IACC Strategic Plan for Autism Research 2010 Update for Question 3

What is new in this research area and what have we learned this past year?

A variety of discoveries have advanced knowledge of the biological underpinnings of autism. It was found that, among individuals with ASD, copy number variants, submicroscopic deletions and duplications in the genome, occur more frequently in areas containing ASD risk genes. Some of these copy variants involved genes previously found to be associated with autism and some involved new rare mutations (Pinto et al, 2010). Neurodevelopmental disorders are more common in infants born prematurely and Johnson and colleagues found that preterm infants are at increased risk of developing autism (Johnson et al., 2010). Studies of environmental contributions to autism have been more difficult. A study of blood mercury levels in 452 children in the Childhood Autism Risk from Genetics and the Environment study showed that total mercury in blood was neither elevated nor reduced in pre-school children with ASD (Hertz-Picciotto et al., 2010). In a separate study (Price et al., 2010), no link was found between the exposure to thimerosal, a mercury-containing preservative used in vaccines, and increased risk for ASD.

New data based on the Autism Treatment Network patient registry and studies of high risk infants indicate that autism is associated with high rates of several physiological conditions, including gastrointestinal dysfunction, sleep disturbance and early signs of fine motor and temperament difficulties. These co-morbid conditions are poorly studied, yet investigating them may reveal unexpected clues to environmental risk factors. For example, nonmotor features associated with Parkinson's disease (e.g., GI problems, olfactory deficits, autonomic abnormalities) have yielded information about Parkinson's disease etiology.

On September 8, 2010, the National Institute of Environmental Health Sciences and Autism Speaks co-sponsored a meeting of scientists from both inside and outside the field of autism to identify novel opportunities and mechanisms to accelerate research on environmental factors and autism. Environmental factors considered included all factors affecting health that are external to the individual (such as, physical, biological, chemical, dietary, social, and cultural), as well as the non-genetic characteristics of an individual (such as age, nutritional status, physical functioning and medical history.) As noted in the meeting report, understanding environmental influences to autism will require both agnostic, discovery-based science as well as hypothesis-driven science in parallel. Strong interdisciplinary teams are needed to move findings back and forth from clinical and epidemiologic settings to mechanistic studies. Research needs and opportunities identified included expansion of epidemiology investigations to capitalize on existing resources, development of a range of model systems that can address the complexity of autism, exploration of bioinformatics and screening approaches to identify environmental chemicals of interest, increased emphasis on neuropathology, enhancement of capacity for measurement of environmental analytes, harmonization of exposure assessment instruments and mechanisms for expanding the workforce.

Technical advances in the past year increase our traction for finding genetic and environmental risk factors. Novel bioinformatics platforms can be used to map genes to specific signaling pathways and to

explore what environmental exposures are most likely to influences those pathways. Toxicogenomics data such as that produced by the National Center for Computational Toxicology could be mined to determine which environmental compounds act on the genes of interest. An important finding this year revealed the extent of "parent of origin" effects – for many genetic variations, risk depends on whether this variation was inherited from the maternal or paternal genome. And recent studies have revealed the importance of epigenetic mechanisms in disease etiology, bringing together genetic and environmental factors for the first time.

Information on the utility of induced pluripotent stem cells and mesenchymal stem cells for exploring the biological basis of ASD is rapidly developing, pointing to the opportunity to use these tools as molecular assays for understanding genetic variation as well as for translational toxicology. Although research this year revealed several differences between these adult-derived stem cells and embryonic stem cells, adult-derived stem cells continue to be one of the most promising new frontiers for understanding risk for ASD.

In a 2009 Report by the National Vaccine Advisory Committee (NVAC), it was recommended that, in the context of immunization research, the ASD clinical subset of particular interest is regressive autism. Although the NVAC stressed that the temporal occurrence of this regression and the immunization schedule is not evidence of a causal relationship, regressive autism warrants further research in rigorously defined subsets of ASD. The NVAC noted that studies in this subpopulation might involve comparison of immune cytokine profiles between regressive and non-regressive ASD to screen for differential immune system profiles, or prospective immunization responsive profiling in siblings of children with regressive ASD. In addition, the NVAC recommended that studies assess whether adverse events following immunization (e.g. fever and seizures) correlate with risk of ASD, and that immune response profiles be examined in ASD cases with history of adverse events following immunization.

The 2009 research portfolio analysis was presented this year, reporting that 32.7% of studies funded corresponded to question 3. The majority of funding was directed toward the identification of genetic risk factors, $37,043,410 and less funding and attention was reported for environmental research. This analysis suggests that environmental research is an understudied area that has been given insufficient attention and requires a heightened priority.

Several specific recommendations for research objectives and needed resources were made, which are reflected in the new objectives listed below.

What gap areas have emerged since last year?

Suitable model systems, and those that offer better high-throughput capabilities, for the study of environmental risk factors and their interaction with genetic susceptibility are needed. For example, models such as *Drosophila melanogaster* (fruit flies) and *Danio rerio* (zebra fish) have been extremely useful in identifying environmental contributors to other conditions, such as Parkinson's and Alzheimer's disease. The genetics and biology of synapse formation and function are increasingly well-understood, underscoring the potential utility of vertebrate and invertebrate models for exploring how environmental exposure can affect brain function at cellular and molecular levels.

Expansion and integration of epidemiological studies using different designs and types of data are needed. Combining data from multiple studies will be necessary to enhance statistical power, requiring standardization of protocols, instrument development and data harmonization methods. This should also include standardized protocols on biological specimen collection, storage and analysis. International studies offer unique opportunities to examine populations with different genetic and environmental exposure backgrounds. It would be helpful to create an autism "atlas" to examine differences in autism prevalence as a function of geography. Such analysis has proven useful in both cancer and asthma research.

There is a need for greater collaboration between genetic and environmental science investigators. Studies collecting genetic information should include data on environmental exposures and vice-versa; large data sets are needed allowing mapping of detailed genetic, detailed environment and detailed phenotypic information, including medical comorbidities, inflammatory markers, pattern of onset and developmental course, family history, and so on.

To accelerate our understanding of the role of epigenetics in autism etiology, further development and application of sensitive assays to measure DNA methylation,histone modification, and other epigenetic marks are needed. Studies are also needed to examine how exposures may act on maternal or paternal genomes via epigenetic mechanisms to influence risk for ASD.

The lack of adequate postmortem brain tissue continues to be a major barrier to progress in understanding the neurobiology of ASD, including the potential influence of environmental factors in the functional pathways involved in ASD.

Efforts to increase analytical capacity and core facilities are needed. For example, adding an environmental, immune or animal models core to an already existing multidisciplinary team that studies autism would be beneficial. Access to these core facilities and services could encourage individual scientists to expand the scope of their studies to address environmental hypotheses.

What new research opportunities and research objectives have emerged?

- Support at least three epidemiological studies that take advantage of special populations to inform our understanding of environmental risk factors for ASD in pregnancy and the early postnatal period by 2012. Such studies include comparisons of populations differing in geography, gender, ethnic background, exposure history (e.g. prematurity, maternal infection, nutritional deficiencies, toxins),

and migration patterns. Emphasis on environmental factors that influence prenatal development is particularly of high priority with special attention to racial and ethnically diverse populations.

- Support at least three epidemiological studies that capitalize on existing that could be mined or expanded to identify ASD cases and make use of or add exposures information and/or biosamples (e.g. placenta, blood spots, cord blood) by 2013.
- Support at least three studies that explore the use of newly emerging bioinformatics platforms and technologies, including toxicogenomics data bases by 2013.
- Support at least three studies that explore differences in phenotype, such as cytokine profiles, among special populations of children with ASD for which environmental risk factors may play a role, including children with autistic regression, adverse events following immunization (such as fever and seizures), and mitochondrial impairment, and siblings of children with regressive ASD by 2013.
- Support at least three studies that examine potential differences in the microbiome of individuals with ASD versus comparison groups by 2012.
- Support at least three studies that focus on the role of epigenetics in the etiology of ASD, including studies that include assays to measure DNA methylations and histone modifications and those exploring how exposures may act on maternal or paternal genomes via epigenetic mechanisms to alter gene expression by 2012.
- Support studies and workshops that facilitate the development of vertebrate and invertebrate model systems for the exploration of environmental risks and their interaction with gender and genetic susceptibilities for ASD by 2012.
- Support at least three epidemiologic studies that combine data from multiple existing studies to provide enhanced statistical power of analyses of environmental risk factors for ASD by 2012, especially enhancing investigation of individual risk factors that may have a relatively low prevalence and investigation of gender differences in ASD risk from environmental factors. Such efforts should capitalize on combining data from existing studies of comparable designs, methodologies and data types but differing in geography, ethnic background, exposure history (e.g. prematurity, maternal infection, nutritional deficiencies, toxins), and migration patterns. Emphasis on environmental factors that influence prenatal development is particularly of high priority.

References

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