

Chapter 2

DRUG DISCOVERY STRATEGIES AIMED AT REDUCING PHASE II ATTRITION

As discussed in Chapter 1, in their quest to discover and develop innovative drugs that can address unmet medical need in the complex diseases that are the focus of the pharmaceutical/biotechnology industry today, companies are increasingly focusing on unprecedented targets. For example, among drug candidates entering clinical trials between 2000 and 2004, 67% were novel targets. However, drugs that address unprecedented targets are much more likely to fail in Phase II (by a factor of 2–4 fold) than are drugs that address precedented targets.⁸ The most common reason for this attrition is failure to demonstrate significant differences in clinical effects from treatment with a placebo (*i.e.*, efficacy failures).

Strategies to reduce the risk in Phase II due to addressing unprecedented targets involve: 1) identifying those targets that have the best chance of success in the discovery phase, and 2) employing early-stage proof-of-concept (POC) clinical trials to weed out targets that do not achieve POC. As a result, drugs that address risky targets should fail prior to entering Phase IIIb, thus reducing R&D costs and improving productivity. This chapter focuses on the first part of this strategy: Selecting the best targets in drug discovery in order to reduce the risk of attrition as early as possible. Later chapters will address POC clinical trials and other types of early-stage human studies aimed at reducing Phase II attrition.

Selecting the best targets for drug discovery is commonly referred to as “target validation.” 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. Genomics and proteomics have provided researchers with an overabundance of potential targets. Little or nothing is known about the biological function or role in disease pathways of the vast majority of them. The difficulty of selecting

inclusions that contain ubiquitinated TDP-43 [described earlier].) The role of these mutations in these diseases provides strong evidence that abnormalities in tau can cause neurodegeneration. Moreover, specific haplotypes of *MAPT* are linked to several of the sporadic tauopathies.⁵¹

In normal physiology, tau binds to and stabilizes microtubules in the polymerized state. In the case of neurons, this microtubule-binding function promotes axonal transport, which is necessary for the function and survival of neurons. In AD and the tauopathies, tau becomes abnormally hyperphosphorylated and can no longer bind to microtubules. This hyperphosphorylated tau is insoluble and aggregates to form NFTs.

There are also human neurodegenerative diseases that appear to be caused by α -synuclein pathology in the absence of amyloid plaque. These include dementia associated with Parkinson's disease, as well as the disease known as dementia with Lewy bodies (DLB).⁵¹ However, the biology of α -synuclein remains poorly understood. Therefore, researchers have been focusing on the tau pathway, as well as the amyloid pathway, in developing therapeutic strategies for AD.

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Studies in Mouse Models Transgenic For Tau

The Lee/Trojanowski group, as well as other researchers, has been using singly-transgenic tau-overexpressing mouse models in efforts aimed at 1) discovering and developing drugs that target tau pathways in AD and human tauopathies, and/or 2) understanding these pathways. These models are simpler than the doubly-transgenic models described above, and thus allow researchers to study, for example, the effects of drugs on the tau pathway without confounding effects of another pathway such as amyloid or α -synuclein. As discussed below, unlike APP transgenic mouse models, tau transgenics exhibit neurodegeneration.

We discussed some of these studies, done prior to 2006, in an earlier Insight Pharma Report.⁵² Because of tau's role in stabilizing microtubules, researchers hypothesize that pharmacological stabilization of microtubules may ameliorate the effects of tau pathology in AD and other tauopathies and thus slow the rate of neurodegeneration.

The Lee/Trojanowski group performed studies to test this hypothesis in a transgenic mouse model in which the shortest human tau isoform, T44, was overexpressed in the neurons of the CNS.⁵³ Neurons of these mice

In general, translational studies are especially applicable to drugs that address unprecedented targets. These drugs as well as the strategy of addressing particular unprecedented targets lack proof that they can do anything useful in terms of treating human disease. Translational studies are especially focused on providing that proof, or alternatively disproving therapeutic hypotheses based on using these drugs and addressing these targets. Well-designed translational studies may enable drugs that do not work in humans (and especially those that address “bad targets”) to fail early, at a much lower cost than if they were taken into full-scale Phase IIb or Phase III trials.

Translational studies are generally aimed at answering four questions,⁶² as outlined in Table 4.1.

Table 4.1. Questions To Be Answered In Translational Studies

- Which patient subsets will respond best to treatment and which are nonresponders?
- What is the optimal dosing regimen?
- Can researchers identify early, sensitive markers of efficacy?
- Can researchers identify patient subsets likely to experience adverse effects?

Source: Haberman Associates; based on Hurko O, Rutkowski L. Translational medicine breaks bottlenecks. Drug Discovery and Development. November 9, 2005.

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4.1. Defining Responder and Nonresponder Populations

The first question is concerned with responder or nonresponder subpopulations. Most primary care drugs, such as those to treat hypertension, are efficacious in large subsets of patients, but many patients are weak responders. These drugs have usually been approved without studies to define responder populations, but physicians may easily compensate for this by trying another drug if the first one does not work. In the case of cancer, however, treating with the wrong drug may allow tumors to grow and metastasize to the point where they are untreatable. Therefore, studies on responder and nonresponder populations have been mainly focused on cancer. However, other disease areas may also benefit from studies to define responder subpopulations.

In cancer, defining responder populations to a targeted therapy, such as a MAb or a kinase inhibitor, has involved defining biomarkers for response. Examples of such biomarkers include Her2 overexpression in

Question 5 asks what the respondents see as the major reasons for low productivity and high cost of drug development; again, they could give more than one answer. Of the 32 respondents who answered the question, the largest numbers cited poorly predictive animal models (53.1%) and the increasing difficulties and expense of conducting clinical trials (53.1%). Other answers with the largest responses include the increasing caution of regulatory agencies in approving drugs (50%), and defensive design of clinical trials to deal with late-stage and postmarketing safety issues (40.6%). All other choices listed in Question 5 got significant numbers of answers.

Question 5: What do you see as the major reasons for low productivity and high cost of drug development?



n = 32

Source: Insight Pharma Reports' Phase II Attrition Survey—January/February 2009

IPR: Do you also see the need for more predictive biomarkers to improve the results of translational medicine for accelerating drug development?

Dr. Lassota: This is an area where, despite the tremendous progress made in recent years, there are still many challenges to meet. Biomarkers have many flavors. We need better markers for early detection of diseases, particularly cancers, in order to improve therapeutic outcomes. Looking for circulating tumor cells holds a promise here. Also, the emerging field of microRNAs may give us new insights into early diagnosis. We are in need of surrogate markers of efficacy, and FDG and FLT PET, as well as MRI, proved to be extremely useful there. Finally, pharmacodynamic markers used in preclinical drug discovery and development will accelerate moving the compounds through the pipeline. Here, Caliper's non-invasive, visible light imaging technology provides the tools for real-time pharmacodynamic readouts, which, in my view, will be displacing traditional IHC-based approaches.

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Insight Pharma Reports (IPR): Do you agree that Phase II attrition is a major issue in the pharmaceutical and biotechnology industries?

Dr. Littman: Yes, I think Phase II attrition is the major problem facing most companies right now. There is not a lot of evidence yet that the approaches taken to address Phase II attrition have been working sufficiently well. However, I don't believe there has been enough time to test all of the changes that have been made throughout the industry in the last few years. Many of those changes involve work that gets done fairly early in projects. Those projects might not have even reached their Phase II starts yet, or they may just be reaching that point now.

One thought I have, which I think is worth mentioning, has to do with one of the changes occurring in the industry now, where individual therapeutic areas are being spun off, almost as separate business entities. I think that can have a really negative effect on Phase II attrition.

From a scientific point of view, before a compound enters Phase II, you have to be sure that it's having its intended pharmacology at a well-tolerated dose. That's the approach that most companies have taken