Boston Taiwanese Biotechnology Association (BTBA)

June 6-7, 2015

BOSTON TAIWANESE BIOTECH SYMPOSIUM

Abstract Book

BTBATW.ORG/2015

Welcome Message

Welcome to the 3rd Boston Taiwanese Biotechnology Symposium 2015!

The Boston Taiwanese Biotechnology Association (BTBA) was established by a group of young scientists, including graduate students, postdoctoral researchers and professionals working in biotechnology related fields in the greater Boston area. We work closely with Harvard GSAS Taiwan Student Association. Our annual symposiums in the past two years attracted over 300 attendees to discuss cutting-edge research topics and exchange ideas about career development. In addition, we have been hosting bi-weekly academic seminars and biotechnology industry workshops to serve as an information platform and stimulate interactions among the community.

The goals of Boston Taiwanese Biotechnology Symposium 2015 are to:

- Discuss the frontiers in biotechnology and how the advances in the field can impact upon human health
- Facilitate networking and interdisciplinary communications
- Strengthen the connections among biotechnology communities in Taiwan, Asia-Pacific and the U.S.

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 research abstracts. We greatly appreciate the dedication of all the speakers and panelists to this event. We are also very grateful for 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), Cesari and McKenna, LLP, Taiwanese Association of America, Boston Chapter (波士頓台灣同鄉會), PosterSmith.com, and generous friends for supporting the symposium financially.

Please email us at btba.tw@gmail.com or visit our facebook group “Boston Taiwanese Biotechnology Association”, if you have any questions or comments about BTBA, or if you would like to get more involved! We hope you will enjoy the symposium and the time in Boston.

Sincerely,
Sherry Lee
Fu-Kai Hsieh
Organizing Committee Co-Chair,
Boston Taiwanese Biotechnology Association

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List of Organizers and Sponsors

Organizers

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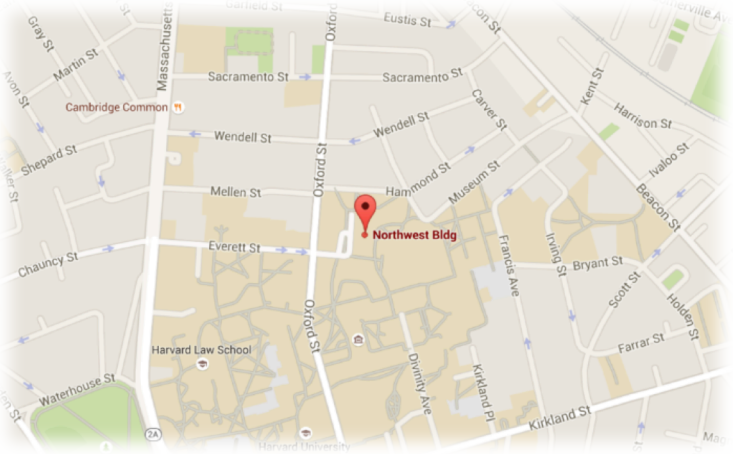
Direction

Northwest Building, Harvard University

52 Oxford St., Cambridge, MA, 02138



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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):

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We recommend you to use Harvard Campus Services online purchase system to purchase parking permit: https://www2.uos.harvard.edu/cgi-bin/permit/purchase.pl

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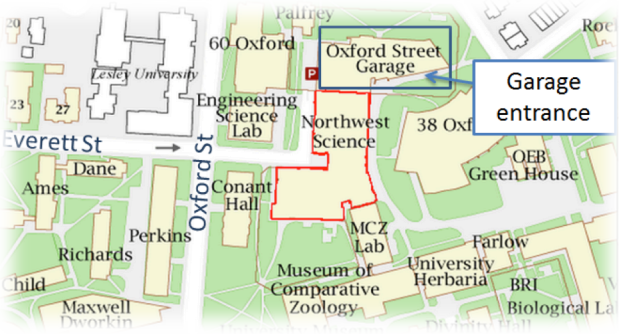

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15. Enjoy the symposium!

Agenda

Day 1 (06/06/2015)

08:30-09:00	**Registration and Poster Setup**
09:00-09:10	**Opening Remarks**
09:10-10:10	**Keynote** **Dr. Yuan-Tsong Chen, Distinguished Research Fellow and Academician, Institute of Biomedical Sciences, Academia Sinica, Taiwan**
10:10-10:40	**Coffee Break**
10:40-12:00	**Academic Panel Discussion** **Moderator: Hsiao-Ying (Monica) Wey** **Dr. Gene-Wei Li, MIT** **Dr. Chia-Kuang (Frank) Tsung, Boston College** **Dr. Li-San Wang, University of Pennsylvania** **Dr. Ronglih Liao, BWH/Harvard Medical School** **Dr. Tun-Hou Lee, Harvard School of Public Health**
12:00-13:30	**Lunch Break & Networking**
13:30-14:40	**Research Talks: Basic Research (Room B103)** (*L represents 8 min long talk. **P represents 90 sec talk with a poster.) **Chichao Chen** *L01*. Identifying essential AML maintenance genes in Ras pathway using shRNA screen* **Tai-Yen Chen** *L02. Regulation by Modulating Transcription Factor Unbinding Kinetics in Live Bacteria* **Wei-Chien Hung** *L03. Confinement Affects Cell Migration via Modulating Protein Kinase A* **Sherry Lee** *L04. PPARα and glucocorticoid receptor synergize to promote erythroid progenitor self-renewal* **Chien-Ling Lin** *L05. Genome-wide Lariat profiling reveals the Structure and Function of Branched Intermediates of Splicing* **Kun-Yu Teng** *L06. Ihhibition of Liver Tumorigenesis by CCL2-CCR2 AXIS, a Target of MIR-122* **Anne H.-H. Tseng** *L07. SIRT3 Crosstalks with FOXO3 Acetylation-Phosphorylation-Ubiquitination to Mediate Mitochondrial Homeostasis and Hypoxic Adaptation*

Po-Lin Chiu

*P08**. Structural studies of lipid-protein interactions using electron crystallography*

Ran-Der Hwang

P12. The Neuroprotective Effect of Human Uncoupling Protein 2 (hUCP2) Requires cAMP dependent Protein Kinase in a Toxin Model of Parkinson's Disease

Kun-Po Li

P14. Levels of the pro-apoptotic molecule Bim are determined early in the response and positively correlated with memory T cell fate.

Jia-Ren Lin

P18. Highly multiplexed high-throughput imaging of single-cell using CycIF cyclic immunofluorescence

Sheng-Hsuan Lin

P19. Parametric mediational g-formula approach to mediation analysis with time-varying exposures, mediators and confounders: an application to smoking, weight, and blood pressure

Research Talks: Applied Research (Room B101)

Ying-Chou Chen

L08. Randomized CRISPR-Cas transcriptional perturbation screening identifies novel genes that protect against alpha-synuclein toxicity in yeast and human cells*

Melody Cheng

L09. Modeling Parkinson's Disease Using Human Induced Pluripotent Stem Cells

Wan-Ping Lee

L10. A Next-Generation Sequencing Aligner for A Graph Genome Reference

Yen-Chun Lu

L11. Design Complex Hydrogel Microparticles for Scalable 3D cell Culture, Co-Culture and Microtissue Production

Chia-Hung Tsai

L12. Platelet count control in immune thrombocytopenic purpura patient: optimum romiplostim dose profile

Yane-Shih Wang

L13. Polyspecific pyrrolysyl-tRNA synthetases from directed evolution

Studies on the Role of Interleukin-6 in Prostate Cancer Development

Shu-Han Yu

L14. Studies on the Role of Interleukin-6 in Prostate Cancer Development

Hsiao-Rong Chen

*P05**. A computational method that identifies repositioned drug candidates by finding inversely correlated cellular functions under disease and drug perturbations*

Jung-Ting Chien

P07. A novel innovation of highly accurate, scalable sequencing solution for complex nucleotide mixture

Li-Shiuan Hung

P11. The perspective of Genetic Testing Development and Regulatory

	Reform in Personalized Medicine **Christy Tzu-yun Kuo** *P13. T cells Expressing CARs directed against HLA-0201 WT1 peptide complex can effectively eradicate WT1+ A0201+ tumor cells in vitro* **Jia-Wei Yeh** *P26. Stretching tethered single chromatin in nanofluidic channels for detection of epigenetics marks*
14:40-16:00	**Industrial Scientist Panel Discussion** **Moderator: Chen-Yuan (Charlie) Yang** **Dr. Crystal C. Sung, Sanofi** **Dr. Eric Peng, Biogen Idec** **Dr. Wei Lien Chuang, Sanofi** **Dr. Alice Tsai, Vertex Pharmaceuticals** **Dr. Hon-Ren Huang, Intellia Therapeutics**
16:00-17:00	**Coffee Break & Networking: Entry Into the Industry** **Rose Chen, Dennis Wei, Chen-Chen (Rita) Liao, LiangChin (Carla) Chen, Ying-Ja Chen, Wan-Ping Lee, Eric Peng, Amy Shyu, Jay Hsu**
17:00-18:20	**Beyond the Bench Panel Discussion** **Moderator: Chen-Chen (Rita) Liao** **Dr. Jenny Chen, Wolf Greenfield** **Dr. Shen Luan, Thermo Fisher Scientific** **Dr. Shaoyu Chang, Life Science Nation** **Mr. Chance Lai, Life Technologies** **Dr. Yu-Feng Wei, Vizuro**
18:20-20:30	**Poster Session & Reception Dinner**

Day 2 (06/07/2015)

09:00-09:30	**Special Featured Talk** **Dr. Winston Town, Diamond BioFund Inc. & Fountain Biopharma Inc.**
09:30-10:50	**Biotech in Taiwan Panel** **Moderator: Tzu-Hsing (April) Kuo** **Mr. Charley Lu, Taiwan Liposome Company** **Mr. Chia-Chin Sheu, Simpson Biotech co., Ltd.** **Dr. Ko-Chung Lin, PharmaEssentia Corporation** **Dr. Nan-Horng (Stan) Lin, CHO Pharma**
10:50-11:20	**Coffee Break**
11:20-12:20	**Keynote** **Dr. Nancy T. Chang, Angel investor and philanthropist in healthcare and education**
12:20-	**Closing Remarks & Poster Award Ceremony**

Keynote Speaker

Yuan-Tsong Chen, 陳垣崇 博士

Distinguished Research Fellow and Academician, Institute of Biomedical Sciences, Academia Sinica, Taiwan

Dr. Chen is a world-renowned biomedical researcher specializing in genomic and translational medicine. He has published more than a hundred scientific papers in prestigious journals and received multiple awards for his remarkable research and innovation in medicine. One of his most notable works is the invention of Myozyme, the first drug approved by the US Food and Drug Administration and the European Medicines Evaluation Agency to treat Pompe disease (glycogen storage disease type II). He is currently a Distinguished Research Fellow of the Institute of Biomedical Sciences, Academia Sinica, and Professor of Pediatrics at Duke University. Dr. Chen obtained his M.D. from National Taiwan University in 1973 and has been keen on studying the human genome since then. In 1978, he completed his Ph.D. in genetics from Columbia University and became a faculty at Duke University in 1983. He continued his research at Duke until he was recruited by Nobel Laureate Yuan-Tseh Lee（李遠哲）to be the Director of the Institute of Biomedical Sciences in 2001. In the past 14 years, he has contributed tremendously to the collaboration between hospitals and research institutes and laid the groundwork for Taiwan to develop translational medicine and biotech industry. His lab has also devoted to understanding the genetic basis of adverse drug reactions and successfully identified the genes/SNPs associated with the life-threatening Steven-Johnson syndrome. Dr. Chen is also highly admired and respected for his mentorship to many students and young scientists in Taiwan. Many of them continue to thrive and become outstanding scientists in the field.

Keynote Speaker

Nancy T. Chang, 唐南珊 博士

Angel investor and philanthropist in healthcare and education

Dr. Chang, best known as the Co-founder, President, CEO and Chairman of Tanox Inc. until it was bought by Genetech in 2006 with $919 million, is one of the most prominent and influential leaders in the global biotechnology industry. She was born in Taiwan in 1950, and after receiving her B.S. from National Tsing Hua University (Hsinchu, Taiwan) in 1972, she came to the United States to attend graduate school. On the plane ride to U.S., she read James Watson's The Double Helix and was immediately drawn by the beauty of biology, which led to her decision to transfer from Brown University to Harvard University, where she earned her Ph.D. in biochemistry in 1982.

She grew interests in interferon during her Ph.D. study and therefore went to Roche Pharmaceutical Company in New York to work with Dr. Sidney Pestka as a postdoc after graduation. Later she joined Centocor (now Janssen Biotech Inc.) as a diagnostician. However, her passion and determination for research resulted in the birth of several pioneering new projects, including the first HIV/AIDS diagnostic assay, and eventually transformed Centocor into a therapeutic company. She then served as Director of Research at Centocor from 1982 to 1986 before she had to move with her family to Texas, where she became Associate Professor of Molecular Virology at Baylor College of Medicine from 1986 to 1991. She and Dr. Tse Wen Chang co-founded Tanox in 1986 with their family savings to develop treatments for allergic asthma. Besides the success of Xolair – the first biological therapy for allergic asthma, what's worth mentioning is that Nancy's group at Tanox also successfully brought TNX-355, now known as Ibalizumab, to Phase II trial before the acquisition by Genetech. Now Ibalizumab is one of the most promising new drugs to treat AIDS patients and has been put high hopes to eventually prevent HIV infection.

Academic Panelist

Gene-Wei Li, 李勁葦 博士

Assistant Professor, Biology, MIT

Gene-Wei Li received his PhD training in Physics at Harvard University, where he developed single-molecule approaches to probe the dynamics of gene expression in living cells. He then became a Helen Hay Whitney Postdoctoral Fellow at UCSF. There he combined analytical and high-throughput sequencing approaches to reveal the intricate tuning of protein synthesis in relation to a cell's physiology. He became an assistant professor of Biology at MIT in 2015. His laboratory aims to achieve quantitative understanding of how a cell works, with special emphasis on the control of gene expression and protein synthesis. Gene grew up in Hsinchu and received B.S. in Physics from National Tsinghua University.

Chia-Kuang Frank Tsung, 宗家洸 博士

Assistant Professor, Chemistry, Boston College

Prof. Tsung received his B.A. degree in chemistry from the National Sun Yat-Sen University, Taiwan in 1999. After two-year mandatory military service, he began his Ph.D. study with Professor Galen D. Stucky at the University of California, Santa Barbara in 2002 and received his Ph.D. in 2007. In October 2007, he started his joint postdoctoral research in Prof. Peidong Yang's and Prof. Gabor A. Somorjai's groups at the University of California at Berkeley. He joined the chemistry faculty at Boston College in the summer of 2010. His research focuses on heterogeneous catalysis, which is critical for the prosperity of human civilization. It provides access to the range of chemicals, materials, and fuels we use. Tsung's group studies new approaches to enable the molecular-level design of active sites in heterogeneous catalysts. These precise active sites allow fundamentally tuning of molecule sorption behaviors, reaction pathways, and the corresponding rates. Achieving this goal will have a significant impact on the field of heterogeneous catalysis, as well as on the society as a whole.

Academic Panelist

Li-San Wang, 王立三 博士

Associate Professor, Pathology and Laboratory Medicine, University of Pennsylvania

Li-San Wang received his B.S. and M.S. in Electrical Engineering from the National Taiwan University, and his Ph.D. in Computer Sciences from the University of Texas at Austin. Currently he is an Associate Professor of Pathology and Laboratory Medicine and Chair of the Genomics and Computational Biology graduate program at the University of Pennsylvania Perelman School of Medicine. Dr. Wang's research integrates bioinformatics, genomics, and human genetics in the study of Alzheimer's disease and neurodegenerative disorders. He is the principle investigator of the NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS), a data repository supported by the National Institute of Aging for Alzheimer's disease genetics research.

Ronglih Liao, 廖容儷 博士

Associate Professor, BWH / Harvard medical School

Prof. Ronglih Liao is an Associate Professor in the Department of Medicine at Brigham and Women's Hospital, Harvard Medical School. Her research program has centered upon the interrogation of cardiovascular physiology, from the cellular level to the organismal level, to understand the molecular underpinnings of human heart disease. Her research program has centered on two areas of investigation, to define the mechanisms governing the development of amyloid cardiomyopathy and to understand endogenous cardiac regenerative capacity in the adult heart. Her research efforts have universally involved collaboration with local, national and international colleagues. Through this process, her research program has contributed to the scientific knowledge base and education of the next generation of scientists.

Academic Panelist

Tun-Hou Lee, 李敦厚 博士

Professor, Harvard T.H. Chan School of Public Health

Tun-Hou Lee, Professor of Virology at the Harvard T. H. Chan School of Public Health, was born in Taipei, Taiwan. He was a graduate of National Taiwan University and received his doctoral degree from Harvard University and post-doctoral training at the Karolinska Institute of Sweden.

Dr. Lee's major research interests are host-virus interactions with particular focus on human and related primate retroviruses. His work has contributed to the development of serologic testing for the human leukemia virus (HTLV) and human immunodeficiency virus (HIV). He was the first to identify envelope gene products of HTLV-I, HTLV-II and HIV, and demonstrated that the envelope antibody is the most important marker for screening individuals for infection with these human retroviruses. He also identified the putative transforming protein of HTLV-I, which was the first observation of a retrovirus protein linked to a cancer that was not an oncogene product. Other gene products of HIV-1 and HIV-2 identified by Dr. Lee and his co-workers include those encoded by the vpu, vif, vpr,vpx and nef genes. Several patents related to his discoveries have been awarded to Harvard University.

Bench Scientist Panelist

Crystal C. Sung, 宋晶晶 博士

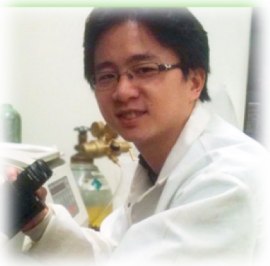
Senior Director Scientific, Clinical Lab Sciences, Sanofi

Dr. Sung has over 14 years of industry experience in biologics development. She is the Scientific Director of Clinical Laboratory Sciences at Sanofi. Dr. Sung is directing a CLIA certified lab, which provides clinical laboratory services and scientific expertise to support global R&D projects and drug development through its life cycle (phase o-IV and post approval commitments).

Dr. Sung received a B.S. degree in Medical Technology from National Taiwan University and a Ph.D. degree in Pathology, College of Medicine at the Ohio State University. She completed her post-doctoral clinical research training at Northwestern University Medical School followed by Clinical Immunology Fellowship at Chicago Medical School/Evanston Hospital/Children's Memorial Hospital. Prior to joining Genzyme, she was an Assistant Professor in Tzu-Chi Medical School, Taiwan.

Crystal is a diplomate of American Board of Medical Laboratory Immunology (ABMLI) and currently holds CLIA lab directorship and New York State Department of Public Health certificate of qualification of Laboratory Director in Diagnostic Immunology and Clinical Chemistry.

Bench Scientist Panelist



Eric Peng, 彭浩帆 博士

Sr. Engineer, Process Development, Biogen Idec

Haofan (Eric) Peng is a senior engineer in the cell culture development group at Biogen Idec. He obtained his chemical engineering BS degree at National Taiwan University. He received his PhD from the SUNY Buffalo in chemical and biological engineering where he focused on regenerative medicine and preclinical animal model. In Biogen Idec, he is team leader in perfusion bioprocessing development cross functionally including Cell line evaluation, medium optimization, process development, filtration integration, operation automation and manufacture scale up to 15,000L world-class facility. He is also working closely with GMP manufacture facility in RTP, North Carolina, and responsible for raw material screening, analytical assay development, quality control bioassay transferring, and supply chain management.

Wei Lien Chuang, 莊維廉 博士

Principle Scientist, Analytical Chemistry, Sanofi

Dr. Chuang has more than fifteen years of working experience in the pharmaceutical industry. In his current position, he focuses on using mass spectrometry and nuclear magnetic resonance to apply lipidomics and metabolomics for biomarker discovery. Another area of interest is discovery bio-analysis with particular focus on protein and antibody pharmacokinetics and toxicology. Prior than that, Dr. Chuang had ten years of experience in academic research. Dr. Chuang received his PhD in Chemistry from the University of California, Riverside. He then completed his postdoctoral research at the University of California, San Francisco. He joined Genzyme/Sanofi in 2004.

Bench Scientist Panelist

Alice Tsai, 蔡婉容 博士

Research Scientist, Vertex Pharmaceuticals

Dr. Alice Tsai is a talented research scientist at the Vertex Pharmaceuticals. She has been working in the industry for seven years, actively involved with drug development projects. Her expertise is in PK/PD (pharmacokinetics and pharmacodynamics), DMPK (drug metabolism) and clinical development. Moreover, she is an insightful team leader. With her passion about pharmaceutical science, she handles team dynamics well and leads the team to reach project goals. Prior to starting her career in the pharmaceuticals and followed by the B.S. degree in Agricultural Chemistry from the National Taiwan University, she received the M.S. degree in Nutrition and Exercise Science and the Ph.D. degree in Pharmaceutical Science from the State University of New York at Buffalo.

Hon-Ren Huang, 黃宏仁 博士

Senior Scientist, Intellia Therapeutics

Dr. Hong-Ren Huang is a senior scientist in Intellia Therapeutics. He has a broad spectrum of knowledge in the high through put drug discovery, including cellular and biochemical assay development. His expertise is in epigenetic drug targets. He has successfully demonstrated the pre-selected small molecules were on target to the pathway of interest at various cellular conditions. Before he joined Constellation Pharmaceuticals, he was a research fellow in Dr. Tom Maniatis lab at Harvard University. He studied innate immune response in Drosophila and discovered an endosomal protein in the Toll signaling pathway, which induce the innate immune response to fight off the fungal and bacterial infection. He received his M.S. and B.S in the department of Life Sciences from National Taiwan University. Then, he completed the Ph.D. program in the department of Biochemistry and Molecular Biology from University of Texas Southwestern Medical Center.

Beyond the Bench Panelist

Y. Jenny Chen, 陳亞華 博士, 律師

Patent Attorney, Wolf Greenfield

Jenny Chen focuses her practice on U.S. and foreign patent prosecution, freedom-to-operate and invalidity opinion work, due diligence studies, post-grant challenges, and counseling clients in the areas of biological, medical, and pharmaceutical sciences. She is currently an Associate at Wolf Greenfield. Jenny has worked on projects related to diagnosis and treatment of various diseases and disorders, vaccine technologies, drug discovery, antibiotic biosynthesis, biosimilars, medical implants, gene- and cell-based therapies, pharmaceutical formulations, and herb extracts. She was named to the 2014 list of Massachusetts Rising Stars by Super Lawyers, an honor reserved for those lawyers who exhibit excellence in practice.

Jenny received her J.D. from Northeastern University School of Law. She is a member of the State Bar of Massachusetts and is registered to practice before the U.S. Patent and Trademark Office. She is a member of the American Intellectual Property Law Association and Boston Patent Law Association. Jenny received her Ph.D. from Baylor College of Medicine and her B.S. from Fudan University.

Beyond the Bench Panelist

Shen Luan, 欒牲 博士

Director of Regulated Products, Thermo Fisher Scientific

Shen Luan is currently Director of Regulated Products at Thermo Fisher Scientific. Shen co-founded Berg Diagnostics (now part of Berg) in 2010. He served as the founding President and CTO and was named as COO in 2011. He led efforts on molecular profiling, pan-omics, CLIA-certified clinical diagnostics laboratory services, and overall technology management related to business operations. Prior to Berg, Shen was Technical Product Manager of Waters Corporation for 5 years responsible for LC/MS system solutions and laboratory informatics and participated in the ISO13485 compliance program. Shen started his career with Thermo Fisher Scientific (originally Thermo Jarrell Ash Corporation) for 9 years and has held various management positions including Engineering Manager, Research Manager, and Product Manager. Shen received a Ph.D. in Analytical Chemistry from Professor Robert Samuel Houk of Iowa State University and a B.S. in Chemistry from Peking University. He holds a Lean - Six Sigma Black Belt certificate. He is a member of BayHelix, an invitation-only organization of leaders of Chinese heritage in the global life sciences and healthcare community.

Beyond the Bench Panelist

Shaoyu Chang, 張劭聿 醫師

Senior Research Analyst, Life Science Nation

Shaoyu is Senior Research Analyst at Life Science Nation, a Boston-based research and consulting firm that connects products, services and capital in the life sciences arena. Shaoyu specializes in investor outreach, market research, and technical review and writing in support of biotech and medtech entrepreneurs with their fundraising campaigns. He also contributes to LSN's Next Phase Newsletter. Prior to LSN, Shaoyu served as Research Scholar at Sanford School of Public Policy of Duke University and worked closely with Prof. Anthony So in Program on Global Health and Technology Access. His research focused on the global R&D of medical innovations against antimicrobial resistant microorganisms. Shaoyu received a Master of Public Health from Harvard Chan School of Public Health and an M.D. from National Taiwan University. Shaoyu is US Regulatory Affairs Certified with extensive experiences in clinical trials and pharmaceutical development.

Chance Lai, 賴青志 企管碩士

Associate Director, BioProduction Division, Life Technologies

As a biotech business professional, Chance Lai has 10+ years of experience in technology transfer, venture capital, and product management. He is now managing the GIBCO cell culture product/service portfolio for Thermo Fisher Scientific. Chance has Bachelor's and Master's degrees in life sciences from National Tsing Hua University, and an MBA from Georgetown University. When he's not running businesses, you can find him experimenting new food in kitchen or playing with his daughter.

Beyond the Bench Panelist

Yu-Feng Wei, 魏宇峰 博士

Co-Founder, Vizuro

Yu-Feng is the co-founder of Vizuro LLC, providing predictive analytics solutions based on cutting-edge machine learning technologies. He has over 16 years of experience in advanced analytics and predictive modeling with clients ranging from manufacturing, government, and service industries. In the past 7 years, he has focused on serving the healthcare sector, working with major hospitals and pharmaceutical companies in the US to improve their operational efficiencies and quality of care. Yu-Feng has a Ph.D. in mechanical engineering from MIT, a M.S. in industrial engineering from University of Wisconsin-Madison, and B.S. in mechanical engineering from National Taiwan University.

Biotech in Taiwan

Charley Lu, 呂全偉 經理
Senior Business Development Manager
Taiwan Liposome Company (TLC) 台灣微脂體

Mr. Lu is currently the Senior Business Development Manager at Taiwan Liposome Company (TLC), a publicly listed specialty biopharmaceutical company focusing on lipid-based nanoparticles drug delivery technologies. He leads business development and alliance management activities. Previously, Mr. Lu served as the Principal of Strategic Initiatives at Carantech, Inc. Carantech was a spinout from the University of California, San Francisco developing neuroprotective therapies for Multiple Sclerosis patients. Mr. Lu shared fundraising and operating responsibilities with the founding team.

Mr. Lu is a member of Mayor's Biotech Advisory Council in San Francisco. He earned his MBA from the Johnson School at Cornell University focusing on venture capital and private equity and his MS from Northwestern University studying bioinformatics and immunology. Prior to Cornell and Northwestern, Mr. Lu independently led autoimmune disease research at the University of California, San Francisco Medical Center while earning his BA in Integrative Biology with emphasis in Neurobiology and Endocrinology from the University of California, Berkeley. He was the award winner at Cornell's Big Idea Business Plan competition and the Jonas Weil Entrepreneurship Fellow.

Mr. Lu is an active and recognized leader in the community. He has received multiple commendations for his public outreach, fundraising, and volunteering efforts at the Greater Bay Area Make-A-Wish Foundation granting wishes to children with life-threatening illnesses.

tlc 台灣微脂體

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 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. Its headquarters is located in Taipei and subsidiaries in the US, the Netherlands, China, Australia, and Japan.

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Biotech in Taiwan

Chia-Chin Sheu, 許嘉欽 總經理
President
Simpson Biotech Co., Ltd. 善笙生物科技股份有限公司

Mr. Chia-Chin Sheu is currently President of Simpson Biotech Co. in Taoyuan, Taiwan, and a member of the board of TahChwen Food Co.(大醇食品-工研醋關係企業) and Kong Yen Food Co.(工研醋). His research and business interests include medicinal fungus fermentation and their downstream processing, early stage drug discovery from fermented and natural products, quality control of fermentation products, fermented natural ingredient for dietary supplements, industrial enzymes and product development, recombinant proteins, enzymes and their purification processes, in vitro diagnostic devices, and microbial rapid test kits. Mr. Sheu holds master's degrees in packaging and food technology from Michigan State University and Iowa State University, respectively.

善笙生物科技股份有限公司
SIMPSON BIOTECH CO.,LTD.

Simpson Biotech Co., Ltd. was established in 1998 and is a privately held company located in Taipei, Taiwan focused on the development and commercialization of fermentation of bioactive natural ingredients. These include some fermented medicinal fungi as dietary supplements and the early stage drug discovery for the active compounds isolated. We also developed a patented platform technology to express and purify recombinant proteins including biologics and industrial enzymes. The company has won numerous awards including the "National Innovation Award" from the Institute for Biotechnology and Medicine in Taiwan and holds 37 issued patents with another 21 pending

Learn more athttp://www.simpsonbiotech.com/

Biotech in Taiwan

Ko-Chung Lin, 林國鐘 博士
Founder and CEO
PharmaEssentia Corporation 藥華醫藥

- Received his Ph.D. from the University of Missouri, postdoctoral research at the University of Michigan
- More than 20 years of successful experience in drug discovery and development
- Worked at Monsanto-Searle (US) on HIV protease inhibitor project resulting in an AIDS drug on the market; and at Biogen (US), where Lin led the team to discover their first drug candidate that was later licensed to Merck. He's also the lead inventor Biogen's PEG-IFN b (Plegridy)
- Inventor of 50 patents

PharmaEssentia Corporation aims to deliver efficacious, safe and cost-effective therapeutic products for the treatment of human diseases while aiming to bring long lasting value to our stakeholders. At PharmaEssentia, our mission is a never-ceasing commitment to the improvement of health and quality of life. PharmaEssentia was founded in 2003 by a group of Taiwanese-American executives and high-ranking scientists from leading biotechnology and pharmaceutical companies in the US, with a goal to develop treatments for myeloproliferative neoplasms, hepatitis and oncology.

Learn more athttp://www.pharmaessentia.com

Biotech in Taiwan

Nan-Horng (Stan) Lin, 林南宏 博士
Senior VP
CHO Pharma

- Executive Director, Development Center of Biotechnology, Taiwan
- Senior Vice President/CTO, Crwon Bioscience, USA
- CSO, Shanghai Medicilon, USA/China
- Research Fellow/Volweiler Society, Abbott Laboratories Inc, USA
- Senior Group Leader, Abbott Laboratories Inc, USA
- Senior Scientist, Bayer USA
- Postdoc, University of California, Irvine.
- Ph.D. from Indana University, Bloomington.
- More than 210 publications: research article/review/presentation/patent

CHO Pharma, located at Nangang Software Park in Taiwan, is a biopharmaceutical company mainly focused on the research, development and commercialization of innovative products based on its proprietary glycan engineering technologies that exclusively licensed from the strategic partner, Academia Sinica in Taiwan. We are committed to glycan scientific innovation to deliver best-in-class targeted and differentiated products. Our goal is to bring advanced, high-quality and affordable medicines、diagnostics and therapies to patients around the world.

Engineered antibodies are antibody based therapeutics, which are gaining increasing attention from various sizes of pharmaceutical company. By 2017, the overall market of monocolonal antibody is estimated to be USD 252 billion which has attracted enthusiasm in delivering the next generation of antibody based therapeutics. CHO Pharma possesses several core technologies including glycoproteins, glycan-based vaccine, glycan array and glyco-probes with more than 30 patents protection. We strive to address unmet medical needs and to deliver medical solutions valuable to patients, physicians and payers. The company has become one of leaders in glycan engineering technologies through an innovative product portfolio, and by

working in partnership with the research as well as medical communities and other stakeholders. CHO Pharma employs more than 30 people in Taiwan.

CHO Pharma is a young, rapidly growing, and full-of-potential biopharmaceutical company. We are actively recruiting passionate talents across the globe to join us and build future success together. If you are looking for a world-class organization that relentlessly pursues excellence, we are definitely your best choice.

Special Featured Speaker

Winston Town, 湯竣鈞 博士

Vice President, Diamond BioFund Inc.,
Chairman and President, Fountain Biopharma Inc.

Winston joined Microbio Group in March 2013 and currently serves as Vice President at Diamond BioFund Inc., a specialized health care venture capital firm with US$300 million under management and Chairman and President of Fountain Biopharma Inc. Winston was formerly Chief Executive Officer of Panacor Bioscience and spearheaded a successful new drug development in the nephrology field in collaboration with pharmaceutical companies in the United States and Japan. Prior to that, Winston served as Senior Vice President with GloboAsia, a drug development consultation company. He has consulted and worked on numerous drug development projects involving multiple collaborative parties worldwide covering Africa, Asia as well as N. America. Winston has in-depth work experience with pharmaceutical companies in Asia and the United States in designing and implementing development and commercialization strategies. He is also well connected in the financial communities around the world.

Diamond BioFund Inc.
Diamond Capital Inc.

Diamond was established in 2013 with USD 300 million under management & the largest evergreen health care fund based in Taiwan. Management team has extensive life science management experiences and product development expertise in the biotech sector.

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Fountain was founded in December 2010 and headquartered in the Nankang Software Park, Taipei, Taiwan. Fountain Biopharma focused on innovative development of humanized & fully human monoclonal antibodies for the treatment of allergic disorders and cancers. The company has instituted needed core technologies for antibody drug discovery and development including fully human antibody phage display, screening bioanalytics, and antibody-guided delivery through collaboration with several leading academic institutes.

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L-01. Identifying Essential AML Maintenance Genes in Ras Pathway using shRNA Screen

Chi-Chao Chen[1]

[1]MSKCC

Acute myeloid leukemia (AML) has the worst 5-year-survival rate of all leukemias. Despite therapeutic improvement in recent decades, AML remains a clinically challenging disease. Ras mutations are frequently observed in AML and are key drivers of proliferation and tumor survival. Since Ras protein is relatively difficult to target, we set out to identify tumor maintenance genes in this broad Ras pathway. Using an Nras overexpressing mouse model, we performed a focused shRNA library screen to identify Ras related targets that are most required for leukemia maintenance.

We chose 75 Ras related genes for use in this library. We designed mRNA-complimentary 22 mer oligonucleotides using the DSIR algorithm. After insertion in the mir30 cassette, 65 shRNAs designed for each gene were tested by a sensor assay (to evaluate the effectiveness of shRNAs) developed in our lab to pick the top 10 scoring shRNAs. Using an Ã¢â‚¬Å“on-chipÃ¢â‚¬Â synthesis strategy, these 750 hairpins were cloned in a pooled format into a doxycycline-inducible, retrovirus compatible vector. The screening was done in three independent cell lines with the same genotype (NrasG12D/MLL-AF9). Raf1 (c-Raf) is the most top-ranking gene with multiple hairpins scoring in all 3 cell lines. We validated the results by using individual Raf1 hairpins. Overall, our results indicated the importance of MAPK pathway in Ras-mutated AMLs and provided a rationale of using MAPK pathway inhibitors in suppressing Ras-mutated tumors.

L-02. Regulation by Modulating Transcription Factor Unbinding Kinetics in Live Bacteria

Tai-Yen Chen[1], Ace George Santiago[1], Won Jung[1], Łukasz Krzemiński[1], Feng Yang[1], Danya J. Martell[1]

[1]Department of Chemistry and Chemical Biology, Cornell University

Binding and unbinding of transcription regulators at operator sites constitute a primary mechanism for gene regulation. While many cellular factors are known to regulate their binding, little is known on how cells can modulate their unbinding for regulation. Using nanometer-precision single-molecule tracking, we study the unbinding kinetics from DNA of two metal-sensing transcription regulators in living Escherichia coli cells. We find that they show unusual concentration-dependent unbinding kinetics from chromosomal recognition sites in both their apo- and holo-forms. Unexpectedly, their unbinding kinetics further vary with the extent of chromosome condensation, and more surprisingly, vary in opposite ways for their apo-repressor vs. holo-activator forms. These findings suggest novel and likely broadly relevant mechanisms for facile switching between transcription activation and deactivation in vivo and in coordinating transcription regulation of resistance genes with the cell cycle. Accepted by Nature communication 2015.

L-03. Confinement Affects Cell Migration via Modulating Protein Kinase A

Wei-Chien Hung[1], Jessica Yang[2], Chris Yankaskas[1], Joy T. Yang[3], Konstantinos Konstantopoulos[1], Jin Zhang[2]

[1]Department of Chemical and Biomolecular Engineering

[2]Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine
[3]Department of Cell Biology, Johns Hopkins University School of Medicine

Cells modulates signaling network to adapt physical environments, thus further modifying wide-array of cellular functions such as cell migration, proliferation, and survival. cAMP-dependent protein, protein Kinase A (PKA) plays a critical role of triggering signaling cascade and is responsible for phosphorylating numerous protein substrates such as ion channels, GTPases, and transcription factors. Moreover, the substrate specificity of PKA is controlled by its subcellular compartmentalization and is mediated by interactions of its regulatory subunits with A-kinase anchoring proteins (AKAPs). Therefore, we employed well-developed Fluorescence resonance energy transfer (FRET)-based PKA activity reporters in conjunction with micro-fabrication technology to explore the real-time modulation of PKA activity in response to physical constraint.

To verify if PKA activity is different in unconfined and confined cells, we utilized a FRET-based PKA activity biosensor (AKAR4) to probe the basal PKA activity levels in unconfined and confined cells. Because we are interested in the population of PKA near the integrins, we specifically used a plasma membrane-targeted version of AKAR4: AKAR4-Kras. CHO-ÃŽÂ±4WT cells were first transfected with AKAR4-Kras and then seeded onto the microchannel devices. To obtain confined cells, a chemoattractant was applied to induce cell migration through the 3ÃŽÂ¼m channels. The basal PKA activity levels were then quantified by measuring the change in the FRET ratio after a 30-minute treatment with a PKA inhibitor, H89. Unconfined cells treated with H89 resulted in significantly larger decrease in PKA activity compared to confined cells. Moreover, time-lapse images show an overall reduction of PKA activity when CHO-ÃŽÂ±4WT cells moved from unconfined to confined spaces. These results strongly suggest that cells are able to modulate PKA activity in response to physical environment.

Investigating signaling modulation in response to physical constraint leads to answer various physiological questions, thus providing the clues for potential therapies to various diseases. Here, we present that the PKA activity is reduced when cells are under physical environment. To further understand how the signaling modulation is triggered, future work will be focused on determining the primary mechanosensor that permits the local and global change of PKA activity.

L-04. PPARα and glucocorticoid receptor synergize to promote erythroid progenitor self-renewal

Sherry Lee[1*], Xiaofei Gao[1*], M. Inmaculada Barrasa[1], Hu Li[2], Russell R. Elmes[1], Luanne Peters[3] and Harvey F. Lodish[1,4]

[1]Whitehead Institute for Biomedical Research

[2]Center for Individualized Medicine, Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic

[3]The Jackson Laboratory

[4]Departments of Biology and Biological Engineering, Massachusetts Institute of Technology

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 the early erythroid progenitor, the burst-forming unit erythroid (BFU-E), and increase the production of terminally differentiated erythroid cells. Here we demonstrate that activation of the peroxisome proliferator-activated receptor alpha (PPARα) by PPARα agonists, GW7647 and fenofibrate, synergizes with 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. We also showed that PPARα± alleviates anemia in a mouse model of chronic 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 early erythroid progenitor cells suggests that the clinically tested PPARα± agonists we used may improve the efficacy of corticosteroids in treating Epo resistant anemias.

L-05. Genome-wide Lariat profiling reveals the Structure and Function of Branched Intermediates of Splicing

Chien-Ling Lin[1], Allison Taggart[1], Barsha Shrestha[1], Wiiliam Fairbrother[1]

[1]Brown University

Pre-mRNA contains short sequences of protein coding exons interrupted by long non-coding introns. The process called splicing connects adjacent exons releasing the intron as a branched RNA lariat. 5′ splice site (5′ss), 3′ splice site (3′ss), together with the Ã¢â‚¬Å“branchpointÃ¢â‚¬Â sequence in the intron, determine the splicing outcome. Malfunction of branchpoint causes splicing defects and are related to human diseases. However, almost all we know about splicing in vivo comes from exon junctions in mRNA; very little is known about the branchpoint. Hundreds of thousands of splice site choices have been mapped from mRNA/genomic alignments, whereas the branchpoint information is lost with the excised intron. Here, by detecting fragmental reversed reads specifically across the lariat branch sites from deep sequencing data, we report our genomic scale detection of the transcript branchpoints in three different species. We present more than 102,479 lariats mapped to human introns and an in depth analysis of branchpoint selection and alternative splicing. This data demonstrates a central role for branchpoint location in alternative splicing.

Our analysis redefines the branchpoint. Traditionally, it is believed that branchpoints are located 18-36 nt upstream to the 3′ss. Our data, however, mapped certain branchpoints hundreds of nucleotides upstream to the 3'ss. These distal branchpoints are conserved and functional in that the disruption of those reduced the splicing efficiency. Remarkably, some 3′ss are used as both branchpoint and splice site, dysregulation of which may be associated with carcinogenesis of leukemia. Within the data, we find several novel alternate modes of spliceosomal U2snRNA and pre-mRNA interactions at the branchpoint sequence, underlying the promiscuous human branchpoint motifs.

Finally, while most lariats are rare and transient, certain species appear to be stabilized in the cell. We consider the possible non-splicing roles these (and other) lariats could perform in the cell, such as expression vehicle for snoRNAs and RNA-binding protein sponges, for the first time at a genomic scale. Utilizing both computational and experimental analysis, our results provide insights of the first step of splicing which directs the splice site choices in the normal and the disease background.

L-06. INHIBITION OF LIVER TUMORIGENESIS BY BLOCKING CCL2-CCR2 AXIS, A TARGET OF MIR-122

Kun-Yu Teng[14], Jianfeng Han[24], Michael A. Caligiuri[24], Samson T. Jacob[34], Jianhua Yu[24], Kalpana Ghoshal[14]

[1]Department of Pathology, College of Medicine

[2]Department of Internal Medicine, College of Medicine

[3]Department of Molecular and Cellular Biochemistry, College of Medicine

[4]The OSU Comprehensive Cancer Center

Hepatocellular carcinoma (HCC) is the most common liver cancer and the third leading cause of cancer related death worldwide due to lack of effective therapy. Loss of miR-122, the most abundant liver-specific miRNA, is associated with poor prognosis in HCC patients. Development of chronic inflammation and spontaneous HCC in miR-122 knockout (KO) mice established it as a tumor suppressor. Previously, our lab reported that recruitment of CD11b+/ GR-1+ monocytes due to the activation of CCL2-CCR2 axis drives inflammation in miR-122 KO livers by producing IL-6 and TNFÃŽÂ±. Since HCC almost always arises in the setting of chronic inflammation, we hypothesize that blocking CCL2-CCR2 axis might be an effective therapy in HCC patients. To this end, we treated miR-122 KO mice with CCR2 inhibitor or CCL2 neutralizing antibody (nAb) to block CCL2-CCR2 signaling. We found liver injury and inflammation were significantly reduced in mice after blocking CCR2 - CCL2 axis. The reduced inflammation correlated with decrease in serum CCL2 and hepatic TNF-ÃŽÂ± and IL-6 levels. In addition, reduced tumor incidence, burden, and proliferation were observed in tumor bearing KO mice treated with CCL2 nAb. Interestingly, population of immune-suppressive CD11b+/GR-1+ MDSCs (myeloid derive suppressor cells) was significantly reduced after CCL2 nAb therapy. These results suggest potential therapeutic application of CCL2 nAb or CCR2 inhibitor in HCC patients. Currently, we are studying the mechanism by which CCL2 nAb affect proliferation, migration or apoptosis of immune (MDSCs) and tumor cells. We expect CCL2 is an essential chemokine to induce liver inflammation and recruits MDSCs to initiate hepatocarcinogenesis. Blocking CCL2-CCR2 axis will be an effective therapeutic approach to suppress hepatocarcinogenesis.

L-07. SIRT3 Crosstalks with FOXO3 Acetylation-Phosphorylation-Ubiquitination to Mediate Mitochondrial Homeostasis and Hypoxic Adaptation

Anne H.-H. Tseng[1234], Ling D. Wang[124]

[1]Taiwan International Graduate Program, Molecular Medicine Program

[2]Institute of Biomedical Sciences

[3]Institute of Biochemistry and Molecular Biology

[4]Institute of Medical Sciences

Progressive accumulation of defective mitochondria is a common feature of aged cells. SIRT3 is a NAD+-dependent protein deacetylase that regulates mitochondrial integrity and metabolism in response to caloric restriction and stress. FOXO3 is a direct target of SIRT3 and functions as a forkhead transcription factor to govern diverse cellular responses to stress. Results showed that SIRT3 is induced by hydrogen peroxide and hypoxia to deacetylate FOXO3 at K271 and K290. The SIRT3-mediated deacetylation of FOXO3 further reduced FOXO3 phosphorylation, ubiquitination and degradation. This reaction leads to the stabilization of FOXO3 and upregulation of a set of FOXO3-dependent genes, essential for mitochondrial homeostasis (mitochondrial biogenesis, fission/fusion and mitophagy) and mitochondrial ROS detoxification system. Consequently, the SIRT3-mediated deacetylation of FOXO3 contributes to the increments in mitochondrial mass, ATP production, clearance of defective mitochondria and ROS detoxification. Thus, mitochondrial quantity and quality are ensured to maintain mitochondrial reserve capacity in response to oxidative stress and hypoxic condition. Maladaptation to environmental stresses is a major risk factor underlying aging and aging-related diseases. Our finding showed that SIRT3-mediated deacetylation of FOXO boosts mitochondrial homeostasis and increases mitochondrial hormesis under oxidative stress and hypoxic condition. Hence, it provides a possible direction for aging-delaying therapies and disease intervention.

L-o8. Randomized CRISPR-Cas transcriptional perturbation screening identifies novel genes that protect against alpha-synuclein toxicity in yeast and human cells

Ying-Chou Chen[12], Fahim Farzadfard [1234], Timothy K. Lu[1234]

[1]Synthetic Biology Group, MIT Synthetic Biology Center

[2]Research Laboratory of Electronics

[3]MIT Microbiology Program

[4]Department of Biological Engineering and Electrical Engineering & Computer Science

The genome-wide perturbation of transcriptional networks with CRISPR-Cas technology has relied on systematic and targeted single-gene modulation. Here, we developed a complementary and distinct high-throughput screening platform based on randomized CRISPR-Cas transcription factors (crisprTFs) that introduce global and bidirectional perturbations within transcriptional networks. We applied this technology to a yeast model of Parkinson's disease (PD) and identified guide RNAs (gRNAs) that modulate transcriptional networks and protect cells from alpha-synuclein (αSyn) toxicity. Global gene expression profiling for a strong protective gRNA revealed a substantial number of differentially expressed genes that could rescue yeast from αSyn toxicity when overexpressed. The majority of these genes have not been previously identified in αSyn screens and belong to families involved a diverse set of processes, including protein quality control, ER/Golgi trafficking, lipid metabolism, mitochondrial function, and stress response. Human orthologs of highly ranked hits from the yeast model were further verified in a human neuronal PD model. For example, we demonstrate that overexpressing human genes PARK7, a redox-dependent chaperone, ALS2, a guanine nucleotide exchange factor (GEF) involved in endocytic regulation, DNAJB1, a chaperone known to suppress polyglutamine toxicity, and GGA1, a Golgi-localized protein that facilitates cargo sorting, protect neurons from αSyn-induced cell death. The discovery of novel genes that rescue yeast and human cells from αSyn-induced toxicity suggests that randomized crisprTF-based screening is an effective tool for the high-throughput and unbiased perturbation of transcriptional networks that underlie complex biological phenotypes.

L-09. Modeling Parkinson's Disease Using Human Induced Pluripotent Stem Cells

Melody Cheng[12], Chris Woodard[2], Brian Campos[2], Matthew Zimmer[2], Aiqun Li[2], Sheng-Han Kuo[1]

[1]Department of Neurology, Columbia University Medical Center

[2]The New York Stem Cell Foundation Research Institute

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1 in 100 people over age 60 in the United States. Approximately 10% of PD cases have been linked to known genetic contributors, including mutations in glucocerebrosidase (GBA). PD pathology is characterized by α-synuclein aggregation in Lewy bodies in midbrain dopaminergic (mDA) neurons and subsequent neuronal death. PD research is challenging because of the inaccessibility of affected human mDA neurons and a scarcity of animal models that mimic the key disease features.

In this study, we developed a platform to reprogram adult human skin fibroblasts into induced pluripotent stem cells (iPSCs) from a set of monozygotic twins harboring the heterozygous GBA mutation (GBA N370S), but clinically discordant for PD. We further differentiated these iPSCs into genuine mDA neurons in defined medium and generated enriched mDA populations by fluorescence-activated cell sorting. Using this revolutionary iPSC technology, we successfully increased the purity of iPSC-derived mDA neurons to approximately 80%.

We found that the mDA neurons from both twins had only ~50% GBA enzymatic activity, ~3-fold elevated α-synuclein expression, and a reduced capacity to synthesize and release dopamine. In addition, levels of lysosomal markers LAMP1 and LAMP2A appeared to be up-regulated in PD-GBA samples, suggesting general lysosomal dysfunction. Furthermore, RNA-sequencing analysis showed that the abnormal expression of these lysosomal markers occurred at the transcriptional level.

In summary, we provide a new platform to study PD pathogenesis in the most native form when primary neuronal cells from patients are unavailable for investigation. It can not only reveal disease phenotypes quickly and robustly, but also enable the automated high-throughput drug screening efficiently. Overall, our iPSC platform can be easily extended to other human diseases caused by genetic mutations.

L-10. A Next-Generation Sequencing Aligner for A Graph Genome Reference

Wan-Ping Lee[1], Kaushik Ghose[1], Ben Murray[2], Deniz Kural[1]

[1]Seven Bridges Genomics Inc., R&D

[2]Seven Bridges Genomics, R&D, London, United Kingdom

The publication of the first, fairly complete, sequence of the human genome by the International Human Genome Sequencing Consortium in 2001, and the development of high throughput, short read sequencing (HTS) has opened the gate for cheap whole genome analysis and a whole host of research and clinical applications are now within reach.

Projects, such as the thousand genomes project, have painstakingly analyzed the genomes of additional individuals, from different populations, allowing us to understand how genomes vary between humans. A key insight from these projects, has been that most of the variants in an individual are shared by the population. This has led to the hypothesis that, by incorporating known variants into the current, linear, reference we can improve alignment of HTS reads and thereby improve variant calling.

We test this hypothesis by developing a graph based whole-genome read mapper. A directed acyclic graph (DAG) is constructed by combining the linear reference genome with a list of variants. Our mapper works in two phases. First, we identify regions where a read is likely to map in the DAG. Secondly, we align the read against the DAG, using a graph-aware extension of a string matching algorithm. We achieve 550 and 6,000 reads per second in the first and second steps. The graph mapper generates standard BAM files ensuring compatibility with the majority of other available bioinformatics tools.

We simulated 18,827 insertions with lengths ranging from 2 to 96 bp. We aligned simulated reads against a DAG constructed with human genome and these variants. We passed the graph aligned BAM files to GATK, Samtools and Freebayes to call variants. The overall insertion detection accuracy improved by 15% (from 78% to 93%) when compared to alignments using a linear mapper (BWA).

Our experiments show that there is a considerable gain in variant calling sensitivity when known variants are incorporated into the alignment step. We demonstrate a working and practical implementation of this idea in our graph aligner.

L-11. Design Complex Hydrogel Microparticles for Scalable 3D cell Culture, Co-Culture and Microtissue Production

Yen-Chun Lu[1], Wei Song[1], Duo An[1], Robert Schwartz[2], Mingming Wu[1], Minglin Ma[1]

[1]Cornell University

[2]Weill Medical College of Cornell University

Cell encapsulation in hydrogel microparticles has been investigated for decades in various bioengineering applications including tissue engineering, and cell therapy. However, most of the time, the cells are encapsulated randomly in whatever material that forms the microparticles, most commonly alginate. The lack of control over the spatial organizations of the cells and the extracellular environment within the microparticles significantly limits for advanced applications. Here we report a novel, multi-fluidic cell microencapsulation approach where 1 or more types of cells are encapsulated in pre-assigned compartments in the microparticles with controlled extracellular matrix. These microparticles can be produced with controllable and nearly monondispersed sizes at rates of over 10,000 microparticles per min and therefore provide a promising platform for high throughput applications. We demonstrated the utilization of these extracellular matrix-supported microparticles for 3D culturing of cells that typically require specific microenvironment to survive such as human umbilical vein endothelial cells (HUVECs) and small intestine stem cells. By taking advantage of the confinement effect, we also showed robust and scalable productions of size-controlled multicellular microtissues. Lastly, to demonstrate the broad applications of these microparticles, we performed proof-of-concept studies on three different co-culture systems including cell segregations under 3D confined space, the supporting role of stromal cells in hepatocyte functions and the paracrine cell signaling in aggregation of endothelial cells, all in a high throughput manner.

L-12. Platelet count control in immune thrombocytopenic purpura patient: optimum romiplostim dose profile

Chia-Hung Tsai[1], James Bussel[2], Allison Imahiyerobo[2], Stanley I. Sandler[1], Babatunde A. Ogunnaike[1]

[1]University of Delaware

[2]Weill Cornell Medical College

Patients with immune thrombocytopenic purpura (ITP), a disease characterized by abnormally low platelet count, are susceptible to excessive bleeding as a direct consequence. While the problem of low platelet count can be addressed fundamentally either by slowing down the rate of platelet destruction or by increasing platelet production, or both, one of the more effective means of treating ITP patients is to increase platelet production with romiplostim, a relatively new drug that has recently been approved for treating patients who have not responded to other treatments. However, current romiplostim treatment strategies tend to result in undesirable responses where platelet counts oscillate between dangerously low values followed extremely high peaks, as a direct consequence of the complex nonlinear dynamics associated with platelet count regulation. The objective of this study is to employ a model-based approach to determine the optimum dose profile of romiplostim required to maintain a steady platelet count of 70Ãƒâ€"109/L for a specific ITP patient.

Using clinical platelet count data obtained from the patient in response to a series of subcutaneously applied doses of romiplostim, a standard pharmacokinetics and pharmacodynamics (PKPD) model was modified, validated, and analyzed first to obtain insight into the patient's physiological characteristics. The customized model was then subsequently used to investigate, via simulation, the performance of three control strategies (Ã¢â‚¬Å"fixed doseÃ¢â‚¬Â open-loop control, Ã¢â‚¬Å"variable doseÃ¢â‚¬Â discrete PI feedback control, and Ã¢â‚¬Å"variable doseÃ¢â‚¬Â open-loop optimal control) implemented for both weekly and biweekly treatment regimens. Our results indicate that with both treatment frequencies, the Ã¢â‚¬Å"fixed doseÃ¢â‚¬Â open-loop control strategy resulted in unacceptable sustained oscillating platelet counts while the PI feedback control and optimal open-loop control led to stable platelet count profiles after about 50 days but only for weekly injections. Additional details concerning the controller designs and performance under various conditions will be discussed along with other notable observations, for example: that the time span required to achieve a stable platelet count is very sensitive to the values of initial doses administered at the very beginning of the treatment; and that, for the specific patient in question, regardless of control strategy, it is nearly impossible to maintain stable, non-oscillatory platelet count with biweekly injections.

L-13. Polyspecific pyrrolysyl-tRNA synthetases from directed evolution

Yane-Shih Wang[1], Dieter Söll[12]

[1]Department of Molecular Biophysics and Biochemistry, Yale University

[2]Department of Chemistry, Yale University

Pyrrolysyl-tRNA synthetase (PylRS) and its cognate tRNA_Pyl have emerged as ideal translation components for genetic code innovation.Variants of the enzyme facilitate the incorporation >150 noncanonical amino acids (ncAAs) into proteins. PylRS variants were previously selected to acylate Ne-acetyl-Lys (AcK) onto tRNA_Pyl. Here, we examine an Ne-acetyl-lysyl-tRNA synthetase (AcKRS), which is polyspecific (i.e., active with a broad range of ncAAs) and 30-fold more efficient with Phe derivatives than it is with AcK. Structural and biochemical data reveal the molecular basis of polyspecificity in AcKRS and in a PylRS variant [iodo-phenylalanyl-tRNA synthetase (IFRS)] that displays both enhanced activity and substrate promiscuity over a chemical library of 313 ncAAs. IFRS, a product of directed evolution, has distinct binding modes for different ncAAs. These data indicate that in vivo selections do not produce optimally specific tRNA synthetases and suggest that translation fidelity will become an increasingly dominant factor in expanding the genetic code far beyond 20 amino acids.

Key words: aminoacyl-tRNA synthetase | genetic code | genetic selection | posttranslational modification | synthetic biology

L-14. Studies on the Role of Interleukin-6 in Prostate Cancer Development

Shu-Han Yu[1], Qizhi Zheng[1], Ajay Vaghasia[2], Charles G. Drake[23], Angelo M. De Marzo[123], Karen S. Sfanos[12]

[1]Department of Pathology

[2]Sidney Kimmel Comprehensive Cancer Center

[3]Department of Urology, James Buchanan Brady Urological Institute

Correlative human studies suggest that the pleiotropic cytokine interleukin-6 (IL-6) contributes to the development and/or progression of prostate cancer. However, the source of IL-6 production in the prostate microenvironment in patients has yet to be determined. The cellular origin of IL-6 in primary and metastatic prostate cancer was examined in formalin-fixed, paraffin-embedded (FFPE) tissues using a highly sensitive and specific chromogenic in situ hybridization (CISH) assay that underwent extensive analytical validation.

CISH analysis indicated that both primary and metastatic prostate adenocarcinoma cells do not express IL-6 mRNA. IL-6 expression was highly heterogeneous across specimens and was nearly exclusively restricted to the prostate stromal compartment: including endothelial cells and macrophages among other cell types. The number of IL-6-expressing cells correlated positively with the presence of acute inflammation. In metastatic disease, tumor cells were negative in all lesions examined and IL-6 expression was restricted to endothelial cells within the vasculature of bone metastases. Finally, IL-6 was not detected in any cells in soft tissue metastases. These data suggest that, in prostate cancer patients, paracrine rather than autocrine IL-6 production is likely associated with any role for the cytokine in disease progression.

Moreover, in this study we also reported a series of allograft studies that provide initial evidence that IL-6 may be involved in early prostate tumor development, but does not play a similar role in other cancer types. Two mouse cancer cell lines were used in allograft studies with C57BL/6J wildtype and IL-6 knockout (IL6-/-) mice: the prostate cancer cell line TRAMP-C2 and a colon cancer line MC38. In this study, there was a significant reduction in TRAMP-C2 allograft take rate and growth rate in IL6-/- mice versus wildtype mice. This trend was not observed for the MC38 cell line, indicating tumor-type specificity to the phenomenon. CISH analysis of the TRAMP-C2 allograft tumors indicated that the tumor cells were not producing IL-6 mRNA. Rather, IL-6 ELISA analyses on the mouse serum showed a significant increase in the circulating levels of IL-6 in mice with TRAMP-C2 tumors and the levels of IL-6 correlated with tumor size.

Our results are consistent with previous studies in prostate cancer patients that demonstrate that high circulating levels of IL-6 tend to associate with a more aggressive clinical course of the disease. Additionally, our studies provide evidence that IL-6 may be required for early prostate tumor development. The results of our IL-6 -/- animal studies indicate that elevated systemic IL-6 levels may play a causal role in tumor initiation and progression, and are not simply caused by or indicative of tumor burden.

P-01. MECHANISM OF DNA REPLICATION THROUGH CHROMATIN

Han-Wen Chang[1], Manjula Pandey[2], Olga I. Kulaeva[1], Smita S. Patel[2], Vasily M. Studitsky[1]

[1]Fox Chase Cancer Center

[2]Department of Biochemistry-RWJMS Rutgers

Accurate maintenance of chromatin structure and associated epigenetic and regulatory histone marks during DNA replication is essential for normal functioning of the daughter cells. However, the mechanisms of maintaining chromatin architecture during replication are unknown. We have studied nucleosome traversal by T7 replisome in vitro. Nucleosome is a strong barrier for replication, with particularly strong pausing of DNA polymerase at the +(27-39) and +(41-63) regions of nucleosomal DNA. After replication ~50% of nucleosomes are translocated to an upstream DNA region. The exonuclease activity of T7 DNA polymerase increases the overall rate of progression of the replisome through a nucleosome, likely by resolving non-productive complexes and by facilitating nucleosome translocation, although it partially compromises the efficiency of nucleosome survival. The presence of nucleosome-free DNA upstream of the replication fork augments progression of DNA polymerase through the nucleosome. Our data suggest a novel mechanism for maintenance of nucleosomes carrying the epigenetic and regulatory codes during replication.

P-02. Molecular dynamics of oncogenic BRaf-induced senescence

Jia-Yun Chen[12], Jose Reyes[1], Peter Sorger[12], Galit Lahav[12]

[1]Department of Systems Biology, Harvard Medical School

[2]Laboratory of Systems Pharmacology, Harvard Medical School

Oncogene-induced senescence (OIS) is a safeguard mechanism that suppresses proliferation upon aberrant oncogene activation in normal cells. Studies have shown that the OIS response is heterogeneous within a population with some cells undergoing senescence while others remain proliferative, eventually proceeding to malignancy. It is therefore crucial to identify the source of heterogeneity and the mechanism by which oncogenic activity is translated by individual cells into distinct cell fates. Here, we use high-content imaging and quantitative time-lapse microscopy to dissect the molecular dynamics of oncogenic BRafV600E-induced senescence in primary human epithelial cells. We show that BRafV600E induction leads to substantial heterogeneity in cell fates with a fraction of cells entering into a prolonged G1-phase arrest while others kept proliferating. Interestingly, in single cells, a preceding burst of proliferation was not observed and is not required for the subsequent long-term arrest. We further show that ERK activity but not BRafV600E expression levels strongly correlate with the growth and divisions of individual cells. We show that a moderate induction of ERK activity accelerates proliferation whereas beyond a certain threshold activity, proliferation is inhibited. Epistasis analysis suggests that the BRafV600E-induced senescence is independent of the canonical p16INK4A-pRB and p53 tumor suppressor pathways. We further identify p38 pathway as an essential component leading to BRafV600E-induced senescence. We are currently examining whether pre-existing differences in ERK activity, cell cycle history, and the temporal dynamics of tumor suppressors determine future cell fates. This knowledge will allow us to understand how cell-to-cell variability at various levels contributes to the establishment of OIS, and explains how OIS is escaped in some cells.

P-03. Protein Aggregation and Pore-formation of a Neurodegenerative Protein

Charles H. Chen[1], Ayesha Khan[2], Joseph J.-T. Huang[3], Martin B. Ulmschneider[12]

[1]Department of Materials Science and Engineering

[2]Institute of NanoBioTechnology

[3]Institute of Chemistry

Neurodegenerative diseases are often associated with protein aggregates, but the molecular mechanism of cytotoxicity remains ambiguous. Transactive response DNA-binding protein (TDP-43) is the major component of neuronal inclusion bodies of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). Amyloid deposits of TDP-43 can accumulate at the intracellular and extracellular spaces in the central nervous system, leading to neurodegenerative disease. Using unbiased atomic-detailed molecular dynamics simulations, we explored the aggregation of C-terminal fragments of TDP-43, which have been suggested to form membrane pores, in the presence of lipid bilayer membranes. The peptide were found to aggregate and form disordered-toroidal pores in a lipid bilayer membrane. The cytotoxicity of TDP-43 can be inferred from the observation that the membrane pores catalyze lipid flip-flop between bilayer leaflets and conduct water and ions at high rates. The disordered nature of the pore suggests that TDP-43 is able to cross the membrane spontaneously, explaining why the peptide is present both in the cytosol and the extracellular matrix in neurodegenerative disease.

P-04. Study design and statistical tests for detecting gene-environment interaction on environmental exposure-defined phenotypes

Chia-Yen Chen[12], Peter Kraft[34], Benjamin M. Neale[12], Jordan W. Smoller[13]

[1]Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital

[2]Analytic and Translational Genetic Unit, Massachusetts General Hospital

[3]Departments of Epidemiology, Harvard School of Public Health

[4]Departments of Biostatistics, Harvard School of Public Health

There is an increasing interest in investigating gene-environment interaction for phenotypes with a prerequisite of certain environmental exposure (e.g. post-traumatic stress disorder, substance dependence). However, the nature of these phenotypes, which exclude the possibility that an individual becomes a case without the required exposure, poses unique challenges in choosing the optimal study design and statistical test for gene-environment interaction analysis. We explored the best strategy to detect gene-environment interaction for environmental exposure-defined phenotypes, where the exposure had four ordered levels (unexposed; and low, medium, high exposure). We compared the statistical power and Type 1 error of 4 different tests that are commonly used in this context: 1) gene main effect test (G); 2) conventional gene-environment interaction test (GE); 3) case-only gene-environment interaction test (CO); 4) joint test of both the gene main effect and the interaction (GGE). We considered factors that may affect the power and Type 1 error of these tests, including: genetic risk allele frequency; environmental exposure frequency; genotype-exposure correlation in the population; effect sizes of exposure, gene and gene-environment interaction; and exposure misclassification. Finally, we compared analyses for non-exposure-defined phenotype and exposure-defined phenotype with both exposed and non-exposed controls, or with exposed controls only. When only main effects were present with no interaction effect, the G test showed higher power than the GGE test. When main and interaction effects were present, the CO test showed higher power than the GE test for non-exposure-defined and exposure-defined phenotypes. We note that the power of GE test reduced dramatically when restricting to exposed controls for exposure-defined phenotypes. For non-exposure-defined phenotype, the GGE test showed higher power than the G test (2% increase in power). However, for exposure-defined phenotype, the G test showed higher power than the GGE test (12% increase in power). Restriction to exposed controls improved the power of the G test and the GGE test for exposure-defined phenotype. Based on these results, we recommend the CO test for investigating gene-environment interaction, with a caveat on inflated type 1 error due to G-E correlation, and restriction to the exposed controls for detecting genetic effects on exposure-defined phenotypes.

P-05. A computational method that identifies repositioned drug candidates by finding inversely correlated cellular functions under disease and drug perturbations

Hsiao-Rong Chen[1], Zhenjun Hu[1], Charles DeLisi[1]

[1]Bioinformatics Program, Boston University

Progressively increasing failure rates, high cost, poor safety, limited efficacy, and a lengthy design and testing process associated with drug development have necessitated improvements in current drug discovery approach. Drug repositioning that develops novel indications for Food and Drug Administration (FDA)-approved drugs is a promisingly faster and cost-efficient drug discovery approach. We devise a computational drug repositioning method to uncover multi-targeted drug candidates that may correct aberrant cellular functions in diseases. The method screens repositioned drug candidates that significantly regulate genes interacting with predicted disease causal genes. The method utilizes both a biological pathway database and a functional linkage network to not only discover drug candidates but also comprehensively identify molecular mechanisms underlying drug responses and diseases. In the preliminary results, the method has successfully identified anti-breast cancer drug candidates with high sensitivity and specificity. In combination with further experimental validations, this method can be a fast and cost-efficient drug discovery pipeline. It also has important potential applications in personalized medicine when gene expression data are available in patients.

P-06.

Li-Chun Cheng[12], Christopher Seidel[1], Sean McKinney[1], Alejandro Sanchez Alvarado[12]

[1]Stowers Institute for Medical Research

[2]Howard Hughes Medical Institute

The p53 family of transcription factors consists of p53, p63 and p73 in vertebrates. The first identified member, p53, is best known as a tumor suppressor and is one of the most well studied genes in the human genome. On the other hand, p63 and p73 get less attention even though they are indispensable in the development of epithelial layers (p63), central nervous systems (p73) and immune systems (p73). A long-standing question is whether the function of p53 family in tumor suppression is specific to vertebrate innovation, or what is the function present in an ancestral p53/p63/p73 homolog? Among invertebrates, functional studies of p53 homologs have been limited to model organisms such as Drosophila and C. elegans. It has been demonstrated that fly and nematode p53 homologs mainly regulate apoptosis of germ cells upon genotoxic stress. However, little is known about p53 function in other early animal lineages considering that the existence of the p53-like molecules can be traced back to choanozoa and amoebozoa and the function of p53 may diverge among metazoan. Planarians Schimidtea mediterranea are free-living flatworms that belong to the Lophotrochozoan super-phylum and thus provide a fresh view on the functional evolution of the p53 family. A recent study identified a planarian p53 homolog and its role in tissue homeostasis and regeneration. To gain more insights in p53-mediated stem cell regulation, we performed RNASeq analysis on FACS-sorted neoblasts isolated from p53(RNAi) planarians and identified a cohort of down-regulated genes that are expressed in a subpopulation of neoblasts. Utilizing RNAi and in situ hybridization, we classified planarian p53 as the most upstream molecule in a transcriptional cascade that drives the lineage progression of epidermal progenitors. Interestingly, one of the immediate downstream molecule of planarian p53 shares a conserved C2H2 zinc finger domain with mammalian ZNF750, which is a transcriptional target of mammalian p63 at the epithelial stem cells. In line with the hypothesis that a p63/p73-like molecule may be the last common ancestor in the evolution of vertebrate p53 family members, we suggest that planarian p53 shares an evolutionary conserved function with vertebrate p63 in the epidermis lineage progression from stem cells.

P-07. A novel innovation of highly accurate, scalable sequencing solution for complex nucleotide mixture

Jung-Ting Chien[1], Dario A. Dilernia[1], Daniela C. Monaco[1], Eric Hunter[1]

[1]Emory University

INTRODUCTION. The third generation sequencing technology called SMRT (Pacific Biosciences) provides the longest sequencing reads currently available. However, the relatively high error rate present in each single read has precluded efficient sequencing of genetic mixtures because the true diversity is masked by high background noise. In this sense, sequencing of mixtures of HIV genomes stands as a major challenge for this technology. Our objective was to develop a work-flow of novel computer algorithms that would allow highly-accurate PacBio sequencing of full-HIV genome mixtures.

METHODS. Samples were obtained from the participants of the Zambia Emory HIV Research Project (ZEHRP) discordant couples cohort in Lusaka, Zambia,

Forty Single Genome Amplicons (SGAs) were obtained by limiting dilution RT-PCR from two linked-transmission pairs. Library preparations were performed following standard protocols (Pacific Biosciences Inc). Sequencing reads were initially filtered and then aligned using SMRT Analysis v2.2.0 in UBUNTU 10.04. The analytical algorithms presented here were developed in MATLAB v2012a.

RESULTS. By comparison with DNA sequence of the same SGAs obtained by Sanger sequencing, our results indicate that our analytical algorithm is able to derive the DNA sequence of each of the 40 full HIV genome variants exhibiting various numbers of single-nucleotide variations, present in a mixture, with an accuracy of >99.9%. This goal was achieved using one single SMRT Cell and desktop computing power. All the sequencing was performed in duplicate and in every replicate the results was identical. Neither in silico artificial sequences nor in silico recombination between different genetic variants were observed in the output. It is important to note that the algorithm does not require the a priori definition of the number of sequences in order to get an accurate result and it is able instead to explore the entire data set and provide the real number of unique genetic variants present in the original sample. This remains true even for variants differing by one single nucleotide. In addition, the methods described here did not require the barcoding of each SGA.

CONCLUSIONS. This novel approach can revolutionize HIV sequencing making it more cost-effective to sequence the entire genome using PacBio Next-Generation Sequencing than just limited segments by Sanger sequencing. It also opens the possibility of solving complex sequencing tasks that currently lack a solution.

P-08. Structural studies of lipid-protein interactions using electron crystallography

Po-Lin Chiu[1], Thomas Walz[1]

[1]Harvard Medical School

Aquaporin-0 (AQP0) permeates water molecules and also forms thin junctions between the lens fiber cells. AQP0 forms a two-dimensional array in the native lens membranes. The previous structural studies of AQP0 with dimyristoyl phosphatidylcholine (DMPC) and E. coli polar lipid (EPL) found that the reconstituted AQP0 2D crystals are double layered, and the interacting tetramers in two opposing crystalline layers are exactly in register, resulting in a p422 plane symmetry. Comparison of the DMPC and EPL bilayers suggested that the lipid head groups do not play an essential role in the interaction of annular lipids with AQP0. However, the 2D crystals of AQP0 with dimyristoyl phosphatidylglycerol (DMPG) showed different plane symmetries other than the normal p422 symmetry, resulting from translational shifts between the two crystalline layers. To test if the net negative charge on the PG head group was the reason to this destabilization of the interactions between two crystalline layers, we also reconstituted AQP0 with other anionic phospholipids, dimyristoyl phosphatidylserine (DMPS) and dimyristoyl phosphatidic acid (DMPA), and the results suggested that the crystalline layer shift is due to the specific chemistry of PG head group, not simply the negative charge. Next, to answer the question of how AQP0 forms membrane array in vivo, we crystallized AQP0 with lens lipids, which are mostly sphingomyelin and cholesterol, the raft lipids. Two crystal structures of AQP0 with raft lipids at the lower and the higher cholesterol ratios have been determined at 2.5-Ãƒâ€¦ resolution using electron crystallography. The overlapping positions of the annular cholesterols may suggest the cholesterol specific binding sites, and this specific lipid-protein interaction may be the driving force of the native array formation in lens membranes. This finding may help us to extend the knowledge of how the formation of lipid raft domain occurs.

Keywords: cryoEM, lipid-protein interaction, electron crystallography, aquaporin-0, lipid raft

P-09. O-GlcNAcylation Stabilizes Nod2, an Innate Immune Receptor Involved in Crohn's Disease

Ching-Wen Hou, Natasha E. Zachara, Catherine L. Grimes

[1]University of Delaware

[2]The Johns Hopkins University School of Medicine

[3]University of Delaware

Nucleotide-binding oligomerization domain2 (Nod2) is an intracellular receptor that can sense bacterial components, such as, Muramyl dipeptide (MDP). MDP is a peptidoglycan fragment from bacterial cell wall that can activate NF-kB, a transcriptional factor that induces the production of inflammatory molecules such as cytokines. In 2001, a genetic linkage analysis revealed three major mutations in Nod2 were linked to Crohn's disease. Crohn's-associated Nod2 variants have a loss of function phenotype where they display a decreased ability to turn on NF-kB. Recently, using the classic cycloheximide stabilization assay, we showed that Crohn's-associated Nod2 variants have lower half-life compared with wild type Nod2 in cells. To further characterize this protein, the objective of this study is to determine if Nod2 is post translationally modified. GlcNAcylation is one of post translational modifications in which O-GlcNAc transferase (OGT) transfers N-acetylglucosamine (GlcNAc) from UDP-GlcNAc to selected serine and threonine residues of a target protein. As GlcNAc is a major component of peptidoglycan of bacterial cell wall and a large amount of GlcNAc is released from bacterial cell wall during cell wall remodeling, we hypothesized that Nod2 could be O-GlcNAcylated. Preliminary data show that wild type Nod2 and Nod2 variants are O-GlcNAcylated by using O-GlcNAc antibody (CTD110.6). In addition, increasing the O-GlcNAcylation level can increase the half- life of Nod2 in wild type Nod2 and affect Nod2 mediated NF-kB pathway .In future experiments, we will determine which residue of Nod2 is GlcNAcylated and investigate if this modification affects Nod2 mediated NF-kB pathway in Crohn's-associated Nod2 variants.

P-10. Using inducible and reversible transgenic RNAi to reveal on-target effects associated with CDK9 inhibition in vivo

Chun-Hao Huang[12], Darjus F. Tschaharganeh[1], Ana Banito[1], Kevin P. O'Rourke[13], Chi-Chao Chen[12], Scott W. Lowe[124]

[1]Memorial Sloan-Kettering Cancer Center

[2]Weill Cornell Graduate School of Medical Sciences

[3]Weill-Cornell/ Rockefeller/Sloan Kettering Tri-Institutional MD-PhD program

[4]Howard Hughes Medical Institute

The MYC oncoprotein is a well-validated but currently undruggable driver in hepatocellular carcinoma (HCC) and other tumor types. Recently we identified CDK9 Ã¢â‚¬â€œ a key component of the Positive Transcription Elongation Factor b (P-TEFb) complex Ã¢â‚¬â€œ as required for the addiction of cancer cells to MYC. Although CDK9 inhibition showed modest impact on non-transformed immortalized mouse embryonic fibroblasts and some low MYC cells, the potential in vivo toxicities associated with targeting factors that control transcription elongation are unclear. Using hydrodynamic tail vein injections of transposons expressing Cdk9 or Myc shRNAs followed by partial hepatectomy, we found their inhibitions did not show significant effects on the proliferation of hepatocytes and liver regeneration. To examine the systemic effects of CDK9 inhibition on normal tissue homeostasis and organ function in adult mice, we generated transgenic mice harboring tetracycline/doxycycline (dox) responsive Cdk9 or control luciferase miR-E shRNAs coupled with GFP that allows temporal and spatial control of endogenous gene expression. Furthermore, the shCdk9 transgenic mice can be applied to studying the anti-cancer and -inflammatory properties of CDK9 inhibition by combined with Myc transposon/p53 CRISPR/Cas9 or Dextran Sodium Sulfate (DSS)-induces colitis models, respectively. Successful completion of these studies will provide important insight into CDK9 function in normal and diseased tissues and may predict potential outcomes associated with sustained CDK9 protein inhibition.

P-11. The perspective of Genetic Testing Development and Regulatory Reform in Personalized Medicine

Li-Shiuan Hung[1]

[1]Department of Biological Sciences, Columbia University, NY

The United States health care system is facing the unprecedented challenges in high expenditures, resource wasting and ineffective treatments for patients. To address the issues, the development of biomarker-related genetic testing provides an evidence-based approach to achieve customized, and personalized diagnosis for optimal clinical decision- making. In order to resonate with the U.S. health care legislations and the Precision Medicine Initiative (PMI) announced by the President of the United States Barack Obama in January 2015, herein, find a review intended to explore the existing examples of personalized medicine, and the current development of genetic testing from the perspective of sequencing methods, including the newly adoption of Next-Generation Sequencing technology, the genomic databases, and the regulatory reform to embrace the pioneering shift for the entire pharmaceutical industry in attempting to provide tailed information for diseases or medical conditions diagnosis, prevention, and treatment in personalized medicine.

P-12. The Neuroprotective Effect of Human Uncoupling Protein 2 (hUCP2) Requires cAMP dependent Protein Kinase in a Toxin Model of Parkinson's Disease

Ran-Der Hwang, Yih-Woei Fridell

Parkinson's disease (PD), caused by selective loss of dopaminergic (DAergic) neurons in the substantia nigra, is the most common movement disorder with no cure or effective treatment. Exposure to the mitochondrial complex I inhibitor rotenone recapitulates pathological hallmarks of PD in rodents and selective loss of DAergic neurons in Drosophila. However, the mechanisms underlying rotenone toxicity are not completely resolved. We previously reported a neuroprotective effect of human uncoupling protein 2 (hUCP2) against rotenone toxicity in adult fly DAergic neurons. In the current study, we show that increased mitochondrial fusion is protective from rotenone toxicity whereas increased fission sensitizes the neurons to rotenone-induced cell loss in vivo. In primary DAergic neurons, rotenone-induced mitochondrial fragmentation and lethality is attenuated as the result of hucp2 expression. To test the idea that the neuroprotective mechanism of hUCP2 involves modulation of mitochondrial dynamics, we detected preserved mitochondrial network, mobility and fusion events in hucp2 expressing but not control DAergic neurons exposed to rotenone. hucp2 expression also increased intracellular cAMP levels. Thus, we hypothesized that cAMP-dependent protein kinase (PKA) might be an effector that mediates hUCP2- associated neuroprotection against rotenone. Indeed, preserved mitochondrial integrity, movement and cell survival observed in hucp2 expressing DAergic neurons exposed to rotenone were blocked by PKA inhibitors. Taken together, my work provides strong evidence identifying a hUCP2-PKA axis that controls mitochondrial dynamics and survival in DAergic neurons exposed to rotenone implicating a novel therapeutic strategy in modifying the progression of PD pathogenesis.

P-13. T cells Expressing CARs directed against HLA-0201 WT1 peptide complex can effectively eradicate WT1+ A0201+ tumor cells in vitro

Tzu-Yun Kuo[12], Aisha Hasan[2], Qi Zhao[2], Dimiter Tassev[2], Nai-Kong Cheung[2], Richard J O'Reilly[1]

[1]Weill Cornell Graduate School of Medical Sciences

[2]Department of Pediatrics, Memorial Sloan-Kettering Cancer Center

Adoptive transfer of ag specific T-cells can effectively eradicate viral infections and tumors. T-cells can be targeted to specific ags expressed on tumor cells by genetic modification to express chimeric ag receptors (CARs); which are fusion proteins incorporating an ag recognition moiety (ab) and T-cell activation domains. Human T-cells genetically modified to express a CD19-targeted CAR have been demonstrated to successfully eradicate CD19+ B cell malignancies in patients with refractory disease. The CARs developed thus far have been directed against native cell-surface antigens, such as CD19, that are recognized through antibody-derived antigen-binding motifs, independently of antigen processing or MHC-restricted presentation. However, tumor associated intracellular antigens such as WT-1 require processing following which antigenic epitopes are presented on the tumor cell surface in complex with HLA class-I or class-II. A strategy for targeting T-cells to specific peptide epitopes expressed on tumor cells involves genetically introducing TCR mimic CARs containing a scFv ab directed against the specific peptide-MHC complex. CARs containing a Fab directed against an HLA-A0201-NY-ESO-1 epitope have been generated, but functional data is lacking. We generated a TCR-like CAR containing a scFv specific for an HLA/peptide complex; the WT-1 RMFPNAPYL peptide presented by HLA-A0201 (A2-RMF CAR). The original A2-RMF ScFv, isolated using phage display technology, had a low binding affinity (Kd= 2.3 x 10-7 M). T-cells were transduced to express the A2-RMF CAR using MSCV retroviral vector. However, CAR transduced T-cells bearing the low affinity A2-RMF ScFv did not demonstrate any binding to the A2-RMF tetramers, and did not demonstrate any in-vitro cytotoxic activity against A2+/WT-1+ tumor cell targets. We subsequently developed an affinity matured ScFv (Kd= 3.08 x 10-9 M) to determine if ScFv binding affinity correlated with functional activity. T-cells transduced to express CARs bearing the affinity matured A2-RMF ScFv demonstrated strong binding to the A2-RMF tetramer in all transduced cells. The affinity matured A2-RMF CAR modified T-cells were able to kill A2+/WT-1+ solid tumor or B cell leukemia cell lines (29% -40% specific lysis) at E:T ratios of 50:1 and 20:1, in comparison to 1-4% specific lysis for HLA A2-/WT-1+ or A2+/WT-1- control tumor cell lines. These data demonstrate that a TCR-mimic CARs bearing scFv against an A2-RMF complex, can bind to A2-RMF tetramers and effectively lyse tumor cell targets co-expressing HLA A2 and WT1 in an HLA restricted and antigen specific manner. The results also suggest that the binding affinity of the antibody is important for effective functional activity of CAR modified T-cells directed against epitopes of self tumor associated antigens.

P-14. Levels of the pro-apoptotic molecule Bim are determined early in the response and positively correlated with memory T cell fate

Kun-Po Li[12], Allyson Sholl[1], David Hildeman[12]

[1]Cincinnati Children's Hospital Medical Center

[2]University of Cincinnati

We and others have shown that the pro-apoptotic molecule Bim plays a critical role in controlling the contraction of T cell responses. Paradoxically, T cells destined to become memory (pre-memory) cells have higher levels of Bim than their effector counterparts. Similarly, after memory development, central memory (TCM) cells have higher levels of Bim relative to their effector memory (TEM) counterparts. However, due to the intracellular location of Bim, sorting and subsequent tracking of T cells based on Bim expression has been challenging. To circumvent this issue and determine the relationship between Bim expression and cell fate, we generated Bim-mCherry reporter mice, inserting an IRES-mCherry cassette into the 3'-UTR of the Bim gene. Similar to intracellular staining for Bim, mCherry levels were higher in pre-memory cells and TCM cells than their effector or TEM counterparts. In addition, the expression and function of Bim in T cells is not altered in Bim-mCherry reporter mice. The transfer of Bim(hi) or Bim(lo) T cells on the basis of mCherry expression favored their development into TCM or TEM cells, in recipient animals, respectively. Further, the levels of mCherry (and Bim) remained stable in the transferred mCherry(hi) or mCherry(lo) T cells across contraction of the response. These data suggest that the levels of Bim in CD8 T cells are determined at an early stage of infection and are paradoxically positively correlated with T cells having a memory fate.

P-15. Parametric mediational g-formula approach to mediation analysis with time-varying exposures, mediators and confounders: an application to smoking, weight, and blood pressure

Sheng-Hsuan Lin[12], Eric J. Tchengen Tchengen[12], Tyler J. VanderWeele[12]

[1]Department of Epidemiology, Harvard School of Public Health

[2]Department of Biostatistics, Harvard School of Public Health

Mediation analysis with time-varying mediators and confounders is a common but challenging problem with longitudinal cohort data, and standard mediation analysis approaches are generally inapplicable. The mediational g-formula is a new approach to address this question. In this paper, we develop a parametric approach to provide methods for the mediational g-formula to implement it with data, including a feasible algorithm and a Statistical Analysis System (SAS) macro. We apply this method to Framingham Heart Study dataset to examine pathways for the effect of smoking on blood pressure mediated by and independent of weight change for a 10-year follow-up period. Compared with non-smoking, smoking 20 cigarettes per day for 10 years increases blood pressure by 2.87 (95 % C.I. 0.36, 5.38) mm-Hg. The direct effect in fact increases blood pressure by 3.06 (95 % C.I. 0.65, 5.47), and the mediated effect is -0.19 (95 % C.I. -0.28, -0.08). This provides evidence that weight change in fact partially conceals the detrimental effect of cigarette smoking on blood pressure. This work represents the first application of the mediational g-formula in an epidemiologic cohort study.

P-16. A Genetic Screen for miRNAs involving in Metastatic Behavior in Drosophila

Ching-Jung Lin[1], Fernando Bejarano[2], Eric C. Lai[2]

[1]Weill Cornell Graduate School of Medical Science

[2]Sloan-Kettering Institute, Department of Developmental Biology

MicroRNAs are 20-23 nucleotide length noncoding RNAs that could regulate the stability of mRNA through complementary binding between the position 2-8 nucleotides seed sequence with the 3'-untranslated region of their target mRNAs. Although computational strategies and experimental profiling could now predict hundreds to thousands of direct targets per miRNA, such data rarely provide clear insight into the biological function of individual miRNAs in vivo. In a previous study, we have described a collection of around 200 Drosophila miRNA transgenes and found that missexpression of individual miRNAs often induced specific development defects.

The Notch signaling plays an important role in the development and regeneration of many tissues and has been associated with tumorigenesis in recent years. Ectopically expression of the fly miRNA library in the Drosophila eye under Notch activated condition, we identify 22 miRNAs from 203 miRNAs screened could cooperate with Notch resulting in tumor-like phenotype of the eye with significant overgrowth and furrowing. Among them, 6 miRNAs could give metastatic-like phenotype including basement membrane degradation, loss of E-cadherin expression and secondary tumor formation in the brain, neck, notum or abdomen. Moreover, 12 candidate miRNAs are highly conserved in mammals. These data suggest that the gain-of-function study in animal could provide more information to functions of miRNAs during development and disease conditions, such as cancer.

P-17. Automated detection of diabetic retinopathy: using fundus images and machine learning algorithms

Pei Lin[1]

[1]Anthem HealthCore

Diabetic retinopathy (DR) is one of the leading causes of blindness in the developed countries. The most effective treatment for DR needs to be administered in the early stages of the disease. Detecting DR requires a trained clinician to examine and evaluate color fundus photographs of the retina. As instruments for retinal images get advanced and become popular in recent years, a new algorithm to automate the detection of abnormalities in retinal images is needed. This paper explains the algorithm to determine the severity of DR with color fundus photography as input. The algorithm contains two stages: the first step is to use pattern recognition methods to identify features in the fundus images including macula, exudate, optic disc, and haemorrhage. The second step is to train a machine learning model with thousands of clinician-reviewed images to predict the severity of DR. The research demonstrates a way to examine the fundus images automatically and to detect DR at its early stages.

P-18. Highly multiplexed high-throughput imaging of single-cell using CycIF cyclic immunofluorescence

Jia-Ren Lin[1], Mohammad Fallahi-Sichani[2], Peter K Sorger[12]

[1]HMS LINCS Center Laboratory of Systems Pharmacology

[2]Department of Systems Biology, Harvard Medical School

Single cell analysis reveals aspects of cellular physiology not evident from population-based studies, particularly in the case of highly multiplexed methods such as mass cytometry (CyTOF) that measure the levels of multiple signaling, differentiation and cell fate markers simultaneously. Immunofluorescence (IF) microscopy adds information on cell morphology and the microenvironment that are not easily obtained using flow-based techniques but the multiplicity of conventional IF is limited. This has led to the development of imaging methods that require specialized instrumentation, exotic reagents or proprietary protocols that are difficult if not impossible to recreate in most laboratories. Here we report a public-domain method for achieving high multiplicity single-cell IF using cyclic immunofluorescence (CycIF), a simple and versatile procedure in which four-color staining alternates with chemical inactivation of fluorphores to progressively build a multi-channel image. Because the method uses standard commercial reagents and instrumentation and is no more expensive than conventional IF, it is both easy to perform and suitable for high-throughput and high-content assays.

P-19. Parametric mediational g-formula approach to mediation analysis with time-varying exposures, mediators and confounders: an application to smoking, weight, and blood pressure

Sheng-Hsuan Lin[12], Eric J. Tchengen Tchengen[12], Tyler J. VanderWeele[12]

[1]Department of Epidemiology, Harvard School of Public Health

[2]Department of Biostatistics, Harvard School of Public Health

Mediation analysis with time-varying mediators and confounders is a common but challenging problem with longitudinal cohort data, and standard mediation analysis approaches are generally inapplicable. The mediational g-formula is a new approach to address this question. In this paper, we develop a parametric approach to provide methods for the mediational g-formula to implement it with data, including a feasible algorithm and a Statistical Analysis System (SAS) macro. We apply this method to Framingham Heart Study dataset to examine pathways for the effect of smoking on blood pressure mediated by and independent of weight change for a 10-year follow-up period. Compared with non-smoking, smoking 20 cigarettes per day for 10 years increases blood pressure by 2.87 (95 % C.I. 0.36, 5.38) mm-Hg. The direct effect in fact increases blood pressure by 3.06 (95 % C.I. 0.65, 5.47), and the mediated effect is -0.19 (95 % C.I. -0.28, -0.08). This provides evidence that weight change in fact partially conceals the detrimental effect of cigarette smoking on blood pressure. This work represents the first application of the mediational g-formula in an epidemiologic cohort study.

P-20. MicroRNA-150 regulates pathologic ocular neovascularization by modulating endothelial cell function

Chi-Hsiu Liu[1], Ye Sun[1], Jie Li[1], Jing Chen[1]

[1]Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, Boston, MA

Purpose

Pathologic ocular angiogenesis is a major cause of blindness in several vascular eye diseases. In order to develop effective targeted therapeutics, it is critical to define factors dysregulated in pathologic neovessels. MicroRNAs are small non-coding RNAs regulating gene expression at the post-transcriptional level, and may mediate pathologic angiogenesis. Here we investigated the potential role of a specific microRNA, miR-150, in regulating ocular angiogenesis.

Methods

Two mouse models of pathologic ocular angiogenesis were used: the oxygen-induced retinopathy (OIR) and the laser-induced choroidal neovascularization (CNV). In OIR, neonatal mice were exposed to 75% O2 from postnatal day 7 to 12. MicroRNA array was performed with OIR retinas compared with normoxic controls, followed by verification with RT-PCR and localization with laser capture microdissected (LCM) retinal neural and vascular layers. Pathologic retinal neovascularization (NV) in OIR was quantified in miR-150 knockout (miR-150-/-) and wild type (WT) mice, and WT mice injected intravitreally with miR-150 mimic and negative control. For CNV model, adult miR-150-/- and WT mice were treated with laser photocoagulation and CNV lesions were analyzed at 1 week post laser. Effects of miR-150 on endothelial cell function were analyzed in human retinal microvascular endothelial cells (HRMECs). Putative target genes of MiR-150 were validated in both retinas and HRMECs.

Results

Expression of miR-150 was found highly enriched in LCM retinal blood vessels isolated from normal retinas compared with retinal neurons, and significantly suppressed in pathologic NV isolated from OIR retinas. OIR-treated miR-150-/- retinas revealed increased retinal NV compared with WT. Intravitreal injection of miR-150 mimic significantly decreased NV in OIR. In laser-induced CNV, miR150-/- mice showed significantly larger CNV lesions compared with WT. HRMECs treated with miR-150 mimic revealed substantially decreased levels of cell proliferation, migration, and tubular formation. Loss of miR-150 led to strong upregulation of predicted target angiogenic genes (Cxcr4, Dll4, Fzd4, Plxnd1, and Kdr) in OIR retinas in vivo and in HRMECs in vitro.

Conclusions

Our findings indicate that vascular-enriched miR-150 is a novel endogenous inhibitor of pathologic ocular NV. MiR-150 may represent a potential therapeutic target to develop treatments for neovascular eye diseases.

P-21. Design Complex Hydrogel Microparticles for Scalable 3D cell Culture, Co-Culture and Microtissue Production

Yen-Chun Lu[1], Wei Song[1], Duo An[1], Robert Schwartz[2], Mingming Wu[1], Minglin Ma[1]

[1]Cornell University

[2]Weill Medical College of Cornell University

Cell encapsulation in hydrogel microparticles has been investigated for decades in various bioengineering applications including tissue engineering, and cell therapy. However, most of the time, the cells are encapsulated randomly in whatever material that forms the microparticles, most commonly alginate. The lack of control over the spatial organizations of the cells and the extracellular environment within the microparticles significantly limits for advanced applications. Here we report a novel, multi-fluidic cell microencapsulation approach where 1 or more types of cells are encapsulated in pre-assigned compartments in the microparticles with controlled extracellular matrix. These microparticles can be produced with controllable and nearly monondispersed sizes at rates of over 10,000 microparticles per min and therefore provide a promising platform for high throughput applications. We demonstrated the utilization of these extracellular matrix-supported microparticles for 3D culturing of cells that typically require specific microenvironment to survive such as human umbilical vein endothelial cells (HUVECs) and small intestine stem cells. By taking advantage of the confinement effect, we also showed robust and scalable productions of size-controlled multicellular microtissues. Lastly, to demonstrate the broad applications of these microparticles, we performed proof-of-concept studies on three different co-culture systems including cell segregations under 3D confined space, the supporting role of stromal cells in hepatocyte functions and the paracrine cell signaling in aggregation of endothelial cells, all in a high throughput manner.

P-22. Computational studies of functional interactions and collaboration between ClpB ATPase and associated co-factors DnaK/GrpE during protein disaggregation

Yu-Hsuan Shih[1], Shannon M. Doyle[2], Shankar Shastry[2], Andrea Kravats[2], Marika Miot[2], Joel R. Hosk[2], George Stan[1], Sue Wickner[2]

[1]Department of Chemistry, University of Cincinnati, Cincinnati, OH

[2]Laboratory of Molecular Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD

The ClpB chaperone, which belongs to first class of ATPases Associated with diverse cellular Activities (AAA+) superfamily, plays an essential role for protein disaggregation. Co-factors, such as DnaK/GrpE, collaborate with ClpB to suppress aggregates under stress conditions. In order to understand the molecular mechanism for ClpB/DnaK/GrpE (BKE) collaboration, computational modeling and proteinprotein docking approaches are utilized to inspect those strong binding contacts at the interfaces. We construct a hexameric model of ClpB by using constraints derived from an asymmetric cryoEM map and crystal structure of monomeric fragments.

Our results indicate GrpE and ClpB bind mutually exclusive to DnaK, which are consistent with biochemical studies in vivo and in vitro. Interestingly, we predict a multivalent binding of DnaK to ClpB assembly, suggesting potential functional regions and residues involved in protein disaggregation. Further studies are underway to validate our computational predictions. Altogether, these results provide a more complete picture of multi-chaperones collaboration during protein disaggregation.

P-23.

Derek J. C. Tai[123], Ashok Ragavendran[13], Alexei Stortchevoi[13], Catarina M. Seabra[12], James F. Gusella[14], Michael E. Talkowski[1234]

[1]Molecular Neurogenetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA

[2]Department of Neurology, Harvard Medical School, Boston, MA

[3]Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, and Department of Psychiatry, Massachusetts General Hospital, Boston, MA

[4]Program in Medical and Population Genetics, Broad Institute of Harvard and MIT

Recurrent genomic disorders involve large copy number variations (CNV) generated from non-allelic homologous recombination (NAHR) mediated by segmental duplications. These reciprocal microdeletions and microduplications are a major cause of human disease, often producing phenotypically distinct syndromes. However, their investigation has been limited by the uniform size of the recurrent lesion, which can encompass many genes, the diverse genetic backgrounds of patients, and the lack of accessible tissues. The capacity to generate large reciprocal CNVs in an otherwise isogenic pluripotent stem cell could overcome these obstacles and provide an invaluable tool for modeling these recurrent genomic disorders. Here, we used CRISPR/Cas9 genome engineering methods to achieve this goal for the common 16p11.2 microdeletion/microduplication syndrome as a proof-of-principle for NAHR-mediated disorders. Using a dual-guide RNA strategy, we first demonstrate the capability to ablate the 575 kb unique genic segment spanning the 16p11.2 microdeletion region. We then developed a single-guide RNA approach that targets the flanking segmental duplications and achieved accurate reproduction of NAHR-mediated reciprocal microdeletion and microduplication, modeling the in vivo mechanism, with the expected three and five copies of the flanking segmental duplications, respectively. Copy number analysis, chromosomal microarrays, and transcriptome sequencing revealed that the method efficiently generates DNA dosage changes (14.8% of all clones screened), and that gene-expression patterns recapitulate those of human subjects harboring the CNV. Our data suggest that this genome engineering approach provides an efficient method to model recurrent, reciprocal genomic disorders, producing a cell resource that can be differentiated to any cell type of relevance. These models can be compared with cells subjected to more traditional single-gene editing to define the functional genetic contributors to the characteristic clinical phenotypes, and to suggest potential therapeutic target pathways. With further optimization and development, these methods may also permit efficient correction of these defects.

P-24. LIN28 cooperates with Wnt signaling to drive invasive intestinal and colorectal adenocarcinoma in mice and humans

Ho-Chou Tu[1], Sarah Schwitalla[1], Zhirong Qian[2], Grace LaPier[1], Shann-Ching Chen[3], George Q. Daley[14]

[1]Boston Children's Hospital

[2]Dana Farber Cancer Institue

[3]Thermo Fisher Scientific Inc.

[4]Howard Hughes Medical Institute

Colorectal cancer (CRC) remains a major contributor to cancer-related mortality. LIN28A and LIN28B are highly related RNA-binding protein paralogs that regulate biogenesis of let-7 microRNAs and influence development, metabolism, tissue regeneration, and oncogenesis. Here we demonstrate that overexpression of either LIN28 paralog cooperates with the Wnt pathway to promote invasive intestinal adenocarcinoma in murine models. When LIN28 alone is induced genetically, half of resulting tumors harbor Ctnnb1 (B-catenin) mutation. When overexpressed in ApcMin/+ mice, LIN28 accelerates tumor formation and enhances proliferation and invasiveness. In conditional genetic models, enforced expression of a LIN28-resistant form of the let-7 microRNA reduces LIN28-induced tumor burden, while silencing of LIN28 expression reduces tumor volume and increases tumor differentiation, indicating that LIN28 contributes to tumor maintenance. We detected aberrant expression of LIN28A and/or LIN28B in 38% of a large series of human CRC samples (n=595), where LIN28 expression levels were associated with invasive tumor growth. Our late-stage CRC murine models and analysis of primary human tumors demonstrate prominent roles for both LIN28 paralogs in promoting CRC growth and progression, and implicate the LIN28/let-7 pathway as a therapeutic target.

P-25. The role of cigarette smoke in modulating the inflammatory status of lymphocytes during the pathogenesis of rheumatoid arthritis (RA)

Chien-Huan Weng, Gupta Sanjay, Patrick Geraghty, Robert Foronjy, Alessandra B. Pernis

Cigarette smoke (CS) has been shown to be one of the potential environmental factors contributing to the development of many autoimmune diseases, including rheumatoid arthritis (RA). Evidences from epidemiology research also cast a strong correlation between the incidence of RA and tobacco exposure. Thereby, we launched to investigate whether cigarette smoke had any effect in modulating the inflammatory status of CD4+ lymphocytes. Our preliminary in vitro data from mouse interestingly suggest a negative regulatory effect of CS in regulating pro-inflammatory cytokine production, specifically interleukin-17 (IL-17), through decreasing the Rho-associated Kinase (ROCK) activity and the phosphorylation of the downstream substrate of ROCK- the interferon regulatory factor 4 (IRF4)- in CD4+ T lymphocytes. The decreased ROCK kinase activity mediated by cigarette smoke is possibly resulted from an yet unknown effect of CS in weakening the interaction between RhoA and Rho guanine nucleotide exchange factor 1 (ARHGEF1 or p115), evidenced by our mass spectrometry data. Further investigations, including in vivo experiments, are still ongoing to characterize the role of cigarette smoke in the development of RA.

P-26. Stretching tethered single chromatin in nanofluidic channels for detection of epigenetics marks

Jia-Wei Yeh, Harvey Tian, Kylan Szeto, Harold G. Craighead

[1]Cornell University

Epigenetic modifications around the genome are linked to cellular behavior, human development and disease. Histone modification is one of the most abundant forms of epigenetic modifications; to date, there have not been reliable methods available for imaging and analysis histone modifications on individual chromatin molecules. A nanofluidic device was used to electrophoretically stretch and image single native chromatin fibers and DNA attached to microspheres held at the entrance to a nanoslit. The field-extension of tethered chromatin and DNA polymers in the nano-confinement slits was measured and described using 3D and 2D worm-like chain field-extension models. Chromatin fragments extracted from human cancer cells (HeLa) were stretched and held in the nanoslits and histone modification (H3k79me2) was optically detected by the binding of fluorescently labeled antibodies.

Attendee

Name	Affiliation
CAI, ERICA	Joslin Diabetes Center
CHANG, BART YI-CHIEN	Boston University
CHANG, CHIA-CHIH	UMass-Amherst
CHANG, CHIA-JUNG	Harvard/MIT
CHANG, CHIEN-I	
CHANG, CHI-HSUAN	Baylor College of Medicine
CHANG, DEKUAN	DFCI
CHANG, FENG-MING JAMES	Indiana University
CHANG, HAN-WEN	Fox Chase Cancer Center
CHANG, HUI-HSIN	Brigham and Women's Hospital
CHANG, PAUL	Cornell University
CHANG, SHENG-WEI	Ohio State University
CHANG, SHIOU-CHI	MIT
CHANG, WEI	Regenerative Technologies
CHANG, WEI TING	Northeastern University
CHANG, YI-PIN	The Forsyth Institute
CHAO, CHUN-CHEIH	Brigham and Women's hospital
CHEN, CHARLES	Johns Hopkins University
CHEN, CHEN-HAO	Harvard
CHEN, CHIA-YEN	Massachusetts General Hospital
CHEN, CHICHAO	MSKCC
CHEN, CHIH-HUNG	
CHEN, CHING-HUAN	Indiana University Bloomington
CHEN, CHUN-TI	Boston College
CHEN, EMMA	Fuqua School of Business, Duke University
CHEN, GRACE	Albert Einstein college of medicine

CHEN, HO-CHUNG	
CHEN, HSIAO-RONG	Boston University
CHEN, HSI-JU	UMMS
CHEN, HSIN-CHIEN	Eaton-Peabody Lab, Mass Eye and Ear
CHEN, HUEI-MEI	Harvard University
CHEN, JIA-YUN	Harvard Medical School
CHEN, JUNG-KUEI	UT Austin
CHEN, KAIYU	UCLA
CHEN, KAI-YUAN	Cornell University
CHEN, LIANGCHIN	Bioss Inc
CHEN, PO-HSUEN	Schepens Eye Research Institute
CHEN, ROSE	Sanofi
CHEN, SHENG-HONG	Harvard Medical School
CHEN, SOPHIA	Senberger Investment Co., Ltd.
CHEN, TA-CHING	Department of Ophthalmology, National Taiwan University Hospital
CHEN, TAI-YEN	Cornell University
CHEN, WAN-HSUAN	Tulane University School of Public Health and Tropical Medicine
CHEN, WEI-CHIANG	Biogen
CHEN, YEN-HUA	Columbia University in the City of New York
CHEN, YI-HSUAN	
CHEN, YI-JU	University of Pennsylvania
CHEN, YING-CHOU	MIT
CHEN, YING-JA	Pronutria Biosciences
CHEN, YI-SHAN	Duke University
CHEN, YU-FAN	Department of Cellular and Molecular Pharmacology, Graduate School of Biomedical Sciences at RWJMS, Rutgers University
CHEN, YUWEI	Genzyme
CHENG, LI-CHUN	Stowers Institute
CHENG, MELODY	Columbia University Medical Center
CHENG, MENG-TZU	

CHENG, YENFU	Harvard Medical School
CHENG, YUNG-CHIH	Boston Children's Hospital / Harvard Medical School
CHIANG, MATHEW	
CHIANG, MENGCHUN	Cambridge Health Alliance/Harvard Medical School
CHIANG, NING	Rutgers University - New Brunswick
CHIANG, YING-LING	Cornell University
CHIEN, CHENG-HAO	Tufts University
CHIEN, JUNG-TING	Emory University
CHIU, JOYCE	
CHIU, LI-YA	
CHIU, PO-LIN	Harvard Medical School
CHIU, SHIHYU	Columbia University
CHOU, HUI-TING	Department of Cell Biology, Harvard Medical School
CHOU, MINDY	Cold Spring Harbor Laboratory
CHOU, SHAO-PEI	Cornell University
CHOU, YI-YING	Harvard Medical School
CHU, AN-HSIANG	
CHUANG, KAI-YUN (KAY)	GenScript
CUI, DONGYAO	MGH
DENG, MANQI	Harvard University
FANG, CHRISTOPHER	Amaris Partners
FANG, DAVID	
FANG, YA-LIN	
FU, SHIH-CHEN	Icahn School of Medicine at Mount Sinai
GAO, XIAOFEI	Whitehead Institute for Biomedical Research
HAN, CHIA-JUNG (JOY)	
HAO, PENGYING	
HAO, YUNGCHIA	
HO, KELLY	

HO, LI-LUN	
HO, YI-YUN	
HOU, CHING-WEN	University of Delaware
HSIAO, CHIN-JU	
HSIAO, YA-LUAN	Johns Hopkins School of Public Health
HSIEH, FU-KAI	MGH/HMS
HSIEH, MIN-KANG	Columbia University
HSIEH, YU-YING PHOEBE	Harvard MCB
HSU, HUNGLUN	
HSU, JAY	GSK
HSU, JESSIE	Boston Children's and Dana-Farber Cancer Institute
HSU, WEI-LUN	
HSUEH, YI-CHING	
HU, CHENG-TSUNG	Boston University
HU, YU-JIE	UMASS MEDICAL SCHOOL
HUANG, CHIA LUN	Columbia University
HUANG, CHUN-HAO	Memorial Sloan-Kettering Cancer Center
HUANG, CYNTHIA	Education Division, Taipei Economic and Cultural Office in Boston (TECO Boston)
HUANG, ELISE	Bristol Myers Squibb
HUANG, HAO	Princeton University
HUANG, HSIN-HO	MIT
HUANG, HUBERT (HAI-TSANG)	DFCI - Cancer biology
HUANG, JIA-HSIN	
HUANG, JING-YING	
HUANG, NAI-JIA	Whitehead Institute
HUANG, WEITING	Education Division, Taipei Economic and Cultural Office in Boston (TECO Boston)
HUANG, YUNG-CHI	UMass Medical School
HUNG, ANDY	Northwestern University
HUNG, CINDY	

HUNG, HUI-FANG	UmassMed
HUNG, KUO-CHAN	NEW ENGLAND BIOLABS
HUNG, LI-SHIUAN	Columbia University
HUNG, LUNG-HSIN	Bio-Rad Digital Biology Center
HUNG, WEI-CHIEN	Johns Hopkins University
HWANG, RAN-DER	University of Connecticut
KU, SHENG-YU	Roswell Park Cancer Institute
KUNG, CHIA-YU	Stony Brook University
KUNG, LING HSUAN	
KUO, CHARLES	University of Maryland
KUO, CHRISTY TZU-YUN	Weill Cornell Medical college
KUO, SZU-YU	Harvard University
KUO, TZU-HSING (APRIL)	Brigham and Women's Hospital/Harvard Medical School
LAI, CHARCHANG	Sanofi Pasteur
LAI, JIANN-JYH	UMASS Medical School
LAI, YI-JU	Tulane University
LAN, CHEN WEI	
LAN, CHENWEI	
LEE, CHIUCHING	TYCCNE
LEE, CHUN-TEH	Harvard School of Dental Medicine
LEE, I-JU	Dana-Farber Cancer Institute/Harvard Medical School
LEE, JENG-SHIN	AB Biosciences
LEE, PRISCILLA	
LEE, SHERRY	Whitehead Institute for Biomedical Research
LEE, WAN-PING	Seven Bridges Genomics
LEE, YI-YING	Institute of Marine and Environmental Technology
LEE, YUAN-CHO	New York University
LEE, YU-CHI	Dartmouth College
LI, HSIN-JUNG	Princeton University

LI, JU-MEI	
LI, KUN-PO	Cincinnati Children's Hospital Medical Center
LI, PEI-HSUAN	
LI, PI-CHUN	
LIANG, CHIA-PIN	MGH
LIANG, CHUN-CHI	
LIAO, CHEN-CHEN (RITA)	Berg
LIAO, JOSHUA	
LIN, CHIA-CHING	Baylor College of Medicine
LIN, CHIEN-LING	Brown University
LIN, CHING-JUNG	Weill Cornell Graduate School of Medical Sciences
LIN, CHIN-TI	Columbia University
LIN, HANK	Pfizer Inc.
LIN, HSIAO-CHUN	MEEI
LIN, JIA-REN	Harvard Medical School
LIN, KE-CHIH	Princeton University
LIN, LEESA	Harvard University
LIN, MENG-YUN	BU
LIN, PAO	MIT
LIN, PEI	HealthCore
LIN, SHENG-HSUAN	Harvard School of Public Health
LIN, TSUNG-YI	Albert Einstein College of Medicine
LIN, WAN-JUNG	Department of Biomedical Engineering, Carnegie Mellon University
LIN, YING-JOU	WuXi AppTec
LIN, YU-CHENG	Columbia University
LIN, YU-MIN	BIDMC/Harvard Medical School
LIN, YU-SHIH	Cenezyme LLC
LIU, CATHERINE	
LIU, CHI-HSIU	Boston Children's Hospital

LIU, GINA	
LIU, HAIPING	MCB
LIU, TIFFANY	
LIU, YIFEN	Cornell University
LU, YEN-CHUN	Cornell University
LU, YI-FEN	Boston Children's Hospital
MAK, HUEY-MING	
MIN, YI-LI	UT Southwestern Medical Center
PAI, CHI-FENG	Massachusetts Institute of Technology
PENG, SHENG-SHIANG	Broad Institute
SHEN, HANNAH	Harvard MCB
SHIH, TA-LIN	Taipei Economic and Cultural Office in Boston
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SHU, CHRISTINA	Yale University
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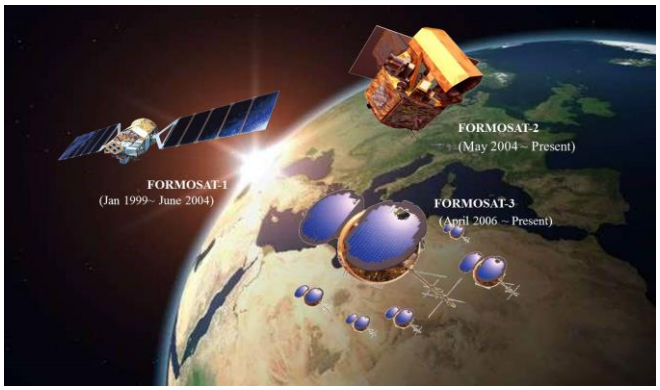

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電話：617-737-2055/6
電郵：education@tecoboston.org
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Please Contact

Jeannie Wu (吳菁菁)
jcw@c-m.com
台北市幸安國民小學畢業
M.I.T., B.S.
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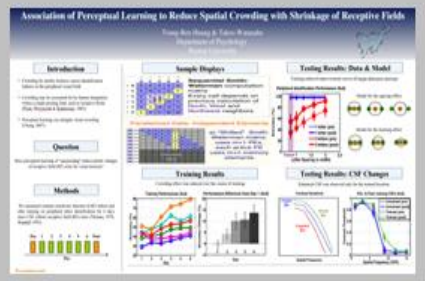

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