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INTRODUCTION

Surviving and Thriving in the High Throughput Environment

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This set of papers provides perspectives on the evolution of technologies that increasingly drive both pharmaceutical discovery and fundamental discovery in biology. This past decade is unparalleled in the introduction of novel tools that increase productivity by orders of magnitude. Combinatorial chemistry, for example, stimulated the automation of chemical synthesis to the point where century old pharmaceutical companies were, overnight it seems, synthesizing more new chemical entities in a single year than had been synthesized in the prior history of the companies. One challenge met, another created; this required the same quantum jump in biomolecular screening capabilities. This was met with engineering advances at all levels: instrumentation capable of a quarter million assays per day, miniaturization to hold down cost of reagents and facilities, and improved assays that can determine outcome of interactions between compound and target in the intracellular environment, enabling for example, co-assessment of bioavailability and activity. Another challenge met, still another challenge created: How do you visualize results of tens of thousands of assays and plan the next round of chemical synthesis time effectively? Chemical informatics meets bioinformatics; fortunately, computers were already up to the task and newer and more effective generations of algorithms have increased both the speed and effectiveness in analysis and prediction.

Given the desirability of capabilities that accomplish far more at substantially reduced unit cost, additional efforts at enhancing the overall drug discovery and development processes abound. Later stage steps in drug development can be moved forward so that earlier assessments of potential toxicity can be incorporated into decision processes for chemical synthesis. This enhancement side steps potentially costly dead ends. Transcription array analysis of drug candidate activity can provide greatly improved views of mechanism that were out of reach only a few years ago. Scaleable proteomics technologies complement and extend this information. The knowledge level provided by the sum of these scaleable methods is subject only to the ingenuity of a new breed of computational biologists and chemists who have taken up firm residence at interfaces between discovery processes.

If the science and art of drug development are not your primary forte, you may wish to begin your reading of these papers with the contribution by Prabha Fernendes who has participated substantially in the high throughput revolution. Figure 1 of her paper describes the overall process of drug development, though she cautions that components of the process are often as much matrix related as straight lined. So fortified you will be better prepared for what follows. Shankar Balasubramanian describes combinatorial chemistry approaches to synthesis of classes of compounds that possess interesting biological activities. Robert Goodnow contributes a clear picture of how combinatorial chemistry and medicinal chemistry are evolving together. Clearly, the diversity of chemical libraries is greatly enhanced when an optimal number of suitable scaffolds is selected for combinatorial embellishment, as opposed to sole reliance on combinatorial approaches with a single or few scaffolds. David Hunter describes the evolution of automated chemical laboratory design that incorporates flexibility to drive scaleable synthetic approaches that find the

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best line between multiple scaffolds and combinatorial strategies. Randall King and his colleagues introduce chemical genetics which itself introduces a dilemma. Is this chemistry or screening? It is both and epitomizes the level of integration that is frequently achieved in problem solving approaches that proceed with selection of highly active small ligands from large and diverse libraries.

The second section of this issue examines the interplay between biomolecular screening and bioinformatics in target identification. The cellular biochemist requires little introduction to the technologies and systems employed here. The technologies for screening range from protein-ligand to protein-protein to protein-nucleic acid as well as to ligand-induced modifications in the latter two. Donghui Ma and Min Li introduce the analytical back end of display methodologies that are increasingly powerful driving forces in discovery processes. Keith Joung and Chris Voigt and his colleagues describe co-application of experimentation and computation for optimizing interactions between macromolecules or properties of the macromolecules themselves. Fuyu Tamanoi and his colleagues examine relationships between post-translational protein modification and activity and the Yguerabides describe ultrasensitive capabilities for display at the cellular level employing quantum dots. Erica Golemis and her colleagues address factors that should be considered in drug discovery now that display technologies can begin to analytically address the complexities of biological systems.

Strategies for addressing the nature and specificity of interactions between macromolecules or between ligand and macromolecule are addressed in the third section. Virgil Woods describes direct chemical technology for identifying the site of interaction between ligand and protein as well as sites in proteins that undergo allosteric modification in response to ligand binding. Sem and colleagues describe NMR tools for characterizing protein-ligand interactions that enable construction of focused chemical libraries directed at families of enzymes or receptors. Velaques-Campoy and Freire examine binding site dynamics with a view on developing "adaptive" drug molecules. Given the evolution of target in response to ligand in antiviral and antibacterial therapies and some classes of cancer therapy, is it possible to design ligands that are effective not only with the initial target but also with targets that would otherwise evolve to escape drug action?

The final section focuses on genomic approaches to gene product classification and drug discovery. Mateo Pelligrini and colleagues have developed predictive clustering approaches by which protein products of genes that have no described function(s) can be associated with described pathways. This has substantial relevance to today's discovery environment in which half the products of described genes of many organisms have yet to be described functions. Juergen Hammer and his colleagues comment on three examples of functional genomics applications in the drug discovery process: identification of drug targets, identification of prodrug-converting enzymes associated specifically with disease tissue (prodrug development) and vaccinomics (computational models for simulating and predicting disease specific epitopes). Eric Schadt, Cheng Li, Byron Ellis and Wing Wong describe the DNA-Chip Analyzer, consisting of algorithms for enhancing low level analysis of oligonucleotide array experiments. This validated software is available in beta version through their website. The capstone paper by Irwin Chaiken draws widely on components presented throughout this issue in examining high throughput strategies for designing ligands that modify receptor behavior. He ends with a plea for even more powerful high throughput tools.

The articles in this issue are contributed primarily by authors participating in 5th Lake Tahoe Symposium, an annual meeting focused on high throughput innovations in drug discovery. Drs. Irwin Chaiken, Prabha Fernandes, Fred Fox, Paul Hoeprich, Douglas Livingston, and Robert Pearlman participated in the selection of authors for this issue. Extended abstracts of papers presented at these meetings are freely available on the web at http://laketahoesymposia.org.