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2013 IACC Strategic Plan - Question 2 Draft

"How can I understand what is happening?" - Volunteer drafter – Walter Koroshetz

INTRODUCTION:

The aspirational goal of Question 2is understanding the biological basis of autism spectrum disorders (ASD) to enable targeted and personalized interventions. Over the course of the last several years a great deal has been learned about altered neurodevelopment in ASD, but the knowledge base is still not sufficient to support personalized interventions, although a few interventions are in early phase testing. Question2 has also evolved as the science has provided more insight into the complexity of ASD. Specifically, there is a better sense of the role of the immune system in brain development and potentially in autism. The contribution of gastrointestinal symptoms, sleep disorders, and epilepsy to the burden of illness and the biologic mechanisms by which specific gene mutations cause syndromic autism are better understood. Additionally, the development of technological advances in brain imaging has furthered the mapping of the structure and measurement of activity as the brain develops.

PROGRESS TOWARDS THE STRATEGIC PLAN OBJECTIVES: The 2009 Strategic Plan, which was revised in 2010 and 2011, included 9 objectives under the heading of Question 2 which include 7 short-term objectives and 2 long-term objectives designed to address gaps in current research on the biological basis of autism. The 2011-2012 Portfolio Analysis performed a long range evaluation of public and privately funded autism research. Based on this analysis, the cumulative investment from 2008-2012 was $362M. Approximately 50% of the investments which align with Question 2 were not specific to the gap-targeted objectives. This represents a long-standing substantial investment in understanding the biology of autism outside of specifically identified gap areas.

Of the 9 objectives in Question 2, four objectives addressing fever and immune system interactions with the CNS, biological pathways of genetic conditions related to autism, biological mechanisms of co-occurring conditions, and specific genotypes that underlie ASD phenotypes met or exceeded the recommended budget and fulfilled the recommended number of projects. The remaining 5 objectives including studies on females with ASD, raising awareness of brain and tissue donation, characterization of regression, application of biosignatures to diagnosis, and large scale study longitudinal studies of diverse populations with ASD were below the recommended budget and number of projects, however, some progress has been made on all objectives. .

LONGITUDINAL aND COMPREHENSIVE EXAMINATION oF THE BIOLOGICAL, CLINICAL, aND DEVELOPMENTAL PROFILES oF INDIVIDUALS WITH ASD: Autism is considered a neurodevelopmental disorder that begins in early life and longitudinal study is critical to understand how brain function is altered throughout the lifespan. Indeed much science points to the prenatal period and the first years of life as the critical window for onset and development of ASD. Recent gene expression studies demonstrated that key ASD-related genes and genetic pathways are activated during specific times in fetal development, and epidemiological studies found that prenatal conditions and exposures found that some factors, such air pollution and certain medication use, are associated with increased risk, while prenatal vitamin use appears to reduce risk[1,2,3,4,5,6,7]. A recent small, longitudinal study of infants

demonstrated normal eye tracking behavior that then declined over 2-6 months after birth predicted later development of autism[8]. Another study found that white matter tracts in infants who develop ASD are detectably different from those of neurotypical children at 6-24 months of age[9]. Additionally, a number of imaging studies have demonstrated greater brain volume in ASD, but only during a specific early developmental stage. Other functional and structural imaging studies are beginning to uncover correlates of ASD differences in processing of visual and language inputs. New sophisticated techniques such as resting state MRI, resting state EEG, magnetoencephalography, and evoked related potentials are being used to noninvasively interrogate neural circuits in ASD Repeated over time, these measures can help chart neurodevelopment. Such techniques hold the potential for early diagnosis as well as serving as potential targets for therapies that harness neuroplasticity to improve functional deficits.

FEVER, METABOLISM and IMMUNITY: Research on the potential relationship between the immune system and ASD has grown considerably over the past 2 years, resulting in several major breakthroughs. In the realm of basic developmental research, immune cells and immune signaling molecules have been identified as central to establishment of stable connections between neurons. Brain tissue studies of the expression patterns of genes showed differences in immune pathways in those with autism compared to typically developed individuals. Of note, the role of immune genes was not detected in population genetic studies suggesting a non-genetic basis for the immune differences. Specific autoantibodies targeting fetal brain proteins have been found in mothers and in some children with ASD. These maternal autoantibodies appear to alter neurodevelopment in non-human primate studies.[10] Further, children born to mothers with the autoantibodies were found to have an abnormal brain enlargement on MRI studies compared to the typically developing controls and persons with ASD without the antibodies[11].

NEURODEVELOPMENT in FEMALES: While ASD affects more males than females, there is a growing awareness that ASD in females may be missed, possibly because they have less disruptive behavioral disorders. Multiple familial and genetic studies suggest female gender protects against autistic behavior and more genetic disruptions are required to cause autism in females. An ACE center is now devoted to understanding this potential "female protective factor".

BRAIN aND TISSUE DONATION: The research community is in extreme need of brain and other types of tissue to enable important studies. One example of the value of brain tissue is the recent study using modern stereological techniques, researchers blind to subject diagnosis found young children with autism have a 67% excess neuron in prefrontal cortex – the part of the brain centrally involved in higher-order social and communication behavior[12]. Since prefrontal neurons are generated in the second trimester, this neuron excess indicates abnormal brain development in autism begins before birth. These types of studies can only be performed if appropriate brain tissue is available. The Autism BrainNet initiative is a multi-site effort supported by Autism Science Foundation, Simons Foundation, Autism Speaks and the Nancy Lurie Marks Family Foundation that will target autism specifically and will include and autism-specific brain donation outreach campaign to address this need. In the public sector, NIH recently launched the NIH Neurobiobank which includes samples for research on autism as well as other brain disorders and has an associated online publication "Why Brain Donation? A Legacy of Hope" to increase awareness about brain donation. The lack of brain tissue is considered a major factor

impeding progress in ASD research. The collection of biological samples from very young children at risk for ASD is a potential opportunity to facilitate multidisciplinary efforts to establish biomarkers of ASD risk.

GENETIC CONDITIONS RELATED tO AUTISM; The greatest explosion of knowledge related to Question 2 has come from studies of the biologic processes regulated by genes that either cause syndromic autism (Fragile X syndrome, Rett syndrome, Tuberous Sclerosis) or are associated with increased risk of non-syndromic autism. Overlap has been uncovered in the biological mechanisms that give rise to ASD especially at the level of synaptic function. For instance, deletion or mutation of the SHANK3 gene causes autism and the Shank3 protein was found to play a critical role in glutamatergic synapses[13]. Glutamatergic neurotransmission was also found to be altered in Fragile X and Tuberous Sclerosis. A variety of other rare genetic mutations associated with autism have been found to affect synaptic function raising the question of whether a common synaptic deficit with multiple causes results in autism. After finding these functional deficits at the synapse, investigators have asked whether it is possible to reverse functional deficits at the root cause of ASD and indeed this has been demonstrated in some animal models. Indeed, early stage clinical trials have been mounted to treat Tuberous Sclerosis with rapamycin[14], and non-syndromic autism with specific synaptic glutamate receptor antagonists[15].

The new field of epigenetics, the study of gene modifications that occur over time, has also been brought to bear on ASD. Recent publications have found that the methylation of DNA occurs in several brain regions in autism[16]. One report determined that the DNA in typically developing females is less methylated than in ASD females, with a similar trend for normal males compared to ASD males[17].

CO-OCCURRING CONDITIONS WITH AUTISM : A number of genetic abnormalities have been found to be associated with autism, epilepsy and intellectual disability suggesting that all are related to the same neurodevelopmental abnormality. A recent NIH workshop on epilepsy and ASD offers recommendations for next steps and research opportunities. Studies identified genetic mutations, malfunctioning ion channels, interneuron deficits and other factors that may play a critical role in ASD with co-occurring disorders[18]. A very recent study found three distinct patterns of specific co-morbid conditions which suggests they may represent distinct etiologies with different genetic and environmental contributions[19]. Abnormalities in circadian rhythms have been identified as potential cause of sleep disorders in ASD. On the other hand, there is very limited knowledge regarding the biological mechanisms underlying the serious problems of elopement, GI dysfunction, and wandering in persons with ASD.

PROGRESS TOWARDS THE QUESTION 2 ASPIRATIONAL GOAL: The challenges to understanding what is happening in the body that results in ASD are substantial. One opportunity for expanding the research horizon in ASD understanding the gender-associated protective factors in females as this might lead to therapeutic breakthroughs. The role of the immune system in autism both for its “good” role in sculpting neural circuits and its “bad” inflammatory role in upsetting neural circuits, needs to be elucidated. It is especially important to be able to gauge the effects of maternal immune processes on the developing fetal brain. Careful longitudinal studies of important neurodevelopmental processes are clearly required as studies of single time points are likely to miss the point in this dynamic period of

brain development. There is still very little known about why certain children with autism are noted to deteriorate over relatively short periods of time. Ongoing longitudinal studies of high risk children may lead to a better understanding of regression and whether it is a distinct syndrome, or part of the continuum of neurodevelopmental abnormalities in ASD. The underlying basis for specific disabilities (i.e. verbal vs. non-verbal ASD), specific behaviors, heterogeneity in severity, sleep disorders, gastrointestinal disturbances, et cetera remain poorly understood and without effective treatments. A systems biology approach seems necessary to understand the multifaceted disturbances that we know occur in ASD.

This is an exciting time in brain research with exciting new tools that further reveal biologic basis of ASD. Launched in 2013, The President's BRAIN initiative, which aims to map the interactions of individual brain cells and complex neural circuits, is focused on neurotechnology development. It will advance the ability to characterize the cellular differences in ASD vs. typically developing individuals. It also promises to substantially improve the ability to record brain circuit activity that would be helpful to monitor neurodevelopment or to guide therapy in ASD. Induced pluripotent stem cell technology is another revolutionary tool, which enables scientists to convert cells taken from a simple skin biopsy into nerve cells enabling the search for the autistic biologic phenotype, (i.e. synaptic dysfunction), and even to screen drugs for their ability to ameliorate the autistic phenotype. Breakthroughs in RNA sequencing and epigenetics now allow powerful new studies of gene regulation in brain tissue. In the world of imaging, the NIH's Human Connectome Project aims to produce a detailed map of brain connections in those with ASD and to visualize how this map changes over time from infancy through childhood. These and other techniques bring together tremendously large amounts of data from a variety of tissues and cells to enable systems biology approaches to understand the connections between different systems—genetics, brain circuits, immune system, metabolism, microbiome, etc. The richness of the data and the variety of tools call for a coordinated approach in which findings are replicated and the tools validated so that they can become clinically useful.

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