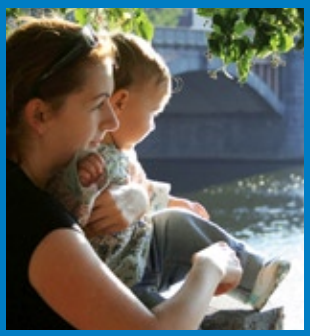
CDMRP

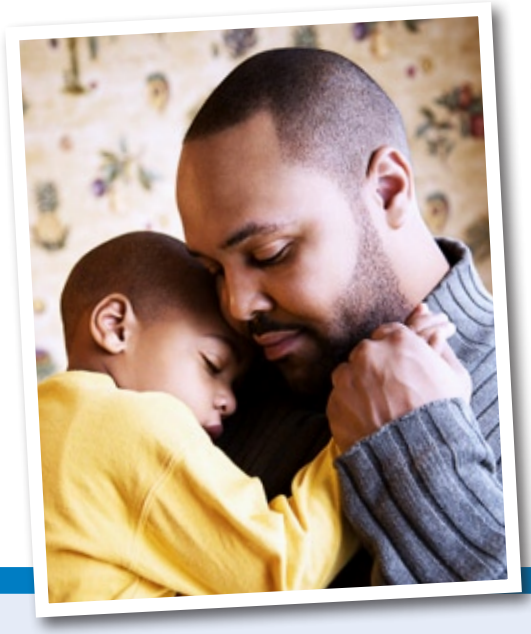
Department of Defense

Autism Research Program



U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs



HISTORY

In 1992, the Office of the Congressionally Directed Medical Research Programs (CDMRP) was born from a powerful grassroots effort led by the breast cancer advocacy community that convinced Congress to appropriate funds for breast cancer research. This enabled a unique partnership among the public, Congress, and the military. Created within the U.S. Army Medical Research and Materiel Command (USAMRMC) to manage these critical funds, the CDMRP has grown to encompass multiple targeted programs and has received more than $6 billion in appropriations from its inception through fiscal year 2009 (FY09). Funds for the CDMRP are added to the Department of Defense (DOD) budget where support for individual programs such as the Autism Research Program (ARP) is allocated via specific guidance from Congress.

Proposal Review Process

The CDMRP uses a two-tier review process for proposal evaluation. The first tier of evaluation is a scientific peer review of proposals weighed against established criteria for determining scientific merit. The second tier of evaluation is a programmatic review conducted by an Integration Panel (IP). Programmatic review is a comparison-based process where IP members take into consideration relevant innovation, impact, portfolio balance, and adherence to the intent of the award mechanism of each proposal. IP members also recommend an annual investment strategy that targets underfunded and underrepresented areas of research and encourages research into those areas that are considered the most critical to patients, consumers, clinicians, and laboratory researchers.

Both steps involve dynamic interactions among scientists, clinicians, and consumers. Scientific reviewers and other professionals are selected for their subject matter expertise while consumer reviewers provide a perspective that is complementary to the scientific expertise. For the ARP, consumers are individuals with an autism spectrum disorder (ASD) or family members of individuals with an ASD. Their firsthand experience with autism provides a unique perspective that helps researchers better appreciate the human side of the disease and supports funding recommendations that reflect the concerns and needs of individuals with ASD, their families, and clinicians.

Autism Research Program

VISION:

Improve the lives of individuals with ASD now.

MISSION:

Promote innovative research that advances the understanding of ASD and leads to improved treatment outcomes.

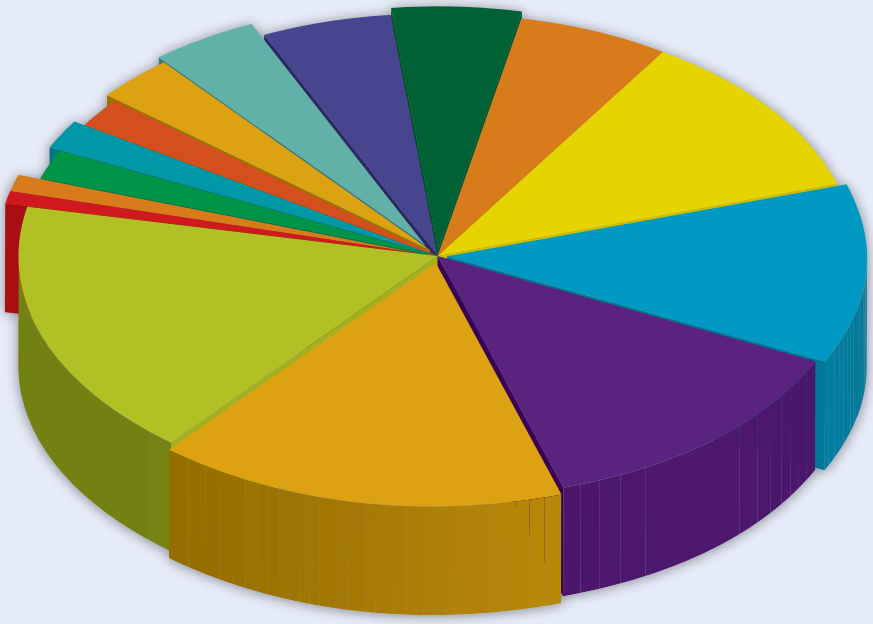
HISTORY:

Efforts by autism consumer advocates led to a congressional appropriation of $7.5 million (M) in FY07 to establish the DOD Autism Spectrum Disorder Research Program, which was renamed the ARP in FY08. The ARP received $6.4M in FY08, $8.0M in FY09, and $8.0M in FY10.

The autism spectrum includes the pervasive developmental disorders (PDD), including classic autism, Asperger's syndrome, Rett syndrome, childhood disintegrative disorder, and PDD-not otherwise specified. Many other disorders and syndromes may show autistic-like behaviors.

Autism Research Program Portfolio

Since inception, the ARP has offered award mechanisms that have supported conceptually innovative basic, translational, and clinical research, clinical trials, and scientific collaborations. The ARP has funded across a diverse range of focus areas.



ARP Investment Portfolio (FY07–FY09)

- Computational Biology **1%**
- Research Resources **1%**
- Endocrinology **2%**
- Health Care Delivery **2%**
- Primary Prevention **2%**
- Immunology **3%**
- Cell Biology **4%**
- Clinical and Experimental Therapeutics **5%**
- Complementary and Alternative Medicine **5%**
- Pathobiology **6%**
- Biobehavioral Sciences **11%**
- Genetics and Molecular Biology **12%**
- Neuroscience **13%**
- Epidemiology **16%**
- Detection and Diagnosis **17%**

Andrew Bolte, son of Ellen Bolte, with ASD

For the entire trip, I was absorbed in the ARP process: Getting to know the others involved, thinking about important autism issues, and making wonderful connections with people all over the country whose work touches on autism. That was valuable beyond words. Often it seems that emotions—not science—are the driving force behind autism treatments. I believe that peer-reviewed research will change this and lead to treatments that are evidence based.

Ellen Bolte, ARP Consumer Reviewer, FY09-FY10

My experience on the panel has been highly rewarding and educational. It is exciting to see the breadth of excellent science, ranging from the basic to the more applied and clinical, that the ARP is attracting. Working with such a diverse group of scientists and consumer advocates has helped me better realize how all of the science the ARP is funding impacts the lives of families and people with autism spectrum disorders.

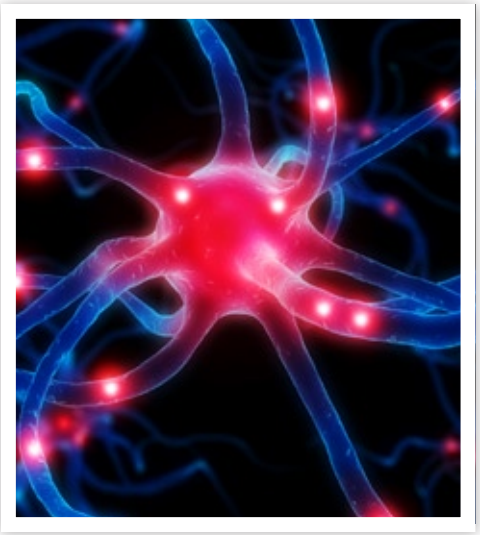
Christopher J. Stodgell, Ph.D., Integration Panel Member, FY08–FY10

Redox Abnormalities as a Vulnerability Phenotype for Autism and Related Alterations in CNS Development

Mark Noble, Ph.D., University of Rochester, Rochester, New York

S. Jill James, Ph.D., Arkansas Children's Hospital Research Institute, Little Rock, Arkansas

Maria Hepel, Ph.D., Department of Chemistry, State University of New York, Potsdam, New York



Early intervention has been shown to improve outcomes for individuals with ASD. Unfortunately, because ASD diagnosis is based on behavioral observations, it often takes several years to make a definitive diagnosis, missing the crucial window of opportunity for intervention (18 months to 3 years). Drs. Mark Noble, S. Jill James, and Maria Hepel received funding in FY07 to investigate oxidative abnormalities in children with ASD. Their goals are to understand the role of oxidative imbalance on the developing brain and to provide new options for earlier detection and treatment of such abnormalities.

Dr. James is testing the hypothesis that children with regressive autism and high-risk (developmentally delayed) children have low systemic redox potential. She hopes to identify a biomarker in primary immune cells that will be predictive for regressive autism and develop a treatment to increase redox potential and methylation capacity that will improve immune function in children with ASD.

Dr. Noble is analyzing the correlation between oxidative abnormalities in cells of the peripheral blood and developing brain to determine if a target can be identified in the bloodstream that can predict the oxidative status of precursor cells in the developing brain. He will test whether these redox abnormalities can (1) explain the differences in myelination observed in children with ASD and (2) cause enhanced sensitivity to physiological stressors.

Dr. Hepel is developing sensors for oxidative stress biomarkers such as glutathione, glutathione disulphide, cysteine, cystine, and homocysteine. The analytical tools developed in this project will provide a sensitive and cost-effective means of measuring redox potential that can be used to identify children at increased risk for ASD due to expression of a more oxidized phenotype.

Gestational Neuro-Immuno-Pathology Hypothesis

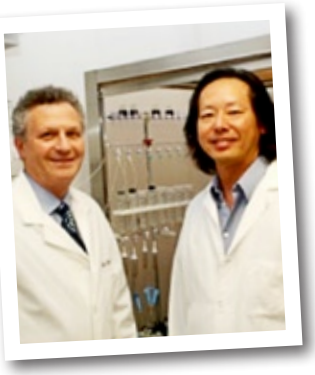
Robert Vogt, Ph.D., Centers for Disease Control and Prevention, Atlanta, Georgia

Dr. Anand Swamy and Ms. Sharon Kerr, scientists in Dr. Vogt's lab.

Dr. Robert Vogt, recipient of an FY07 Idea Development Award, and his team are developing and evaluating assays to search for biomarkers of increased risk for ASD in newborn dried blood spot (DBS) samples. The researchers are testing the Gestational Neuro-Immuno-Pathology hypothesis, which proposes that autoimmune or cross-reactive antibodies in pregnant women transverse the placenta to the fetus and may disrupt normal development by reacting with brain tissue. To date, the assay that Dr. Vogt developed has been used to measure nerve tissue antigen-specific IgG antibodies in over 390 DBS samples from children who developed ASD, over 390 children with mental retardation, and over 625 matched controls. Unexpectedly, the researchers found that higher levels of the nerve tissue antigen-specific IgG antibodies were associated with a reduced risk of ASD. Specifically, this trend was observed in brain-derived neurotropic factor, glial fibrillary axonal protein, and myelin basic protein IgG antibodies. These findings may be attributed to the placentally transferred IgG acting as a blocking antibody and highlight the need for further studies.

Finding a Genetic Path Toward Understanding Autism

Stuart A. Lipton, M.D., Ph.D., and **Nobuki Nakanishi, Ph.D.,** Sanford-Burnham Medical Research Institute, La Jolla, California



Drs. Stuart Lipton and Nobuki Nakanishi, recipients of an FY08 Synergistic Idea Award, hypothesize that the proper activation of myocyte enhancer factor 2C (MEF2C) leads to normal brain development, but altered expression of MEF2C may contribute to ASD pathogenesis or other neurological diseases. In their research, Drs. Lipton and Nakanishi have shown that the MECP2 protein, a mutation of which causes Rett syndrome, negatively regulates MEF2 activity in cultured neurons. Additionally, they have created a MEF2C-heterozygous mouse model and observed that these mice have abnormal amygdaloid morphology and exhibit ASD-like behaviors. Based on their findings and recent results from human genetic studies, which suggest that ASD and related disorders may result from MEF2C haploinsufficiency, Drs. Lipton and Nakanishi surmise that their research may lead to a new animal model for ASD, intellectual/developmental disorders, and epilepsy.

It is a privilege to serve on the Integration Panel. This unique collaboration between scientists and consumers allows the funding of research projects of the highest scientific standard with relevance to families impacted by autism.

Diane Chugani, Ph.D.,
Integration Panel Member, FY10

It has been my privilege to serve on the Integration Panel for 2 years now and to chair it for this past year. Participation in the ARP continues to be an exceptionally rewarding, yet challenging, experience. We have learned so much in the last decade, and the rate of progress continues to accelerate to produce new knowledge at an incredible pace for a research field. However, we all recognize that this rate is still too slow to meet the needs of children and adults with autism today. Our vision challenges us to work even harder to identify those research areas that can make a difference sooner rather than later.

Cynthia Molloy, M.D.,
Integration Panel Member, FY09–FY10, and Integration Panel Chair, FY10

Autism and Folate Deficiency

Richard H. Finnell, Ph.D., Texas A&M University, Houston, Texas

Folate deficiency is a possible risk factor for autism. Dr. Richard Finnell and colleagues at Texas A&M University hypothesized that folate deficiency secondary to genetic manipulation would cause both decreased cerebral spinal fluid (CSF) folate and altered (autistic-like) behavioral phenotypes and that supplemental folate may remediate the phenotypes. Mouse models of altered intracellular folate transport and metabolism exist (Folr1, Folr2, Mthfr, and Pcft1). Specifically, proton-coupled folate transporter (Pcft1) and folate receptor alpha (Folr1) were of particular interest, as they are involved in folate transport from the blood into the CSF, and patients with Folr1 mutations have been observed to have both cerebral folate deficiency and profound progressive cognitive deficiencies. Furthermore, specific variations in the methylenetetrahydrofolate reductase (NAD(P)H) gene (Mthfr) have been associated with autism risk in a highly complex fashion.

Heterozygous breeding pairs of Folr1, folate receptor beta (Folr2), Pcft1, and Mthfr mice were crossed to generate offspring of three different genotypes: wild type (WT), heterozygotes (het), and nullizygotes (null). All treatment groups were evaluated between 12 and 20 weeks of age using four different neurobehavioral assays: nest building to assess behavioral deficits, marble burying for perseverative/impulsive behaviors, three-chambered box for social interaction, and tube test for social dominance. CSF has been collected and is currently being analyzed by immunohistochemistry to determine if CSF folate levels are associated with observed behavioral abnormalities. This study may lead to both prognostic biomarkers and treatments for individuals living with ASD.

Normal nest built by Folr2 wild-type mouse.

Folr2 null mice displayed a deficiency in nest building that was corrected by pre- and postnatal folate supplementation.

The DOD program has been a great success in providing funding for established investigators, like myself, to explore new ideas and concepts about the disease. I just wish that Congress could provide more funds via DOD to this noble cause.

Chris Lau, Ph.D, ARP Concept Award Recipient, FY07

The ARP peer review process is ideal in many ways because it leaves so much room for questions and discussion. The panel truly wants to hear from the parents, and we all learned from each other. Feeling both relaxed and fascinated, I also felt that my group was going to move autism research ahead, which is just a breathtaking notion.

Susan Senator, ARP Consumer Reviewer, FY09–FY10

Characterization of the Pathological and Biochemical Markers That Correlate to the Clinical Features of Autism

Jerzy Wegiel, Ph.D., Thomas Wisniewski, M.D., and **Abha Chauhan, Ph.D.**
New York State Institute for Basic Research in Developmental Disabilities, Staten Island, New York

Drs. Jerzy Wegiel, Thomas Wisniewski, and Abha Chauhan, recipients of an FY07 ARP Idea Development Award, have been studying morphological and biochemical markers of autism. Postmortem brains of autistic subjects and control subjects were examined to detect morphological and biochemical patterns of altered development, maturation, and aging of neurons. The application of standardized clinical, genetic, and neuropathological inclusion criteria resulted in the largest unbiased postmortem study of the brain of autistic subjects.

The integrated efforts of the three research groups with clinical studies have resulted in (a) identification of brain neurons, neuronal networks, and brain regions with developmental defects; (b) characterization of the type and severity of these alterations; and (c) detection of links between the structural and functional defects. The detection of signs of partial correction of the developmental defects in some of the affected brain structures suggests that therapeutic acceleration/enhancement of these natural processes may contribute to functional improvements.

The review process runs smoothly, and the review panels gather a diverse group of people with a wide range of clinical, scientific, and personal experience in the subject area. The deliberations within the CDMRP review panels are always enlightening and provoke fascinating interchange that often positively impacts how I approach the problem scientifically in the lab and how we relate to people affected by the clinical problem. The diversity of viewpoints represented in a CDMRP review panel helps to ensure that the highest quality research is recommended for funding consideration.

John Welsh, Ph.D., ARP Peer Reviewer, FY09

Serving as a consumer reviewer provided so much encouragement and hope for the future of those affected by autism because I learned how much extensive research was being done to understand and combat this disorder, and I liked being able to shape the vision of this research. My outlook regarding autism became more positive once I understood how many resources are dedicated to helping today's families, caregivers, and educators.

Debra Vines, ARP Consumer Reviewer, FY09–FY10

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09-2010