Strategies to Move Beyond Target Validation

Targets and Druggability for Small and Large Molecule Drugs

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Genomics and proteomics have made thousands of potential targets available to drug discovery researchers. These researchers utilize a number of target identification and validation technologies, ranging from comparative genomics to gene expression profiling to RNA interference (RNAi) to animal models, in order to sort through the host of potential targets and select validated ones.

Target validation refers to the determination that a target is critically involved in a disease process and that modulating the target is likely to have a therapeutic effect.

Compounds that modulate these validated targets may then be taken into preclinical and clinical studies. However, the high rate of efficacy failures of drugs in the clinic, especially in the later stages of clinical development, have made many pharmaceutical and biotechnology companies question the ability of laboratory target validation tests to adequately predict efficacy.

Mark Fishman and Jeffrey Porter of **Novartis** that target validation does not take one year (as usually shown in drug development timelines) but decades.[1]

If drug discovery researchers can utilize a target derived from basic biological and medical research, this eliminates the need to sort through hundreds or thousands of targets using target identification and validation technologies. However, many, and perhaps the majority of such well-validated targets, are not deemed to be druggable. Some pathways contain no druggable elements.

For example, the central, or intrinsic pathway of apoptosis is typically blocked in cancer cells. Many companies would like to develop drugs that overcome these blocks and thus induce programmed cell death in the cancer cells. However, all of the potential targets in the intrinsic pathway of apoptosis are undruggable protein-protein interactions. As a result, the majority of pro-apoptotic agents in clinical trials are antisense compounds.

Given the drug delivery and other issues with antisense drugs, companies would prefer to develop small molecule compounds. In this and many other cases, expanding the universe of druggable targets would allow drug discovery researchers to access well-validated targets rather than attempting to utilize targets of largely unknown value.

Selected Marketed Drugs Whose Targets Were Validated Via Basic Biological and Medical Research

Drug	Company	Target	Disease
SMALL-MOLECULE DRUGS			
Gleevec/Glivec (imatinib)	Novartis	Abl, c-Kit, and PDGFR kinases	Cancer (marketed for CML and gastrointestinal stromal tumors)
Tarceva (erlotinib)	OSI/Genentech	EGFR	Cancer (marketed for NSCLC)
Velcade (bortezomib)	Millennium	The proteasome	Cancer (marketed for multiple myeloma)
LARGE-MOLECULE DRUGS			
Rituxan (rituximab)	Genentech/Biogen Idec	CD20 receptor	Non-Hodgkin's lymphoma
Herceptin (trastuzumab)	Genentech	HER2 receptor	HER2-positive cancer metastatic breast
Avastin (bevacizumab)	Genentech	VEGF (a key angiogenic factor)	Cancer (marketed for colorectal cancer)
Remicade (infliximab)	Johnson & Johnson/ Centacor	TNF-a	Inflammatory diseases
Humira (adalimumab)	Abbott/Cambridge Antibody Technology	TNF-a	Inflammatory diseases
Enbrel (etanercept)	Amgen/Wyeth	TNF-a	Inflammatory diseases

Source: Haberman Associates

PDGFR: platelet derived growth factor receptor, CML: chronic myelogenous leukemia, EGFR: epidermal growth factor receptor, NSCLC: non-small-cell-lung cancer, VEGF: vascular endothelial growth factor , TNF-a: tumor necrosis factor-alpha

"Powering Discovery Through Target Evaluation: Moving Beyond the Validation Paradigm" (Cambridge Healthtech Advisors Advances Reports, August 2005) discusses strategies for moving beyond the current target validation paradigm in order to improve the effectiveness of drug discovery and development.

These include such strategies as biology-driven drug discovery, whole-pathway based drug discovery, discovering therapies that address multiple targets, genetic- and biomarker-based disease stratification, translational medicine, and improved animal models. This article is based on one chapter of that report.

Validated Targets

The very best validated targets have been identified as the result of extensive studies of the biology of disease pathways, usually over years and even decades, by academic and biotechnology company researchers. The targets for the majority of breakthrough drugs that have reached the market in recent years were identified via such research. *Table 1* lists examples of such drugs and their targets.

In contrast, not one marketed drug has so far resulted from large-scale target identification and validation testing. This disparity is reflected in the statement in a recent article by

A pragmatic definition of druggability is that researchers have the appropriate science and technology in hand to develop antagonists to a particular target. In the case of small molecule drugs, druggable targets are those that can be addressed with currently available medicinal chemistry. These targets especially include those belonging to protein families that are targeted with currently marketed drugs—specifically G-protein coupled receptors, ion channels, nuclear receptors, proteases, phosphodiesterases, kinases, and other key enzymes.

Druggable targets for large molecule drugs are the secreted proteins, both those expressed on the cell membrane and those secreted into extracellular fluids, especially blood plasma. Cell surface receptors are targets for development of monoclonal antibodies (Mabs) and recombinant fusion proteins that carry protein ligands for the receptors.

Recombinant versions of extracellularly secreted proteins may be used as therapeutic proteins such as erythropoietin (**Amgen's** Epogen and Aranesp), granulocyte colony-stimulating factor (Amgen's filgastrim and pegfilgastrim), and interferons (**Berlex'** betaseron [interferon beta-1b] and **Biogen Idec's** Avonex [interferon beta-1a]).

Medicinal chemists have a useful body of science and experience that predicts druggability of targets as well as drug-like properties of small molecule compounds that may interact with these targets.

However, what constitutes druggability has undergone expansion in recent years. For example, protein kinases were traditionally considered undruggable. However, there are now several protein kinase inhibitors on the market and many more in development, and nearly all big pharmas and many biotechnology companies have kinase discovery and development programs.

Protein phosphatases present greater difficulties to medical chemists because their natural substrates are highly charged; mimetics of such polar substrates will be expected to have difficulty entering into cells. However, such companies as **Pfizer**, **Roche**, **Abbott**, and **Incyte**, as well as academic groups, are making apparent headway in exploring novel approaches to discovery of phosphatase inhibitors.

High-Quality Targets

Most drug developers consider the druggable genome to consist of 3,000–5,000 targets. However, **Lexicon Genetics** and some other companies, on the basis of extrapolation from targets of existing drugs, have determined that the number of high-quality new targets is only about 100–150. High-quality targets are those that are expected to give rise to large-selling drugs.

However, as discussed in detail in our report, determining the true value of a target depends on extensive research, including both laboratory and clinical studies. Informatics-based calculations of the number of high-quality druggable targets have a high degree of uncertainty, and this approach may lead drug developers only to what seem like obvious candidates.

Given the relative scarcity of truly well-validated targets in terms of function and disease role, such an approach may leave a company at a disadvantage compared with competitors that pursue disease-focused or biology-driven approaches to drug discovery and development.

An object lesson is the case of Gleevec and its initial target, Bcr-Abl in CML. Prior to the development of this drug, it did not seem like a high-quality candidate because it appeared to address a small market.

However, because of Gleevec's ability to target several other kinases structurally related to Abl, the drug has now been approved for another type of cancer and is in clinical trials for several other indications. Gleevec sales surpassed $1 billion in 2003, giving the drug blockbuster status.

Hard Targets

Targets that cannot be addressed with currently available medicinal chemistry are called hard targets. The prototypical hard targets for development of small molecule antagonists are domains of intracellular signaling proteins involved in protein-protein interactions.

Such interactions include, for example, those between signaling proteins and those between cytokine or growth factor receptors and their protein ligands. Researchers often cite the theoretical issue that protein-protein interactions involve interactions over large surface areas, which is expected to make inhibition by small molecule agents difficult.

However, there are natural products that disrupt protein-protein interactions, which in a few cases have been developed and marketed. For example, the fungal product FK506 (tacrolimus, **Fujisawa's** Prograf) disrupts the interactions between the intracellular domains of type I receptors for transforming growth factor-beta (TGF-b) and FK-binding protein-12 (FKBP-12).

Several companies also have discovered novel small molecule drugs that target protein-protein interactions. For example, **Ariad** discovered small molecule, nonpeptide compounds that target the interaction between SH2 domains in many signaling proteins and their recognition sites, which are specific phosphotyrosine-containing amino acid sequences in proteins[2].

Ligand Pharmaceuticals discovered small molecule drug candidates that serve as cytokine agonists. The company has been collaborating with **GlaxoSmithKline** (GSK) to develop a class of oral small molecule nonpeptide thrombopoietin mimetics for use in treatment of thrombocytopenia (which results in low platelet count).

In February 2005, Ligand received a $1 million milestone payment from GSK, upon entry of the thrombopoietin mimetic SB-497115 into Phase II trials.

In Phase I trials, the agent increased platelet counts in a dose-dependent fashion when administered to healthy volunteers. Other companies that are developing small molecule nonpeptide drugs that modulate protein-protein interactions include Abbott, **BioImage**, **Genentech**, and **Infinity Pharmaceuticals**.

These examples indicate that, whatever the theoretical issues that make protein-protein interactions the prototypical hard target, the inability of companies to develop small molecule modulators of these targets is likely due in part to limitations in current medicinal chemistry paradigms.

The determination of a target's druggability will depend in part on how much a company is willing to invest in time and in money to develop (or partner for) novel strategies for developing these compounds and on the creativity of the company's researchers.

Some classes of targets that are not readily amenable to small molecule drug discovery can be addressed with recombinant protein or Mab drugs. This applies to many cell surface receptors that are involved in disease processes, including cytokine or growth factor receptors. Examples of such large molecule drugs are listed in *Table 1*.

In most cases, biotechnology companies develop Mab and recombinant protein drugs. However, Big Pharma companies have gained commercial access to such products—and thus to the hard targets for small molecule drug development that they address—through partnerships or acquisitions. GEN

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