

Recent Patents on Cell Signaling Systems

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Abstract: A new biological paradigm, Systems Biology, has emerged with the completion of the Human Genome Project. The Human Genome Project has advanced the view that biological information operates on multiple hierarchical levels and is processed in complex networks.

In this paradigm, cumulative knowledge will be used to build models, providing positive externalities to researchers who can use this knowledge to generate new products. As systems biology is likely to become the dominant paradigm in biology, central to the development of medically viable products is ensuring accessibility to systems-based knowledge for multiple researchers.

In this paper, we have selected seven systems based on their biological significance including: the Akt (Protein Kinase B), BCR-ABL, GPCR (G-Protein-Coupled Receptor), JAK/STAT (Janus Kinase/Signal Transducers and Activators of Transcription), MAP Kinase, NF- κ B (Nuclear Factor Kappa B), and Phospholipase C signaling pathways. For each system we provide a complete list of patents, including categorization and institutional ownership; we also review specific patents for each system from the perspective of type of assignee, breadth of claims, and focus—namely whether the focus of the patent is on upstream knowledge regarding the signaling pathway or downstream on pharmaceutical or biological drug development, screening assays, or diagnostics.

Keywords: Systems biology, Cell signaling pathways, Signal transduction, Akt (Protein Kinase B), BCR-ABL, GPCR (G-Protein-Coupled Receptor), JAK/STAT (Janus Kinase/Signal Transducers and Activators of Transcription), MAP Kinase, NF- κ B (Nuclear Factor Kappa B), Phospholipase C.

INTRODUCTION

A new biological paradigm, Systems Biology, has emerged with the completion of the Human Genome Project. The Human Genome Project has advanced the view that biological information operates on multiple hierarchical levels and is processed in complex networks. Systems biology does not simply focus on the individual genes and proteins of a system, but focuses on the behavior and relationships of all components in a particular biological system from a functional perspective [1,2]. Biological systems are fundamentally composed of information: genes, their encoded products, and the regulatory components controlling the expression of these genes [3]. Targets that function across systems will be selected to develop drugs that either augment or suppress the associated biological systems, thereby enabling for disease intervention.

In the systems biology paradigm, the focus of intellectual property rights will also gradually shift to the patenting of information [4]. This information perspective must incorporate an understanding of the impact of enclosing hierarchical and complementary, basic biological knowledge, on the technological opportunities available for the development of novel medical products.

THE SYSTEMS BIOLOGY PARADIGM

Systems biology research begins with the identification of the structures of a system including: genes, proteins, the regulatory relationships of genes, the interactions between proteins that enable signal transduction, metabolic pathways as well as the physical structures of an organism such as cells, tissue networks, and organs. Once the structures of a system are identified, the behavior of a system is analyzed as a function of external perturbation [5]. This analysis provides information regarding system characteristics as well as important insights for medical intervention. The knowledge gained from structure identification and system analysis can then be applied in downstream development activities once research has been conducted into controlling the state of biological systems. [5] It is anticipated that biological systems will eventually be controlled and designed with the aim of intervening in disease onset and progression [1,3,5].

Cell Signaling Systems-Tracing the Route from Membrane to Nucleus

Biological signaling pathways interact with one another to form complex networks. This complexity arises from the number of components, many with partially overlapping functions, from the connections among components, and from the spatial relationship between components [6]. Researchers are beginning to identify a myriad of molecules that interact and interface with different signaling pathways

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to form a signaling network integrating multiple receptors, signal-transducers, and second messengers [7].

Regulation of cell growth can be mediated by receptors belonging to different super families that include: G-protein-coupled receptors, receptor tyrosine kinases, cytokine receptors, cell adhesion receptors, and antigen receptors [7]. Researchers are tracing the signaling routes from these cell surface receptors to the nuclear events leading to cell proliferation through the maze of small GTPases, kinase signaling-modules, non-receptor tyrosine kinases, and transcription factors [7]. While unique sets of regulatory molecules insulate the respective signaling pathway from the adjacent pathways, overlapping sets of regulatory molecules such as small GTPases, tyrosine kinases, and kinase signaling-modules integrate cell signaling between these different signaling pathways [6,7]. The observation that multiple effector molecules can be activated by a single receptor and that the signals from different receptors can be integrated, substantiate the view that multiple signaling inputs are required to commit cells to the critical pathways involved in cell growth.

These effector molecules, which include enzymes (for example, adenylate cyclases; phospholipases) and ion channels, regulate the generation of second messenger molecules [7,8]. The most important function for second messengers is to regulate the degree of phosphorylation of intracellular proteins [7,8]. Second messengers promote phosphorylation of protein substrates by activating protein kinases, or by reversing this process through protein phosphatases [7,8].

Sensing the Signal

The reversible phosphorylation events that are triggered by a ligand binding to its receptor modify protein function. For example, such signals can alter the biological activity of a protein by changing its conformation, can disrupt or enhance its interaction with other regulatory molecules, or can change the protein's cellular location. Protein kinases actually mediate most of the signal transduction in eukaryotic cells [8]. Furthermore, the substrates of protein kinases are often cell specific. Serine/threonine kinases phosphorylate either serine or threonine residues within their target proteins. Protein tyrosine kinases (PTKs) phosphorylate tyrosine residues within proteins. These molecules have been subdivided into two categories, receptor tyrosine kinases (RTKs) and nonreceptor PTKs [8].

Signal Transduction

Protein kinase cascades are extremely useful in signal transduction mechanisms as they allow for amplification, feedback, crosstalk, and branching [8]. A limited number of enzymes can therefore, regulate very precisely a large number of cellular processes. The most important group of serine/threonine kinases, upon which many other signals converge, are the mitogen activated protein kinases (MAPKs) [8]. The mammalian MAPKs are divided into at least five families: ERK1/2 (extracellular regulated kinases), the p38mapks, the c-jun N-terminal kinases (JNKs), ERK3/4, and ERK5. The most widely studied MAPKs of recent years are ERK1/2, which are components of the so called "classical" MAPK cascade. Through their effects on

phosphorylation, these kinases directly affect the activities of key cytoplasmic molecules, and modify acute cellular functions, as well as promote phosphorylation of nuclear proteins [8]. In this sense, these kinases are involved in signal transduction from membrane to nucleus [8].

Cell Signaling Systems and Disease

From the perspective of disease, the malfunctioning of a single entity often does not cause problems, but the combined effects of multiple malfunctioning complexes can be significant. An understanding of how individual components function within the context of the entire cell signaling system, under a variety of situations, should be helpful in understanding why interactions between aberrant signaling pathways often result in pathophysiology [6, 7, 8].

ORGANIZATIONAL HIERARCHY OF INFORMATION IN CELL SIGNALING SYSTEMS:

Cell signaling networks, the associated pathways, and their components are strategic knowledge-based assets [9-12]. The importance of these knowledge-based assets, combined with the increased complexity of molecular and systems-based knowledge, is encouraging the view that drug discovery and development should be viewed centrally from a knowledge-based perspective.

The Human Genome Project has advanced the view that biological information operates on multiple hierarchical levels [3]. From this perspective, it is no longer sufficient to develop a model and perform analysis at only one or two levels of biological information. Information storage, information processing, and the execution of the various cellular programs occur at the level of cell's genome, transcriptome, proteome, and metabolome. These building blocks organize themselves into recurrent patterns i.e. pathways and motifs in genetic-regulatory networks [13]. These pathways and motifs form functional modules or groups of nodes that are responsible for cellular function [13]. Key nodes and intervention points will be sought for medical intervention during target model development. Fig. (1)

Currently, the central task is to integrate and analyze these data for the purpose of biological and pharmacological discoveries. Clustering of data based on structure, function, patterns of expression, interactions, and association with biological system has become a key feature of systems biology. The attempt to capture systems-level laws governing cells is in fact a search for the common patterns that apply to complex systems and networks in general. A modular framework for biology will organize systems into classes that share a common set of characteristics performing a common function [4, 13].

INTELLECTUAL PROPERTY IN THE SYSTEM BIOLOGY PARADIGM

For many industries, concern has been expressed where the research process is primarily knowledge based, the process of invention may be cumulative and iterative, with downstream research dependent on upstream research [14]. A patent system that was developed for a discrete model of innovation and an essentially linear relationship between knowledge elements may no longer be optimal for a

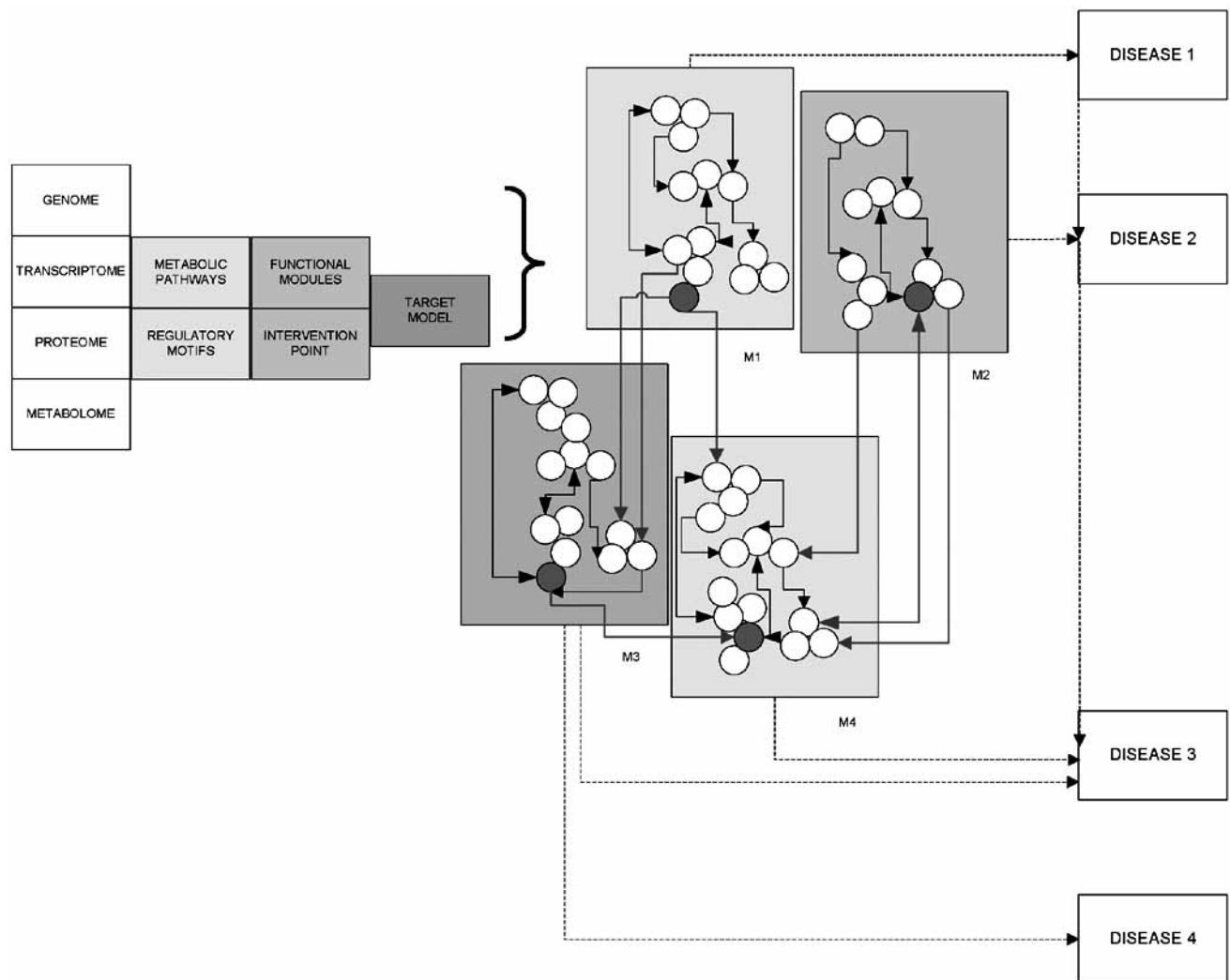


Fig. (1). Hierarchy of Information in Systems Biology

Adopted from Oltvai, Z. N., & Barabási, A. 2002. Life's complexity pyramid. *Science*, 298: 763-764.

Legend:

- M=Modules;
- Black Arrow=Internal System Relationship;
- Grey Arrow=External System Relationship;
- Dashed Arrow=Putative Association between System and Disease;
- White Circle=Signaling Pathway Component;
- Grey Circle=Putative Intervention Point.

knowledge-based, cumulative model of innovation. The notion of biological entities as being composition of matter from the chemistry perspective tends to support the view that extending patent protection to biotechnological inventions, including life forms, is nothing new but simply a matter of expanding an existing logical patent category.

Currently, under existing patent law, biological information is considered a new article of manufacture or composition of matter [15]. However, patent examiners are increasingly finding it difficult to apply the chemical patent law doctrines to biological information. The consequence of this has been the granting of and enforcement of broad patents on domains of knowledge critical for subsequent research and development activities.

In the systems biology paradigm, researchers seek to understand the interactions and informational flow between structures in the cell. Data from various hierarchical levels of biological information will be incorporated into the modeling of systems. Each level of information builds on information found at lower levels in this hierarchy. [3, 4] Consequently, system biology uses cumulative knowledge to build models, providing positive externalities to researchers who can use this knowledge to generate and embody the knowledge in new products. Despite the fact that existing patent law allows a researcher who has discovered a new, nonobvious and useful process, machine, article of manufacture, or composition of matter to receive a patent, is the discovery of a system and putative function enough to

enclose not only the system but also all possible medical developments that arise from the system? By staking out claims to biological pathways, if the claims in a patent cover more than the territory of innovation of a first innovator, subsequent innovations (by other innovators based on the first innovation) can be blocked. If the first innovator cannot or chooses not to fully exploit all technological opportunities presented by the patent, high private costs exist for those follow-on innovators who cannot "get around" such patents [16,17].

Furthermore, research activities are characterized by high levels of risk and uncertainty in terms of generating knowledge and then in terms of downstream applicability. For example, a great deal of uncertainty exists with respect to the role of genes in disease susceptibility and progression, the hierarchy of proteins in any system, as well as the function of such genes and proteins during drug intervention. The simple discovery of a gene and its sequence does not provide this information. In one case, the knowledge may have a limited, specific role in one disease or system and in another scenario, the gene and its encoding products may have a central role across multiple diseases or drug intervention pathways. It is difficult then to assess ex-ante the economic value stemming from the putative application of the knowledge in downstream activities [18,19]. Bargaining stalemates are especially likely when the first innovator has been awarded a broad upstream patent covering follow-on development.

ANALYZING PATENTS ON CRITICAL CELL SIGNALING SYSTEMS

In this paper, we have selected seven systems based on their biological significance including: the Akt (Protein Kinase B), BCR-ABL, GPCR (G-Protein-Coupled Receptor), JAK/STAT (Janus Kinase/Signal Transducers and Activators of Transcription), MAP Kinase, NF- B (Nuclear

Factor Kappa B), and Phospholipase C signaling pathways. We searched the United States Patent and Trademark Office (USPTO) database specifically for patents with these cell signaling systems mentioned in their titles. Patents have been categorized by target area: structural patents with reference to the 2-dimensional and 3-dimensional structure of the key system component(s) as well localization of the key system component(s); method or assay patents targeting the cell signaling systems; activator, modulator, or inhibitor patents with reference to the cell signaling systems; and usage patents that specifically refer to pharmaceutical compositions, disease intervention, or process/production patents with respect to the cell signaling systems. A closer scrutiny of these patents reveals in which target area the greatest number of patents have been filed—an indication of the research trajectory as well as ownership patterns. Table 1 provides a collective summary of our analysis across the cell signaling systems.

In some cases, there appears to be a primary area of focus for research. For example, in the case of the GPCR signaling pathway, the focus of research is on the upstream structural components of the signaling pathway and/or the receptor itself followed by methods or assays associated with the signaling pathway and uses including the treatment of disease. In the case of the Akt, JAK, Map Kinase, and NF- B signaling pathways, the emphasis appears to be on downstream techniques/technologies that activate, modulate, or inhibit the associated pathway.

In terms of patent assignee, as a proxy for determining the sector where research is being conducted, the private sector is the primary location of research concerning the Akt, GPCR, Map Kinase, and Phospholipase C cell signaling pathways. However, the public sector dominates in terms of research on the BCR and JAK pathways. Interestingly, the private and public sectors have their attention equally focused on the NF- B pathway.

Table 1. Patent Statistics for Cell Signaling Systems

| Cell Signaling System | USPTO Patents | Publication Dates | S _{USPTO} | MA _{USPTO} | AMI _{USPTO} | U _{USPTO} | PR _{USPTO} | PUB _{USPTO} | IND _{USPTO} |
|-----------------------|---------------|-------------------|--------------------|---------------------|----------------------|--------------------|---------------------|----------------------|----------------------|
| Akt | 10 | 1999-2006 | 1 | 0 | 7 | 2 | 10 | 0 | 0 |
| BCR | 5 | 1994-2003 | 0 | 1 | 2 | 2 | 1 | 5 | 0 |
| GPCR | 133 | 1993-2006 | 71 | 26 | 10 | 26 | 92 | 43 | 5 |
| JAK | 14 | 1998-2006 | 0 | 1 | 13 | 0 | 1 | 13 | 0 |
| MAP Kinase | 27 | 1997-2006 | 8 | 3 | 14 | 2 | 21 | 6 | 0 |
| NF- B | 13 | 1998-2006 | 2 | 1 | 9 | 2 | 7 | 7 | 0 |
| Phospholipase C | 14 | 1994-2006 | 4 | 2 | 6 | 2 | 12 | 2 | 0 |

Legend:

- USPTO Patents=Based on USPTO Title Search;
- Categorization of Patents: S=Structural, MA=Method or Assay, AMI=Activator, Modulator, Inhibitor, U=Use;
- Patent Assignee: PR=Private Entity, PUB=Public Entity, IND=Individual;
- Totals may not add correctly due to multiple category placement of patents;

In the sections that follow, we review specific patents for each signaling pathway including an analysis of the breadth of claims for each patent as well as downstream implications for product development. As part of the supplementary material attached with the paper, we provide a complete list of patents for each signaling pathway, including categorization and institutional ownership (see appendix).

AKT (PROTEIN KINASE B)

Akt signaling regulates cell proliferation and survival, cell growth (size), glucose metabolism, cell motility, and angiogenesis. Aberrant regulation of these processes result in cellular perturbations considered hallmarks of cancer, and numerous studies testify to the frequent hyperactivation of Akt signaling in many human cancers [20-25]. Akt is now known to include a family of three closely related, highly conserved cellular homologues: Akt1, Akt2, and Akt3. The encoded proteins are serine/threonine kinases that belong to the protein kinase B (PKB) family, and the Akt1, Akt2 and Akt3 proteins are also referred to as PKBa, PKBb and PKBg, respectively [26]. Akt has been shown to be the target of platelet derived growth factor-activated phosphatidylinositol 3-kinase (PI3K) [27]; Akt kinases are now known to be key mediators of signal transduction pathways downstream of activated growth factor and cytokine receptors and PI3K [20, 23,26]. Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns(3,4,5)-P₃), which in turn binds to and induces the activity of a AH/PH-domain [21,23,28,29]. Inhibitors of PI3K or dominant negative Akt mutants abolish survival-promoting activity of these growth factors or cytokines. Introduction of constitutively active PI3K or Akt mutants promote cell survival under conditions in which cells normally undergo apoptotic cell death [20,30].

In U.S. Patent No. 6881555, Guo *et al.* describe isolated nucleic acids encoding human Akt3, vectors containing them, and their therapeutic uses, in particular for gene therapy. Akt3 polypeptide produced recombinantly or by chemical synthesis, and fragments or other derivatives or analogs thereof, including fusion proteins, may be used as antigens or immunogens to generate antibodies that agonize or antagonize the activity of Akt3 polypeptides [31].

The invention also provides for methods of inhibiting apoptosis or necrosis of a cell by administering to the cell a nucleic acid as described in the patent. Guo *et al.* further describe the use of these nucleic acids or vectors for the preparation of pharmaceutical compositions intended for the surgical and/or therapeutic treatment of the human or animal body. Candidate molecules may be either agonists or antagonists of Akt3. The nucleic acids of the invention and the pharmaceutical compositions containing them may be used for the treatment of many pathologies. Compositions may comprise an Akt protein or polypeptide or a nucleic acid encoding an Akt protein or polypeptide, and a pharmaceutically acceptable carrier or vehicle. The compositions are particularly suitable for formulation of biological material for gene therapy [31].

U.S. Patent No. 6881555 is assigned to Aventis Pharmaceuticals Inc. (Bridgewater, NJ). Although this patent claims upstream knowledge of Akt3 in the form of isolated

nucleic acids encoding Akt3 or polypeptides, the invention clearly also relates to downstream methods of treating myocardial infarction or ischemia reperfusion injury by administering to a patient suffering therefrom a nucleic acid as described in the invention. Preferably, the nucleic acid is administered to cardiac myocytes of a patient [31].

Owens *et al.* describe compounds which inhibit the activity of Akt in U.S. Patent No. 7098208. The invention not only provides for chemotherapeutic compositions containing the compounds, but also methods for treating cancer via the administration of the compounds [32].

The compounds are selective inhibitors whose efficacy is dependent on the PH domain.

In another embodiment of the invention, the instant compound is a selective inhibitor whose inhibitory efficacy is dependent on the region of the proteins between the PH domain and the kinase domain referred to as the hinge region. In this embodiment, the compound exhibits a decrease in *in vitro* inhibitory activity or no *in vitro* inhibitory activity against truncated Akt proteins lacking the PH domain and the hinge region [32].

Such an inhibitor that is dependent on either the PH domain, the hinge region or both, provides a particular advantage since the PH domains and hinge regions in the three Akt isoforms lack the sequence homology that is present in the rest of the protein, particularly the homology found in the kinase domains (which comprise the catalytic domains and ATP-binding consensus sequences). It is therefore observed that certain inhibitor compounds as described in the invention are not only selective for one or two isoforms of Akt, but also are weak inhibitors or fail to inhibit other kinases, such as PKA and PKC, whose kinase domains share some sequence homology with the kinase domains of the Akt/PKB isoforms. Both PKA and PKC lack a PH domain [32].

This is an example of downstream patent assigned to Merck and Co., Inc.

Also claimed is a method of treating cancers including: ovarian, pancreatic, and breast cancer via the administration of a therapeutically effective amount of the compounds described in this invention [32].

BCR-ABL

Activation of the oncogenic potential of normal cellular proteins such as protein tyrosine kinases may occur by alteration of the proteins' corresponding enzymatic activities, their inappropriate binding to other cellular components, or both.

For example, the BCR-ABL protein tyrosine kinase oncoprotein may transform cells via changes in enzyme activity and/or altering of noncovalent protein-protein interactions [33]. The gene encoding the BCR-ABL oncoprotein is a chimeric oncogene generated by the translocation of sequences from the ABL protein tyrosine kinase on chromosome 9 into BCR sequences on chromosome 22 [34, 35]. The BCR-ABL oncogene has been implicated in the pathogenesis of Philadelphia chromosome (Ph^{sup.1}) positive human leukemias. Specifically, the kinase activity

of ABL in the abnormal BCR-ABL protein becomes activated and unregulated, thereby driving uncontrolled cell growth [36].

Bcr-Abl inhibits apoptosis induced by cytokine deprivation, DNA damage, and a variety of chemotherapeutic agents [37-43]. However, Bcr-Abl does not prevent apoptosis induced by natural killer cells or in response to X-irradiation in some cell types [44, 45].

There are a variety of cellular substrates of the BCR-ABL kinase that may be involved in cellular transformation. BCR-ABL is associated with the cytoplasm as part of a large signaling complex. Some of the downstream factors in BCR-ABL signaling include PI3 kinase/AKT, and STAT transcription factors. The ability of BCR-ABL to block apoptosis is dependent on its ability to activate ras [46]. The activation of BCR/ABL also represses apoptosis through induction of anti-apoptosis factors such as Bad, allowing transformed cells to divide [33].

Although the ability of BCR-ABL to inhibit apoptosis is an important component of its transforming activity, several studies suggest that BCR-ABL may also signal to affect cell proliferation [47].

In U.S. Patent No. 6066463, Schlessinger *et al.* describe compositions and methods for the prevention and treatment of cell proliferative disorders involving protein tyrosine kinase (PTK) or protein tyrosine phosphatase (PTP) capable of complexing with a member of the SH2- and/or SH3-containing family of adaptor proteins. This invention is based on the discovery that the adaptor protein, GRB-2, binds the intracellular BCR-ABL tyrosine kinase product *in vivo* and is necessary for the activation of the oncogenic potential of the BCR/ABL product. The invention further describes protein tyrosine kinase/adaptor protein complexes and the uses of these complexes for the identification of agents capable of decreasing or inhibiting the interaction between the members of such complexes [33].

The inventors indicate their priority in demonstrating the physiological relevance of the interactions between the members of a signal transduction pathway, in part by showing that disruption of this signal transduction can result in the reversal of the transformed phenotype of cells and inhibit tumor growth in animals. Disruption of the GRB-2 signal transduction for example, can reverse the transformed phenotype of cells and reduce tumor growth in animals [33].

Described are some of the uses to which the binding of such PTKs and adaptor proteins and/or PTPs and adaptor proteins can be put for the treatment of cell proliferative disorders involving such complexes. The uses focus on, but are not limited to, the identification of agents capable of disrupting such complexes (i.e., decreasing or inhibiting the interaction between the component PTK or PTP, and adaptor members of the complexes), and the utilization of such compounds for the treatment of cell proliferative disorders involving a PTK or a PTP capable of complexing with a member of the SH₂- and/or SH₃- containing family of adaptor proteins [33].

U.S. Patent No. 6066463 is assigned to New York University (New York, NY), Duke University (Durham, NC), and Sugen, Inc. (South San Francisco, CA). The patent

has a downstream focus on the oncogenic potential of the BCR/ABL product. Downstream claims include compounds to be tested for the ability to modulate a cell proliferative disorder involving a protein tyrosine kinase polypeptide/GRB-2 adaptor polypeptide complex. Specifically, the compound disrupts a BCR/ABL polypeptide/GRB-2 adaptor polypeptide complex or modulates a cell proliferative disorder involving a BCR/ABL polypeptide/GRB-2 adaptor polypeptide complex. Cell proliferative disorders include chronic myelogenous leukemia, acute lymphocytic leukemia, and acute myelogenous leukemia [33].

GPCR (G-PROTEIN-COUPLED-RECEPTOR)

G-protein-coupled receptors (GPCRs) constitute a major class of proteins responsible for transducing a signal within a cell and are a major target for drug action and development. Upon binding of a ligand to an extracellular portion of a GPCR, a signal is transduced within the cell that results in a change in a biological or physiological property of the cell.

Following activation by an external signal, the GPCR physically engages an inactive heterotrimeric G protein complex, composed of α , β , and γ subunits. It catalyzes the dissociation of GDP from the α subunit, which allows binding of GTP-which is at relatively high concentrations in the cell-and the rapid dissociation of the activated G α subunit from the β and γ subunits. Both the GTP-bound subunit and the $\beta\gamma$ complex are then free to act as cell signaling effectors [48].

The GPCR protein superfamily can be divided into five families: Family I, receptors typified by rhodopsin and the beta.2-adrenergic receptor and currently represented by over 200 unique members [49]; Family II, the parathyroid hormone/calcitonin/secretin receptor family [50, 51]; Family III, the metabotropic glutamate receptor family [52]; Family IV, the cAMP receptor family, important in the chemotaxis and development of *D. discoideum* [53]; and Family V, the fungal mating pheromone receptors such as STE2 [54].

In U.S. Patent No. 7057028, Glucksmann *et al.* describe a newly identified receptor belonging to the superfamily of G-protein-coupled receptors. The invention provides for polynucleotides encoding the receptor and methods for using the receptor polypeptides and polynucleotides as a target for diagnosis and treatment in receptor-mediated disorders, specifically, cardiovascular diseases, including congestive heart failure. The inventors also describe drug-screening methods using the receptor polypeptides and polynucleotides to identify agonists and antagonists for diagnosis and treatment. The patent provides for modulation of receptor polypeptide activity, especially using screened compounds to treat conditions related to expression of the receptor polypeptides [55].

U.S. Patent No. 7057028 is assigned to Millennium Pharmaceuticals, Inc. (Cambridge, MA). The patent is one of many upstream patents filed on the GPCR family-clearly focusing on the upstream knowledge discovery of this protein, although several uses are discussed including: biological assays related to GPCRs; drug screening assays, in cell-based or cell-free systems; identification of compounds that modulate receptor activity; diagnosing active disease, or predisposition to disease, in a patient having a

variant receptor protein; monitoring the effectiveness of modulating compounds on the expression or activity of the receptor gene; testing an individual for a genotype that while not necessarily causing the disease, nevertheless affects the treatment process; use in pharmaceutical compositions; antibody preparation from the polypeptides for screening for gene expression in diseased tissues *in vitro* or *in vivo*, modulating gene expression, and treating disorders associated with the receptor polypeptides, especially cardiovascular diseases [55].

In U.S. Patent No. 7119190, Liaw *et al.* describe transmembrane receptors, more particularly a human G-protein-coupled receptor and mutated (non-endogenous) versions of the human GPCRs providing evidence of constitutive activity. Liaw *et al.* claim polynucleotides encoding a non-endogenous, constitutively activated version of a wild-type G protein. In some embodiments, the constitutively activated GPCRs can be used for the direct identification of candidate compounds as receptor agonists or inverse agonists having applicability as therapeutic agents. Agonists and agonists are ideal candidates as lead compounds in drug discovery programs for treating diseases related to this receptor [56].

Other upstream uses of these versions of GPCRs are also provided for in this patent. For example, *in vitro* and *in vivo* systems incorporating GPCRs can be utilized to further elucidate and understand the roles these receptors play in the human condition, as well as to understand the role of constitutive activation as it applies to the signaling cascade. In some embodiments, the modified, non-endogenous GPCRs can be used to understand the role of endogenous receptors in the human body before the endogenous ligand is identified. Such receptors can also be used to further elucidate known receptors and the pathways through which they transduce a signal [56].

U.S. Patent No. 7119190 is assigned to Arena Pharmaceuticals, Inc. (San Diego, CA). This patent describes both upstream structural knowledge of the G-protein coupled-receptor as well as downstream drug screening and development programs [56].

Kuliopulos *et al.* provide for G-protein-coupled-receptors and in particular agonists and antagonists of G protein receptors in U.S. Patent No. 6864229- a patent assigned to New England Medical Center Hospitals, Inc. (Boston, MA). In terms of upstream knowledge of the receptor, Kuliopulos claim chimeric polypeptides that have a first domain that are either extracellular or intracellular portions of a G-protein-coupled-receptor (GPCR), and at least a second domain, attached to the first domain. The second domain is a hydrophobic moiety which is either naturally or non-naturally occurring. Furthermore, the first domain does not comprise a native extracellular ligand of said GPCR [57].

Within a GPCR fusion peptide, the peptide fragment from a GPCR can correspond to all or a portion of a GPCR protein without containing native extracellular ligand. In one embodiment, a GPCR fusion peptide comprises at least one biologically active portion of a GPCR protein. In another embodiment, a GPCR fusion peptide comprises at least two biologically active portions of a GPCR protein. The non-GPCR polypeptide can be fused to the N-terminus and/or C-

terminus of the GPCR polypeptide. Such fusion peptides can be utilized in screening assays for compounds that modulate GPCR activity [57].

Downstream provisions include methods for identifying a potential therapeutic agent for use in treatment of a pathology, wherein the pathology is related to aberrant expression or aberrant physiological interactions of a GPCR. Kuliopulos *et al.* include methods of treating or preventing a pathology associated with a GPCR, wherein a polypeptide of the invention is administered to a subject in which such treatment or prevention is desired in an amount sufficient to treat or prevent the pathology. Preferably, the subject is a human. Pharmaceutical compositions may contain any of the polypeptides and/or nucleic acids of the invention and a pharmaceutically acceptable carrier. Accordingly, the invention includes methods for screening for a modulator of the receptor [57].

JAK/STAT (JANUS KINASE/SIGNAL TRANSDUCERS AND ACTIVATORS OF TRANSCRIPTION)

In mammals, the JAK/STAT pathway is the principal signaling mechanism for a wide array of cytokines and growth factors. JAK activation stimulates cell proliferation, differentiation, cell migration, and apoptosis [58]. These cellular events are critical to hematopoiesis, immune development, mammary gland development and lactation, adipogenesis, sexually dimorphic growth, and other processes. Mutations that reduce JAK/STAT pathway activity affect these processes [59,60]. Conversely, mutations that constitutively activate or fail to regulate JAK signaling properly cause inflammatory disease, erythrocytosis, gigantism, and an array of leukemias [58].

In mammals, the JAK family comprises four members: Jak1, Jak2, Jak3, and Tyk2. JAK activation occurs upon ligand-mediated receptor multimerization because two JAKs are brought into close proximity, allowing *trans*-phosphorylation. The activated JAKs subsequently phosphorylate additional targets, including both receptors and major substrates such as STATs. STATs are latent transcription factors that reside in the cytoplasm until activated. The seven mammalian STATs bear a conserved tyrosine residue near the C-terminus that is phosphorylated by JAKs. This phosphotyrosine permits the dimerization of STATs through interaction with a conserved SH₂ domain. Phosphorylated STATs can then enter the nucleus. Once in the nucleus, dimerized STATs bind specific regulatory sequences to activate or repress transcription of target genes [61].

In U.S. Patent No. 6969760, Ihle *et al.* describe the JAK family of kinases and their role in the cellular response to the binding of cytokines to their respective receptors. The invention specifically refers to the cytokine-induced activation of at least one member of a JAK kinase family (Jak3), to the identification of interactions between specific cytokines and members of the JAK kinase family, and to compounds, compositions, and methods relating to the regulation of this interaction. Ihle *et al.* describe the complete DNA and amino acid sequence for particular JAK kinases. Cytokines are also described whose activity is mediated by at least one JAK kinase. JAK kinases mediate cytokine activity through their tyrosine phosphorylation (i.e. activation) in response to

cytokine-receptor binding. Thus, cytokines may be identified on the basis of their ability to cause the tyrosine phosphorylation (i.e. activation) of one or more members of the JAK kinase family [58].

Ihle *et al.* describe cytokines whose activity is mediated by a member of the JAK kinase family, which includes, but is not limited to, Jak1, Jak2, Jak3 and Tyk2. Cytokines include those which function by binding to members of the cytokine receptor superfamily, and also those which function by binding to members of the tyrosine kinase receptor superfamily. More specifically, these cytokines include, but are not limited to, at least one selected from the group consisting of: interleukin-3 (IL-3), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 6 (IL-6), interleukin 7 (IL-7), interleukin 9 (IL-9), interleukin 11 (IL-11), oncostatin M (OSM), leukemia inhibitory factor (LIF), granulocyte-macrophage specific colony stimulating factor (GM-CSF), erythropoietin (EPO), granulocyte colony stimulating factor (G-CSF), interferon-gamma (IFN-gamma), prolactin hormone, and growth hormone [58].

Ihle *et al.* also provide for methods for regulating JAK kinase activity that may be applied to treating disease conditions caused by an abnormal cellular response to a cytokine whose activity is mediated by the activation of a JAK kinase. In particular, disease conditions caused by excessive proliferation of eukaryotic cells may be treated by inhibiting JAK kinase activity where this excessive proliferation occurs in response to a cytokine whose activity is mediated by the activation of a JAK kinase [58].

U.S. Patent No. 6969760 is assigned to St. Jude Children's Research Hospital and claims the DNA and amino acid sequence for Jak3 kinases, the regulation of cytokines whose activity is mediated by the activation of a JAK kinase, and the identification of compositions capable of inhibiting the biological response of a eukaryotic cell to a cytokine whose activity is mediated by the activation of a JAK kinase. In this case, we have a broad upstream-based patent held by public organization. Downstream possibilities include the treatment of disease conditions caused by excessive proliferation of eukaryotic cells [58].

Uckun *et al.* describe inhibitors of Jak3 kinase for the treatment of allergy in U.S. Patent No. 6933300. In this downstream patent assigned to Parker Hughes Institute (Roseville, MN), Uckun *et al.* claim a method for inhibiting Jak3 tyrosine kinase activity comprising contacting Jak3 tyrosine kinase with the compounds described in the invention. Furthermore, the invention provides for a method for treating asthma comprising administering to a patient a therapeutically effective amount of the compounds [62].

Treatment with Jak3 inhibitor reduces and/or prevents allergic reactions and anaphylaxis. Jak3 inhibition results in reduced or inhibited degranulation and proinflammatory mediator release. Thus, targeting Jak3 with a specific inhibitor provides a new and effective treatment and prevention for mast-cell mediated allergic reactions [62].

Jak3 is found to be abundantly expressed in mast cells. Allergic disorders associated with mast cell activation include: Type I immediate hypersensitivity reactions such as allergic rhinitis (hay fever), allergic urticaria (hives), angioe-

dema, allergic asthma, and anaphylaxis, i.e., anaphylactic shock [62]. The invention provides a method comprising inhibiting mast cell activation or degranulation by contacting the mast cell (*in vitro or in vivo*) with an effective amount of a Jak3 inhibitor.

Uckun *et al.* also provide for the use of a substance that inhibits Jak3 for the manufacture of a medicament for the treatment of a condition that is associated with mast cell activation or degranulation [62].

MAP KINASE (MAPK)

The mitogen-activated protein kinase (MAP kinase) pathways consist of four major groupings and numerous related proteins which constitute interrelated signal transduction cascades activated by stimuli such as growth factors, stress, cytokines, and inflammation. The four major groupings are the ERK, JNK or SAPK, p38 and the Big MAPK or ERK5 cascades [63].

MAPK activity is regulated through three-tiered cascades composed of a MAPK, MAPK kinase (MAPKK, MKK or MEK), and a MAPKK kinase or MEK kinase (MAPKKK or MEKK) [63]. MAPKs are evolutionary conserved enzymes connecting cell-surface receptors to critical regulatory targets within cells [63]. For example, signals from cell surface receptors such as GPCRs and growth factor receptors are transduced, directly or via small G proteins such as ras and rac, to tiers of protein kinases that amplify these signals and/or regulate each other. The endpoints of these cascades include the MAPK activated protein kinases (MAPKAPK) and some of the numerous transcription factors that regulate genes involved in apoptosis, inflammation, cell growth, and differentiation [8, 63].

In U.S. Patent No. 6900043, Belmont *et al.* novel describe JNK activating phosphatase polypeptides and nucleic acid molecules encoding the same including vectors, host cells, antibodies, and methods for producing JNK activating phosphatase polypeptides. The invention also provides for methods for the diagnosis and treatment of diseases associated with JNK activating phosphatase polypeptides.

Belmont *et al.* specifically describe novel JNK activating phosphatase nucleic acid molecules and encoded polypeptides including derivatives of the JNK activating phosphatase polypeptides of the invention, fusion polypeptides comprising the JNK activating phosphatase polypeptides of the invention, and antibodies specifically binding to the JNK activating phosphatase polypeptides included in the disclosure. Compositions may include therapeutically effective amounts of the nucleotides or polypeptides of the invention, and methods of using the polypeptides and nucleic acid molecules [64].

The inventors further outline methods for activating or modulating the response of JNK to cytokines and other stimuli including a polypeptide (a phosphatase) involved in the JNK signal transduction pathway. The modulation of JNK activity includes inhibitory or stimulatory effects. In some cases, augmentation of JNK activity is desirable, e.g., induction of apoptosis. Agents used to modulate JNK activity, include polynucleotides, polypeptides, and other

molecules such as antisense oligonucleotides and ribozymes. Included in the disclosure are also methods for determining whether molecules are agonists or antagonists of a JNK activating phosphatase polypeptide [64].

With respect to the diagnosis and treatment of diseases, JNK activating phosphatase polypeptides and nucleic acid molecules can be used screen for therapeutic agents to treat, prevent, and/or detect conditions relating to JNK-mediated disorders.

Belmont *et al.* describe means for treating a JNK-mediated disorders by administering to a subject in need thereof an effective dose of a therapeutic agent that modulates (inhibits or enhances, as required) the activity of JNK. Agents that stimulate a JNK signal transduction pathway can be used in a number of ways, including inducing programmed cell death (apoptosis) in tissues. For example, the elimination of UV damaged cells can be used to prevent cancer [64].

U.S. Patent No. 6900043 assigned to Amgen Inc. (Thousand Oaks, CA) is a broad patent that covers both upstream knowledge discovery and downstream application development of this signal transduction pathway, namely the upstream identification novel polypeptides and nucleic acid molecules encoding the same which have downstream diagnostic or therapeutic benefit. Upstream claims include: isolated nucleic acids, a process for producing polypeptides encoded by the nucleic acids, and methods for producing the JNK-activating phosphatase comprising the amino acid sequence. Downstream uses described in this patent include: regulating JNK activation and modulating JNK-mediated signal transduction, screening therapeutic agents as being agonists or antagonists, and treating disease (the list provided of such diseases is comprehensive) [64].

Interest in phosphatases has stemmed from the concept that phosphatases serve to "turn off" what kinases "turn on". The requirement for JNK activating phosphatase in stimulus-induced JNK activation is a novel observation among MAP kinase phosphatases. This, along with the other unusual characteristics of JNK activating phosphatase, supports a more complex role of phosphatases in MAP kinase signaling than as a simple "off switch" [65].

Cheng *et al.* describe compounds that are p-38 MAP kinase inhibitors, including pharmaceutical compositions containing them, methods for their use, and methods for preparing these compounds in U.S. Patent No. 6630485. [66].

TNF and IL-1 have been shown to be central players in the pathological processes underlying many chronic inflammatory and autoimmune diseases. Studies have demonstrated that p38 MAP kinase plays an important role in the translational control of TNF and IL-1 and that p38 MAP kinase is also involved in the biochemical signaling of these molecules [67]. Compounds that bind to p38 MAP are effective in inhibiting bone resorption, inflammation, and other immune and inflammation-based pathologies. The characterization of the p38 MAP kinase and its central role in the biosynthesis of TNF and IL-1 have made this kinase an attractive target for the treatment of diseases mediated by these cytokines [67].

Cheng *et al.* describe that the compounds provided for in this patent are p38 MAP kinase and JNK inhibitors and compositions containing them are useful in the treatment of diseases such as: rheumatoid arthritis, osteoarthritis, spondylitis, bone resorption diseases, sepsis, septic shock, toxic shock syndrome, endotoxic shock, tuberculosis, atherosclerosis, diabetes, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, fever, periodontal diseases, ulcerative colitis, pyresis, Alzheimer's and Parkinson's diseases [66].

In U.S. Patent No. 6630485, assigned to Syntex LLC. the inventors clearly claim downstream applications of the MAP kinase signaling pathway. The inventors demonstrate the ability of the compounds claimed to inhibit p38 MAP kinase via *in vitro* assays. The ability of the compounds to inhibit the release of TNF- α . is also demonstrated by *in vitro* and the *in vivo* assays [66].

NF- B (NUCLEAR FACTOR KAPPA B)

The Nuclear Factor - B (NF- B) cell signaling pathway is a key biological component described in more than 5,000 scholarly papers and a convergent pathway for a number of stimuli that impact cells. There is a great deal of interest in this signal transduction pathway in the biopharmaceutical industry. Given the central effector role that this pathway occupies for a number of cell-surface receptors, it is an important drug target as well as proxy for other effector molecules located on the pathway. The Nuclear Factor - B is a nuclear transcription factor that regulates the expression of a large number of genes that are critical for the regulation of cell death, viral replication, tumorigenesis, inflammation, and various autoimmune diseases [68]. Companies are researching how to prevent the activation of NF- B and the subsequent expression of select disease-associated genes responsible for the onset and progression of cancer, autoimmune, inflammatory, neurological, and cardiovascular diseases [68]. Various small molecule inhibitors are being sought to modulate or inhibit targets within this signal transduction pathway.

The primary regulation of the NF- B pathway is through the association of NF- B complexes with I B inhibitor proteins. [69] As with NF- B complexes, there are multiple human I B proteins. Activation of the NF- B pathway proceeds via phosphorylation of I B at two N-terminal serines (Ser-32 and Ser-36) by the I B kinase (IKK). This promotes ubiquitination of I κ B by the SCF- TrCP complex and its degradation by the proteasome [69]. After degradation of I B, the liberated NF- B complex is free to bind to appropriate target genes. However, the activity of NF- B transcription complexes can also be modulated by a variety of post-translational modifications and interactions with other proteins, such as other transcription factors or coactivators [70]. Studies indicate that given the diversity of inducers of NF- B, many different signal transduction pathways originating from a wide variety of inducing mechanisms converge on a single target, i.e., the NF- B/I B complex [70].

In U.S. Patent No. 6410516, Baltimore *et al.* describe human lymphoid-cell nuclear factors which bind to gene elements associated with regulation of the transcription of Ig

genes and to methods for identification and for isolation of such factors. The factors are involved in the regulation of transcription of Ig genes. Four different factors which bind to transcriptional regulatory DNA elements of Ig genes were identified and isolated in nuclear extracts of lymphoid cells. Two of the factors, IgNF-A and E, are constitutive; two IgNF-B and κ -3 (otherwise known in the patent as NF- κ .B) are lymphoid cell specific [71].

This invention specifically describes the transcriptional regulatory factors, the genes encoding the four factors associated with transcriptional regulation, reagents (e.g., oligonucleotide probes, antibodies) which include or are reactive with the genes or the encoded factors and uses for the genes, factors, and reagents. It further relates to NF- B inhibitors, including isolated I κ B, the gene encoding I κ B and agents or drugs which enhance or block the activity of NF- B or of the NF- B inhibitor (e.g., I κ B) [71].

Baltimore *et al.* further describe methods of regulating (inducing or preventing) activation of NF- B and other genes whose expression is controlled by NF- B (e.g., HIV). The invention also provides for methods of regulating NF- B-mediated gene expression in the cells and systems in which it occurs [44]. The methods and compositions described are designed to make use of the role of NF- B as a mediator in the expression of genes in a variety of cell types. The expression of a gene having a NF- B 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- B. NF- B-mediated gene expression can also be selectively regulated by altering the binding domain of NF- B in such a manner that binding specificity and/or affinity are modified. Cellular interactions between NF- B and a gene or genes whose expression is mediated by NF- B activity and which have, for example, medical implications (e.g., NF- B/ cytokine interactions) can be altered or modified [71].

In addition, 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- B 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- κ B is present [71].

U.S. Patent No. 6410516 is assigned to Harvard College (Cambridge, MA), the Massachusetts Institute of Technology (Cambridge, MA), and the Whitehead Institute for Biomedical Research (Cambridge, MA). The patent claims cover methods of treating human disease by regulating NF- B activity, methods of treating disease by inhibiting NF- B, and methods useful for treating various disease conditions through modulation of NF- B activity. The associated patent on the upstream system itself was awarded in 2002, with claims that may cover almost every downstream application of this fundamental signaling pathway. Licensed to Ariad Pharmaceuticals in 2002, Ariad sued Eli Lilly, arguing that Lilly's Evista and Xigris products for osteoporosis and sepsis, approved in 1997 and 2001 respectively, infringe upon their patent since the drugs work via the NF- B pathway [72]. A federal jury ruled on May 4th 2006 that Eli Lilly & Company had infringed the NF- B

patent covering drugs that work on this basic biological pathway, and ordered Lilly to pay \$65.2 million in back royalties to Ariad Pharmaceuticals [72]. A separate trial, or bench trial, however, commenced before the judge on August 7th 2006 on certain defenses asserted by Lilly relating to the validity and enforceability of the claims of the patent [73]. These assertions must be addressed before the Court enters a final judgment in this lawsuit. Industry experts however claim that the lawsuit is problematic since Ariad did not conduct research on the pathway itself and this is a case of a very broad upstream patent being asserted against companies that actually developed the downstream technology and products without the benefit of an upstream patent.

In U.S. Patent No. 6660268, assigned to The President and Fellows of Harvard College (Cambridge, PA), Palombella *et al.* also claim methods for regulating the activity of NF- B through the use of certain proteasome inhibitors. Since NF- B has been shown to be required for a number of genes involved in the inflammatory response, such as the TNF- α and cytokine genes such as IL-2, IL-6, G-CSF, and IFN- β , Palombella specifically claim methods for treating inflammatory conditions caused by NF- B activity, through the use of a selective inhibitor of proteasome function or ubiquitin conjugation in an amount sufficient to reduce NF- B activity. [74] The inflammatory conditions described are characterized by elevated IL-6 or TNF- α levels. Therefore, treatment involves the use of a selective inhibitor of proteasome function or ubiquitin conjugation at a level sufficient to reduce NF- B activity, whereby IL-6 or TNF- α levels are reduced. In this downstream patent, the inventors provide specific structures for the proteasome function or ubiquitin conjugation inhibitor [74].

PHOSPHOLIPASE C

Phospholipase C (PLC) belongs to a family of enzymes, also known as disulfide isomerases, which play an important role in mediating signal transduction pathways [75]. Many extracellular signaling molecules including hormones, growth factors, neurotransmitters, and immunoglobulin bind to their respective cell surface receptors and activate PLCs. [76] Its main function is to hydrolyze phosphatidylinositol-diphosphate into diacylglycerol (DG) and inositoltriphosphate (IP3). DG is necessary for further activation of Protein Kinase C (PKC) while IP3 leads to the release of intracellular calcium. PKC activation is known to be involved in diverse array of cellular responses in endocrine, exocrine, nervous, muscular, inflammatory, and immune systems [77, 78].

In U.S. Patent No. 6897056, Meyers *et al.* describe discovery of a novel human phospholipase, referred to as "32544". The nucleotide sequence of a cDNA encoding 32544 and the amino acid sequence of a 32544 polypeptide are provided in this patent. Isolated 32544 proteins, fusion proteins, antigenic peptides, and anti-32544 antibodies as well as diagnostic methods utilizing compositions of the invention are provided. The invention further includes a process for modulating 32544 polypeptide or nucleic acid expression or activity, e.g. using screened compounds [75].

With respect to downstream claims, specifically included are polypeptides and biologically active or antigenic fragments that are useful as reagents or targets in assays applicable to treatment and diagnosis of 32544-mediated or related disorders. Methods involve treatment of conditions related to aberrant activity or expression of the 32544 polypeptides or nucleic acids, such as conditions involving aberrant or deficient cellular proliferation or differentiation [75].

U.S. Patent No. 6897056 is a broad upstream patent assigned to Millennium Pharmaceuticals, Inc. (Cambridge, MA). The patent however also describes many downstream uses for the invention. Meyers *et al.* stipulate that the nucleic acid molecules, proteins, protein homologues, and antibodies described in the invention can be used in one or more of the following methods: a) screening assays; b) predictive medicine (e.g., diagnostic assays, prognostic assays, monitoring clinical trials, and pharmacogenetics); and c) methods of treatment (e.g., therapeutic and prophylactic) [75].

Screening assays include methods which bind to 32544 proteins, have a stimulatory or inhibitory effect on, for example, 32544 expression or 32544 activity, or have a stimulatory or inhibitory effect on, for example, the expression or activity of a 32544 substrate. Compounds thus identified can be used to modulate the activity of target gene products (e.g., 32544 genes) in a therapeutic protocol, to elaborate the biological function of the target gene product, or to disrupt normal target gene interactions. Sequences can be used to: (i) map their respective genes on a chromosome e.g., to locate gene regions associated with genetic disease or to associate 32544 with a disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. Diagnostic assays, prognostic assays, and clinical trials can be used for prognostic (predictive) purposes to treat an individual. Generally, the invention provides a method of determining if a subject is at risk for a disorder related to a lesion in or the misexpression of a gene which encodes 32544 [75].

Ducker *et al.* claim Phospholipase C delta 5 (PLCD5) polypeptides and polynucleotides as well as methods for producing such polypeptides by recombinant techniques in U.S. Patent No. 6958152. The inventors also provide for methods for utilizing phospholipase C delta 5 (PLCD5) polypeptides and polynucleotides in diagnostic assays. Furthermore, phospholipase C delta 5 (PLCD5) polypeptides and polynucleotides may be useful in identifying compounds that may be agonists or antagonists for therapeutic purposes. Diseases to be treated including but are not limited to: deep vein thrombosis, instable angina pectoris, PTCA (percutaneous transluminal coronary angiography), thrombo embolic insult, disseminated intravascular coagulation, arteriosclerosis, epilepsy, depression, neurodegenerative diseases, stroke, seizure, rheumatoid arthritis and immune disorders [79].

The inventors of U.S. Patent No. 6958152-a patent assigned to Merck Patent GmbH (Darmstadt, DE), claim both upstream knowledge in the form of DNA, RNA and peptide sequences, as well as downstream uses including chromosome localization studies, tissue expression studies, identification of compounds, screening methods, antibody

production, vaccine use, diagnostic assays, and other therapeutics uses [79].

CURRENT & FUTURE DEVELOPMENTS

It is expected that in-depth knowledge of the dynamic informational processes of a cell will drastically change medicine. The development of system models will revolutionize the drug discovery process. These models will enable for multiple drug target identification and the high-throughput virtual screening of compounds. It will become possible to identify feedback mechanisms that offset the effects of drugs and predict systemic side effects. Multiple drug systems will be used to guide the state of a cell from a diseased to healthy state with minimal side effects. By being able to identify a series of effector points for drugs it may be possible to more effectively control the status of a cell.

Patient models and disease models will be precisely based on the cellular model, rather than on a simple empirical model. Drug design and treatment procedures will reflect the precise systems dynamics of each patient, enabling for the assessment and simulation of disease risk and drug response. Pre-emptive medicine is likely to be one of the major applications of systems biology research [1,2,5].

On a more complex level, the ability to develop organs using sophisticated monitoring and control mechanisms may become a reality. Using special incubation systems, organ growth can be monitored and the biochemical status of the incubation systems used to guide the growth of the organ [1].

Building system, cell, organ or even patient models will require the integration of biological information, simulations, as well as the biological and clinical testing of models. Multiple hierarchies of models, including gene regulation networks, biochemical networks, tissue networks, models of organs and patient system profiles, will be integrated for the purpose of drug discovery.

From the perspective of intellectual property, patents can exist at level in this biological hierarchy. Depending on the breadth of patents filed at a particular level, these patents can dominate over other hierarchical levels of biological information [4]. Dominance of patents filed earlier in time, at the lowest levels of the biological information hierarchy, can hinder the incentive to progress into the higher levels of the hierarchy where appropriation may not be possible. Furthermore, if multiple researchers own patents over the structures or subsystems comprising a system, the system may become so fragmented that other researchers may no longer be able to exploit the system in its entirety. The transaction costs associated with recombining the elements that comprise the system, for downstream exploitation, may be too high for a downstream developer. [29, 80] From our analysis, of concern are patents filed on the GPCR signaling pathway. US Patent No. 6,410,516 filed on the NF- κ B signaling pathway provides ample evidence that even one patent can be detrimental to downstream product development. Given the number of upstream patents filed on the GPCR signaling pathway, it will be important to monitor downstream development issues related to the GPCR pathway.

Appendix 1.

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|---|
| 7,122,527 | Use of antisense oligonucleotides to inhibit the expression of human Akt-1 | USE | PRIVATE | Rexahn Corporation (Potomac, MD) |
| 7,098,208 | Inhibitors of Akt activity | INH | PRIVATE | Merck & Co., Inc. (Rahway, NJ) |
| 7,071,316 | Human Akt-3 | STRUCTURAL | PRIVATE | Janssen Pharmaceutica N.V. (Beerse, BE) |
| 7,034,026 | Inhibitors of Akt activity | INH | PRIVATE | Merck & Co., Inc. (Rahway, NJ) |
| 6,960,584 | Inhibitors of Akt activity | INH | PRIVATE | Merck & Co., Inc. (Rahway, NJ); Merck Sharp & Dohme Limited (Hertfordshire, GB) |
| 6,958,334 | Inhibitors of Akt activity | INH | PRIVATE | Merck & Co., Inc. (Rahway, NJ) |
| 6,881,555 | AKT nucleic acids, polypeptides, and uses thereof | USE | PRIVATE | Aventis Pharmaceuticals Inc. (Bridgewater, NJ) |
| 6,187,586 | Antisense modulation of AKT-3 expression | MOD | PRIVATE | Isis Pharmaceuticals, Inc. (Carlsbad, CA) |
| 6,043,090 | Antisense inhibition of human Akt-2 expression | INH | PRIVATE | Isis Pharmaceuticals Inc. (Carlsbad, CA) |
| 5,958,773 | Antisense modulation of AKT-1 expression | MOD | PRIVATE | Isis Pharmaceuticals Inc. (Carlsbad, CA) |

Appendix 2.

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|---|
| 6,537,804 | BCR-ABL directed compositions and uses for inhibiting Philadelphia chromosome stimulated cell growth | INH | PUBLIC | Board of Regents, The University of Texas Systems (Austin, TX) |
| 6,107,457 | Bcr-Abl directed compositions and uses for inhibiting Philadelphia chromosome stimulated cell growth | INH | PUBLIC | Board of Regents, The University of Texas System (Austin, TX) |
| 6,066,463 | Method and compositions for treatment of BCR-ABL associated leukemias and other cell proliferative disorders | USE | PUBLIC/PRIVATE | New York University (New York, NY); Duke University (Durham, NC); Sugen, Inc. (South San Francisco, CA) |
| 5,652,222 | Selective inhibition of leukemic cell proliferation by BCR-ABL antisense oligonucleotides | USE | PUBLIC | Temple University-of The Commonwealth System of Higher Education (Philadelphia, PA) |
| 5,369,008 | Methods for the detection of BCR-ABL and abnormal ABL proteins in leukemia patients | METHOD | PUBLIC | Board of Regents, The University of Texas System (Austin, TX) |

Appendix 3.

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|---|
| 7,122,570 | Tetrahydrocarbazol derivatives as ligands for G-protein-coupled receptors (GPCR) | USE | PRIVATE | Zentaris AG (Frankfurt, DE) |
| 7,119,190 | Endogenous and non-endogenous versions of human G protein-coupled receptors | STRUCTURAL | PRIVATE | Arena Pharmaceuticals, Inc. (San Diego, CA) |

(Appendix 3) Contd....

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|---|
| 7,115,724 | Murine genomic polynucleotide sequence encoding a G-protein coupled receptor and methods of use therefor | USE | PRIVATE | Wyeth (Madison, NJ) |
| 7,115,377 | Cell-based assays for G-protein-coupled receptor-mediated activities | METHOD | PRIVATE | Atto Bioscience, Inc. (Rockville, MD) |
| 7,108,991 | Human orphan G protein-coupled receptors | STRUCTURAL | PRIVATE | Arena Pharmaceuticals, Inc. (San Diego, CA) |
| 7,105,488 | G protein-coupled receptor antagonists | INH | PUBLIC | The United States of America as represented by the Department of Health and Human Services (Washington, DC) |
| 7,097,969 | Non-endogenous, constitutively activated known G protein-coupled receptors | MOD | PRIVATE | Arena Pharmaceuticals, Inc. (San Diego, CA) |
| 7,094,593 | Method for improving the function of heterologous G protein-coupled receptors | METHOD | PUBLIC/PRIVATE | BASF Aktiengesellschaft (DE)/The United States of America as represented by the Department of Health (Washington, DC) |
| 7,094,572 | Polynucleotide encoding a novel human G-protein coupled receptor variant of HM74, HGPRBMY74 | STRUCTURAL | PRIVATE | Bristol-Myers Squibb (Princeton, NJ) |
| 7,087,735 | Bivalent binding molecules of 7 transmembrane G protein-coupled receptors | STRUCTURAL | PRIVATE | Gilead Sciences, Inc. (Foster City, CA) |
| 7,084,259 | G-protein coupled receptors | STRUCTURAL | PRIVATE | Amgen Inc. (Thousand Oaks, CA) |
| 7,081,360 | Expression of G protein-coupled receptors with altered ligand binding and/or coupling properties | USE | PRIVATE | Cadus Technologies, Inc. (New York, NY) |
| 7,063,966 | Chimeric G protein coupled receptors | STRUCTURAL | PRIVATE | SRI International (Menlo Park, CA) |
| 7,057,028 | 14273 Receptor, a novel G-protein coupled receptor | STRUCTURAL | PRIVATE | Millennium Pharmaceuticals, Inc. (Cambridge, MA) |
| 7,049,096 | Polynucleotides encoding a novel human G-protein coupled receptor splice variant HGPRBMY29sv1 | STRUCTURAL | PRIVATE | Bristol-Meyers Squibb Company (Princeton, NJ) |
| 7,037,891 | Methods of modulating G-protein-coupled receptor kinase-associated signal transduction | MOD | PUBLIC/PRIVATE | Children's Medical Center Corporation (Boston, MA)/Yissum Research and Development (Jerusalem, IL) |
| 7,033,773 | Screening assays for G protein coupled receptor agonists and antagonists | METHOD | PUBLIC | The General Hospital Corporation (Boston, MA) |
| 7,018,812 | Modified G-protein coupled receptors | STRUCTURAL | PUBLIC | Duke University (Durham, NC) |
| 6,998,255 | Human G-protein coupled receptor | STRUCTURAL | PRIVATE | Solvay Pharmaceuticals B.V. (CP Weesp, NL) |
| H2,136 | Nucleic acids encoding G protein-coupled receptors | STRUCTURAL | PRIVATE | Affymetrix, Inc. (Santa Clara, CA) |
| 6,902,902 | Human G protein-coupled receptors and modulators thereof for the treatment of metabolic-related disorders | USE | PRIVATE | Arena Pharmaceuticals, Inc. (San Diego, CA) |
| 6,893,827 | Receptor function assay for G-protein coupled receptors and orphan receptors by reporter enzyme mutant complementation | ASSAY | PRIVATE | Applera Corporation (Bedford, MA) |

(Appendix 3) Contd....

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|---|-----------------------|-------------------------|---|
| 6,890,731 | Isolated human G-protein coupled receptors that are members of the aminergic subfamily, nucleic acid molecules encoding human GPCR proteins, and uses thereof | STRUCTURAL | PRIVATE | Applera Corporation (Bedford, MA) |
| 6,887,683 | Human G-protein coupled receptors | STRUCTURAL | PRIVATE | Human Genome Sciences, Inc. (Rockville, MD) |
| 6,864,229 | G protein coupled receptor (GPCR) agonists and antagonists and methods of activating and inhibiting GPCR using the same | INH | PUBLIC | New England Medical Center Hospitals, Inc. (Boston, MA) |
| 6,855,807 | Heterodimeric opioid G-protein coupled receptors | STRUCTURAL | PUBLIC | New York University (New York, NY) |
| 6,855,550 | Expression of G protein coupled receptors in yeast | USE | PUBLIC | Duke University (Durham, NC) |
| 6,838,275 | Human G-coupled protein receptor kinases and polynucleotides encoding the same | STRUCTURAL | PRIVATE | Lexicon Genetics Incorporated (The Woodlands, TX) |
| 6,838,258 | G protein-coupled receptor up-regulated in prostate cancer and uses thereof | USE | PRIVATE | Agensys, Inc. (Santa Monica, CA) |
| 6,835,546 | Drosophila G protein coupled receptors, nucleic acids, and methods related to the same | STRUCTURAL | PRIVATE | Pharmacia & Upjohn Company (Kalamazoo, MI) |
| 6,824,990 | Methods of detecting and modulating oligomerization of G protein-coupled receptors | METHOD | PUBLIC | Washington University (St. Louis, MO) |
| 6,821,950 | Cyclic agonists and antagonists of C5a receptors and G protein-coupled receptors | MOD | PUBLIC | The University of Queensland (Brisbane, AU) |
| 6,806,061 | G protein-coupled receptor gene and methods of use therefor | USE | PUBLIC/PRIVATE | Children's Medical Center Corporation (Boston, MA); Millennium Pharmaceuticals, Inc. (Cambridge, MA); Brigham and Women's Hospital (Boston, MA) |
| 6,806,054 | Non-endogenous, constitutively activated known G protein-coupled receptors | STRUCTURAL | PRIVATE | Arena Pharmaceuticals, Inc. (San Diego, CA) |
| 6,800,749 | G-protein coupled receptor | STRUCTURAL | PRIVATE | AstraZeneca Canada Inc. (Mississauga, CA) |
| 6,800,445 | Systems for sensitive detection of G-protein coupled receptor and orphan receptor function using reporter enzyme mutant complementation | METHOD | PRIVATE | Applera Corporation (Bedford, MA) |
| 6,790,631 | G protein-coupled receptor up-regulated in prostate cancer and uses thereof | USE | PRIVATE | Agensys, Inc. (Santa Monica, CA) |
| 6,733,990 | Nucleic acid encoding 15571, a GPCR-like molecule of the secretin-like family | STRUCTURAL | PRIVATE | Millennium Pharmaceuticals, Inc. (Cambridge, MA) |
| 6,709,830 | Methods for modulating the activation of a lymphocyte expressed G protein coupled receptor involved in cell proliferation, autoimmunity and inflammation | MOD | PUBLIC | The Regents of the University of California (Oakland, CA) |
| 6,699,965 | Peptides that activate the G-protein coupled receptor protein, OTT175 | ACTIVATOR | PRIVATE | Takeda Chemical Industries, Ltd. (Osaka, JP) |
| 6,696,257 | G protein-coupled receptors from the rat and human | STRUCTURAL | PUBLIC | National Research Council of Canada (Ottawa, CA) |

(Appendix 3) Contd....

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|---|
| 6,696,244 | G-coupled receptors associated with retroviral entry into cells, and therapeutic uses thereof | USE | PUBLIC | New York University (New York, NY) |
| 6,682,886 | Bivalent binding molecules of 7 transmembrane G protein-coupled receptors | STRUCTURAL | PRIVATE | Gilead Sciences, Inc. (Foster City, CA) |
| 6,653,086 | Endogenous constitutively activated G protein-coupled orphan receptors | STRUCTURAL | PRIVATE | Arena Pharmaceuticals, Inc. (San Diego, CA) |
| 6,638,733 | G-protein coupled receptors amplified in breast cancer | STRUCTURAL | PRIVATE | Tularik Inc. (South San Francisco, CA) |
| 6,635,741 | G-protein coupled receptor BCA-GPCR-3 | STRUCTURAL | PRIVATE | Tularik Inc. (South San Francisco, CA) |
| 6,632,621 | G protein-coupled receptor-like receptors and modulators thereof | MOD | PRIVATE | Pharmacia & Upjohn Company (Kalamazoo, MI) |
| 6,620,615 | G-protein coupled receptor-encoding nucleic acids | STRUCTURAL | PRIVATE | CuraGen Corporation (New Haven, CT) |
| 6,607,906 | Heterologous G protein coupled receptors expressed in yeast, their fusion with G proteins and use thereof in bioassay | USE | PRIVATE | BASF Aktiengesellschaft (Ludwigshafen, DE) |
| 6,602,699 | Promotor for functional characterization of G-protein coupled receptors in the yeast <i>saccharomyces cerevisiae</i> | STRUCTURAL | PRIVATE | Aventis Pharma Deutschland GmbH (Frankfurt, DE) |
| 6,586,205 | 43239 a novel GPCR-like molecule and uses thereof | USE | PRIVATE | Millennium Pharmaceuticals, Inc. (Cambridge, MA) |
| 6,569,995 | Identification of a G protein-coupled receptor transcriptionally regulated by protein tyrosine kinase signaling in hematopoietic cells | METHOD | PUBLIC | The Regents of the University of California (Oakland, CA) |
| 6,538,107 | G protein coupled receptor protein production, and use thereof | USE | PRIVATE | Takeda Chemical Industries, Ltd. (Osaka, JP) |
| 6,521,418 | G protein-coupled receptor with an enlarged extracellular domain | STRUCTURAL | PUBLIC | The Scripps Research Institute (La Jolla, CA) |
| 6,518,480 | Selective target cell activation by expression of a G protein-coupled receptor activated superiorly by synthetic ligand | ACTIVATOR | PUBLIC | The Regents of the University of California (Oakland, CA) |
| 6,518,414 | Molecular cloning and expression of G-protein coupled receptors | USE | INDIVIDUALS | |
| 6,514,696 | Transcriptionally regulated G protein-coupled receptor G2A | STRUCTURAL | PUBLIC | The Regents of The University of California (Oakland, CA) |
| 6,500,934 | Bivalent agonists for G-protein coupled receptors | STRUCTURAL | INDIVIDUALS | |
| 6,448,005 | 14723 Receptor, a novel G-protein coupled receptor | STRUCTURAL | PRIVATE | Millennium Pharmaceuticals, Inc. (Cambridge, MA) |
| 6,444,456 | Human G-coupled protein receptor kinases and polynucleotides encoding the same | STRUCTURAL | PRIVATE | Lexicon Genetics Incorporated (The Woodlands, TX) |
| 6,420,563 | Small molecule modulators of G protein-coupled receptor six | MOD | PRIVATE | Arena Pharmaceuticals, Inc. (San Diego, CA) |
| 6,406,871 | Method for detecting ligand binding to G protein coupled receptors | METHOD | PRIVATE | BASF Aktiengesellschaft (Ludwigshafen, DE) |

(Appendix 3) Contd....

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|---|-----------------------|-------------------------|--|
| 6,403,767 | Polypeptide molecules of the G protein-coupled heptahelical receptor superfamily and uses therefor | USE | PRIVATE | Millenium Pharmaceuticals, Inc. (Cambridge, MA); CRC Technology Limited (London, GB) |
| 6,403,305 | Methods of identifying peptide agonists or negative antagonists of a G protein coupled receptor | METHOD | PUBLIC | Cornell Research Foundation, Inc. (Ithaca, NY) |
| 6,395,877 | 14273 receptor, a novel G-protein coupled receptor | STRUCTURAL | PRIVATE | Millennium Pharmaceuticals, Inc. (Cambridge, MA) |
| 6,383,778 | Nucleic acids encoding a G-protein coupled receptor involved in sensory transduction | STRUCTURAL | PUBLIC | The Regents of the University of California (Oakland, CA) |
| 6,383,761 | Methods and compositions for identifying modulators of G-protein-coupled receptors | METHOD | PUBLIC | The Regents of the University of California (Oakland, CA); National Institutes of Health (Rockville, MD) |
| 6,383,760 | Transcriptionally regulated G protein-coupled receptor | STRUCTURAL | PUBLIC | The Regents of the University of California (Oakland, CA) |
| 6,368,848 | Compositions to identify plant proteins that function in G-protein coupled systems | USE | PRIVATE | BASF Aktiengesellschaft (DE) |
| 6,361,967 | Axor10, a G-protein coupled receptor | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA); SmithKline Beecham plc (Brentford, GB) |
| 6,344,342 | Human G protein coupled lysophosphatidic acid receptor | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 6,300,312 | Antagonists of G-protein-coupled receptor | STRUCTURAL | PUBLIC | Hôpital Sainte-Justine (Montreal, CA) |
| 6,291,177 | Assay for agents which alter G-protein coupled receptor activity | ASSAY | PRIVATE | Millennium Pharmaceuticals, Inc. (Cambridge, MA) |
| 6,287,801 | Nucleic acids encoding the G-protein coupled receptor HNFDS78 | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 6,280,934 | Assay for agents which alter G-protein coupled receptor activity | ASSAY | PRIVATE | Millennium Pharmaceuticals, Inc. (Cambridge, MA) |
| 6,258,527 | Methods of identifying G-coupled receptors associated with macrophage-trophic HIV, and diagnostic and therapeutic uses thereof | METHOD | PUBLIC | The Aaron Diamond Aids Research Center (New York, NY); New York University (New York, NY) |
| 6,255,069 | Compositions and methods for modulating the activity of G protein-coupled receptor kinases GPK5 and GRK6 | METHOD | PUBLIC | Thomas Jefferson University (Philadelphia, PA) |
| 6,255,059 | Methods for identifying G protein coupled receptor effectors | METHOD | PRIVATE | Cadus Pharmaceutical Corporation (Tarrytown, NY) |
| 6,251,582 | Alternative G-coupled receptors associated with retroviral entry into cells, methods of identifying the same, and diagnostic and therapeutic uses thereof | USE | PUBLIC | New York University (New York, NY) |
| 6,242,572 | Human G protein coupled lysophosphatidic acid receptor | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 6,232,123 | Monoclonal antibodies against leucocyte-specific G protein-coupled receptors | USE | INDIVIDUALS | |

(Appendix 3) Contd....

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|---|
| 6,218,376 | Uracil compounds as P2-purinoreceptor 7-transmembrane G-protein coupled receptor antagonists | USE | PRIVATE | AstraZeneca UK Limited (London, GB) |
| 6,214,562 | Transcriptionally regulated G protein-coupled receptor | STRUCTURAL | PUBLIC | The Regents of the University of California (Oakland, CA) |
| 6,207,412 | Identification of a G protein-coupled receptor transcriptionally regulated by protein tyrosine kinase signaling in hematopoietic cells | USE | PUBLIC | The Regents of the University of California (Oakland, CA) |
| 6,183,974 | Screening assays for G protein coupled receptor agonists and antagonists | ASSAY | PUBLIC | The General Hospital Corporation (Boston, MA) |
| 6,168,927 | Expression of G protein coupled receptors in yeast | USE | PUBLIC | Duke University (Durham, NC) |
| 6,114,139 | G-protein coupled receptor protein and a DNA encoding the receptor | STRUCTURAL | PRIVATE | Takeda Chemical Industries, Ltd. (Osaka, JP) |
| 6,111,076 | Human G-protein coupled receptor (HIBCD07) | STRUCTURAL | PRIVATE | Takeda Chemical Industries, Ltd. (Osaka, JP) |
| 6,096,868 | ECR 673: A 7-transmembrane G-protein coupled receptor | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 6,090,575 | Polynucleotides encoding human G-protein coupled receptor GPR1 | STRUCTURAL | PRIVATE | Human Genome Sciences, Inc. (Rockville, MD) |
| 6,087,115 | Methods of identifying negative antagonists for G protein coupled receptors | METHOD | PUBLIC | Cornell Research Foundation, Inc. (Ithaca, NY) |
| 6,071,722 | Nucleic acids encoding a G-protein coupled 7TM receptor (AXOR-1) | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 6,071,719 | DNA encoding ECR 673: A 7-transmembrane G-protein coupled receptor | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 6,063,596 | G-protein coupled receptors associated with immune response | STRUCTURAL | PRIVATE | Incyte Pharmaceuticals, Inc. (Palo Alto, CA) |
| 6,060,272 | Human G-protein coupled receptors | STRUCTURAL | PRIVATE | Human Genome Sciences, Inc. (Rockville, MD) |
| 6,048,711 | Human G-protein coupled receptor polynucleotides | STRUCTURAL | PRIVATE | Takeda Chemical Industries, Ltd. (Tsukuba Ibaraki, JP) |
| 6,020,158 | Isolated polynucleotide for novel G-protein coupled receptor | STRUCTURAL | PRIVATE | Allelix Biopharmaceuticals, Inc. (Ontario, CA) |
| 6,013,479 | Human Emr1-like G protein coupled receptor | STRUCTURAL | PRIVATE | Incyte Pharmaceuticals, Inc. (Palo Alto, CA) |
| 6,001,972 | Splicing variant of the epstein-barr virus-induced G-protein coupled receptor | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 5,998,164 | Polynucleotides encoding human G-protein coupled receptor GPRZ | STRUCTURAL | PRIVATE | Human Genome Sciences, Inc. (Rockville, MD) |
| 5,994,097 | Polynucleotide encoding human G-protein coupled receptor | STRUCTURAL | PRIVATE | Incyte Pharmaceuticals, Inc. (Palo Alto, CA) |
| 5,985,584 | Method to identify plant proteins that function in G protein coupled systems and compositions therefor | METHOD | PRIVATE | American Cyanamid Company (Madison, NY) |

(Appendix 3) Contd....

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|---|-----------------------|-------------------------|--|
| 5,955,575 | Antagonists of G-protein-coupled receptor | STRUCTURAL | PUBLIC | Hopital Sainte-Justine (Montreal, CA) |
| 5,955,309 | Polynucleotide encoding G-protein coupled receptor (H7TBA62) | STRUCTURAL | PRIVATE | Smithkline Beecham Corporation (Philadelphia, PA) |
| 5,945,307 | Isolated nucleic acid molecules encoding a G-protein coupled receptor showing homology to the 5HT family of receptors | STRUCTURAL | PRIVATE | Millennium Pharmaceuticals, Inc. (Cambridge, MA) |
| 5,942,414 | Polynucleotides encoding human G-protein coupled receptor HIBEF51 | STRUCTURAL | PRIVATE | Human Genome Sciences, Inc. (Rockville, MD) |
| 5,939,320 | G-coupled receptors associated with macrophage-trophic HIV, and diagnostic and therapeutic uses thereof | USE | PUBLIC | New York University (New York, NY); The Aaron Diamond Aids Research Center (New York, NY) |
| 5,932,702 | Human G-protein coupled receptor | STRUCTURAL | PRIVATE | Human Gene Sciences (Rockville, MD); Takeda (Osaka, JP) |
| 5,925,549 | Soluble 7-transmembrane domain G-protein-coupled receptor compositions and methods | METHOD | PUBLIC | The Board of Trustees of the Leland Stanford Junior University (Stanford, CA) |
| 5,912,335 | G-protein coupled receptor HUVCT36 | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 5,910,430 | Isolated nucleic acid encoding G-protein coupled receptor (HTADX50) | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 5,891,720 | Isolated DNA encoding a novel human G-protein coupled receptor | STRUCTURAL | PRIVATE | Millennium Pharmaceuticals, Inc. (Cambridge, MA) |
| 5,882,944 | Methods for G protein coupled receptor activity screening | METHOD | PUBLIC | The Regents of the University of California (Oakland, CA) |
| 5,874,252 | Splicing variant of the Epstein-Barr virus-induced G-protein coupled receptor | STRUCTURAL | PRIVATE | Smithkline Beecham Corporation (Philadelphia, PA) |
| 5,874,245 | Human G-protein coupled receptor (HIBCD07) | STRUCTURAL | PRIVATE | Takeda Chemical Industries, Ltd. (Osaka, JP) |
| 5,871,967 | Cloning of a novel G-Protein coupled 7TM receptor | USE | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 5,869,609 | G protein coupled glutamate receptors | STRUCTURAL | PUBLIC/PRIVATE | Zymogenetics, Inc. (Seattle, WA); The Board of Regents of the University of Washington (Seattle, WA) |
| 5,856,443 | Molecular cloning and expression of G-protein coupled receptors | USE | INDIVIDUALS | |
| 5,834,587 | G-protein coupled receptor, HLTEX 11 | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 5,783,402 | Method of identifying ligands and anatognists of G-protein coupled receptor | METHOD | PUBLIC | The United States of America as represented by the Secretary of the (Washington, DC) |
| 5,763,218 | Nucleic acid encoding novel human G-protein coupled receptor | STRUCTURAL | PRIVATE | Human Genome Science, Inc. (Rockville, MD); Takeda (Osaka, JP) |

(Appendix 3) Contd....

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|--|
| 5,747,267 | Method for identifying a G protein coupled glutamate receptor agonist and antagonist | METHOD | PUBLIC/PRIVATE | Zymogenetics, Inc. (Seattle, WA); The Board of Regents of the University of Washington (Seattle, WA) |
| 5,739,029 | Vectors for expression of G protein coupled receptors in yeast | STRUCTURAL | PUBLIC | Duke University (Durham, NC) |
| 5,721,107 | Antibodies to G protein coupled glutamate receptors | USE | PUBLIC/PRIVATE | The Board of Regents of the University of Washington (Seattle, WA); Zymogenetics, Inc. (Seattle, WA) |
| 5,691,188 | Transformed yeast cells expressing heterologous G-protein coupled receptor | USE | PRIVATE | American Cyanamid Company (Madison, NJ) |
| 5,591,618 | G protein-coupled receptor kinase GRK6 | STRUCTURAL | PRIVATE | ICOS Corporation (Bothell, WA) |
| 5,585,476 | Molecular cloning and expression of G-protein coupled receptors | USE | INDIVIDUALS | |
| 5,576,210 | Mammalian/yeast hybrid G protein-coupled receptors | STRUCTURAL | PRIVATE | ZymoGenetics, Inc. (Seattle, WA) |
| 5,532,157 | Host cell line LVIP2.0Zc, useful in assays to identify ligands and ant agonists of G protein-coupled receptors | ASSAY | PUBLIC | The United States of America as represented by the Secretary, Department (Washington, DC) |
| 5,532,151 | G protein-coupled receptor kinase GRK6 | STRUCTURAL | PRIVATE | ICOS Corporation (Bothell, WA) |
| 5,482,835 | Methods of testing in yeast cells for agonists and antagonists of mammal G-protein coupled receptors | METHOD | PUBLIC | Duke University (Durham, NC) |
| 5,385,831 | Method for producing a mammalian G protein coupled glutamate receptor | METHOD | PUBLIC/PRIVATE | Zymogenetics, Inc. (Seattle, WA); The Board of Regents of the University of Washington (Seattle, WA) |
| 5,284,746 | Methods of producing hybrid G protein-coupled receptors | METHOD | PRIVATE | ZymoGenetics, Inc. (Seattle, WA) |

Appendix 4.

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|--|
| 7,122,552 | Inhibitors of JAK and CDK2 protein kinases | INH | PRIVATE | Vertex Pharmaceuticals Incorporated (Cambridge, MA) |
| 6,969,760 | Jak kinases and regulation of cytokine signal transduction | MOD | PUBLIC | St. Jude Children's Research Hospital (Memphis, TN) |
| 6,933,300 | JAK-3 inhibitors for treating allergic disorders | INH | PUBLIC | Parker Hughes Institute (Roseville, MN) |
| 6,800,649 | Method for inhibiting c-jun expression using JAK-3 inhibitors | INH | PUBLIC | Parker Hughes Institute (St. Paul, MN) |
| 6,452,005 | JAK-3 inhibitors for treating allergic disorders | INH | PUBLIC | Parker Hughes Institute (Roseville, MN) |
| 6,326,373 | JAK-3 inhibitors for treating allergic disorders | INH | PUBLIC | Parker Hughes Institute (Roseville, MN) |
| 6,313,130 | JAK-3 inhibitors for treating allergic disorders | INH | PUBLIC | Parker Hughes Institute (Roseville, MN) |
| 6,265,160 | Method of identifying inhibitors of the Jak-Stat signal transduction pathway | METHOD | PUBLIC | The United States of America as represented by the Department of Health and (Washington, DC) |

(Appendix 4) Contd....

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|---|-----------------------|-------------------------|---|
| 6,210,654 | Jak kinases and regulation of cytokine signal transduction | MOD | PUBLIC | St. Jude Children's Hospital (Memphis, TN) |
| 6,177,433 | JAK-3 inhibitors for treating allergic disorders | INH | PUBLIC | Parker Hughes Institute (Roseville, MN) |
| 6,136,595 | Jak kinases and regulations of cytokine signal transduction | MOD | PUBLIC | St. Jude Children's Hospital (Memphis, TN) |
| 6,080,748 | Therapeutic use of JAK-3 inhibitors | INH | PUBLIC | Parker Hughes Institute (Roseville, MN) |
| 6,080,747 | JAK-3 inhibitors for treating allergic disorders | INH | PUBLIC | Hughes Institute (Roseville, MN) |
| 5,728,536 | Jak kinases and regulation of Cytokine signal transduction | MOD | PUBLIC | St. Jude Children's Research Hospital (Memphis, TN) |

Appendix 5.

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|---|
| 6,984,646 | Imidazopyridinones as p38 MAP kinase inhibitors | INH | PRIVATE | Bayer Healthcare AG (Leverkusen, DE) |
| 6,979,693 | Pyrazole derivatives-p38 MAP kinase inhibitors | INH | PRIVATE | Syntex (U.S.A.) LLC (Palo Alto, CA) |
| 6,962,933 | Method for inhibiting p38 MAP kinase or TNF- α production using a 1,3-thiazole | INH | PRIVATE | Takeda Pharmaceutical Company Limited (Osaka, JP) |
| 6,900,043 | Phosphatases which activate MAP kinase pathways | ACTIVATE | PRIVATE | Amgen Inc. (Thousand Oaks, CA) |
| 6,806,293 | Use of pheromone compounds having MAP kinase modulating activity | MOD | PRIVATE | Darley Pharmaceuticals LTD (Tel Aviv, IL) |
| 6,765,128 | Method of using a pathogen-activatable MAP kinase to enhance disease resistance in plants | USE | PUBLIC | Rutgers, The State University of New Jersey (New Brunswick, NJ) |
| 6,706,869 | Map kinase phosphatases and polynucleotides encoding them | STRUCTURAL | PRIVATE | Wyeth (MA) |
| 6,630,485 | p38 MAP kinase inhibitors | INH | PRIVATE | Syntex (U.S.A.) LLC (Palo Alto, CA) |
| 6,566,511 | MAP kinase phosphatase mutant | STRUCTURAL | PRIVATE | Syngenta Participations AG (Basel, CH) |
| 6,566,081 | Methods of identifying a compound which modulates the non-transcriptional non-map-kinase induced effects of steroid hormones | METHOD | PUBLIC | The Brigham and Women's Hospital, Inc. (Boston, MA) |
| 6,537,996 | Modulators of p38 MAP kinase | MOD | PRIVATE | Iconix Pharmaceuticals, Inc. (Mountain View, CA) |
| 6,479,507 | p38 Map kinase inhibitors | INH | PRIVATE | Syntex (U.S.A.) LLC (Palo Alto, CA) |
| 6,444,696 | Pyrazole derivatives P38 Map kinase inhibitors | INH | PRIVATE | Syntex (U.S.A.) LLC (Palo Alto, CA) |
| 6,376,747 | Plant-derived MAP kinase kinase | STRUCTURAL | PUBLIC | Her Majesty the Queen in right of Canada as represented by the Minister of (CA) |
| 6,376,527 | Pyrazole derivatives-p38 MAP kinase inhibitors | INH | PRIVATE | Syntex (U.S.A.) LLC (Palo Alto, CA) |
| 6,376,214 | DNA encoding a novel homolog of CSBP/p38 MAP kinase | STRUCTURAL | PRIVATE | SmithKline Beecham Corporation (Philadelphia, PA) |
| 6,316,466 | Pyrazole derivatives P-38 MAP kinase inhibitors | INH | PRIVATE | Syntex (U.S.A.) LLC (Palo Alto, CA) |

(Appendix 5) Contd....

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|---|
| 6,316,464 | P38 MAP kinase inhibitors | INH | PRIVATE | Syntex (U.S.A.) LLC (Palo Alto, CA) |
| 6,190,663 | Human MAP kinase homolog | STRUCTURAL | PRIVATE | Incyte Genomics, Inc. (Palo Alto, CA) |
| 6,147,107 | Specific inhibition of the P42/44 mitogen activated protein (MAP) kinase cascade sensitizes tumor cells | INH | PUBLIC | Virginia Commonwealth University (Richmond, VA) |
| 6,033,910 | Antisense inhibition of MAP kinase kinase 6 expression | INH | PRIVATE | Isis Pharmaceuticals Inc. (Carlsbad, CA) |
| 6,010,856 | Assay systems and methods for measuring P38 MAP kinase, and modulators thereof | METHOD | PUBLIC | The Scripps Research Institute (La Jolla, CA) |
| 6,001,580 | Method for assaying ERK2 MAP kinase | METHOD | PRIVATE | Takeda Chemical Industries, Inc. (Osaka, JP) |
| 5,989,885 | Specific mutations of MAP kinase 4 (MKK4) in human tumor cell lines identify it as a tumor suppressor in various types of cancer | STRUCTURAL | PRIVATE | Myriad Genetics, Inc. (Salt Lake City, UT) |
| 5,977,442 | Salicylic acid induced MAP kinase and its use for enhanced disease resistance in plants | USE | PUBLIC | Rutgers, The State University of New Jersey (New Brunswick, NJ) |
| 5,846,778 | Human MAP kinase homolog | STRUCTURAL | PRIVATE | Incyte Pharmaceuticals, Inc. (Palo Alto, CA) |
| 5,663,313 | Human MAP kinase homolog | STRUCTURAL | PRIVATE | Incyte Pharmaceuticals, Inc. (Palo Alto, CA) |

Appendix 6.

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|---|-----------------------|-------------------------|--|
| 7,081,343 | Methods for identifying modulators of NF-KB activity | METHOD | PUBLIC | The Regents of the University of California (Oakland, CA) |
| 6,740,522 | Antibodies against ligand for receptor activator of NF-kB | USE | PRIVATE | Immunes Corporation (Seattle, WA) |
| 6,696,498 | 2-Cyclopenten-1-one and its derivatives as inhibitors of the NF-kB factor | INH | PUBLIC | Consiglio Nazionale Della Richerche (Rome, IT) |
| 6,660,268 | Proteasome regulation of NF-KB activity | MOD | PUBLIC | The President and Fellows of Harvard College (Cambridge, MA) |
| 6,642,215 | Method of modulating NF-kB activity | MOD | PRIVATE | Leo Pharma A/S (Ballerup, DK) |
| 6,545,027 | Methods of modulating NF-kB transcription factor | MOD | PRIVATE | Eli Lilly and Company (Indianapolis, IN) |
| 6,410,516 | Nuclear Factors associated with transcriptional regulation | STRUCTURAL/ USE | PUBLIC/PRIVATE | President & Fellows of Harvard College (Cambridge, MA); Massachusetts Institute of Technology (Cambridge, MA); Whitehead Institute for Biomedical Research (Cambridge, MA) |
| 6,392,100 | 2-Cyclopenten-1-one as inhibitors of the NF-KB factor | INH | PUBLIC | Consiglio Nazionale Delle Richerche (Rome, IT) |
| 6,123,943 | NF-KB activity inhibitor | INH | PRIVATE | Kaken Shoyaku Co., Ltd. (Tokyo, JP) |

(Appendix 6) Contd....

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|---|
| 6,509,377 | Use of a 2-hydroxy-4-trifluoromethylbenzoic acid derivatives as inhibitors of the activation of the nuclear transcription factor NF-kappa.B | INH | PRIVATE | J. Uriach & Cia, S.A. (Barcelona, ES) |
| 6,498,147 | Suppression of nuclear factor-.kappa.b dependent processes using oligonucleotides | INH | PUBLIC | The Scripps Research Institute (La Jolla, CA) |
| 5,981,583 | Inhibition of nuclear transcription factor NF-.kappa.B by caffeic acid phenethyl ester (CAPE), derivatives of CAPE, capsaicin (8-methyl-N-vanillyl-6-nonenamide) and resiniferatoxin | INH | PUBLIC | Research Development Foundation (Carson City, NV) |
| 5,591,840 | Antisense lignonucleotides directed against nucleic acids encoding NFKB transcription factor | STRUCTURAL | PRIVATE | Hoffmann-La Roche Inc. (Nutley, NJ) |

Appendix 7.

| U.S. Patent No. | Patent Title | Patent Categorization | Institutional Ownership | Patent Assignee |
|-----------------|--|-----------------------|-------------------------|--|
| 7,081,343 | Methods for identifying modulators of NF-KB activity | METHOD | PUBLIC | The Regents of the University of California (Oakland, CA) |
| 6,740,522 | Antibodies against ligand for receptor activator of NF-kB | USE | PRIVATE | Immunex Corporation (Seattle, WA) |
| 6,696,498 | 2-cyclopenten-1-one and its derivatives as inhibitors of the NF-kB factor | INH | PUBLIC | Consiglio Nazionale Della Ricerche (Rome, IT) |
| 6,660,268 | Proteasome regulation of NF-KB activity | MOD | PUBLIC | The President and Fellows of Harvard College (Cambridge, MA) |
| 6,642,215 | Method of modulating NF-kB activity | MOD | PRIVATE | Leo Pharma A/S (Ballerup, DK) |
| 6,545,027 | Methods of modulating NF-kB transcription factor | MOD | PRIVATE | Eli Lilly and Company (Indianapolis, IN) |
| 6,410,516 | Nuclear Factors associated with transcriptional regulation | STRUCTURAL/ USE | PUBLIC/PRIVATE | President & Fellows of Harvard College (Cambridge, MA); Massachusetts Institute of Technology (Cambridge, MA); Whitehead Institute for Biomedical Research (Cambridge, MA) |
| 6,392,100 | 2-Cyclopenten-1-one as inhibitors of the NF-KB factor | INH | PUBLIC | Consiglio Nazionale Delle Ricerche (Rome, IT) |
| 6,123,943 | NF-KB activity inhibitor | INH | PRIVATE | Kaken Shoyaku Co., Ltd. (Tokyo, JP) |
| 6,509,377 | Use of a 2-hydroxy-4-trifluoromethylbenzoic acid derivatives as inhibitors of the activation of the nuclear transcription factor NF-.kappa.B | INH | PRIVATE | J. Uriach & Cia, S.A. (Barcelona, ES) |
| 6,498,147 | Suppression of nuclear factor-.kappa.B dependent processes using oligonucleotides | INH | PUBLIC | The Scripps Research Institute (La Jolla, CA) |
| 5,981,583 | Inhibition of nuclear transcription factor NF-.kappa.B by caffeic acid phenethyl ester (CAPE), derivatives of CAPE, capsaicin (8-methyl-N-vanillyl-6-nonenamide) and resiniferatoxin | INH | PUBLIC | Research Development Foundation (Carson City, NV) |
| 5,591,840 | Antisense lignonucleotides directed against nucleic acids encoding NFKB transcription factor | STRUCTURAL | PRIVATE | Hoffmann-La Roche Inc. (Nutley, NJ) |

As systems biology is likely to become the dominant paradigm in biology, central to the development of medically viable products is ensuring accessibility to systems-based knowledge for multiple researchers who can pursue tomorrow's technological opportunities. Academia, government, and industry will all play a role in shaping policies that will enable the broad dissemination of systems-based knowledge.

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