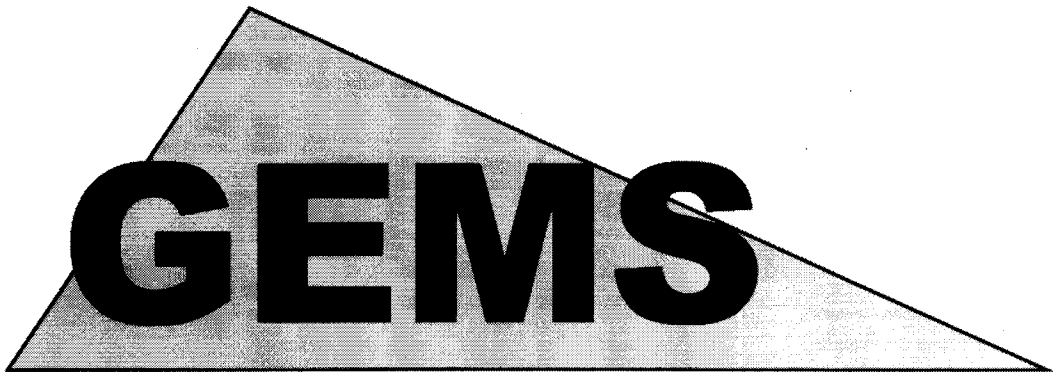

Genetics and Environmental Mutagenesis Society

2007 Spring Meeting

"Integrative Bioinformatics: Systems Biology Approaches to Genetics, Metabolism & Disease"

Monday, April 16th, 2007

U.S. Environmental Protection Agency

109 T.W. Alexander Drive, RTP, NC

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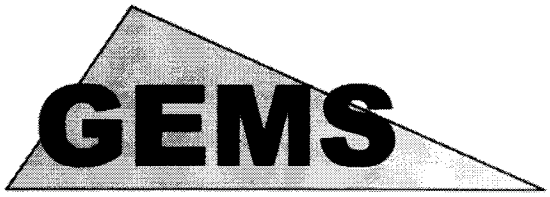


SPRING MEETING
April 16th, 2007

U.S. Environmental Protection Agency
109 T.W. Alexander Drive, RTP, NC

"Integrative Bioinformatics: Systems Biology Approaches to Genetics, Metabolism & Disease"

11:00 - 12:00	Registration and Lunch
12:30 - 1:15	Welcome: Rose Anne McGee, GEMS President-Elect Dr. Bennett Van Houten, Laboratory of Molecular Genetics, National Institute of Environmental Health Sciences *"Systems Approaches To Understanding Friedrich's Ataxia From Yeast To Man"*
1:15 - 2:00	Dr. Christopher J. Portier, Environmental Systems Biology, National Institute of Environmental Health Sciences *"Chipping away at Risk Assessment: Systems Biology, Computer Chips, Gene Chips and Modern Biology"*
2:00 - 2:15	Break
2:15 - 3:00	Dr. William K. Kaufmann, Laboratory of Human DNA Metabolism, University of North Carolina at Chapel Hill *"Systems Biology of Environmental Cancer"*
3:00 - 3:45	Dr. Paul M. Magwene, Department of Biology, Duke University, *"Using Systems Biology to Study Pleiotropy: A Case Study in Yeast"*
3:45 - 4:45	Dr. Michael B. Yaffe, Department of Biology, Massachusetts Institute of Technology, *"A Systems Biology Approach to DNA Damage Signaling"*
4:45 pm	Reception

INVITED SPEAKER PRESENTATIONS

S1. SYSTEMS APPROACHES TO UNDERSTANDING FRIEDRICH'S ATAXIA FROM YEAST TO MAN

Dr. Bennett Van Houten, Ph.D. [1], Astrid C. Haugen [1], Jennifer B. Collins [2], Joel Parker [2], Michael Resnick [1], Nicholas DiProspero [3] and Kenneth Fischbeck [3]

[1] Laboratory of Molecular Genetics, NIEHS, NIH, Research Triangle Park, NC 27709
[2] Microarray Center, NIEHS, NIH, Research Triangle Park, NC 27709
[3] Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, NIH, 35 Convent Drive, Building 35, Room 2A-114, Bethesda, MD 20892.

Friedreich's Ataxia, an autosomal recessive disorder, results in neurodegenerative disease and cardiomyopathy. The *YFH1* gene is the *Saccharomyces cerevisiae* homologue of the human FRDA gene encoding the frataxin protein. Cells lacking *YFH1* exhibit 1) accumulation of iron, which cannot be exported from the mitochondria; 2) oxidation of proteins; 3) oxidative DNA damage, which leads to petite colony formation with defects or loss of mitochondrial DNA and 4) nuclear chromosomal damage (*Human Mol. Gen.* 12:3331-3342, 2003). The cellular impact of mitochondrial iron overload in yeast was determined by global gene expression profiling in a *yfh1Δ* deletion mutant with defective mitochondrial function and no mitochondrial DNA (i.e., rho^0). Mapping these gene expression changes onto the yeast regulatory network of 22,605 protein-protein/protein-DNA interactions visualized through the tool, Cytoscape, revealed Rcs1/Aft1, Mrps5, Hap4, Mrp4, Cox9, and Cad1 as important centers of gene activity. Interestingly, the *yfh1Δ* profile harbored a large number of downregulated mitochondrial ribosomal proteins. In order to more closely recapitulate the human disease, we also conducted transcription profiling on a yeast strain with a rheostatable system that can progressively shutdown the *YFH1* gene. We found similar network responses occurring within 4-6 generations of reduced frataxin levels. Using a systems biology approach we have knocked out key transcription factors to further validate the importance of these response networks.

Based on these yeast results we are testing the hypothesis that Friedreich's ataxia (FRDA) patients: 1) accumulate mitochondrial DNA (mtDNA) damage in peripheral lymphocytes; and 2) share common gene expression patterns unique to the pathogenesis of the disease. Both primary peripheral white blood cells and lymphoblastoid cell lines were examined. Mitochondrial DNA (mtDNA) damage, an indicator of oxidative stress, was measured using a quantitative PCR (QPCR). No significant level of basal DNA lesions was found in the lymphoblastoid cells from FRDA patients, but preliminary data showed more mtDNA damage in FRDA cell lines following treatment with hydrogen peroxide than in age-matched control cell lines. As part of a phase II clinical study, lymphocytes from 48 FDRA patients were assessed for mtDNA damage using the QPCR assay and revealed a range of lesions spanning 0 to over 1 lesion per 10 kb of mtDNA. However, no positive correlation with mtDNA lesions and repeat length or severity of the disease was observed. Gene expression profiling (using a 22,000 oligonucleotide gene array Agilent chip) of lymphoblastoid cells from FRDA patients and controls as analyzed using Ingenuity Pathways analysis, revealed global transcriptional changes associated with cell death, cardiovascular disease, neurological disease, and muscular and skeletal disorders. Gene expression profiles of white blood cells from the 48 FRDA patients display many of the same patterns observed in the lymphoblastoid cell lines. Our long term objective is to develop quantitative biomarkers for disease progression.

S2. CHIPPING AWAY AT RISK ASSESSMENT: SYSTEMS BIOLOGY, COMPUTER CHIPS, GENE CHIPS AND MODERN BIOLOGY

Dr. Christopher J. Portier, Ph.D. [1], Julia Gohlke [1], Fred Parham [1], Marjo Smith [2] and Hiroyoshi Toyoshiba [3]

[1] Environmental Systems Biology, National Institute of Environmental Health Sciences, Research Triangle Park, Research Triangle Park, NC 27709
[2] Constella Group, Durham, NC
[3] Takeda Corporation, Osaka, Japan

The evaluation of health risks from exposure to environmental agents goes through a fairly formal process that involves multiple steps, two of which are the identification of a hazard and the analysis of response as a function of the level of exposure. "Omics" technologies focusing on mRNA expression (genomics), protein expression (proteomics) and metabolite profiling (metabonomics) offer the opportunity to study some of the key events leading to the onset of disease following exposure. Systems biology has developed as a tool to use this information to understand cellular biochemistry and focuses on the development of model structures on the computer to describe a system or part of a system. These tools will eventually play an important role in guiding decisions about health risks. In this talk, we examine the ways in which systems biology could impact on hazard identification and dose-response analysis. The first part of the talk will focus on defining the pathways to disease and the second part will discuss quantifying these pathways.

S3. SYSTEMS BIOLOGY OF ENVIRONMENTAL CANCER

Dr. William K. Kaufmann, Ph.D., Laboratory of Human DNA Metabolism, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599

The mantra of systems biology is the essential properties of a system emerge when all parts in the system and the way they interact are known. With the development of "omic" technologies that permit system-wide analysis of cellular genes, proteins and metabolites, it is possible to imagine a day when the malignant features of cancer can be attributed to specific genetic alterations that alter cellular phenotypes. Malignant melanoma is a skin cancer of environmental origin; sunlight-induced sunburns in childhood constitute a major risk factor. Melanoma is characterized by severe chromosomal instability suggesting that during its development there was deregulation of the systems of response to DNA damage that guard the genome and suppress the development of chromosomal damage. The systems of response to DNA damage include the various pathways of DNA repair and cell cycle checkpoints. We are testing a hypothesis that an early step in melanomagenesis is the development of a chromosomal mutator phenotype that degrades the systems of response to UV-induced DNA damage thereby increasing the likelihood that sunlight-induced damage culminates in chromosomal aberrations. In this talk I will present data showing that normal human melanocytes express effective checkpoint responses to DNA damage, melanoma cell lines display significant defects in checkpoint responses, and selected oncogene mutations in the melanoma lines appear to determine which checkpoint responses are disturbed. Analysis of global gene expression defined signatures that predicted defects in checkpoint function in the melanoma lines. Current results support our hypothesis as the defects in G1 and G2 checkpoint function that were seen in melanoma lines are expected to increase UV-induced chromosomal aberrations. Systems biology also incorporates computational modeling and we have developed models of nucleotide excision repair and the G2 checkpoint. These models enable us to simulate the function of the system after various perturbations of its parts with a goal to discover new alleles that protect against UV-induced chromosomal damage.

S4. USING SYSTEMS BIOLOGY TO STUDY PLEIOTROPY: A CASE STUDY IN YEAST

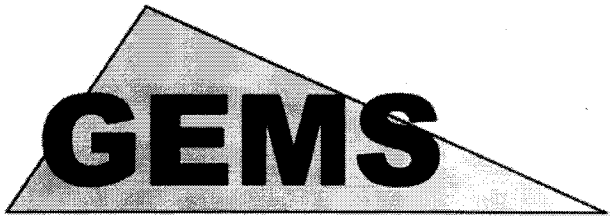
Dr. Paul M. Magwene, Ph.D., Assistant Professor, Department of Biology, Duke University, Durham, NC 27708

Pleiotropy is a common feature of most genetic systems. Mechanistic explanations for pleiotropy lie in the description of how mutations impact the structure and dynamics of gene networks. I describe a model system for studying pleiotropy, and discuss the experimental and computational approaches that my research group is employing to understand how genetic architecture, genetic variation, and evolutionary history shape and influence pleiotropic effects.

S5. SYSTEMS BIOLOGY APPROACHES TO DNA DAMAGE SIGNALING

Dr. Michael B Yaffe, M.D., Ph.D., Howard S. and Linda E. Stern Associate Professor, Center for Cancer Research, Departments of Biology and Biological Engineering, Associate Member, Broad Institute, Massachusetts Institute of Technology, 77 Massachusetts Ave., E18-580, Cambridge, MA 021329, and the Division of Trauma and Critical Care, Department of Surgery, Beth Israel Deaconess Medical Center, 300 Brookline Ave., Boston, MA 02215

Many protein kinases along with phosphoserine/threonine-binding domains such as 14-3-3 proteins, WW domains, FHA domains, Polo-box domains, and BRCT domains function together within signaling networks to control cell cycle progression, the response to DNA damage, and the onset of apoptosis. How signals emerging from these pathways are integrated and processed as a network is unclear. To address this, we have been developing systems models of signaling where kinase activities, protein phosphorylation, binding of substrates to phosphoserine/threonine binding domains, and cellular responses such as cell cycle arrest and apoptosis are quantitatively measured at densely sampled points in time, and related mathematically using partial least squares regression and principal components analysis. Using cytokine-induced apoptosis in HT-29 cells as a starting point, we used this approach to construct a systems model of 7980 intracellular signaling events that directly links measurements to 1440 response outputs associated with apoptosis. The model accurately predicted multiple time-dependent apoptotic responses induced by a combination of the death-inducing cytokine tumor necrosis factor (TNF) with the pro-survival factors epidermal growth factor (EGF) and insulin. The model revealed new molecular mechanisms connecting signaling to apoptosis including the role of unsuspected autocrine circuits activated by TGF-α and IL-1α, All of the molecular signals could be divided along two primary signaling axes that constitute fundamental dimensions (molecular "basis axes") within the apoptotic signaling network. Projections of different stimuli along these axes captures the entire observed apoptotic response, suggesting that cell survival is determined by signaling through this canonical basis set. We have developed a new technique termed "network breakpoint analysis" to probe essential features of information transfer in signaling pathways. Applying this approach to TNFα-induced cell death revealed that the p38MAPK-MAPKAP Kinase-2 pathway is optimally 'tuned' to maximize apoptosis in response to pro-death stimuli while minimizing death in their absence. We are currently applying this methodology to study signal transduction events that control cell cycle arrest and apoptosis in response to DNA damage, underlying the importance of these processes in cancer and cancer treatment. Preliminary data indicates that, in addition to the ATM-Chk2 and ATR-Chk1 pathways, p53-defective tumor cells have re-wired the checkpoint signaling network to incorporate the p38MAPK-MAPKAP Kinase-2 pathway as an essential component of the DNA damage response.



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