Boston Taiwanese Biotechnology Association

2014

Boston Taiwanese Biotechnology Symposium

Welcome Message

Welcome to the 2nd Boston Taiwanese Biotechnology Symposium 2014!

The Boston Taiwanese Biotechnology Association (BTBA) was established by a group of young Taiwanese scientists, including graduate students, postdoctoral researchers and fellows working in biotechnology-related fields in the greater Boston area. We work closely with the Harvard GSAS Taiwan Student Association (HTSA). Our first symposium held last year attracted nearly 300 participants to discuss exciting new ideas in research and career development. Since then, we have held bi-weekly academic seminars and career talks to provide the community an environment to continue the conversation.

The goals of the Boston Taiwanese Biotechnology Symposium 2014 are to:

- Discuss the future of biotechnology and how we can contribute to it
- Share career information including advancement in academia, transition to industry, and moving between Taiwan, Asia-Pacific and the U.S.
- Facilitate research discussion and collaboration

The organization of a symposium requires the support of many people. We would first like to thank all the participants for coming and authors for submitting their papers. This year we have 3 keynote speakers, 3 career panels and a career fair. We would like to thank all the speakers and panelists for their time and dedication to the symposium. We also want to thank kind help from our sponsors: Taiwanese-American Foundation of Boston (波士頓台美基金會), the Ministry of Science and Technology, Taiwan (中華民國科技部), Science and Technology Division, Taipei Economic and Cultural Representative Office in the U.S (駐美國台北經濟文化代表處科技組), Education Division, Taipei Economic and Cultural Office in Boston (駐波士頓台北經濟文化辦事處教育組), PosterSmith, Taiwanese Association of America, Boston Chapter (波士頓台灣同鄉會) and generous friends for supporting the symposium financially.

Please email us at btba.tw@gmail.com if you have any questions, comments, or would like to get involved. We hope you will enjoy the symposium and have a great time in Boston!

Sincerely,

Ho-Chou Tu
Ching-Han Shen
Organizing Committee Co-Chair,
Boston Taiwanese Biotechnology Association

BTBA
Biweekly Academic Seminar Series
Oct, 2014-May, 2015

Call For Speakers

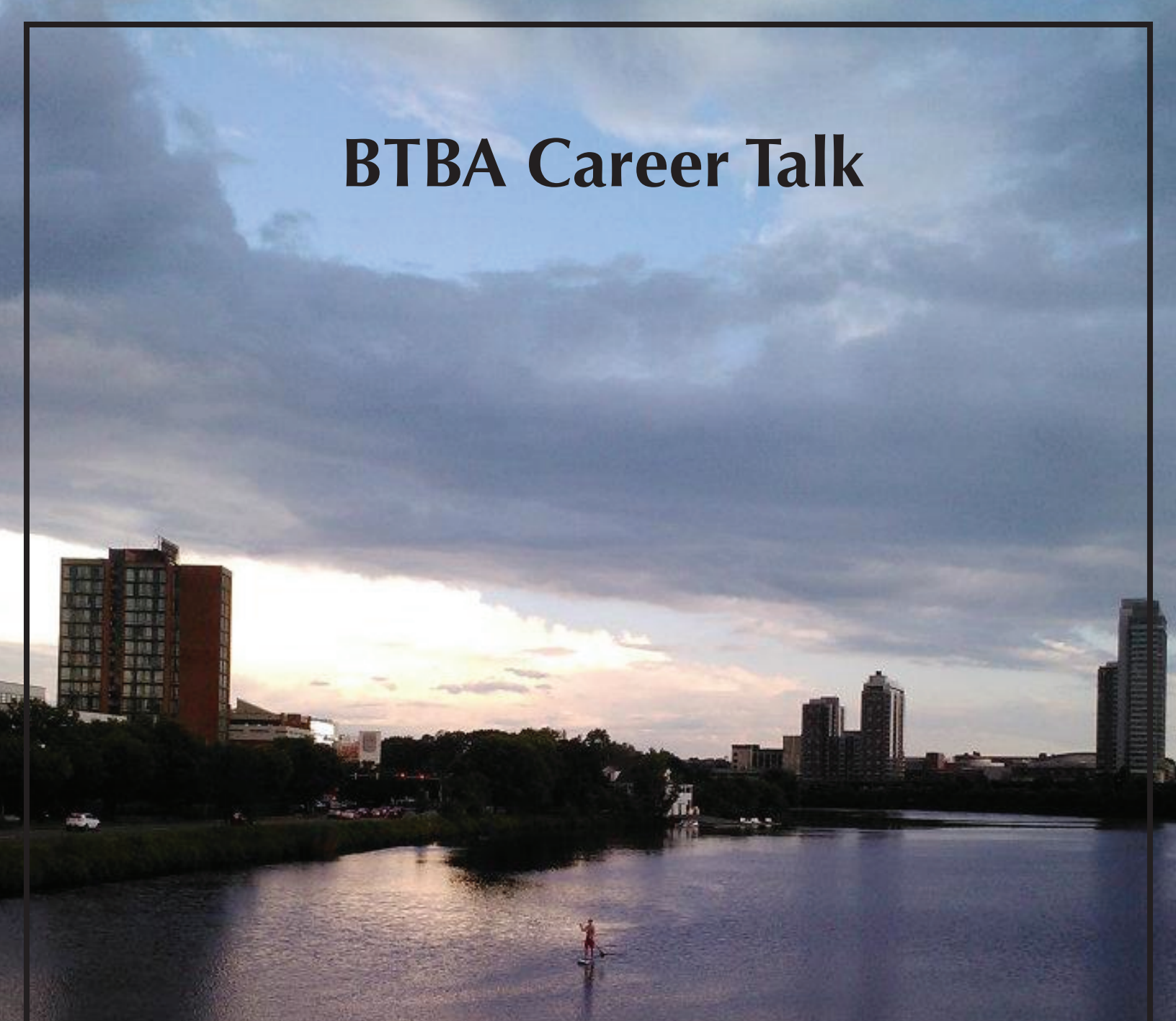
Deadline: September 15, 2014

The biweekly seminars will be held at
6:30pm every 2nd Tuesday@ Longwood
2:00pm every 4th Sunday @MIT

Next BTBA biweekly academic series is coming in October! Last series, 20 speakers from BU, Children's Hospital, Harvard, MGH, MIT, UMass and Whitehead Institute shared their research experience. It is a great opportunity for networking, looking for collaboration and meeting new friends.

The seminar will be held at 6:30pm on the 2nd Tuesday in Longwood and 2:00pm on the 4th Sunday in MIT each month. The presentation should be around 30 minutes, and there will be some Q&A time afterwards. If you are interested in presenting your work, please contact us at btba.tw@gmail.com before Sep 15 and let us know your preferred date and location. More information will be announced soon on BTBA facebook and website.

BTBA Career Talk



Finding the first job in bio-industry
is like paddling on Charles River...
... a long and lonely way.

BTBA is calling for friends who are willing to share their Industrial Experience in our monthly career talk. Please email: btba.tw@gmail.com

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Organizers

Boston Taiwanese Biotechnology Association

Harvard GSAS Taiwan Student Association

Gold Level Sponsorships

Taiwanese-American Foundation of Boston (波士頓台美基金會)

Ministry of Science and Technology, Taiwan, R.O.C. (中華民國科技部)

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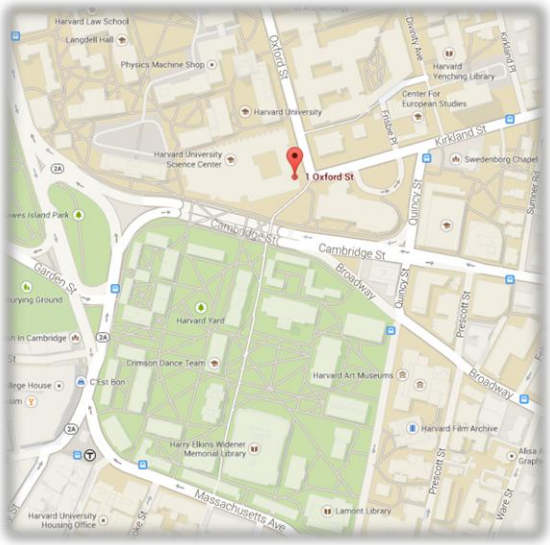
Direction

Science Center, Hall B, Harvard University

1 Oxford St., Cambridge, MA, 02138



Direction

By Subway: Take the RED Line to Harvard Square. The entrance of Science Center is right across Harvard Yard, at the intersection of Oxford and Kirkland Streets.

By Train or Bus: Amtrak and the bus terminal are located at South Station on the Red Line. Take the RED Line to Harvard Square.

By Car:

From the Massachusetts Turnpike:

Take Exit 18 (Allston or Brighton/Cambridge). At 2nd traffic light, turn left onto Storrow Drive (Soldiers Field Road). Exit at Harvard Square. Turn right to cross the bridge and you will be on JFK Street headed into Harvard Square.

From the South (I-93 North):

Head north on Route 93, take the Mass Pike.

From the North (I-93 South)

Head south on Route 93 exit onto Storrow Drive west. Take Harvard Square/Cambridge exit. Turn right to cross the bridge and you will be on JFK Street headed into Harvard Square.

From Logan Airport:

As you leave the airport, follow signs to Rt. 90, Mass Turnpike West.

Parking:

On-street parking is scarce in Cambridge, but there are several public parking lots and garages around the square.

Attendants can use Harvard Campus Services to purchase one-day permit for parking on or near campus.

Agenda

Day 1 (06/14/2014)

08:30-09:00	**Registration and Poster Setup**
09:00-09:10	**Opening Remarks**
09:10-10:10	**Keynote** **Dr. David Ho, The Rockefeller University** *Random Reflections of an HIV Scientist (from Taiwan)*
10:10-10:55	**Contributed Talks** **Chair: Yi-Dong Lin** **Poshen Chen** *L01*. Genome-Wide Measurement of Chromatin Accessibility by RED-Seq* **Jia-Yun Chen** *L02. Dosage of Dyrk1a Shifts Cells within a p21-cyclin D1 Signaling Map to Control the Decision to Enter the Cell Cycle* **Chien-Ling Lin** *L03. An Ancient Class of Structured Intron Demonstrates a Widespread Role for Dinucleotide Repeats in Vertebrate Gene Expression* **Hui-Ting Chou** *P10**. Molecular Organization of the GARP Vesicle Tethering Complex* **Chien-Der Lee** *P21. The PUF Protein Puf3 Toggles the Translational Fate of Bound mRNA Transcripts to Regulate Mitochondrial Biogenesis* **Hsu-Yang Lee** *P23. Single Molecule Studies on the Mechanism of Chromatin Remodeling by Rad54* **See-Yeun Ting** *P32. Understanding the Molecular Architecture of the Hsp70-Based Mitochondrial Protein Import Machinery* **Yang-Hui Yeh** *P40. How Could a Mitogenic proIGF-I E-Peptide Induce Cancerous Cell Death?*
10:55-11:25	**Coffee Break**
11:25-12:45	**Academic Panel Discussion** **Moderator: Yi-Ying Chou** **Dr. Theresa Chang, Rutgers, The State University of New Jersey** **Dr. Yen-Tsung Huang, Brown University** **Dr. Tony Ip, University of Massachusetts Medical School** **Dr. Ya-Chieh Hsu, Harvard University**
12:45-14:00	**Lunch**

*L represents 10 min long talk.

** P represents 1 min short talk with a poster.

14:00-14:45	**Contributed Talks** **Chair: Tzu-Hsing April Kuo** **Kun-Hsiang Liu** *L04. Probing Nitrate Signaling in Arabidopsis* **Ming-Ru Wu** *L05. B7H6-Specific Chimeric Antigen Receptors (CARs) Lead to Tumor Elimination and Host Immunity* **Chun-Te Chiang** *P07. Nanoliposome-Assisted Combination Strategy for Pancreatic Cancer* **Yu-Jie Hu** *P16. JumonjiC Domain-Containing Protein 6 (Jmjd6) is Required for Adipogenic Differentiation in Mouse Mesenchymal Cells* **Yu-Chieh Kao** *P19. Can Cortical Spreading Depolarization Serve as a Marker for Tissue Plasminogen Activator (tPA) Toxicity for Stroke Treatment?* **Chun-Chi Richard Liang** *P27. TorsinA hypofunction Causes Abnormal Twisting Movements and Sensorimotor Circuit Neurodegeneration* **Shu-Lin Liu** *P29. MMP-12 is an Essential Mediator of Arterial Stiffening in Vascular Remodeling and Atherosclerosis* **Chi-Chao Chen** *P04. In vivo Leukemia Clonality Tracking Using Neutral shRNA Library* **Sheng-hong Chen** *P05. Mdmx Buffers against p53 Oscillations to Affect Cell Fate Decisions* **Yi-Hsuan (Elisha) Ho** *P12. The Inferred Stress-Activated Signaling Network from Yeast: Coordination, Interconnectivity, and a Novel NaCl Network Hub, Cdc14 Phosphatase* **Chun-Hao Huang** *P17. CDK9-Mediated Transcription Elongation is Required for MYC Addiction in Hepatocellular Carcinoma* **Yane-Shih Wang** *P34. Exploring the Substrate Range of Wild-Type and Evolved Aminoacyl-tRNA Synthetases*
14:45-16:05	**Bench Scientist Panel Discussion** **Moderator: Yung-Chih Cheng** **Dr. Tsun-Kai Chang, Genentech** **Dr. Chase Shen, Biogen Idec** **Dr. Chi-Li Chen, TetraPhase Pharmaceuticals** **Dr. Hsin-Pei Shih, Vertex Pharmaceuticals**
16:05-16:35	**Coffee Break**

16:35-17:35	**Keynote** Dr. Morgan Sheng, Genentech ***Science in biotech industry: a deubiquitinase with relevance to Parkinson's disease***
17:35-19:00	**Taiwan Recruitment Information Panel** **Moderator: Ying-Ja Chen** **Dr. Yuh-Jyh Jong, National Chiao Tung University** **Dr. Chung Hsuan Chen, Academia Sinica** **Dr. Soo-Chen Cheng, Academia Sinica** **Dr. Tuan-Hua David Ho, Academia Sinica** **Dr. Lie-Fen Shyur, Academia Sinica** **Dr. Wayne Liao, Taiwan Liposome Company**
19:00-21:00	**Poster Session, Career Fair & Reception Dinner**

Day 2 (06/15/2014)

09:00-10:00	**Keynote** **Dr. Jennie Shen, DuPont Pioneer** *If I could turn back time: My hindsight, your foresight*
10:00-10:45	**Contributed Talks** **Chair: Fu-Kai Hsieh** **Chun-Wan Yen** *L06. A Rapid, Multiplexed, Mobile Phone-Enabled Point-of-Care Diagnostic Device to Detect Infectious Diseases* **Yung-Chi Huang** *L07. A Gain-of-Function UNC-2/CaV2 Channel Induces Behavioral Hyperactivity and an Imbalance in Excitatory-Inhibitory Signaling* **Chi Lu** *L08. Control of Spinal Cord Function with Optoelectronic Integrated Polymer Fiber Probes* **Ching-Han Shen** *L09. Control Interneuron Activity in Caenorhabditis elegans to Evoke Chemotactic Behavior*
10:45-11:15	**Coffee Break**
11:15-12:35	**Beyond the Bench Panel Discussion** **Moderator: Wan-Ping Lee** **Dr. Jeffery Tsao, McKinsey & Co.** **Dr. Paul Lu, Lazard** **Dr. Vivide Chang, L.E.K. Consulting** **Dr. Wayne Peng, KnowledgePoint360 Group**
12:35-12:45	**Poster Award Ceremony**

Keynote Speaker

David Ho, 何大一院士

Scientific Director & Chief Executive Officer
Aaron Diamond AIDS Research Center
The Rockefeller University

Dr. David Ho has devoted himself to HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome) research for more than 30 years and published more than 400 scientific papers on HIV/AIDS. During his residency at UCLA medical center, Dr. Ho saw some of the first documented cases of AIDS where he found unusual opportunistic infections on several young men. As it turned out to be the result of a completely new type of virus infection, i.e. HIV-1, without any cure available, Dr. Ho realized that the best way to combat the disease is to gain the knowledge of HIV as best and as fast as we could. In 1996, his observation on the early dynamics of HIV replication led to the development of HAART (highly active anti-retroviral therapy), which remains the standard and the only treatment for HIV infection nowadays. HAART substantially inhibits HIV replication and increases the survival rate of HIV-1-infected patients. TIME magazine therefore named him "Man of the Year" in the same year and "The Man Who Could Beat AIDS" in the following interview in 2010. In recent years, Dr. Ho has shifted his research focus from treatment to the early prevention of the HIV infection, hoping to eradicate HIV one day entirely from the human society.

What's worth mentioning is that the battleground between Dr. Ho and HIV is not only limited in the test tubes. Dr. Ho is a strong advocate of bringing affordable drugs to the AIDS patients in the developing world. Feeling the need to equip the public with the necessary knowledge to fight AIDS, Dr. Ho has also helped to establish several initiatives to raise global awareness of HIV/AIDS and to eliminate the stigma and the discrimination imposed on HIV carriers. Born and growing up in Taichung, Taiwan before moving with his family to the United States, Dr. Ho has relentlessly contributed to the growth and the development of biological research as well as biotechnology industry in Taiwan. He was elected to be one of the Academicians by Academia Sinica in 1998.

Keynote Speaker

Morgan Sheng, 沈華智博士

Vice President
Neuroscience & Molecular Biology
Genentech

"As a neuroscientist with a medical background, I am inspired to understand how the brain works from the level of molecule to cognitive behavior, and to tackle serious brain diseases based on understanding of biological mechanisms."

I started at Genentech in September 2008. Prior to that, I spent 14 years in academia focused on molecular and cellular neuroscience - first at Massachusetts General Hospital/Harvard Medical School and then at Massachusetts Institute of Technology (MIT), where I was the Menicon Professor of Neuroscience and an Investigator of the Howard Hughes Medical Institute. Before I got into research I completed a residency in general medicine in London, U.K. So I have seen human disease from two sides - as a scientist investigating basic mechanisms and as a medical doctor treating patients. I came to Genentech because I believe this company is best equipped to translate our increasing knowledge of the basic causes of disease into potential treatments for serious brain disorders. I am energized by the people at Genentech, who have the right combination of know-how, creativity and motivation to make a difference for patients.

Research Focus

At Genentech, we have built a world-class Neuroscience Department and research program committed to understanding the mechanisms underlying major diseases of the nervous system and discovering drugs for these disorders. My lab's research is broadly divided into three areas: (i) the molecular mechanisms of synapse weakening and loss (which are characteristic of neurodegenerative disorders such as Alzheimer's); (ii) the molecular regulation of synapses on inhibitory interneurons (dysfunction of which is implicated in schizophrenia and autism); (iii) uncovering fresh insights into the pathogenesis of Alzheimer's disease, Parkinson's disease and frontotemporal dementia, starting from identification of novel human gene mutations that increase the risk of these disorders. These directions of research should yield new mechanisms and pathways that are of wide scientific interest and that might be a strategy for neurodegenerative and neurodevelopmental diseases.

Keynote Speaker

Jennie B. Shen, 沈碧君博士

Senior Director
Business Affairs & Business Development
DuPont Pioneer

Dr. Jennie B. Shen serves as Strategy & Business Development Director for DuPont business Pioneer Hi-Bred in China, which is based in Beijing. In this role, she is responsible for planning, developing and establishing strategic partnerships with public and private sectors, and facilitating innovative collaborations to improve research productivity and farmer profitability. In addition, she also manages Pioneer China's business affairs, including industry relations, external communications and public outreach programs.

Jennie began her career at DuPont in 1989 as a Research Scientist in the Ag Biotech Department. After Pioneer Hi-Bred became DuPont's fully-owned subsidiary in 1999, she served as Strategy Director for DuPont's Agriculture and Nutrition, devoted her efforts to optimizing biotech research strategy and process (Six Sigma) and was instrumental in strategizing and implementing the Global R&D concept. In that role, she led the establishment of the first MNC biotech research JV (Beijing Kaituo DNA Biotech Research Center Co., Ltd.) in China, partnering with Beijing Weiming Kaituo Crop Design Center Co., Ltd. She currently serves on the Board and as Managing Director for the research JV.

Before Jennie relocated to Beijing in 2011, she was the Business Development Director for Pioneer's Asia Pacific business. She established numerous germplasm and trait collaborations across various AP countries.

Jennie holds B.S. and M.S. degrees from National Taiwan University in Agricultural Chemistry and Horticulture, respectively. She later earned her Ph.D. in Plant Molecular Biology from the University of Illinois, Urbana-Champaign, in 1989. Jennie also holds an Executive MBA degree concentrated in Finance, from the University of Delaware, in 1999.

Career Fair

Yuh-Jyh Jong, 鐘育志院長
Dean
國立交通大學生物科技學院
College of Biological Science and Technology, National Chiao Tung University

National Chiao Tung University College of Biological Science and Technology

Department of Biological Science and Technology
(Master and Doctoral degree programs)
Institute of Molecular Medicine and Bioengineering
(Master and Doctoral degree programs)
Institute of Bioinformatics and Systems Biology
(Master and Doctoral degree programs)
Bioinformatics Research Center

We are dedicated for academic excellence and academia-industry collaborations

Features of Development

In light of our excellent achievement in electronic engineering and computer sciences at National Chiao Tung University, we are looking to bringing this well-established experience into the biomedical research.

1. A milestone in Taiwan academic research, which integrates the multidisciplinary scientists from the field of engineering, mechanics, computer sciences, physics, chemistry, biochemistry, molecular biology, microbiology, biotechnology, bioinformatics and medicine into a team-oriented research.
2. Enhancement of the international academic standing
3. Promoting international exchange-student programs
4. Collaboration with domestic universities, institutes and local industry

Current Goals

1. To incubate students who are pursuing biological sciences and technology and related fields as future career
2. To identify the causes and the genes involved in genetic and neurologic disorders
3. To delineate the pathogenic mechanisms for important domestic diseases
4. To establish the molecular targets that may potentially be used for diagnostic and therapeutic intervention
5. To explore the biomarkers for early diagnosis in preventive medicine
6. To establish environmental safety and engineering program
7. To understand the structure-dynamics-function relationships of proteins and their correlation to genetic properties
8. To establish a bioinformatics center for focused promotion of both bioinformatics research and education
9. To develop platform technology in photoelectronics and mechanics used in biology and medical related sciences
10. To provide the theory in photoelectronics mimicking biological vision system
11. To establish a brain research center in collaboration with Yang Ming, Tsing-Hua, and Central University

Career Fair

Chung Hsuan (Winston) Chen, 陳仲瑄主任
Director
中央研究院基因體研究中心
Genomics Research Center, Academia Sinica

Genomics Research Center (GRC) was established in 2003. At present GRC composes of 40 full-time faculty members including both senior scientists as well as energetic and talented junior researchers. Their specialties cover a broad range of fields from physics, chemistry, engineering, computation, biology, to medicine. We have also assembled a large team of specialists to support technology development. These two unique features enable GRC to facilitate advanced interdisciplinary research. In addition to regular research staff, two other tremendous talent pools, Scientific Advisory Board (SAB) and Joint Research Fellows, complement our research projects. All members in SAB are renowned scientists in the world who advise GRC in both research and strategic planning on a regular basis. More than 40 joint research fellows from major research institutes in Taiwan are a very valuable asset for interdisciplinary research.

In our effort to screen new drug leads for various diseases, GRC has set a chemical library of more than two-million compounds and the most efficient high throughput drug screening facility in Asia. GRC has also established critical facilities for cell biology and biomedical technology development, including mass spectrometer proteomic facility, NMR and X-ray facility for structure determination, microarray and high throughput genome sequencer for genomic research, cell sorter and microscopy for cell biology, and phytotron for agricultural biotechnology. A new animal laboratory is also among the highlights. These facilities can significantly advance frontier biotechnology development and drug discovery.

The major focus of GRC's research is on the understanding of genes associated with diseases and their functions. Through new discoveries, new diagnosis tools and new therapeutic strategies are expected to be developed. Increased efforts will be placed on the pursuit of fundamental scientific advances through interdisciplinary programs, and the extension of basic discoveries to translational research. Therefore, we organize three Divisions: Chemical Biology Division to develop new tools and molecules to target cancer and infectious diseases, Medical Biology Division to pursue clinical potential for new medicines, and Physical and Computational Genomics Division to develop data analysis for drug prediction, and novel biomedical technology development. In addition to these research Divisions, GRC has also established the Biotechnology Incubation Center (BIC) for pursuing technology transfer to convert important discoveries into commercial opportunities. Some of the scientific pursuits in GRC with great

potential to be among the world leading research include new drug design based on structure research of membrane protein, carbohydrate chemistry and structure biology, the relationship of molecular biology and disease, high throughput technology for drug discovery, infectious disease research, vaccine development, immunotherapy, evolutionary bioinformatics, cancer stem cell, biological mass spectrometer development and fast biomarker search. We strive continuously to make GRC a place that inspires as well as fulfills innovative ideas.

To foster young and promising students to join the field of advanced research, GRC currently has joint PhD programs with two top universities - National Defense Medical Center and National Yang-Ming University. GRC faculties have also been participating in the Taiwan International Graduate Program (TIGP) and other degree-given programs collaborated by Academia Sinica and local universities.

Up to present, GRC members have published around 700 papers and have filed over 200 patents. GRC is very competitive compared to all peer institutes in Taiwan and Asia. To date, BIC has recruited 14 highly respectable biotechnology companies that licensed technologies from Academia Sinica. Several of these new companies have commercially produced proprietary products and hence become independent to build up their own manufacturing facilities. With rapid increase of inventions at Academia Sinica and the more favorable industrial environment for start-up biotech companies in Taiwan, we expect that the number of these successful start-up companies will grow rapidly in the foreseeable future.

We will continue to pursue fundamental scientific research through interdisciplinary programs. The basic discoveries will then be extended to translational research. Our future perspective is to play a more critical role in pharmaceutical and biomedical device industry in Taiwan.

Career Fair

Soo-Chen Cheng, 鄭淑珍所長

Director

中央研究院分子生物研究所

Institute of Molecular Biology, Academia Sinica

The Institute of Molecular Biology at the Academia Sinica is a dynamic research institute engaging in cutting-edge research at the molecular and cellular levels in diverse fields of biology. The Institute currently has 35 principle investigators, and their research topics cover the areas of nucleic acid and chromosome biology, developmental biology and neuroscience, structural biology, plant science, virus-host interactions, and biochemistry and cellular physiology, using yeast, Drosophila, zebra fish, mouse and Arabidopsis as model systems. The Institute is very well equipped, and has also established several core facilities for demanding research need of high technology. The imaging core composes of several confocal microscopes of different variants and electron microscopes, providing services for acquisition and analysis of high-resolution images. The mouse facilities are set up to host mouse experiments with high standards but at very reasonable price. Other facilities, including X-ray, FACS, transgenic mice, microarray, sequencing and q-PCR facilities, are all well set up to facilitate scientific progress in the IMB.

IMB holds a regular seminar series to facilitate collaborations with domestic and international scientific communities, and to apprise our fellow members of current research advances. To promote interactions between each other, the faculty members get together once every week in a lunch meeting to discuss each other's research work, and each year the Institute also holds a retreat to include all research staffs for scientific interactions. The Institute has also established graduate training programs with Nation Yang Ming University and National Defense Medical Center for training of the next generation of young scientists for careers in the field of molecular biology. There are also programs for summer internship to educate undergraduate students and promote their interest in research.

Career Fair

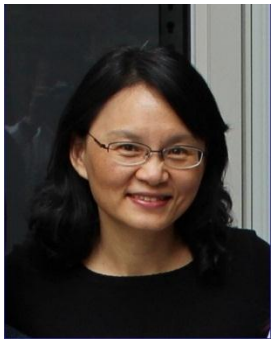
Tuan-Hua David Ho, 賀端華院士

Academician

中央研究院植物暨微生物研究所

Institute of Plant and Microbial Biology, Academia Sinica

Career Fair



Lie-Fen Shyur, 徐麗芬副主任
Vice Director
中央研究院農業生物科技中心
Agricultural Biotechnology Research Center, Academia Sinica

The Agricultural Biotechnology Research Center (ABRC) of Academia Sinica, Taiwan pursues basic and applied mission-oriented research in agricultural biotechnology, and fosters the development of the BioAgricultural industry in Taiwan. The ABRC was established to allow a multidisciplinary approach to our research program, bringing constant innovation to bear on the development of a biotechnology industry that builds on those features unique to Taiwan and can compete with the best of the rest of the world. We are continuing to recruit suitable principal investigators and research specialists to consolidate our four research themes of Integrative Plant Stress Biology, Herbal Medicine Research, Molecular Vaccine Technology and Enzyme Biotechnology. Establishment of these thematic programs is to strengthen the organization and function of the ABRC, and will allow large-scale projects in collaboration with various Institutes and Research Centers of the Academy.

ABRC maintains several state-of-the-art and shared-use core facilities, including metabolomics, proteomics, microarray, plant technology, laboratory animal, and confocal microscopy core facilities. The efficient utilization of the core facilities and our other platforms such as cell/tissue culture and transformation or transgenic technology for both plants and animals are a key part of our ability to conduct innovative research. We are actively engaged in research in new agricultural biotechnologies and food security related to environmental or global warming issues. We generate useful and platform-based patents, innovative products, and publish high-impact scientific or technical papers. ABRC emphasizes crosstalk and collaboration in research at both national and international levels, and provides networking opportunities and information systems to serve the technological needs of the biotechnology industry in Taiwan.

Career Fair

Wayne Liao, 廖文曄博士

Director, US Operations

台灣微脂體股份有限公司

TLC Biopharmaceuticals, Inc.

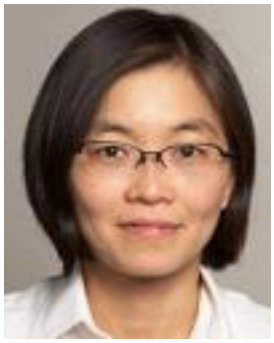
TLC Biopharmaceuticals, Inc. is the US subsidiary fully owned by Taiwan Liposome Company, LTD. The website is the same as Taiwan Liposome Company: http://www.tlcbio.com/en-global/

The followings are the two paragraphs that briefly describe Taiwan Liposome Company:

Taiwan Liposome Company (TLC) is a biopharmaceutical company focused on the research, development and commercialization of innovative pharmaceutical products based on its proprietary drug delivery technologies. Our strengths lie in lipid-based formulation and scale-up for parenteral drugs using micelles and nanoparticles to optimize the pharmacokinetics of drugs for better efficacy and lower toxicity, and thus prolong the product lifecycle of branded drugs.

TLC is dedicated to maximizing the benefits of medications for patients and improving their quality of life through constantly advancing our technology and know-how. We strives to become a global leading biopharmaceutical company, to contribute more towards making a difference in the healthcare industry and make Taiwan biotechnology industry visible in the global arena. Currently TLC is expanding its operation globally and we are actively seeking for talents to join our team. You are cordially invited to submit your application to our HR department or talk to our representative in the 2014 BTBA symposium.

Academic Panelist



Theresa L. Chang, 張璨云博士

Principal Investigator, Public Health Research Institute
Associate Professor, Department of Microbiology and Molecular Genetics
Rutgers Biomedical and Health Sciences, New Jersey Medical School

Dr. Chang received her Ph.D at New York University and did her post-doctoral trainings at Yale University and Aaron Diamond AIDS research Institute, Rockefeller University. She worked at a start-up company, Osel, Inc. before joining Mount Sinai School of Medicine as Assistant Professor. Currently, she is Principal Investigator at Public Health Research Institute, and Associate Professor at Department of Microbiology and Molecular Genetics, Rutgers Biomedical and Health Sciences. Her research interests include the role of innate immunity, hormone, and microbiome in HIV pathogenesis and transmission, the interaction between HIV and human peritoneal macrophages, and development of nanographenes as anti-HIV therapeutics.

Yen-Tsung Huang, 黃彥棕博士

Assistant Professor of Epidemiology
Brown University

Dr. Yen-Tsung Huang is an Assistant Professor of Epidemiology at Brown University. Dr. Huang earned a Doctor of Medicine degree from the National Taiwan University, Taiwan. After the two-year military service, Dr. Huang went to Harvard University for Master of Public Health in quantitative methods and Master of Science in biostatistics. Dr. Huang earned dual doctorate in Epidemiology and Biostatistics at Harvard in 2012. His research experience and goals focus on cancer genomics, statistical genetics, high-dimensional statistical learning and genetic/molecular epidemiology of cancer."

Academic Panelist

Tony Ip, 葉亦棟博士

Professor of Molecular Medicine
University of Massachusetts Medical School

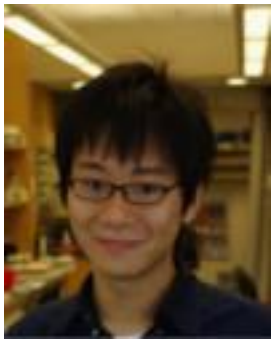
Dr. Tony Ip received his BS from the National Defense Medical Center, Taipei, ROC in 1984 and his PhD from the University of Iowa in 1989. He was a Hoffmann-LaRoche postdoctoral fellow of the Life Sciences Research Foundation from 1991-1994 at the University of California at San Diego. In 1994, he joined the University of Massachusetts Medical School faculty. He was a recipient of a Scholar Award of the Leukemia Society of America in 1996-2001. He is currently a Professor of Molecular Medicine at UMMS. His research interest is the mechanism of stem cell-mediated regeneration, using the genetic model organism *Drosophila* to identify conserved regulatory networks that control regeneration in the adult intestine.

Ya-Chieh Hsu, 許雅捷博士

Assistant Professor, Department of Stem Cell and Regenerative Biology
Harvard University

Ya-Chieh Hsu received her B.S. from Department of Life Sciences, National Tsing-Hua University. She completed her Ph.D. in Dr. Kwang-Wook Choi's lab at Baylor College of Medicine, where she studied the control of growth and proliferation using *Drosophila* as a model. For her postdoctoral research she joined the laboratory of Dr. Elaine Fuchs at the Rockefeller University, investigating how signals from the microenvironment regulate mouse hair follicle stem cells. She will become an assistant professor at the Department of Stem Cell and Regenerative Biology at Harvard University from spring, 2014. In her laboratory, she will explore how various cell types interact and coordinate with one another during development and regeneration to produce functional organs.

Bench Scientist Panelist



Tsun-Kai Chang, 張惇凱博士

Postdoctoral Research Fellow
Genentech

Dr. Tsun-Kai Chang received his BS and MS from National Taiwan University and National Yang-Ming University, respectively. He joined the laboratory of Dr. Eric Baehrecke in the Department of Cancer Biology at the University of Massachusetts Medical School and earned his PhD degree in 2013. He then worked as a postdoctoral research fellow in the Department of Research Oncology at Genentech. Dr. Chang is most interested in the cell death regulation and autophagy. Currently, he resides in San Francisco with his wife and son.

Chase Shen, 沈慶鴻博士

BioMolecule Scientist, Development Translational Medicine Division
Biogen Idec

Chase Shen is a scientist in the Department of Translational Sciences at Biogen Idec. He is involved in bioanalysis of biomarkers and immunogenicity in response to drugs to support pre-clinical and clinical studies. He has also worked previously on predictive immunogenicity in response to novel biologics at Pfizer Inc. He obtained his M.S (NYMU) and B.S. (NTU) in Taiwan and his Ph.D. from UMass Medical School in 2000. He then joined the Koch Institute for Integrative Cancer Research for his postdoctoral training and later worked as Research Scientist at MIT prior to joining Pfizer as Principal Scientist.

Bench Scientist Panelist

Chi-Li Chen, 陳豈禮博士

Research Scientist II

TetraPhase Pharmaceuticals

Chi-Li Chen is a Research Scientist in both process and medicinal chemistry at TetraPhase Pharmaceuticals, a clinical-stage company using its proprietary chemistry technology to create novel antibiotics for serious and life-threatening multidrug-resistant (MDR) infections. He works on synthetic route optimization and scale-up, transferring the synthetic technology to CRO/CMO, managing the external production, the development of highly convergent synthesis toward tetracycline analogs for the SAR studies, and the synthesis of a wide range of molecules to improve the potency of tetracyclines. Prior to the industrial job, he had completed several projects in synthesis of natural products and development of new synthetic methodologies. He was a postdoctoral research fellow at Harvard University working under the direction of Professor Yoshito Kishi (2007-2008), and received a Ph.D. degree under the direction of Professor Stephen F. Martin at the University of Texas at Austin (2002-2007).

Hsin-Pei Shih, 施心沛博士

Senior Research Scientist

Vertex Pharmaceuticals

Hsin-Pei Shih is currently a senior scientist at Vertex Pharmaceuticals. His current focus is to employ informatics to facilitate drug discovery, especially in scientific intelligence and chemical biology. Prior to Vertex, he served as a scientist at EnVivo Pharmaceuticals (now Forum Pharmaceuticals). His research led to a proprietary organism-based small molecule screening platform and several discovery programs for Huntington's disease. He later served as a lead scientist directing a collaboration program with Cure Huntington's Disease Initiative. Shih received his B.S. degree in Botany at National Taiwan University, and earned his Ph.D. degree in Biology from University of North Carolina at Chapel Hill.

Beyond the Bench Panelist

Jeffery Tsao
Engagement Manager
McKinsey & Co

Paul Lu, 盧柏源博士
Healthcare Investment Banking Associate
Lazard

Paul Lu studied Neuroscience at Washington University School of Medicine. While pursuing his PhD, he co-founded and ran a biotech consulting firm - The BALSA Group - that advises entrepreneurs and small businesses in market research and business development. Under his tenure as President, BALSA grew to 80 participating consultants and engaged in 15 ~ 20 projects on a yearly basis. Later, he did venture capital investing for Washington University and FinServe Tech Angels, focusing on healthcare and finance tech start-ups. He also worked in healthcare investment banking at Lazard Frères & Co. in New York, specializing in M&A.

Paul received a PhD in Neuroscience from Washington University in St. Louis, B.Sc. in Biological Sciences and Chemistry from University of Waikato in New Zealand, and is an MBA candidate and Kaplan Life Sciences Fellow at Harvard Business School. He is the Founder and CEO of Precursor Advisors, which enable Immigrant Investors qualify for green cards faster and receive a superior return through investments in small businesses and real estate.

Beyond the Bench Panelist

Vivide Chang, 張端強博士

Consultant

L.E.K. Consulting

Vivide is a Consultant in L.E.K.'s Boston office and specializes in life science engagements. Vivide joined L.E.K. in 2011 and has worked in L.E.K. Boston and Shanghai offices. Dr. Chang provides services to clients on corporate, portfolio, R&D and commercialization strategy for a wide range of biopharmaceutical, medical devices, and life science tools clients. Recent engagements include: -diabetes franchise strategy for a leading global pharma -CV business development strategy for leading device company -post-acquisition R&D portfolio prioritization strategy for two life science tools companies Vivide received his Ph.D. in Biomedical Engineering from Duke University. His doctoral research was focused on developing optical diagnostic tools for early cancer screening. Vivide also holds a B.A.Sc. in Engineering Physics with a Minor in Commerce from the University of British Columbia.

Wayne Peng, 彭賢巍博士

Medical Writer

KnowledgePoint360 Group

Wayne Peng strives to facilitate scientific and medical communications—not only among researchers but also between scientists and non-scientists stakeholders. He received a Ph.D. from Columbia University, where he studied the function of an oncogenic transcription factor complex in progenitor cell fate decision. After defending his thesis, Wayne moved to Nature Publishing Group to pursue a career in the interface between science and business. Besides serving as a scientific liaison to marketing and digital technology teams, he started the Drug Pipeline column in Nature Biotechnology in 2010, and served as a scientific editor at Nature and Nature Genetics in 2011–2012. After four years in publishing, Wayne switched career gear and joined a medical education agency in Sudler & Hennessey, where he devised launch strategy and created promotional materials for an investigational drug for type 2 diabetes. He recently moved to KnowledgePoint360 Group to serve a wider range of biopharma clients working on diverse therapeutic areas.

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L01. Genome-Wide Measurement of Chromatin Accessibility by RED-Seq

Poshen B. Chen, Lihua J. Zhu, Sarah J. Hainer, Kurtis N. McCannell, and Thomas G. Fazzio
UMass Medical School

Differential accessibility of DNA to nuclear proteins underlies the regulation of numerous cellular processes. DNA accessibility is primarily determined by the presence or absence of nucleosomes. At present, methods for mapping the positions and occupancy of nucleosomes genome-wide (MNase-seq) have uncovered the nucleosomal landscapes of different cell types and organisms. Conversely, methods specialized for the detection of large nucleosome-free regions of chromatin (DNase-seq, FAIRE-seq) have uncovered numerous gene regulatory elements. However, these methods are less successful in measuring the accessibility of DNA sequences within nucelosome arrays. Here we describe a new genome-wide method, RED-seq (deep sequencing analysis of Restriction Enzyme Digestion), that measures chromatin accessibility in an unbiased way. Using this method, we identified differences in chromatin accessibility between populations of cells, not only in broadly nucleosome-depleted regions of the genome (e.g., enhancers and promoters), but also within the more widespread regions of nucleosomal occupancy. Furthermore, RED-seq identified both large differences in chromatin accessibility in distinct cell lineages and subtle changes observed during differentiation of mouse embryonic stem cells (ESCs). Most notably, using RED-seq, we detected differences in accessibility among sequences occupied by distinct nucleosome variants. Therefore, RED-seq provides unique insights into genome-wide chromatin dynamics.

L02. Dosage of Dyrk1a Shifts Cells within a p21-cyclin D1 Signaling Map to Control the Decision to Enter the Cell Cycle

Jia-Yun Chen[a,b], Jia-Ren Lin[a,b], Feng-Chiao Tsai[a], and Tobias Meyer[a]
[a]Department of Chemical and Systems Biology, Stanford University, Stanford, CA 94305, USA.
[b]Laboratory of Systems Pharmacology, Harvard Medical School, MA, 02115, USA.

Mammalian cells have a remarkable capacity to compensate for heterozygous gene loss or extra gene copies. One exception is Down syndrome (DS) where a third copy of chromosome 21 mediates neurogenesis defects and lowers the frequency of solid tumors. Here we combine live-cell imaging and single-cell analysis to show that increased dosage of chromosome 21-localized Dyrk1a steeply increases G1 cell cycle duration through direct phosphorylation and degradation of cyclin D1 (CycD1). DS-derived fibroblasts showed analogous cell cycle changes that were reversed by Dyrk1a inhibition. Furthermore, reducing Dyrk1a activity increased CycD1 expression to force a bifurcation, with one subpopulation of cells accelerating proliferation and the other arresting proliferation by co-stabilizing CycD1 and the CDK inhibitor p21. Thus, dosage of Dyrk1a repositions cells within a p21-CycD1 signaling map, directing each cell to either proliferate or to follow two distinct cell cycle exit pathways characterized by high or low CycD1 and p21 levels.

L03. An Ancient Class of Structured Intron Demonstrates a Widespread Role for Dinucleotide Repeats in Vertebrate Gene Expression

Chien-Ling Lin[a], Kian Huat Lim[a], Allison J Taggart[a], Luciana Ferraris[a], Kamil J Cygan[b], and William G Fairbrother[a,b]

[a]Molecular Biology, Cell Biology and Biochemistry, Brown University, Providence 02912

[b]Center for Computational Molecular Biology, Brown University, Providence 02912

RNA secondary structure plays an integral role in catalytic, ribosomal, small nuclear, micro, and transfer RNAs. Discovering a prevalent role for secondary structure in pre-mRNAs has proven more elusive. By utilizing a variety of computational and biochemical approaches, we present evidence for a class of nuclear intron that relies upon secondary structure for correct splicing. These introns are defined by simple repeat expansions of complimentary AC and GT dimers that co-occur at opposite boundaries of an intron to form a bridging structure that enforces correct splice site pairing. Remarkably, this class of intron does not require U2AF65, a core component of the spliceosome, for its processing. Phylogenetic analysis suggests that this mechanism was present in the ancestral vertebrate lineage prior to the divergence of tetrapods from teleosts. While largely lost from land dwelling vertebrates, this class of introns is found in 11% of all zebrafish genes.

L04. Probing Nitrate Signaling in *Arabidopsis*

Kun-Hsiang Liu[a,b], Yajie Niu[a,b], Matthew McCormack[a,b], and Jen Sheen[a,b]
[a]Harvard Medical School
[b]Massachusetts General Hospital

Nitrogen is the basic element in all organisms. In agriculture, nitrogen availability is the key factor that limits crop productivity. Plants prefer to use the inorganic form of nitrogen source, nitrate, as their nitrogen source. In nitrogen cycle, plants play a critical role in converting inorganic to organic form of nitrogen for supporting animal nitrogen source. Thus, understanding nitrate signaling in plants is not only important for improving plant growth but also benefits the whole biosphere. Despite the importance, little is known about how plants sense nitrate in order to regulate plant morphology and nitrate assimilation. Here, we use both genetics and functional genomics approaches to discover and dissect novel components involved in nitrate signaling in Arabidopsis. By performing the genetic approach, we developed a dual genetic screen and successfully isolated three novel nitrate signaling mutants. To identify the causative mutation, we have developed a targeted parallel sequencing (TPSeq) simultaneously identify mutations in these mutants. Furthermore, we have elucidated the molecular mechanism of one of these genes function in nitrate signaling. By performing functional genomics approach, we developed an integrated cell-based and genetic screening method for identifying novel signaling components and transcription factors involved in nitrate signaling. Strong evidence obtained from cell-based screens and genetic analyses indicated that Group III CDPKs (Calcium-Dependent Protein Kinase) participate in nitrate signaling.

L05. B7H6-Specific Chimeric Antigen Receptors (CARs) Lead to Tumor Elimination and Host Immunity

Ming-Ru Wu, Tong Zhang, and Charles L. Sentman
Dartmouth College

CAR T cell therapies have demonstrated durable and potentially curative therapeutic efficacy against B cell leukemia in clinical trials. This CAR strategy can target any tumor surface antigens as long as a tumor-specific receptor can be generated. New CARs which target solid tumors and have the potential to target multiple tumor types are needed. In this study, we utilized a NK cell activating receptor, NKp30, to design CARs which can target multiple tumor types. NKp30 recognizes two major ligands, B7H6 and BAG-6. B7H6 is expressed on various primary human tumors, including leukemia, lymphoma, and gastrointestinal stromal tumors (GISTs). Gene expression data also indicated some ovarian cancers, brain tumors, breast cancers, renal cell carcinomas, and sarcomas potentially expresses B7H6. Furthermore, it is not constitutively expressed on normal tissues. However, BAG-6 is expressed on immature dendritic cells (iDCs) and leads NKp30-based CARs responses against autologous iDCs. To eliminate this self-reactivity, we further created CARs specific to B7H6. B7H6-specific CAR T cells have robust cellular cytotoxicity and IFN-g secretion when co-cultured with B7H6+ tumor cells, and they exhibit little self-reactivity to iDCs. These T cells produce a variety of effector molecules that can alter the local tumor microenvironment. In vivo, B7H6-specific CAR T cells greatly enhanced the survival of RMA/B7H6 lymphoma bearing mice. The long-term survivor mice were protected against a B7H6-deficient RMA tumor re-challenge. This therapy also decreased tumor burden in a murine ovarian cancer model. In conclusion, B7H6-specific CARs have the potential to treat B7H6+ hematologic and solid tumors.

L06. A Rapid, Multiplexed, Mobile Phone-Enabled Point-of-Care Diagnostic Device to Detect Infectious Diseases

Chun-Wan Yen[a,b], Helena de Puig Guixe[a], Justina Tam[a,b], Patrick Regan[b], Charles Clavet[b], Kimberly Hamad-Schifferli[c], and Lee Gehrke[a]

[a]Institute for Medical Engineering and Science, Massachusetts Institute of Technology

[b]FDA Winchester Engineering and Analytical Center

Medical countermeasures surveillance and reporting during and after a public health emergency event require detection/diagnostic methods and devices. We propose to design, build and test a rapid, multiplexed diagnostic device directed at identifying three biological threats; that is, Dengue virus, Yellow Fever Virus, and Ebola virus infections. The device will be designed for field use by the layperson, without need for refrigeration, specialized training, specialized equipment or chemicals. During a public health emergency, the location of identified pathogens is critically important for predicting spread, and for mobilizing public health responses. To accomplish this goal, the diagnostic device, covering 8-10 pathogen markers, will be photographed with a mobile phone camera, and the image will be uploaded by multimedia messaging service or short message service to a server for results quantification and analysis, followed by geospatial data mapping for real time epidemiology. The technical specifications of diagnostic device are based on lateral flow chromatography, a well-established technology.

L07. A Gain-of-Function UNC-2/CaV2 Channel Induces Behavioral Hyperactivity and an Imbalance in Excitatory-Inhibitory Signaling

Yung-Chi Huang[a], Jennifer K. Pirri[a], Diego Rayes[a], Shangbang Gao[b], Mei Zhen[b], Cornelia I. Bargmann, Michael M. Francis[a], and Mark J. Alkema[a]

[a]Department of Neurobiology, University of Massachusetts Medical School, Worcester, MA

[b]Lunenfeld- Tannenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada

Animal behaviors are fine-controlled by precise interplay between excitatory and inhibitory synapses. Imbalance between excitatory and inhibitory synaptic transmission have been associated with several neurologic disorders, such as seizure, epilepsy and migraine. Ion channels are central to synaptic transmission and highly conserved from invertebrate to humans. The nematode, Caenorhabditis elegans, with its well-defined neuronal wiring and amenability to genetic analysis, offers an opportunity to study the channel functions and how synaptic modifications alter behaviors at the molecular and cellular level. Here we report a novel gain-of-function mutation in the unc-2 gene, encoding the conserved α1 subunit of the neuronal voltage-gated calcium channel (CaV2), causes increased CaV2 activity and behavioral hyperactivity. Electrophysiological data shows that unc-2(gf) mutants have an increased frequencies of total synaptic signaling events. Surprisingly, unc-2(gf) mutants show a marked reduction of inhibitory signaling events resulting in a raised excitation-inhibition ratio. Analysis of the synaptic markers showed that unc-2(gf) mutants have an increased expression of the excitatory acetylcholine receptors, and a strikingly decreased expression of the inhibitory GABA receptors. Our data suggests that excitatory and inhibitory synapses have different regulation in response to the elevated CaV2 activity, which leads to excitation-Inhibition imbalance. In the human CaV2 gene, gain-of-function mutations result in the Familial Hemiplegic Migraine (FHM). Interestingly, transgenic animals that express FHM mutations recapitulate the behavioral hyperactivity of unc-2(gf) mutants suggesting unc-2(gf) mutants may provide insights on circuit malfunction in CaV2 channelopathies.

L08. Control of Spinal Cord Function with Optoelectronic Integrated Polymer Fiber Probes

Chi Lu[a,b], Ulrich P. Froriep[b], and Andres Canales[a,b]
[a]Department of Materials Science and Engineering, Massachusetts Institute of Technology
[b]Research Laboratory of Electronics, Massachusetts Institute of Technology

Restoration of sensory and motor functions in paralyzed spinal cord injury patients requires simultaneous stimulation and recording of neural activity in the spinal cord. However, the flexible and fibrous structure of the spinal cord and the heterogeneity of surrounding tissues including the vertebrae pose technical challenges to the development of spinal neural probes. To address these challenges, we developed highly flexible neural probes consisting entirely of polymers, including polycarbonate (PC) and cyclic olefin copolymers (COC), which form a high refractive index contrast pair and conductive polyethylene (CPE), for combined optical stimulation and recording of neural activity in the spinal cord. By employing thermal drawing, which is commonly used in the optical fiber industry, we simultaneously processed different polymers and reduced the size of a macroscopic probe template to a microscopic fiber probe, while preserving its cross-sectional geometry. Our fiber probes exhibit low optical losses (0.5-2 dB/cm) and their flexible design (bending stiffness <10 N/m) enables recording and stimulation functions at deformation angles up to 270° and radii of curvature down to 500 µm. With our fiber probes, we successfully demonstrated simultaneous recording and optogenetic stimulation of neural activity in the spinal cord of transgenic mice expressing the blue-light (λ = 473 nm) sensitive cation channel channelrhodopsin 2 (ChR2). Neural activitiy corresponding to optical stimulation were robustly evoked and recorded in the spinal cord with our integrated probes. Furthermore, the observed optically evoked activity in the spinal cord induces on-demand lower limb movements that correlate with the electromyographic (EMG) activity of the gastrocnemius muscle. To our knowledge, this is the first observation of in vivo optogenetic stimulation in the rodent spinal cord using a flexible polymer fiber probe.

L09. Control Interneuron Activity in *Caenorhabditis elegans* to Evoke Chemotactic Behavior

Ching-Han Shen[a,b], Askin Kocabas[a,b], Zengcai V Guo[c], and Sharad Ramanathan[a,b,d,e,f]
[a]Department of Molecular and Cellular Biology, Harvard University
[b]FAS Center for Systems Biology, Harvard University
[c]Janelia Farm Research Campus, Howard Hughes Medical Institute
[d]Allen Institute for Brain Science
[e]Harvard Stem Cell Institute, Harvard University
[f]School of Engineering and Applied Sciences, Harvard University

One way to test how well we understand a biological system is to control its inner machinery to generate desired outputs. To do so, we need to know how the nodes are connected and how the dynamics of activity between nodes affect the outputs. Here we aim to produce chemotactic behavior in *Caenorhabditis elegans* by controlling the activity in interneurons. To do so, we have to understand which sets of interneurons to control and what activity patterns to evoke in these neurons. We first deduced the neural activity patterns triggered during chemotaxis by studying animals that move toward a bacterial lawn. Based on the head-bending angle of the animal and the direction of the gradient, sensory signals received by the animal can be separated into symmetric and asymmetric components. To drive the activity of neurons with desired patterns, we expressed light-gated ion channels on them. Further, we developed a setup to stimulate neuron(s) of interest even when light-gated ion channels are expressed in multiple neurons. Among the interneurons we tested, one interneuron pair, AIY, control reversal frequency during symmetric activation and elicited gradual turning during asymmetric activation. Since both behaviors AIY control are required for chemotaxis, we wanted to test whether we could directly control the activities in AIY to produce chemotactic behavior. We designed a virtual light gradient to modulate both symmetric and asymmetric activation levels of AIY and discovered that controlling the dynamics of AIY activity was sufficient to force the animal to locate, turn toward, and track virtual light gradients.

P01. Discriminating Multiplexed GFP Reporters in Primary Articular Chondrocyte Cultures Using Image Cytometry

Leo Chan[a], Jianping Huang[b,c], Yusuke Hagiwara[b,c], Leonardo Aguila[b,c], and David Rowe[b,c]
[a]Department of Technology R&D, Nexcelom Bioscience LLC, Lawrence, MA 01843
[b]Center for Regenerative Medicine and Skeletal Development, Department of Reconstructive Sciences, School of Dental Medicine
[c]Department of Immunology, School of Medicine, University of Connecticut Health Center, Farmington, CT 06030

Flow cytometry has become a standard tool for defining a heterogeneous cell population based on surface expressed epitopes or GFP reporters that reflect cell types or cellular differentiation. The introduction of image cytometry raised the possibility of adaptation to discriminate GFP reporters used to appreciate cell heterogeneity within the skeletal lineages. The optical filters and LEDs were optimized for the reporters used in transgenic mice expressing various fluorescent proteins. In addition, the need for compensation between eGFP and surrounding reporters due to optical cross-talk was eliminated by selecting the appropriate excitation and emission filters. Bone marrow or articular cartilage cell cultures from GFP and RFP reporter mouse lines were established to demonstrate the equivalency in functionalities of image to flow cytometry analysis. To examine the ability for monitoring primary cell differentiation, articular chondrocyte cell cultures were established from mice that were single or doubly transgenic (Dkk3eGFP and Col2A1GFPcyan), which identify the progression of superficial small articular cell to a mature chondrocyte. The instrument was able to rapidly and accurately discriminate cells that were Dkk3eGFP only, Dkk3eGFP/Col2A1GFPcyan, and Col2A1GFP, which provides a useful tool for studying the impact of culture conditions on lineage expansion and differentiation.

P02. Next-Generation Sequencing Reveals the Biological Consequences of Ethenoguanine Lesions *in vivo*

Shiou-chi Chang[a], Jie Wu[a], Bogdan Fedeles[a], Linlin Zhao[b], F. Peter Guengerich[b], and John Essigmann[a]
[a]MIT
[b]Vanderbilt University School of Medicine

Damaged DNA, when left unrepaired, can block replication or lead to mutations. The traditional biochemical approach of investigating the biological consequences of DNA lesions is expensive and tedious. Inspired by the ability of next-generation sequencing to perform massively parallel sequencing, we have applied this technique to investigate ethenoguanine lesions *in vivo*. By using unique barcodes for different lesions and cell strains, multiple lesions can be studied in multiple cell strains simultaneously, making this a multiplex approach. Here we show that both 1,N2-εG and N2,3-εG are strong blockers of replication, with 1,N2-εG being more potent. 1,N2-εG is also a potent inducer of deletion mutations, whereas N2,3-εG primarily generates G to A point mutations. Interestingly, induction of the SOS response of *E. coli* dramatically reduces the level of deletions while increasing the frequency of point mutations. Moreover, AlkB, a DNA repair protein, appears to repair all the etheno- DNA lesions (εA, εC and 1,N2-εG) except N2,3-εG. This result provides an explanation for the persistency of N2,3-εG in cells and suggests N2,3-εG may be contributing to the GC to AT mutations found in vinyl chloride induced tumors. Furthermore, our results demonstrate the feasibility of utilizing next-generation sequencing to investigate the biological consequences of DNA lesions *in vivo*.

P03. Functional Dissection of the *Toxoplasma gondii* Mitotic Apparatus

Chun-Ti Chen
Boston College

Toxoplasmosis is an opportunistic infectious disease caused by the protozoan parasite *Toxoplasma gondii*. It is a cyst forming apicomplexan parasite that may cause only minor symptoms to healthy individuals upon infection. However, acute acquisition of parasites or reactivation from chronic infection could develop into severe inflammatory diseases, and could be fatal to both immunocompetent and immunocopromised persons. The pathology and severity of toxoplasmosis is tightly linked to the rapid replication of parasite asexual form, the tachyzoites. Tachyzoites replicate through a unique process of internal budding. In this process, daughter cytoskeletal components assemble and elongate to encapsulate the dividing nucleus and organelles. Like in other eukaryotes, the centrosome serves as the node coordinating mitosis and cytokinesis. In *T. gondii*, these two processes occur concomitantly whereas the daughter budding initiates around the duplicated centrosomes, and the mitotic spindle assembles inside the nucleus. However, the molecular mechanisms providing the spatio-temporal cue are largely unknown. Here, we characterize several novel proteins that are crucial for parasite division. We have shown that TgNek1 regulates centrosome segregation and nuclear division. Failing to separate the duplicated centrosomes results in formation of single daughter bud. To better understand the dynamic of mitotic spindle, we studied a microtubule binding protein, TgEB1, where it binds to the spindle microtubule. When overexpressing a dominant negative mutant TgEB1-Q117A, the mutant protein bundles spindle microtubules and disrupt nuclear division. In all, our studies highlight the molecular mechanism that orchestrates parasite division.

P04. *In vivo* Leukemia Clonality Tracking Using Neutral shRNA Library

Chi-Chao Chen[a,b], Zhen Zhao[b], and Scott Lowe[a,b,c]
[a]Weill Cornell Graduate School of Medical Sciences Cornell University
[b]Cancer Biology and Genetics Program, Memorial Sloan-Kettering Cancer Center, New York
[c]Howard Hughes Medical Institute

With its origin not fully understood, tumor heterogeneity remains a major obstacle in cancer therapy.

Most of effective cancer therapeutics eventually select out either preexisting or newly-evolved resistant tumor cell clones. Several fluorescence-based technologies have been developed to track tumor clones. These methods are convenient in visualizing different clones, while the number of clones tracked is limited. To monitor the proliferation of different clones in a large scale setting, we used a 1000 hairpin neutral library to barcode each cell clone and track them in an *in vivo* leukemia mouse model. Using a retroviral vector with MOI<0.1, typically a single copy of shRNA (22 mers) barcode is stably integrated into each infected cell. In an effort to offset integration site bias, at least 1000 cells were to be infected by one shRNA sequence. A week after tumor transplant into recipient mice, we confirmed *in vivo* leukemogenesis by luciferase imaging. Bone marrow and spleen samples were harvested at either early, late, or chemo-relapse time points. Genomic DNA was extracted from tissue samples of more than 3 biological replicates. shRNA sequences were amplified and prepared for Hiseq (Illumina) sequencing and barcode representation was compared to pre-transplantation cell population.

Our results show higher noises between biological replicates than previously in-vitro studies. Initially, we reasoned that variable results across replicates are possibly due to different engraftment, niche-interaction, or immuno-responses in different mice. Following *in silico* modeling suggests that heterogeneity of *in vivo* microenvironment could be a major contributor to barcodes representation changes, which implies a more heterogeneous growth environment *in vivo*. Interestingly, our data from 2 independent experiments also indicated that spleen provides a more homogenous microenvironment than bone marrow does under chemotherapy. This work implies the importance of environmental niche in tumor growth in a more physiological context.

P05. Mdmx Buffers against p53 Oscillations to Affect Cell Fate Decisions

Sheng-hong Chen and Galit Lahav
Harvard Medical School, Department of Systems Biology

Cells sense and integrate signals that lead to various cellular decisions including proliferation, differentiation and death. The tumor suppressor p53 plays an important role in regulating these outcomes. Mdmx binds to p53 and regulates its activity and abundance. Here, we used live cell imaging to study the role of Mdmx in p53 dynamics in single cells. Knockdown of Mdmx leads to cell cycle arrest and oscillatory patterns of p53 in the absence of DNA damage. Upon UV-irradiation, inhibition of Mdmx alters a single p53 pulse response to an oscillatory behavior. This change in p53 dynamics converts the cellular fate from apoptosis to cell cycle arrest. Our results show that Mdmx functions as a controller for p53 dynamics, and for diverging cell fate decisions.

P06. A Tyrosine-Phosphorylated Type III Secretion Effector Mediates Recruitment of a Host Scaffolding Protein to the Pathogenic Vacuole of *Chlamydia trachomatis*

Yi-Shan Chen[a, b], Robert J. Bastidas[b], Kristian L. Richards[c], Gregory V. Plano[c], and Raphael H. Valdivia[b]

[a]Department of Biochemistry, Duke University

[b]Department of MGM, Duke University

Chlamydia trachomatis, the causative agent of trachoma and sexually transmitted infections, employs a type III secretion (T3S) system to deliver effector proteins into host epithelial cells to establish a replicative vacuole ("inclusion"). Aside from the phosphoprotein TARP, a *Chlamydia* effector that promotes actin re-arrangements, very few factors mediating bacterial entry and early inclusion establishment have been identified or characterized. Like many T3S effectors, TARP requires a chaperone (Slc1) for efficient translocation into host cells. In this study, we defined proteins that associate with Slc1 in invasive *Chlamydia* elementary bodies (EB) by immunoprecipitation coupled with liquid chromatography-tandem mass spectrometry (LC-MS/MS). In this manner, we identified a previously uncharacterized protein, which we renamed TEPP (Translocated early phosphoprotein), as a new T3S effector. We show that TEPP is translocated early during bacterial entry into epithelial cells and is phosphorylated at tyrosine residues. During infection, phosphorylated TEPP co-immunoprecipitated with CrkI-II, isoforms of a SH2 and SH3 domain-containing host scaffolding protein, that were recruited to bacteria entry sites. This association remained till the nascent inclusions had trafficked to microtubule organizing center. Importantly, a *Chlamydia* mutant lacking TEPP failed to recruit CrkI-II to inclusions, providing genetic confirmation of a direct role for this effector in the recruitment of this signaling scaffolding protein. We propose a model wherein TEPP acts as a "scaffolder" of scaffolding proteins to initiate and amplify signaling cascades important for establishing a replicative niche for *Chlamydia*.

P07. Nanoliposome-Assisted Combination Strategy for Pancreatic Cancer

Chun-Te Chiang, Huang-Chiao Huang, Srivalleesha Mallidi, Zhiming Mai, Joyce Liu, and Tayyaba Hasan

Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, Boston, MAMassachusetts

Pancreatic cancer (PanCa) is associated with the poorest prognosis of all malignancies and has a 5-year survival less than 5%. Gemcitabine-based chemotherapy regimens given as first-line treatment for advanced PanCa patients with metastasis are standard but have modest response rates. Phase 2 trial of liposomal irinotecan (MM-398) demonstrates moderate antitumour activity but with a manageable side effect profile. A recent completed phase 3 trial (NAPOLI-1) shows the promise of combing MM-398 with 5-fluorouracil (5-FU) and leucovorin for metastatic, gemcitabine-refractory advanced PanCa patients. Photodynamic therapy (PDT) is an emerging treatment for cancer which involves excitation of nontoxic photosensitizer by harmless visible light leading to the production of toxic reactive oxygen species (ROS) that kill cancer cells. PDT has been approved for clinical use in a number of countries. Clinical PDT of inoperable, advanced localized PanCa demonstrates substantial improvements in patient survival. Based on our findings that PDT decreases the expression of the putative resistance markers for irinotecan (drug efflux transporter ABCG2 and anti-apoptosis protein survivin), we hypothesized that combining PDT can enhance the efficacy of irinotecan for PanCa. In two orthotopic PanCa xenograft models, a single, low-dose combination of PDT and liposomal irinotecan dramatically inhibited the primary tumor growth without acute systemic toxicity. Furthermore, we found that irinotecan reduces tumor hypoxia and creates a favorable microenvironment for PDT. In summary, we demonstrated a rationally designed nanoliposome-assisted combination strategy can potentially improve PanCa treatment outcome.

P08. L-Tryptophan Dioxygenation Activity of human Indoleamine 2, 3 Dioxygenase 2

Bing-Yu Chiang
Albert Einstein college of Medicine

Indoleamine 2, 3 dioxygnease 1 (IDO1) is an important immunosuppressive heme-containing enzyme that catalyzes dioxygenation reaction of L-Tryptophan. Recently a new isoform of indoleamine 2, 3 dioxygenase, IDO2, was discovered and shown to exhibit high amino acid sequence similarity (43%) to IDO1. Although most of the active site residues critical for L-Tryptophan binding in IDO1 are conserved in IDO2, the L-Tryptophan dioxygenation activity of IDO2 is much lower than IDO1 - with x-fold lower kcat and x-fold higher Km. Amino acid sequence alignment studies show that F269 and Q270 in IDO1, which form part of the heme binding site, are replaced by L274 and H275, respectively, in IDO2. To evaluate the structural roles of the two residues, we have constructed and purified L274F and/or H275Q mutants of IDO2, and examined their spectroscopic and functional properties. Our data revealed that L274F and/or H275Q mutations in IDO2 rescued the Trp dioxygenation activity of IDO2 by modulating the conformation of the heme prosthetic group. This study provides important information about the structural factors that control the dioxygenation activity of IDO

P09. Design and development of glucose-responsive insulin derivatives

Danny Chou[a,b], Matthew Webber[a,b], Benjamin Tang[a,b], Amy Lin[a,b], Robert Langer[a,b], and Daniel Anderson[a,b]

[a]Department of Chemical Engineering, MIT

[b]Koch Institute for Integrative Cancer Research, MIT

The emergence of exogenous insulin to treat diabetes has dramatically improved the prospects for patient survival. However, standard insulin therapy must be strictly regimented, and even with perfect compliance serious complications can arise. Previous work has established various chemically modified insulin analogues in order to alter the kinetics of insulin activity and enable more patient-specific tuning of therapy. We demonstrate the use of a chemical modification strategy intended to promote both long-term and glucose-mediated insulin activity. The insulin analogues designed here incorporate a hydrophobic domain intended to facilitate binding with serum albumin along with a phenylboronic acid (PBA) moiety intended to bind to glucose, thereby rendering the modification more hydrophilic. These insulin analogues exhibit glucose-mediated albumin binding and demonstrate active control of blood glucose in vivo following glucose challenge. This approach could afford long-term and glucose-mediated insulin activity, reduce the number of administrations required for insulin therapy, and improve glycemic control in a diabetic state.

P10. Molecular Organization of the GARP Vesicle Tethering Complex

Hui-Ting Chou, Melissa Chambers, Tom Walz
Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA

The steps in intracellular trafficking include vesicle budding, movement, tethering and fusion with the target membrane. The first physical interaction between a transport vesicle and its target membrane is mediated by tethering factors, which are recruited to the membrane by Rab GTPases and facilitate the assembly of SNARE complexes. These three components determine the specificity and efficiency of vesicle fusion. Here, we focus on GARP (Golgi-associated retrograde protein), the multisubunit tethering complexes (MTCs) on the *trans*-Golgi membrane tethering the vesicles derived from endosomes. GARP contains 4 subunits (Vps51, Vps52, Vps53 and Vps54) and its association with the Golgi apparatus is mediated by the Rab GTPase Ypt6. In mice, the point mutant L967Q in Vps54 can cause degeneration of motor neurons, resulting in progressive muscle weakness, atrophy and contractures similar to the human disease amyotrophic lateral sclerosis (also known as Lou Gehrig's disease). We are using single-particle electron microscopy to study the structure and molecular organization of GARP in an effort to understand how each subunit contributes to tethering, GTPase binding and SNARE complex assembly.

P11. Kin Recognition Protects Social Amoeba from Cheaters

Hsing-I Ho[a], Shigenori Hirose[b], Adam Kuspa[a, b], and Gad Shaulsky[a]
[a]Department of Molecular and Human Genetics, Baylor College of Medicine
[b]Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine

The evolution of sociality and altruism is enigmatic because cooperators are constantly threatened by cheaters who benefit from cooperation without incurring its full cost. Kin recognition is the ability to recognize and cooperate with genetically close relatives. It has also been proposed as a potential mechanism that limits cheating, but there has been no direct experimental support for that possibility. Here we show that kin recognition protects cooperators against cheaters. The social amoebae *Dictyostelium discoideum* cooperate by forming multicellular aggregates that develop into fruiting bodies of viable spores and dead stalk cells. Cheaters preferentially differentiate into spores while their victims die as stalk cells in chimeric aggregates. We engineered syngeneic cheaters and victims that differed only in their kin-recognition genes, tgrB1 and tgrC1, and in a single cheater allele, and found that the victims escaped exploitation by different types of non-kin cheaters. This protection depends on kin-recognition-mediated segregation, because it is compromised when we disrupt strain segregation. These findings provide direct evidence for the role of kin recognition in cheater control, and suggest a mechanism for the maintenance of stable cooperative systems.

P12. The Inferred Stress-Activated Signaling Network from Yeast: Coordination, Interconnectivity, and a Novel NaCl Network Hub, Cdc14 Phosphatase

Yi-Hsuan Elisha Ho, Deborah Chasman, Matthew E. MacGilvray, James Hose, Anna E. Merrill, Joshua J. Coon, Mark Craven, and Audrey P. Gasch
University of Wisconsin-Madison, Madison, WI

Stressed cells coordinate a multi-faceted response spanning many levels of physiology. Yet knowledge of the complete stress-activated regulatory network as well as principles for signal integration remain incomplete. We developed an experimental and computational approach to integrate available protein interaction data with gene fitness contributions, mutant transcriptome profiles, and phospho-proteome changes in cells responding to salt stress, to infer the salt-responsive signaling network in yeast. The inferred subnetwork presented many novel predictions by implicating new regulators, uncovering unrecognized crosstalk between known pathways, and pointing to previously unknown 'hubs' of signal integration. We exploited these predictions to show that Cdc14 phosphatase plays a central role in integrating the response. We found that the cdc14-3 mutant at the non-permissive temperature had a distinct defect in NaCl transcriptome changes that significantly overlapped with targets of the Hog1 kinase. Based on the predictions of the network, we showed that Cdc14 is required for normal nuclear localization of Hog1 upon salt stress. We also found that Cdc14 interacts with another implicated regulator, the CK2 kinase, which together with Hog1 is required for normal induction of salt-responsive targets of the regulator Hot1. Surprisingly, we discovered that the cdc14-3 mutant aberrantly induced G1- and S-phase genes upon NaCl treatment, even though the cells were arrested in M-phase, suggesting that it is required to suppress signaling to the cell cycle network. The network predicted that this crosstalk was mediated by the Snf1 kinase. We found that the aberrant induction was abrogated with snf1 deletion in the cdc14-3 background. Together, our results demonstrate the central role of Cdc14 in coordinating cellular signaling upon osmotic shock, while showcasing the predictive power of our inferred subnetwork.

P13. Activation of STAT3 by TBK1 Modulates the Cellular Responses to Cytosolic DNA

Hung-Ching (Gloria) Hsia[a,c], Jessica Hutti[b], Zhigang Zheng[c], Charles Stopford[c], Blossom Damania[c], and Albert Baldwin[a,c]

[a]Cell Biology and Physiology, UNC-CH

[b]Abbvie

[c]Lineberger Comprehensive Cancer Center, UNC-CH

In the mammalian immune system, mislocalized macromolecules are often seen as danger-associated molecular patterns (DAMPs. The detection of DAMPs by cellular receptors triggers innate immune and inflammatory responses. Cytosolic DNA derived from undigested engulfed materials or intracellular pathogens is a potent DAMP. The recognition of cytosolic DNA by cellular receptors activates TANK-binding kinase 1 (TBK1), which phosphorylates and activates the transcription factor IRF3. This then leads to the production of interferons and initiation of innate immune responses.

Here we identified the transcription factor STAT3 as an additional factor governed by TBK1 in response to cytosolic DNA. Activation of STAT3 leads to production of inflammatory cytokines and counteracts the innate immune responses mediated by a closely related protein, STAT1. Consistently, STAT3 null cells express higher STAT1-dependent interferon-stimulated genes (ISGs) and are more resistant to a DNA virus, herpes simplex virus-1 (HSV-1). Moreover, we identified that TBK1 directly phosphorylates STAT3 in its transactivation domain, potentially regulating its transcriptional activity. In addition, phosphorylated STAT3 has distinct subcellular localization, suggesting transcription-independent functions. The exact functional consequences of this phosphorylation are currently under investigation.

In summary, we identified STAT3 as a negative regulator of innate immunity and a positive contributor to inflammation in response to cytosolic DNA. Cytosolic DNA is not only implicated in DNA pathogen-mediated infectious diseases but also autoimmunity, in which inflammation often contributes to pathogenesis. Our discovery of TBK1-STAT3 signaling axis will elucidate the molecular basis of both infectious diseases and autoimmunity.

P14. Intravascular Ultrasound and Photoacoustic Imaging

Bao-Yu Hsieh, and Pai-Chi Li
National Taiwan University

Photoacoustic (PA) imaging combines good ultrasonic resolution with high optical contrast. Integration of intravascular ultrasound (IVUS) and photoacoustic (IVPA) imaging was proposed for diagnosis of cardiovascular diseases. The hypothesis is that ultrasound (US) provide anatomical details of vessels, while the atherosclerotic and normal vessels can be differentiated by the photoacoustic (PA) techniques. In this research, we constructed a dual-modality imaging system for IVUS/IVPA imaging. A high-speed pulsed laser was used to increase the imaging frame rate for real-time IVUS/IVPA imaging. An optical fiber with an axicon-like distal tip was designed for omni-directional excitation, eliminating the need of fiber rotation. Also, we developed two types of integrated imaging probes. One is an imaging scanhead with piezoelectric ring-shaped transmitter and the other is an all-optical IVUS/IVPA transducer. Both can be made sufficiently small for intravascular applications and a polymer microring, an optical based ultrasound sensor, was used for acoustic detection. Note that the all-optical design is suitable for one-time, disposable use. In the first all-optical design, the US signal is induced by impinging the laser energy on the substrate of the microring. A subband imaging method is subsequently applied to separate the PA signals from the US signals. In the second all-optical design, a dichroic filter is located at the outlet of the optical fiber to switch between US and PA imaging modes. The green laser pulse was absorbed by the red dichroic filter to induce an acoustic signal for US transmission, while the red laser light penetrated through the dichroic filter and illuminated the sample directly for PA imaging. The image resolution and the contrast can be further improved by applying the synthetic aperture focusing technique. In summary, the study has realized effective IVUS/IVPA imaging methods for cardiovascular diseases diagnosis. The contributions include development of a dual-modality imaging system and various kinds of integrated imaging probes. Future works include high-frame-rate imaging techniques to achieve real-time 2D and 3D IVUS/IVPA imaging by integration of omni-directional excitation with a ring array transducer.

P15. Integrating Regioselective Silyl Exchange Technology (ReSET) and Glycosyl Iodide Glycosylation to Achieve Step-Economical Syntheses of Tumor-Associated Carbohydrate Antigens (TACAs) and Immunogenic Glycolipids

Hsiao-Wu Hsieh, and Jacquelyn Gervay-Hague
Department of Chemistry, University of California, Davis

Carbohydrates mediate a wide range of biological interactions, and understanding these processes benefits the development of new therapeutics and chemical biology research tools. Isolating sufficient quantities of carbohydrates and glycolipid from biological samples remains a significant challenge; as well as chemical synthesis which usually require multiple steps and purifications. Two methodologies, Regioselective Silyl Exchange Technology (ReSET) and glycosyl iodide glycosylation, have now been combined to simplify the synthesis of the globo series trisaccharide (globotriaose and isoglobotriaose) and alpha-lactosylceramide (alpha-LacCer). These glycoconjugates are tumor-associated carbohydrate antigens and immunostimulatory glycolipids that hold promise as potential immunotherapeutics. Glycosyl iodide can also be further functionalized by using trimethylene oxide (TMO) to introduce iodopropyl linker at the anomeric carbon as a chemical handle. The terminal iodide can be converted to corresponding azide followed by copper-catalyzed azide-alkyne cycloaddition to afford multivalent glycoconjugates of Gb3 for further investigation as anti-cancer vaccine.

P16. JumonjiC Domain-Containing Protein 6 (Jmjd6) is Required for Adipogenic Differentiation in Mouse Mesenchymal Cells

Yu-Jie Hu, Houda Belaghzal, and Anthony N. Imbalzano
Department of Cell and Developmental Biology, University of Massachusetts Medical School, Worcester, MA

Cellular differentiation is essential for embryonic development and adult tissue homeostasis. The initiation of differentiation requires the activation of tissue-specific transcription factors and the function of multiple classes of nuclear enzymes to facilitate chromatin alteration and gene expression. JumonjiC domain-containing protein 6 (Jmjd6) is a nuclear protein involved in histone modification, transcription, and RNA processing. It was previously showed that the lack of Jmjd6 leads to widespread defects during mouse embryonic development due to poor differentiation in multiple tissues. However, the link between Jmjd6's molecular function and its role in any given differentiation process is still underexplored. In the present study, we examined the requirement of Jmjd6 in mesenchymal lineage differentiation using the well-established multipotent mouse C3H10T1/2 cell line and determined that it is required for adipogenic differentiation. We found that knockdown of Jmjd6 prevented both gene and protein expression of key adipogenic regulators, PPARγ and C/EBPα, and that compromised the expression of their downstream targets. In contrast, without an effect on the mRNA levels, knockdown of Jmjd6 reduced the protein expression of C/EBPβ and C/EBPδ, two early regulators that required for the activation of PPARγ and C/EBPα, due to a decrease in de novo synthesis. We also found that the binding of C/EBPβ at PPARγ and C/EBPα locus was decreased when Jmjd6 was depleted. The decrease of C/EBPβ binding associated with a decrease in chromatin accessibility and RNA polymerase II loading on the promoters. Moreover, ectopic expression of Jmjd6 promoted PPARγ and C/EBPα expression, and over-expression of PPARγ and C/EBPα are able to rescue the differentiation deficiency that caused by the depletion of Jmjd6. These results suggest that Jmjd6 is a crucial epigenetic regulator for lineage-specific gene expression during fat cell differentiation through both transcriptional and post-transcriptional mechanisms.

P17. CDK9-Mediated Transcription Elongation is Required for MYC Addiction in Hepatocellular Carcinoma

Chun-Hao Huang[a,b,c], Amaia Lujambio[a,c], Johannes Zuber[c,d], Thomas Kitzing[a,c], Nan Zhu[a], Scott A. Armstrong[a], Charles J. Sherr[e,f], and Scott W. Lowe[a,b,c,e]

[a]Memorial Sloan-Kettering Cancer Center, New York, 10065, New York, USA

[b]Cell & Developmental Biology Program, Weill Graduate School of Medical Sciences, Cornell University, New York, 10065, New York, USA

[c]Cold Spring Harbor Laboratory, Cold Spring Harbor, 11724, New York, USA

[d]Research Institute of Molecular Pathology, Vienna, 1030, Austria

[e]Howard Hughes Medical Institute

[f]St. Jude Children's Research Hospital, Memphis, 38105, Tennessee, USA

One-year survival rates for newly diagnosed hepatocellular carcinoma (HCC) are below 50% and unresectable HCC carries a dismal prognosis owing to its aggressiveness and undruggable nature of its main genetic drivers. By screening a custom library of short hairpin RNAs (shRNAs) directed towards known drug targets in a genetically-defined Myc-driven HCC model, we identified Cdk9 as required for disease maintenance. Pharmacological or shRNA-mediated CDK9 inhibition led to robust antitumor effects that correlated with MYC expression levels and depended on the role that both CDK9 and MYC exert in transcription elongation. Our results establish CDK9 inhibition as a therapeutic strategy for MYC-overexpressing liver tumors and highlight the relevance of transcription elongation in the addiction of cancer cells to MYC.

P18. Identification of enhancer and target gene interactions in the human genomes

Yih-Chii Hwang, Chiao-Feng Lin, Otto Valladares, John Malamon, Qi Zheng,
Brian D. Gregory, and Li-San Wang
University of Pennsylvania

GWAS have shown the majority of disease-associated DNA variations lie within non-coding regions of the human genome. One class of DNA non-coding regulatory elements is enhancer elements. Because an enhancer element can be linearly distal and orientation-independent from the gene it regulates, probing all possible pairs of enhancer–target gene contacts in the genome would be laborious and remain largely unsolved. To systematically identify all enhancers and the genes they regulate, we reanalyzed Hi-C datasets of human and mouse cells with between 60M and 1,612M reads. We identified DNA—DNA interactions by extracting DNA intervals between restriction sites with significant read levels referred to as restriction fragment peaks. We then identify candidate enhancer elements as restriction fragment peaks that overlap with known enhancer-associated histone modification sites and have paired reads overlapping a gene promoter in Hi-C experiments. We have identified between 2,540 and 13,867 enhancer/target-gene interactions throughout the human and mouse genomes. These enhancers are highly enriched with p300 binding activity (17-fold) and their target promoters are 20% more likely to be near RNA polymerase II binding sites. This comprehensive enhancer—target gene catalog will allow us to identify disease-linked polymorphisms that lie within enhancer elements, and study the evolution of enhancer-mediated regulatory mechanisms. Our analysis pipeline is highly optimized and can analyze multiple Hi-C experiments efficiently. The pipeline can be installed on local high-performance clusters or run on the Amazon Elastic Compute Cloud, and is available upon request.

P19. Can Cortical Spreading Depolarization Serve as a Marker for Tissue Plasminogen Activator (tPA) Toxicity for Stroke Treatment?

Yu-Chieh Jill Kao[a, b, c], Wenjing Li[a, b, c], Weili Lin[a, b, c, d], and Yen-Yu Ian Shih[a, b, c, d]
[a]Experimental Neuroimaging Laboratory, University of North Carolina at Chapel Hill
[b]BRIC, University of North Carolina at Chapel Hill
[c]Department of Neurology, University of North Carolina at Chapel Hill
[d]Department of Biomedical Engineering, University of North Carolina at Chapel Hill

Thrombolysis by intravenous recombinant tissue plasminogen activator (tPA) is the only proven therapy for stroke but is limited to only a subset of patients because of the effective duration (~4.5 h) and the risk of causing hemorrhage. Identifying a marker to monitor tPA effect during the treatment is of great clinical importance to prevent tPA-induced damage. Cortical spreading depolarization, a series of propagated waves that shut-down the neuronal activity, is primarily caused by sodium and calcium influx and occurs at hyperacute phase of stroke. CSD is known to exacerbate ischemic damage, as the number of CSDs correlates with final infarct volumes and suppressing CSDs improves functional outcomes. We'd like to address the question that whether CSD could serve as a marker for tPA toxicity, since tPA stimulates glutamate receptors and excess glutamate results hyperpolarization of neurons causing CSD and eventually leading apoptosis. We developed a novel rat model of photothrombotic ischemia using a miniature implantable optic fiber that allows lesion induction inside the magnetic resonance imaging (MRI) scanner. We were able to precisely control the location and the size of the ischemic lesion, and continuously monitor dynamic perfusion and diffusion MRI signal changes at high temporal resolution before, during and after the onset of focal ischemia for the first time. tPA was infused for 30 min under different injury severity to examine the tPA effect on the characteristics of CSDs.

This study introduces a novel platform to study CSDs with high reproducibility using high resolution MRI. We demonstrated that by modulating stroke induction parameters, the lesion severity, diffusion-perfusion mismatch, final infarct volume, and the number of CSDs can be manipulated. We also demonstrated that the size of perfusion-diffusion mismatch (approximate penumbra) can be controlled in our model and the number of CSDs was correlated with a larger mismatch area, but not the final infarct volume. Interestingly, our data showed that infusing tPA evoked 3-fold more CSDs in severe ischemic lesion, but instead suppressed CSDs in mild ischemic lesion in the same subject (both $P<0.05$). Significant difference in permeability was observed between two ischemic conditions, indicating that tPA-induced CSD changes might be related to blood-brain-barrier integrity. Our future studies will address the question that whether glutamatergic antagonist (e.g., Topiramate) modifies CSD signatures during tPA treatment in the hyperacute phase of stroke. Ultimately, this study should provide strong implications for

clinical decision-making because clinicians can determine whether or not to terminate tPA infusion (usually ~1 h) for a stroke patient when multiple CSDs occur or co-administer a glutamate antagonist/anti-epileptic drug to reduce tPA tissue toxicity.

P20. Therapeutic Combination Strategies for Translocation Renal Cell Carcinoma

Sheng-Yu Ku[a,b], Swathi Ramakrishnan[a,b], Eric Ciamporcero[e], Gissou Azabdaftari[a,c], and Roberto Pili[a,d]

[a]Genitourinary Program, Roswell Park Cancer Institute, Buffalo NY

[b]Department of Cancer Prevention and Pathology, Roswell Park Cancer Institute, Buffalo NY

[c]Therapeutic combination strategies for translocation renal cell carcinoma

[d]Department of Medicine. Roswell Park Cancer Institute, Buffalo NY

[e]Department of Medicine and Experimental Oncology, University of Turin, Turin, Italy

Background: Xp11 translocation renal cell carcinoma (tRCC) is a subtype of kidney cancer, which harbors gene fusions involving the TFE3 transcription factor on chromosome X. It is a rare, very aggressive disease refractory to standard treatment for clear cell RCC in adult patients, and it accounts for one-third of pediatric RCC. The tumor biology and optimal treatment for tRCC remain unclear. We have successfully generated a cell line and patient-derived xenograft from a tRCC patient to develop rational therapeutic strategies

Methods: We have utilized a feeder layer containing a ROCK inhibitor to successfully generate a cell line, 277T, from a young translocation RCC patient. Also, we have implanted tumor samples from the patient into SCID mice to generate a patient-derived xenograft model, RP-R-07. Cells were treated with different drugs, and then growth inhibition and cell death were assessed MTT assay and PI uptake. TFE3 expression in cells and tumors were detected by immunofluorescence and immunohistochemistry.

Results: Our preliminary results showed that TFE3 is predominately in the nucleus of 277T cells and RP-R-07 tumor model compared to other subtypes of RCC by immunofluorescence and immunohistochemistry, respectively. Previous publications have suggested that TFE3 fusions increase c-met expression. Thus, we have treated 277T cells with a c-met inhibitor, crizotinib. Standard proliferation assay revealed that 277T cells have greater response to crizotinib than 786-O cells, a clear cell RCC cell line. Moreover, during our drug screening, combined HDAC and mTOR inhibitors revealed a strong inhibitory effect on 277T compared to standard chemotherapy agents used for this disease. *In vivo* experiments to test the preclinical efficacy of these combinations are ongoing.

Conclusions: Overall our results indicate that tRCC is sensitive to c-met inhibition. Moreover, combination of a c-met inhibitor with HDAC and mTOR inhibitors provides a promising therapeutic strategy for tRCC.

P21. The PUF Protein Puf3 Toggles the Translational Fate of Bound mRNA Transcripts to Regulate Mitochondrial Biogenesis

Chien-Der Lee and Benjamin Tu
Department of Biochemistry UT Southwestern Medical Center

PUF proteins are conserved post-transcriptional regulators that bind in a sequence-specific manner to the 3'UTRs of mRNA transcripts. Paradoxically, PUF proteins have been proposed to promote both degradation of their target mRNAs and their translation. Herein, we show how a yeast PUF protein Puf3p responds to glucose availability to switch the fate of its bound transcripts that encode proteins required for mitochondrial biogenesis. Upon glucose depletion, Puf3p becomes phosphorylated, associates with polysomes, and actively promotes translation of its target mRNAs. Strikingly, a Puf3p mutant that prevents its phosphorylation cannot promote mRNA translation and becomes trapped in intracellular PUF-bodies that dominantly poison the cell in an mRNA-dependent manner. Our results reveal that nutrient-responsive phosphorylation toggles the activity of Puf3p to promote either degradation or translation of pre-existing mitochondrial mRNAs. Such activation of mRNA translation might enable rapid adjustment to environmental changes without the need for de novo transcription.

P22. Photoperiodic Regulation of the C-repeat Binding Factor (CBF) Cold Acclimation Pathway and Freezing Tolerance in *Arabidopsis thaliana*

Chin-Mei Lee[a,b,c] and Michael Thomashow[b]
[a]Department of Biochemistry and Molecular Biology, Michigan State University
[b]MSU-DOE Plant Research Laboratory, Michigan State University

The CBF (C-repeat binding factor) pathway has a major role in plant cold acclimation, the process whereby certain plants increase in freezing tolerance in response to low nonfreezing temperatures. In *Arabidopsis thaliana*, the pathway is characterized by rapid cold induction of CBF1, CBF2, and CBF3, which encode transcriptional activators, followed by induction of CBF-targeted genes that impart freezing tolerance. In addition to low temperatures, photoperiod is another environmental factor that regulates freezing tolerance in woody deciduous trees. As summer turns to fall, plants sense the shortening of day length and initiate developmental program that results in cessation of growth and an increase in freezing tolerance. Whereas this phenomenon has been well-documented in woody species, the underlying mechanism is elusive. Here, we establish that the shortening day length result in up-regulation of the CBF pathway and increased freezing tolerance in preparation for coming cold temperatures. Genetic analysis indicated that photoperiodic regulation of CBF pathway is mediated by phytochrome B (PHYB) and two phytochrome-interacting factors, PIF4 and PIF7.

P23. Single Molecule Studies on the Mechanism of Chromatin Remodeling by Rad54

Hsu-Yang Lee[a,b] and Stephen C. Kowalczykowski[a,b]
[a]Department of Microbiology and Molecular Genetics, University of California, Davis, California 95616, USA
[b]Biophysics Graduate Group, University of California, Davis, California 95616, USA

DNA double strand break (DSB) is regarded as the most serious type of DNA damages in a cell, which can result from the attack of cell metabolites such as free radicals, ionizing radiation, or DNA replication through a DNA lesion. If left unrepaired, DSB leads to genomic instability, causing cell apoptosis or cancer. Cells of all kind of species have evolutionarily conserved pathways for repairing DSB, and they are usually found disabled in cancer cells. Among these pathways, homologous recombination (HR) is the one that has highest fidelity, because it utilizes intact homologous DNA as a template to recover lost sequence at the broken site, when there exist more than one copy of DNA in the cell. HR is accomplished by many proteins; the key factor, Rad54, can translocate on double stranded DNA, and increase DNA accessibility on chromatin to facilitate homology search. However, it is still unclear how Rad54 remodels chromatin and the fate of nucleosomes after remodeling. We utilized optical tweezers to grab a single nucleosomal DNA at the ends, and watched what happens when a Rad54 protein translocating on it runs into the nucleosome array. Our preliminary results suggest Rad54 slow down when encountering nucleosomes, but finally are able to dissociate them from DNA.

P24. Synergism between PPARα and Glucocorticoid Receptor Signaling Promotes Self-Renewal of BFU-E Erythroid Progenitors and Increases Red Cell Production

Sherry Lee[a], Xiaofei Gao[a], Inma Barrasa[a], Hu Li[c], Russell Elmes[a], and Harvey Lodish[a, b]
[a]Whitehead Institute for Biomedical Research
[b]Departments of Biology and Biological Engineering, MIT

Many acute and chronic anemias, including hemolysis, sepsis, and genetic bone marrow failure diseases such as Diamond-Blackfan Anemia (DBA), are not treatable with erythropoietin (Epo), because the colony-forming unit erythroid progenitors (CFU-Es) that respond to Epo are either too few in number or are not sensitive enough to Epo to maintain sufficient red blood cell production. Treatment of these anemias requires a drug that acts at an earlier stage of red cell formation and enhances the formation of Epo-sensitive CFU-E progenitors. Recently we showed that glucocorticoids specifically stimulate self-renewal of early erythroid progenitor, burst-forming units erythroid (BFU-Es), and over time increase the production of terminally differentiated erythroid cells. Here we demonstrate that activation of the peroxisome proliferator-activated receptor alpha (PPARα) by two PPARα agonists, GW7647 and fenofibrate, synergizes with activation of the glucocorticoid receptor (GR) to promote BFU-E self-renewal. Over time these agonists greatly increase production of mature red blood cells in cultures both of mouse fetal liver BFU-Es and of mobilized human adult CD34+ peripheral blood progenitors, the latter employing a new and effective culture system that generates normal enucleated reticulocytes. While PPARα-/- mice show no hematological difference from wild-type mice in both normal and phenylhydrazine (PHZ)-induced stress erythropoiesis, PPARα agonists facilitate recovery of wild-type mice, but not PPARα-/- mice, from PHZ-induced acute hemolytic anemia. Finally, both in control and corticosteroid- treated BFU-E cells PPARα co-occupies many chromatin sites with GR; when activated by PPARα agonists additional PPARα is recruited to GR-adjacent sites and presumably facilitates GR-dependent BFU-E self-renewal. Our discovery of the role of PPARα agonists in stimulating self-renewal of an early erythroid progenitor cells suggests that the clinically tested PPARα agonists we used may become novel therapeutics for Epo-resistant anemias.

P25. A Genetically Encoded Acrylamide Functionality Directs Diverse Bioorthogonal Protein Modification

Yan-Jiun Lee, Bo Wu, and Wenshe R. Liu
Department of Chemistry, Texas A&M University

Nε-acryloyl-L-lysine, a noncanonical amino acid with an electron deficient olefin, is genetically encoded in Escherichia coli using a mutant pyrrolysyl-tRNA synthetase-tRNA_CUA^Pyl pair. The acrylamide moiety is stable in cells, whereas it is active enough to perform a diverse set of biocompatible and unique reactions for protein modifications in vitro. These reactions include Michael addition, radical polymerization and 1,3-dipolar cycloaddition. We demonstrate that a protein incorporated with Nε-acryloyl-L-lysine is efficiently modified with thiol-containing Michael donors at slightly alkali conditions and the acrylamide moiety also allows rapid radical copolymerization of the same protein into a polyacrylamide hydrogel at physiological pH. At physiological conditions, the acrylamide functionality undergoes a fast 1,3-dipolar cycloaddition reaction with diaryl nitrile imine to show turn-on fluorescence. We have used this observation to demonstrate site-specific fluorescent labeling of proteins incorporated with Nε-acryloyl-L-lysine both in vitro and in living cells. This critical development allows easy access to an array of modified proteins for applications where high specificity and reaction efficiency are needed.

P26. Surface Viscosity and Temperature Dependence in the Function of *Proteus mirabilis* fliL and Swarming

Yi-Ying Lee and Robert Belas
Department of Marine Biotechnology, University of Maryland Baltimore County

Proteus mirabilis is a dimorphic Gram-negative enterobacterium and well-known for its ability of move over agar surfaces by flagellar-dependent swarming motility. In liquid culture, *P. mirabilis* cells are uniformly 1.5-2.0 μm rods with 4-6 flagella, called swimmer cells. When *P. mirabilis* encounters a highly viscous environment or a solid surface, swimmer cells differentiate into elongated (10-80 μm), highly flagellated swarmer cells that lack of septa and contain multiple nucleoids. The bacteria detect a surface by monitoring the rotation of their flagellar motors. Conditions that prevent rotation of swimmer cell flagella trigger production of swarmer cells. This process involves a ubiquitous but functionally enigmatic flagellar basal body-associated protein called FliL. *fliL* is often the first gene in a class II operon (*fliLMNOPQR*) encoding proteins of C-ring (FliM and FliN) and flagellar export apparatus (FliO, FliP, FliQ and FliR), which are essential for bacterial flagellation and motility, and the function of the leading gene *fliL* remains obscure. Unlike other flagellar proteins, whose functions are conserved across motile bacterial species, *fliL* defects produce species-specific phenotypic changes. Previous studies suggested that FliL is essential for swarming and important for flagella stability in enterobacteria. In this study, we constructed a mutant with an in-frame deletion of the *fliL* gene (*fliL*Δnt4-456; encoding a *fliL* product with deletions of residues 2-153) in the genome of *P. mirabilis* to characterize the role of the FliL protein. Similar to previously shown, *P. mirabilis* Δ*fliL* is motile (Swm$^+$) on semi-solid agar and produces "pseudoswarm" cells, a swarmer cell-like cell type, in broth (Elo$^+$). Surprisingly, the Δ*fliL* strain does swarm (Swr$^+$) proficiently on LB with 1.5% agar at the wild-type level. Further, we discovered that Δ*fliL* cells exhibit non-wild-type viscosity dependence on swarming. On LB with 0.9% agar, Δ*fliL* cells swarm precociously while the wild-type swarms poorly; on semi-solid agar, Δ*fliL* cells have slightly reduced motility. The precocious swarming of Δ*fliL* cells is not due to overexpression of flagella as the expression of the flagellar regulatory and structural genes (*flhD*, *fliA* and *flaA*) and the production of flagellin (FlaA) protein in the Δ*fliL* cells are all at the wild-type level on LB with 0.9% agar. Rather, the increased elongated cells production in the Δ*fliL* population may contribute the precocious initiation of swarming on LB with 0.9% agar. Moreover, the motility of *P. mirabilis* Δ*fliL* cells is temperature-dependent: low temperature (< 30^{o}C) severely reduces swimming and prevent swarming. It indicates that Δ*fliL* cells are defective in flagellar function and have faults in sensing the torque generated by flagellar rotation on a surface.

P27. TorsinA hypofunction Causes Abnormal Twisting Movements and Sensorimotor Circuit Neurodegeneration

Chun-Chi Liang and William T. Dauer
University of Michigan

The inability to create a genetic model of primary dystonia exhibiting dystonic-like twisting movements has stymied identification of the cellular and molecular underpinnings of the disease. The classical familial form of primary dystonia is caused by the DYT1 mutation in TOR1A that encodes torsinA, a AAA+ ATPase resident in the endoplasmic reticular/nuclear envelope lumen. We find that conditional CNS deletion (Nestin-Cre;Tor1aflox/-) or isolated CNS expression of DYT1 mutant torsinA (Nestin-Cre;Tor1aflox/△E) cause striking abnormal twisting movements. These animals develop perinuclear accumulation of ubiquitin and the E3 ubiquitin ligase Hrd1 in discrete sensorimotor regions, followed by neurodegeneration that is significantly milder in Nestin-Cre;Tor1aflox/ΔE than Nestin-Cre;Tor1aflox/- animals. Similar to the neurodevelopmental onset of DYT1 dystonia, the behavioral and histopathological abnormalities emerge and become fixed during CNS maturation. Our results establish the long-sought genetic model of primary dystonia that is overtly symptomatic, and link torsinA hypofunction to neurodegeneration and abnormal twisting movements. These findings provide a cellular and molecular framework for how impaired torsinA function selectively disrupts neural circuits, and raise the possibility that discrete foci of neurodegeneration may contribute to the pathogenesis of DYT1 dystonia.

P28. Identification of the Newly-Synthesized Proteins Required for Synaptic Plasticity *in Xenopus laevis*

Han-Hsuan Liu[a], Wanhua Shen[a,b], Lucio Schiaparelli[a], Daniel McClatchy[a], John R. Yates III[a], and Hollis T. Cline[a]

[a]The Scripps Research Institute, La Jolla, CA 92037, USA

[b]Hangzhou Normal University, Hangzhou, Zhejiang, China

De novo protein synthesis is dynamic, in corresponding to the changes in the environment. It plays an important role in synaptic transmission and plasticity. We are interested in knowing what proteins are being synthesized while the synaptic efficacy is changing. Some studies are examining if the proteins known to be required for synaptic plasticity are being synthesized or degraded dynamically. A systematic search for newly synthesized proteins during specific types of brain activity in the intact animals has not been done yet. In order to do so, we take the advantage of recently developed bioorthogonal noncanonical amino acid tagging (BONCAT) and the well-established visual conditioning and behavior test on *Xenopus* in our lab. The newly synthesized proteins with their methionine being replaced with the non-canonical amino acid azidohomoalanine (AHA) are tagged with biotin through click reaction and analyzed by multidimensional protein identification technique (MudPIT). We have maximized the detection coverage by modifying the protein extraction method and improving the efficiency of the click reaction. The first MS/MS experiment on the brains of tadpoles labeled with AHA showing that we are able to detect not only cytoplasmic protein, but also membrane proteins and nucleus proteins. Further studies will aim to utilize the method we established here to examine the role of de novo protein synthesis in neurons under different inputs from the environment.

P29. MMP-12 is an Essential Mediator of Arterial Stiffening in Vascular Remodeling and Atherosclerosis

Liu S.L., Bae Y.H., Castagnino P., Hawthorne E.A., and Assoian R.K.
Penn; University of Pennsylvania

Background--- Increased arterial stiffening is a hallmark of vascular remodeling and a common consequence of atherosclerosis. The mechanisms mediating changes in vascular stiffness remain poorly understood. We have combined vascular injury, genome-wide profiling, and mouse modeling to identify the molecular mechanism(s) responsible for arterial stiffening during vascular remodeling.

Methods and Results---Vascular remodeling induced by fine-wire femoral artery injury was investigated in SMA-GFP mice. In this transgenic line, the SMα-actin promoter drives GFP expression, so vascular smooth muscle cell dedifferentiation at sites of injury can be visualized by loss of GFP fluorescence. Analysis of these injury sites by atomic force microscopy (AFM) revealed increased stiffening coincident with vascular remodeling. We then microdissected the GFP-negative (stiff areas) and GFP positive (soft areas) of injured and uninjured arteries, respectively, and performed an Affymetrix-based microarray analysis to identify stiffness-regulated genes. The microarray data showed dramatically high induction of MMP-12 mRNA in injury sites as compared to uninjured control. We then compared arterial stiffness after arterial injury in wild-type and MMP-12 KO mice. AFM analysis showed that arterial stiffening was largely eliminated in MMP12 KO mice (Injured / uninjured control : 1.04 fold) compared to WT mice (Injured / uninjured control : 4.88 fold). The ratio of neointimal to medial areas is also decreased in the MMP-12 KO mice as compared to WT mice. In addition to vascular injury, arterial stiffening occurs in atherosclerosis. To determine the functional importance of MMP-12 in arterial stiffness and atherosclerosis, we compared arterial stiffness and lesion formation in fat-fed LDLR-null mice that were either wild-type (MMP-12+/+;LDLR-/-) or null for MMP-12 (MMP-12-/-;LDLR-/-). Deletion of MMP-12 strongly inhibited arterial stiffening and the development of atherosclerosis without changing the plasma lipid level. We then analyzed the composition of these atherosclerosis lesions. CD68-staining revealed that macrophage abundance in lesions was markedly reduced in the MMP-12-/-;LDLR-/- mice. Further in the in vitro assay, we then used extracellular matrix-coated hydrogels to mimic the stiffness of healthy and diseased arteries and found the adhesion of primary mouse peritoneal macrophages was affected by substratum stiffness.

Conclusion--- These results raise the possibility that pharmacological control of arterial stiffness by suppressing MMP-12 may complement the effect of using cholesterol-lowering drugs in treating atherosclerosis.

P30. Microscopic Visualization of Membrane Domains in *Mycobacterium smegmatis*

Chu-Yuan Luo[a], Taroh Kinoshita[b], and Yasu S. Morita[a]
[a]Department of Microbiology, University of Massachusetts, Amherst, USA
[b]Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

Unlike eukaryotic cells, it is generally considered that bacterial cells do not require membrane-bound compartments to organize cellular processes. Nevertheless, bacteria must process numerous cellular reactions that take place at membranes including transport of macro and micro molecules, energy production, sensing/signaling, and cell wall assembly. In fact, recent evidence indicates that a number of these processes are compartmentalized to particular domains of the plasma membrane in several bacterial species. *Mycobacterium smegmatis* has a unique multilayered cell wall, and the plasma membrane is fundamental for the biosynthesis of the cell wall components. Sucrose density gradient fractionation of *M. smegmatis* cell lysate showed that different lipid biosynthetic activities are enriched in two distinct membrane-containing fractions. Based on their chemical compositions, we termed these membrane compartments PMf (plasma membrane free of cell wall components) and PM-CW (plasma membrane associated with cell wall). Here we visualized these membrane compartments in mycobacteria by fluorescent microscopy. We first identified several major proteins associated with PMf by peptide mass fingerprinting, and then expressed one of the newly identified PMf-associated proteins as a GFP fusion. We confirmed the correct localization of the marker protein to PMf by density gradient fractionation. The PMf marker was visualized by fluorescent microscopy as patches throughout the cell with frequent enrichment at the growing poles of the cells. In contrast, a PM-CW marker showed circumferential and more homogeneous fluorescent patterns. Thus, our data suggest that PMf and PM-CW membrane compartments are spatially distinct and PMf membrane domain might play a role in the growth of mycobacterial cells.

P31. The Impact of Effective Radii and Entropy on MM/PBSA, MM/GBSA, QM-MM/GBSA methods in *Francisella tularensis* Enoyl Acyl Reductase (FabI)

Pin-Chih Su, Shahila Mehboob, Kirk Hevener, and Michael E Johnson
Center for Pharmaceutical Biotechnology, University of Illinois at Chicago, Chicago IL 60607

Francisella tularensis (*F. tularensis*) is a Gram-negative bacterial pathogen that causes tularemia, and is a viable biological weapon that could cause mass causalities due to its ease of cultivation and aerosolization. Currently available treatments are either only available in intravenous injection or hampered by their toxicity, motivating the search for new antibiotics. The bacterial fatty synthesis pathway (FAS-II) is an appealing and essential pathway for antibiotic design against *F. tularensis*, as the enoyl acyl carrier protein (ACP) reductase, FabI, is an essential antibiotic enzymatic target in the FAS-II system because it catalyzes a key and rate-limiting step of fatty acid production. In prior studies, we identified benzimidazole FabI inhibitors that showed low microgram/mL antibacterial activities against *F. tularensis*, and our crystal structures have shown the benzimidazole inhibitors to exhibit a unique binding mode. Herein, we carefully chose 16 benzimizadole ligands to optimize our *in silico* lead optimization protocol. In our small molecule: protein system, we firstly compared the effect of effective radii on three implicit solvent methods, molecular mechanics / Poisson-Boltzmann Surface Area (MM/PBSA), molecular mechanics / Generalized Born Surface Area (MM/GBSA), and quantum mechanics molecular mechanics / Generalized Born Surface Area (QM-MM/GBSA), which haven't been extensively explored by the molecular modeling community. Our results suggested that various effective radii settings changed the inhibitor affinities ranking and QM-MM/GBSA together with the GBneck2 and mbondi2 effective radii generate the best agreement with experimental values in the benzimidazole FabI system (r^2= 0.88). Furthermore, MM/PBSA, MM/GBSA, and QM-MM/GBSA can only accurately provide inhibitors' relative affinities but not absolute affinities partly due to large fluctuating entropy calculation results. The protocol developed here will be applied to subsequent large scale *in silico* benzimidazole scaffold prediction.

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P32. Understanding the Molecular Architecture of the Hsp70-Based Mitochondrial Protein Import Machinery

See-Yeun Ting, Brenda Schilke, Masaya Hayashi, and Elizabeth Craig
University of Wisconsin - Madison

Approximately 99% of the proteins residing in mitochondria are encoded by nuclear DNA. Proteins destined for the mitochondrial matrix are synthesized as preproteins in the cytoplasm and transported into mitochondria through channels in the outer and the inner membranes, TOM and TIM23 complex, respectively.

Translocation of the preprotein across the TIM23 complex, consisting of the transmembrane proteins Tim23 and Tim17, requires the action of the matrix- localized, Hsp70-based import motor. The motor complex has four components, Tim44, Pam16, Pam18, and Pam17 in addition to Hsp70 (called Ssc1 in yeast). Interaction between TIM23 and the motor complex is critical for Hsp70 to provide an inward-directed movement of the incoming preprotein. However, sites of interaction have not been defined and regulatory mechanisms are not understood.

We are performing genetic and *in vivo* site-specific photo cross-linking analysis to gain a better understanding of the overall architecture of the import machinery. Both Tim23 and Tim17 expose a relatively large (~24 residue) hydrophilic loop to the matrix. Specifically we are testing the hypothesis that both loops are important for interaction between the two complexes.

P33. The Pluripotency Factor LIN28 Promotes Intestinal and Colorectal Tumorigenesis and Progression

Ho-Chou Tu[a,b], Sarah Schwitalla[a,b], Grace Lapier[a,b], Alena Yermalovich[a,b], Srinivas Viswanathan[a,b], Hao Zhu[e], Zhirong Qian[d], Samar Shah[a,b], Shuiji Ogino[d], Charles Fuchs[d] and George Q. Daley[a,b,c]

[a]Division of Pediatric Hematology/Oncology, Boston Children's Hospital and Dana Farber Cancer Institute, Boston, MA, USA

[b]Harvard Stem Cell Institute, Boston, MA, USA

[c]Howard Hughes Medical Institute, Boston, MA, USA

[d]Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA

[e]Chidren's Medical Center Research Institute, University of Texas Southwestern, TX, USA

LIN28A and LIN28B are RNA-binding protein paralogs highly expressed in embryonic stem cells and in early developing tissues. Through blocking the terminal processing of let-7 miRNAs and regulating the translation of a number of mRNA binding targets, LIN28 controls an array of targets that mediate proliferation, pluripotency, differentiation and metabolism in embryonic stem cells. While LIN28A/B are highly expressed in embryonic stem cells and in the early embryos, they are downregulated as differentiation and development proceed. However, aberrant overexpression of LIN28A and LIN28B is often observed in human malignancies especially those with poor prognosis. We have demonstrated that LIN28 promotes cellular transformation in vitro, yet it is unknown how LIN28 regulates tumorigenesis *in vivo*. Here, we investigate the role of LIN28 in colorectal cancer (CRC) development in humans and in animal models. We first investigated the status of LIN28A and LIN28B in a cohort of 1000 CRC patients and observed a 35-60% of the CRC samples express LIN28A and/or LIN28B. In order to model CRC development *in vivo*, we generated intestinal-specific LIN28 overexpressing animals. Interestingly, these animals developed intestinal adenoma as well as invasive adenocarcinoma that highly resemble the histology of human CRCs. Moreover, in Apcmin/+ animals, additional LIN28 expression significantly increased tumor incidence and accelerated disease onset, as their tumors appear to be poorly differentiated and more invasive compared with tumors derived by Apc mutation alone. Together, our study shows that LIN28 drives tumorigenesis and promotes the progression of tumor development into a more malignant state in the intestinal epithelium. CRC is one of the major contributors to cancer-related mortality; however, current mouse models seldom progress to later stages of the disease, a situation that greatly impedes efforts to developing more effective therapies. Our data suggests LIN28 as an important factor for CRC initiation and progression. Based on the knowledge gained from this research, we hope to provide novel insights into designing therapeutics targeting late-stage CRC.

P34. Exploring the Substrate Range of Wild-Type and Evolved Aminoacyl-tRNA Synthetases

Yane-Shih Wang[a] and Dieter Söllll[a, b]
[a]Department of Molecular Biophysics and Biochemistry, Yale University
[b]Department of Chemistry, Yale University

We tested the substrate range of four wild-type *Escherichia coli* aminoacyl-tRNA synthetases (AARSs) and evolved *Methanosarcina mazei* pyrrolysyl-tRNA synthetases (PylRSs) with a library of non-standard amino acids (nsAAs). While the AARSs can discriminate efficiently against the other canonical amino acids, they were able to use many nsAAs as substrates. Genetic selection provided PylRS variants with a broad range of specificity for diverse ncAAs. Our results also indicated that *E. coli* tryptophanyl-tRNA synthetase (TrpRS) and tyrosyl-tRNA synthetase have overlapping substrate range. In addition, we found that the anticodon sequence of the tRNA_Trp isoacceptor altered the substrate range of TrpRS; this implies that the sequence of the anticodon affects the TrpRS amino acid binding pocket. These results highlight again that inherent AARS polyspecificity will be a major challenge to the goal of incorporating multiple different amino acids site-specifically into proteins.

P35. The Yeast Guanine Nucleotide Dissociation Inhibitor (GDI) Enforces Singularity by Enhancing Competition between Polarity Sites

Chi-Fang Wu[a], Natasha Savage[b], Trevin Zyla[a], and Daniel J. Lew[a]
[a]Duke University
[b]University of Liverpool

Polarity establishment employs an evolutionarily conserved machinery centered around the Rho-family GTPase Cdc42. In response to cell cycle cues, Saccharomyces cerevisiae concentrates active GTP-bound Cdc42 at the presumptive bud site. The local concentration of GTP-Cdc42 grows as a result of a Bem1p complex-mediated self-amplifying positive feedback mechanism. A negative feedback loop is also present in the polarity circuit that buffers the level of GTP-Cdc42 and stops clusters from growing too large. When cells begin to polarize, they can grow several clusters of polarity factors. However, the clusters then appear to compete rapidly with each other, leaving only a single winning cluster after 2-3 min, which becomes the bud site. We are trying to understand how competition between clusters occurs. We find that the yeast guanine-nucleotide dissociation inhibitor (GDI), Rdi1, is needed for rapid competition between clusters. In the absence of Rdi1p the initial clustering of polarity factors is slowed, and competition is also much slower: in some cases cells still have two clusters at the time of bud emergence and they form two buds. We suggest that in the absence of Rdi1, the clusters compete for a limiting pool of Cdc42, and that slow exchange of Cdc42 on and off the membrane in rdi1Δ cells leads to slow competition. Overexpression of Cdc42p in the rdi1Δ background restored rapid competition. We suggest that with ample Cdc42, other components (e.g. the Bem1 complex) become limiting, and that because these components readily exchange between membrane and cytoplasm, competition for that limiting pool is more rapid. A mathematical model can recapitulate several aspects of our observations.

P36. Effects of 2-Methylhopanoids on Biophysical Properties of Membranes

Chia-Hung Wu[a, b], Maja Bialecka-Fornal[a], and Dianne K. Newman[a, b, c]
[a]Division of Biology and Biological Engineering, Caltech
[b]Howard Hughes Medical Institute
[c]Division of Geological and Planetary Sciences, Caltech

Hopanoids are sterol-like lipids found in the membranes of some bacteria. Earlier genetic and phenotypic studies have established the role of hopanoids in bacteria resistance to antibiotics, extreme pH, high temperature, and high osmotic stress. Furthermore, the carbon backbones of hopanoids are well preserved in fossils dated back to at least 1.7 billion years ago, which allows the potential application of using hopanoids as biomarkers to better understand the evolution of microbes and the environment in early Earth. To better understand the biological roles of individual hopanoids and provide insights to better interpret these molecular fossils, here we present the application of modern LC-MS/MS and GC-MS techniques to quantify hopanoids and determine their distribution in the inner and outer membranes of a hopanoid model organism, Rhodopseudomonas palustris TIE-1. The results showed that the hopanoid content in the outer membrane is ~3-fold higher than that in the inner membrane. Furthermore, the ratio of extended (C35) to short (C30) hopanoids is ~4-fold higher at the outer membrane compared to the inner membrane. To better understand the impact on the membrane biophysical properties such as membrane fluidity due to these differences in the hopanoid distributions, 2-methylated and unmethylated extended or short hopanoids were purified from R. palustris TIE-1 and reconstructed into small unilamellar vesicles using native inner or outer membranes. The results indicated that the 2-methylation of both extended and short hopanoids is the strongest factor that makes the membrane more rigid. However, such property was only observed at concentrations much higher than the ones determined by the MS quantifications. These results suggest that direct attenuation of membrane fluidity by hopanoid 2-methylation may not be physiologically relevant in R. palustris TIE-1 under normal growth conditions. The combination of robust MS quantification techniques and in vitro biophysical studies provides valuable tools to elucidate the function of hopanoids.

P37. A Combinatorial Algorithm to Identify Independent and Recurrent Copy Number Aberrations across Cancer Types

Hsin-Ta Wu, Iman Hajirasouliha, and Benjamin J. Raphael
Department of Computer Science and Center for Computational Molecular Biology, Brown University

Somatic copy number aberrations (SCNAs) are frequent in cancer genomes, but many of these are random events that do not contribute to the cancer phenotype. A common strategy to distinguish functional, driver events from such random passenger events it to identify recurrent aberrations shared by multiple samples. However, the extensive variability in the length and position of copy number aberrations makes the problem of identifying recurrent aberrations notoriously difficult.

We introduce a new algorithm, RAIG (Recurrent Aberrations from Interval Graphs), to identify independent and recurrent SCNAs by considering the composition and the correlation between all SCNAs on a chromosome across a set of samples. We derive independent and recurrent SCNAs as maximal cliques in an interval graph constructed from overlaps between aberrations. In contrast to existing approaches that deconvolve the recurrence score of the recurrent SCNAs on markers (probes), RAIG analyzes the combinatorial structure of the underlying intervals, and thus explicitly models the dependencies between values of the recurrence score. RAIG uses a dynamic programming algorithm to optimize a rigorous objective function for the selection of recurrent aberrations. RAIG is very efficient, as maximal cliques in an interval graph can be efficiently enumerated. Also, RAIG is readily adaptable for both microarray and high-throughput sequencing data.

We compared RAIG with four existing approaches: GAIA, JISTIC, GISTIC and GISTIC2 on three simulated data sets, including a simple model with the introduction of spatial noise, a simulated model for examining the power of detecting secondary events, and a simulated model for demonstrating the power of separating two driver SCNAs that contain different fraction of overlap. The results demonstrate RAIG outperforms other approaches on all three simulated data sets. Furthermore, because RAIG is fast, we used RAIG to perform a Pan-Cancer analysis of somatic copy number aberrations in 4,976 samples from 12 cancer types from The Cancer Genome Atlas (TCGA). Significantly recurrent SCNAs were observed in 112 regions, including 59 amplified regions and 51 deleted regions. A total of 54 recurrent SCNAs were reported in recently published pan-cancer analysis, including amplifications of KRAS, CCND1, CDK4, ERBB2, MDM2, MDM4, FGFR3, PDGFRA, EGFR and MYC; and deletions of PTEN, RB1, NF1, ARID1A, CDKN2A, PTPRD and MLL3. Moreover, RAIG identified some regions with known mutated genes uniquely, e.g. amplifications of ERBB3, SMARC4, MECOM and ESR1, and deletions of MAP2K4 and SLIT2.

P38. Improved Stability and Half-Life of Fluorinated Phosphotriesterase Using Rosetta

Ching-Yao Yang[a], P. Douglas Renfrew, PhD[a], Andrew J. Olsen[a], Michelle Zhang[a], Carlo Yuvienco[a], Richard Bonneau, PhD[a], and Jin Kim Montclare[a, d]
[a]NYU
[b]SUNY Downstate Medical Center

Organophosphates (OPs) are widely adopted in agriculture and military industries. However due to effects to environment and public health, the disposal and management of OPs represents a significant challenge. The current approach to remove OPs involves incineration and chemical neutralization, which produce toxic by-products and is costly. Phosphotriesterase (PTE) enzymes from multiple organisms have been identified and employed as biocatalytic scavengers and deactivators of OPs that perform optimally under physiological temperatures and conditions. Recently, our lab demonstrated that incorporating p-fluorophenylalanine (pFF) into particular variants of PTE enzymes dramatically improves the refoldability of the protein, leading to enhanced stability and function at elevated temperatures. To further improve the stability of the fluorinated enzyme, Rosetta was used to identify multiple potential stabilizing mutations. We report one such variant, pFF-F104A, that exhibited enhanced activity at elevated temperatures and also maintained activity over multiple days in solution at room temperature.

P39. Endocytosis and the Role for ESCRT Protein Bro1 in Vesicle Formation at the Endosome

Athena Yi-Chun Yeh, Mike W. Henne, and Scott D. Emr
Cornell

Through membrane receptors, a cell responds to signals from the extracellular environment, such as nutrients or hormones. To respond to these signals, the endocytic pathway down regulates membrane receptors to prevent their hyper-activation. The failure of membrane receptor degradation results in imbalanced cellular physiology, which leads to numerous diseases and cancers.

Down-regulation of cell surface receptors is mediated by a series of vesicle trafficking steps: Ub (ubiquitin)-mediated endocytosis, ESCRTs (endosomal sorting complex required for transport)-mediated Ub-cargo recognition and packaging event, which first sequesters and then sorts cargoes into the intraluminal vesicles (ILVs) inside endosomes, and endosome-lysosome fusion. Finally, receptors are degraded in lysosomes. During these steps, ILV formation is crucial to successful cargo sorting and is conducted by the ESCRTs, which were initially discovered in Dr. Scott Emr's lab.

One ESCRT protein, denoted Bro1 (Alix in humans), is a critical player in cytokinesis and HIV viral budding, which both require similar membrane remodeling as ILV biogenesis. Bro1 has N-terminal Bro1 domain, the middle V domain and the C-terminal PRD domain. Previous studies showed that the PRD domain recruits the Ub hydrolase, Doa4, to endosome to remove Ub from cargoes before they are sorted into ILVs. This de-Ub process maintains the cytosolic pool of Ub. Intriguingly, bro1Δ cells exhibit sorting defects that are more severe than doa4Δ cells. This suggests Bro1 may have additional functions in the endocytic pathway.

Snf7, the major subunits in ESCRTs, polymerizes into filaments. The Snf7 filaments act as a "molecular fence" to sequester Ub-cargoes at the limiting endosomal membrane. This first ensures Ub can be removed from cargoes efficiently by Bro1-mediated de-Ub process, and then further guarantees that cargoes cannot escape from endosomes after removing Ub's. Snf7 cycles between a "closed" monomer in cytosol and an endosome-bound "opened" subunit with polymerization ability. Though we can reconstitute Snf7 filaments *in vitro*, how the Snf7 monomer is activated remains poorly understood.

Interestingly, our SILAC data together with previous studies have shown that Bro1 directly interacts with Snf7. I will present data, which further suggests Bro1 promotes Snf7 filament formation *in vitro*. Thus, I hypothesize the novel role of Bro1 in endocytosis: Bro1 activates Snf7 monomers to facilitate the steps of ESCRT-mediated cargo sequestration and sorting. Further experiments will test the activator role of Bro1 *in vivo*, and the mechanism for Snf7 activation *in vitro*.

P40. How Could a Mitogenic proIGF-I E-Peptide Induce Cancerous Cell Death?

Yang-hui (Jimmy) Yeh, Thomas T. Chen, Chun-Mean Lin, and Wei-Ting Huang
University of Connecticut

Most peptide hormones are matured from pre-pro-peptide, which comprises signal sequence, mature peptide, and proteollytically cleaved portion. Besides matured hormone itself, cleaved portion, which were long thought to be “junk” are now gaining more spotlight. Evidentially, they exert biological function, similar or not, to it’s hormonal counterpart. E-peptide is that proteollytically cleaved portion of the pre-pro-IGFI. The mature IGF-I plays many different roles in promoting growth, metabolism, differentiation, and neuroendocrine regulation in all vertebrates. As for E-peptides, they also have mitogenic activity, as well as promoting cell attachment and morphological change. They also inhibit colony formation in soft agar, angiogenesis, and metastasis of various types of cancer cells. Potentially, E-peptide might direct cancer cells toward to program cell death, apoptosis. This study is focusing on what potential mechanism is behind the action of E-peptide. It’s showing here that E-peptide binds to cell “surface” and been endocytosed mainly through clathrin-mediated pathway. Once reaching to critical concentration(between 0.25 μM to 0.5 μM), it enhances cell attachment, changing their morphology rapidly upon seeded at least partly mediated through integrin. Even more, when E-peptide is in dimer form, it kills some type of cancerous cell fairly quick at higher concentration possibly via permeabilizing cell membrane, similar fashion as antimicrobial peptide, and can be enhanced when endocytosis is blocked.

P41. Caspase-Dependent Regulation of the Ubiquitin-Proteasome System through Direct Substrate Targeting

Ting-Chun Yeh[a,b], and Shawn B. Bratton[a]

[a]The Virginia Harris Cockrell Cancer Research Center at the University of Texas MD Anderson Cancer Center, Science Park, Department of Molecular Carcinogenesis, Smithville, TX, 78957

[b]The University of Texas at Austin, Institute for Cellular and Molecular Biology, Austin, TX, 78712,

Drosophila inhibitor of apoptosis 1 (DIAP1) is an E3 ligase that regulates apoptosis in flies, in large part through direct inhibition and/or ubiquitination of caspases. IAP antagonists, such as Reaper, Hid, and Grim, are thought to induce cell death by displacing active caspases from baculovirus IAP repeat (BIR) domains in DIAP1, but can themselves become targets of DIAP1-mediated ubiquitination. Herein, we demonstrate that Grim is ubiquitinated by DIAP1 at Lys136 in an UbcD1-dependent manner and that K48-linked chains are added almost exclusively to BIR2-bound Grim due to its structural proximity to DIAP1's RING domain. Nevertheless, active caspases can simultaneously cleave Grim at Asp132, removing the lysine necessary for ubiquitination, and in doing so, enhance the stability of Grim and initiate a feed-forward amplification loop. Thus, Grim represents the first caspase substrate whose cleavage promotes apoptosis by limiting, in a target-specific fashion, its ubiquitination and turnover by the proteasome.

P42. CRISPR/CAS9 Targeted Mutagenesis in Mouse Cells and Embryos

Shuo-Ting Yen[a, b], Jian Min Deng[b], Shireen J. Usman[b], Luis A. Cedeño-Rosario[c], James F. Martin[a], Jan Parker-Thornburg[d], and Richard R. Behringer[b]

[a]Program in Developmental Biology, Baylor College of Medicine, Houton, TX

[b]Department of Genetics, UT MD Anderson Cancer Center, Houton, TX

[c]Chemistry Department, University of Puerto Rico – UPRH1, Humacao, PR

[d]Department of Biochemistry and Molecular Biology, UT MD Anderson Cancer Center, Houston, TX

The CRISPR/Cas9 system is an adaptive immune system found in all Archea and some bacteria. This system has been engineered and applied to plant and animal cells as a mutagenesis tool. Various model organism systems have begun to adopt this technology for genetic manipulations. In mouse, we first tested this system in embryonic stem cells and a hepatocarcinoma cell line (Hepa1-6). Exon 1 of Hprt was targeted by four small guidance RNAs (sgRNAs). Cells were transfected with an expression plasmid and selected for HPRT deficiency by culture in 6-thioguanine (6-TG) medium. Among the 6-TG resistant clones, we found mutations, including small indels and larger deletions (>100 bp). We then attempted generating mutant mice by pronuclear or cytoplasmic injection of Cas9 mRNA and sgRNA to Tyrosinase (Tyr). Tyrosinase is the rate-limiting enzyme for the production of melanin. A lack of functional tyrosinase results in albinism. Mice resulting from the zygote injections included albinos and a complete range of albino mosaisim. Albinos were obtained injecting into wild-type and Tyr heterozygous zygotes. Genotyping identified a series of mutations localized to the sgRNA target sites. These visual phenotypes highlight the somatic mosaicism of founders that likely occurs for other genes during CRISPR/Cas9-mediated genome editing by zygote injection.

P43. The Effect of Akt Isoforms in Tumorigenesis and Glucose Homeostasis *in vivo*

Wan-Ni Yu[a]
[a]University of Illinois at Chicago

Akt is hyperactivated in many human cancers. Germ line Akt1-deficient mice are resistant to cancer development which is driven by hyper-activation of PI3K-Akt signaling in mouse model. However, it is not clear whether Akt1 is required for tumor maintenance, and whether systemic Akt1 deficiency can block tumor progression in the mouse. It is also not known whether Akt1 deficiency could hinder tumorigenesis which is not driven by hyper-activation of PI3K-Akt signaling. Here, we use Akt1f/fRosa26CREERT2 mice, in which Akt1 could be systemically deleted after tamoxifen administration. These mice were crossed with p53-/-mice which are tumor prone. Systemic whole body Akt1-deficient mice substantially increased survival of these mice. Thymic lymphoma cell lines isolated from the mice undergone cell death and cell cycle arrest following by Akt1 deletion. Xenograft tumors of these mice are inhibited after Akt1 deletion. PI3K-Akt signaling is frequently activated in human cancer. Therefore, Akt is a popular target for cancer therapy. However, the long-term effect is not well known since most of tests were done in the xenograft model. Here we used Akt1f/f; Akt2-/-; Rosa26CREERT2 mice and Akt1f/f; Akt2-/-; Albumin-Cre mice to generate combined Akt1 and Akt2 deleted adult mice and liver-specific deleted mice in order to mimic drug therapy condition. Akt1f/f; Akt2-/-; Rosa26CREERT2 adult mice could not survive after tam administration and Akt1hep-/-Akt2-/- mice developed severe diabetes and hepatocellular carcinoma (HCC). Thus, using Akt inhibitors that target both Akt1 and Akt2 need to be aware of the side effects.

Attendee

Name	Affiliation
Chan, Kun-Wei	PhD Student, NYU Medical Center
Chan, Leo	Marketing Technology R&D Manager, Nexcelom Bioscience
Chang, Ally	Global Product Manager, Corning Inc.
Chang, Che-Wei	Ph.D. student, University of Wisconsin Madison
Chang, Chien-I	Research Scientist , UMASS Medical School
Chang, Chun-Chieh	PhD student, University of Michigan
Chang, Feng-Ming	Research Assistant, Indiana University
Chang, Hsiao-Han	Postdoc, Harvard School of Public Health
Chang, Hsin-Wen	Graduate student, Cornell University
Chang, Jun	Graduate Student, Weill Cornell Medical College
Chang, Keng-Ming	Ph.D. graduate, University of Texas at Austin
Chang, Marie	
Chang, Shaoyu	Student, Tufts University
Chang, Shiou-chi	Graduate student, MIT
Chang, Shu-Wei	PhD candidate, MIT
Chang, Ting-Jung	Public Affairs and Marketing Intern, Stony Brook Medicine
Chang, Ya-Chu	Research assistant, National Taiwan University
Chang, Yi-Chien	Student, BU
Chao, Yi-Sheng	Postdoctoral Fellow, Universite de Sherbrooke
Chen, Chen-Hao	Graduate student, Harvard Medical School
Chen, Chia-Hui	Graduate Student, Rutgers University
Chen, Chiao-Lin	Postdoctoral Fellow, Harvard Medical School
Chen, Chia-Yen	Postdoctoral research fellow, Massachusetts General Hospital
Chen, Chi-Chao	PhD student, Memorial Sloan-Kettering Cancer Center, New York
Chen, Chi-Li	Research Scientist, TetraPhase Pharmaceuticals, Inc
Chen, Ching-Huan	Graduate student, Indiana University Bloomington

Chen, Chun-Hau (Howie)	Research Fellow, Harvard Medical School
Chen, Chun-Liang	
Chen, Chun-Ti	Post-doctoral researcher, Boston College
Chen, Guan-Yu	Postdoc Fellow, Whitehead Institute for Biomedical Research
Chen, Hsiao-Wei	Sr. Research Technician, Memorial Sloan-Kettering Cancer Center
Chen, Hsi-Ju	PhD Student, University of Massachusetts
Chen, Hsin-Yi	Postdoctoral fellow, The Wistar Institute
Chen, Hsiuyi	Graduate student, UMASS medical school
Chen, Huai-Chun	Postdoc, University of Colorado
Chen, Huei-Mei	
Chen, Jia-Yun	Postdoc fellow, Harvard Medical School
Chen, Kai-Chun	Postdoc, University of Michigan
Chen, Kai-Yuan	Graduate Student, Cornell University
Chen, Kowa	Postdoc, Massachusetts Institute of Technology
Chen, Kuchuan	Graduate student, Baylor College of Medicine
Chen, Michael	Post-doc, Boston Children's Hospital
Chen, Pan-Yu	Graduate student, Massachusetts Institute of Technology
Chen, Poshen	Graduate Student, UMASS Medical School
Chen, Rose	Research Associate, Genzyme.Sanofi
Chen, Sam	Student, Stony Brook University
Chen, Shann-Ching	Staff Scientist, Bioinformatics, Thermo Fisher Scientific
Chen, Sheng-hong	Postdoctoral fellow, Harvard Medical School
Chen, Shih-Pin	Postdoctoral fellow, Massachusetts General Hospital
Chen, Ting-Hsuan	PhD Student, Cornell University
Chen, Tzu-Chieh	Student, UC Berkeley
Chen, Wen Yu	Lab Manager, University of Texas at Austin
Chen, Ying-Chou	Postdoc Fellow, Massachusetts Institute of Technology
Chen, Ying-Ja	Scientist, Pronutria
Chen, Yi-Shan	Postdoc, Duke University

Chen, Yi-Ju	Postdoctoral Researcher, University of Pennsylvania
Chen, Yu-Fan	Graduate student, Rutgers University
Chen, Yu-Tsung	Graduate Student, Duke University
Cheng, Chieh-Yang	PhD Student, Cornell
Cheng, Han Ling	
Cheng, Melody	Postdoctoral Research Scientist, Columbia University
Cheng, Nai-Lin	
Cheng, Ting-Wen	Postdoc Fellow, Pfizer Inc
Cheng, Yenfu	PhD student, MIT
Cheng, Yung-Chih	Postdoctoral Research Fellow, Boston Children's Hospital/Harvard Medical School
Chi, Alicia	PhD candidate, University of Cape Town
Chiang, Bing-Yu	Postdoc, Albert Einstein college of medicine
Chiang, Chang-Ying	Graduate student, Harvard Medical school
Chiang, Chun-Te	Research Fellow, Massachusetts General Hospital
Chien, Miao-Ping	Post-doctoral fellow, Harvard University
Chiu, Chen-Jui	Manufacturing engineer, Arteriocyte Medical System, Inc.
Chiu, Joyce	Senior Project Leader, Honeywell Safety Products
Chiu, Po-Lin	Postdoctoral Fellow, Harvard Medical School
Chiu, Shang-Yi	Postdoctoral fellow, Dana-Farber Cancer Institute
Chou, Chia-Ching	PhD candidate, MIT
Chou, Danny	JDRF Postdoctoral Fellow, MIT
Chou, Hsin-Jung	Graduate student, UMass Medical School
Chou, Hui-Ting	Postdoc Fellow, Harvard Medical School
Chou, Shao-Pei	Graduate Student, Cornell University
Chou, Szu-Ting	Student, University of Maryland
Chou, Wen-Chi	Postdoc, Harvard Medical School
Chou, Yi-ying	Post doctoral fellow, Boston Children's Hospital/Harvard Medical School
Chow, Philicia	Formulations Development Intern, Blend Therapeutics
Chu, Heng-Hsuan	Postdoc, Dartmouth College

Chung, Tai-Chun	Graduate Student, State University of New York at Buffalo
Fan, Jessy YY	Postdoc, Pfizer
Fang, Chi-Chun	PhD student, UT Austin
Fu, Shih-Chen	PhD student, Icahn School of Medicine at Mount Sinai
Guo, Fang-Ting	Student , Johns Hopkins University
Han, Tina	Postdoctoral Fellow, UC San Francisco
Hao, Pengying	Graduate student, Boston University
Ho, Hsing-I	Graduate student, Baylor College of Medicine
Ho, Li-Lun	Postdoc, MIT
Ho, Tammy Szu-Yu	Graduate student, Baylor College of Medicine
Ho, Yi-Hsuan (Elisha)	Doctoral Candidate, University of Wisconsin-Madison
Ho, Yi-Yun	Research Technician, Cornell University
Ho, Yu-Jui	Graduate Student , Cold Spring Harbor Laboratory
Hsia, Hung-Ching	Graduate Student, University of North Carolina at Chapel Hill
Hsiao, Chinghan	Master Student, Brown University
Hsiao, Chinju	Sr. Postdoc Fellow, Ipsen
Hsiao, Stephanie	Senior research fellow, Mass General Hospital
Hsiao, Wen-Yu	Graduate Student, UMASS
Hsieh, Bao-Yu	Postdoctoral Fellow, North Carolina State University
Hsieh, Fu-Kai	Postdoctoral researcher, Mass General Hospital/Harvard Medical School
Hsieh, Hsiao-Wu	PhD Candidate / Graduate Research Assistant, University of California, Davis
Hsieh, Tsung-Han	Graduate student, UMass Medical School
Hsieh, Tsungying	Student, Duke University
Hsieh, Wen-Chuan	Research assistant, Chang Gung Medical Foundation
Hsieh, Yu-Ying	
Hsiung, Jenny	Student, Harvard Business School
Hsu, Carolyn	
Hsu, Huang-Che	Staff, sbux
Hsu, Hui-Ting	Student, Harvard University

Hsu, Hunglun	Graduate Student, Cornell University
Hsu, Tsung-Ta (David)	Graduate Research Associate, The Ohio State University
Hsu, Wei-Lun	
Hu, Yu-Jie	Graduate Student , UMass Medical School
Hu, Zhuting	Graduate student, Dartmouth College
Huang, Chia-Ling	Instructor, Boston University
Huang, ChiaYi	
Huang, Chun-Hao	PhD Candidate, Memorial Sloan-Kettering Cancer Center
Huang, Hai-Tsang	Graduate Student, Harvard University
Huang, Jia-Hsin	Postdoc, Cornell University
Huang, Nai-Jia	Postdoc, MIT
Huang, Po Yu	Student, Stony Brook University
Huang, Rex	Of Counsel, Fish and Richardson
Huang, Ting-Hao	Grad student, UMass Worcester
Huang, Ya-Shu	Postdoc, Georgia State University
Huang, Yen-Tsung	Assistant Professor, Brown University
Huang, Yu-Hwa	Postdoc, BWH
Huang, Yung-Chi	Graduate Student, UMass Medical School
Hung, Cindy	Research Fellow, Harvard Medical School/MGH
Hung, Hui-Fang	Student, Umass Med
Hung, Kuo-Chan	Postdoc, New England Biolabs
Hung, Lung-Hsin	Microfluidics Engineer, GnuBIO
Hung, Ruei-Jiun	Postdoc, Harvard Medical School
Hung, Tony	
Hwang, Yih-Chii	PhD Candidate, University of Pennsylvania
Kang, Yuan-Lin	Postdoctoral research fellow, Harvard university
Kao, Yu-Chieh	Postdoctoral researcher, University of North Carolina at Chapel Hill
Ke, Iou-Sheng	Senior Chemist, Dow Chemical
Ke, Jia-Yu	Graduate Research Associate, The Ohio State University

Ku, Sheng	Pre-doctoral trainee, Roswell Park Cancer Institute
Kung, Chia-Yu	College students, Stony Brook
Kuo, Meredith	Student, Harvard University
Kuo, Tzu-Hsing	Postdoctoral Research Fellow, Brigham and Women's Hospital/Harvard Medical School
Lai, Jiann-Jyh	PostDoc, UMASS Medical School
Lai, Julia	Student, Boston university
Lai, Natalie DanYu	Project Developer, Mirimus
Lan, Yu-Han	Graduate Student, Rutgers University
Lee, Cheng-Sheng	Student, Brandeis University
Lee, Chien-Der	Graduate student, UT Southwestern Medical Center
Lee, Chin-Mei	Postdoctoral Researcher, University of Pennsylvania
Lee, Chung-Tsai	Technician, UPenn
Lee, Chung-Wei	Postdoc, Brigham and Women's Hospital
Lee, Chun-Teh	
Lee, Hsiao-Ju	Graduate student, Texas A&M University
Lee, Hsu-Yang	Graduate student, University of California, Davis
Lee, Nick	MBA , Duke University
Lee, Sherry	Postdoc, Whitehead Institute for Biomedical Research
Lee, Wan-Ping	Senior Lead Scientist, Seven Bridges Genomes, Inc.
Lee, Yan-Jiun	Graduate Student , Texas A&M University
Lee, Yi-Ying	Postdoctoral Research Associate, University of Maryland Baltimore County
Lee, Yu-Ru	Research fellow, Beth Israel Deaconess Medical Center
Liang, Richard	Research Investigator, University of Michigan
Liao, Chen-Chen	Research Associate, Berg
Liao, Julie	Post-doctoral researcher, Biofilm Research Group, Binghamton University
Liao, Meichen	Post-doctoral Fellow, Brigham & Women’s Hospital
Lin, Chien-Ling	Postdoctoral Research Associate, Brown University
Lin, Hungyun	Principal Scientist, Pfizer Inc.
Lin, Jia-Ren	Postdoc, Harvard Medical School

Lin, Lih-Ling	Director, Pfizer
Lin, Pao	Postdoc, Massachusetts Institute of Technology
Lin, Ruei-Zeng	Research Fellow, Boston Children's Hospital
Lin, Sheng-Hsuan	Doctoral student, Harvard School of Public Health
Lin, Steve	Postdoctoral fellow, University of Texas at Austin
Lin, Tsung-Yi	PhD, UMASS-Amherst
Lin, Yi-Chun Kelly	Research Assistant, Indiana University
Lin, Yi-Dong	Postdoctoral Fellow, MIT
Lin, Yi-Fen	PhD Student, UMASS
Lin, Yu-Min	Post-Doc, Harvard Medical School
Lin, Zhenxin	
Liu, Han-Hsuan	Graduate Student, Scripps research institute
Liu, Harris	Research Assistant, Massachusetts Institute of Technology
Liu, Kun-Hsiang	Assistant in Molecular Biology, Mass General Hospital
Liu, Shu-Lin	Post doctoral, University of Pennsylvania
Liu, Wan-Ju	Postdoc, Stony Brook University
Liu, Ya-Ting	Marketing Associate, CDF
Liu, Yen-Liang	Ph.D. student, The University of Texas at Austin
Liu, Yen-Ting	Postdoctoral fellow, University of Texas at Austin
Lu, Chi	Grad Student, MIT
Lu, Tsai-Yi	Graduate Student, University of Massachusetts Medical School
Lu, Tzongshi	Instructor in Medicine, Harvard Medical School
Lu, Yen-Chun	PhD student, Cornell University
Lu, Yi-Fen	Research fellow, Boston Children's Hospital
Luo, Chu-Yuan	Graduate student , UMASS-Amherst
Mak, Huey-Ming	Graduate student, Northwestern University
Nieh, Mu-Ping	Professor, University of Connecticut
Ou, Yi-Hung	Research Fellow, Harvard Medical School
Peng, Haofan	

Peng, Sheng-Shiang	Graduate Student, Rutgers University
Poh, Yu-Ping	PostDoc, UMass Med School
Rwei, Alina	Student, MIT
Shen, Ching-Han	Graduate Student, Harvard University
Sheu, Yi-han	Research Assistant, Harvard University
Shih, Han-Yu	Postdoc, NIAMS/NIH
Shyu, Amy	Research, Novartis
Su, Chienwen	Instructor, MGH
Su, Jay	Business Development Manager, Genzyme
Su, Pin-Chih	Graduate Student, University of Illinois at Chicago
Sung, Crystal	Scientific Director, Sanofi
Sung, Yun-shao	Bioinformatician, MSKCC
Tai, Jui-Cheng	Research Fellow, MGH
Teng, Chi-Hse	Director, Novartis
Ting, See-Yeun	Graduate student, University of Wisconsin-Madison
Tsai, Chia-Lun Jack	Research Team Leader, Mass General Hospital
Tsai, Ching-Yi	Postdoc, UPENN
Tsai, Pei-Ling	Postdoctoral Associate, Yale University
Tsai, Pei-Yun	Student, Harvard
Tsai, Tony	Post-doc, Harvard Medical School
Tsai, Wei-Wen	Associate Scientist, The Dow Chemical Company
Tsai, YuCheng	Postdoc, UPenn
Tseng, Hsien-Chung	Research Scientist, Manus Biosynthesis
Tseng, Kuang-Ching	Graduate Student, University of Rochester
Tseng, Wei-Ju	Research Specialist, University of Pennsylvania
Tseng, YiJu	Postdoc fellow, Boston Children's Hospital
Tu, Ho-Chou	Research Fellow, Boston Children's Hospital
Tung, Kuei-Ling	Student, Cornell
Tzeng, Te-Chen	Post doc, UMASS

Wang, Chen-Yu	Graduate Student, Harvard University
Wang, Chien-Chung	Postdoc, Harvard University
Wang, Chih-Chieh	PostDoc, Harvard Medical School
Wang, Shuen-Shiuan	Grad student, University at Buffalo
Wang, Sih-han	Postdoctoral Fellow, University of Texas MD Anderson Cancer Center
Wang, Ting-Yi	Graduate Student, Texas A&M University
Wang, Yane-Shih	Postdoctoral Associate, Yale University
Wang, Yaoyu	Associate Director, Dana-Farber Cancer Institute
Wei, Pei-Chi	Research Fellow, Harvard Medical School/Boston Children's Hospital
Wei, Pinghung	Sensor Engineer, MC10 Inc.
Wei, Shuo	Postdoctoral Fellow, BIDMC
Wei, Wei-Shao	PhD student, UPenn
Wu, Chia-Chien	Postdoc, UMass Boston
Wu, Chia-Hung	Research Associate, Caltech/HHMI
Wu, Chia-Jung	Associate Senior Consultant Engineer, Eli Lilly & Company
Wu, Chia-Ling (Leslie)	Postdoc research associate, Boston University Medical Campus
Wu, Chi-Fang	Postdoctoral fellow, Duke University
Wu, Hai-Yin	Ph.D. student, Harvard University
Wu, Hsin-Ta	PhD candidate, Brown University
Wu, I-Hui	Graduate Student, UTSW
Wu, Kuen-Phon	Postdoctoral research fellow, St. Jude Children's Research Hospital
Wu, Ming-Ru	Graduate student, Dartmouth College
Wu, Shu-Pei	Research Scientist 1, Vertex pharmaceuticals
Wu, Wei-Pu	Research Assistant, Columbia University
Yang, Chihsheng	Postdoctoral Fellow, Harvard University
Yang, Ching Yao	PhD Fellow, New York University
Yang, Yeuan Ling	Graduate Student, Cornell University
Yao, Li-Chin	
Yaung, Stephanie	PhD Candidate, Harvard Medical School & MIT

Ye , Chun-Wan	Postdoctoral Research Fellow, MIT
Yeh, Athena Yi-Chun	Graduate student, Cornell University
Yeh, Danny	Associate Director, Biogen Idec
Yeh, Johannes	Research Fellow, Harvard Medical School
Yeh, Ting-Chun	Postdoc fellow, UT MD Anderson Cancer Center
Yeh, Yang-Hui	Ph.D student, University of Connecticut
Yen, Shuo-Ting	Graduate Student, Baylor College of Medicine
Yu, Che-Hang	Graduate Student, Harvard University
Yu, Wan-Ni	Postdoctoral Research Fellow, University of Illinois at Chicago
Yuan, CC	Postdoctoral Scientist, Constellation Pharmaceuticals
Yuan, Wei-Chien	Research Fellow, Boston Children's Hospital
Yueh, Han	Postdoctoral Associate, Boston University

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Ho-Chou Tu, 杜荷洲, Research Fellow
Boston Children's Hospital, Harvard Medical School

Ching-Han (Hannah) Shen, 沈敬涵, Graduate student
Molecular and Cellular Biology, Harvard University

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Electrical Engineering and Computer Science, MIT

Chia-Yen Chen, 陳家彥, Postdoctoral Fellow
Massachusetts General Hospital/Broad Institute

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Sherry Lee, 李湘盈, Postdoctoral Fellow
Whitehead Institute for Biomedical Research, MIT

Wei-Yu Chen, 陳威宇, Assistant Professor
Center for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital

Hai-Yin Wu, 吳海茵, Graduate student
Applied Physics, Harvard University

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Massachusetts General Hospital, Harvard Medical School

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Ying-Ja Chen, 陳映嘉, Scientist
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Whitehead Institute for Biomedical Research, MIT

Yi-Ying Chou, 周怡吟, Postdoctoral Fellow
Boston Children's Hospital, Harvard Medical School

Yi-Dong Lin, 林意棟, Postdoctoral Fellow
Koch Institute, MIT

Academic Panel

Tsai-Yi Lu, 呂采宜, Graduate Student
Biomedical Sciences, University of Massachusetts Medical School at Worcester

Tzu-Hsing (April) Kuo, 郭姿杏, Postdoctoral Research Fellow
Brigham and Women's Hospital, Harvard Medical School

Meredith Kuo, 郭思妤, Graduate student
Molecular and Cellular Biology, Harvard University

Chun-Te (Patrick) Chiang, 江俊德, Postdoctoral Research Fellow
Massachusetts General Hospital, Harvard University

Bench Scientist Panel

Yung-Chih Cheng, 鄭永志, Postdoctoral Research Fellow
Boston Children's Hospital, Harvard Medical School

Larry Lo, 羅志鴻博士, Director
Translational Sciences and Technologies, Biogen Idec

Beyond the Bench Panel

Wan-Ping Lee, 李婉萍, Senior research associate
Department of Biology, Boston College

Hank Lin, 林弘昀, Principal Scientist
Safety Biomarker and Clinical Pathology, Pfizer Inc.

Website

Wen-Fan Hsieh, 謝汶芳, Graduate student
Computer Information Science, Boston University

Sky Tien-Yun Huang, 黃天韻, Graduate Student
Massachusetts College of Art and Design

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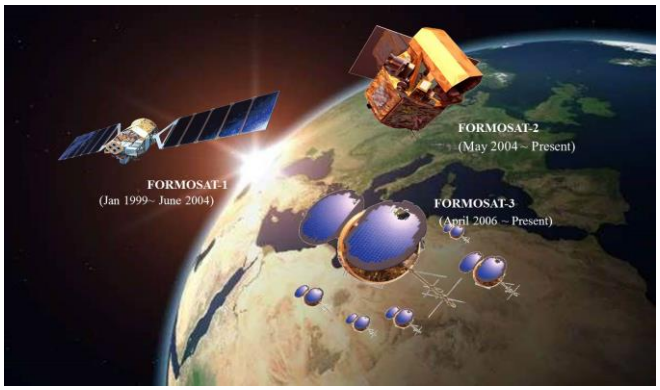

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- 參與並協助海外科技社團舉辦之科技活動
  To support the activities of Chinese-American S&T community organizations
- 協助國內蒐集科技資訊
  To help collect S&T information
- 服務區域包括大華府地區、美東地區、美東北地區、美東南地區及美中地區共 25 州
  Service area including 25 states(ME, VT, NH, MA, CT, NY, RI, PA, NJ, DE, MD, VA, WV, NC, SC, GA, TN, AL, FL, KY, OH, MI, IL, IN, D.C.)

➢ 國內人才海外培訓計畫：

- 千里馬計畫(Graduate Students Study Abroad Program) 博士生至國外研究
  http://www.most.gov.tw/int/ct.asp?xItem=22495&ctNode=4522
- 龍門計畫(Dragon Gate Program)
  台灣研究團隊赴國外尖端研究機構進行合作
  http://www.most.gov.tw/int/ct.asp?xItem=18969&ctNode=4522
- 赴國外頂尖機構從事博士後研究計畫 (Postdoctoral Research Abroad Program)
  http://www.most.gov.tw/int/ct.asp?xItem=22494&ctNode=4522

➢ 海外人才延攬培訓計畫：

- 台灣暑期研究生計畫
  Summer Institute in Taiwan
  美國研究生暑假赴台研究
  www.nsf.gov/eapsi
- 候鳥計畫 Taiwan Tech Trek
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  www.most.gov.tw/ttt/

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駐波士頓臺北經濟文化辦事處教育組
Education Division,
Taipei Economic and Cultural Office in Boston

我們是...

教育組是中華民國教育部派駐於美國新英格蘭地區的單位，主要任務為促進臺灣與新英格蘭地區間各級教育學術交流。

與我們聯絡

電話：617-737-2055/6
電郵：education@tecoboston.org
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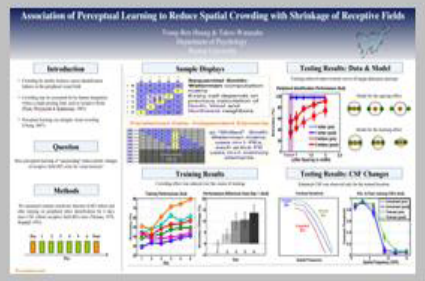

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