IACC Strategic Plan Question 2 Outline
January 2017

Question 2: What is the Underlying Biology of ASD?

Aspirational Goal: **Discover how alterations in brain development and nervous system function lead to ASD in order to enable the development of effective targeted interventions and societal accommodations that improve quality of life for people on the autism spectrum.**

Introduction:

Over the course of last decade there is considerable new knowledge related to:

a) the role of genetic contributions to the risk of developing ASD that has enabled a greater understanding of:
    a. Mechanisms by which highly penetrant mutations disturb brain development and brain function in the syndromic forms of ASD.
    b. How the many common genetic variants that affect the risk of ASD converge on disordered synaptic dysfunction as a common mechanism
b) Differences in brain development in persons with ASD as compared to typical development
c) Nature and prevalence of comorbidities in persons with ASD

In almost all cases however our knowledge is incomplete and significant gaps in science have stymied attempts to develop therapies to improve QOL for those suffering with ASD. Over the course of the last decade there have been considerable advances related to the identification of rare mutations of large effect that are highly likely to be causally related to autism in humans. However, the mechanisms by which these gene mutations disrupt the underlying neural circuitry of the brain remain virtually unknown. Autism-associated gene mutations include chromatin remodeling factors, ion channels and synaptic proteins and little is known about how such a diversity of gene mutations cause a common set of human disease phenotypes. Documented differences at the synaptic, cellular and circuit level in animal models of autism, based on human disease associated gene mutations, remain largely correlative in all but a few instances and there is very little information regarding how observed cellular deficits are causally connected with behavioral outcomes. While there have been advances in the nature and prevalence of comorbidities in persons with ASD, much work remains to be done.

Objective 1: To foster research to better understand the neurodevelopmental changes, molecular mechanisms, and brain circuitry that contribute to the structural and functional basis of ASD.

1) **Molecular mechanisms by which gene mutations or common variants lead to ASD** – we have learned more about monogenic forms, but still have much to learn about polygenic forms of ASD. Our understanding of what is happening in the brain to cause ASD and its varying symptoms is informed in large part by studies of the implicated gene effects in cellular or animal models. These genetic findings are the subject of Question 3; the mechanistic studies of the genes' effects, however, are within Q2.

    a) The function of the normal and mutated protein in syndromic forms of ASD, TSC, Retts, Phelan McDermott, SCN1, Fragile X
    b) The function of genes implicated by large GWAS studies
    c) neural effects of genes implicated in ASD. Studies can **now** be performed in cells from persons with syndromic and potentially non -syndromic autism which have been reprogramed to IPSCs and then differentiated into neural cells or even neural tissue. These can then be compared to genetically corrected identical cells (syndromic ASD) or to cells or tissues derived from typical developing controls.
        i. Establish a differentiating phenotype in neurons, glia
            a. Synaptic dysfunction, firing properties, epileptogenesis, etc.
        ii. Explore development and cellular differentiation in brain organoids

    Explore these models for effects of XX vs. XY, sex hormones

2) **Brain Structure and Function in ASD**. Brain imaging technologies to examine brain structure and function in humans has identified differences in brain development and brain connectivity in persons with ASD.
    a) Brain overgrowth during a specific period in development

    Work is ongoing to link these to the core features of ASD:
    a) Difficulties in social interaction
    b) Difficulties in verbal and non verbal communication
    c) Repetitive behaviors

    As well as with other neurological manifestations such as:
    a) Anxiety
    b) Intellectual disability
    c) Epilepsy
    d) Difficulties with motor control
    e) Difficulties with attention
    f) Sleep disorders
    g) Sensory processing

h) Special skills in some persons with autism, ie math, visual, memory

Greater knowledge of the structural and molecular changes in ASD brain is needed. Studies of post mortem brain tissue to uncover developmental abnormalities in brain structure as well as activation of cellular responses especially by the immune system.

a) BRAIN Initiative has as its goal the development of a census of cell types and would be important to compare it with the census of cell types in ASD brain.
b) There is a need to understand the role of the immune system in ASD. RNA studies in ASD brain have identified changes in the brain's immune system. Immune cells in the brain have been recently shown to have a major role in shaping the connections between neurons in development as well as in neurodegeneration.
c) Chromatin remodeling
d) Somatic mutations in brain have **now** been found to occur much more commonly than previously thought. What is their role in ASD?
e) Search for adaptive changes that may be attempts at compensation for a developmental disturbance, either beneficial or with net harm.

3) **Brain Circuitry** Greater knowledge of the brain circuit abnormalities implicated in ASD in animal models which can **now** be explored in detail using techniques to map neural connections, record from large number of neurons during a behavioral task, precisely turn on or turn off specific types of neurons to understand the nature of the brain circuit abnormalities caused by biologic mechanisms tied to ASD, ie. genetic mutations, immune challenge,
    a) Attempt to understand the synaptic dysfunction implicated by the GWAS studies.
    b) Attempt to understand what changes are reversible
    c) Explore these models for the effects of XX vs. XY, sex hormones
    d) Explore how abnormal sensory input and processing affects neurodevelopment

Objective 2: To support research to understand the underlying biology of co-occurring conditions in ASD

4) **Co-Occurring Conditions** Studies of persons with ASD has led to a greater appreciation of the contribution that comorbidities make to a decreased QOL for persons with ASD.
    a) GI dysfunction, microbiome
    b) Seizures
    c) Sleep disorders
    d) Psychiatric disorders
    e) Immune/metabolic differences

5) **Phenotypes, Subtypes and Natural History of ASDs**. More inclusive and more in depth knowledge of the difficulties experienced by persons with ASD is needed to better define and quantify important aspects of the disorder. Phenotyping studies can **now** employ non-invasive monitoring of speech (automatic language processing), motor activity, eye tracking, interactions with others and the environment.
   To better understand the course of the disorder and its variability
   a) Characterize and quantify effect of comorbidities in persons with ASD.
      i. Bowel function, abd pain, sleep patterns, wandering, emotional swings.
   b) Identify phenotypic subtypes to link to genetic differences
   c) Develop algorithms to predict course of the disorder. (precision medicine)
   d) Develop clinical measures that would be useful in intervention trials
   e) Better understand the changes across the lifespan including transition to adulthood and aging.
   f) Differences in phenotype across genders?

Objective 3: To support large scale longitudinal studies that can answer questions about the development of ASD from pregnancy through childhood and the natural history of ASD across the lifespan, and XYZ (could enumerate ways in which large cohort studies could be used to further understanding of ASD – even including science that may overlap with other chapters of the Strategic Plan, as this is a common goal of several working groups)

6) **Brain development and developmental trajectories** Greater knowledge of brain development through longitudinal imaging studies using standardized acquisition parameters to enable comparability across studies and with robust data sharing policies to enable expert analysis of the data by a variety of computational scientists.
   a) Beginning in utero and throughout the first two years of life in persons at high risk of developing ASD.
   b) At time of diagnosis and in the years following ASD diagnosis
   c) MRI techniques to examine brain development are now more powerful. The 'baby connectome" project will establish norms in typically developing infants and toddlers to compare with data from young children with signs of ASD.
   d) Search for adaptive brain changes in response to a developmental disturbance. These adaptive changes may be beneficial or incur net harm. Search for adaptive changes in brain activity/structure that predict response to interventions (CBT).

Barriers to research (try to describe the barriers under each scientific category):

1) There is a need for innovative single center studies to continue, but there is now a greater need to prospectively plan to standardize data elements, data acquisition parameters to enable greater comparability between studies and the establishment of large, high quality databases of genetic, phenotypic and imaging data.
2) As brain development in ASD occurs over many years there is a need for longitudinal studies; and less need for small cross sectional studies.
3) Validated animal models.
    a) Relevant biology
    b) Relevant behaviors?
    c) NHP—marmoset is now target for new genetic tools currently confined to mouse.
4) We have little knowledge of the environmental influences that must be out there
    a) In utero
    b) Infancy
5) We have little knowledge of how to design therapeutic interventions to improve brain function.
6) Few targets for therapeutic development.
7) Distinguishing between correlation and causation.
    a) Extending animal studies to humans.
    b) Correlations from imaging studies.
    c) Need large studies that look earlier in development and integrate diff modalities of investigation, starting in infancy before comorbidities occur.
    d) Need to stratify by subgroups to deal with heterogeneity, since causation won't apply broadly to all types of autism.

Research Policy issues:

1) Inclusion of persons on autism spectrum in research plans and messaging Quality of life needs to be tracked across the lifespan
2) Need to address replicability of findings by
    a) Follow-up validation studies,
    b) prospective guidelines for ASD research
        i. Standardization of data acquisition
        ii. Prospectively planned data sharing
        iii. Standardization of behavioral measures
3) Need to move to larger team studies for certain types of research
    a) Longitudinal patient studies
4) Attract more diverse workforce

a) Engineering, machine learning, monitoring device engineers, bioinformatics, etc.

3 Objectives:

Objective 1) Foster research to better understand the genetic and non-genetic components that contribute to the structural and functional basis of ASD.

Objective 2) Support research to understand the underlying biology of co-occurring conditions in ASD and to understand the relationship of these conditions to ASD.

Objective 3) Support large scale longitudinal studies that can answer questions about the development of ASD from pregnancy through adulthood and the natural history of ASD across the lifespan.