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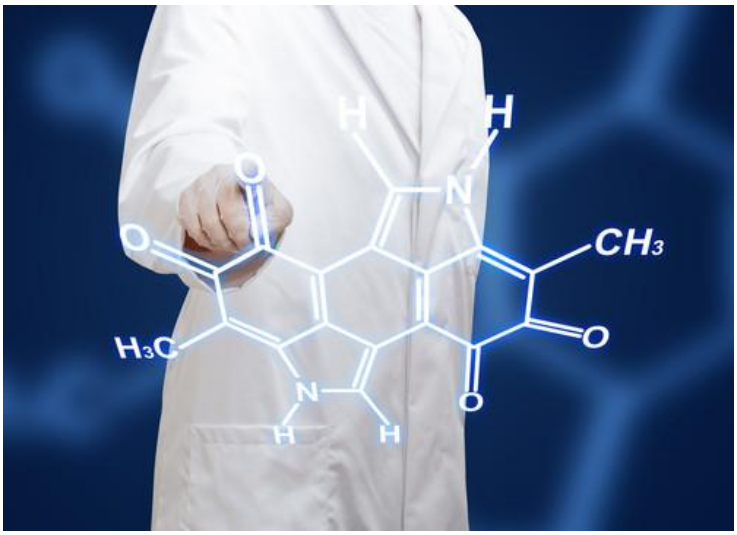
The Future of Drug Discovery: Two Required Supplements to Current Practices

23 July 2013 in Articles



A massive restructuring is currently taking place within pharmaceutical industry drug discovery sector. Consequently, we suggest that phenotypic screening and drug repositioning will need to be increasingly utilized to uncover new therapeutics.

A convergence of forces in the pharmaceutical/biopharmaceutical industry continues to drive rapid rates of business restructuring in 2013. Although US regulatory policy issues, healthcare costs, globalization and other forces all contribute to this morphogenesis, the patent cliff that we are working through now has been a tremendous contributor as roughly $100 billion in sales have or will go off patent from 2010 to 2014. This massive loss in pharmaceutical companies' top line is naturally flowing down to an array of cost-cutting measures in the industry, but drug discovery R&D is the true "canary in the coal mine."

Since 2000, the pharmaceutical industry has eliminated about 300,000 jobs — as many people as currently work at the three largest drug makers (Pfizer, Merck and GSK) — combined.1 A significant portion of these are chemists, biologists and other scientists who participated in drug discovery. Large portions of R&D process have been outsourced to third-party, offshore contractors, raising criticism that true innovation, vital for drug discovery, is being significantly compromised.2 And although some have argued that drug discovery will increasingly shift into small to mid-sized biotechnology

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companies, and even academia, these sectors are also reeling from disruptions in the venture capital markets and pressures on the federal budget.

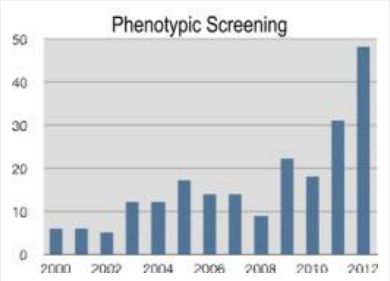
Andrew Reaume

Christopher Lipinski

These disruptions and the restructuring of drug discovery across the industry have not significantly affected later stage, clinical programmes, as observed in rates of new drug application (NDA) fillings and new drug approvals, which have remained relatively stable (and even improved) in the last few years. It seems, however, quite likely that a day of reckoning is lurking on the horizon when opportunities for new drug candidates may begin to dry up. As a consequence, the industry has become very pragmatic about cost-effective strategies to drug discovery. Our experience indicates that strategic approaches such as phenotypic screening and drug repositioning will continue to be increasingly adopted in this new cost-effectiveness driven era of drug discovery.

Phenotypic Screening

The first of these strategies, phenotypic screening, can be viewed either as a departure or a complement to our existing standard paradigm for drug discovery — the target-based medicinal chemistry approach that runs central to all pharma R&D operations and has done since the 1980s and 1990s. The current approach, in a reductionist way of thinking, relies on our current understanding about biochemical pathways and their relationship to disease processes.



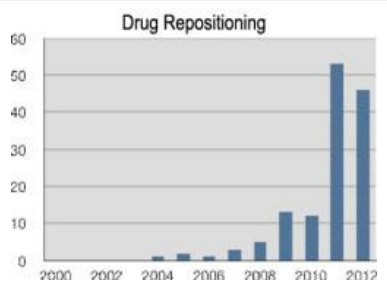
Literature Occurrences of Phenotypic Screening

Hypotheses are developed as to what enzyme or receptor should be modulated (inhibited or activated) to effect a positive outcome on a disease process. By contrast, phenotypic screening is, by its nature, not hypothesis-based, but instead is an empirical approach that relies upon observations of drug candidate activity in a system, such as an animal model of a disease process, independent of any initial hypothesis of why or how that candidate may be therapeutic towards the disease. One can make the argument, as have many pundits who have commented on the productivity gap in the pharmaceutical industry, that given the extreme complexity of biochemical pathways within intact higher organisms, that our hypotheses are too often wrong and the cost of testing them is too expensive leading to higher and higher R&D investments without concomitant productivity.3–5

The seminal publication by Swinney and Anthony showed, that despite an industry essentially focused on new drug discovery using the target-based approach, most first-in-class small molecule drugs were discovered by phenotypic screening.6 A possible criticism of phenotypic screening is that it will discover off-target effects that then need to be followed-up through additional hypothesis-based research. Based on our own mechanism of agnostic phenotypic screening of more than 200 drugs, we strongly believe that most (75–90%) of new biology uncovered by phenotypic screening is driven by on-target effects.7 An unbiased phenotypic screen is far more likely to uncover unexpected biology for a known mechanism than it is to discover new biology because of an off-target effect. Some companies such as Eli Lilly have been pursuing phenotypic drugs for close to a decade as a complement to mechanism/target-based drug discovery. Nevertheless, in our opinion, there is considerable opportunity to incorporate an increased balance of phenotypic to mechanistic screening in drug discovery. The barriers to increased phenotypic screening are partially the cultural familiarity with the mechanistic approach and in the case of cell-based assays the technical challenges of incorporating high-density data readouts into higher throughput assays.

Drug Repositioning

The second strategic element that is increasingly being adopted to increase cost-effective drug discovery is drug repositioning. It turns out that the famous words of Sir James Black: "The most fruitful basis for the discovery of a new drug is to start with an old drug" has a sound biological rationale that Black could not have fully appreciated at the time. From the point of view of molecular evolution, we now know that nature 'recycles' protein motifs again and again, and for this reason the chemical universe of biologically active compounds is characterized by dense spaces of hotspots with vast amounts of chemistry space that is biologically empty.8



Literature Occurences of Drug Repositioning

Although this finding is useful for medicinal chemists seeking to design new chemical entities, it also has a corollary, namely that compounds designed for one therapeutic area often have therapeutic benefit in other areas. In fact, it turns out that about 30% of approved drugs are labelled for indications other than the indication for which they were originally developed.9 Moreover a Thomson-Reuters Integrity database analysis shows that a drug in development for a single indication is the exception and that pursuit of multiple indications is the rule.10

Identifying new drug candidates from within the existing pharmacopeia (drug repositioning) has the well-recognized benefits of short cutting development, and thereby significantly reducing costs, by virtue of utilizing pre-existing preclinical and clinical drug development data. In most cases the first clinical studies for a new candidate can be in disease patients thereby obviating the time, expense and risk associated with Phase I studies. Although composition-of-matter patents typically are unavailable to provide exclusivity for repositioned candidates chosen from previously studied drugs, method-of-use patents, in many contexts, can be as rigorous (for compounds that have never had market approval). Also, with the lower costs to market it can be the case with many therapeutic product opportunities that the required commercialization thresholds may be met with the 5 years of data exclusivity available in the US and 10 years available in Europe through Trade-Related Aspects of Intellectual Property Rights (TRIPs) (again applies to compounds that have never had market approval).11 At a recent Washington DC drug repositioning conference there was audience unanimity that increasing the data exclusivity period was the single event most likely to enhance the drug repositioning field.

Conclusion

The significant economic pressures creating the need for changes in the drug discovery paradigm are reflected in the increasing literature on drug repositioning and phenotypic screening. Figure 1 shows the number of papers each year since 2000 citing 'drug repositioning' or 'phenotypic screening.' If the inflection shown in this figure is any indication it may be that we are at the dawning of a new era of how drugs are discovered.

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8. C.A. Lipinski, "A Perspective on the Evolution of Collaborative Drug Discovery and Future Challenges," in R. Chaguturu (Ed.), Collaborative Drug Discovery: Strategies for Academic, Industry and Government Partnerships (John Wiley & Sons Inc., 2013).
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11. M.S. Saporito, C.A. Lipinski and A. Reaume, "Phenotypic In Vivo Screening to Identify New, Unpredicted Indications for existing Drugs and Drug Candidates," in M.J. Barratt and D. Frail (Eds.) Drug Repositioning: Bringing New Life to Shelved Assets (John Wiley & Sons Hoboken, NJ, USA, 2012).

For more information

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