF$_2$ receptors which are encoded by a nucleic acid sequence defined in (a) or (b).

5. The isolated nucleic acid molecule according to claim 1 wherein said molecule encodes a human CRF$_2$ receptor.

9. A recombinant expression vector, comprising a promoter operably linked to a nucleic acid molecule according to any one of claims 1-8.

11. A host cell containing a recombinant expression vector according to claim 9 or 10.

12. An isolated CRF$_2$ receptor or variant thereof encoded by a nucleic acid sequence according to claim 1.

13. The isolated CRF$_2$ receptor according to claim 12 having the amino acid sequence of Sequence I.D. No. 4, from amino acid number 1 to amino acid number 411.
Biological targets – Some examples

27. A method for detecting the presence of a compound which binds to a CRF₂ receptor, comprising:

   (a) exposing one or more compounds to cells or cell membranes that express CRF₂ receptors encoded by a nucleic acid sequence according to claim 1 under conditions and for a time sufficient to allow binding of said compounds to said receptors; and
   (b) isolating compounds which bind to said receptors, such that the presence of a compound which binds to a CRF₂ receptor may be detected.

30. A method for determining whether a selected compound is a CRF₂ receptor agonist or antagonist, comprising:

   (a) exposing a selected compound to cells which express CRF₂ receptors encoded by a nucleic acid sequence according to claim 1 under conditions and for a time sufficient to allow binding of the compound and an associated response through a response pathway; and
   (b) detecting either an increase or decrease in the activity of the response pathway, as compared with the activity of the response pathway prior to step (a) and thereby determining whether said selected compound is a CRF₂ receptor agonist or antagonist.

34. The method according to any one of claims 30 to 33 wherein said response pathway is the adenylate cyclase response pathway.

35. Use of a CRF₂ receptor antagonist for the manufacture of a medicament for treating a CRF₂ receptor-associated disease by prevention or decrease of stimulation of a CRF₂ receptor response pathway, wherein said disease is a cerebrovascular disorder, and wherein said CRF₂ receptor is encoded by a nucleic acid sequence according to claim 1.
Protein 3-D structures & in silico screening

- Rise in the number of 3-D structures of proteins elucidated → expected increase in patent filings

- Types of claims that may be seen in this type of patent applications:
  - Computer model of protein
  - Data array comprising atomic coordinates of protein
  - Computer-readable storage medium with atomic coordinates of protein
  - Pharmacophore
  - Protein defined by its tertiary structure
  - Crystalline form of protein
  - Binding pockets and protein domains
  - In silico screening methods
  - Compounds identified by in silico screening methods
  - Compounds defined by a pharmacophore

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Protein 3-D structures & in silico screening - Examples

- WO 03/092607  Vertex Pharmaceuticals

(43) International Publication Date

(10) International Publication Number
WO 03/092607 A2

(51) International Patent Classification: A61K

(21) International Application Number: PCT/US03/13605

(22) International Filing Date: 1 May 2003 (01.05.2003)

(54) Title: CRYSTAL STRUCTURE OF AURORA-2 PROTEIN AND BINDING POCKETS THEREOF

(57) Abstract: The present invention provides crystalline molecules or molecular complexes which comprise binding pockets of Aurora-2 or its homologues. The invention also provides crystals comprising Aurora-2. The present invention also relates to a computer comprising a data storage medium encoded with the structural coordinates of Aurora-2 binding pockets and methods of using a computer to evaluate the ability of a compound to bind to the molecule or molecular complex. This invention also provides methods of using the structure coordinates to solve the structure of homologous proteins or protein complexes. In addition, this invention provides methods of using the structure coordinates to screen for and design compounds, including inhibitory compounds, that bind to Aurora-2 or homologues thereof.
We claim:

1. A crystal comprising an unphosphorylated Aurora-2 kinase domain or unphosphorylated Aurora-2 kinase domain homologue thereof.

2. The crystal according to claim 1, further comprising a chemical entity.

9. A crystalline molecule or molecular complex comprising a binding pocket defined by structure coordinates of a set of amino acid residues that correspond to Aurora-2 amino acid residues L139, L194, L210, E211, A213, L263 and W277 according to any one of Figures 1-4, wherein the root mean square deviation of the backbone atoms between amino acid residues of said molecule or molecular complex and said Aurora-2 amino acid residues is not greater than about 3 Å.
21. A computer comprising:
   (a) a machine-readable data storage medium, comprising a data storage material encoded with machine-readable data, wherein said data defines the binding pocket or protein according to any one of claims 9-20;
   (b) a working memory for storing instructions for processing said machine-readable data;
   (c) a central processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine-readable data and means for generating three-dimensional structural information of said binding pocket or protein; and
   (d) output hardware coupled to said central processing unit for outputting three-dimensional structural information of said binding pocket or protein, or information produced using said three-dimensional structural information of said binding pocket or protein.
25. **A method for designing, selecting and/or optimizing a chemical entity** that binds to all or part of the binding pocket or protein according to any one of claims 9-20 comprising the steps of:

(a) providing the structure coordinates of said binding pocket or protein on a computer comprising the means for generating three-dimensional structural information from said structure coordinates; and

(b) designing, selecting and/or optimizing said chemical entity by performing a fitting operation between said chemical entity and said three-dimensional structural information of all or part of said binding pocket or protein.
Protein 3-D structures & in silico screening - Examples

WO 2005/119230 Univ Minnesota & Janssen Pharmaceutica

(43) International Publication Date
15 December 2005 (15.12.2005)

(10) International Publication Number
WO 2005/119230 A2

(51) International Patent Classification7:
G01N 24/00

(21) International Application Number:
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(22) International Filing Date:
20 May 2005 (20.05.2005)

(25) Filing Language:
English

(26) Publication Language:
English

(30) Priority Data:
10/854,904 27 May 2004 (27.05.2004) US

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ijd. P.A., P.O. Box 581415, Minneapolis, MN 55458-
1415 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, EZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KM, KP, KR, KZ, LC, LK, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ,
OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL,
SM, SV, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC,
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ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM).

(54) Title: PHARMACOPHORES FOR NOCICEPTIN, METHODS OF OBTAINING AND USING IN SCREENING FOR NO-
CICEPTIN MIMICS

(57) Abstract: Nociceptin pharmacophores, methods of determining a nociceptin pharmacophore, nociceptin solution structures, and methods of identifying compounds as potential nociceptin mimics are provided.
WHAT IS CLAIMED IS:

1. A method of determining a nociceptin pharmacophore, the method comprising:
   collecting nuclear magnetic resonance (NMR) data of nociceptin or a peptide analog thereof in an aqueous composition;
   determining distances and angles between atoms of nociceptin from the NMR data;
   computer modeling the three-dimensional structure of nociceptin in the aqueous composition based on the NMR data; and
   conducting a structure-activity analysis to identify pharmacophore elements of the solution structure of nociceptin.

16. A method of identifying a nociceptin mimic, the method comprising:
    determining a nociceptin pharmacophore comprising:
    collecting nuclear magnetic resonance (NMR) data of nociceptin in an aqueous composition;
    determining distances and angles between atoms and features of nociceptin from the NMR data;
computer modeling the three-dimensional structure of nociceptin in the aqueous composition based on the NMR data; and conducting a structure-activity analysis to identify pharmacophore elements of the solution structure of nociceptin; supplying a three-dimensional structure of a test compound; comparing the structural features of a test compound to the pharmacophore to determine if it is a potential nociceptin mimic; and evaluating the binding capacity of the potential mimic to a nociceptin receptor, wherein a nociceptin mimic inhibits the binding of labeled $^{125}$I-nociceptin to human nociceptin receptor (ORL-1) on HEK-293 cell membranes by 50% or more at a concentration of 10 µM.

25. A nociceptin pharmacophore comprising at least three elements comprising two hydrophobic features and one polar feature or a feature capable of electrostatic interaction.

29. A nociceptin pharmacophore comprising a three-dimensional structure represented by the Cartesian coordinates listed in Table 5.
**Protein 3-D structures & in silico screening - Examples**

- WO 2006/055959 Bioquanta & Univ René Descartes

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**International Publication Date**
26 May 2006 (26.05.2006)

**International Patent Classification:**
G06F 19/00 (2006.01)

**International Application Number:**
PCT/US2005/042386

**International Filing Date:**

**Title:** PF4 PHARMACOPHORES AND THEIR USES

**Abstract:** The invention provides a novel PF4 pharmacophore that is useful, *inter alia*, for identifying peptidomimetics and other compounds capable of modulating PF4 activity (*e.g.*, as inhibitors, agonists or antagonists). Mutant PF4 polypeptide sequences are also provided that modulate PF4 activity in cells.
WHAT IS CLAIMED IS:

1. A compound that modulates PF4 activity comprising a plurality of functional groups that are each selected from a functional group of an amino acid side chain in the PF4 sequence set forth in Figure 1C (SEQ ID NO:1), which amino acid side chains comprise: Asp7, Leu8, Gln9, Leu11, Val13, His23, Gln18 and is not PF4, IL-8, a PF4 mutant or a peptide having the amino acid sequence selected from the group consisting of SEQ ID NOS:34-156.

13. A compound that modulates PF4 activity comprising functional groups I, II, III, IV, VIII, IX and X wherein the distances between the functional groups in three-dimensions are about:

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<td>6.03 ± 1.37 Å</td>
<td>between groups I and III;</td>
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<tr>
<td>6.92 ± 1.60 Å</td>
<td>between groups I and IV;</td>
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<tr>
<td>8.57 ± 2.60 Å</td>
<td>between groups I and VIII;</td>
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<tr>
<td>14.20 ± 1.53 Å</td>
<td>between groups I and X;</td>
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<td>12.54 ± 1.51 Å</td>
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<td>14.45 ± 0.24 Å</td>
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<tr>
<td>7.25 ± 0.49 Å</td>
<td>between groups IX and X</td>
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32. **A method for identifying a compound that modulates PF4 activity**, which method comprises comparing:

(a) a three-dimensional structure of a candidate compound, to

(b) a three-dimensional structure of a PF4 pharmacophore,

wherein similarity between the three-dimensional structures of the candidate compound and the PF4 pharmacophore is indicative of the candidate compound’s ability to modulate PF4 activity.

37. **The method according to claim 32 wherein the PF4 pharmacophore comprises a plurality of functional groups**, each functional group being selected from a functional group of an amino acid side chain in the PF4 sequence set forth at **Figure 1C** (SEQ ID NO:1), which amino acid side chains comprise: Asp7, Leu8, Gln9, Leu11, Val13, His23, Gln18 and **is not PF4, IL-8, a PF4 Mutant or a peptide having the amino acid sequence selected from the group consisting of SEQ ID NOS:34-156.**
Recent litigation re research tool patents

- University Rochester vs. Searle (COX-2 inhibitors)
- Ariad vs. Lilly (NF-κB modulators)
- Housey vs. Bayer
- Integra vs. Merck
Univ. Rochester vs. Searle – COX-2 inhibitors

• Univ. Rochester scientists discovered that there are 2 isoforms of cyclooxygenase (COX) and that inflammation is mediated by COX-2

• Rochester filed patent applications directed to COX-2 in 1992

• In 2000, when several selective COX-2 inhibitors had already been marketed, a US patent was granted to Rochester (US 6048850) covering methods of treatment using any compound that was a selective COX-2 inhibitor, although none were actually identified in the patent

• The day after the patent was granted, Rochester sued Searle, the manufacturer of Celebrex® (celecoxib), for infringement
METHOD OF INHIBITING PROSTAGLANDIN SYNTHESIS IN A HUMAN HOST

Inventors: Donald A. Young, 540 Clover Hills Dr., Rochester, N.Y. 14618; Michael K. O'Banion, 3613 Clover St., Pittsford, N.Y. 14653; Virginia D. Winn, 139 Raleigh St., Rochester, N.Y. 14620

Appl. No.: 08/487,744
Filed: Jun. 7, 1995

Related U.S. Application Data

Division of application No. 08/487,752, Jun. 7, 1995, and a continuation-in-part of application No. 08/034,143, Mar. 22, 1993, abandoned, which is a continuation of application No. 07/840,780, Sep. 22, 1992, abandoned, said application No. 08/487,752, is a continuation-in-part of application No. 08/231,456, Apr. 20, 1994, abandoned, which is a continuation-in-part of application No. 08/054,364, Apr. 28, 1993, abandoned, which is a continuation-in-part of application No. 07/983,835, Dec. 1, 1992, abandoned, which is a continuation-in-part of application No. 07/949,780.

Han et al., 1990, “Persistent induction of cyclooxygenase in p60^cmyc^-transformed 3T3 fibroblasts”, Proc Natl Acad Sci 87:3373–3377.
Jones et al., 1993, “Molecular cloning of human prostaglandin endoperoxide synthase type II and demonstration of
**Univ. Rochester vs. Searle**

- **US 6048850** – the claims at issue:

What is claimed is:

1. A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment.

2. The method of claim 1 in which the compound inhibits the enzymatic activity of the PGHS-2 gene product, and has minimal effect on enzymatic activity of PGHS-1.

3. The method of claim 1 in which the activity of PGHS-1 is not inhibited.

4. The method of claim 3 in which the compound is a non-steroid anti-inflammatory drug.

5. A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product in a human host in need of such treatment, wherein the activity of the non-steroidal compound does not result in significant toxic side effects in the human host.

6. A method for selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product in a human host in need of such treatment, wherein the ability of the non-steroidal compound to selectively inhibit the activity of the PGHS-2 gene product is determined by:

   a) contacting a genetically engineered cell that expresses human PGHS-2, and not human PGHS-1, with the compound for 30 minutes, and exposing the cell to a pre-determined amount of arachidonic acid;

   b) contacting a genetically engineered cell that expresses human PGHS-1, and not human PGHS-2, with the compound for 30 minutes, and exposing the cell to a pre-determined amount of arachidonic acid;

   c) measuring the conversion of arachidonic acid to its prostaglandin metabolite; and

   d) comparing the amount of the converted arachidonic acid converted by each cell exposed to the compound to the amount of the arachidonic acid converted by control cells that were not exposed to the compound, so that the compounds that inhibit PGHS-2 and not PGHS-1 activity are identified.

7. The method of claims 1, 3 or 4, which is used to treat inflammation.

8. The method of claims 1, 3, or 4, in which the inhibition of prostaglandin synthesis has anti-inflammatory action in the human host.
The patent was invalidated at District Court for failing to comply with the written description requirement. According to the court, the patent was nothing more than a research plan, an invitation to experiment, not a completed invention

Decision was maintained following appeal (Fed Cir 2004)
Ariad vs. Lilly – the NF-κB story

• NF-κB is a prolific transcription factor implicated in many diseases including cancer, inflammation, immune diseases, osteoporosis and sepsis

• Discovered in 1986 by Nobel prize winners David Baltimore and Phillip A. Sharp, among others

Source: Science 2006, 311, 1855-1857
Ariad vs. Lilly

- Patent was filed in 1986 by MIT, Whitehead Institute and Harvard University. Exclusively licensed to Ariad in 1991

- US patent granted in June 2002

- Shortly after, Ariad sued in the USA Eli Lilly for infringement by the sale of its products Evista® (raloxifene, for osteoporosis) and Xigris® (recombinant human activated Protein C, for sepsis)
### Ariad vs. Lilly

- **Drugs that inhibit NF-κB:**

<table>
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<tr>
<th>Drug</th>
<th>Company</th>
<th>Putative mechanism</th>
<th>Primary indications</th>
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<tr>
<td>Enbrel (etanercept)</td>
<td>Amgen</td>
<td>Inhibits tumor necrosis factor (TNF), inactivating IKK</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Lipitor (atorvastatin)</td>
<td>Pfizer (New York)</td>
<td>Reduces NF-κB in macrophages and vascular smooth muscle cells</td>
<td>High cholesterol</td>
</tr>
<tr>
<td>Remicade (infliximab)</td>
<td>Johnson &amp; Johnson (New Brunswick, New Jersey)</td>
<td>Inhibits TNF, inactivating IKK</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Humira (adalimumab)</td>
<td>Abbott (Abbott Park, Illinois)</td>
<td>Inhibits TNF, inactivating IKK</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Premarin (conjugated estrogens)</td>
<td>Wyeth (Madison, New Jersey)</td>
<td>Blocks IκB degradation</td>
<td>Hormone replacement therapy, osteoporosis</td>
</tr>
<tr>
<td>Neoral/Sandimmune (cyclosporine)</td>
<td>Novartis (Basel)</td>
<td>Various mechanisms</td>
<td>Autoimmune disease, organ transplantation</td>
</tr>
<tr>
<td>Prograf (tacrolimus)</td>
<td>Fujisawa (Osaka)</td>
<td>Blocks NF-κB DNA binding in T cells</td>
<td>Organ transplantation</td>
</tr>
<tr>
<td>Prednisone (prednisone)</td>
<td>Roxane (Columbus, Ohio)</td>
<td>Enhances IκB production</td>
<td>Various steroid-responsive conditions</td>
</tr>
<tr>
<td>Decadron (dexamethasone)</td>
<td>Merck (Whitehouse Station, New Jersey)</td>
<td>Enhances IκB production</td>
<td>Various steroid-responsive conditions</td>
</tr>
<tr>
<td>Velcade (bortezomib)</td>
<td>Millennium (Cambridge, Massachusetts)</td>
<td>Blocks IκB degradation</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Clinoril (sulindac)</td>
<td>Merck</td>
<td>Blocks IκB phosphorylation</td>
<td>Osteoarthritis and rheumatoid arthritis</td>
</tr>
<tr>
<td>Accupril (quinapril)</td>
<td>Pfizer</td>
<td>Reduces NF-κB in macrophages and vascular smooth muscle cells</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Revlimid (thalidomide)</td>
<td>Celgene (Summit, New Jersey)</td>
<td>Interferes with IKK activity</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Cozaar (losartan)</td>
<td>Merck</td>
<td>Blocks IκB degradation</td>
<td>High blood pressure</td>
</tr>
</tbody>
</table>

**Table 1:** Selected marketed prescription drugs that inhibit NF-κB

**Source:** Nature Biotechnol, 2006, 24(7), 737-739

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Ariad vs. Lilly

- The patent at issue: contains 203 claims

**United States Patent**

**Baltimore et al.**

**Patent No.:** US 6,410,516 B1

**Date of Patent:** Jun. 25, 2002

**NUCLEAR FACTORS ASSOCIATED WITH TRANSCRIPTIONAL REGULATION**

**Inventors:** David Baltimore, New York, NY (US); Ranjan Sen, Cambridge; Phillip A. Sharp, Newton, both of MA (US); Harinder Singh, Chicago, IL (US); Louis Staudt, Silver Springs, MD (US); Jonathan H. Labowitz, Zionsville, IN (US); Albert S. Baldwin, Jr., Chapel Hill, NC (US); Roger G. Clerc, Binningen (CH); Lynn M. Corcoran, Port Melbourne (AU); Patrick A. Baeuerle, Eichanau (DE); Michael J. Lenardo, Poziomac, MD (US); Chen-Ming Fan, San Francisco; Thomas P. Maniatis, Belmont, both of MA (US)

**Assignees:** President & Fellows of Harvard College; Massachusetts Institute of Technology; Whitehead Institute for Biomedical Research, all of Cambridge, MA (US)

**Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(a)(5) by 0 days.

**Appl. No.:** 08/464,364

**Other Publications**


Ariad vs. Lilly

• The relevant claims: 80, 95, 144 and 145

• **Claim 80**: A method 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 by reducing binding of NF-κB to NF-κB recognition sites on genes which are transcriptionally regulated by NF-κB such that NF-κB-mediated effects of external influences are modified

• **Claim 95**: A method of reducing, in human 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
Ariad vs. Lilly

- Lilly’s arguments:
  - Evista® and Xigris® discovered and marketed without consideration to NF-κB activity
  - Claims unpatentable because they cover a natural phenomenon
  - Claims inherently anticipated since old products (aspirin, estrogens, red wine, cyclosporin A and others) reduce NF-κB activity
  - Claims invalid for lack of written description and enablement (no inhibitors of NF-κB disclosed)

BIOMEDICAL PATENTS

Broad Patent Faces Narrow Odds in Court Battle

Upstream biotech patents face a crucial test in April in a trial with implications for future drug development

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Science, 2006, 311, 1855
Ariad vs. Lilly

• The jury decision (4 May 2006):
  ✓ Claims considered to be valid and infringed
  ✓ Awarded damages of 65.2 million US$ plus 2.3% royalty on sales of Evista® and Xigris® up to 2019 (expiry of patent)

Decision on NF-κB Patent Could Have Broad Implications for Biotech

In what one patent expert called a potentially “huge, huge case,” a federal jury last week unanimously upheld a biotechnology patent that critics describe as exceptionally broad. If the verdict survives appeal, it could set a new precedent for the enforcement of patents on biological discoveries upstream of actual drugs.

Judge Rya Zobel to decide certain legal challenges to the patent’s validity and enforceability. Lilly vows to appeal last week’s verdict if the judge rejects these arguments. And in late April, Angen, a biotechnology company in Thousand Oaks, California, filed suit against Ariad to

Patently absurd?

Ariad Pharmaceuticals’ surprise victory against Lilly on NF-κB patent infringement has drug companies and legal experts wondering about the future of biotech patenting. Ken Garber reports on the aftermath of the surprising decision.
Not yet the end of the story...

- Separate bench trial on certain issues (August’06) is awaiting decision

- Lilly can appeal the jury decision if bench trial negative

- Amgen filed in April’06 a lawsuit seeking a declaration that its antiarthritis drugs Enbrel® (etanercept) and Kineret® (anakinra) do not infringe

- Reexamination of the patent requested by Lilly and other parties in April 2005. Recently a first opinion issued and most claims, including the claims involved in the ruling against Lilly, deemed to be invalid on the grounds that:

  ✓ They use over-broad functional language
  ✓ Are anticipated by a variety of prior art, including the Bible!
Rights conferred by a patent

- Right to exclude others from making, using, selling or offering a patented product, or importing the product for any such use. If patent is for a process, right to prohibit use of patented process → direct product obtained using the patented process is also protected.

- Not in itself a right to do → even if having a patented invention, one must be careful not to infringe third parties patents (Freedom to operate).

- Certain exceptions to rights conferred by a patent:
  - Acts done for private and non-commercial purposes
  - ... 
  - Acts done for experimental purposes
**Experimental use exemption**

- Europe: acts done for experimental purposes relating to the subject matter of the invention do not infringe a patent
  - Key issue is whether the patented invention is the object of the research or whether the invention is the means/tool used to carry out the research. The latter is not exempted.
  - Universities also at risk

- USA - very narrow exception: applies only to activity conducted “solely for amusement, to satisfy idle curiosity, or for strict philosophical inquiry” (Madey vs Duke Univ, Fed Cir 2002) → of no practical use for R&D today
Bolar-type clauses

- Bolar-type clauses: legislation enacted to allow the preparation and submission of generic marketing applications before patent expiry
- In force in USA since 1984
- Recently implemented into EU law (Medicines Directive 2004/27/EC)
- It is uncertain whether it will apply to new drugs or research tools:
  - USA: Integra vs Merck (US Supreme Court 2005): not limited to generic products. However, patents involved were not regarded as RT patents by SC → no conclusions can be drawn
  - Europe: differences in scope from country to country. RT most probably not covered. In Spain, Bolar limited to generic products

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**Patent term extensions & Pediatric legislation**

- Laws enacted to extend the duration of pharma patents beyond 20 years to compensate for regulatory delays in reaching the market.
- Available in US, EU, JP and some other countries. In EU called Supplementary Protection Certificates (SPCs).
- Each country applies a different system to calculate extension to be granted. Maximum extension in EU, US and JP is 5 years.
- Pediatric legislation: intended to promote the study of the effect of drugs in children. Incentives given:
  - EU: 6 month extension of SPC (not yet in force; expected by beginning 2007)
  - USA: 6 months of market exclusivity at the end of patent term.
Hot topics in pharma patenting – Further reading

If some one is interested in further reading:


  - Biotechnology patent practices: reach-through claims
  - Protein 3-dimensional (3-D) structure related claims

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• Thank you for your attention!

• Any questions?