Vision:
Improve the lives of individuals with autism spectrum disorders now

Mission:
Promote innovative research that advances the understanding of autism spectrum disorders and leads to improved outcomes

Background and History
The office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since the inception of the Autism Research Program in fiscal year 2007 (FY07), appropriations of $53.4 million (M) have been directed toward promoting innovative research to advance the understanding of Autism Spectrum Disorder (ASD). The immediacy of the ARP Vision — to improve the lives of individuals with autism now — has imparted a strong sense of action and continues to steer the investment strategy for the ARP.

ASD encompasses a range of complex developmental disorders characterized by mild to severe challenges to social, emotional, and communication abilities. Recent reports by the Centers for Disease Control and Prevention indicated that the prevalence of ASD may be as high as 1 in 68. According to the report (Morbidity and Mortality Weekly Report 63 [2014] 2-24), an estimated 1 in 42 boys and 1 in 189 girls are affected and, thus, are identified as living with ASD. The causes of ASD are unknown; however, progress is being made on several fronts, and the answers related to autism will likely be the same as the disorder itself, which is multifaceted. Through the program’s areas of interest, the ARP seeks to improve diagnosis, treatment, and the study of psychosocial factors for affecting key lifetime transitions to independence and a better life for those with autism and their families.
The ARP strives to achieve and maintain a research portfolio of studies addressing gaps as defined by the scientific and consumer communities. The Areas of Interest (see figure below) are topics identified for increased emphasis and need in the scientific setting or in consumers’ daily lives. The Areas of Interest are revisited every fiscal year and adjusted to keep pace with the current needs of the community and may vary depending on the type of solicitation. For example, the Clinical Trial Award focuses on clinical application that may emerge from laboratory findings, while the Idea Development and Pilot Awards both seek novel studies that may shift paradigms and yield impact on the field of autism.
Yun-Fai Lau, Ph.D., of the Veterans Affairs Medical Center, UCSF discovered a potential cause of sexual bias in autism by showing that the Y chromosome-encoded transcription factor sex-determining region Y (SRY) regulates the X chromosome-encoded monoamine oxidase A, an important enzyme in deamination of neurotransmitters. This demonstrates a novel mechanism of sexual dimorphism for neural function and potential disorders.


John Shoffner, M.D., of Georgia State University found that children with defects in the genes of the mitochondrial oxidative phosphorylation pathway are at risk for neurological regression during periods of high fever; therefore, screening for mitochondrial diseases may aid in therapies that could minimize neurological regression associated with fever.


Armin Alaedini, M.D., from Columbia University used samples from a cohort of well characterized patients diagnosed with autism, their unaffected siblings, and unrelated controls to find that patients with autism had Immunoglobulin G antibodies to gluten linked to gastrointestinal symptoms distinct from those of celiac disease. Dr. Alaedini received an FY13 Idea Development Award for Proteomic Mapping of the Immune Response to Gluten in Children with Autism.


http://cdmrp.army.mil/arp/research_highlights/14alaedini_highlight.shtml

Brooke Ingersoll, Ph.D., from Michigan State University developed an internet-based training program, ImPACT Online, a highly innovative, web-based, distance learning program that teaches parents to support their child’s social communication development using a novel blend of evidence-based intervention techniques. ImPACT Online uses effective adult learning tools to help parents learn the intervention techniques and integrate them into their daily interactions with their child.


http://cdmrp.army.mil/arp/research_highlights/13ingersoll_highlight.shtml

Andrew Feinberg, M.D., M.P.H., and Walter Kaufmann, M.D., of Johns Hopkins Medical Center and Children’s Hospital, Boston (respectively) isolated differentially methylated regions within the genome of patients with autism as compared to their monozygotic twin. These epigenetic changes may help to determine if environmental factors influence the development of neurological disorders such as autism.


http://cdmrp.army.mil/arp/research_highlights/14feinberg_kauffman_highlight.shtml
Environmental Risk

Placental Vascular Tree as Biomarker of Autism/ASD Risk

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Research Foundation for Mental Hygiene, Inc., at the New York State Office for People With Developmental Disabilities’ Institute for Basic Research in Developmental Disabilities, Staten Island

Autism spectrum disorder (ASD) is the term for the range of complex neurodevelopmental disorders characterized by difficulties in social interactions, impaired verbal and nonverbal communication, and repetitive behaviors. Diagnosis of ASD at a young age is crucial for early intervention strategies to be implemented early enough to improve developmental outcomes. However, because current diagnostic procedures are based solely on behavioral assessments, diagnoses of ASD usually cannot be made until a child is at least 2 years old. The availability of additional criteria to identify individuals at risk for ASD, such as the identification of novel biomarkers, would have an enormous impact in improving the lives of individuals with autism and on the field of autism studies.

Dr. Carolyn Salafia of the Research Foundation for Mental Hygiene, Inc. is working to characterize placental changes in order to identify early biomarkers for ASD. Evidence suggests that prenatal exposures (e.g., environmental factors or certain drugs) may contribute to the onset of ASD. The placenta is the “first responder” to such stressors; therefore, it may be a useful tool to identify changes that represent ASD.

With support from an FY09 Idea Award, Dr. Salafia and her team accessed placentas from the Avon Longitudinal Study of Parents and Children, which studied from birth 8,403 children born in 1991 and 1992, and analyzed them for morphological differences. The placentas studied were from 56 children with ASD, 168 children without ASD but diagnosed with developmental delay and requiring special education needs, and 168 children with normal childhood development. Through this analysis, Dr. Salafia identified changes in the chorionic surface vasculature in the placentas of children with ASD that were significantly different from those of neurotypically developing children. Furthermore, she found that the placentas of children with ASD had a quite distinct chorionic surface shape and a reduced maximum radius. Dr. Salafia’s research team also observed a significant reduction in placental weight in female ASD cases. Taken together, these findings support her hypothesis that ASD placentas show alterations of branching structures known to be determined by the mid-trimester.

In addition to conducting morphological assessments of placentas, Dr. Salafia also developed specific immunohistochemical staining procedures to identify possible markers of prenatal exposures to acute and chronic inflammation. This ongoing biochemical analysis, in combination with the comprehensive morphological assessments of placentas, provides the basis for the development of powerful, noninvasive screening tools for earlier diagnosis of ASD.
Therapeutic Targets

Excessive Cap-Dependent Translation as a Molecular Mechanism Underlying ASD

Eric Klann, Ph.D.
New York University

Autism spectrum disorders (ASD) are characterized by deficits in social interactions, impaired communication, and repetitive behaviors. Several cases of ASD in unrelated families were found to have the same genetic mutation in the eIF4E gene promoter region. It is known that the cap-binding translation factor eIF4E takes part in regulating the translation process of genes to proteins in the cell. Mutations or changes in the promoter region of eIF4E could lead to higher eIF4E protein levels. Dr. Eric Klann of New York University sought to further elucidate the link between this gene and ASD. Through his study of the eIF4E gene and consequent linking of the cap-dependent translation to ASD, Dr. Klann has made significant progress in the ASD field.

With support from an FY10 Idea Development Award, Dr. Klann’s team studied a mouse model that overexpresses eIF4E. Dr. Klann performed behavioral tests on the mice, including tests to look at repetitive self-grooming and digging patterns, and as measures of the repetitive behaviors associated with ASD. He found that the eIF4E mutant mice displayed significant increases in both repetitive behaviors compared with their wild-type control littermates. Dr. Klann also performed a choice reversal Y-maze task in which the mice first had to learn and remember the location of an exit, and then when the exit was moved, to learn the new location. This test effectively measures the animal’s resistance to change, which was significantly lower in the eIF4E mutant mice than in controls. To look at impairments in social behavior, Dr. Klann assessed the mice in tests to determine their interaction time with other mice versus inanimate objects. In these experiments, the eIF4E mutant mice showed no preference for the mice and the inanimate objects, an indication of social interaction deficits. Dr. Klann then utilized an inhibitor of the eIF4F initiation complex for treatment of the eIF4E mutant and control mice. This inhibitor reversed all of the abnormal behaviors exhibited by the eIF4E mutant mice such that they behaved similarly to the wild-type mice. These results provide, for the first time, a clear link between exaggerated cap-dependent translation and behaviors associated with ASD. Moreover, this suggests that the eIF4F initiation complex may be a viable target for the treatment of ASD symptoms. Furthermore, the promising results from this study have led to a collaboration with Egenix Pharmaceuticals to pursue preclinical testing of additional compounds that target eIF4E and the eIF4F initiation complex for ASD treatment.

Excessive grooming in the eIF4E transgenic mice results in loss of facial hair compared to a wild-type mouse at the bottom.

Trista Matascastillo
Peer Reviewer (consumer)
Autism spectrum disorders (ASD) are a range of neurodevelopmental disorders that are characterized by impairments in social interaction, verbal and nonverbal communication deficits, and repetitive interests and behaviors. Adults with ASD experience significant impairments in social and nonsocial information processing, which often results in unemployment or underemployment, poor academic performance, limited social functioning, and poor quality of life. Despite advances in early detection and intervention approaches to limit the impact of ASD, few efforts have focused on interventions for adults with ASD. In fact, no interventions currently exist for adults that effectively remediate the broad range of information processing impairments characteristic of ASD. Drs. Nancy Minshew and Shaun Eack of the University of Pittsburgh sought to address this research gap and test new intervention strategies for the adult ASD population.

With support from an FY10 Clinical Trial Award, Drs. Minshew and Eack initiated a pilot trial in which they randomized 54 adults with ASD to either Cognitive Enhancement Therapy (CET) or Enriched Supportive Therapy (EST). Both of these interventions have been shown to be effective in improving adaptive function in schizophrenia patients but have never before been tested in individuals with ASD. CET integrates computer-based training focusing on attention, memory, and problem solving, with a small group-based curriculum to facilitate the development of adult social-cognitive milestones. EST, an emotion management intervention that provides psychoeducation about ASD and condition management skills, was used as a control to account for the non-specific effects of CET.

To assess cognitive and behavioral outcomes, the research team used a battery of standardized neuropsychological tests and clinical interviews before and after implementation of either intervention strategy. Preliminary analysis of 33 participants in the study indicates that after 18 months of either CET or EST, adults with ASD had significant increases in neurocognition, social cognition, and social adjustment compared to baseline measures, although increases were highest in the CET group (see figure below). Improvements in neurocognition were seen particularly in the areas of processing speed/attention and cognitive flexibility. Furthermore, although CET is not an employment-based treatment, it resulted in significant gains in employment in the adult ASD population that was not observed with EST treatment.

Drs. Minshew and Eack next used functional magnetic resonance imaging (fMRI) to analyze brain images of the individuals undergoing either CET or EST while completing established perspective-taking and emotion regulation tasks. In the CET treatment group, they found significant differential increases in prefrontal brain function, signifying improvements in perspective-taking, and front-medial temporal connectivity, suggesting an increase in emotion regulation.

The results of the trial thus far show that both CET and EST are effective at improving cognition and adaptive function in adults with ASD compared with baseline measures. Additional advantages have been seen with CET intervention, including greatly improved neurocognitive and social-cognitive measures, increased employment, and increased prefrontal brain plasticity in the fMRI studies. Taken together, these results highlight the feasibility of using CET as a new, effective approach to treat cognitive impairments in adults with ASD.
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