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Division of Immunology
Project Inventory

2008
Project Inventory

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Lynda Schneider, MD
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An investigation of the safety and efficacy of Elidel 1% cream in atopic disease modification, assessed in a 3-year randomized double-blind vehicle controlled phase to evaluate effects on atopic dermatitis in infants, and a 2-3 year open-label phase to evaluate the effect of early intervention versus delayed
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Open-label extension study of CE1145 (Human pasteurized C1 esterase inhibitor concentrate) in subjects with congenital C1-INH deficiency and acute HAE attacks


The role of hormone infertility therapy in the development of childhood peanut allergy

Robert Sidbury, MD, MPH
Hypersensitivity reactions to hydroxychloroquine in juvenile dermatomyositis patients

Vitamin D Supplementation for wintertime Atopic Dermatitis: A randomized controlled trial

Robert Sundel, MD
A prospective, randomized, double-blind, active controlled, parallel group, multi-center trial to assess the efficacy and safety of mycophenolate mofetil (MMF) in inducing response and maintaining remission and renal function in subjects with lupus nephritis

Trial of Early Aggressive Therapy in Juvenile Idiopathic Arthritis (TREAT JIA trial)

Dale Umestu, MD, PhD
Lab summary
**Project Inventory**

**Title:** A Registry of Patients with Primary Immunodeficiency Diseases

**Principal Investigator:** Francisco A. Bonilla, MD, PhD

**Researchers Involved:** Raif Geha, MD - Lynda C. Schneider, MD - Hans Oettgen, MD - Anahita Dioun, MD – Fatma Dedeouglu, MD - Rima Rachid, MD - Dale Umetsu, MD - Wanda Phipatanakul, MD - Sachin Baxi, MD - Douglas R. McDonald, MD – Manish Butte, MD – Susan Kim, MD – Mary Beth Son, MD –Michael Pistiner, MD - John Lee, MD - Rajashri Shuba Iyengar, MD - William Sheehan, MD - Perdita Permaul, MD - Jolan Walter, MD - Janet Chou, MD - Susan Rudders, MD - Ari Fried, MD - Arturo Borzutzky, MD - Lisa M. Stutius, MD - Erin M. Janssen, MD - Andrew I. Shulman, MD - Luigi Notarangelo, MD - Irene Borrás Coughlin, CCRC

**Abstract:** The United States Immunodeficiency Network (USIDNET) is a NIH-funded consortium of investigators of primary immunodeficiency diseases (PIDD). The consortium has established 6 Committees to organize, manage, and accomplish the overall aims and goals of the consortium. The Committees are: Senior Advisory, Advisory, Steering, Education/Mentoring, Repository, and Registry. This protocol is for the establishment of Children’s Hospital Boston as a participating center for the collection and submission of clinical and demographic data on our PIDD patients to the USIDNET Registry.

**Funding Sources:** USIDNET (NIH-funded consortium)

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Title: Association of anti-IgA antibodies with adverse reactions to gamma globulin infusion.

Principal Investigator: Francisco A. Bonilla, MD, PhD

Researchers Involved: Rima Rachid, MD - Irene Borras Coughlin, CCRC

Abstract:
1. To conduct a pilot study at Children’s Hospital Boston of a possible correlation between the presence of serum IgG or IgE anti-IgA antibodies in IgA-deficient patients and the occurrence of adverse reactions to gamma globulin administration in patients with primary immunodeficiency.

2. To compare results of ELISA methods for the determination of IgG anti-IgA antibodies with commercially available passive hemagglutination and immunoradiometric methods.

3. To examine the persistence of anti-IgA antibodies over a 6 month period.

Funding Sources: Talecris Biotherapeutics, Inc.

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Title: Studies of Immunological Deficiency Syndromes

Principal Investigator: Francisco A. Bonilla, MD, PhD

Researchers Involved: Raif Geha, MD - Lynda C. Schneider, MD - Hans Oettgen, MD - Anahita Dioun, MD - Fatma Dedeouglu, MD - Rima Rachid, MD - Dale Umetsu, MD - Wanda Phipatanakul, MD - Sachin Baxi, MD - Douglas R. McDonald, MD – Manish Butte, MD – Susan Kim, MD – Mary Beth Son, MD – Melissa Hazen, MD – Michael Pistiner, MD - John Lee, MD - Rajashri Shuba Iyengar, MD - William Sheehan, MD - Perdita Permaul, MD - Jolan Walter, MD - Janet Chou, MD - Susan Rudders, MD - Ari Fried, MD - Arturo Borzutzky, MD - Lisa M. Stutius, MD - Erin M. Janssen, MD - Andrew I. Shulman, MD - Sung-Yun Pai - Luigi Notarangelo, MD - Irene Borrás Coughlin, CCRC - Richard Grand, MD - Athos Bousvaros, MD, MPH

Abstract: This is a repository protocol for the purpose of collecting, storing, and sharing a variety of types biological specimens from patients/subjects with primary immunodeficiency diseases, or who are being evaluated for possible defects of immune system function

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Title: (multiple, see abstract)

Principal Investigator: Raif Geha, MD

Researchers Involved: Miguel de la Fuente, MD - Michiko Oyoshi, PhD - Lalit Kumar, PhD - Koduru Suresh, PhD - Narayanaswamy Ramesh, PhD - Rima Rachid, MD - Francisco Bonilla, MD, PhD - Rui He, PhD

Abstract: The Geha laboratory investigates the molecular mechanisms of primary immunodeficiency diseases and atopic dermatitis. It cloned a WASP interacting protein in the yeast two-hybrid system and named it WIP. WIP inhibits WASP function in vitro and binds both G and F actin. WIP KO were made and were shown to have a severe T cell activation defect. WIP shuttles WASP to the immune synapse and is critical for IL-2 responsiveness, WIP functions as a chaperone for WAP. WASP protein, but not mRNA, levels were severely diminished in T cells from WIP/- mice, and were restored by introduction of WIP. Calpain and proteasome inhibitors restored WASP levels in T cells from WIP/- mice and from WAS patients with missense mutations that disrupt WIP binding, and corrected the defect in actin polymerization. Current efforts are directed towards constructing mice that expressa small 39 a.a. Wip fragments that restores WASP levels in WWIP KO mice and that disrupts the WASP-WIP interaction in WT T cells. Three other knockouts of genes that are in the WASP WIP pathway have been performed and are being characterized.

The Geha lab has recently conducted a series of studies on the TNF family molecules BAFF and APRIL and showed that they induce isotype switching, particularly to IgA, mostly via TACI, but also via BAFF-R receptors engaged by both APRIL and BAFF. APRIL KO were also generated and were found IgA deficient. Very recently mutation in TACI were found in patients with common variable immunodeficiency (CVID) and IgA deficiency. We are constructing TACI knockin mice to examine the molecular and biochemical effects of human TACI mutations.

LRRC8 is a gene implicated in agammaglobulinemia because a patient with no B cells was found to have a balanced translocation that involves LRRC8 deleting a segment of its extracellular domain. We knocked out LRRC8 Surprisingly the knockout has a severe block in thymic differentiation at the very early double negative stage but normal
B cell development indicating that the human mutation is not a dominant negative and suggesting a central role of LRRC8 in thymic development. Further characterization of the Ko is in progress. A knockin that mimics the human mutation is planned.

The Geha lab developed, 7 years ago, a mouse model of atopic dermatitis (AD) elicited by epicutaneous (EC) sensitization with ovalbumin. We have used and continue to use this model to understand the local factors elicited by mechanical skin injury caused by scratching that modulate the strong Th2 and the Th17 response observed following EC sensitization. We are also studying mice deficient in the skin protein fillagrin, which is mutated in 15% of patients with AD.

Dr Geha heads the Animal Consortium of NIH Atopic Dermatitis Vaccinia Network (ADVN), a multicenter study aimed at understanding the basis of the susceptibility of patients with AD to eczema vaccinatum (EV) and vaccinia dissemination. He has 2 projects: one aims to establish an EV model in mice, the other to understand the role of cells cytokines and skin mediators in the EV model.

**Funding Sources:**
NIH/NIAID
March of Dimes
NIH/NIAMS

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Title: Biological Phenotyping of Juvenile Arthritis

Principal Investigator: Peter Nigrovic, MD

Researchers Involved: Robert Sundel, MD - Robert Fuhlbrigge, MD – David Leslie, MD - Fatma Dedeoglu, MD - Susan Kim, MD – Daniel Brown, MD - Mary Beth Son, MD – Melissa Hazen, MD- Ari Fried, MD - Arturo Borzutzky, MD - Bebe Samler; RN - Maria Benoit; RN – Irene Borras Coughlin, CCRC

Abstract:
This study aims to collect clinical information and biological specimens from children with newly-diagnosed arthritis in order to define critical steps in the development of joint inflammation. We will create a repository of specimens for study here at Children’s Hospital and to share with researchers at other institutions. The research that will be performed with these specimens will include biochemical and/or genetic tests related to arthritis and inflammatory diseases only.

Funding Sources: Children’s Hospital Faculty Pilot Grant

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**Title:** Developing a Novel Strategy to Cure Human Congenital Immunodeficiencies: Using Tailored Endonucleases to Correct Human RAG1 Mutations

**Principal Investigator:** Luigi D. Notarangelo, MD

**Researchers Involved:** Itai Pessach, PhD - Frederick Alt, MD - George Daley, MD - Silvia Giliani, MD (Brescia, Italy) - Frederic Paques, MD (Romainville, France)

**Abstract:** The RAG1 and RAG2 proteins form a complex that initiates V(D)J recombination, an essential step in the development of T and B lymphocytes. Accordingly, mutations in either RAG1 or RAG2 result in T- B- NK+ severe combined immune deficiency (SCID) in humans. In spite of advances in the treatment of SCID and related disorders, the outcome of haploidentical stem cell transplantation for T- B- NK+ SCID remains problematic, with about 50% mortality rate, especially for patients with hypomorphic mutations that allow for residual T cell immunity. Overall, there is a need to better define the consequences of various RAG mutations on the disease phenotype, and to develop alternative forms of treatment for these disorders. This project involves a group of investigators with a specific expertise that will assist in the development of a highly innovative approach to understanding and targeting of RAG-associated disorders.

We have built a repository of cell samples from patients carrying various RAG1 mutations. We will take advantage of cutting-edge iPS technology to compare for the first time, in a head to-head fashion, the ability of iPS derived from patients with various RAG1 mutations to support T-cell development. This will provide important insights into the molecular and cellular mechanisms that contribute to the phenotypic heterogeneity of RAG1-associated disorders in humans and may serve as the platform to develop novel therapeutic approaches.

Since retrovirus-mediated gene transfer has offered proof-of-principle of the potential benefits of gene therapy for SCID, but carries significant risks associated with random integration, we will explore a novel approach for gene correction in SCID based on targeted DNA cleavage and homologous recombination.

Homing endonucleases (HE) are sequence-specific endonucleases that recognize large (>12bp) DNA target sequences. Recent technologies have led to the development of artificial HEs tailored to target specific DNA sequences. We intend to exploit the ability of a newly engineered and RAG1-specific HE to correct a RAG1 mutation (del nt 368-369), that in humans results in Omenn syndrome. We anticipate that RAG1-specific HE...
will correct the human RAG1 del368-369 mutation and restore RAG1 expression and function. Safety of this approach will be monitored by studying genotoxicity. We will take advantage of our ability to generate iPS and to drive them to differentiation into hematopoietic progenitor cells to explore the ability of RAG1-specific HE-mediated gene correction to restore T cell development in vitro, following culture on OP9-DL1 stromal cells. These studies may pave the way for novel and safer innovative therapeutic approaches to RAG deficiency and other human genetic diseases.

**Funding Sources:** March of Dimes

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Abstract: Omenn syndrome (OS) is a combined immunodeficiency associated with severe damage of peripheral tissues (skin, gut, liver) due to infiltrating, activated and oligoclonal T lymphocytes, that are poorly responsive to CD3 crosslinking. In addition, patients with OS typically have a virtual lack of circulating B lymphocytes and profound hypogammaglobulinemia, but normal or elevated serum IgE. We have previously found that most patients with OS carry hypomorphic mutations of the RAG genes that decrease but do abolish V(D)J recombination. We have also found that the transcription factor Aire and tissue-specific transcripts are poorly expressed in the thymus of patients with OS, raising the possibility that negative selection of autoreactive T cells may not be properly in place. In addition, development of regulatory T cells (Tregs) is likely to be altered in OS, as the thymus of these patients lacks Hassall’s corpuscles, which are involved in Tregs development.

Finally, environmental factors may also be involved in the pathophysiology of OS, as it has been shown that the disease phenotype in infants with hypomorphic RAG mutations can be dramatically modified by exposure to pathogens.

Taking advantage of a murine model of OS with a hypomorphic Rag2 mutation (RAG2R229Q), that has been recently developed by our collaborator Dr. Anna Villa, we now intend to investigate the cellular and molecular pathophysiology of the disease.

Our overall hypothesis is that central and peripheral tolerance is defective in OS, and that environmental factors may modify the disease phenotype.

To test this hypothesis, we will analyze central tolerance and negative selection, as well as development, distribution and function of nTregs and of iNKT cells in rag2R229Q/R229Q mice, and assess the effect of challenge of rag2R229Q/R229Q mice and of rag1S723C/S723C mice with selected pathogens.
We expect that detailed characterization of this unique animal model will provide critical information to understand the pathophysiology of OS, but also of other, more common, disorders of immune regulation. The information that will be collected might be useful also for development of novel and more appropriate forms of treatment of this severe condition of immune deficiency and immune dysregulation.

**Funding Sources:** NIH/NIAID

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**Title:** Primary Immune Deficiency Treatment Consortium

**Principal Investigator:** Morton Cowan, MD (USCF)

**Co-PI:** Luigi D. Notarangelo, MD, Donald Kohn (CHLA), MD, Jennifer Puck (USCF), MD

**Researchers Involved:** Sung-Yun Pai, MD

**Other collaborators:** Rebecca Buckley, MD - Richard O’Reilly, MD - Harry Malech, MD - Alexandra Filipovich, MD - Thomas Fleisher, MD - William Shearer, MD - Hans Ochs, MD - Doug Rizzo, MD - Mary Eapen, MD

**Abstract:** Primary immune deficiencies (PIDs) are a group of rare life-threatening inherited defects in the immune system. The focus of the PID Treatment Consortium (PIDTC) will be on three forms of PIDs which can be cured with hematopoietic cell transplantation (HCT) or gene therapy: Severe Combined Immunodeficiency (SCID), Wiskott-Aldrich Syndrome (WAS) and Chronic Granulomatous Disease (CGD). The objectives of the consortium are to define the critical factors and biologic markers that determine the outcome of children with SCID, WAS and CGD following HCT and other therapies; to characterize the long term outcomes and late effects in children with SCID, WAS and CGD who undergo HCT and other therapies; to prove the feasibility of newborn screening for SCID in Athabascan-speaking Native Americans, and to provide training to physician/scientists in the treatment of PID with HCT. Project 1, A Cross-Sectional Retrospective Study of SCID will focus on patient- and transplant-related factors that affect long term survival, immune reconstitution, late effects and quality of life. Project 2, Prospective Study of SCID Infants Who Receive Hematopoietic Cell Therapy will aim at identifying early biomarkers and other disease- or transplant-related factors that may affect engraftment, early immune reconstitution and early survival. Project 3, Early and Long–term Outcomes Following Hematopoietic Cell Transplantation (HCT) of Wiskott-Aldrich syndrome and Chronic Granulomatous Disease will evaluate the effect of donor source and degree of engraftment on short and long-term outcome and disease correction. In addition, we will aim to identify patients with CGD who are most likely to benefit from an HCT. The Pilot Study of newborn screening for SCID will determine the efficacy of a novel test using newborn blood spots for the early detection of
SCID among Navajo Indians in which there is a high incidence of SCID. We have identified 15 major centers that care for ~80% of all SCID, WAS and CGD patients in North America. These centers bring together a group of transplant physicians and immunologists with broad expertise in PIDs including genetics, molecular biology, immunology and use of HCT, gene therapy or medical management. Parent advocacy groups will participate in the Consortium operation and oversight, recruitment of subjects as well as the dissemination of information resulting from our studies. These studies will resolve critical questions concerning HCT for these disorders and form the basis for future prospective clinical trials.

**Funding Sources:** NIH

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Project Inventory

**Title:** Role of WASP and N-WASP in B cell maturation, homing and function

**Principal Investigator:** Luigi D. Notarangelo, MD

**Researchers Involved:** Miguel de la Fuente, Rima Rachid, Lisa Westerberg, Frederick Alt,

**Collaborators:** Raif Geha, MD - Scott Snapper, MD - John Hartwig, MD - Silvia Giliani MD (Brescia, Italy) - Thomas Kirchhausen, MD - Richard Malley, MD - Hans Ochs (Seattle), MD - Klaus Rajewsky, MD - Michael Reth, MD - (Freiburg Germany) - Timothy Springer, MD

**Abstract:** The Wiskott-Aldrich syndrome (WAS) is a severe immune deficiency, caused by mutations of WASP that belongs to a family of proteins that control de novo actin nucleation. It is unclear whether defects in humoral immunity observed in patients with WAS and in WASP-/- mice reflect a B-cell intrinsic role of WASP for B cell differentiation, and function, and whether N-WASP may play a compensatory role in these processes.

We will test the hypothesis that lack of expression of WASP and/or N-WASP affects B lymphocyte maturation, homing and function in a cell-intrinsic fashion.

To this purpose, we will study in vivo competition models between WASP+ and WASP- cells in humans and mice. We will also develop conditional knock-out models in which expression of WASP and/or N-WASP is ablated in B lymphocytes. Specifically, we will:

1) Analyze the role of WASP in B cell development and maturation, through the analysis of in vivo competition models both in mice and in humans. The proportion of memory and naïve B cells will be analyzed among WASP+ and WASP- cells in carriers of XLT and in WAS patients with gene reversion. We will also analyze the role of WASP in germinal center reaction and somatic hypermutation following immunization in WASP+/-- mice and in WASP+/- mice in which expression of N-WASP is deleted in B cells.

2) Test the hypothesis that the B-cell specific lack of WASP and/or N-WASP affects B cell maturation, homing and function in vivo. To this purpose, we will develop a
conditional model of WASP deficiency in B cells. We will test the peripheral distribution and homing of B cells, and response to immunization in mice with B-cell specific lack of WASP and/or N-WASP.

3) Test the hypothesis that the B-cell specific lack of WASP and/or N-WASP affects B cell function in vitro.

To this purpose, chemotaxis, activation and class-switch recombination will be studied in vitro in B cells from mice with B-cell specific lack of WASP and/or N-WASP. We anticipate that the results of this project will allow a better understanding of the biology of WAS, and will be important for development of novel forms of treatment of WAS, including gene therapy.

**Funding Sources:** NIH/NHLBI

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Title: Study of Rag1 hypomorphic mice and their rescue by lentiviral-mediated gene transfer

PI: Gustavo Mostoslavsky, MD (Boston University)

Co-PI: Luigi D. Notarangelo, MD

Researchers Involved: Francesca Rucci, PhD

Abstract: The major goal of this project is to use lentiviral-mediated gene transfer to correct RAG1 deficiency in mouse models. In particular, the impact of including different regulatory elements in the construct will be analyzed. Expression of the murine RAG21 gene will be driven by constitutive promoters (PGK, EF1a), and the specific role of endogenous RAG1 T- or B-cell specific enhancers will be assessed. In addition, use of a suitable hypomorphic mouse model of RAG1 deficiency (Rag1 S723C mice), in which a mutant form of Rag1 is expressed, will allow to assess the effects of simultaneously expressing endogenous mutant RAG1 as well wild-type RAG1 molecules. This will be the first attempt to provide correction in a murine model of leaky SCID.

Funding Sources: NIH

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Project Inventory

**Title:** IgE Antibodies and Mast Cell Homeostasis

**Principal Investigator:** Hans C. Oettgen, M.D., Ph.D.

**Researchers Involved:** Clinton Mathias, Ph.D. - Dimtri Poddighe, M.D. - Diana Kombe

**Summary:** Mast cells are key effectors of allergic responses. IgE antibodies arm these cells for allergen-triggered mediator release in classical immediate hypersensitivity reactions. We and others have observed that IgE antibodies also exert potent effects on mast cell phenotype and homeostasis. Mast cell biology in allergic disease is optimally studied *in vivo*. A number of well-characterized murine models for asthma exist but attempts to use them to study mast cell function have been hampered by the fact that mouse airways contain very few mast cells either at baseline or following exposure to standard asthma models. In order to overcome this limitation, we have characterized a vigorous mast cell induction in the airways of mice subjected to repeated intranasal instillation of the naturally-occurring mold allergen, *Aspergillus fumigatus* (*Af*). Our data establish that IgE antibodies are critical for this mast cell expansion. The IgE effect on mast cell homeostasis is at the level of fully-differentiated cells; *Af*-induced recruitment of mast cell progenitors (MCp) occurs independently of IgE antibodies but the survival of mature mast cells absolutely requires the presence of IgE antibodies. The main goals of this project now are to examine the roles of mast cells and basophils (which are much more rapidly induced in this model) in the initiation and regulation of allergic responses in the airways.

**Funding Source(s):** NIH

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Project Inventory

**Title:** Immune responses to vaccinia virus in a murine model of eczema vaccinatum

**Principal Investigator:** Hans C. Oettgen, M.D., Ph.D.

**Researchers Involved:** Eva-Jasmin Freyschmidt, Ph.D.

**Summary:** Patients with atopic dermatitis (AD) have a genetically determined diffuse allergic inflammation of the skin that arises spontaneously, often in early infancy. When exposed to the smallpox vaccine (vaccinia virus [VV]), patients with AD can develop a severe, overwhelming, and potentially lethal infection called eczema vaccinatum (EV). The goal of this project is to reproduce this severe VV infection in mice which, like humans with AD, are genetically predisposed to the spontaneous development of diffuse allergic skin inflammation without exogenous manipulation. The two strains of focus are Relb<sup>−/−</sup> and FoxP3<sup>−/−</sup>. Such genetic models exhibit spontaneous onset of skin inflammation unlike standard allergen-driven models of AD in which allergic skin inflammation is elicited in the otherwise unaffected skin of normal mice by repeated allergen application and injury.

**Funding Source(s):** NIH

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Title: A 5-year prospective study in infants with atopic dermatitis to determine risk factors, with a focus on pets and pests, on the development of asthma and allergic diseases

Principal Investigator: Wanda Phipatanakul, MD

Researchers Involved: Jonathan Gaffin, MD – Lynda Schneider, MD

Abstract: This is a substudy of a multicenter trial of Pimecrolimus to alter the progression of atopic diseases in children. We will evaluate 350 patients with atopic dermatitis for risk factors for developing other allergic diseases. Periodic questionnaire data will be obtained on each subject to ascertain allergic exposures, specifically looking at pet and pest exposure, and the presence of allergic outcome measures, such as asthma, allergic rhinitis, allergic conjunctivitis and food allergy. Our objective will be to determine risk factors (such as parents’ atopic history, smoking during pregnancy, perinatal factors, sex, race, maternal age at birth, breast-feeding, family income, existence of siblings, pets [dogs, cats] in the household, signs of pests [mice, rats, cockroaches], attendance of day-care, smoke exposure) on the development of asthma, allergic rhinitis, food allergy, and allergic conjunctivitis in infants with atopic dermatitis. We will particularly focus on the role of pets and pests.

Funding Sources: Novartis Pharmaceuticals

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Title: A Randomized, Double-Blind, Parallel Trial on the Effect of Budesonide/Formoterol and Inhaled Budesonide Alone on Exercise-Induces Asthma

Principal Investigator: Wanda Phipatanakul, MD

Researchers Involved: Jon Gaffin, MD

Abstract: Budesonide/Formoterol (Symbicort) is a relatively new combination inhaled corticosteroid (ICS)/Long Acting Beta Agonist (LABA) used in the treatment of persistent asthma. There is some evidence that combination ICS/LABAs improve bronchoreactivity associated with exercise induced asthma. The aim of this study is to evaluate the effect of Budesonide/Formoterol vs Budesonide alone in improving exercised induced asthma as measured by change in FEV-1 during a routine exercise-induced asthma challenge. Secondary outcomes will be morning peak flow measurements and asthma symptoms recorded in a daily asthma diary. Data on exhaled nitric oxide and beta adrenergic gene polymorphisms will also be collected in this population.

Funding Sources: Astra Zeneca

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Title: Allergens in Inner-City Schools and Childhood Asthma

Principal Investigator: Wanda Phipatanakul, MD, MS

Researchers Involved: Lynda Schneider, MD - William Sheehan, MD - Diane Gold, MD, MPH - Michael Muilenberg, MA - Jonathan Gaffin, MD - Christine Rogers

Abstract: Allergic asthma is the most common chronic disease of childhood in the United States. Asthma is also the number one cause of school absences in America. The role of indoor allergen exposure in homes and asthma development and morbidity has been extensively studied. Because children spend a significant amount of time in school, the school classroom environment may be as significant a source of allergen exposure and consequent asthma morbidity as allergen exposure in the home. However, little is known about the role of allergen exposure in schools and asthma morbidity. We hypothesize that exposure to common indoor allergens in the classroom will increase the risk of asthma morbidity in inner-city children with asthma, even after controlling for home allergen exposures. In a longitudinal study of 600 elementary school-aged children with asthma from multiple classrooms in 25 Boston inner-city schools, we will examine the following specific aims: 1) to test whether elevated levels of allergens in the classroom increase the risk of asthma morbidity, even after controlling for allergen exposure in the home; and 2) to test whether the risk of increased asthma morbidity in relation to elevated classroom levels of a specific allergen will be highest for those specifically sensitized to that allergen. An understanding of exposure risk factors specific to the school classroom is critical, because the school classroom environment could potentially be considered as an effective target for prevention of inner-city asthma morbidity by reducing exposures to many symptomatic children through school-based interventions. While the potential importance of the classroom environment to the health of asthmatic children has been recognized nationally, study of this area has lacking. This unique proposal will build on important collaborations between the Channing Laboratory at the Brigham and Women’s Hospital, Children’s Hospital Boston, the Harvard School of Public Health, the University of Massachusetts Amherst, and the Boston Public School System. Our multidisciplinary research group has significant expertise in asthma epidemiology and environmental epidemiology (Drs. Phipatanakul and Gold), environmental assessment (Drs. Phipatanakul, Gold, Muilenberg, and Rogers), and statistics (Drs. Ryan, Hoffman, and Sankaranarayanan [Subramanian]). In addition to its
public health relevance, this proposal will recruit a unique school pediatric cohort that will facilitate future hypothesis testing.

**Funding Sources:** NIH/ NIAID

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Title: Characterizing Sesame Allergy: Role of Specific IgE and Skin Prick Testing in Predicting Food Challenge Results

Principal Investigator: Wanda Phipatanakul, MD, MS

Researchers Involved: Perdita Permaul, MD - Lisa Stutius, MD - P. Rangsithienchaisri, MD - Jolan Walter, MD - Michael Young, MD - Frank Twarog, MD - Lynda Schneider, MD

Abstract:

RATIONALE: Sesame is an emerging food allergen in the American pediatric population, with a significant risk of severe reaction including anaphylaxis. Little is known about the role of sesame-specific IgE levels and skin prick testing (SPT) in predicting the outcome of oral food challenges to sesame. We examined the correlation of sesame-specific IgE levels and SPT results with oral sesame challenge outcomes.

METHODS: This was a retrospective chart review of all children who received a serum sesame-specific CAP RAST IgE level, SPT, and oral sesame challenge at Children’s Hospital Boston and several affiliated allergy clinics. A positive RAST was defined as > 0.35 kU/L and a positive SPT was defined as a wheal ≥ 3 mm larger than the negative control.

RESULTS: 27 oral sesame challenges were conducted from January 2004 to March 2008. Of the 27 oral sesame challenges, 18.5% (N=5) failed and 81.5% (N=22) passed. A positive RAST demonstrated: 80% sensitivity, 32% specificity, 21% PPV, and 88% NPV. A positive SPT demonstrated: 60% sensitivity, 55% specificity, 23% PPV, and 86% NPV. A sesame RAST > 3.50 kU/L and SPT wheal ≥ 6 mm both demonstrated specificity > 90%.

CONCLUSIONS: Based on our sample, positive sesame-specific IgE level and positive sesame SPT are not good predictors of true sesame allergy as determined by the gold standard test of an oral sesame challenge. However, there may be certain RAST levels and SPT wheal sizes that are helpful in predicting a negative sesame food challenge.
**Funding Sources:** NIH Training Grant

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Title: Characterizing the Relationship Between Peanut and Sesame Allergy in Children

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Researchers Involved: Perdita Permaul, MD - Lisa Stutius, MD - P. Rangsithienchai, MD - Jolan Walter, MD - Michael Young, MD - Frank Twarog, MD - Lynda Schneider, MD

Summary:
Rationale: Sesame is an emerging food allergen in the US. There is hypothesized cross-reactivity between peanut and sesame, making sesame allergy a potential risk for peanut-allergic children. As a result, many allergists are screening peanut-allergic children for sesame allergy. We examined the relationship between sesame and peanut sensitization by skin prick test (SPT) and parent/guardian report of allergic reactions.

Methods: We performed a retrospective chart review of all children who underwent SPT to sesame at our program from December 2006 to March 2008. In these patients, we obtained SPT data for several other common food allergens and determined history of allergic reaction to peanut or sesame from the medical record.

Results: We identified 190 children who underwent SPT to sesame. Of these, 122 underwent SPT to peanut. The prevalence of sesame sensitivity in our cohort was 36.3% (N=69). Children sensitized to sesame had a high prevalence of sensitization to other foods, with peanut being the most common: peanut 84.8%, hazelnut 82.9%, egg 81.5%, walnut 80.6%, almond 76.3%. Further, 52.7% of children sensitized to peanut were sensitized to sesame. Children sensitized to peanut were significantly more likely to be sensitized to sesame (OR 6.53, 95% CI 2.59-16.42, p<0.001). Children with reported history of peanut reaction were not more likely to have reported history of sesame reaction (OR 1.37, 95% CI 0.54-3.51, p=0.5).

Conclusions: Children with peanut sensitivity are more likely to be sensitized to sesame. However, there does not appear to be a significant relationship between reported history of clinical reaction to peanut and sesame.
Funding Sources: NIH

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**Project Inventory**

**Title:** Higher Incidence of Pediatric Anaphylaxis in Southern Areas of the United States

**Principal Investigator:** Wanda Phipatanakul, MD, MS

**Researchers Involved:** William Sheehan, MD - Dionne Graham, MD - Lin Ma, MD

**Abstract:**

**Rationale:** Previous studies have suggested a north-south gradient of anaphylaxis with increased rates further from the equator. We examined the rates of pediatric anaphylaxis in the US, focusing on a north-south comparison.

**Methods:**
We searched the Pediatric Health Information System (PHIS), a billing database of US free-standing pediatric hospitals, for all cases of anaphylaxis. All hospitals providing inpatient and ED information from 2003-2007 were studied and divided at the 39° longitude creating 12 northern and 13 southern pediatric hospitals. Anaphylaxis rates (per 1,000 visits) were analyzed for north-south differences.

**Results:** There were 16,629 anaphylaxis cases (56.7% male, median age 6.2 years) among 8.5 million patient encounters. Anaphylaxis incidence was 1.96 per 1,000 encounters. Sting anaphylaxis was five times more common than food anaphylaxis (1.13 vs. 0.20 per 1,000; OR=5.79; 95%CI = 5.49-6.09; p < 0.001). Southern pediatric hospitals had higher anaphylaxis rates in the ED (2.08 vs. 1.87 per 1,000; p < 0.001) and admissions (2.13 vs. 1.60 per 1,000; p < 0.001) compared to northern hospitals. Sting anaphylaxis was more common in the south (1.44 vs. 0.83 per 1,000; p < 0.001). In contrast, food anaphylaxis was twice as likely in the north (0.26 vs. 0.13 per 1,000; OR=2.02; 95% CI=1.82-2.23; p < 0.001), although this represented a small proportion of the total cases.

**Conclusion:** The incidence of anaphylaxis was 0.2% of all pediatric hospital visits. Overall anaphylaxis and sting specific anaphylaxis were higher in southern US cities. Food anaphylaxis was much less common overall, but occurred more frequently in northern US cities.
**Funding Sources:**
Phipatanakul: NIH
Sheehan: NIH NRSA

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Title: Mouse Allergen And Asthma Intervention Trial (MAAIT)

Principal Investigator: Wanda Phipatanakul, MD, MS

Researchers Involved: Irene Borras Coughlin, CCRC

Abstract: The study is a randomized, controlled trial of a mouse-targeted integrated pest management (IPM) intervention in childhood asthma. There will be two parallel arms; one arm will receive IPM, education, and room air filters (IPM Group) and the other arm will receive IPM education alone (Education Group). The IPM Group will receive two IPM visits 4 weeks apart after randomization and subsequent IPM visits will be driven by continuing or recurring evidence of mouse infestation. The Education Group will receive one intensive education visit within 4 weeks of randomization. Clinical outcomes will be assessed every three months and followed for a total of 12 months in both groups. Home environments will be assessed every three months for a total of 12 months in both groups. Mouse-specific IgG levels will be quantified at baseline and 12 months as a biomarker of mouse allergen exposure. At the end of the 12 month period, the Education Group will receive IPM and room air filters.

Funding Sources: NIH

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Title: Preschool Children’s Ability to Perform Useful Pulmonary Function Tests

Principal Investigator: Wanda Phipatanakul, MD

Researchers Involved: Jonathan Gaffín, MD - Nancy Shotola - Thomas Martin, MD

Abstract: Spirometry has been performed and standardized for children six years old and older. Recent prospective studies have shown that preschool age children, age 3-5 years old are able to produce useful spirometry maneuvers. The American Thoracic Society (ATS) has recently published suggested guidelines for establishing adequacy and reproducibility standards for this population. We aim to review our PFT experience (Pulmonary Division records) for children 3-5 years old to determine the proportion of children who fit the current criteria. We will also look at the clinical utility of PFTs to diagnose asthma and detect early changes in lung function associated with cystic fibrosis.

Funding Sources: None

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Title: Prevalence of Aeroallergen Sensitization in Pediatric Patients Referred for Allergy Evaluation

Principal Investigator: Wanda Phipatanakul, MD, MS

Researchers Involved: William Sheehan, MD, Pitud Rangsithienchai, MD, Sachin Baxi, MD

Abstract:
Rationale: The decision to skin test depends on the clinical history, the severity of atopic disease, and the expected yield of testing. Our study evaluates rates of sensitization to environmental inhalant allergens (aeroallergens).

Methods: Retrospectively, we reviewed skin test results for consecutive pediatric patients referred to our allergy program. Sensitization was defined by a positive skin prick test to the following aeroallergens: mouse, cockroach, dog, cat, dust mite, tree, grass, and ragweed. Prevalence of sensitization, by age, was calculated for each aeroallergen.

Results: 1394 patients were skin tested during the period and grouped by age. 57.2% of all subjects were sensitized to at least one aeroallergen with a higher rate of sensitization in males as compared to females (60.1% vs. 53.2%; p = 0.010). In children less than 2 years of age, 26.5% were sensitized with the most prevalent sensitizations including dog (15.5%) and cat (9.2%). Additionally, tree sensitization was demonstrated in the youngest ages (7.8% at 0-2 yrs; 17.1% at 2-4 years). Sensitization rates to dust mites and trees were the highest in all age groups above 4 years with a peak tree sensitization of 56.4% in the 10-12 yr group and a peak dust mite sensitization of 56.8% in the >12 yr group. Overall, we observed increasing sensitization rates throughout childhood for indoor and outdoor aeroallergens (p<0.001; Pearson Chi-Square).

Conclusion: Sensitization rates to indoor and outdoor aeroallergens increase during childhood. In addition to the clinical history, knowledge of these sensitization rates may assist in the decision to perform skin testing.
**Funding Sources:**
Phipatanakul: NIH
Sheehan: NIH NRSA

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Title: Prevalence of Asthma in the Food Allergic Pediatric Population

Principal Investigator: Wanda Phipatanakul, MD, MS

Researchers Involved: Gaffin JM - Sheehan WJ - Sawicki G - Twarog F - Young M - Schneider LC

Abstract: Children with food allergies often go on to develop asthma. Our objective is to determine if specific food allergies are associated with a higher prevalence of asthma. We will use the Food Allergy and Fertility study database to evaluate the association between food allergy and asthma. The database contains information on over 1300 children with food allergies who are seen in local allergy clinics.

Funding Sources: The Jordan Family Fund for Allergy Research

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Title: Prevalence of Coconut Allergy in Children with Tree Nut and Peanut Allergies

Principal Investigator: Wanda Phipatanakul, MD, MS

Researchers Involved: Pitud Rangsithienchai, MD - William Sheehan, MD - Lisa Stutius, MD - Lynda Schneider, MD - Michael Young, MD

Abstract:
Rationale: The U.S. F.D.A. recently updated their tree nut allergen list to include coconut. This labeling has created confusion among tree nut allergic patients. Our objective was to examine the prevalence of coconut allergy in pediatric patients with and without tree nut and peanut allergies.

Methods: We performed a retrospective chart review of all pediatric patients who underwent coconut skin prick testing (SPT) in our allergy program from January to December, 2007. Patients were analyzed for coconut, tree nut, and peanut allergies based on SPT results and physician-diagnosed allergy.

Results: 37 subjects (7 months to 16 years old, median age 4.0 years) underwent coconut SPT. Of the 37 children skin tested to coconut, 21.6%, 37.5%, and 58.8% were sensitized and 24.3%, 67.6%, and 70.3% were diagnosed as allergic to coconut, tree nuts, and peanut, respectively. Children diagnosed as allergic to tree nuts were not more likely to be positive on SPT to coconut compared to those who were not diagnosed as tree-nut allergic (24.0% vs. 16.7%; p=1.00). Similar results were found comparing patients with and without diagnosed peanut allergy (23.1% vs.18.2%; p=1.00). Furthermore, children with diagnosed tree nut allergy were not more likely to be diagnosed with coconut allergy compared to those who were not diagnosed as tree-nut allergic (28.0% vs. 16.7%; p=0.69). Again, similar results were found when comparing patients with and without diagnosed peanut allergy (30.8% vs. 9.1%; p=0.23).

Conclusions: Based on our study, there is no evidence of increased coconut allergy in children allergic to tree nuts or peanuts.
**Funding Sources:** Bunning Food Allergy Research Fund

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Title: Skin Testing with Water Buffalo Milk in Patients Allergic to Cow Milk

Principal Investigator: Wanda Phipatanakul, MD, MS

Researchers Involved: William Sheehan, MD - Andrea Gardynski, MD - Pitud Rangsithienchai, MD

Abstract: Food allergy is one of the most common medical conditions in pediatrics, estimated to occur in approximately 8% of children. Specifically, the prevalence of food allergy to cow milk is estimated to be 2-3% of children in the first 2 years of life. Alternatives to drinking cow’s milk include soy milk or rice milk. Additionally, other mammalian sources of milk have been tried in children with allergy to cow milk, such as goat milk and sheep milk. A number of studies have shown that goat milk and sheep milk are not a tolerated substitute in the majority of patients allergic to cow milk.

In this study, we will begin to test water buffalo milk as a milk substitute for patients who are allergic to cow milk. For this trial, we will only perform skin testing as a preliminary test to evaluate the possibility of allergy to water buffalo milk. We will be choosing patients (ages 6 months to 8 years) who are known to be allergic to cow milk.

The primary goal of this study is to evaluate the safety of skin testing with water buffalo milk. The secondary goal of this study is to determine percentage (prevalence) of cow milk allergic patients who have negative skin tests to water buffalo milk. This is a pilot study that will give us preliminary data on the clinical cross-reactivity between cow milk and water buffalo milk.

Funding Sources:
Phipatanakul: NIH
Sheehan: NIH NRSA

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Title: ADVN Biomarker Registry Study

Principal Investigator: Lynda Schneider, MD

Researchers Involved: Irene Borras-Coughlin, CCRC - William Sheehan, MD - John Lee, MD

Abstract: This protocol describes the development of the Atopic Dermatitis and Vaccinia Immunization Network (ADVN) Biomarker Registry Study. The proposed Registry is a database with a minimum of 1,000 subjects who have voluntarily agreed to provide medical and demographic information about themselves and their health status. These data will be collected through the end of the funding period and will be used to identify potential subjects for future studies designed to improve scientific understanding of the increased risk of complications after exposure to the smallpox vaccine for people with atopic dermatitis (AD). In addition, enrolled subjects will be asked to provide a blood sample for evaluation of biomarkers, and permission for blood sample storage to support future analyses.

Funding Sources: NIH

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Title: An investigation of the safety and efficacy of Elidel 1% cream in atopic disease modification, assessed in a 3-year randomized double-blind vehicle controlled phase to evaluate effects on atopic dermatitis in infants, and a 2-3 year open-label phase to evaluate the effect of early intervention versus delayed intervention with Elidel on the incidence of asthma in children.

Principal Investigator: Lynda C. Schneider, MD

Researchers Involved: Wanda Phipatanakul, MD - Karol Timmons, CPNP - William Sheehan, MD - Irene Borras Coughlin, CCRC

Abstract:

Summary of Main Study: The current protocol is testing the hypothesis that Elidel® 1% cream (1% pimecrolimus cream) has atopic disease-modifying capabilities. Due to the natural course of atopic disease, an investigation of atopic disease modification will entail an assessment of effects on atopic dermatitis (AD) and on asthma, the two principal clinical manifestations of atopy which are typically seen at different ages: eczema in early infancy and asthma some 5-6 years later.

This is a randomized, double-blind, vehicle-controlled, multi-center, parallel-group study. Infants between the ages of 3 to 18 months with atopic dermatitis (AD) and a family history of atopic disease were enrolled between January 2004 and December 2004. The study has two phases; during phase one, which all subjects are currently participating in, subjects are given either Elidel® 1% cream or a placebo cream. In the second phase of the study all subjects who qualify will receive open-label Elidel® 1% cream for up to 33 months. Subjects will participate until shortly after their 6th birthdays.

We also hope to develop a better understanding of AD through investigation of the association of filaggrin mutations with different phenotypes of AD, other cutaneous features associated with AD, and systemic allergic manifestations. We also would like to evaluate how subjects with AD (and/or with AD who subsequently develop asthma) with and without filaggrin mutations respond to pimecrolimus cream 1%.

In order to gain a better understanding of additional factors that may contribute to the development of AD and asthma, information about the patient’s breastfeeding history and the patient’s family’s history of atopy will be collected.

Summary of Substudy: Allergic diseases such as atopic dermatitis, asthma, and allergic rhinitis are among the most common chronic diseases in the developed world. It is also well known that
childhood atopic diseases are associated with allergy to one or more indoor and outdoor allergens, and that indoor allergens, particularly pets and pests appear to be highly important in disease development. However, despite much study, the full role of various risk factors, i.e. environmental allergen exposure, on disease development is still unclear, and it is thought that multiple environmental, genetic, and medical therapeutic factors may determine whether an individual goes on to develop an allergic disease. This epidemiological substudy will take the opportunity of evaluating risk factors for developing asthma and allergic diseases in a cohort of patients which are prospectively followed the main study.

**Funding Sources:** Novartis Pharmaceuticals

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Title: APPLES: A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis

Principal Investigator: Lynda C. Schneider, MD

Researchers Involved: Karol Timmons, CPNP - Irene Borras Coughlin, CCRC

Abstract: Over 4,500 pediatric subjects aged 2 to 16 years have been exposed to tacrolimus ointment in clinical studies, including 400 children followed for more than 3 years. In large open-label study of 0.1% tacrolimus ointment including over 4,000 children with AD, the adverse event profile was consistent with that of children with atopic allergies and was comparable to that reported in the package insert. Minimal systemic absorption of tacrolimus has been observed following topical application.

This is a phase 4, prospective, multinational, observational cohort study to assess the long-term safety of tacrolimus ointment 0.03% or 0.1% in the treatment of subjects with atopic dermatitis under actual use conditions, including the risk of developing cutaneous or systemic malignancies. Each subject will be followed for 10 years in this study.

Funding Sources: Astellas Pharma Us, Inc. (Successor in interest to Fujisawa Healthcare, Inc.)

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**Title:** Immune Response to Varicella Vaccination in Subjects with Atopic Dermatitis Compared to Nonatopic Controls

**Principal Investigator:** Lynda Schneider, MD

**Researchers Involved:** Irene Borras-Coughlin, CCRC - William Sheehan, MD - John Lee, MD

**Abstract:** Children with eczema (atopic dermatitis/AD) are more vulnerable to viral skin infections such as severe cold sores (herpes simplex virus [HSV]) and vaccinia (smallpox). Eczema patients given the smallpox vaccine may have a severe life-threatening infection called eczema vaccinatum. The reason why children with eczema have more difficulty with smallpox and other viral infections is currently unknown. In case smallpox vaccinations are needed, it may be important to find out why children with eczema get eczema vaccinatum due to smallpox vaccinations. In order to understand the immune response to a viral vaccine, we will study children who have received the chicken pox (varicella) vaccine. This study is examining the immune response to the chicken pox (varicella) vaccination and may provide important information about changes in the body’s immune response to live virus vaccines in children with eczema. Understanding the different responses in children with and without eczema may allow for the creation of safer vaccines for smallpox and better treatments for vaccine complications. Participation will consist of 1 visit, approximately 3 weeks after the child has been vaccinated with the chicken pox (varicella) vaccine

**Funding Sources:** NIH

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Project Inventory

**Title:** Open-label extension study of CE1145 (Human pasteurized C1 esterase inhibitor concentrate) in subjects with congenital C1-INH deficiency and acute HAE attacks

**Principal Investigator:** Lynda C. Schneider, MD

**Researchers Involved:** Francisco A. Bonilla, MD, PhD - Hans Oettgen, MD - Anahita Dioun, MD - Rima Rachid, MD - Dale Umetsu, MD - Wanda Phipatanakul, MD - Sachin Baxi, MD - Douglas R. McDonald, MD – Mary Beth Son, MD – Melissa Hazen, MD - Michael Pistiner, MD - John Lee, MD - Rajashri Shuba Iyengar, MD - William Sheehan, MD - Perdita Permaul, MD - Jolan Walter, MD - Janet Chou, MD - Susan Rudders, MD - Ari Fried, MD - Arturo Borzutzky, MD - Lisa M. Stutius, MD - Erin M. Janssen, MD - Andrew I. Shulman, MD - Irene Borrás Coughlin, CCRC

**Abstract:** The study is an open-label extension study for subjects who were enrolled in study CE1145_3001 (CH Protocol # 05-07-104). After subjects have participated in CE1145_3001, they can be enrolled in this extension trial. Subjects will be treated with 20 U C1-INH per kg body weight, and will be observed until relief of symptoms. Following the first treatment with the study medication there are two visits for virus safety assessment at approximately one week and 3 months after study medication treatment. Patients can be treated multiple times. There is no limit to the number of treatments that a subject can receive. The study duration is planned for 24 months or until the product receives licensing, whichever comes first.

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Abstract: This is a multi-center open-label study that will evaluate the efficacy and safety of C1INH-nf as a therapeutic agent for repeated use to treat acute Hereditary Angioedema (HAE) attacks. Patients will receive treatment for HAE attacks and will have a 3 month follow visit for Laboratory Safety. Patients also have the option of receiving C1-INH-nf as a prophylaxis treatment for surgical or dental procedures.

This study will be providing the study medication, C1INH-nf concentrate, as a compassionate treatment for patients who are suffering a HAE episode. This study will continue to collect safety and supportive data related to the hypothesis set forth in the Blinded Study, which was completed and is under FDA review.

Funding Sources: LevPharmaceuticals

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Title: The role of hormone infertility therapy in the development of childhood peanut allergy

Principal Investigator: Lynda C. Schneider, MD

Researchers Involved: Michael Young, MD - Francis Twarog, MD - Mark Hornstein, MD - John Lee, MD - Stacey Missmer, Sc.D. - Irene Borras Coughlin, CCRC - Munevver Cinar, MD

Abstract: Peanut allergy is a life-threatening allergy now affecting as many as 1% of children. The prevalence of peanut allergy has risen dramatically in the last 10 years (1). This diagnosis has a significant impact on the quality of life of the patient and family (2, 3). The reason for this dramatic increase remains unknown (4). Factors associated with increased peanut allergy have included the allergenicity of roasted forms of peanut, exposure in utero, early feeding of solid foods, use of topical ointments containing peanut, and possibly use of soy formula (4, 5). A recent report suggested that advancing maternal age could be a factor (6). The rate of allergic sensitization and atopic disease in general has also increased.

Dr. Schneider and Dr. Young have noted that the parents of approximately twenty children with food allergy report that conception of the child was by IVF. During IVF prospective mothers inject progesterone support emulsified in peanut oil. This has not previously been evaluated as a risk factor for peanut allergy. The goal of this study is to determine whether IVF conception and in particular the use of peanut oil containing progesterone support increases the risk of childhood peanut allergy.

Funding Sources: Jordan Foundation

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References:
Title: Hypersensitivity reactions to hydroxychloroquine in juvenile dermatomyositis patients

Principal Investigator: Robert Sidbury MD, MPH

Researchers Involved: Peter Lio, MD - Mary Beth Son, MD - Robert Sundel, MD - Harley Haynes, MD

Summary: It has been noted by our adult dermatologist colleague at the Brigham and Women's Hospital (Dr. Harley Haynes) that a very large percentage of adult dermatomyositis patients develop a hypersensitivity reaction to plaquenil. There is one paper in the literature that supports this observation in adult patients noting a frequency of 31% (Pelle MT, Arch Dermatol, 2002;138:1231) This is not a phenomenon that has been observed anecdotally in pediatric patients by either the dermatology service (RSi, PL) or the rheumatology service (MBS, RSu) at Children's Hospital Boston. Similarly, there is nothing in the pediatric literature about this potential reaction. Juvenile dermatomyositis (JDMS) has well accepted differences from adult dermatomyositis (DM). Among the principle differences are the following: 1) DM is considered to be a paraneoplastic condition whereas JDMS is not 2) JDMS patients have increased incidence of calcinosis relative to DM patients. We hypothesize that the tendency to develop a hypersensitivity reaction to plaquenil may be yet another such difference. We plan to review the charts of over 60 patients followed by the Dermatology and Rheumatology Services at Children's Hospital Boston. All of these patients have taken or are taking plaquenil. We will document the proportion of patients with a history of such a reaction to plaquenil and compare this to historical controls (Pelle paper) We will also record additional demographic data to try and identify subgroups that may be more susceptible to hypersensitivity reaction.

Funding Source(s): N/A

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Title: Vitamin D Supplementation for wintertime Atopic Dermatitis: A randomized controlled trial

Principal Investigator: Carlos Camargo MD, PhD

Researchers Involved: Robert Sidbury MD, MPH - Ashley Sullivan, MS - Ravi Thadhani MD - Carlos Camargo MD, PhD

Summary: AD is a common pediatric skin disease occurring in 17.2% of the U.S. population. AD is known to be a T-cell mediated inflammatory disease with well-characterized cutaneous barrier abnormalities. The relative contribution of these two pathophysiologic features has historically been poorly understood. Recent basic advances have refocused AD investigation on skin barrier abnormalities. Vitamin D effects on cutaneous differentiation and metabolism are well characterized though not in the context of AD. Elucidation of the role of Vitamin D in human susceptibility to bacterial infection and its interaction with cytokines involved in innate immune pathways and the cutaneous inflammatory response have suggested a possible connection to AD pathogenesis.

We propose a randomized, double blind, placebo-controlled pilot trial. The intervention will be 800 IU/day of vitamin D in pill or liquid form. The Placebo will be made up by the Children’s Hospital Boston Pharmacy to be indistinguishable from Vitamin D. The intervention will simply be added to their baseline therapeutic regimen. In addition, both the intervention and placebo groups will receive a packet containing one month’s supply of emollient and teaching materials about appropriate skin care for patients with atopic dermatitis.

Patients aged 2-17 years with AD diagnosed by Hanifin/Rajka criteria [13] will be recruited from the dermatology clinic.

Funding Source(s): Center for D-Receptor Activation Research

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Project Inventory

**Title:** A prospective, randomized, double-blind, active controlled, parallel group, multi-center trial to assess the efficacy and safety of mycophenolate mofetil (MMF) in inducing response and maintaining remission and renal function in subjects with lupus nephritis

**Principal Investigator:** Robert Sundel, MD

**Researchers Involved:** Mary Beth Son, MD - Fatma Dedeoglu, MD - Susan Kim, MD - Irene Borras-Coughlin, CCRC

**Abstract:** The study is designed as a prospective, randomized, active controlled, parallel group, international multicenter, two arm comparison study of MMF vs. cyclophosphamide during induction (open label), followed by a randomized double-blind comparison of MMF vs. azathioprine during maintenance. After screening and determination of eligibility, subjects with lupus nephritis will enter the induction phase of the study and be randomized to receive, in an open-label fashion, either oral MMF (1.5 g BID) or IVC (monthly bolus doses of 0.5 to 1.0 g per square meter of body surface area) for 24 weeks. At the end of the open-label induction phase, subjects meeting the criteria for response (Section 4.4 of the Protocol) or complete (renal) remission (Section 4.5 of the Protocol) will be re-randomized to receive either oral MMF (1.0 g BID) or azathioprine (2mg.kg.day), in a double-blinded fashion until 144 treatment failures are observed or until the last subject has been followed for 36 months. A protocol amendment will be written extending the maintenance phase duration if any subject is required to be followed beyond 36 months. Dose adjustments for efficacy and safety will be allowed during the maintenance phase. Subjects also will receive concomitant treatment with corticosteroids at specified initial dosing and taper (Section 6.1 of the Protocol). Subjects in selected countries who enter the maintenance phase will also be asked to enter a long-term registry under a separate protocol.

**Funding Sources:** Aspreva Pharmaceuticals Corp. - PPD Inc

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Project Inventory

Title: Trial of Early Aggressive Therapy in Juvenile Idiopathic Arthritis (TREAT JIA trial)

Principal Investigator: Robert Sundel, MD

Researchers Involved: Mary Beth Son, MD - Fatma Dedeoglu, MD - Susan Kim, MD - Robert Fuhlbrigge, MD - Arturo Borzutzky, MD - Erin Janssen, MD - Andrew Shulman, MD - Lisa Stutius, MD - Bebe Samler, RN - Maria Benoit, RN - Irene Borras Coughlin, CCRC

Abstract: This study is being conducted to determine if treatment early in the disease course of children with polyarticular juvenile idiopathic arthritis (JIA) (within 12 months from onset of disease) with an aggressive combination of medications can result in Inactive Disease (ID) in a greater proportion of children than treatment with one medication. Initial treatment with Methotrexate will be compared to the combination of methotrexate, prednisone and etanercept together. All of these medications are routinely used to treat poly JIA and are all considered to be first-line agents, but are usually added together slowly after the disease has been present for a long time. This trial will study their effectiveness given together very early in the disease process.

Funding Sources: NIH/NIAMS; Amgen, Inc.

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Project Inventory

Title: Umetsu/DeKruyff Laboratory

Principal Investigator: Dale T. Umetsu, MD, PhD

Researchers Involved: Rosmarie DeKruyff, PhD - Omid Akbari, PhD - Lee Albacker, PhD - Ya-Jen Chang, PhD - Yee-Ling “Elaine” Chim, PhD - Hye Young Kim, PhD - Hyun-Hee Lee, PhD - Ponpan Matangkasombut, BS - Muriel Pichavant, PhD

Abstract:

The laboratory focuses on understanding innate and adaptive immunity, using models of allergy, asthma, autoimmunity and tolerance. These studies involve analysis of subpopulations of human and murine CD4+ T cells, T cells with restricted cytokine profiles (Th1, Th2 and Th0 cells), antigen-specific regulatory T cells (T_{Reg}), subpopulations of Natural Killer T (NKT) cells and subpopulations of dendritic cells. The laboratory is interested in the cellular, molecular and genetic mechanisms that control the interaction of T cells and NKT cells with dendritic cells and other antigen presenting cells, resulting in inflammatory responses versus tolerance, and the development of, or protection against, disease.

Ongoing studies deal with the examination of:

- The function of members of the TIM gene family, a family that we recently discovered, and that regulates the development of Th1/Th2 responses, T cell activation, tolerance, asthma and autoimmunity.
- Costimulatory molecules that drive polarization of cytokine synthesis in memory and naive populations of effector CD4+ T cells and T_{Reg} cells.
- The role and characteristics of subsets of NKT cells in allergy and asthma.
- How NKT cells become activated; and what are the glycolipids that activate NKT cells.
- How dendritic cells regulate respiratory tolerance induction, T_{Reg} cell development and NKT cell function.
- The influence of innate immunity to infection with influenza A virus, hepatitis A virus and Listeria monocytogenes on adaptive immunity, asthma and tolerance.
- The role of apoptosis/programmed cell death in regulating inflammatory responses and inducing tolerance.
• Methods to induce, and mechanisms of, antigen-specific tolerance in patients with allergy and food allergy.
• Subsets of CD4+ T cells, T_{Reg} cells in regulating the development of Th2 responses, respiratory tolerance and asthma.

**Funding Sources:** NIH and others

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