CANDIDATE STATEMENT – 2011: Susan Gunst, PhD

Members of the Chancellor's Professorship Selection Committee:

I am much honored to be nominated for a Chancellor's Professorship from IUPUI and I very much appreciate the committee's consideration of my candidacy. Indiana University has done much to contribute to the successes that I have had in my professional career, and I believe that the Chancellor's Professorship would enhance my opportunities to contribute to Indiana University and the IUPUI community.

I joined the School of Medicine Faculty in 1989 as an Associate Professor of Physiology and Biophysics (now Cellular and Integrative Physiology). There has been tremendous growth and development of IUPUI since I became a member of the faculty, and I am very pleased that I have been able to participate in the growth and development of this institution. I have endeavored to serve the mission of IUPUI through the development of a strong scientific research program, by contributing to the educational missions of the university and to the training and education of new scientists, and by service to the university community and to national scientific and medical communities. I will try to provide an overview of my professional activities with respect to the IUPUI mission.

The research in my laboratory has been focused on determining biological and physiological processes that regulate the bronchial airways and the pathophysiologic processes that contribute to asthma. My laboratory has been continuously funded by grants from the NIH for this work since 1984. Excessive constriction of the bronchial airways is a cardinal feature of asthma, a common and deadly disease. The studies in my laboratory have employed a multidisciplinary approach that has integrated studies at the cellular and molecular level with *in vitro* and *in vivo* physiologic approaches. Early studies from my laboratory demonstrated that the mechanical forces that are imposed on the bronchial tree during inflation and deflation of the lungs and airways during normal breathing provide an important homeostatic mechanism that prevents the airways from constricting, and that this motion is important for the maintenance of a normal low level of airway reactivity. We found that mechanical stretch of airway smooth muscle and of isolated bronchi that are similar to that which occurs during normal breathing reduces the contractile responsiveness of the airways, and that this inhibits airway reactivity and airway narrowing. Our *in vitro* observations have been explored *in vivo* in animal models through a long-running collaborative NIH-funded project (with Dr. Robert Tepper in the Dept. of Pediatrics at IUSM), in which we have extensively evaluated the effects of acute and chronic mechanical maneuvers on lung and airway responsiveness. The most recent renewal of this project includes human studies to evaluate the effectiveness of mechanical interventions as a therapy for airway hyperreactivity. The project has also led to the development of a recent proposal for a multi-center clinical trial on asthmatic subjects in which the effectiveness of mechanical therapy using nocturnal PEEP (positive end expiratory pressure) in reducing airway hyperreactivity in asthmatics will be evaluated. We hope that these studies may lead to development of a new non-pharmacologic therapy that is effective in mitigating the symptoms of asthma.

A major focus of my research has centered on investigating the molecular mechanisms involved in regulating the contraction of smooth muscle. I found that many of the properties of airway smooth muscle that we observed *in vitro* could not be explained by currently accepted theories for the molecular basis of muscle contraction. The widely accepted explanation for smooth muscle contraction has relied on the presumption that the sliding movement of contractile filaments (actin and myosin) is solely responsible for the generation of tension and muscle contraction. However our studies have demonstrated that other non-contractile cytoskeletal proteins that determine the cellular structure of muscle cells are very dynamic under physiologic conditions. We found that these proteins are activated during contractile

stimulation to reorganize and form structural connections within the cell that are essential for the muscle to develop tension or shorten. We believe that a dynamic and adaptable cytoskeletal structural organization is the basis for the ability of airway smooth muscle to modulate its tension and relax in response to the mechanical stretch that occurs during breathing or lung inflation.

In order to explore the physiologic functions of cytoskeletal proteins that may contribute to the functional properties of airway smooth muscle, we developed a new technique for the introduction of genetic material into intact live smooth muscle tissues. Molecular studies of the physiology of muscle have long been constrained by technical barriers to applying modern molecular genetic approaches because intact muscle tissues are notoriously difficult to transfect, making it difficult to use molecular interventions to analyze the functions of individual proteins. The results of our molecular studies resulted in the development of a novel model for the physiologic regulation of smooth muscle contraction involving cytoskeletal processes that were previously not understood to contribute to muscle contraction. Evidence from other laboratories suggests that the paradigm we described is likely to be applicable to other smooth muscle tissue types. This opens up a multitude of potential new molecular targets for the modulation of smooth muscle function that can be exploited to develop new therapeutic approaches for the treatment of diseases that involve smooth muscle pathology, such as asthma and hypertension. Recently, we have been focusing on the feasibility of using a synthetic inhibitor of a cytoskeletal regulatory protein, (p21-activated kinase, or PAK), as a novel approach for asthma therapy. Our preliminary studies suggest that this may be successful in inhibiting both airway smooth muscle hypercontractility and the airway inflammation that is characteristic of asthma, because PAK is also key to the normal physiologic functions of inflammatory cells. We are very excited about the potential of this approach. In 2010 at the international meeting of the American Thoracic Society (ATS), the major professional organization of pulmonary physicians and scientists, I organized a symposium designed to highlight novel new approaches to asthma therapy that are currently under development (entitled “Frontiers in Asthma Therapy”). The symposium was very highly attended, and our studies describing the potential of PAK inhibitors and mechanical interventions (such as PEEP) as new therapeutic modalities for asthma generated a lot of interest. At the 2010 conference the American Thoracic Society also presented me with the Parker B. Francis Award for “outstanding contributions to pulmonary medicine and science”, and I presented the Parker B. Francis lecture.

My participation in national professional societies and organizations has provided me with opportunities to provide national and international leadership in my field. I have been very active in the American Thoracic Society for many years: I have served on the ATS Board of Directors, as Chairperson of the Assembly on Respiratory Structure and Function (RSF) –the respiratory physiology section of the ATS, and I have served on or chaired many committees within the ATS organization. I regularly present lectures, chair scientific sessions and participate in scientific forums at the annual international conferences. I am also quite active in the American Physiological Society (APS): I served as Chair of the Respiration Section of the APS and I have chaired and served on a number of committees within the APS. I have also served as Associate Editor for 2 journals published by the APS: I was an Associate Editor of the Journal of Applied Physiology from 2000-2009 and since 2009 I have been an Associate Editor of American Journal of Physiology; Lung, Cellular and Molecular Physiology. Recently, I was asked to coordinate the writing of the chapter on “Airway Smooth Muscle” for the most recent edition of “Comprehensive Physiology” an exhaustive review of physiological science published by the APS every 10 years. I also participate on numerous review committees for the National Institutes of Health (NIH): I served a 4 year term on Respiratory and Applied Physiology review committee from 1996-2000 and I completed a 4 year term on the Lung Cellular, Molecular and

Immunobiology review committee in June 2010. I also serve regularly on other NIH review committees on an ad hoc basis.

I believe that the university's mission of educating and training of new scientists is an extremely important responsibility. I have participated actively in the development of graduate training programs in the Dept of Cellular and Integrative Physiology and the IUSM, and I have taught in a wide range of graduate and professional courses within IUSM and other Schools on the IUPUI campus (Biology, Dental, Nursing, School of Allied Health). I have also developed and directed several graduate courses, including a new graduate level course in systems physiology for PhD students introduced in 2004, that was included as a required course in physiology of the new unified IUSM PhD program in 2008. I expend significant effort nurturing the careers of the students and fellows in my laboratory. Many of my trainees have been successful in obtaining their own grants and fellowships and have received awards in recognition for their work. I am especially pleased that a number of my former trainees have developed successful independent scientific careers; several are faculty members at other institutions as where they have established their own laboratories and successfully competed for extramural support from the NIH and other national organizations. I am regularly asked to contribute to the mentoring of graduate students, fellows, and junior faculty from other laboratories within Indiana University and at other institutions. For example, I am currently serving a second 5 year term on the external advisory panel for an NIH COBRE grant for faculty development at the University of Nevada School of Health Sciences, which convenes annually to mentor junior faculty in the development of their research programs.

In 2003-2004 I served as Chair of the Search Committee for selection of a new Dean for the Graduate School at IUSM. My committee was also charged with making recommendations for the conversion of the old departmentally-based IUSM PhD programs to a new unified PhD training program, now known as "The Indiana University School of Medicine BioMedical Gateway (IBMG)" program. The recommendations of the search committee formed a basis for the formulation of many aspects of the initial blueprint for the new graduate program that was ultimately implemented by Dr. Simon Rhodes when he assumed the position of Associate Dean of the Graduate School. I am very pleased that Dr. Rhodes has been extremely effective in this position. Our committee also made recommendations for revisions and expansion of the responsibilities for the Graduate School Dean, including the establishment of an Office of Postdoctoral Affairs. It has been gratifying to see the success of the IBMG PhD program and the successful implementation of many of our committee's recommendations.

I have devoted time to service on a number of IUPUI committees that contribute to the educational and service missions of IUPUI. To highlight a few: I have been a standing member of the IUSM faculty Promotion and Tenure Committee since 2004, where I regularly review and evaluate the academic progress of individual faculty members within the IUSM and contribute to the development of criteria for the assessment of the achievements and productivity. I have also been a long time member of the Institutional Animal Care and Use committee (IUCAC), and I was recently agreed to participate as a member of the IUPUI Sabbatical Leaves Committee. I also served on the search committee for the Dean of the Dental School, which was successful in attracting Dr. John Williams who assumed the position in July 2010.

I have enjoyed my career as a member of the IUPUI faculty and I feel that the university has fostered a productive environment for my professional activities. I would be honored to be able to further serve the IUPUI community as a Chancellor's Professor. Thank you for considering me for this appointment.

Susan Gunst, PhD
Professor of Cellular and Integrative Physiology
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