

# Autism Research Program



# 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 \$5.4 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.

# Autism Research Program

## VISION:

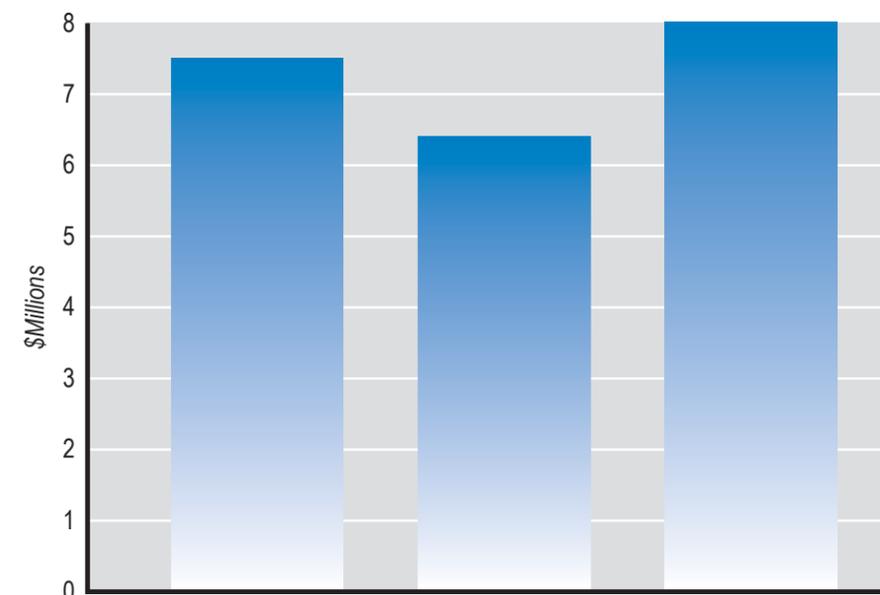
Improve the lives of individuals with autism spectrum disorder now.

## MISSION:

Promote innovative research that advances the understanding of autism spectrum disorder and leads to improved treatment outcomes.

## HISTORY:

Efforts by autism consumer advocates led to a congressional appropriation of \$7.5M in FY07 to establish the DOD Autism Spectrum Disorder Research Program (ASDRP), which was renamed the Autism Research Program (ARP) in FY08.



Congressional Appropriations for the ARP FY07–FY09

## Proposal Review Process

The CDMRP uses a two-tier review process for proposal evaluation, with both steps involving dynamic interactions among scientists, clinicians, and consumers. For the ARP, consumers are individuals with an autism spectrum disorder (ASD) or family members or caregivers of individuals with an ASD. 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. The consumer group evaluates proposals based on the impact the research will have on the autism community and how it will translate effectively to individuals with autism. Overall, consumer reviewers bring a sense of urgency to the discussions.

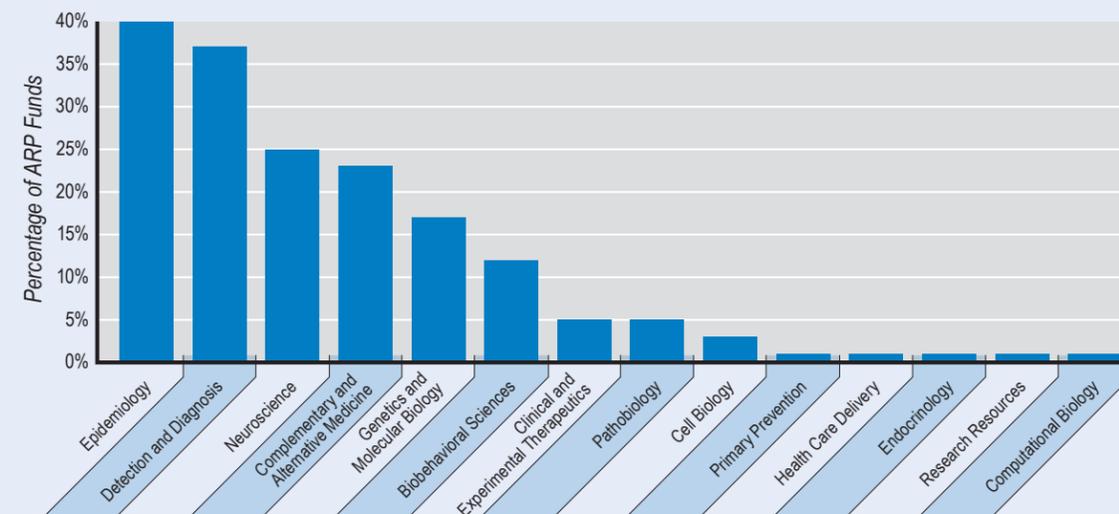


The first tier of evaluation is a scientific peer review of proposals weighed against established criteria for determining scientific merit. The second tier of evaluation is a programmatic review conducted by an Integration Panel (IP). The ARP IP is composed of visionary scientists, clinicians, and consumer advocates who are committed to serving the interests of the ASD community. Individual panel members recommend program priorities, innovative investment strategies, and a broad portfolio of research projects for funding.

## 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 research across a diverse range of focus areas.

ARP Funds (FY07 - FY08) Invested By Focus Area\*



\*Individual awards may be represented in more than 1 focus area.

# Consumer Involvement Voicing the Research Needs of the Consumer Community

## A Unique Feature of the ARP – Consumer Participation

The unique voice and experiences of consumers play a pivotal role in the ARP. As active members of the program, consumers work with expert scientists and clinicians to establish program priorities, participate in proposal review, and make funding recommendations. Their firsthand experience with autism provides a unique perspective that helps scientists and clinicians 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. Equally important, consumers take what they have learned from participation in the ARP back to their communities to increase awareness of the importance of autism research. This communication helps to strengthen the relationship between the scientific community and the consumer advocate community.



“I participated as a consumer reviewer and found it to be an invaluable experience. As a parent of a child with autism, I used to be frustrated at the pace of science and unappreciative of the fundamental building blocks that needed to be put in place before effective interventions could be designed. Participating as a consumer reviewer led me to meet and talk with the best and brightest in the field and learn just how carefully the two-tier review process sifts through the proposals to fund only the best and most critical studies.”

Ann Gibbons, Peer Review Consumer Reviewer, FY07 and FY09

“I am honored to serve on the Integration Panel for the Autism Research Program for the Congressionally Directed Medical Research Programs. It is the one federal research program that takes consumer input seriously. If we are to solve the “autism puzzle” in the near future, there is no question that it will come sooner when scientists and vested stakeholders (i.e., parents) can work together to address the complexity of autism.”

Peter Bell, Integration Panel Member, FY07–FY09, and Integration Panel Chair, FY07



“I knew very little about autism before my son regressed in 1996. I devoured PubMed, only to find that there was precious little in the medical literature that fit his clinical situation well. Over a decade later, autism has not “gone away,” and it is long past time for no stone to be left unturned; autism spectrum disorders must be understood. The Autism Research Program of the Congressionally Directed Medical Research Programs is designed to support novel, potentially groundbreaking research, and I was thrilled to be invited to participate as a consumer reviewer as it was an opportunity for me to give back to the autism community—a community I respect greatly. It was also a heartening experience because I found that there are researchers who are listening to us and scrutinizing our children carefully. Their proposals demonstrate that they have doubts about the validity of the traditional dogma regarding autism, and doubt is good. I am grateful to the researchers and to the CDMRP’s Autism Research Program, and I believe this may be the one that funds groundbreaking autism research.”

Deborah Darnely-Fisch, Peer Review Consumer Reviewer, FY08–FY09



“I can think of nothing more devastating than discovering that your child has a serious developmental disorder, except the news that there is no research going on into the disorder that has robbed your child of his future. In 2007, the Department of Defense Office of Congressionally Directed Medical Research Programs announced a new program that would focus on autism research. I was honored to be chosen to serve as a consumer reviewer for the first round of the CDMRP-ARP grants.”

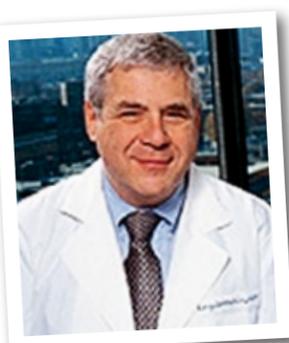
Portia Iversen, Peer Review Consumer Reviewer, FY07





“The opportunity to serve on the ARP Integration Panel has been a truly enriching one. Panel members come from very diverse backgrounds, but each brings a passion and commitment to do what we can as a group to advance the understanding of autism. This is reflected in every step of the process, from discussions of programmatic priorities to finding the right proposals to address those priorities. I have already learned so much from this group of dedicated scientists and advocates. With respect for what each brings to the table, they put tremendous effort into working together to provide a perspective to the ARP to promote good science that is firmly connected to the real-world experience of autism.”

Dr. Cynthia Molloy, Integration Panel Member, FY08–FY09



“I have had the pleasure of being a member of the Autism Integration Panel for 3 years, since its beginning, and to chair the Panel. The projects chosen for funding are high quality, diverse, and hold great promise for improving the lives of individuals with autism. It is an honor to serve.”

Dr. Gary Goldstein, Integration Panel Member, FY07–FY09, and Integration Panel Chair, FY08–FY09



# Supporting Collaborations

## Maternal Risk Factors for ASD in Children of the Nurses’ Health Study II

In 2005, participants in the Nurses’ Health Study II (NHS II) cohort, a large U.S. national sample, were asked to report whether they had any children with an ASD. The NHS II has a wealth of data on maternal factors collected prospectively and without any relationship to a child’s condition that will be utilized by ARP FY07 Idea Development Award recipients Drs. Alberto Ascherio, Susan Santangelo, and Marc Weisskopf to investigate the role of both maternal dietary factors and environmental toxins in relationship to ASD. The study will analyze samples from study participants to examine genetic and environmental components that may lead to autism. Success in this study will increase the understanding of how demographic and reproductive factors could influence obstetric practice. Investigating maternal dietary factors could reveal as-yet-unidentified risk factors for ASD, thereby impacting public health recommendations for nutrition for women of child bearing age.



## Developing Treatment, Treatment Validation, and Treatment Scope in the Setting of an Autism Clinical Trial

It is believed that autism may be caused by interactions of multiple genetic and environmental factors. Some of the genes identified are related to oxidative stress, which supports that oxidative stress may be a mechanism that contributes to autism. A key omega-3 fatty acid called docosahexaenoic acid (DHA) is a normal substance that is present in large amounts in the brain and has properties that oppose oxidative stress. Therapeutic trials of agents containing DHA appear promising in autism.

Drs. William Johnson, Peter Stein, and Sherie Novotny received FY07 ARP Idea Development Awards to investigate if DHA treatment can beneficially affect the autism clinical phenotype. Specifically, Drs. Johnson, Stein, and Novotny’s research aims to develop a new therapy for children with autism, to develop means of validating and monitoring therapeutic responses assessed through clinical phenotype and lipid biomarker excretion, and to develop means for selecting children with autism likely to respond to this therapy.



## Discordant Monozygotic Twins as a Model for Genetic-Environmental Interaction in Autism



While environmental factors have long been suspected to play an important role in autism, they have been very difficult to identify, and their gene targets are still unknown. One of the possible mechanisms by which the environment could influence autism is through epigenetic changes. Epigenetics refers to all modifications to genes other than changes in the DNA sequence itself. A major component of epigenetics is DNA methylation, a chemical change in DNA that is reproduced during cell division and is associated with gene silencing. DNA methylation is affected by a variety of environmental factors including diet.



FY08 ARP Synergistic Idea Award Recipients Drs. Andrew Feinberg and Walter Kaufmann will explore the contribution of epigenetic abnormalities to the etiology of autism. They hypothesize that genetically identical twins are often discordant for autism. Drs. Feinberg and Kaufmann are testing this idea by studying DNA methylation in such monozygotic twins and have already discovered genes that are abnormally methylated in the more affected twin. They will then determine whether the identified epigenetic changes are present in autistic subjects in the general population. This project will combine novel and sensitive high-throughput epigenomic strategies developed by Dr. Feinberg, a pioneer in epigenetics, with detailed phenotypic analyses by Dr. Kaufmann, a leader in the study of autism in genetic disorders. These studies may help to better define autism's clinical heterogeneity by identifying epigenetic changes and genetic abnormalities relevant to autism.

## Identifying Biomarkers

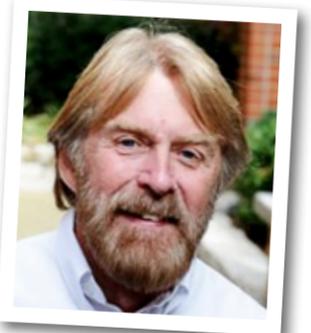
### Multiplexed Suspension Arrays to Investigate Newborn and Childhood Blood Samples for Potential Immune Biomarkers of Autism



Antibodies are formed by the immune system as part of the normal host defense activity that is essential for life. FY07 ARP Idea Development Award recipient Dr. Robert Vogt is testing the theory that a subset of antibodies in pregnant women and infants may cross-react with brain tissue, leading to disruption of normal infant development. Dr. Vogt and his team will analyze dried blood spot (DBS) samples obtained from public health newborn screening programs. To date, they have tested more than 500 archived DBS samples of newborn babies who later developed autism and more than 1,500 others who developed normally or had other types of behavioral disorders. Their results show that different types of antibodies can be detected at a high level in some newborns. They are currently analyzing the data obtained to determine if there is a relationship between antibody levels and autism, and they are developing new methods to find out more about the antibodies they have detected.

## Improving Diagnosis

### Reliability and Validity of Autism Assessments and Diagnosis Using Telemedicine



Evaluations for ASD are particularly needed in rural communities as these areas have fewer qualified specialists. Dr. Matthew Reese from the University of Kansas Medical Center Research Institute was awarded an FY07 ARP Concept Award to explore the innovative use of telemedicine (interactive TV) to diagnose ASD in children. Dr. Reese will determine whether young children can receive an appropriate assessment and diagnosis through telemedicine. Telemedicine overcomes several barriers faced by families living in rural areas, including traveling for appointments, missing work, and accessing services from qualified specialists. This project highlights the need to empirically evaluate the use of telemedicine for delivery of services to children with autism living in underserved areas.



# Exploring Innovative Research Ideas



## Prostaglandins and Brain Development: A Link Between Inflammation and Autism

Pathologies of the cerebellum are frequently and strongly associated with ASD. Autism exhibits a strong gender bias toward males and is susceptible to environmental perturbations. Included among the critical environmental variables is inflammation early in life, either in utero or postnatally. Fever is an integral component of inflammation and is induced and maintained by prostaglandins. Prostaglandins are membrane-derived lipids synthesized from arachidonic acid by the cyclooxygenase enzymes, COX-1 and COX-2. Inhibitors of the COX enzymes are among the most widely used over-the-counter medications on the market today.

Dr. Margaret McCarthy of the University of Maryland, Baltimore, received an FY08 ARP Concept Award to explore the hypothesis that prostaglandins associated with inflammation and/or the inhibition of prostaglandin synthesis by fever-reducing medications are a contributor to the enhanced vulnerability to autism following early life illness. Dr. McCarthy and her team have found that inhibition of prostaglandin synthesis stunts the development of Purkinje neurons, the principal neuron of the cerebellum. They have also found that estradiol, a steroid that can be synthesized locally in the cerebellum, has the same effect. Preliminary evidence suggests that prostaglandins stimulate estradiol synthesis and the estradiol then retards Purkinje neuronal growth. These experiments will be informative about basic mechanisms leading to the risk of developing autism and may influence clinical practice regarding the treatment of inflammation during critical periods of development.

## Etiology of Sleep Disorders in ASDs: Role for Inflammatory Cytokines



Children diagnosed with ASD experience high rates of sleep disorders that typically include night-time arousals. There have been relatively few reports that address the underlying cause for these disruptions. Alterations in sleep have been linked with cognitive and behavioral deficits as well as stress and anxiety. The initiation of the stress axis may feed back and exacerbate the sleep dysregulation, which may further worsen the behavioral deficits. A consequence of increased anxiety is a dysregulation of cytokines, which are cellular signaling molecules. Long-term exposure to high levels of cytokines can disrupt sleep patterns, and elevated cytokine levels have been reported in children with ASD.

Dr. Jessica Mong received an FY08 ARP Concept Award to identify and understand the sleep disorders that are potentially compounding autistic behaviors. Dr. Mong's research team plans to test the prediction that increased levels of proinflammatory cytokines are present in ASD and underlie the dysregulation of sleep patterns.

## Three-Dimensional Facial Pattern Analysis for Autism

While clinical observations indicate that autism is a heterogeneous disorder, there are no readily available means to differentiate subtypes within the patient population. Distinguishing the subtypes would aid in the development and utility of more individualized therapies and a better understanding of different etiologies. ARP FY07 Concept Award recipient Dr. Ye Duan proposes to determine if there is a consistent facial pattern in the core group of idiopathic autism patients, which is often referred to as essential autism. If such a pattern is confirmed, in addition to defining a subgroup of autism patients, Dr. Duan believes it will indicate that essential autism is a neurodevelopmental syndrome and may provide a prescreening tool to assist in early diagnosis.





For more information, visit

<http://cdmrp.army.mil>

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