Screening the Drug Target with Genome High Throughput Screen (DNA Chip Technology)

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Pharmacceutical companies, perceiving an "innovation deficient," are working to increase their output of new drugs. The perceived innovation deficit is perhaps better reflected by the fact that R&D expenditures as a percentage of sales rose from 11-12% in the 1970s to 19-21% in the 1994-1999 period. A revolution in the way new drugs are discovered and developed appears necessary for the continued health of the industry. Areas needing improvement include the time and costs required for drug discovery ans development. Significant improvements in both times and costs might be possible with higher quality drug targets, the ability to eliminate compounds at earlier stages in the overrall process, and improvements in the selection of clinical trial populations. Each of these factor is addressable by pharmacogenomics. In its efforts to make crucial improvements in R&D productivity, the pharmaceutical industry is in the process of adopting two related perspectives: 1) the industrialization of drug discovery and development and 2) the application of genomics and genetics to drug discovery and development. Drug discovery began as a predominantly empirical science from which a large body of heuristic knowledge emerged. Advances in molecular biology and related sciences led to the identification of molecular targets and increasingly rational approaches to drug discovery. Advances in combinatorial chemistry produced a plethora of compounds to test with the growing collection of targets, leading to what has been termed the "industrialization" of drug discovery. The chief strategy (Fig. 1) is to focus on revolutionizing drug discovery and development technology through industrialization. In its current state, the process needs a lot of improvement, and we have worked on developing and integrating a large number of technologies and information systems so we can continue to optimize productivity. By applying

technologies such as high throughput screening(DNA chip technology) back in discovery, we can begin to predict and perhaps limit those failures that occur in clinical trials. Finally, Pharmacceutical companies are often thought of as a genomics company – Pharmacceutical companies focusing on genes and targets, but they are aggressively moving to apply our technologies downstream. It is believed there are very significant applications for genomic-type technologies and information tools to be applied at later stages in discovery and development. The idea is to leverage our technology and know-how from gene to patient. In reality the R&D process in its current state is very inefficient. It takes ten to fifteen years to complete the product cycle of discovery-to-market. It is also very expensive. Current estimates show that the discovery-to-market effort costs about $600 million per drug, with most of that cost comprised of funds consumed by drug candidates that fail in clinical trials. Such a high cost and rate of failure in product development would be blamed on an extremely inefficient process, and in the pharmaceutical industry it is inefficient. Industry executives need to start thinking about how we can improve the odds of developing a successful drug, and how we can improve the overall productivity of the process. We are making a significant effort to move our initial hits from a high throughput screen toward pre-clinical candidates of higher quality. How do we better predict toxicity, whether it is acute or long-term toxicity, for example? How do we predict the various aspects of pharmacokinetics, such as oral absorption or blood-brain barrier permeability? These are areas that many companies have worked on for years, but we have some significant tools available to us today. We now have information tools and very sensitive *in vitro* measures of some of these parameters. For example, we are using transcriptional and protein profiling to look at pharmacokinetics and toxicity. As we look at different drug candidates, we see significant changes at a very small fraction of the MIC. This is very indicative. By using these fingerprinting methods, we can determine what kinds of effects compounds have besides efficacy. We can determine these effects at a very early stage, using only small amounts of material. We need to develop algorithms to be able to understand how these early measurements translate into animal or human response. This is a major focus for us. We want to be able to have a lead series that goes into animal studies and succeed with higher frequency throughout clinical trials. Drugs fail in the clinic either because they do not work, or because the trial was not appropriately designed. We believe more information can be gathered from animal studies and early-phase clinical trials, and applied to later-stage clinical studies by using bioinformatics technology. How can this information help us to determine what the

inclusion criteria should be for a clinical study? Which clinical endpoints should we choose in order to maximize the chance for success? The overall strategy has been to transform R&D and make a conscious effort to think about the entire process that extends from discovery to the clinic, as opposed to focusing narrowly on one or two technologies. Yet such industrialization really needs to provide more than just vast acceleration to an imperfect, less-than-fully-rational process. The drive towards rationality, coupled with the rise of genomics, the emergence of effective knowledge management systems and the need to improve R&D cost-efficiency, leads inevitably towards the adoption of gene-based technologies, discoveries, and perspectives. The ability of genomics to discover new drug targets is tempered by the realization that genetically complex, high-incidence diseases may involve defects in several genes acting in concert with environmental factors to produce disease. A new paradigm is evolving based on the intersection of emerging new technologies, shifting market realities, and evolving pharmaceutical industry economics. Pharmaceutical companies are staking claims to the new territory. Scientists believe that a Mother Lode of pharmacogenomic-based treasure may well exist, waiting only to be discovered. Early indications are favorable, but nothing really dramatic has yet been accomplished to prove the existence of such a treasure trove. As will be seen, the enterprise rests in large measure on a fundamental genetic hypothesis that has yet to be verified. A major part of the effort being expended by small, medium, and large-sized companies is being directed toward the testing of this hypothesis. Rapid advances in genomics have touched off a commercial race to identify new gene targets, which become subjects of big pharma's "industrialized" drug discovery assembly lines in a race to alleviate the innovation deficient. The story does not end there, because genomic advance have reignited interest in genetic variability and its application to the study of drug response variations among individuals. It is hoped that such studies can provide new drugs and diagnostics that can enhance safety and efficacy, while reducing the costs accompanying inappropriate drug therapy and adverse drug reactions. The emerging field of pharmacogenomics promises to satify these requirements, perhaps at the cost of reducing the size of the market for resulting drugs.

Fig. 1. High throughput intergration: Industrialization of process