TWENTY-SECOND ANNUAL

UNIVERSITY OF ROCHESTER

GENETICS DAY

Friday, May 7th, 2010

Flaum Atrium
University of Rochester Medical Center

10:00 AM – 5:00 PM
22nd Annual Genetics Day Lectures
Class of ‘62 Auditorium

Morning session: 10:00 – 12:45pm

Dr. Alan V. Smrcka
Professor, Department of Pharmacology and Physiology
“Small Molecule Modulation of Protein-Protein Interactions In G Protein Signaling”

Dr. Bradford Berk
CEO, University of Rochester Medical Center
Senior Vice President for Health Sciences
Professor - Department of Medicine
“Genetics of Vascular Remodeling”

Dr. Rudi Fasan
Assistant Professor, Department of Chemistry
“Molecular Discovery with Engineered P450 Enzymes”

Dr. Charles Thornton
Professor, Department of Neurology
“Antisense Therapeutics for Genetic Disease: New Luster on Old Magic Bullet”

Afternoon session: 4:00 – 5:00

8th Annual Fred Sherman Lecture

Dr. Stuart L. Schreiber
Harvard University
Howard Hughes Medical Institute
“Relating the genetic features of cancers to drug efficacies using small-molecule probes”
The Fred Sherman Lecture

Dr. Fred Sherman, Ph.D. served as Chairman of the Department of Biochemistry and then of the Department of Biochemistry & Biophysics between 1982-1999. During this period and before he led international efforts to firmly establish yeast as the premier genetic eukaryotic model system. The NIH has funded Fred for a remarkable 44 years, during which time he has published over 280 papers, with more on the way. In 1970 Fred initiated the famous yeast course at Cold Spring Harbor, which has trained scores of today’s leading investigators. He served as an instructor in this course for 17 years. Fred’s many landmark contributions to several fields of molecular biology were recognized by his election to National Academy of Sciences in 1985. A few of his recent awards include the Arthur Kornberg Research Award (1999); Honorary Doctorate degree, University of Minnesota (2002); AAAS Fellow (2006); George W. Beadle Award, Genetic Society of America (2006); and the Lifetime Achievement Award, Genetic Society of America (2006). We are proud to acknowledge Fred’s leadership role at the University of Rochester by establishing this named lecture in his honor.

Past Sherman Lecturers

2009 Robert Tjian
2008 Michael Snyder
2007 C. David Allis
2006 Ruth Lehmann
2005 Rudolf Jaenisch
2004 Cynthia Kenyon
2003 Fred Sherman
G proteins are critical transducers of signals downstream of G protein coupled receptors. G protein βγ subunits mediate many of these signals and have potential as therapeutic targets for treatment of a number of diseases. Compounds that bind to and inhibit G protein βγ subunit protein-protein interactions were identified by small molecule library screening using purified Gβγ as the target. Select compounds were shown to alter G protein βγ subunit signaling to modify GPCR signals and have efficacy in animal models of disease. To understand how these compounds alter protein-protein interactions, biochemical and biophysical techniques, coupled with structure-activity analysis were employed to reveal multiple mechanisms for inhibition and potentiation of protein-protein interactions. Co-crystallization reveals a binding mode in the protein-protein interaction “hot spot” and suggests a mechanism by which compounds alter the activity of Gβγ. These data will be important for directing future compound design and screening efforts as well as reveal novel mechanisms for modulating Gβγ signaling.
Research in the Berk lab focuses on defining the mechanisms by which cells in the vascular wall respond to hemodynamic and hormonal stimuli. The four major research projects ongoing in the laboratory include 1) Mechanisms by which blood vessels sense changes in blood flow and modulate vessel size and tone. 2) The cellular mechanisms that cause hypertension are being investigated by analysis of the role of the renin angiotensin system and the kinases that regulate intracellular sodium. 3) The mechanisms by which changes in cellular redox state alter blood vessel function 4) A genetic model of vascular remodeling in the rat has been established. We recently demonstrated significant mouse strain-specific variation in the inflammatory response during carotid intimal (arterial) thickening in response to low flow. Our hypothesis is that the carotid inflammation leading toward intimal thickening is a genetically regulated trait. We identified three novel quantitative trait loci (QTLs) on chromosomes (chr) 2, 11, and 18 that control intimal formation in a genetic cross between C3HeB/FeJ (C3H) and SJL mice. We tested our hypothesis by applying a whole genome approach using infiltration of leukocytes to the carotid intima as a quantitative trait. We conclude that the genetic regulation of leukocyte infiltration in the carotid localizes to a previously published Im2 locus (chr 11) by our group. This observation reveals an important mechanistic relationship between leukocyte infiltration and intimal proliferation in response to decrease blood flow.
The ubiquitous nature of aliphatic C-H bonds in biologically active natural and synthetic compounds make them most attractive sites for the chemical manipulation of organic molecules in order to improve or modulate their pharmacological properties. Selective functionalization of unreactive, aliphatic C-H bonds remains however one of the most challenging transformations in chemistry. Our approach to this problem involves the use of engineered P450 enzymes and P450-mediated aliphatic C-H bond oxidation as an alternative and concise synthetic strategy for functionally elaborating organic molecules of medical interest. This strategy was applied for the selective fluorination of various small-molecule pharmacophores. Fluorination is a useful tool for fine-tuning the pharmacokinetic and pharmacological properties of drugs and lead compounds but current fluorination methods are limited in scope. P450-based chemoenzymatic synthesis enabled the rapid identification of fluorinated drug derivatives with enhanced membrane permeability and increased resistance against metabolic breakdown. Our current efforts focus on probing the versatility of this method for manipulating complex structures and accelerating the discovery of natural product derivatives with improved or even novel biological activities.
Now that we have detailed genetic information about Mendelian disorders, the expectation to “do something about it” becomes more urgent. Genetic diagnosis and counseling are critically important, but ultimately these cannot eradicate genetic disease. What, then, are the options for helping people who currently have or soon will develop symptoms of a genetic disorder? The field of neurogenetics can furnish some recent examples, both in terms of spectacular failures and hopeful signs of future success. This presentation will focus on treating genetic disease by using antisense oligonucleotides (ASOs) to target RNA. The general approach is not new, but the technology is maturing and the design is getting more sophisticated and diverse. Extensive analysis of the human transcriptome, coupled with the application of bio-organic chemistry to modify the hybridization and metabolic properties of oligonucleotides, has led to the development of ASOs with improved efficacy, toxicology and pharmacology. By using ASOs to modulate RNA processing or translation, or to block RNA-protein interactions, some promising results have been achieved in preclinical testing and early clinical trials.
**1:00 – 3:30**

**Poster Session, Flaum Atrium**

*Presenter(s) listed in italics*

* Student poster competition  △ Post-Doctoral poster competition*

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<table>
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</thead>
</table>
| **1** | Electron Microscope Research Core  
Imaging Applications in Biomedical and Genetics Research  
Karen L. Bentley, Director  
Pathology and Laboratory Medicine |
| **2** | The Rochester Human Immunology Center and Core Laboratory at the University of Rochester School of Medicine and Dentistry  
David H. Smith Center for Vaccine Biology and Immunology,  
Department of Microbiology and Immunology |
| **3** | Very-high-throughput ("Next Generation") sequencing at the Functional Genomics Center  
Michelle Zanche, Meghann McBennett, ChinYi Chu, Steve Welle  
Functional Genomics Center |
| **4** | Multi-Photon Core Facility  
Anita Sun, Gheorghe Salahura, Maria Jepson, Karl Kasischke  
Department of Neurology, Center for Neural Development and Disease, URMC Research Core Facilities |
| **5** | URMC Confocal and Conventional Microscopy Core: Development of a full access state-of-the-art facility  
Linda M. Callahan  
Pathology/CNDD/URMC Core Facilities Program |
| **6** | The URMC Flow Cytometry Core Facility  
Timothy Bushnell, Matt Cochran, Dave Fuller, Mitchele Au, Matt Balys, Jason Curran and Ashley Adams  
Center for Pediatric Biomedical Research |
| **7** | Mass spectrometry approaches to characterizing proteins in your experimental or clinical system  
Kevin Welle, Jennifer Hryhorenko, Alan Friedman, and Fred Hagen  
Biochemistry & Biophysics and Environmental Medicine |

We are pleased to note that the URMC Core Facilities Program is presenting posters 1-7.

The University of Rochester School of Medicine and Dentistry (URSMD) is committed to provide shared instrumentation and core facilities in support of basic, translational and clinical research across departments and centers. Poster presentations by university core facilities will highlight key shared resources, state of the art instruments and expertise available through the cores to support research.
| 8 | * Regulation of apoptosis, growth and development by CG3313 in Drosophila  
   *Dae-Sung Hwangbo, Benoit Biteau, Sneha Rath, Heinrich Jasper*  
   Department of Biomedical Genetics, Department of Biology |
|---|---|
| 9 | * Chemotherapeutic agents negatively affect CNS progenitor cells and behavior in the mouse  
   *Nunes, A; Han, R; Sprentall, K; Santoni, O; Noble, M.,*  
   Department of Pharmacology and Physiology, and Department of Biomedical Genetics |
| 10 | * Forward Genetic Screens for the Isolation and Characterization of Novel Structural Neonatal Models of Human Disease: A Multi-species Approach  
   *GL Coles, X Zhang, L Wiggins, L Baglia, LA Metlay, BI Goldman, J Cassady, JR Miles, GA Rohrer, JL Valet, and KG Ackerman*  
   Department of Biomedical Genetics, Pediatrics |
| 11 | * Wilms Tumor 1 contributes to both the mesothelium of the anterior and posterior diaphragm and is associated with a variety of diaphragmatic hernia phenotypes  
   *Nicole Paris, Laurel Baglia, Xiaoyun Zhang, William T Pu, Kate G Ackerman*  
   Pediatrics and Biomedical Genetics |
| 12 | ∆ Interplay of Wnt and Fgf signaling determines the mesenchymal stem cell fate in skeletal development and disease  
   *Takamitsu Maruyama, Hsiao-Man Ivy Yu, Anthony J Mirando, Chu-Xia Deng and Wei Hsu*  
   Center for Oral Biology |
| 13 | Characterization of the human biliverdin reductase gene structure and regulatory elements: Promoter activity is enhanced by hypoxia and suppressed by TNF-alpha-activated NF-kB  
   *Peter E.M. Gibbs, Tihomir Miralem and Mahin D. Maines*  
   Biochemistry and Biophysics |
| 14 | * Hypersensitivity to contact inhibition as a clue to the extraordinary cancer resistance of Naked Mole-Rats  
   *Andrei Seluanov, Christopher Hine, Jorge Azpurua, Marina Feigenson, Michael Bozzella, Zhiyong Mao, Kenneth Catania, Karen L. de Mesy Bentley, and Vera Gorbunova*  
   Department of Biology, University of Rochester; Department of Biochemistry and Biophysics, University of Rochester School of Medicine and Dentistry; Department of Biological Sciences, Vanderbilt University |
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</table>
| 15 | ∆ | Neonatal Oxygen Treatment Results in an Impaired CD8⁺ T-cell Response to a Pulmonary, but not Systemic Influenza Challenge  
*Matthew Giannandrea, Michael A. O’Reilly, Shauna H. Marr, Min Yee, Lisbeth Boule, B. Paige Lawrence*  
Departments of Environmental Medicine, Pediatrics, and Microbiology & Immunology |
| 16 | * | A novel bipotential progenitor in the murine olfactory epithelium  
*Mridula Vinjamuri, Catherine Ovitt*  
Biomedical Genetics |
| 17 | * | Jabba mediates sequestration of histones on embryonic lipid droplets  
*Zhihuan Li, Michael Welte*  
Department of Biology |
| 18 | ∆ | Klarsicht interacts with kinesin-1 and cytoplasmic dynein through separable domains  
*Yanxun V. Yu, Sean L. Cotton, Michael A. Welte*  
Department of Biology |
| 19 | * | CG7172 as a putative tumor suppressor gene  
*Su Jun Lim, Pranab Dutta, Willis X. Li*  
Department of Biomedical Genetics |
| 20 | * | The role of dCRIF in RNAi and heterochromatin formation  
*Su Jun Lim, Willis X. Li*  
Department of Biomedical Genetics |
| 21 | ∆ | SIRT6 promotes DNA double strand break repair by mono-ADP-ribosylating PARP1 under oxidative stress  
*Zhiyong Mao, Christopher Hine, Amita Vaidya, Michael Bozzela, Andrei Seluanov and Vera Gorbunova*  
Department of Biology |
| 22 | ∆ | The determinants of the structure and stability of yeast heterochromatin  
*Qun Yu, Xinmin Zhang, Lars Olsen and Xin Bi*  
Department of Biology |
| 23 |   | Gene Expression Changes in NIH3T3 Fibroblast Cells During Notch Mediated Cellular Transformation  
*Joshua Travers, John Dankert, Jeffrey Kamperman, and Bochiwe Hara-Kaonga*  
School of Biological and Medical Sciences, Rochester Institute of Technology |
| 24 |   | Using Behavioral Procedures to Test for Genetic Differences  
*Troy Zarcone, Debbie Cory-Slechta*  
Environmental Medicine |
| 25 | * | Halo controls lipid-droplet motion via physical interactions with Kinesin-1 and Dynein  
*Michael A. Welte, Susan L. Tran, Gurpreet K. Arora* |
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<table>
<thead>
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<tbody>
<tr>
<td>26</td>
<td>Δ</td>
<td>Acetylation of Dna2 and FEN1 by p300 promotes formation of long flaps favoring DNA stability. <em>Lata Balakrishnan, Jason A. Stewart, Piotr Polaczek, Judith L. Campbell and Robert A. Bambara</em> Biochemistry and Biophysics.</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>*</td>
<td>Cartilage-specific Notch signaling regulates chondrocyte maturation and coordinates osteoblast differentiation. <em>Anat Kohn, Yufeng Dong, Alana Jesse, Tasuku Honjo, Regis J O’Keefe, Matthew J Hilton</em> Department of Biomedical Genetics, Department of Orthopaedics.</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td></td>
<td>A Novel Mouse Model of Enhanced NF-κB Activity. <em>Kathleen Gillespie</em>, Mary Hankin, Eijiro Jimi, Jie Dong, Sankar Ghosh, Brian Poligone. †Department of Dermatology and the James P. Wilmot Cancer Center, University of Rochester School of Medicine. ‡Departments of Immunobiology and Dermatology, Yale University School of Medicine. New Haven, CT.</td>
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<td>30</td>
<td>*</td>
<td>The Redox/Fyn/c-Cbl pathway and its interaction with Cool-1: A novel pathway that regulates chemo-sensitivity in Glioblastoma. <em>Brett M. Stevens</em>, Christopher J. Folts, Wanchang Cui, Mark Noble. †Department of Pharmacology and Physiology and Department of Biomedical Genetics.</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Δ</td>
<td>Studies of the biology and protection of adverse neurological effects of systemic chemotherapy treatment in an animal model. <em>Ruolan Han, Kelcie Sprentall, Margot Mayer-Pröschel and Mark Noble</em> Biomedical Genetics.</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Δ</td>
<td>Core neuronal circuitry modulates the behavioral output of sex-specific neurons in C. elegans. <em>Renee M. Miller, William R. Mowrey, and Douglas S. Portman</em> Center for Neural Development and Disease, Department of Biomedical Genetics.</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td></td>
<td>Insulin signaling pathway genes facilitating the maintenance of thermotolerance and protein homeostasis. <em>Andrew V. Samuelson, Christopher Carr, and Gary Ruvkun</em> Department of Biomedical Genetics.</td>
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<tr>
<td>34</td>
<td>Multicolor Flow Cytometry-based Analysis of the Glial Lineage in the Developing Spinal Cord</td>
<td>Jonathan D. Cherry, Frederick G. Strathmann, Brendan C. Carlin, Ollivier Hyrien, Margot Mayer-Pröschel</td>
<td>Department of Biomedical Genetics, Department of Statistics and Computational Biology, University of Rochester, Rochester, New York USA 14625, Department of Laboratory Medicine Chemistry Division, University of Washington, Seattle 98195.</td>
</tr>
<tr>
<td>35</td>
<td>R2 Retrotransposons Encode a Self-Cleaving Ribozyme</td>
<td>Danna Eickbus and Thomas Eickbus</td>
<td>Biology</td>
</tr>
<tr>
<td>36</td>
<td>fs5: A Mutant that Disrupts Development of the Ray Sensory Neurons in C. elegans</td>
<td>Margaret Casazza and Douglas Portman</td>
<td>Biomedical Genetics</td>
</tr>
<tr>
<td>37</td>
<td>∆ GPR56 Inhibits VEGF Secretion and Suppresses Melanoma Angiogenesis</td>
<td>Liquan Yang¹, Guangchun Chen¹, Glynis Scott², Sonali Mohanty¹, Shahinoor Begum¹, Richard O. Hynes³, Lei Xu¹²</td>
<td>¹Department of Biomedical Genetics, ²Department of Dermatology, University of Rochester Medical Center, Rochester, NY 14642, ³Howard Hughes Medical Institute and Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02193</td>
</tr>
<tr>
<td>38</td>
<td>∆ Modulation of IL-8 Activity Upon Lipid Raft Disruption and Nanoparticle Exposure</td>
<td>Chia T. Thach and Jacob N. Finkelstein</td>
<td>Environmental Medicine</td>
</tr>
<tr>
<td>39</td>
<td>∆ SUMO-like domain containing Esc2p regulates global protein sumoylation and transcriptional silencing</td>
<td>Holly Kuzmiak-Ngiam, Lars Olsen, and Xin Bi</td>
<td>Biology</td>
</tr>
<tr>
<td>40</td>
<td>∆ Identification of a novel gene, Rpl17, in vascular remodeling using integrative transcriptomic and genomic approaches</td>
<td>Elaine M. Smolock¹², Vyacheslav A. Korshunov¹², Galina Glazko³, Xing Qiu³, Keith Connolly⁴, and Bradford C. Berk¹</td>
<td>Aab Cardiovascular Research Institute¹, Departments of Medicine² and Biostatistics and Computational Biology³, University of Rochester School of Medicine and Dentistry and Department of Biochemistry⁴, University of Rochester</td>
</tr>
</tbody>
</table>
| 41 | Δ | Reciprocal regulation of Wnt and Gpr177/mouse Wntless is required for embryonic axis formation  
**Jiang Fu**, Ming Jiang, Anthony J. Mirando, Hsiao-Man Ivy Yu, and Wei Hsu  
Center for Oral Biology, Department of Biomedical Genetics |
| 42 | * | Extracellular Matrix Protein CCN1 (Cyr61) Promotes Neutrophil Recruitment to the Lung  
**Katherine Ringo**, Rosemary Norman, and Jennifer L. Young  
Department of Pediatrics, Division of Neonatology |
| 43 | Δ | The T1α promoter mediates nuclear import of plasmid DNA into alveolar epithelial type I cells  
**Lynn F. Gottfried** and David A. Dean  
Department of Pediatrics |
| 44 | * | Design, Synthesis and Biological Activity of Small Molecules Targeting CUG<sup>exp</sup> repeat RNA  
**Leslie O. Ofori**, Jason Hoskins, Charles A. Thorton and Benjamin L. Miller  
Chemistry, Dermatology, Neurology |
| 45 | Δ | SUMO-specific protease 2 is essential for trophoblast development  
**Eri O Maruyama**, Shang-Yi Chiu, Naoya Asai, Frank Costantini, Wei Hsu  
Department of Biomedical Genetics, Center for Oral Biology, James P Wilmot Cancer Center |
| 46 | * | Long-term CNS Sequelae of Gestational Iron Deficiency  
**Dawn L. Lee**<sup>1</sup>, Frederick G. Strathmann IV<sup>1</sup>, Jacob Mitchell<sup>1</sup>, Mahlon Johnson<sup>1</sup>, Joseph Walton<sup>4</sup>, Margot Mayer-Pröschel<sup>1</sup>  
<sup>1</sup>Department of Pathology and Laboratory Medicine, <sup>2</sup>Department of Biomedical Genetics, <sup>3</sup>Department of Neuroscience-UR, <sup>4</sup>Department of Surgery |
| 47 | * | Cisplatin negatively affects CNS progenitor cells and behavior in the adult mouse  
**Nunes, A**; **Han, R**; **Sprentall, K**; **Santoni, O**; **Noble, M.**  
Department of Pharmacology and Physiology, and Department of Biomedical Genetics |
| 48 | * | Metabolic differences between Cancer Stem Cells and the non-stem cell tumor population  
**Julie Babulski**<sup>1</sup>, **Brett Stevens**<sup>1,2</sup>, **Christopher Folts**<sup>1</sup>, **Mark Noble**<sup>1</sup>  
<sup>1</sup>Biomedical Genetics, <sup>2</sup>Department of Pharmacology and Physiology |
| 49 | * | Understanding the mechanism of chemo-resistance in breast cancer  
**Hsing-Yu Chen**, **Yin Yang**, **Brett Stevens**, and **Mark Noble**  
Biomedical Genetics, Pathology, Pharmacology and Physiology |
| 50 | * | A Role for the Redox/Fyn/c-Cbl Pathway in Modulating Oxidant-Induced Cell Cycle Arrest in Oligodendrocyte Precursor Cells  
*Christopher J. Folts, Mark Noble  
Department of Biomedical Genetics! |
| 51 | The sequences in U3 of Human Immunodeficiency Virus 3’ LTR contribute to efficient minus strand transfer in the cell  
*Dorota Piekna-Przybylska*, Carrie Dykes, Lisa M. Demeter, Robert A Bambara  
Department of Biochemistry and Biophysics, and Infectious Diseases Division, Department of Medicine |
| 52 | * | Regulation of Polyamine Metabolism Essential for Malignant Transformation  
*Aslihan Petenkaya* and Hartmut Land  
Department of Biomedical Genetics |
| 53 | * | Deregulation of the Cholesterol Transporter ABCA1 as a Causal Factor in Malignant Transformation  
*B. Smith*, H. McMurray, E. Sampson, H. Land  
Department of Biomedical Genetics |
| 54 | * | Microtubule Acetylation Enhances Binding of Plasmid DNA in Gene Transfer  
*MA Badding*, EE Vaughan, and DA Dean  
Departments of Environmental Medicine and Pediatrics |
| 55 | * | The Odd-skipped Family Transcription Factors Osr1 and Osr2 Control Synovial Joint Development  
*Yang Gao,* Yu Lan, Han Liu, Catherine E. Ovitt, Rulang Jiang  
Department of Biomedical Genetics and Center for Oral Biology |
| 56 | The Mds1-Evi1 locus regulates hematopoietic stem cell dormancy in the mouse  
*Yi Zhang,* Charles Wuertzer, Fernando Camargo, and Archibald S. Perkins  
Department of Pathology and Laboratory Medicine |
| 57 | Regulation of ICAM-1 Expression in Endothelial Cells via Syk-Dependent Recruitment of p300 and Acetylation of RelA/p65  
*Kaiser M. Bijli,* Fabeha Fazal, Mohammad Minhauddin and Arshad Rahman  
Pediatrics |
| 58 | * | Role of Small Maf in CncC/dKeap1 (Nrf-2/Keap1) Mediated Stress Response and Aging  
*M. Mahidur Rahman*, Gerasimos Sykiotis, Dirk Bohmann  
1Department of Biomedical Genetics, University of Rochester Medical Center, Rochester, NY 14642, 2Reproductive Endocrine Unit, Massachusetts General Hospital, Boston, MA 02114 |
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<tbody>
<tr>
<td>59</td>
<td>* Drosophila as a genetic model to study the effects of cigarette smoke</td>
<td>Olga Stolpnik, Nirmalya Chatterjee and Dirk Bohmann</td>
<td>Department of Biomedical Genetics</td>
</tr>
<tr>
<td>60</td>
<td>* Identification of Cancer Initiating Cells in Malignant Melanoma</td>
<td>Shweta Tiwary, Sonali Mohanty, Brad Martin, Xuan Li, Lei Xu</td>
<td>Department of Biomedical Genetics</td>
</tr>
<tr>
<td>61</td>
<td>∆ Mechanisms by which yeast Trm7 methylation of tRNA regulates cell</td>
<td>Michael P. Guy and Eric M. Phizicky</td>
<td>Department of Biochemistry and Biophysics</td>
</tr>
<tr>
<td></td>
<td>growth</td>
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</tr>
<tr>
<td>62</td>
<td>* Definitive erythroid precursors with extensive self-renewal capacity</td>
<td>Samantha England, Kathleen E. McGrath, Jenna Frame, James Palis</td>
<td>Department of Biomedical Genetics and the Department of Pediatrics and the Center for Pediatric Biomedical Research</td>
</tr>
<tr>
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<td>emerge from the early mammalian embryo</td>
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</tr>
<tr>
<td>63</td>
<td>* Expression analysis of leukemia stem cells (LSCs) in acute myeloid</td>
<td>Tzu-chieh Ho and Michael W. Becker, M.D. Pathology</td>
<td>Department of Biomedical Genetics and the Department of Pediatrics and the Center for Pediatric Biomedical Research</td>
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<td>leukemia (AML) with chromosome 5q deletion</td>
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<tr>
<td>64</td>
<td>* Regulation of DNA double-strand break repair by NPAT</td>
<td>Michael DeRan, Mary Pulvino, Jiyong Zhao</td>
<td>Department of Biomedical Genetics, Department of Biochemistry and Biophysics</td>
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<tr>
<td>65</td>
<td>∆ Small molecules that affect yeast replicative lifespan and reduce</td>
<td>Matan Rapoport, Boris Zybailov and David S. Goldfarb</td>
<td>Department of Biology</td>
</tr>
<tr>
<td></td>
<td>inflammation in mammalian models</td>
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<tr>
<td>66</td>
<td>* An integrated in vivo and cell-based approach to study oxidative</td>
<td>Nirmalya Chatterjee, Kerstin Spirohn, Michael Boutros and Dirk</td>
<td>Department of Biomedical Genetics, University of Rochester Medical Center, Division Signaling and Functional Genomics, German Cancer Research Center</td>
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<td>stress-responsive signaling in Drosophila melanogaster</td>
<td>Bohmann</td>
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</tr>
<tr>
<td>67</td>
<td>∆ STAT and heterochromatin protect genome stability</td>
<td>Shian-Jang Yan, Su Jun Lim, Amy Tsurumi, Song Shi, Anthony</td>
<td>Department of Biomedical Genetics</td>
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<td>Scott, Pranabananda Dutta, and Willis X. Li</td>
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<td>RNA Pseudoknots and Multibranch Loops</td>
<td></td>
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</tr>
<tr>
<td>69</td>
<td>Saccharomyces cerevisiae tRNA&lt;sup&gt;His&lt;/sup&gt; undergoes modification changes under different conditions</td>
<td>Melanie A. Preston&lt;sup&gt;1&lt;/sup&gt;, Kady Krivos&lt;sup&gt;2&lt;/sup&gt;, Patrick A. Limbach&lt;sup&gt;2&lt;/sup&gt;, and Eric M. Phizicky&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1Department of Biochemistry and Biophysics, University of Rochester Medical Center, Rochester, NY, 2Department of Chemistry, University of Cincinnati, Cincinnati, OH</td>
</tr>
<tr>
<td>70</td>
<td>Identification of the enzyme responsible for the 3-methylcytidine modification at position 32 of tRNA&lt;sup&gt;Threonine&lt;/sup&gt; in budding yeast</td>
<td>Sonia D'Silva, Steffen Haider, and Eric M. Phizicky</td>
<td>Department of Biochemistry and Biophysics</td>
</tr>
<tr>
<td>71</td>
<td>Reconstitution of Base Excision Repair in a Telomere Environment</td>
<td>Adam S. Miller, Lata Balakrishnan, Patricia L. Opresko, Robert A. Bambara</td>
<td>Biochemistry &amp; Biophysics</td>
</tr>
<tr>
<td>72</td>
<td>Inappropriate aryl hydrocarbon receptor activation during development leads to immune system reprogramming</td>
<td>Bethany Winans, Shauna Marr and B. Paige Lawrence</td>
<td>Department of Environmental Medicine</td>
</tr>
<tr>
<td>73</td>
<td>Coordinated Control of Multiple Features of Malignant Transformation through Cooperation Response Genes, Essential Downstream Targets of Cooperating Oncogenic Lesions</td>
<td>H. R. McMurray&lt;sup&gt;1&lt;/sup&gt;, A. Petenkaya&lt;sup&gt;1&lt;/sup&gt;, L. Newman&lt;sup&gt;1&lt;/sup&gt;, V. Balakrishnan&lt;sup&gt;1&lt;/sup&gt;, J. Aldersley&lt;sup&gt;1&lt;/sup&gt;, B. Smith&lt;sup&gt;1&lt;/sup&gt;, E.R. Sampson&lt;sup&gt;1&lt;/sup&gt;, M. Cassazza&lt;sup&gt;1&lt;/sup&gt;, P. Salzman&lt;sup&gt;1&lt;/sup&gt;, H. Land&lt;sup&gt;1,3&lt;/sup&gt;</td>
<td>1Department of Biomedical Genetics, 2Department of Biostatistics and Computational Biology, 3James P. Wilmot Cancer Center, University of Rochester, School of Medicine and Dentistry, Rochester, NY, USA</td>
</tr>
<tr>
<td>74</td>
<td>Morphological Evolution in Nasonia Species through Multiple Noncoding Changes</td>
<td>David W. Loehlin and John H. Werren</td>
<td>Biology</td>
</tr>
<tr>
<td>75</td>
<td>Notch Signaling is Required for the Generation of Hair Cells and Supporting Cells in the Mammalian Inner Ear</td>
<td>Wei Pan, Ying Jin, Ben Stanger, and Amy Kiernan</td>
<td>Department of Ophthalmology</td>
</tr>
<tr>
<td>76</td>
<td>Upregulation of the Nrf-2 antioxidant pathway decreases α-synuclein-dependent neurotoxicity in a Drosophila model of Parkinson’s disease</td>
<td>Maria Cecilia Barone and Dirk Bohmann</td>
<td>Biomedical Genetics</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
<td>Departments</td>
</tr>
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<td>------------------------------------------------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>77</td>
<td>Osr2 interacts with the Pax9-Bmp4 pathway to pattern the tooth</td>
<td>Jing Zhou, Zunyi Zhang, Yuan Zhang, Yang Gao, Jin. A. Baek, Yu Lan, Rena N. D’Souza and Rulang Jiang</td>
<td>Center for Oral Biology</td>
</tr>
<tr>
<td>78</td>
<td>Replicating plasmids as tools for revealing the genes for negative</td>
<td>Ausaf Ahmad, Anatoliy Kravets and Elena Rustchenko</td>
<td>Department of Biochemistry &amp; Biophysics</td>
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<td>and positive regulation of the metabolic SOU1 gene in human pathogen</td>
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<td>Candida albicans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>Importin α4 Mediates Thrombin-Induced ICAM-1 Expression in</td>
<td>Fabeha Fazal, Kathryn Levy, Mohammad Minhajuddin, Kaiser M. Bijli, Jacob N. Finkelstein and Arshad Rahman</td>
<td>Department of Pediatrics, Division of Neonatology, Lung Biology and Disease Program</td>
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<td>Endothelial Cells by Facilitating RelA/p65 Nuclear Translocation</td>
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<tr>
<td>80</td>
<td>Schnurri regulates tissue damage response in Drosophila</td>
<td>Ellen Miriam Kelsey, Henri Jasper</td>
<td>Department of Biomedical Genetics, Department of Biology</td>
</tr>
<tr>
<td>81</td>
<td>IL-22 production by pulmonary natural killer cells and the potential</td>
<td>Hailong Guo, David J Topham</td>
<td>Department of Microbiology and Immunology and the David H. Smith Center for Vaccine Biology and Immunology</td>
</tr>
<tr>
<td></td>
<td>role of IL-22 during primary influenza infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>Development mechanism of Cleft Lip Pathogenesis in the Dancer</td>
<td>Shihai Jia, Jeffrey O. Bush, Zunyi Zhang, Rulang Jiang</td>
<td>Center for Oral Biology</td>
</tr>
<tr>
<td></td>
<td>Mutant Mice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>83</td>
<td>The Rapid tRNA Decay Pathway Monitors the Structural Integrity of</td>
<td>Joseph M. Whipple, Elizabeth Lane, Sonia D'Silva, Eric M. Phizicky</td>
<td>Department of Biochemistry and Biophysics</td>
</tr>
<tr>
<td></td>
<td>Mature tRNAs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>Inflammation is a genetically regulated mechanism contributing to</td>
<td>Dietrich E. Machleder, Vyacheslav A. Korshunov, and Bradford C. Berk</td>
<td>Aab Cardiovascular Research Institute, University of Rochester School of Medicine and Dentistry</td>
</tr>
<tr>
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<td>the intimal thickening in the SJL/J mouse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85</td>
<td>Interactions between adjacent CGA codons affect translation</td>
<td>Kimberly M. Dean, Daniel P. Letzring, and Elizabeth J. Grayhack</td>
<td>Department of Biochemistry and Biophysics</td>
</tr>
<tr>
<td></td>
<td>efficiency in Saccharomyces cerevisiae</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 86 | ∆ | Progenitor cells reversibly exit the cell cycle upon treatment with IFN-γ. 
*Daniel C Tanner, Jonathan D Cherry, and Margot Mayer-Pröschel*  
Biomedical Genetics |
| 87 | Delineation of chromosome 5 contigs from diploid assembly 19 of *C. albicans* genomic sequence. 
*Anatoliy Kravets, Han Wool John Sung, Elena Rustchenko*  
Biochemistry and Biophysics |
| 88 | Identification of Pathways for Carotid Artery Intima Formation: Integration of Mouse Genetics and Global Gene Expression Data. 
*Vyacheslav A Korshunov, Galina Glazko, Xing Qiu, Bradford C Berk*  
Aab Cardiovascular Research Institute, Department of Medicine |
| 89 | Derivation of Astrocytes from Human Embryonic Stem Cell (hESC) for Spinal Cord Injury Therapy. 
*Chung-Hsuan Shih*¹,², Matthew Mavissakalian²³, Michelle Cooney², Mark Noble²³, and Christoph Pröschel²³  
¹Graduate Program in Pathology, ²Institute for Stem Cell and Regenerative Medicine, ³Department of Biomedical Genetics, University of Rochester Medical Center |
| 90 | Development and Analysis of a Mitochondrial-DNA Haplogroup Database. 
*Syafrul Azfar Rosly, Eric Stevens, Kyle Dewey, Michael Osier, Dina L. Newman*  
School of Biological and Medical Sciences, Rochester Institute of Technology, Rochester, NY |
| 91 | Small Molecule Antagonists of HIV Vif Dimerization, Leads for Anti-HIV Therapeutics. 
*Ryan Bennett, Harold Smith*  
Biochemistry Dept. |
| 92 | Activating APOBEC3G, a Potent Innate Inhibitor of HIV-1 Infection. 
*Prohaska, Kimberly, M.; Smith, Harold, C.*  
Biochemistry and Biophysics |
| 93 | RNA dependent inhibition of APOBEC3G deaminase activity. 
*William M. McDougall, Harold C. Smith*  
Biochemistry and Biophysics |
8th Annual Fred Sherman Lecture

Dr. Stuart L. Schreiber
Harvard University
Howard Hughes Medical Institute

"Relating the genetic features of cancers to drug efficacies using small-molecule probes"

The ability to understand and to modulate cancer genomes provides a radically new foundation for creating the medicines we’ve only imagined since declaring the war on cancer decades earlier – the ones needed to take out this disease. We’ve learned the power of linking genetic signatures of cancers to drug sensitivities – and that the extraordinary consequences of exemplars like imatinib/Gleevec are not restricted to this drug and its genetically matched leukemia, CML. Recent studies, for example, show unprecedented response rates with genetically matched drugs targeting extremely challenging cancers such as melanoma. These advances are encouraging, but they still only affect a tiny subset of patients suffering today from cancer. So where do we go from here, how do we exploit our new foundation and insights comprehensively so that all cancer patients are affected?

We must exploit this unprecedented opportunity for treating cancer rapidly and effectively. So, we must be wise in planning our next steps. In my lecture, I will offer one simple idea. I find this idea attractive since it addresses the challenge comprehensively and it is on a direct path to cancer patients. In fact, it’s an idea that starts with patients.

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Thank you for your participation!

Please send any comments or suggestions to:
Dr. David S. Goldfarb, Genetics Cluster Co-Chair, or
Jill Van Atta, Department of Biomedical Genetics Administrative Assistant

Telephone: 273-1447, Fax: 273-1450
E-mail: jill_vanatta@urmc.rochester.edu