Recommendations for Revisions to the NIH IACC Autism Research Matrix of December 2003 as Described in the *Congressional Appropriations Committee Report on the State of Autism Research* of April 2004.

For Consideration by the IACC Science Panel

Submitted by
SafeMinds & the National Autism Association

August 9, 2006

Background

The NIH Autism Research Matrix of December 2003 was created three years ago as a planning mechanism for autism research at NIH at the request of Congress. The Matrix was developed by an external panel of experts convened by the IACC in July 2003. It categorized the most promising areas of research into content area, risk level, and time frame for accomplishment. After completion, the Matrix was presented to the public at the Autism Summit Conference and then formally adopted by the IACC in November 2003.

The Matrix is intended to be dynamic, to be "revised and expanded as current goals are achieved and new goals identified." Given that the Matrix is three years old and the field of autism research has advanced during this time, Dr. Tom Insel of NIMH has agreed to reconvene a panel of experts to update and revise the document. The panel is expected to meet in September 2006. The panel recommendations will be a topic of discussion at the November 2006 IACC meeting.

Several advocacy groups have been in communication with NIH about revising the Matrix, including SafeMinds and the National Autism Association (NAA). Both groups have a strong interest in the biomedical research of autism as it relates to environmental factors and treatment. These organizations have made three requests to Dr. Insel concerning the Matrix update: (a) to expand the panel membership to include scientists and clinicians with expertise in environmental factors and biomedical interventions; (b) to include representatives from advocacy groups on the panel; and (c) to submit to the panel for consideration a list of recommendations that pertain to environmental and biomedical treatment content areas. SafeMinds and NAA also request that, going forward, the external panel, comprised of scientists, clinicians, and advocates, convene at least annually to review Matrix progress and revise goals and activities as warranted in light of new findings and hypotheses.

This document contains the content area recommendations for the environmental contributors and biomedical treatments.. For ease of adoption, the recommendations have been distributed to the current Matrix content areas as appropriately as possible given the way the Matrix is now organized. Consideration for reorganizing the content areas might be given during the update process. The recommended activities have not, however, been assigned a risk level or timeframe. Autism is a national emergency. Any promising activity that scientific findings suggest could lead to treatment, prevention, or recovery should be addressed within an immediate timeframe and without consideration of risk. Sufficient resources must be applied to undertake these promising activities.

These recommendations, like the Matrix itself, are subject to ongoing revision as new findings and ideas arise. Input from a variety of sources, including the involved institutes at NIH, is welcome.

Roadblocks

- Good epidemiology that retrospectively tracks trends in prevalence and addresses causal factors in addition to counting.
- Restricted access by credentialed researchers to medical databases that could advance understanding of causal factors.
- Insufficient numbers of post-mortem brains for research and lack of access to existing brains for legitimate research.
- In general, an incomplete commitment to open resources, whether biological repositories or databases.
- Lack of systematic collection of exposure history data among autistic individuals and matched controls, and incomplete medical examination of ASD individuals that might detect past, persistent, or ongoing exposures.
- Lack of rigorous subgrouping that can indicate what treatments are most likely to be effective in a given individual.
- Unwillingness by NIH and scientists to investigate environmental factors in autism, including those that relate to vaccines and vaccine components.
- Perpetuation of a belief system that autism is fixed prenatally and immutable postnatally, rather than as a condition that arises from preventable pre- or postnatal exposures and is amenable to treatment after birth.
- Insufficient numbers of scientists with toxicological and environmental health expertise working in the field of autism.
- Advancement of animal models that represent environmental exposures and can elucidate complex environmental factor interaction and gene-environment interaction. Incipient animal models exist but they need to be expanded.
- Lack of support and standards for clinicians working in the area of biomedical interventions for autism.
- Inadequate funding for autism research and lack of a sense of urgency given the magnitude of the emergency.

Update Recommendations

Overall implementation

These research goals and activities would have the greatest likelihood of implementation if NIH made them priorities in practice. The means to accomplish them are (a) to include these activities as an item to be scored when reviewing grant proposals; (b) to list them as program project grants; and (c) to require Autism Centers of Excellence to address them as part of their center designation and to consider such project proposals when scoring center proposals. The activities should be undertaken by external independent institutions without conflicts of interest. Input from autism advocacy group representatives would enhance the process by insuring that the research is meeting the needs of autism individuals in an expedited fashion and that the results of the research will be accepted by the community.

Specific recommendations
The titles below are taken from the current Matrix, pages 11-22. Bulleted points are research goals and activities that would need to be added to the Matrix from the vantage point of a model that explores how autism is environmentally triggered and biomedically treated. In addition to enhancing the existing Environmental Factors and Treatment sections, the recommendations are embedded in each of the other content sections as appropriate.

* * *

CHARACTERIZATION OF AUTISM SPECTRUM DISORDERS AND ASSOCIATED GENETICS

Goals

- The title should be changed to "Characterization of autism spectrum disorders, co-occurring conditions, associated genetics, and associated exposures".
- Enhance the section that pertains to characterization of medical conditions. Enhance by adding science that investigates recovery and significant improvements of individuals with a previous PDD diagnosis.
    - Study autism as a dynamical process with intra-individual variability in severity that may be transient or persistent, and that may include improvement, loss of diagnosis and recovery; the mechanisms of dynamism may point toward treatment targets.
    - Look for biomarkers relevant to plasticity (including brain metabolism, brain neurophysiology, and systemic metabolism as well as behavior) that could track treatment response
- Identify the environmental factors that increase risk for PDD and might give rise to subtypes within the PDDs, depending on the exposure, exposure interactions, timing, and individual genetics.
    - Identify genetic vulnerabilities to environmental exposures, for example, from the environmental genome project, that would be of particular relevance to autism.
    - Special attention to detoxification pathways, including glutathione and cysteine levels, is warranted.
    - Conduct DNA methylation and epigenetics studies among autistic children.
    - Investigations into environmental triggers should not wait until the genetics of autism is characterized. Rather, these investigations can be used to inform genetics research and can be done prior to or simultaneous to genetics investigations.
    - Pre- and postnatal exposure history should be part of the medical work up and a key component of subtyping and phenotyping efforts. Exposures captured should include methylmercury, ethylmercury, mercury vapor from maternal amalgams, and small particle airborne and soil-based mercury. A study of Rh-blood type mothers who were exposed to ethylmercury from immune globulins should be part of such investigations.

- Toxicology studies that find biomarkers in non-autistic exposed individuals or animals should be applied to autism.
- Exposure histories among PDD individuals that identify multiple exposures that might lead to interaction effects or "double hit" effects should be used to generate hypothesis for research on such effects in autism.

Activities

- Autism phenome project defined and planned and resources established
  - Incorporate response to treatment as phenotype characteristic
  - Incorporate recovery/improvement trajectory as phenotype characteristic
  - Add exposure history to database so that phenotype and genotype can be linked to exposures, exposure interaction, and timing.
- Toxicological literature and databases are reviewed for susceptibility gene candidates and potential biomarkers.
- Using toxicological review, peripheral biomarkers are screened among well characterized ASD subgroups, with subgroups based on phenotype, genotype, or exposure history. Build on promising immune system findings to more clearly understand the role of immune alterations in ASD and how these alterations might arise from environmental exposures, both chemical and viral.
- Toxicologically-relevant susceptibility genes are screened among ASD subgroups.
- Animal models are developed using exposures relevant to the ASD population based on exposure history, factoring in susceptibility genes as appropriate.
- Longitudinal study of baby siblings is amended to add an exposure history; identify differences in exposure between siblings developing autism and those developing normally, and identify any differences in autism subtype based on differences in exposures.
- Pre-natal exposures can be captured via medical records, maternal surveys, and cord blood examinations.
- Databases of phenotype characteristics should cover not just behaviors and core deficits but also a comprehensive list of co-occurring medical and psychiatric conditions and systems alterations including CNS, sensory/perceptual, metabolic, immune, renal, and gastrointestinal. Metabolic alterations should include detoxification pathways, cell signaling, methylation, apoptosis, growth factors, and porphyrin profiles. How these characteristics change over time should be captured.

SCREENING

Goals

- Include physiologically meaningful exposure measures and intermediary metabolism measures (e.g. measures from body compartments and with laboratory measures sensitive to chronic or persistent as well as acute exposures) that could inform identification of biomarkers and development of biomarker profiles that will aid in screening.

- Gain a better understanding of the degree to which those with "early signs" progress to an actual ASD diagnosis, the reasons for progressing/not progressing, and whether progression varies by exposure history.
- Modify wording of current Matrix so that the goal to prevent autism is not to find "effective techniques for detecting autism as early as possible", but rather to find "effective techniques for detecting the early signs that might indicate an infant susceptible to a later ASD diagnosis and determine the exposures that might be prevented or the interventions that might be employed to avert the early signs from evolving into ASD."

Activities

- Screening tools – modify so that screening tools detect "at risk" signs and not just predict a subsequent ASD diagnosis.
- Longitudinal cohort for research – modify so that the cohort can be used to track exposures and subtype based on early signs that progress to ASD compared to early signs that resolve. Ensure that educational modules cover reduction in potentially harmful environmental exposures to at-risk infants.
- Biological and behavioral markers to develop indices of risk for ASD: modify goal to include environmental factors research along with genetic, neurobiological, and molecular biology research. Include environmental exposures and immune system molecules in the list of possible markers.

EARLY INTERVENTION

Goals

- Remove the emphasis on early intervention before age 3. While it is recognized that the earliest intervention is a lower risk and shorter term goal, it should not mean that the goal should be weakened for older individuals, only that intervention in older individuals may take longer to achieve and there is less research to support a positive outcome.
- The goal should recognize that treatments may be educational, therapeutic, or biomedical, and that the latter might include nutritional, dietary, and detoxification approaches as well as pharmaceutical ones.

Activities

- Develop intervention methods for older individuals with autism.
- Prevent 25% of autism cases: modify this goal so that the prevention of cases is set at 75%. If environmental factors play a key role in the majority of ASD cases, then eliminating or reducing exposures should prevent the majority of cases.

SPECIFIC TREATMENTS

Goals

- Overall, research should shift from a focus on "damage" towards a focus on "plasticity", or what can be corrected or modified to achieve recovery or gain of function.
- Treatment research should be viewed as urgent and the goal should be to find effective treatments for as many individuals as possible as quickly as possible.
- Modify the goal so that it is recognized that studies on effectiveness are conducted among meaningful subgroups, as certain interventions may work among some but not others.
- Modify the goals to recognize that complex, combined interventions and not single interventions may work best for ASD, and clinical trial methodologies must be developed that can accurately ascertain effectiveness for such regimens.
- The goals should recognize that treatments may be educational, therapeutic, or biomedical, and that the latter might include nutritional, dietary, and detoxification approaches as well as pharmaceutical ones.
- Treatment databases should be established that can link effectiveness of a given regimen on a given outcome (eg speech, anxiety) with patient information such as phenotype, genotype, and exposure history. Such learning can be used to understand pathways and mechanisms, which in turn can be used to develop more effective interventions.

Activities

- Develop biological outcome measures, such as intermediary metabolism measures in blood, urine or cerebrospinal fluid; electrophysiology; brain perfusion; and metabolic markers. These can be employed in clinical trials and in development of a treatment algorithm.
- Create a linked database that can be used by clinicians to record patient information, treatments tried, and outcomes, for use in research on interventions from which hypotheses can be generated for the most promising treatments and optimal subgroups for randomized clinical trials.
- Develop arrays related to intermediary metabolism that may underpin environmental vulnerabilities; these do not have to be specific to autism, just implicated in the pathophysiology.
- Efficacious drug treatments that target core symptoms: include other promising interventions besides pharmacology, and indicate that treatment may encompass complex regimens.

ROLE OF THE ENVIRONMENT IN AUTISM

Goals

- Rigorous and independent studies on historical autism prevalence rates over time and across geographies will aid in determining the extent of the autism epidemic, the role of changes in diagnostic practices, the extent to which environmental factors play a causal role in any increase, and what future services might be needed given the true increase in autism rates.
- Study environmental factors not only in relation to direct measures of exposure but also in relation to metabolic impacts to aid in developing potential treatments. Investigations of differential sensitivity, metabolic alteration, and pharmacokinetics to toxicants and other xenobiotics among ASD cases compared to controls would help in identifying toxicants, mechanisms, and doses of relevance.
- Research is showing that cumulative and synergistic effects of multiple exposures can have a far greater impact than a single exposure. Investigations of "multiple hits" are warranted.
- Other goals and activities listed in other sections of this document.

Activities

- Conduct a prevalence study comparing rates of autism and ASDs among school age children age 8 to 18.
- Conduct a study in a well defined population of autism rates before and after documented removal of thimerosal from infant vaccines.
- Retain twin registry; specify collection of complete pre- and postnatal exposure history including vaccines and other medical products.
- Implement a study of the rate and severity of ASD outcomes in vaccinated compared to unvaccinated populations.
- Conduct studies of the rate and severity of ASDs by geography, and link these geographic areas to databases of pollutants.
- As listed above, add exposure component to baby sibling longitudinal study.
- Conduct cell culture studies among autistic and control lymphocytes after exposure to thimerosal and other relevant chemicals. Look at pathways and gene expression that are differentially altered such as apoptosis, detoxification, methionine, etc.
- Create animal models based on single exposures, multiple exposures, and multiple exposures over time, both pre- and postnatally, to substances and viruses that ASD children have been exposed to in the doses to which they were exposed. Use these animal models to understand genetic susceptibility, pharmacokinetics, mechanisms (including effects at the cellular level and systems level such as GI, immune, and brain), retention and localization of body burden, and response to potential treatments. Toxicants studies should include methylmercury, ethylmercury, mercury vapor from maternal amalgams, and small particle airborne mercury. Viruses should include measles and chicken pox.

NEUROSCIENCE

Goals

Neuroinflammation and immune system effects on brain development should be added to the list of areas to be studied. An understanding of how toxicants alter brain function during various stages of development is needed, especially if linked to examination of autism brains and how they are different from controls. Investigations on how the brain "repairs" itself would aid in treatment approaches.

Activities

- Study not only brain regional changes but pervasive volumetric changes
- Study classes of tissue changes such as inflammation, microglial activation, oxidative stress, and hypoperfusion, and the effect these might have at varying stages of development.
- Study neuromodulator alterations that could be associated with plasticity and that could be altered by treatments.
- Study dynamic features of brain function (e.g. with EEG, MEG, fMRI or SPECT) that may show alterations that might be caused by toxicants and track function that may improve with treatment.
- Examine post mortem brain tissue for direct and indirect indications of environmental exposures. Brains must be made available for such investigations.

SCHOOL AND COMMUNITY INTERVENTIONS

- Add environmental interventions such as reducing pesticide and other chemical use in schools, service settings, and homes, as well as sale of low-nutrient, high-additive junk food in schools, where vulnerable children experience reduction in level of function in relation to such exposures.
- Educate school, institutional and community personnel about accommodating and supporting restrictive or prescriptive biomedical interventions including nutritional approaches.
- Expand definition of intervention in this section to include biomedical as well as behavioral/educational approaches.

EPIDEMIOLOGY

- Studies have shown that the largest increase in autism rates occurred in the late 1980s and early to mi-1990s. Epidemiology should investigate these birth cohorts and not just prospective cohorts.
- See other sections for additional epidemiology recommendations.

COMMUNICATION & COLLABORATION

- Institute CME courses in autism treatment nationwide.
- Create standards of care for autism treatment.
- Create capacity for randomized clinical trials, including studies of complex regimens that may or may not be pharmacological.
- Ensure that biological collections are open resources, and expand available resources.
- Encourage collaboration among clinical practices and medical institutions on database development and autism registries.