

# Autism Research Program



Congressionally Directed Medical  
Research Programs

# CDMRP

Department of Defense



U.S. Army Medical Research  
and Development Command



## Vision:

Improve the lives of individuals with ASD now

## Mission:

Promote innovative research that advances the understanding of ASD and leads to improved outcomes for Service members, their families, and the American public

## Application Review Process

The CDMRP uses a two-tier review process, with both tiers involving dynamic interaction among scientists and disease survivors. Scientific peer review determines the scientific merit of the application, while programmatic review compares applications 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.



It was an awesome experience to be a part of the ARP Peer Review. I loved networking with experts in different fields, with different perspectives, but all on one accord passionately working towards the same goal of how to better service the autism community.

**Dana Bryant, Consumer Peer Reviewer**

# Congressionally Directed Medical Research Programs Autism Research Program

## Background and History

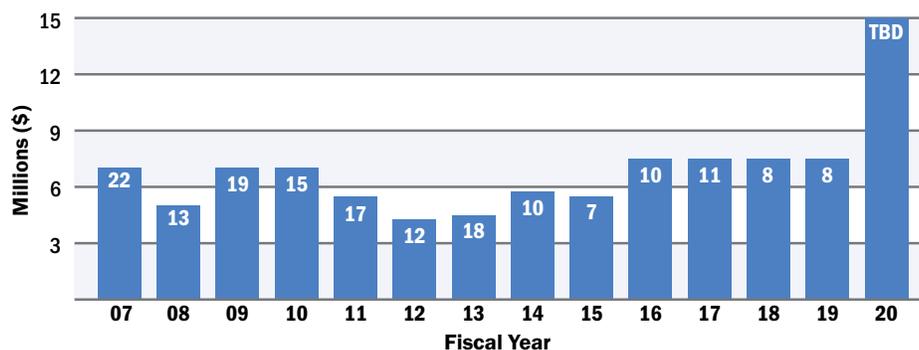
The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a Congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since that time, Congress has added additional research programs and topics. Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs such as the Autism Research Program (ARP) is allocated via specific guidance from Congress. Since its inception in fiscal year 2007 (FY07) and on through FY20, appropriations totaling \$104.4 Million have been directed to the ARP by the Peer-Reviewed Autism Research Congressional appropriation.

Autism Spectrum Disorder (ASD) encompasses a wide range of complex developmental disorders characterized by mild to severe challenges in social, emotional, and communication abilities. Additionally, many individuals living with ASD are afflicted with co-occurring conditions (e.g., anxiety, gastrointestinal [GI] issues, sleep disorders, and aggression) that are not well understood. The causes of ASD are unknown; however, progress is being made on several fronts and the answers related to autism are expected to be, like the disorder itself, multifaceted.

Recent reports by the Centers for Disease Control and Prevention indicated that the prevalence of ASD may be as high as 1 in 54.<sup>1</sup> An estimated 1 in 34 boys and 1 in 145 girls are affected and thus are identified as living with ASD.<sup>1</sup> The cost of caring for Americans with ASD reached \$268 billion in 2015 and could rise to \$461 billion by 2025.<sup>2</sup>

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 has placed emphasis on research that assists ASD individuals in their transition to adulthood, as well as research aimed at improving healthcare delivery to adults with ASD. The ARP also focuses on ways to improve diagnosis, treatment, and co-occurring conditions to enable a better life for those with autism and their families.

## ARP Appropriations and Number of Awards



<sup>1</sup> Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years – Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States. 2016. *Surveillance Summaries*. March 27, 2020, 69(4):1-12.

<sup>2</sup> Leigh, JP and Du J. 2015. Brief Report: Forecasting the Economic Burden of Autism in 2015 and 2025 in the United States. 2015. *J Autism Dev Disord*. 45:4135-4139. <https://doi.org/10.1007/s10803-015-2521-7>.

# Research Portfolio

The ARP strives to obtain a balanced research portfolio focused on the 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 and Clinical Translational Research Awards will have Areas of Interest that are related to dissemination and implementation of clinically validated interventions, whereas the Idea Development Award will have Areas of Interest focused on the use of preclinical models for assessments of novel therapeutics.

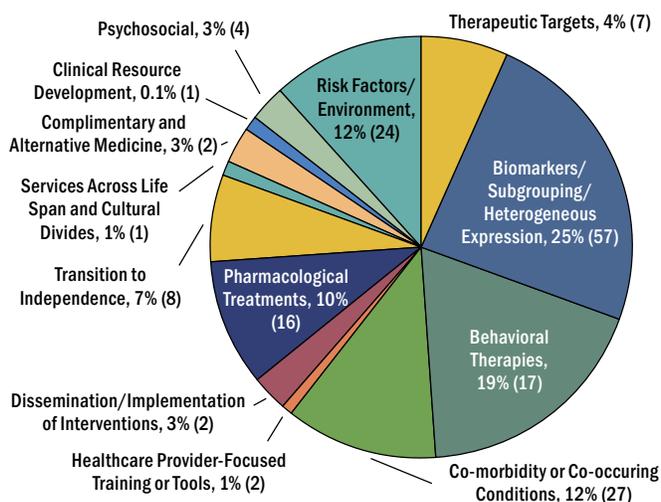
## ARP FY07-FY20 Areas of Interest through the Years

	FY07-09	FY10-12	FY13-16	FY17-18	FY19	FY20
Clinical resource development	✓	✓				
Co-morbidity or co-occurring conditions	✓	✓	✓	✓	✓	✓
Identification and/or validation of therapeutic targets	✓	✓*	✓**	✓**	✓**	✓**
Biomarkers, subgrouping and mechanisms of heterogeneous expression and response to treatment	✓	✓	✓	✓	✓	✓
Risk factors/environment	✓	✓	✓	✓	✓	✓
Pharmacological treatments/interventions		✓	✓	✓	✓	✓
Psychosocial research and/or interventions		✓				
Complementary and alternative medicine		✓				
Behavioral and/or other non-pharmacological therapies/interventions		✓	✓	✓	✓	✓
Dissemination/Implementation of interventions			✓	✓	✓	✓
Key transitions to independence			✓	✓	✓	✓
Healthcare provider-focused training or tools				✓	✓	✓
Diagnosis and access to services across life span and cultural divides				✓	✓	✓
Factors influencing quality of life during geographic relocation					✓	✓
Mechanisms underlying sex differences in diagnosis						✓

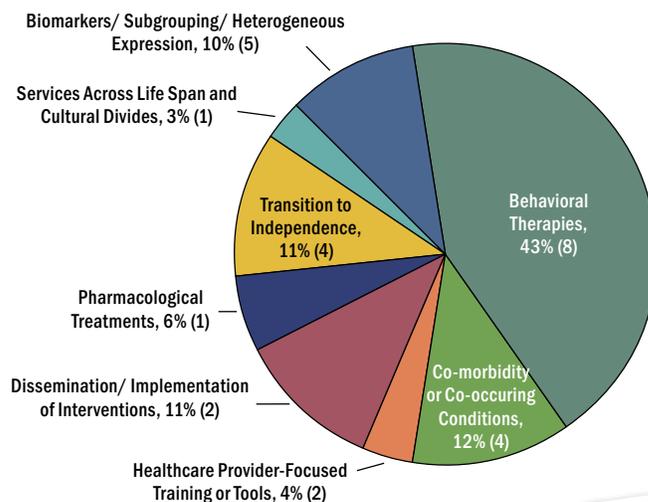
\*Excluding gene discovery | \*\*In preclinical models

## ARP Portfolio Categorized by Areas of Interest

ARP Investments in AOIs FY07-FY19  
(Number of Awards)



ARP Investments in AOIs FY17-FY19  
(Number of Awards)



# ARP-Funded Research in Depth



## The Development of Novel Drugs to Treat the Core Symptoms of ASD

**Raymond Booth, Ph.D., Northeastern University; Clinton Canal, Ph.D., Mercer University**

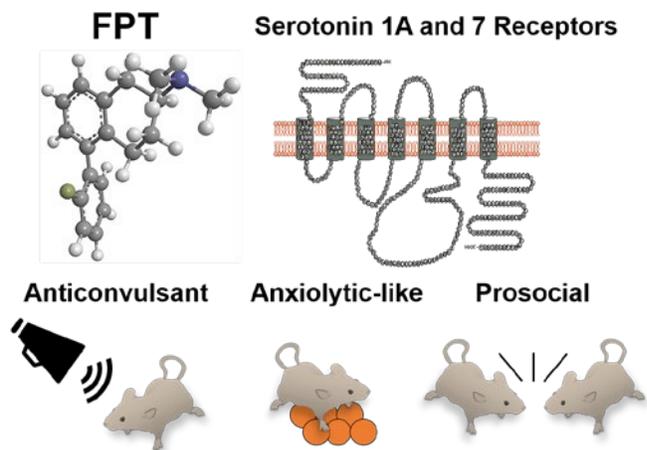
Currently, there is no approved pharmacotherapy for the core debilitating symptoms of ASD, which are impaired social interactions, communication difficulties, and repetitive behaviors. The option of pharmacologic interventions could be monumental for many individuals with ASD, allowing them to function better and improve their quality of life. The complexity of ASD has made the development of pharmacotherapy for ASD challenging. A number of factors, including genetic, infectious, immunologic, metabolic, nutritional, and toxic factors are thought to be involved. Moreover, different brain areas, neuronal connections, neuronal receptors, and neuronal proteins may be affected.



Evidence suggests that imbalances in the ratio of excitatory to inhibitory neurons contribute to the core symptoms of ASD. Serotonin (5-HT) is a chemical that helps stabilize a person's mood and has been linked to ASD. Blood 5-HT levels have been shown to correlate with repetitive behaviors and diet-induced reduction of 5-HT increases these behaviors. Thus, the 5-HT receptors are poised as viable targets for ASD pharmacotherapy. There are 14 distinct 5-HT receptors. The 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptors in particular are expressed in regions of the brain that control behaviors altered in ASD, and there is preclinical evidence that partial agonists to each receptor improves ASD symptoms. Drs. Raymond Booth and Clinton Canal postulated that targeting both receptors together may realize greater success.

The ARP awarded Drs. Booth and Canal a FY16 Idea Development Award to explore the development of novel drugs targeting serotonin receptors to treat ASD using mouse models. The team set out to design and synthesize compounds that target the 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> serotonin receptors, yielding varying degrees of receptor activity. The team had previously identified a compound that partially activates 5-HT<sub>7</sub> and 5-HT<sub>1A</sub> receptors; with ARP support they next investigated structural modifications of the lead compound that might impact 5-HT<sub>7</sub> and 5-HT<sub>1A</sub> selectivity and improve the effectiveness of the compound. The team uncovered three new 5-HT<sub>1A</sub> and 5-HT<sub>7</sub> receptor compounds with unique functional pharmacology and varying degrees of efficacy at 5-HT<sub>1A</sub> and 5-HT<sub>7</sub>. The three new compounds attenuate repetitive behaviors in normal mice. One lead compound, 5-fluorophenyl-2-aminotetralin (FPT), modulated several behaviors in a genetic mouse model of ASD, including increasing social interactions, decreasing repetitive and anxiety-like behaviors, and preventing seizures caused by auditory stimuli. Furthermore, after FPT administration, c-Fos expression selectively increased in the amygdala of the autism mouse model, which might be a neural signal of reduced anxiety.

These results demonstrate that the team has identified a compound that targets serotonin receptors and yields receptor activity that corrects the ASD core symptoms of repetitive behavior and impaired social interactions. The team will continue testing their lead compound as well as other top candidates in mouse models of ASD. They are on track to obtain an Investigational New Drug Application, a request for authorization from the Food and Drug Administration to administer an investigational drug to humans. New pharmacotherapy options addressing core symptoms of ASD are in urgent need. Drs. Booth and Canal's research provides hope to the autism community that new medicines for relieving autism's most disabling symptoms are on the horizon.



A model of the lead compound, FPT, is depicted. The structure of the seven transmembrane domain serotonin receptors is also shown, and FPT binds to the subgroup serotonin 1A and 7 receptors. FPT prevents seizures elicited by loud sounds in a genetic mouse model of autism. FPT also reduces anxious behaviors, such as marble burying, and promotes social interactions in the autism mouse model and in normal ("wild-type") mice.



## Evidence-Based Social-Emotional Therapy Using Augmented and Virtual Reality on Google Glass to Improve Employability and Job Skills in Adults with Autism

**Ned T. Sahin, Ph.D., Brain Power, LLC**

Essential funding and services necessary for people with ASD to thrive and survive “age out” around age 23, resulting in an overall lack of resources for adults

with ASD. An important way to support these individuals is to provide them with the tools to manage their symptoms and learn key social-emotional skills that can help them obtain meaningful employment. This is essential, as the most protective factor against lifetime negative mental health outcomes is being employed.

The ARP recognizes the need for helping individuals with ASD obtain employment and has made it an Area of Interest for the program. The ARP awarded a FY16 Idea Development Award to Brain Power, LLC, and Dr. Ned T. Sahin (Principal Investigator) to encode principles of neuroscience and behavioral sciences into augmented reality and virtual reality software for head-mounted display computers like Google Glass. The software is designed to aid in the successful transition of individuals with ASD into employment.

Dr. Sahin and his team developed augmented reality and virtual reality software technology (“Empowered Brain”) aimed at improving the symptoms of social interaction disorders such as ASD. With Empowered Brain, individuals look through a computer screen (e.g., Google Glass) that incorporates virtual reality displays to provide the user with experiences that will help them cope with real life situations.

With ARP support, the team has developed software modules to teach job-related skills of particular use in the ASD population. The new technology allows wearers to be safely digitally immersed in work environments through Google Glass to aid in transition to adulthood. This allows individuals with ASD to experience and prepare for different workplaces and helps them determine whether a job could be appropriate for them.

Brain Power has used the FY16 ARP award not just to conduct studies, but also to successfully produce tangible output in terms of science-based apps and to bring them into the real world with school districts as customers. For instance, the team has been working with Newton Public Schools, one of the largest public school districts in Massachusetts, to implement the technology in their job placement effort known as the Transition Planning Program. Additionally, several public school districts throughout Massachusetts, as well as in other states, have procured Brain Power’s augmented reality/virtual reality social-emotional learning apps suite. In this way, the tangible benefit resulting from the ARP funding has been extended to a broad range of students with ASD already, and the benefit from ARP will continue to compound rapidly in the future.

The Empowered Brain system has had great success. This 2016 award marked the first ARP award to a company, rather than a research university, in recognition that Dr. Sahin and his Brain Power team offered a unique approach and the promise of a tangible, real-world outcome. The investigators have published 10 peer-reviewed articles on use of the technology and its capacity to aid in developing social and behavioral skills for individuals with ASD. The Empowered Brain system has also received news coverage by media outlets such as NPR, PBS, CNN, Wired, Tech Crunch, New York Times, and others. With this exciting technology, ASD individuals can better prepare for transitions to adulthood by obtaining jobs that are better suited for them. A meaningful job is a major step in establishing success and independence for adults with ASD as well as assuring positive mental health outcomes.



Part of Empowered Brain’s great success may be due to the fact that Brain Power is also an employer of autistic individuals. Through their autism employment program, Brain Power prioritizes hiring individuals with autism. They are a company where individuals on the ASD spectrum feel accepted and where the focus is on talent, not social skills.

Eleanor joined the Brain Power family 5 years ago as an autistic intern. One of the apps that Brain Power has developed with the assistance of the ARP award, Transition Master, particularly resonates with her, since she struggles with transitions to new places. “It allows me to see a place before going there. Being able to see the office and practice helps me feel less worried.”

Eleanor’s colleague, Julie, is another example of the importance of the Brain Power autism employment program. Julie has Asperger’s Syndrome and struggled finding meaningful employment until she was offered a position as a graphic artist at Brain Power. Julie’s raw talent was enough to land her a position at Brain Power. She has finally found employment she enjoys and feels passionate about. Julie says, “In prioritizing hiring people on the spectrum, Brain Power recognizes that autistic kids become autistic adults.”



# FUNDING HIGH IMPACT RESEARCH



## **Developmental Pathways and ASD**

**Dr. Alan Brown, Columbia University Medical Center**

This study utilizes biospecimens, namely archived maternal prenatal serum from the Finnish Maternity Cohort and data collected from medical records and registries on children born in Finland. Serum specimens drawn during pregnancy in mothers of children with and without ASD were assayed for prenatal risk factors including biomarkers of inflammation, thyroid antibody, and smoking. Measures of the children's developmental milestones and head circumference from child health clinics, as well as data from Finnish registry linkages, were also collected. Using this information, Dr. Brown's group is currently investigating the complex relationships between prenatal environment, family psychiatric history, and postnatal developmental indicators in order to identify factors leading to increased risk of development of ASD in offspring.



## **Predicting Situational Onset of Aggression**

**Dr. Matthew Goodwin, Northeastern University and Dr. Matthew Siegel, MaineHealth/Tufts University School of Medicine**

Minimally verbal individuals with ASD (MV-ASD) may engage in aggression stemming from distress. This project seeks to investigate whether peripheral physiological biomarkers combined with machine learning algorithms can predict aggressive outbursts before they occur. The researchers are estimating study participants' physiological arousal levels using wrist-worn biosensing technology that measures heart rate, sweating, and motor activity. Findings from this study could facilitate prediction and forewarning of aggressive behavior in MV-ASD individuals that may enable more effective behavioral interventions. Current results with 20 participants suggest that aggression can be predicted 3-4 minutes into the future with 95% accuracy.



## **The Prenatal Origins of ASD**

**Dr. Jennifer Straughen, Henry Ford Health System**

The etiology of ASD is increasingly attributed to the prenatal environment. Angiogenesis, the formation of new blood vessels, is an important process for normal neurodevelopment; thus, altered angiogenesis in the child beginning in the prenatal period could impact neurodevelopment and increase the risk of ASD. This study will examine whether altered placental and neonatal angiogenic markers are associated with an increased risk of ASD. In addition, it will examine whether placental histopathology is associated with severity of ASD symptoms. These findings may be used to identify children at high risk of ASD.



## **The Influence of Social, Educational, and Work Experiences on Psychological Health**

**Dr. Julie Taylor, Vanderbilt University Medical Center, and Dr. Somer Bishop, University of California San Francisco**

Individuals with ASD face difficulties on a day-to-day basis, and these challenges might be linked to the higher lifetime rates of depression observed in this group. The goal of this project is to use existing data from the Simons Simplex Collection national registry and conduct surveys and interviews to identify specific day-to-day experiences associated with depressive symptoms and quality of life. Data will be collected predominantly from adolescents and young adults with ASD. Knowledge from this work will lay the foundation for a better understanding of how to alleviate depression by means of enhanced interventions for individuals with ASD.



## **Mechanisms That Underlie Improvement in Microbiota Transfer Therapy Patients**

**Dr. Stephen Walker, Wake Forest University Health Sciences**

Microbiota transfer therapy (MTT) has recently gained interest due, in part, to the publication of a small pilot study that reported sustained improvements in both GI and behavioral issues in children with ASD who underwent MTT therapy. Using peripheral blood samples collected at multiple time points from a larger number of adults with ASD in a follow-up MTT clinical trial, this molecular study will evaluate changes in host-gene expression and blood metabolite content. Through this co-expression analysis, Dr. Walker and his team hope to identify changes that track with and may underlie symptom improvement experienced with MTT therapy.

# Idea Development

# ACROSS THE RESEARCH CONTINUUM



## A Daily Living Skills Intervention for High Schoolers with ASD

**Dr. Amie Duncan, Children's Hospital, Cincinnati**  
Individuals with ASD often have difficulty obtaining independence and making a successful transition into adulthood. This pilot randomized clinical trial will examine the effectiveness of an intervention developed to teach daily living skills (hygiene, cooking, cleaning, laundry, managing money, etc.) to high schoolers with ASD without an intellectual disability. Previous studies have found that adolescents increase their daily living skills by 2-3 years after completing the intervention. Researchers hope to translate the intervention to various other age groups with ASD and comorbid intellectual disabilities in the future.



## Emotion Awareness and Skills Enhancement Program for ASD

**Dr. Carla Mazefsky, University of Pittsburgh**  
Many individuals with ASD have difficulty regulating their emotions. This two-site randomized controlled trial will evaluate the efficacy of the Emotion Awareness and Skills Enhancement (EASE) program. The 16-week program is intended to use behavioral therapy and mindfulness to improve emotion regulation capabilities and lessen depression, anxiety, and aggression in young individuals with ASD and aid in their successful transition to adulthood. Researchers will utilize direct testing, electroencephalogram, questionnaires and interviews with the subjects and their parents, and ratings from interviewers who are naïve to condition assignment to evaluate efficacy of the EASE program.



## Increasing Functional Independence During Aging in ASD

**Dr. Nicole Matthews,**

**Southwest Autism Research & Resource Center, Dr. B. Blair Braden, Arizona State University, and Dr. Leslie Baxter, Mayo Clinic Arizona**  
In this pilot randomized clinical study, researchers are seeking to improve independence and quality of life across the life span in adults with ASD. They will examine the effectiveness of combining PEERS\* an evidence-based social skills program, with personalized cognitive compensation training, mindfulness-based emotional regulation, and support groups for adults with ASD and their support companions. Participants will also be able to access guided lessons on a website to support long-term maintenance of functional gains.



## Targeting Insomnia in Children with ASD

**Dr. Christina McCrae, The Curators of the University of Missouri**

Insomnia is a common issue for children with ASD that can cause decreased quality of life, problems with learning and cognition, and increased parent stress. This project aims to examine the effects of standard (in-person) and remote cognitive behavioral treatment for insomnia in school-aged children with ASD. Researchers will analyze child and parent sleep, daytime functioning, quality of life, and physiological arousal, as well as parent stress/burden. If successful, the remote version of this brief (four-session) treatment would be more accessible to children and families suffering from ASD insomnia-related difficulties compared to standard care.



## Clinicianless Training in Autism Treatment

**Dr. Ty Vernon, University of California, Santa Barbara**  
Gold standard autism treatments greatly improve the developmental outcomes of young children

with autism, but access to these treatments remains a nationwide problem. The use of a smartphone app-based training program may help, as it could facilitate wide-spread dissemination of treatment tools directly to families, regardless of location or financial means. The objective of this investigation is to evaluate the use of a self-directed app to teach parents Pivotal Response Treatment, a highly effective early intervention that leverages motivation to improve social communication skills. Interactive lessons, paired with the ability to record and self-monitor treatment delivery, will be used to train parents without any direct clinician involvement. This app-based program has the potential to significantly enhance existing parent training paradigms and child developmental outcomes.



## An Employment-Related Social Skills Training Program for Youth with ASD

**Dr. Connie Sung, Michigan State University**

This project evaluates the efficacy of the Assistive Soft Skills and Employment Training (ASSET) program. The ASSET program is a manualized training program developed to improve work-related social skills, confidence, independence, job readiness, and mental health of youth with ASD transitioning to adulthood. A randomized controlled trial will evaluate the school-based 10-week group intervention (90 minutes per session) for students with ASD in Michigan and Illinois schools. The program specifically targets the development of work-related interpersonal skills to promote a successful transition to adulthood.

\* Sanderson J, Tucci L, Bates S. 2014. The ABC's of teaching social skills to adolescents with autism spectrum disorder in the classroom: the UCLA PEERS (®) Program. *J Autism Dev Disord.* 44(9):2244-2256. doi:10.1007/s10803-014-2108-8.

**Translational Research**

**Clinical Trials**



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