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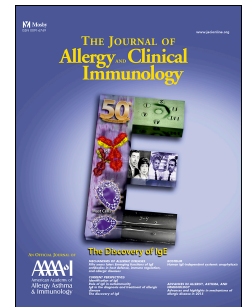
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Editorial:

The future of Allergy/Immunology: Promising Young Investigators

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In a previous report, the AAAAI Task Force on “The Future of Allergy” emphasized the need to foster and encourage young investigators.¹ As Co-Editors-in-Chief, we consider fostering and promoting the development of our junior colleagues as one of our core missions. ² This core value is also shared by the AAAAI Foundation which was established in 1988 as the Education Research Trust (ERT) and began awarding support in 1993. The \$3.25 million awarded to date have generated \$54.25 million in additional research support as of 2016. Many of the awardees have gone on to have stellar academic careers, and were featured in the presidential plenary session at the 2017 AAAAI Annual Meeting in Atlanta, Georgia.

In keeping with this core mission, JACI will begin featuring the research projects of the recipients of the AAAAI “Faculty Development Awards”. By doing so, we hope to help speed their development and success by making the Allergy/Immunology community aware of these amazing young investigators.

In this Editorial, we are giving a platform for the the 2017 AAAAI Foundation Faculty Development Award Recipients to summarize their projects in text and Graphical Abstract. The three recipients are: Lora G. Bankova, MD, Kirsten Kloepper MD, MS and

Timothy P. Moran MD, PhD.

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Lora G. Bankova, M.D (Brigham and Women's Hospital, Harvard Medical School)

(Photograph of Bankova to go here)

Title: "A novel cysteinyl leukotriene pathway for control of epithelial cell differentiation and function."

Cysteinyl leukotrienes (cysLTs) are potent mediators of bronchoconstriction and airway inflammation. Leukotriene E₄ (LTE₄) is the stable cysLT, detected in the biologic fluids of patients with asthma triggered by allergen, aspirin and respiratory viruses. LTE₄ elicits both airflow obstruction and basophil and eosinophil recruitment to the lungs in patients with asthma, which is incompletely blocked by the antagonist to the type 1 cysLT receptor (CysLT₁R). It was hypothesized that the LTE₄ receptor GPR99 controls epithelial cell activation and differentiation in the lung and downstream innate type 2 pulmonary inflammation (Figure 1). Dr. Bankova's research has been planned to include *Alternaria* and LTE₄ models to delineate the role of GPR99 in epithelial cell function and in innate type 2 pulmonary inflammation. GPR99 function will be assessed in patients with aspirin-exacerbated respiratory disease, a cysLT-driven asthma endotype. This will allow the researchers to make inferences about the contribution of GPR99 to human airway disease. Their initial findings now demonstrate that GPR99 regulates type 2 inflammation and inflammation-dependent goblet cell expansion in the lung in response to *Alternaria* or to exogenous LTE₄, suggesting that activation of GPR99 has broad effects on both epithelial cell fate and the development of type 2 immunity.³

Figure 1. GPR99 for the control of epithelial cell differentiation and function.

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Kirsten Kloepper, MD, MS (Indiana University)

(Photograph of Kloepper to go here)

Title: Microbial Influence on Airway Function and Inflammation.

Recurrent wheeze is associated with an overabundance of pathogenic bacteria in the airway often referred to as dysbiosis. Previous studies focused on high-risk infants ≥ 2 months of age and have not utilized metagenomic sequencing to investigate all pathogens (bacteria, viruses and fungi). Delineating the airway in infants within the first weeks of life is critical to define if airway dysbiosis (including bacteria, viruses and fungi): 1) is present at birth or within the first few weeks of life; 2) precedes local inflammatory cytokine expression; and 3) precedes lung function changes. Dr. Kloepper has hypothesized that airway dysbiosis precedes local inflammatory changes and decreases in lung function in infants who subsequently develop wheeze within the first year of life (Figure 2). Her research approach includes the recruitment of two groups of newborns: infants with a maternal history of asthma (high-risk for wheeze), and infants lacking a parental history of asthma, allergies or eczema (low-risk). Nasopharyngeal (NP) swabs and nasal fluid samples are being collected at four time points: birth, one, three and 12 months of age. 16S rRNA sequencing and metagenomics shotgun sequencing are being performed on NP swabs; Luminex Multiplex analysis is being performed to assess cytokine levels in nasal fluid samples. Passive respiratory mechanic measurements assess baseline lung function on all participants at one month of age. At three and 12 months of age, the low-risk group are repeating the passive respiratory mechanic measurements, while the high-risk group are participating in sedated lung function measures that assess forced expiratory flows. Her Preliminary data from the high-risk group (n=10) reveals that decreased airway diversity at 3 months of age is associated with physician diagnosis of wheeze within the first 6 months of life. Infants with decreased diversity of airway bacteria had lower z-scores for FEF₇₅ (median

0.91 vs. -1.24, $p=0.004$); and FEF_{25-75} (median 0.06 vs. -0.85, $p=0.05$); with a trend for significance of $FEV_{0.5}$ (median 0.45 vs. 0.06, $p=0.08$).

Figure 2. Dysbiosis and airway inflammation

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Timothy P. Moran, MD, PhD (University of North Carolina School of Medicine)

(Photograph of Moran to go here)

Title: Role of neuropilin-2 in allergic asthma pathogenesis

Through their ability to inhibit inflammation and induce antigen-specific FoxP3⁺ regulatory T cells (Treg), alveolar macrophages (AM) play a critical role in maintaining tolerance to inhaled antigens. Exposure to allergens and microbial products can activate AM via Toll-like receptors (TLR) and impair their ability to generate Treg. Therefore, AM activation must be tightly regulated, but the key molecules that inhibit pro-inflammatory responses of AM remain elusive. Their group has recently discovered that neuropilin-2 (NRP2), a pleiotropic transmembrane receptor for class III semaphorins and vascular endothelial growth factors⁴, is expressed in human and murine AM following exposure to endotoxin and house dust extracts, which contain a mixture of environmentally-relevant allergens and microbial products. Furthermore, allergen-induced airway eosinophilia is exacerbated in NRP2-deficient mice, suggesting that NRP2 expression by AM is necessary for suppressing allergic inflammation and maintaining airway tolerance. Dr. Moran has hypothesized that NRP2 signaling inhibits TLR-mediated activation of AM and induces expression of suppressive molecules (e.g. TGF-beta and retinoic acid) that promote Treg development, which is necessary for airway tolerance to inhaled antigens (Figure 3). They plan to investigate the ability of NRP2 to suppress AM activation in response to TLR ligands and allergens, and define inflammatory signaling pathways regulated by NRP2. They will determine if airway tolerance is impaired in NRP2-deficient mice, and whether NRP2 signaling is required

for antigen-specific Treg induction by AM. Finally, Dr. Moran is planning to examine the therapeutic efficacy of NRP2 ligands in allergic airway inflammation. It is expected that these studies will explore a previously uncharacterized role of NRP2 in regulating inflammatory responses in the lungs, and may identify a novel therapeutic target for allergic asthma.

Figure 3. Regulatory function of neuropilin-2 in alveolar macrophages

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We offer our congratulations to all three awardees and wish them successful and productive careers. We look forward to their future submissions to JACI.

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