KANSAS CITY AREA LIFE SCIENCES INSTITUTE, INC.

Regional Strategic Assessment Neuroscience Working Group
Neurodevelopment Subcommittee Meeting Agenda

Date and Time: Wednesday, March 30, 2016 from 1:00 – 3:00 pm
Location: Children's Mercy Kansas City, Adele Hall Campus
2401 Gillham Road, Conference Room 21

Attendees:

David Beversdorf, MD
University of Missouri
Wayne O. Carter, DVM, PhD, DACVIM
Kansas City Area Life Sciences Institute
John Colombo, PhD,
University of Kansas
Keith A. Gary, PhD
Kansas City Area Life Sciences Institute
Matthew W. Mosconi, PhD (Chair)
University of Kansas
Sarah Soden, MD
Children's Mercy
Steven Shapiro, MD, MSHA
Children's Mercy
Zohreh Talebizadah, PhD
Children's Mercy
Kathy Thiemann-Bourque, PhD,
University of Kansas
Steven F. Warren, PhD
University of Kansas

Minute taker: Sharon Newman, Kansas City Area Life Sciences Institute

Welcome and Introductions

Attendees represent a broad range of expertise, from animal models and preclinical approaches all the way through applied clinical interventions. While the group has interests in neurodevelopmental disorders in general, there are also specific interests in autism spectrum disorders, Fragile X syndrome, and communications disorders. It will be our challenge to determine whether to keep a broad view of neurodevelopmental disorders or focus on specific disorders. Attendees were asked to introduce themselves and share some information about their specific programs:

David Beversdorf, MD, (MU)
Associate Professor, Departments of Radiology, Neurology, Psychology and the Thompson Center, University of Missouri

Works in areas of autism research:

1. Prenatal stress
2. Interaction between medical comorbidities and stress reactivity in autism – there are a couple of papers coming out soon
3. Psychopharm where we are looking at propranolol as an agent for autism. Just two weeks ago he was awarded a $1.5M DOD grant for this research project.
4. Former KCALSI grant recipient.

Sarah Soden, MD (CMH)
Developmental and Behavioral Medicine
Director, Genome Center at Children's Mercy Hospital

Research interests include neurodevelopmental disabilities, mostly diagnosable monogenetic rare disorders. She is involved with KU researchers in a gene discovery project looking at the etiology of Tourette syndrome.

Zohreh Talebizadah, PhD, (CMH)
Director, Autism and Neurodevelopmental Disorders Laboratory, Section of Genetics, Children's Mercy Hospital
Associate Professor, University of Missouri-Kansas city School of Medicine,

Dr. Talebizadeh's research interest is on investigating the underlying genetic and epigenetic factors in the etiology of autism and to find ways to subtype this heterogeneous population with the focus on: identification of autism spectrum subtypes and examination of gene regulatory processes, including alternative splicing, noncoding RNAs and X chromosome inactivation.

She is currently working on a collaborative project with Dr. Beversdorf. She has a newly funded DOD project focused on genetic approaches to determine if obesity is a comorbidity of autism. Recently Dr. Talebizadah received a PCORI engagement award to form an advisory committee and develop a roadmap for incorporating genetic studies in outcomes research projects. She also has a larger PCORI methodology proposal under review.

Steven Shapiro, MD, MSHA, (CMH, UMKC, KUMC)
Division Director, Neurology, Children's Mercy Hospital
Professor of Pediatrics, University of Missouri-Kansas City School of Medicine and KUMC in pediatrics and neurology

Dr. Shapiro is interested in broad number neurodevelopmental and neurological disorders and partnering with genomics. His personal research interest is in Kernicterus newborn disorder, a form of brain damage caused by excessive jaundice. We believe that it can cause more subltle underdevelopment disabilities at more subtle levels.

John Colombo, PhD, (KU)
Professor Psychology
Director, KU Lifespan Institute (Schiefelbusch Institute for Life Span Studies),
He has research programs in early attention and identifying bio-behavioral markers in autism. He also works in a KUMC lab looking at prenatal nutritional status and supplementation with DHA on cognitive development through childhood.

Kathy Thiemann-Bourque, PhD, (KU)
Associate Research Professor, Juniper Gardens Children's Project, KU Life Span Institute, Her research focuses on preschool children with autism and employing iPads as voice outlet and communication devices. She is a co-investigator on a project with Nancy Brady in an NIH funded Communication Success and AAC Project.

Steven F. Warren, PhD (KU)
Professor, Speech-Language-Hearing: Sciences and Disorders, KU Lifespan Institute, Hs is previous vice chancellor of research graduate studies for a while and the director of the Lifespan Institute.

Dr. Warren has been focused on neurodevelopment disabilities, autism, Down syndrome and especially fragile X syndrome. He is a behavioral scientist and has performed many intervention studies using randomized clinical trials. For the past 17 years has had been researching a natural history study of fragile X syndrome along with Nancy Brady, PhD. They received funding to do a five-year study on the effects of parenting in the development in fragile X syndrome in fifty five children who are spread out across the country. They visit the families in their homes every 18 months and record 30-35 minutes of observation that involve the mother and child interacting in a variety of scenarios. This data has been powerful in terms of results that show different aspects of parenting having impact on these children accumulatively, including controlling for autism and other effects. Recently, their grant was extended for five more years into its third cycle.

Matthew W. Mosconi, PhD (KU: Committee Chair),
Associate Professor, Clinical Child Psychology Program and Life Span Institute,

Regional Strategic Assessment Update/Questions

Wayne O. Carter, DVM, PhD, DACVIM
President and CEO, Kansas City Area Life Sciences Institute
Wayne reviewed the process and outcomes of the Path to 2025 strategic assessment. As we consider developing ecosystems, there may be opportunities in the overlap between outcomes research/health IT and neurodevelopment. As a group, we need to strategically assess what ecosystem components are missing and how to grow existing strengths.

There are a few companies in the area that are in the neurodevelopmental space

- AB Pathfinder acquired Ensure Billing and now operates as Pathfinder Health Innovations. In addition to serving as a back-end for autism clinics, the company's platform allows collection/quantitation of outcomes data. They have over 128 clients, many of whom are outside this region. They have accumulated a significant amount of quantitative data and recognize the value of the data, but it has received little attention to-date.
- LEKA is a startup company at the Sprint Accelerator that developed an interactive smart toy designed to stimulate children with developmental disorders (autism, Down syndrome, Multiple Disabilities).
- Netsmart, a Cerner spinoff, recently announced a joint venture between San Francisco-based equity firm GI Partners and Chicago-based Allscripts Healthcare Solutions Inc. to buy Netsmart for $950 million. Netsmart expects to add 250-300 people at its headquarters this year.

As we think about developing an ecosystem around this space, we want to consider including companies that can take technology and discoveries to commercialization. Dr. Carter referred to the list of specific deliverables and special considerations for the scientific areas. The Neuroscience Working Group and subgroups should also develop goals and metrics to identify if we are achieving goals. If we determine that autism spectrum disorder (ASD) is a regional strength, we want to set goals. We need to ask how we are going to grow this strength as a region. He noted that both he and Dr. Gary continue to see ASD strengths rise to the surface, as represented by Elsevier analytics.
What are other examples of establishing regional ecosystems.

- The Outcomes Research/health IT will be working with payors to create value-based healthcare. The neurosciences effort can link into the Outcomes Research/hIT; specifically the Outcomes Research/hIT and phenotyping go well together.
- The Kansas City Proteomics Consortium (KCPC) was described as an example of regional collaboration establishing significant proteomics infrastructure. After convening key stakeholders to define specific proteomics equipment and personnel needs, KCALSI vigorously pursued federal earmarks for these stakeholders through legislative advocacy at

the federal level and assisted in securing more than $16 million for facilities and equipment in support of the KCPC. The burden for making strategic personnel hires was the responsibility of individual academic institutions. There was insufficient attention given to bioinformatics component of this initiative.

Round-Robin Asset Identification, Networks, Collaborations

University of Missouri

Dr. Beversdorf is involved with the Thompson Center for Autism and Director of the Neuroscience PhD program, with 12 students currently enrolled.

- Thompson Center for Autism - University of Missouri is a large clinic, involving a large population and research.
    - Drs. Stephen Kanne and Micah Mazurek just completed an R01 and have developed an assessment tool to measure the success of autism treatments.
    - Member, Autism Treatment Network, a multi-institutional program that is building a large patient network for potential trials, with subsets to fund small subgrants.
    - Dr. Beversdorf is sole developmental researcher at the Thompson Center that is primarily focused on ASD with a basic/translational focus.
    - DOD funded a propranolol trial using an animal model for its behavioral effects. Propranolol is non-selective, if you do this with beta 1 and beta 2 agents you could identify a possible use for a selective agent going forward if this trial is successful. This is a patient focused clinical trial, and has 2 age groups, the 7-14 mentioned, and also 15 and older who could have autism etiology. <u>It is clear that we need biomarkers to specify who will respond.</u> Currently, only FDA approved autism drugs are anti-psychotic Two multi-site trials failed. Clinical trials to-date have focused on two strategies: NMDA antagonists to decrease hyperglutamatergic tone and a GABA ergic agonist to increase GABA ergic tone, and both failed. There is a subset of responders.
    - The European Union has put together a $2B EU for the "European Autism Interventions - A Multicentre Study for Developing New Medications (EU-AIMS) and this could represent a government/industry partnership opportunity (e.g., Alzheimer's Disease Neuroimaging Initiative). Missouri Republican Senator is the head of one of the committees that makes NIH funding decisions. He has openly said he wishes to increase NIH funds. There could be an industry/academic/NIH partnership that could include the Kansas and Missouri area. Interstate collaboration helps us compete for funding dollars. In Kansas, Senator Moran is on the Appropriations Committee and favorable to increasing NIH funding.

Summary:

- The University of Missouri is has a large clinical population ripe as a resource for clinical trials.
- Biomarker development has hindered the field in areas of fragile X and autism. Perhaps other regional institutions could provide this resource. Dr. Beversdorf will share a “position paper” that is under review describing this large scale opportunity.

Children’s Mercy

- A discussion on drug development should also be included. Steven Leeder and Scott Weir’s groups have so many strengths when it comes to pharmacologic compounds that can be repurposed and the pharmacogenomics and the metabolism of drugs that are often left out of the trials.
- Drs. Soden and Leeder are working with Hogland Institute to make a fluorine imaging helmet. A large number of drug compounds possess fluorine as a stabilizer for pharmacologic compounds. Hogland is uniquely capable of measuring fluorine concentrations in the brain.
- Andrea Gaedigk, PhD is the world’s expert on CYP2D6.

- CMH has strength in epilepsy, and genetic causes of epilepsy, and has plans for multicenter trials in the future.
- CMH has strength with Tourette Syndrome Clinic. Tourette Syndrome Association (TSA) as recognized Children's Mercy as a TSA Center of Excellence (one of ten nationally).
- CMH has an active cognitive behavioral intervention for tics (CBIT) program and collaborates with Marco Bortolato at University of Kansas.
- CMH has a heart center with state-of-the art home monitoring, and neurocognitive outcomes of these children is becoming a major part of this home monitoring.
- CMH has four Neurodevelopmental treatment (NDT) boarded staff.
- CMH Genomic Center has been doing clinical genome and large panel tests for some time. Recently we brought up clinical symptom driven exomes and a variety of Next Gen sequencing panels and these are now clinically available.
- Dr. Soden is doing an outcomes research tech project looking at the clinical impact of doing Next Gen sequencing diagnostics very early in the workup of families. We are sequencing them on their second visit and following up with them every six months. She is using philanthropic funding for this project.
- Children's Genomic Center performs whole-genome sequencing in its Neonatal Intensive Care Unit (NICU) using STAT-Seq for neonates with any suspected genomic disorder, and many have neurological defects.
- CMH is bring up including transcriptomics, metabolomics, single cell sequencing. Single cell sequencing is a good way to get information whether mutation or germ DNA are present in a heterogeneous population.

University of Kansas

- Kansas Intellectual and Developmental Disabilities Research Center (KIDDRC) has been funded by the National Institute of Health and Human Development for the past 45 years and is internationally recognized.
- KU Life Span Institute has at least 55 grants that are relevant to intellectual development disabilities. Dr. Colombo noted that some of these grants are not listed on the handout list of NIH funding/University Centers. The grants are organized in terms of themes that represent longstanding strengths; including language and intellectual disability; intervention and risk (intervention biomarkers and early identification); access of preclinical work on reproductive biology. The longstanding strengths have been around measurement; behavioral markers, behavioral characterization, and development of animal assays, and preclinical assays around animal work that have branched out to genetic phenotyping. There is no other place in country that has this access of measurement. Juniper Gardensis actively looking to commercialize an assessment package for evaluating whether children who enteredz into a program need to have things changed. This demonstrated a translational cycle, and could be the theme of our strengths,
- Dr. Colombo has been involved in nutritional compounds as a direct outgrowth of the measurement strengths. Clinical research organizations worldwide are looking for outcome measures to harmonize their clinical trials to get outcomes to determine whether their interventions work before children reach the ages of 8 -9.
- Dr. Mosconi added that they recently submitted for a multisite grant to study Phelan-McDermid Syndrome, a rare disorder with moderate to severe intellectual disability. They need multiple sites to move this into clinical trials and get enough candidates.

Discussion

- Consider developing a *translational measurement corridor* that goes from preclinical to human to application with a health IT/outcomes component.

- Group consensus leans toward a broader approach rather than a focus on autism (biomarker aspect and gene regulation). More important is the dense characterization of individuals both intellectually and behaviorally.
- Understand the intersection between genetic markers and neurodevelopmental behavior and being able to define differential outcomes at that behavioral level that informs genetic approaches or understanding the differences.
- Emphasis of NIH and DOD RFAs are less focus on pure gene identification for autism. Genetic approaches need to integrate with other approaches to identify subsets responding to a particular treatment. This is consistent with current outcomes research methodologies.
- Dr. Soden expressed concern about pitting the region against stiff external competition if we are too narrowly focused on autism spectrum disorders. There are much larger research teams with significant funding playing in this space. Dr. Carter noted that:
    - This group needs to determine their strength and focus, and incorporate this into existing strengths such as outcomes research/hIT. It makes sense to integrate the neurodevelopment research into the outcomes research/health IT.
    - The region has a large concentration of contract research organizations (CROs). Could the region consider developing a network of pre-enrolled, pre-certified well-charaterized ASD (or other) patients?
- Should other institutions be invited to participate on the committees' efforts, specifically the Washington University. John Constantino, MD at Washington University is familiar with Kansas City assets and has some existing collaborations. He expressed interest in being kept apprised of progress. Dr. Beversdorf noted that MU is part of Wash U's CTSA.

Collaborate2Cure

The Collaboration Task Force recommended a model to promote collaboration across the region, similar to 1MillionCups at Kauffman Foundation. You need two things to collaborate, 1) a well-defined problem, 2) an incentive. KCALSI will be launching Collaborate2Cure, a weekly event that will rotate to various venues with two speakers providing a TED-like talk followed by Q&A and networking. This topic may be pursued for 6-8 weeks, with the first topic likely on Lymphoma. Within the process there will be natural connections that will develop.
Is this of interest to the Neurodevelopmental working group?

Summary of Regional Strengths

1. Drug discovery and pharmacogenetics.
2. Behavioral measurement.
3. Research Outcomes and Health IT.

Moving forward we will need to leverage these strengths and come up with reasonable goals and timelines.

Next Steps

- *KCALSI will distribute meeting minutes and work with Dr. Mosconi to define actions.*
- *KCALSI will invite Pathfinder Health Innovations to future meetings.*
- *John Colombo will develop a one page concept paper on the vision for a translational continuum for neurodevelopmental research.*
- *Dr. Beversdorf will share the "position paper" that is under review.*