2013 IACC Strategic Plan - Question 2 Draft

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

Introduction:

The aspirational goal of Question 2 is to understand the biological basis of autism spectrum disorder (ASD) so that targeted and personalized interventions may be developed to reduce disabling symptoms and increase quality of life for people across the spectrum. Over the course of the last several years a great deal has been learned about altered neurodevelopment in ASD and a few interventions are in the early phases of testing, but the knowledge base is still not sufficient to support personalized interventions. Objectives within Question 2 have also evolved as the science has provided more insight into the complexity of ASD. Specifically, through recent groundbreaking brain mapping and brain imaging research, much has been learned about how the brain develops and how autism unfolds in early development, and insights from syndromic forms of ASD have provided clues about the general mechanisms and genetic pathways that are affected in ASD. There is also a better sense of the role of the immune system in brain development and potentially in autism, and progress has been made in understanding and developing guidelines to address co-occurring conditions such as gastrointestinal (GI) symptoms, sleep disorders, and epilepsy that can greatly impact quality of life for people with ASD. Finally, the biological mechanisms by which specific gene mutations cause syndromic autism are now better understood.

Progress Toward the Strategic Plan Objectives:

The 2009 IACC Strategic Plan, which was revised in 2010 and 2011, included nine objectives under the heading of Question 2, encompassing seven short-term objectives and two long-term objectives designed to address gaps in current research on the biological basis of autism. IACC Portfolio Analysis data from 2008-2012 indicated that the cumulative investment in research categorized under Question 2 during this period was $362M. Approximately 50% of the investments that align with Question 2 were made in gap areas identified in the IACC Strategic Plan objectives, while the other 50% were invested in other/core research activities on the underlying biology of autism. The substantial activity in other/core research areas indicates long-standing investment in research toward understanding the biology of autism that has been augmented by growth in emerging areas of scientific research.

Of the nine objectives in Question 2, four objectives addressing fever and immune system interactions with the central nervous system (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 five objectives (studies on females with ASD, raising awareness of brain and tissue donation, characterization of regression, application of biosignatures to diagnosis, and large scale 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.

Of note, in 2009, NIH received funds from the American Recovery and Reinvestment Act (ARRA) that were used to support a series of initiatives totaling $122 million over two years on key scientific areas including the heterogeneity of ASD, which encompasses work on topics such as basic biology of ASD, biomarkers, risk factors and treatments, that were responsive to the newly released IACC Strategic Plan

for ASD Research (http://iacc.hhs.gov/portfolio-analysis/2010/index.shtml#appendixc). This infusion of new funds helped jumpstart efforts to address Strategic Plan objectives and is reflected in the portfolio across all Questions of the Strategic Plan.

Progress in 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 studies are 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[1,2]. Furthermore, epidemiological studies have found that prenatal conditions and environmental exposures, such as air pollution and certain medication use, are associated with increased risk, while prenatal vitamin use appears to reduce risk[3–8]. 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[9]. 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[10]. Additionally, a number of imaging studies have demonstrated greater brain volume in ASD, but only during a specific early developmental stage[11]. Other functional and structural imaging studies are beginning to uncover correlates of ASD differences in processing of visual[12] and language[13] inputs. New sophisticated techniques such as resting state magnetic resonance imaging (MRI), resting state electroencephalography (EEG), and magnetoencephalography (MEG) and magnetic resonance spectroscopy (MRS) are being used to noninvasively examine neural circuits in ASD. Repeated over time, these measures can help chart neurodevelopment. Such techniques hold the potential for early diagnosis as well as measurement of efficacy of therapies that harness neuroplasticity to improve functional deficits.

Progress in the Fields of 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 essential for establishing stable connections between neurons during early brain development[14,15]. Brain tissue studies of the expression patterns of genes have indicated differences in immune pathways in those with autism compared to that of typically developed individuals[16,17]. Of note, the role of immune genes was not detected in population genetic studies, suggesting a non-genetic basis for the immune differences[1,18]. Specific autoantibodies targeting fetal brain proteins have been found in a subgroup of mothers of children with ASD and in some children with ASD[19]. These maternal autoantibodies appear to alter neurodevelopment in non-human primate studies[20]. Further, children born to mothers with these autoantibodies were found to have an abnormal brain enlargement on MRI studies compared to that of typically developing controls and persons with ASD without the antibodies[21]. Preliminary research findings suggest that metabolic and immune factors may play a role in ASD in some individuals[22–27]. Reports of improved behavior in persons with ASD during periods of fever still remain unexplained, warranting further efforts in this area[28].

In addition, there have been intriguing new findings with regard to the role of metabolism in autism. For example, a rare hereditary form of autism is caused by mutation of a gene that codes for the enzyme BCKD-kinase, which prevents the body from breaking down the essential branched-chain amino acids leucine, isoleucine and valine after eating food[26]. When BCKD is inactivated, individuals cannot maintain adequate levels of the above mentioned amino acids and they experience a deficiency. The problem can be addressed through amino acid supplementation, but research is needed to determine whether supplementation can reverse the autism symptoms associated with this disorder. In a separate study, preliminary findings have linked a rare form of autism with a gene defect that interferes with the body's ability to manufacture carnitine, an amino acid that helps convert fat into energy, suggesting that another form of autism also may be potentially be amenable to treatment through nutritional supplements[27]. Further work in this emerging field may yield new insights into the mechanisms of ASD and potential for novel treatments.

Progress in Understanding Neurodevelopment in Females:

While ASD affects more males than females, there is a growing awareness that ASD in females may be underdiagnosed, potentially due to differences in the manifestations of ASD in females, such as less disruptive behavioral disorders and stronger ability to recognize emotions in facial expressions, which mask symptoms[29,30]. Multiple familial and genetic studies suggest that female gender may protect against autistic behavior and that more genetic disruptions are required to cause autism in females[31]. The abnormal brain growth patterns that have been observed in people with ASD are also more pronounced in females than in males[11]. One of the newly funded NIH Autism Centers of Excellence (ACE) networks, including Yale University, UCLA, Harvard, and the University of Washington, is now devoted to understanding this potential "female protective factor"[32].

Progress in the Field of 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. In these studies, researchers observed that young children with autism have 67% more neurons in the prefrontal cortex – the region of the brain centrally involved in higher-order social and communication behaviors[33]. Since prefrontal neurons are generated in the second trimester, this neuron excess indicates that 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, a multi-site private effort supported by the Autism Science Foundation, the Simons Foundation, Autism Speaks, and the Nancy Lurie Marks Family Foundation, will target autism specifically and will include an 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. As efforts to collect brain tissue progress, the collection of other biological samples from very young children at risk for ASD is another potential opportunity to facilitate multidisciplinary efforts to establish biomarkers of ASD risk.

Progress in Understanding Genetic Conditions Related to Autism and synaptic function:

The largest area of scientific progress related to Question 2 has come from studies of the biological 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 – those synapses that transmit neuronal signals using the excitatory neurotransmitter glutamate[34]. Glutamatergic neurotransmission was also found to be altered in Fragile X and Tuberous Sclerosis[35,36]. 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 synaptic deficits and indeed this has been demonstrated in some animal models[37]. Moreover, early stage clinical trials have been mounted to treat Tuberous Sclerosis with rapamycin, a drug that affects synaptic transmission via effects on mTOR signaling[38], and non-syndromic autism with specific synaptic glutamate receptor antagonists[39]. Recent studies that have shown that oxytocin can alter synaptic function and that the oxytocin receptor gene may be mutated or epigenetically altered in people with ASD[40–42]. Consistent with these findings, exciting new clinical trial data suggest that intransal oxytocin can improve social function in ASD[43,44].

The new field of epigenetics, the study of DNA modifications that change over time and affect gene expression, has also been explored in ASD-related research. Recent publications have found that the methylation of DNA occurs in several brain regions in autism[45]. One report determined that the DNA in typically developing females is less methylated than that of females with ASD. A similar trend is observed in neurotypical males compared to males with ASD[46]. Furthermore, new data suggests that there are various genetic alterations and mutations in neurons that may occur during development[47]. Evidence suggesting that DNA hypermethylation may be involved in the development of cerebellar abnormalities associated with ASD has also emerged, thus reinforcing the value of integrative genomic approaches in better understanding the etiology of ASD[48].

Progress in Understanding Conditions Co-occurring with Autism:

Much progress has been made in understanding the prevalence and biology of conditions that commonly co-occur with ASD, including epilepsy, sleep disorders, gastrointestinal (GI) disturbances, attention deficit hyperactivity disorder and other psychiatric comorbidities[49–54]. A recent study found three distinct patterns of specific co-occurring conditions in persons with ASD, which suggests that such groupings of symptoms may represent distinct etiologies with different genetic and environmental contributions[55]. A 2012 NIH workshop on epilepsy and ASD offered recommendations for next steps and research opportunities to better understand seizure disorders in ASD[56]. The workshop report reviewed several studies that identified genetic mutations, malfunctioning ion channels, interneuron deficits, and other factors that may play a critical role in ASD with co-occurring seizure disorders. Abnormalities in circadian rhythms have been identified as potential cause of sleep disorders in ASD[57]. Several recent studies have pointed to differences in gut microbiota as playing a potential role in ASD[58–60]. In a recent finding, the common co-occurring issue of gastrointestinal (GI) dysfunction was linked to ASD and treatment with a probiotic ameliorated the bacterial, GI and behavioral changes in a mouse model[59], suggesting the possibility of probiotic treatments to help a subset of individuals whose ASD is accompanied by GI symptoms. Another common issue among those with ASD is the propensity to wander. Currently, though wandering presents an important safety issue for families with children on the spectrum, there is very limited knowledge regarding the biological basis of this behavior, and thus further research is needed in this area.

Progress Toward the Aspirational Goal:

The challenges to understanding the underlying mechanisms of ASD are substantial. One opportunity for expanding the research horizon in ASD is to understand the gender-associated protective factors in females, as this might lead to therapeutic breakthroughs. The roles of the immune system in sculpting neural circuits and in neuroinflammation and response to stress also need further elucidation. 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 needed as studies examining single time points are likely to miss important occurrences 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 various disabilities (e.g. verbal vs. non-verbal ASD), specific behaviors, heterogeneity in severity, sleep disorders, and gastrointestinal disturbances remain poorly understood and lack effective treatments. A systems biology approach is thus necessary to understand the multifaceted disturbances that occur in ASD.

Many new tools to further reveal the biological basis of ASD are emerging. Launched in 2013, the President's Brain Research through Advancing Innovative Neurotechnologies (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 compared to 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. One such tool that will promote advances relevant to the BRAIN initiative is Clear, Lipid-exchanged, Anatomically Rigid, Imaging/immunostaining compatible, Tissue hYdrogel (CLARITY), a new technology that aids in the visualization of the human brain structure as well as the localization of proteins, neurotransmitters, and gene expression patterns. This neurotechnology is already being used to study the brain of a person affected by autism[62]. Induced pluripotent stem cell (iPSC) technology is another revolutionary tool, which enables scientists to transform cells (drawn from simple skin biopsies) into nerve cells[63,64]. Such methods can be used to research biological phenotypes observed in autism (i.e. synaptic dysfunction)[34,65,66], examine specific genes and pathways that are differentially regulated, and screen drugs for their ability to ameliorate autistic phenotypes[67]. 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, including genetics, brain circuits, the immune system, metabolism, and the microbiome. The richness of the data and the variety of tools needed 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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