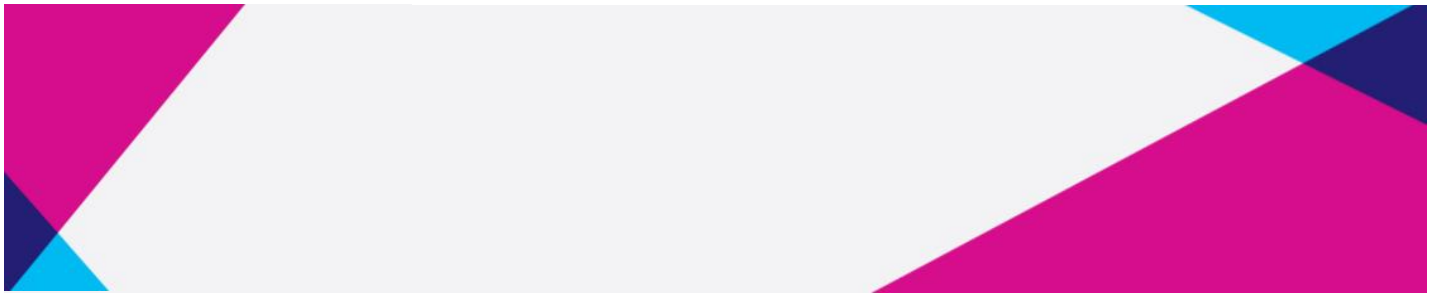
Icahn School of Medicine at Mount Sinai

Graduate School of Biomedical Sciences

UNDERGRADUATE RESEARCH SYMPOSIUM in Biological, Chemical, Structural, and Computational Sciences

September 17, 2016

SYMPOSIUM PROGRAM



Event Schedule

9:00 am (ongoing)
Symposium Check-In

10:00 am – 10:15 am
Opening Remarks & Welcome Address
(Deans of Graduate School & Organizing Committee)

10:15 am – 11:30 am
Morning Poster Session*
(Groups A, C, E)

11:30 am – 12:45 pm
Plenary Talks
(Current students of the Graduate School of Biomedical Sciences)

12:45 pm – 1:15 pm
Lunch
(Provided by the Graduate School of Biomedical Sciences)

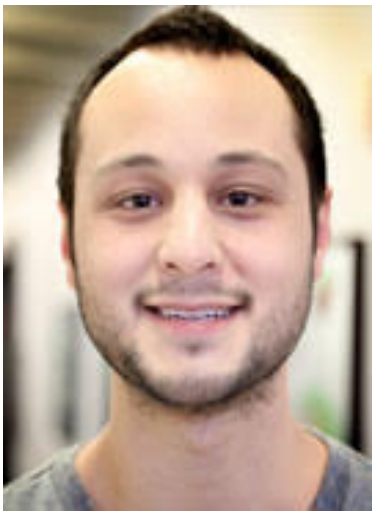
1:15 pm – 2:30 pm
Afternoon Poster Session*
(Groups B, D, F)

2:30 pm – 3:30 pm
Data Blitz
(Current students of the Graduate School of Biomedical Sciences)

3:30 pm – 4:00 pm
Award Presentations and Closing Remarks

Plenary Lecture Speakers

Ted Pak
Y5 MD/PhD Candidate
Biomedical Sciences

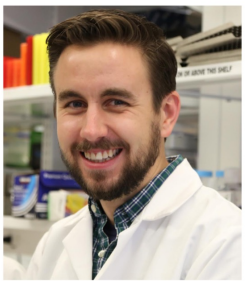


Efrain Riberio
Y4 MD/PhD Candidate
Neuroscience Neuroscience

Keith Sigel, MD, MPH
Assistant Professor of Medicine
PhD in Clinical Research

Data Blitz Speakers

Jennie Altman
Y2 PhD Candidate
Microbiology



Evan Bardot
Y3 PhD Candidate
Developmental Biology

Kamilah Castro
Y4 PhD Candidate
Neuroscience

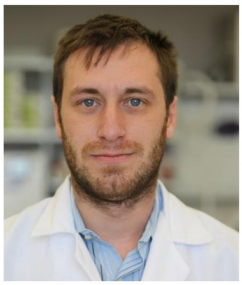
Neil Dhawan, MS, PhD
Dual Therapeutics
Co-Founder

Jim Duehr
Y3 PhD Candidate
Microbiology

Helya Ghaffari
Y5 MD/PhD Candidate
Oncological Sciences

Jennifer Hamilton
Y4 PhD Candidate
Microbiology

Joshua Mayourian
Y3 MD/PhD Candidate
Biotechnology



Michael Miller, PhD
Y7 MD/PhD Candidate
Neuroscience

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**equal contribution*

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1. REMOVING SPURIOUS ASSOCIATIONS IN MICROBIOME ANALYSIS

Vivek Ramanan[1,2], Rajita Menon[3], Kirill Korolev[3]

[1]Department of Biology and Computer Science, Swarthmore College, 500 College Avenue, Swarthmore PA, 19081.

[2]Boston University BRITE Bioinformatics REU Program, Summer 2016, 24 Cummington Mall, Boston MA 02215

[3]Department of Physics and Bioinformatics, Boston University, 590 Commonwealth Avenue, Boston MA 02215.

Microbes play many essential roles in the human body, ranging from digestion to protection from harmful antigens. Imbalances in bacterial abundances are associated with many diseases from inflammatory bowel disease to cancer. Recently, several large-scale efforts have been undertaken to characterize microbial dysbiosis and detect disease-causing taxa. Current statistical methods however do not account for microbial interactions and are likely to produce spurious correlations. Indeed, if microbe A suppresses microbe B, then changes in A's abundance due to disease will affect B's abundance even if B is not directly involved in the disease. To circumvent this problem, we developed an inference approach based on maximum entropy models in statistical physics. In synthetic data, our method successfully identifies direct associations with the disease and removes spurious associations due to microbial interactions. We applied this novel analytical tool to RISK, the largest pediatric cohort (700 samples) of controls and patients with Crohn's disease. The number of detected associations was reduced by about ten fold, but the strength of associations increased. Thus, our approach can help clinicians sieve through the large number of taxa correlated with Crohn's disease by narrowing the search for disease-causing microbes.

Acknowledgement Statement:

This work was funded in part by a startup fund from Boston University to Kirill Korolev and by the Boston University BRITE Bioinformatics REU Program (Director Gary Benson).

2. DEVELOPMENT OF MICROFLUIDIC SENSORS FOR MONOCLONAL ANTIBODY DETECTION AND PURIFICATION

Natalija Tasovac, Mengxin He, Mehnaz Mursalat and Sagnik Basuray
Otto H. York Department of Chemical Engineering, Newark College of Engineering, New Jersey Institute of Technology, Newark, New Jersey 07102

Due to the extraordinary binding affinity and specificity, there is the vast usage of monoclonal antibodies (mAbs) for the treatment of multiple diseases including cancer (no aggressive chemotherapy), rheumatoid arthritis, and cardiovascular diseases. This demands the improvement of current purification and detection techniques of mAbs. A new microfluidic lab-on-a-chip device can be introduced for this purpose which is quick, simple, reliable and cost-effective and sensitive to a wide range of molecules and can achieve lower limits of detection.

Two devices are fabricated: Device 1 – this uses functionalized carbon nanotubes (CNTs), Device 2 – this uses functionalized polycarbonate membrane (POC).

Device 1 – The CNT device has interdigitated gold electrodes that use dielectrophoresis to trap CNTs with functionalized antigen on the surface. At lower flow rates, the mAbs bind with the CNT-antigen complex while the cell debris and other impurities get washed away. Following this mAbs filtration step, increased flow rate which translates into higher shear force will be used to strip the weakly bonded mAbs from the CNT-antigen complex. Thus this modified microfluidic affinity based separation protocol can be used to obtain purified mAbs.

Device 2 – For the second device, a gold coated POC membrane placed between interdigitated gold electrodes is functionalized by EDH-NHS chemistry which creates a platform of thiols to react with mAbs; and dielectrophoresis enhances their binding at low flow rates. Due to developed gold electrodes and increased localized dielectrophoresis force the amount of mAbs collected is higher compared to traditional methods. A biosensor usage as a sandwich ELISA is also shown with higher sensitivity and selectivity than using classical plating methods.

The antibody – antigen links formed in both device is characterized by electrochemical impedance spectroscopy (EIS) through observation of changes in EIS signal or by enzyme-linked immunosorbent assay (ELISA) which uses color/fluorescent changes to identify the substance.

3. TOWARDS IMPROVED DRUG DELIVERY VECHICLES THROUGH PROTIEN ENCAPSULATION WITHIN HYBRID NANOPARTICLES

Suiying Huang [1], Mark Payawal [1], Uri Samuni [2]
[1]Department of Chemistry and Biochemistry, Queens College, City University of New York, Flushing, NY, 11367
[2]Department of Chemistry and Biochemistry, Queens College, City University of New York, Flushing, NY, 11367

Proteins/enzymes can be encapsulated within silica based sol-gel matrices and remain structurally and functionally intact. Furthermore, the solgel matrix environment can enhance the stability of the encapsulated proteins. For example Hemoglobin or Myoglobin encapsulated within sol-gel matrices retain reversible oxygen binding even under conditions of high temperature. Crosslinked polymeric sol-gel based nanoparticles (nanogels) with an interior network for incorporation and protection of biomolecules, offer unique advantages for polymer based drug delivery systems. We aim to synthesize sol-gel based hybrid nanogels by means of silicification reactions including the use of polycationic peptides, like polylysine, as capping agents. Transmission Electron Microscopy, dynamic light scattering and Zeta potential were utilized to characterize the nanogels size distribution, shape and aggregation. We are exploring how changes in the conditions of the synthesis and primarily of the capping agents used may allow better control on the properties of the resultant nanogels.

Acknowledgement:
This research was supported by PSC-CUNY TRAD-A 69513-00 47 and UR/ME Research Award, Queens College and the Core Facility for Imaging, Cellular & Molecular Biology at Queens College.

4. ORGAN-ON-CHIP: MICROFLUIDIC IN-VITRO BLOOD-BRAIN BARRIER MODEL

Victoria Harbour[1], Nikki Rodriguez[1], Bhuvana Mohanlal[1], Sagnik Basuray[1]
[1]Department of Chemical, Biological & Pharmaceutical Engineering, New Jersey Institute of Technology, 323 Dr Martin Luther King Jr Blvd, Newark, NJ 07102

Organ-on-chip devices are an emerging class of *in vitro* models that combine microfabrication and spectroscopic techniques with cell culture to study organ physiology. We have developed an organ-on-chip model of the blood-brain barrier (BBB), the μTRANS chip, that analyzes real-time BBB dynamics in a controlled microenvironment. The μTRANS chip incorporates human brain endothelial cells (hBECs), astrocytes and neuronal cell lines to mimic the molecular selectivity of the BBB as a component of the neurovascular unit (NVU). The device contains a pair of 30nm gold deposited, interdigitated electrodes that form the top and bottom layers of the μTRANS chip. Each electrode is flush to a 500μm by 1800μm microfluidic channel, laser cut from diagnostic PMMA tape. The top and bottom electrode/channel pairs sandwich a pre-coated Transwell ® membrane seeded on one side with hBECs and on the other with neurons/astrocytes, respectively forming the luminal and basal sides of the NVU. The microfluidic channels give rise to flow generated shear across the hBECs, astrocytes and neurons. Flow generated shear is a key component of the *in vivo* BBB environment.

The fabricated device is characterized using optical imaging, permeability assays, such as fluorescence microscopy, and electrical impedance spectroscopy (EIS). Optical imaging confirms hBEC adhesion and confluency. Fluorescence microscopy is used to signify presence of key BBB proteins and membrane permeability. EIS is used to measure resistance and capacitance across the seeded hBEC membrane. A resistance value of ~1000Ω indicates a functional BBB. EIS measurements are advantageous because they provide real-time capacitance and resistance measurements of transient BBB activities. Additionally, EIS capacitance data distinguishes transcellular resistance from paracellular resistance. This novel approach provides insight to transcellular BBB kinetics as well as paracellular (tight junction) kinetics. In future, the μTRANS chip will be used to characterize the interaction and mechanistic pathway for drug-loaded nanoparticles.

Wholehearted thanks to my mentors Dr. Sagnik Basuray and Dr. Bhuvana Mohanlal as well as the generosity of NJIT's Provost grant funding whose support and guidance have made my work possible.

5. PNP PINCER LIGAND COMPLEXES OF VANADIUM

Noriyo Onishi[1], Daniel Unruh[2], Michael Findlater[2], Colin D. Abernethy[1]
[1]Department of Chemistry, Sarah Lawrence College, 1 Mead Way Bronxville, NY 10708
[2]Department of Chemistry & Biochemistry, Texas Tech University, 2500 Broadway Lubbock, Texas 79409

PNP (2,6-bis(di-*tert*-butylphosphinomethyl)pyridine) is a commonly used pincer ligand. Pincer ligands are a class of tridentate ligands that have three electron-donor sites that can bond to a metal atom or ion. In PNP, these are two phosphorous atoms and one nitrogen atom. Pincer ligands are widely employed in the design of transition metal-based catalysis. However, to-date, PNP-vanadium complexes have not been reported in literature.

Herein, we report the first structurally characterized PNP-vanadium complex, which was formed by the reaction of PNP with $VCl_3(thf)_3$ in tetrahydrofuran. The structure of this complex will be discussed and compared with other vanadium (III) complexes containing similar pincer ligands.

6. IRON CYCLING IN A STIMULATED EUROPEAN OCEAN

Jovan Mirkovic, Dr. Robin Schneider
Department of Chemistry, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439

The European ocean is considered a top candidate for a second source of life because of the abundant salts and organic materials found on its surface. The Galileo Spacecraft previously identified hydrogen peroxide and iron (III) concentrations, which are large enough to produce a redox cycle that could support primitive life. The redox reaction between hydrogen peroxide and iron (III) is performed either by hydrogen peroxide dependent microbes or geothermal processes in the deep ocean. We created an aqueous system analogous to that of the European ocean in an Erlenmeyer flask filled with artificial seawater and iron while pumping in hydrogen peroxide at a known rate of 60nM per second. At the same rate, we collected an outflow solution containing certain concentrations of hydrogen peroxide and oxidized iron. Understanding the kinetic mechanism behind the redox reaction that could host life on Europa allows us to better understand the possible microbial community and their significance to the hydrogen peroxide cycling in the European ocean.

7. CUED FEAR MEMORY RETRIEVAL (IN)ACCURACY OVER TIME

Gabrielle A Pollack[1] and Hadley C Bergstrom[2]

[1]Program in Neuroscience and Behavior, Vassar College, 124 Raymond Ave, Poughkeepsie, New York, 12604.

[2]Department of Psychological Science; Program in Neuroscience and Behavior, Vassar College, 124 Raymond Ave, Poughkeepsie, New York, 12604.

The ability to discriminate and generalize fear conditioned stimuli is adaptive in a continuously changing external environment. The passage of time is one factor that influences memory generalization. Fear conditioned contextual stimuli are well-known to generalize over time. Surprisingly little is known about the accuracy of fear conditioned auditory stimuli with the passage of time. Further, the brain-wide neuronal activity patterns underlying cued fear memory performance at very long time retention intervals following learning is unknown. The present study sought to establish an auditory fear conditioned stimulus discrimination gradient at 1-day (recent) and 30-days (remote) following learning. Adult male C57BL/6 mice were fear conditioned with three auditory conditioned stimuli (CS; 75 dB, 5 kHz, 20 s) that each co-terminated with a foot shock unconditioned stimulus (US; 0.5 s, 0.6 mA) in context A. One day after fear conditioning, mice were assigned to one of five different tone frequencies (2, 3, 5, 8, or 12 kHz; 75 dB, 20s), and played the tone in a novel context (context B). 30 days later, the mice were placed into context B again and replayed the tone. 60 min following the CS test, brains were processed for Arc/Arg 3.1 immunohistochemistry. Results showed mice discriminated most auditory frequencies (all but 8 kHz) at the recent frame (24 hrs). When the stimulus was presented again 30 days later, mice were still able to discriminate the stimuli, suggesting a high degree of accuracy for fear memory retrieval over time. In a second experiment, the tone (2, 3 and 5 kHz) was not played at a recent time point but presented 30 days later. Results showed a flattening of the generalization gradient, indicating a recent tone cue improves remote stimulus discrimination. Brain-wide Arc/Arg 3.1 mapping is ongoing.

Acknowledgements: We thank the Undergraduate Research Summer Institute (URSI) at Vassar College for funding this research.

8. EFFECTS OF MILD SIMULATED BLUR AND CONTRAST REDUCTION ON THE PERCEPTION OF ORIENTED PATTERNS

Monika Devi[1], Zena Dakmak[2], Byron Johnson[2], Deborah Watman[2], Bryan Richgruber[2], Silvia Calderon[2], Ayesha Shahab[2], Kimberly Paredes[2], and Andrea Li[2]

[1]Department of History, Brooklyn College, 2900 Bedford Avenue, Brooklyn, NY 11210

[2]Department of Psychology, Queens College CUNY, 65-30 Kissena Blvd, Flushing, Queens, NY 11367

Visual impairment is reduced vision that results from aging, disease, or injury that cannot be corrected by corrective lenses or surgery. We aim to understand how visual impairment affects the way individuals visually perceive objects and how it thus affects interaction with the environment. The brain is well equipped to perceive the orientation, or tilt, of object boundaries. We explore the effects of simulated visual impairment conditions on tilt perception in individuals with normal or corrected-to-normal vision. Gaussian blur and reduced contrast are applied to oriented Gabor stimuli to measure tilt threshold, the smallest amount of tilt that is still detectable, at 1.5 and 4.5 cpd, around both vertical and horizontal orientations. Results suggest that mild contrast reduction, which reduces visual acuity to 20/40, significantly decreases orientation sensitivity for low and high spatial frequency stimuli, but equivalently mild levels of blur have no effect on orientation perception. The lack of effect of mild blur is likely due to the fact that the blur we implemented largely filters out frequencies greater than 4.5 cpd, thus the blurred stimuli are visually similar to the unimpaired stimuli. These results suggest that any visual impairment, such as cataracts, that results in the reduction of visual acuity to 20/40 (which is still sufficient to obtain a driver's license) may affect the perception of the orientation of object boundaries and thus might affect the perception of and interaction with objects. Plans to test the perception of more complex stimuli include measuring the effects of similarly mild visual impairment on 2-D shape discrimination (e.g. squares vs. circles) and orientation thresholds to better understand everyday object recognition for the visually impaired.

Acknowledgements

We would like to thank Macaulay Honors College and the HMNS program at Queens College, Mathworks, and Cambridge Research Systems for helping to make this research possible. This work was supported by a grant from the City of New York PSC-CUNY Research Award Program (PSC- 68197-00 46) to Dr. Li.

9. OPTOGENETIC DISSECTION OF BDPP-MEDIATED RESILIENCE AGAINST SLEEP DEPRIVATION INDUCED COGNITIVE IMPAIRMENT

Justin S. Brathwaite[1], Chad C. Smith[1], Giulio M. Pasinetti[1,2,3]

[1]Department of Neurology, [2]Department of Psychiatry, Icahn School of Medicine, One Gustave Levy Place, Box 1137 New York, NY 10029

[3]Geriatric Research Education Clinical Center at James, J. Peters VA Medical Center, 130 W Kingsbridge Rd, Bronx, NY 10468 Bronx, NY

Sleep deprivation (SD) adversely impacts neurocognitive performance such as attention, memory, and learning. SD is reported to reduce CamKII/CREB and other signaling pathways and downregulate expression of immediate early genes (IEGs) including c-fos, which play important roles in plasticity, learning, and memory. We have found that oral administration of Bioactive Dietary Polyphenol Preparation (BDPP) promotes resilience to SD-induced cognitive deficits through increased CamKII/CREB signaling and upregulation of *c-fos.* We aim to determine mechanistically how BDPP confers resilience to SD in neurons activated by behavioral testing and confirm the role that *c-fos* plays in sleep deprivation induced cognitive deficits.

We will utilize the c-fos-tTA/TRE-ChR2 optogenetics system which directly couples the *c-fos* promoter to the tetracycline transactivator tTA. This novel system has recently been used to develop false memories in the contextual fear conditioning (CFC) paradigm. In the absence of Dox, training-induced neuronal activity selectively labels *c-fos*-expressing neurons in the dentate gyrus with ChR2-mCherry, allowing for reactivation by light stimulation during testing. The use of ChR2 allows for *c-fos*-expressing neurons to respond to training experiences and for recapitulation of learned behavior. *C-fos* promoter activity should be decreased by SD, causing fewer neurons to be labeled with ChR2; conversely, BDPP-induced resilience should improve performance in behavioral testing reflected by increased recapitulation of learned behavior. ChR2 activation in the CFC probe trial will induce freezing/fear behavior in a context not previously associated with footshock, but freezing behavior will occur less frequently in SD-animals as opposed to non-SD and SD + BDPP diet. Immunohistology will identify signaling pathways and effector proteins upregulated by BDPP in memory bearing neurons. Due to the prevalence of SD in our society, a mechanistic understanding of SD-induced cognitive impairment is of great importance.

Botannical Dietary Supplement Research Center, Diversity Training Supplement to P50 AT008661-01, National Center for Complementary and Integrative Health NCCIH

10. TESTING THE EFFECTS OF CG85 BINDING ON A CHIMERIC ALPHA-GALACTOSIDASE DIMER

Sachita Ganesa[1], Derrick Deming[2], Scott Garman[1,2]
[1]Department of Biochemistry & Molecular Biology, University of Massachusetts Amherst, 710 N Pleasant Street, Amherst, MA 01545
[2]Molecular & Cell Biology Graduate Program, University of Massachusetts Amherst, 710 N Pleasant Street, Amherst, MA 01545

Mutations in the *GLA* gene, which encodes the lysosomal enzyme α-galactosidase (α-GAL), lead to a build up of the substrate globotriaosylceramide (GB3) in affected tissues, ultimately resulting in Fabry disease. Mutations in the *NAGA* gene, which encodes the lysosomal enzyme α-N-acetylgalactosaminidase (α-NAGAL), result in Schindler/Kanzaki disease. These lysosomal storage diseases lead to progressive deterioration of organs, including the liver and kidney, and eventually result in death. Because lysosomal storage diseases are caused by defects in single proteins, they are in principle repairable and thus active topics of clinical research. To date, enzyme replacement therapy, pharmacological chaperone therapy, substrate reduction therapy, and gene therapy have been approved or tested. Pharmacological chaperones (PC) stabilize their target proteins to increase the amount of enzyme activity in the lysosome.

Previously, we have engineered the human α-GAL dimer to contain two α-NAGAL-like active sites (α-GAL$^{E203S/L206A}$). Extending from this result, we have designed a chimeric version of the α-GAL dimer, with one α-GAL active site and one α-NAGAL active site. We hypothesize that the chimeric molecule can be chaperoned in one active site, increasing the activity of the other active site of the heterodimer. We have designed the chimeric molecule to have two distinct affinity tags, allowing purification by tandem affinity chromatography, using nickel and streptavidin columns. Then, we will test our chaperoning hypothesis, using the PC 2-acetamido-1,2-dideoxy-D-*galacto*nojirimycin (DGJNAc). We predict that binding of chaperone to one half of the chimeric molecule will increase enzymatic activity in the other active site, 50Å away.

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11. ROLE OF *rab-10* AND *rme-1* IN AUTOPHAGY

Natalie Rosario[1], Mateusz Wysocki[1] , N. J. Palmisano[1], B. Grant, and A. Meléndez[2]
[1]Department of Biology, The Graduate Center, City University of New York, New York, NY; [2]Biology Department, Queens College, CUNY, Flushing, NY; [3]Department of Molecular Biology and Biochemistry, Rutgers University, Piscataway, NJ

Autophagy is an evolutionarily conserved degradative process, which involves the formation of a double-membrane vesicle called the autophagosome that engulfs protein aggregates and/or organelles. Endocytosis mediates the sorting and transport of cargo to specific areas of the cell, through the formation of intracellular vesicles termed endosomes. Endocytosis and autophagy are important to maintain cellular homeostasis, and crosstalk between them has been shown to exist. However, the extent to which endocytic proteins function in autophagy, and how they contribute to autophagy is not fully understood.

To investigate further the connection between autophagy and endocytosis, we conducted an RNAi screen for genes that altered GFP::LGG-1 expression and blocked tissue remodeling in Insulin-like IGF-1 receptor *daf-2/IIR* mutants. *daf-2/IIR* mutants display a dauer phenotype and have an increase in autophagy, as determined by the increase in GFP::LGG-1 positive foci, the autophagy reporter. We identified RAB-10, a GTPase that regulates basolateral endocytic trafficking in *C. elegans*, as a gene required for GFP::LGG-1 positive structures in *daf-2/IIR* mutants, and we have found that RAB-10 is required for autophagy flux.

We will report on our studies to determine if the recycling endosome marker, RFP::RAB-10, and the autophagosome marker, GFP::LGG-1, colocalize under low and moderate levels of autophagy activity, as well as under disrupted autophagy conditions. ATG-9 is the only transmembrane protein involved in autophagosome biogenesis. Loss of *rab-10* increased or decreased the size of GFP::ATG-9 positive structures in *daf-2/IIR* dauer (high autophagy) or non-dauer animals (low autophagy), respectively. Additionally, we will report on the role of the endocytic recycling protein RME-1 in autophagy.

12. INVESTIGATING THE ROLE OF HISTIDINE KINASE PLEC IN ASYMMETRICAL DIVISION OF *CAULOBACTER CRESCENTUS*

Cindy Lin[1,2] and Kathleen Ryan[2]

[1]Department of Biological Sciences, St. John's University, 8000 Utopia Pkwy, Jamaica, NY 11439

[2]Department of Plant and Microbial Biology, University of California, Berkeley, 111 Koshland Hall, Berkeley, CA 94720

The division of a single cell to yield cells with distinct identities and fates is fundamental to the generation of a multi-cellular organism from a unicellular organism. However, asymmetrical division is observed not only in complex organisms, but also in the alpha-proteobacterium *Caulobacter crescentus*, providing a simplified system to study the mechanisms that govern this process. *Caulobacter* divides into two distinct daughter cells: a sessile, replication-competent stalked cell and a motile, non-replicating swarmer cell. These different cell fates are determined by the localization of distinct regulatory proteins at each pole of the *Caulobacter* predivisional cell, resulting in unequal inheritance upon division. However, the mechanisms by which these regulatory proteins interact and organize themselves to control replication, transcription, and division in the correct spatiotemporal pattern remain unclear.

We are investigating how the *Caulobacter* predivisional cell is able to mediate the conflict between two opposed signaling pathways, one that activates and one that inhibits chromosome replication. To resolve this paradox, we are studying the bifunctional histidine kinase PleC, which inhibits regulatory protein DivK to directly prevent replication. PleC may inhibit DivK by dephosphorylating it, or by acting as a kinase and sequestering phosphorylated DivK. To distinguish between these models, we constructed a *pleC* (T614A) mutant which retains kinase activity, but lacks phosphatase activity. We have begun to biochemically and morphologically characterize this mutant in comparison to wildtype *pleC* (k+ p+), PleC-F788L (k- p+), and PleC-T614R (k- p-). We expect severely compromised growth and deficient PleC developmental functions.

13. INVESTIGATING THE EFFECT OF ABT-737 ON PRO-APOPTOTIC BAX

Stephanie Crowley[1], Mark P.A. Luna-Vargas[1,3], Jerry E. Chipuk[1, 2, 3, 4, 5]
[1] Department of Oncological Sciences, [2] Department of Dermatology, [3] The Tisch Cancer Institute, [4] Graduate School of Biomedical Sciences, [5] The Diabetes, Obesity, and Metabolism Institute
Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029

Cancer cells often circumvent apoptosis to maintain survival and resist chemotherapeutics. BH3-mimetics (e.g., ABT-737) are a valuable class of drugs designed to block anti-apoptotic BCL-2 family function (e.g., BCL-2 and BCL-xL). However, these targeted therapies show varying efficacy in clinical trials. ABT-737 was designed to target the hydrophobic groove of BCL-2 and BCL-xL, but it may also bind to the pro-apoptotic effector BAX to block apoptosis. Previous lab studies have shown that ABT-737 directly binds BAX to inhibit mitochondrial outer membrane permeabilization (MOMP), the key event in apoptotic initiation. We hypothesize that ABT-737 binds to BAX in its conserved hydrophobic groove containing alpha helices 2, 3, 4, and 5. An *in silico* molecular modeling simulation (SwissDock) was used to identify 14 residues in BAX that are key for ABT-737 binding. The goal of this work is to utilize structural and biochemical approaches to identify and examine mutations in the BAX hydrophobic groove that disrupt ABT-737 binding. Over the course of the summer, these BAX mutants were cloned, expressed in BL21(DE3) cells, and examined for disruption of ABT-737 binding and MOMP activity. The conclusions of this study will be used to edit the current repertoire of BH3-mimetics in order to improve their clinical efficacy.

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14. THE STERIC CORRELATION WITH AMYLIN

Shukantha Zubayer[1], Aileena Khan[1], Dr. Adam Profit[2]
Department of Biology, York College, City University of New York, 94-20 Guy R Brewer Blvd, Jamaica, NY 11451
Department of Chemistry, York College, City University of New York, 94-20 Guy R Brewer Blvd, Jamaica, NY 11451

Human islet amyloid polypeptide (hIAPP), also known as amylin, is a 37 residue peptide hormone that is stored and co-secreted with insulin. hIAPP plays a pivotal role in type 2 diabetes (adult onset diabetes or diabetes mellitus) and is the major component of amyloid deposits found in the pancreas of over 95% of patients afflicted with the disease. The self-assembly of hIAPP and the formation of amyloid is linked to the death of insulin producing beta cells and hyperglycemia. One potential avenue of therapeutic intervention is the development of amyloid inhibitors that prevent the self-assembly of hIAPP. The 22-29 region of hIAPP, which corresponds to the sequence NFGAILSS, is known as the “amyloidogenic core” and has been demonstrated to self-assemble on its own. Our laboratory is pursuing an electrostatic repulsion approach to the development of inhibitors and modulators of hIAPP self-assembly. Due to the aromaticity that phenylalanine possesses in the 23rd region of hiAPP, it creates a hydrophobic environment, which can help promote the pi electrons to interact with electron donating groups, EDG, in amylin to create further stability of these aggregations through resonance and inductive effects. It is hypothesized that introduction of a series of charged amino acids to the N- or C-terminal of the NFGAILSS sequence may produce compounds capable of arresting amylin aggregation. These compounds will be prepared by solid phase peptide synthesis methods and their ability to inhibit hIAPP aggregation characterized using kinetic aggregation assays, vibrational spectroscopy and transmission electron microscopy. Manipulating the sequence of NFGAILSS with the addition of charged amino acids in the terminals will be the focus in future experimentation to determine the role sterics play in the aggregative properties of amylin.

15. EFFECT OF MICRORNA DOSAGE IN THE GENE REGULATION OF THE MeCP2 PROTEIN

Andres Villegas[1], Heather McGowan[1], and Zhiping Pang[2]
[1] Department of Cell Biology & Neuroscience, Rutgers, State University of NJ, Piscataway, NJ,
[2]Rutgers Robert Wood Johnson Medical School, The Child Health Institute of NJ, New Brunswick, NJ 08901

MicroRNAs (miRNAs), small non-coding RNAs, function primarily by patrolling the cytosol in search for complementary messenger RNA (mRNA) targets. In doing so, miRNAs are able to establish mRNA threshold levels and thereby allow fine-tuning of gene expression. Pathology can result when miRNAs are expressed at abnormal levels. In order to elucidate the effects of miRNA dosage on the developing and maturing Central Nervous System (CNS), a model of the endogenous aberrant miRNA expression is needed. Such a model is provided by Trisomy 21 (T21), whereby afflicted inherit three copies of chromosome 21 (HSA21) and as a result individuals display ranging cognitive deficits. Of special note is the methyl-CpG-binding protein 2 (MeCP2) that has been implicated to be vital for synaptogenesis and plasticity in the developing brain. In particular, converging evidence point to the synapse as a focal point for the cognitive disability phenotype seen in T21. We propose that since certain miRNAs, overexpressed by the extra HSA21, target the MeCP2 mRNA its expression level should be decreased accordingly, and provide a novel explanation for the cognitive abnormalities seen in T21 via synaptic dysfunction. My role in this ongoing investigation is to facilitate experimentation by investigating MeCP2 expression level in induced pluripotent stem cells (iPSC) and Neuronal coverslips by using basic cell culture techniques, immunostaining, western blotting, and luciferase analysis. Preliminary data indicates that MeCP2 expression is indeed downregulated in overexpressed iPS cells further augmenting the known literature on the causes and possible treatment for T21.

16. INVESTIGATING INTERACTIONS BETWEEN IFI16 AND CGAS IN RESPONSE TO DNA

Jessica L. Shannon[1], Tyler J. Dorrity[1], Uma Kantheti[1], Molly S. Murphy[1], Constantinos J. Bacas[1], Brianne R. Barker[1]

[1]Department of Biology, Drew University, 36 Madison Avenue, Madison, NJ 07940

Pattern recognition is a vital component of the innate immune system, allowing infected cells to sense pathogen invasion and induce an inflammatory response. Pattern recognition receptors that sense DNA have been shown to play an important role in responses to DNA viruses and retroviruses. Two DNA sensors, IFI16 and cGAS, have been implicated in the inflammatory response to retroviral DNA. IFI16, a member of the ALR gene family, is localized in the nucleus and has been shown to be necessary for interferon production and pyroptosis following HIV infection. cGAS is a cytosolic enzyme that produces the small molecule cGAMP as a second messenger to lead to interferon production following the detection of HIV DNA. cGAS has been shown to associate with a binding partner, PQBP1, which is also necessary for the interferon response to HIV DNA. Much of the literature in the field indicates that cGAS is the predominant pathway in DNA sensing, and some have suggested that ALRs may not play a major role in this pathway. Given the similarities in the data on IFI16 and cGAS in DNA sensing and the overlap in many of the downstream signaling molecules in these pathways, we hypothesize that IFI16 and cGAS are both members of a single signaling cascade.

This hypothesis prompted the present study to investigate the interactions between DNA sensors. Using co-immunoprecipitation and western blotting, interactions between members in this pathway were investigated following stimulation with DNA. In addition, cytokine production and cell death in response to DNA stimulation was investigated in cells deficient in members of this signaling pathway. Our results indicate that there are interactions between members of the IFI16 and cGAS pathways, which challenges the two currently accepted pathways and indicates that ALRs do play a role in interferon production in response to DNA.

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17. REGULATION OF THE CLASS II TRANSACTIVATOR BY 14-3-3β

Hagerah Malik[1], Drew Cressman[1]
[1]Department of Biology, Sarah Lawrence College, 1 Mead Way, Bronxville, NY 10708

The Class II Transactivator (CIITA) is an important transcription factor of Major Histocompatibility II (MHC II) genes. Defects in CIITA, as occur in bare lymphocyte syndrome, lead to the loss of MHC II expression and subsequent inability to activate an immune response. Accordingly, CIITA has often been termed the master switch of the immune system. Its underactivation results in immunodeficiencies whereas its overactivation may lead to autoimmune disorders. Therefore, the activity of CIITA must be tightly regulated through multiple mechanisms including phosphorylation and ubiquitination to ensure proper levels of activation.

We identified a sequence within CIITA from amino acids 283 to 289 that matches a consensus 14-3-3 binding site motif: RxxxpTxP. We decided to explore the effects of 14-3-3β on CIITA. CIITA co-transfected with increasing amounts of 14-3-3β showed a steady decrease in activity, increasing cytoplasmic localization, and decreased stability. We created seven different mutants of the binding site and performed a similar series of experiments. Compared to wild type CIITA, the mutants show lower activity levels and higher cytoplasmic localization. Co-transfection of the mutants with 14-3-3β resulted in decreased activity, increased nuclear localization, and more stability.

We hypothesize that 14-3-3β is regulating CIITA by scaffolding it to a cellular factor, leading to post translational modifications and thus altering transactivation potential and localization. Much work remains to be done to completely elucidate the complexities of the interaction between CIITA and 14-3-3β.

18. DIFFERENT SEROTYPES OF DENGUE AS WELL AS THEIR NS4A PROTEINS PROTECT MDCK BY UPREGULATING AUTOPHAGY THROUGH MULITPLE PATHWAYS

J Landazuri Vinueza, S Ghosh Roy, N Zali, E Datan , A Ramnauth, R A Lockshin, Z Zakeri

Department of Biology, Queens College and Graduate Center of the City University of New York, Flushing, New York 11367

Dengue is the most potent flavivirus and is capable of infecting 40% of the global population. In vitro studies reveal that the virus exerts differential effect on the survival/death pathways in different cell types. In case of Dengue, we have shown that the whole virus (Dengue-induced autophagy, virus replication and protection from cell death require ER stress pathway activation Cell Death Dis. 2016 Mar 3;7:e2127) as well as the NS4A viral protein (present study) trigger autophagy in canine kidney (MDCK) cells through an ATM-dependent mechanism. This enhances virus replication and also protects the infected cells against toxins and other agents. This is in stark contrast to several neuronal and immune cells that undergo apoptotic cell death (World J Biol Chem. 2014 May 26;5(2):93-105ref: Regulation of cell survival and death during Flavivirus infections). In the present study, we looked at the four different serotypes known to affect humans (DEN1, 2, 3, 4) and found that the ability to protect cells is conserved among them. We also transfected/overexpressed NS4A from all the serotypes in MDCK and recorded similar observations. Flaviviruses often exhibit persistence following the acute phase of infection. Here we report that dengue persistence can be modeled in vitro, with traces of viral RNA, protein and mature virions found in MDCK after 6 weeks of infection. In a different cell line (VERO), we report the persistent infection of DEN 2,3,4 for up to one week after infection. Since the homology among the NS4A is fairly high (~72%), our findings can contribute to a pan- Dengue therapy that can override the infamous antigenic sin/antibody dependent enhancement associated with multiple infections.

19. BLAST EXPOSURE INDUCES CEREBRAL VASCULAR DEGENERATION DEVOID OF GENERALIZED INFLAMMATION IN A RAT MODEL OF mTBI

Heidi Sosa[1,2,4,10], Danielle C. Vargas[1,2,4], Courtney J. Searcy[1,2,4], Georgina Perez Garcia[2,3,8], Rita De Gasperi[2,4,8], William Janssen[6,8], Patrick R. Hof[6,7,8], Stephen T. Ahlers[9], Gregory A. Elder[3,4,5,8], Miguel A. Gama Sosa[2,4,8]

[1]Northeast Regional Alliance (NERA) MedPrep Program, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Research & Development and [3]Neurology Services, James J. Peters VA Medical Center, Bronx, NY, 10468; Departments of [4]Psychiatry, [5]Neurology, [6]Neuroscience and [7]Geriatrics, Icahn School of Medicine at Mount Sinai, New York, NY, 10029; [8] Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, [9]Department of Neurotrauma, Operational and Undersea Medicine Directorate, Naval Medical Research Center, Silver Spring, MD 20910 and [10]Columbia University, New York, NY, 10027

Mild traumatic brain injury (mTBI) is a common occurrence in the war theaters of Iraq and Afghanistan. Blast-induced mTBI has been associated with chronic neurological and psychiatric dysfunctions linked to post-traumatic stress disorder (PTSD) including memory, behavioral, and cognitive impairments.

In previous studies using a rat model of blast-induced mTBI, we found focal lesions including tissue tears that followed the course of penetrating cortical vessels as well as vascular degenerative processes in the brains of blast-exposed animals. The aims of the present study are to determine in a rat model whether blast exposures trigger generalized brain inflammation (gliosis and astrocytosis) as well as abnormalities in the blood. Brains of 74.5 kPa blast-exposed (4 months post-exposure) and control rats were analyzed by immunohistochemistry (IHC) using specific antibodies against microglia (Iba1) and activated astrocytes (GFAP).

Stereological analyses of $Iba1^+$ microglia in the prelimbic cortex and hippocampus showed no significant differences between control and blasted rats. Similarly, no significant differences were observed in the brain distribution of GFAP immunostaining. Morphological analyses of blood smears from blast-exposed animals (72 hrs post-blast) presented amorphous, potentially occlusive material resembling platelet aggregates in addition to RBC structural abnormalities. Additionally, we could not confirm the increased expression of phosphorylated Tau (Ser_{202}) in the brains of blast-exposed animals by IHC as has been shown in other studies.

Our results indicate that the behavioral and cognitive impairments linked to blast-induced mTBI cannot be attributed to generalized chronic inflammation nor to increased phosphorylated Tau but instead are likely due to circulatory deficiencies associated with vascular degeneration. These findings provide a new lens for the development of treatments for vascular dysfunctions associated with blast-induced PTSD.

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20. THE ROLE OF DOPAMINE RECEPTOR 1 (D_1) AND *PPP1R1B*$^+$ BASOLATERAL AMYGDALAR (BLA) NEURONS IN FEAR EXTINCTION

Eudorah Vital[1]; Joshua Kim[2]; Xiangyu Zhang[2]; and Susumu Tonegawa[2], Ph.D.
[1]Department of Biological Sciences, University of Maryland, Baltimore County, Baltimore, MD 21250;
[2]Picower Institute for Learning and Memory at MIT, Cambridge, MA 02139

Fear extinction is the extinguishment of the fear response by repeated exposure to a conditioned stimulus. A key player in fear extinction is the Basolateral Amygdala (BLA). Previous fear extinction studies in the BLA demonstrated that while neurons which previously responded to fear reduce their firing, additional distinct populations of BLA neurons are also recruited during fear extinction. Fear extinction is also thought to involve dopamine signaling in the BLA, based on the expression of dopamine receptor 1 (D_1) in the BLA, and pharmacological studies which implicated D_1 in extinction (Abraham et al. 2013). In this study, we examined the role of D_1 in a distinct population of neurons recruited to the BLA during fear extinction in mice. Within the BLA there are two separate populations of neurons, *Ppp1r1b*$^+$- and *Rspo2*$^+$-expressing neurons, that define the posterior and anterior BLA, respectively. *Ppp1r1b*$^+$ neurons, mediate reward-related behaviors, whereas *Rspo2*$^+$ neurons mediate fear-related behaviors. Furthermore, these two populations have a reciprocal inhibitory relationship - when one is active the other is proportionally inactive. Here, we demonstrate that in response to fear extinction, *c-Fos* – an immediate early gene that correlates with neural activity - is expressed in the posterior BLA, which corresponds to the *Ppp1r1b*$^+$ neurons. Concurrently, *c-Fos* expression is reduced in anterior BLA, which corresponds to *Rpso2*$^+$ neurons. This suggests that the neurons that are recruited during fear extinction may include *Ppp1r1b*$^+$ neurons or a subset of them. In order to couple the function of D_1 to *Ppp1r1b*$^+$ neurons in extinction, we are currently developing genetic targeting strategies to knock down and to enhance D_1 expression in *Ppp1r1b*$^+$ neurons. This will allow us to examine the specific role of D_1 within *Ppp1r1b*$^+$ neurons during extinction. In doing so, we will also further validate the role of *Ppp1r1b*$^+$ neurons in extinction.

Notes:
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21. ROLE OF SHH SIGNALING IN ADULT SPINAL CORD GLI1 CELLS

Michael S. Rallo[1,2], Hui Wang[2], Michael P. Matise[2]

[1]Department of Cell Biology and Neuroscience, Rutgers- The State University of New Jersey, 604 Allison Road, Piscataway, NJ 08854

[2]Department of Neuroscience and Cell Biology, Rutgers- Robert Wood Johnson Medical School, 675 Hoes Lane W, Piscataway, NJ 08854

Spinal cord injury (SCI) and demyelinating ailments (e.g. multiple sclerosis) are debilitating insults affecting adults. It is well established that mammalian stem cell reservoirs are present in the ependymal zone (EZ), white matter, and gray matter of the adult mammalian spinal cord. Therefore, the endogenous response to these injuries may provide a therapeutic target for recovery.

Sonic hedgehog (Shh) signaling is critical for the development of the central nervous system (CNS). In addition, Shh expression is maintained in many adult tissues and is upregulated following CNS injuries. The role Shh plays in both intact and injured adult CNS tissues is not well understood. The goal of this study is to identify and characterize a population of cells in the spinal cord expressing Gli1, a target of Shh signaling, and later determine the role of Shh signaling in their response to injury/insult. Conditional mutagenesis and genetic lineage tracing approaches were used to generate adult mice in which cells receiving Shh are marked. Immunohistochemistry using neuronal- and glial-specific antibodies was performed to establish the molecular profile of these cells. Gli1+/eYFP expressing cells were found throughout the gray matter of the spinal cord. These cells expressed astrocyte markers including GFAP and Sox9, but not neuronal markers such as NeuN. Further, BrdU analysis showed that these cells are non-proliferating. We conclude that these $Gli1^{+}$ cells are post-mitotic protoplasmic astrocytes based on their expression profile and morphology.

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22. GROWING AN IDEA *IN VIVO*: OVEREXPRESSION OF COLLYBISTIN IN ADULT MOUSE HIPPOCAMPUS

John Bear, Christopher Fekete, Shanu George, Celia Miralles, Angel de Blas, Ph.D.
Department of Physiology & Neurobiology, University of Connecticut, Storrs, CT, 06268

Epilepsy, the fourth most common neurological disorder, is characterized by increased excitatory electrical activity and decreased inhibition within the nervous system. While epilepsy constitutes a spectrum with many different clinical outcomes depending on the affected area, mesial temporal lobe epilepsy (MTLE) originates in the hippocampus and accounts for the majority of localized seizures in the brain. By manipulating the expression of the GABAergic postsynaptic protein collybistin in hippocampal neurons of adult mice, we explore the possibility of increasing inhibitory potential of GABAergic postsynapses in these cells. Further comparing the presence of the collybistin 2 SH3(-) protein isoform throughout different areas of the rodent CNS, we consider other common focal seizure areas for which it would be possible to supplement endogenous collybistin activity.

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23. A POTENTIAL BRIDGE BETWEEN GLUTAMATE RECEPTORS AND THE NEURO-PROTECTIVE INSULIN/IGF SIGNALING PATHWAY IN A *C. ELEGAN* MODEL OF EXCITOTOXICITY.

Tanzib Razzaki[1], Ayesha Chowdhury[2], and Itzhak Mano[3]
Center for Discover & Innovation, CUNY School of Medicine at City College, 85 St. Nicholas Terrace, New York, NY 10031
Department of Physiology, Pharmacology, and Neuroscience, CUNY School of Medicine at City College, 85 St. Nicholas Terrace, New York, NY 10031

An American dies from a stroke every 4 minutes. A stroke occurs when there is limited supply of blood to the brain, causing reduced levels of energy. This energy deficiency leads to the malfunction of the system that usually clears synapses of excess neurotransmitter, like Glutamate. Consequently, Glutamate Receptors (GluRs) are overwhelmed; neurons are overstimulated; and ultimately this results in neurodegeneration in a process known as excitotoxicity. However, it is not known how neurodegeneration occurs in excitotoxicity, and what processes might mitigate its damaging effects. One pathway that might provide some protection is the Insulin/IGF Signaling (IIS) Pathway, known for its neuro-protective role in cellular aging, mediated via the transcription factor, FoxO. However, studying these intricate pathways in mammals is very challenging. The *C. elegans* model offers many advantages when studying these cascades, such as powerful genetic tools, simplified cascade structure, and strong conservation of relevant signaling pathways like the IIS Pathway. Moreover, *C. elegans* are transparent organisms, which facilitates the localization (in intact animals) of specific proteins labeled with GFP, such as dendritic signaling complexes or transcription factors that shuttle between the cytoplasm and the nucleus. In my project I will study whether synaptic scaffolding proteins might serve as a bridge between GluRs and the IIS Pathway. In order to find that out, I am using a model of excitotoxicity in *C. elegans* and study the function of synaptic scaffolding proteins on the IIS pathway and the transcription factor FoxO/DAF-16. This study holds the potential to identify novel and conserved mechanisms of neuroprotection in stroke-related mode of neuronal damage.

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24. DETERMINING THE EXPRESSION OF DPR AND DIP PROTEINS IN A08A AND DBD NEURONS

Rebekah Rashford[1], Emily Sales[2], Chris Doe[2]
[1]Department of Biological Sciences, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250
[2]Institute of Molecular Biology, University of Oregon, Eugene, OR 97403

The precise wiring of neural circuits during development, a mechanism known as synapse specificity, is critical for proper nervous system function. However, the biological mechanisms underlying synapse specificity are still poorly understood. Our goal is to test the function of two novel cell adhesion protein families, defective proboscis extension response (Dpr) and Dpr-interacting proteins (DIP) in synapse specificity. First, we will determine which Dpr and DIP proteins are expressed by two synaptically coupled neurons in the larval *Drosophila melanogaster*, the A08a interneuron and the dbd sensory neuron. In order to test which proteins are expressed by these neurons, we will tag Dpr and DIP proteins with green fluorescent protein, and the A08a and dbd neurons with red fluorescent protein. Then, to test the function of Dpr and DIP proteins, we will use RNAi to knockdown expression of the Dpr and DIP proteins, as well as use cDNA to misexpress the Dpr and DIP genes and analyze neuron morphology and synapse formation. This work will characterize, for the first time, the role of Dpr and DIP proteins in the establishment of proper neural connectivity in the larval central nervous system.

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25. HYPOXIA-INDUCED REMODELING OF A CHEMOSENSORY NEURON

Jonathan Werner[1], Luis Martinez-Velazquez[2], Julia Brandt[2], Niels Ringstad[2]
[1]University of Maryland Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250
[2]Skirball Institute for Biomolecular Medicine, NYU School of Medicine, 540 1st Avenue, New York, NY 10016

Cells and tissues adapt to reduced oxygen levels (hypoxia). Molecular pathways that mediate hypoxia-responses are implicated in many aspects of cell physiology including the control of cell metabolism and proliferation. Accordingly, these pathways are important therapeutic targets. A canonical hypoxia-response pathway is mediated by the prolyl hydroxylase EGL-9, which uses available oxygen as a substrate to target the transcription factor HIF-1 for degradation. In low oxygen, HIF-1 accumulates and promotes transcription of a battery of hypoxia-response genes. The nematode *C. elegans* uses this same hypoxia-response pathway and expresses homologs of HIF-1 and EGL-9. Through studies of gene expression and protein localization in sensory neurons, we find that expression of a component of the sensory cilium – guanylate cyclase – is upregulated by hypoxia in an EGL-9-dependent manner. In mutants lacking EGL-9, we find that total cyclase levels in both the cell body and the cilium are significantly increased. Strikingly, exposure of *egl-9* mutants to hypoxia triggers relocalization of cyclase out of the cell body and into the cilium, suggesting that an EGL-9-independent hypoxia-sensing mechanism regulates protein trafficking in sensory neurons. To understand this non-canonical hypoxia-sensing mechanism, we are interrogating a panel of candidate genes that encode putative oxygen-binding proteins for roles in hypoxia-triggered trafficking of proteins cargo to the sensory cilium. We will also perform an unbiased mutagenesis screen for genes that function in this process.

26. EFFECT OF DELTA-9 TETRAHYDROCANNABINOID (THC) EXPOSURE ON NGN2-INDUCED NEURONS

Khalifa Stafford[1], Ifeanyi Obiorah[2], Hamza Muhammad[2], Kristen Brennand[2]
[1]Hunter College of CUNY, [2]Icahn school of Medicine at Mount Sinai

The use of cannabis, particularly during pregnancy, is drastically increasing; over 10% of pregnancies are now associated with maternal cannabis exposure and rates are approaching 20% in pregnant teenagers. Despite mounting animal and human epidemiological evidence showing that *in utero* exposure to cannabis and THC (the psychoactive component of cannabis) increases the risk of neurobehavioral and cognitive impairments in children, the effects of cannabinoid exposure on neuronal function remains unresolved. We aim to investigate the effects of delta-9 tetrahydrocannabinoid (THC) exposure on neurons derived from human induced pluripotent stem cells (hiPSCs), which because they are more similar to human fetal brain tissue, are ideal for studying the effects of THC exposure on the developing human brain.

Results from animal studies suggest that THC alters glutamate transmission; thus, we hypothesized that THC exposure on *NGN2*-induced neurons alters glutamate receptor expression via CB1 receptor activation. Using various concentrations of THC, we determined that 5nM THC was sufficient for induced changes in glutamate receptor expression. NGN2 neurons treated with 5nM THC showed reduced expression of glutamate receptor subunits, notably GluA1. We performed colocalization analysis to determine if GluA1 puncta were more prominent on axons or dendrites.

Future studies will aim at determining the molecular mechanisms of THC-induced alteration of glutamate signaling by using pharmacological inhibitors of CB1. We will investigate if blocking CB1 activation restores the glutamate receptor deficits. Ultimately, we hope to use this platform for investigating if cannabis exposure contributes to the molecular and cellular mechanisms underlying psychiatric disorders.

27. PROTISTS AND THE COCKROACH MICROBIOME

Aditya Bhagirath, Dr. Jane Carlton, Julia Maritz
Department of Biology, Genomics and Systems Biology, New York University, 12 Waverly Place, New York, NY 10003

Microorganisms are the most abundant and diverse organisms on earth, living in, on, and around us. Many insects have diverse microbial communities that inhabit their gut and other tissues and contribute to various host functions. However, compared with the human microbiome very little data exists for the microbiomes of urban wildlife or domestic pets. Most of the available data was generated through bacterial surveys from healthy laboratory animals. The goals of my project are to determine what level of protist diversity is present in the German cockroach microbiome and to answer questions of overlap between the microbiomes of whole insects, guts and feces. The plan for this project was to create a protocol for collecting, dissecting and extracting DNA from American cockroaches. Additionally, we would sequence German cockroaches from North Carolina as well as American cockroaches from New York. The methods used for this project were acquiring the cockroaches, dissecting the cockroaches and extracting the DNA from the cockroaches and then using 18S V9 deep amplicon sequencing in order to obtain information about the protist diversity in the microbiome of the cockroach. Through high-output sequencing, I was able to create phylogenetic trees of the protist diversity that is present in the microbiomes of cockroaches. The two sequencing runs that were conducted called 15357180 and 15754000 reads respectively, with mean PHRED scores over 30.

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28. MULTIPLE OSCILLATORS DRIVE FORWARD LOCOMOTION IN *C. ELEGANS*

Shelly Teng[1], Julian Mark[1], Anthony Fouad[1], Christopher Fang-Yen[1]
[1]Department of Bioengineering, University of Pennsylvania, 210 S 33rd St, Philadelphia, PA 19104

The relationship between neural networks and associated behavior in animals has been a compelling field of inquiry for many years. In particular, the mechanisms by which an organism's nervous system controls locomotion is still not well understood. This question is often difficult to answer because the neural circuitry linked to movement is much too complicated to decipher. However, using *C. elegans*, a 1-mm long transparent roundworm, simplifies the problem because of the worm's complete and simple connectome. The current model for *C. elegans* locomotion proposes that a single oscillator in the head generates rhythmic waves that are then propagated along the rest of the body through a reflex-like mechanism.

In order to further test this model, we asked whether the worm could generate multiple independent undulations. When we optogenetically paralyzed small regions of the worm's body, we found that the head and tail were capable of simultaneously oscillating at different frequencies. Similarly, heat-mediated lesioning of the worm's head caused anterior paralysis, but waves persisted in the posterior. The worm's ability to undulate at two-frequencies was not lost when the pre-motor interneurons or most motor neurons were ablated. In fact, ablation of the forward motor neurons just posterior to the head also resulted in two-frequency locomotion. Furthermore, we also found that stimulating the posterior motor neurons while hyperpolarizing all other cholinergic neurons elicited local undulations in the stimulated region.

Our results show that the *C. elegans* forward motor circuitry consists of at least two units capable of independent oscillation, rather than the previously proposed single head oscillator model. Current work aims to identify cells responsible for generating oscillations outside the head.

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29. INVESTIGATE THE EFFECTS OF CYCLOPAMINE ON *DROSOPHILA MELANOGASTER* MODEL OF ALZHEIMER'S DISEASE

Phuong Nguyen[1], Michal Sharoni[1], Nina Latcheva[2], Michelle Krach[1], Katherine Innamorati[2], Aleister Saunders[1], Daniel Marenda[1,2,3]

[1]Department of Biology, Drexel University, 3245 Chestnut Street, Philadelphia, PA 19104

[2] Molecular Cell Biology and Genetics Program, Drexel University College of Medicine, 2900 W Queen Lane, Philadelphia, PA 19129

[3]Department of Neurobiology and Anatomy, Drexel University College of Medicine, 2900 W Queen Lane, Philadelphia, PA 19129

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is the most common cause of dementia in older adults. AD pathology includes formation of amyloid plaques, a major component of which is the Amyloid β peptide (Aβ) generated from sequential proteolytic cleavage of Amyloid precursor protein (APP) by β- and γ-secretases. Aβ accumulation is neurotoxic and leads to synaptic dysfunction, neuronal death, and learning and memory defects.

Our lab identified the Smoothened receptor of the Sonic Hedgehog signaling pathway in a genetic screen as a regulator of APP metabolism. In a later study, Cyclopamine (an antagonist of the Smoothened receptor) was shown to alter the subcellular trafficking of APP C-terminal fragments (substrates for γ-secretase cleavage) in HeLa cells and primary rat cortical neurons. Thus, we hypothesized that Cyclopamine would have a similar mechanism of action in an *in vivo* AD model. To test this, we used transgenic *Drosophila melanogaster* which overexpress human APP and β-secretase in all postmitotic neurons under the control of the Gal4-UAS system.

We showed that Cyclopamine rescues a number of defective phenotypes observed in our AD *Drosophila* model including external morphology, larval locomotion, adult motor reflex, and neuroanatomy. These data suggest Cyclopamine can be investigated further for AD therapeutics.

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30. POTENTIAL COLLABORATORS OF DAPK IN THE EXCITOTOXIC NECROSIS PATHWAY IN *C. ELEGANS*

Adem Idrizi,[1,2] Itzhak Mano[2]

[1]Undergraduate Program in Biology, City College of New York, 160 Convent Ave, New York, NY 10031

[2]Department of Physiology, Pharmacology, and Neuroscience, CUNY School of Medicine at City College, 85 St. Nicholas Terrace, New York, NY 10031.

A central neurodegenerative process in stroke is excitotoxicity, where excessive synaptic levels of glutamate overstimulate the post-synaptic neuron. This overstimulation induces lethal levels of calcium influx into the cell and causes neuronal cell death. The molecular mechanism of neuronal necrosis in excitotoxicity is fiercely debated, and mediators of the toxic effect of Ca^{2+} remain bone of contention. Recent evidence suggests that a key mediator of this is the calcium regulated Death Associated Protein Kinase (DAPK), but the mechanism by which it regulates neuronal necrosis in excitotoxicity remains unclear. In order to unravel the role of DAPK in excitotoxicity, we use the genetic animal model system of the nematode *C. elegans*, as it has simplified cascades that regulate key decisions like cell death & survival, and it exhibits conserved structure and function of DAPK and the mediators of glutamate signaling. We found that a number of pathways that were suggested to mediate DAPK's action in excitotoxicity are not significant in nematode excitotoxicity, suggesting that they are not key conserved processes in this type of neurodegeneration. Searching for alternative mediators, we noticed that previous mammalian studies revealed that in other signaling cascades, DAPK interacts with downstream proteins through its death domain. We now ask if DAPK uses its Death Domain to mediate necrotic neurodegeneration under excitotoxic conditions. We will analyze the possible involvement of various proteins by determining the effect of genetic knockouts (*ko)* on the extent of necrotic neurodegeneration (determined by counting swollen neurodegenerative cells in live animals subjected to excitotoxicity). We hope that identifying key novel and conserved DAPK-partners in excitotoxic signaling in the nematode will help focus future research on steps that are critical in this type of neurodegeneration across species, and facilitate the development of novel therapeutic intervention in excitotoxicity and stroke.

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31. TRANSCRIPTIONAL REPRESSION MECHANISMS IN PLANT STEM CELL MICROENVIRONMENTS

Aaron Weiner[1] and Naden Krogan[1]
[1]Department of Biology, American University, 4400 Massachusetts Ave NW, 20016

In multicellular organisms, the identity and function of a cell depends on which genes are expressed ("turned on") or repressed ("turned off"). This regulation is conferred by protein complexes comprised of transcription factors that bind DNA. In the model plant *Arabidopsis thaliana*, two such factors are the co-repressor TOPLESS (TPL) and the histone deacetylase HDA19, which cooperatively "turn off" genes in stem cell microenvironments. Neither of these two factors binds DNA directly, so their ability to repress genes depends on their association with other unknown DNA-binding proteins. Using yeast one-hybrid assays, we have identified candidate DNA-binding factors that recruit TPL and HDA19 to repress genes and maintain stems cells in an undifferentiated state. This work will elucidate the composition of novel protein complexes required to repress genes in plant development and will increase our understanding of how gene regulation impacts stem cell function.

32. THE POSITIVE EFFECT OF NEUTRIENT-RICH DIET ON LONGEVITY OF *C.elegans* WITH METABOLIC DEFECT

Min Kyung Shin[1], James Clark[1], Cathy Savage-Dunn[1]
[1]Department of Biology, Queens College of City University of New York,
65-30 Kissena Blvd, Flushing, NY 11367

Background: Longevity is influenced by both environmental and genetic factors, but how these factors interact is poorly understood. The nematode *Caenorhabditis elegans* is one of the principle model organisms used to study longevity because of its excellent genetics and short lifespan of three weeks. TGF-β signaling is a transduction pathway responsible for cell growth, cell differentiation and apoptosis. DBL-1 is TGF-β-related ligand in Sma/Mab pathway and SMA-3 is one of the signal transducers in Sma/Mab pathway. Our lab has recently discovered that *sma-3* mutants have defects in fat metabolism. *C. elegans* feed on bacteria; HB101 and DA837 are two commonly used *E.coli* strains in a laboratory setting. A previous study revealed HB101 contains more protein, fatty acids, and carbohydrates than DA837. However, it is not known whether a nutrient-rich diet affects the longevity of *C. elegans* with metabolic defects.

Approach/ Principal Findings: The complete lifespan of wildtype and *sma-3* mutant strains were recorded while fed either HB101 or DA837. The median lifespan of *sma-3* mutants fed HB101 was significantly longer than *sma-3* mutants fed DA837, 10 days and 8 days respectively. This result indicates that a nutrient-rich diet may positively affect the metabolic defect of *sma-3* mutants, resulting in a longer lifespan. In ongoing experiments, we are quantitating levels of fat storage using Oil Red O which stains neutral lipids. In addition, we are testing whether the DBL-1 and insulin pathways interact in lifespan regulation.

Conclusions: Our studies demonstrate that high nutritional diet may support the metabolism-defective *C.elegans* to overcome their shorter lifespan, suggesting the interaction between Sma/Mab pathway and major nutrients at the molecular level.

33. OPTOGENETIC INVESTIGATION OF *NEISSERIA* SPECIES MOTILITY DURING THE FORMATION OF MICROCOLONIES

Ioannis Eugenis[1], Kevin Gardner[2], and Nicolas Biais[1,3]

[1]Department of Biology, Brooklyn College, 2900 Bedford Avenue, Brooklyn, NY 11210.

[2] CUNY Advanced Research Science Center, 85 St Nicholas Terrace, New York, NY 10031.

[3]Graduate Center of CUNY, 365 5th Ave, New York, NY 10016.

Bacterial motility plays an important role in the attachment to and colonization of a host. However, the twitching motility of bacteria caused by the retraction of their Type IV pili is an understudied biological phenomenon. Here, an optogenetic system was cloned into the genome of both *Neisseria gonorrhoeae* and *Neisseria elongata* to study their motility and to assay the role of bacterial movement during the formation of microcolonies, the precursors to biofilms. Optogenetics, a technique notably used in neuroscience to regulate the expression of genes with light, was applied to bacteria in this experiment. Using this method, pilT, an ATPase motor protein responsible for the retraction of pili and thus the twitching motility, was put under the control of a promoter responding to blue light. Gibson Assembly, a molecular tool that allows for the joining of DNA fragments, was used to create DNA constructs containing the genes encoding pilT and EL222, a light-sensitive protein that binds to a specific sequence of DNA and allows for the transcription of downstream genes. This tool allows for the precise spatial and temporal control of the motility behavior of the bacteria upon the activation of the pilT gene. The optogenetic control of pilT, and thus of the twitching motility, in *N. gonorrhoeae* and *N. elongata* also allows for the measurement of the dynamics of pili turnover.

34. OXIDATIVE STRESS SUSCEPTIBLE GUANINE NUCLEOTIDE EXCHANGE FACTOR 1 (OSG-1) MEDIATED THERMOTOLERANCE IN THE HEAT SHOCK RESPONSE OF *C.ELEGANS*

Rahul Patel[1], Sindhu Sriramoji[1], and Federico Sesti[1]
[1]Department of Neuroscience and Cell Biology, Rutgers-Robert Wood Johnson Medical School, 683 Hoes Lane West, Piscataway, NJ 08854

All cells, including neurons, have programs that mitigate damage caused by extreme temperatures, exposure to toxins, inflammation, infection, starvation, and hypoxia. Maintenance of these programs plays a critical role in both normal physiology and pathology, as several pathological states are either characterized by loss of function or reduced efficacy of these cellular responses. Disturbances in the thermodynamic equilibrium specifically recruit molecular chaperones of the heat shock protein family, which are also implicated in neurodegenerative diseases such as Huntington's disease, which play a central role in the molecular response to thermal insult.

Using *Caenorhabditis elegans* as a model system we have identified the role of a recently discovered modulator of the actin cytoskeleton during aging, oxidative stress susceptible guanine nucleotide exchange factor 1 (OSG-1), in the heat shock response of *C. elegans*. Notably, OSG-1 KO worms exhibit impaired tolerance to thermal stress, presumably through interaction with the Rho family of GTPases. Survival is similarly affected by suppressing actin binding proteins ARX-3 and ARX-5, *C. elegans* orthologs of human Arp2/3 complex. Additionally, sequestration of calcium signaling prior to thermal insult mediates changes in actin cytoskeletal dynamics as well. Taken together our data indicates that stabilization of the actin cytoskeleton is crucial to promote survival under conditions of cellular stress and during aging.

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35. AUDITORY FEAR CONDITIONING IN A MOUSE MODEL OF FRAGILE X SYNDROME (FXS)

Alexander Koo[1], Dr. Bojana Zupan[1]
[1]Department of Psychology, Vassar College, 124 Raymond Avenue, Poughkeepsie, NY, 12604
[2]Department of Psychology, Vassar College, 124 Raymond Avenue, Poughkeepsie, NY, 12604

Sociability varies widely among individuals and depends on a number of developmental factors. As social animals, mice are a good model for studying sociability and the factors that affect it. Mice modeling Fragile X Syndrome (FXS), a genetic mutation-induced condition characterized by intellectual disability and social anxiety, display abnormal sociability. Yet previous research in our lab found that abnormal sociability is not only dependent on the organism's genotype, but also on that of its mother. This suggests that sociability may be developmentally programmed by nongenetic factors. Sociability is in part regulated by the amygdala as inhibition of certain amygdaloid projections increases social interaction in mice. In FXS mice, defects in synaptic plasticity and neurotransmission in the amygdala have also been reported. We therefore asked whether increased sociability observed in our mice is associated with maternal genotype-dependent changes in amygdala function. Using cued fear conditioning, a classical amygdala-dependent learning task, we assessed whether maternal or offspring FXS mutation alters acquisition and/or extinction of fear memory. We found no effect of maternal nor, surprisingly, offspring's own genotype on fear learning. This finding fails to replicate published data showing deficits in expression of fear memory in FXS mice. However, differing mouse strains may explain our inability to replicate these results as our mouse has very low if any freezing behavior in response to fear conditioning. We are currently reassessing our results using locomotor activity as a behavioral measure of fear learning. If our findings are confirmed, the lack of differences in fear learning would suggest that abnormal sociability is not mediated by amygdala dysfunction. However, we can't rule out the possibility that the indiscriminate social approach observed in our mice may be at least in part mediated by a more nuanced deficit in processing of aversive social cues.

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36. THE ROLE OF GLUA1 AND GLUA3 TRAFFICKING IN THE BASOLATERAL AMYGDALA DURING PAVLOVIAN REWARD CONDITIONING

Diego Alvarado Mateo[1,4], Roseanna M. Zanca[3,4], Jorge A. Avila[3,4], Andrew Delamater[2], and Peter A. Serrano[3,4]

[1]Biology, York College 94 - 20 Guy R. Brewer Blvd., Jamaica, NY 11451;
[2]Psychology, Brooklyn College, 2900 Bedford Ave, Brooklyn, NY 11210;
[3]The Graduate Center of CUNY, 365 Fifth Ave, New York City, NY 10016;
[4]Psychology, Hunter College, 695 Park Ave NY, NY 10065

Pavlovian Conditioning (PC) is a behavioral model for learning that occurs through associations. In our present study, we used PC to examine the molecular mechanisms in the brain that underlie the association of a conditioned stimulus (CS), a tone, and an unconditioned stimulus (US), a food reward. Previous work has revealed that the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAr) subunit GluA1 is preferentially trafficked in the hippocampus shortly after spatial-memory acquisition. Furthermore, the AMPAr subunit, GluA3, is preferentially trafficked in the lateral amygdala during fear-memory consolidation. Thus, we hypothesized that PC could also mediate differential AMPAr subunit trafficking in the Basolateral Amygdala (BLA). The BLA is a region in the brain known to processes the value of the US. To address our hypothesis, we measured the expression of AMPAr subunits within the BLA of rats that received PC, PC + Extinction, or No-PC. Rats underwent 8 days of PC conditioning, followed by 5 days of extinction training or no-stimulus delivery. Rats were subsequently tested for 4 consecutive trials, sacrificed, and their brains were retrieved. Micro-dissections of the BLA were conducted, synaptic fractions were obtained for tissue samples, and Western Blots were run to analyze the expression of AMPAr subunits. Our results reveal that GluA1 is elevated in our PC + Extinction group only, GluA3 was elevated in our PC group, and GluA2 was elevated in both PC and PC + Extinction groups. Our current data reveal that appetitive Pavlovian conditioning mediates the differential trafficking of AMPAr subunits in the BLA, and suggest that the plasticity in this region could be pivotal to PC learning and extinction. Future work will address the necessity of GluA 1/2 AMPAr for extinction, the necessity of GluA 2/3 AMPAr for consolidation, as well as identify the neuron populations that mediate PC and PC + Extinction, separately.

37. FUNCTION OF NPAS4 IN VISUAL RECOGNITION MEMORY

Shadia Farah[1], Xiaochen Sun[2] and Yingxi Lin[3]
[1]Department of Psycholoy, Queens College CUNY
[2,3]Department of Brains & Cognitive Sciences, Massachusetts Institute of Technology

Neuronal PAS domain protein 4 (Npas4) is an immediate early gene that functions as an important molecular link between neuronal activity and memory. It is selectively activated by neuronal activity, modifies synaptic connections, is involved in circuit homeostasis and plays a role in memory formation. However, very little is known about how Npas4 in the neural circuits may underlie memory formation, specifically recognition memory. Here, we investigate the requirement of Npas4 in visual recognition memory. We found that Npas4 total knockout animals are impaired in visual object recognition, suggesting that Npas4 is necessary for novel object recognition. To understand the cell-type specific requirement of Npas4 in recognition, Emx-Cre or Gad2-Cre mice were crossed to Npas4$^{f/f}$ mice to generate animals that lack Npas4 specifically in excitatory or inhibitory neurons, respectively. The Emx-Cre mice portrayed competence in visual object recognition while the Gad2-Cre mice portrayed impairment. This may indicate that disruption of Npas4 inhibitory networks leads to a disruption in visual object recognition. Furthermore, pilot data indicates that acute deletion of Npas4 in the V1 led to disrupted orientation-selective habituation (OSH), a behavioral paradigm for visual recognition memory. In addition, Npas4 acute deletion in the V1 decreases inhibition following either 10 days or 30 days after the injection, suggesting inhibition may play a very important role in recognition memory.

38. SESTD1KO MICE SHOW A BEHAVIORAL PHENOTYPE CONSISTENT WITH BIPOLAR DISORDER SYMPTOMALOGY.

Anastasia Pluish[1, 2], Pierre Martin. Ph.D.[2], Benjamin N.R. Cheyette, MD, Ph.D[2].
[1]Department of Psychology, Brooklyn College, 2900 Bedford Ave, Brooklyn NY 11210.
[2]Department of Psychiatry, University of California San Francisco, 1550 4th St, San Francisco, CA 94158

Bipolar disorder affects 2.6% of the US population, manifests in cycles of depression and mania, and has a substantial heritable component, but little is known about the responsible genes. A recent genome-wide association study identified Sestd1 as a likely risk gene for lithium-responsive bipolar disorder (Song et.al, 2015). Studies using Sestd1KO mice point to a role for Sestd1 in synapse formation (Yang et.al, 2016, unpublished). We hypothesized that Sestd1KO mice (conditionally in the forebrain) would exhibit behaviors relevant to bipolar disorder (e.g. abnormal spontaneous locomotor activity, motivation, impulsivity), and that lithium administration would rescue behavioral abnormalities. 43 mice (13-mutants, 30-wild-type) underwent behavioral phenotyping: open field, marble burying, o-maze, digging, light/dark box, y-maze, hyponeophagia, forced swim. Compared to controls Sestd1KO mice buried more marbles and spent more time digging, entered the open zone sooner in the o-maze, spent more time in the light zone of the light/dark box, consumed more novel food in the hyponeophagia test (trend), and swam less in the forced swim task (trend). The same cohort was injected with lithium and repeated behavioral tests (results forthcoming). Our findings support a possible role for Sestd1 in the psychophysiology of bipolar disorder. Future work will replicate and extend analyses of behavioral phenotype in this mouse model.

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39. VALIDATING THE EXPRESSION LEVELS OF MAPT EXONS IN POST-MORTEM ALZHEIMER'S BRAIN

Derian Pugh[1], Kathryn Bowles[2], Dr. Alison Goate, DPhil[3]

[1]Department of Neuroscience, Xavier University of Louisiana, 1Drexel Dr, New Orleans, LA 70125

[2]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029

The microtubule - associated protein tau (MAPT) gene encodes for the protein Tau, which is abundant in the neurons of the central nervous system. Tau is responsible for stabilizing microtubules, which supply essential nutrients to the cell, and it participates in cell division. Tau can aggregate to form neurofibrillary tangles that ultimately end up disintegrating this vital transport system, resulting in cell death. Diseases that are associated with defective Tau are referred to as tauopathies. In an effort to understand MAPT expression, splicing, and regulation in the human brain on the exon level, we designed and optimized primers for each of the different MAPT exons. We then carried out qRTPCR on 18 RNA samples derived from the dorsolateral prefrontal cortex of ROSMAP (Religious Order Study/Memory and Aging Project) participants in order to validate the expression levels that have previously been calculated using RNA-seq data from the full ROSMAP cohort. We validated the pattern of expression for the majority of the exons, but there were a few targets that did not match the ROSMAP data. The reasons for this are currently unknown, and further investigation and optimization of these exons is required. We plan to use this assay in the future to better characterize and understand the alternative splicing events that have been associated with several other tauopathies such as Alzheimer's disease (AD), frontotemporal dementia (FTD), and progressive supranuclear palsy (PSP).

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40. EPIGENETIC DYSREGULATION IN AUTISM SPECTRUM DISORDER

Mohamad A. Nasrallah[1], Josefa Sullivan[2], Melanie von Schimmelmann[2], Naama Volk[2], and Anne Schaefer[2]

[1]University at Albany, Department of Biological Sciences

[2]Laboratory of Brain Epigenetics, Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY

Autism spectrum disorders (ASDs) are complex neurodevelopmental disorders characterized by repetitive stereotypic behaviors, cognitive inflexibility, and dysfunctions in social interactions. Studies investigating ASDs have revealed diverse genetic origins of the disorder. Despite extensive genetic research, little is known about the epigenetic mechanisms associated with ASD. Using a pharmacological approach, we previously identified the bromodomain and extraterminal domain-containing protein family (BETs) as epigenetic regulators of genes involved in ASD-like behaviors in mice. There are three BET proteins expressed in the brain, Brd2, Brd3, and Brd4, and each exhibits a unique structure and temporal expression profile, suggesting that they may have distinct functions during brain development. Here, we propose to investigate which member of the BET family is the primary regulator of the ASD-like phenotypes previously described. We identify direct BET target genes by using neuron-specific chromatin immunoprecipitation coupled with deep sequencing (ChIP-seq) from mice striatum to understand how each BET protein interacts with the chromatin landscape. We also investigate the contribution of each BET protein to the neuronal transcriptome using genetic knockout, knockdown, and gene expression analyses *in vitro* and *in vivo*. Collectively, our work will help elucidate the mechanism by which BET proteins epigenetically control ASD-related gene networks and the development of autism-like behavioral abnormalities.

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41. HORMONAL CHANGES AND OUTCOMES OF PREGNANCIES IN WOMEN WITH NON-CLASSICAL CONGENITAL ADRENAL HYPERPLASIA

Tanushree Laud[1,2], Emily Huang[1,2], Mabel Yau M.D.[2]
[1]New York University, New York, NY 10003
[2]Division of Adrenal Steroid Disorders, Department of Pediatrics, Icahn School of Medicine at Mount Sinai Hospital, New York, NY. 10029

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders of steroidogenesis. CAH is classified into two forms, the severe classical form and the milder non-classical form (NC). The classical form results in cortisol deficiency and genital ambiguity in affected females. Adult women with CAH are often met with infertility. Maintaining normal adrenal androgen and 17 hydroxyprogesterone (17-OHO) concentrations through glucocorticoid treatment is vital to achieve fertility and maintain a healthy pregnancy. The objectives of this study were to observe hormone levels in pregnant women affected with NC-CAH, pregnancy outcomes in women with NC-CAH, and birth outcomes of their fetuses.

In a retrospective review, charts of female subjects with NC-CAH due to a 21-hydroxylase deficiency were screened. We compared 17-hydroxyprogesterone, androstenedione, and testosterone levels in pregnant women with NC-CAH to the hormone levels of pregnant women who were clinically unaffected with CAH. The mean serum concentration of 17-OHP is 840.23 ng/dl during the first trimester. The serum concentrations of 17-OHP during the first trimester are significantly higher compared to the second trimester ($p = 0.028$). The mean serum concentrations of androstenedione were 296.1 ng/dl during the first trimester, 271.3 ng/dl during the second trimester, and 289.25 ng/dl during the third trimester. The mean serum concentration of testosterone is 98.26 ng/dl during the first trimester, 107 ng/dl during the second trimester, and 120.59 ng/dl during the third trimester.

Significantly higher serum concentrations of 17-OHP were observed during the first trimester and androgen levels were normal to low throughout the pregnancies of women affected with NC-CAH. No fetuses were born with virilization. Of all pregnancies observed, 87% were carried to term. Dosages of hydrocortisone from at least 1.5 mg/m^2 to 9.03 mg/m^2 were sufficient for maintaining a healthy pregnancy and androgen levels within normal range.

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42. MUTATIONAL ANALYSIS TO DETERMINE THE ROLE OF FYN DURING CHLAMYDIAL PATHOGENESIS

Trevor Wolf[1], Jeffrey Mital[1]
[1]Department of Biomedical Sciences, Quinnipiac University, 275 Mt. Carmel Ave, Hamden, CT 06518

The obligate intracellular bacteria *Chlamydiae* cause several different diseases, including ocular trachoma and sexually transmitted diseases. Additionally, chlamydial infection is associated with an increased risk of reproductive cancers. Due to the prevalence of these diseases, it is imperative to elucidate the molecular biology involved in chlamydial pathogenesis. Src family kinases (SFKs) may be part of these disease pathways, as kinases (phosphorylating enzymes) are involved in cellular signal transduction, cellular growth control, differentiation, cytoskeletal arrangements, secretion, and voltage- and ligand-gated channel function.

Previous research has shown that the SFK Fyn co-localizes with proteins and lipids within the membrane of Chlamydia's intracellular vacuole, as well as the host cell centrosomes. SFKs have also been shown to have specie-specific roles during chlamydial infection and development. To better understand SFK's role in chlamydial pathogenesis, FYN has been modified to be expressed as a null, dominant-negative, and constitutively active mutant. These plasmids were then transfected into HeLa and murine SYF (SFKs knockout) cell lines, which were subsequently infected with *Chlamydia caviae* and the differences were noted.

To further investigate the role of Fyn, other mutations at different loci in FYN are being constructed; for example, membrane trafficking mutants. Progeny counts, Western blotting, and cell lines expressing various SFKs will be used to make direct comparison in order to elucidate the role of Fyn during chlamydial pathogenesis.

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43. HEART RATE VARIABILITY BIOFEEDBACK FOR ASTHMA

Agratta Sharma[1], Karen Kaur, Paul Lehrer Ph.D.[2]
[1]Department of Psychiatry, Robert Wood Johnson Medical School, 671 Hoes Lane, Piscataway, NJ 08854

We conducted a two-center trial on 71 steroid-naive patients with mild or moderate asthma to test the role of heart rate variability (HRV) biofeedback in asthma therapeutics. Compared with a group receiving EEG biofeedback, music therapy, and paced breathing at a relaxed rate, we found significantly greater improvement for HRV biofeedback on twice-daily home peak flow recordings, daily symptoms, and the Asthma Control test. Although there were no significant between-groups differences in methacholine reactivity, PC20FEV1 (the dose of methacholine producing a 20% drop in pulmonary function as measured by the volume of air exhaled in the first second of a forced expiratory maneuver from maximum vital capacity) improved significantly only in the HRV biofeedback group. This is considered to be a 'gold standard' measure of asthma severity, and reflects sensitivity of the airways to parasympathetic stimulation, which produces constriction of the smooth muscles in the central airways. Both groups improved significantly in asthma quality of life, and generalized anxiety symptoms.. There were no significant changes in either group in albuterol (a bronchodilator) use, airway inflammation measured by exhaled nitric oxide, hyperventilation symptoms, or perceived stress. More volunteers than expected were excluded because they were taking inhaled steroids, counter to literature estimates of 50% nonadherence rates. Details of this intervention and results will be described in several papers. We will present hypotheses about possible mechanisms of biofeedback effects.

44. TARGETING APP TRANSLATION FOR ALZHEIMER'S DISEASE PREVENTION AND THERAPY

Chiamaka Ekwunazu[1], Cassidy Reich[2], Joanna Pankiewicz[2], Martin Sadowski[2]
[1]Department of Biological Sciences, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, MD 21250
[2] Departments of Neurology, Psychiatry, and Biochemistry & Molecular Pharmacology, New York University School of Medicine, 450E 29th St., Room 830 New York, NY 10016

Alzheimer's disease (AD) is a neurodegenerative disorder that currently affects 5.5 million people ages 65 and older in the US. Pathology of AD is characterized by the progressive accumulation of β-amyloid (Aβ) in the brain, which over time leads to synaptic loss, formation of neurofibrillary tangles within neurons, and inflammatory glial response. Aβ is a peptide which is inherently hydrophobic and prone to self-aggregation into synaptotoxic oligomers and amyloid fibrils. Aβ is a natural proteolytic metabolite of amyloid precursor protein (APP), a cell membrane protein involved in synapse formation and plasticity. In sporadic AD, Aβ accumulates in the brain due to a mismatch between Aβ production and clearance. We and others have previously shown that Aβ production can be reduced by targeting APP mRNA and limiting efficiency of its translation into protein. We have identified a small, brain penetrant, molecular compound, 2-([pyridine-2-ylmethyl]-amino)-phenol (2-PMAP). In an AD transgenic mice model it decreased Aβ brain deposition, preventing these mice from developing memory deficit. The goal of my project is to determine the structure activity relationship of 2-PMAP. We have obtained a library of 12 2-PMAP chemical derivatives, which passed a toxicity screen in SY5Y human neuroblastoma cells. We are now developing an enzyme-linked immunosorbent assay (ELISA), allowing us to compare the dose-response effect of 2-PMAP derivatives on APP levels in SY5Y cells.

This ELISA assay will move the structure-activity relationship study of 2-PMAP forward, and ultimately help develop a therapy for the many people who suffer from Alzheimer's disease.

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45. REGULATION OF PTF1A IN DIFFERENTIATING HORIZONTAL CELLS PROGENITORS

Kazi Hossain[1], Pooja Dutta[1], Twinkle Jacobs[1], Kevin Gonzalez[1], Diego Buenaventura Nathalie Jean-Charles, Sruti Patoori, Miruna Ghinia, and Mark Emerson[2]
Department of Biology, City College of New York, 160 Convent Ave, New York, NY 10031

The vertebrate retina is a complex structure and understanding the molecular mechanisms that underlie the generation of specific neuronal cell types will elucidate how this structure is formed. The retina consists of six types of neurons and one type of glia. The structure originates from a population of dividing progenitor cells. It has been found that these cells generate specific neuronal cell types with unique gene expression patterns. Thrb is a gene that is expressed in a specific progenitor cell population. This population generates mainly horizontal cells or cone photoreceptors. The goal of this project is identify the genes and pathways that control the generation of horizontal cells.

Our approach is to identify the earliest known factor specifically expressed in horizontal cells and to investigate how this specific expression arises. One such factor is Ptf1a, which is crucial for the differentiation of horizontal cells and amacrine cells. To identify how Ptf1a is expressed in this population, we looked for the cis-regulatory elements that control Ptf1a transcription. These will provide a map of the regulatory events that occur to produce horizontal cells. Comparison of DNA sequences among different vertebrate species resulted in identification of twenty-eight evolutionarily conserved regions (ECRs) around the Ptf1a gene. To determine which ECRs were active in our cell populations of interest, ECR's were amplified by PCR and cloned into vectors containing reporter proteins (GFP). These experimental constructs were then coelectroporated with control constructs into chick retina to determine its activity. ECR22 showed GFP expression in regions of the retina that was electroporated. This suggests that ECR22 is a possible cis-regulatory element for the Ptf1a gene. Analysis of these sequences could reveal the molecular mechanisms driving Ptf1a expression and their respective horizontal cell fates. In addition, these reporter constructs will allow isolation of these cells for further studies.

46. CHARACTERIZATION OF THE LIN28 PARALOGS THROUGHOUT EMBRYONIC DEVELOPMENT

Kemi Akinnola[1], Jihan Osborne[2], George Daley[2]
[1]Department of Biological Sciences, University of Maryland, Baltimore County, 1000 Hilltop Circle, Baltimore, Maryland 21250
[2]Department of Hematology/Oncology, Boston Children's Hospital, Harvard Medical School, 1 Blackfan Circle, Boston, MA 02115

Lin28 was first discovered in C. elegans as a regulator of the L1 to L2 transition during larval development and is specifically expressed in the hypodermal seam cells. Hypodermal seam cells give rise to the nervous system and skin. Worms breathe through their skin, making it analogous to the mammalian respiratory system. During mammalian development, the lung undergoes the reiterative process of branching morphogenesis to give rise to the complex bronchial tree.

In mammals, there are two Lin28 paralogs that are homologous to the C. elegans Lin28: Lin28a and Lin28b. They are highly expressed early in development but decrease as the organism matures into adulthood. Loss of function of Lin28a and b in mammals lead to embryonic lethality. We did an in-depth analysis of several organs from early to late embryonic development in the mouse. We found that Lin28a expression was as previously shown, highly expressed early and decreased throughout maturation. Lin28b expression was high early in development but did not extinguish like Lin28a expression. Instead, it persisted into later embryonic time points. These two points taken together led us to hypothesize a role for Lin28a and b in the developmental process of lung branching morphogenesis.

To study the role of Lin28a/b in lung development, we created various inducible and knockout transgenic mice using a lung-specific Cre. We observed a loss of branching in the lungs of Lin28a/b double knockout mice. We will continue to characterize the role of Lin28a/b in lung branching morphogenesis as well as analyze other organs that undergo branching.

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47. TARGETING MYC ONCOGENE TO OVERCOME CHEMORESISTANCE IN NOVEL PRECLINICAL MODEL OF MUSCLE INVASIVE BLADDER CANCER

Seonghee (Joy) Park[1], Guilhem Roubaud M.D.[1,2], Geoffrey Bryant[1], John Sfakianos, M.D.[1], David Mulholland Ph.D.[1]

1 Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai,
2 Department of Medical Oncology, Institut Bergonié, Bordeaux, France

One of the main reasons for poor survival for patients with metastatic bladder cancer (BCa) is the onset of cisplatin resistance and associated toxicity. While several human BCa cell lines exist, such 2D systems may not accurately reflect (1) the complexity of human BCa and (2) adaptation to treatments due to divergent evolution during the long-term in-vitro culture. To overcome this challenge, we have developed a novel mouse model of cisplatin (CDDP) resistant BCa capable of in-vivo tumorigenesis.

Donor mice were treated with carcinogen OH-BBN (0.1%, N-Butyl-N-4-hydroxybutyl nitrosamine). Following resection and dissociation of the bladder, tissues were injected subcutaneously to immune incompetent *nude/nude* mice. Allografts were implanted as chunks for before subsequent passage. BBN tumors were treated with CDDP, the most widely used chemotherapy drug for BCa. During the CDDP treatment it was observed that the BCa tumor was showing CDDP resistance.

OH-BBN induced BCa has basal phenotype, which then has p63 and MYC overexpression. MYC signaling, in other cancer types in which CDDP chemotherapy is commonly used, has been identified as a possible cause of resistance and a plausible therapeutic target. With this knowledge, we used a MYC inhibitor, JQ1, to observe the effects of combining a MYC inhibitor with CDDP. A combined treatment of CDDP and JQ1 were done for nude mice who had tumor cells passed from the donor mice showing resistance to CDDP. This combined treatment was also done on a cohort with nude mice who had CDDP resistant tumor grafts implanted from human patients.

We derived novel OH-BBN induced BCa models that are amenable to studying cisplatin resistance. Combining the CDDP treatment with JQ1 showed the flexibility of this model. With the use of this novel model, we look to show that the p63 signaling pathway drives MYC signaling to regulate progression and chemoresistance in basal muscle invasive BCa.

48. PRESENCE OF eEF3-LIKE PROTEINS IN NON-FUNGAL ORGANISMS

Alexandra Garino[1], Justyna Pupek[1], McClellan Knapp[1] Kia Bourdot[1], Sarah Colmer[1], Maria K Mateyak[2], Terri-Goss Kinzy[2], Stephen Dunaway[1]

[1] Department of Biology, Drew University, 36 Madison Avenue, Madison, NJ 07940

[2] Department of Biochemistry and Molecular Biology, Rutgers University, 675 Hoes Lane West, Piscataway, NJ 08854

In most organisms, translation elongation requires two highly conserved elongation factors eEF1A and eEF2. Fungal systems are unique in requiring a third factor, essential for translation elongation and cell viability, the eukaryotic Elongation Factor 3 (eEF3). For decades, eEF3, a ribosome-dependent ATPase, was considered “fungal-specific”, however, recent genome sequencing results indicate it may be widely distributed among other unicellular eukaryotes. In order to determine whether these eEF3-like proteins from other organisms can provide the essential functions of budding yeast eEF3, we cloned the eEF3-like proteins from the green algae, Chlamydomonas reinhardtii and potato blight, Phytophthora infestans. Both these eEF3-like proteins are approximately 62% similar to S. cerevisiae eEF3. This level of similarity is equal to that observed in C. neoformans eEF3, which has been shown by others to substitute for S. cerevisiae eEF3 in vivo. Initial experiments suggest that P. infestans eEF3-like protein can support the growth of S. cerevisiae in the absence of yeast eEF3. These experiments will help identify the distribution of eEF3 function among eukaryotes and will further the understanding of the evolution of elongation from prokaryotes to eukaryotes and within eukaryotic phyla.

49. ASSESSING THE IMPACT OF MATERNAL SMOKING DURING PREGNANCY ON CHILD DEVELOPMENT

Karen Go,[1,2,3*] Jin Rong Pan,[4*] Jessica Buthmann,[3] Jackie Finik,[3] and Yoko Nomura[1,3]

**equal contribution*

[1]Mount Sinai Hospital, 1 Gustave L. Levy Pl. New York, NY 10029

[2]Macaulay Honors College, 35 W 67th St. New York, NY s10023

[3]Department of Psychology, Queens College, City University of New York, 65-30 Kissena Blvd., Flushing NY 11367

[4] Brandeis University, 415 South St. Waltham, MA 02453

Previous studies have shown that maternal smoking during pregnancy (MSP) is associated with several adverse child development such as low birth weight, ADHD, obesity and asthma (Suzuki et al., 2010). However, few studies have examined the adverse effects of MSP on specific childhood development competencies. The present study utilized a subsample of 103 women and their offspring participating in a larger birth cohort (SIP Study, PI Nomura). Participants were recruited at the OB/GYN clinics of Mount Sinai Hospital and New York Presbyterian Queens, and followed through pregnancy and as their children develop. MSP was ascertained by self-report during the 2nd trimester, while their offspring's cognitive, communication, physical, social-emotional, and adaptive development were evaluated using the Bayley Scales of Infant and Toddler Intelligence (Bayley III) between ages 18 and 42 months. We hypothesized that MSP would be associated with lower child developmental functioning in general. Using a multivariable general linear model, we found that MSP was associated with lower communication ($p = .010$), poorer home living ($p = .030$), poorer health and safety ($p = .002$), suboptimal self-care ($p = .004$), lower self-direction ($p = .035$), lower social ($p = .003$), and lower motor functioning ($p = .019$). Furthermore, gender difference on the effects of MSP in expressive communication, communication, community use, functional pre-academics, home living, health and safety, leisure, self care, self direction and social was found where affected males have the lowest mean scores and affected females have the highest mean scores, demonstrating clear interactions by gender. These findings suggest that MSP significantly affects childhood development competencies, leading to suboptimal neurodevelopment specifically in males. If replicated in different cohorts in the future, these findings could be critical factors for clinicians to identify high-risk population and present a more persuasive argument to alter modifiable risk (smoking) among pregnant women in the interest of optimal child development.

50. IMMUNE RESPONSE OF THE *ASTYANAX MEXICANUS*

Jennifer Rutkowski[1, 2], Robert Peuss[2], Nicolas Rohner[2]
[1]School of Science, Marist College, 3399 North Road, Poughkeepsie, NY 12601
[2]Stowers Institute for Medical Research, 1000 E 50th Street, Kansas City, MO 64110

Diseases relating to stress and immunity have been at the forefront of research. Cave dwelling *Astyanax mexicanus* is being studied to better understand how stress induces the evolutionary pathway of phenotypes associated with the immune response, with regards to inflammatory and anti-inflammatory responses.

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51. VALIDATING ALTERNATIVE SPLICING EVENTS IDENTIFIED THROUGH ISOFORM SEQUENCING IN POST-MORTEM BRAINS

Felicity J. Emerson[1,2], Nancy J. Francoeur[3,4], and Dalila Pinto[3,4]
[1]Summer Undergraduate Research Program (SURP), Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029
[2]Department of Neuroscience and Behavior, Mount Holyoke College, 50 College Street, South Hadley, MA 01075
[3]Departments of Psychiatry and [4]Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029

Alternative splicing (AS) is a key mechanism in the regulation of gene expression that can occur when pre-mRNA is processed into mature mRNA via the excision of introns and the adjoining of exons. AS events such as intron retention have the potential to alter gene expression and diversify protein function by generating different mRNA and protein isoforms. Although a variety of AS events occur in all cells throughout development, aberrant splicing, particularly in the brain, has been linked to neurodevelopmental disorders such as autism spectrum disorders (ASD).

Identifying AS events in RNA-seq data from healthy post-mortem human brain samples using both short- and long-read sequencing technologies allows for the characterization of AS events that occur in typically developed brains. Making use of long-read Isoform Sequencing data on *SH-SY5Y*, a neuroblastoma-derived cell line, and a post-mortem human dorsolateral prefrontal cortex (DLPFC) sample, novel retained introns (RIs) were identified in *SF3B1* (*splicing factor 3B subunit 1*) and in *CRBN* (*cereblon*), two genes implicated in neurodevelopmental disorders.

These AS events were experimentally validated using semi-quantitative PCR, gel electrophoresis, and Sanger sequencing. Specifically, primers were designed to target a RI in *SF3B1* between exons 4 and 5 and two RIs in *CRBN* between exons 6 and 8 and between exons 7 and 9. After PCR protocol refinement, RIs in *SF3B1* and *CRBN* were validated using cDNA from *SH-SY5Y* and two additional post-mortem DLPFC samples from healthy individuals. Using the DLPFC cDNA PCR products from *CRBN* between exons 7 and 9 and *SF3B1* between exons 4 and 5, gel electrophoresis bands were extracted and prepared for confirmation with Sanger sequencing. Ultimately, these results may be used for the comparison of RI expression in post-mortem brains from ASD cases and controls, which may have important implications for understanding the genetic mechanisms underlying neurodevelopmental disorders.

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52. MESENCHYMAL STEM CELL-DERIVED EXOSOMES IN THE DE-DIFFERENTIATION OF BREAST CANCER 'PROGENITOR' CELLS

Sheena Kapoor[1, 2], Oleta A. Sandiford[3], Lauren S. Sherman[2, 3], Garima Sinha[2,3], Pranela Rameshwar[3]

[1]University of California, Santa Cruz, 1156 High Street, Santa Cruz, CA 95064

[2]Graduate School of Biomedical Sciences, Rutgers Biomedical and Health Sciences, 185 South Orange Avenue, Newark NJ 07103

[3]Dept. of Medicine, Division of Hematology/Oncology, New Jersey Medical School, Rutgers Biomedical and Health Sciences, 185 South Orange Avenue, Newark NJ 07103

Breast cancer (BC) resurgence often occurs after years of remission. The resurgent cancer cells are drug resistant, and are mostly cancer stem cells (CSCs). These CSCs appear to exit quiescence and resurge from the bone marrow (BM). The BM has been identified as the major organ of metastatic BC cells (BCCs). Upon entering the BM, the BCCs interact with the mesenchymal stem cells (MSCs), which act as "gatekeepers" monitoring afferent and efferent flow of cells from the central vessels. The interaction between BCCs and MSCs could be direct and indirect through soluble factors and microvesicles, such as exosomes. Our studies show BCCs priming MSCs to release exosomes with a different miRNA profile. The exosomes then enter BCCs to impart cell quiescence as well as drug resistance. In this study we tested the hypothesis that the exosomes (i.e. miRNA, lipids, proteins, and/or RNA) initiate a de-differentiation process, whereby the cancer progenitors take on a CSC phenotype and become drug resistant. Through the use of immunostaining and flow cytometry we have proven that the addition of exosome initiates an increase in expression of stem cell genes in the otherwise non-CSCs, which we designate as BC progenitors. The addition of exosomes increased the frequency of cells with stem cell properties, supporting the dedifferentiation of BC progenitors by MSC-derived exosomes. Future studies will be to functionally characterize the de-differentiated cells, use time-lapse microscopy to follow single cells and to understand the changes in single cell sequencing. Increased understanding of the de-differentiation process could result in the development of new treatments to prevent cancer dormancy, and to prolong the time of resurgence in survivors - perhaps even eradication of cancer.

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