

DDTP Symposium Biophysics in Drug Development

Friday, March 2, 2012

8:30 AM to 12:30 PM

Faculty Club, McGill University

presented by

**McGill-CIHR
Drug Development
Training Program**



Schedule

8:30 - 9:00 **Coffee/Registration**

9:00 -10:00 **Dr. Ernesto Freire**

Achieving Extremely High Affinity and
Selectivity in Drug Design

10:00 -10:15 **Coffee**

10:15 -11:15 **Dr. Elizabeth Vadas**

Selection of a Drug Development Candidate and Dosage Form Design - Know Thy Physical Chemistry!

11:15 -12:15 **Dr. Lipinski**

Times of Change in Drug Discovery and
Chemical Biology: Hard Lessons from the
Last Decades

Chair: **Dr. Anthony Mittermaier**



Dr. Ernesto Freire

Department of Biology
Johns Hopkins University
Baltimore, MD

Achieving Extremely High Affinity and Selectivity in Drug Design

Extremely high affinity and selectivity are two of the most sought after properties of drug molecules. Since the binding affinity originates from the sum of enthalpic and entropic contributions to the Gibbs energy of binding, it is apparent that optimization strategies that maximize both contributions should be preferred. Recently, the concept of thermodynamic optimization plots (TOPs) was introduced. TOPs provide an easy way of organizing enthalpy, entropy and Gibbs energy data obtained by isothermal titration calorimetry (ITC) in order to accelerate the affinity optimization of drug candidates. While traditional structure/activity relationships rely solely on binding affinity, TOPs expand the range of correlations to enthalpic and entropic coordinates. TOPs identify affinity bottlenecks and provide effective solutions directed to achieve extremely high affinity. By providing a precise structural mapping of enthalpic and entropic effects, TOPs also provide a way to optimize or modify the thermodynamic signatures of lead candidates. Another key property of drug molecules is selectivity or specificity. Selectivity is difficult to achieve, especially for targets that belong to large families of structurally and functionally related proteins. There are essentially two ways of improving selectivity during lead optimization: 1) a chemical modification of the lead compound improves the affinity towards the target to a higher extent than to off target molecules; and, 2) a chemical modification of the lead compound actually lowers its affinity towards off target molecules. Maximal selectivity is achieved when both situations apply simultaneously. Analysis of several protease inhibitors that

vary by a single functionality indicates that non-polar functionalities can follow either mechanism while polar functionalities follow the second one. The actual mechanism reflects the balance of desolvation and target interactions and is revealed in changes in thermodynamic signature. These results indicate that ITC can be used as an important tool for affinity and selectivity optimization. This work was supported by grants from the National Institutes of Health (GM56550 and GM57144) and the National Science Foundation (MCB0641252).



Dr. Elizabeth Vadas

Owner
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Selection Of A Drug Development Candidate And Dosage Form Design - Know Thy Physical Chemistry!

The Holy Grail of drug discovery is to find the perfect molecule that can fulfill all requirements of specificity, potency, safety and efficacy resulting in a major breakthrough in targeting a specific disease. While achieving this goal is indeed the major motivation that brings medicinal chemists, biologists, biochemists and other discovery scientists to the laboratory day after day, it must be recognized that finding the “perfect” molecule maybe an elusive goal.

A newly discovered molecule must fulfill a number of other requirements before it can become a viable development candidate. These requirements include having the appropriate biopharmaceutical and pharmacokinetic properties, as well as physicochemical characteristics such as solubility, stability in the solid state and in solution and the potential for a scalable, commercially viable synthetic route, just to name a few.

Upon examination of the different requirements corresponding to the needs of each of the scientific disciplines that play a role in developing a molecule into a viable therapeutic entity, it becomes clear that the best development candidate is unlikely to be the ideal molecule. Most likely the molecule will be a best compromise. Using a team approach, discovery and development scientists must jointly evaluate the risks inherent in the molecule, decide what imperfections of the molecule may be tolerated, what the costs of these imperfections are, and then design a strategy to minimize risks during the development process.

Understanding and exploiting the physicochemical properties is one of the potential ways to accommodate imperfections and to minimize risks to the development program. This understanding must be arrived at within the context of the disease, the target patient population, the clinical needs, the appropriate dosage form(s) and the safe and efficacious doses to be developed.

The dosage form concerns include route of administration, dose range and dose strengths, crystallinity, solubility, chemical and physical stability alone and in the presence of excipients, biopharmaceutical properties, and the analytical methods that will need to be developed and the processes by which the formulations will be made.

The presentation will use real life examples of how approaches in dosage form design rooted in principles of physical chemistry can advance a molecule in development. Low aqueous solubility, multiple crystal forms, the presence of ionisable groups on the molecule may represent hurdles to development. Conversely, these properties may represent opportunities for innovative approaches in dosage form development resulting in safe and efficacious medicines.



Dr. Chris Lipinski

Scientific Advisor
Melior Discovery
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Times of Change in Drug Discovery and Chemical Biology: Hard Lessons from the Last Decades

In 2012, we have lists of rules and structural filters to avoid problematic chemistry functionality and we have consistent published reports from multiple companies spanning hundreds of clinical candidates on the association of relatively simple physicochemical properties with compound survival in the clinic. Despite this level of knowledge, drug discovery is not getting easier. Why is this?

To me it is clear that several widely held beliefs over the last few decades in the biology realm are charitably speaking flawed, or more bluntly are outright wrong. The truly selective and potent single ligand for a single target reductionist drug discovery approach is fundamentally flawed. Multi targeted drug discovery, phenotypic screening and drug repositioning are all in ascendancy. People are only recently beginning to realize that problems of bias and error long known and painfully addressed in the clinical realm are huge problems in the pre-clinical space. Hypothesis driven biology research is a recipe for error. Better than half of academic target identification is completely wrong.

Similar chemistry translates to similar biology; right or wrong? Wrong, network maps for targets and network maps for ligands do not superimpose particularly well. As a consequence, it is really important to do chemistry due diligence around a hit or lead. Similar chemistry drug motifs tend to reoccur across targets with quite different biology. Biologically active compounds are most definitely

not evenly distributed in chemistry space. As a result, screening truly diverse chemical libraries is the worst way to discover a drug.

Disciplines involved in drug discovery / chemical biology can be sorted into two classes; those with broad scope and generality, eg. medicinal chemistry and those with narrower and more precise focus, eg biology, whether in-vitro target / mechanism or in-vivo readout. Of the broader disciplines, medicinal chemistry has the longest history and therefore in some ways is the best understood. Depth in understanding translates to better control especially since the compound structure and resulting properties dictate the pK / pD and clinical effects both positive (as in efficacy) and negative (as in toxicity). With understanding comes responsibility, namely not to squander opportunities in chemical biology and drug discovery by progressing flawed compounds.

Directions

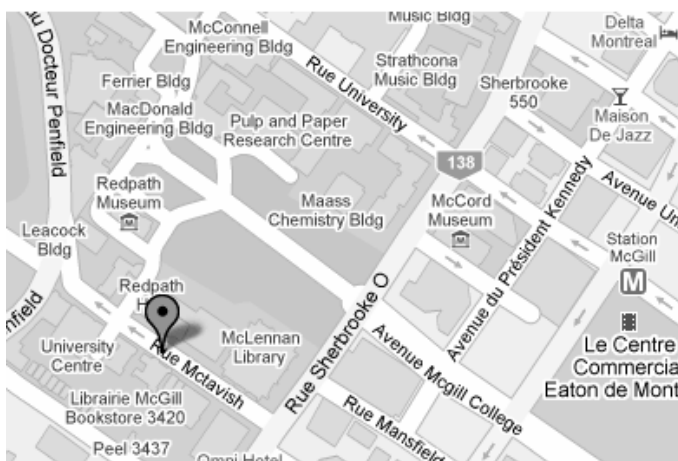
The symposium will take place in the ballroom at the Faculty Club of McGill University located at:

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Faculty Club



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