

1999 - NAAR

David R. Cool, Ph.D.

Wright State University, Dayton, OH

"Neuro-Endocrine Peptide Hormones are Implicated in Social Behavior Development: Oxytocin Involvement in Autism".

Two-Year Award: \$60,000

Research Partner: Autism Society of Cincinnati

Research Partner: Solving the Mystery of Autism Foundation

2001 - NAAR

Karl Herrup, Ph.D.

Case Western Reserve University, Cleveland, OH

"CNS Pattern Formulation and the Etiology of Autism."

Two-Year Award: \$99,000

2003 – NAAR

Kenneth Campbell, Ph.D.

Children's Hospital Research Foundation, Cincinnati, OH

Genetic Control of Mammalian Amygdalar Development

Two-year award - \$120,000

Karl Herrup, Ph.D.

Case Western Reserve University, Cleveland, OH

The Engrailed-2 Mutant as a Model of the Neuropathology of Autism

Two-year award - \$120,000

Research Partner: Autism Coalition for Research and Education

2003 - CAN

Immune Phenotypes in Autism Spectrum Disorder

Cynthia A. Molloy, M.D., M.S., Cincinnati Children's Hospital (Pilot Project)

Research on the etiology of autism spectrum disorders (ASD) has been hindered by the heterogeneity of the population with this behaviorally defined condition. Previous studies have suggested the possibility that distinct phenotypic subgroups of ASD may be defined, based on history of immune disorders and measurable immune responses. The adaptive immune response involves the proliferation of T helper cells along two divergent, antagonistic lines. The resulting subsets, TH1 and TH2, are distinct immune phenotypes characterized by the particular cytokines they produce and the immune response mediated by those cytokines. The TH1 immune phenotype is associated with organ specific autoimmunity. The TH2 phenotype predominates in an atopic response. Different

investigators have reported either TH1 or TH2 predominance in ASD. This molecular epidemiologic pilot study seeks to address this apparent paradox. Our proposed study uses a case control design, comparing children with ASD (cases) to children with other developmental disorders (Control A) and children with neurotypical development (Control B). The specific aims of the study are to 1) compare the histories of atopy and familial autoimmunity between cases and controls, 2) measure peripheral blood cytokines and compare the distribution of TH1 and TH2 phenotypes between cases and controls and 3) examine the relationship between immune phenotype, history of atopy and familial autoimmunity, and the clinical characteristics of ASD. By addressing important methodologic issues such as unbiased selection of cases and controls, and measurement of both medical history and cytokine levels, this study will contribute significant new information about immune phenotypes in ASD.

2005 – NAAR

David Beversdorf, M.D.

The Ohio State University Research Foundation

Pharmacological Modulation of Functional Connectivity in Autism Spectrum Disorder

Two-Year Award: \$113,740

2006 – AUTISM SPEAKS (administered by Dana Foundation)

Cincinnati Children's Hospital Medical Center

Marsha Wills-Karp, Ph.D., Cynthia M. Malloy M.D., and Patricia Manning-

Courtney, M.D.

\$100,000

Does immune system dysfunction play a role in autism?

Recent evidence suggests that the immune system, which normally protects the body against many diseases, may malfunction in people with autism and actually contribute to or produce this disorder. "Adaptive" immune "T" cells are summoned by 'innate" immune cells to attack invaders. Immune T cells in some people, however, mistake the body's own tissues as foreign and attack them, a process called "autoimmunity." Immune T cells also can over-react to otherwise harmless substances, such as pollen, and produce allergies. Usually these potentially errant responses by immune T cells are kept under control by 'regulatory T cells." Regulatory T cells are produced by the *Foxp3* gene. According to the collaborating researchers, who combine expertise in autism, immunity, and patterns of disease ("epidemiology"), a disproportionate number of children with autism have immune system malfunctions that are similar to those seen in autoimmunity, allergy, or both conditions. They hypothesize that regulatory T cells in people with autism may be too few, or too weak, to provide a generalized ability to control errant immune responses, which contributes to, or causes, autism.

The collaborators will study immune T cells, which circulate through the bloodstream, in blood samples taken from 20 children with autism and 20 healthy ("control") children. They will compare the number of regulatory T cells, and how effectively these cells control the "attacker" T cells, in blood samples from the two groups of children. The investigators also will find out whether differences exist in the two groups of blood samples in the amount of chemicals, called "cytokines," produced by attacking T cells. Excessive amounts of these cytokines, suggesting incomplete control of T cells by their regulators, may have consequences for the brain, providing a link between immune dysfunction and autism. Alternatively, some other factor may be common to both immune regulation and to autism.

Significance: If this study indicates that a failure to properly regulate immune T cells is involved in autism, the research will provide a better understanding of immune system involvement in autism. The findings also may provide an immune "marker" to diagnose autism, and lead to development of specific immune-based therapies to prevent or treat autism.

2006 AUTISM SPEAKS - "Augmentation" Grants Designed to Supplement or Expand the Scope of Existing Projects

L. Eugene Arnold, M.D.
Ohio State University, OH
\$97,659.00 for one year

Risperidone and Behavior Therapy in Children with Pervasive Developmental Disorder: Long Term Follow-up

Based on an earlier study by Dr. Arnold and his colleagues in the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, the FDA recently approved the use of the antipsychotic drug risperidone to treat irritability and aggression in children with autism. The Network—led by Dr. Arnold at Ohio State and including teams from Yale University and Indiana University—are now working on an NIH-funded follow-up study. The new study will examine whether risperidone combined with parent management training (PMT) can boost the effectiveness of risperidone and help lower relapse rates once patients stop taking the medication. The research team will randomly assign 120 children with pervasive developmental delay (PDD) to either treatment with risperidone alone or risperidone plus PMT. They will then evaluate autism-related behaviors. This grant will provide funding for a one-year follow up to examine the long-term effects of PMT and risperidone.

What this means for people with autism: Results from this study will provide clinicians with important information about the long-term effectiveness of combining drug therapy with parent training for treating aggression and irritability in children with autism. Since prolonged use of antipsychotic drugs poses some risks to children, it will be extremely

helpful to examine whether parent training can help reduce the need for medication over time.

2007 – AUTISM SPEAKS basic and clinical awards

Cynthia Molloy, M.D.
Cincinnati Children's Hospital Medical Center
\$449,742 for 3 years

Genome-wide Association Study of Autism Characterized by Developmental Regression

By some estimates, up to 30% of children with autism experienced developmental regression characterized by the acquisition and subsequent loss of social and communication skills. Dr. Molloy plans to explore the genetic component of this devastating phenomenon by analyzing and comparing the genetic “profile” of children with autism affected by regression with normally developing counterparts. By focusing on a more homogenous subset of the population, she and her colleagues hope to identify autism susceptibility genes, especially those that might be related to regression.

What this means for people with autism: If the subset of children who are likely to experience regression can be identified genetically, it could provide biomarkers for earlier diagnosis and aid in the development of intervention strategy related to those gene changes.

2007 treatment grants – autism speaks

Eugene Arnold, M.D., M.E.D.
Ohio State University
\$173,219 for 3 years

Neuronal Nicotinic Receptor Modulation in the Treatment of Autism: A Pilot Trial of Mecamylamine

There is currently no FDA-approved medication for the core symptoms of autism. New directions for therapy need to be based on understanding the central neurobiology of autism. One consistently identified abnormality in autism is a reduction in one of the receptors (nicotinic) for the neurotransmitter acetylcholine. The proposed pilot trial aims to test the response of individuals with autism to agents that target this receptor type, thus changing acetylcholine signaling.

There is one nicotinic agent that has been shown to be safe in other childhood-onset disorders, including Tourette's syndrome and attention-deficit/hyperactivity disorder (ADHD). This agent will be pilot-tested in children with autism. Twenty children with autism spectrum disorder will receive the drug or placebo over 13 weeks in a controlled (placebo double-blind) trial. The outcome will be assessed by standard clinical rating scales which will measure a range of behavioral and communicative functions, including

attention. Computerized testing will also be used to assess changes in attention objectively.

What this means for people with autism: This controlled pilot trial will provide essential evidence required to evaluate the potential of nicotinic-receptor therapy in the treatment of the core symptoms of autism.

Connie Wong, Ph.D.
Cleveland State University
\$119,536 for 2 years

A Play and Joint Attention Intervention for Preschool Teachers and Young Children with Autism

Research has shown both symbolic play and joint attention are delayed and deficient in young children with autism, and predictive of their later language and social development. However, these skills are not often directly addressed in early intervention programs. The proposed treatment study tests an intervention focused on change in play and joint attention interactions between teachers and preschoolers with autism. Specific aims of the study include assessing the degree in which teachers implement the principles and strategies outlined in the treatment, assessing changes in the children's symbolic play and joint attention skills, and exploring teacher and child characteristics affecting optimal treatment outcomes.

The methodology includes 16 preschool special education classroom teachers to be randomly assigned to an immediate treatment or a wait-list control group. The treatment utilizes principles of applied behavioral analysis and milieu teaching. Teachers will be observed in the preschool classroom interacting with the children in the classroom in unstructured and structured settings before and after the treatment. During the observations, researchers will code the teacher's implementation of the curriculum as well as the child's joint attention and symbolic play skills. This project advances the state of knowledge in autism by attempting to bridge the gap between research and practice.

What this means for people with autism: The absence of social communication abilities in children with autism represents a core area of deficit. Findings from the study will enable researchers to understand the effectiveness of a joint attention training model for teachers of young children with autism and will help determine characteristics that affect treatment outcomes.

CTN Trial: Memantine

Through a Treatment Initiative Award given to Evdokia Anagnostou, M.D. in 2005, Cure Autism Now sponsored the first CTN clinical trial, which evaluated the effects of memantine (marketed as Namenda) on motor skills and expressive language in autism.

Memantine is a glutamate antagonist that is an FDA-approved pharmaceutical for treatment of memory loss in moderate to severe Alzheimer's disease. CTN will be conducting a double-blind, placebo-controlled trial of 60 children with ASD to formally examine the benefit of memantine in motor planning and expressive language. While the preliminary data strongly support the rationale for a trial, the formal methodology must be used if memantine is to ever be considered effective by traditional medical standards. *(Research Partner: Sallie and Tom Bernard)*

Current List of Participating Sites

The following sites are participating in the memantine trial:

Mount Sinai School of Medicine, NY, NY: Evdokia Anagnostou, M.D.

North Shore-Long Island Jewish Health System, Long Island, NY: Joel Bregman, M.D.

University of Medicine and Dentistry of New Jersey (UMDNJ), Newark, NJ: Charles Cartwright, MD

Southwest Autism Research and Resource Center (SARRC), Phoenix, AZ: Raun Melmed, M.D.

University of North Carolina, Chapel Hill, NC: Lin Sikich, M.D.

Yale Child Study Center, New Haven, CT: Lawrence Scahill, MSN, Ph.D.

Ohio State University, Columbus, OH: Michael Aman, Ph.D.

University of Washington, Seattle, WA; Bryan King, M.D., Ph.D.

ATN site:

Cincinnati Children's Hospital Medical Center (Cincinnati, OH)

Patricia Manning-Courtney, MD

Cynthia Molloy, MD, MS