

CDMRP



Department of Defense

Autism Research Program



U.S. Army Medical Research and Materiel Command



Vision:

Improve the lives of individuals with autism spectrum disorder now

Mission:

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

Application Review Process

The ARP employs the CDMRP's two-tier review process for application evaluation, with both tiers involving dynamic interaction among scientists, clinicians, psychologists, and disease survivors. The first tier of evaluation is the scientific peer review of applications to measure the scientific merit and gauge the impact of the submissions against established criteria. The second tier is a programmatic review conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, and consumer advocates. The Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit, potential impact, adherence to the intent of the award mechanism, relevance to program goals, and portfolio composition.

Congressionally Directed Medical Research Programs Autism Research Program

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 then, the CDMRP has grown to encompass multiple targeted programs and has received over \$7.5 billion in appropriations from its inception through fiscal year 2015 (FY15). Since its inception in FY07 through FY15, appropriations added to the DoD budget and totaling \$58.86M have been directed to the Autism Research Program (ARP) to promote innovative research that advances the understanding of Autism Spectrum Disorder (ASD) and to improve the lives of those living with 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.

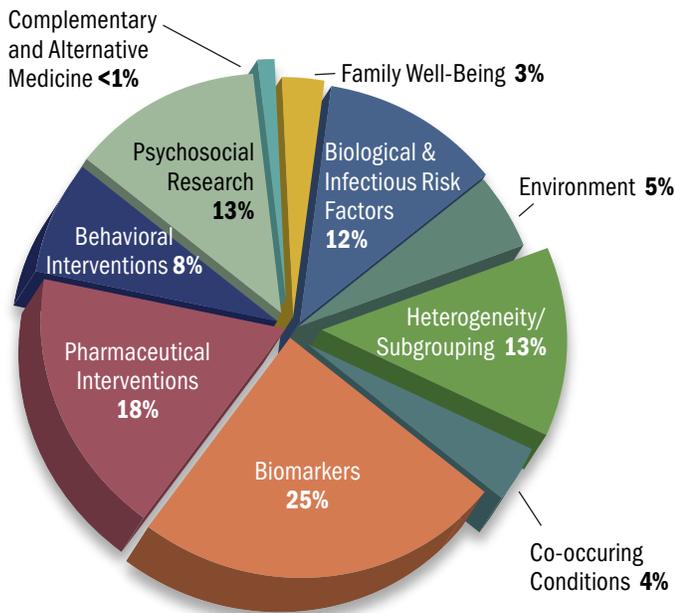
ASD encompasses a range of complex developmental disorders characterized by mild to severe challenges to social, emotional, and communication abilities. Recent reports by the Centers for Disease Control and Prevention indicated that the prevalence of ASD may be as high as 1 in 68. According to the report (*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 associated national cost of ASD is estimated to be \$35-\$90 billion dollars. 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—multifaceted. The ARP focuses on improving the lives of those living with ASD by funding innovative and highly impactful research. Through the program's areas of interest, the ARP seeks to improve diagnosis, treatment, and study of psychosocial factors for affecting key lifetime transitions to independence and a better life for those with autism and their families.



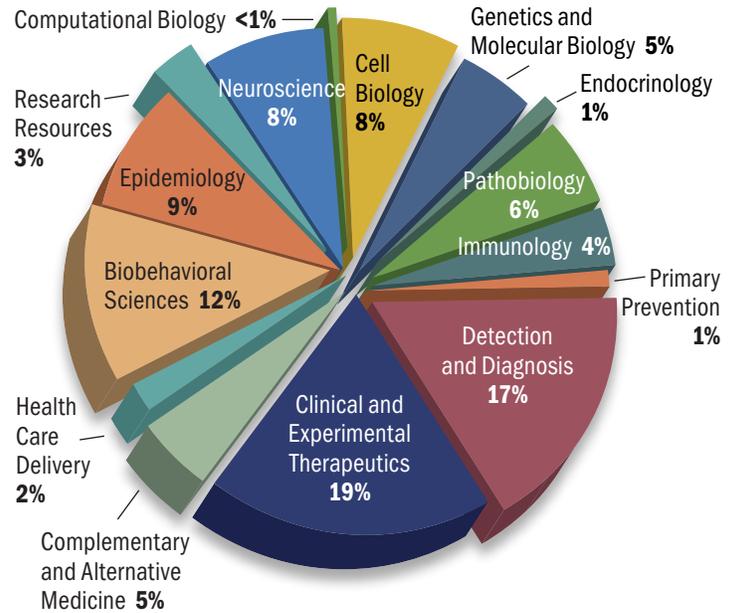
Research Portfolio

The ARP strives to find a research portfolio balance composed of studies focused on gaps 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 the consumers' daily lives. The Areas of Interest are revisited every fiscal year and are changed according to the current state of need. Additionally, the Areas of Interest may be different, depending on the type of solicitation. For example, the Clinical Trial Award will have Areas of Interest that are related to applying laboratory findings in the clinic, whereas the Idea Development or Pilot Award will have Areas of Interest focused on pursuing novel information for future impact on the field of autism.

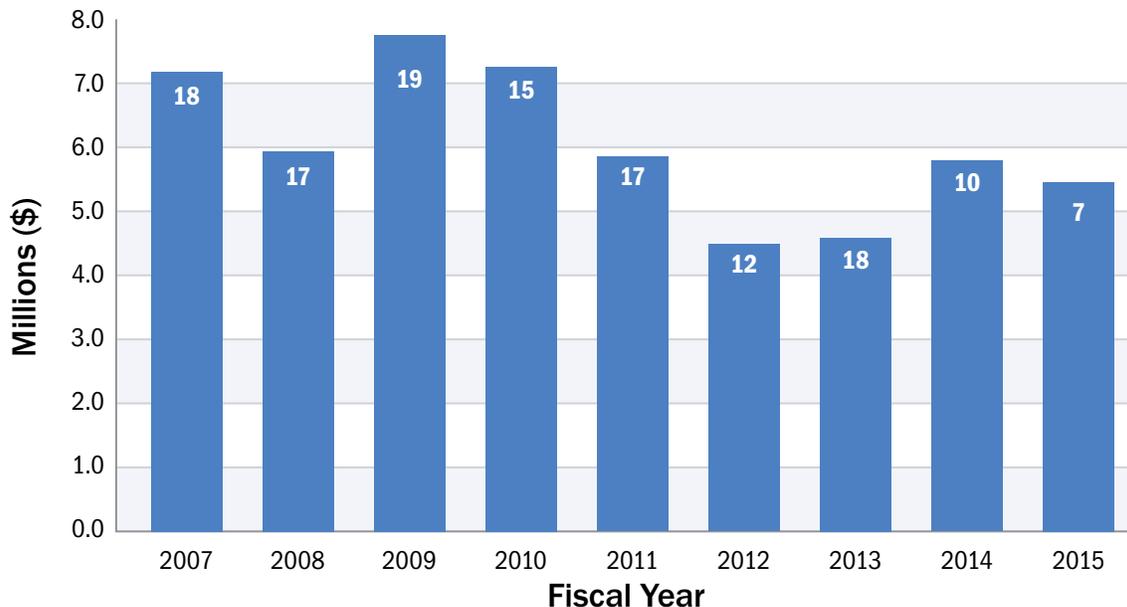
ARP FY07–FY15 Portfolio by Area of Interest (by Dollars)



ARP FY07–FY15 Research Portfolio (by Dollars)



ARP Appropriations and Number of Awards



ARP Research In Depth

Neural Basis of Empathy and Its Dysfunction in ASD, Therapeutic Interventions



"I have been impressed with the broad range of research proposals submitted to the CDMRP, as well as the thoughtful and careful review and discussion by the scientific reviewers on the panel. As a consumer reviewer, I have been able to bring the perspective of the community to those peer reviews and to discuss the relevance and potential impact of each proposal to our community's concerns and needs. I am extremely grateful to the scientific reviewers and their commitment and dedication to improving the lives and possible outcome for individuals with autism, and I applaud the Department of Defense CDMRP for developing this program for Autism Spectrum Disorders and committing the funds to move necessary research proposals forward."

Claire Bothwell

National Autism Association
FY14 Peer Reviewer (Consumer)



Michael Platt, Ph.D., University of Pennsylvania

Children with ASD struggle with social interactions that include understanding other people's feelings. The biological reason for this social dysfunction remains poorly understood; however, current evidence suggests that social impairments may involve the neuronal circuitry that motivates behaviors aimed at other people. These other-regarding preferences (ORPs) are defined as a concern for the welfare or the benefit of others. It is believed that ORP may rely on empathy, a social-cognitive function that is compromised in individuals with ASD.

Dr. Michael Platt of the University of Pennsylvania is working toward understanding how the various regions of the brain interact as an individual receives a reward and how naturally occurring chemicals may enhance this process. With support from an FY10 Idea Development Award, Dr. Platt's research team developed an animal model using rhesus macaques to characterize the role of certain brain regions in the prefrontal cortex and the role of oxytocin (OT), a naturally occurring hormone, in social behaviors.

Dr. Platt's study found that rhesus macaques were excellent models for studying particular social behaviors. Results showed that the rhesus macaques preferred to deliver juice rewards to another monkey rather than no monkey and also displayed an increased attention to the recipient monkey. This model was used to determine specific regions of the prefrontal cortex that respond to self-rewards, reward allocations to another monkey, or both. Dr. Platt's research team also explored the effects of OT on monkeys' concerns for others. OT itself has been known to increase trust in people; it has been suggested that abnormalities in the neural pathways for OT may contribute to issues with social interactions observed in ASD. The research team found that OT, when administered effectively, can enhance prosocial behavior and social attention in rhesus monkeys.

Overall, this work holds promise for understanding both the basic mechanisms that support complex social behavior and translating that knowledge to improve treatment avenues for individuals with ASD. Ultimately, these results could inform both pharmacological and behavioral interventions to improve the lives of people living with ASD.



Risk Factors, Comorbid Conditions, and Epidemiology of Children with Autism in Military Families



Maj Cade Nylund, M.D., USAF, Uniformed Services University of the Health Sciences

With funding provided by a 2011 Pilot Award from the CDMRP ARP, Dr. Cade Nylund and his team from the Uniformed Services University of the Health Sciences examined Department of Defense Military Health System medical records to understand the comorbid conditions and risk factors for autism.

The researchers studied the records of 48,762 children with ASD, ages 2-18, and 243,810 children without ASD, age- and gender-matched, who enrolled in the Military Health System during 2000-2013. Using this data set (one of the largest of military families in the world), Dr. Nylund and his colleagues were able to identify multiple key conditions that are more common in children with autism and a combination of prenatal and early infancy risk factors for the later development of ASD.

Specifically, the researchers found that children with ASD are at considerably increased nutritional risk. They found that children with ASD were more than twice as likely to be obese and to suffer from its complications, including hypertension, high cholesterol, type II diabetes, and fatty liver disease, than matched controls. The research suggests that medications prescribed to children with ASD may play a part. Children with ASD also are at risk for nutritional deficiencies in macro- and micronutrients, including iron, vitamin A, calcium, vitamin D, and protein. Counterintuitively, some children with ASD are also at increased risk for being underweight.

Common childhood conditions such as ear infections, urinary tract infections, and appendicitis are more likely to have complications in children with ASD. Children with ASD have difficulty in communicating their physical concerns to parents and physicians, which leads to missed or late diagnosis.

The researchers found that over 80% of children with ASD were diagnosed with a mental health condition compared to 30% of controls. Over 65% of children with ASD were on psychiatric medications at some point in the study and for more than 9 times as many days compared to children without ASD, which is particularly noteworthy, as there is no FDA-approved medication to cure the behavioral and social deficits of ASD. Twenty percent of children with ASD experienced one or more seizures between the ages of 2-18, compared to 4% of children without ASD. Thirty percent of children with ASD had sleep disorders that required treatment.

The research team was able to examine the records of more than 8,000 children, starting from birth, and even before birth by studying their mother's medical records during pregnancy. The large data set allowed the researchers to explore the impact of more than 50 potential risk factors at one time. Infants with seizures in the first 90 days of life were seven times more likely to be diagnosed with ASD. In the perinatal period, birth asphyxia, preterm birth, low birth weight, newborn infections, and newborn complications were also associated with increased risk of ASD. A number of maternal medical conditions were associated with eventual diagnosis of ASD, including high blood pressure, asthma, mental health problems, and obesity. The use of assisted fertility treatments and procedures and labor and pregnancy complications were also associated with increased risk of ASD. Finally, the use of medications during pregnancy was associated with ASD. These included exposure to antibiotics, antivirals, asthma medications, muscle relaxants, cardiac medicine, anticonvulsants, mental health medications, anti-vomiting medications, diabetes medications, and fertility drugs.



"As a CDMRP reviewer and as a [former] review panel chair, I have been very impressed with the time and effort scientific reviewers put into assuring that ARP's funded work asks important questions and is of the highest methodological quality. Working with fellow panelists who are consumer reviewers has been a great experience that all scientists should have to better enable them to propose research most valued by the families we aim to help."

Bryna Siegel, Ph.D.
University of California,
San Francisco
FY15 Peer Reviewer

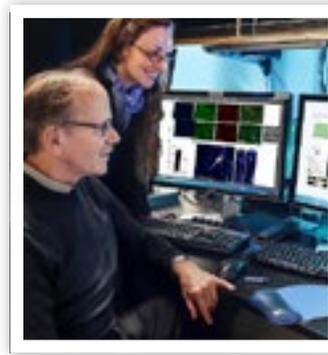


"From understanding how genes and proteins play a role in causing ASD to helping adults with ASD learn to drive and find jobs, the CDMRP's ARP has helped scientists conduct groundbreaking research on ASD over the last decade. As the chair of the Programmatic Panel, I am excited to work with our dynamic group of stakeholders and scientists and our program's dedicated support staff to ensure the ARP's wide range of research support will continue to help families and individuals with ASD across their lifespans."

Christopher Stodgell, Ph.D.
University of Rochester
Programmatic Panel Member
(Chair)

Testing Brain Overgrowth and Synaptic Models of Autism Using Neuroprogenitor Cells and Neurons from Patient-Derived Induced Pluripotent Stem Cells

Fred H. Gage, Ph.D., Salk Institute for Biological Studies, Basic Research



ASD involves complex neurodevelopmental disabilities distinguished by impairments in social interactions and communication and/or the presence of repetitive behaviors. The biological basis for the development of ASD is not known, but recent evidence suggests that two factors, early childhood brain overgrowth and neuronal synaptic dysregulation, may play roles in the development of ASD.

Brain overgrowth is abnormal enlargement of the brain, and MRI studies conducted in ASD patients found a correlation between this condition and ASD. Neuronal synapses operate as network components in the brain's circuit board, conveying electrical impulses from one neuron to an adjacent neuron to send a message to accomplish a specific activity. Some ASD patients have genetic mutations that adversely affect neuronal synapse growth or function, suggesting neuron communication issues may correlate with the development of ASD. However, a paucity of relevant research models has made it difficult to determine the importance of both brain overgrowth and neuronal synapse dysregulation in ASD, prompting Dr. Fred Gage of The Salk Institute for Biological Studies and colleagues from the University of California, San Diego and the Cleveland Clinic to create a cellular model of ASD to aid in the study of these abnormalities.

With support from an FY12 Idea Development Award, Dr. Gage and his colleagues biopsied skin cells from ASD patients and reprogrammed them to behave like stem cells known as induced pluripotent stem cells (iPSCs). iPSCs are capable of becoming many different cell types, so Dr. Gage and his colleagues devised experimental conditions that promote their development into early brain cells, called neuroprogenitor cells (NPCs), and neurons. He then examined these ASD patient-derived NPCs for signs of brain overgrowth and found that the population size of cultured ASD NPCs doubled almost twice as quickly as control NPCs. To dig deeper into the reasoning behind the enhanced ability of ASD NPCs to proliferate, Dr. Gage and his colleagues analyzed the genetic and molecular pathways within neuronal cells that control cell growth, division, and function. He found that ASD NPCs had a lower activity of beta-catenin, a cell signaling molecule that helps maintain the structural organization of tissues and controls the expression of developmentally critical genes.

In additional studies, Dr. Gage and his colleagues further differentiated NPCs into neuron cells to investigate whether ASD patient-derived neuron function is altered compared with those of normal individuals. A multielectrode array analysis, which can measure neuronal network changes in cultured cells, revealed that neuronal communication is deficient in ASD patient-derived neuron cells. Genetic analyses of these developing ASD neurons showed abnormal expression patterns of genes that control voltage-gated cation channels involved in helping neurons fire properly. Treating ASD patient neuron cells with the drug insulin growth factor 1, which has been shown to improve synaptic function in some specific subsets of ASD patients, improved neuronal activity in many, but not all, ASD patient samples.

Dr. Gage's research provides critical insight into the underlying biology for the occurrence of brain overgrowth and alterations in the function of neuronal synapses in patients with ASD. His results may also provide helpful information that could be used in screening patients for future therapeutic intervention studies.



"I am so honored to serve on the Programmatic Panel of the CDMRP ARP, which embraces consumers as an integral part of the process in selecting research that is most relevant to our community. Our input is valued in equal measure by our scientific and clinical community counterparts. Allowing this type of cross-pollination gives our community a voice to explain what life beyond the laboratory and treatment rooms is like for families living with autism. That improved understanding helps all of us focus on our ultimate mission and vision of improving the lives of those with ASD now, in real time, to improve their ability to grow up and live independent, meaningful, and fulfilling lives."

Shelley Hendrix, B.A.

Unlocking Autism
Programmatic Panel Member
(Consumer Advocate)

Highlights of ARP Achievements



Jaime A. Pineda, Ph.D., of the University of California, San Diego, and Ralph-Axel Mueller, Ph.D., of San Diego State University provided neurofeedback training (NFT) and mental exercises aimed at promoting greater neural plasticity to ASD patients exhibiting deficits in social cognition and abnormal electroencephalogram (EEG) mu rhythms (8-13 Hz) compared with typically developing controls. ASD children who underwent 30 hours of NFT demonstrated improvements in mu rhythm desynchrony and brain organization, as detected by functional magnetic resonance imaging. They also showed improvement in several validated behavioral measures, including the

Autism Treatment Evaluation Checklist, which consists of 4 subtests gauging speech/language communication, sociability, sensory/cognitive awareness, and health/physical behavior.

Fishman I, Keown CL, Lincoln AJ, et al. 2014. Atypical cross talk between mentalizing and mirror neuron networks in autism spectrum disorder. JAMA Psych 71(7):751-60.



Sarkis K. Mazmanian, Ph.D., and Paul H. Patterson, Ph.D., of the California Institute of Technology determined in a mouse model of ASD that animals exhibiting ASD-like behavior also display gastrointestinal abnormalities similar to those found in ASD patients. Treating young mice harboring disrupted gut bacteria with *Bacteroides fragilis*, a commensal bacterium found in humans and known to promote immune homeostasis, improved gut function and alleviated ASD-like behaviors in mice. These findings suggest that probiotic therapy may be a useful treatment for individuals with ASD and may soon lead to promising clinical trials.

Hsiao EY, McBride S, Chow J, et al. 2012. Modeling an autism risk factor in mice leads to permanent immune dysregulation. PNAS 109:12776-12781.

Hsiao EY, McBride SW, Hsien S, et al. 2013. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 155(7):1451-1463.



Emma Allen-Vercoe, Ph.D., of the University of Guelph discovered that children with autism have an altered fecal metabolic profile and that ASD individual-derived fecal extracts are more immunostimulatory compared with normal individuals. This may reflect an imbalanced microbial ecosystem in the intestines, providing a scientific foundation for parental reports of “disturbed gut” in ASD children.

Elisa Hill-Yardin, Ph.D., of the University of Melbourne studied gastrointestinal (GI) nerve function in an autism mouse model harboring a mutation in neuroigin 3 (NL3), a gene associated with autism that is required for proper function of neuronal synapses in the brain. The research team used these mice to characterize the localization and function of NL3 in myenteric nerves in the GI tract, which may be linked to digestive difficulties experienced by ASD patients.



Dwight German, Ph.D., of the University of Texas Southwestern Medical Center used a novel peptoid library screening procedure to search for an antibody blood biomarker to identify children with ASD. He found one peptoid, ASD1, which recognized significantly lower levels (over 50%) of an antibody in the blood of ASD boys compared with typically developing boys. This peptoid was 66% accurate in identifying ASD. When the peptoid was used along with another protein biomarker (thyroid stimulating hormone), Dr. German found that the predictive accuracy of the two biomarkers rose to 73%. The identification of blood biomarkers for ASD will make it possible in the future for initiation of therapeutic treatments at an early age.

Zaman S, Yazdani U, Deng Y, et al. 2016. A search for blood biomarkers for autism: peptoids. Scientific Reports 14(6):19164



For more information, visit:

<http://cdmrp.army.mil>

or contact us at:

CDMRP.PublicAffairs@amedd.army.mil

301-619-7071

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