

Pharmaceutical Industry at the Post-Genomic Junction

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The pharmaceutical industry is in disarray, notwithstanding the enticing promises of the post-genomic era. Drug discovery appears to be harder and riskier than ever [1]. Projects get unexpectedly terminated in mid-stage clinical trials, new targets are getting harder to find, and successful therapeutic agents are often recalled as idiosyncratic side effects affecting small patient subpopulations are discovered [2]. Exploiting the huge output of post-genomic studies to address such problems has proven to be far harder than anticipated. More than ever, the lead in the pharmaceutical industry depends on the ability to harness innovative research. In this regard, wrapping [2-15], a basic concept stemming from fundamental bio molecular research, may well hold potential to broaden the technological base of the industry and enable a vigorous recovery.

Wrapping is a relatively novel category in structural biology, in which the 3D-structure of the target protein is examined not by itself but in relation to the surrounding solvent [2-5]. More specifically, wrapping describes the extent to which a protein is capable of protecting its native structure from water attack or better still, from competing backbone hydration. It has been recently shown that wrapping provides the basis for a rational translational approach to molecular targeted therapy since wrapping defects are fairly unique to the protein targets [6]. These deficiencies are less conserved across proteins of common ancestry than the fold, which tends to be shared across homologs. Thus, a "wrapping drug", that is, a drug that corrects the wrapping defects of the target upon binding to it, should in principle permit a better control of specificity [6]. This idea heralded the advent of the so-called "wrapping technology" with the overarching goal of designing safer drugs with reduced side effects [7-11].

The wrapping technology stands at the antipodes of current discovery endeavors based on high-throughput screening and trial-and-error approaches. Before incarnating as a molecular design concept, wrapping has been explored from a biophysical and evolutionary perspective. Thus, wrapping becomes particularly insightful as we try to characterize the protein-water interface. The emerging drug-discovery platform is rooted in fundamental principles that shape our current understanding of biological water. The wrapping technology is implemented with the aid of a bioinformatics toolbox that enables us to explore the bio molecular and evolutionary basis of drug specificity.

While such a transformative concept is in principle capable of broadening the technological base of the pharmaceutical industry, a sobering note is in order. Despite the fact that wrapping designs are physically sound, ultimately, only clinical trials can fully assess their therapeutic value and safety. In this regard, and from a practical perspective, current business models in the pharmaceutical R&D may not be supple enough to accommodate this type of innovation.

Current business models developed around prevalent discovery paradigms appear to be getting progressively obsolete and are certainly inadequate to exploit the output of post-genomic forays. More than ever, the lead in the pharmaceutical industry will depend on alternative models with the flexibility to incorporate innovative research and harvest its fruits. On the other hand, the business context required for the efficient exploitation of fundamental breakthroughs remains elusive, and perhaps requires a new breed of leadership.

Standing at the cross roads of drug discovery and academic pursuit, the wrapping concept may well address basic integrative and functional problems of the pharmaceutical industry. The success of this and other key translational concepts depends pivotally on the perceived business imperatives of the industry leadership.

References

1. Cures for an Industry Crisis: Big Pharma Scrambles to Find New Ways to Develop Drugs Faster. Health Economics, Knowledge at Wharton.
2. Fernández A (2010) Transformative Concepts for Drug Design: Target Wrapping. Springer, Heidelberg, Berlin, ISBN: 978-3-642-11791-96.
3. Fernández A, Rogale K, Scott R, Scheraga HA (2004) Inhibitor design by wrapping packing defects in HIV-1 proteins. *Proc Natl Acad Sci* 101: 11640-11645.
4. Fernández A (2004) Keeping dry and crossing membranes. *Nat Biotechnol* 22: 1081-1084.
5. Fernández A (2005) Incomplete protein packing as a selectivity filter in drug design. *Structure* 13: 1829-36.
6. Chen J, Zhang X, Fernández A (2007) Molecular basis for specificity in the druggable kinase: sequence-based analysis. *Bioinformatics* 23: 563-572.
7. Fernández A, Sanguino A, Peng Z, Crespo A, Ozturk E, et al. (2007) Rational drug redesign to overcome drug resistance in cancer therapy: imatinib moving target. *Cancer Research* 67: 4028-4033.
8. Fernández A, Sanguino A, Peng Z, Ozturk E, Chen J, et al. (2007) An anticancer C-Kit kinase inhibitor is re-engineered to make it more active and less cardiotoxic. *Journal of Clinical Investigation* 117: 4044-4054.
9. Crespo A, Fernández A, (2007) Kinase packing defects as drug targets. *Drug Discovery Today* 12: 917-923.
10. Zhang X, Crespo A, Fernández A (2008) Turning promiscuous kinase inhibitors into safer drugs. *Trends Biotechnol* 26: 295-301.
11. Fernández A, Crespo A (2008) Protein wrapping: a molecular marker for association, aggregation and molecular drug design. *Chemical Society Reviews* 37: 2373-2382.
12. Fernández A, Bazan S, Chen J (2009) Taming the induced folding of drug-targeted kinases. *Trends in Pharmacological Sciences* 30: 66-71.
13. Fernández A, Lynch M (2011) Non adaptive origins of interactome complexity. *Nature* 474: 502-505.
14. Fernández A, Sessel S (2009) Selective antagonism of anticancer drugs for side-effect removal. *Trends in Pharmacological Sciences* 30: 403-410.
15. Sessel S, Fernández A (2011) Selectivity filters to edit out side effects in molecular anticancer therapy. *Current Topics in Medicinal Chemistry* 11: 788-799.

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