UCSD SALK
Biology Retreat 2018

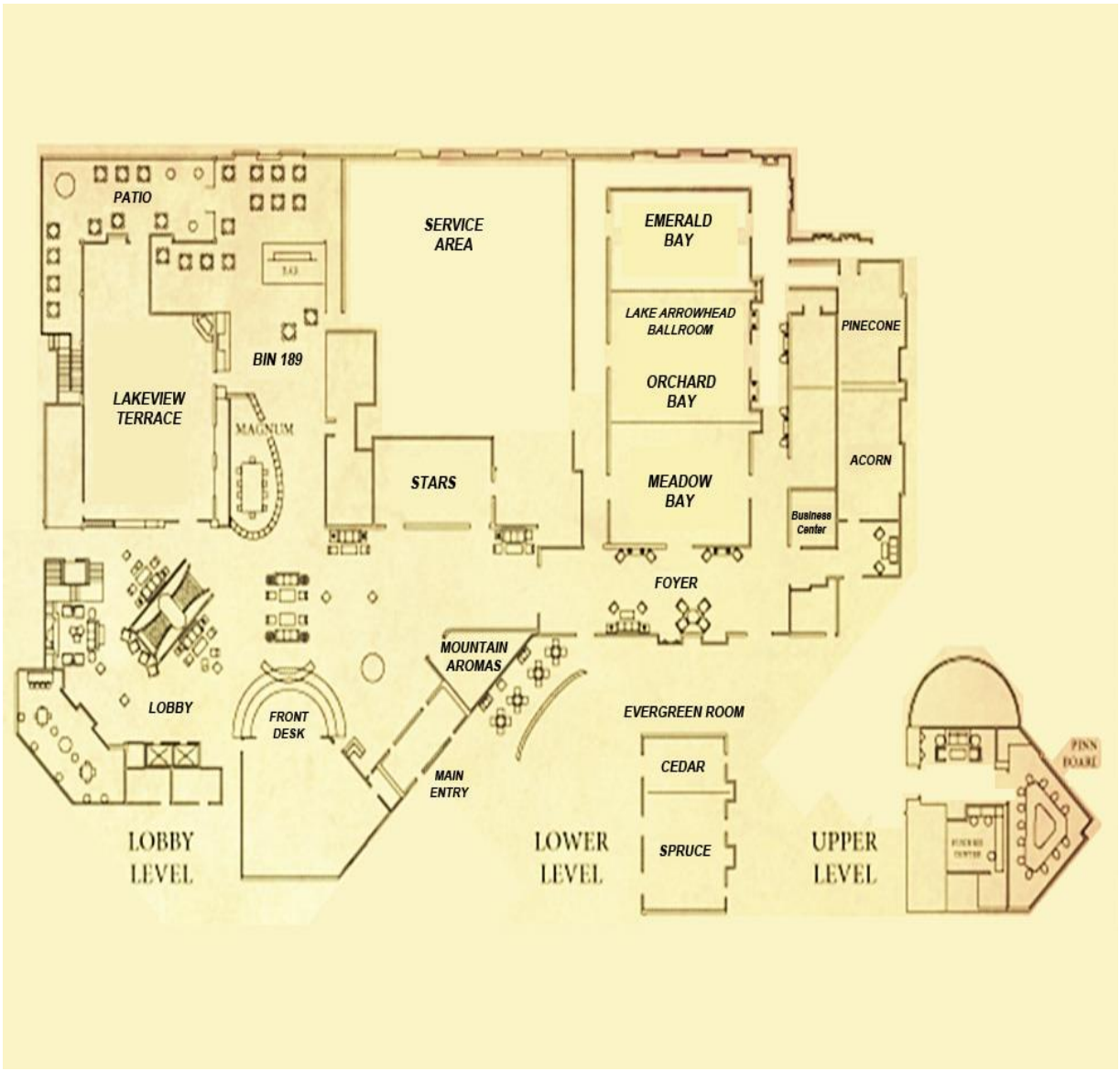
Lake Arrowhead Resort and Spa
Lake Arrowhead, CA

September 16 - 18, 2018

Retreat cover designed by: Audrey Menegaz Proenca

UC San Diego
Biological Sciences

salk®
Where cures begin.


PATIO
SERVICE AREA
EMERALD BAY
LAKE ARROWHEAD BALLROOM
PINECONE
BIN 189
ORCHARD BAY
LAKEVIEW TERRACE
MAGNUM
ACORN
STARS
MEADOW BAY
Business Center
FOYER
MOUNTAIN AROMAS
LOBBY
FRONT DESK
EVERGREEN ROOM
CEDAR
MAIN ENTRY
SPRUCE
LOBBY LEVEL
LOWER LEVEL
UPPER LEVEL

2018 UCSD Division of Biological Sciences-Salk Institute Annual Retreat Schedule

SUNDAY, SEPTEMBER 16

Arrival Lunch (Lakeside Lawn) 12:00-1:00

Welcome and Announcements (Arrowhead Ballroom) 1:10-1:20
By Justin Meyer (Chair)

Faculty Session 1
Chaired by Nan Hao (Arrowhead Ballroom)

1. Brenda Bloodgood
The rules of life are encoded in the genome 1:20-1:35

2. Susan Golden 1:35-1:50
How cyanobacteria tell time

3. Kenta Asahina 1:50-2:05
Neurogenetic basis of behavioral choice during social interactions

4. James Nieh 2:05-2:20

An elegant evolutionary bind: poison, alarm, and honey bee olfactory eavesdropping

Break 2:20-2:35

Postdoc Session
Chaired by Matt Banghart (Arrowhead Ballroom)

1. Gabriele Sulli 2:35-2:50
Pharmacological activation of REV-ERBs is lethal in cancer and oncogene-induced senescence

2. Jessica Sowa 2:50-3:05
Mechanisms of Intracellular Pathogen Detection in C. elegans

Room Check-in/Poster Set-up/Free Time 3:20-4:45
(Poster Set-up in Lakeview Terrace)

SUNDAY, SEPTEMBER 16 (CONTINUED)

Faculty Session 2
Chaired by Axel Nimmerjahn **(Arrowhead Ballroom)**

1. Omar Akbari 4:45-5:00
Innovating genetic technologies to combat human disease vectors

2. Elsa Cleland 5:00-5:15
Invasion alters ecosystem response to drought via shorter growing seasons and lower carbon capture

3. Dong-Er Zhang 5:15-5:30
Regulation of immune responses and tumorigenesis by protein ISGylation

4. Stanley Lo 5:30-5:45
Developing a common framework for assessing scientific arguments in biological sciences

Introduction of first year students and new faculty 5:45-6:00
By Dean Kit Pogliano

Dinner (Ballroom Foyer/Pinecone/Acorn) 6:00-7:30

Keynote Speaker **(Arrowhead Ballroom)**

Introduction by Matt Banghart 7:40-7:50

Keynote Speaker Terry Sejnowski 7:50-8:50
The Deep Learning Revolution

Social Time and Poster Viewing 9:00-11:00
(Social in Ballroom Foyer, Posters in Lakeview Terrace, Hospitality Suite in Stars Room)

MONDAY, SEPTEMBER 17

Breakfast (Ballroom Foyer) 8:00-9:00

Student Session

Chaired by Jens Lykke-Andersen (Arrowhead Ballroom)

1. Danielle Garshott 9:15-9:30
USP21 and OTUD3 antagonize regulatory ribosomal ubiquitylation and ribosome-associated quality control

2. Anusorn Mudla 9:30-9:45
Decoupling Priming and Desensitization in Response to Pulsatile Stimulations of IFN-alpha

3. Kanika Khanna 9:45-10:00
Visualizing molecular architecture of engulfment in Bacillus subtilis using in situ cryo-electron tomography

4. Audrey Proenca 10:00-10:15
Age structure landscapes emerge from the equilibrium between aging and rejuvenation in bacterial populations

5. Hannah Grunwald 10:15-10:30
Super-Mendelian inheritance mediated by CRISPR/Cas9 in the female mouse germline

Break 10:30-10:55

Faculty Session 3

Chaired by Omar Akbari (Arrowhead Ballroom)

1. Sonya Neal 10:55-11:10
ERADicating Integral Membrane Substrates Through a Novel Route of Retrotranslocation

2. Cressida Madigan 11:10-11:25
Immune-mediated nerve damage in leprosy: insights from a zebrafish model

3. Stacey Glasgow 11:25-11:40
Lineage specific chromatin architecture governs NFIA expression and glioma tumorigenesis

Lunch (Lakeside Lawn) 12:00-1:00
Tables on deck for networking with new faculty

Free Time / Poster Viewing 12:00-3:00
(Posters in Lakeview Terrace)

Student Only Session: Navigating mental health issues in graduate school (Evergreen Room) 12:00-1:30
(Organized by Andy Ryan)

MONDAY, SEPTEMBER 17 (CONTINUED)

Hike (Meet at lobby) 12:30-2:30
(Organized by GSA Reps)

Breakout session: practicing chalk talks (Acorn/Pinecone Rooms) 1:00-2:30

Poster Session and Poster Judging	**3:00-6:00**
Organized by Matt Banghart	**(Lakeview Terrace)**
Posters lettered A presented 3:00-4:00	
Posters lettered B presented 4:00-5:00	
Posters lettered C presented 5:00-6:00	

Dinner (Ballroom Foyer/Pinecone/Acorn) 6:15-7:15
Random seating assigned by drawing Uno cards

Award for Excellence in Graduate Research Speaker Introduced by Yishi Jin

Ipshita Zutshi 7:30-8:00
Generating a grid cell: Role of recurrent networks within the medial entorhinal cortex

Awards / Announcements	**8:00**
(Arrowhead Ballroom)	

Best Graduate Student/Postdoc Talks

Best Graduate Student/Postdoc Posters

TA Awards

Graduate Student Mentorship Award

Faculty Mentorship Award

Faculty Attendance Award

Break 8:30-8:45

Faculty Entertainment
Presented by TBA

Student video
Presented by the 2nd Year Students

Party, Hospitality Suite 10:00-12:00
Party in Lakeview Terrace, Hospitality Suite in Stars

TUESDAY, SEPTEMBER 18

Breakfast (Ballroom Foyer) 8:00-9:30

Checkout

Talk Abstracts

The rules of life are encoded in the genome

Brenda Bloodgood

Stimulus-dependent gene regulation is a core feature of robust and flexible biological systems – central to the function of all cell types, at every developmental stage, and in every organism. The first wave of a stimulus-dependent transcriptional response includes the expression of immediate-early gene transcription factors (IEG-TFs) which in neurons are expressed in response to depolarization and the associated calcium influx. Substantial progress has been made in elucidating the signaling pathways that link global depolarization to the expression of IEG-TFs. Yet, neurons do not experience depolarization as a stimulus that is uniformly distributed over the plasma membrane. Rather, membrane potential fluctuations are heterogeneously distributed in space across the axon, soma, and dendritic subdomains of a neuron. Moreover, depolarization is used to carry information about both the neuron's output, in the form of action potentials (APs), and inputs, in the form of excitatory postsynaptic potentials (EPSPs). While APs and EPSPs are inherently inter-related, they encode distinct information and it is unclear if the induction of an IEG-TF reflects changes in neuronal inputs, output, or both. I am going to share with you bits and pieces of the incredibly beautiful cell biology that allows neurons to deconstruct neural activity into multifaceted gene regulation through AP- and EPSP-specific IEG-TF induction. If time permits (and this really depends on my mood) I might tell you a little about what this is good for.

How cyanobacteria tell time

Susan S. Golden

Cells of diverse organisms, from cyanobacteria to humans, execute temporal physiological programs that are driven by circadian oscillators. The circadian clock of the cyanobacterium *Synechococcus elongatus* regulates global patterns of gene expression, the timing of cell division, and metabolism. We use *S. elongatus* as a model to understand how a cell keeps track of time, executes activities according to a temporal program, and synchronizes the internal clock with the external solar cycle. The components of the circadian oscillator are known (proteins KaiA, KaiB, and KaiC), their structures have been solved, and the rhythm in phosphorylation of KaiC can be reconstituted *in vitro*. One oscillator component, KaiB, undergoes a metamorphosis to a new protein fold – a rare event that is key to the slow progression of the circadian cycle. Furthermore, fold-switched KaiB initiates the “night” phase of the oscillator, and connects the Kai complex to the downstream components that broadcast time to the cell. These processes involve partner switching, in which fold-switched KaiB binds to KaiC, displacing a kinase (SasA) that activates a master transcription factor, RpaA; once bound, KaiC-associated KaiB recruits a kinase called CikA, turning on its RpaA-phosphatase activity. This transition from active SasA kinase to active CikA phosphatase causes a marked temporal peak in phosphorylated RpaA that is reflected in rhythms of transcripts from downstream genes. The mechanisms of the oscillator and generation of downstream transcription rhythms were captured accurately in an animation created by an undergraduate team as part of a course, the BioClock Studio, supported by a grant from the Howard Hughes Medical Institute.

Neurogenetic basis of behavioral choice during social interactions

Kenta Asahina

The fruit fly (*Drosophila melanogaster*) shows robust and stereotypical aggressive behaviors when it encounters conspecifics of the same sex. The intensity of aggressive interactions depend on the availability of food, relative body size differences, outcomes of the past fight and so on, making *Drosophila* an ideal model organism to investigate the genetic and neural mechanisms underlying these context-dependent action choice during aggressive interactions. Here, I will specifically discuss the function of the gene *nervy*, which encode a scaffold protein for chromatin modifying proteins, on the *Drosophila* aggression. Brain-specific knockdown of *nervy*, as well as its null mutation, results in abnormally high levels of aggression both in males and females. Although the smaller fly rarely attack the larger opponent, the smaller nervy mutant males fight against the larger male fly. Interestingly, the *nervy* mutant males attack females, which is rarely observed in wild type males. These results suggest that *nervy* is necessary for the flies to modulate the levels of aggression in a context-dependent manner. We are taking multidisciplinary approaches, from single-cell RNAseq, CRISPR-mediated genome editing, and functional calcium imaging, to illuminate how the *nervy* protein influences the function of specific neurons in the fly brain to maintain the proper levels of aggression.

An elegant evolutionary bind: poison, alarm, and honey bee olfactory eavesdropping

James C. Nieh

An evolutionary arms race between hornet predators and Asian honey bees, has led to a remarkable defence, heat-balling, which suffocates hornets with heat and carbon dioxide. The sympatric Asian honey bee species, *Apis cerana* (Ac), formed heat balls in response to Ac and hornet (*Vespa velutina*) alarm pheromones, demonstrating eavesdropping. The allopatric species, *Apis mellifera* (Am), only weakly responded to a live hornet and not to hornet or Am alarm pheromones. Hornets released sting venom when initially attacked. Once heat balls were formed, guards released honey bee sting alarm pheromones: isopentyl acetate, octyl acetate, (*E*)-2-decen-1-yl acetate, and benzyl acetate. In addition, only Ac heat-balled in response to realistic bee alarm pheromone component levels, <1 bee-equivalent (1 µg), of isopentyl acetate. Further, only Ac, not Am, formed heat-balls in response to a synthetic blend of hornet alarm pheromone. Finally, only Ac antennae showed strong, consistent responses to hornet alarm pheromone compounds and venom volatiles. These data provide the first evidence that the sympatric Ac, but not the allopatric Am, can eavesdrop upon *V. velutina* alarm pheromone and uses this information, in addition to its own alarm pheromone, to heat-ball hornets. Evolution has likely given Ac this eavesdropping ability.

Pharmacological activation of REV-ERBs is lethal in cancer and oncogene-induced senescence

Gabriele Sulli
(Satchin Panda Lab)

The circadian clock imposes daily rhythms in cell proliferation, metabolism, inflammation and DNA damage response. Perturbations of these processes are hallmarks of cancer and chronic circadian rhythm disruption predisposes individuals to tumour development. This raises the hypothesis that pharmacological modulation of the circadian machinery may be an effective therapeutic strategy for combating cancer. REV-ERBs, the nuclear hormone receptors REV-ERBα (also known as NR1D1) and REV-ERBβ (also known as NR1D2), are essential components of the circadian clock. Here we show that two agonists of REV-ERBs—SR9009 and SR9011—are specifically lethal to cancer cells and oncogene-induced senescent cells, including melanocytic naevi, and have no effect on the viability of normal cells or tissues. The anticancer activity of SR9009 and SR9011 affects a number of oncogenic drivers (such as HRAS, BRAF, PIK3CA and others) and persists in the absence of p53 and under hypoxic conditions. The regulation of autophagy and *de novo* lipogenesis by SR9009 and SR9011 has a critical role in evoking an apoptotic response in malignant cells. Notably, the selective anticancer properties of these REV-ERB agonists impair glioblastoma growth *in vivo* and improve survival without causing overt toxicity in mice. These results indicate that pharmacological modulation of circadian regulators is an effective antitumour strategy, identifying a class of anticancer agents with a wide therapeutic window. We propose that REV-ERB agonists are inhibitors of autophagy and *de novo* lipogenesis, with selective activity towards malignant and benign neoplasms.

Mechanisms of Intracellular Pathogen Detection in C. elegans

Jessica Sowa
(Emily Troemel Lab)

Understanding the mechanisms of pathogen recognition is vital to combat both infectious disease and autoimmunity. The nematode worm *C. elegans*, with its relatively simple immune system and powerful genetics, provides an excellent system to study pathogen detection. Several natural intracellular pathogens of *C. elegans* have been identified, including the Orsay virus, a positive-strand RNA virus that infects the intestine (Félix et al., 2011). *C. elegans* lacks many of the canonical Pattern Recognition Receptors found in other organisms, and so far no Pathogen-Associated Molecular Patterns (PAMPs) have been shown to trigger immune response in worms. However, *C. elegans* are able clear several intracellular pathogens, including the Orsay virus.

Previously, our lab profiled the *C. elegans* transcriptional response to intracellular pathogens, and identified a set of highly upregulated genes, which we have termed the Intracellular Pathogen Response genes (IPR). I am now using this gene expression signature to investigate the specific events during intracellular pathogenesis. I found that IPR activation by Orsay virus does not require the native infection route, and can be induced by microinjection of the virus directly into intestinal cells. I further found that intact viruses were not required, and that microinjection of a dsRNA corresponding to a small portion of Orsay virus RNA1 was sufficient to induce IPR gene expression. My results suggest that *C. elegans* recognize viruses via the detection of viral-associated dsRNAs. These results provide some of the first evidence for recognition of pathogens via PAMPs in *C. elegans*.

Innovating genetic technologies to combat human disease vectors

Omar Akbari

Insects act as vectors for diseases of plants, animals and humans. Replacement of wild insect populations with genetically modified individuals unable to transmit disease provides an environmentally friendly, sustainable, and self-perpetuating method for disease prevention. However, transgenes that mediate disease refractoriness are unlikely to confer an overall fitness benefit on insects that carry them. Additionally, wild populations are large, partially reproductively isolated, and dispersed over wide areas. Therefore, population replacement requires a gene drive mechanism in order to spread linked genes mediating disease refractoriness through wild populations at greater than Mendelian frequencies. To address this problem, we previously reported on the creation of several synthetic selfish genetic elements able to drive population replacement. Here I plan to give a broad overview the many approaches we are developing to combat human disease vectors.

Invasion alters ecosystem response to drought via shorter growing seasons and lower carbon capture

Elsa Cleland

Invasive species can display greater phenological sensitivity to climate compared to native species, potentially influencing ecosystem responses to climatic changes such as drought. We manipulated rainfall on plots dominated by native shrubs or exotic annual plants, and measured canopy greenness as a proxy for photosynthetic carbon gain. Drought caused vegetation to senesce earlier where exotic species dominated, shortening the growing season and reducing potential ecosystem carbon gain more than in areas dominated by native vegetation. These results demonstrate that invasion can alter ecosystem responses to climate change, especially when native and invading species have differing phenological sensitivity to environmental cues.

Regulation of Immune Responses and Tumorigenesis by Protein ISGylation

Dong-Er Zhang

Interferon stimulated gene 15 (*ISG15*) is one of the most up regulated genes upon Type I interferon (IFN) induction related innate immune responses, such as pathogen infection and cancer development. Its 17 kDa protein product, ISG15, was the first ubiquitin-like modifier identified, and is similar to a ubiquitin linear dimer. As ISG15 modifies proteins in a similar manner to ubiquitylation, protein conjugation by ISG15 is termed ISGylation. Interestingly, in addition to ISG15, both conjugating and deconjugating enzymes of protein ISGylation are encoded by interferon inducible genes. Therefore, protein ISGylation is tightly regulated by the interferon signal transduction, implying its important role in modulating innate immune responses. However, relative to protein ubiquitylation, the biological function of ISGylation is still poorly understood. Using publically available human cancer datasets, we analyzed the expression of *UBA7*, a gene of a critical enzyme, UBE1L, for protein ISGylation in human normal and cancer samples, and also examined correlation of the *UBA7* expression to cancer patient survival. We further used the MMTV-PyVmT mouse model to examine whether protein ISGylation plays any role during cancer progression. Data will be presented.

Developing a common framework for assessing scientific arguments in biological sciences

Stanley M. Lo

Scientific arguments are used to make sense of data, draw conclusions, and construct hypotheses. Although they are critical in biological sciences, these skills are rarely taught explicitly to undergraduates. A recent survey of college educators found that a common barrier to teaching scientific argumentation is the lack of assessment tools. We developed a common rubric to assess scientific arguments by combining two frameworks: the Toulmin argumentation framework and Biggs' Structure of the Observed Learning Outcome (SOLO). Biggs' SOLO is broken down into five levels of increasing complexity, and these levels can be applied to connect the three main components of the Toulmin framework: conclusion, evidence, and reasoning. We developed this rubric through iterations of testing and refinement on arguments written by students. With the final form of the rubric, we achieved high reliability between two coders (86-95% agreement for all codes). We characterized the argumentation abilities of a stratified sample (based on course grade) of upper-division genetics students (n = 120), with two writing samples per student (n = 240). While nearly half of the arguments (48%) were able to describe multiple pieces of data and make individual conclusions, only 28% of the arguments relate multiple pieces of data together into a coherent conclusion. Less than 2% of the arguments made forward-looking hypotheses and predictions that would potentially explain the observed data. In our presentation, we will discuss these findings and implications of this rubric in terms of using it as a scaffold to develop targeted interventions and as an assessment tool for scientific argumentation.

Keynote Speaker

The Deep Learning Revolution

Terry Sejnowski

Artificial intelligence (AI) is a branch of engineering that has traditionally ignored brains, but recent advances in deep learning have dramatically changed AI and made it possible to solve difficult problems in vision, planning and natural language. Deep learning is based on general principles of neural computation from the 1980s, but only recently has enough computer power been available to train networks with a hierarchy of layers similar to that found in the cerebral cortex. This recent convergence of AI and neuroscience is having a major impact on our everyday lives: If you talk to Alexa or use Google translate, you have experienced deep learning in action. This lecture will explore the past, present and future of deep learning.

USP21 and OTUD3 antagonize regulatory ribosomal ubiquitylation and ribosome-associated quality control

Danielle M. Garshott
(Eric Bennett Lab)

Maintaining cellular protein homeostasis is critical to the overall health and survival of an organism. Cells are frequently exposed to various proteotoxic stressors, including the translation of mRNAs into aberrant protein products. Failure to remove these defective nascent proteins results in a proteome imbalance and can lead to the accumulation of deleterious protein aggregates. Translation is a closely monitored process that is tightly-regulated by numerous cellular quality control pathways to ensure cellular homeostasis. When the progression of an actively elongating ribosome is halted by a defect within an mRNA or nascent chain the ribosome-associated quality control (RQC) pathway is initiated. The RQC is responsible for the rescuing and recycling of stalled ribosomes and the degradation of the defective mRNA and nascent polypeptide. We have previously demonstrated that conserved monoubiquitylation events on specific 40S ribosomal proteins are required for downstream RQC events following the translation of polyA sequences. We identified the E3 ubiquitin ligase, ZNF598, which is responsible for initiating RQC by catalyzing the regulatory ribosomal ubiquitylation (RRub) of RPS10 (eS10) and RPS20 (uS10). Ubiquitylation of RPS2 (uS5) and RPS3 (uS3) are additional RRub events triggered upon activation of the unfolded protein response (UPR), and function within the RQC pathway. The reversibility of all four RRub events suggests regulation by deubiquitylating enzymes (Dubs). Here, we utilized a poly(A) translational readthrough reporter to identify OTUD3 and USP21 as deubiquitylating enzymes, when overexpressed, enhance readthrough of poly(A) sequences which would normally induce RQC events. We demonstrate that OTUD3 and USP21 directly antagonize ZNF598-mediated RRub and specifically deubiquitylate 40S ribosomal proteins following RQC induction. Interestingly, overexpression of either USP21 or OTUD3 allows for readthrough of poly(A) sequences to a greater extent than that observed in cells with point mutations within RPS10 (eS10) or RPS20 (uS10). This result suggests that ubiquitylation of both RPS10 and RPS20 is required for optimal resolution of RQC events. At steady-state, cellular ZNF598 is in vast excess relative to OTUD3 and USP21 which suggests that the constrained stoichiometric balance may be needed to facilitate rapid 40S ubiquitylation upon RQC activation.

Decoupling Priming and Desensitization in Response to Pulsatile Stimulations of IFN-alpha

Anusorn Mudla
(Nan Hao Lab)

Interferon-alpha (IFN-a) is a major cytokine produced in response to viral infection and clinically important in anti-viral and anti-cancer therapy. Although several key components of the interferon pathway have been characterized, their dynamics in response to repetitive stimulation remain elusive. Pretreating cells with IFN-a increases the rate of downstream gene activation and antiviral response upon second treatment known as priming effect. However, prolonged IFN-a priming can lead to desensitization dampening the response to the efficiency of further IFN-a treatments. Here, we systematically studied the dynamics of priming and desensitization in response to IFN-a in single cells. We used CRISPR/Cas9 to fluorescently tagged signal transducer and activator of transcription 1 (STAT1) protein to monitor its nuclear translocation and used microfluidics to precisely control the durations of the IFN-a stimulation, the break-time and the second stimulation. Single cell quantification from time-lapse microscopy revealed that the strength of STAT1 nuclear translocation was negatively correlated with the priming duration. The rate of interferon regulatory factor 9 (IRF9), a downstream reporter, increased with longer priming time but was significantly suppressed by 24hr priming. We then knockdowned ubiquitin specific protease 18 (USP18), a known negative regulator of IFN-a signaling, using shRNA and found that STAT1 nuclear translocation was restored and IRF9 induction rate was significantly higher. Treating the cells with 3-pulses of 8 hour IFN-a resulted in higher expression of IRF-9 than prolonged 24-hour treatment. Our preliminary data highlight the role of USP18 in desensitization of IFN-a signaling and potentially provide insight information to improve pharmacokinetic of IFN-a delivery for effective viral-infected disease and cancer therapy.

Visualizing molecular architecture of engulfment in Bacillus subtilis using in situ cryo-electron tomography

Kanika Khanna
(Elizabeth Villa Lab)

An important factor that limits the study of cell biology is the difficulty in visualizing cellular structures at high spatial resolution within their native cellular context. Here, we have visualized the developmental process of sporulation in the bacterium *Bacillus subtilis* using cryo-electron tomography (cryo-ET), a technique that allows the 3D reconstruction of pleiomorphic structures, including cells and organelles in near-native state at molecular resolution. During sporulation, an asymmetrically-positioned septum divides the cell into a larger mother cell and a smaller forespore. Subsequently, the mother cell phagocytes the forespore in a process called engulfment, which entails dramatic rearrangements of the peptidoglycan (PG) cell wall around the forespore. By imaging wild-type sporulating cells, engulfment mutants, and sporulating cells treated with peptidoglycan synthesis inhibitors, we show that the initiation of engulfment entails a thin, flexible septal PG layer that curves toward the mother cell. Then, the mother cell migrates around the forespore by forming tiny finger-like projections, the formation of which requires both PG synthesis and degradation. We also show that chromosome translocation is essential for engulfment by inflating the forespore like air in a balloon. Overall, our data provides the basis to build mechanistic models of various specific aspects of endospore formation.

Additional contributors:
Javier Lopez Garrido, Ziyi Zhao, Yuan Yuan, Kit Pogliano, Elizabeth Villa

Age structure landscapes emerge from the equilibrium between aging and rejuvenation in bacterial populations

Audrey M. Proenca
(Lin Chao Lab)

The physiological asymmetry between daughters of a mother bacterium is produced by the inheritance of either old poles, carrying non-genetic damage, or newly synthesized poles. However, because bacteria display long-term growth stability leading to physiological immortality, there is controversy on whether asymmetry corresponds to aging. Here we show that deterministic age structure landscapes emerge from physiologically immortal bacterial lineages. Through single-cell microscopy and microfluidic techniques, we demonstrate that aging and rejuvenating bacterial lineages reach two distinct states of growth equilibria. These equilibria display stabilizing properties, which we quantified according to the compensatory trajectories of continuous lineages throughout generations. Finally, we show that the physiological asymmetry between aging and rejuvenating lineages produces complex age structure landscapes, resulting in a deterministic phenotypic heterogeneity that is not artifact of starvation, neither a strategy induced by extrinsic damage. These findings indicate that physiological immortality and cellular aging can coexist in a single cellular context.

Super-Mendelian inheritance mediated by CRISPR/Cas9 in the female mouse germline

Hannah Grunwald
(Kim Cooper Lab)

A gene drive biases the transmission of a particular allele of a gene such that it is inherited at a greater frequency than by random assortment. Recently, a highly efficient gene drive was developed in insects, which leverages the sequence-targeted DNA cleavage activity of CRISPR/Cas9 and endogenous homology directed repair mechanisms to convert heterozygous genotypes to homozygosity. If implemented in laboratory rodents, this powerful system would enable the rapid assembly of genotypes that involve multiple genes (e.g., to model multigenic human diseases). Such complex genetic models are currently precluded by time, cost, and a requirement for a large number of animals to obtain a few individuals of the desired genotype. However, the efficiency of a CRISPR/Cas9 gene drive system in mammals has not yet been determined. Here, we utilize an active genetic “CopyCat” element embedded in the mouse *Tyrosinase* gene to detect genotype conversions after Cas9 activity in the embryo and in the germline. Although Cas9 efficiently induces double strand DNA breaks in the early embryo and is therefore highly mutagenic, these breaks are not resolved by homology directed repair. However, when *Cas9* expression is limited to the developing female germline, resulting double strand breaks can be efficiently resolved by homology directed repair that copies from the homologous chromosome and leads to super-Mendelian inheritance of the CopyCat allele.

ERADicating Integral Membrane Substrates Through a Novel Route of Retrotranslocation

Sonya Neal

My newly-established lab strives to understand the basic biology of ER-associated protein degradation (ERAD), a critical pathway which removes misfolded proteins both from the ER membrane and lumen. *Retrotranslocation* of misfolded ubiquitinated substrates for later cytosolic degradation is a universal feature of eukaryotic cells. Despite intense efforts, the mechanism of ER retrotranslocation for integral membrane substrates has remained contentious and unclear. Using a self-ubiquitinating substrate (SUS) and the new microarray library to query all yeast genes, I discovered a central factor in membrane protein retrotranslocation, the rhomboid derlin protein Dfm1. Indeed, Dfm1 is required for retrotranslocation of multiple types of misfolded integral membrane substrates. Surprisingly, *dfm1*Δ *cells* undergo rapid suppression, which revealed the existence of a second stress-induced ER membrane protein retrotranslocation pathway, this time mediated by the E3-ligase Hrd1. It has become increasingly clear that the conserved retrotranslocation process is critical to the health of cells and organisms. Accordingly, we are interested in studying the mammalian retrotranslocation pathway in both a cellular and organismal context. Knowledge of the proteins involved in retrotranslocation will open avenues for therapeutic approaches to attack diseases upregulated in retrotranslocation (cancers), or to ameliorate diseases where proteins are prematurely retrotranslocated (cystic fibrosis).

Immune-mediated nerve damage in leprosy: insights from a zebrafish model

Cressida Madigan

Leprosy, caused by *Mycobacterium leprae*, is the only bacterial skin infection that causes widespread destruction of peripheral nerves. Over time, this nerve damage causes the stigmatizing deformities of leprosy, including loss of fingers and blindness. How does leprosy cause nerve damage? To determine how *M. leprae* infection damages the nerve axons and their myelin insulation, we developed a new zebrafish model of leprosy to observe real-time nerve infection in a living animal. We found that *M. leprae* infects nerve macrophages, which aggregate into an inflammatory structure, or granuloma. In response to an unusual *M. leprae*-specific outer membrane lipid, heavily infected nerve macrophages up-regulate inducible nitric oxide synthase to produce copious amounts of nitric oxide. The result is local damage to axon mitochondria and associated myelin. Our findings provide a new understanding of leprosy as an inflammatory neurodegenerative disease. Further, they set the stage for our lab to use live imaging in zebrafish to examine how infection and inflammation contributes to neurodegeneration.

Lineage specific chromatin architecture governs NFIA expression and glioma tumorigenesis

Stacey Glasgow

Long-range enhancer interactions are fundamental components of gene expression, yet how their activities oversee diverse developmental states and associated diseases remain nascent. Using regulation of the transcription factor NFIA in the developing CNS as a model, we identified long-range enhancers that recapitulate its expression across diverse lineages *in vivo*. Complementary genetic studies found that Sox9/Brn2 and Isl1/Lhx3 regulate NFIA expression across glial and neuronal lineages. Chromatin conformation analysis revealed that these enhancers and regulatory factors form distinct architectures within these lineages. Applying these findings towards glioma, we found that NFIA forms the glial-specific architecture in tumors and these enhancers are required for its expression and glioma formation. Our studies identify lineage specific chromatin architectures and associated genetic mechanisms that regulate cell fate determination and tumorigenesis.

EXCELLENCE IN GRADUATE RESEARCH

Generating a grid cell: Role of recurrent networks within the medial entorhinal cortex

Ipshita Zutshi
(Stefan Leutgeb Lab)

Specialized cells in the medial entorhinal cortex (mEC), such as speed cells, head direction (HD) cells, and grid cells are thought to support spatial navigation. To determine whether these computations are dependent on local circuits, we recorded neuronal activity in mEC layers II and III and optogenetically perturbed locally projecting layer II pyramidal cells. We found that sharply tuned HD cells were only weakly responsive while speed, broadly tuned HD cells, and grid cells showed pronounced transient excitatory and inhibitory responses. During the brief period of feedback inhibition, there was a reduction in specifically grid accuracy, which was corrected as firing rates returned to baseline. These results suggest that sharp HD cells are embedded in a separate mEC sub-network from broad HD cells, speed cells, and grid cells. Furthermore, grid tuning is dependent on local processing, but also rapidly updated by HD, speed, or other afferent inputs to mEC.

Poster Abstracts

Determining factors that affect biofilm formation in *Synechococcus elongatus* using randomly barcoded transposon insertion site sequencing and comparative genomics

Marie Adomako
(Susan Golden Lab)

Cyanobacteria are important photosynthetic members of biofilm communities in diverse environments, and their biofilms have potential applications in wastewater purification, bioremediation efforts, and combating biofouling. The cyanobacterium *Synechococcus elongatus* PCC 7942 is a tractable model organism used to research photosynthesis and circadian rhythms in prokaryotes. A novel strain of *S. elongatus* recently isolated from environmental samples-designated WC-1-forms robust biofilms and exhibits phototaxis, phenotypes the PCC 7942 strain does not normally display, although PCC 7942 will form biofilms upon mutation of specific genes. We have sequenced the genome of WC-1, and the average nucleotide identity of WC-1 with PCC 7942 is 98.46%, indicating they are the same species. However, compared to PCC 7942, WC-1 has novel insertions and deletions, as well as 43,025 single nucleotide polymorphisms and different plasmids. The genetic similarity between the two strains, despite their distinct phenotypic differences, gives the opportunity to use comparative genomics to study complex phenotypes in *S. elongatus*. A randomly-barcoded transposon mutant (RB-TnSeq) library in PCC 7942 generated in our lab is a robust tool for unbiased genetic screens; a complimentary RB-TnSeq library will be created in WC-1, and a comparative genetics approach using the results from screens in both libraries will be used to study the genetic basis of phototaxis and biofilm behaviors in *S. elongatus.* The comparison of a lab-adapted strain and a wild isolate of the same species will also aid the understanding of the role cyanobacteria in environmental communities and the processes of microbial domestication.

POSTER POSTION 1A

Effect of pH on pairwise interactions in a model cheese rind community

Brooke Anderson
(Rachel Dutton Lab)

The formation of a model cheese-rind biofilm involves a reproducible succession of bacteria and fungi. As the growing biofilm breaks down cheese proteins and releases ammonium, the pH of the cheese increases drastically, from pH 5 to pH 8. This dynamic abiotic environment can modulate the nature of interactions between biofilm residents in two possible ways: either by removing or imposing a reliance on another species, or by altering the mechanism by which two species interact. As a multi-species biofilm undergoes such abiotic and biotic dynamics, it can be expected that the structure of the biofilm will reflect and further impact these dynamics.

Using a 7-member *in vitro* cheese rind community as a model, growth assays of all pairwise combinations reveal species pairs that interact in a pH-dependent versus pH-independent manner. To understand how these changing interactions are reflected in the spatial organization of species pairs and whether these patterns are maintained in a complete community, fluorescence in situ hybridization methods have been optimized to visualize *in vitro* cheese rind biofilms consisting of two- to seven-microbe biofilms. These results may have implications for the resultant pattern of succession observed in the complete 7-member community.

POSTER POSTION 1B

Title

Wendy Chen
(Gen-Sheng Feng Lab)

POSTER POSTION 1C

Divergent Roles of the miRNA Argonaute Proteins in *C. elegans* Aging

Laura Chipman
(Amy Pasquinelli Lab)

Although highly related proteins often perform redundant functions, there are rare cases of homologous proteins taking on opposing roles in certain contexts. We discovered one such example where the activities of Argonaute-like-gene 1 *(alg-1*) and *alg-2* diverge in adult *C. elegans*. These Argonaute (AGO) proteins are specific to the miRNA pathway and seem to perform overlapping and complementary roles in regulating gene expression during embryogenesis and larval development. Surprisingly, we found that loss of *alg-1* leads to a shorter lifespan and loss of *alg-2* results in an extended lifespan. Gene expression analyses revealed that distinct sets of genes are misregulated in each of the AGO mutant backgrounds. Consistent with the longevity phenotypes of *alg-1* and *alg-2* mutant animals, many of the differentially expressed genes are regulated by the insulin/ IGF1 signaling (IIS) pathway. Furthermore, genetic experiments demonstrate that the long lifespan of animals deficient in insulin receptor activity (*daf-2* mutants) is partially dependent on *alg-1*, while the extended lifespan of *alg-2* mutants requires the FOXO DAF16 transcription factor. These findings prompt the question of how two proteins that are over 80% identical in amino acid sequence and exhibit similar expression patterns and functions during development take on opposing roles in adulthood. To address this problem, we have used CRISPR to fuse fluorescent tags to the endogenous *alg-1* and *alg-2* genes, which will enable detailed analyses of the expression and activity of these AGOs in aging animals. These strains will allow us to test the hypothesis that in adults ALG-1 and ALG-2 bind distinct miRNAs and targets, which contributes to their opposing longevity roles. To understand the molecular basis for the different activities of these two AGOs, regulatory and coding sequences will be swapped between *alg-1* and *alg-2* to identify the elements responsible for their divergent roles in adult animals. Overall, I aim to elucidate how two miRNA AGOs promote opposite longevity fates in *C. elegans.*

POSTER POSTION 2A

In vitro and *in vivo* approaches to study translation as a regulator of gene expression during stress

Anna Guzikowski
(Brian Zid Lab)

Translation of eukaryotic mRNAs into protein is performed sequentially in three distinct stages: initiation, elongation, and termination. Proper regulation of each step is necessary for cells to quickly alter patterns of gene expression in order to adapt to a changing environment, particularly when conditions are unfavorable for cell survival. Upon exposure to glucose starvation, yeast cells rapidly suppress overall levels of translation. Traditionally, it has been thought that the initiation step of translation was key to mediating the down-regulation of translation in response to this stress. Surprisingly, we find that differential translation elongation is another crucial mechanism that allows preferential translation of certain genes during stress amidst the global reduction in protein production. To study the stages of translation of mRNAs in yeast we have developed an extract-based *in vitro* translation system. Notably, our system recapitulates the reduced translational capacity observed during glucose starvation when compared to cells in log-phase growth. Additionally, we have observed occupancy of ribosomes *in vivo* across the genome during glucose starvation and found that a subset of transcriptionally upregulated mRNAs have high rates of translation initiation but poor translation elongation, and therefore low protein production. We are currently utilizing a combination of these *in vitro* and *in vivo* approaches to analyze the roles that cellular factors have in regulating translation during glucose starvation and speculate that elongation and initiation serve as two distinct means cell use to fine-tune gene expression and regulate the translation of specific mRNAs in response to stress.

POSTER POSTION 2B

Investigating Microglial TAM Receptors as Modulators for Alzheimer's Pathology

Youtong Huang
(Greg Lemke Lab)

TAM receptor tyrosine kinases – Tyro3, Axl, and Mer - are essential regulators of apoptotic cell (AC) clearance and immune homeostasis in macrophages, dendritic cells, and immune sentinels throughout the body. Our lab recently demonstrated that these receptors play equivalent roles in microglia, the specialized tissue macrophages of the central nervous system, where they are required for the clearance of the ACs generated during adult neurogenesis. Alzheimer's disease (AD) features formation of neurotoxic Aβ oligomers and deposition of plaques, along with prominent neuroinflammation, that give rise to synapse and neuronal loss and cognitive decline in patients. Recent transcriptomic studies show that microglial *Axl* mRNA is dramatically up-regulated in both AD and its mouse models. In addition, nuclear receptor (e.g., PPARγ) agonists, which elevate both Mer expression and phagocytosis in microglia and macrophages, have been shown to ameliorate mouse AD pathology in a Mer-dependent fashion. These findings notwithstanding, the biological role of microglial TAMs signaling in Alzheimer's disease remains unclear. We hypothesize that microglial TAM receptor signaling restrains AD by (a) microglial production of neurotoxic proinflammatory cytokines and (b) promoting microglial phagocytosis of neurotoxic Aβ peptides and plaques. Here we show that the TAM signaling system is strongly activated and its expression upregulated in mouse models of AD. Preliminary data suggests that the loss of Mer and Axl signaling has profoundly deleterious effects on the development of disease in AD mouse model. This study highlights the importance of understanding TAM action in AD with respect to therapeutic intervention of neurodegenerative diseases.

Additional Authors: Youtong Huang[1,2], Kaisa Happonen[1], Patrick Burrola[1] and Greg Lemke[1,3]

1. Molecular Neurobiology Laboratory, the Salk Institute for Biological Studies, 10010 North Torrey Pines, La Jolla, CA 92037, USA
2. University of California San Diego, Department of Biological Sciences, 9500 Gilman Drive, La Jolla, CA 92093, USA
3. Immunobiology and Microbial Pathogenesis Laboratory, the Salk Institute for Biological Studies, 10010 North Torrey Pines, La Jolla, CA 92037, USA

POSTER POSTION 2C

Investigating microbiota species that influence postnatal growth

Yujung Michelle Lee
(Janelle Ayres Lab)

The intestinal microbiome influences host gastrointestinal development, nutritional status, and mucosal immunity, and thus plays important functions in health and disease [1,2]. However, under some conditions, constituents of the microbiota can become pathogenic to the host and cause disease [3,4]. The factors that maintain the mutualistic relationship between the host and microbiota and those that drive microbial virulence remain incompletely understood. To identify such factors that promote microbial virulence, we will investigate the relationship between the developmental stage of the host and microbial virulence of intestinal microbes. Dissection of these host-microbial interactions will improve our understanding of the connection between developmental stage, microbial virulence and commensalism of intestinal microbes. Here, we present identification of a strain of *E. coli* that behaves as a commensal when colonizing the adult murine intestine, but when colonizing the neonate intestine, this *E. coli* strain appears to be pathogenic to the host as indicated by the impaired neonatal development of the host. By using a gnotobiotic mouse model, we are investigating the mechanism by which this microbe employs virulence to negatively impact the health of the host during its early developmental stage.

Yujung Michelle Lee[1,2], Daniela Michel[1], Janelle S. Ayres[1]*

[1]Nomis Center for Immunobiology and Microbial Pathogenesis, The Salk Institute for Biological Studies, La Jolla, CA 92037, USA; [2]Division of Biological Sciences, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA.
*Corresponding author

References

1 Sommer, F. & Backhed, F. The gut microbiota--masters of host development and physiology. *Nat Rev Microbiol* **11**, 227-238, doi:10.1038/nrmicro2974 (2013).
2 Smith, M. I. *et al.* Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. *Science* **339**, 548-554, doi:10.1126/science.1229000 (2013).
3 Baumler, A. J. & Sperandio, V. Interactions between the microbiota and pathogenic bacteria in the gut. *Nature* **535**, 85-93, doi:10.1038/nature18849 (2016).
4 Cameron, E. A. & Sperandio, V. Frenemies: Signaling and Nutritional Integration in Pathogen-Microbiota-Host Interactions. *Cell Host Microbe* **18**, 275-284, doi:10.1016/j.chom.2015.08.007 (2015).

POSTER POSTION 3A

Post-transcriptional Regulation of Nuclear-Encoded Mitochondrial mRNAs

Ben Lewis
(Tony Hunter Lab)

Expression of the genes required for functional mitochondria is dependent on mRNA transcripts that are transcribed from nuclear-encoded genes, translated by cytosolic ribosomes and imported into the mitochondria. Experiments in yeast have shown that certain mRNAs localize to the mitochondria to varying degrees and that while both post-translational and co-translational incorporation of proteins into the mitochondria occur, for a subset of proteins co-translational import is preferred. Significant differences exist between the mitochondria of yeast and of metazoans, this project aims to expand on previous yeast studies by moving into the mammalian system and identifying mRNAs enriched in the vicinity of the mitochondria as well to characterize the translation activity in vicinity of the mitochondria in mammalian cells. To circumvent the drawbacks of classical subcellular fractionation, new methods based on proximity labeling technology to capture subcellular distributions of RNA as well as localized transitional within the cytosol, are in the final stages of development. For the analysis of RNAs localized to the vicinity of the mitochondria APEX proximity labeling has been integrated with cross-linking and immunoprecipitation RNA sequencing (CLIP-seq) techniques. In addition, I am also developing APEX2 based methods for proximity-specific ribosomal profiling to analyze translational dynamics in the vicinity of the mitochondria. An additional objective of this project is to perform a functional analysis of LARP4 QK1 RNA-target binding, which was analyzed by CLIP-seq and shown to be enriched for nuclear-encoded mitochondrial mRNAs and also to colocalize to the mitochondria. Together these studies will shed light on the how human cells post-transcriptionally regulate the expression of nuclear-encoded mitochondrial genes a relatively unexplored and potentially fundamental cellular process.

POSTER POSTION 3B

β-Catenin Deficiency in Hepatocytes Aggravates Hepatocarcinogenesis Driven by Oncogenic β-Catenin and MET

Yan Liang
(Gen-Sheng Feng)

Both activating and inactivating mutations in catenin β1 (ctnnb1), which encodes β-Catenin, have been implicated in liver tumorigenesis in humans and mice, although the underlying mechanisms are not fully understood. Herein, we show that deletion of endogenous β-Catenin in hepatocytes aggravated hepatocellular carcinoma (HCC) development driven by an oncogenic version of β-Catenin (CAT) in combination with the hepatocyte growth factor receptor MET proto-oncogene receptor tyrosine kinase (MET). Although the mitogenic signaling and cell cycle progression was modestly impaired after CAT/MET transfection, the β-Catenin-deficient livers displayed changes in transcriptomes, increased DNA damage response, expanded Sox9+ cells, and up-regulation of protumorigenic cytokines, including interleukin-6 and transforming growth factor β1. These events eventually exacerbated CAT/MET-driven hepatocarcinogenesis in β-Catenin-deficient livers, featured by up-regulation of extracellular signal-regulated kinase (Erk), protein kinase B (Akt), and Wnt/β-Catenin signaling and cyclin D1 expression. The resultant mouse tumors showed similar transcriptomes to human HCC samples with concomitant CTNNB1 mutations and MET overexpression. Conclusion: These data argue that while dominantly activating mutants of β-Catenin are oncogenic, inhibiting the oncogenic signaling pathway generates a pro-oncogenic microenvironment that may facilitate HCC recurrence following a targeted therapy of the primary tumor. An effective therapeutic strategy must require disruption of the oncogenic signaling in tumor cells and suppression of the secondary tumor-promoting stromal effects in the liver microenvironment.

POSTER POSTION 3C

Tyrosine Phosphatase Shp2 Is Required for Hepatocarcinogenesis Driven by Oncogenic β-Catenin, PIK3CA and MET

Jijun Jacey Liu
(Gen-Sheng Feng Lab)

Shp2 is an SH2-tyrosine phosphatase acting downstream of receptor tyrosine kinases (RTKs). Most recent data demonstrated a liver tumor-suppressing role for Shp2, as ablating Shp2 in hepatocytes aggravated hepatocellular carcinoma (HCC) induced by chemical carcinogen or Pten loss. We further investigated the effect of Shp2 deficiency on liver tumorigenesis driven by classical oncoproteins MET, β-Catenin(CAT) and PI3K(PIK). Shp2 deletion in hepatocytes suppressed liver tumor development driven by overexpression of oncogenic proteins MET/CAT or MET/PIK. Shp2 loss inhibited proliferative signaling from MET/ERK, Wnt/β-Catenin and PI3K/Akt pathways, but induced cell senescence following exogenous expression of the oncogenes. The suppression of proliferative signals and oncogene-induced tumorigenesis was rescued by exogenous reconstitution of Shp2 in Shp2-genetically depleted liver. Collectively, we demonstrated the requirement of Shp2 for hepatocyte-intrinsic oncogenic signaling from MET, β-Catenin and PI3K, despite that Shp2 deficiency induces a tumor-promoting hepatic microenvironment. Our study suggested a new and more effective therapeutic strategy for HCCs driven by oncogenic RTKs and other upstream molecules, by inhibiting Shp2 and also suppressing any tumor-enhancing stromal factors produced due to Shp2 inhibition. Further, we are testing the efficacy of this proposed strategy in vivo.

Jacey J. Liu[1], Yanjie Li[1,2], Wendy S. Chen[1], Yan Liang[1], Gaowei Wang[1], Min Zong[1], Kota Kaneko[1], Ruiyun Xu[2], Michael Karin[1] and Gen-Sheng Feng[1]

[1]University of California, San Diego; [2]The Third Affiliated Hospital of Sun Yat-Sen University

POSTER POSTION 4A

Modifications to Plant Defense Metabolites Alter Antibiotic Mechanism of Action

Roland Liu
(Joseph Pogliano Lab)

It is generally accepted that structurally similar antibiotics exhibit the same or similar antibiotic mechanism of action (MOA). Chemical modifications and alterations to the backbone structures of antibiotics are thought to adjust pharmacological properties of these drugs, such as bioavailability, resistance to degradation, potency, and specificity. We used Bacterial Cytological Profiling, a fluorescence-based microscopy technique able to determine the MOA of an antibiotic molecule within hours, to examine the MOAs of a group of plant metabolites called flavones. Our results suggest that the addition or removal of single hydroxyl or methoxyl groups from the flavone background can completely change the molecule's cellular target and thus its MOA. This could have significant effects in understanding the plant-bacterial interface as well as in drug discovery of new antibiotics.

POSTER POSTION 4B

Developmental Control of Nuclear Positioning of EBF1 in B Cell Commitment

Hanbin Lu
(Cornelis Murre Lab)

B cell commitment from multi-potent progenitors is dictated by B cell lineage specific transcription factor, early B cell factor 1 (EBF1). EBF1 locus tethering to the transcriptionally inert nuclear lamina is repressed in the progenitors to avoid mis-activation. It is unknown what controls EBF1 locus repositioning to the nuclear interior for activation in response to B cell differentiation signal. Recent studies indicate transcription is able to cause nuclear repositioning and refold the local chromatin 3D structure. We identify the transcription units, including distal and proximal promoters and super-enhancer related ncRNA in the EBF1 locus. Knockout mice of these units are generated to systematically analyze their contribution to the EBF1 repositioning. Preliminary data shows the distal promoter exerts a dominant effect in EBF1 repositioning in early B cell development.

POSTER POSTION 4C

Identification of a novel functional domain in the bZip transcription factor CEBP-1

Rose Malinow
(Yishi Jin Lab)

Transcriptional control is one of the most versatile molecular mechanisms regulating gene expression. All transcription factors have DNA binding domains that recognize specific DNA elements, and regulatory domains that interact with other factors to enable transactivation or modulation. The *C. elegans* bZip protein CEBP-1 is a conserved transcription factor required for multiple processes including synapse development, neuronal stress response, and axon regeneration. Here, we took advantage of genetic interaction screening to uncover a putative trans-activation domain of CEBP-1. We previously reported that loss of function of *cebp-1* fully suppresses the larval lethality in null animals of *nipi-3* [1], which encodes a conserved Tribbles pseudokinase and is required for animal development and innate immunity. We designed a highly efficient scheme to select for suppressor mutations of *nipi-3(0)* and were able to characterize many functional mutations in *cebp-1.* Many mutations affected the canonical bZip domain in the C-terminal region of CEBP-1, while several missense mutations were clustered in the N-terminal region of CEBP-1. All these mutations behave similarly as genetic null of *cebp-1*. Our data reveal a stretch of 10-12 amino acids, independent of bZip, are essential for CEBP-1's function. Additionally, we have identified a novel suppressor of *nipi-3(0)*, that does not affect any of the genes previously identified. We will present further studies of this mutation using whole genome sequencing and SNP mapping.

Additional Contributors:
Kyung Won Kim[1], Yishi Jin[1]

1. Kim, K. W., Thakur, N., Piggott, C. A., Omi, S., Polanowska, J., Jin, Y., & Pujol, N. (2016). Coordinated inhibition of C/EBP by Tribbles in multiple tissues is essential for Caenorhabditis elegans development. *BMC biology*, *14*(1), 104.

POSTER POSTION 5A

Bacterial Cytological Profiling (BCP) Reveals 24F3 and Derivatives as Peptidoglycan Inhibitors

Elizabeth T. Montaño
(Joseph Pogliano Lab)

A library comprised of 1,800 synthetic small molecules was screened for antibacterial activity against *E. coli* **Δ***tolC* using the broth microdilution method at 100 µg/mL. One of these molecules, 24F3, was found to have an MIC of 45 µM. To gain insight into the mechanism of action (MOA) of this compound, BCP was used to examine the effect of treating *E.coli* **Δ***tolC* with 1X, 2X, 3X, and 5X the MIC at 30 minutes and 2 hours. Over time, at these concentrations, cells treated with 24F3 became swollen, severely misshapen, and eventually lysed. These results strongly suggest that 24F3 inhibits peptidoglycan biogenesis. Potent derivatives of 24F3 were identified and have multiple MOAs including peptidoglycan biogenesis. To identify the specific target within the peptidoglycan synthesis pathway, resistant mutants to compounds 24F3 and potent derivatives were isolated. The untreated cytological profile of 24F3 resistant mutants revealed obvious cell division or cell wall defects. The locus of the mutations existing among these mutants is expected to unveil the specific target of 24F3 and its derivatives.

POSTER POSTION 5B

Short Poly(A) Tails are a Conserved Feature of Highly Expressed Genes

Angela Nicholson
(Amy Pasquinelli Lab)

The poly(A) tails appended to the 3' ends of most eukaryotic mRNAs play important roles in translation and stability. However, recent genome-wide studies concluded that poly(A) tail length was generally not associated with translational efficiency in non-embryonic cells. To investigate if poly(A) tail size might be coupled to gene expression in an intact organism, we used an adapted TAIL-seq protocol to measure poly(A) tails in larval stage *Caenorhabditis elegans*. Surprisingly, we found that well-expressed transcripts contain relatively short, well-defined tails that would likely accommodate only 1-2 poly(A) binding proteins (PABPs). This attribute appears dependent on translational efficiency, as transcripts enriched for optimal codons and ribosome association had the shortest tail sizes, while non-coding RNAs retained long tails. Across eukaryotes, short tails were a feature of abundant and well-translated mRNAs. However, for these genes and almost all others, we were still able to detect transcripts with tail lengths consistent with the very long (>200 nt) poly(A) tails synthesized on nascent mRNAs. The finding that genes with the highest frequencies of optimal codons were represented by mRNAs that spanned the entire range of detectable tail sizes, but were strongly biased for short tailed species, suggests that well-expressed mRNAs undergo poly(A) tail shortening to an optimal length, which we refer to as pruning. The hallmarks of pruning are that poly(A) tails are well-defined and relatively short, while tails on mRNAs enriched for suboptimal codons are more heterogeneous and less defined, showing a spread across the range of possible sizes. Although this seems to contradict the dogma that deadenylation induces translational inhibition and mRNA decay, it instead suggests that well-expressed mRNAs accumulate with pruned tails that accommodate a minimal number of PABPs, which may be ideal for protective and translational functions.

POSTER POSTION 5C

The Dynamic Cellular Responses to Loss of Sir2 Activity During Aging

Julie Paxman
(Nan Hao Lab)

Sir2, a conserved NAD-dependent histone deacetylase, plays a dynamic role in regulating heterochromatin silencing in yeast. Temporal silencing patterns of the heterochromatic ribosomal DNA (rDNA) locus, which are governed by Sir2 activity, directly influence cellular aging—driving cells towards two distinct aging paths and death phenotypes. In one aging path, cells produce elongated daughter cells near the end of their lifespan and exhibit a dramatic loss of Sir2 activity that precedes cellular death. How loss of Sir2 activity causes rapid cellular decline and death with elongated daughter morphology remains unknown. We propose that loss of Sir2 activity during aging affects homeostasis of ribosomal biogenesis leading to amino acid starvation and loss of cellular proteostasis. When cells experience amino acid starvation, the transcription factor GCN4 upregulates expression of amino acid biosynthesis genes. Here I show that MET3, a gene necessary for methionine biosynthesis, has increased expression in cells that die from loss of Sir2 activity, and expression is particularly increased upon production of elongated daughter cells. Furthermore, I find that the protein disaggregase HSP104 forms foci, indicating a loss of proteostasis, almost exclusively in the subgroup of cells that die from loss of Sir2 activity. Together these data suggest that there is indeed a dynamic interplay between Sir2, amino acid biosynthesis and cellular proteostasis during aging. Ongoing work will further investigate the underlying mechanisms and the relationship to ribosomal biogenesis.

POSTER POSTION 6A

Mechanisms of Bacterial-Fungal Interactions in a Model Microbiome

Emily Pierce
(Rachel Dutton lab)

In their native environments, microbes grow in close association not only with other members of the same species but frequently with many species. Microbes in these communities have evolved complex interaction systems. Bacterial-fungal interactions, in particular, are key factors in determining the composition and function of many microbiomes, and are relevant to medicine, soil health, and the texture, taste, and smell of fermented foods. Understanding bacterial-fungal interactions will be vital to our ability to predict responses of these microbial communities to disturbances or to push these communities toward desired outcomes. In this work, we use RB-TnSeq (a variation of traditional TnSeq) to identify genes important for bacterial-fungal interactions in a model microbiome (cheese). Pairwise assays have been performed by growing a bacterial barcoded transposon mutant library either alone or with one of 8 fungal members of the cheese ecosystem on in vitro cheese medium for seven days. The fitness effect of each mutation was determined and compared across conditions to identify the genes and pathways important for species interactions. These assays have been performed with a barcoded mutant E. coli library as well as a library created in the cheese-associated Pseudomonas psychrophila. By using a diverse set of interaction partners (molds and yeasts, five different fungal genera) with multiple bacterial mutant libraries, it is possible to determine the relative conservation or specificity of genetic mechanisms of bacterial-fungal interactions. We identified both general and specific microbial interaction mechanisms across diverse interaction combinations, which include responses to both nutritional and toxic stresses.

POSTER POSTION 6B

Uncovering the Genetic Basis of Maize Sensitivity to Herbivore-Associated Fatty-acid Amino-acid Conjugates

Elly Poretsky
(Alisa Huffaker Lab)

Billions of dollars are lost annually due to damage of crops caused by herbivorous caterpillars, posing a major threat to global food security that is expected to become increasingly severe due to amplified pressures occurring with climate change. Plants recognize and respond to herbivory with protective responses, and understanding the mechanisms by which this occurs is essential for developing crop varieties with increased resistance to herbivores. N-linolenoyl L-glutamine (Gln-18:3) is a fatty-acid amide conjugate (FAC) present in the oral secretions of Lepidopteran herbivores. FACs are potent inducers of innate immune responses that protect against herbivores, but the mechanism by which plants perceive these molecules remains unknown. Comparison of two maize inbred lines revealed a genotype-dependent differential sensitivity to Gln-18:3. Association mapping of FAC-induced responses in a biparental mapping population derived from the two parents led to identification of a single genetic locus associated with Gln-18:3 sensitivity. Fine-mapping of this locus, analysis of sequence variations, and sorting of genes with herbivory-associated expression profiles allowed for the prioritization of 2 candidates from the original list of 132 genes within the locus, including one encoding a Toll-like pattern recognition receptor. To test whether these candidate genes play a role in FAC sensitivity we are using a Virus-Induced Gene Silencing system (VIGS) to knock-down their expression in maize and expressing each in heterologous systems to observe whether they can confer sensitivity.

POSTER POSTION 6C

Investigating the role of the Neuron Navigator 1 in cytokinesis

Regina Powers
(Shelley Halpain Lab)

The neuron navigators (Nav1, Nav2 and Nav3) are a group of cytoskeleton-associated proteins most highly expressed in the developing nervous system. In particular, the navigators have been identified as +TIP proteins that regulate neurite outgrowth, though not much else is known about their role in the cell. I have identified a potential novel role of the navigators in cytokinesis. Nav1, 2, and 3 localize to the midbody ring in cell lines and human iPSC-derived neural progenitor cells, and the microtubule associated domain of Nav1 specifically is necessary and sufficient for that localization. My preliminary data also indicate that Nav1 plays a functional role in abscission. These data represent a new potential role for the navigators in regulating cytokinesis, opening up new avenues of investigation into, for example, the role of the navigators in regulating the neural progenitor pool in the developing brain, as well as in cancer.

POSTER POSTION 7A

C. elegans defensive responses to a predator

Amy Pribadi
(Shrek Chalasani Lab)

Sensing environmental threats and conducting the appropriate defensive responses are basic survival skills for any animal. We are analyzing a predator-prey interaction between *Pristionchus pacificus* (predator) and *Caenorhabditis elegans* (prey). *P. pacificus* has a pair of teeth that it uses to bite *C. elegans*. We have developed a conditioning assay where *C. elegans* receives non-lethal bites as an unconditioned stimulus in the presence of a mildly attractive odor (butanone) as a conditioned stimulus. After receiving bites for 3 hours in the presence of butanone, *C. elegans* decreases its response toward butanone in a single-worm chemotaxis assay. We plan to further characterize this conditioned response and dissect its neural components through the development of CaMPARI, and its genetic components through single-worm RNA-seq.

POSTER POSTION 7B

Drought in Southern California coastal sage scrub reduces biomass of exotic species more than native species, but exotic growth recovers quickly when drought ends

Chandler Puritty
(Elsa Cleland)

Semi-arid regions with Mediterranean-type climates harbor exceptional biodiversity, but are increasingly threatened by invasion by annual exotic species and climatic changes, including drought. Studies in these systems find antecedent conditions, or lag effects, often influence plant growth, but the role of lag effects from drought on the growth of native and exotic species remains largely unexplored. From 2013-2016 we imposed experimental rainfall treatments (average rainfall, moderate or severe drought) in plots dominated by shrubs or herbaceous vegetation, and quantified growth (peak biomass) and abundance (cover) of native and exotic herbaceous species. In the following year we quantified recovery from the drought treatments (2017). We found exotic biomass was less resistant to drought (declined more than native biomass), but was more resilient (increased more than native biomass in the year following drought), especially in open areas unshaded by a shrub canopy. These responses were strongly correlated with life history; annual species responded more negatively to drought in the open than perennial species. Antecedent factors had little influence on plant growth; during the drought litter had a positive effect on exotic, but not native, biomass. Previous year's rainfall had only marginally significant influences on biomass during the drought, and no antecedent factors predicted biomass in the recovery year. This study demonstrates that when native and exotic species differ in life history, as they do in Mediterranean climate ecosystems, they may respond differently to future climate changes such as drought, and can also have different responses to antecedent factors such as litter accumulation.

POSTER POSTION 7C

High-throughput method to discover regulatory network in novel microorganism

Bijie Ren
(Stephen Mayfield Lab)

The world faces global warming, high cost of therapeutic antibody and natural products, serious pollution in developing countries, and potentially energy crisis in next 100 years. One of solutions to solve above problems is to discover useful genetic elements and enzymes from novel abundant microorganisms in the nature, build a specific cell factory and perform state-of-art bioprogramming. However, it's time-consuming to discover and identify these useful molecular elements. Here we develop a pipeline that uses Dynamic Mode Decomposition to analyze time course diurnal RNAseq data in C.reinhardtii, cluster genes with similar expression pattern and use one-time-for-all sequencing to identify Transcription factor binding to our interested promoters in a high-throughput manner. Such pipeline will help us to understand the fundamental regulation of photosynthetic cell and build a reliable whole cell modeling, which will be used for bioprogramming.

POSTER POSTION 8A

Investigating roles of spinal ascending pathway in sensorimotor transformation

Xiangyu Ren
(Martyn Goulding Lab)

The spinal cord plays a central role in sensorimotor transformation. Neurons in the spinal dorsal horn have been recognized as major receivers and processors of different sensory modalities, including pain, itch, touch, temperature and body position (Braz et al. 2014; Andrew J. Todd 2010; Abraira and Ginty 2013). Spinal dorsal neurons relay somatosensory information from primary afferent neurons to different downstream targets, including ventral spinal cord neurons to control movement (spinal reflex pathways), or to supraspinal structures to generate affective behaviors (spinal ascending pathways) (Andrew J. Todd 2010). Recently, great progress has been made in the characterization of spinal dorsal neuron populations with molecular and genetic approaches to significantly improve our understanding of the morphological, electrophysiological and molecular properties as well as the functional role of these neurons (Duan et al. 2014; Steeve Bourane et al. 2015; S. Bourane et al. 2015; Watanabe et al. 2017). However, most of these studies preferentially focused on spinal reflex pathways instead of spinal ascending pathways, making the functional roles of spinal ascending pathways in sensorimotor transformation still elusive. For my thesis project, I will use intersectional genetic strategy to selectively target and manipulate of most important spinal projection neurons, especially the post-synaptic dorsal column neurons, trying to explicit their locational and molecular properties and functional roles in sensorimotor transformation.

POSTER POSTION 8B

Rapidly evolving PARP proteins act as both positive and negative regulators of the antiviral response

Andy Ryan
(Matthew Daugherty Lab)

Viral manipulation of cellular post-translational modifications (PTMs) can be key to their survival and replication. One understudied PTM that has been implicated in the antiviral response is ADP-ribosylation. To manipulate this modification, several viral families encode for a macrodomain capable of binding and removing ADP-ribosylation. Importantly, disruption of this function can lead to reduction in pathogenesis or increases in sensitivity to the host interferon response. While the family of host proteins capable of catalyzing ADP-ribosylation, known as PARPs, is large, a subset show multiple signs of rapid evolution, including gene duplication and loss as well as recurrent sequence changes. Focusing in on these genes, we have found that the long isoform of PARP13 is acting directly to inhibit Sindbis virus, a member of the macrodomain-containing alphavirus family. The full antiviral activity requires the presence of the PARP domain in addition to proper localization. In contrast to this, the short isoform acts as a negative regulator of the interferon response by binding and degrading Interferon mRNAs. The balance between antiviral and proviral functions creates a novel dynamic that is potentially more resistant to viral antagonism. We are now exploring the role of ADP-ribosylation in modulating these two phenotypes.

POSTER POSTION 8C

Differential Control of Functionally Distinct Sympathetic Outputs

Gokhan Senturk
(Samuel Pfaff Lab)

Despite the prevailing notion that the sympathetic nervous system (SNS) acts in a diffuse way to stimulate all its effector organs at once, many studies have found different patterns of sympathetic activity under various physiological conditions. This suggests that the SNS can differentially activate its effector organs. However, *the degree to which* the sympathetic efferent pathways are segregated to enable differential control remains to be unknown. We aim to answer this question by using the sympathetic innervation of the head as a model system in mice. To this end, we have established the circuit tracing tools and a mouse line for SNS that will enable us to dissect out the SNS efferent circuitry.

POSTER POSTION 9A

Global Identification of Non-coding RNA Targets of 3’ Processing Enzymes

Tim Shaw
(Jens Lykke-Andersen Lab)

The 3’ ends of non-coding RNA (ncRNAs) are dynamic battlegrounds of post-transcriptional regulation. Certain classes of exonucleases and polymerases are capable of shaping that 3’ end in order to affect biogenesis, decay, and ultimately the proper functioning of ncRNAs in the cell. Identification of these trimming and extension events and the enzymes responsible for them is complex. Recent studies have focused mainly on known 3’ events and searched for candidate enzymes responsible for them in a low-throughput manner. In this work, we use a next generation sequencing approach to assess the composition of the 3’ ends of ncRNAs in the cell after knockdown of a 3’ processing enzyme. ncRNAs that are altered in length after knockdown are identified as candidate targets for processing by that enzyme. This approach was applied to TOE1, a deadenylase we recently discovered to be responsible for trimming snRNAs to their mature length. Our experimental pipeline confirmed snRNAs as a strong hit. Using this assay, we hope to extend this pipeline to other 3’ processing enzymes to find novel 3’ modification events in the cell and further illuminate their complex biogenesis and regulation.

POSTER POSTION 9B

Single cell elongation asymmetry in *E.coli*

Chao Shi
(Lin Chao Lab)

Aging is a typical phenomenon in cellular organisms. The mechanism of aging and its evolutionary significance is a long-debating topic. Publications show that the cellular aging and rejuvenation caused by asymmetric damage distribution among the daughter cells, which is originated from more damage in mother cell's old pole.

E.coli has recently been reported to show a strong correlation between elongation rate and the amount of inclusion body. But little is known about this relationship in subcellular level. Here, we applied a cell wall marker on elongating bacteria to track local elongation event, and tested relation of subcellular damage distribution and local elongation. By tracking local elongation rate of a single cell, we found elongation rate is asymmetrical in a single cell and bias towards the new pole. And the degree of asymmetry is correlated to the age asymmetry of the cell.

Three-D deconvolution is used for the first time to correct both diffraction and fluorescent scatter coming from a reflective substrate.

POSTER POSTION 9C

Coordination of theta and slow oscillations across medial septum, hippocampus, olfactory bulb and prefrontal cortex

Sunandha Srikanth
(Stefan Leutgeb Lab)

It has been proposed that communication between the sensory cortices and the hippocampus during memory acquisition and retrieval is coordinated by oscillations (Buzsáki, 1996). Furthermore, hippocampal oscillations are thought to be synchronized by subcortical inputs from the medial septal area (MSA). To investigate whether MSA may coordinate oscillations across a larger cortical network, we recorded local field potentials (LFPs) across brain regions with prominent oscillations in the theta range. These regions not only include the hippocampus and prefrontal cortex, but also the olfactory bulb (OB) where oscillations in the theta band (3-12 Hz) closely follow the respiratory frequency (Rojas-Líbano et al., 2014). In particular, the respiration rhythm and the dorsal and ventral hippocampal theta rhythms are coherent during odor learning and discrimination tasks (Macrides et al., 1982; Kay, 2005). The olfactory respiration rhythm may thus couple to theta band rhythms in the limbic-cortical network and contribute to sensory processing. To begin to understand the mechanisms for theta coupling, we simultaneously recorded LFP signals from the OB, MSA, dorsal hippocampus (dHpC), ventral hippocampus (vHpC), and medial prefrontal cortex (mPFC). We compared these signals between different periods when mice were running on a figure 8 maze, actively sniffing a neutral odor presented at an odor port, or sleeping in the home cage following behavior. As expected, we found that the oscillations in the MSA and dHpC were coordinated in the theta range (7-9 Hz) throughout all the phases of behavior (odor sniffing, running and sleep). However, septal oscillations were coherent with the vHpC only during sleep and odor presentation, but not during running. During sleep, the OB and mPFC oscillations were highly coherent to each other and to the other three regions in the 3-5 Hz range, but this coherence shifted to higher frequencies (5-7 Hz) during odor presentation. Oscillations are thus differentially coordinated between these regions during each behavioral epoch, such that task-dependent functional subnetworks emerge, which can each use frequencies in the theta range for coupling.

Biskamp J, Bartos M, Sauer J-F (2017) Organization of prefrontal network activity by respiration-related oscillations. Scientific Reports, Published online: 28 March 2017; | doi:101038/srep45508.

Buzsáki G (1996) The hippocampo-neocortical dialogue. Cereb Cortex 6:81-92.

Fontanini A, Spano P, Bower JM (2003) Ketamine-xylazine-induced slow (< 1.5 Hz) oscillations in the rat piriform (olfactory) cortex are functionally correlated with respiration. J Neurosci 23:7993-8001.

Fujisawa S, Buzsáki G (2011) A 4 Hz oscillation adaptively synchronizes prefrontal, VTA, and hippocampal activities. Neuron 72:153-165.

Kay LM (2005) Theta oscillations and sensorimotor performance. Proc Natl Acad Sci U S A 102:3863-3868.

Macrides F, Eichenbaum HB, Forbes WB (1982) Temporal relationship between sniffing and the limbic theta rhythm during odor discrimination reversal learning. J Neurosci 2:1705-1717.

Rojas-Líbano D, Frederick DE, Egaña JI, Kay LM (2014) The olfactory bulb theta rhythm follows all frequencies of diaphragmatic respiration in the freely behaving rat. Front Behav Neurosci 8:214.

Yanovsky Y, Ciatipis M, Draguhn A, Tort AB, Brankačk J (2014) Slow oscillations in the mouse hippocampus entrained by nasal respiration. J Neurosci 34:5949-5964.

POSTER POSTION 10A

Chlamydomonas reinhardtii as a new recombinant protein factory: making way for the underdog

Yasin Torres-Tiji
(Stephen Mayfield Lab)

Biotechnological derived high value product market size has shown a tremendous increase over the past decades, and it is expected to continue to do so. The traditional approach to generate these products has been to focus on the model organisms for biotechnology such as *Escherichia coli*, *Saccharomyces cerevisiae*, *Pichia pastoris*, CHO cells, etc. However, even if those organisms have proven very useful in biotechnology, they do have their limitations such as: cost, complexity of products that can be made, GRAS status, etc. Green algae have the potential to join those traditionally used organisms in biotechnology and complement their limitations. Being able to produce highly complex recombinant proteins, unique valuable metabolites, and being able to be grown at a fraction of the cost of other complex systems like CHO cells and not needing much product purification due to their GRAS status, green algae are an option that cannot be ignored anymore.

Despite all its potential, the state of the art for high value molecules production in algae is still behind of what it should be for this technology to be competitive. The two single most important issues that need to be addressed for this to be achieved are the development of strong and inducible synthetic promoters and genetic tools, and the development of high cell density culture techniques.

POSTER POSTION 10B

Intermittent hypoxia and hypercapnia, a hallmark of obstructive sleep apnea, alters the gut microbiome and metabolome

Anupriya Tripathi
(Rob Knight and Pieter Dorrestein Labs)

Obstructive sleep apnea (OSA) is a common disorder characterized by episodic obstruction to breathing due to upper airway collapse during sleep. OSA has been associated with adverse cardiovascular and metabolic outcomes, although data regarding potential causal pathways are still evolving. Because O2 and CO2 affect the ecology of the gut microbiota and the microbiota has been shown to contribute to various cardio-metabolic disorders, we hypothesized that the downstream physiological consequences of OSA are linked to functional alterations in the gut ecosystem. Here, we model human OSA and its cardiovascular consequence using atherosclerosis-prone (Ldlr -/-) adult mice fed high-fat diet (resembling western dietary practices). As episodic hypoxia and hypercapnia mimic the changes in blood gases that occur in OSA, these mice were longitudinally exposed to intermittent hypoxia and hypercapnia (IHH; analogous to chronic OSA) in a computer-controlled atmosphere chamber system (treatment group; n=8) or housed in room air (control group; n=8), and examined for 6 weeks. We had previously shown that IHH exacerbates atherosclerosis plaque formation in this model system. Fecal samples, a representative of the gut ecosystem, were collected at baseline and twice each week thereafter, and microbiome and metabolome were profiled using 16S rRNA amplicon sequencing and LC-MS/MS-based untargeted mass-spectrometry, respectively. We estimated relative abundances of microbial features (using QIIME2) and molecular features (using GNPS and MZmine2) per sample and compared OSA-mimicking and control mice using multivariate statistical models. Starting from a highly congruent gut composition at baseline, both microbiome and metabolome of IHH-exposed mice cumulatively diverged from controls and co-varied with increasing duration of IHH-exposure. We noted significant compositional changes in both microbial (>10%, mostly increases in Clostridia) and molecular (>22%) species in the gut. Furthermore, top molecules altered in abundance included microbe-derived secondary bile acids, enterolignans and fatty acids (identified to the highest level of annotation per metabolomics standards), highlighting the impact of IHH on host-commensal co-metabolism in the gut. Thus, we present the first evidence that IHH functionally perturbs the gut ecosystem, setting the stage for understanding its involvement in associated cardio-metabolic disorders.

POSTER POSTION 10C

Evolution-guided discovery of viral protease cleavage targets in primates

Brian Tsu
(Matthew Daugherty Lab)

The Daugherty lab aims to understand how host innate immune defenses evolve against viruses, and on the other side, how viruses evolve to subvert these defenses for increased infectivity. Because viruses have to subvert innate immune factors to succeed, I assert that we could use signatures of viral antagonism to chase down host innate immunity proteins relevant to a given infection. One classical example of a viral antagonism strategy we use is site-specific proteolytic cleavage of host antiviral proteins via proteases. By using evolutionary signatures of conflict and viral protease cleavage motif discovery as a guide, we have begun to identify potential primate host targets in conflict with viral proteases and are currently working to assess whether cleavage susceptibility of these targets results in increased infectivity in humans.

POSTER POSTION 11A

Fine-scale mapping of local ancestry across Africanized honeybee genomes collected across a broad geographic gradient

Daniela Zarate
(Joshua Kohn Lab)

Admixture, the novel mixture of two distinct genetic pools, acts as a creative evolutionary force through previously unrealized combination of genes on which selection can act. Admixture holds the potential to generate high levels of genetic diversity, provide pathways to adaptive evolution, and produce novel ecological traits. The hybridization of European (EHB) and African honeybees (AHB) (subspecies of Apis mellifera) that gave rise to the Africanized honeybee (AfrHB) is one of the most extensively studied cases of admixture. In what is often termed the most spectacular biological invasion ever documented, the African honeybee subspecies Apis mellifera scuttelata, brought from southern Africa to Brazil in 1956, escaped experimental breeding apiaries and quickly expanded across the continent. Throughout their expansion, African honeybees successfully interbred with preexisting European honeybees creating an aggressive Africanized honeybee hybrid that has posed serious concerns to both the agricultural and apiary industries. Hybridization between AHB and EHB is largely characterized by the overall displacement of EHB traits by AHB ones. Admixture is characterized by the domination of African genetic material (70-80%) and the hybrids typically resemble the African subspecies in both behavior and biology. While admixture ratios in Africanized honeybees have been relatively well studied, fine-scale genomic mapping of local ancestry is much less common. Here, we have sampled and sequenced 60 Africanized honeybee genomes across the hybrid's geographic range expansion in the Americas. To our knowledge this is the first study undertaking a genomic mapping of local ancestry in Africanized honeybees across a broad geographic gradient which parallels the advancement of the hybrid across the continents and thus provides unique windows through which to study admixture on a fine scale across the entire hybridization process.

POSTER POSTION 11B

Asymmetric lateral inhibition in the initial of olfactory processing

Ye Zhang
Chih-Ying Su Lab

Olfactory receptor neurons (ORNs) housed in the same sensory hair in *Drosophila* can inhibit each other non-synaptically. Here we provide experimental evidence that direct electrical interaction, or ephaptic coupling, is sufficient to mediate lateral inhibition between ORNs. Moreover, in most sensilla, we find that ephaptic interactions between these neurons are asymmetric. Interestingly, volume electron microscopy of genetically identified ORNs shows that the physically larger ORN in a pair corresponds to the dominant neuron in ephaptic interactions, in agreement with our electric circuit model that considers morphometric differences between compartmentalized ORNs. By revealing the asymmetric nature of this circuit interaction, our findings bring functional insights into how information is processed in the first neurons of an insect olfactory circuit.

POSTER POSTION 11C

Geometry of the olfactory space

Yuansheng Zhou
(Tatyanna Sharpee Lab)

The reason that the sense of smell can be used to avoid poisons or estimate a food's nutrition content is that biochemical reactions create many by-products. Thus, the production of a specific poison by a plant or bacteria will be accompanied by the emission of certain sets of volatile compounds. An animal can therefore judge the presence of poisons in the food by how the food smells. This perspective suggests that the nervous system can classify odors based on statistics of their co-occurrence within natural mixtures rather than from the chemical structures of the ligands themselves. We show that this statistical perspective makes it possible to map natural odors to points in a hyperbolic space. Hyperbolic coordinates have a long but often underappreciated history of relevance to biology. For example, these coordinates approximate distance between species computed along dendrograms, and more generally between points within hierarchical tree-like networks. In the hyperbolic natural odor space, we identify three axes that are aligned with odor pleasantness, molecular boiling point and acidity. In addition to natural odors, we find that human perceptual descriptions of smells can also be described using a three-dimensional hyperbolic space. This match in geometries can avoid distortions that would otherwise arise when mapping odors to perception.

POSTER POSTION 12A

Investigating the mechanism of promoter-driven mRNA localization and translational control during glucose starvation

Yang Sophie Chen
(Brian Zid Lab)

Adaptive responses to unpredictable stress conditions are necessary for survival across biological systems. One conserved mechanism is the overall down-regulation of gene expression to conserve resources, but up-regulation of a group of selective genes that are important for survival against stress. During multiple types of stresses, conserved from budding yeast to mammals, cells undergo rapid phase transitions and form compact, membrane-less messenger ribonucleoprotein (mRNP) granules to sequester and store mRNA transcripts that are not actively translated. Two well-known membrane-less, phase-dense and gel-like mRNP granules related to stress responses are P-bodies and stress granules (SGs). This rapid mRNA localization change is beneficial for cell to alter its cellular composition efficiently during stress. Although it was generally thought that the specificity of mRNA cytoplasmic localization is majorly determined by *cis*-acting mRNA sequence elements. Previously, we found that, during glucose starvation in budding yeast, mRNA localization with regard to mRNP granules was independent of *cis*-acting mRNA sequence elements, but instead controlled by non-transcribed promoter elements. It suggested that there might be an alternative promoter-driven mechanism dictating the translatability and localization of transcripts during stressful conditions. To answer the question of how does promoter in nucleus specify the cytoplasmic fate of mRNA during stress, we performed an unbiased identification of factors potentially involved in the process and tested the function of candidates by utilizing the power of yeast genetics, biochemical techniques, microscopy and next-generation sequencing.

POSTER POSTION 12B

Structure-Misfunction" Analysis of a Cytoplasmic Enzyme: Exploring the Structural Envelope of Protein Quality Control

Matthew Flagg
(Randy Hampton Lab)

To maintain cellular proteostasis, the ubiquitin-proteasome system (UPS) must recognize, ubiquitinate, and degrade misfolded proteins while sparing folded ones. This selective process, referred to as protein quality control, is key to the maintenance of cellular functions and organismal health. Indeed, malfunctions in quality control mechanisms underlie a growing list of human diseases, ranging from Parkinson's to cystic fibrosis.

To achieve the exquisite specificity required for functional quality control, the UPS employs E3 ubiquitin ligases, enzymes that preferentially bind to and ubiquitinate misfolded substrates. It is known that quality control ligases can discern between normal proteins and a surprisingly large array of mutated, truncated, and mislocalized substrates, but the structural features these substrates posses that allow them to be recognized as misfolded remain unclear.

We therefore set out to examine substrates of a highly conserved and central pathway of cytosolic quality control mediated by the Ubr1 and San1 E3 ligases. Although we know that Ubr1 and San1 have a very broad range of misfolded substrates, we do not know what criteria these E3 ligase uses to make the critical decision to ubiquitinate a protein. We have therefore designed and executed a "structure-misfunction" screen to identify enzymatically functional, minimally misfolded mutants of Lys1, a normally stable cytosolic enzyme with a known and well-studied structure and function. By harnessing yeast genetics and a plate-based, optical approach, we have assayed for degradation of roughly 19,000 randomly mutated versions of *LYS1*. By doing so, we have identified a range of individual point mutations that destabilize Lys1 but do not ablate its function.

These mutants were subsequently mapped to the Lys1 structure and tested for their E3 ligase specificity. To our surprise, different quality-control pathways can be elicited by destabilizing different secondary structures within a single domain. A mutation to the final alpha helix of Lys1, which resides on the first domain, causes San1-Ubr1 mediated degradation. On the other hand, mutations to the first alpha helix of the protein, which also resides on the first domain, cause recognition by additional ligases, perhaps including but not limited to Doa10 and Ltn1.

To better understand these mutations and others, we have begun make use of site-directed and saturation mutagenesis. We hope to model the structural perturbations caused by an array of different amino acids substitutions at a single position and to thereby uncover specific structural changes that are recognized by E3 ligases. In particular, we hope to discover a difference (or lack thereof) between canonical San1-Ubr1 substrates and those that are degraded by an as yet unidentified proteasomal pathway.

POSTER POSTION 12C

Investigating the Role of the microRNA Pathway in the Heat Shock Response

Delaney Pagliuso
(Amy Pasquinelli Lab)

The microRNA (miRNA) pathway plays an important regulatory role in a variety of cellular processes. These small (~22nt) RNA molecules target messenger RNAs through imperfect base-pairing to repress their expression. Each miRNA has the potential to regulate multiple targets by recruiting specific factors to promote mRNA degradation or translational inhibition. While the targets and biological functions of some miRNAs have been determined, the roles of most miRNAs are yet to be elucidated, especially in the context of disease or stress. To investigate the role of the miRNA pathway in stress conditions, we are studying miRNA expression and function during heat shock in last larval stage (L4) *Caenorhabditis elegans*, Using small RNA profiling, we identified a subset of miRNAs that are significantly up- or down-regulated in response to heat shock (HS). Thus far, we have determined that some of these miRNAs are important for recovery from an episode of HS. To examine how miRNA target recognition is affected by HS, I will use InfraRed Crosslinking and Immunoprecipitation (irCLIP) to compare targeting of the miRNA complex under control versus HS conditions. By coupling this assay with RNA expression and Ribosome Profiling, I aim to gain new insights into miRNA regulation of gene expression during HS. Overall, we hope this work will improve our understanding about how the miRNA pathway contributes to stress tolerance and reveal new roles for specific miRNAs.

POSTER POSTION 13A

Immunity in Eusocial Mammals

Alexandria M Palaferri Schieber
(Janelle Ayres Lab)

Social Immunity entails a group response to parasite infection and insult, in which others may gain health and fitness benefits of the collective immune system, and may include social group-living animals, insects, and microbes. Studying eusocial animals, considered to have the highest form of sociality, can provide a relevant and useful tool for elucidating more about social immunity. Due to close living proximity and genetic relatedness, eusocial animals are expected to be prime hosts for transmissible parasite infections. Ants, Bees, and other eusocial insects have been shown to display altruism and social immunity, including leaving the colony when diseased or infected with pathogen, sacrificing themselves in order to protect the colony from disease spread. It can be hypothesized that the eusocial mammal, *Heterocephalus glaber*, commonly termed Naked Mole Rat (NMR), has evolved the collective parasite defense mechanisms of social immunity. Little is known about NMR innate and behavioral immunity to parasites. As eusocial animals, NMRs are inherently cooperative, displaying altruistic breeding and brood care as well as division of labor; in our colony we have even observed cooperative fighting against a challenger. Despite this, NMRs are known to exert aggressive behaviors such as shoving and climbing over lower caste animals while traveling in their tunnels, pushing workers to work harder, and fighting or displaying social dominance. I will perform experiments with infectious agents and parasites in NMRs, analyzing behavioral and physiological responses at individual and group host level, as well studying results of perturbing social dynamics of the group. I suggest there may be a role for both cooperative, and antagonistic behaviors, as a means of social immunity, and further hypothesize that they may have different physiological and social drivers, as well as different outcomes for the individual or the group. As a novel and exotic model for social immunity, research with the eusocial NMR would provide insights into mammalian social immunity that may differ from that of insects.

POSTER POSTION 13B

Mutant p53 regulates the cancer cell epigenome through interactions with the histone methyltransferase MLL4

Homa Rahnamoun
(Shannon Lauberth Lab)

Enhancers contribute to gene regulation during development and signal-dependent cellular responses. The location and activity state of enhancers is well correlated with particular epigenetic signatures. Specifically, monomethylation of histone H3 lysine 4 (H3K4me1) is enriched at enhancers that are primed for activation, and the accumulation of H3K4me1 and H3 lysine 27 acetylation (H3K27ac) denotes active enhancers. It has been well-established that MLL3 (KMT2C) and MLL4 (KMT2D) constitute the major mammalian histone monomethyltransferases (HMTs) that function at enhancers. While the enrichment of these HMTs is well correlated with and predictive of enhancer activity, the factors and mechanisms governing MLL3 and MLL4 recruitment to cell-type and signal-specific enhancers remain poorly understood. Here, through global profiling analysis in colon cancer cells, we demonstrate that tumor promoting mutant p53 regulates H3K4me1 levels in response to chronic immune signaling. We show that mutant p53 and MLL4 colocalize at a subset of enhancers and form functional associations to enhance the binding of this HMT at active enhancers upon chronic TNF signaling. Furthermore, we establish that mutant p53 directly interacts with MLL3/4 *in vitro* to enhance its binding and subsequent H3K4 monomethylation activity on reconstituted chromatin templates. Lastly, we demonstrate that loss of mutant p53-directed MLL4 binding at active enhancers results in alterations in the epigenetic landscape that include decreased deposition of the H3K4me1 histone mark and lower levels of enhancer transcription at these cancer cell-specific enhancers which ultimately lead to downregulation of mutant p53-dependent gene expression programs. Our results provide new insights into gain-of-function activities of mutant p53 and define a molecular mechanism for mutant p53-MLL4 interactions in directing epigenetic signatures that are linked to aberrant enhancer and tumor promoting gene activation.

POSTER POSTION 13C

Investigating immunometabolism in host parasite interactions

Samuel Redford
(Janelle Ayres Lab)

Adipose tissue is increasing being recognized for its role in signaling between the immune system and metabolic responses. This role has become evident as many of the morbidities associated with obesity, such as dysregulated metabolic responses, can be associated with improper immune activation within the adipose tissue. These responses are typically detrimental to the individual but have not been extensively studied within host pathogen interactions. Adipose tissue may play a role in coordinating the metabolic responses to infection. I am proposing to utilize *Trypanosoma brucei*, which is an extracellular eukaryotic parasite that localizes to adipose tissue, to investigate the metabolic responses to a chronic infection and determine the immune origin of the responses. Through genetic knockout models of mice, drug administration, and dietary intervention, the importance of host metabolic and immune molecular signaling will be determined.

POSTER POSTION 14A

Metabolic differentiation and intercellular nourishing underpin *Bacillus subtilis* endospore formation

Eammon Riley
(Kit Pogliano Lab)

Intercellular nutrient exchange underlies complex biological phenomena such as the formation of multispecies microbial communities and bacterial development. Although an intercellular nourishing relationship has long been hypothesized to occur during spore formation in *Bacillus subtilis*, the nature and extent of this relationship remain poorly characterized. Here, taking advantage of a recently developed technology called spatiotemporally regulated proteolysis (STRP) to inactivate biosynthetic pathways in a cell-specific manner, we demonstrate that spore formation entails a profound metabolic interaction between two cells arising from a polar cell division event: the forespore, which becomes a metabolically dormant spore, and the mother cell, which lyses upon the completion of sporulation. We show that the forespore and mother cell become metabolically differentiated shortly after sporulation initiation, with enzymes functioning in central metabolism, amino acid biosynthesis, and nucleotide biosynthesis becoming highly enriched in the mother cell. Furthermore, using bio-orthogonal non-canonical amino acid tagging (BONCAT) and click chemistry in conjunction with STRP, we demonstrate that forespore protein synthesis becomes dependent on mother cell-derived metabolic precursors and Q-A, a transenvelope complex bridging the forespore and mother cell membranes. Interestingly, fluorescence recovery after photobleaching (FRAP) data reveal that Q-A also mediates the movement of small molecules from the mother cell to the forespore. Altogether, our findings suggest that metabolic differentiation and intercellular nourishing allow the mother cell to assume the burden of precursor biosynthesis during spore formation, and to nurture the forespore as it transitions to dormancy.

POSTER POSTION 14B

Investigating the role of muscle wasting during infection: Why do muscles waste when we're sick?

Alicia Romero
(Janelle Ayres Lab)

During infection, hosts endure significant metabolic changes that can dramatically influence host defense responses and pathogen behavior. Muscle wasting is one of the most highly conserved metabolic changes observed across a wide range of infections and across the animal kingdom; but current evidence and clinical data suggest that muscle wasting decreases host survival and impairs recovery from severe infections. Alternatively, it has been proposed that muscle wasting is a host metabolic response that modulates energy allocation during infection. Nonetheless, a function of muscle wasting during infection has not been investigated experimentally, and it is unclear *how* muscle wasting negatively affects the outcome of infections.

Using a transgenic murine model that is protected from muscle wasting, this work aims to elucidate how muscle wasting negatively affects the outcome of systemic *Salmonella* infection.

POSTER POSTION 14C

How to trigger pexophagy? - Molecular mechanism of action of the pexophagy-specific receptor complex

Katarzyna Zientara-Rytter
(Suresh Subramani Lab)

Macroautophagy/autophagy is a highly conserved process in which subcellular components destined for degradation are sequestered within autophagosomes. The selectivity of autophagy is determined by autophagy receptors, such as *Pichia pastoris* Atg30 (autophagy-related 30), which controls the selective degradation of peroxisomes (pexophagy) through the assembly of a receptor-protein complex (RPC). Previously, we proved that the peroxisomal acyl-CoA-binding protein, Atg37, and the highly conserved peroxin, Pex3, are required for RPC formation and efficient pexophagy. Here, we will describe how these two proteins regulate the assembly and activation of the pexophagic RPC. We will show that Atg30 requires both Atg37 and Pex3 to recruit key autophagic proteins, Atg8 and Atg11, to the pexophagic RPC. However, due to close proximity of Atg37- and Pex3-binding sites in Atg30, the binding of these proteins to Atg30 is mutually exclusive. We also show that direct binding of Pex3 or Atg37 to Atg30 regulates its phosphorylation by the Hrr25 kinase, negatively or positively, respectively. Based on these results, we will present a model that clarifies the assembly and activation of the pexophagic RPC through the phosphoregulation of Atg30.

POSTER POSTION 15A

Poster Presenters

Poster Position	Name	Lab		Poster Position	Name	Lab
1A	Marie Adomako	S. Golden		**7C**	Chandler Puritty	Cleland
1B	Brooke Anderson	Dutton		**8A**	Bijie Ren	Mayfield
1C	Wendy Chen	Feng		**8B**	Xiangyu Ren	Goulding
2A	Laura Chipman	Pasquinelli		**8C**	Andrew Ryan	Daugherty
2B	Anna Guzikowski	Zid		**9A**	Gokhan Senturk	Pfaff
2C	Youtong Huang	Lemke		**9B**	Tim Shaw	Lykke-Andersen
3A	Yujung Michelle Lee	Ayres		**9C**	Chao Shi	Chao
3B	Benjamin Lewis	Hunter		**10A**	Sunandha Srikanth	Leutgeb
3C	Yan Liang	Feng		**10B**	Yasin Torres-Tiji	Mayfield
4A	Jijun Liu	Feng		**10C**	Anupriya Tripathi	Knight
4B	Roland Liu	K. Pogliano		**11A**	Brian Tsu	Daugherty
4C	Hanbin Lu	Murre		**11B**	Daniela Zarate	Kohn
5A	Rose Malinow	Jin		**11C**	Ye Zhang	Su
5B	Elizabeth Montano	J. Pogliano		**12A**	Yuansheng Zhou	Sharpee
5C	Angela Nicholson	Pasquinelli		**12B**	Yang Sophie Chen	Zid
6A	Julie Paxman	Hao		**12C**	Matthew Flagg	Hampton
6B	Emily Pierce	Dutton		**13A**	Delaney Pagliuso	Pasquinelli
6C	Elly Poretsky	Huffaker		**13B**	Alexandria Palaferri Schieber	Ayres
7A	Regina Powers	Halpain		**13C**	Hoda Rahmamoun	Lauberth
7B	Amy Pribadi	Chalasani		**14A**	Samuel Redford	Ayres

Poster Position	Name	Lab		Poster Position	Name	Lab
14B	Eammon Riley	K. Pogliano		**14C**	Alicia Romero	Ayres
15A	Katarzyna Zientara-Rytter	Subramani				