

Summer Student Research Program
Project Description

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PROJECT TITLE (200 Characters max):

Cytokine regulation in the pathogenesis of autism

HYPOTHESIS:

Autism is a neurodevelopmental disorder that has a strong genetic influence. Environmental factors can activate cells of the immune system to secrete a variety of cytokines that can influence brain development and behavior. Clinical and experimental evidence indicates that activation of the maternal immune system increases vulnerability to psychiatric disorders that involve repetitive and stereotypic behavior

Earlier studies in the laboratory, using a murine pre-natal model to investigate the contribution of immunologic mechanisms to autism, have shown that administration of polyclonal stimuli (e.g., poly I:C and LPS) that induce pro-inflammatory cytokines, or the direct injection of such cytokines (e.g., IL-2 or IL-6) to pregnant dams causes immunologic changes, as well as long-term behavioral abnormalities in the offspring in comparison to the offspring of control pregnant mice injected with vehicle (PBS).

Activated cells of the immune system secrete cytokines that influence brain development and behavior. Studies show that pro-inflammatory cytokines such as Interferon – gamma (IFN-gamma) and Tumor Necrosis Factor – alpha (TNF-alpha) are elevated in patients with autism spectrum disorders (ASD). Genetic polymorphisms in the regulatory regions of cytokine genes have a positive or negative influence on the level of protein produced. Single nucleotide polymorphisms (SNP's) in the promoter regions of cytokine genes including IFN-gamma, TNF-alpha, IL-1, IL-6 and IL-10 affect the level of transcription of the protein. Numerous studies have documented the dysregulation of cytokines as etiological factors in children with ASD, but there has been far less focus on the parents of autistic children.

Our preliminary investigation on the analysis of cytokines showed significant differences in the frequency of SNPs between controls versus mothers and controls versus autistic children in the following pro-inflammatory cytokines: IFN-gamma, IL-1, IL-6, IL-12 and the anti-inflammatory cytokine, IL-10. The results of this pilot study suggested that the immunogenetic profiles of autistic children and their mothers show a trend towards a pro-inflammatory phenotype.

The aim of the current investigation is to extend the analysis of SNP's to unaffected siblings and biological fathers (if available) of the autistic children. Such a comprehensive analysis will help to further understand the immunogenetic role of cytokines in the pathogenesis of autism.

PROJECT DESCRIPTION (Include design, methodology, data collection, techniques, data analysis to be employed and evaluation and interpretation methodology)

Paired DNA samples from forty-six children with autism /ASD and their mothers, obtained from Autism Genetic Resource Exchange (AGRE) have been tested previously in our laboratory. The mothers selected for the study exhibited the following criteria: a diagnosis of

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allergies and inflammatory gastrointestinal problems, which indicate an overactive immune system. In the current study we wish to extend the analysis to unaffected siblings of autistic children. If available we will also analyze the biological father of the autistic children in the study.

Cytokine SNP (single nucleotide polymorphism) typing for the determination of cytokine polymorphisms in the DNA samples will be performed using the Cytokine SNP Typing kit (TEPNEL). In addition to TNF- α and IL-10 we will analyze the SNP's in the pro-inflammatory cytokines IL-1 and IL-12 and the anti-inflammatory cytokine TGF- β . The assay will be performed on the Luminex 200 system, a multiplex bead array that works on the principle of direct DNA hybridization after PCR amplification.

Data analysis will be done using Chi-squared or Fishers exact test.

SPONSOR'S MOST RECENT PUBLICATIONS RELEVANT TO THIS RESEARCH:

Ponzio NM, Servatius R, Beck K, Marzouk A, Kreider T: Cytokine levels during pregnancy influence immunological profiles and neurobehavioral patterns of the offspring. *Ann NY Acad Sci.* 1107:118-128, 2007.

Ramanathan M, Ponzio NM and Fernandes H: Maternal Cytokine Regulation in the Pathogenesis of Autism. *Abstract - Asia Pacific Congress for Maternal-Fetal Medicine.* 2009.

IS THIS PROJECT SUPPORTED BY EXTRAMURAL FUNDS?

Yes or No

(IF YES, PLEASE SUPPLY THE GRANTING AGENCY'S NAME)

THIS PROJECT IS: Clinical Laboratory Behavioral Other

THIS PROJECT IS CANCER-RELATED

Please explain Cancer relevance

THIS PROJECT IS HEART, LUNG & BLOOD- RELATED

Please explain Heart, Lung, Blood relevance

THIS PROJECT INVOLVES THE USE OF HUMAN SUBJECTS

PENDING APPROVED IRB PROTOCOL # M0120060177

THIS PROJECT IS SUITABLE FOR:

UNDERGRADUATE STUDENTS ENTERING FRESHMAN
SOPHOMORES ALL STUDENTS

THIS PROJECT IS WORK-STUDY: Yes or No

THIS PROJECT WILL BE POSTED DURING ACADEMIC YEAR

FOR INTERESTED VOLUNTEERS?: Yes or No

WHAT WILL THE STUDENT LEARN FROM THIS EXPERIENCE?

The student will be exposed to several state of the art techniques that are applicable to basic research as well as clinical diagnostics. In addition, the student will learn to analyze and interpret data as well as the potential of translational research.