

## QUESTION 2: HOW CAN I UNDERSTAND WHAT IS HAPPENING?

### IACC Strategic Plan Objectives

### Planning Group Summary

### Funding 2008-2013

**2.S.A.** Support at least four research projects to identify mechanisms of fever, metabolic and/or immune system interactions with the central nervous system that may influence ASD during prenatal-postnatal life by 2010 (Fever studies to be started by 2012).

*IACC Recommended Budget: \$9,800,000 over 4 years*

**Funding:** The recommended budget for this objective was met and many projects were funded in this area, but the field is still developing and emphasis on this objective should continue in the future.

**Progress:** Scientific advances have been made in linking maternal innate immune function and immune-system challenge to aspects of ASD. Methodological advances in the field include the development of animal models for study of the role of the immune system in ASD and PET ligands for imaging microglial activation.

**Remaining Gaps, Needs and Opportunities:** There is a need for a well-designed, multi-site clinical study of clinical effects of fever and to develop standard measures of fever and behavioral/cognitive outcomes. Questions about fever could be integrated into funded epidemiological studies. There is also interest in further work on metabolic and mitochondrial issues, but there is a need for validated assessment of oxidative stress and mitochondrial function. More guidance is needed on the key questions for this field to answer – a workshop to define these methodologies may be helpful. One of the key questions is to determine whether it is the body temperature associated with fever or some consequence of immune activation and production of the febrile state that leads to amelioration of cognitive function.

\$16,997,853

**2.S.B.** Launch three studies that specifically focus on the neurodevelopment of females with ASD, spanning basic to clinical research on sex differences by 2011.

**Funding:** The recommended budget for this objective was partially met, and more than 3 studies were launched, but further work is needed in this area.

**Progress:** Studies have identified the need for a higher genetic load in females suggesting a gender-associated protective effect.

**Remaining Gaps, Needs and Opportunities:** Studies of protective and compensatory effects in females and differential response to treatment based on gender are promising areas that could help with future prevention and effective, personalized treatment efforts. Beyond genetic differences, it is important to determine whether other biological features, such as differences in neuropathology, are found in the two sexes.

\$5,856,783

*IACC Recommended Budget: \$8,900,000 over 5 years*

**2.S.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*

**Funding:** The recommended budget for this objective has been partially met as of 2012. **Progress:** In 2013, Loss of autism brain samples due to a freezer malfunction at a major brain bank in 2012 has caused a loss of progress and there is a need for new samples to replace and build the amount of available brain tissue for ASD research. The Autism BrainNet initiative is a multi-site privately funded effort that will target autism specifically and will include and autism-specific brain donation outreach campaign that addresses this objective. NIH launched the NIH Neurobiobank (\$5M), 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. Both of these initiatives are not yet reflected in the Portfolio analysis, because they began in 2013.

\$856,031

**Remaining Gaps, Needs and Opportunities:** There is an ongoing and urgent need to raise awareness of the importance of brain and tissue donation for research, to standardize the methodology of collection and to increase the supply of such tissues. Autism BrainNet, a private outreach and postmortem brain donation program dedicated to research on autism and related disorders will commence operation.

**2.S.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.

**Funding:** The recommended budget for this objective has been met and a large number of projects funded that address this objective.

**Progress:** Investment in this area has doubled since 2009, and there is an ACE center focused on tuberous sclerosis. Much is being learned about conditions related to autism that can be applied to autism. This objective is on track.

**Remaining Gaps, Needs and Opportunities:** The next step will be to translate findings in this area into clinically useful therapies.

\$53,147,645

*IACC Recommended Budget: 9,000,000 over 5 years*

**2.S.E.** Launch three studies that target the underlying biological mechanisms of co-occurring conditions with autism, including seizures/epilepsy, sleep disorders, wandering/elopement behavior, and familial autoimmune disorders, by 2012.

**Funding:** The recommended budget for this objective was met, and more than twenty projects were funded.

**Progress:** Scientific advances in this area include mechanistic and mutation linkages of epilepsy and ASD-like behaviors, as well as circadian rhythm disruptions downstream of ASD-associated mutations.

**Remaining Gaps, Needs and Opportunities:** While studies on co-occurring conditions have been initiated, a greater depth of understanding is needed. Further efforts are needed, especially on wandering, metabolic and immune conditions related to ASD, as

\$16,531,078

well as a systems-biology approach to understand how these co-occurring conditions are related to ASD. In order to more accurately assess progress, wandering/elopement should be considered separately from seizures/epilepsy/sleep. Familial autoimmune disorders could be moved to 2.S.A to be grouped with other immune-related issues.

*IACC Recommended Budget: \$9,000,000 over 5 years*

**2.S.F.** Launch two studies that focus on prospective characterization of children with reported regression to investigate potential risk factors by 2012.

**Funding:** The recommended budget for this objective has been partially met. The number of recommended projects has been met and progress is being made, but further work is needed to understand how autism develops.

**Progress:** Some recent data suggest that regression may be more of a continuum than regression vs. non-regression as distinct types of autism, and several studies have provided new descriptions of ASD developmental trajectories. Other studies, however, have found some differences between children with reported regression vs. children without reported regression.

\$993,134

**Remaining Gaps, Needs and Opportunities:** Further work is needed to better understand subtypes and potential biomarkers. High-risk siblings may present an opportunity for studying regression prospectively.

*IACC Recommended Budget: \$4,500,000 over 5 years*

**2.S.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.

**Funding:** The recommended budget for this objective has been met.

**Progress:** Over 40 projects have been funded in this area, and the projects cover the areas described, so the objective appears to be on track.

\$41,777,028

**Remaining Gaps, Needs and Opportunities:** With so many studies initiated, the next step is to encourage multi-site collaboration in order to achieve the large number of subjects required for meaningful data interpretation.

*IACC Recommended Budget: \$22,600,000 over 5 years*

**2.L.A.** Complete a large-scale, multidisciplinary, 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.

**Funding:** The recommended budget for this objective was partially met and several projects have been funded in this area.

**Progress:** The ACE Network continues to collect data relevant to this objective.

\$20,661,641

**Remaining Gaps, Needs and Opportunities:** More clinical studies are needed over a longer trajectory to identify issues faced as people with ASD age, especially with regard to risk factors for other medical conditions. Another remaining need is that of standardization of data collection and analysis methods.

*IACC Recommended Budget: \$126,200,000 over 12 years*

**2.L.B.** Launch at least three studies that evaluate the applicability of ASD phenotype and/or biological signature findings for performing diagnosis, risk assessment, or clinical intervention by 2015.

**Funding:** The recommended budget for this objective was partially met, and more than 3 studies were launched, but more funding and work in this area is needed.

**Progress:** Imaging studies have developed activity signatures of the ASD brain.

\$3,628,406

**Remaining Gaps, Needs and Opportunities:** This objective also requires standardization of data collection and analysis methods, as well as collaboration among investigators to pool data. Increased emphasis must be placed on conducting biological evaluations of very young children at risk for ASD. Increased effort should be addressed to collecting biological samples from these young children that enable research into the establishment of biomarkers or risk markers of very young children.

*IACC Recommended Budget: 7,200,000 over 5 years*  
Not Specific to Objectives (Core Activities)

\$201,661,561

**Total funding for Question 2**

\$362,111,160