

1st Annual FSU Life Sciences Symposium

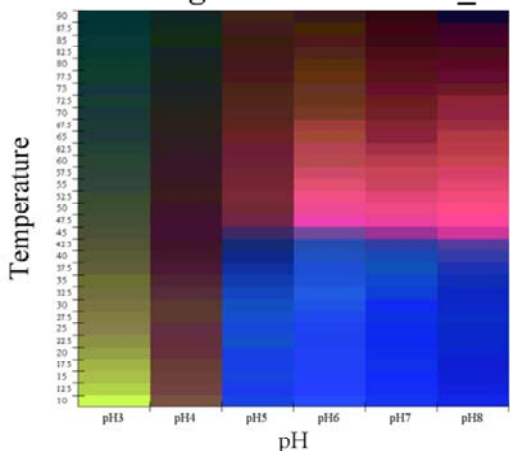
From Molecules to Medicine

January 7th – January 8th, 2011

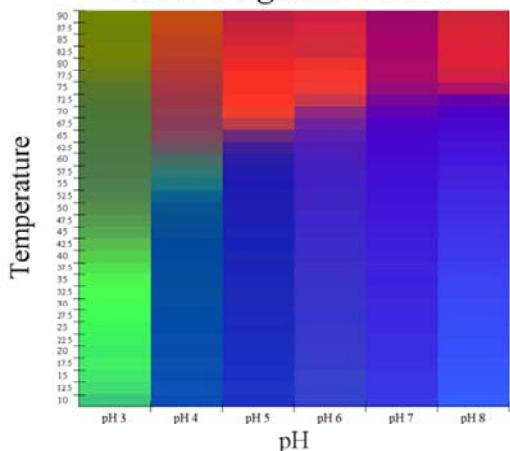
College of Medicine

Florida State University

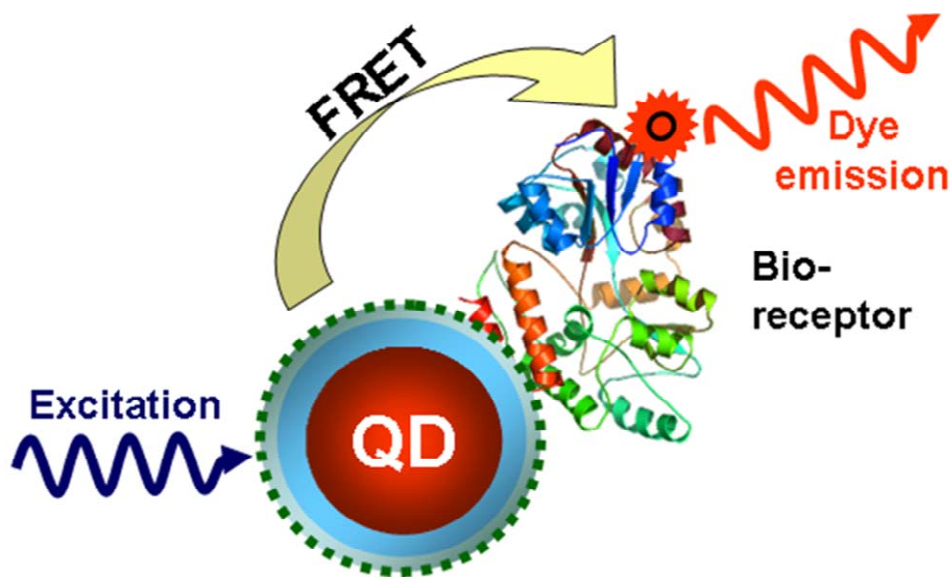
Phase Diagram: FGF-1 WT_All



Phase Diagram: SYM6



Promoting the broad spectrum of biomedical science research at FSU, the Life Sciences Symposium is intended to provide a venue for faculty, postdoctoral fellows and students to present their research, to promote collaborations, and to foster professional development.



MESSAGE FROM THE PROGRAM CHAIR



The idea for this symposium grew from the tremendous changes that have occurred over the past several years at FSU in the area of life sciences. Physical infrastructure has been the most obvious change, with new science buildings in the College of Medicine, and departments of Biological Science, Psychology and Chemistry all springing up over the past several years. Less obvious, but perhaps more importantly, life sciences research is being pursued by a wide variety of investigators, and in departments that you might not normally associate with such research. New approaches, as well as solutions to old problems, can emerge from collaborative interactions between such faculty, postdocs, students and staff – but, only if we can successfully raise awareness of this wide diversity of life sciences research. That is the goal for this symposium. I would like to thank the Department of Biomedical Sciences, the Office of Research, the symposium steering committee, the administrative staff of the department of Biomedical Sciences, and our corporate and university sponsors for their support in making the symposium actually happen. I would like to thank everyone in attendance; hopefully, the symposium will prove useful.

Dr. Michael Blaber

Chair, 2011 FSU Life Sciences Symposium Organizing Committee
College of Medicine, Florida State University



Welcome! The Department of Biomedical Sciences is pleased to sponsor the inaugural 2011 FSU Life Sciences Symposium "From Molecules to Medicine". Our hope is to highlight the accomplishments of biomedical science researchers at FSU. We wish to bring together faculty, postdoctoral fellows, graduate students and staff to listen and learn from each other and from outside speakers. We hope to generate an atmosphere of excitement about the life sciences at FSU, and a view of a future in which we have a shared vision amidst a growing atmosphere of collaboration. Most of all we hope that all of you will leave here with a feeling of camaraderie and community. The organizing committee was selected to represent the diversity among the FSU Life Sciences community. I commend them for the extraordinary program they have assembled. I look forward to an exciting two-day symposium during which I expect both to learn a great deal and to make many new friends. I trust you will do the same.

Dr. Richard Nowakowski

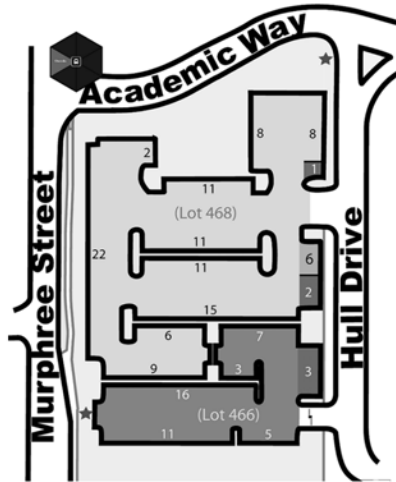
Chair, Biomedical Sciences
College of Medicine, Florida State University

2011 FSU Life Sciences Symposium

OFFICIAL PROGRAM

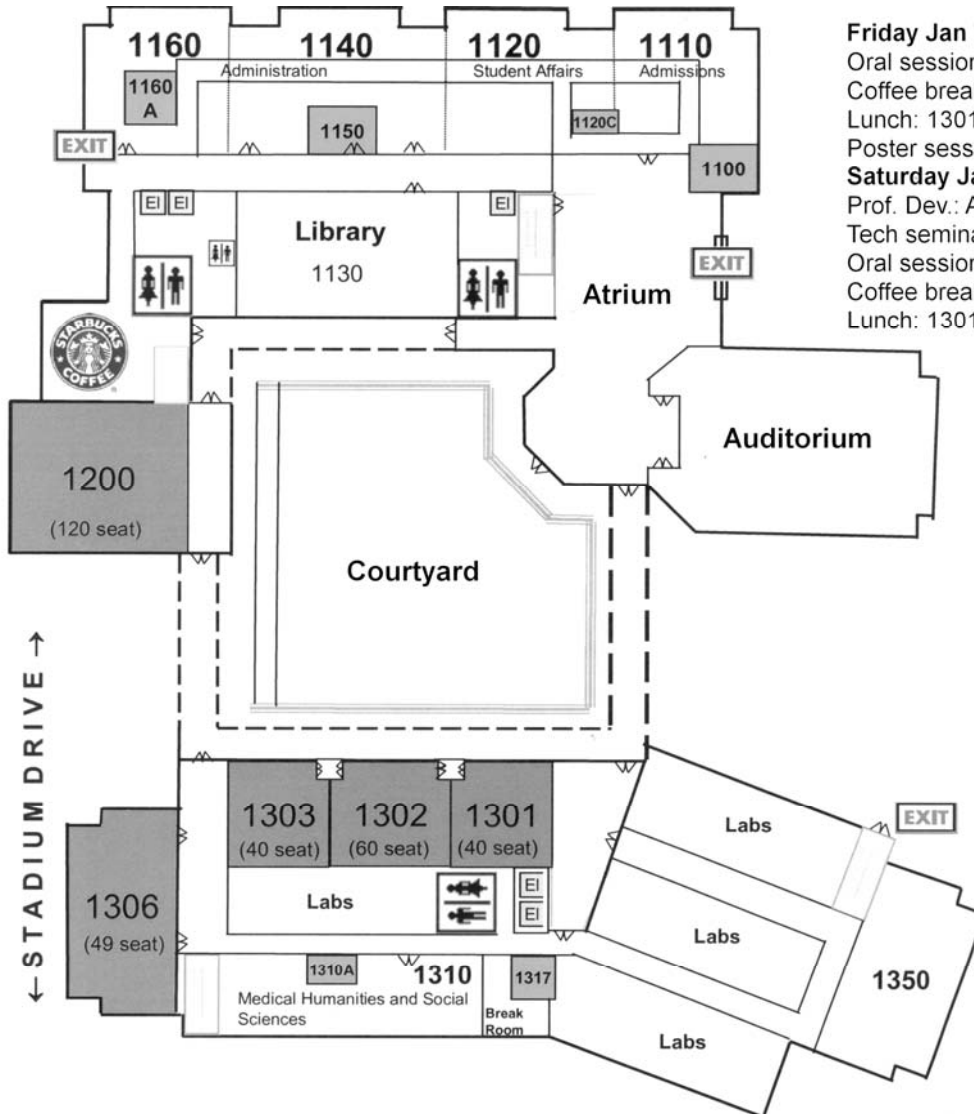
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SITE MAP



Parking for vendors, MagLab, Engineering, and other off-site attendees will use the "Stone-R" lot

"Stone-R" (Lot 466)
 (7:30AM-5:00PM)
 42 3



Friday Jan 7:
 Oral sessions: Auditorium
 Coffee breaks: Atrium
 Lunch: 1301
 Poster session: Atrium
Saturday Jan 8:
 Prof. Dev.: Auditorium
 Tech seminars: 1302/1303
 Oral sessions: Auditorium
 Coffee breaks: Atrium
 Lunch: 1301

MEETING AT A GLANCE

Day 1 – Friday Jan 7 2011

- 8:30 – 8:45** **Welcome**
- 8:45 **Morning Session I (Auditorium)** Session chairs: Scott Stagg and Hedi Mattoussi
- 8:45 – 9:30 **Michael Dustin**, NYU medical school
How Killer T Lymphocytes Lock onto Tumor Cells
- 9:30 – 10:00 **Joe Schlenoff**, FSU Dept. Chemistry & Biochemistry
Cells in Tune with Surfaces
- 10:00 – 10:30 **Geoffrey Strouse**, FSU Dept. Chemistry & Biochemistry
Nanomaterials to Treat Genetic Disorders
- 10:30** **Break/coffee (Atrium)**
- 10:45 – 11:15 **Anant Paravastu**, FSU Dept. Chemical & Biomed. Eng.
Solid State NMR Structural Characterization of Disease Related and Designer Protein Self-Assembly
- 11:15 – 11:45 **Tim Cross**, FSU Dept. Chemistry & Biochemistry
Opportunities, Challenges and Urgency for the Characterization of Membrane Protein Drug Targets
- 11:45 – 12:15 **Scott Stagg**, FSU Dept. Chemistry & Biochemistry/Institute of Molecular Biophys.
Structure and Heterogeneity of the COPII Coat
- 12:15 - 1:15** **Lunch** (Box lunch in 1301 for registered attendees)
- 1:30 **Afternoon Session I (Auditorium)** Session chairs: Hengli Tang and Tim Megraw
- 1:30-2:15 **Val Sheffield**, HHMI/ University of Iowa
Human Genetics of Bardet-Biedel Syndrom (BBS)
- 2:15-2:45 **David Houle**, FSU Biological Science
Phenomics: the Next Challenge
- 2:45-3:15 **Jonathan Dennis**, FSU Biological Science/Institute of Molecular Biophysics
The Regulatory Organization of the Human Genome
- 3:15** **Break/coffee (Atrium) Group Photo – Atrium**
- 3:30 – 4:00 **Beth Stroupe**, FSU Biological Science/Institute of Molecular Biophysics
Structure and Activity in Bacterial Sulfite Reductase
- 4:00 – 4:30 **Brian Chadwick**, FSU Biological Science
Exploring the Role of Macrosatellites in Genome Biology and Disease Susceptibility
- 4:30 – 5:00 **David Gilbert**, FSU Biological Science
SPACE AND TIME IN THE NUCLEUS: Replication Timing Reflects the Stable Alterations in 3D Chromosome Organization During Development and Disease
- 5:00 – 5:30 **Tim Megraw**, FSU Dept. Biomedical Sciences
Cell Biology of MCPH: a Neural Stem Cell Disease
- 5:30 – 7:00 **Posers/vendors/Wine & Cheese refreshments (Atrium)**

Day 2 – Saturday Jan 8 2011

Concurrent Sessions

8:30 – 9:20

9:25 – 10:15

Room 1400	Jeff W. Garis , FSU Career Center <i>C.V./resume Preparation</i>	Jeff W. Garis , FSU Career Center <i>Interview Skills</i>
Room 1302	Joel Silfies , Nikon Instruments Inc. <i>Detection, Resolution and Imaging Beyond the Abbe Diffraction Limit</i>	Juergen von der Heiden , Hunt Optics and Imagine <i>CARS and SHG: Multiphoton Excitation without Fluorophores!</i>
Room 1303	Tim Sackos and Manju R. Sethi , Thermo Scientific <i>The Future of QPCR: Best Practices, Standardization, and the MIQE Guidelines</i>	Kirsteen Maclean , Genomics Division, Thermo Scientific <i>Advances in qPCR and PCR Assays</i>

10:15 **Break/coffee** (Atrium)

10:30 **Morning Session II** (Auditorium) Session chair: Mike Blaber

10:30 – 11:15 **Peter Sarnow**, Stanford U

MicroRNAs in Viral Hepatitis

11:15 – 11:45 **Branko Stefanovic**, FSU Dept. of Biomedical Sciences

Progress towards Discovery of Antifibrotic Drugs

11:45 – 12:15 **Yoichi Kato**, FSU Dept. of Biomedical Sciences

Notch a Victory over Diseases

12:15 - 1:30 **Lunch** (Box lunch in 1301 for registered attendees)

1:30 **Afternoon Session II** (Auditorium) Session chair: Richard Hyson

1:30-2:15 **Stephen Dalton**, UGA

Cardiovascular Progenitors Derived from Human Pluripotent Cells

2:15-2:45 **Karen Berkley**, FSU Dept. of Psychology/Program in Neuroscience

Neural mechanisms of Pelvic Pain: Lessons from Translational Research on Endometriosis

2:45-3:15 **Carlos Bolaños**, FSU Dept. of Psychology/Program in Neuroscience

Extracellular Signal-Regulated Kinase-2 (ERK2) as a Potential Target for Drug- and Mood-Related Co-Morbid Behaviors

3:15 **Break/coffee** (Atrium)

3:30 – 4:00 **Mohamed Kabbaj**, FSU Dept. of Biomedical Sciences

Individual Differences in the Effects of Social Defeat in Rats: the HR/LR Model

4:00 – 4:30 **Josh Rodefer**., FSU Dept. of Psychology/Program in Neuroscience

Neuropharmacology and Cognitive Flexibility: Implications for Neuropsychiatric Disorders

4:30 – 5:00 **Michael Blaber**, FSU Dept. of Biomedical Sciences

Protein Engineering for Human Therapeutics

5:00 – 5:30 **Roger Mercer**, FSU Dept. of Biomedical Sciences

Translation in Transition: Building a New Translational Science Lab at FSU

5:30 – 5:45 **Closing remarks**

ORAL SESSION ABSTRACTS

Friday Jan 7 2011

Session I Morning

HOW KILLER T LYMPHOCYTES LOCK ONTO TUMORS

Michael Dustin, Maria Grazia Ruocco, Kaushik Choudhuri, Noriko Kawashima, Silvia Formenti and Sandra Demaria

Pathology, NYU School of Medicine, New York, NY, 10016

Synergy of radiation and anti-CTLA-4 blockade has been shown to induce CD8-driven tumor regression in a mouse model of breast cancer. To understand the mechanism, we employed intravital 2-photon imaging techniques that allow us to characterize the interactions between T cells and tumor cells in the tumor microenvironment. In order to visualize T cells, we used a transgenic mouse line in which the green fluorescent protein was expressed under the CXCR6 promoter. CXCR6 is a chemokine receptor expressed on effector T cells. To visualize tumor cells, we transduced 4T1 cells with a retroviral vector expressing the cyan fluorescent protein. We analyzed tumor bearing mice that were 1) untreated, 2) treated with radiation therapy alone, 3) treated with anti-CTLA-4 alone and 4) treated with a combination of radiation therapy and anti-CTLA-4. We found that anti-CTLA-4 mAb (9H10) as monotherapy increased T cell motility in vivo, preventing the formation of stable interactions between T cells and tumor cells. In contrast, the combination of radiotherapy and anti-CTLA-4 mAb promoted arrest of T cells with tumor cells. We found that the expression of the NKG2D ligand Rae-1 on tumor cells is increased following radiation therapy in vivo. We identified the interaction between radiation-induced Rae-1 and NKG2D receptor expressed on T cells as an important co-stimulatory signal that counteracts the go signal provided by anti-CTLA-4. Blocking this interaction prevented T cell arrest in vivo and tumors continued to grow even when treated with radiation and anti-CTLA-4. Our results suggest that Rae-1/NKG2D is a critical contributor to the formation of stable junctions between T cells and tumor cells. The radiation induced Rae-1/NKG2D interaction is a required co-factor for 4T1 eradication and provides a molecular mechanism underlying the effectiveness of combined radiation and anti-CTLA-4 treatment.

CELLS IN TUNE WITH SURFACES

Joe Schlenoff, Tom Keller, Jessica Martinez, Ali Lehaf and Maroun Moussallem

Chemistry & Biochemistry, FSU, Tallahassee, FL, 32306

In collaboration with the Keller group in the Department of Biological Sciences we are looking at how cells respond to the surfaces on which they grow. To provide the most control over the surface properties, we use thin polymer films, which we make from water-soluble polymers. Both chemical and physical properties can be systematically varied to control cell adhesion, growth, movement and proliferation. This interdisciplinary project involves cell biology, nanotechnology and polymer science.

IS THERE A PLACE FOR NANOSCIENCE IN BIOMEDICINE? THE USE OF NANOMATERIALS FOR TRACKING AND CONTROLLING GENE DELIVERY

Geoffrey F. Strouse

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL, 32306-4390

Nanomaterials (quantum dots, gold nanoparticles, SPIOs, lipoplexes, etc) are widely used today in biological, biophysical, and medical research. Recent developments include the use of NSET to track the release of a gene from a gold nanometal to induce in-vitro targeted gene expression via a controlled delivery mechanism. In addition, the ability to utilize the nanomaterial in-vivo as a tracer allows use of MRI methods to follow the delivery of the material and its fate. Such advances are opening the potential to manipulate protein expression levels in-vivo and provide a tracking modality once the nanoplex is delivered. Discussion of advances in controlled gene delivery and use of advanced optical and spectroscopic methods to track nanomaterial delivery will be discussed.

SOLID STATE NMR STRUCTURAL CHARACTERIZATION OF DISEASE RELATED AND DESIGNER PROTEIN SELF-ASSEMBLY

Anant Paravastu, Ashley Cormier, Serena Danting Huang, William Tay and Terrone L. Rosenberry

Chemical and Biomedical Engineering, Florida State University and Florida A&M Universtiy, Tallahassee, FL, 32310

In biology, protein self-assembly is associated with the formation of nanostructured materials (e.g., extracellular matrices) and disease-associated plaques (e.g., amyloid deposits). Recent work on amyloid fibril forming proteins suggests that soluble oligomeric structures play a key role in cellular toxicity. We seek an atomic level understanding of protein self-assembly in order to design synthetic self-assembling peptides (small proteins) capable of supporting tissue repair while avoiding formation of toxic structures. Towards this goal, we have performed solid state NMR measurements on two designer self-assembling peptides from the literature and a stable oligomeric form of the 42-residue variant of the Alzheimer's β -amyloid peptide. Unlike in-vivo derived peptides, the designer self-assembling peptides have very simple repetitive amino acid sequences designed to promote specific secondary structures. NMR spectra unexpectedly indicate a high degree of structural order in these systems, suggesting highly ordered supramolecular organization despite the repetitive sequences. Hydration effects on observed NMR linewidths suggest a critical role of water in stabilizing self-assembled structures. Oligomeric β -amyloid, in contrast, seems to have a structure that is not stabilized by water. However, the presence of water in oligomeric β -amyloid does introduce site-dependent molecular motion that has not been observed in fibrillar β -amyloid.

OPPORTUNITIES, CHALLENGES AND URGENCY FOR THE CHARACTERIZATION OF MEMBRANE PROTEIN DRUG TARGETS

Timothy A. Cross, Sharma, M., Huajun, Q., Petersen, E., Busath, D., Yi, M, Dong, H. & Zhou, H.-X

Department of Chemistry and Biochemistry, Department of Physics, Institute of Molecular Biophysics, National High Magnetic Field Laboratory, Florida State University, Department of Physiology and Developmental Biology, Brigham Young University

More than 50% of all drug targets are membrane proteins and yet this is the least well understood class of proteins. They have multiple conformations generating multiple opportunities for drug development. Both their conformation is influenced by their environment as Anfinsen's thermodynamic hypothesis states "that the native conformation (of a protein) is determined by the totality of inter-atomic interactions and hence by the amino acid sequence in a given environment." Too often these last four words are ignored and therefore many membrane protein structures in the Protein Data Bank are distorted and not representative of their native conformation. Today, there is a great urgency to develop new classes of antimicrobial agents and while membrane proteins provide great opportunities the challenge of obtaining structural characterizations of these proteins are great. A new approach using NMR spectroscopy of lipid bilayer preparations has considerable promise. Here, I will show our first success with the characterization of the conductance domain of M2 protein from Influenza A in a liquid crystalline lipid bilayer environment. This protein is a proven drug target but the virus has recently mutated such that both the seasonal flu and the swine flu pandemic were resistant to the drugs that target this essential protein for the viral life cycle.

THE STRUCTURE AND HETEROGENEITY OF THE COPII COAT

Scott Stagg, Jason O'Donnell and Nilakshee Bhattacharya

Institute of Molecular Biophysics, Florida State University, Tallahassee, FL, 32306

The COPII proteins Sar1, Sec23/24 and Sec13/31 are involved in transporting cargo from the endoplasmic reticulum to the Golgi apparatus. In recent years several structures have been solved that elucidate the mechanisms employed by the individual COPII proteins. In order to transport the large variety of cargo in the cell, the COPII coat must be capable of expanding and contracting. We have used electron tomography to quantify the range of conformations accommodated by the Sec13/31 cage. Moreover, we have reconstructed a structure of a COPII coat cage assembled from Sec13/31 and Sec23. The assemblies form at least two geometries, and the most common size is 600 Å, similar to what has been observed for Sec13/31. We will discuss how the orientation of Sec23 may dictate cage geometry and orient Sar1 to participate in the fission of COPII coated vesicles in the cell.

Session I Afternoon

MOLECULAR MECHANISMS INVOLVED IN BARDET-BIEDL SYNDROME, A HUMAN OBESITY DISORDER

Val Sheffield, Qihong Zhang and Seongjin Seo

Pediatrics/ Medical Genetics, University of Iowa/ HHMI, Iowa City, IA, 52242

Bardet-Biedl Syndrome (BBS) is an autosomal recessive disorder resulting in obesity, polydactyly, retinal degeneration, renal abnormalities, diabetes, hypertension, and cognitive impairment. Our laboratory has focused on identifying genes involved in BBS, determining the functions of BBS proteins, and developing BBS animal models to aid in the understanding of the pathophysiology of BBS-related phenotypes. Fifteen genes have been reported to be involved in BBS. Among the known BBS proteins, seven proteins form a stable complex known as the BBSome, which mediates vesicle trafficking to the ciliary membrane. Three BBS proteins (BBS6, BBS10, BBS12) form a second complex with the CCT/TRiC family of group II chaperonins. This complex mediates BBSome assembly. BBS3 (ARL6), a member of Ras super family of small GTPases, is not required for BBSome assembly but controls BBSome recruitment and ciliary entry. Many receptor proteins and signaling molecules localize to cilia, and the BBSome is involved in transporting at least some of these proteins in and out of the cilia. In addition, the BBSome is involved in some functions not clearly related to ciliary trafficking including leptin receptor signaling. In an effort to understand how BBSome function is regulated, we have identified BBSome interacting proteins in vivo. This work has led to the identification of a novel negative regulator of BBSome trafficking, which has potential implications in the treatment of BBS phenotypes.

PHENOMICS: THE NEXT CHALLENGE

David Houle

Biological Science, Florida State University, Tallahassee, FL, 32308

A key goal of biology is to understand phenotypic characteristics, such as health, disease, and evolutionary fitness. Phenotypic variation is produced through a complex web of interactions between genotype and environment, the genotype-phenotype map. The map is inaccessible to study without detailed phenotypic data that allows these interactions to be studied. Despite this need, our ability to characterize phenomes, the full set of phenotypes of an individual, lags our ability to characterize genomes. Phenomic data will allow us to address three key phenomena: the pleiotropic effects of genetic variation, the full range of causes of variation in phenotypic traits, and important interactions that do not have genetic causes. I will present examples of phenomic studies using *Drosophila melanogaster* as a model organism.

THE REGULATORY ORGANIZATION OF THE HUMAN GENOME

Jonathan Dennis and Brian Spetman

Biological Science, The Florida State University, Tallahassee, FL, 32306

Understanding the functional organization of the genome remains one of the biggest challenges in biology. A large body of research has emerged on the modifications of chromatin and their role in gene regulation; however, the underlying structure of chromatin is less well characterized, despite its importance as the substrate for DNA-templated reactions. Genome-wide nuclease-sensitivity and nucleosome-position information is critically important for understanding of genomic processes, yet this information is nonexistent across a variety of human cell lines. In order design new diagnostics and therapies for chronic disease and fully understand chronic disease progression, we need better descriptions of the chromatin-structural characteristics of these disease states. To address this shortcoming, we have developed cost-effective microarray-based nuclease-sensitivity and nucleosome-position mapping platforms to analyze chromatin structure. We have used cell lines latently infected with HIV as a model for understanding the relationship that HIV has with the human genome. We have assayed genome-wide chromatin accessibility and have identified significant changes within hours of HIV reactivation HIV at multiple loci throughout the human genome. Additionally, we have the measured changes in nucleosome position and occupancy of 505 immunity-related genes. We suggest that both large scale and local chromatin structural changes may play a significant role in the reactivation of HIV.

CRYO-EM STRUCTURE OF THE ACTIN-TROPOMYOSIN FILAMENT

M. Elizabeth Stroupe, Duncan Sousa, Roger Craig, Larry S. Tobacman, William Lehman and M. Elizabeth Stroupe

Biological Science, Florida State University, Tallahassee, FL, 32303

Tropomyosin is a key factor in the molecular mechanisms that regulate the binding of myosin motors and numerous cytoskeletal proteins to actin filaments in most eukaryotic cells. This regulation is achieved by the azimuthal repositioning of tropomyosin along the thin filament in order to block or expose binding sites on actin. In regulating muscle contraction, tropomyosin couples Ca^{+2} activation of troponin to myosin-binding on thin filaments. Depending on the activation state of troponin as well the binding state of myosin, tropomyosin occupies either blocked, closed, or open positions on actin. While the corresponding azimuthal positions of tropomyosin on actin are well known, the changing interactions between tropomyosin and the actin filament at the amino acid level remain uncertain. In fact, current ~ 20 Å-resolution 3DEM of negatively stained actin-tropomyosin cannot resolve tropomyosin's coiled-coil structure directly, which complicates precise fitting of high resolution striate muscle tropomyosin structures. Details about the interactions of the remaining 40 tropomyosin isoforms found in non-muscle cells are even less certain; thus the atomic structures of these actin-tropomyosin complexes cannot be related to their unique cellular functions. Using native cryogenic 3DEM, we have now directly resolved and visualized the striated muscle tropomyosin on F-actin, which will lead to the elucidation of the atomic details of this complex.

EXPLORING THE ROLE OF MACROSATELLITES IN GENOME BIOLOGY AND DISEASE SUSCEPTIBILITY

Brian Chadwick, Deanna Tremblay, Shawn Moseley, Andrea Horakova, Raed Rizkallah and Myra Hurt

Biological Science, Florida State University, Tallahassee, FL, 32306

Macrosatellites are among the largest tandem repeat DNA in the human genome. Each array is composed of near identical individual repeat units of several kilobases that are organized in an uninterrupted head-to-tail arrangement spanning 10-100's of kb. The precise number of repeat units varies from one individual to the next and therefore the array sizes are polymorphic in the general population. What purpose these sequences have in genome biology remains unclear. However, their relevance to human health is clearly demonstrated by the chromosome 4 macrosatellite D4Z4 that is responsible for fascioscapulohumeral muscular dystrophy (FSHD) when the array contracts to fewer than ten 3.3kb repeat units on a common haplotype. We are focused on exploring the role of the X-linked macrosatellite DXZ4, an array of 20-100 3kb GC rich repeat units at Xq13. By virtue of its location on the X chromosome, DXZ4 is hemizygous in males and exposed to the epigenetic process of X chromosome inactivation in females, the mammalian form of dosage compensation. Gene silencing on the chosen inactive X chromosome (Xi) is achieved by repackaging the DNA into facultative heterochromatin. However, DXZ4 does not conform to this new chromatin arrangement, and instead adopts a euchromatic conformation bound by the zinc finger proteins CTCF and YY1. Strikingly, chromatin changes observed at DXZ4 on the Xi closely resemble those seen at the contracted D4Z4 array in FSHD patients.

SPACE AND TIME IN THE NUCLEUS: REPLICATION TIMING REFLECTS STABLE ALTERATIONS IN 3D CHROMOSOME ORGANIZATION DURING DEVELOPMENT AND DISEASE

David Gilbert

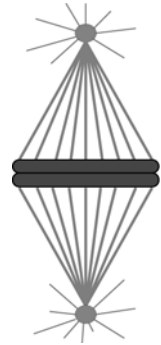
Biological Science, FSU, Tallahassee, FL, 32306

All eukaryotic cells replicate segments of their genomes in a defined temporal sequence. In multicellular organisms, at least half the genome is subject to changes in this temporal sequence during development. We find that this temporal sequence and its developmentally regulated changes are conserved in mouse and human, suggesting that it either represents or reflects something biologically important. We recently demonstrated a remarkably strong genome-wide correlation between replication timing and chromatin interaction maps, indicating that sequences localized near each other replicate at similar times. This provides molecular confirmation of longstanding cytogenetic evidence for spatial compartmentalization of early and late replicating DNA, and supports our earlier model that replication timing is re-established in each G1-phase coincident with the anchorage of chromosomal segments at specific locations within the nucleus (Timing Decision Point; TDP). I will review the evidence linking the replication program to 3D chromatin architecture, discuss what such a link might mean for the mechanism and significance of a developmentally regulated replication program. I will also discuss some of the abnormalities in the replication program found in disease, and the potential of replication profiling to serve as a novel biomarker for the presence of genetic and epigenetic lesions associated with disease.

Tim Megraw

Biomedical Sciences, Florida State University, Tallahassee, FL, 32309

Primary autosomal recessive microcephaly (MCPH) is an inherited developmental disorder of the centrosome. Afflicted individuals have reduced development of the cerebral cortex due to defective division of the neural stem cells. Neural stem cells divide with a regulated polarity that is crucial to the control of neurogenesis. Polarized mitosis in neural progenitors requires coordination between polarization determinants that define the apical and basal poles of the axis early in mitosis, and alignment of the mitotic spindle along this axis. We use mouse and *Drosophila* models to investigate how specific centrosomal proteins coordinate with the polar axis of the cell to orient the spindle at mitosis. Disruption of centrosomin (*cnn*) in *Drosophila* results in random spindle orientation in neural stem cells. *Cdk5rap2*, one of the two human *cnn* homologs, is mutated in MCPH. *Cdk5rap2* mutant mice lose control of centriole duplication. Mutation of *Drosophila* *cnn* and mouse *Cdk5rap2* produced defects in neural stem cell division, yet apparently by different mechanisms. We present a model to explain why both defects impact the polarity of neural stem cell divisions. In addition, we have discovered a novel conserved partner of CNN that is required for spindle orientation and proper localization of polarizing determinants on the cell cortex. This novel molecule may coordinate the polarization axis with the orientation of the mitotic spindle within neural stem cells.



Saturday Jan 8 2011 **Session II Morning**

DETECTION, RESOLUTION AND IMAGING BEYOND THE ABBE DIFFRACTION LIMIT

Joel S. Silfies

Product and Marketing, Nikon Instruments, Inc. , Melville, NY, 11747

We will review the concepts of object detection versus resolution. Then we will see how new techniques have been developed to use light microscopes to resolve structures and features beyond the traditional Abbe limit of diffraction. Specifically we will explore the new techniques of STORM - Stochastic Optical Reconstruction Microscopy and SIM - Structured Illumination Microscopy. This talk will illustrate how these techniques work to allow super resolution imaging and how current microscopes systems are adapted for SIM and STORM imaging.

CARS AND SHG: MULTIPHOTON EXCITATION WITHOUT FLUOROPHORES!

Juergen von der Heiden

Imaging specialist, Hunt Optics and Imaging

Second Harmonic Generation (SHG) is a label-free method of imaging certain structures in tissue using a pulsed near infra-red (NIR) laser. The signal has a very sharp spectral peak at exactly half the wavelength of the incident light and requires the intense photon density found at the focal plane of a multiphoton excitation system. SHG, alone and in combination with TPEF (Two-Photon Excitation Fluorescence), offers novel opportunities for investigating the 3D structure of macromolecules within living tissue. SHG has the advantage over TPEF of determining molecular orientation as well as reduced toxicity. This is because the photobleaching of fluorescent dyes creates toxic free radicals, whereas SHG uses no fluorophores and therefore shows no bleaching and associated toxicity. CARS is an acronym for COHERENT ANTI-STOKES RAMAN SCATTERING Microscopy. It is a non-staining method for the detection of particular types of molecules in a sample. The wavelengths of laser light and unique molecular vibration of chemical bonds determine which types of molecules are detected with either the Non-Descanned Detectors or Forward Detectors of the MPE system. Applications of CARS include: Lipid Domains in Model Membranes- The study of lipid distribution in biological membranes and their role in signal transduction, membrane trafficking and disease; In-Vivo imaging- taking advantage of the fact that CARS is a non-staining technique. There is no toxicity due to staining; Imaging of the myelin sheath, which is a plasma membrane which wraps around an axon; Study of Multiple Sclerosis; Obesity and Cardiovascular Disease; Skin and Cosmetic research, drug delivery and polymers.

THE FUTURE OF QPCR: BEST PRACTICES, STANDARDIZATION, AND THE MIQE GUIDELINES

Tim Sackos and Manju R. Sethi

Marketing, Thermo Scientific, Spring Hill, FL, 34608

This presentation is an installment from the popular Science/AAAS webinar series and is designed to raise your understanding of quantitative polymerase chain reaction (qPCR) technology. Using the recently published MIQE guidelines as a foundation. The purpose will not be directed at the actual process of data collection but rather the adoption of a standardized method of reporting the data for peer review. A panel of experts will address qPCR best practices, with the goal of providing researchers with more consistent and reliable data.

ADVANCES IN QPCR AND PCR ASSAYS

Kirsteen Maclean

Field Application Specialist, Thermo Fisher Scientific, Lafayette, CO, 80026

The use of quantitative real-time PCR (qPCR) is now a routine laboratory technique for the measurement of DNA or RNA that exceeds the limitations of traditional end-point PCR methods by allowing rapid and efficient quantification of the PCR product during each amplification cycle rather than simple detection on a gel. Important attributes for high quality qPCR and RT-qPCR assays that must be considered during experimental design and assay selection include: specificity, dynamic range, amplification efficiency, and assay reproducibility. In this seminar we will discuss assay design and considerations applicable to general qPCR. Furthermore, we will demonstrate applications for the variety of available PCR polymerases for improved fidelity, processivity in order to amplify with accuracy and speed previously unattainable with standard PCR enzymes. Technologies for gene specific qPCR detection have been limited by complex assay selection, lack of target sequence information, requirements for the user to individually design gene-specific assays, and lack of target specificity. To address these concerns we also discuss the use of Solaris™ qPCR Gene Expression Assays which represent a novel approach to gene-specific qPCR detection. The assays are pre-designed on a genome-wide scale using a novel, tier-based algorithm to detect all variants of a given gene and distinguish among closely related family members. Here, we describe the application of this new probe/primer qPCR detection technology through examples highlighting design benefits, demonstrating the performance of Solaris™ assays in comparison to traditional reagents, and providing specific support for the value of these assays in common research workflows.

MICRORNAS IN VIRAL HEPATITIS

Peter Sarnow, Erica Machlin, Kara Norman and Selena Sagan

Microbiology & Immunology, Stanford University, STanford, CA, 94305

In general, microRNAs interact with sites residing in 3' noncoding regions in target mRNAs, leading to posttranscriptional downregulation of mRNA expression. In contrast, liver-specific microRNA miR-122 is known to bind at two adjacent sites that are close to the 5' end of the hepatitis C virus (HCV) RNA genome, resulting in upregulation of viral RNA abundance. We discovered that the location of the miR-122 binding site in the viral genome dictates its effect on gene regulation, because insertion of the miR-122 binding site into the 3' noncoding region of a reporter mRNA leads to downregulation of mRNA expression. Curiously, defined mutations at distinct locations in miR-122 abolished upregulation of viral RNA, yet functioned well in microRNA-dependent downregulation of reporter mRNA expression. This finding suggests that the HCV-miR-122 complex is distinct from RISC-miR-122 complexes that regulate cellular target mRNAs in the liver. Extensive analyses have shown that miR-122 regulates the turnover of HCV RNA, with only minimal effects on viral mRNA translation or rates of replication. To explore the feasibility of antiviral intervention by targeting an oligomeric microRNA-HCV complex, it is important to understand the roles for miR-122 in the liver. We have discovered that a major target for miR-122 is Insig1 mRNA. Insig 1 functions as an inhibitor of liver-specific transcription factor SREBP that modulates the transcription of many genes in cholesterol biosynthesis.

PROGRESS TOWARDS DISCOVERY OF ANTIFIBROTIC DRUGS

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• Fibrosis is a major health problem affecting 30% of world population. It is characterized by excessive synthesis of type I collagen in parenchymal organs. There is no cure for fibrosis and development of antifibrotic drugs targeting collagen has been hampered by the lack of knowledge of the regulatory steps specific for type I collagen. We have discovered that synthesis of type I collagen critically depends on the interaction between the two molecules; the 5' stem-loop structure (5'SL) present in collagen mRNAs and the protein LARP6. 5'SL is a unique sequence element found only in collagen mRNAs. LARP6 binds 5'SL with high specificity and affinity and this binding is critical for high expression of type I collagen. Knock down of LARP6 decreased collagen expression from human lung and scleroderma fibroblasts. Fibroblasts from knock-in mice in which the 5'SL was mutated in the context of endogenous collagen $\alpha 1(I)$ gene produced.

NOTCH A VICTORY OVER DISEASES

Yoichi Kato

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The Notch signaling pathway is an evolutionally conserved intracellular signaling pathway and regulates downstream responses, such as cell-fate specification, progenitor cell maintenance, boundary formation, cell proliferation and apoptosis. Importantly, dysfunction of this pathway leads to a variety of human diseases including cancer formation and vascular diseases. Recently, we identified B-cell leukemia/lymphoma 6 (BCL6), a transcriptional repressor, as a Notch-associated factor by an interaction-based screen. BCL6 was originally found as a gene responsible for B-cell non-Hodgkin lymphoma. In our study, BCL6 has been shown as an inhibitory factor of Notch signaling in patterning of left-right body axis during embryonic development. To inhibit the Notch activity, BCL6 prevents the intracellular domain of Notch1 receptor from recruiting Mastermind-like 1, a co-activator, into the transcriptional complex on the promoters of Notch-target genes to activate Notch-mediated transcription. Our data also suggest that this regulatory mechanism of Notch signaling by BCL6 is important for the differentiation of neuron as well as the protection from apoptosis. In my presentation, I will discuss the importance of this regulatory mechanism of Notch signaling in the biological processes and possible relevance to human diseases.

Session II Afternoon

CARDIOVASCULAR PROGENITORS DERIVED FROM HUMAN PLURIPOTENT CELLS

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Human pluripotent cells represent a valuable tool for the development of cell-based therapies because they can be easily expanded and differentiated into a wide-range of cell types. We have taken advantage of these properties by developing approaches for the generation of cardiovascular lineages, using human pluripotent cells as a starting point. This presentation will focus on the generation of a specific type of cardiovascular progenitor found in the pro-epicardium, a mesoderm-derived tissue that plays critical roles in cardiac development, homeostasis and repair. These findings have major implications for the utilization of pluripotent cell-derived cardiovascular progenitors for cell therapeutic applications and drug discovery.

NEURAL MECHANISMS OF PELVIC PAIN: LESSONS FROM TRANSLATIONAL RESEARCH ON ENDOMETRIOSIS

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Endometriosis (endo) is an estrogen-dependent disorder defined by extrauterine growths of endometrial tissue. Symptoms range from severe dysmenorrhea to chronic pelvic pains that co-occur with other pain disorders. How the growths relate to pain is unknown (no correlation), and the pain is difficult to alleviate without using hormones that often produce intolerable side effects, or surgery that fails to help. Studies with a rat model provide clues for mechanisms & treatments. Growths in the model & women recruit sensory & sympathetic nerve branches that sprout from nearby fibers, creating an interaction between growths & CNS. The new fibers are affected by estradiol & become sensitized. This peripherally-dynamic condition produces local & remote CNS sensitization & affects CNS estrogen receptors. Thus, the dynamic & estradiol-responsive nervous system is directly involved in endo, allowing generation of pains that can become independent of the growths. Stimulated by patient reports, other studies show that cannabinoid receptors are located on neurons innervating the growths, and that treatment with cannabinoids alleviates endo-induced pains. Overall, the findings support a change in focus from pathology to pain, acknowledging that the origin of pain is the CNS. This change encourages a multi-therapeutic approach to treatment and recognition that translational research that includes basic scientists, clinicians & patients can bring about productive advances.

EXTRACELLULAR SIGNAL-REGULATED KINASE-2 AS A POTENTIAL TARGET FOR DRUG- AND MOOD-RELATED CO-MORBID BEHAVIORS

Carlos Bolanos

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Substance abuse and major depressive disorders often co-occur, yet the neurobiological mechanisms underlying this comorbidity are poorly understood. Neurotrophic factors and their signaling pathways have been implicated in the regulation of mood and the neurobiological adaptations in response to stress and drugs of abuse. Chronic exposure to cocaine or unpredictable stress increases the activity of extracellular signal-regulated kinase (ERK 1/2) in the ventral tegmental area (VTA), an important substrate for motivation, drug reward, and stress. However, the functional significance of changes in ERK activity in this brain region is unknown. Using viral-mediated gene transfer to alter ERK2 activity within the rat VTA, we show that overexpressing ERK2 increases preference for environments previously paired with cocaine and also increases sensitivity to stressful stimuli. In contrast, blocking ERK2 activity in the VTA blunts cocaine preference, whereas it induces an antidepressant-like phenotype. Together, these results highlight a role for ERK signaling in the VTA as a key mediator of responsiveness to drugs of abuse and stressful stimuli, and point to the possibility that ERK2 activation in this brain region may mimic comorbid conditions such as substance abuse and major depressive disorder.

INDIVIDUAL DIFFERENCES IN THE EFFECTS OF SOCIAL DEFEAT IN RATS:THE HR/LR MODEL

Mohamed Kabbaj

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Chronic social stress has been linked to anxiety and depression disorders in humans. The mechanism behind this process, as well as the variable nature of these stress-induced pathologies, has not yet been clearly elucidated. Social defeat in rodents is a model of social stress that centers on intraspecies conflict and provides an ethological and ecological method to study the relation between chronic stress and depression without the complication of habituation. In order to examine the role that individual differences might play in stress-induced disorders we used naïve male Sprague-Dawley rats classified as either high (HR) or low (LR) responders according to their locomotor activity in a novel environment. During the meeting we will present data showing how social defeat affects HR and LR rats' drug addiction, anxiety, depression and learning and memory. We will also present some data on the neurobiological bases that may underlie some of the behavioral changes seen after social defeat in HR and LR rats.

NEUROPHARMACOLOGY AND COGNITIVE FLEXIBILITY: IMPLICATIONS FOR NEUROPSYCHIATRIC DISORDERS

Joshua Rodefer

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Cognitive impairment is one of the most functionally debilitating aspects of neuropsychiatric and neurodegenerative disorders, such as schizophrenia and Alzheimer's disease. Yet this problem persists, remaining an unmet need because no effective pharmacotherapies approved for use currently exist. There is emerging evidence that selective novel drug treatments improve cognition in both human and nonhuman species and this has sparked interest in the development of new rodent models to evaluate neuropsychological traits. The investigation of novel antipsychotics and nicotinic compounds (among others) suggests these compounds mediate improvement in attention, learning and working memory. When compared with existing pharmacotherapies, these specific drugs may represent unique targets for the treatment of neuropsychiatric and neurodegenerative disorders that feature cognitive impairment as a key symptom.

PROTEIN ENGINEERING FOR HUMAN THERAPEUTICS

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Protein therapeutics target over 200 human diseases and although still an overall minority, they are the fastest-growing category of new drug approvals. Proteins as therapeutics present new challenges in comparison to traditional small molecules due to their ability to adopt alternative conformations – which can result in altered function, solubility, aggregation and immunogenicity. Maintaining protein integrity during all stages of production, transportation, storage, reconstitution and delivery has typically been approached by formulation additives. However, since the underlying basis of conformational change is thermodynamic stability, the opportunity exists to modulate this property by specific mutation. I will describe an interaction between protein thermostability and buried free-cysteine residues that can substantially affect the in vitro functional half-life of fibroblast growth factor-1 (FGF-1). Furthermore, this interaction can be modulated by specific mutagenesis to produce a set of FGF-1 mutants with a wide-range of functional half-lives. The results suggest a protein design strategy whereby "second-generation" forms of protein therapeutics might have specifically-tailored functional half-lives to accomplish specific therapeutic goals.

TRANSLATION IN TRANSITION: BUILDING A NEW TRANSLATIONAL SCIENCE LAB AT FSU

Roger Mercer

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The FSU College of Medicine has created a Translational Science Laboratory (TSL) that will build scientific programs that focus on the study of human diseases – particularly neurodegenerative diseases and cancer – with the goal of translating basic science discoveries into treatment of disease. The TSL will provide support for projects arising in the labs of investigators in the basic sciences from across the campus and throughout the region and will support projects originating with clinicians in the College's Clinical Research Network as it comes fully online. The TSL will provide instrumentation, expertise and services that will enable biomarker discovery and validation, high end protein identification and characterization, differential proteomic analysis, and small molecule identification and quantitation including metabolomic analyses. In addition to providing turnkey services for these analyses, the TSL will also emphasize training of students, postdoctoral fellows and faculty to enable researchers to conduct their own investigations using state-of-the-art analytical technology. This presentation will address the mission of the TSL, outline implementation plans and timing, discuss the rollout of capabilities in the areas discussed above, and provide a look at the first major instrument to be installed – a nanoelectrospray LC –MS/MS system with high resolution and mass accuracy, suitable for protein identification as well as differential proteomic analysis.

POSTER SESSION ABSTRACTS

A SINGLE-CONSTRUCT APTAMER-NP CONJUGATE FOR THE SENSITIVE OPTICAL DETECTION OF ATP

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Aptamer beacon systems have recently become popular due to their high target selectivity, functionalizability, and wide-range of applications. In the biomedical field, they are utilizable as detection assays, binding agents, molecular delivery systems, etc. Here we report a highly sensitive ($K_d = 76\text{nM}$) hairpin aptamer-gold nanoparticle conjugate for the optical detection of ATP with a low minimum detection limit of $\sim 0.5\text{ nM}$. Utilizing NSET (nanometal surface energy transfer) between the nanoparticle and a fluorescent dye, this aptamer beacon system is able to detect and measure ATP concentration based upon the conformational change of the hairpin aptamer when ATP-bound. In the ATP-unbound state, a fluorescent-quenching ("off" state) is observed, whereas a fluorescent "on" state is observed in the presence of ATP. This aptamer beacon system shows promise in biomedical monitoring systems due to its high sensitivity and its potential for simultaneous multi-target detection, as it incorporates multi-functionalizable nanoparticles.

INTERACTION OF RESVERATROL AND THE ALZHEIMER'S A β PEPTIDE

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The Alzheimer's amyloid β (A β) peptide exists in multiple association states, including monomeric, oligomeric and fibrillar. Recent evidence shows that this structural diversity translates into different degrees of A β neurotoxicity, with the oligomeric state thought to be the most harmful. Consequently, any factors that modify the A β association state have a potential to affect the neuronal survival. Direct binding of small molecules to the various forms of the amyloid β perturbs the relative distribution of the amyloid states, thus impacting the resulting neurotoxicity. The mechanisms involved in this process are still not fully understood and appear to involve more than one A β self-association pathway. Resveratrol, a stilbene derivative and a potent antioxidant present in red wine shown to have a neuroprotective effect, is being investigated in this study. This molecule is of special interest, as it has been shown to play a role in the newly-proposed "off-pathway" mechanism of the A β self-association and neurotoxic species formation. In this study, the resveratrol/A β interaction and the corresponding A β conformational states are being investigated using circular dichroism (CD) spectroscopy, fluorescence, and Western blot approaches. The resulting findings provide new understanding of the alternative pathways involved in A β neurotoxicity, which may ultimately serve as a gateway to development of novel approaches halting progression of the Alzheimer's disease.

NEURAL TOPOGRAPHY OF A LEARNED SEQUENTIAL BEHAVIOR

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Male zebra finches learn a specific sequence of syllables (a song) during a sensitive period of juvenile development. Although two distinct regions of songbird pre-motor cortex can drive vocalization (LMAN and HVC), the learned adult syllable pattern is encoded only in HVC. Here, we used a transection technique to investigate the neural mapping of the adult vocal pattern in HVC. Adult males first received bilateral ablation of LMAN, so that all subsequent singing was driven exclusively by HVC. Birds then received either rostro-caudal or medio-lateral transection of HVC bilaterally. We found that rostro-caudal transection of HVC had no effect on vocal patterning (N=3), while medio-lateral transection severely disrupted vocal patterning (N=3) or resulted in no singing at all (N=2). Interestingly, partial transection (~50%) along the medio-lateral axis of HVC produced selective loss of only one or two syllables from the vocal pattern, as well as shifts in spectral features of other notes (N=3). These data indicate that the learned syllable sequence is produced by streams of neural activity that are oriented along the rostro-caudal axis of HVC, and suggest that specific syllables may be encoded by localized clusters of neurons within HVC.

CO-EXPRESSION OF Δ FOSB IN NEURONAL NITRIC OXIDE SYNTHASE-EXPRESSING CELLS OF THE NUCLEUS ACCUMBENS AND MEDIAL PREEPTIC AREA

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The transcription factor Δ FosB functions in reinforcing rewarding behaviors, including drug addiction and natural rewards such as sexual behavior. Repeated sexual experience increases Δ FosB immunoreactive (ir) positive cells in the nucleus accumbens (NAc). However, little is known regarding the role of Δ FosB in the medial preoptic area (MPOA), an area essential for the regulation of male sexual behavior. Recent studies in our lab have shown that Δ FosB-ir cells in the MPOA increases significantly after the first sexual experience, with smaller increases elicited after multiple experiences. Nitric oxide (NO), also expressed in the MPOA, facilitates sexual behavior. Given that Δ FosB is expressed in the MPOA after sexual experience, we investigated whether it is co-expressed in NO-containing cells that facilitate sexual behavior. Adult male rats were given one sexual experience. 18-24 hours after ejaculation, animals were deeply anesthetized, perfused and 40 μ m tissue sections collected from the NAc and MPOA. Using double-label immunohistochemistry, sections were immuno-labeled for FosB (1:500; Santa Cruz Biotechnology) and neuronal nitric oxide synthase (nNOS 1:1000; Invitrogen). Δ FosB was significantly increased in the MPOA following one sexual experience; however, FosB/nNOS co-expression was barely observed in the MPOA and NAc. These findings suggest that any actions of Δ FosB on sexual behavior may not be mediated by changes in nNOS-expressing cells of the MPOA.

ENDOMETRIOSIS (ENDO) IN THE RAT: SYMPATHETIC AND SENSITIZED SENSORY INNERVATION OF THE ECTOPIC GROWTHS DEVELOPS IN PARALLEL WITH ENDO-INDUCED VAGINAL HYPERALGESIA

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Endometriosis is a painful disorder defined by extrauterine endometrial growths. How the growths contribute to pain symptoms is poorly understood. A rat model of endometriosis is created by autotransplanting on abdominal arteries pieces of uterus (ENDO), which form vascularized and innervated cysts. ENDO induces vaginal hyperalgesia (i.e., dyspareunia, common in women with endo). Here we tested the hypothesis that the innervation of the cysts contributes to hyperalgesia symptoms by examining the relationship between the developmental time courses of the vaginal hyperalgesia, the innervation, and neurogenic activity in the sensory C-fibers innervating the cysts after ENDO surgery. Four studies were done. 1. Rudimentary sensory and sympathetic innervation appeared in the cysts by TWO WEEKS after ENDO surgery, increasing dramatically in density by 4 wks. 2. Neurogenic activity became significant by THREE WEEKS after ENDO surgery, remaining elevated thereafter. Significant vaginal hyperalgesia appeared FOUR WEEKS after ENDO surgery, increased during the next 4 wks, then stabilized. Removing the cysts before innervation was in place prevented hyperalgesia from developing. Cyst removal after innervation was in place eliminated the hyperalgesia that had developed. These findings strongly support the hypothesis that sensitization of C-fiber innervation of the ectopic growths (cysts) in endometriosis contributes to the development of ENDO-associated vaginal hyperalgesia.

STRUCTURE OF THE SEC13/31 + SEC23 COPII COAT CAGE

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COPII coated vesicles are responsible for packaging and transporting newly synthesized proteins from the endoplasmic reticulum to the Golgi apparatus. The COPII coat consists of Sec13/31, Sec23/24, and Sar1. Mutation in these coat protein cause medical conditions like Anderson disease, chylomicron retention disease and cranio-lenticulo-sutural dysplasia, which highlights the biological relevance of the coat proteins. Previously we solved two different COPII structures (Stagg et. Al., Nature 2006 and Stagg et. Al., Cell 2008) that suggest that the hinge region formed by the four heterotetramer can direct cage expansion to accommodate cargo of various sizes. Recently a tubular structure of Sec 13/31 solved where the tubules were formed by the concatenation of individual sec13/31 cage (O'Donnell et. Al, J. STruc. Biol.). Earlier, we hypothesized that the distribution of Sec23/24 dictates the geometry of the COPII coat. We now show that Sec23 by itself influences the outer geometry of the cage. We have reconstructed a structure of a COPII coat cage assembled from Sec13/31 and Sec23. The assemblies form at least two geometries, and the most common size is 600 Å, similar to what has been observed for Sec13/31/23 density forming an inner core. We will discuss how the orientation of Sec23 may dictate cage geometry and orient Sar1 to participate in the fission of COPII coated vesicles in the cell.

STRUCTURAL ELEMENTS AND THEIR ROLE IN THE CELLULAR PRION PROTEIN N-TERMINAL DOMAIN

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The prion protein is a “Jekyll and Hyde” molecule. It can adopt two distinct conformations that translate into dual and strikingly opposite fates of this protein. In stark contrast to a form notoriously known for its pathology, the cellular, non-pathological prion protein (PrP) has been implicated in a number of critically important cellular functions that include signal transduction, neuroprotection, and angiogenesis. While much research has focused on the PrP pathology, the molecular mechanisms involving the cellular prion protein remain elusive and are the focus of this study. The functional significance of the PrP N-terminal domain (N-PrP) presents a conundrum since this domain has thus far been classified as “largely unstructured”. This study tests a hypothesis that the prion N-terminal domain, although lacking a well-defined architecture, contains “flickering” structural elements that facilitate PrP function(s) in the cell. A multifaceted biophysical analysis of N-PrP and its fragments is being carried out with the goal to understand this domain’s structural elements and their role in biomolecular interactions. Since this research revolves around aspects of protein structure, physiological function, and macromolecular recognition, the resulting findings also provide new insights into the fundamental knowledge involving “intrinsically disordered”, but functionally important proteins and their domains.

A DROSOPHILA MODEL FOR ADENOVIRUS E1A ONCOPROTEIN PATHOGENESIS

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The DNA tumor viruses share in common the ability to transform vertebrate cells through the action of virus-encoded tumor oncoproteins that interfere with normal cell physiology. We created a genetic model to dissect the pathogenesis and tumorigenesis produced by Adenovirus-5 (Ad-5), using the GAL-4 system to control the tissue-specific expression of the Ad-5 oncoprotein E1A in *D. melanogaster* during development. Expression of E1A in the eye resulted in a ‘glassy’ eye phenotype that is amenable to genetic modifier screens, which was then used to identify individual gene mutations that modify (suppress or enhance) the eye phenotype, allowing the discovery of potential interacting proteins and elucidation of the pathways involved in cancer and other aspects of E1A pathogenesis. Screening of 400 hairpin RNAi “TRiP” lines and 200 deficiency mutations on the second chromosome has yielded 15 potential genes that interact with the E1A pathway. The novel genes that were found to enhance the E1A phenotype are reported here. Mutations in the domains that elicit known E1A functions are under investigation. Cytology and biochemistry will be implemented to elucidate how these genes promote or suppress pathogenesis of E1A. This *Drosophila* model for E1A pathogenesis offers a promising way for efficient screening of genes that interact in the E1A pathway, allowing further investigation of how the DNA tumor viruses lead to tumor growth.

DIFFERENCES IN ASTRAL VS ANASTRAL MITOSIS REVEALED BY GENETIC AND PROTEOMIC APPROACHES

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Centrosomes are the major microtubule-organizing centers in animal cells, and contribute dominantly to spindle assembly at mitosis. Centrosomin (Cnn) is a core centrosome component that recruits protein components including γ -tubulin and other regulators of spindle assembly to centrosomes. In *cnn* mutants, cells assemble mitotic spindles, divide, and complete zygotic development through deployment of an alternative, "centrosome-free" or anastral pathway, producing viable adults. Using genetic and proteomic approaches, we used 2D-Difference Gel Electrophoresis (2D-DIGE) between wild type and *cnn* mutant brains and embryos, and identified at least four proteins that are differentially expressed or modified. As a complementary approach, we used mass spectrometric global proteome analysis from brain and embryo lysates, and identified proteins unique to both wild type and *cnn*, as well as proteins with significant up or down regulation. As an alternative approach, we used a genetic screen and isolated 22 mutants that are synthetic lethal with *cnn*. At least one of these mutants is required for proper spindle assembly in *cnn* mutant cells but not in wild type cells. Together, the two approaches will provide an understanding of the differences between astral and anastral division, paving the way toward a mechanistic understanding of these two pathways for mitotic spindle assembly *in vivo*. In future studies these finding may lead to new means to halt cell division in therapeutic settings.

THE EFFECT OF TESTOSTERONE IN DEPRESSIVE-LIKE BEHAVIORS

Nicole Carrier and Mohamed Kabbaj

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Sex differences in anxiety and depression, where females are more than twice as likely as men to suffer, are widely accepted. In the open-field and social interaction tests for anxiety-like behaviors, we found the levels of estrogen in females to have no effect. Similarly, we found that anxiety-like behaviors were not dependent upon estrus cycle stage in the female. These results prompted us to test the hypothesis that testosterone may be associated with decreased anxiety and depressive-like behaviors in males. In a preliminary study, we found that male rats that were castrated and implanted with a placebo pellet exhibited significant signs of anhedonia and depressive-like symptoms and these deficits were reversed with testosterone replacement. The anti-depressive mechanisms of testosterone, including the possible effects on neurotrophic factors, are currently being investigated.

VIMENTIN FILAMENTS BIND AND STABILIZE COLLAGEN MRNAS

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Excessive collagen production is the hallmark of all fibroproliferative disorders. The 5' stem-loop (5'SL) in the 5' UTR of collagen $\alpha(1)$ and $\alpha(2(I))$ mRNAs is the key element regulating stability and translation of collagen mRNAs. LARP6 is the RNA binding protein which exhibits high affinity binding to the 5'SL of collagen $\alpha(1)$ and $\alpha(2(I))$ mRNAs. Here we report that vimentin filaments associate with type I collagen mRNAs in a 5'SL and LARP6 dependent manner. This association is needed for stabilization of type I collagen mRNAs. Vimentin knockout mouse fibroblasts produce reduced amount of collagen due to decreased stability of mRNAs encoding type I collagen. Disruption of vimentin filaments using drugs or expressing a dominant negative intermediate filament markedly reduced production of type I collagen. This was also primarily due to decreased stability of collagen mRNAs. Our RNA-FISH experiments showed that collagen I mRNAs colocalize with vimentin filaments. SiRNA knock down of LARP6 abrogated the interaction of type I collagen mRNAs with vimentin filaments. We also found that LARP6 interacts and colocalizes with vimentin filaments. We mapped the domain of LARP6 needed for interaction with vimentin to be the La-domain. We conclude that vimentin intermediate filaments may play a key role in the development of tissue fibrosis by stabilizing type I collagen mRNAs that subsequently contributes to increased collagen synthesis. This finding will serve as a basis for targeting vimentin in the development of novel anti-fibrotic therapies.

A NOVEL CENTROSOMIN PARTNER REGULATES SPINDLE ORIENTATION AND CELL POLARITY IN NEURAL STEM CELLS

Jieyan Chen and Timothy Megraw

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Asymmetric division is a crucial aspect of stem cell division to regulate cell differentiation during development. During neurogenesis in *Drosophila melanogaster*, asymmetric mitosis of the neuroblast gives rise to a renewed daughter neuroblast and one differentiated ganglion mother cell (GMC), while asymmetric division in sensory organ precursor cells (SOPs) produce specified cells of the external sensory organ. To ensure proper asymmetric division, fate determinants in the cell must be appropriately polarized, and then the mitotic spindle must orient correctly along the polar axis in order to accomplish polar division. We have identified a novel protein that is required for proper spindle orientation and cell polarization. Homozygous mutants exhibit doubled bristles and sockets on the notum, indicating defects in SOP asymmetric division. Additionally, cell fate determinants were mislocalized in asymmetrically dividing mutant larval neuroblasts, and there is a delay in spindle orientation along the apical-basal axis. These effects on asymmetric division may involve the centrosome as we have identified a physical interaction between this novel protein and Centrosomin, a centrosome core component. However, astral microtubules, are not overtly disrupted in mutant neuroblasts. Other phenotypes include wing defects and maternal effect lethality. We will present a model for how this novel molecule links coordination of activities at the centrosome to polarization of stem cells.

SCARECROW PROMOTES ROOT MERISTEM ACTIVITY BY SUPPRESSING SUGAR SIGNALING

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SHR and SCR are key regulators of stem cell renewal and radial patterning in the Arabidopsis root. There is evidence that SHR and SCR control the two processes through distinct mechanisms, but the molecular basis has been unknown. To dissect the SHR/SCR developmental pathway, we have determined genome-wide locations of SHR targets using a ChIP/chip method. Among the top-ranked targets we identified not only genes that are involved in development but also genes that respond to stresses. This observation has led us to the unexpected finding that SCR also plays a critical role in modulating glucose signaling through a pathway that involves ABI4 and ABA2 but not HXK1. Interestingly, the stem cell and short root phenotype, but not the radial pattern defect, of scr mutant was partially rescued by the glucose insensitive mutant aba2, suggesting that one mechanism by which SCR promotes root growth is by suppressing glucose signaling.

CELL FATE SPECIFICATION, REPROGRAMMING AND SUGAR SIGNALING IN PLANTS

Hongchang Cui, Jiao Sima and Yueling Hao

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A fundamental question that our lab is interested in is how different cell types in multi-cellular organisms are generated from a single zygotic cell. We are dissecting the mechanisms that control cell fate specification in plants using the Arabidopsis root as a model system and a variety of methods ranging from molecular genetics to genomics and epigenomics. The Arabidopsis root is particularly useful for high throughput studies, because individual cell types can be isolated by the fluorescence-assisted cell sorting technique. We are particularly interested in plants because they have the potential to regenerate new individual plants from differentiated cells. Our recent studies showed that sugar signaling also plays a role in stem cell renewal and we are studying two proteins that appear to coordinate plant development and sugar signaling.

COMPUTATIONAL MODEL OF MICROCIRCUIT DYNAMICS UNDERLYING BIRD SONG IN THE ZEBRA FINCH

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Sequences of motor activity are fundamental elements of animal and human behavior. One of the touchstone questions in neuroscience is how the brain learns and generates these complex sequences; this question entails understanding of the underlying complex neural circuitry responsible for producing these patterns. Like humans, songbirds learn to produce highly stereotyped complex sequences of vocal gestures; their songs. This renders the songbird an excellent model system for studying sequential behavior and complex learned patterns. The learned song pattern is generated by the HVC, a telencephalic nucleus that is in some ways analogous to pre-motor cortical regions in mammals. The HVC contains three neural populations: neurons that project to the telencephalic motor output for song (RA), neurons that project to the avian striatum (Area X), and interneurons. These three populations are interconnected, with specific patterns of excitatory and inhibitory connectivity. We have developed a simple ionic current-based computational model that replicates this neural architecture, with the goal of understanding the mechanism for the rhythmic firing patterns that occur in all three neural populations during singing. The mathematical model reproduces these patterns, and shows how the sequence of activity can be stored and directed by the specific excitatory and inhibitory connections between these three types of neurons within the HVC microcircuit. (Supported by NIH, DC002035)

ENDOMETRIOSIS (ENDO)-INDUCED HYPERALGESIA IN THE RAT: CONTRIBUTION OF NERVE GROWTH FACTOR (NGF) AND TRKA IN DORSAL ROOT GANGLION (DRG) NEURONS INNERVATING THE ECTOPIC GROWTHS.

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Endometriosis is a painful disorder defined by extrauterine endometrial growths. How the growths contribute to pain symptoms is poorly understood. A rat model of endometriosis is created by autotransplanting on abdominal arteries pieces of uterus (ENDO). ENDO, but not surgical control induces vaginal hyperalgesia. We recently showed that sensitized activity in C-fiber innervation of the cysts contributes to the development of ENDO-associated vaginal hyperalgesia. Here, we tested the hypothesis that increased expression of NGF and its receptor trkA contribute to this sensitization. The study was done using single- and double-labeling immunohistochemistry to assess expression of NGF and trkA in T9-T10 DRGs harvested from rats 1 - 6 wks after ENDO surgery and from control rats. (The T9-T10 DRGs contain the sensory neurons whose axons sprout to innervate the cysts.) RESULTS: The expression in DRG neurons of NGF, trkA or both antibodies began to be greater than the expression in control rats by 1 wk after ENDO surgery, increased further by 2 wks after ENDO surgery, and then stabilized. This time course is similar to the development of the cysts' sensory (and sympathetic) innervation (Berkley et al., this meeting). CONCLUSION: These results support the hypothesis that upregulation of NGF and its receptor trkA contribute both to the sensitization of afferent neurons whose axons sprout to innervate the cysts and to the accompanying hyperalgesia that develops after ENDO surgery.

INDIVIDUAL DIFFERENCES IN SOCIAL DEFEAT-INDUCED DEPRESSIVE-LIKE BEHAVIOR

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Depression is a major neuropsychiatric disorder deeply affecting mood and behavior, and exhibiting marked variations between patients in response to treatments, with some individuals remaining resistant. Such individual variations in depressive states can also be found in rodents. Indeed, according to their locomotor activity in response to novelty, naïve male rats can be classified as either high (HR) or low responders (LR), predicting subsequent differences in behavioral sensitivity to stress, anxiety and depression. Social defeat is a model of psychosocial stress inducing, in rodents, severe alterations in stress responsiveness, social behaviors, and specific changes in gene expression together with variations of histone acetylation in a time-, tissue- and histone-specific manner. Interestingly, these histone modifications follow a distinct pattern between HR and LR rats, suggesting an epigenetic contribution to individual differences in depressive-like symptoms. In order to identify the mechanisms directing these individual differences, male Sprague-Dawley rats were socially defeated for one or four consecutive days by a Long-Evans resident male, and sensitivity to defeat was measured in HR and LR rats using several behavioral paradigms, followed by an analysis of epigenetic factors in depression-related brain areas. By providing behavioral and molecular clues, these data strengthen the importance of considering individual differences in depression-related investigations.

TITIN KINASE INTERACTION WITH HAX1 IN NONMUSCLE CELLS

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In striated muscles, the large multifunctional elastic protein titin plays important roles in assembling and maintaining the contractile sarcomere structure and as a mechanosensor that signals changes in protein turnover and gene expression. Our lab discovered that isoforms of titin exist in nonmuscle cell structures including stress fibers, where the cellular titin (c-titin) may play similar structural and signaling roles. C-titin, like striated muscle titin, contains a kinase domain near its C-terminus. Yeast two hybrid (Y2H) screening of a HeLa cell cDNA library revealed that the c-titin kinase domain interacts with several overlapping clones of the C-terminal end of Hax1. Hax1 is a ubiquitously expressed multifunctional protein that interacts with a variety of other proteins and plays a variety of roles in cells from modulating apoptosis to regulating the actin cytoskeleton formation. Additional Y2H, alanine mutagenesis, and GST-Pull Down analyses showed that a beta-strand cap region of the titin kinase domain interacts with a short highly conserved region of Hax1 near a possible phosphorylation site. Western blot analysis using an anti-phosphoserine/threonine antibody demonstrated that the titin kinase domain phosphorylates Hax1 in vitro. Immunolocalization revealed that some titin kinase domain and Hax1 colocalize in lamellipodia, where the interaction between the titin kinase domain and Hax1 may regulate actin cytoskeleton formation and cell migration.

CHECKPOINT KINASE DEPENDENT TRANSCRIPTIONAL REPRESSION OF HISTONE GENES UPON REPLICATION INHIBITION IN BUDDING YEAST

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In eukaryotic cells DNA replication and histone synthesis are tightly coordinated with each other. Interference with replication leads to downregulation of the histone transcripts. In budding yeast this process is mainly regulated by transcriptional repression and is dependent on the checkpoint kinases Mec1, Tel1 and Rad53. To further understand the molecular mechanisms underlying this regulation we are exploring the potential downstream targets of these checkpoint kinases. We propose that the checkpoint kinases stabilize Hpc2, a subunit of the histone regulatory complex Hir which is required for histone gene repression.

BINDING AND ACTIVATION OF P90 RIBOSOMAL S6 KINASE (RSKS) BY ORF45 ARE REQUIRED FOR KSHV LYTIC REPLICATION AND EPISOME VIRAL GENOME MAINTENANCE

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KSHV immediate-early and tegument protein ORF45 is in the forefront of coping with the host cellular environment because of its unique expression. We have shown that ORF45 causes sustained activation of ERK and p90 ribosomal S6 kinases (RSKs) through formation of complexes with RSKs. We have identified the critical region of KSHV ORF45 that is involved in RSK interaction and activation. We found that the loosely conserved ORF45s of γ -2 herpesviruses share the core RSK-binding motif and all activate RSK to different extents. Alanine scanning mutagenesis revealed that a single F66A point mutation abolished binding of ORF45 to RSK, and consequently its ability to activate the kinases. We introduced the mutation into the BAC36 genome, producing BAC-45F66A. We also repaired the mutation and obtained a revertant BAC-45res-A66F. We transfected the BAC DNAs and obtained cells that all carry latent episomal KSHV genomes. When the cells were treated under different conditions to induce lytic replication, we found that the BAC-45F66A behaved similarly as the ORF45-null BAC-stop45 and produced 5-10 fold fewer progeny viruses than the wild type and the revertant. When the cells were continuously passaged, we found that the BAC-45F66A and BAC-stop45 lost their episomal genomes much more rapidly than the wild type and the revertant. These results indicate that the ORF45/RSK axis plays critical roles in not only lytic replication but also episomal viral genome maintenance of KSHV.

ORF45 OF KAPOSI SARCOMA-ASSOCIATED HERPESVIRUS ACTS AS A MOLECULAR SCAFFOLD FOR CELLULAR AND VIRAL PROTEINS DURING LYTIC REPLICATION PHASE

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ORF45 of Kaposi's sarcoma-associated herpesvirus (KSHV) is gamma herpesvirus-specific, immediate-early, and tegument protein. Our genetic studies have revealed its crucial roles in both early and late stages of KSHV infection. To characterize the ORF45-containing complexes, we immunoprecipitated (IP) 35S-labeled TPA-induced BCBL1 cell lysates with a panel of monoclonal antibodies. In addition to the previously identified RSK1/2 proteins, we found several other copurified proteins. The ORF45 and associated cellular and viral proteins were immunoaffinity purified with IgG-conjugated magnetic Dynabeads. The identities of these proteins were revealed by LC-MS/MS and confirmed by western blot. Among them, ORF33 is an essential and highly homologous viral tegument protein present in all herpesviruses; USP7 is a cellular deubiquitination enzyme known to interact with p53 and MDM2. We mapped the ORF33-binding domain to the very C-terminal end of ORF45 and also confirmed binding of USP7 to ORF45 and mapped the binding domain to the aa210-237 region of ORF45. Further experiments revealed that the prominent cellular proteins and ORF33 can bind to ORF45 independently and that ORF45 is required for the assembly of ORF33, RSK, ERK, and USP7 into a larger complex. In conclusion, ORF45 forms diverse complexes with viral and cellular proteins during the lytic cycle. Further dissection of these complexes will be essential for understanding the critical roles of ORF45 in KSHV life cycle.

THE TYPE I TGFSS RECEPTOR ALK-1 FUNCTIONS IN TGFSS-MEDIATED SIGNALING IN ANGIOGENESIS

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Activin-Like Kinase 1 (ALK1, TSR1), a type I transforming growth factor (TGF β) family receptor found in endothelial cells is involved in angiogenesis (new blood vessel formation). Control of angiogenesis is critical in diseases such as tumor formation as tumors can induce their own blood supply. We show that expression of ALK-1 but not the ubiquitous ALK 5 type I receptor increased dramatically in endothelial cells after tube formation stimulated by TGF β + fibroblast growth factor (FGF) in serum-free medium on collagen gels. FGF-2 and TGF β also both upregulate cell surface expression of ALK1 and downregulate expression of ALK5 in human microvascular endothelial cells (HMVEC). This suggests a critical role for the ALK-1 receptor in endothelial tube formation. Furthermore we show that TGF β signals through a complex of ALK 1, the ALK signaling protein Smad1, and the accessory receptor endoglin. Three ligands, TGF β , activin, and bone morphogenetic protein 9 (BMP-9) have been shown to bind ALK-1. We present evidence that endogenous activin binds ALK 1 and can be displaced by exogenous TGF β . Antisense RNA that targets both ALK 1 and ALK 5 disrupts tube formation. To explore the roles of each receptor type in more detail we are generating kinase defective and kinase deletion mutants of ALK-1 and ALK-5 to test their roles in angiogenesis and growth factor signal transduction. We hope to dissect the role of ALK-1 and TGF β family ligands in angiogenesis of tumors.

OXYTOCIN INDUCES AN ACUTE PROLACTIN RESPONSE THAT ACTS IN THE BRAIN TO INDUCE A PROLACTIN SECRETORY RHYTHM

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We have previously shown that a single intravenous injection of oxytocin (OT) in ovariectomized rats can induce a prolactin (PRL) secretory rhythm similar to that initiated by mating or artificial cervical stimulation. This consists of an early morning surge in PRL release followed by an early evening surge, repeated for up to 12 days. We hypothesized that OT releases PRL, and that peripheral PRL crosses into the central nervous system to trigger the PRL secretory rhythm. To test this, we injected OT intravenously into OVX rats and collected blood samples to monitor the timing of the OT-evoked PRL release from lactotrophs. We found that OT induced a biphasic PRL response, with first an acute and sharp increase 5 min after the OT injection and a delayed and more prolonged elevation after 6 h. We then injected OT peripherally while a PRL antagonist was infused into the lateral ventricle. The OT injection induced a rhythmic release of PRL, but the blockage of the PRL action in the brain at the time of the injection prevented the initiation of the rhythmic PRL surges, even after clearance of the drug. Taken together, our results suggest that the peripheral injection of OT acts directly on pituitary lactotrophs to stimulate PRL release, which is transported into the brain where it acts to trigger the OT-induced circadian PRL secretory rhythm.

BEHAVIORAL AND MOLECULAR INVESTIGATIONS INTO SUSCEPTIBILITY TO DEPRESSION IN RATS

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Stress has been linked with such psychological disorders as major depression and post-traumatic stress disorder (PTSD). There are individual differences in the response to stress where some appear more vulnerable to its effects than others. As the most common stressors are psychological in nature, we investigated individual vulnerabilities in depressive-like behavior following repeated social defeat stress. Social defeat in rodents is a model of social stress that centers on intraspecies conflict and provides an ethological and ecological method to study the relation between chronic stress and depression without the complication of habituation. As evidence for individual variation, we were able to classify an outbred population of male Sprague-Dawley rats as either susceptible or unsusceptible to the effects of repeated social defeat using the social approach and avoidance test. We compared the behavior of these two groups to non-defeated controls to assess for the presence of depressive-like symptoms. We found that rats that scored as “susceptible” in the social approach and avoidance test showed several other depressive-like changes in behavior, while those that scored as “unsusceptible” appeared similar to non-defeated controls. As the mechanisms behind such variation in behavior have yet to be elucidated, we are exploring epigenetic mechanism underlying these phenotypes.

IDENTIFICATION OF RK6 INHIBITOR IN RAT BRAIN

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The human kallikrein 6 (KLK6) homologue, rat myelencephalon-specific protease (MSP), has been reported to be abundantly expressed in the CNS and has been implicated in demyelinating disease, like multiple sclerosis (MS). In addition, the inhibition of KLK6 in experimental models of MS has resulted in reduced severity of symptoms. The regulation of this protein, therefore, is of particular interest to the medical community. Our goal is to identify the major CNS-specific inhibitor of rat kallikrein 6 (rK6) and characterize a human homologue. Purified rat brain homogenate was 'spiked' with recombinant rK6 to promote inhibitor/KLK6 complex formation and then analyzed on SDS-PAGE. An α -MSP polyclonal antibody was used to probe and identify rK6 in two high molecular mass bands. The presence of these bands suggests a complex formation between rK6 and another protein. Since the proteins in the two higher mass bands indicate stability to SDS, it is possible that the rK6 is in complex with a member of the serpin (serine protease inhibitor) family. This project will investigate the identity of the protein in complex with rK6 further using co-immunoprecipitation techniques and mass spectrometry. The identification of proteins that associate with MSP is useful in understanding the regulation of this protein in inflammatory CNS disease.

HISTONE GENE DOSAGE MODULATES DNA REPAIR VIA THE HOMOLOGOUS RECOMBINATION PATHWAY

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In eukaryotes, multiple genes encode histones proteins that package genomic DNA and regulate its accessibility. Due to their positive charge, histones can also bind non-specifically to the negatively charged DNA and affect its metabolism, including DNA repair. We have investigated the effect of altering histone gene dosage on DNA damage and repair in the budding yeast *Saccharomyces cerevisiae*. An increase in histone gene dosage resulted in enhanced DNA damage sensitivity, while a reduction in histone H3 and H4 gene dosage resulted in resistance to DNA damaging agents, even in mutants defective in the DNA damage checkpoint. This effect is due to an increase in the efficiency of repair via the Homologous Recombination (HR) pathway upon a reduction in histone gene dosage. Cells with reduced histone gene dosage experience greater histone loss around a DNA Double Strand Break (DSB), while the recruitment of HR factors is concomitantly enhanced. We propose that histones compete with the HR machinery and reduce its efficiency. Our findings may have major implications for DNA repair, genomic stability carcinogenesis and aging in human cells that have dozens of histone genes.

TURN STRUCTURE IN THE TRANSITION STATE OF FIBROBLAST GROWTH FACTOR-1

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The ability of a protein to perform its biological function hinges on successful attainment of the native conformation. Many of the fundamental protein folds exhibit tertiary structural symmetry, implying that a symmetric architecture is compatible with a foldable polypeptide. However, little is known about the role of tertiary structural symmetry in protein folding. To better understand the interaction between protein folding and symmetry, Fibroblast Growth Factor-1, a β -trefoil protein with a pseudo threefold axis of symmetry, was subjected to a phi-value analysis of its 11 turn regions. Analysis of kinetic and equilibrium data revealed that the large majority of mutants satisfied the assumptions of two-state folding and were analyzed further to extract structural information about the transition state ensemble. The resulting phi-values were polarized with nearly all positions being either folded or unfolding in the transition state ensemble. Turns related by tertiary structural symmetry did not fold concurrently despite the gross structural similarities of their environment. Eight of the 10 analyzed turns exhibited native-like structure or intermediate structure in the transition state ensemble, underpinning the structural importance of turns for the folding of a globular protein. Interestingly, the only two turns identified as being fully denatured-like in the transition state ensemble were those closest to the termini, suggesting that closure of the termini happens late in the folding pathway. The results of this study clearly indicate that tertiary structural symmetry in the native-state conformation is not retained in the transition state. Instead, the hallmark symmetry of this β -trefoil is established after the barrier crossing event.

DEVELOPMENTAL EXPOSURE TO A SEROTONIN AGONIST PRODUCES SUBSEQUENT BEHAVIORAL AND NEUROCHEMICAL CHANGES IN THE ADULT MALE PRAIRIE VOLE

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It has been previously shown that 5-HT acts as a developmental signal in the rat. In rat pups, 5-HT manipulation during early development induces abnormal development in various brain regions with an associated increase in abnormal behaviors. The present study was conducted on the socially monogamous prairie vole (*Microtus ochrogaster*). Previous studies have shown that the complex social behaviors displayed by prairie voles are regulated by a variety of neurotransmitters, and thus this rodent model may provide an excellent opportunity to study neurochemical mechanisms underlying a complex psychiatric disorder, such as autism. In this study, prairie voles received perinatal injections of either saline or 5-MT daily (1mg/kg). Subjects were then behaviorally tested at approximately PND 80. Compared to saline controls, 5-MT-treated males spent less time in side-by-side contact with a conspecific male in a social affiliation test. Further, 5-MT-treated males entered the open arms fewer times and spent less time there in an elevated plus maze test and spent more time in the corners of an open field test. These data suggest that developmental exposure to 5-MT impaired social affiliation and increased anxiety-like behavior in male prairie voles. Interestingly, 5-MT males had fewer 5-HT immunoreactive neurons in the dorsal raphe nucleus of the brain compared to saline controls, suggesting that such altered 5-HT system may play a role influencing social and anxiety-like behaviors.

A NOVEL ROLE OF RNA HELICASE A IN TRANSLATION REGULATION OF TYPE I COLLAGEN

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Type I collagen is the most exuberant polypeptide in mammals, composed of a heterotrimer of two $\alpha 1$ and one $\alpha 2$ polypeptides. Type I collagen contains a 75 nucleotides (nt) from the 5'-terminal 7-methylguanine cap, a discrete stem-loop (5'SL) structure that resembles the PCE-like region described in many retroviruses as a regulatory mechanism enhancing translation efficiency. For translation to progress to elongation, numerous initiation factors cooperate to ensure the unwinding of the secondary structure in the 5'UTR. The complexity of the 5' UTR of the type I collagen makes collagen mRNAs poor substrates for translation. To establish a 100 fold increase of type I collagen synthesis during fibrogenic proliferation a coordination between RHA and Larp6, a collagen 5'SL binding protein is required. This makes RHA an important regulatory molecule in stimulating fibrogenesis. Our data reveals a novel role of RHA with cooperative binding to Larp6 as an enhancer required in translation of type I collagen mRNAs during fibrogenesis. This is the first description of the role of RHA in synthesis of extracellular matrix proteins and may have profound implications to the future development of antifibrotic drugs.

ENDOMETRIOSIS (ENDO) IN THE RAT: INDIVIDUAL DIFFERENCES IN SENSORY AND SYMPATHETIC INNERVATION OF THE ECTOPIC GROWTHS CORRELATES WITH INDIVIDUAL DIFFERENCES IN THE SEVERITY OF HYPERALGESIA

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Endometriosis is a painful disorder defined by extrauterine endometrial growths. How the growths contribute to pain symptoms is poorly understood. A rat model involves autotransplanting on abdominal arteries pieces of uterus (ENDO), which form vascularized cysts. ENDO induces vaginal hyperalgesia (i.e., dyspareunia, common in women with endo). Vaginal hyperalgesia in the rat develops by 4 wks after ENDO surgery, increasing and stabilizing by 8 wks. The cysts become innervated by branches of sensory and sympathetic fibers that sprout from nearby nerves. In support of the hypothesis that these fibers contribute to the hyperalgesia is that the development of innervation after ENDO surgery parallels the development of the hyperalgesia. Another aspect of the developing hyperalgesia is that there are large individual differences in hyperalgesic severity 4 wks post-ENDO. If the hypothesis that the innervation contributes to the hyperalgesia is correct, then the density of this innervation should correlate with the hyperalgesic severity at this time. Here we report pilot data from 6 rats showing that the correlation between the sensory innervation and hyperalgesia was $r=0.73$, between the sympathetic innervation and hyperalgesia was $r=0.77$, and that a significant correlation was obtained for the total sensory+sympathetic innervation, $r=0.81$, $p<0.05$. These data not only support the hypothesis but suggest further that sensory-sympathetic coupling may be a predominant mechanism.

TRANSCRIPTIONAL REGULATION OF SEXUAL BEHAVIOR IN MALE RATS: EFFECTS OF Δ FOSB AND Δ JUND IN THE MPOA

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Previous sexual experience sensitizes male rats to sexually-relevant stimuli and facilitates copulatory efficiency. In the nucleus accumbens (NAc), repeated sexual behavior increases the expression of the transcription factor Δ FosB to a greater extent than a single sexual experience and overexpression of Δ FosB in the NAc facilitates sexual behavior. We recently found the opposite result of sexual experience on Δ FosB in a different brain area, the medial preoptic area (MPOA), an integral site for the regulation of male sexual behavior. We theorize that in the MPOA up-regulation of Δ FosB may inhibit, and down-regulation may facilitate, male sexual behavior. In the present study, adeno-associated virus (AAV) vectors for Δ FosB (AAV- Δ FosB), Δ JunD (AAV- Δ JunD), or a control expressing only green fluorescent protein (AAV-GFP) were microinjected bilaterally into the MPOA of sexually naïve male rats. Δ FosB heterodimerizes with JunD to form an activator protein-1 transcription factor (AP-1); Δ JunD is a dominant negative antagonist of such transcription. Copulatory testing revealed that administration of AAV- Δ JunD in the MPOA facilitated sexual function, whereas AAV- Δ FosB impaired sexual function, compared to animals that received AAV-GFP. Additionally, Δ FosB animals displayed increased levels of aggression toward stimulus females during copulation testing, compared to both AAV-GFP and AAV- Δ JunD males. These data support the hypothesis that Δ FosB in the MPOA impairs male sexual behavior.

INTRAGENIC TRANSCRIPTION IN RESPONSE TO STRESSFUL DNA REPLICATION

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The function of a given gene can be regulated at multiple levels and one of the most important is at the transcriptional level. Regulation can occur by the increase or decrease of mRNA levels or by the use of alternative promoters to generate different gene products from a single gene with distinct functions. The use of an alternative promoter can allow intragenic transcription, whereby the initiation of transcription occurs within the coding region of a gene. Our data indicates a previously uncharacterized example of intragenic transcription in response to stressful DNA replication. Interestingly, when DNA synthesis is blocked with the drug Hydroxyurea (HU), we observe two shorter forms of Ase1 protein, a spindle midzone component. We demonstrated that the smaller Ase1 protein is a result of intragenic transcription because we verified the expression of a shorter ASE1 mRNA. We also found that the presence of the short forms of Ase1 depends on the S-phase checkpoint, which is essential for cell cycle arrest and the integrity of replication forks in response to DNA synthesis block. We propose that a group of genes is subjected to intragenic transcription as part of the S-phase response and that this may be due to the change in chromatin structure. This uncharacterized regulatory mechanism for gene function may be crucial for genome integrity, and higher eukaryotes may use a similar mechanism to respond to stressful DNA synthesis.

DESIGN OF MULTIDENTATE CATECHOL- AND POLYETHYLENE GLYCOL- DERIVATIZED OLIGOMERS FOR BIOCOMPATIBLE IRON OXIDE NANOPARTICLES

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Iron oxide nanoparticles (NPs) offer great promises for use in biomedical applications, including magnetic resonance imaging and magnetic separation bioassays. Effective synthetic strategies, based on high temperature reaction of organometallic precursors, have been developed to prepare high quality iron oxide NPs that are mainly hydrophobic. Cap exchange with hydrophilic ligands is a reliable strategy to transfer them to buffer media and to endow them with biocompatibility. It has recently been reported that catechol derivatives, such as dopamine and L-3,4-dihydroxyphenylalanine, exhibit strong affinity to metal oxides nanoparticles. We demonstrate the design and preparation of a new set of hydrophilic catechol-derivatized oligomeric ligands. These ligands consist of a short oligomer backbone, several dopamine anchoring groups, several hydrophilic poly(ethylene glycol) segments, and reactive lateral groups for coupling to biological receptors. We found that rapid ligand exchange of hydrophobic iron oxide NPs with these multidentate ligands takes place and the resulting NPs were easily dispersed in buffer media with greatly enhanced colloidal stability. We will describe the synthesis routes for these ligands, where the density of anchoring groups, intrinsic ligand structure and the type of end reactive groups can be tuned, and apply them to cap and transfer iron oxide NPs to buffer media. We will also outline a few demonstrations using these NPs for contract imaging.

UNDERSTANDING THE ROLE OF THE NONSTRUCTURAL PROTEIN NS5A IN THE LIFE CYCLE OF HEPATITIS C VIRUS

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Hepatitis C virus (HCV), which affects 170 million people worldwide, is a major cause of primary hepatocellular carcinoma. HCV is also associated with higher risk of non-Hodgkin lymphoma and multiple myeloma, a type of blood cancer that affects plasma cells. Since there is no available vaccine and current forms of treatment are not effective due to the presence of several genotypes, and due to resistance issues, there is an urgent search for new anti-HCV drugs. The HCV life cycle depends on both viral and cellular proteins. The viral life cycle is defined by two major steps: first, the replication of the viral RNA which involves translation of the viral RNA to produce viral proteins which also help in production of new viral RNAs. Second, viral assembly where RNA is packaged and viral particles are assembled before being released through the cellular surface. For RNA viruses, such as HCV, high mutation rates and great diversity makes cellular factors a better target for developing anti-HCV drugs. Cellular protein cyclophilinA (CyPA) interacts with viral nonstructural protein NS5A and is susceptible to anti-HCV drug CsA. NS5A is instrumental to both steps of viral life cycle, replication and assembly, by yet-unknown mechanism. Using an engineered virus that carries an exogenous tag on NS5A, NS5A associated complexes are isolated and identified through mass spectroscopy. These factors are individually studied for their roles in HCV infection.

MELATONIN HAS NEUROPROTECTIVE ACTIONS IN A CELLULAR MODEL OF ALZHEIMER'S DISEASE

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Some important pathological elements of Alzheimer's disease (AD) include cerebral plaques dense in β -amyloid peptide ($A\beta$), neurofibrillary tangles, inflammation and oxidative damage. In AD, dysfunctional mitochondria release reactive oxygen species that cause oxidative stress. The neurohormone melatonin (MEL) has frequently been reported to exert anti- β -amyloid aggregation, antioxidant, and anti-inflammatory actions in various in vitro and animal models including transgenic mice expressing the mutated human Swedish amyloid precursor protein (sweAPP). (cf Olcese et al. 2009) In the current study, we utilized wild-type murine neuroblastoma (N2a-wt) cells as compared to N2a cells stably transfected with the sweAPP gene (N2a-sweAPP), which leads to neurotoxic levels of $A\beta$ fragments in human AD. These $A\beta$ fragments can cause alterations in specific gene expression, some of which likely contribute to neurodegeneration. We employed gene microarrays, qPCR, immunoblotting, enzyme assays and mitochondrial studies to examine N2a-sweAPP cells after exposure to either vehicle or physiological and pharmacological levels of the receptor ligands Iodo-MEL and MEL. Evaluation of gene and protein expression of standard anti-oxidant markers such as superoxide dismutase, catalase and glutathione peroxidase indicate that I-MEL reduces oxidative stress and assessment of respiratory function and reactive oxygen species after I-MEL treatment demonstrate restored mitochondrial function.

POLYETHYLENE GLYCOL-BASED MULTIFUNCTIONAL OLIGOMERS FOR INTERFACING GOLD AND SEMICONDUCTOR NANOCRYSTALS WITH BIOLOGICAL MEDIA

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Inorganic nanocrystals, such as semiconductor quantum dots (QDs) and Au nanoparticles, exhibit unique size-dependent photophysical properties. They are very attractive for use in sensor design and live cell imaging. Interfacing these inorganic nanoparticles with biology involves the combination of basic chemistry with biomolecular engineering. In general, high quality QDs synthesized from organometallic precursors, are dispersible in hydrophobic solvents and AuNPs are often made via citrate-reduction. Thus, post-synthetic surface modification is required to render these nanocrystals stable in aqueous media and biologically compatible. We have previously developed a set of molecular scale ligands based on bi-dentate and multidentate dihydrolipoic acid (DHLLA) motifs, and each was made of a strong anchoring head, a tunable poly(ethylene glycol) segment and a terminal functional group; the latter promoted biocompatibility of the nanocrystals. Recently, we have developed a new set of compact multifunctional ligands that contain each an oligomer coupled to several copies of a short poly(ethylene glycol) (PEG)-appended thioctic acid (TA) or DHLLA. Here the insertion of several PEG segments promotes water solubility, while TA and DHLLA groups provide multidentate anchoring onto Au and ZnS-overcoated semiconductor QDs, respectively. We will discuss the ligand design, preparation, capping of the nanocrystals, coupling to target biomolecules to design some specific biological sensor.

THE LONG-TERM EFFECT OF NICOTINE ON CRYSTALLIZED SONG IN THE ADULT MALE ZEBRA FINCH

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The zebra finch (*Taeniopygia guttata*) is a well-known animal model to study cognitive processes using the natural occurring song pattern as a parameter for synaptic plasticity. The song pattern of the male zebra finch crystallizes approx. 120 days after hatching, and remains constant for the entirety of the animal's life. In this study, we examine the effect of nicotine on the quality of the crystallized song of adult male zebra finches. Sixteen mature (>120 days old) male birds were selected at random, and housed individually in recording cages to monitor song production. After baseline recording and control injections were made, nicotine or saline was given. Our results show that the crystallized song pattern in nicotine-exposed animals is significantly degraded, in which the overall structure of the song remains constant, but the finer features vanish from the spectrogram beginning approximately three weeks following the cessation of the nicotine treatment, and continuing for two months until the end of the experiment. Age matching controls did not show this effect. These results indicate a long-term change in the crystallized song, which is caused by the 7-day administration of nicotine. We propose two hypotheses: 1) nicotine interferes with auditory feedback pathways and creates a form of deafness in the animals 2) a genetic change in the song nuclei occurs, in which case injection of nicotine after a latency period would reverse the song deterioration.

THE REGION-SPECIFIC REGULATION OF NEURONAL DEVELOPMENT IN THE MEDULLARY DORSAL HORN

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Neurons located in the Vc (subnucleus caudalis) relay noxious input from the skin and/or deep tissues to higher brain centers and has therefore been designated as the "medullary dorsal horn". Recent work in our lab has demonstrated numerous developmental differences in dissociated cultures of Vc and DH (spinal dorsal horn) neurons. When compared with DH neurons, the growth of neurons located in the Vc was significantly slower: the number of primary processes was fewer and the total length of processes of Vc neurons was shorter. Furthermore we found that small (non-protein) ninhydrin-reacting molecules purified from DH-conditioned medium promoted neuronal growth; whereas the corresponding ninhydrin-reacting molecules from Vc-conditioned medium inhibited neuronal growth. In order to better understand the mechanisms involved in the delayed development of Vc cultures, immunocytochemical studies of Vc and DH dissociated cultures at Day 7 were performed using co-labeling with Hoechst 33342 and Tuj1, NeuN, MAP2, NK-1R or GFAP antibodies. When compared with DH neurons, significantly more mature Vc neurons, detected with NeuN or MAP2 antibody, showed abnormal nuclear staining, but no difference was found in young neurons. Taken together these data strongly suggest that through locally released factors the development and function of Vc neurons can be region-specifically regulated. Thus a novel insight is provided for investigating neurodegenerative disease and facial pain.

SUBUNIT-SPECIFIC DIFFERENCES IN NMDA RECEPTOR FUNCTION AT EXCITATORY SYNAPSES ONTO LAYER 5 PYRAMIDAL NEURONS IN SOMATOSENSORY BARREL CORTEX

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NMDA receptors (NMDARs) are implicated in diverse cellular phenomena ranging from learning and memory to inflammation and pain. Contrary to common assumptions, subunit composition of synaptically expressed NMDARs on excitatory neurons appears to be input-specific. To test the generality of these observations, we assayed NMDAR subunit composition in individual layer 5 pyramidal neurons in the somatosensory barrel cortex. We stimulated in VPM of the thalamus or striatum to activate TC afferents and in layer I to activate fibers from the primary whisker motor cortex (M1) / posterior medial nucleus (POM) (Petreanu et al, 2009) designated IC. Typical decay time constants (τ) for NMDAR-mediated EPSCs in barrel cortex (~20 ms) were significantly faster than those observed in the frontal cortex (~75 ms) suggesting a preponderance of NR2A at barrel cortex synapses. However, decay time constants and half-widths (HW) for normalized IC responses (at +30 mV in aCSF) were significantly larger than those for TC responses (τ_{IC} : 18.6 ± 1.8 vs τ_{TC} : 13.4 ± 1.4 ms; HW_{IC} : 16.9 ± 2.1 vs HW_{TC} : 11.4 ± 1.2 ms; $p < 0.05$ for both, t-test, $n = 12$ cells), while rise times (RT) were similar at both positive and negative holding potentials (RT_{TC} : 1.8 ± 0.2 vs RT_{IC} : 2.3 ± 0.3 ms at +30 mV; RT_{TC} : 2.1 ± 0.3 vs RT_{IC} : 2.2 ± 0.3 ms at -70 mV; $p > 0.8$). Thus while TC and IC inputs most likely contain the NR2A subunit that might be responsible for speeding-up responses.

SLK19-MEDIATED CENTROMERE COHESION ALLOW FOR FAITHFUL CHROMOSOME SEGREGATION

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Before chromosome segregation, kinetochores (KT) are attached by spindle microtubules (MT) emanating from opposite spindle poles to establish bipolar attachment. Defects in the KT-MT interaction cause chromosome mis-segregation and aneuploidy, a hallmark of cancer. The bipolar attachment generates force on chromosomes which is counter-acted by the cohesin complex at the centromeric region. Interestingly, a 'breathing' phenomenon occurs when the sister centromeres separate and come back together, suggesting a unique role for centromere cohesin. The mechanism of how and why centromeric breathing occurs and its potential role in the KT-MT interaction remains unclear. Slk19 is a protein that is located at the kinetochore where it likely has a role in KT-MT attachments due to its genetic interaction with spindle assembly checkpoint proteins. Our preliminary data which uses various genetic and biochemical techniques show that Slk19 provides peri-centromeric-specific cohesion which allows for faithful KT-MT interactions. Additionally, we show that there is an interaction between separate cohesin complexes and this interaction is nearly abolished in slk19 mutants. Currently, we are testing the novel hypothesis that Slk19 can bridge separate cohesin molecules around the centromere to provide a centromeric-specific holding force to aid chromosome bipolar attachment.

DUAL-MODALITY QUANTUM DOT-MRI CONTRAST AGENTS FOR IN-VITRO AND IN-VIVO DELIVERY

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Quantum Dots (QDs) have attracted huge attention over the past two decades with untold numbers of applications. Herein, we report the use of QDs as a platform for delivery of MRI contrast agents in cell tissues as well as live animal. InP/ZnS quantum dots were synthesized via CEM microwave technologies and water-solubilized via ligand exchange with a short peptide sequence. Through a simple condensation reaction, the chelating ring of the contrast agent was appended to the QD-peptide construct. Finally, the lanthanide was incubated with the QD-peptide-chelating ring complex to form the final, dual-modality system. The system was tested in solution, in which T1, T2 and T2* contrast measurements were observed. Injection into the ventricles of a rat brain displayed T1 24 hours later. This QD-MRI system shows promise for enhancing contrast delivery within live animal systems.

DIFFERENCES IN DELTA-FOSB PROTEIN ACROSS BRAIN REGIONS AFTER CHRONIC COCAINE ADMINISTRATION

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The buildup of the transcription factor Δ FosB occurs in the NAc after exposure to euphoriant drugs and natural rewards such as sex. Our lab has previously shown that the MPOA displays a different pattern of Δ FosB expression following sexual reward. Here, Δ FosB induction in the MPOA was greater following the first sexual experience than after repeated sexual experiences and this induction was transient. The current study tests whether this pattern was specific to sexual behavior or generalized to DAergic stimuli. We administered repeated injections of cocaine or saline to rats with a schedule identical to that of the sex study and measured Δ FosB protein and locomotor activity. Cocaine induced a similar but nonsignificant pattern of Δ FosB expression in the MPOA, suggesting that a DAergic mechanism may exist, but that the MPOA DA response to cocaine is insufficient to produce the same magnitude of response (there are relatively few DA transporters in the MPOA for cocaine to inhibit). Additionally, the NAc displayed an abnormal Δ FosB expression pattern - acute induction was robust, while chronic accumulation was minimal. The level of Δ FosB expression matched the pattern of drug-induced locomotor activity, which has also been correlated with Δ FosB expression by other groups. These data suggest a temporal pattern of Δ FosB expression that is both region- and stimulus-specific. Additionally, stimulus schedule may play an important role in regulating its long-term buildup.

COFACTOR-INDEPENDENT MUTANT (COFIM) SCREENING: PROOF-OF-CONCEPT STUDIES WITH
CYCLOPHILIN A AND HCV RECEPTORS

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Successful completion of the life cycle of a virus depends not only on the function of proteins encoded by the virus but also on cellular cofactors. Since the advent of genome-wide small interfering RNA screening, large numbers of cellular cofactors important for viral infection have been discovered. Here we report a new, unbiased genetic approach to the identification of the viral target through which a cellular cofactor functions to exert its effect on viral infection. Cell lines expressing small hairpin RNAs targeting cellular cofactors are first established and tested for viral inhibition. Viral escape mutants are then selected to isolate variants that can infect the knockdown cells lines which are refractory to infection by the wildtype virus. Mutations responsible for the escape phenotype are then identified and characterized using reverse genetics. In proof-of-concept studies, we chose two groups of clinically relevant cellular cofactors for HCV: CyPA and entry receptors claudin-1 and SR-BI. For CyPA, we isolated a mutant virus that replicated higher in CyPA-knockdown cells than in the control cells. The mutations responsible for the reduced CyPA-dependence mapped to a proline-rich region of NS5A. For the second group of cofactors, selection of viral mutants in cell lines with individual receptor knockdown produced escape mutants that showed general reduced dependence on all four receptors, albeit to different levels. Taken together, we believe that CoFIM screen can complement genome-wide siRNA projects to identify viral targets of cellular cofactors in the absence of small molecule compounds or prior knowledge of protein function.

DISSOCIABLE PRO-COGNITIVE CONTRIBUTIONS OF SOCIAL INTERACTION AND ENVIRONMENTAL ENRICHMENT ON COGNITIVE FLEXIBILITY IN DEVELOPING MALE RATS

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Pro-cognitive benefits of environmental enrichment provide insight into the neural substrates by which cognitive dysfunction develops. While enhancing environmental novelty and complexity during development has been demonstrated to be effective in a wide array of behavioral assays assessing cognitive functioning, the ambiguity of currently used enrichment paradigms encourages the need to identify potentially dissociable pro-cognitive contributions of enrichment components. As such, we examined the effects of two of these components—social interaction and environmental complexity—on cognitive performance in a well-validated rodent model of cognitive flexibility. We administered phencyclidine to male rats using a regimen that we have demonstrated to be reliable and effective in the production enduring deficits in cognitive flexibility. Animals experienced one of four rearing conditions where animals were socially isolated (SI) or pair-housed (PH) in either an impoverished (IE) or enriched (EE) environment. After a drug washout period, animals were tested on novel object recognition (NOR) learning and attentional set-shifting (SS) discrimination problems to assess the effects of rearing condition on behavioral impairment. Results indicate that regardless of social exposure, daily access to a running wheel in a novel and complex environment was sufficient to attenuate PCP-induced cognitive impairment in both NOR and SS procedures.

CHROMATIN REGULATORY CONTROL OF TLR7-STIMULATED INNATE IMMUNE RESPONSE

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In human cells, three meters of DNA is organized within a five micrometers nucleus. The cell is able to compensate for this length of DNA by packaging it into chromatin. This organization into chromatin, affects all DNA-templated processes. One well-characterized gene that is regulated through changes in chromatin structure is IFN beta, an inflammatory protein that is produced when cells are stimulated by viral pathogens. Such a mechanism could possibly be generalized to other genes in the inflammatory response. Pattern recognition receptors are a family of proteins essential for the innate immune response to pathogens. TLR7 is a receptor that recognizes molecular patterns associated with viral infections. We sought to investigate if TLR7 stimulation exerts its regulatory effects through changes in chromatin structure. After treating human macrophage-like cell lines with the TLR7 agonist imiquimod, chromatin was prepared to determine nuclease sensitivity as a readout for higher order chromatin structure, using an innovative application of whole genome tiling microarrays. This work provides the first insights into the chromatin regulatory control of the TLR7-mediated innate immune response. We expect that these descriptions of chromatin structure remodeling will help describe TLR7-mediated gene expression, and furthermore will provide a platform for future studies involving the regulation of chromatin in immunity and inflammation.

AURORA KINASE IPL1 COORDINATES SPINDLE POLE BODY REDUPLICATION WITH CHROMOSOME SEGREGATION IN YEAST MEIOSIS

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During meiotic interphase I, the microtubule-organizing center, called the spindle pole body (SPB) in yeast, is duplicated when chromosomes replicate. A pair of sister SPBs establishes a bipolar spindle that facilitates the segregation of homologs in meiosis I. To form two independent spindles for sister-chromatid separation in meiosis II, SPBs are reduplicated at interphase II where DNA replication is absent. Here we report that the Aurora kinase Ipl1, which protects sister-chromatid cohesion, is also required for maintaining sister-SPB cohesion in yeast meiosis. Premature loss of cohesion leads to SPB overreduplication and the formation of multipolar spindles. The Polo-like kinase Cdc5 promotes SPB separation, is necessary for SPB reduplication, and interacts antagonistically with Ipl1 at the SPB. Finally, we present evidence that meiotic cohesin plays a role in regulating SPB cohesion and reduplication. Our data suggest that a shared regulatory mechanism coordinates SPB dynamics with chromosome segregation during yeast meiosis.

POSTTRANSLATIONAL REGULATION OF CORE HISTONE PROTEINS IN HUMAN CELLS

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Histones are required by the cells to package the replicating DNA during S phase of the cell cycle. However, histone levels must be tightly regulated so as to maintain proper stoichiometry with the amount of DNA available. Thus, histone genes are mainly expressed during S phase. Until recently, histones were considered to be extremely stable proteins. Using the budding yeast as a model system, we have previously shown that the essential DNA damage checkpoint kinase Rad53 regulates histone protein levels by targeting excess histones for degradation. Since the basic regulatory mechanisms are highly conserved among eukaryotes, it is likely that a similar mechanism for the regulation of histone protein levels exists in higher organisms including humans. Chk2 is the mammalian homolog of Rad53 and it is known to be the major DNA damage checkpoint kinase along with Chk1. It is possible that like its yeast counterpart, Chk2 may be playing a role in regulating histone levels as well. We will present evidence to support the hypothesis that like budding yeast, histone levels are regulated posttranslationally in human cells. This pathway is very important in maintaining genomic integrity as excess histone dose is not only cytotoxic but can also lead to genomic instability which is a hallmark of carcinogenesis.

GAS CHROMATOGRAPHY-MASS SPECTROMETRY METABOLOMIC AND ¹³C-ISOTOPE TRACER EXPERIMENTS APPLIED TO GOLD NANOPARTICLE TRANSFECTED HEK293 CELLS

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Nanoparticles are emerging in the field of gene therapy as vehicles for the delivery of proteins and/or nucleic acid. Gold is an attractive nanoparticle for such purposes due to its ease of synthesis, FDA approval for human usage, and unique imaging potential. While nanoparticle synthesis, ligand conjugation, and ligand release have been studied, the cellular metabolic processes associated with nanoparticle transfection remain poorly understood. We performed experiments to determine the metabolic changes that occur during nanoparticle uptake using gas chromatography-mass spectrometry to establish metabolic profiles of human embryonic kidney (HEK) 293 cells pre- and post-transfection with 6 nanometer gold nanoparticles. Principal component analysis clearly distinguished between the control and transfected samples. The metabolic pathways which were most affected in terms of metabolite concentrations were determined using the loadings plot and further investigated by observing the label accumulation of their corresponding metabolites following incubation with U-¹³C-glucose and 1-¹³C-glucose to assess the relative flux through these pathways. This study shows that significant changes to the cellular metabolome occur following uptake of gold nanoparticles and that these changes are observed in glucose metabolizing pathways.

THE PROTECTIVE ROLE OF VITAMIN B12 IN ALZHEIMER'S DISEASE

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The Alzheimer's disease (AD) is a fatal neurodegenerative disorder that afflicts millions of people world-wide. A hallmark, and a putative cause, of AD is the self-association of the amyloid- β ($A\beta$) peptide that leads to formation of toxic $A\beta$ species and insoluble plaques within AD patients' brains. Vitamin B12 (B12) has been postulated to play an important role in the pathology of AD, but the mechanism of this involvement has not been elucidated. This study tested a hypothesis that a direct binding between B12 and $A\beta$ impacts the $A\beta$ peptide self-association, affecting the Alzheimer's disease pathology. A biophysical approach utilizing surface plasmon resonance (SPR) and fluorescence was used to characterize the interaction of $A\beta$ with B12. The protective role of B12 was tested in hippocampal tissue culture, demonstrating physiological relevance and efficacy of B12 in alleviating the neurotoxicity inflicted by $A\beta$. The specific questions asked were: (1) What are the characteristics of the B12 interaction with the $A\beta$ peptide? (2) Does the B12 binding to a monomeric $A\beta$ prevent formation of toxic $A\beta$ species? Conversely, can B12 dissociate the $A\beta$ fiber and shift the $A\beta$ species equilibrium towards the non-toxic, monomeric $A\beta$ form? and (3) Does B12 alleviate the $A\beta$ neurotoxic effects in the hippocampal neurons? This study characterized the neuroprotective B12/ $A\beta$ interaction on a molecular level and provided insights into potential B12-based therapeutics for Alzheimer's disease.

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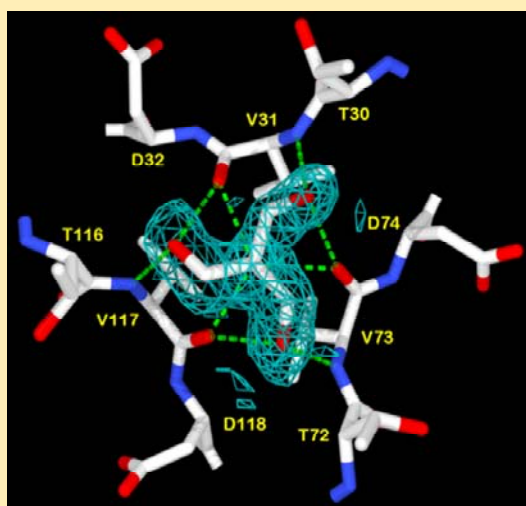
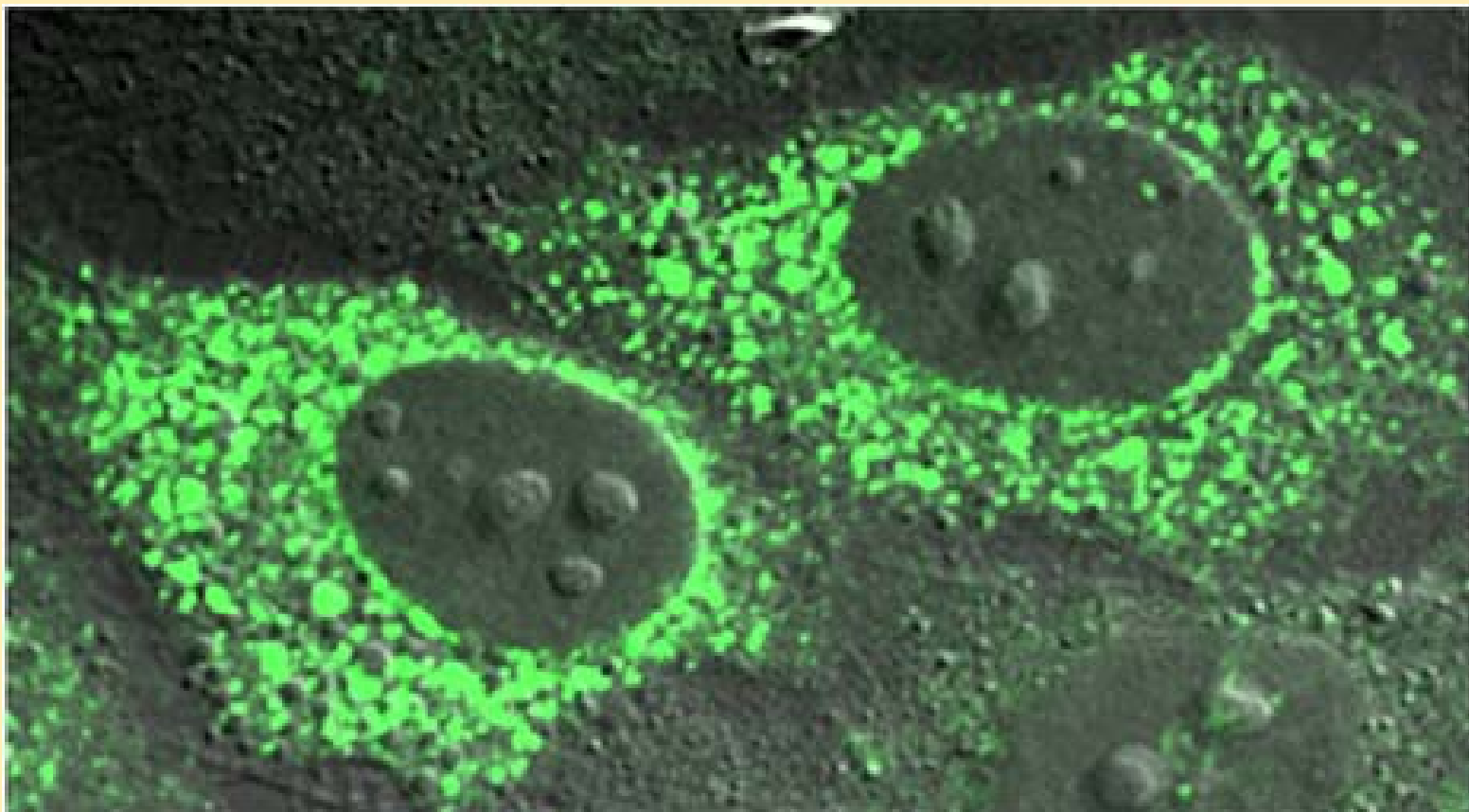
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