

**NOMINATION COVER SHEET**

2016 Virginia Outstanding Faculty Awards

<p>1. <u>NAME</u>                  Full (Legal): Lawrence B. Schwartz, M.D, Ph.D. Preferred First Name: Larry</p>	
<p>2. <b><u>INSTITUTIONAL INFORMATION</u></b>                  Institution: Virginia Commonwealth Univ                  Rank/Position Title: Charles &amp; Evelyn Thomas Professor of Medicine and Chair, Division of Rheumatology, Allergy &amp; Immunology                  Year Rank/Title Attained: 1989                  Years at Institution: 32                  Campus Email Address:                  Campus Phone: 828-9685                  Campus Mailing Address: Box 980263                  Campus Communications Contact:                  -Name:                  -E-mail:</p>	<p>3. <b><u>PROFESSIONAL INFORMATION</u></b>                  Academic Discipline: Medicine                  Specialization/Field: Microbiology &amp; Immunology, Pediatrics                  Type of Terminal Degree: M.D. Ph.D.                  Year Awarded: 1976 (Medicine, Biochemistry)                  Awarding Institution: Washington University</p> <hr/> <p>4. <b><u>PERSONAL INFORMATION</u></b></p>

***Please check only one box:***

- RESEARCH/DOCTORAL INSTITUTION NOMINEE: XX**  
**MASTERS/COMPREHENSIVE INSTITUTION NOMINEE:**   
**BACCALAUREATE INSTITUTION NOMINEE:**   
**TWO-YEAR INSTITUTION NOMINEE:**   
**RISING STAR NOMINEE:**

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## **EXCERPTS FROM MISSION STATEMENT**

### **Excerpted Mission Statement of Virginia Commonwealth University**

As the premier urban, public research university in Virginia, VCU's mission is to advance knowledge and student success through its commitments to:

- an engaged, learner-centered environment that fosters inquiry, discovery and innovation in a global setting;
- research that expands the boundaries of new knowledge and creative expression and promotes translational applications to improve human health;
- interdisciplinary collaborations that bring new perspectives to complex problems and mobilize creative energies that advance innovation and solve global challenges;
- health care that strives to preserve and restore health for all people, to seek the cause and cure of diseases through groundbreaking research, and to educate those who serve humanity;
- diversity that provides a climate of inclusion, a dedication to addressing disparities wherever they exist, and an opportunity to explore and create in an environment of trust;
- sustainable, university-community partnerships that enhance the educational, economic and cultural vitality of the communities VCU serves in Virginia and around the world.

## SUMMARY OF ACCOMPLISHMENTS

Lawrence Schwartz, MD, PhD, the Charles and Evelyn Thomas Professor of Medicine and Chair of the Division of Rheumatology Allergy and Immunology, is an innovative and leading translational research investigator who has made fundamental discoveries about mast cells and basophils, publishing over 350 manuscripts, and bringing his bench discoveries to the bedside. Noteworthy accomplishments include the discovery of human  $\alpha/\beta$  tryptases, proteases selectively expressed by mast cells, creation of clinically useful immunoassays for tryptases as biomarkers of disorders involving mast cells, development of in vitro conditions for the differentiation of human mast cells from progenitors and for culturing tissue-derived human mast cells, and the identification of two types of human mast cells. **His assay for total tryptase is now used throughout the world to facilitate the diagnosis of systemic mastocytosis (a WHO criterion and FDA approved for this purpose). Importantly, by bringing greater sensitivity and precision to screening for mastocytosis with a simple blood test, this disorder has revealed itself in many patients for whom this problem might otherwise have remained undiagnosed. The assay is also used to help diagnose systemic anaphylaxis, a severe allergic reaction, with greater precision than previously possible.** His contributions as Program Director of Allergy and Immunology from 1983-2014 exemplify his excellence in teaching, and his service activities both within the VCU community, and for national and international organizations frame his excellence in service

Dr. Schwartz has been recognized by VCU by with an endowed chair and awards for research (Triennial Award for Sustained Research Excellence, Internal Medicine, 1998) and innovation (VCU Billy R Martin Innovation Award 2008); nationally by his research grants, including continuous NIH funding for over 30 years, including an NIH MERIT award, and most recently as the recipient of the 2015 Distinguished Scientist Award from the American Academy of Allergy Asthma and Immunology ([www.AAAAI.org](http://www.AAAAI.org)) and the 2015 Scientist of the Year Award from the European Competence Network on Mastocytosis ([www.ECNM.net](http://www.ECNM.net)). He has been elected to honorary societies, i.e., the American Society for Clinical Investigation and the Association of American Physicians, and to leadership positions, i.e., Chair of the American Board of Allergy and Immunology (2001; [www.ABAI.org](http://www.ABAI.org)), President of the Clinical Immunology Society (2011-12; [www.clinimmsoc.org/](http://www.clinimmsoc.org/)), Chair of the AAAAI Program Directors Assembly (2010-12) and Grant Review Committee (2002-7), and Chair of the NIH Immunological Sciences (1992-4) and NIAID Inner City Asthma Consortium (2002) study sections; and internationally by his numerous invitations to lecture and collaborate.

### Teaching

For Dr. Schwartz, formal teaching occurs at VCU in the classroom, laboratory and clinic, and outside of VCU in lectures, seminars, workshops and debates. He has taught the immunology of hypersensitivity disorders to both graduate and medical students, and advanced immunology to graduate students, and developed video presentations of patients describing either their rare (x-linked agammaglobulinemia; i.e., genetically unable to make their own antibodies to fight infections) or their common (asthma) immunologic disorder that were shown to medical students during immunology. By caring for patients with disorders involving mast cells, such as anaphylaxis, as well as being involved in both research and the development of guidelines for such disorders, he brings a unique educational perspective to the classroom.

In the laboratory he has mentored 3 graduate students, about 35 postdoctoral/clinical fellows, research faculty and visiting scholars in research related to mast cells or basophils. He served a

sponsor for three K awardees. Anne-Marie Irani, MD, (K08), Wei Zhao, MD, PhD, (K08) and Greg Gomez, PhD (K01). Drs. Irani and Zhao both serve on the faculty at VCU in the Department of Pediatrics. Dr. Gomez is now an Assistant Professor at the University of South Carolina. Chris Kepley, PhD, now an Associate Professor at the Joint School of Nanoscience and Nanotechnology, Greensboro, NC, as a graduate student developed the first monoclonal antibody (mAb) that selectively detects human basophils. Marianna Castells, MD, PhD, who as a fellow made key observations on human mast cells and basophils, is now an Associate Professor of Medicine at Harvard's Brigham and Women's Hospital where she is internationally renowned for her work on immunologic desensitization of mast cells. Joud Hajjar MD, Kelly Maples MD, Karen Demuth MD, and Rand Arnaout MD, each of whom completed a fellowship in Allergy/Immunology at VCU, have been recruited to faculty positions as clinician-educators at Baylor (Houston), Kings Daughters Hospital (Norfolk), Emory (Atlanta) and King Faisal (Saudi Arabia) Hospitals, respectively. Dr. Schwartz's caring and effective mentorship is reflected by the fact that 3 of the 4 faculty in the Allergy/Immunology program at VCU (not including himself) have been trained by him and elected to remain at VCU to pursue their academic careers.

In the clinical setting, Dr. Schwartz has mentored residents and fellows since 1983, teaching about common allergic diseases, such as asthma, rhinitis, dermatitis, conjunctivitis, anaphylaxis and drug allergy, and also about rare immunologic disorders, such as primary or iatrogenic immune deficiencies, autoimmune chronic urticaria, hereditary angioedema due to a deficiency of C1inh, hypereosinophilic syndromes and mastocytosis/mast cell activation syndromes. His students have benefitted from patients coming to VCU from across the US and the world to be evaluated by Dr. Schwartz, as he is a recognized international expert in the diagnosis and treatment of hypereosinophilic disorders and systemic mastocytosis. As such, VCU has been designated a "Center of excellence for systemic mastocytosis. During his 31-year tenure as Program Director for Allergy/Immunology from 1983-2014, 100% of allergy/immunology residents passed their ABAI certification examination on their first attempt, compared to a national average of 89%.

Dr. Schwartz has presented on numerous occasions at the weekly Rheumatology Allergy and Immunology journal club and grand rounds conferences, aimed at fellows, residents and faculty, departmental grand rounds on topics of common interest to the Departments of Internal Medicine, Dermatology, Oral and Maxillofacial surgery, and to the Cancer Center. He has presented seminars and spoken at grand rounds outside of VCU over 100 times. In 2015, this includes Allergy Grand rounds at Johns Hopkins University, Boston Citywide Allergy Grand Rounds, Allergy/Immunology Grand Rounds at Mount Sinai Hospital in New York, the Genentech Immunology Discovery Seminar in South San Francisco, and the Swineford Conference at the University of Virginia; plenary international lectures at a Symposium to honor Paul Ehrlich at the University of Vienna in Austria, at the European Competence Network on Mastocytosis in Munich, Germany, and at the European Mast Cell and Basophil meeting in Marseille, France. Previous lectures of note have been the Jerry Dolovich Memorial Lecture at the AAAI (2011), The Karolinska Nobel Forum on Mast Cells in Karolinska (2010), and keynote speaker at the Australian Society of Clinical Immunology and Allergy in Adelaide, Australia (2009).

## **Discovery**

Dr. Schwartz is recognized internationally as a leading investigator of human mast cells and basophils. With over 350 publications, being named an ISI Highly Cited Researcher in 2001 and having had continuous NIH funding for over 30 years, his productivity has been outstanding. When entering into the field of mast cells in 1978, mast cells were known to store histamine and heparin in cytoplasmic secretory granules, which were released when these cells were

sensitized with IgE and activated with the allergen recognized by that IgE. Dr. Schwartz began to ask questions about mast cells such as what tools were needed to better understand when and how mast cells participate in human biology and disease, and what other attributes mast cells had that distinguished them from other cell types.

In 1978, to study mast cell activation and degranulation, the amount of histamine released by such cells was measured by using fresh ileum (small bowel) obtained from guinea pigs, and measuring the strength of the smooth muscle contraction, a bioassay that was tedious and variable, and required the sacrifice of numerous guinea pigs. Dr. Schwartz found that in addition to histamine, secretory granules of rat mast cells contained abundant amounts of the enzyme called  $\beta$ -hexosaminidase, an enzyme that could be measured using a commercial chemical substrate, permitting rapid and quantitative measures of the release of  $\beta$ -hexosaminidase as a biomarker for mast cell degranulation. He then extended this assay to measure degranulation from human lung mast cells. After Dr. Schwartz's two publications with rat and human mast cells, most mast cell research labs throughout the world soon abandoned the cumbersome histamine bioassays for the  $\beta$ -hexosaminidase enzyme assay to measure mast cell degranulation in vitro.

Dr. Schwartz then decided to focus his attention on the human rather than the rat experimental system, because he thought this was feasible and more relevant to the human condition. A key experiment was to compare to protease activities released by rat mast cells to those of human. Rat peritoneal mast cells released primarily chymotrypsin-like activity, whereas human lung mast cells released trypsin-like activity. Utilizing skills of protein purification learned in graduate school, Dr. Schwartz purified the enzyme responsible for the trypsin-like activity to homogeneity, naming it tryptase, and showing that tryptase was released from human lung mast cells in parallel with histamine and  $\beta$ -hexosaminidase, providing another biomarker for mast cell degranulation. This observation led him to ask whether this tryptase was unique to mast cells, or, like  $\beta$ -hexosaminidase, present in other cell types.

To answer this question Dr. Schwartz utilized the then relatively new field of monoclonal antibodies (mAbs) to make an anti-human tryptase mAb that would specifically recognize tryptase. Once such mAbs were made, it appeared that only mast cells contained significant amounts of tryptase. This meant that if tryptase levels could be precisely measured in serum or other body fluids, they would provide a means of assessing mast cell activation occurring in vivo. Accordingly, Dr. Schwartz developed assays using one mAb attached to a solid surface to capture tryptase in solution, and another non-competing anti-tryptase mAb for detection. Early data indicated that tryptase levels in serum, nasal or bronchial lavage fluid or tears were elevated when mast cells were activated compared to baseline levels in normal control subjects. Furthermore, baseline serum levels were also elevated in patients with a clonal mast cell disease called mastocytosis.

Subsequently, Dr. Schwartz led his laboratory's effort to clone tryptase cDNAs, and found two types, reflecting what became known as the  $\alpha$ -tryptase and  $\beta$ -tryptase genes, about 90% identical to one another at the DNA and protein levels. Both genes led to the formation of an immature protryptase that could be converted to mature tryptase. It turned out that one of the tryptase immunoassays recognized only mature tryptase, while all of the others recognized both mature and pro forms of the enzyme. In the 1990s, VCU licensed the tryptase immunoassay technology to Pharmacia Diagnostics, a company in Uppsala, Sweden, which is now part of Thermofisher. VCU's Innovation Gateway Office continues to collect royalties from

ThermoFisher, and shares them with Dr. Schwartz. In addition to the tryptase assay licensed to ThermoFisher, the Dr. Schwartz has produced mAbs used to recognize various proteins in mast cells and basophils that have been licensed to Millipore Pharmaceutical Co., Santa Cruz, Biologend, Hycult, and eBiosciences, also through the VCU Innovation Gateway Office.

**The current assay, which measures all forms of tryptase, sometimes called the total tryptase assay, is currently used by clinicians and clinical investigators throughout the world to assess mast cell involvement in various clinical situations.** Levels in healthy subjects range from 1 to 11 ng/ml in serum. Both the WHO and the FDA have endorsed its use in the diagnostic workup of systemic mastocytosis, whereby baseline levels greater than 20 ng/ml meet one of the four minor diagnostic criterion. Having a precise biomarker detectable in peripheral blood, reflecting the mast cell burden, when elevated raises the suspicion of mastocytosis, providing justification for a bone marrow biopsy, and leading to the diagnosis of mastocytosis in many patients who otherwise might have remained undiagnosed with unexplained symptom of dizzy spells, brain fog, episodic diarrhea, flushing or pathologic bone fractures. Further, the tryptase assay provides a surrogate marker for chemotherapy effectiveness, declining tryptase levels reflecting a reduced mast cell burden in systemic mastocytosis. Another important application of the serum tryptase assay is its inclusion in consensus guidelines from the Allergy and Immunology professional societies for the diagnosis of systemic anaphylaxis (a severe allergic reaction), whereby acute levels in blood drawn within 4 hours of the clinical event should be equal to or greater than  $2 + 1.2 \times \text{baseline tryptase level}$  to be considered clinically significant and consistent with a mast cell activation event. Using this formula, the specificity of the tryptase measurement for systemic anaphylaxis is very high, and has been particularly helpful when the severity of the reaction is high, when the allergen is administered parenterally, e.g., insect sting or intravenous drug administration, and when the blood is collected 30-60 min after the acute event. On the other hand, the sensitivity of the assay is low when the clinical severity of low, when the trigger is food allergen ingestion and when the time of blood collection is greater than 4 hours after the acute event.

Tryptase levels at local sites has also been used to assess mast cell involvement. High levels of tryptase in bronchoalveolar lavage fluid have been instrumental in showing mast cell activation in asthma and during adenosine- and exercise- induced bronchospasm. High levels in tears in allergic conjunctivitis or after an allergen challenge, in nasal fluid of subjects with allergic rhinitis or after an allergen challenge, or in skin blister fluid after an allergen challenge have been used to show mast cell activation at these sites.

Dr. Schwartz has also led his laboratory in making fundamental contributions to understanding human mast cell biology and the biochemistry of tryptase. Techniques were developed to grow human mast cells from fetal liver or cord blood progenitors. Human mast cells in culture have been used to study desensitization, a procedure allergists use to induce tolerance in a patient allergic to a particular drug, to understand why adenosine administered to patients causes wheezing but not hives, i.e., mast cell activation in the lungs but not in the skin, and to study the response of mast cells to IgG complexes. Most recently, Dr. Schwartz's graduate student, Sahar Lotfi-Emran, and fellow, Brant Ward, MD, PhD, discovered that human mast cells could be transformed by interferon- $\gamma$  to a cell expressing MHCII and co-stimulatory molecules, becoming capable of taking up, processing and presenting antigen to T cells. These findings have opened up a new area of research into the biologic role of mast cells in human immunology, namely that mast cells can contribute to the development of immunity as well as causing allergic reactions.

Techniques were also developed using mAbs to identify two types of human mast cells, named MC<sub>T</sub> and MC<sub>TC</sub>, initially based on differences in the expression of human chymase, cathepsin G and carboxypeptidase A3, but later extended to include different responses to the complement anaphylatoxins C3a and C5a, to adenosine, and to positively charged proteins and drugs. These techniques are now used by researchers around the world to identify the type of mast cell involved in a specific diseased tissue.

Although tryptase was initially purified by standard chromatographic techniques, one of the low affinity anti-tryptase mAbs has been used since then to purify tryptase from human tissues, mostly lung or skin. Furthermore, different forms and types of recombinant human tryptases have been expressed in a standard insect system. Dr. Schwartz's laboratory showed that protryptases are converted to mature tryptases predominantly by cathepsins B or L, that conversion of tryptase monomers to tetramers is reversible, and that tryptase tetramers and monomers exhibit much higher proteolytic activities at acidic (pH 6) than neutral (pH 7.4) pH values.

Another exciting development was the demonstration by Dr. Schwartz that one of his anti-tryptase mAbs is a highly potent and specific non-competitive inhibitor of tryptase, raising the possibility of potential therapeutic effects in mast cell-mediated diseases. Indeed, a pharmaceutical company has recently signed a licensing contract with VCU's Innovation Gateway Office to humanize this murine mAb, such that its use can be tested in humans as an inhibitor of tryptase activity, specifically targeting diseases such as asthma, where tryptase is over-secreted in and around the asthmatic airways.

In summary, it is clear that Dr. Schwartz's outstanding productivity in the research arena has led to lasting contributions that have significantly improved the care of patients with mast cell-mediated disorders as well as in the sharing of reagents and techniques helpful to researchers around the world.

### **Knowledge Integration**

Dr. Schwartz's activities in teaching, discovery and service have had a substantial impact on the broader knowledge base. His teaching of clinical fellows over the past 30 years, practitioners who have carried the knowledge, professionalism and self-learning skills from VCU to their postgraduate endeavors, fulfills the mission to educate those who serve humanity to improve human health. His service activities on professional and lay organizations, national and international committees to develop diagnostic or therapeutic guidelines, and VCU committees to foster research, education and discovery facilitate the mission of knowledge integration as well. Given his expertise on mast cells, he has written multiple review articles for journals and books on topics within the field of allergy and immunology. For example, he has written the chapter on anaphylaxis for the last three editions of Cecil's Textbook of Medicine and a chapter in UpToDate on the Use of Laboratory Tests to Support the Clinical Diagnosis of Anaphylaxis, providing information that is taught to physician educators, clinicians and investigators throughout the world. Dr. Schwartz's discovery and development of tools to identify mast cells and basophils, to measure tryptase levels that help diagnose mastocytosis or anaphylaxis, and to potentially inhibit tryptase activity in asthma, have extended his research work well beyond his laboratory, expanding the boundaries of new knowledge and reflecting translational research that has improved human health through more precise and accurate diagnostic tests and, potentially, of a new therapeutic intervention. Leading a group of talented investigators from the

Department of Biology in the College of Humanities and Sciences and from Internal Medicine, Biochemistry, Pediatrics and Microbiology & Immunology in the School of Medicine, VCU successfully competed for a prestigious 5-year \$7 million NIH-sponsored Asthma and Allergic Diseases Cooperative Research Center award in 2008, integrating research from five departments through interdisciplinary collaborations and conferences with Dr. Schwartz being the Principal Investigator.

### **Service**

In addition to excellence in service related to research and educational activities, Dr. Schwartz has contributed countless hours to serving the University as well as the Allergy/Immunology Specialty and the community. At VCU, he has served as chair of the Division of Rheumatology Allergy and Immunology in the Department of Internal Medicine since 2000, as Director of the adult Allergy/Immunology clinics since 1983, as the VCU Allergy/Immunology Program Director from 1983 to 2014, on the VCU Research Advisory Council from 1996-2003, as chair for the School of Medicine ABIM Physician-Scientist program from 2008-2011, as chair of the School of Medicine Sponsored Research Advisory committee since 1999, and as a member of the MD, PhD Program Committee (1987-95, 1998-2000, 2003-present). He was the Principal Investigator and Director of VCU's NIH-funded Asthma & Allergic Diseases Cooperative Research Center from 2008-2014.

On a national level, Dr. Schwartz has served on 15 different NIH study sections, chairing two of them; and on 5 NIH task forces. Dr. Schwartz also has served on editorial boards for the Journal of Immunology (1986-93, Section Editor 1997-2001), Journal of Clinical Immunology (1993-96), Clinical and Experimental Allergy (1988-2000), Journal of Allergy and Clinical Immunology (2010-13), and Journal of Clinical Immunology (Associate Editor, 2011-Present). Dr. Schwartz has reviewed numerous manuscripts from about 20 journals, including the New England Journal of Medicine, Immunity, Journal of Clinical Investigation and Journal of Experimental Medicine.

For the American Academy of Allergy Asthma and Immunology, Dr. Schwartz has served on their Board of Directors (2000-2003), and as a member of the Program Directors Board (2007-14, President 2010-12), Xolair-Associated anaphylaxis committee (2008-9), PRACTALL on anaphylaxis (2007) and on exercise-dependent asthma and anaphylaxis (2008) committees, member of the cells and cytokine committee (1992—present), anaphylaxis committee (2006-present), grant review committee (2008, 2010-present), J Allergy Clin Immunol Liaison committee (Chair, 2002-8); and the annual meeting Program Committee (1988-9).

Dr. Schwartz's service activities extend to the community where he has served on the board of directors of the Asthma & Allergy Foundation of America (2008-13), a lay organization representing those with asthma and allergic diseases, chairing their research program and their grant review committee, and currently serving on their Medical-Scientific Research Council. For the Mastocytosis Society, a lay organization representing people with mastocytosis and mast cell activation disorders, he serves on the Medical Advisory Board. He also served on the Virginia SIDS Alliance Board of Directors (1996-7), and the Board of Directors of the Richmond Montessori School (1987-95).

## PERSONAL STATEMENT

When I arrived at VCU in 1983, my primary goals were to develop a strong research program and to strengthen an existing fellowship program that trains physicians in Allergy and Immunology. Also, I wanted to provide excellent care for patients with allergic and immunologic disorders and to teach graduate and medical students about such disorders and the science behind them. These goals fit with the current mission statement of VCU as a public research university, including to foster 'discovery and innovation in a global setting', 'research that...promotes translational applications to improve human health', 'interdisciplinary collaborations', and 'health care that strives to preserve and restore health for all people, to seek the cause and cure of diseases through groundbreaking research, and to educate those who serve humanity'.

**Teaching:** An early challenge in my career was to improve the existing fellowship program in Allergy and Immunology, which was struggling with less than half of the trainees able to pass their board certification exam at first try. I was proud and gratified to witness the success of teaching initiatives I put in place. Indeed, all fellows who have trained in Allergy and Immunology under my direct supervision over the past 30 years were certified by the American Board of Allergy and Immunology after their first attempt at passing the certification exam, enabling them to practice this medical discipline as board-certified specialists. Several techniques may have led to this accomplishment, each engaging fellows to learn from active involvement. Fellows chose and presented two journal club articles per week, one from among the top clinical journals, the other covering basic science articles related to the discipline, again from the highest impact journals. For each of the clinical journal club articles, fellows were asked to write a board-type 'stump the chump' question— me being the chump, who would critique and try to answer the question. Fellows were strongly encouraged to enroll in and complete the basic immunology class for graduate students. Fellows were presented with various projects and asked to identify the research questions they were most interested in answering. Most importantly, the door to my office was open any time the fellows had questions, whether related to patient care, journal articles or research. I believe that these strategies work better than simply lecturing our trainees on what one thinks they need to know or providing them with reading assignments. Further, while in training, fellows were appreciative of their opportunities to see patients with rare disorders, such as mastocytosis, as well as more common problems such as asthma, which allowed them to easily adapt to various postgraduate clinical settings and be prepared to provide the best possible care for their patients.

**Discovery:** When I began to study mast cells as a fellow-in-training at Harvard, a cell that resides in body tissues, not in the circulation, it became clear that one could consider this cell type to be the organ of allergy, just as the heart is to cardiology. However, there were no precise laboratory tests to detect mast cell involvement in various disorders, leaving their clinical diagnosis somewhat vague. Also, only about 20% of the population has allergic diseases, even though everyone has mast cells – what roles do these cells play outside of allergic reactions? I presumed that potential biomarkers of mast cells could identify disorders of mast cell activation, e.g., anaphylaxis with fainting from low blood pressure, or of increased numbers of mast cells, e.g., mastocytosis, with greater precision than vague symptoms. Of the numerous enzymes I found to reside in human mast cells, I focused on tryptase because of its preferential expression by this cell type, its presence in all mast cells, and its great abundance in mast cells. Also, the unique tetrameric structure I discovered protected it from biologic protease inhibitors,

allowing it to be detected in the circulation for hours after its release from mast cells. The result was an FDA approved tryptase assay which is commercially available and used by clinicians and researchers around the world. I discovered techniques to develop human mast cells from progenitor cells in vitro, and to grow mast cells in the laboratory, thus allowing my lab and others the opportunity to study this cell outside of the body. Further, the various monoclonal antibodies against constituents of mast cells and basophils developed in my lab have been used by us and other labs throughout the world to identify these cells in tissue biopsies from patients with a variety of conditions, identifying such cells with greater precision and sensitivity than previously available histochemical stains, and often leading to improved understanding of the pathogenesis of such conditions. Finally, I developed an anti-tryptase monoclonal antibody capable of inhibiting tryptase activity, proposing it as a potential therapy for diseases such as asthma, where tryptase is over-produced. This has led the Innovation Gateway Office at VCU to license the rights to this antibody for such a purpose. Thus, my work is aligned with VCU's mission to 'foster discovery and innovation that has a global impact by developing translational applications to improve health'.

**Service:** In each of my service activities, I try to imagine what accomplishment might have the greatest impact, consider its feasibility, and work hard on it. I have helped develop guidelines for the diagnosis of mastocytosis and anaphylaxis, and for the treatment and prevention of anaphylaxis. As a Board member of professional organizations, including the American Academy of Allergy Asthma and Immunology (AAAAI) and the Clinical Immunology Society (CIS), I led efforts to improve their control of their academic journals. For AAAAI, this led to ownership of their journal, facilitating the introduction of changes that have elevated the journal's impact factor from 4 to 11, among the highest in the world for a subspecialty journal. For the CIS, this provided a critical revenue stream. As a board member of the Asthma and Allergy Foundation of America, a lay organization, I encouraged collection of outcome data from their education programs to better show their impact, advised them on legislative issues and formulated their program to sponsor research to cure or prevent asthma. At VCU, I chair the School of Medicine Sponsored Advisory Committee, which provides bridge funds to support promising research of faculty whose funding has lapsed, enhancing funding of their resubmitted proposals. These service activities are typically interdisciplinary, mobilizing creative energies that innovate and solve local or regional challenges.

**Knowledge Integration:** The impact of one's work in teaching, discovery and service depends upon its integration into the broader knowledge base. In this sense, my teaching of clinical fellows, practitioners who have carried the knowledge, professionalism and self-learning skills from VCU to their postgraduate endeavors, fulfills this mission. So does the discovery and development of tools to identify mast cells and basophils, to measure tryptase levels that help diagnose mastocytosis or anaphylaxis, and to potentially inhibit tryptase activity in asthma, extending the impact of my research well beyond VCU. Leading a group of talented investigators from the Department of Biology in the College of Humanities and Sciences and from Internal Medicine, Biochemistry, Pediatrics and Microbiology & Immunology in the School of Medicine, we successfully competed for a prestigious 5-year \$7 million NIH-sponsored Asthma and Allergic Diseases Cooperative Research Center award in 2008, integrating research from five departments through interdisciplinary collaborations and conferences. Finally, service activities on professional and lay organization, committees to develop diagnostic or therapeutic guidelines, and VCU committees to foster research, education and discovery also facilitate knowledge integration.

## ABBREVIATED CURRICULUM VITAE

Schwartz, Lawrence B, MD, PhD	Professor of Medicine, Microbiology & Immunology, & Pediatrics		
INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
University of Illinois, Urbana, IL	BS (Summa cum laude)	1970	Chemistry
Washington University, St. Louis, MO	MD, PhD	1976	Medicine, Biochemistry
Barnes Hospital, St. Louis, MO	Intern/ Resident	1976-1978	Internal Medicine

### A. Teaching Experience

#### Harvard Medical School; Boston, Massachusetts

1978-1980 Fellow, Allergy/Immunology & Rheumatology

1980-1983 Instructor/Assistant Professor of Medicine

#### Virginia Commonwealth University

1983-1989 Associate Professor of Medicine, Microbiology and Immunology and Pathology

1989-Present Professor of Medicine, Microbiology & Immunology; Pediatrics

2000-Present Chair, Division of Rheumatology, Allergy and Immunology

### B. Scholarly Works (selected from over 350) and Activities

Schwartz LB, Lewis RA, Seldin D, Austen KF: Acid hydrolases and tryptase from secretory granules of dispersed human lung mast cells. *J Immunol* 126:1290-1294, 1981

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Gomez G, Zhao W, Schwartz LB. Disparity in Fc $\epsilon$ RI-induced degranulation of primary human lung and skin mast cells exposed to adenosine. *J Clin Immunol* 31:479-87, 2011.

Le QT, Gomez G, Zhao W, Hu J, Xia HZ, Fukuoka Y, Katunuma N, Schwartz LB. Processing of human protryptase in mast cells involves cathepsins L, B and C. *J Immunol* 187:1912-8, 2011.

Zhao W, Gomez G, Macey MR, Kepley CL, Schwartz LB. In vitro desensitization of human skin mast cells. *J Clin Immunol* 32:150-60, 2012.

Lyons JJ, Sun G, Bai Y, et al. Mendelian inheritance of elevated serum tryptase, atopy, and connective tissue abnormalities. J Allergy Clin Immunol 133:1471-4, 2014.

### **C. Public and Academic Service**

1987-1995 Board of Directors, Richmond Montessori School  
1992-1994 Chair, NIH Immunological Sciences Study Section  
1997-1997 Board of Directors, Virginia SIDS Alliance  
1999-present Chair, School of Medicine Sponsored Research Advisory Committee  
2000-2003 Board of Directors, American Academy of Allergy Asthma and Immunology  
2001 Chair, American Board of Allergy and Immunology  
2008-2013 Board of Directors, Asthma and Allergy Foundation of America  
2010-2012 President, Allergy/Immunology Program Directors Assembly  
2011-2012 President, Clinical Immunology Society  
2011-Present Associate Editor, Journal Clinical Immunology

### **D. Awards**

1987 American Society for Clinical Investigation  
1990 NIH Merit Award  
1991 Association of American Physicians; Charles and Evelyn Thomas Professor of Medicine  
1998 Triennial Award for Sustained Research Excellence, Internal Medicine, VCU  
2008 Billy R. Martin Innovation Award, VCU  
2009 Plenary Speaker, Australasian Society of Clinical Immunology and Allergy  
2011 J Dolovich Memorial Lectureship, AAAAI Annual Meeting  
2015 AAAAI Distinguished Scientist Award  
2015 European Competency Network for Mastocytosis Researcher of the Year Award

### **E. Other Significant Contributions**

1983-present Director, VCU Adult Allergy and Immunology Clinics  
1983-2014 Program Director, VCU Allergy and Immunology  
2014-present Assistant Program Director, VCU Allergy and Immunology

### **Selected Grants**

1982-90, 2001-6 NIH R01 AI-20487 (PI) Biochemistry of mast cell secretory granule enzymes  
1990-2001 NIH MERIT R37 AI20487 (PI) Biochemistry of mast cell secretory granule enzymes  
1988-2011 NIH R01 AI27517 (PI) Characterization of different types of human mast cells  
1998-2003 NIH R01 AR45441-01 (PI) Evaluation of basophil involvement in human disease  
2008-14 NIH U19 A1077435 (PI) Cellular & Inflammatory pathways in asthma & allergic diseases: from ige to cells & mediators  
2006-present Glaxo Smith Kline MHE104317 (VCU PI) Compassionate use of mepolizumab for patients with hypereosinophilic syndrome  
2015-present CSL Behring: CSL830\_3002 (VCU PI) An open-label, randomized study to evaluate the long-term clinical safety and efficacy of subcutaneous administration of human plasma-derived C1-esterase inhibitor in the prophylactic treatment of hereditary angioedema  
2016-17 Merck: MISP 52707 (Co-PI) Desensitization and cross-desensitization during oral grass or ragweed pollen immunotherapy

## LETTERS OF SUPPORT (excerpted)

Dr. Schwartz embodies the mission and vision of the VCU Quest for Distinction. Our mission to advance knowledge through seeking the “cause and cure of diseases through groundbreaking research and educating those who serve humanity and research that expands the boundaries of new knowledge ... and promotes translational application to improve human health.” Without reservation or exception Larry’s 30 year career exemplifies the mission and vision of VCU. Over thirty years of continuous award-winning research and highly successful student mentorship and teaching have indeed supported this mission. The translation of the bench research into assays that help to identify the presence of a rare disease, continuous funding through the National Institute of Health and International recognition of the contributions of his work all support the acknowledgement of his substantial contributions to the Commonwealth and the world. **Michael Rao Ph.D., President VCU and VCU Health Systems.**

Dr. Schwartz’s work on the orphan disease, systemic mastocytosis, has facilitated the creation of an assay to more rapidly diagnose this difficult to diagnose disease. He has received continuous funding through the National Institutes of Health for over thirty years. This sustainability in research funding, through difficult funding years, indicates the strength and value of this work. Larry has been recognized by VCU with numerous awards for excellence. He has been an NIH Merit award, and has received the distinguished scientist award from the AAAAI. His numerous awards for excellence and distinction have been bestowed both nationally and internationally. His award winning research informs his teaching. He is a caring clinician and a highly effective mentor to graduate and medical research students alike. His numerous awards and recognitions give testament to the high caliber of his research and service. He is a valued member of VCU and an asset to the Commonwealth. **Dr. Gail Hackett, Ph.D. Provost and Vice President of Virginia Commonwealth University**

Dr. Larry Schwartz's research has led to discoveries that have changed medical practice throughout the world. His work on the discovery, purification, cloning and characterization of human  $\alpha/\beta$  tryptases and the use of immunoassays for tryptases as biomarkers has led to improved diagnosis of mastocytosis (a diagnostic tool adopted by the World Health Organization (WHO) and approved by the FDA) and the risk of systemic anaphylaxis. The ability to diagnose this disease more quickly and precisely has had marked impact on patients, allowing quicker treatment and reduced instance of severe allergic reactions that can result in death. He has trained dozens of scientists at all levels, from students to visiting scholars, who are building on his work to improve human health. His record of service to the profession and to lay organizations is exemplary. **Jerome F. Strauss, III, M.D., Ph.D., Interim Vice President for Health Sciences, Interim CEO, VCU Health System, Dean, School of Medicine.**

Dr. Schwartz is an outstanding scholar whose world renown work on mast cells includes discovering antibodies that are used worldwide in clinical diagnostic and research care and an anti-tryptase monoclonal antibody which has been licensed for development in treatment. Dr. Schwartz has been a vital VCU faculty member leading efforts to train the next generation of researchers and stellar clinicians in allergy, immunology and rheumatology. He has played leadership roles in our MD/PhD program and research education across the school. **John Nestler, MD, William Branch Porter Professor of Medicine, Chair, Department of Internal Medicine**

I have admired Larry's high level of excellence and his leadership in our subspecialty as a teacher and scientist since he joined the faculty at VCU over 30 years ago. In 1983, I began my training in allergy/immunology and Larry was my mentor and teacher in the adult allergy/immunology clinics at VCU. He is at the my top list of teachers who shared his fund of

knowledge and his passion for helping patients with allergic disorders and immune-deficiencies. For many years, he has been mentoring, encouraging, and motivating students at all levels of training who have been working in his clinics and laboratory. He also has been the director of a highly successful training program for fellows in our subspecialty for many years.

As an academic scientist, Larry has devoted his career to deciphering the role of mast cells in the pathogenesis of allergic disorders. His discovery of tryptase as an important mast cell degranulation product that can be measured to facilitate the diagnosis of anaphylaxis is known worldwide and is now used commonly in clinical laboratories throughout the world. He truly has earned a national and international reputation for this work. This, of course, has been of great benefit to VCU, the state of Virginia, and to many patients who are at risk for life-threatening anaphylaxis. His success as a clinician/scientist, has also led to sustained funding from the NIH for Larry's research on the faculty at VCU. It is an honor for me to support with enthusiasm the nomination for Dr. Schwartz for the 2016 Virginia outstanding faculty award. **Peter W. Heymann, MD, Head, Pediatric Allergy and Immunology, Asthma and Allergic Diseases Center, University of Virginia Health System**

Dr. Schwartz had made two historic contributions to the field of allergy and immunology. The first is the discovery and development of the human serum tryptase assay for the documentation of anaphylaxis and the diagnosis of systemic anaphylaxis. The second is the identification and characterization of two types of human mast cells. In addition to this body of work, Larry has made additional observations relating to basophil and mast cell biology of major importance, including the development of the beta-hexosaminidase assay for the measurement of mouse and human mast cell degranulation, exploration of the multiple functions of human proteases, development of human mast cells from umbilical cord blood cells, and the documentation of basophil interleukin-4 production. **Dean D. Metcalfe, M.D., Chief, Laboratory of Allergic Diseases, Chief, MCBS/LAD NIAID, NIH, Bethesda, MD**

Dr. Lawrence (Larry) Schwartz is one of the leading allergists in the US. His work on the mast cell enzyme tryptase is internationally recognized and has been critical to helping unravel the pathobiology of anaphylaxis, a potentially fatal acute allergic response. He has not only developed an assay for this important molecule but has also taught an entire generation of allergists and immunologists how to use tryptase to understand disease and improve patient care. **Stephen Wasserman MD, FAAAAI, FACP, Professor of Medicine, University of California, San Diego, President of the American Board of Allergy and Immunology**

Larry Schwartz has been a prominent investigator of mast cell biology and this cell's role and contribution in allergic disease. His findings have been at the forefront of research for over thirty years. An example of how his research has had direct translation to patient care and improved treatment of mast cell disease has been his development of a clinical assay to measure, mast cell tryptase. Tryptase is a major mediator of the mast cell and is released when the mast cell is activated in allergic reactions, such as anaphylaxis, an acute potentially life threatening allergic reaction. The development of clinical methodology to measure mast cell activation by the detection of serum tryptase has revolutionized the diagnosis of anaphylaxis and other mast cell diseases like systemic mastocytosis. A key diagnostic feature of systemic mastocytosis is an elevated tryptase level. Prior to the availability of the tryptase assay, this disease could not be readily diagnosed and patients would continue to suffer and be at risk for acute allergic reactions and even death. Larry's contribution in detection methods has changed the capability and capacity to diagnose this disease, which is a major accomplishment.

Larry Schwartz has been a teacher and mentor at many levels in education – didactic, conferences, but, perhaps, most importantly his advisory and mentoring contributions in

research. His “students” include post-graduate, pre-graduate, post-doctoral, visiting scholars, and faculty. The list of his students is long, distinguished and well-recognized. Larry has been stalwart in Allergy and Immunology at VCU for over 30 years. His contributions to VCU start with his distinguished research career and his longstanding extramural support. He has been an outstanding educator in formal classwork and as a mentor. Larry has also given and provided considerable service to VCU – Chair of the Division of Rheumatology, Allergy and Immunology, Program Director of the training program, and Director of the Adult Allergy/Immunology Clinic. Larry Schwartz is a model for all of us in Allergy and Immunology, and in my opinion, an outstanding nominee for the 2016 Virginia Outstanding Faculty Award. **William W. Busse, M.D., Professor of Medicine, University of Wisconsin School of Medicine and Public Health, Allergy, Pulmonary and Critical Care Medicine**

Dr. Schwartz is an excellent clinician and teacher. I have enjoyed working with him in clinics and inpatient service during my 2 years fellowship in the allergy and immunology at VCU. He is very caring clinician and I have learned a lot from his bedside manners. He is as well a great teacher who encourages self learning and critical thinking. He is supportive in career advancement and provided great advices and letters of recommendations. Dr. Schwartz is a world authority in mast cells biology and it was a great opportunity to work under his mentorship. **Joud Hajjar MD, Assistant Professor of Medicine, Baylor College of Medicine and Texas Children's Hospital, Section of Immunology, Allergy & Rheumatology**

It gives me great pleasure to recommend Lawrence B. Schwartz, MD, PhD for the 2016 Virginia Outstanding Faculty Award for the State Council of Higher Education for Virginia. I have known Larry for my entire academic career. He truly is an example of the quintessential physician scientist. In 1981, while an Assistant Professor at Harvard, he purified tryptase, the predominant neutral protease in human mast cell secretory granules. He has continued in this concentration and has characterized human alpha and beta tryptase and developed immunoassays that help clinicians diagnose systemic mastocytosis and to assess anaphylactic risk. As recently as 2014 he published that the human tryptase locus on chromosome 16 contains one gene encoding only beta-tryptase and another encoding either beta-tryptase or the homologous alpha-tryptase, providing an alpha:beta gene ratio of 0:4, 1:3 or 2:2 in the diploid genome. Beta tryptase levels generally reflect the magnitude of mast cell activation and are elevated during most cases of systemic anaphylaxis. Dr. Lawrence Schwartz has had numerous honors that are included on his CV. I will not be repetitive and delineate them. What I will say is the fact that it was an honor and a pleasure to have him present Allergy Grand Rounds at Hopkins on Wednesday, June 10, 2015. In summary, I can think of no one more qualified to receive the 2016 Virginia Outstanding Faculty Award for the State Council of Higher Education for Virginia. **Susan M. MacDonald, MD, Professor of Medicine, Johns Hopkins University School of Medicine, Interim Director: Division of Allergy and Clinical Immunology**

I trained under Dr. Schwartz for my Allergy/Immunology fellowship from 2008-2010. I felt I was getting great training while going through my fellowship. However it wasn't until after I graduated and started my own Allergy/Immunology department in a large Multispecialty Group that I realized exactly how excellent my training was. I received outstanding clinical training and felt very confident in my knowledge and ability to evaluate and treat the simple common conditions as well as the very complex atypical conditions that came my way. Most importantly under Dr. Schwartz's training I learned how to critically evaluate articles and research studies to continuously further my knowledge. I will always feel indebted to Dr. Schwartz for giving me the ability to provide the best possible care for my patients. My past, present and future patients all thank you Dr. Schwartz. **Jigisha Morosky, M.D., Allergy/Immunology, Connecticut Multispecialty Group**

