INAUGURAL ROSE F. KENNEDY INTELLECTUAL AND DEVELOPMENTAL DISABILITIES RESEARCH CENTER SYMPOSIUM

Tuesday, April 30, 2013
9:00 am to 6:00 pm
Price Center /Block Research Pavilion
8:30 – 9:00am  Continental Breakfast (available in Lower Lobby)

**Workshop in LeFrak Auditorium**

9:00 – 9:15am  Welcome and Introduction to the Program by Dr. Steven Walkley

9:15 – 9:50am  Talk title: “The neuronal methylome at the interface of genetic and environmental factors in autism risk” by Janine LaSalle, Ph.D. (Chair, Genetics Graduate Group, Medical Microbiology and Immunology, Genome Center, and MIND Institute, UC Davis School of Medicine) with introduction by Dr. Francine Einstein

9:50 – 10:00am  Questions/Discussion

10:00 – 10:15am  Selected poster presentation: “Alterations in the hepatic and hypothalamic epigenome of mice exposed to a maternal high fat diet” by Lyda Williams

10:15 – 10:50am  Talk title: “Hypo or hyper? The hype and promise of connectivity research in ASD” by Ralph-Axel Müller, Ph.D. (Brain Development Imaging Laboratory, Dept. of Psychology, San Diego State University) with introduction by Dr. John Foxe

10:50 – 11:00am  Questions/Discussion

11:00 – 11:15am  Selected poster presentation: “Oscillatory neural mechanisms during deployment of intersensory selective attention in high functioning children with Autism” by Jeremy Murphy

11:15 – 11:50am  Talk title: “Fragile X Syndrome: synaptopathy, signalopathy and therapeutic intervention” by Gary Bassell, Ph.D. (Departments of Cell Biology and Neurology, Emory University School of Medicine) with introduction by Dr. Steven Walkley

11:50 – 12 Noon  Questions/Discussion

12 Noon – 12:15pm  Selected poster presentation: “The DNA replication program is altered at the FMR1 locus in fragile X embryonic stem cells” by Jeannine Gerhardt, Ph.D.

12:15 – 1:30pm  Informal Luncheon (Lower Lobby) and Poster Session (Upper Lobby)

1:30 – 2:05pm  Talk title: “Brain development, plasticity and re-organization in deafness: Evidence from children with cochlear implants” by Anu Sharma, Ph.D. (Speech Language and Hearing Science, University of Colorado at Boulder) with introduction by Dr. Elyse Sussman

2:05 – 2:15pm  Questions/Discussion

2:15 – 2:30pm  Selected poster presentation: “Aberrant Cx26 hemichannels and keratitis-ichthyosis-deafness syndrome” by Helmuth Sanchez, Ph.D.

2:30 – 6:00pm  Poster session in the upper lobby (open to the entire Einstein community)

2:30 – 4:00pm  Breakout sessions for IDDRC members with invitation to selected conference rooms by research theme (Room 251 for ASD cluster; Room 351 for Neurogenetics & Seizure Disorders cluster; Room 451 for Deafness & Communication Disorders cluster; and Room 551 for Nutritional & Environmental Determinants of Brain Development cluster)

4:00 – 5:00pm  Breakout groups reconvene in the Auditorium for summary wrap-up by cluster leaders

5:00 – 6:00pm  Closing reception (available in Lower Lobby)
Title: The neuronal methylome at the interface of genetic and environmental factors in autism risk

Abstract: Autism is an increasingly common disorder of complex etiology, affected by multiple genetic and environmental influences. Epigenetic mechanisms represent a critical link at the interface between genetic and environmental factors. Sequencing the epigenetic marks of DNA methylation at base-pair resolution (MethylC-seq) have provided large-scale methylation domain maps of a variety of human tissues and are expected to be relevant to interpreting and directing future investigations into genetic and epigenetic etiologies of autism. Commercial flame retardants commonly used in electronics, bedding, carpeting, and furniture contain persistent organic pollutants called polybrominated diphenyl ethers (PBDEs). Organic pollutants such as PBDEs and PCBs persist in lipid-rich tissues such as brain and are therefore a concern for human brain development. We used a perinatal PBDE exposure of mouse dams and tested the long-term effect on behavior of their offspring into adulthood. Interactions with genetic mutation in MeCP2 were also tested, as well as epigenetic consequences on brain DNA methylation. Perinatal exposure of mutant mice to PBDE at a dose comparable to average human levels negatively impacted sociability, learning, and early growth of female offspring. A high PBDE dose at the level of the highest observed human exposure negatively impacted fertility. Female offspring perinatally exposed to PBDE showed reduced DNA methylation in brain in adulthood, corresponding to the defects in social and cognitive learning behaviors. These and other studies suggest a new paradigm of “integrative genetics” in which environmental factors may influence the genomic saturation of DNA methylation and impact the development of the social brain.

Title: Hypo or hyper? The hype and promise of connectivity research in ASD

Abstract: Brain biomarkers for autism spectrum disorder (ASD) remain unknown, although there is growing consensus that atypical network organization may be a hallmark of the disorder. The large quantity of studies reporting hypo-connectivity in ASD has led to the misperception of a ‘firm finding.’ However, many recently reported divergent findings, with often robust hyper-connectivity in ASD, suggest that greater awareness of methodological fine print in functional connectivity MRI (fcMRI) studies and a more nuanced model of connectivity in ASD are needed. I will review recent results on functional and anatomical connectivity in ASD, with some focus on the promise of data-driven approaches for the detection of biomarkers.
Title: Fragile X Syndrome: synaptopathy, signalopathy and therapeutic intervention

Abstract: Fragile X syndrome is a neurodevelopmental brain disorder characterized by aberrant signal transduction. FXS is caused by loss of the fragile X mental retardation protein (FMRP), an mRNA binding protein shown to regulate the translation of specific target mRNAs. Previous work in FXS animal models has demonstrated that signaling through group 1 metabotropic glutamate receptors (mGlu1/5) is exaggerated and dysregulated in the absence of FMRP, but the precise molecular mechanisms underlying dysregulated mGlu1/5 signaling in FXS are not fully understood. We hypothesize that aberrant expression of proteins encoded by FMRP target mRNAs contributes to the defects in signal transduction. Recently, evidence has been emerging that FMRP directly regulates the phosphoinositide-3-kinase/mammalian target of rapamycin (PI3K/mTOR) signaling pathway, leading to dysregulated PI3K/mTOR signaling in FXS animal models and patient cells. Recently, we have observed that mGlu5-associated PI3K activity is selectively increased in the brains of Fmr1 KO mice. Moreover, the PI3K catalytic subunit p110β and PI3K enhancer PIKE display increased protein expression in the absence of FMRP. We show that pharmacological and/or genetic reduction of the PI3K complex can rescue FXS-associated phenotypes in a mouse model. These results suggest that loss of FMRP-mediated control of expression of PI3K/mTOR pathway components regulating signaling downstream of mGlu5 and other G-protein coupled receptors might contribute to altered neuronal signal transduction and synaptic impairments in FXS. Our work provides rationale that pharmacological treatments reducing signaling through the PI3K/mTOR complex might be promising therapeutic strategies for FXS.
Title: Brain Development, Plasticity and Re-organization in Deafness: Evidence from Children with Cochlear Implants

Abstract: Our group is investigating the deterioration, development, plasticity and re-organization of the human central auditory pathways in deaf children who regain hearing after being fitted with cochlear implants. Electrophysiological and brain imaging techniques have delineated the time course of, and constraints on development of the central auditory pathways following stimulation with cochlear implants. In a series of experiments, we have established sensitive periods for development of the central auditory pathways. If stimulation is delivered within a period of 3.5 years, cortical response latencies reach age-normal values within months following the onset of stimulation. However, if stimulation is withheld for more than 7 years, we find reduced plasticity as evidenced by abnormal cortical responses. This lack of central auditory development in congenitally deafened late-implanted children is correlated with relatively poor development of speech and oral language skills. The findings for sensitive periods for cortical auditory plasticity in humans are consistent with those reported from animal models which suggest that primary auditory cortex may be (completely or partially) functionally decoupled from higher-order cortical areas in long term congenitally deafened cats. Another aspect of plasticity that works against late-implanted children is the re-organization of higher order cortex by other sensory modalities. In long-term congenital deafness, somatosensory and visual stimuli activate higher-order auditory areas. Cross-modal re-organization is correlated with poor speech and language outcomes. A better understanding of cortical development and re-organization in children who experience auditory deprivation may have important clinical implications for optimal intervention and habilitation of these children.
Breakout Session (2:30 – 4:00pm)

Autism Spectrum Disorders (ASD) Cluster
Facilitated by: Drs. John Foxe and Sophie Molholm
Room: 251

Neurogenetic & Seizure Disorders Cluster
Facilitated by: Drs. Robert Marion and Steven Walkley
Room: 351

Deafness and Communication Disorders Cluster
Facilitated by: Drs. Elyse Sussman and Vyto Verselis
Room: 451

Nutritional and Environmental Determinants of Brain Development Cluster
Facilitated by: Drs. Francine Einstein and Maureen Charron
Room: 551
Poster Session

Autism Spectrum Disorders (ASD)

- Experimental therapeutics of fever and inflammation in ASD: Hot tubs, locus coeruleus and helminths (Eric Hollander, Bonnie Taylor, Casara Ferretti, Emma Racine, Genoveva Uzunova, Jon Kirsch, Rachel Noone)
- Hand stereotypies distinguish Rett syndrome from autism disorder (Sylvie Goldman, Teresa Temudo)
- Oscillatory neural mechanisms during deployment of intersensory selective attention in high functioning children with autism (Jeremy W. Murphy, John J. Foxe, Joanna Peters, Sophie Molholm)
- Parental Stress in families of children with autism and other developmental disabilities: Associations with ethnic groups and child-comorbid symptoms (Maria Valicenti-McDermott, Kathryn Hottinger, Katharine Lawson, Rosa Seijo, Meryl Schechtman, Lisa Shulman, Shlomo Shinnar)
- Severe multisensory speech integration deficits in high-functioning school-aged children with an autism spectrum disorder (ASD) and their resolution during early adolescence (John J. Foxe, Sophie Molholm, Victor A. Del Bene, Daniella Blanco, Hans-Peter Frey, Dave Saint-Amour, Lars A. Ross)
- Stereotyped behaviors and restricted interests in toddlers with ASD: Prevalence and diagnostic significance (Lisa Shulman, Kate Hottinger, Rosa Seijo, Deborah Meringolo, Nancy Tarshis)
- Variation at ACSM1, but not other neurocognitive-disease related risk alleles, is associated with altered white matter integrity (Young Jae Woo, Tao Wang, Sophie Molholm, John J Foxe, Brett S. Abrahams)

Neurogenetic & Seizure Disorders Cluster

- Aberrant cofillin signaling in a mouse model of Fragile X syndrome (Alexander Pyronneau, R. Suzanne Zukin)
- Aberrant regulation of GluA2 mRNA abundance in dendrites of Fragile X neurons (Andrea Gompers, Adina Buxbaum, Robert Singer, R. Suzanne Zukin)
- Autophagy dysfunction in Lysosomal disease (Matthew C. Micsenyi, Nafeeza Ali, Gloria Stephney, Sharon Zhou, Kostantin Dobrenis, Steven U. Walkley)
- CPP-115, a new GABA transaminase inhibitor, suppresses infantile spasms in the rat multiple-hit model (Stephen W Briggs, Tomonori Ono, Solomon L Moshé, Aristeia S Galanopoulou)
- Differential rewiring of signaling networks in hippocampus vs cortex of Fragile X mice (Kirsty Sawicka, R. Suzanne Zukin)
- Genetic causes of intellectual disability in 22Q11DS syndrome patients (Tingwei Guo , Tao Wang, Bernice Morrow)
- Long-term follow-up of the multiple-hit rat model of symptomatic infantile spasms (Ozlem Akman, Stephen W. Briggs, and Aristeia S. Galanopoulou)
- Oculomotor control in Rett syndrome (Hans-Peter Frey, John J. Foxe, Aleksandra Djuikic)
- Recombinant tetanus toxin peptide tags for efficient CNS neuronal lysosomal enzyme targeting in the treatment of neuronopathic lysosomal storage diseases (Kostantin Dobrenis, Ryan Lippell, Pancrazio Papapietro, Adela Yang, Shannon Odell, Daniel Murphy)
- Regulation of dendritic spine remodeling by group I metabotropic glutamate receptors (Magdalena Kalinowska, Catherine Castillo, Anna Francesconi)
• Serotonin uptake transporter in heterologous neurons controls cortical patterning during neonatal brain development (Xiaoning Chen, Sofia Jurgensen Hartke, Kostantin Dobrenis, Pablo Castillo, and Ji Ying Sze)
• The DNA replication program is altered at the FMR1 locus in fragile X embryonic stem cells (Jeannine Gerhardt, Mark J. Tomishima, Nikica Zaninovic, Zi Yan, Qiansheng Zhan, Dilek Colak, Zev Rosenwaks, Samie R. Jaffrey and Carl L. Schildkraut)
• Towards an understanding of gene x environment interactions in neurocognitive disease (Rebecca A. Nebel, Herb Lachman, Brett S. Abrahams)
• Visual attention and recognition memory in girls with Rett syndrome (Susan A. Rose, Aleksandra Djukic, Jeffery J. Jankowski, Judith F. Feldman, Iris Fishman, and Maria Valicenti-McDermott)

**Deafness and Communication Disorders Cluster**

• Aberrant Cx26 hemichannels and keratitis-ichthyosis-deafness syndrome (Helmuth A. Sanchez, Miduturu Srinivas, Thomas W. White, Vytautas K. Verselis)
• Effectiveness of late implantation in children with prelinguistic deafness (PLD) (Janie Chobot-Rodd)
• Functionally impaired pulvinar-cortical pathways for sustained attention processing in children with ADHD (Xiaobo Li, Ariane Sroubek, Mary S. Kelly, Iris Lesser, Elyse Sussman, Craig A. Branch, John J. Foxe)

**Nutritional and Environmental Determinants of Brain Development Cluster**

• Alterations in the hepatic and hypothalamic epigenome of mice exposed to a maternal high fat diet (Lyda Williams, Y Seki, M Suzuki, X Guo, D Zheng, JM Greally, EB Katz, MJ Charron)
• Altered CpG methylation at blood pressure and body weight QTLs in human CD3+ T lymphocytes from intrauterine growth restricted newborns (Yoshinori Seki, L Williams, F Delahaye, M Suzuki, X Guo, D Zheng, J Greally, F Einstein, MJ Charron)
• Conditional vitamin D receptor (VDR) deletion delays puberty and permanently disrupts reproductive physiology in females only (Thomas Fisher, Fangyin Meng, Joseph Davis, Jun Shu, Genevieve Neal-Perry)
• Early life vitamin D deficiency programs sex differences in hypothalamic and pituitary gene expression (Fangyin Meng, Thomas Fisher, Joseph Davis, Jun Shu, and Genevieve Neal-Perry)