Determining the Efficacy and Value of Immunotherapy on the likelihood of peanut tolerance: The DEVIL Study

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PURPOSE OF THE STUDY

Peanut allergy is an increasingly common and potentially severe problem, and no active treatment is currently available. The current standard of care is strict dietary elimination and emergency preparedness with an anaphylaxis kit in the event of an accidental reaction. Despite the constant state of vigilance required by families, accidental reactions are common and can be severe, leading to anxiety and impaired quality of life. Because the disease is life-long in over 80% of affected patients, an active form of therapy is needed. Traditional injection immunotherapy (allergy shots) with peanut has been studied as a treatment option. Although effective, the rate and severity of significant systemic side effects was unacceptably high, and this approach has been abandoned. Mucosal immunotherapy (MIT), which takes advantage of the normally suppressive environment of the gut, has been used for the treatment of nasal allergies and food allergy, as well as drugs such as antibiotics and biological agents. In recent case reports and uncontrolled studies on oral immunotherapy in patients with milk, nut, egg, or fish allergy the majority of patients successfully completed the treatment regimen, and the mild side effects associated with treatment were generally controlled by the occasional use of antihistamines. However, many of these studies were simply descriptive and did not employ rigorous study design or immunologic investigation, and the long-term effectiveness of such treatments are unknown. Many unanswered questions remain about the possible mechanism(s) and optimal treatment schedule (dose, timing, route, duration) of food allergen immunotherapy,

This randomized, double blinded, dose-finding study proposal is designed to find out if we can use peanut mucosal immunotherapy (PMIT) in young subjects allergic to peanuts, and to better characterize the appropriate dose of PMIT. Our hypothesis is that mucosal peanut immunotherapy will make subjects who have peanut allergy less allergic and induce changes in their immune system. The goal of this proposal is to produce a new treatment that would benefit these subjects by lowering the risk of anaphylactic reactions (**desensitization**), and changing the peanut-specific immune response in subjects who have peanut allergy (**tolerance**). By initiating PMIT in infants and toddlers shortly after their initial reaction to peanuts, we aim to interrupt the allergic immune response to peanut prior to the development of life-long immunologic memory. We anticipate being able to make these subjects less allergic to peanuts and cause long-term immune changes in their peanut allergic response. The specific aims for this proposal are to: (1) use PMIT to treat subjects with peanut allergy to lower the risk of anaphylactic reactions and induce tolerance to peanut (2) determine the effect that PMIT has on the peanut-specific immune response.

BACKGROUND AND SIGNIFICANCE

Food allergic reactions have generated increasing concern in the U.S., with prospective studies indicating that 6-8% of children less than four years of age experience IgE-mediated food allergic reactions. These data were recently confirmed by a Centers for Disease Control report, which also documented an 18% increase in food allergies among U.S. children over the past 10 years. A recent survey in the U.S. found that 1.3% of the total population is allergic to peanuts or tree nuts, and the average age at peanut allergy diagnosis in our local population is 14 months, a significant decrease over the past 5 years. Despite increased recognition and understanding of food allergies, food-induced anaphylaxis remains the single-most common cause of anaphylaxis in hospital emergency departments, accounting for about one third of anaphylaxis cases seen. Each year in the US, food allergy causes an estimated 125 000 emergency department visits, with anaphylaxis occurring in approximately 15 000 cases, leading to 3100 hospitalizations. Though food-induced anaphylaxis-induced deaths are rare, they do continue to occur, and remain the fundamental threat to all families dealing with food allergy. Fatal reactions are caused by peanut or tree nut allergy in over 80% of cases, and not surprisingly peanut allergy causes significant anxiety and impairment in quality of life for patients and their families.

PROJECT DESCRIPTION

We expect to develop a treatment that lowers the risk of anaphylactic (allergic) reactions and alters peanut-specific immune responses in peanut-allergic children. This proposal seeks to determine the effect that peanut mucosal allergen immunotherapy (PMIT) has on the allergic response to peanuts in young children. Our ultimate goal is determine whether PMIT will protect the allergic child from a potentially fatal reaction (by **desensitization**) and induce children to outgrow their allergy to peanuts (by **tolerance**).

GOALS, HYPOTHESIS AND OBJECTIVES

The **goal** of this proposal is to produce a new treatment that would benefit these subjects by lowering the risk of anaphylactic reactions (**desensitization**), and changing the peanut-specific immune response in subjects who have peanut allergy (**tolerance**). *This project is designed to study the innovative idea that PMIT, begun early in life, will desensitize subjects with peanut hypersensitivity by regulating their mucosal and systemic immune reactivity and cause long-term tolerance.*

The present research plan draws upon our extensive knowledge of the allergens involved in peanut hypersensitivity; it is also based upon evidence demonstrating the effectiveness of peanut oral immunotherapy (OIT) in preliminary research studies. Previous attempts to utilize peanut-specific immunotherapy (IT) subcutaneously have failed primarily because of the side effects of therapy. We expect PMIT to have fewer side effects than the non-mucosal systemic desensitization method, and this proposal will compare a high dose regimen to a low dose regimen, which may improve the safety profile of PMIT. We propose to test the efficacy of PMIT in young peanut-allergic subjects; we believe that early intervention with PMIT, prior to the development of sustained immunologic memory, may offer an optimal treatment for affected subjects.

Our **hypothesis** is that mucosal peanut immunotherapy will make subjects who have peanut allergy less allergic and induce changes in their cellular and humoral immune system.

The proposed study has two primary **objectives**:

Objective #1: To treat peanut-allergic subjects with PMIT and to determine whether this protocol lowers their risk of anaphylactic reactions and causes long-term tolerance.

Objective #2: To determine the effect that PMIT has on the peanut-specific cellular and humoral response in peanut-allergic subjects.

Objective #1: To determine whether PMIT reduces peanut induced anaphylactic reactions and induces long-term tolerance in peanut-allergic subjects.

Purpose and expectations:

These studies are designed to test the feasibility and effectiveness of using PMIT to desensitize subjects with peanut allergy, and to optimize the appropriate treatment dose. We expect to demonstrate the effectiveness of PMIT by showing that subjects on PMIT will have negative double-blind placebo-controlled food challenges (DBPCFC) to peanuts following completion of a 36-month course of PMIT. We will compare the effects of high-dose PMIT (3000mg) and low-dose PMIT (300mg) against untreated controls, and we expect that PMIT will induce a significant decrease in: (a) wheal (swelling) size from a titrated skin prick test to peanut protein, (b) serum-specific IgE to peanut, and (c) adverse effects with accidental peanut ingestion. In this study we will test the hypothesis that low-dose PMIT is as successful in tolerance induction as high-dose PMIT in a young cohort of newly diagnosed subjects.

The studies under Objective #1 will determine the feasibility of utilizing PMIT for peanut-allergic subjects early in life, and help to define an optimal treatment dose, which will minimize potential side effects and thus enhance the safety of PMIT. At the present time, strict avoidance of food allergens and ready access to self-injected epinephrine is the "standard of care" for food allergy. Unfortunately, this method does not work well for young patients with peanut allergy. The ubiquity of peanut-containing foods, especially in children's diets, makes the possibility of inadvertent ingestion great; moreover, children are often in circumstances in which epinephrine injection would prove logistically difficult. If, however, we can demonstrate that PMIT is effective for peanut-allergic children, the treatment would provide an immediate and feasible *preventive* option for averting potentially life-threatening reactions to accidental peanut exposure (desensitization). Additionally, we may be able to cause peanut-allergic children to lose their allergic reactivity to peanuts (tolerance).

Objective #2: To determine the effect that PMIT has on the peanut-specific cellular and humoral activity/response in peanut-allergic subjects.

Purpose and expectations:

Objective #2 seeks to understand the mechanism(s) of PMIT's effect on the cellular and humoral response to peanut. To do this, we will: (a) analyze the regulatory T-cells (types of white blood cells) induced following PMIT, (b) measure the cytokines (chemicals) produced by peanut-specific T-cells after PMIT, (c) determine the type and quantity of peanut IgE-specific B cells (antibody-producing white blood cells), and (d) examine the peanut-specific IgE, IgG and IgG4 response (in blood) and secretory IgA response (in stool). We anticipate that the effect of PMIT will occur by one or both of the following mechanisms: (1) the induction of regulatory T-cells, or (2) a shift from a Th_2 (allergic) to Th_1 (non-allergic) lymphocyte response (as evidenced by cellular changes and changes in peanut-specific IgE and IgG). The induction of regulatory T-cells would modify the subject's immune response to peanuts by modifying peanut-specific T cell proliferation and cytokine production. Both CD4+/CD25+ and CD4+/CD25+/CTLA+ T cells have been demonstrated in humans after mucosal antigen delivery, and there is extensive evidence in animals that T cells with regulatory properties develop upon repeated exposure to antigen and form the basis of low dose tolerance. The conversion from a Th_2 to Th_1 lymphocyte response would have a similar clinical effect of making the subject less sensitive to peanuts, but would accomplish this by a different immune mechanism. These mechanisms may have overlapping effects and both have been reported to occur following allergen specific immunotherapy. Additionally, stool analysis will evaluate the potential of PMIT to induce the production of allergen-specific secretory IgA antibodies in the gastrointestinal tract that prevent allergens from accessing the systemic immune system and inducing allergic symptoms.

Our expectation is that the balance of immunoglobulin isotype response and the epitope diversity within each isotype (IgE, IgG subtypes, and IgA) is reflective of the antigen-specific immune response. We anticipate that the identification of antigen-specific immunoglobulin responses may give better insight into mechanisms of immediate hypersensitivity reactions (e.g., "blocking" antibodies) and mediators of immune tolerance induction (e.g., IL-10 induced IgG4 as a marker of a modified Th2 response).

STUDY DESIGN, DOSAGE SCHEDULE, AND ACCIDENTAL REACTIONS

We will utilize a modified MIT schedule for this PMIT study with a randomized, double-blinded study based on our previous experience with peanut-allergic subjects. Active peanut allergy will be confirmed in all interventional subjects with open oral food challenge prior to entry into the study. Control subjects may be offered a confirmatory food challenge if the diagnosis is uncertain. We will enroll 80 children in the intervention group. The active subjects will be randomized into either a high dose group (final maintenance dose of peanut 3000mg, N=40) or a low dose group (final maintenance dose of peanut 300mg, N=40) (see Figure 1). Forty additional subjects will be followed as control subjects and will not receive any type of study protein. All subjects in the active group will undergo a one-day peanut desensitization protocol designed to enable the subject to tolerate a daily dose of peanut protein (modified rush phase) (Table 3). If the subject has a mild reaction to one of the doses, the next dose would be determined at the discretion of the investigator. The options open to the investigator are to administer the last previously tolerated dose, or wait an additional amount of time between doses, or repeat the current dose. Once this determination of the dosage amount is made, the desensitization process resumes as outlined. Upon completion of the modified rush phase to peanut, the subject is observed for a minimum of 2 hours. If there is no evidence of an allergic reaction the subject is discharged home.

If the subject requires treatment for symptoms during the initial escalation protocol with antihistamines on one occasion, then the rest of the protocol may be followed. If the subject requires more than one medication or multiple doses of antihistamines or requires other rescue medications, the initial desensitization phase should be stopped. If the subject has tolerated either the 3 mg or 6mg dose, the subject will be eligible to return on Day 2 to proceed with the build-up phase.

After the first day of desensitization, subjects will return to the research unit to begin the build-up phase of the study. The subject will ingest 6 mg, or a lower amount based on the reaction to the modified rush phase. After the subject is observed for a minimum of 30 minutes for symptoms to the study protein ingestion, he or she will be discharged from the research unit and will continue to consume the study protein at home daily for a minimum of ten to fourteen days (+7 days). The family receives the study protein doses as a powder that they give to the child each day by sprinkling it on a previously tolerated food (e.g., applesauce). Subsequently, subjects will return to the clinical research unit every ten to fourteen days to monitor their adherence to the dosage administration and increase the dose to the next escalation amount (see Table 4). The subject's response to the new dose escalation amount will be monitored for a minimum of 30 minutes after dose administration. Vital signs are performed prior to the dose administration, prior to the completion of the observation period before discharge, and anytime symptoms occur. If attempts at blood pressure measurement have been very disturbing and traumatic to a young child, the study team will rely on observation, heart rate and respiratory rate and the physical assessment to determine the subject's response. If the study team feels that a longer observation time is warranted based on the prior dosing history of the subject or their current physical status, the subject will be observed for a longer period of time. If symptoms occur that do not require treatment, the subject will be observed until they resolve. If symptoms occur that require diphenhydramine or albuterol, the subject will be observed a minimum of 2 hours or until symptoms resolve. If symptoms occur that require epinephrine, the subject will be observed at least 4 hours or until symptoms resolve. If symptoms do not fully resolve after 6 hours or if new symptoms occur, the subject will be transferred to UNC Children's Hospital to be observed overnight. Subjects will then take that dose daily for a period of 10 to 14 days (+ 7 days) after which they will return to the clinical research unit to have the daily dose increased proportionately at each visit until the maximum daily dose of study protein (3000mg) is consumed. All active subjects will build up to 3000mg of study protein. To maintain blinding, the subjects randomized to the 300mg peanut dose will have additional placebo flour added to the study protein during buildup by unblinded study personnel. Laboratory studies will be done at the beginning of the study, when the subject reaches the 156 milligram dose, when the subject reaches the 749 milligram dose, and when the subject reaches the 3000mg dose, and annually thereafter until the end of the study. The laboratory studies will consist of blood tests to monitor the immune response to the peanut protein. Stool studies will be performed at the beginning of the study and the end of the study. Control subjects will have visits for medical history, physical exam, titrated skin prick testing and blood and stool laboratory studies associated with the study at entry and then yearly. This control group will be seen yearly over the length of the study.

Each subject is given multiple ways to contact study staff when they are enrolled in the study. This is reviewed at the end of each visit. The families are told to contact the study staff if they have any questions or concerns before the next visit or at any time during the study. Study contact information given to families include the office phone number, pager number, and email address of the PI's, study coordinators, and research nurses in addition to the pager number of

the on-call allergist who has the personal cell numbers of the study staff. Subjects who have any symptoms during observed dosing, food challenges, or those who express any specific concerns are given a follow up phone call on the day after dose escalation.

After completing the escalation schedule (*build up phase* to 3000 mg study protein), the subjects will continue to receive their maintenance dose of study protein daily for the next 36 months of the study (*maintenance phase*). Once subjects enter the maintenance phase, assessment of the primary endpoint will occur conditionally (i.e., upon achievement of defined immunological benchmarks), and/or at the chronological end of 36 months of maintenance. These two possible scenarios are discussed further below. After 12 months of maintenance, the subject will have the peanut-specific IgE measured. In the first conditional scenario, at any point after this measurement, if the peanut IgE is 15 kU/L or less, the skin test is 8mm or less, and there have been no severe symptoms following PMIT doses or accidental peanut exposure in the previous 6 months, at the discretion of the investigator, the subject will stop the daily dosing and have a DBPCFC the next day. This cohort of subjects will then stop the daily dosing for the next 4 weeks and then return for a 2nd DBPCFC to peanut to assess long term tolerance to peanut. If these food challenges are negative (i.e., successfully completed), they will be followed by an open peanut challenge. The open challenge will occur in a 1 to 2 hour window after the successful completion of the tolerance challenge, and the study will be completed for that participant if the open challenge is successful. If any of the challenges are positive or inconclusive (i.e., not successful), the participant will resume OIT dosing until the next 12 months, or at the end of the 36 month treatment period. In the second (i.e. chronological) scenario, all remaining subjects will be assessed for the primary endpoint once they have completed 36 months of maintenance treatment, regardless of their immunologic parameters and/or their performance in past challenges, if applicable. If either challenge at the end of 36 months are positive or inconclusive (i.e., not successful), the participant will be considered as having completed the study and will return to standard of care.

Subjects who miss one to two days of the daily dose will continue at their current dose at home. The PI will determine where the next dose of study protein is given for those who miss three to four days of the daily dose based on the length of time on study, the daily dose amount, the subject's reaction history and the amount of time since the last reaction to a dose in order to assure safety with dosing. Those who miss more than four days will return to the clinical research unit for evaluation by the study team in order to determine the best course of action for the subject. Options open to the investigator include repeat desensitization, observed dosing at a dosing level previously tolerated by the subject, or a change from active subject to control subject . To monitor subjects for adherence, any accidental ingestion, any symptoms related to daily dosing and any unintended side-effects of daily dosing, the families will be asked to keep a simple daily diary to record the requested information. A copy of the daily diary is included on page 16 of the protocol.

We will monitor accidental reactions to peanuts in each subject during the PMIT trial. We will note any reaction that occurs in a subject after the ingestion of peanuts, and record the type of symptoms (i.e., skin, respiratory, gastrointestinal, or cardiovascular). Pilot data from our previous studies indicate that home dosing is safe, with infrequent reactions which are typically mild. These data have identified several risk factors for reactions, which include dosing on an empty stomach, fever/illness, and activity/exercise shortly after dosing. Families of subjects will be asked to administer the study protein with additional food such as at snack or meal times, and during illness to hold the study protein and contact study personnel for instruction.

Because of the extreme risk to subjects, those experiencing severe symptoms during dosing or challenges such as respiratory failure, hypotension or other symptoms requiring ICU care will be withdrawn from the study. Additionally any subjects who have had an accidental peanut ingestion and developed anaphylaxis with respiratory failure or hypotension during the time on PMIT will be dropped from the active portion of the study. Subjects that do not complete the study because of an accidental reaction to peanut will be followed in the control group.

Study Stopping Rules

The following stopping rules will be used throughout the study. If a subject at any time point experiences a serious adverse event as described by the FDA or an unanticipated event of grade 3 or above as defined by the CTC III scale, the trial will be halted and the IRB and FDA will be consulted. If symptoms as noted above occur in 2 or more subjects, the study will be stopped and the situation reviewed. In addition, the study will not resume until the FDA has been notified and given the approval for the study to continue.

Subjects will come to the UNC Food Allergy Study Center (FASC) for a double-blind, placebo-controlled food challenge (DBPCFC) at the end of the 36 month maintenance treatment period, or sooner if challenge criteria are met. The DBPCFC may either occur on 1 day or over a 2 day period. The food challenges will be administered by the study coordinators or research nurses associated with the study. In a double-blind, placebo controlled challenge, two challenges, one containing placebo (which will be oat flour) and one containing peanut, will be performed in the same day Randomization and preparation of the challenge materials will be performed by the dietitian or a representative from Dr. Burks' laboratory. Prior to the food challenge, subjects will be asked to restrict the use of antihistamines (short acting, 72 hours: long acting, 7 days), beta-agonists (12 hours), theophylline (12 hours), and cromolyn (12 hours). One challenge will consist of six doses of peanut given every 10-20 minutes in increasing amounts up to a total weight of 5 grams of peanut protein. The other challenge will consist of placebo material given also in six doses. The cumulative dose of peanut protein given is 5 grams (10 gram weight of peanut flour). Both challenges will start by first touching the patient's lip/tongue with a small amount of the test material. The first ingested dose will be 0.5 grams (5 %), then increasing to 1 gram (10%), 2 grams (20%), 2.0 grams (20%), 2 grams (20%), and 2.5 grams (25%). During food challenges, vital signs will be performed prior to the challenge, between the two parts of the challenge, at the end of the challenge day, and anytime symptoms occur. Prior to each challenge, the patient will have a medical history and physical exam performed, during which emphasis will be placed on active respiratory symptoms such as wheeze and cough. The challenge will be administered by a nurse or physician who is blinded to the testing material. The supervising investigator will also be blinded to testing material.

If the subject ingests all of the challenge material without significant symptoms, the treatment will be stopped for 4 weeks, and the DBPCFC will be repeated, using the same procedure as described above. At the end of these challenges, **all negative challenge results will be confirmed by open challenge to peanut. Approximately 5 grams of peanut protein will be the quantity of peanut given in the open challenge.**

After each challenge the patient will be observed for a minimum period of 1 hour. Reactions will be scored using a Food Challenge Symptom Score sheet (page 24 and 25 of the protocol). If the patient begins to have any objective symptoms or subjective symptoms deemed clinically significant, the food challenge will be terminated and the patient will be given appropriate treatment. Symptoms which would result in discontinuation of the ongoing part of the DBPCFC include diffuse hives, throat/tongue swelling, wheezing, respiratory distress, emesis, moderate to severe abdominal pain and hypotension. These would be treated with the appropriate emergency medication and the subject would enter a minimum 2 hour observation period or until symptoms resolve. If no symptoms are reported during the first part of the DBPCFC, the subject would enter the observation period. If the subject is stable after the observation period, the second part of the DBPCFC would then commence. If epinephrine is required to treat symptoms, the subject would be observed for a minimum of 4 hours and the second part of the challenge will be deferred until the next day. The subjects who are not symptomatic will be observed for a minimum of 2 hours after the challenges are completed before being discharged from the FASC. All food challenges will be performed under physician supervision.

If the subject fails the tolerance challenge after being off the study protein for 1 month, the subject will be discharged home to continuing daily dosing on the highest tolerated dose of the challenge. The subject will continue this dose and have the desensitization and tolerance challenges repeated in one year or at the chronological end of their 36 month maintenance period, whichever comes first.

Individual Stopping Rules

Subjects will be dropped from the arm of the study ingesting daily maintenance dose of peanut protein if they are having moderate to severe clinical symptoms (GI, respiratory or skin) at home after taking the daily dose of peanut protein. Additionally, any subjects who have an accidental peanut ingestion and have anaphylaxis during the time on oral desensitization, will be dropped from the arm of the study ingesting daily maintenance dose of peanut protein. Subjects who experience peanut-related hypotension as evidenced by a 15 % drop in their blood pressure from their baseline, nontransient oxygen desaturation below 90%, recurrent abdominal pain, or recurrent emesis which is felt by the PI to be potentially dose related will be stopped from participating in the study.

Any subject who has a serious adverse event which is felt by the PI to be potentially a result of participation in the study will be dropped from the study.

SAFETY MONITORING

This section defines the types of adverse events that should be reported. It outlines the procedures for the appropriate collection, grading, recording and reporting of the events.

Procedures and Monitoring

All unexpected serious adverse events related to the experimental procedures will be reported to the IRB, DCRU, DSMB, and FDA in a manner consistent with 21 CFR 312.32. All other adverse events related to the experimental procedures will also be reported to the IRB and DCRU in an expedited manner if they are Grade 3 and above in severity. Participant deaths are reportable within 24 hours. The expedited report sent to other organizations will be copied to the DCRU. The investigator will continue to follow or obtain documentation of the resolution course of such an event. A copy of the annual report of adverse events submitted to the IRB will be copied to the DCRU. Reactions to dosing of the study product will be recorded on a dosing log and will not be reported separately as adverse events. Any reaction that meets the criteria for a serious adverse event will be reported both on the dosing log and on an adverse event case report form.

Definitions

Adverse Event (AE) or Medical Event

An adverse event is a new, undesirable medical event or occurrence or worsening of an existing condition (including an abnormal laboratory finding) in a subject that occurs during treatment and throughout the study, whether or not it is considered to be study related. Adverse events or medical events and toxicities are treatment emergent signs and symptoms.

Potential adverse reactions seen in subjects treated with peanut OIT and subjects undergoing DBPCFC include the following: skin manifestations such as pruritus, urticaria, or angioedema; respiratory symptoms such as wheezing, coughing, nasal congestion/rhinorrhea, cough and hoarseness; and gastrointestinal manifestations such as vomiting, diarrhea, or abdominal pain. Anaphylaxis is a potential risk involving any of the above symptoms plus hypotension and circulatory collapse.

Serious Adverse Event

A serious adverse event is defined as any adverse therapy experience occurring at any dose that results in the following (21 CFR 312.32):

1. Death: A death occurring during the study, or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy whether or not considered treatment related, must be reported.

2. Life-threatening: Any adverse therapy experience that places the subject or subjects, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death).

3. In-patient hospitalizations or prolongation of existing hospitalization.

4. Persistent or significant disability or incapacity.

5. Congenital anomaly/birth defect.
6. An event that required intervention to prevent permanent impairment or damage.

Unexpected Adverse Event

An adverse event is considered "unexpected" when its nature (specificity) or severity is not consistent with applicable product information, such as safety information provided in the protocol or consent.

TOXICITY GRADING

Toxicity grades are assigned by the study site to indicate the severity of adverse experiences and toxicities using the NCI-CTCAE version 3.0. Toxicity grading for allergic reactions including anaphylaxis is modified from the NCI-CTCAE system to be more appropriate for this study population, and is displayed in Appendix 2. The NCI-CTCAE has been reviewed specifically for this protocol and is otherwise appropriate for this study population. The purpose of using the NCI-CTCAE system is to provide standard language to describe toxicities and to facilitate tabulation and analysis of the data and assessment of the clinical significance of treatment-related toxicities.

Adverse events not included in the CTCAE listing should be recorded and graded 1-5 according to the General Grade Definition provided below:

Grade 1	Mild	Transient or mild discomforts (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain).
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible.
Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical/therapy intervention required, hospitalization or hospice care probable.
Grade 5	Death	Death.

Relationship to Procedure Definitions

Associated: There is a reasonable possibility that the adverse event may have been caused by the test product and/or procedure. This definition applies to those adverse events that are considered definitely, probably or possibly related to the procedure.

1. Definitely related: An adverse event that follows a temporal sequence from administration of the test product and/or procedure; follows a known response pattern to the test article and/or procedure; and, when appropriate to the protocol, is confirmed by finitely related: An adverse event that follows a temporal sequence from administration of the test product and/or procedure; follows a known response pattern to the test article and/or procedure; and, when appropriate to the protocol, is confirmed by improvement after stopping the test product (positive rechallenge: and by reappearance of the reaction after repeat exposure [positive rechallenge]); and cannot be reasonably explained by known characteristics of the subject's clinical state or by other therapies.
2. Probably related: An adverse event that follows a reasonable temporal sequence from administration of the test product and/or procedure; follows a known response pattern to the test product and/or procedure, is confirmed by improvement after rechallenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state or other therapies.
3. Possibly related: An adverse event that follows a reasonable temporal; sequence from administration of the test product and/or procedure and follows a known response pattern to the test product and/or procedure, but could have been produced by the participant's clinical state or by other therapies.

Not associated: An adverse event for which sufficient information exists to indicate that the etiology is not related to the test product and/or therapy.

1. **Unrelated**: An adverse event that does not follow a reasonable temporal sequence after administration of the test product and/or procedure and most likely is explained by the participant's clinical disease state or by other therapies. In addition, a negative rechallenge to the test article and/or procedure would support an unrelated relationship.

ADVERSE EVENTS COLLECTION PROCEDURES

The Principal Investigator is responsible for collecting and recording all clinical data. As these results are collected, all toxicities and adverse events will be identified and reported to the principal investigator. Adverse events will be reported as described above. The Principal Investigator will determine relationship of the event to the study intervention and decide course of action for the study participant.

Recording and Reporting Procedures

Monitoring will be conducted semi-annually via Internal Audits with a Research Safety Committee known as the UNC Food Allergy Initiative (UNC FAI) Data Safety Monitoring Board DSMB). Yearly reports will be made to the proper Institutional Committees, as required. All adverse events will be kept in a file by numerical identifier.

SAE Recording and Reporting Procedures

All serious adverse events are recorded on the appropriate case report forms.

SERIOUS ADVERSE EVENT NOTIFICATION

The research staff will notify the sponsor/investigator of any serious adverse event immediately on learning about the event.

SIZE OF POPULATION (AGE, GENDER, ETHNICITY, SOURCE OF SUBJECTS, RECRUITMENT PROCESS)

We will recruit 120 subjects between 9 to 36 months of age who have EITHER diagnosed peanut allergy, based on (1) the presence of IgE specific to peanuts (a positive skin prick test >3mm wheal size) to peanuts or a positive *in vitro* IgE [CAP-FEIA] > 0.35 kU/L and (2) a convincing history of an allergic reaction (defined as significant clinical symptoms occurring within 60 minutes after ingesting peanuts) within 6 months prior to enrollment, OR probable peanut allergy, defined as (1) positive skin prick test and (2) CAP-FEIA ≥ 5 kU/L, in a child with no known history of peanut ingestion. We will confirm the diagnosis of peanut allergy in all interventional subjects with graded open (unblinded) oral food challenge to 4 grams of peanut protein prior to enrollment. Subjects with a known wheat food allergy will be excluded because of cross contamination of oat with wheat. We will recruit subjects from the Duke Pediatric Allergy Clinics and subjects from colleagues of the investigators in the surrounding community based on our clinic's demographics; we expect to enroll subjects in equal numbers of females and males, with approximately 20% under-represented minorities. Subjects will participate in the study for a period of up tp 72 months.

Inclusion Criteria

Subjects who meet *all* of the following criteria are eligible for enrollment as study participants:

- Age 9-36 months of either sex, any race, any ethnicity at the time of the initial visit
- EITHER a positive skin prick test to peanuts (diameter of wheal ≥ 3.0 mm) or positive *in vitro* IgE [CAP-FEIA] > 0.35 kU/L] PLUS a history of a clinical allergic reaction (defined as significant clinical symptoms occurring within 60 minutes after ingesting peanuts) within 6 months of screening

- OR a positive prick skin test to peanuts and CAP-FEIA > 5 kU/L when there is no history of allergic reaction and no known peanut exposure
- Provision of signed informed consent
- Development of symptoms characteristic of IgE-mediated food allergy (urticaria, angioedema, respiratory distress/wheeze/cough, vomiting/diarrhea, anaphylaxis) during initial open oral food challenge

Exclusion Criteria

Subjects who meet *any* of these criteria are *not* eligible for enrollment as study participants:

- History of severe anaphylaxis to peanut as defined by hypoxia, hypotension, or neurological compromise (Cyanosis or SpO_2 < 92% at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence)
- Currently participating in a study using an investigational new drug
- Participation in any interventional study for the treatment of food allergy in the past 12 months
- Subjects with a known wheat food allergy will be excluded because of cross contamination of oat with wheat
- Subjects with a known oat allergy will be excluded because oat flour will be added to the peanut flour for those subjects who are randomized to receive the dose of 300 mg of peanut
- Severe atopic dermatitis
- Currently being treated with greater than medium daily doses of inhaled corticosteroids, as defined by the NHLBI guidelines
- Inability to discontinue antihistamines for skin testing and OFCs

EXPECTED IMPACT

The significance of this proposal is several-fold. First, a treatment for peanut-allergic children is badly needed. A therapeutic option such as PMIT would greatly benefit subjects both immediately, by preventing anaphylactic or significant allergic reactions to small amounts of peanuts in other foods, and long-term, by laying the groundwork for development of an optimal vaccine for peanut allergy. Second, an understanding of the cellular and humoral dynamics following PMIT will allow us to determine if this is an appropriate initial step in the eventual development of a safe and efficacious vaccine/treatment for peanut-allergic subjects. This proposed study would also generate important new pharmacodynamic information about PMIT by targeting newly diagnosed young patients. We believe that the initiation of treatment soon after diagnosis and early in life, as well as the comparison of doses, will generate novel data that are likely to impact the safety and efficacy of future PMIT therapies. Additionally, targeting young populations with PMIT may also generate useful insights about tolerance that could be applied to implementation of primary prevention strategies before peanut allergy develops. If PMIT does not induce complete tolerance, it may be partially effective and useful in augmenting other types of therapy including antihuman IgE or other peanut-specific vaccines. Finally, a better understanding of the immunologic process by which allergen desensitization occurs during PMIT can later be applied to other food allergies.

1. <u>Urgent need for an effective treatment/prevention strategy</u>

It is estimated that over 50% of individuals who are allergic to peanuts will have an accidental reaction to peanuts over a two-year period. Previous studies have examined traditional and rush allergen IT in peanut-allergic subjects. Given the partial rate of response and the high rate of adverse reactions in these studies, and considering the frequent occurrence of accidental peanut ingestion, alternative forms of immunotherapy are necessary for this potentially fatal allergy.

Novel immunotherapeutic strategies designed to alter the immune system's response to food allergens are being examined as potential treatment modalities for food allergy. These include cytokine-modulated immunotherapy, immunostimulatory sequence-modulated immunotherapy, plasmid DNA immunotherapy, allergen-peptide immunotherapy, and "engineered" (mutated) allergen protein immunotherapy. All of these approaches strive to elicit a Th_1-type response or tolerance from the immune system in response to a specific food allergen. Unfortunately all of these therapeutic options are costly, technically demanding, and several years from becoming available to peanut-allergic subjects. Data from our preliminary studies indicate that PMIT is effective in creating a state of desensitization, whereby treatment raises the threshold for clinical reactivity to peanut ingestion. This PMIT-induced change can protect subjects in the event of an accidental peanut exposure, which could be potentially dangerous. *The proposed project is designed to develop a peanut-specific MIT that could be made immediately and readily available to peanut-allergic infants, toddlers, and older children.*

2. Importance of elucidating cellular and humoral mechanisms in order to develop vaccine/treatment

Understanding the cellular and humoral dynamics following PMIT will allow us to determine if this strategy represents an appropriate initial step toward developing a safe and efficacious vaccine for peanut allergy. Even if PMIT does not induce complete tolerance, it may nonetheless be partially effective. Delineating its specific effects on the immune response will enable us to determine its utility and define its role in conjunction with other types of therapy,

Ultimately, we hope to develop a vaccine that lowers the risk of anaphylactic reactions and down-regulates peanut-specific IgE and peanut-specific T and B cells in peanut-allergic children. By specifically targeting patients who are at risk for life-long peanut sensitivity, we intend to develop a therapy that permanently desensitizes patients or that induces long-term immune modulation of their allergic response to peanuts. Beginning PMIT early in life and shortly after diagnosis may promote reshaping of the immune response to peanut prior to the development of long-lasting immune memory. Targeting newly diagnosed subjects early may also permit lower dosing which could improve the safety and effectiveness of PMIT.

3. Relevance of project results for treatment/prevention of other food allergies

If PMIT proves effective, then there is reason to believe that a similar approach could be used to treat individuals with allergies to other common food allergens such as milk, egg, tree nuts, fish, shellfish, wheat, and soy. Additionally, if PMIT is effective in infants and toddlers, and if we can understand the immune responses that cause it to be effective, we will be able to design clinical trials for young children prior to their development of food allergy, to prevent the emergence of food allergy. Mucosal immunotherapy may also modify the systemic responses to non-food allergens and possibly affect the development of new respiratory allergies and asthma, as has been shown for traditional subcutaneous injection immunotherapy in children with dust mite allergy.

SPECIFIC LABORATORY PROCEDURES.

Overview

We hypothesize that PMIT will induce immunologic changes characterized by either (1) a conversion from a Th2 to Th1 response or (2) the induction of regulatory T cells, or both. The specific laboratory procedures are outlined in the section below. In brief, peripheral blood mononuclear cells (PBMCs) will be isolated from whole blood drawn at all time points. PBMCs will be cultured with the major peanut allergen *Ara h 2*, crude peanut extract (CPE), and the positive control Concanavalin A and assessed for proliferative responses to these various stimuli. In addition, supernatants from these stimulated PBMCs will be analyzed for the production of the cytokines IFN-γ, IL-4, IL-5, IL-10, IL-13, TGF-β and TNF-α. In addition to measuring the composite cytokine profile in the circulation, the ELISPOT technique will allow us to follow the cytokine levels of peanut-specific T cells on a per-cell basis over time. Using flow cytometry, we will determine the presence of regulatory T cells in a subject's blood sample from each time point, and we will assess their function with additional coculture techniques. In the event that a subject's blood sample from any given time point does not have enough cells to perform all studies outlined, we will prioritize our studies to focus first on the cytokine and initial proliferation studies, then assessing the presence of T regulatory cells, then functional regulatory T cell assays.

We expect to find one or both of the two patterns described below.

Th2 to Th1 conversion: Protective responses to PMIT mediated by a shift from a Th_2 response to a Th_1 response would be expected to result in decreased concentrations of Th_2 cytokines IL-4 and IL-5, and increased concentration of the Th_1 cytokine IFN-γ in cells cultured at later time points compared to cells cultured at entry. However, Th_2 to Th_1 conversion will result in no significant change in the magnitude of allergen-specific proliferative responses from cells isolated at entry compared to cultures of cells from follow-up time points.

Induction of regulatory T cells: The pattern from the studies described in the overview section that would suggest a role for T regulatory cells would include proliferation data demonstrating hyporesponsiveness of desensitized allergen-specific T cells in conjunction and/or elevated levels of regulatory cytokines (IL-10 and/or TGF-β). If suppression is indeed observed, we will concentrate on the role of regulatory T cells by phenotypic and functional analyses.

Allergy Skin Tests

Allergy prick skin testing with standard 1:20 peanut allergen extract will be performed at the beginning of the study and yearly thereafter. The wheal will be outlined in ink on transparent tape and then transferred to the permanent record. Skin prick testing to environmental allergens (dust mites, cat, grass mix, tree mix, and weed mix) and pecan will be performed at entry into the study and at the end of the study as well.

Skin testing is routinely done in the Allergy Clinic for patients with possible allergies.

Measurement of serum peanut specific IgG and IgE levels

Sera will be collected and stored at –80°C. Levels of peanut-specific IgE and IgG will be measured by ELISA. Briefly, plates will be coated with CPE incubated overnight at 4°C, and then blocked and washed. Samples (1:10 dilutions for IgE, 1:500 dilutions for $IgG_)$ will be added to the plates and incubated overnight at 4°C. For IgE measurement, plates will be washed and sheep anti-human IgE will be added and incubated for 1 h. After washing, biotinylated donkey anti-sheep IgG will be added for 1 h. After washings, avidin peroxidase will be added for an additional 15 min at room temperature. The reactions will be developed and read at 405 nm. For peanut specific IgG measurements, biotinylated rat anti-human IgG_1, and IgG_2 monoclonal antibodies (0.25 g/ml) will be used as the detection antibodies. Subsequent steps will be done as same as those in IgE measurement. Equivalent concentrations of PN-specific IgE and IgG will be calculated by comparison with a generated reference curve.[15] Additionally, a CAP-FEIA (Pharmacia) for peanut specific IgE and IgG4 will de done at each time point.

Stool peanut-specific secretory IgA

We will utilize ELISA assays to evaluate host antibody responses to *Ara h 2* in stool and serum in samples collected before, during and after completion of PMIT. Stool samples will be tested at an initial dilution of 1:4 followed by serial 2-fold dilutions until we are able to determine an endpoint titer. An endpoint titer will be calculated as the last sample dilution that has an ELISA reading (fluorescent relative light units) 3-fold great than the RLU of the same sample tested against ELISA plates that are not coated with antigen. Once the antigen-specific endpoint titers are calculated, we will quantitate the total concentration (µg/ml) of IgA in each stool sample and report the antigen-specific responses as a "titer/µg of total antibody".

Cytokine Measurements

Cells will be collected, isolated, and suspended in complete medium containing RPMI 1640 plus 10% FBS, 1% penicillin/ streptomycin, and 1% glutamine. Cell suspensions will be cultured in 24-well plates (4×10^6 /well/ml) in the presence or absence of *Ara h 2*, CPE (10 µg/ml) or Con A (2 µg/ml). Culture supernatants will be harvested after 24-, 48- and 96-hrs of culture. Levels of cytokines IFN-γ, IL-4, IL-5, IL-10, IL-13, TGF-β and TNF-α will be determined by either Cytometric Bead Array (Becton Dickinson, CA) or ELISA according to the manufacturer's instructions (R&D systems, Minneapolis for IL-13; PharMingen, San Diego for all others). All analyses will be performed in duplicate with cytokine concentrations calculated by comparison with standard curves generated using reference cytokine preparations. Samples will be analyzed on a Bio-Mek 1000 Automated ELISA Workstation or Luminex multiplex analyzer.

Protection from anaphylaxis mediated by conversion from a Th_2 response to a Th_1 response would be expected to result in decreased concentrations of the Th_2 cytokines IL-4, IL-5, and IL-13, and increased measured concentration of the Th_1 cytokine IFN-γ in cells isolated at

entry compared to cultures in follow up every 4 months. Alternatively, protection mediated by tolerance induction would likely result in low levels of all cytokines tested. Elevated levels of IL-10, TGF-β, and or IL-4 in conjunction with proliferation data demonstrating suppression of allergen-specific T cell proliferation in treated subjects would suggest a mechanism of tolerance involving regulatory cells.

T cell phenotype and proliferation

Cells isolated at entry and every 4 months from individual patients will be incubated for 6 days in triplicate (1 x 10^6/well in 0.2 ml complete medium) in the presence or absence of *Ara h 2*, CPE (10 μg/ml) or Con A (2 μg/ml). Cells will then be pulsed for 18 h with 1 μCi [^{3}H] thymidine, harvested, and incorporated radioactivity measured in a β-scintillation counter. Results will be expressed as geometric mean cpm +/- SE with significant proliferation above background ($p<0.05$) determined by a t test. Protection from anaphylaxis due to Th_2 to Th_1 conversion will result in no significant change in the magnitude of allergen-specific proliferative responses from cells isolated at entry compared to cultures in follow up every 4 months. However, protection mediated by tolerance induction will result in diminished proliferation in peanut-desensitized patients. If diminished proliferation is observed, cultures will be setup in the presence of exogenous IL-2 to distinguish whether decreased proliferation is due either to anergy, which should respond to exogenous IL-2, or due to tolerance, which should not. The presence of CD4+ CD25+ FoxP3+ regulatory T cells will be assessed by flow cytometry. Additionally, we will use ELISPOT kits to quantify the number of IL-10+ peanut-specific T cells over time to determine if this inducible Tr1 type of regulatory T cell develops in treated subjects.

PRELIMINARY RESULTS

Preliminary data from current trials suggest that oral and mucosal immunotherapy for food allergy is safe and effective. 28 subjects (mean age 4.8 years) were enrolled in an initial study of unblinded peanut oral immunotherapy at Duke and the University of Arkansas Medical Sciences Center. Comorbid allergic disease was prevalent in this cohort, with 68% having asthma, 64% atopic dermatitis, and 61% allergic rhinitis. 20 of 28 have completed the three phase protocol; four subjects dropped out of the study for personal reasons, one due to the development of eosinophilic esophagitis, and three remain in the build-up or maintenance phase.

The final dose of the initial modified rush desensitization in this study was 50 mg. In this study, the risk of experiencing some symptoms during the initial desensitization was 93%, but most were mild. Three subjects were treated with epinephrine for cough &/or mild wheeze (Tables 1 & 2). **None of the subjects had any cardiovascular symptoms such as hypotension or bradycardia**. Subsequent study designs have capped the top dose on initial desensitization day at 6 mg of peanut to minimize reactions.

The risk of developing any symptoms during subsequent buildup doses at DCRU was less than 50%, and fewer than 2% required any treatment. Home doses were very well-tolerated, with fewer than 1% of over 10,000 home doses requiring any treatment (Tables 1&2).

Table 1: Risk of Symptom Occurrence with 95% Confidence Intervals during the Initial Escalation Day, the Build-up Phase and the Home Dosing Phase

	Initial Escalation Day	Build-up Phase	Home Dosing Phase
Any Symptom	93% (77%, 99%)	46% (37%, 56%)	3.5% (2.3%, 5.1%)
Upper Respiratory	79% (59%, 92%)	29% (20%, 41%)	1.2% (0.6%, 2.5%)
Skin	61% (41%, 79%)	24% (17%, 32%)	1.1% (0.7%, 1.8%)
Abdominal	68% (48%, 84%)	5.5% (3.2%, 9.2%)	0.9% (0.6%, 1.4%)
Chest	18% (6%, 37%)	1.7% (0.6%, 5.1%)	0.3% (0.1%, 0.4%)

Table 2: Frequency of Treatment during the Initial Escalation Day, Build-up Phase and Home Dosing Phase of Peanut Oral Immunotherapy

Treatment	Percent of Initial Escalation Days	Percent of Build-up Doses	Percent of Home Doses
Any	71% (20/28)	1.7% (5/301))	0.7% (67/10,184)
Diphenhydramine Alone	50% (14/28)	1% (3/301)	0.4% (45/10,184)
Albuterol Alone	0%	0%	0.04% (4/10,184)
Diphenhydramine + Albuterol	7% (2/28)	0.7% (2/301)	0.2% (18/10,184)
Diphenhydramine + Epinephrine	11% (3/28)	0%	0%
Diphenhydramine + Albuterol +Epinephrine	4% (1/28)	0%	0.02% (2/10,184)

100% (9/9) of the subjects who have undergone follow-up food challenges after maintenance OIT treatment have become clinically desensitized. Of these nine subjects, six had IgE levels < 2, suggesting they may have become tolerant. 100% (6/6) of these subjects passed a follow-up food challenge after discontinuing treatment, indicating tolerance to peanut. These subjects now freely consume peanut in their diet without symptoms. Median peanut IgE of all subjects treated to date has significantly decreased over time while median peanut IgG4 has significantly increased, indicating that peanut OIT may actively reshape the immune response to peanut. A double-blinded, placebo-controlled PMIT study is currently underway to better assess the contribution of peanut immunotherapy on the immune response, and further mechanistic work is ongoing.

DATA STORAGE AND CONFIDENTIALITY

All records generated during the visits will be stored in the Division of Allergy and Immunology Food Allergy data base or the individual subject's research study binder. The subject's information is accessible only to the investigator or his designated colleagues by individual password or direct viewing of the research record. In addition, patients will be assigned a unique subject identification number that will be used to assure anonymity for any data retained in the research record or stored in the microcomputer. The research records will be kept in a locked closet in the investigator's office suite. Subject information which will be shared with the other institution participating in the research will only be shared using the unique subject identification number. All other identifiers of the subject will be removed prior to the release of the information. If the results of the trial are published, the participant's identity will remain confidential. Study records will be retained until the subject reaches age 21. At that point, any data not in the medical record will be destroyed.

Figure 1. Peanut Study Overall Schematic

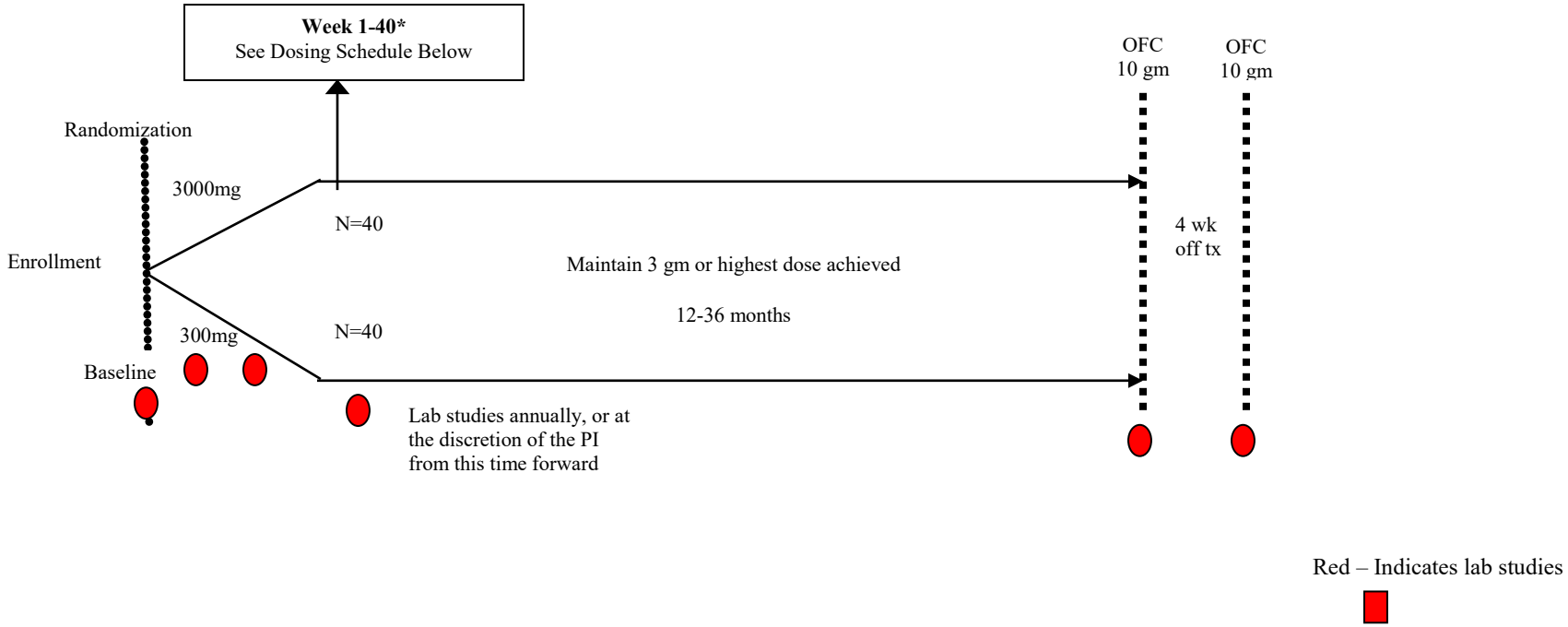

Table 3 – Modified Rush and Daily Home Schedule

Modified Rush – Day One

Dose #	Dose	Interval (minutes)	% Increase
1	0.1mg	30	100
2	0.2mg	30	100
3	0.4mg	30	100
4	0.8mg	30	100
5	1.5mg	30	100
6	3mg	30	100
7	6mg	30	100

Daily Dosing and Increase

Dose #	Dose	Interval (weeks)	% Increase
7	6mg		Rush escalation to 6 mg
8	12mg	2	100%
9	25mg	2	108%
10	50mg	2	50%
11	75mg	2	33%
12	100mg	2	25%
13	125mg	2	25%
14	156mg	2	25%
15	195mg	2	25%
16	245mg	2	25%
17	306mg	2	25%
18	383mg	2	25%
19	479mg	2	25%
20	599mg	2	25%
21	749mg	2	25%
22	936mg	2	25%
23	1170mg	2	25%
24	1463mg	2	25%
25	1829mg	2	25%
26	2286mg	2	25%
27	3000mg	2	31%

Tolerance of Daily Study Protein Dose Diary

Child's Name_____

Date							
Dose taken (Yes or No)							
Accidental ingestion (Yes or No)							

Using the following scale, please enter the appropriate number in each box
0 = None 1 = Mild 2 = Moderate 3 = Excessive

Vomiting							
Diarrhea							
Hives							
Itching							
Runny Nose							
Wheezing							
Other							

Comments:

DEVIL Screening Form

Screening Date_____
Recorded by _____

Informed consent obtained and witnessed prior to obtaining information: Yes No

Copy of informed consent given to parent: Yes No

Name_____ Unit #_____

Parent's Name_____

Address_____

Telephone number that we can personally reach you: (H)_____
(W)_____ (Cell) _____

DOB_____ Age_____ (between 9 and 36 months of age)

Sex: Male Female Race: Afr-American Caucasian Hispanic Other

Weight_____ (lb kg) Height_____ (in cm)

Ever eaten peanut? Yes No Not Sure
Describe reactions to peanut and other foods:
_____
_____

Eligibility Criteria

_____ Subject between 9 and 36 years of age
_____ Peanut allergy diagnosis within the last 6 months: CAP > 0.35 or PST > 3mm with history of peanut ingestion &
convincing IgE-mediated symptoms within 60 minutes
date of reaction: _____
date of testing (and results): PST_____(_____)_ CAP_____(_____)

Or

_____ Probable peanut allergy diagnosis within the last 6 months: CAP > 5 and PST > 3mm with NO history of peanut ingestion
date of testing (and results): PST_____(_____)_ CAP_____(_____)

Exclusion

_____Subjects with a history of severe, anaphylaxis to peanut
_____Medical history that would prevent a DBPCFC/OFC to peanut

Desensitization Day

Initial Medical History & Physical Exam

Subject Name:_____ D.O.B:_____

Subject #_____ Race:_____

Atopic History: (Symptoms, triggers, current treatment, date of onset/diagnosis)

Rhinitis_____

Atopic Dermatitis_____

Food Allergy _____

Drug/Venom allergy_____

Asthma_____

Patient has a current in-date EpiPen
Yes: □ Date expires _____
No: □
Patient was given an EpiPen
Yes: □ Date expires _____
No: □
Episodic symptoms/brief and intermittent with complete clearing/ greater than twice a week/continuous?

_____*Coughing* _____*Chest Tightness* _____*Wheezing* _____*SOB*
Peak Flow:___>80% baseline _____*60-80% baseline* _____*<60%*
*PF variability :*_____
Nighttime symptoms: _____*always* _____*exacerbations only* _____*never*
*ER visits in past 6 months*_____
Exercise symptoms: _____*routine activities* _____*vigorous exercise* _____*none*

Significant Medical History: (Skin/skeletal, neuro, endocrine, respiratory, cardiac, renal, gastrointestinal), Hospitalizations, surgeries

_____

_____

Family History of Atopy: (Immediate family members)

_____

_____

Physical Exam:

General:_____

HEENT:_____

Respiratory:_____

Cardiac:_____

Abdomen:_____

Skin/Extremities:_____

Diagnostic Tests:
PST_____
RAST_____
PFT's _____
Lab_____
Other_____

All Current Medications:

Medication	Dose	Indication

Comments:_____

_____

_____

_____

Study Coordinator Signature:_____date:_____

Investigator Signature:_____date:_____

Follow-Up Visit History
&
Physical Exam

Subject Name:_____ DUMC#_____

Interval History:

_____

_____

_____

_____

Accidental ingestion/reaction: _____

_____

Physical Exam:

General:_____

HEENT:_____

Respiratory:_____

Cardiac:_____

Abdomen:_____

Skin/Extremities:_____

All Current Medications:

Last antihistamine given/indication_____

Medication	Dose	Indication

Comments:_____

_____

Study Coordinator Signature:_____date:_____

Investigator Signature:_____date:_____

DEVIL

Desensitization/ Challenge Sheet

(*Record time in 24 hour clock)

Subject Number_____
Date of visit____/_____/_____ Randomization number: _____

Date of Desensitization____/____/____

Food used for desensitization_____; Use 1 Tablespoon per dose of peanut.

Clock time*	Running time (Minutes)	Amount Food Challenge	***SKIN***				***UPPER RESPIRATORY***				***CHEST***	***ABDOMEN***	
			% Area Rash **IA**	Rash **IB**	Pur. **IC**	Urt/Ang. **ID**	Sneez/ Itch **IIA**	Nasal/ Cong **IIB**	Rhin **IIC**	Laryn. **IID**	Wheeze **IIIA**	Subj Comp **IVA**	Obj Comp **IVB**
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(Continued) **DEVIL**

Desensitization/ Challenge Sheet

(*Record time in 24 hour clock)

Subject Number_____
Date of visit____/_____/_____ Randomization #_____

Clock time*	Running time (Minutes)	Amount Food Challenge	***SKIN***				***UPPER RESPIRATORY***				***CHEST***	***ABDOMEN***	
			% Area Rash **IA**	Rash **IB**	Pur. **IC**	Urt/Ang. **ID**	Sneez/ Itch **IIA**	Nasal/ Cong **IIB**	Rhin **IIC**	Laryn. **IID**	Wheeze **IIIA**	Subj Comp **IVA**	Obj Comp **IVB**
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[1]Mucosaldose approximately doubled every 30 minutes.
[2]If the subject has a clinical reaction to one of the doses, the next dose is the previously tolerated dose.

Skin: + - Time of the initial response after food challenge: _____(minutes)
Respiratory: + - Antihistamine administered Yes No Route: PO IV
GI: + - Epinephrine administered Yes No Route: IM IV
Time (minutes from initiation of challenge):_____

Comments:_____

DEVIL

Dosage Escalation Sheet

(*Record time in 24 hour clock)

Subject Number_____
Date of visit____/_____/_____
Date of Desensitization____/____/____
Randomization #:_____
Current Daily Dose _____
Dose to be given today _____

Food used for dosage escalation_____; Use 1 Tablespoons per dose of peanut.

Clock time*	Running time (Minutes)	Amount Food Challenge	***SKIN***				***UPPER RESPIRATORY***				***CHEST***	***ABDOMEN***	
			% Area Rash **IA**	Rash **IB**	Pur. **IC**	Urt/Ang. **ID**	Sneez/ Itch **IIA**	Nasal/ Cong **IIB**	Rhin **IIC**	Laryn. **IID**	Wheeze **IIIA**	Subj Comp **IVA**	Obj Comp **IVB**
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Comments:_____
_____

Symptom Scoring Sheet for Desensitization, Dosage Escalations, and Oral Food Challenges

I. Skin

A. Erythematous rash - _____% area involved

B. Rash
- 0 Absent
- 1 Mild – few areas of faint erythema
- 2 Moderate – areas of erythema, macular and raised rash
- 3 Severe – generalized erythema (>50%), extensive raised lesions (>25%)

C. Pruritus
- 0 Absent
- 1 Mild – occasional scratching
- 2 Moderate – scratching continuous for more than 2 minutes at a time
- 3 Severe – generalized involvement

D. Urticaria/Angioedema
- 0 Absent
- 1 Mild – less than 3 hives
- 2 Moderate – greater than 3 but less than 10 hives
- 3 Severe – generalized involvement

II. Upper Respiratory

A. Sneezing/Itching
- 0 Absent
- 1 Mild – rare bursts
- 2 Moderate – less than 10 bursts, intermittent rubbing of nose and/or eyes
- 3 Severe – continuous rubbing of nose and/or eyes, periocular swelling and/or long bursts of sneezing

B. Nasal Congestion
- 0 Absent
- 1 Mild – some hindrance to nasal breathing
- 2 Moderate – nostrils feel blocked; breathes through mouth most of the time
- 3 Severe – nose runs freely despite sniffling and tissues

C. Rhinorrhea
- 0 Absent
- 1 Mild – occasional sniffling
- 2 Moderate – frequent sniffling, requires tissues
- 3 Severe – nose runs freely despite sniffling and tissues

D. Laryngeal
- 0 Absent
- 1 Mild – throat clearing, cough
- 2 Moderate – hoarseness, frequent dry cough
- 3 Severe – inspiratory stridor

III. Chest

A. Wheezing
- 0 Absent
- 1 Mild – expiratory wheezing to auscultation
- 2 Moderate inspiratory and expiratory wheezing
- 3 Severe – dyspnea, use of accessory muscles, audible wheezing

IV. Abdomen

A. Subjective complaints
- 0 Absent
- 1 Mild – complaints of nausea or abdominal pain, no change of activity
- 2 Moderate – frequent complaints of nausea or pain, decreased activity
- 3 Severe – patient in bed; crying or notably distressed

B. Objective complaints
- 0 Absent
- 1 Mild – 1 episode of emesis or diarrhea
- 2 Moderate – 2 to 3 episodes of emesis or diarrhea or 1 of each
- 3 Severe- more than 3 episodes of emesis or diarrhea or greater than 1 of each