plasmid and a plasmid containing the IFN-β promoter linked to the luciferase reporter gene. Cells were stimulated with the appropriated ligand and harvested to measure luciferase activity.

RESULTS: Depending on the viral dose used, pDCs produced 1.5 to 3.5-fold higher levels of IFN-α in response to rhMPV- ΔSH compared to rhMPV-WT. Treatment of pDC with chloroquine completely blocked hMPV-induced IFN-α, suggesting the requirement of an intact endosomal compartment for signaling. Expression of isolated SH protein was sufficient to inhibit TLR7-dependent, but not TLR9-dependent gene transcription in 293 cells.

CONCLUSIONS: Our study indicates that hMPV SH protein is a newly discovered inhibitor of IFN type I, likely by targeting the pDC TLR7 signaling pathway.

L5 Serum Levels of Soluble IL6R are Genetically Regulated and Correlate with Lung Function in Asthmatics: Severe Asthma Research Program (SARP)

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RATIONALE: The IL6 pathway is a major regulator of inflammation. Soluble IL6R (sIL6R) can activate the IL6 pathway by binding IL6 and then interacting with constitutively expressed gp130 in cells that do not express IL6R, a process called transsignaling. Increased IL6R serum levels have been identified in several inflammatory diseases and have been associated with the IL6R coding SNP rs2228145 (Asp358Ala).

METHODS: Serum sIL6R levels were measured (ELISA) in asthmatics from the Severe Asthma Research Program (SARP). Relationships between serum sIL6R and IL6R genetic variation (6 IL6R tagging SNPs) and pulmonary function were investigated.

RESULTS: Serum measurements of sIL6R were significantly associated with the coding SNP rs2228145 ($p<10\text{-}12$) and IL6R haplotype pairs ($p<0.0001$) in non-Hispanic whites ($n=100$). Significant associations were also observed in African Americans ($N=17$) for rs2228145 ($p<0.001$) and haplotype pairs ($p=0.034$). Significant differences in serum sIL6R measures were also observed between novel asthma phenotype clusters ($p=0.028$) as defined by SARP (Moore et al, Am J Respir Crit Care Med. 2009(ePub)). Non-Hispanic whites with high serum sIL6R tended to have lower %predicted FEV1, lower (FEV1/FVC)2, lower log PC20, and higher reversibility. Similar trends were observed in African Americans.

CONCLUSIONS: Serum sIL6R, which is genetically regulated, may be an important biomarker to delineate asthma severity. The relationship between trends in pulmonary function measures and sIL6R serum levels is a possible indicator that sIL6R transsignaling might regulate the IL6 pathway in cells such as airway smooth muscle cells, and may influence lung function.

Support: HL69167, HL089992, HL077916, HL87665

L6 Egg Oral Immunotherapy (OIT) Induces Clinical Desensitization in a Double-Blind, Placebo-Controlled (DBPC) Trial in Egg Allergic Children from the Consortium of Food Allergy Research (CoFAR)

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RATIONALE: The goals of our study are to investigate the safety, clinical effectiveness and immunologic effects of OIT for egg allergy.

METHODS: This is a multi-center, randomized, DBPC study in egg-allergic children (5-18 yrs). Subjects were randomized to receive egg white solid OIT (eOIT)($n=40$) or placebo ($n=15$). There were 3 study phases: initial escalation, build-up, and maintenance (2000mg), followed by oral food challenge (OFC) at ~44 weeks to determine the percentage of subjects achieving desensitization to egg (5g).

RESULTS: Fifty-five subjects were enrolled; 7 withdrew from the protocol (5-12.5% eOIT;2-13.3% placebo) before OFC. At the time of OFC, 52.5% eOIT (21/40) and 0% placebo (0/15) passed the 5g OFC ($p<0.001$). Mean cumulative dose consumed at OFC was 4,580±170mg (eOIT) vs. 660±270mg (placebo)($p<.001$). During the OFC, 33 eOIT and 1 placebo ingested >2750mg. Symptoms during dosing phases were mild to moderate with symptom-free dosing reported in 74.87% eOIT (11,802 doses) vs. 96.14% placebo (4014 doses). Predominant dosing reactions with eOIT were oral/pharyngeal (15.46% eOIT; 0.22% placebo) while respiratory, gastrointestinal and skin symptoms were seen less frequently. In eOIT vs. placebo groups, there were significant reductions in egg-IgE levels (mean -12.66 vs. -1.26; $p=0.02$) and egg PST (-6.5mm vs. 0.1mm; $p=0.001$). A significant reduction in basophil activation was seen in eOIT compared to placebo at the time of OFC ($p<0.001$).

CONCLUSION: In this first multi-center trial, eOIT induced clinical desensitization after 44 weeks of treatment, with significant decreases in egg IgE and egg-specific basophil and mast cell responses. Immune profiles and long-term tolerance are being monitored.

L7 Genetic Polymorphisms of NAT2, CYP2C9, CYP2C19, CYP2D6 and CYP2E1, and Antituberculosis Drugs Induced Maculopapular Eruption

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RATIONALE: Cutaneous drug reaction, such as maculopapular eruption (MPE), is one of the major adverse reactions induced by the first line antituberculosis drugs (ATD). Genetic polymorphisms in drug metabolizing enzymes can be closely related with the development of cutaneous adverse reactions induced by ATD as in ATD-induced hepatitis. In this study, we aimed to investigate associations between drug metabolizing enzymes gene polymorphisms and ATD-induced MPE.

METHODS: We compared genotype distributions of single nucleotide polymorphisms in promoter and exons and haplotypes in five drug metabolizing enzyme genes (*NAT2, CYP2C9, CYP2C19, CYP2D6* and *CYP2E1*) between 62 patients with ATD induced MPE and 159 patients tolerant to ATD.

RESULTS: -1565C>T of *CYP2C9* showed significant association with ATD-induced MPE. Frequency of genotypes carrying minor alleles (CT or TT) was lower in case group compared to controls ($P = 0.011$, OR = 0.23, 95% CI 0.07-0.78). Another significant association was found in W212X of *CYP2C19*. Significantly lower number of subjects had GA or AA in patients with ATD induced MPE compared to controls ($P = 0.021$, OR = 0.27, 95% CI 0.09-0.82). In analysis of *CYP2C19-CYP2C9* haplotypes [-1418C>T_W212X_-1565C>T_-1188C>T], ht3[T-A-T-C], carrying both two significantly associated SNPs showed significant association with the development of ATD-induced MPE ($P = 0.004$, OR = 0.13, 95% CI 0.03-0.57). There was no significant association between the other genotypes and ATD-induced MPE.

CONCLUSIONS: These findings suggest that *CYP2C19-CYP2C9* haplotype is significantly associated with ATD-induced MPE and the genetic variants in *NAT2, CYP2D6* and *CYP2E1* are not closely related with the development of this adverse reaction.

L8 Novel Gene-Environment Associations with Diisocyanate Induced Asthma

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RATIONALE: Risk and susceptibility factors for Diisocyanate Asthma (DA) are poorly defined. We used candidate gene approaches to define genetic susceptibility for DA in workers exposed to hexamethylene-(HDI), methylene diphenyl-(MDI) or toluene-(TDI) diisocyanate.

METHODS: DNA was collected from HDI, MDI or TDI exposed symptomatic workers with: DA (n=103) confirmed by specific inhalation challenge (SIC); non-DA defined by negative SIC (n=115). Asymptomatic HDI exposed workers (CTRL) (n=150) were also studied. Genotyping was performed with the following SNPs: IL-4 receptor alpha (IL4RA) (I75V, E400A, Q576R); IL-13 (R130Q); CD14 (C159T); glutathione transferases (GSTP1/Ile-Val, GSTT1/deletion, GSTM1); superoxide dismutase2 (MnSOD/A-V); epoxide hydrolase (EPHX Exon3, EPHX Exon4). DNA microarray was used to assess associations with 52 candidate asthma genes (772 SNPs) using a gene centric analytic approach.

RESULTS: Among HDI workers, workers with DA were more likely to have IL4RA II/CD14 CT (OR=3.1; 95%CI: 1.3, 7.3) and IL4RA II/IL13RR/CD14CT (OR=4; 95% CI: 1.4, 11.6) combined genotypes versus non-DA workers. The same combined genotypes were significantly associated with DA when compared with HDI CTRL workers. The MnSOD/VV genotype was individually associated with DA ($p<0.05$). Microarray data using gene centric analysis revealed three genes associated with DA: hydroxyacid oxidase/HAO1 (p= .01), plasminogen activator inhibitor 1/SERPIN1 (p= .05), and serine peptidase inhibitor B3/SERPINB3 (p=.05).

CONCLUSIONS: Genotype combinations of SNPs associated with Th2 cytokines, anti-oxidant enzymes (MnSOD, HAO1), the innate immune response (CD14), airway remodeling (SERPIN1, SERPINB3), and HDI exposure may define susceptibility to DA.

L9 Effectiveness of Food Allergen Avoidance During Late Pregnancy and Beyond In High Risk Families

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RATIONALE: This study investigated the effectiveness of comprehensive advice given to mothers of food allergic ('index') children regarding dietary and environmental food allergen avoidance during late pregnancy, lactation and beyond, with the aim of reducing the risk of developing food allergy in subsequent children, particularly to peanut.

METHODS: Siblings of 274 index cases were evaluated at age 18 months (N=313) and again at 36 months (N=117). Outcome measures were allergen sensitization (skin prick test $\geq$ 2x2 mm) and symptoms of allergic disease (eczema, asthma). Siblings were divided into an 'avoidance' (A) group whose mothers chose to follow the dietary advice (65% at 18 months; 62% at 36 months), and a 'no avoidance' (NA) group whose mothers maintained an unrestricted diet.

RESULTS: Siblings in group A had a significantly lower prevalence of peanut and egg sensitization than those in the NA group at 18 months (9*vs*37%; 23*vs*50%) and 36 months (16*vs*52%; 34*vs*75%). Group A siblings were also significantly less likely to develop symptoms of asthma at both time points (9*vs*23%; 11*vs*43%). Rates of dust mite sensitization and eczema were reduced at 18 months (14*vs*24%; 49*vs*62%) but not significantly different at 36 months.

CONCLUSIONS: Comprehensive dietary and environmental avoidance measures were shown to significantly reduce the prevalence of peanut and egg sensitization at both 18 months and 3 years of age. Although delayed in onset, dust mite sensitization and eczema were no different by 3 years of age; however there was a persistent and highly significant reduction in asthma.

L10 Efficacy and Safety of Grass Allergy Immunotherapy Tablet (AIT) in a North American Pediatric Population

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RATIONALE: One European sublingual immunotherapy trial with grass AIT has shown efficacy and tolerability in children with allergic rhinoconjunctivitis (ARC). This phase III trial investigated daily administration of SQ-standardized grass AIT (oral lyophilisate, *Phleum pratense*, 2,800 BAU, 75,000 SQ-T, ~15 μg Phl p 5) in a North American grass-allergic pediatric population.

METHODS: 345 children (ages 5-17 years) with grass pollen ARC were randomized 1:1 to once-daily treatment with grass AIT or placebo >8 weeks prior to and throughout the 2009 grass pollen season (GPS). Rescue medications and symptoms were recorded in e-diaries daily from randomization with efficacy measured during GPS. The primary efficacy endpoint comprised the total combined daily symptom score (DSS) and daily medication score (DMS). Secondary endpoints were individual DSS, DMS and the Juniper (pediatric or adolescent) Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). Immunological endpoints included specific IgG_4 and IgE-blocking factor. Safety was assessed by adverse events (AEs).

RESULTS: 89% of the subjects were multisensitized. The AIT group had a statistically significant improvement (26%, $P=0.001$) in total combined score compared to the placebo group. The DSS (25%, $P=0.002$), DMS (32%, $P=0.066$), and RQLQ (mean difference 0.32 (18%, $P=0.028$) also improved for the active group. The majority of treatment-related AEs were local, application site reactions, with no reports of anaphylactic shock.

CONCLUSIONS: This was the first successful phase III trial in North America investigating grass AIT in children. Once-daily administration of grass AIT preseasonally and during GPS is clinically effective, well-tolerated, and may be a new therapeutic modality for children with grass pollen allergy.