



# **The Lilly Phenotypic Drug Discovery Initiative: A New Paradigm for Open Innovation**

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## Background

The present environment for drug discovery is complicated by many concurrent challenges. Rising costs of R&D, poor productivity as measured by a declining number of new drug approvals per dollar investment, patent expirations, increasing regulatory restrictions, etc., are exerting unprecedented pressure on pharmaceutical companies. Ironically, this environment follows on the heels of two decades of transformational breakthroughs in the understanding of disease biology. Furthermore, the demand for new therapies has never been higher, fueled by unmet medical need, an aging population that will live longer and the growth of emerging markets such as China and India. Pharmaceutical companies have taken varied approaches to address this challenge. These include in-licensing of development-stage molecules, consolidation through mergers and acquisitions and aggressive cost-cutting measures such as outsourcing of work to low-cost providers. While these approaches have merit, they provide short-term benefits if not supported by scientific innovation that can be translated into clinical opportunities.

One area that has historically been a fertile ground for innovation is the interface between industry and academia. In many cases, these collaborative interactions have focused on the exchange of basic science across discovery disciplines that have found applicability in the drug discovery process. A few examples include molecular and cellular biology, biophysical sciences, pharmacology, computational science and synthetic chemistry. There are however a few examples of clinical success stories that trace their origins to a direct collaborative interaction between industry and academia on specific molecules. These relationships have successfully negotiated the challenges posed by alignment of business and scientific objectives, sharing of intellectual property, and the high risk and time horizon for converting basic science into clinical outcomes. The circumstances that brought industry and academic partners together were a mutual desire to advance innovative science and create medicines to help patients. It is on the foundation of these successful experiences that we propose to engage the global academic community through a new open innovation drug discovery initiative. Our goal is to identify novel molecules active in relevant disease biology models that can serve as the foundation for collaborative work between Lilly and external investigators.

While the business environment is transforming the way the pharmaceutical industry operates, the climate in academia is ideal for such opportunities as well. Many academic investigators have increasingly turned their interest to the interface of chemical and biological science and are participating in programs (such as the NIH Roadmap Initiative) that are attempting to advance the discovery of biomedical breakthroughs.

## The Lilly Phenotypic Drug Discovery Initiative

Phenotypic drug discovery is a complement to target-based drug discovery (Figure 1). The latter focuses on evaluating a disease hypothesis through the process of discovery and clinical testing of a molecule designed to interact with a specific genomic target believed to be involved in the disease pathogenesis. With the sequencing of the human genome and the development of many high throughput and complementary drug discovery technologies, target-based drug discovery has emerged as the primary strategy of many pharmaceutical companies during the past 20 years. While significant R&D dollars have been invested in this paradigm, relatively few new drugs have been approved. Many reasons have been ascribed to the poor success of this approach; however a possible cause is the

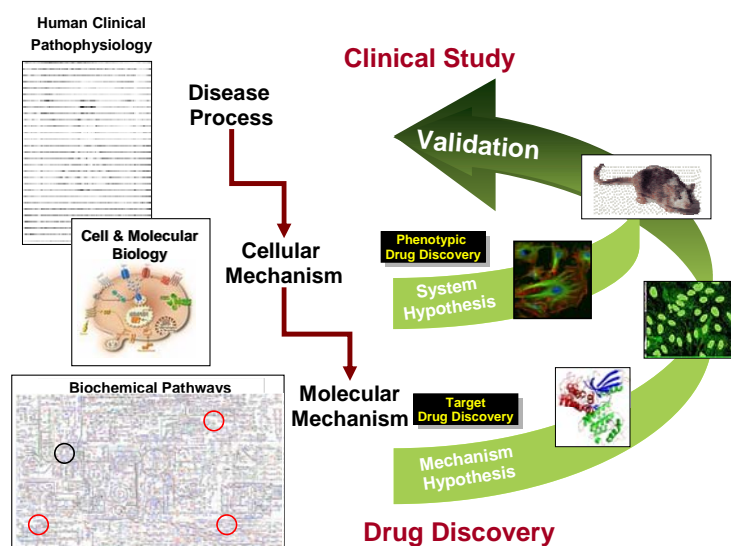


Figure 1

lack of translational medicine approaches to provide differentiation among many possible targets as well as validation for any single mechanism to serve as a primary intervention point for disease modulation.

Phenotypic drug discovery provides an alternative approach that begins by querying more complex cellular systems instead of specific targets. The possible advantage resides in the fact that a relevant biological context is interrogated without predisposed bias toward mechanism(s). Thus an opportunity is created to identify compounds that may interact with one or more targets or pathways not anticipated by a single mechanism-driven hypothesis. In essence, phenotypic approaches screen multiple mechanisms and targets simultaneously. Furthermore, since the initial readouts from cellular assays are more information-rich, the connection of compound action to disease-relevant phenotypes is established earlier in the drug discovery process. The challenge with phenotypic drug discovery ultimately lies in the complexity of fully understanding and assessing compound differentiation and elucidating with greater resolution the possible mechanisms of action. Fortunately, this complexity has been substantially reduced with the development of advanced assay technologies and informatics tools that make these challenges tractable for drug discovery.

Over the last 10 years, cellular assay technologies have become an important experimental tool to investigate complex biological processes. Lilly has invested significant resources to develop a panel of disease-related phenotypic assay modules (primary cellular phenotypic screens with secondary assays for thorough characterization) representing therapeutic areas of long-standing strategic interest. As a complement to target-based drug discovery, these assay modules will be used to screen internal compound collections and, as premise for this initiative, molecules submitted from research universities, institutes and biotech. Lilly will make these phenotypic assay modules available **without charge** to global external investigators for evaluation and characterization of their compounds in a manner where all generated data and intellectual property rights will be retained by the submitting investigator/institute (*Figure 2*). As described below, Lilly will maintain a first right to negotiate access to the molecules or partner with the investigator to further advance promising discoveries. The goal is to not promote a random, high volume submission of compounds; rather to stimulate the testing of compounds that represent novel structural diversity and molecular hypotheses that are thoughtfully considered in light of the biology associated with each assay.

As a point of emphasis and strategy, we have elected to employ phenotypic assays for this initiative and not specific biological targets. Our goal is to identify compounds with unique molecular signatures that impart the desired, observable phenotype and that are distinct from molecules we would likely identify otherwise. Thus the phenotypic assay provides an unbiased net to capture compounds with one or more potential mechanisms of action that elicit a desirable response. For compounds that display the desired phenotype, the follow-up paradigm will aid in further elucidating the underlying pharmacology. While the initial focus of the initiative is synthetic compounds and natural products, we are actively considering possible future scope expansions such as peptides and biologics.

The following process illustrates how Lilly will enable investigators in the global community to submit compounds and in return receive a phenotypic data report on molecular activity. The process will begin with registration through a third party website ([pd2.lilly.com](http://pd2.lilly.com)) and the signing of

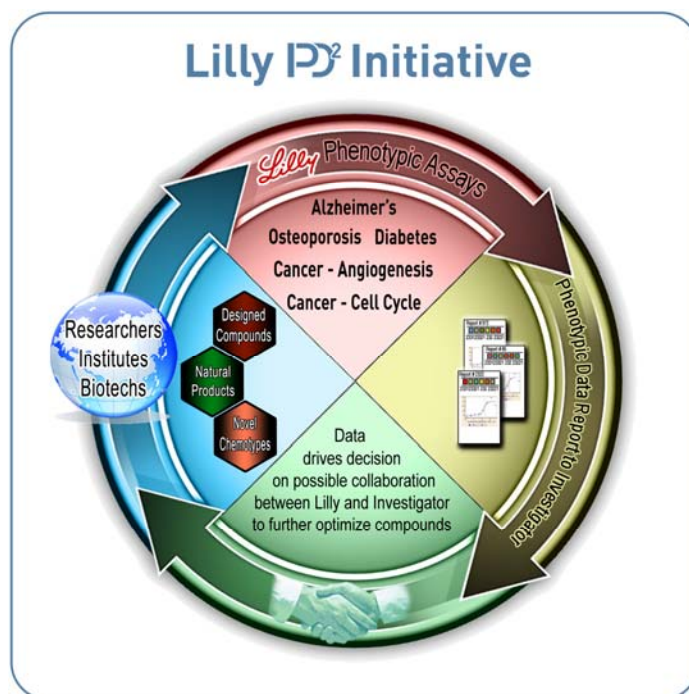
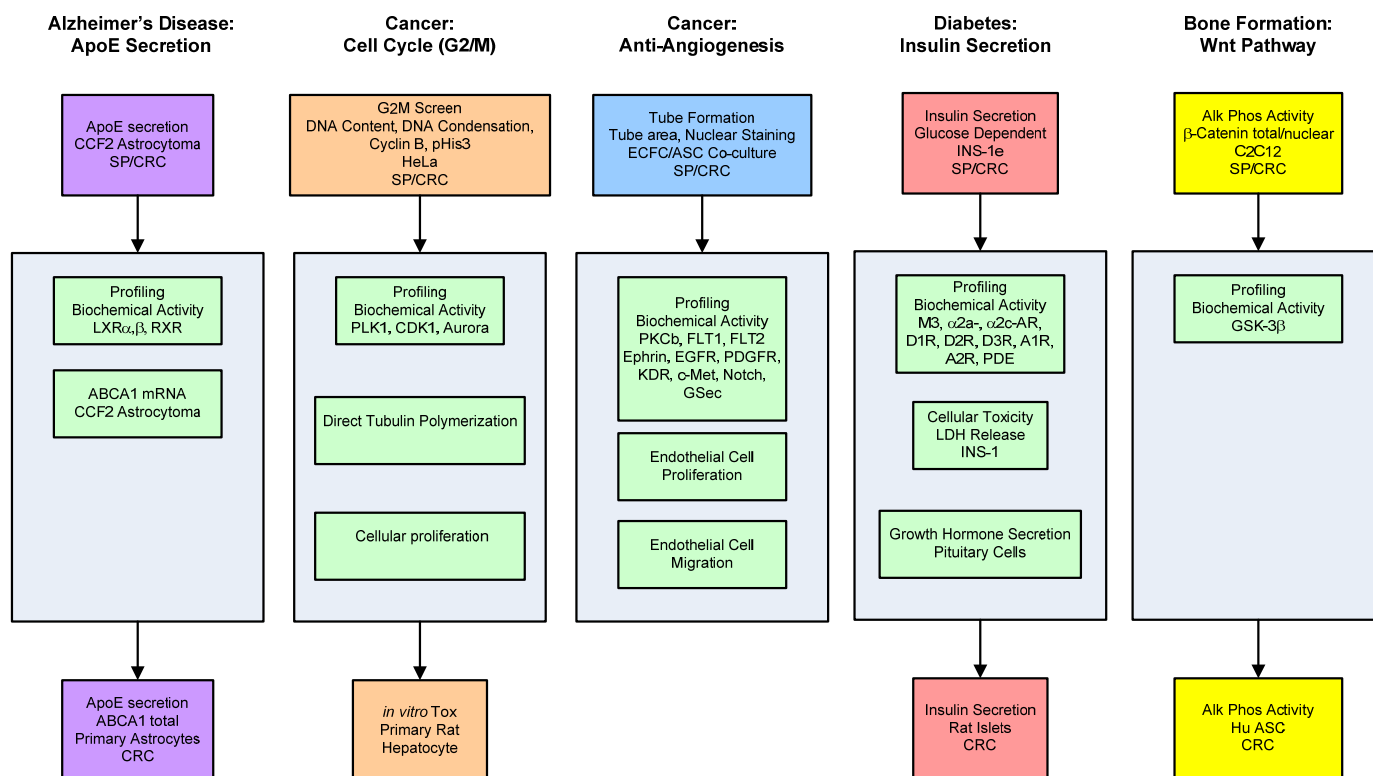


Figure 2

a standardized Material Transfer Agreement (MTA). The design and wording of the MTA was developed through a close partnership with AUTM (Association of University Technology Managers). The leadership of AUTM is a critical component, eliminating the need to establish individual agreements with each investigator/institute and providing broad access and exposure to this initiative through their global network.

Once registered, investigators will be guided through the process for submission of compounds via the website. Confidentiality of three-dimensional molecular structures will be maintained with the submitter. The website contains cheminformatic tools that will enable external investigators to submit compound structures for an initial computational evaluation using a set of proprietary algorithms focused on drug-like properties and structural novelty without disclosure of the actual structures to Lilly. These algorithms will determine if the submitted structures meet Lilly-defined minimum criteria used to trigger the next step, which is submission of a physical sample for biological testing. For selected compounds, Lilly will provide barcoded vials and shipping instructions for easy, no-cost compound submission.

Upon receipt of the compounds, Lilly will test for activity in the five phenotypic assay modules. Any compound demonstrating confirmed activity in the initial phenotypic assay will then be tested in the secondary assays outlined in *Figure 3*. After sample evaluation, the investigator will receive a report with a complete biological profile of the compounds across the five phenotypic assay modules. This report will also include data from known reference standards relevant to the individual phenotypic assay. For compounds demonstrating interesting assay profiles, Lilly will have a set timeline defined by the MTA to exclusively negotiate with the investigator for enhanced compound access. As all intellectual property rights will remain with the investigator, these discussions will focus on how both parties can best leverage the research through collaboration or licensing. Further biological characterization will proceed only after disclosure of compound structure to Lilly and establishment of a collaboration or licensing agreement. If a decision is made by Lilly or the investigator not to enter into an agreement, the investigator will be free to use the data to refine a hypothesis, publish or use in a grant application.



SP= Single Point  
CRC= Concentration Response Curve

Figure 3

## The Lilly Phenotypic Drug Discovery Evaluation Panel

The initial Lilly Phenotypic Panel is comprised of five assay modules, as represented in *Figure 3*. Each module starts with the primary phenotypic assay followed by secondary biochemical and cellular assays (in green boxes), and concludes with a confirmatory assay for the desired phenotype. These modules are part of a testing paradigm that is currently used to identify compounds to probe disease biology and to serve as relevant starting points for drug discovery.

**Alzheimer's Disease (AD) – ApoE Secretion:** Alzheimer's Disease (AD) is a progressive degenerative dementia that usually begins with memory impairment and progresses to involve a severe loss of multiple areas of cognitive function. The  $\epsilon$  4 allele of the apolipoprotein E gene was identified as an important genetic risk factor for the development of the most prevalent form of AD (sporadic). Subsequent studies indicate that apoE suppresses early amyloid-beta ( $A\beta$ ) deposition by facilitating the clearance of  $A\beta$  from the brain. The Alzheimer's phenotypic module measures secretion of apoE from a human astrocyte cell line. Confirmed actives are tested in primary astrocytes and in biochemical nuclear hormone receptor assays. Compounds of interest selectively enhance apoE secretion through a non-LXR $\beta$  mechanism.

**ApoE Promotes the Proteolytic Degradation of Ab.** Qingguang Jiang *et al*, *Neuron*, 58, 681–693 (2008).

**Liver X Receptor-Mediated Gene Regulation and Cholesterol Homeostasis in Brain: Relevance to Alzheimer's Disease Therapeutics.** Guoqing Cao *et al*, *Current Alzheimer Research*, 4, 1567-2050 (2007).

**Cancer – Cell Cycle G2/M Arrest:** The Cell Cycle G2/M Arrest phenotypic module uses a multiplexed, high throughput cell imaging assay to identify compounds that arrest HeLa cells in G2 or M phase. Compounds that block the cell cycle in G2/M are further tested for inhibition of cell cycle kinases and for direct effects on tubulin polymerization/depolymerization. Finally, compounds which are G2/M blockers and utilize a non-tubulin mechanism are tested for cell cycle-dependent cytotoxicity using non-proliferating primary hepatocytes. Compounds of interest block the cell cycle in G2 or M phase, are selectively anti-proliferative to rapidly growing cells, and act through non-tubulin mechanisms.

**To Cycle or Not To Cycle: A Critical Decision in Cancer. (Abstract)** M. Malumbres and M. Barbacid, *Nature Reviews Cancer*, 1, 222-231 (2001).

**Cancer – Anti-Angiogenesis:** The Anti-Angiogenesis phenotypic module utilizes the co-culture of human endothelial progenitor cells (ECFCs) with adipose-derived adult stem cells (ADSCs) to measure angiogenesis. Compounds which inhibit angiogenesis without affecting feeder cell viability are followed up in a panel of biochemical kinase and cell-based assays. Compounds of interest inhibit angiogenesis but do not show inhibition of known angiogenic receptor tyrosine kinases.

**VEGF-Targeted Therapy: Mechanisms of Anti-Tumor Activity.** Lee M. Ellis and Daniel J. Hicklin, *Nature Reviews Cancer*, 8, 579-591 (2008).

**Angiogenesis: an Organizing Principle for Drug Discovery? (Abstract)** Judah Folkman, *Nature Reviews Drug Discovery*, 6, 273-286 (2007).

**Diabetes – Insulin Secretion:** The Diabetes phenotypic module tests for compounds that enhance glucose-dependent insulin secretion. Glucose dependence is confirmed in the presence of a non-stimulatory and a stimulatory concentration of glucose. The preferred molecule acts only in the presence of glucose and would have a novel mechanism of action. Active molecules are further characterized relative to signaling pathways and cell-surface receptors known to modulate insulin secretion. Follow-up assays test for non-specific compound effects on cell permeability and non-selective hormone secretagogue activity. Activity for compounds of interest is confirmed in primary rat islets. Compounds of interest act as glucose-dependent, insulin specific secretagogues.

**Novel Aspects of the Molecular Mechanisms Controlling Insulin Secretion.** L Eliasson *et al*, *J Physiol*. 586(14), 3313-24 (2008).

**Beta-Cell Failure as a Complication of Diabetes.** KJ Chang-Chen *et al*, *Rev Endocr Metab Disord*. 9(4), 329-43 (2008).

**Bone Formation – Wnt Pathway:** The Bone Formation phenotypic assay module tests compounds for their ability to differentiate murine C2C12 cells, a cell line with multi-lineage potential, to an osteoblast-like phenotype through  $\beta$ -catenin-dependent stimulation of alkaline phosphatase activity. Secondary assays confirm the osteogenic activity of the compounds in both rodent and human multi-potential cell populations. Compounds of interest increase osteoblast formation in rodent and human cellular assays through a non-glycogen synthase kinase (GSK) mechanism.

**Wnt Pathway, an Essential Role in Bone Generation.** Y. Chen and B.A. Alman, *J Cell Biochem.* 106(3), 353-62 (2009).

## Final Comments

In summary, it is our hope that the implementation of this open innovation program will provide academic and biotech investigators access to sophisticated *in vitro* model systems while simultaneously increasing Lilly's partnership with top global research talent. We expect that investigators from all over the world will take advantage of this resource and that it will open new venues to test novel therapeutic hypotheses and deepen our understanding of complex biological systems. Through this initiative and others like it, our steadfast goal remains focused on the discovery of novel therapeutics that improve patient's lives. This will be our ultimate measure of success.