Legends of Allergy/Immunology: Robert P. Schleimer

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Word Count: 1004 words Conflicts of interest: AK reports a consultant fee from Astellas Pharma and a gift for his research from Lyra Therapeutics. WWS served on advisory boards for GlaxoSmithKline, GenenTech, and Bristol Myers Squibb and on a speaker's bureau for GlaxoSmithKline. BSB receives publication-related royalty payments from Elsevier and UpToDate. He receives remuneration for consulting services (Glaxo SmithKline, Sanofi/Regeneron) and for serving on the scientific advisory board of Third Harmonic Bio, Inc. and Allakos, Inc. He also own stocks in Allakos. BSB is a co-inventor on existing Siglec-8–related patents and thus may be entitled to a share of royalties received by Johns Hopkins University during development and potential sales of such products. BSB is a co-founder of Allakos, Inc. which makes him subject to certain restrictions under University policy. The terms of this arrangement are being managed by Johns Hopkins University and Northwestern University in accordance with their conflict of interest policies. *Address correspondence to Atsushi Kato, Ph.D., Division of Allergy and Immunology, Northwestern University Feinberg School of Medicine, 240 E. Huron, Room M304, Chicago, IL 60611 USA.

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Major contributions

- Purification, characterization and function of human lung mast cells (1982).
- Inhibitory effects of glucocorticoids on basophils, mast cells and eosinophils (1981-1991) and other cells during allergic inflammation (1981-)
- Demonstrated that pro-inflammatory cytokines like IL-1 and TNF cause endothelial cells to acquire adhesiveness for granulocytes (1986) while type 2 cytokines selectively induce adherence of eosinophils and basophils, but not neutrophils, to endothelium via induction of VCAM-1 (1992)
- Role of airway epithelial cells in allergic diseases (1995-)
- Understanding pathogenesis of chronic rhinosinusitis (2005-)
- Mentorship of over 50 trainees including more than 10 full professors

This issue honors Robert (Bob) Paul Schleimer, PhD for his scientific accomplishments. Bob has been studying the mechanisms of inflammation, especially in the context of disease of the airways of humans, for over 40 years and is a world-renowned expert on the role of immune and structural cells in type 2 inflammatory diseases including asthma, allergic rhinitis and chronic rhinosinusitis (CRS). Bob was born on

April 8, 1952 in New York City. He received his PhD in pharmacology and toxicology at the University of California, Davis in 1980 followed by a postdoctoral fellowship at The Johns Hopkins University School of Medicine under the primary mentorship of Dr. Lawrence Lichtenstein. Bob first became interested in the role of basophils and mast cells, key effector cells in the allergic response. Importantly, Bob was on the team that developed the first method to purify human mast cells from lung tissue. For over 30 years Bob has studied basophils and mast cells and published many important and impactful papers describing the regulation of their signaling, activation and products especially in human allergic diseases.

One of his key contributions to this field was the discovery of the action of glucocorticoids in allergic reactions. Bob was the first to demonstrate that glucocorticoids inhibit human basophil-mediated, but not mast cell-mediated, allergic release of histamine (Figure 1).[1,2] This very important finding explains why glucocorticoid treatment does not interfere with the allergen-induced immediate early phase response by mast cells but does inhibit the basophil's contribution to the late phase response. Bob has continued to study the mechanisms of action of glucocorticoids in allergic diseases for over 30 years as a principal investigator in NIH research grants and received a MERIT award focusing on this subject.

Recruitment of leukocytes by adhesion and migration is a key event to induce an inflammatory cascade. Bob was the first to show that cytokines including TNF and IL-1 cause endothelial cells to acquire adhesiveness for neutrophils.[3] This important finding ultimately led other groups to clone endothelial adhesion molecules such as E-selectin and VCAM-1. Together with one of his early mentees Bruce Bochner, Bob then focused on the mechanisms of selective recruitment for eosinophils and basophils in allergic diseases and identified several important mechanisms such as the fact that IL-4 and IL-13 selectively induced VCAM-1 on endothelial cells, a ligand for VLA-4 on eosinophils and basophils but not neutrophils.[4] His laboratory was the first to characterize the adhesion molecules and chemokines that mediate transendothelial migration, including work by Motohiro Ebisawa and others.[5] These findings contributed to the rationale for drug discovery that targeted CCR3, IL-4, IL-13, IL-4Rα, VCAM-1 and α4 integrins (ligands for VCAM-1). Indeed, many such drugs are under development or are already approved for the treatment of allergic and other diseases.

In the mid 1990s, Bob continued to explore chemokine biology and began to focus on the role of airway epithelial cells in allergic diseases. Besides working with Lisa Beck to show that RANTES caused eosinophil accumulation in the skin, his lab was actually among the first to describe epithelial cells as important producers of chemokines including MCP-4 (discovered by Cristiana Stellato in the Schleimer laboratory), RANTES and eotaxin.[6,7] His laboratory also found that type 2 cytokines, especially in the presence of proinflammatory cytokines, induce expression of MCP-4 and eotaxin as well as an adhesion molecule VCAM-1 in airway epithelial cells. Expression and induction of these molecules in epithelial cells are now widely recognized as an essential event in leukocyte recruitment in both physiological and disease situations. Bob's group also made the important observation that glucocorticoids enhanced innate immunity and host defense molecules in airway epithelial cells while they reduced pro-inflammatory mediators. In addition, his laboratory was among the first to describe that airway epithelial cells are an important source of cytokines including BAFF, TSLP and IL-36 that directly and indirectly activate innate and adaptive immune cells and participate in several airway diseases, including work by Atsushi Kato.

In the late 1990's, the Schleimer laboratory, once again working together with Bruce Bochner's laboratory, co-discovered Siglec-8 (or sialoadhesin factor-2, SAF-2).[8] Siglec-8 is selectively expressed on human eosinophils and mast cells, and the engagement of Siglec-8 with a monoclonal antibody or its natural ligands induces the death of eosinophils and inhibits mast cell degranulation. Anti-Siglec-8 antibody (AK002, lirentelimab) is currently in clinical trials for several eosinophilic disorders.[9]

In 2004, Bob moved to Northwestern University Feinberg School of Medicine and became the chief in the division of Allergy and Immunology and a Roy & Elaine Patterson Professor of Medicine. Although there was only a CLIA laboratory in this division before his arrival, Bob successfully recruited multiple faculty members and developed several research laboratories in this division. Bob, together with Dr. Robert Kern, a surgeon and Chairman of the Department of Otolaryngology, developed the Sinus and Allergy Center at Northwestern to focus on translational research in chronic rhinosinusitis (CRS). At the time, basic research

in CRS was far behind compared to other airway inflammatory diseases including asthma and allergic rhinitis especially in the US. Bob contributed to the CRS field for 16 years and has published over 100 manuscripts on CRS.[10] He also currently serves as the program director for the Chronic Rhinosinusitis Integrative Studies Program funded by NIH/NIAID. Bob is now one of the key leaders in this field in the world.

Dr. Schleimer has published over 390 peer-reviewed papers with an H index of 88 and has been recognized by the ISI as being among the top 0.5% of the most highly cited investigators over the last 20 years. He actively contributes to research on the mechanisms of allergic diseases and chronic rhinosinusitis, and true to his background in pharmacology, several of his discoveries served as underpinnings for drug development in allergic and other diseases. Between his time at Johns Hopkins and at Northwestern, he trained over 50 highly successful scientists, many of whom are full professors and leaders in Allergy/Immunology/Respiratory/Dermatology fields throughout the world. His impact on current and future generations of physicians and scientists will be long-lasting.

Figure Legends

Figure 1. Glucocorticoids inhibit basophil-mediated but not mast cell-mediated release of histamine upon IgE-mediated activation in humans.

Inhibition of basophil histamine release by triamcinolone acetonide (closed triangle), dexamethasone (open circle), 9α-fluorocortisone (open square) and hydrocortisone (closed circle) is shown (A) (from reference 1). Incubation for 24 hours with 10^{-6} M dexamethasone had no inhibitory effect on the release of histamine from anti-IgE stimulated human lung mast cells (B). Result (B) was adapted from reference 2.

Photo

Robert Schleimer (center) with Bruce Bochner (left) and Lawrence Lichtenstein (right) in 2013.

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