Restoring Systemic GDF11 Levels **Reverses Age**-Related Dysfunction In Mouse Skeletal Muscle *Vascular And Neurogenic* **Rejuvenation** *Of The Aging Mouse Brain By Young Systemic Factors* Reversal Of Diabetes With **Insulin-Producing** Cells Derived In Vitro From Human Pluripotent **Stem Cells** *Generation Of Functional Human* **Pancreatic Β** *Cells In Vitro* Bidirectional Switch Of The Valence Associated With A **Hippocampal** Contextual Memory Engram *Creating A* **False Memory** *In The Hippocampus* A **Semi-Synthetic Organism** With An **Expanded Genetic Alphabet** *Designer Microbes Expand Life's Genetic Alphabet* A Three-Dimensional Human **Neural Cell Culture** Model Of Alzheimer's Disease **Sleep** *Drives Metabolite Clearance From The Adult Brain* The Dizzying Journey To A New Cancer Arsenal *Double Nicking By RNA-Guided* **CRISPR Cas9** *For Enhanced Genome Editing S*_____ High-Frequency Off-Target Mutagenesis Induced By CRISPR_____ In Human Cells *The* **Intestinal Microbiota** *Modulates The* _____ *Effects Of Cyclophosphamide*

# SYMPOSIUM 2015

## Texas Taiwanese Biotechnology Association

## November 21, Houston

# 2016 TTBA Symposium

**DALLAS**

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**TEXAS**

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## About

# Texas Taiwanese Biotechnology Association

Texas Taiwanese Biotechnology Association (TTBA) is a young non-profit organization established by a vibrant group of PhD students from *Baylor College of Medicine, UT Austin, UT Southwestern, UT MD Anderson Cancer Center, Texas A&M University,* and *Rice University*. Our mission is to facilitate intellectual conversation and networking among young Taiwanese biomedical scientists, and foster their career development in the US and Taiwan.

The aims of TTBA symposium are to:

- Encourage in-depth communication, networking and collaboration among the Taiwanese scientific communities.

- Provide a conversation platform to facilitate interdisciplinary discussion about the current and future scientific landscape.

- Provide opportunities for well-established Taiwanese scientists and entrepreneurs to share global views and experiences in career development.

## Agenda

### SATURDAY, November 21, 2015

| 8:30 a.m. | **Registration and Poster Setup** |
|---|---|

| 9:00 a.m. | **Opening Remarks** |
|---|---|

| 9:10 a.m. | **Keynote 1**<br>Session Chair: Yu-Mei Huang<br>**Dr. Shu Chien, The University California, San Diego**<br>*Life and Science: A Case History and General Thoughts* |
|---|---|

| 10:10 a.m. | **Panel 1: Academic Career Development**<br>Moderator: Tsung-Wei Ma<br>**Dr. Ching-Shih Chen,** The Ohio State University<br>**Dr. Jer-Tsong Hsieh,** The University of Texas Southwestern Medical Center<br>**Dr. Jen Liou,** The University of Texas Southwestern Medical Center<br>**Dr. J. Jack Lee,** The University of Texas MD Anderson Cancer Center<br>**Dr. Ian Y. Lian,** Lamar University |
|---|---|

| 11:10 a.m. | **Coffee Break** |
|---|---|

| 11:30 a.m. | **Elevator Talk** |
|---|---|

| 12:00 p.m. | **Poster and Lunch** |
|---|---|

| 2:00 p.m. | **Panel 2: R&D Jobs in Industry**<br>Moderator: Yi-Li Min<br>**Dr. Keelung Hong,** Taiwan Liposome Company (TLC)<br>**Mr. Alex Li,** Fluidigm<br>**Dr. Diane D.-S.Tang-Liu,** Supra Integration and Incubation Center (Si2C)<br>DTL BioPharma Consulting<br>**Dr. Ming-Chi Wu,** Development Center for Biotechnology (DCB)<br>The University of North Texas Health Science Center |
|---|---|

| 3:00 p.m. | **Keynote 2:** |
|---|---|
| | **Session Chair: Min-Shan Chen** |
| | **Dr. Michael Chang, OBI Pharma, Inc.** |
| | *Trend and recent development of Biotech Industry in Taiwan* |

| 4:00 p.m. | **Coffee Break** |
|---|---|

| 4:30 p.m. | **Panel 3: Beyond The Bench** |
|---|---|
| | **Moderator: Shu-Hui Chuang** |
| | **Dr. Elaine F. Chan,** Medical Metrics, Inc. |
| | **Dr. Carol Chuang,** The University of Texas MD Anderson Cancer Center |
| | **Dr. Ying-Ja Chen,** Pronutria Biosciences, Inc. |
| | **Dr. Po-Tsan Ku,** The University of Texas at Austin |

| 5:30 p.m.<br>6:00 p.m. | **Closing Remarks & Poster Award Ceremony** |
|---|---|

## Life and Science: A Case History and General Thoughts
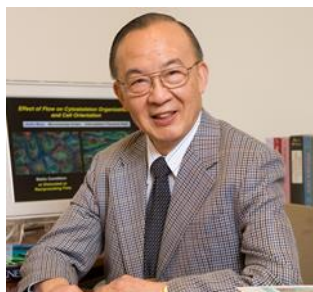
**Shu Chien** 錢煦

*Director, Institute of Engineering in Medicine, UC San Diego*

Professor Shu Chien is University Professor at the University of California San Diego, with research focuses on molecular, cellular and integrative bioengineering. He has served in leadership position in many professional organizations, including Federation of American Societies of Experimental Biology and American Institute for Medical and Biological Engineering. He is a member of National Academy of Sciences, National Academy of Engineering, National Academy of Medicine, and American Academy of Arts and Sciences, as well as Chinese Academy of Sciences and Academia Sinica. He has received many awards and medals, including the Presidential Prize in life sciences in Taiwan, ROC, and the National Medal of Science, the highest honor for scientists and engineers in USA, bestowed by President Obama.

## Trend and recent development of Biotech Industry in Taiwan

**Michael Chang** 張念慈

*Chairman & Founder, OBI Pharma, Inc.*

Dr. Michael Chang is the world's top chemist and entrepreneur. He found five pharmaceutical companies in U.S. and Taiwan and raised more than $1 billion. He served as President and Chief Executive Officer at Optimer Pharmaceuticals, Inc. from 1998 to 2009. From 1998 to 2000, Dr. Chang was the Chief Scientific Officer of Nu Skin Enterprises, Inc. In 1995, Dr. Chang co-founded Pharmanex, Inc., a natural healthcare company, where he was employed as Senior Vice President, Research and Development and Chief Science Officer. Before Pharmanex, Dr. Chang worked for 15 years in the pharmaceutical industry, at Merck & Co, Inc., Rhone-Poulenc Rorer Inc., and ArQule, Inc. In 2002, he brought his extensive experience back to Taiwan and found OBI Pharma, Inc.（台灣浩鼎）focusing on the immunotherapy in cancer and infectious diseases. Now the OBI Parma is the most valuable biotech company. His devotion lights up the future of biotechnology in the Taiwan.

## Panel 1: Academic Career Development
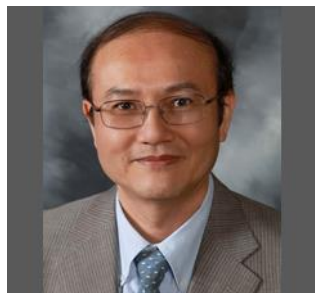
**Ching-Shih Chen** 陳慶士
*Professor, College of Pharmacy, The Ohio State University*

Professor Chen received his B.S. (1978) and M.S. (1980) degrees from National Taiwan University, and Ph.D. (1986) from University of Wisconsin-Madison. He then worked at University of Wisconsin as a postdoctoral fellow. He started his independent career as Assistant Professor of Pharmaceutical Science at University of Rhode Island in 1987 and became Associate Professor in 1991. He moved to University of Kentucky as Associate Professor in 1995 and was promoted to Professor in 1998. He joined the medicinal chemistry faculty at the Ohio State University Medical Center in 2001, and is the holder of the Lucius A. Wing Chair of Cancer Research and Therapy (2004-present). Since August 2014, he has been Director of Institute of Biological Chemistry at Academia Sinica, and Professor of Medicinal Chemistry at the Ohio State University and Professor of Biochemical Sciences at National Taiwan University. Professor Chen was a recipient of NIH Shannon Award, The V Foundation-AACR Translational Cancer Research award, Prostate Cancer Foundation award, Hearst Foundation award, and several awards at the Ohio State University. He is an elected fellow of American Association for the Advancement of Science and National Academy of Inventors. His recent work involves the development of novel cancer therapeutic agents that target KRAS signaling, cancer cachexia, cell surface receptor recycling, Notch and Hippo signaling pathways, as well as host-targeted broad-spectrum antiviral agents.

**Jer-Tsong Hsieh** 謝哲宗
*Professor, Department of Urology, UT Southwestern*

Dr. Hsieh received his B.S. degree from the National Taiwan University in 1982 and an M.S. degree from National Yang-Ming Medical College in Taipei, Taiwan. He received his Ph.D. in 1989 from the University of Wisconsin at Madison. Dr. Hsieh then did a post-doctoral fellowship at MD Anderson Cancer Center. Dr. Hsieh is now John McConnell Distinguished Chair Professor in Prostate Cancer Research and the Director of the Jean H. and John T. Walter, Jr., Center for Research in Urologic Oncology at UT Southwestern. He has received several awards including: the Gillson Longenbaugh Research Award; SBUR/Merck Young Investigator Award. These interests include: signaling pathways leading to cancer metastasis; develop of novel treatment strategies of advanced prostate cancer; and non-invasive molecular imaging.

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## Panel 1: Academic Career Development

**Jen Liou** 劉珍

*Assistant Professor, Dapartment of Physiology, UT Southwestern*

Dr. Jen Liou received her PhD in Microbiology and Immunology from University of California at San Francisco with a focus on dissecting signaling transduction events in lymphocyte activation using biochemical and genetic approaches. During her postdoctoral training under Dr. Tobias Meyer at Stanford University, Dr. Liou studied cellular signaling using systems biology and quantitative live-cell imaging approaches. She is now an assistant professor in Department of Physiology at UT Southwestern. Her studies are aimed at developing a better understanding of calcium transportation in cells and the dynamics at the organelle junctions.

**J. Jack Lee** 李君愷

*Associate Vice Provost, Quantitative Research, MD Anderson*

J. Jack Lee is professor of biostatistics, Kenedy Foundation Chair in Cancer Research, and Associate Vice Provost in Quantitative Research at MD Anderson. Dr. Lee received his dental degree in 1982 from the National Taiwan University and Ph.D. in biostatistics from UCLA in 1989. He joined UT MD Anderson Cancer Center in 1991. Dr. Lee' is active on developing and applying novel biostatistical methods for translational research, particularly in incorporating biomarkers and implementing Bayesian adaptive designs for clinical trials. He is a statistical editor for Journal of the National Cancer Institute and Cancer Prevention Research and an elected Fellow of American Statistical Association.

## Panel 1: Academic Career Development

**Ian Y. Lian  連裕仁**

*Assistant Professor, Department of Biology, Lamar University*

Dr. Lian conducted his undergraduate study in engineering physics and bioengineering, and mentored by Dr. Shu Chien during his graduate study in UCSD. To compliment his training in the engineering field, Dr. Lian receives his postdoc apprenticeship under Dr. Kun-Liang Guan in the area of cancer and stem cell biology. As an independent investigator at Lamar University, Dr. Lian combines basic science and engineering approaches to study the effect of microenvironment on the metastatic potential of cancer cells. In addition, his lab collaborated with teams in UCSD and Rice University to develop an amplification free nucleic-acid detection platform for the purpose of early cancer detection.

## Panel 2: R&D Jobs in Industry

**Keelung Hong  洪基隆**
*Founder, Chairman & CEO of Taiwan Liposome Company*
台灣微脂體

Dr. Hong's longstanding interest in improving cancer therapy has led to a series of breakthroughs and a number of patents in drug carrier technology for improving drug and gene delivery. After being a consultant to several biotech companies, Dr. Hong founded Taiwan Liposome Company in Taiwan and its subsidiary, TLC Biopharmaceuticals in United States. He currently serves as Chairman & CEO. Dr. Hong has built a team to pursue the dream of becoming a Taiwanese pharmaceutical company having drugs developed and made in Taiwan for global market. Under his leadership, TLC has been selected by Red Herring as a Winner of Asia Top 100 Company in 2006 and a Finalist of Global Top 100 in 2007.
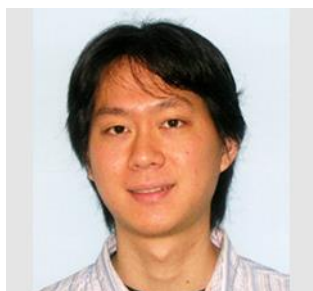
**Alex Li  李介元**
*Scientist, Fluidigm*

Chieh-Yuan Li (Alex) graduated from UC Berkeley with a B.S. in Chemical Biology and has several years of experience in biotechnology companies including Life Technologies by Thermo Fisher Scientific and Roche Molecular Diagnostics. As an R&D scientist, he was involved in developing genomic assays and technologies such as single-cell RNA-Seq, targeted-resequencing, gene expression, genotyping qPCR and IVD use assay. Alex is also the author of several patents and inventor of Ion Torrent's isothermal NGS sample preparation technology. Currently, Alex is pursuing a Ph.D. at the University of Texas MD Anderson Cancer Center.

## Panel 2: R&D Jobs in Industry

**Diane D.-S.Tang-Liu 湯丹霞**
*Scientific Advisor Board Member, Supra Integration and Incubation Center 台灣生技整合育成中心*
*CEO & President, DTL BioPharma Consulting*

Dr. Tang-Liu received B.S. in Pharmacy from National Taiwan University, and Ph.D. in Pharmaceutical Chemistry from the University of California, San Francisco. She is a full adjunct professor of Pharmacology and Pharmaceutical Sciences at the University of Southern California, and of Bioengineering and Therapeutic Sciences at the University of California, San Francisco. Diane was elected AAPS Fellow and ACCP Fellow. Dr. Tang-Liu is the CEO of DTL BioPharma Consulting, Inc., which provides strategic advice, operational expertise, and consulting services to biotechnology and pharmaceutical companies. Diane has co-founded Allgenesis, Inc.（新源生物科技），which develops NCEs and therapeutic proteins for global markets. She has 30 years of experience in pharmaceutical development with Allergan, Inc., and spent over 20 years in R&D executive and portfolio management.

**Ming-Chi Wu 吳明基**
*Former President/CEO, Development Center for Biotechnology 財團法人生物技術開發中心*
*University of North Texas Health Science Center at Fort Worth*

Dr. Wu received his BS degree in Agricultural Chemistry, National Taiwan University (1963), Ph.D. in Biochemistry, University of Wisconsin-Madison (1970), and postdoctoral training at Johns Hopkins Medical School and University of Pittsburgh Medical School. He started his academic career at University of Miami Medical School/Howard Hughes Medical Institute and later moved to University of North Texas Health Science Center at Fort Worth until his retirement in 2006. He then moved back to Taiwan to serve as President/CEO at Development Center for Biotechnology until 2008. His research involves in studying the structure, function and mechanism of hematopoiesis, plasminogen activator (coagulation) and its possible roles in cancer metastasis, as well as the potential applications of bone marrow, cord blood or mesenchymal stem cells in tissue repair and/or replacement. In addition to serving as a consultant on several biotech projects, he is a co-founder of a start-up company that engages in the process of developing a universal pneumonia vaccine.

## Panel 3: Beyond The Bench

**Elaine F. Chan** 陳芳婷

*Client Services Manager, Medical Metrics, Inc.*

Dr. Elaine Chan is a bioengineer and scientist by training. She received her bachelor's degree from Rice University and her Ph.D. from the University of California at San Diego, with a research focus in cartilage tissue engineering and 3-D statistical shape modeling. Her research interests include imaging and analysis of orthopedic medical devices and treatments, and her professional goal is to foster cross-cultural collaborations and assist Asia-based biotech companies to enter the US market. She currently works as a Client Services Manager at Medical Metrics, Inc., an imaging core lab for clinical trials.

**Carol Chuang** 莊可柔

*Clinical Research Program Coordinator, MD Anderson*

Dr. Chuang received her Ph.D. in biomedical sciences from Baylor College of Medicine with a focus on molecular and cellular biology. Prior to joining the Department of Investigational Therapeutics at MD Anderson Cancer Center (MDACC), she was a patent research analyst at Global Patent Solutions and a postdoctoral fellow in the Department of Translational Molecular Pathology at MDACC. Dr. Chuang joined MDACC as a regulatory coordinator in September 2014. Her various experiences have provided her with the tools to efficiently process clinical protocols to meet tight deadlines and to effectively communicate expected timelines and deliverables to the study Sponsor/CRO.

## Panel 3: Beyond The Bench
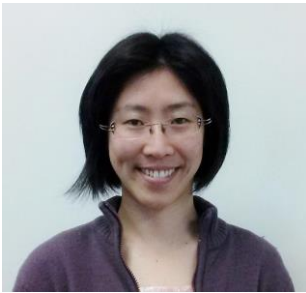
**Ying-Ja Chen 陳映嘉**

*Patent Agent, Pronutria Biosciences, Inc.*

Dr. Ying-Ja Chen is a Patent Agent at Pronutria Biosciences, a Boston-based biotech startup developing first-in-class oral biologics. Her role at Pronutria Biosciences transitioned from research in discovery science, where she focused on protein engineering, into intellectual property, where she develops strategies and prosecutes patent applications. She holds a BS. In Electrical Engineering from National Taiwan University, a Ph.D. in Bioengineering from the University of California, San Diego working with Dr. Xiaohua Huang on genome sequencing, and completed postdoctoral training at MIT with Dr. Christopher Voigt in synthetic biology.

**Po-Tsan Ku 辜博燦**

*Graduate Student and Postdoctoral Career Development Specialist, College of Natural Sciences, UT Austin*

Dr. Po-Tsan Ku is a Career Development Specialist at the University of Texas at Austin. He counsels graduate students and postdocs in career exploration, job searches and professional development. Before coming to UT Austin, he has been a product marketing manager with over thirteen years of experience in the biotechnology industry, including Ambion, Life Technologies and EMD Millipore. Prior to joining biotech industry, he completed postdoctoral training at UT Austin and Baylor College of Medicine. He received a MBA from UT Austin, PhD in Cell and Developmental Biology from Harvard University, and BS in Biology from University of South Florida.

## Elevator Talks

Poster Number: 11

## Scratching the Surface of Allergic Itch: More than Just Histamine

Cheng-Chiu Huang[1, 2] and Qin Liu[1, 2, 3] *

[1]Center for the Study of Itch, [2]Department of Anesthesiology, [3]Department of Ophthalmology & Visual Sciences, Washington University School of Medicine, St. Louis, MO

*Keywords: allergic conjunctivitis, ocular itch, histamine-independent, TRPA1, platelet-activating factor*

*INTRODUCTION* Ocular itch is the cardinal symptom of allergic conjunctivitis and afflicts 15-20% of the population worldwide. Histamine produced by mast cells has been implicated as the principal mediator of allergic ocular itch via TRPV1 activation. However, antihistamines cannot completely relieve ocular itch in many cases, suggesting the involvement of a histamine-independent itch pathway.

*RESULT AND DISCUSSION* TRPA1 channel mediates neuronal and behavioral responses to many histamine-independent pruritogens (itch-inducing molecules). Conjunctival mucosa is richly innervated by TRPA1^{+} sensory neurons. TRPA1-mediated neural pathway is required for ocular itch in allergic conjunctivitis, partly due to the platelet-activating factor secreted from mast cells upon allergen challenge. TRPA1 signaling complements the histamine-dependent pathway mediated by TRPV1 and confers severe itch sensation in ocular allergy. Genetic deletion or pharmacological blockade of both pathways abolishes allergic ocular itch in a mouse model. Interestingly, TRPA1 and TRPV1 play significantly reduced roles in urticaria, suggesting potential mechanistic differences between cutaneous and ocular itch. At the 1st TTBA symposium, I will also present our latest findings regarding the neural basis for ocular surface itch sensation.

*CONCLUSION* Pharmacological antagonism of TRPA1 channel is a novel therapeutic strategy for treating ocular itch in various allergic conditions.

# Elevator Talks

Poster Number: 17

## Sclerostin Antibody (Scl-Ab) Increases Bone Mass and Strength in a Mouse Model of Osteogenesis Imperfecta Caused by Wnt1 Mutation

<u>Yi-Chien Lee</u>[1], Kyu-Sang Joeng[1], Hao Ding[2], Xiaohong Bi[2], Catherine Ambrose[3] and Brendan Lee[1] *
[1]Department of Human and Molecular Genetics, Baylor Collage of Medicine, Houston, TX 77030, USA,
[2]Department of Nanomedicine and Biomedical Engineering, University of Texas Health Science Center at Houston, Houston, Texas 77030, USA, [3] Department of Orthopaedic Surgery, University of Texas Health Science Center at Houston, Houston, Texas 77030, USA

***Keywords: Anti-Sclerostin antibody, Osteogenesis Imperfecta, Wnt1, Wnt signaling, bone formation and homeostasis***

**BACKGROUND** Osteogenesis Imperfecta (OI) is a brittle bone disease characterized by low bone mass and multiple bone fractures. Recently, our laboratory and others have identified *WNT1* mutations in patients with OI. We have also established and described a mouse model of OI caused by *WNT1* mutations (*swaying* mouse model). Current treatment options for OI mostly focus on bisphosphonate therapy; however, because of its questionable efficacy in some OI patients and concerns about long-term administration, it is necessary to explore new treatment strategy. Sclerostin is a potent inhibitor of WNT signaling, and several studies have shown that the inhibition of sclerostin greatly enhances bone formation. Therefore, we hypothesized that Scl-Ab treatment could be beneficial for treating *WNT1* related OI and tested this hypothesis using our *swaying* mouse model.

**METHODS** In this study, we followed two treatment regimens: from week 3 to week 8 (the early treatment group) and from week 9 to week 14 (the late treatment group). *Swaying* mice and wild-type littermates were subcutaneously administered vehicle or 25 mg/kg Scl-Ab twice a week for 6 weeks (n=4-10 per group). Bone mass was assessed by ☐CT, bone strength by three-point bending, and matrix composition by Raman spectroscopy.

**RESULTS** First, the Scl-Ab treated *swaying* mice in the early treatment group exhibited reduced fracture rate from 90% (vehicle treated *swaying* mice) to 12.5% fracture rate (Scl-Ab treated *swaying* mice). ☐CT analysis showed that Scl-Ab treated *swaying* mice exhibited significantly increased bone volume per tissue volume in both the femur and lumbar spine (p-value < 0.01) in both early and late treatment groups. Three point bending analysis at the femur confirmed that the Scl-Ab treated *swaying* mice show increased bone strength parameters including maximum load, stiffness, and post-yield energy. Finally, Raman analysis demonstrated that the Scl-Ab treated *swaying* mice have increased bone collagen content in bone matrix.

**CONCLUSIONS** These results suggest that Scl-Ab treatment significantly rescued the low bone mass phenotype and increased bone strength in *swaying* mice. These results support future investigations of a potential clinical benefit of Scl-Ab in the management of OI patients with *WNT1* mutations.

# Elevator Talks

Poster Number: 20

## Microbe-Host Chemical Communication Regulates Host Metabolic Adaptation to Environmental Variations

Chih-Chun J. Lin[1, 2] and Meng C. Wang[1, 2] *

[1]Huffington Center on Aging, Baylor College of Medicine, Houston, TX 77030, USA, [2]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA

***Keywords: microbe-host interaction, environment, lipid metabolism***

Microbes residing in the host gut actively produce various metabolic molecules that exert crucial effects on host metabolic health. Environmental factors not only shape the composition of the host's resident microbes, but also modulate their metabolism. However, the exact molecular relationship among the environment, microbe-derived metabolites and host metabolism remains largely unknown. Here, we show that environmental methionine tunes bacterial methyl metabolism to regulate host mitochondrial dynamics and lipid metabolism in *Caenorhabditis elegans* through NR5A nuclear receptor-NHR-25 signaling. We demonstrate that methionine deficiency in bacterial medium decreases the production of bacterial metabolites that are essential for phosphatidylcholine synthesis in *C. elegans.* Reduction of diundecanoyl and dilauroyl phosphatidylcholines suppresses the activation of their receptor NHR-25, leading to increased lipid accumulation by promoting mitochondrial fragmentation. Together, our work reveals an environment-microbe-host metabolic axis that controls mitochondrial dynamics and lipid metabolism with critical consequence for host health and survival.

## Elevator Talks

Poster Number: 22

## Battle between Influenza A Virus and A Newly Identified Antiviral Activity of The PARP-containing ZAPL Protein

Chien-Hung Liu, Ligang Zhou, Guifang Chen, and Robert M. Krug*
Department of Molecular Biosciences, Center for Infectious Disease, Institute for Cellular and Molecular Biology, University of Texas, Austin, TX 78712

*Keywords: ZAPL PARP domain, influenza A virus polymerase protein subunits, proteasomal degradation, ubiquitination, poly(ADP-ribosylation).*

Previous studies showed that ZAPL (PARP-13.1) exerts its antiviral activity via its N-terminal zinc fingers that bind the mRNAs of some viruses, leading to mRNA degradation. Here we identify a different antiviral activity of ZAPL that is directed against influenza A virus. This ZAPL antiviral activity involves its C-terminal PARP domain, which binds the viral PB2 and PA polymerase proteins, leading to their proteasomal degradation. After the PB2 and PA proteins are poly(ADP-ribosylated), they are associated with the region of ZAPL that includes both the PARP domain and the adjacent WWE domain that is known to bind poly(ADP-ribose) chains. These ZAPL-associated PB2 and PA proteins are then ubiquitinated, followed by proteasomal degradation. This antiviral activity is counteracted by the viral PB1 polymerase protein, which binds close to the PARP domain and causes PB2 and PA to dissociate from ZAPL and escape degradation, explaining why ZAPL only moderately inhibits influenza A virus replication. Hence influenza A virus has partially won the battle against this newly identified ZAPL antiviral activity. Eliminating PB1 binding to ZAPL would be expected to substantially increase the inhibition of influenza A virus replication, so that the PB1 interface with ZAPL is a potential target for antiviral development.

# Elevator Talks

Poster Number: 25

## Engineered Primate L-Methioninase for Therapeutic Purposes.

Wei-Cheng Lu[1,3], Wupeng Yan[2], Olga Paley[1], Kendra Garrison[1], Andrew Ellington[2], Yan Zhang[2], Everett Stone[1,3], and George Georgiou*[,1,3]

[1]Department of Chemical Engineering, University of Texas at Austin, Austin, TX, [2]Department of Biochemistry, University of Texas at Austin, Austin, TX, [3]Aeglea BioTherapeutics, Austin, TX

***Keywords: Cystathionine γ-lyase, Methionine γ -lyase, Methionine deprivation***

In cancer biology research, it has been found that cancer cells exhibit different metabolism compared to normal cells and it has been shown that some types of cancer cells, such as glioblastomas, medulloblastomas and neuroblastomas are much more sensitive than normal cells to methionine starvation. Past studies have shown that methionine-dependent tumor cells are not able to survive if the serum methionine is decreased to ≤ 5uM. Systemic depletion of serum methionine can be achieved by *Pseudomonas putida* methionine gamma-lyase (pMGL) but it has proven to be rapidly inactivated *in vitro* and be highly immunogenic in primate models. In order to apply systemic methionine depletion to human cancer therapy, we engineered human cystathionine γ-lyase to accept methionine as a substrate and have isolated several human Methioninase (hMETase) variants with high activity. Several active hMETase variants isolated from a phylogenetic analysis library and the best variant, hMETase V8.4 showed a 10-fold improved $K_M$ (12.2 vs. 1.8mM) and 10-fold better $k_{cat}/K_M$ values (0.59 to 5.3 1/s.1/mM) in degrading methionine compared to our previous version of variant, hMETase V3.1. Furthermore, hMETase V8.4 showed greater stability in thermal melting analyses (melting temperature: 63.2 vs. 70.2°C) and also in serum stability (half-life: 75 vs. >100 hours) compared to hMETase V3.1. In pharmacodynamic analyses, hMETase V8.4 efficiently lowered serum methionine concentration from 75 μM to ~15 μM in 48 hours without the requirement of a methionine restricted diet (one dose: 50 mg/ kg). In addition, we tested the efficacy of hMETase V8.4 on C57L/6 mice bearing A375 melanoma xenografts and it significantly improved the median survival from 35 – 43 days compared to the control group. The hMETase V8.4 efficiently lowered serum methionine concentration in pharmacodynamic analyses. Also, it significantly improved the survival time of C57L/6 mice bearing fA375 melanoma xenografts. The hMETase V8.4 is a promising therapeutic enzyme candidate for systemic methionine depletion in cancer therapy.

## Elevator Talks

Poster Number: 27

## Architecture of The TIM23 Inner Mitochondrial Translocon and Interactions with The Hsp70-based Import Motor

See-Yeun Ting, Brenda A. Schilke, Masaya Hayashi, Elizabeth A. Craig*
Department of Biochemistry, University of Wisconsin, Madison, WI

*Keywords: Mitochondria, protein translocation, TIM23, import motor, protein-protein cross-linking*

Approximately 99% of the proteins residing in mitochondria are encoded by nuclear DNA and synthesized on cytosolic ribosomes. Therefore, mitochondrial biogenesis and function depend on efficient protein import mechanism. Proteins destined for the mitochondrial matrix are transported into mitochondria through channels in the outer and the inner membranes, TOM and TIM23 complex, respectively. Translocation of the proteins across the TIM23 complex, consisting of the transmembrane proteins Tim23 and Tim17, requires the action of the matrix localized, Hsp70-based import motor. The association of the import motor with the import channel (TIM23 complex) is key to efficient protein translocation. However, the organization of the motor machinery is ill-defined, and little is understood about the critical regulatory changes that occur during protein translocation.

We have utilized site-specific *in vivo* photo-crosslinking, along with genetic and co-immunoprecipitation analyses, to understand the interactions between the import motor and the translocon. We found that when Tim23 had a photoactivable cross-linker in a matrix exposed residue, it could be cross-linked to Tim44, an essential motor subunit that plays a central role in recruiting and "organizing" Hsp70 and other motor components at the translocon. When alterations were made in this loop, it destabilized the interaction of Tim44 with the translocon. Analogously, when Tim17 had a photoactivable cross-linker in a matrix exposed residue, it could be cross-linked to a regulatory subunit, Pam17, and alterations in this loop caused destabilization of the interaction of Pam17 with the translocon. In order to further understand the network interactions, we identified Tim44 residues directly involved in Hsp70 interaction using the same site-specific crosslinking approach. We found extensive interaction of Hsp70 with a region of Tim44 previously shown by genetic studies to be involved in motor regulation and thus, positioned at a site conducive for responding to conformational changes in the translocon upon a translocating polypeptide entering the channel.

# Elevator Talks

Poster Number:  30

**Membrane oxidation and oxidized lipids mediate efficient delivery of cell-penetrating peptides into live cells**

Ting-Yi Wang, Yusha Sun, Nandhini Muthukrishnan, Alfredo Erazo-Oliveras, Kristina Najjar, and Jean-Philippe Pellois*
Department of Biochemistry and Biophysics, Texas A&M University, College Station, TX

**Keywords: oxidation, cell delivery, oxidized lipids, plasma membrane translocation**

Cell-penetrating peptides (CPPs) are promising tools to deliver biologically active molecules or probes into live cells. However, the underlying mechanism by which CPPs translocate across cellular membrane is not thoroughly understood. This impedes their applications for cell biology studies and for therapeutic treatments. Here we describe a novel mechanism of cell penetration of polyarginine CPPs. For the first time, we reveal that the cell delivery of CPPs is dependent upon cellular oxidative stress and on the presence of oxidized lipids at the plasma membrane of human cells. Oxygen tension and antioxidants can dramatically impact cell penetration of the peptide, which involves in direct membrane translocation. We also show that naturally occurring oxidized lipids within the plasma membrane directly mediate the rapid and efficient transport of the peptide across this biological barrier by forming inverted micelles with CPPs. Our findings thereby provide new fundamental insights on the process of cell membrane translocation. This novel mechanism also leads to new opportunities for rationale design of highly efficient cell-permeable compounds and drug delivery strategies.

## Poster Abstracts

Poster Number:  1

## Lin-28 Promotes Symmetric Stem Cell Division And Drives Adaptive Growth in The Adult Drosophila Intestine

Ching-Huan Chen[1], Arthur Luhur[1] and Nicholas Sokol*
Department of Biology, Indiana University, Bloomington, IN; [1]These authors contributed equally to this work

*Keywords: Lin-28, Symmetric renewal, Intestinal stem cell, Drosophila*

Stem cells switch between asymmetric and symmetric division to expand in number as tissues grow during development and in response to environmental changes. The stem cell intrinsic proteins controlling this switch are largely unknown, but one candidate is the Lin-28 pluripotency factor. A conserved RNA-binding protein that is downregulated in most animals as they develop from embryos to adults, Lin-28 persists in populations of adult stem cells. Its function in these cells has not been previously characterized. Here, we report that Lin-28 is highly enriched in adult intestinal stem cells in the Drosophila intestine. lin-28 null mutants are homozygous viable but display defects in this population of cells, which fail to undergo a characteristic food-triggered expansion in number and have reduced rates of symmetric division as well as reduced insulin signaling. Immunoprecipitation of Lin-28-bound mRNAs identified Insulin-like Receptor (InR), forced expression of which completely rescues lin-28-associated defects in intestinal stem cell number and division pattern. Furthermore, this stem cell activity of lin-28 is independent of one well-known lin-28 target, the microRNA let-7, which has limited expression in the intestinal epithelium. These results identify Lin-28 as a stem cell intrinsic factor that boosts insulin signaling in intestinal progenitor cells and promotes their symmetric division in response to nutrients, defining a mechanism through which Lin-28 controls the adult stem cell division patterns that underlie tissue homeostasis and regeneration.

## Poster Abstracts

Poster Number: 2

## Tumor Suppression in Carcinogen-Induced And Genetic Models of Colon Cancer: Potential Role of The Lin28/let-7 Axis in Rats Fed Dietary Spinach

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*Keywords: Colon cancer, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), Polyposis in rat colon (Pirc), miRNAs.*

Environmental carcinogen exposure and gene mutations are known contributors to human colon cancer risk. In epidemiology studies, dietary vegetable intake has been associated with reduced rates of neoplasia in the GI tract and in other tissues. We investigated the chemopreventive efficacy of dietary spinach, a high chlorophyll-containing vegetable, in two different rodent models. In the first study, tumors were initiated using a cooked meat heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), which is a known multi-organ carcinogen in the rat. The second investigation used the polyposis in rat colon (Pirc) model, which carries a target-selected Apc mutation and develops tumors spontaneously in colon. Highly significant suppression of tumor formation was observed by dietary spinach in both genetic and carcinogen-induced rat models. Previous studies identified the miRNAs dysregulated in PhIP-induced rat colon tumors. Notably, the loss of mir-29c, mir-215, and several let-7 family members was "normalized" by dietary spinach treatment, in colon tumors and in the tumors from other target organs. Mechanistic studies implicated the Lin28/let-7 axis, which is under intense scrutiny from a therapeutic standpoint because the downstream targets have central roles in the etiology of colon cancer (e.g., c-myc).

# Poster Abstracts

Poster Number:  3

## NanoCluster Beacons Enable Enzyme-Free and Hybridization-Based $N^6$-Methyladenine Detection

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***Keywords: methyladenine-specific NanoCluster Beacon, $N^6$-methyladenine, silver cluster probe, enzyme-free detection, DNA methylation***

$N^6$-methyladenine (m6A) is an inheritable modification of DNA in bacteria, where it exerts essential functions in defense against virus, DNA replication, mismatch repair and gene transcription. Recent studies revealed the presences and roles of m6A in eukaryotes, suggesting its potential as an epigenetic mark. However, it has been challenging to identify a single m6A in a nucleic acid target. Here we introduce a simple, robust, enzyme-free and hybridization-based method. By using a novel silver nanocluster (Ag NC) probe, termed methyladenine-specific NanoCluster Beacon, maNCB, it is able to detect a single m6A in DNA targets. There are two components in maNCB, a Ag NC bearing DNA strand (NC probe) and a guanine-rich (G-rich) DNA strand (enhancer probe). Each DNA component has two regions: one is for recognizing (i.e. hybridizing with) the target, and the other, Ag NC bearing region and G-rich region in NC probe and enhancer probe, respectively, is for fluorescing once the target-probe complex is formed. The fluorescent spectrum of the maNCB varies in accordance with the alignment states of the Ag NC bearing region and the G-rich region. Our design utilized a guanine site on NC probe and an abasic site on enhancer probe. Both sites are in close proximity to the adenine/m6A residue in the target. The strength of interaction of guanine-adenine differs from that of guanine-m6A, which results in different alignment states of maNCB. By analyzing the fluorescent spectrum, we demonstrated that maNCB is able to detect m6A in a single base level; furthermore, maNCB can quantify the extent of methylation in a heterogeneous sample. To date, our method is the only hybridization-based technique with high reproducibility and robustness.

## Poster Abstracts

Poster Number: 4

**Switching the Fate of mRNA for Mitochondrial Biogenesis**

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***Keywords: Pumilio, PUF, post-transcriptional regulation, RNA-protein granule***

PUF proteins are post-transcriptional regulators that bind to the 3′ UTRs of mRNA transcripts. Herein, we show how a yeast PUF protein, Puf3p, responds to glucose availability to switch the fate of its bound transcripts that encode proteins required for mitochondrial biogenesis. Upon glucose depletion, Puf3p becomes heavily phosphorylated within its N-terminal region of low complexity, associates with polysomes, and promotes translation of its target mRNAs. Such nutrient-responsive phosphorylation toggles the activity of Puf3p to promote either degradation or translation of these mRNAs according to the needs of the cell. Moreover, activation of translation of pre-existing mRNAs might enable rapid adjustment to environmental changes without the need for de novo transcription. Strikingly, a Puf3p phosphomutant no longer promotes translation but becomes trapped in intracellular foci in an mRNA-dependent manner. Our findings suggest that the inability to properly resolve Puf3p-containing RNA-protein granules via a phosphorylation-based mechanism might be toxic to a cell.

## Poster Abstracts

Poster Number:  5

## Molecular Mechanisms of Ganaxolone Modulation of Neuronal Synaptic and Extrasynaptic GABA-A Receptors in the Hippocampus

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*Keywords: epilepsy, GABA-A receptor, tonic current, neurosteroid, ganaxolone.*

***INTRODUCTION*** Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one, GX) is the 3β-methylated synthetic analog of the endogenous neurosteroid allopregnanolone (AP). Neurosteroids are allosteric modulators of GABA-A receptors acting through high-affinity binding sites. GX has broad-spectrum anticonvulsant activity in seizure models and has been approved for epilepsy clinical trials. Although GX was previously tested in *Xenopus* oocytes expressing $\alpha1\beta2\gamma2L$ GABA-A receptors, its precise mechanism of action on native neurons remains largely unknown.

***OBJECTIVE*** In this study, we sought to characterize the allosteric and direct effects of GX on GABA-A receptor-mediated currents in native, acutely-dissociated hippocampal neurons from adult male mice. We also recorded the extrasynaptic receptor-mediated tonic currents in hippocampal slices.  Concentration-response profiles of GX were compiled in two distinct cell types: (i) $\delta$-containing dentate gyrus granule cells (DGGCs) and (ii) $\gamma$-containing CA1 pyramidal cells (CA1PCs).

***RESULTS*** GX displayed concentration-dependent, significantly greater GABA-evoked chloride currents of DGGCs (5-fold potentiation at 1 μM) than CA1PCs (2-fold potentiation at 1 μM). GX-potentiated GABA-gated currents were completely blocked by the dual synaptic and extrasynaptic GABA-A receptor antagonists bicuculline and gabazine, and also by the putative extrasynaptic-specific inhibitor zinc ($Zn^{2+}$). In direct activation of receptors, GX evoked inward currents in both DGGCs (EC50, 5.4 μM) and CA1PCs (EC50, 5.6 μM). In hippocampus slices, GX potentiated the extrasynaptic GABA-A receptor-mediated tonic currents in DGGCs. The tonic currents responses were diminished in $\delta$KO DGGCs, indicating a high selectivity for $\delta$-subunit receptors.

***CONCLUSIONS*** These results provide emerging evidence that GX is a potent allosteric modulator of GABA-A receptor-mediated inhibition in native ($\delta$-rich) DGGCs that regulate neuronal excitability and seizure susceptibility. These findings provide a mechanistic rationale for the use of GX in seizure disorders.

# Poster Abstracts

Poster Number: 6

## Comparison Between Ion Chamber And Solid State Radiation Detectors in Dosimetric Measurement Using Fluoroscopic Machine

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***Keywords: ion chamber, solid state detector, radiation dose.***

Ion chamber detector has been the gold standard for measuring radiation dose for many decades. For the past 10 years, solid state radiation detectors have been more commonly used in medical physics and biomedical engineering fields. In this study, we compared the outputs from ion chamber with solid state detectors for fluoroscopic machine dose measurement.

An ion chamber (Radcal, Model: MDH1015) and two solid state detectors (Unfors Xi and Raysafe X2) were tested in this study. GE OEC 9800 mobile fluoroscopic machine was used to generate the x-ray radiation. Copper sheets with thicknesses ranging from 1 mm to 4 mm and a 0.5 mm thick lead sheet were placed in the x-ray beam to make the automatic exposure rate control system of the fluoroscopic machine gradually increase the amount of x-ray radiation.

The results show good agreement among the three systems except in the low and very high level exposure rates (R/min). Unfors Xi over-responded in very low and high radiation level while Raysafe X2 over-responded in very high radiation level. The variations in measurements are due to the inherent differences in the detector technology used.
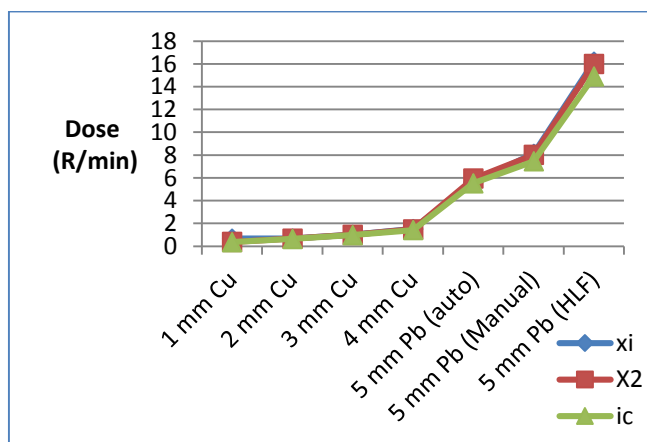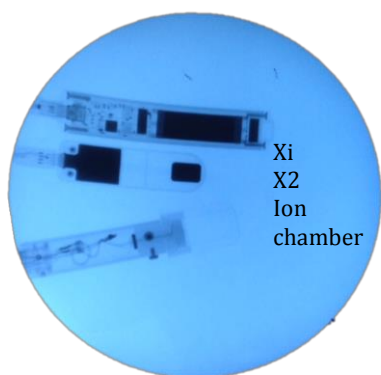


Figure 1: Detector setup under fluoroscopy



Figure 2: Radiation output measured by detectors

# Poster Abstracts

Poster Number: 7

## The Interaction of Oncogenic Phosphatase WIP1 and p27$^{Kip1}$ in DNA Damage Response

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*Keywords: WIP1, p27$^{Kip1}$, ATM, Cell cycle, DNA Damage Response*

**BACKGROUND** A mammalian cell undergoes the DNA Damage Response (DDR) after encountering various types of genotoxic stresses which result in single or double-stranded breaks in the DNA. The sensor kinases ATM and ATR detect this damage and activate downstream effectors through phosphorylation cascades to promote various cellular responses, including cell cycle arrest. Once DNA repair is complete, the expression of Wild-type p53-induced phosphatase 1 (WIP1) is induced to return the cell to a homeostatic state. WIP1 has been shown to dephosphorylate and downregulate various DDR mediators and effectors, including p53, CHK1, CHK2, ATM, ATR, and H2AX.

Currently, our knowledge of the function of WIP1 is mainly limited to its role in the DDR pathway. Preliminary data from our lab suggests that WIP1 may play a role in cell cycle regulation. An *in vitro* phosphatase screen was conducted in our lab to elucidate novel target sites of WIP1, including cell cycle targets that have previously been implicated in DNA Damage Response and ATM phosphorylation. Through this screen, we found that WIP1 may target known inhibitors of the cell cycle, including p27$^{Kip1}$.

We hypothesize that WIP1 dephosphorylates p27$^{Kip1}$ after completion of DNA Damage Response to promote cell cycle progression. To investigate the role of p27$^{Kip1}$ in DDR, we are examining the ability of WIP1 to target a phosphorylation site implicated in DDR signaling by ATM kinase on p27$^{Kip1}$, and testing the ability of WIP1 to promote cell cycle progression.

**MATERIAL AND METHODS** An *in vitro* phosphatase screen was performed incubating bacterially-purified recombinant WIP1 with 11-amino acid phosphopeptides designed with the surrounding sequence of potential targets. An ATM *in vitro* kinase assay was performed using immunopurified 15Gy IR activated-ATM from HEK 293 cells and recombinant p27. WIP1 and p27$^{Kip1}$ co-overexpression assays were conducted in 10Gy IR-treated HEK 293 cells with FLAG and Myc-tagged constructs, respectively.

**RESULTS** Our current results indicate that WIP1 targets a specific phosphorylation site on p27$^{Kip1}$ *in vitro* and in WIP1-overexpressed HEK 293 cells. ATM kinase appears to phosphorylate p27$^{Kip1}$ at the same site *in vitro* and during DDR in HEK 293 WT. These results partially validate our proposed model of WIP1 in cell cycle inhibition by p27$^{Kip1}$.

## Poster Abstracts

Poster Number: 8

## Morphometrics of Calcification and Relationships to FIbrous Cap in Carotid Endarterectomy Tissue

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*Keywords: atherosclerotic plaque, calcification, carotid endarterectomy, fibrous cap*

**BACKGROUND** Arterial calcification plays a significant role in the pathogenesis of a carotid atherosclerotic plaque development. The aim of this study was to provide a detailed analysis of calcification morphology based on histological features in carotid endarterectomy (CEA) specimens. Emphasis has been focused on calcium particle size and shape, particularly their relation to tissue anatomical location, lumen morphologies and fibrous cap thickness. These studies will help to understand the mechanisms of the arterial calcification process and elucidate the vulnerability fibrous cap.

**MATERIALS/METHODS** Representative frozen sections were cut from the common, bifurcation, internal and external segments obtained from 20 CEA samples. Histological Von Kossa stains were used to visualize the calcific particles and tissue compositions. The digitized images of sections were warped when necessary to achieve closure of the vessel wall. Image analysis was to determine the morphologies of calcium particles (size, shape and perimeter), lumen (area and perimeter), tissue (area and compositions) and fibrous cap thickness using ImageJ.

**RESULTS** Calcified particles ranged in size from smaller than 0.1mm2 to larger than 1.0mm2. Particles could be found in each of the 20 CEA tissues. Calcified areas were most abundant in the bulb segment followed by the internal segment and the common segment (p=0.001). The lumen area in the bulb segment deviated from a patent circular shape. The thin fibrous caps were associated with larger calcium particles, but the fibrous cap in the bulb segment was thicker.

**CONCLUSIONS** Calcified areas of various sizes were found in all CEA tissues. These areas were predominantly located at/near the bifurcation. The internal branches were more prone than external branches to calcification. As calcified area increased in size, the area shape became more elongated. The presence of various sized calcified particle, suggests that very small particles coalesce with neighboring particles to form larger patches (p=0.0001). The larger calcified particles were accompanied with thin fibrous caps.

# Poster Abstracts

Poster Number: 9

## Fat Percentage as Important Covariate on Propofol Pharmacokinetics in Pediatric Obese Population

Cheng-Hui Hsiao[1,3], Olutoyin Olutoye[2], David Lazar[2], Lei Wu[1], Dong Liang[3] and Diana S-L. Chow[1] *
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*Keywords: Propofol, Obesity, Pharmacokinetics, Pediatric, Anesthesia*

**PURPOSE** Propofol is widely used as anesthesia reagent in surgery. Current propofol dosing is calculated only based on total body weight without considering obese factor. However, lipophilic propofol may extensively distribute into adipose tissues which will result in different pharmacokinetic (PK) behavior among patients with diverse obese levels. The goal of this study is to determine the impact of obesity on propofol PK in pediatric population.

**METHODS** Patients between ages of 3 to 12 years old presenting for ambulatory surgery at Texas Children's Hospital could be our recruited subjects. BMI between 25th and 84th percentile were categorized as non-obese group (N=10), while patients of BMI>95 percentile were defined as obese (N=8). Propofol was administrated by IV bolus at a dose of 3 mg/kg and then Blood samples (0.5 ml) were collected at 0, 2, 15, 30 min, 4, 8, 12, and 24 hr after dosing. Propofol concentrations in plasma were analyzed by a validated LC-MS/MS assay. PK parameters were derived from propofol time-concentration profiles by population pharmacokinetic analysis using Phoenix WinNonlin 6.3. Age, body weight, fat percentage, BMI and BMI percentile covariates were evaluated for the impacts on propofol PK.

**RESULTS** Three-compartment open model with first-order elimination without a lag time best fitted the data, and primary parameters V, V2, V3 CL, CL2 and CL3 were estimated. Residual variability was best described by a log-additive error model. In continuous covariate model, CL3 typical value was 3.30 L/(kg*hr) for individuals with 22% of fat. Each 1% fat increase was corresponding to a 0.16 L/(kg*hr) decrease in CL3.

**CONCLUSIONS** Fat percentage is an important covariate which has an impact on propofol CL3 significantly in our obese pediatric model, while other demographic characters fail to affect propofol PK. Higher levels of obesity will lead to greater reductions of CL3. Our study suggests that fat percentage should be included into propofol dose calculation, beside body weight in obese pediatric population. Reduced maintenance dose for obese pediatric population decreases the risk of propofol accumulation in fat for long-term IV infusion. Start the text of your abstract here. Do not insert line spaces between paragraphs. Left justify all text and use Arial 11 point, except for affiliation information and keywords, which should be in 10 point. Please underline the name of the presenting author and make sure your abstract fits on one page of US Letter size paper with 1" margins on four sides.

## Poster Abstracts

Poster Number: 10

## Independent AMPK and SIRT1 Signaling Regulate C2C12 Differentiation and Metabolic Adaptation

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*Keywords: AICAR, NAD, nampt, PGC-1α*

Muscle metabolism changes ATP and NAD availability and has been associated with phenotypic plasticity. Some studies have suggested that AMPK-dependent plasticity may be an indirect consequence of increased NAD synthesis and SIRT1 activity. The primary goal of this study was to assess the interaction of AMP and NAD dependent signaling in adaptation of C2C12 myotubes. We compared changes in myotube developmental and metabolic gene expression following the combination of AICAR and nicotinamide mononucleotide (NMN). AICAR showed no effect on NAD pool, but significantly reduced GLUT1, COX2 and MYH3 expression and reduced myotube numbers. In contrast, NMN supplementation for 24 hours increased NAD pool by 45% but did not promote mitochondrial gene expression. The combination of AMP and NAD signaling did not induce further metabolic adaptation, but NMN ameliorated AICAR-induced myotube reduction. We interpret these results as indication that AMPK and SIRT1 regulate C2C12 differentiation and metabolic adaptation independently.

# Poster Abstracts

Poster Number:  11

## Scratching the Surface of Allergic Itch: More than Just Histamine

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***Keywords: allergic conjunctivitis, ocular itch, histamine-independent, TRPA1, platelet-activating factor***

***INTRODUCTION*** Ocular itch is the cardinal symptom of allergic conjunctivitis and afflicts 15-20% of the population worldwide. Histamine produced by mast cells has been implicated as the principal mediator of allergic ocular itch via TRPV1 activation. However, antihistamines cannot completely relieve ocular itch in many cases, suggesting the involvement of a histamine-independent itch pathway.

***RESULT AND DISCUSSION*** TRPA1 channel mediates neuronal and behavioral responses to many histamine-independent pruritogens (itch-inducing molecules). Conjunctival mucosa is richly innervated by TRPA1^{+} sensory neurons. TRPA1-mediated neural pathway is required for ocular itch in allergic conjunctivitis, partly due to the platelet-activating factor secreted from mast cells upon allergen challenge. TRPA1 signaling complements the histamine-dependent pathway mediated by TRPV1 and confers severe itch sensation in ocular allergy. Genetic deletion or pharmacological blockade of both pathways abolishes allergic ocular itch in a mouse model. Interestingly, TRPA1 and TRPV1 play significantly reduced roles in urticaria, suggesting potential mechanistic differences between cutaneous and ocular itch. At the 1st TTBA symposium, I will also present our latest findings regarding the neural basis for ocular surface itch sensation.

***CONCLUSION*** Pharmacological antagonism of TRPA1 channel is a novel therapeutic strategy for treating ocular itch in various allergic conditions.

## Poster Abstracts

Poster Number:  12

## Progressive Changes in A Distributed Neural Circuit Underlie Breathing Abnormalities in Mice Lacking MeCP2.

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***Keywords: Rett syndrome, MeCP2, respiratory network, breathing, apnea***

Rett syndrome (RTT) is a neurodevelopmental disorder caused by mutations in Methyl-CpG-binding protein 2 (*MECP2*). Severe breathing abnormalities are common in RTT, and are reproduced in mouse models of RTT. Previously, we found that removing MeCP2 from the brainstem and spinal cord in mice causes early lethality and abnormal breathing. To determine whether loss of MeCP2 in functional components of the respiratory network cause specific breathing disorders, we used the Cre/LoxP system to differentially manipulate MeCP2 expression throughout the brainstem respiratory network, specifically within HoxA4-derived tissues which include breathing control circuitry within the nucleus tractus solitarius and the caudal part of ventral respiratory column but do not include the pacemaker, pre-Bötzinger complex (preBötC), and components rostral to it. Surprisingly, we found that MeCP2 expression in the HoxA4 domain alone is critical for survival. To determine whether respiratory phenotypes manifested in animals with MeCP2 removal from specific pons-medullary respiratory circuits, we performed whole body plethysmography and electrophysiological recordings from in vitro brainstem slices from mice lacking MeCP2 in different circuits. Our results indicate that MeCP2 expression in the medullary respiratory network is sufficient for normal respiratory rhythm and preventing apnea. However, normal circuits within pontine respiratory group to preBötC are neither sufficient to prevent the hyperventilation nor abnormal ventilation hypoxic response, and our data show those functions require MeCP2 in other components of the respiratory network. Our study reveals that MeCP2 is differentially required in respiratory components for different aspects of respiratory functions, and collectively for the integrity of this network functions to maintain proper respiration.

# Poster Abstracts

Poster Number: 13

## Spectrin Cytoskeleton Orchestrates Peripheral Nervous System Node of Ranvier Assembly and Axon Integrity

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*Keywords: Spectrins, axon degeneration, node of Ranvier*

Spectrins are a family of cytoskeletal proteins that provide structural support of the cell membrane, link membrane-associated proteins to actin and serve as platforms for cell signaling. Spectrins consist of α and β subunits, forming heterotetramers to function as a complex. Among the spectrins, αII-spectrin is the only α-spectrin expressed in the nervous system. αII-spectrin is also implicated in neurological disorders, including traumatic brain injury, spinal cord injury, neurodegenerative diseases and West syndrome. Moreover, embryonic lethality of constitutive knockout mice with nervous system malformation highlights the importance of αII-spectrin in the nervous system.

Here, we investigate the function of the spectrin cytoskeleton in the brain by generating αII-spectrin conditional knockout (cko) mice. The central nervous system (CNS) cko animals (*Nestin-cre*) have profound neurological phenotypes and die perinatally. Loss of αII-spectrin results in dramatic reduction in all brain β-spectrins.

To specifically interrogate the spectrin function in neurons and to bypass the perinatal lethality observed in *Nestin-cre; αII-spectrin* cko mice, we generated sensory neuron specific αII-spectrin cko mice using *advillin-cre.* By electron microscopy (EM), we found that large diameter axons are more susceptible to degeneration in peripheral sensory neuron KO mice. Furthermore, by staining injury maker, ATF3, we observed ATF3^{+} dorsal root ganglia (DRG) neurons in cko mice beginning at P10 and increasing with age. Consistent with EM results, ATF3^{+} neurons are mostly large diameter neurons. The preferential degeneration of large diameter neurons accounts for the ataxic phenotype caused by deficits in proprioception while nociception remains unaffected. In addition, immunofluorescence shows that mutant mice have fewer nodes of Ranvier and sodium channel intensity at node is decreased. Moreover, paranodal junctions, flanking nodes, are extensively disrupted. Altogether, axon degeneration and disrupted node of Ranvier subdomain formation account for the reduction in nerve conduction in cko mice. Above all, we show that neuronal αII-spectrin is crucial for proper axonal functions, node of Ranvier assembly and axon integrity.

## Poster Abstracts

Poster Number: 14

## The Role of Chaperone in ATM Signaling

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*Keywords: ATM, Hsc70, Hsp70*

The Ataxia-Telangiectasia Mutated (ATM) protein kinase plays a critical role in both double-strand break repair and oxidative stress signaling. ATM belongs to the PIKK family and regulates many substrates in cell-cycle arrest, apoptosis, and DNA repair by phosphorylation. Our phosphoproteome and proteome mass spectrometry analysis using ATM-deficient cells from Ataxia Telangiectasia patients expressing separation of function alleles reveals phosphorylated substrates that are specifically regulated by different types of ATM activation. The results suggest that ATM control the phosphorylation of different substrates and may regulate intermediates that also regulate downstream kinases. With so many substrates, the chaperone family is our target based on previous results showing that heat shock proteins (Hsp70s) bind to ATM stoichiometrically in recombinant ATM preparations and that Serine 153 (S153) in constitutively expressed Hsp70 cognates (Hsc70) is phosphorylated during DNA damage. Hsc70 is one of the members of the Hsp70 family and contributes to protein folding and autophagy. Hsp70 and Hsc70 have high similarity in protein sequence and structure including the SQ/TQ motif at S153. The structure of Hsp70 relatives (Hsp110, Sse1) from yeast shows us that the location of the Hsp70 SQ/TQ site in yHsp110 may regulate substrate binding and/or ATP and ADP exchange. These findings inspire us to study the role of human Hsp70 and Hsc70 in oxidative stress and DNA damage activated ATM signaling. We propose that DNA damage or oxidation-activated ATM phosphorylates Hsc70 and possibly Hsp70, and that the phosphorylation controls chaperone activity. The chaperones can be the key that ATM uses to control multiple functions, because the association with many downstream substrates determines the direction of ATM downstream signaling and may further affect cancer development, immunodeficiency or neurodegenerative disease.

## Poster Abstracts

Poster Number: 15

## To Wnt or Not To Wnt: Tcf3 In Skin Tumorigenesis

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*Keywords: b-catenin, Wnt signaling, Lef/Tcfs, oncogene-induced senescence, skin cancer, squamous cell carcinoma*

The transcription factor Tcf3 (or Tcf7l) belongs to Lef/Tcf gene family, which forms transcriptional complex with nuclear β-catenin in the canonical Wnt signaling pathway. Tcf3 is also one of the embryonic stem cell signature genes that are upregulated in multiple aggressive cancer types, including non-melanoma skin cancer. Although alteration of β-catenin pathway and Tcf3 dysregulation have been implicated in skin cancer, Tcf3's role hasn't been defined as a β-catenin coactivator or TLE/Groucho co-repressor in the tumorigenic process. A well-established two stage chemical carcinogenesis model of mouse cSCC provides a platform to study how Tcf3 contributes to skin tumorigenesis. In this work, we show that Tcf3 acts as a tumor promoter in the chemical-induced model of mouse cSCC. Furthermore, we found that TCF3 overexpression increases tumor growth whereas loss of function of TCF3 and TCF4 reduces tumor growth in a xenograft model of human skin SCC. Using different Tcf3 deletion mutants (Tcf3ΔN, loss of β-catenin binding domain; Tcf3ΔG, loss of TLE/Groucho binding domain; Tcf3*, mutations at DNA-binding HMG box), we further demonstrate that Tcf3's tumorigenic role is independent of its binding to β-catenin, suggesting that Tcf3 functions primarily as a co-repressor to promote tumor growth. We also found that Tcf3 enhances cell migration and overrides RAS-induced senescence independently of its role as a β-catenin cofactor. Our findings establish a causal role for Tcf3 as a transcriptional repressor in skin tumorigenesis and elucidate the mechanisms underlying its tumorigenic capacity.
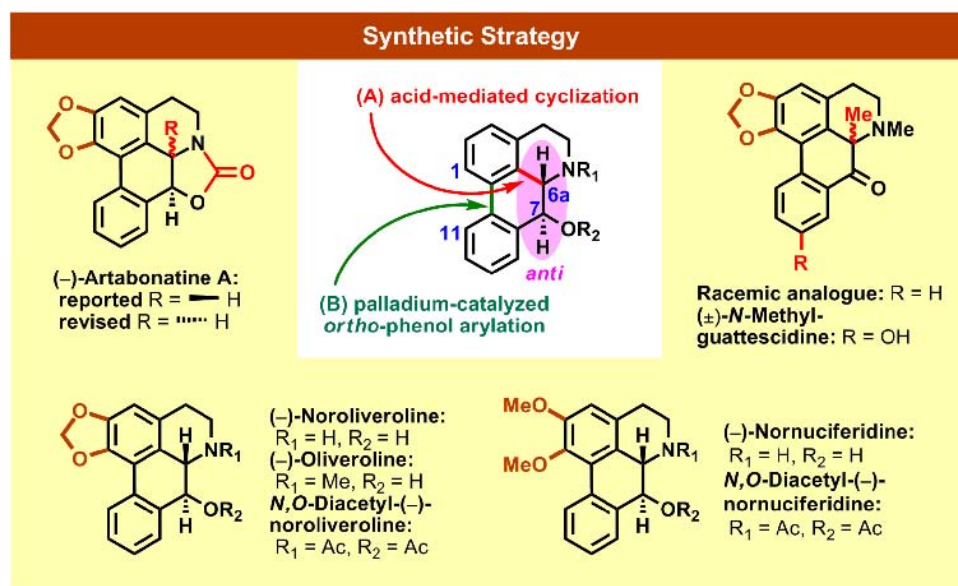
# Poster Abstracts

Poster Number: 16

## Synthetic Studies and Biological Evaluation of 7-Oxygenated Aporphine Alkaloids

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***Keywords: Aporphine, alkaloids, G protein-coupled receptor, adrenergic receptor***

Aporphine alkaloids are a privileged scaffold as GPCRs and monoamine transporter ligands. A series of 7-oxygenated aporphine alkaloids possessing anti-configuration between protons 6a and 7 have been identified in nature, but their pharmacology has not been extensively studied. In order to explore their bioactivities, a synthesis was established by utilizing a diastereoselective one-pot reductive acid-mediated cyclization followed by palladium-catalyzed ortho-arylations. Moderate catalyst loading (10 mol %) and short reaction times (30 min) were sufficient for the XPhos precatalyst to mediate the arylations in excellent yields. Five alkaloids in the families of noroliveroline and nornuciferidine were successfully prepared. However, the configuration of the natural product (−)-artabonatine A was revised from anti to syn based on comparison of NMR spectral data and specific rotations. In addition, (±)-artabonatine A and anti-(±)-artabonatine A demonstrated different in vitro pharmacological activities, and the enantiomer of (−)-nornuciferidine was discovered to be a potent antagonist of adrenergic β1 and β2 receptors. These results highlight the benefit of preparing natural products and non-natural isomers.



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# Poster Abstracts

Poster Number: 17

## Sclerostin Antibody (Scl-Ab) Increases Bone Mass and Strength in a Mouse Model of Osteogenesis Imperfecta Caused by Wnt1 Mutation

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*Keywords: Anti-Sclerostin antibody, Osteogenesis Imperfecta, Wnt1, Wnt signaling, bone formation and homeostasis*

**BACKGROUND** Osteogenesis Imperfecta (OI) is a brittle bone disease characterized by low bone mass and multiple bone fractures. Recently, our laboratory and others have identified *WNT1* mutations in patients with OI. We have also established and described a mouse model of OI caused by *WNT1* mutations (*swaying* mouse model). Current treatment options for OI mostly focus on bisphosphonate therapy; however, because of its questionable efficacy in some OI patients and concerns about long-term administration, it is necessary to explore new treatment strategy. Sclerostin is a potent inhibitor of WNT signaling, and several studies have shown that the inhibition of sclerostin greatly enhances bone formation. Therefore, we hypothesized that Scl-Ab treatment could be beneficial for treating *WNT1* related OI and tested this hypothesis using our *swaying* mouse model.

**METHODS** In this study, we followed two treatment regimens: from week 3 to week 8 (the early treatment group) and from week 9 to week 14 (the late treatment group). *Swaying* mice and wild-type littermates were subcutaneously administered vehicle or 25 mg/kg Scl-Ab twice a week for 6 weeks (n=4-10 per group). Bone mass was assessed by CT, bone strength by three-point bending, and matrix composition by Raman spectroscopy.

**RESULTS** First, the Scl-Ab treated *swaying* mice in the early treatment group exhibited reduced fracture rate from 90% (vehicle treated *swaying* mice) to 12.5% fracture rate (Scl-Ab treated *swaying* mice). CT analysis showed that Scl-Ab treated *swaying* mice exhibited significantly increased bone volume per tissue volume in both the femur and lumbar spine (p-value < 0.01) in both early and late treatment groups. Three point bending analysis at the femur confirmed that the Scl-Ab treated *swaying* mice show increased bone strength parameters including maximum load, stiffness, and post-yield energy. Finally, Raman analysis demonstrated that the Scl-Ab treated *swaying* mice have increased bone collagen content in bone matrix.

**CONCLUSIONS** These results suggest that Scl-Ab treatment significantly rescued the low bone mass phenotype and increased bone strength in *swaying* mice. These results support future investigations of a potential clinical benefit of Scl-Ab in the management of OI patients with *WNT1* mutations.

## Poster Abstracts

Poster Number:  18

## Fast And Large-scale Genetic Screen in *Dictyostelium*

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*Keywords:  whole-genome sequencing, chemical mutagenesis, genetic screen*

*Dictyostelium discoideum* is a social amoeba that straddles both the unicellular and the multicellular life forms. *Dictyostelium* cells proliferate as solitary cells by binary fission while feeding on bacteria. Upon starvation, up to 100,000 cells aggregate together and undergo multicellular development to form a fruiting body. During aggregating development, two immunoglobulin-like adhesive proteins, TgrB1 and TgrC1, play key roles in initiating morphogenesis. Cells with defective *tgrB1* or *tgrC1* gene are developmentally lethal and fail to undergo cell differentiation and morphogenesis. Despite the crucial roles of the TgrB1-TgrC1 system during development, little is known about the underlying signaling pathways.

In *Dictyostelium*, most of the genetic screens in the past 25 years were done by insertional mutagenesis. We used this method to look for genetic modifiers of the *tgrC*-defective phenotype but found very weak modifiers. Therefore, we developed a new method for genetic screens by integrating chemical mutagenesis and whole-genome sequencing, and developed tools to streamline the identification of SNVs (single nucleotide variants). As a proof-of-concept, we screened for and found chemically mutagenized cells with chemotaxis-defects or photo-killing resistance. We then applied the methods to screen for suppressor of the *tgrC1*-defective phenotypes. We found 63 suppressor mutants and sequenced their genomes. There were about 20 mutations per genome and nine candidate genes were mutated independently three times or more. Interestingly, we found two recurrent mutations (G275D and G307D) in the first immunoglobulin domain of TgrB1. Ectopic expression of the mutant alleles, *tgrB1*[G275D] or *tgrB1*[G307D], partially rescued the development of the *tgrC1*-defective cells. Therefore, the G275D and G307D mutations in *tgrB1* are causative, dominant gain-of-function mutations.

In this study, we developed a novel genetic screen pipeline in *Dictyostelium* by coupling chemical mutagenesis and whole-genome sequencing. We also demonstrated that our method allows us to saturate the screen with a relatively small number of mutants and to identify the causative mutations. This new screening strategy is less labor intensive, fast (<6 months) and relatively inexpensive ($100 per genome with 20X coverage) with lots of potential applications, such as drug screens and understanding the mechanisms of drugs with unknown targets.

## Poster Abstracts

Poster Number: 19

## How Does Experience Affect Visual Search in 2D vs. 3D Environments?

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***Keywords: visual search, memory, eye-tracking, immersive virtual reality***

Memory is likely an important determinant of attention allocation during daily human behaviors. Previous studies have shown that memory guides visual search in 2D images. However, it is unclear how these findings extend to 3D environments and whether experience affects visual search differently in 2D and 3D platforms. We developed a 3D immersive virtual reality experiment and a 2D experiment in parallel, and recorded eye movements as a measure of attention deployment. Subjects explored one 3D room or viewed 2D snapshots for one minute and then searched for a series of targets in the same platform. The number of fixations required to locate the targets decreased rapidly and was similar in both 2D and 3D. Interestingly, most of the improvement reflects learning to choose the correct room to look for a given target. Once in the correct room, search is very rapid and objects were located within 3-5 fixations in either environment. As experience grows, higher proportions of fixations are made to local regions that contain the targets. Previous exposure (one minute) to the context did not facilitate subsequent search in both 2D and 3D. In addition, there was little or no effect of experience with the environment on subsequent search for contextual objects in the scene. Incidental fixations made during previous trials also do not seem to benefit search much. Thus, search in both 2D and 3D environments is comparable, and the primary effect of experience on search depends on task relevance (i.e., previously searched objects are easily remembered but not otherwise). We speculate that the effects of context either require much more extensive experience, or else a pre-exposure that immediately precedes the search episode.

## Poster Abstracts

Poster Number: 20

## Microbe-Host Chemical Communication Regulates Host Metabolic Adaptation to Environmental Variations

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***Keywords: microbe-host interaction, environment, lipid metabolism***

Microbes residing in the host gut actively produce various metabolic molecules that exert crucial effects on host metabolic health. Environmental factors not only shape the composition of the host's resident microbes, but also modulate their metabolism. However, the exact molecular relationship among the environment, microbe-derived metabolites and host metabolism remains largely unknown. Here, we show that environmental methionine tunes bacterial methyl metabolism to regulate host mitochondrial dynamics and lipid metabolism in *Caenorhabditis elegans* through NR5A nuclear receptor-NHR-25 signaling. We demonstrate that methionine deficiency in bacterial medium decreases the production of bacterial metabolites that are essential for phosphatidylcholine synthesis in *C. elegans.* Reduction of diundecanoyl and dilauroyl phosphatidylcholines suppresses the activation of their receptor NHR-25, leading to increased lipid accumulation by promoting mitochondrial fragmentation. Together, our work reveals an environment-microbe-host metabolic axis that controls mitochondrial dynamics and lipid metabolism with critical consequence for host health and survival.

## Poster Abstracts

Poster Number:  21

## Identification of Putative Biomarkers and Drug Targets by Multi-omics Analyses of Breast Cancer Metabolism

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***Keywords: cancer metabolism, multi-omics, biomarkers, drug targets, somatic mutation, gene expression, RNA-Seq, breast cancer, metabolite ratio.***

Cancer cells alter metabolism to meet their high demands on energy and supplies, and such dysregulated metabolism plays a central role in carcinogenesis. It has been hypothesized that targeting altered metabolism would halt cancer progression. However, it is unclear how the cancer metabolism alters and what effects these alterations have on carcinogenesis. Therefore, I propose to integrate multi-omics data to determine the impactful metabolism changes and to identify putative drug targets and prognostic markers in breast cancer. Combining somatic mutation and RNA-Seq data in the breast cancer cohort of The Cancer Genome Atlas (TCGA), I found that *TP53* mutants correlate with high expression of *GLUT1*, the glucose transporter as an initiator of glycolysis. The result indicates that functionally impaired *TP53* reduces the repression of *GLUT1*, which is consistent with the previous finding in the rhabdomyosarcoma cell line. More importantly, the expression level of *GLUT1* separates patient survival in breast cancer wild type *TP53* subcohort. This result implies that elevated *GLUT1* expression may promote the import of glucose, lead to more energy production through glycolysis, and contribute to carcinogenesis and poor survival. In addition, I also determined the metabolite ratios that are different among subtypes by Wilcoxon rank-sum test. Based on the hierarchical clustering of top 50 significant different metabolite ratios (false discovery rate <=0.02), the results show that patients of more aggressive subtypes (i.e., HER2-positive and basal subtypes) are clustered together under a huge clade. The data suggest that metabolite ratios are potential subtype classifiers and survival predictors, and may hint drug target candidates. Overall, the current findings demonstrate the importance of altered metabolism in carcinogenesis, shed light on breast cancer metabolism and may accelerate the development of treatments targeting dysregulated cancer metabolism.

## Poster Abstracts

Poster Number:  22

**Battle between Influenza A Virus and A Newly Identified Antiviral Activity of The PARP-containing ZAPL Protein**

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***Keywords: ZAPL PARP domain, influenza A virus polymerase protein subunits, proteasomal degradation, ubiquitination, poly(ADP-ribosylation).***

Previous studies showed that ZAPL (PARP-13.1) exerts its antiviral activity via its N-terminal zinc fingers that bind the mRNAs of some viruses, leading to mRNA degradation. Here we identify a different antiviral activity of ZAPL that is directed against influenza A virus. This ZAPL antiviral activity involves its C-terminal PARP domain, which binds the viral PB2 and PA polymerase proteins, leading to their proteasomal degradation. After the PB2 and PA proteins are poly(ADP-ribosylated), they are associated with the region of ZAPL that includes both the PARP domain and the adjacent WWE domain that is known to bind poly(ADP-ribose) chains. These ZAPL-associated PB2 and PA proteins are then ubiquitinated, followed by proteasomal degradation. This antiviral activity is counteracted by the viral PB1 polymerase protein, which binds close to the PARP domain and causes PB2 and PA to dissociate from ZAPL and escape degradation, explaining why ZAPL only moderately inhibits influenza A virus replication. Hence influenza A virus has partially won the battle against this newly identified ZAPL antiviral activity. Eliminating PB1 binding to ZAPL would be expected to substantially increase the inhibition of influenza A virus replication, so that the PB1 interface with ZAPL is a potential target for antiviral development.

## Poster Abstracts

Poster Number: 23

## Dynamics of EGFR trafficking from membrane into deep cytoplasm revealed by a spatiotemporally multiplexed 3D tracking microscope

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***Keywords: EGFR, two photon microscope, single particle tracking, biomolecule trafficking***

Important discoveries in the last decades have changed our view of the plasma membrane organization and dynamics using 2D single-molecule or single-particle tracking. However, the extent of epithelial growth factor receptor (EGFR) trafficking from plasma membrane into deep cytoplasm is controversial due to the lack of 3D tracking capacity. Here we use a spatiotemporally multiplexed imaging method, termed **T**racking of **S**ingle particles **U**sing **N**onlinear **A**nd **M**ultiplexed **I**llumination (**TSUNAMI**), for visualization of EGFR trafficking from membrane into deep cytoplasm on live cells. The trafficking of membrane proteins is often characterized by transient behaviors such temporary confinement in a particular zone followed by periods of random diffusion or directed movement. To scrutinize the possible transient behaviors of EGFR trajectories, five motion modes (Brownian, corralled, hop, cage, and directed diffusions) were simulated and evaluated as the references, and the dissection of the complex trajectories and the classification of transient subtrajectories were achieved using temporal mean-squared displacement analysis and confinement detection. The dynamic parameters were then extracted by fitting the curves of MSD versus time to analytical forms. Here we characterize and classify the motion signature of EGFRs from cell membrane to cytoplasm into four phases which can be clearly differentiated in the acquired 3D trajectories. Our approach successfully recovered the diffusion coefficients of Brownian diffusion ($0.0012 \pm 0.0004$ µm$^2$/s) and that of confined diffusion ($0.0010 \pm 0.0002$ µm$^2$/s), the length of confinement area ($67 \pm 92$ nm), and the velocity of directed motion ($0.52 \pm 0.33$ µm/s) from the EGFR trajectories with the stimulation of epithelial growth factor (EGF). We believe that the present strategy may represent a useful asset for future research on membrane protein trafficking.

## Poster Abstracts

Poster Number: 24

## SPDEF Enforces Tumor Quiescence by Shifting The Transcriptional Targets of Activated β-catenin

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*Keywords: colorectal cancer, TCF/LEF factors, chromatin, xenograft, adenoma, tumorigenesis, tumor suppressor, transcription, tumor initiating cell, quiescence*

**BACKGROUND** Colorectal cancer (CRC) carcinogenesis is driven by a series of genetic and epigenetic changes that results in the oncogenic transformation of normal colonic mucosa. Canonical Wnt/β-catenin signaling pathway activation, with resultant high β-catenin transcriptional activity, is frequently implicated human CRC (~ 90% of CRC); however, there are currently no treatments targeting this pathway. We have previously reported that SAM Pointed Domain Ets transcription Factor (SPDEF) is lost in the majority of CRC, and suggest that it is a colonic tumor suppressor that negatively regulates canonical Wnt/β-catenin signaling. In agreement with the tumor repressor role of SPDEF, the absence of SPDEF enhances intestinal tumor formation, while re-expression of SPDEF inhibits colon adenocarcinoma proliferation in both genetic (Apc$^{min/+}$) and colitis-associated (AOM/DSS) CRC models. *However, the molecular mechanism by which SPDEF mediates colorectal tumor repression is still largely unknown.* Here we aim to elucidate the molecular mechanism that SPDEF-mediated repression of canonical Wnt/β-catenin signaling in CRC.

**MATERIALS AND METHODS** To achieve our goal, we directly analyzed the effects of SPDEF expression in β-catenin-driven intestinal tumors *in vivo* using a new inducible mouse model (*Lgr5$^{CreERT2}$; β-catenin$^{exon3}$; Rosa26$^{rtta-ires-EGFP}$; TRE-Spdef*) and human colon cancer xenografts. Moreover, wildtype or truncated SPDEF mutants were used for β-catenin transcriptional activity assay, co-immunoprecipitation, and chromatin immunoprecipitation in human colon cancer cell lines.

**RESULTS** In this study, we find that the transcription factor SAM Pointed Domain containing ETS transcription Factor (SPDEF) is sufficient to inhibit β-catenin-driven intestinal tumorigenesis and restrict established tumor growth in both transgenic mice and xenografted human colon cancer cells. SPDEF inhibits canonical β-catenin transcriptional activity through protein-protein interaction, which appears to be distinct from the traditional function of SPDEF as a DNA-binding transcription factor. We find that SPDEF disrupts the binding between β-catenin and its DNA binding partners TCF1 and TCF3, selectively displacing β-catenin from the promoter/enhancer regions of cell cycle genes without affecting stem cell signature genes. Consistent with this observation, re-expression of SPDEF enforces a quiescent state on β-catenin-driven tumor cells *in vivo*. *Taken together, for the first time, we unveil a novel mechanism in which SPDEF shifts the transcriptional targets of activated β-catenin to regulate the active and quiescent switch in tumor initiating cells.* These findings provide insights into the mechanisms that can regulate tumor initiating cells quiescence, and offer a novel angle for targeting canonical Wnt/β-catenin transcriptional machinery as a therapeutic strategy.

# Poster Abstracts

Poster Number:  25

## Engineered Primate L-Methioninase for Therapeutic Purposes.

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*Keywords: Cystathionine γ-lyase, Methionine γ -lyase, Methionine deprivation*

In cancer biology research, it has been found that cancer cells exhibit different metabolism compared to normal cells and it has been shown that some types of cancer cells, such as glioblastomas, medulloblastomas and neuroblastomas are much more sensitive than normal cells to methionine starvation. Past studies have shown that methionine-dependent tumor cells are not able to survive if the serum methionine is decreased to ≤ 5uM. Systemic depletion of serum methionine can be achieved by *Pseudomonas putida* methionine gamma-lyase (pMGL) but it has proven to be rapidly inactivated *in vitro* and be highly immunogenic in primate models. In order to apply systemic methionine depletion to human cancer therapy, we engineered human cystathionine γ-lyase to accept methionine as a substrate and have isolated several human Methioninase (hMETase) variants with high activity. Several active hMETase variants isolated from a phylogenetic analysis library and the best variant, hMETase V8.4 showed a 10-fold improved $K_M$ (12.2 vs. 1.8mM) and 10-fold better $k_{cat}/K_M$ values (0.59 to 5.3 1/s.1/mM) in degrading methionine compared to our previous version of variant, hMETase V3.1. Furthermore, hMETase V8.4 showed greater stability in thermal melting analyses (melting temperature: 63.2 vs. 70.2°C) and also in serum stability (half-life: 75 vs. >100 hours) compared to hMETase V3.1. In pharmacodynamic analyses, hMETase V8.4 efficiently lowered serum methionine concentration from 75 µM to ~15 µM in 48 hours without the requirement of a methionine restricted diet (one dose: 50 mg/ kg). In addition, we tested the efficacy of hMETase V8.4 on C57L/6 mice bearing A375 melanoma xenografts and it significantly improved the median survival from 35 – 43 days compared to the control group. The hMETase V8.4 efficiently lowered serum methionine concentration in pharmacodynamic analyses. Also, it significantly improved the survival time of C57L/6 mice bearing fA375 melanoma xenografts. The hMETase V8.4 is a promising therapeutic enzyme candidate for systemic methionine depletion in cancer therapy.

## Poster Abstracts

Poster Number:  26

# Intramolecular Allosteric Communication in Dopamine D2 Receptor Revealed by Evolutionary Amino Acid Co-variation

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***Keywords: allostery, G-protein-coupled receptors, residue co-variation***

The structural basis of allosteric signaling in G-protein-coupled receptors (GPCRs) is important in guiding design of therapeutics and understanding phenotypic consequences of genetic variation. The Evolutionary Trace (ET) algorithm previously proved effective in redesigning receptors to mimic the ligand specificities of functionally distinct homologues. We now expand ET to consider mutual information, with validation in GPCR structure and dopamine D2 receptor (D2R) function. The new algorithm, called ET-MIp, identifies evolutionarily relevant patterns of amino acid co-variations. These improve predictions of structural proximity from co-evolution, and D2R mutagenesis demonstrates that ET-MIp predicts functional interactions between residue pairs, especially with regard to the potency and efficacy of activation by dopamine. Remarkably, although most of the residue pairs chosen for mutagenesis are neither in the binding pocket nor in contact with each other, many exhibited functional interactions, implying predominantly at-a-distance coupling. Equally striking, the extent of functional interaction between the coupled pairs correlated best with the evolutionary coupling potential derived from D2R orthologs, just 44 sequences, rather than broader sets of GPCR sequences. These data suggest that the allosteric communication responsible for dopamine responses is resolved by ET-MIp, conserved, and best discerned within a short evolutionary distance. Most double mutants restored dopamine response to wild-type levels, also suggesting that tight regulation of the response to dopamine drove the co-evolution and intramolecular communications between coupled residues. Our approach provides a general tool to identify evolutionary co-variation patterns in small sets of close sequence homologs and to translate them into functional linkages between residues.

## Poster Abstracts

Poster Number: 27

## Architecture of The TIM23 Inner Mitochondrial Translocon and Interactions with The Hsp70-based Import Motor

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***Keywords: Mitochondria, protein translocation, TIM23, import motor, protein-protein cross-linking***

Approximately 99% of the proteins residing in mitochondria are encoded by nuclear DNA and synthesized on cytosolic ribosomes. Therefore, mitochondrial biogenesis and function depend on efficient protein import mechanism. Proteins destined for the mitochondrial matrix are transported into mitochondria through channels in the outer and the inner membranes, TOM and TIM23 complex, respectively. Translocation of the proteins across the TIM23 complex, consisting of the transmembrane proteins Tim23 and Tim17, requires the action of the matrix localized, Hsp70-based import motor. The association of the import motor with the import channel (TIM23 complex) is key to efficient protein translocation. However, the organization of the motor machinery is ill-defined, and little is understood about the critical regulatory changes that occur during protein translocation.

We have utilized site-specific *in vivo* photo-crosslinking, along with genetic and co-immunoprecipitation analyses, to understand the interactions between the import motor and the translocon. We found that when Tim23 had a photoactivable cross-linker in a matrix exposed residue, it could be cross-linked to Tim44, an essential motor subunit that plays a central role in recruiting and "organizing" Hsp70 and other motor components at the translocon. When alterations were made in this loop, it destabilized the interaction of Tim44 with the translocon. Analogously, when Tim17 had a photoactivable cross-linker in a matrix exposed residue, it could be cross-linked to a regulatory subunit, Pam17, and alterations in this loop caused destabilization of the interaction of Pam17 with the translocon. In order to further understand the network interactions, we identified Tim44 residues directly involved in Hsp70 interaction using the same site-specific crosslinking approach. We found extensive interaction of Hsp70 with a region of Tim44 previously shown by genetic studies to be involved in motor regulation and thus, positioned at a site conducive for responding to conformational changes in the translocon upon a translocating polypeptide entering the channel.

## Poster Abstracts

Poster Number: 28

## Yki Interacts with the JNK Pathway to Regulate Epidermal Wound Healing in Drosophila Larvae

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***Keywords: wound healing, Hippo pathway, JNK pathway***

To cope with inevitable injury, organisms possess efficient wound healing mechanisms to maintain tissue integrity and guard against infection. However, the cellular and molecular details by which wound healing is accomplished remain poorly defined. Drosophila melanogaster serves as a great model organism to study wound healing because of the versatile genetic tools available and the simple anatomy of the epidermal barrier. Upon larval epidermal wounding, epidermal cells around the wound elongate and migrate in the absence of cell division to ultimately close the wound. Using the wound closure assay we established, we found the Hippo downstream transcriptional regulator, Yorkie (Yki) and its TEAD binding partner Scalloped (Sd) to be required for epidermal wound healing. Intriguingly, unlike in other regenerative contexts, Yki does not regulate the balance of mitosis or apoptosis in the healing larval epidermis. Rather, it seems to regulate actin polymerization in the migrating wound-edge epidermal cells. Moreover, with a series of genetic analyses, we found that Yki has a strong genetic interaction with another wound closure signaling, the Jun N-terminal Kinase (JNK) pathway. Our results suggest that there is a positive feedback loop between these two pathways to facilitate proper epidermal wound healing.

# Poster Abstracts

Poster Number: 29

## The Cell-Adhesion GPCR Brain-Specific Angiogenesis Inhibitor 1 Regulates Dendritic Spine Morphology and Synaptogenesis.

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*Keywords: Synaptogenesis, Cell-Adhesion G Protein-Coupled Receptors, Neurodevelopment, Signaling, Dendritic Spines, Cell Shape Change,*

Synapses are specialized sites that mediate communication between neurons. Most excitatory synapses in the brain reside on actin-rich structures called dendritic spines. The formation, regulation and maintenance of excitatory synapses are crucial for normal cognitive function.

Recently, we have identified the adhesion G protein-coupled receptor (GPCR) brain-specific angiogenesis inhibitor 1 (BAI1) as a key regulator of synapse development. We show that BAI1 is highly localized to spines. Furthermore, knockdown of BAI1 results in decreased spine and synapse density in both cultured hippocampal neurons and cortical neurons from intact mouse brains. Synaptic loss caused by BAI1 knockdown can be rescued by full-length BAI1, but not by a BAI1 truncation mutant, which fails to interact with the Par3/Tiam1 polarity complex. Tiam1 is a Rac1-guanine nucleotide exchange factor (GEF) that promotes spine and synapse development by inducing Rac1-dependent actin remodeling. Tiam1 is restricted to spines by the polarity protein Par3, enabling for spatial control of Rac1 activation. We show that BAI1 regulates spine and synapse development by recruiting the Par3/Tiam1 complex to spines, resulting in localized Rac activation and actin polymerization. Although these findings elucidate how BAI1 signals inward to promote post-synaptic development, it is unclear whether BAI1 also signals across the synapse to induce pre-synaptic differentiation. Utilizing a COS7 cell-neuron co-culture system, we show that BAI1 increases pre-synaptic termini formation on the axons of cultured hippocampal neurons that contact BAI1-expressing COS7 cells. These results indicate that BAI1 can induce pre-synaptic as well as post-synaptic development. Our future investigations are two-fold: (1) We have also shown that BAI1 interacts with important ligands that regulate synaptic development such as Neuroligin-1 and the complement factor C1ql3. Investigating the importance of N-terminal domains that interact with these ligands will further elucidate mechanisms for BAI1's regulation of synaptogenesis. (2) Given that the two other BAI family members are also highly expressed in the brain, affect neuron morphology, and have been linked to neurological disease, we are investigating their role as regulators of spine and synapse development. Results from our study should help to elucidate the mechanisms that regulate excitatory synapse development, and provide potential therapeutic targets for the treatment of neurological disease.

## Poster Abstracts

Poster Number:  30

**Membrane oxidation and oxidized lipids mediate efficient delivery of cell-penetrating peptides into live cells**

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***Keywords: oxidation, cell delivery, oxidized lipids, plasma membrane translocation***

Cell-penetrating peptides (CPPs) are promising tools to deliver biologically active molecules or probes into live cells. However, the underlying mechanism by which CPPs translocate across cellular membrane is not thoroughly understood. This impedes their applications for cell biology studies and for therapeutic treatments. Here we describe a novel mechanism of cell penetration of polyarginine CPPs. For the first time, we reveal that the cell delivery of CPPs is dependent upon cellular oxidative stress and on the presence of oxidized lipids at the plasma membrane of human cells. Oxygen tension and antioxidants can dramatically impact cell penetration of the peptide, which involves in direct membrane translocation. We also show that naturally occurring oxidized lipids within the plasma membrane directly mediate the rapid and efficient transport of the peptide across this biological barrier by forming inverted micelles with CPPs. Our findings thereby provide new fundamental insights on the process of cell membrane translocation. This novel mechanism also leads to new opportunities for rationale design of highly efficient cell-permeable compounds and drug delivery strategies.

## Poster Abstracts

Poster Number: 32

**The Global Regulator WetA Governs Fungal Development and Secondary Metabolism**

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***Keywords: Asexual Development, WetA, Aspergillus, Conidiation, Sporogenesis***

WetA is an evolutionary conserved central developmental regulator in certain Ascomycetes. In this study, we characterized WetA function in *Aspergillus* species and further investigated the underlying molecular regulatory mechanism in *A. nidulans*. The *wetA*-null mutant forms wet and white asexual spores (conidia), which have reduced viability and autolyzes in few days. The *wetA*-null conidium has a smaller size, lacks of the crenulated structure, and eventually loses the spore content. Loss of *wetA* leads to decreased trehalose level in conidia, which is a major conidia content and a protectant against various environmental stresses. Consistently, the *wetA*-null conidia show reduced viability under heat, UV, salt, and oxidative stresses. Interestingly, WetA acts differently in regulating conidiation timing in different *Aspergillus* species. The *wetA*-null mutant shows reduced growth rate, suggesting that WetA is not only involved in asexual development, but also in vegetative growth. Loss of WetA reduces the aflatoxin accumulation in *A. flavus*, suggesting that WetA is involved in secondary metabolism. To elucidate the molecular regulatory mechanism of WetA, we carried out time-course Northern blot analyses, conidia RNA-seq, and conidia ChIP-PCR. The results shows that WetA has a global regulatory role in *A. nidulans* conidiogenesis, especially controlling expression of genes associated with sporulation, cell wall organization, pigmentation, asexual spore wall assembly, and autolysis. WetA is a negative regulator of its upstream regulators, *brlA* and *abaA*, exerting feed-back control for development. The ChIP-PCR results show that WetA binds to the upstream region of *brlA*, suggests that WetA may be a DNA-binding transcription factor. Further studies are undergoing to validate the predicted WetA DNA-binding domain and to identify the WetA-response *cis* elements in *A. nidulans*.

## Poster Abstracts

Poster Number:  34

## Cell Behaviors during Müllerian Duct Formation

Shuo-Ting Yen[1,2], Cheng-Chiu Huang[1,2], and Richard R. Behringer[*, 1, 2]

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***Keywords: Tubulogenesis, Müllerian duct, Time-lapse imaging***

Tubulogenesis is a fundamental developmental process that is essential for the formation of many organ systems, including the female reproductive tract. The Müllerian duct is an epithelial tube that along with its adjacent mesenchyme gives rise to the female reproductive tract. The Müllerian duct forms in an intriguing manner because its elongation depends upon the Wolffian duct. We are applying new imaging methodologies to elucidate the cellular mechanisms of Müllerian duct formation. By fluorescent time-lapse imaging of the fetal mouse gonad-mesonephros (Wnt7a-Cre; R26R-YFP) in organ culture, we have observed digit-like cell processes at the tip of the forming Müllerian duct and changes in duct diameter. Genital ridge cell tracing of transgenic mice with a photo-convertible fluorescent protein, KikGR, indicates bulk anterior-posterior movement of Müllerian duct cells. However, time-lapse imaging of fluorescent clones of Müllerian duct cells using the MADM genetic mosaic system indicate more complex cell behaviors. Some cells actively migrate from anterior to posterior when dividing whereas others remain at a relatively constant position. Single-cell resolution characterization was achieved by mosaic analysis of Wnt7a-Cre; R26R-Confetti Müllerian duct cells. Reconstructed 3D images of these cells show mesenchymal morphology. Cell polarity and size also varies along the forming duct. Cytoneme-like cell processes that point toward the neighboring mesonephric mesenchyme cells are found in numerous ductal cells. Cells sending out lamellipodia along the anterior-posterior axis are also observed. These observations show highly dynamic cell behaviors and heterogeneity of the forming Müllerian duct.

## Poster Abstracts

Poster Number: 35

## Overexpression of Semaphorin-3E enhances pancreatic cancer cell growth and is associated with poor patient survival

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**Keywords: Pancreatic cancer, Semaphorin**

**BACKGROUND** Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer death in the US with a 5-year survival rate of less than 6%. There is an urgent need for a better understanding of PDAC in order to find better therapeutic targets. Two recent large-scale genomic analyses of human PDAC have uncovered increased copy numbers of an axon-guidance gene SEMA3E that codes for Semaphorin-3E (Sema3E). Several recent reports have implicated Sema3E in metastasis of breast and colon cancers, particularly in promoting tumor cell migration and invasion, as well as inducing epithelial-to-mesenchymal transition (EMT). Here, we evaluated Sema3E expression levels in human pancreatic cancer tissue samples and correlation with patient survival; we further studied roles of Sema3E in pancreatic cancer cell proliferation.

**MATERIALS AND METHODS** To determine expression levels of Sema3E in PDAC, qPCR analysis and immunohistochemical (IHC) analysis were performed on human PDAC tissues. To study the effects of Sema3E on pancreatic cancer cell lines, Sema3E-overexpressing and Sema3E-knockdown stable cells were generated using Sema3E-expressing lentivirus and the CRISPR/Cas9 system targeting *SEMA3E* gene, respectively. To assess the effects of Sema3E on pancreatic cancer pathogenesis, assays for cell proliferation, survival and migration were performed. *In vivo* tumor growth was assessed via orthotopic implantation of Sema3E-overexpressing cells into nude mice.

**RESULTS** Using qPCR, Sema3E was found to be upregulated in about 50% of human PDAC samples (n=24), while IHC analysis revealed higher Sema3E expression in tumors compared to normal pancreas (n=54). Interestingly, Sema3E was concentrated in the nuclei of tumor cells while it has been reported to be a secreted protein. High Sema3E expression was also positively correlated with poor patient survival (p<0.01). Overexpression of Sema3E in a PDAC cell line resulted in enhanced cell proliferation and migration *in vitro* as well as increased tumor growth *in vivo*, while knock down of Sema3E resulted in reduced cell proliferation and migration *in vitro*.

**CONCLUSIONS** Our findings indicate that Sema3E is overexpressed in PDAC and is associated with poor survival. Sema3E may play a pathogenic role in PDAC progression by enhancing tumor cell proliferation and migration. These findings suggest that Sema3E could be an attractive novel therapeutic target for PDAC.

# Acknowledgement

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