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DATE XXXXXX

George Q. Daley, M.D., Ph.D.
Dean of the Faculty of Medicine
Harvard Medical School
25 Shattuck Street
Boston, Massachusetts 02115

Dear Dean Daley:

It is with utmost enthusiasm that we propose **Dr. XX XXX, Ph.D.** for consideration of promotion from Instructor of Anesthesia to Assistant Professor of Anesthesia at Harvard Medical School by the area of excellence of Investigation. Dr. XXX has a distinguished record of contribution in Investigation through his theoretical and experimental work in respiratory physiology, lung imaging, and the development of new and innovative means to monitor capillary blood flow with significant supporting activity in Teaching and Education through his teaching efforts of junior investigators in his laboratory.

Review of Current Activities

Dr. XXX is currently Instructor in Anaesthesia at Harvard Medical School and Assistant in Biomedical Engineering at the Massachusetts General Hospital, where he leads an active and independently funded research program in pulmonary physiology examining complex mechanisms of bronchial constriction. He is currently a Principle Investigator for an exploratory grant from the Boston-based Center for Integration of Medicine and Innovative Technology (CIMIT) and lends his special expertise as an essential Co-Investigator on four major Projects funded by the National Institutes of Health (NIH). Dr. XXX is recognized internationally for his research in pulmonary imaging, modeling, and experimental pulmonary studies and is frequently invited to lecture on these topics around the world. He has organized a number of national research meetings and is currently serving as Chair at the Annual Fall Meeting of the Society of Biomedical Engineering, where he is responsible for organizing this national meeting as a whole. Dr. XXX serves as an expert scientific reviewer for The Swiss National Science Foundation, as guest editor for two premier journals in physiology and biomedical engineering, and as a reviewer for eight national and international scientific journals. At present, Dr. XXX also serves on the scientific advisory committee of a large multi-center grant. Dr. XXX is widely published with much of his work appearing in journals with the highest impact factors; both the ac of his publication and the impact of his work based on citation metrics show a continuous increase over the last several years. Dr. XXX teaches several topics each

year in the classroom at the Massachusetts Institute of Technology and Harvard Medical School and currently serves as the direct mentor in the laboratory for a doctoral candidate.

Background and Training

Dr. XXX is a native of Germany and completed his undergraduate and graduate studies with distinction, gaining great expertise in respiratory physiology and mathematical modeling. He received a Doctorate in Philosophy from Dresden University of Technology, Dresden, Germany in 2001, graduating *summa cum laude*. His doctoral studies in the Department of Computer Science at Dresden University focused on developing a unified model of the respiratory system combining ventilation mechanics, gas exchange, gas transport, and metabolism, and the identification the parameters for this new model in mechanically ventilated patients. His work ultimately led to publication of his doctoral thesis, *Identification of a unified model of ventilation mechanics and gas exchange during mechanical ventilation*. In parallel to his doctoral studies, he worked at the University Hospital Carl Gustav Carus in Dresden, Germany, on research projects and on the development of a novel monitor to measure pulmonary capillary blood flow in mechanically ventilated patients.

At the conclusion of his doctoral studies in 2001, Dr. XXX received the prestigious Deutsche Forschungsgemeinschaft scholarship, an award from the leading research foundation in Germany. This scholarship allowed him to join the laboratory of Dr. Jose Venagas in our department. At the occlusion of his productive scholarship work in the Venegas laboratory in 2003, we were exceptionally pleased to offer Dr. XXX a position as Assistant in Biomedical Engineering at Massachusetts General Hospital and Instructor in Anaesthesia at Harvard Medical School.

Area of Excellence: Investigation

Contributions, achievement and impact

Dr. XXX's research projects have been highly interdisciplinary throughout his career, combining biomedical engineering, respiratory physiology, and computer science. His work shows an exceptional integration of theory and direct experimentation. He has demonstrated continuously high standards in scientific innovation and, since 2009, has received funding from the *Asthma and Allergy Foundation of America* and from the NIH (R01). His unique expertise in modeling, system theory, parameter identification, image processing, data analysis, and computer programming has contributed substantially to the success of other grant applications and scientific projects. His collaboration has allowed three other young investigators in the laboratory to publish papers in high-ranking journals; all three have since become independent investigators. In the following paragraphs I will describe Dr. XXX's major scientific achievements.

While working at the University Hospital Carl Gustav Carus Dresden, Dr. XXX conducted research in the Department of Anesthesia and Intensive Care Medicine. His main project during this time was the investigation of a method to measure pulmonary capillary blood flow using partial CO_2 re-breathing. This method derives blood flow from a fundamental equation in pulmonary gas exchange: the relationship between the CO_2 pressure at the end of expiration and the rate of CO_2 elimination. The setup requires only a CO_2 sensor, a flow sensor and a computer-controlled valve attached to a tube to briefly reduce CO_2 elimination. In mechanically ventilated patients, accurate measurements of pulmonary capillary blood flow allow non-invasive monitoring of the amount of cardiac output that contributes to gas exchange. The method also helps to determine which ventilator settings

provide higher blood flows in ventilated areas and, thus, a better match between ventilation and perfusion. Dr. XXX's work was central to the development of a commercial monitor using this CO_2 re-breathing method. His work led to two papers (Publications #3 and #5) and was featured in a number of University press releases and articles in the lay press describing the new technology. He also conducted detailed investigations on the effects of vaporized perfluorocarbon on gas exchange and ventilation mechanics in acute lung injury, which led to co-authorship on a paper detailing the findings (Publication #2). In this animal model of acute respiratory distress syndrome (ARDS), vaporized perfluorocarbon resulted in significant improvements in oxygenation, lung compliance, and peak airway pressure while avoiding liquid perfluorocarbon ventilation. Additionally, Dr. XXX's work resulted in a first author patent (Technological Innovation #3), *Assembly for reducing consumption during the application of gaseous substances*. This assembly led to a dramatic reduction of perfluorocarbon consumption that increased the efficiency and reduced potential effects on the environment. The universal principle of his patented assembly has the potential for wide application to reduce the consumption of gases or aerosols in inhalation therapy.

Since joining the Venegas laboratory here at MGH, Dr. XXX has developed highly original methods for functional Positron Emission Tomography (PET) and PET/CT imaging of the lung. Specifically, he has devised means to use PET to produce images of blood flow and ventilation distribution in the lungs. Using his experience in the computational modeling of lung physiology, Dr. XXX developed novel methods for imaging analysis that have become fundamental for state-of-the-art PET imaging research and gained publication in leading journals, including the *American Journal of Respiratory and Critical Care* and *The Journal of Nuclear Medicine* (Publications #4, 5-8, 10-15,19-23). Dr. XXX has applied these novel imaging techniques to determine regional inflammation and fluid accumulation in the lungs, leading to a better understanding of heterogeneous inflammatory disease processes, including adult respiratory distress syndrome (ARDS). This work led to two publications in high-impact journals detailing their pioneering work, both with Dr. XXX as senior author: *The Journal of Nuclear Medicine* (Publication #17) and *Academic Radiology* (Publication #18). A patent for this new method is pending (Technological Innovation #4).

Dr. XXX, together with Dr. Venegas, has built on his insights from the laboratory to construct an advanced computational model of bronchial constriction in asthma that links the behavior of airways to the behavior of the lung as a whole. This model was the first model able to predict the emergence of ventilation defects and the self-organized patchiness in ventilation that his research group had previously found on imaging studies. The unique predictions of this model have led to new insights and better understanding of asthma and the impact of this work is evidenced by publication in the premier journal *Nature* (Publication # 9). Dr. XXX went on to demonstrate that their new model could predict paradoxical behaviors of the lung that appear during bronchial constriction, including the critical lung volume where severe airway constriction and ventilation defects emerge, the appearance of both airway constriction and dilation following airway smooth muscle stimulation, and the delay in central airway dilation compared to peripheral airways (Publication #16). The agreement between the XXX-Venegas Model's behavior and these seemingly paradoxical observations not previously thought to be linked implies that the model captures a unifying principle and may well be valid for predicting lung responses across a broad range of conditions.

These findings have led to a shift in the paradigm in asthma research; to date, researchers have assumed that the behavior of each airway is independent from other airways and that the global behavior of the lungs reflects nothing more than the average of the individual airways' responses. Dr. XXX's results demonstrate that parallel and serial interdependencies among airways of the bronchial tree lead to complex, but predictable behaviors that are consistent with experimental data.

Currently, Dr. XXX is working on broad characterization of the complex lung behaviors that appear during bronchial constriction. The ability to characterize and predict such complex behaviors will undoubtedly serve as the critical underpinnings in development of novel approaches for the treatment of asthma.

Dr. XXX has gone on to achieve funding as an independent investigator. In 2009, the NIH awarded Dr. XXX his first R01 as Principle Investigator, *A complex system's approach to bronchoconstriction in asthma.* As a Principal Investigator, he has also received an Investigator Award Grant from the Asthma and Allergy Foundation of America. He is currently a Principle Investigator for an exploratory grant from CIMIT and lends his special expertise as an essential Co-Investigator on four major NIH grants. In the CIMIT grant, he will study *High-resolution optical frequency domain imaging and computed tomography imaging of the pulmonary airways*. The aim of is to test and validate a fiber-optical sensor for measurements of airway diameter and structural properties of tissues within the airway walls. Dr. XXX's collaboration in NIH grants includes: 1) *Regional gas trapping in bronchoconstricted asthmatics:* studying the phenomenon of airway closure and gas trapping in asthmatics by combining functional images from positron emission tomography (PET) and structural images from CT; 2) *Alterations in regional pulmonary perfusion, ventilation, and inflammation following burn and smoke inhalation:* designed to test if sub-clinical changes in regional lung perfusion, ventilation and activation of inflammatory cells can anticipate the clinical manifestation of respiratory failure after smoke and/or burn exposure; 3) *Regional inflammation-dysfunction in acute lung injury:* to study the mechanisms that produce acute lung injury and to develop methods to investigate, prevent and treat this condition; and 4) *Redistribution of pulmonary perfusion during bronchoconstriction in asthma:* to understand the mechanism of, and factors that modify, the regional perfusion redistribution during bronchoconstriction in asthma.

Recognition and Reputation

Dr. XXX's research in pulmonary imaging, modeling, and experimental pulmonary studies is internationally recognized. He has been invited to lecture on his work both nationally and internationally including presentations at *Annual Meetings of the Biomedical Engineering Society*, at *Johannes-Gutenberg University* (Mainz, Germany), *University Hospital Carl Gustav Carus* (Dresden, Germany), *Dresden University of Technology* (Dresden, Germany), *Dresdner Medizintechnik-Symposium* [Dresden Symposium of Medical Technology] (Dresden, Germany), *University of Vermont* (Burlington, VT), *New England Complex Systems Institute* (Cambridge, MA), and *Massachusetts General Hospital* (Boston, MA). Dr. XXX was invited to chair an invitation-only workshop of experts at the *National Mathematical Biosciences Institute* (Columbus, OH), and has organized and chaired numerous sessions at annual meetings of the Biomedical Engineering Society.

Additional evidence of Dr. XXX's growing international reputation comes from the growing number of invitations he has received to serve as an expert scientific reviewer. He has served as an *ad-hoc* grant reviewer for The Swiss National Science Foundation. He is also a member of the scientific advisory committee of a NIH funded multi-center project, *Airway Hyper-responsiveness: From Molecule to Organ*, guest reviewer for the *Journal of Applied Physiology* and *Annals of Biomedical Engineering*, and *ad-hoc* reviewer of several national and international journals including *Advances in Physiology Education*, *Simulation in Healthcare*, *IEEE Transactions on Medical Imaging*, *European Respiratory Journal*, *Journal of the Royal Society Interface*, *Biomedical Engineering Online*, *PLoS ONE*, and *Journal of Breath Research*. Finally, he serves as a member of the abstract selection committee of the Society of Biomedical Engineering.

Scholarship

Dr. XXX is author of 24 peer-reviewed original articles in high-impact journals of including, *Nature*, the *Journal of Nuclear Medicine*, the *American Journal of Respiratory and Critical Care Medicine*, the *Journal of Applied Physiology*, the *European Respiratory Journal*, *Anesthesiology*, *Respiratory Physiology and Neurobiology*, *Critical Care Medicine*, *Intensive Care Medicine*, and the *International Journal of Clinical Monitoring and Computing*. Dr. XXX is also the author of a review article in *Drug Discovery Today: Disease Models* and a book chapter in Outstanding Dissertations of 2000 (*Ausgezeichnete Informatikdissertationen 2000*). Dr. XXX's doctoral thesis was published as a stand-alone book in 2000. Thomson Reuters' online service ISI Web of Knowledge currently lists 358 citations of his most prominent research papers, with a continuous increase in the rate of citation of his work over the last years (more than 70 citations per year for 2008 and 2009, and an average of 15 citations per paper).

Of particular note is the significant acclaim that Dr. XXX has achieved in connection with his article describing a new model for bronchial constriction in asthma published in *Nature*. The Editors of *Nature* chose the article for electronic pre-publication and featured the article in the highlights section of the journal; both of these actions are reserved for just a few papers the Editors deem to be of particular scientific significance. The article has been summarized in numerous international publications including *Breath*, *Medical Journal Review*, *Pediatrics*, and the *Aerztezeitung* and has been widely cited by other scientists since its publication.

Teaching and Education

Dr. XXX is a sought-after teacher locally, regionally, and nationally and has an excellent record for supervising and mentoring young scientists in the laboratory. Dr. XXX teaches locally in a quantitative physiology course entitled *Organ Transport Systems* at the Massachusetts Institute of Technology (MIT) and in the graduate level course *Respiratory Physiology and Pathophysiology* in the Harvard-MIT Health, Science and Technology (HST) program at HMS. He has lectured and led various international workshops for the continuing medical education of anesthesiologists and critical care physicians including recent symposia held in Dresden, Germany, and Bad Gastein, Austria.

Dr. XXX has collaborated for several years in the multi-center project VaNTH (*Vanderbilt University*, *Northwestern University*, *University of Texas*, and the *Harvard-MIT Division of Health Sciences & Technology*), supported by the National Science Foundation (NSF), that is developing new education methods and course materials for teaching biomedical engineers. Dr. XXX developed course materials for a respiratory biomechanics laboratory conducted a study to assess the impact of the new course module including computer simulation, realistic simulator, and educational style on the students' learning achievements; their results were published in the proceeding of the *American Society for Engineering Education* (ASEE) (Proceedings #1).

In his senior position in the Venegas laboratory, Dr. XXX successfully mentored and trained undergraduate engineering students, doctoral candidates, and post-doctoral research fellows. In the laboratory, he interacts daily with his trainees, guides their work during weekly lab meetings, and holds individual meetings to guide their research progress. His teaching includes basic and advanced image processing, computer programming, data analysis, and modeling, and preparation of scientific presentations and manuscripts. Since his arrival in Boston, Dr. XXX has mentored 8 trainees at various levels, and has always had at least 1-2 trainees under his tutelage. Without exception, each of his research fellows and doctoral students has successfully published at least one manuscript and/or

presented a research abstract at a scientific conference, with many of these appearing in leading journals. Of particular note is Dr. XXX's mentorship of Dr. Schroeder, who completed the research work for his thesis under direct guidance from Dr. XXX and was awarded his doctoral degree from Dresden University of Technology, *summa cum laude*. His current doctoral candidate from Dresden University of Technology, Mrs. Braune, recently received a noteworthy international fellowship from the Roland-Ernst-Stiftung [Roland Ernst Foundation] in Germany. Dr. XXX is well-known as a teacher who can explain even the most difficult concepts and detailed scientific techniques to others with clarity. He is a patient and gifted mentor, able to guide others to significant scientific achievements.

Review of Solicited Letters

Independent letters of reference were solicited on behalf of Dr. XXX. Each referee was asked to comment upon the proposed promotion. Each letter provides strong support for advancing Dr. XXX to Assistant Professor of Anaesthesia.

SUMMARY EXCERPTS FROM LETTERS OF SUPPORT ARE INSERTED HERE

In summary, Dr. XXX has established himself as a notable investigator in the field of pulmonary physiology. He is one of the most talented researchers in the Department of Anesthesia, Critical Care, and Pain Medicine at the Massachusetts General Hospital, with a strong track record of collaborative work and mentorship of young investigators. He has established an international reputation for innovation and gained independent funding as a principle investigator. Dr. XXX has a sustained record of publication in leading scientific journals of his field, and has established his reputation as a scientist at the regional, national, and international levels. Dr. XXX has successfully built a fully supported independent research group, and made substantial scientific contributions. His innovative work in the field of asthma research, where he has successfully modeled complex systems behavior in the lung, is truly exceptional − indeed he has helped to create a new research paradigm in this field. He is a capable and much sought-after teacher and mentor, and is among the very best young mentors in our large research department.

The proposal to forward Dr. XXX to Harvard Medical School for promotion to Assistant Professor of Anaesthesia at Harvard Medical School with an area of excellence of Investigation was approved unanimously and with great enthusiasm by the Massachusetts General Hospital Department of Anesthesia, Critical Care, and Pain Medicine Appointments and Promotions Committee on ___DATE____ and the Harvard Anaesthsia Executive Committee on ___DATE____. We strongly and most enthusiastically support Dr. XXX's promotion to the Rank of Assistant Professor of Anaesthesia at Harvard Medical School and we look forward to your review and favorable response.

Sincerely yours,