2. How Can I Understand What Is Happening?

- What is happening early in development?
- Are there known biological differences that help explain ASD symptoms?
- Can subgroups of people with ASD help us understand the etiology of ASD symptoms?

What do we know?

Researchers, clinicians, and families have long posed questions about the possible biological bases of ASD. Clinicians classify ASD as a developmental brain disorder based on the behavioral features required for diagnosis. Little evidence exists, however, for a specific neurological abnormality beyond reports of an exuberant and transient pattern of brain or head growth (Akshoomoff, Pierce, & Courchesne, 2002; Dawson et al., 2007; Hazlett et al., 2005). While much of the current science suggests that the behavioral features of ASD result from atypical brain structure, wiring or connections, there is no proven neural variance associated with ASD. Nevertheless, there are some promising leads, and projects are underway that have the potential to provide biological signatures of some forms of ASD.

The development of sophisticated imaging methods has enabled researchers to accurately visualize many aspects of brain structure and functioning. For example, many children and adults with ASD perceive and analyze the visual information conveyed by facial expression differently than do other people (Spezio et al., 2007). Other researchers have employed magnetic resonance imaging (MRI) methods to investigate differences in brain anatomy between people with and without ASD, and have found differences in the density of white and gray matter, in some cases linked to specific symptoms of ASD (Craig et al., 2007).

Subsets of people with ASD have been reported to have experienced regression (i.e., the loss of previously acquired language, social, and developmental skills). The phenomenon is poorly understood and may co-occur with medical conditions common to people with ASD such as epilepsy. Recent studies have sought to understand the relationship between regressive symptoms, co-occurring disorders such as epilepsy, and the etiology of ASD.

Regression is not unique to people with ASD and the loss of language skills (acute language regression) can occur in people without the disorder. In one study, researchers found that children with acute language regression (who did not have ASD) were more likely to have associated seizures or epilepsy than were children with regressive autism (which includes language regression, as well as the loss of other social and developmental skills). This suggests that there are different subtypes of language regression and may help to understand the phenomenon and its relationship to ASD (McVicar, et al., 2005).

Currently, the frequency of language regression is unknown in either children with ASD or the general population. Previous studies of regression have been hampered by delayed referral for evaluation after the onset of regressive symptoms (McVicar, et al., 2005).
A few hypotheses regarding how disruptions of the immune system might contribute to ASD and other neurodevelopmental disorders have emerged in recent years. Some recent findings suggest that the immune system differences of parents and their children may affect early brain development and the onset and fluctuation of symptoms in some children with ASD (Pardo, Vargas, & Zimmerman, 2005). For example, some research indicates that maternal autoantibodies directed at fetal brain tissue could interfere with normal brain development (Braunschweig et al., 2008). While such medical symptoms may not be entirely specific to ASD, treating may have significant impact on quality of life, symptom severity, and level of functioning.

Better understanding of the biology of genes linked to ASD and their functions can also provide insight. Recent studies have shown that the MeCP2 gene (mutations in which can cause Rett Syndrome) is involved in forming connections at the synapse. Genes regulated by the Fragile X Syndrome gene, FMR1, also directly affect synapse function by controlling signaling of the neurotransmitter glutamate. In addition, a 2008 study found that the two genes that cause tuberous sclerosis complex (TSC) impair the formation of axons. Recently, several groups reported remarkable success with targeted therapies in animal models of these disorders showing the ability to reverse the underlying neuroanatomical and even behavioral deficits in the adult (Dolen et al., 2007; Ehninger et al., 2008; Guy et al., 2007). Understanding how MeCP2, TS1, FMR1, TSC1, and TSC2 regulate the growth and function of neurons may help scientists understand related disorders like autism.

What do we need?

Exploring the biological basis of ASD requires access to biospecimens of people with and without ASD. Some progress has been made to establish the necessary infrastructure for the collection and preservation of post-mortem tissue from people with ASD. Nevertheless, the tissues currently available are insufficient for the needs of researchers. Educational campaigns, through contact with healthcare providers and the internet, may be useful to increase public awareness. New technology is expanding biological research beyond post-mortem tissue. For example, it is now possible to create pluripotent stem cells from skin fibroblasts of individual patients to create neuronal cell lines for study.

One of the greatest barriers to progress in determining the biological bases of ASD has been the heterogeneity of the spectrum. A clear need exists to advance understanding of the many phenotypes of ASD, including studies that link genotype to phenotype, investigations of natural and treated history, analyses of genetic interaction with environmental exposures, and studies of co-occurring behavioral and medical conditions. Different autism phenotypes may have different etiologies. There is a need to combine genotyping and functional analysis to better understand the contribution of specific genotypes with functional or structural subtypes. To determine the earliest discernable onset of ASD, experts have expressed the need for an intensive, multidisciplinary study starting at early ages that examines biomedical, neurodevelopmental, and behavioral trajectories of children with ASD. A parallel multidisciplinary analysis of typically developing children and children with non-ASD developmental disorders would be especially enlightening, as limited normative information is currently available. An evaluation of differences in the interplay of biology and environmental exposures for children with and
without ASD is also needed. Understanding early trajectories may lead to targeted interventions aimed
at mitigating behavioral and medical challenges and improving outcomes through adulthood.

Another understudied arena of ASD research is gender differences. Many studies of autism
preferentially enroll males, which, due to a 4:1 increased prevalence, are easier to recruit. Without
additional information about the biological features of ASD in females, it remains unclear whether the
course of ASD is similar and whether currently used interventions are appropriate for females. It is
critical to determine how sex is related to etiology, protective factors, diagnosis, and trajectory. In
addition, many studies of autism preferentially enroll higher functioning individuals who do not have
cognitive impairment, because of their ability to cooperate and participate in study related tasks.
However, these individuals represent only a subset of all individuals with autism and lessons learned
from them may or may not be generalizable to all individuals with ASD. Priority must be made to
develop studies looking at the underlying etiology of non verbal individuals and to understand the
impact of and etiology of co-occurring language and cognitive impairment.

**ASPIRATIONAL GOAL: DISCOVER HOW ASD AFFECTS DEVELOPMENT WHICH WILL LEAD TO TARGETED
AND PERSONALIZED INTERVENTIONS.**

**Research Opportunities**

- Multi-disciplinary, longitudinal, biobehavioral studies of children, youths, and adults beginning
during infancy that characterize neurodevelopmental and medical developmental trajectories
across the multiple axes of ASD phenotype and identify ASD risk factors, subgroups, co-occurring
symptoms, and potential biological targets for intervention. Such studies could include:
  - High-risk siblings of children, youths, and adults with ASD, children without a family
    history of ASD, and typically developing children.
  - Multi-disciplinary assessments of brain imaging, metabolic and immune markers,
    microbiomics, electrophysiology, and behavior.

- Research on females with ASD to better characterize clinical, biological and protective features.

- Human and animal studies that examine immune, infectious and environmental factors in the
  occurrence of ASD.

- Research on the unique strengths and abilities of people with ASD with evaluation of functional
  and biological mechanisms behind social, linguistic, and cognitive profiles.

- Research on individuals with ASD who are nonverbal and /or cognitively impaired

- Research targeting the underlying biology of co-occurring syndromes and co-occurring

conditions.
• Prospective research on children with language regression, both with and without autistic regression, including potential underlying genetic and other risk factors including seizures and epilepsy.

**Short-Term Objectives**

A. Support at least four research projects to identify mechanisms of metabolic and/or immune system interactions with the central nervous system that may underlie the development of ASD during prenatal-postnatal life by 2010. *IACC Recommended Budget: $9,800,000 over 4 years.*

B. Launch three studies that specifically focus on the neurodevelopment of females with ASD, spanning basic to clinical research on sex differences by 2011. *IACC Recommended Budget: $8,900,000 over 5 years.*

C. Identify ways to increase awareness among the autism spectrum community of the potential value of brain and tissue donation to further basic research by 2011. *IACC Recommended Budget: $1,400,000 over 2 years.*

**New Objective**

D. Launch three studies that target improved understanding of the underlying biological pathways of genetic conditions related to autism (e.g. Fragile X, Rett syndrome, tuberous sclerosis complex) and how these conditions inform risk assessment and individualized intervention by 2012. *IACC Recommended Budget: $9,000,000 over 5 years.*

**New Objective**

E. Launch three studies that target the underlying biological mechanisms of co-occurring conditions with autism including seizures/epilepsy, sleep disorders and familial autoimmune disorders by 2012. *IACC Recommended Budget: $9,000,000 over 5 years.*

**New Objective**

F. Launch two studies that focus on prospective characterization of children with reported regression, to investigate potential risk factors by 2012. *IACC Recommended Budget: $4,500,000 over 5 years.*

**New Objective**

G. Support five studies that associate specific genotypes with functional or structural phenotypes, including behavioral and medical phenotypes (e.g., nonverbal individuals with ASD and those with cognitive impairments) by 2015. *IACC Recommended Budget: $22,600,000 over 5 years.*

**Long-Term Objectives**

A. Complete a large-scale, multi-disciplinary, collaborative project that longitudinally and comprehensively examines how the biological, clinical, and developmental profiles of individuals, with a special emphasis on females, youths, and adults with ASD, change over time.
as compared to typically developing people by 2020. **IACC Recommended Budget: $126,200,000 over 12 years.**

**New Objective**

B. Launch at least three studies which evaluate the applicability of ASD phenotype and/or biological signature findings for performing diagnosis, risk assessment, or clinical intervention by 2015. **IACC Recommended Budget: $7,200,000 over 5 years.**

¿Qué progreso se está haciendo para cumplir con los objetivos?

(Please provide 1-2 paragraphs to summarize progress.)

*Note: Objectives labeled “New Objective” are either entirely new additions to the 2010 Strategic Plan or significantly modified objectives from the 2009 Strategic Plan. Objectives from the 2009 Strategic Plan that did not change or that have been slightly modified for clarification purposes are unmarked.*