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# Next-generation therapeutics

## Editorial overview

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Tudor Oprea graduated as a general practitioner from the Victor Babes University of Medicine and Pharmacy, Timisoara, Romania in 1990. He holds a PhD in molecular physiology from the same university (1992). He had pre- and post-doctoral appointments at the University of Utrecht (The Netherlands), Washington University in St Louis and at Los Alamos National Laboratory in Los Alamos (USA), before taking a position as research scientist at AstraZeneca R&D in Mölndal, Sweden (1996–2000). He served as Associate Director in Enabling Sciences and Technology at AstraZeneca R&D Mölndal (2000–2002), where he was in charge of the compound collection enhancement. Dr Oprea joined the University of New Mexico School of Medicine in August 2002, where he is Professor of Biochemistry and Molecular Biology and Chief, Division of Biocomputing, at the same Department. His research focuses on drug discovery, with particular interest in cheminformatics, virtual screening, lead identification and biocomputing.

There has never been a more rational approach to preclinical drug discovery than we are witnessing today. Our ability to understand requirements for therapeutic manipulation of choice targets has dramatically improved in the past decade, an effort that is partly due to our increased ability to design, make and test molecules. We have the ability to identify novel targets and novel chemotypes in a rational manner, and *in silico* methods are now deep-rooted in the process of systematic discovery. Two seemingly unrelated works contributed to this change: a book by Walter E Sneader [1] on drug prototypes, and a paper on the ‘rule of five’, a computational alert procedure suggested by Christopher A Lipinski and co-workers [2]. Sneader’s book, a historical overview of drug discovery from a medicinal chemistry perspective, clearly pointed out that 243 drug prototypes (emerging from animals, plants, microorganisms, screening and serendipity) are responsible for 959 launched drugs. Prototypes continue to be a major source of new drugs, and emerging technologies are expected to help generate novel prototypes. Lipinski’s ‘rule of five’ described methodology implemented at Pfizer’s Groton laboratories, where computational criteria were applied to newly synthesized compounds, as they entered the Pfizer compound collection. These criteria, designed to assist chemists with seemingly intractable pharmacokinetic properties, were derived from (and applicable to) oral bioavailability. These efforts inspired the development of leadlikeness [3], a concept applied today in most pharmaceutical projects, and had a positive effect in encouraging the dialogue between cheminformatics and molecular modeling specialists, on one hand, and practicing chemists or biologists, on the other hand. This issue is a living example of how both aspects of scientific endeavour (i.e. experiment and theory) are required to achieve a balanced effort in the quest for novel therapeutics.

Target identification and validation, key requirement to any preclinical drug discovery effort, are discussed by Chang and co-workers. Their review provides an update on microarray techniques, bioinformatics approaches, antisense technology, chemical genomics and other methodologies used by the drug-discovery community.

Three reviews in this issue are devoted to virtual screening (VS) technologies. VS epitomizes the use of computational tools to identify and evaluate bioactive molecules *in silico*, and is becoming a complementary and alternative method to high-throughput screening of existing molecules. Oprea and Matter describe how VS has the potential to evaluate enormous numbers of *in silico* compounds, saving time in lead discovery. This power can only be realized if it integrates accurate models for multiple response surface optimization, from physical organic chemistry to pharmacology, physiology to toxicology. The authors focus on eight recently confirmed

VS hits and appraise the techniques of target-based and ligand-based VS. Jansen and Martin describe how target bias can be included in the scoring and/or selection step of a structure-based VS protocol, effectively addressing the problem of false positives and false negatives. A third review by Alvarez looks at VS from the docking perspective, with focus on success stories. As lead discovery is a multiple response surface optimization, it is important to predict, at the earliest stage possible in discovery, how a molecule will behave in humans. Davis and Riley describe predictive ADMET (absorption, distribution, metabolism, elimination and toxicology) as the new 'hip' area of preclinical drug discovery. They describe various methods of projecting ADMET data from *in silico* models, inter-species studies and *in vitro-in vivo* methods.

Erlanson and Hansen discuss the Tethering technique, a combination of site-directed and fragment-based lead discovery used to rapidly develop high affinity ligands from known or random fragments, using easily accessible (e.g., sulfur) chemistry. Villar, Yan and Hansen describe how pervasive NMR techniques have become in drug discovery, in areas such as target validation, ADMET, lead discovery and optimization.

Blake examines the integration of cheminformatics analyses and combinatorial synthesis, following the continuing development of post-'rule of five' computational alert procedures, as key physicochemical properties of database compounds can guide the choice of which compounds to synthesize and pursue in lead discovery.

Savchuk *et al.* review chemogenomics approaches from the perspective of using annotated libraries as chemical design starting points. An ever-increasing number of potential drug targets require integrated biological and chemical data. Annotated chemical libraries provide a strong basis for the design of target-directed combinatorial libraries.

Pagliari *et al.* provide a chemical analysis of protein-protein interaction inhibitors, with a focus on small-molecule intervention. As well as reviewing recent successes, the authors also comment on the screening assays used to discover such inhibitors.

Sklar and co-workers take a look at new developments in flow cytometry. Advances in this mature technique have dramatically increased the speed of sample handling and

data analysis. They argue that flow cytometry is now an attractive analysis platform for high-throughput, high-content screening in drug discovery.

Key to the success of combinatorial chemistry in the context of high-throughput screening is ascertaining the presence of the intended compounds and their purity. Keneth and Coldiron review recent progress in the development of methods for high-throughput analytical characterization and quality control of discrete, small-molecule combinatorial libraries.

Chemical biology, as represented by diversity-oriented synthesis, and targeted (biased) libraries are discussed by Auer and co-workers in the context of conformational diversity and informational complexity. They remind us that although various groups have achieved chemical and biophysical characterization of new 'target compound pairs', most approaches have yielded only two out of the three key pieces of information: target, compound and mode of action.

Anti-angiogenic therapy is an important insight that emerged from tumor biology. Numerous anti-angiogenic small molecules, most of them inhibitors of receptor tyrosine kinases, are currently in clinical trials as novel anti-cancer therapeutics. Mazitschek and Giannis discuss the current state of the field.

The above reviews offer an intriguing view of the current state of preclinical drug discovery, as it seeks to reinvent itself by exploring novel technologies or by providing better integration for existing ones. Our increased knowledge in a variety of seemingly unrelated phenomena, from atomic level issues related to drug-receptor binding to bulk properties of drugs and ADMET profiling, is likely to lead us on a better path for the discovery of orally bioavailable drugs, while paving the way for novel, unexpected therapeutics.

## References

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