Chemogenomics: Metabolism and Toxicology for Chemistry and Biology

When: **November 29th, 8:30 am**
Where: **San Diego Super Computer Center - Main Auditorium**
Who should attend: **Chemists, Medicinal Chemists, Biologists, Toxicologists, Genomics and Proteomic Scientists, & ADME/Tox and Pharmacokinetic Scientists**

Agenda:

8:30-9:00am **Registration and breakfast**

9:00-9:45am **"Drug safety: the early detection of drug side effects and toxic responses through gene expression and gene ontologies"**
- **Dr. Jacques Retief, Director of Collaborations, Affymetrix**

9:45-10:30am **"The Rosetta Resolver® System: An Enterprise Solution for Gene Expression Analysis and Predictive Biology"**
- **Dr. Lee Weng, Director of Applied Research, Rosetta Biosoftware**

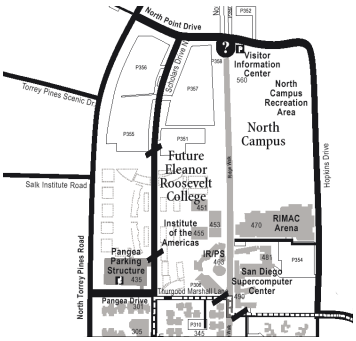
10:30-10:50am **Break**

10:50-11:35am **"A Systems-Based Approach for Predicting Drug Metabolism and Toxicology"**
- **Dr. Sean Ekins, VP Computational Biology, GeneGo Inc.**

11:35-12:20pm **"Signature Networks as Biomarkers. The Method and Applications"**
- **Dr. Yuri Nikolsky, CEO, GeneGo Inc.**

12:20-12:30pm **Wrap Up**

Please RSVP to Laura Brovold at laura@bryant-consulting-group.com or (858)756-7996



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Abstracts

"Drug safety: the early detection of drug side effects and toxic responses through gene expression and gene ontologies"

- Dr. Jacques Retief, Director of Collaborations, Affymetrix

Genome-wide arrays, promise to deliver a comprehensive view of all the molecular processes in the cell. In the field of toxicogenomics such a complete view should enable us to simultaneously monitor the on-target effect of a drug as well as its toxicological side effects and other perturbations of the biological system. To deliver on this promise we need a robust experimental design capable of detecting small, but statistically significant, changes in the gene expression level combined with a biological understanding of the gene functions. We will discuss several case studies where we use Gene Ontology, (GO) classifications with GeneChip® gene expression data to determine the on- and off-target effects of a series of well-studied drugs.

"The Rosetta Resolver® System: An Enterprise Solution for Gene Expression Analysis and Predictive Biology"

- Dr. Lee Weng, Director of Applied Research, Rosetta Biosoftware

It has become more and more difficult and costly to successfully develop a new drug. Compound toxicity is one of the major factors that contribute to the failure of a drug in development. There is an increasing need for more effective methods and tools for predicting the efficacy and safety of drugs. Lately, large-scale data acquisition technologies, such as gene expression microarrays, have provided new opportunities to better understand the biology underlying the drug discovery process. The increasing volume and complexity of data have created demands for more powerful analysis and data management tools. These new tools are developed with the primary goals of creating higher statistical analysis power and discovering more valuable information in the data. This presentation focuses on the use of the Rosetta Resolver system for gene expression data analysis as a vehicle to discuss the challenges in providing tools for the revolution in drug development. The Resolver system serves as a centerpiece in an enterprise environment to routinely process and manage data from hundreds and thousands of high-density microarrays. Although the total amount of data in microarray studies is enormous, the number of replications is usually too small to make reliable statistical inferences based on conventional statistical methods. The error model technology in the Rosetta Resolver system provides a major breakthrough in handling microarray data with low replications. It offers significantly higher power in statistical analysis than the conventional textbook method. To explore the biologically important information hidden in the vast amounts of microarray data, the Resolver system provides unsupervised and supervised data mining capabilities to help biologists gain new

knowledge from the data. One example is demonstrated in the recently published results where a supervised learning tool is used in breast cancer studies to classify and predict patients' prognoses based on their gene expression profiles. Another example shows how the system leverages contents in toxicogenomics databases to help identify potential safety problems in preclinical studies. These case studies show how the Rosetta Resolver system supports data-driven knowledge discovery to improve the drug discovery and development process.

"A Systems-Based Approach for Predicting Drug Metabolism and Toxicology"

- Sean Ekins, VP Computational Biology, GeneGo Inc.

To date computational approaches for ADME/TOX have resulted in models for the individual proteins. I will present an overview of MetaDrug™, a new predictive software platform comprising a database of xenobiotic and endobiotic metabolism as well as methods for predicting metabolites and enzymes involved. In addition I will describe a systems-based approach that uses the accumulated biological data on metabolic, signaling and regulatory networks in order to visualize high throughput data. Ultimately this tool will aid our understanding of metabolism and toxicity of molecules early in the drug discovery progress.

"Signature Networks as Biomarkers. The Method and Applications"

- Yuri Nikolsky, CEO, GeneGo Inc.

Gene signatures are the small gene sets statistically deduced from the large datasets of conditional differential global gene expression. Gene signatures define the minimal list of over- or under-expressed genes characteristic for a certain condition; they are applied as molecular biomarkers but, as a technique, are prone to experimental and statistical errors. We developed an essentially novel approach of "signature interaction networks" (SINs), which overcomes the drawbacks associated with gene signatures. We elucidate SINs from differentially expressed gene sets by mapping the data onto the curated database of human protein-protein and protein-DNA interactions in our MetaCore™ analytical suite, followed by functional analysis and logical operations on the initial networks. We will present the method and the case studies on the SINs for differential drug treatment of the human CSF1 breast cancer cell line and SINs built for different types of toxicity in toxicogenomics studies.

Bios

Dr. Jacques Retief, Director of Collaborations, Affymetrix

Dr. Lee Weng, Director of Applied Research, Rosetta Biosoftware

As the Director of Applied Research, Dr. Weng leads the bioinformatics research and development projects at Rosetta Biosoftware. He leads the effort to develop statistical error models and other microarray analysis tools in the Rosetta Resolver system. These error models and tools provide highly sensitive and specific analysis results for many different gene expression or proteomics technologies. Prior to joining Rosetta Biosoftware in 2000, Dr. Weng served as VP of Advanced Development at Therus Corporation from 1998 to 2000. He was Senior Staff Scientist and Team Lead at Siemens Medical Systems from 1992 to 1998, and R&D manager at Angiosonics from 1990 to 1992. Dr. Weng received his Ph.D. degree in Biomedical Engineering from Drexel University in Philadelphia, PA in 1990.

Sean Ekins, GeneGo Inc.

Dr. Sean Ekins undertook his graduate training in Clinical Pharmacology at the University of Aberdeen; receiving his M.Sc. in 1993 and Ph.D. in 1996. Sean then pursued postdoctoral studies at Lilly Research Laboratories in Drug Disposition. Subsequently, Dr. Ekins has held a number of positions where he honed his interest in computational biology related to drug disposition. These included an appointment at Pfizer (1998-1999), a return to Lilly Research Laboratories (1999-2001), an appointment at Concurrent Pharmaceuticals, Inc. (2001-2004) and lastly his current position with GeneGo. During this period Dr. Ekins has authored or co-authored ~60 peer reviewed papers on in vitro and computational approaches to ADME/Tox. Dr. Ekins also holds several patents in the area of computational biology as related to drug disposition. His expertise has led to appointments as Associate Editor of the Journal of Pharmacological and Toxicological Methods and to the Editorial Board of Drug Metabolism and Disposition.

Yuri Nikolsky, GeneGo Inc.

Yuri Nikolsky is the CEO of GeneGo, Inc. (St. Joseph, MI) from December 2003. Dr. Nikolsky has over ten years of experience in life science, both business and technology. Prior to joining GeneGo, he was a CEO of Chemical Diversity Labs (San Diego, CA), a medicinal chemistry outsourcing company. Prior to that, he co-founded and served as

Vice President for Business Development at Integrated Genomics, Inc. (Chicago, IL), a comparative genomics and bioinformatics company. Dr. Nikolsky has also held positions as a Senior Scientist for Thermogen, Inc. (Chicago, IL) and as Research Associate (Instructor) at the University of Chicago. Dr. Nikolsky holds an MBA degree in Finance from the University of Chicago, a Masters degree in Biology from Moscow State University, and a Doctoral degree in molecular genetics from VNII Genetika Graduate School in Moscow, Russia. Dr. Nikolsky has published over 20 peer-review papers on different aspects of genomics, medicinal chemistry and systems biology.