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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 **____ _____, M.D., Ph.D.** for consideration of promotion from Assistant Professor of Anaesthesia to Associate Professor of Anaesthesia at Harvard Medical School by the area of excellence of Investigation. He has two significant supporting activities: Clinical Expertise and Service to the Community. Dr. _____ has a distinguished record of contribution in each, well as in Teaching and Education.

Dr. _____ received his M.D. from Hunan Medical College, P.R. China and immigrated to the United States, where he enrolled in 1986 in the Ph.D. program of the Graduate School of Biomedical Sciences at the University of Texas Health Science Center. His Ph.D. studies in Prof. Merle S. Olson's laboratory were primarily focused on platelet-activating factor (PAF), a potent pro-inflammatory mediator. He identified PAF biosynthesis and its novel binding sites in hepatic cells, and investigated the role of PAF in tissue injury. He was recognized by awards in Academic Excellence in Doctoral Studies in two consecutive years, documenting his outstanding performance. After completing graduate school in 1991 and a brief postdoctoral fellowship, he joined Professor Roger Spragg's group in the Division of Pulmonary and Critical Care Medicine of UCSD. There, he investigated the regulatory effect of lung surfactant on human neutrophil function, demonstrating crucial experimental evidence and a clear rationale for using lung surfactant as potential therapeutic agents in treating ARDS patients.

We were exceptionally pleased in 1996 to recruit Dr. _____ to HMS and the MGH residency in anesthesiology. He pursued the physician-scientist pathway during residency training, investigating the efficacy of gene transfer in cardioprotection with Dr. Anthony Rosenz_____g of the MGH Cardiovascular Research Center. Following completion of residency in 1999, he joined the HMS faculty as Instructor in Anaesthesia in the Department of Anesthesia and Critical Care at MGH. He established an independent research program in 2003 and has gained consistent research funding including from NIH, American Heart Association, Foundation for Anesthesia Education and Research, and William F. Milton Foundation of Harvard University.

His research team has concentrated on studying the novel role of innate immune Toll-like receptor (TLR) signaling in ischemic cardiac injury. He was promoted to Assistant Professor in Anaesthesia in 2003. In addition to scientific investigation, Dr. _____ devotes 30% of his time to clinical, teaching, and administrative activities. It is particularly noteworthy that Dr. _____ has established a national reputation as an investigator with consistent federal funding in an important basic science area while also contributing to the MGH Department of Anesthesia & Critical Care as an outstanding clinician and teacher.

Investigation

Contributions/Activities

For over 10 years prior to and since his arrival at MGH and Harvard Medical School, Dr. _____'s research has been focused on the mechanisms of tissue inflammation and injury. He has demonstrated consistent scientific innovation, insight, and productivity. His research career and scientific contribution can be summarized in three areas as detailed below.

Defining the hepatic effect of platelet-activating factor (PAF): PAF is a potent phospholipid inflammatory mediator released in many pathological conditions such as asthma, bacterial sepsis, acute lung injury, hepatic injury, and chronic pancreatitis. While he was at the University of Texas, Dr. _____ identified and characterized PAF biosynthesis and its novel receptors in the hepatic system under various pathological conditions. He went on to extensively characterize the regulatory mechanisms of PAF receptors and their role in inflammatory injury in chronic pancreatitis and hepatic injury. These studies provided novel insights into the molecular mechanisms by which PAF signaling is regulated and the specific roles of PAF in tissue injury. These studies resulted in a number of publications in peer-reviewed scientific journals such as *Journal of Biological Chemistry, American Journal of Physiology, American Journal of Pathology, Biochemical Journal, Archive of Biochem and Biophys,* and *Biochem Biophy Acta* (Pub. #3 - #15, and #18 on his CV).

Defining the molecular mechanism by which lung surfactant attenuates neutrophil function: Dr. _____ investigated the regulatory effect of synthetic (KL_4) and native porcine surfactant on respiratory burst oxidase activity in human neutrophils. He demonstrated that porcine lung surfactant inhibited the assembling of cytosolic $p46^{phox}$ and $p67^{phox}$ components and attenuated the activity of NADPH oxidase, the enzyme catalyzing production of superoxide, a free radical released from neutrophils and causing lung injury during ARDS. These pioneering studies provided crucial experimental evidence and a clear rationale for using surfactant, both native and synthetic, as potential therapeutic agents in treating ARDS patients. These studies were published in *Journal of Clinical Investigation (*Pub. *#16)* and *American Journal of Respiratory Cell and Molecular Biology* (Pub. #17).

Ischemic myocardial injury: For the past 10 years, Dr. _____'s research has been focused on ischemic cardiac injury. Ischemic myocardial injury represents a major cause of peri-operative morbidity and mortality and is the leading cause of mortality in the industrialized countries. Since the endogenous regenerative capacity of the heart is inadequate to repair injured myocardium, such injury often leads to the cumulative loss of cardiomyocytes over the lifetime of a patient, and ultimately contributes to the prevalence of heart failure. It is therefore critically important to understand the basic mechanisms governing cardiomyocyte death following ischemia and to identify potential targets for intervention.

Dr. _____ identified that FADD (Fas-associated death domain protein), an adaptor molecule in death receptor pathway, plays a critical role in mediating cardiomyocyte death. Somatic gene transfer of dominant negative FADD *in vitro* and *in vivo* significantly reduced cardiomyocyte apoptosis and myocardial infarction after ischemic injury (*Journal of Biological Chemistry,* 2000, Pub. #19). He also demonstrated that FADD inhibited pro-inflammatory NF-κB signaling by interacting with IKKβ in cardiomyocytes (*American Journal of Physiology*, 2005, Pub. #23). His study clearly demonstrated that blocking FADD signaling confers duel benefits in ischemic myocardium - anti-apoptoic survival and anti-inflammatory actions.

To explore the efficacy of gene therapy in ischemic myocardial injury, Dr. _____ developed the first adenoviral vector that carried the cDNA of insulin-like growth factor-1 (IGF-1), a peptide known for its cardioprotective action, and demonstrated the strategic advantage of adenovirus-mediated cardiac IGF-1 gene expression, compared with systemic administration of IGF-1 peptide, for protecting the heart against ischemic injury. In an animal model of ischemic myocardial injury, he found that Ad. IGF-1 transduction led to a dramatic reduction in myocardial infarct size and attenuated myocardial apoptosis. His elegantly designed studies clearly demonstrated that not only Ad.IGF-1-infected cardiomyocytes, but also adjacent, non-infected cardiomyocytes, were protected from hypoxic injury through paracrine mechanisms (*Journal Gene Medicine*, 2003, Pub. #20).

Since 2003, Dr. _____ and his research team have focused their scientific inquiry on the novel role of innate immune signaling in ischemic myocardial injury. Innate immune system such as Toll-like receptor 4 (TLR4) had been shown to represent the first line of defense against infection, but its role in ischemic myocardial injury was unknown. Dr. _____'s team was the first to demonstrate that transient cardiac ischemia activates innate immune IRAK-1 signaling (*Journal of Biological Chemistry*, 2005, Pub. #22) and using somatic gene transfer and knock-out mouse models, they demonstrated that activation of TLR4 signaling *via* its signaling proteins, NOS2, confers a survival benefit in isolated cardiomyocytes and suggests a potentially important role for TLR4 signaling in modulating cardiomyocyte survival pathways in the setting of ischemic cardiac injury (*American Journal of Physiology - Heart and Circulatory Physiology*, 2006, Pub. #24*)*. These findings are important because identification and characterization of this survival pathway may provide novel targets for intervention in ischemic myocardial injury.

Interestingly, _____'s research team has recently demonstrated that in *in-vivo* conditions, innate immune signaling may also play a deleterious role in ischemic injury as MyD88-deficient mice have a smaller infarction size and better preserved cardiac function compared with wild-type controls (*American Journal of Physiology - Heart and Circulatory Physiology*, 2008, Pub. #26). Since innate immune receptors are present in the heart as well as in immune cells, Dr. _____'s research team has hypothesized recently that TLR4 signaling from both origins may play distinct role in ischemic myocardial injury with cardiac TLR4 being protective while immune cell TLR4 damaging. To test the role of *cardiac* TLR4 signaling, they developed chimeric models as well as a cardiac-specific human TLR4 transgenic model. These on-going studies will certainly provide novel insight into the roles of *cardiac* and *immune* TLR4 signaling in ischemic myocardial injury.

Dr. _____ has also formed collaborations with Dr. Judith Hellman at University of California at San Francisco and Dr. Ulrich Schmidt at MGH to study the molecular mechanisms of cardiac dysfunction during sepsis. Cardiac dysfunction represents a main feature of severe sepsis and contributes to its high mortality. They discovered that stimulation of TLR2 by bacterial peptidoglycan-associated lipopotein activates cardiomyocyte inflammation and contributes to cardiomyocyte dysfunction (*Critical Care Medicine*, 2007, Pub. #25). To further test the hypothesis

that TLR2 signaling is critical for sepsis pathogenesis, Dr. _____'s team has recently developed an animal model of polymicrobial peritonitis, a clinically relevant model of sepsis, and demonstrated that TLR2 signaling is essential for cardiac dysfunction and contributes to the high mortality induced by polymicrobial intra-abdominal sepsis. To delineate the underlying mechanisms, Dr. _____'s team has employed various state-of-the art technologies including a chimeric model (possessing different TLR2 genotypes in the circulating blood cells than in parenchymal tissue cells), flow cytometry, neutrophil mobility assay, and fluorescent bead-based multiplex cytokine/chemokine immunoassay. These studies demonstrated that neutrophil cell and parenchymal tissue TLR2 may play important, but probably different roles in sepsis associated mortality and cardiac dysfunction. Theses studies demonstrate that Dr. _____ and his associates are pursuing this critical area with innovation and success.

Recognition

Dr. _____'s research work that demonstrates the importance of TLR innate immune system in ischemic myocardial injury and cardiomyocyte apoptosis is nationally and internationally recognized. He was invited by the American Journal of Physiology as the only author for a review article on this very topic (*American Journal of Physiology - Heart and Circulatory Physiology*, 2009, Pub #27). Dr. _____ has established his reputation in the specialty of anesthesiology. He has been selected for membership on several important national committees of American Society of Anesthesiologists (ASA). These include Committee on Research, Subcommittees on Clinical Circulation and on Experimental Circulation. He was invited as a moderator of a clinical circulation session and served as an abstract reviewer for the annual meetings of ASA. He is a study section member of American Heart Association (*e.g,* Cardiac Biology / Regulation 1 Clinical Peer Review Committee), a premier national foundation devoted to state-of-the art cardiovascular research. He was invited to present his research work as a visiting professor in other institutions and organizations, such as Medical College of Wisconsin, University of Washington, and Medical College of Georgia. He was also a visiting professor in several prestigious universities and organizations in China such as Fu-Wai Cardiovascular Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, and Xiangya School of Medicine. He is an invited speaker in the upcoming 2009 International Heart Forum in Beijing, China.

Currently, Dr. _____ is Principal Investigator of a NIH R01 grant (2007-2012) and a Grand-in-aid (2007-2010) from American Heart Association. Dr. _____ has served as a study-section member for American Heart Association and American Society of Anesthesiologists. For the past three years, Dr. _____ has been invited by the National Natural Science Foundation of China (NSFC), the largest research-funding agency in China, as a consultant reviewer in two of its study sections (Cardiovascular Pharmacology and Clinical Medicine-Basic Science). Finally, because of his academic achievements, Dr. _____ was elected to membership in the Association of University Anesthesiologists, the most prestigious society of academic anesthesiology in the USA.

Scholarship

The quality of Dr. _____'s research has been demonstrated by the publications in highest quality peer-reviewed journals (*e.g.*, Journal of Clinical Investigation, Journal of Biological Chemistry, and American Journal of Physiology) and by continuous funding support. Dr. _____ was the recipient of MGH-Tosteson Research Award, NHLBI Physician-Scientist Career Development Award (K08), Milton Foundation Research Fund of Harvard University, and

Foundation for Anesthesia Education and Research. Since 2003, Dr. _____ has successfully established himself as an independent investigator. His current funding is via an NIH/NIGMS R01 and a Grant-in-Aid from the American Heart Association. He is also Principal Investigator of several pending NIH grants including a RC-1, a Shared Instrument Grant and a R01 and Co-Investigator of one pending R01 grant. While Dr. _____ was the first author for many of his previous publications, he has been the senior and corresponding author of his last 5 papers. Dr. _____ has an independent laboratory of approximate 1,200 square feet that is located in the Cardiovascular Research Center at the MGH Charlestown Research Facilities. Dr. _____ has served as Reviewer for several national/international scientific and medical journals, including *American Journal of Physiology*, *Anesthesiology, Circulation, Cytokine, Journal Leukocyte Biology, Life Science, and Journal of the American College of Cardiology.*

Merit consideration of proposed promotion/appointment

Dr. _____ clearly merits promotion to Associate Professor of Anaesthesia at Harvard Medical School in the area of excellence of Investigation: (1) he is an independent investigator who has established an active R01-funded research program; (2) he has an excellent track record with high quality scientific publications that have significantly advanced knowledge of innate immunity function and ischemic heart disease; (3) he has a record of consistent grant support, including serving as PI of two NIH grants and several foundation grants; and (4) he has gained national and international reputations by his innovative research. Moreover, Dr. _____ has an outstanding record in teaching, clinical expertise and education, which I will describe in the following sections.

Teaching

Dr. _____ has been a dedicated teacher of students, residents and fellows since joining the faculty of Harvard Medical School and MGH. In addition to his regular clinical teaching of medical students and anesthesia residents in the MGH operating rooms, Dr. _____ has served each summer as a tutor in the highly regarded Clinical Tutorial Program of the MGH Department of Anesthesia and Critical Care. As a tutor, he has dedicated two entire weeks each year, full-time to the introductory clinical education and training of a single incoming resident. He has served as a faculty advisor and preceptor for MGH anesthesia residents. Dr. _____ has delivered and received excellent evaluations for teaching lectures (*e.g.*, Anesthesia Postoperative Care) to the anesthesiology residents as part of our educational curriculum. His excellent teaching skills are revealed by the praise that he receives from the anesthesia residents he supervises in the MGH operating room and on the obstetric floor. Dr. _____ is described in confidential comments to the Chair by the residents as “Excellent teacher, wonderful clinician”, “Excellent supervision/independence balance”, “Stimulating and fun to work with”, “Excellent clinically and very interested in teaching, even basic concepts were made more interesting by his teaching”, “His experience with research gives him unique taste ”, “Excellent instructor, loves to teach, very… efficient. Very patient at teaching central lines”, “Good research experience made him unique”, “Enjoyed working with him, knowledgeable”, “Very helpful and great to work with”.

Dr. _____ has actively participated in the department and hospital education missions. He has given Grand Rounds lectures on topics of ischemic myocardial injury and gene therapy: "*Adenoviral Expression of IGF-I Prevents Cardiomyocyte Apoptosis*" “*Gene Therapy in Ischemic Heart Disease – Targeting Cardiomyocyte Apoptosis*”. He serves as a mock oral anesthesia Board

examiner and has advised senior residents on examination topics. He has enthusiastically served the MGH Office for Research Career Development as a member of its Steering Committee and Poster Review Committee. He was invited to present his research findings in the Nephrology Division, Department of Medicine, MGH and gave scientific presentations at the Harvard Anesthesia Annual Research Symposium that targets audiences that included staff anesthesiologists, cardiologists, neurologists, residents/clinical fellows, researchers, and medical students.

Dr. _____'s teaching activities extend to the laboratory. He has mentored students, research assistants and research fellows who were commencing biomedical research. Specifically, Dr. _____ has mentored eight post-doctoral research fellows and one Harvard pre-med student, supervised one research assistant and 4 summer students. The scientific teaching involves daily interaction with trainees, weekly lab-meeting, and individual meeting, and includes a wide range of activities from experiment trouble-shooting, data analyses, scientific presentation, to manuscript/fellowship grant writing.

Dr. _____'s teaching activities also include the lectures he delivered nationally and internationally. He presented his scientific findings as well as such topics as academic development as a clinician to graduate/medical students, postdoctoral fellows, faculties in many clinical departments and universities in the U.S and in China. He has been invited as visiting professor to give grand rounds and research lectures. Samples of his lecture topics include "Molecular mechanism of surfactant inhibition of neutrophil NADPH oxidase", "Status of anesthesia research in the U.S.", "Physician-scientist pathway in an US academic anesthesia department", "Role of TLR4 in ischemic cardiac injury: defensive or offensive?" "Role of innate immune signaling in ischemic myocardial injury".

Significant Supporting Activities

Clinical expertise

Dr. _____ is qualified by Board certification in both anesthesiology and critical care. He has a particular interest and expertise in anesthesia for orthopeadic surgery, general surgery, and obstetrics. He has consistently practiced clinical anesthesiology ever since completing residency 10 years ago, making his research achievements even more remarkable. At present, he spends about 30% of his time providing clinical anesthesia. His clinical duties include providing perioperative anesthesia care for patients who undergo some of the most complicated surgeries, such as trauma resuscitation, thoraco-abdominal tumor resection, gastric by-pass in morbid obese patients, thoracic-lumbar spinal fusion/instrumentation, and obstetric patients with severe complications of pregnancy. Many of these patients at MGH, often referred and transferred from other hospitals, are critically ill and have a history of severe ischemic cardiac disease. Dr. _____ is tireless and efficient in his clinical work. He is dedicated to his patients, and his clinical excellence has earned him the respect of his clinical colleagues in all associated services. He serves as one of key members on the orthopeadic anesthesia team that provides anesthesia care to one of busiest surgical services at MGH. He is also a member of the obstetrical anesthesia team at MGH, providing pain control for labor and delivery, and anesthesia care for cesarean section and other obstetrical surgeries. Dr. _____ is the senior author of an obstetric anesthesia book chapter on the topic of Local Anesthetic - Pharmacology.

Service to the community

I would like to underscore Dr. _____'s service to the community. He has enthusiastically volunteered his time to serve as a member of the Steering Committee and Poster Review Committee of MGH Office for Research Career Development (ORCD). As a member of the committees, he helped to identify the issues facing MGH research community and helped to organize the annual poster celebration event. Dr. _____ served on the Review Committee for Faculty Scholarship Award of Discovery at Massachusetts College of Pharmacy and Health Sciences in Boston. As a member of the Review committee, he helped to review the research portfolio of their faculty and identify the most innovative research performed by the faculty members. Dr. _____ also serves as a member of several professional societies and communities including the American Heart Association, International Anesthesia Research Society, The American Society for Biochemistry and Molecular Biology, American Physiology Society, and American Society of Anesthesiologist. He has volunteered his time to be a mentor in Harvard Pre-Med Program since 2008.

Letters of Evaluation

Eight letters of reference were received commenting upon the proposed promotion including an impartial. Each letter provides strong support for advancing Dr. _____ to Associate Professor of Anaesthesia.

SUMMARY EXCERPTS OF LETTERS OF SUPPORT WILL BE INSERTED HERE

Thus, all letters of recommendation enthusiastically support the promotion of Dr. _____ _____ to Associate Professor of Anaesthesia with enthusiasm and none reflect any reservations.

In summary, Dr. _____ _____ is one of the most contributory physician-scientists in MGH Department of Anesthesia and Critical Care. Over the years before and since his tenure at our Department, he has demonstrated his vigorous pursuit of research and scientific insight. He is an innovative and independent investigator, with an impressive record of publication in high quality peer-reviewed journals, national and international repute, and a fully supported independent research group. He is truly one of a very few clinical anesthesiologists in our department, even in the country for that matter, who have established a robust research program while maintaining a busy clinical practice. Dr. _____'s contributions to the field of innate immune system and ischemic myocardial injury have gained him a national reputation and have significantly advanced our understanding of ischemic cardiac disease. In addition, Dr. _____ has consistently shown superb skills in teaching and delivering of exceptionally high quality clinical anesthesia, and is an outstanding advisor and mentor. We could not be more enthusiastic in recommending Dr. _____ for promotion to Associate Professor of Anaesthesia at Harvard Medical School with the area of excellence of investigation and a number of significant supporting activities. We therefore support his promotion in the strongest possible terms and look forward to your review, favorable consideration and endorsement.

Sincerely yours,

Carl E. Rosow, M.D., Ph.D.
Provost, Professor of Anaesthesia and
Chairman, DACCPM Promotions Committee

Jeanine Wiener-Kronish, M.D.
Henry Isaiah Dorr Professor of Research
and Teaching in Anaesthetics and Anaesthesia