IACC Subcommittee on Planning the Strategic Plan Updating Process: Template for Updates 10-6-10

Per the vote of the subcommittee, the updates to the IACC Strategic Plan this year will entail preparation of 2010 brief update to each chapter. The instructions and template for preparing each update is below. Please copy the template and fill in text where the *italic font* is located.

TEMPLATE FOR UPDATES

2010 Update for Question 2

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

Over the past year, IACC has nominated several studies that represent advances in what is known about the etiology of ASD with respect to neuropathology, symptoms, and cellular metabolism/ signaling. Schumann et al., (2010) published results of the first longitudinal study of early brain growth in toddlers aged 1.5 to 5. They found evidence of cerebral gray and white matter overgrowth in all regions by age 2.5. After correcting for age and gender, they found almost all brain regions developed at an abnormal rate in ASD. This quadratic trend was more pronounced in girls with ASD. Buie et al., (2010) issued a consensus report about evaluation, diagnosis, and treatment of gastrointestinal disorders in children with ASDs in the Journal *Pediatrics.* While the panel concluded that it was too early to make evidence-based recommendations, the consensus expert opinion was that individuals with ASDs deserve the same thoroughness and standard of care as all patients, and that problem behaviors in ASD may stem from gastrointestinal problems. Ibrahime et. al (Pediatrics 2009) tracked children in Olmsted County Minnesota and reported that the frequency of gastrointestinal symptoms was not different as compared to typically developing children. Mostafa, El-Hadidi, Hewedi, & Abdou (2010) examined oxidative stress in Egyptian children with autism. They found oxidative stress in close to 90% of these children and that this was related to an index of autoimmunity. They suggest that oxidate stress may play a role in autoimmunity, and that this represents a potential treatment target. Altladottir et. Al. (2009) analyzed data from 690 thousand Danish children and reported that families with history of autoimmune disorders, rheumatoid arthritis, type 1 diabetes or celiac disease, are more likely to have ASD. Palmieri and Persico (2010) reviewed the literature and suggested that extant energy metabolism deficits in ASDs are not systematically related to specific genomic or genomic defects. Palmieri et al. (2010), examined gray matter from post-mortem brains of individuals with ASD and found increased levels of oxidized mitochondrial proteins in over half of subjects that was related to high calcium levels. They concluded that interactions between the mitochondrial aspartate/glutamate carrier gene and altered calcium homoestatis may play a role in autism.

Committee members also have pointed to the new focus on metabolic and immune system interactions through studies of mitochondria, oxidative stress, and viral infections; the potential utility of high throughput metabolomics approaches; findings of resolution of autism symptoms with fever (anything published on resolution with fever?); the intensified development of mouse models of autism (Silverman, Lord, & Crawley, 2010); reports of reduced repetitive grooming in a mouse model with administration of an mGluR5 antagonist (Silverman, Toluy, Barkan, & Crawley, 2010); and impaired social abilities in mice with duplication on chromosome seven in a region similar to the 15q 11-13 duplication associated with autism (Nakatani et. al. Cell 2009).

- **What gap areas have emerged since last year?**

One important gap recognized by our Committee is that mismatch between Question 2 objective and actual funding of research in this area. There appears to be little attention given to several of the short-term objectives, namely risk factors in children with regression, neurodevelopmental abnormalities in females with autism and the importance of brain donation. The committee will discuss this further at the upcoming meeting. I have taken a look at this based on the materials we received yesterday. It appears that some studies are misclassified, and/or we lack objectives that are consonant with what researchers have obtained funds to do. Most studies in the unclassified list investigate the underlying neural mechanisms of social perception, motor function, and/or cognition in autism. Some of these studies could be placed under 2.L.A. as they are studies that comprehensively examine biological, clinical, and developmental profiles. Alternatively, we could add a new short-term objective. I have drafted one below. This would be highly consistent with the question "Are there known biological differences that help explain ASD symptoms?" that is at the beginning of Question 2.

A second area highlighted by the Committee is the newly emerging area of metabolomics, which in well controlled studies may provide a way to examine genotype-phenotype relationships; to provide biomarkers; and to monitor treatment effectiveness. A third area suggested by the Committee is increased consideration of structural and functional neuroimaging studies of the development of neural circuitry potentially underlying autism-related symptoms. Finally, it was recommended that the Committee be cognizant of recommendations from other fields to identify "endophenotypes" in autism. Endophenotypes are partial/constituent phenotypes that may be more highly linked to specific genetic causes which may not be appreciated in studies which combine all symptom profiles. Endophenotypes may also aggregate in families and be amenable to deep sequencing genetic studies to identify genetic underpinnings. Endophenotypes also can be common to multiple neurodevelopmental disorders and offer leverage for understanding similarities and differences between different forms of developmental psychopathology.

Public comment points to the need for continued study of regressive autism, and females with ASD. New concerns were raised about the relationship between ASD and epilepsy, liver, and

other diseases. It is also was recommended that we examine inflammation in expectant mothers and apraxia of speech and their relationship to ASD.

Several "implementation" related issues were raised by the Committee. These include the need to add rapidly emerging findings related to cell metabolism, signaling, neuroimaging, genetics, epigenetics, and co-existing medical conditions into existing databases designed to phenotype the "autisms." Finally, the committee recommended that we continue to emphasize the rapid translation of our findings to clinical practice.

- **What new research opportunities and research objectives have emerged?**

Please list new research opportunities first, followed by new research objectives. Opportunities and objectives should each be written in a bullet format. For objectives, please indicate the number of studies and a calendar year that you expect to see accomplishment (e.g., like the current objectives). If you want, you can also suggest the Recommended Budget for the IACC to consider.

The following were recommended as changes to Research Opportunities and Objectives:

Research opportunities:

Revision of the first opportunity, second bullet point to read: "Multi-disciplinary assessments of brain imaging, metabolic and immunity markers, microbiomics, ***metabolomics***, electrophysiology, and behavior."

- Research on children who either regress or improve during episodes of fever.
- Studies to investigate metabolic pathways perturbations that affect immune function, methylation, and redox homeostasis in ASD.

Short-Term Objectives:

- **Supplied by Marjorie**: Support at least 5 studies that use structural, and or functional neuroimaging methods to examine the development of the neural substrates of social, motor, and cognitive functioning in individuals with ASDs and their relationship to autism symptoms. There are quite a few grants listed under Question 1 that use MRI to identify differences in autism. From the titles looks like grants to Piven, Nordahl, Nacewicz, Marco, fit this bill. Also under question two grants to Zeffiro, big one to Just, Steinman, Hazlet, Grodberg, Yoon, **Dager, Lee, Hardan, Herbert, Keinhaus, Vaidya, Rojas, Levitt, Schultz, Conturo, Barbas, Mottron, Mosconi, Barnea-Goraly, Fan, Lainhart, Allen, Pruett, Conturo, Courchesne, Townsend, Dubray, Pierce, Sahin,**
    - **Alternatively, we could fold this into Long-Term Objective A**

Supplied by Marjorie: Support at least 2 studies that examine promising animal models of autism. There are quite a few in the portfolio currently- **Mouse model generation/characterization grant**

to: Rale, Pletnikov, Gambello, devine, Poptani , Kelleher, Huang, Parada, Cheyette, Dulawa, Veenstra-Vanderweele, Carpenter, Jiang, Powell. Malanga, Lewis, Charles, Millonig, Moy, Brodkin, Blakley, Sheng, Orsten, Xiong,

- **Primate model grant to – Baumann, Patterson, Amaral**

- **Supplied by Lyn:** New Objective E: *Change to read* "Launch three studies that target the underlying biological mechanisms of co-occurring conditions with autism including seizures/epilepsy (Walter - didn't see any except Jensens which didn't look like focused on autism), **gastrointestinal**(Walter**:** 5 Gastrointestinal grants to Duffy, Russo, Kushak, Winter,Anderson, **)**, sleep disorders (8 Sleep grants to Anderson, Mayer, Barnes, Hopkins, Dixon, Mong, Glaze, Malow,), **metabolic and mitochondrial dysfunction** (Walter: have a few - Wallace, Shoffner, Wlodarczyk for mito and James & Nelson, for metabolic), **immune dysregulation** (Walter: 13 Immune grants to—Ashwood, Jyonouchi (both small), Elmer, Rall, Hsiao, McAllister, Palmer, Diamond, Carpentier, Swedo, Van der Water, Patterson, Mong **)** , and familial autoimmune disorders by 2012.

- **Supplied by Lyn:** Launch at least one study that focuses on extensive clinical investigations of infants during the process of autistic regression by 2012. **(Lyn-I think the Infant Sib Studies do this…at least I know that it is being done in ours)**

  Supplied by Lyn: Launch two new studies regarding the effect of fever as a potential trigger for autistic regression and for improvement in ASD behaviors.

  Supplied by Lyn: Initiate studies to investigate metabolic pathways perturbations that affect immune function, methylation, and redox homeostasis in ASD. (Walter: Looking at the portfolio see only 2 Redox grants to—Deth, Muratore (no money?), there are 13 grants on immune function though.)

What Progress is Being Made in Fulfilling Objectives?

As exemplified by the progress in the literature and funding as documented by the Portfolio Analysis, autism research is proceeding at a brisk pace. While the allocations in the portfolio analysis do not make this entirely clear, this should not be taken as evidence of failure.There are many promising studies of the neural correlates of autism-related symptoms that have not been classified. Also exciting are the number of young investigators and new investigators from other fields entering autism research as well as the strength of mentoring programs.

Member Assignments and Timeline

Subcommittee members have self-selected specific chapters of the plan. This list of the chapters and subcommittee assignments is included below. Members designated with * are the lead for drafting the update for the chapter. (Note: Lead drafters have not been assigned yet for Chapters 5, 6, and 7, as well as the Introduction.)

Introduction	Thomas Insel, Lyn Redwood, Alison Singer
Chapter 1	Jennifer Johnson, Walter Koroshetz, Coleen Boyle*
Chapter 2	Walter Koroshetz, Lyn Redwood, Marjorie Solomon*, Alison Singer
Chapter 3	Geri Dawson*, Lee Grossman, Thomas Insel, Walter Koroshetz, Lyn Redwood,
Chapter 4	Geri Dawson*, Lee Grossman, Ari Ne'eman, Stephen Shore, Lyn Redwood
Chapter 5	Ellen Blackwell, Lee Grossman, Ari Ne'eman
Chapter 6	Ellen Blackwell, Ari Ne'eman, Marjorie Solomon
Chapter 7	Geri Dawson, Coleen Boyle, Alison Singer

Timeline

- Lead drafters for Chapters 1, 2, 3, and 4 will send first drafts to the subcommittee **no later than Thursday, October 15th**.
- Subcommittee comments are **due by noon Monday October 18th**.
- Final drafts from the lead drafter are **due to OARC no later than 3:00 pm EDT Tuesday, October 19th**.
- OARC will format the drafts (including any light copy-editing), make hard copies for the IACC, and make slides for the public to view in time for the Friday October 22nd IACC meeting.