This is an example of a Chairman's letter that was written in support of a faculty member whose scholarship is mainly in basic science and translational research who has also made significant contributions to mentoring; the candidate is also an interventional cardiologist .

Dear Dean Miller,

I hereby propose the promotion of Michael Smith, MD to Associate Professor of Medicine in the Johns Hopkins School of Medicine. Dr. Smith has held the rank of Assistant Professor for the last eight years. **The promotion is merited on the basis of Dr. Smith's research contributions in the field of vascular biology, with considerable secondary emphasis on his clinical service as an interventional cardiologist.**

Research contributions and recognition. Dr. Smith's research accomplishments relate both to basic science and to clinical investigation. In conjunction with his cardiology training here at Hopkins, Dr. Smith spent over two years as a post-doctoral fellow at the NIH. While there, he developed expertise in the vascular aspects of coagulation as well as in the then-emerging techniques of viral-mediated gene transfer. His investigation into the role of thrombin in mediating neointimal hyperplasia after arterial injury earned him a first author publication in *Nature Medicine*, a paper which has been cited 110 times. After joining the Hopkins faculty, Dr. Smith has continued to pursue many of these same research interests. He has a first-author publication on retroviral vector design and four senior-author publications related to the molecular aspects of thromboregulation in several highly rated journals; two of these papers have received >100 citations since they appeared. One of these manuscripts, focusing on the hemodynamic regulation of thrombomodulin expression, was sufficiently regarded that it was the subject of an editorial comment in *Circulation Research*, the foremost journal of cardiovascular science. In addition to these more basic investigations, Dr. Smith is also a recognized clinical investigator. He is the senior author on two manuscripts arising from investigator-initiated clinical studies and was a principal investigator and middle-author on two landmark multi-centered gene therapy clinical trials which employed adenovirus-mediated gene transfer to stimulate cardiac angiogenesis. Through his collaborations, Dr. Smith is also a coauthor on several high profile publications in *The New England Journal of Medicine, Nature Medicine and Circulation.*

Dr. Smith's primary focus of investigation centers on efforts to genetically modify vein grafts to resist thrombosis. This work was supported by an American Heart Association Scientist Development Grant, a Charitable Trust Research Grant as well as an unrestricted gift from Baxtor Biosciences. It has also produced a patent application that is currently pending. In the course of this translational investigation, he made the observation that the expression of thrombomodulin, a potent anticoagulant molecule expressed by vascular endothelial cells, was markedly inhibited in vein segments following implantation into the arterial circulation and directly resulted in a local hypercoagulable state. These findings may help to explain the high rate of early thrombotic occlusion observed clinically after coronary and peripheral artery bypass surgery. Follow-up mechanistic studies in Dr. Smith's laboratory subsequently identified

pressure-induced vascular stretch as the critical inhibitory stimulus for thrombomodulin expression. This is a significant finding because it represents a completely novel regulatory pathway for this molecule. Hemodynamic-mediated dysregulation of thrombomodulin is not confined solely to vein grafts, but appears to be a more widespread physiologic phenomenon. Notably, Dr. Smith has recently found that elevated cardiac filling pressures inhibit thrombomodulin expression by the endocardial endothelium and results in microthrombus formation in the cardiac chambers. This is an exciting finding that may help explain why patients with heart failure are at increased risk for thromboembolic events, an association historically attributed to blood stasis within dilated cardiac chambers. This work, which is currently under peer review in *Nature Medicine,* represents a fundamental shift in our understanding of thrombogenesis complicating not only heart failure but potentially atrial fibrillation and valvular heart disease as well. Identification of the molecular signaling pathways regulating thrombomodulin expression may provide unique therapeutic opportunities to prevent pathologic thrombosis in these conditions without the use of systemic anticoagulants. Dr. Smith has recently been awarded an RO1 grant from the NHLBI to study this important new area.

Dr. Smith has not neglected the implications of his basic research for clinical investigation. For example, his interest in vein graft disease led him to initiate an ambitious study aimed at identifying novel risk factors for early vein graft thrombosis following coronary artery bypass surgery. This is multi-center study based here at Hopkins that is examining the effects of aspirin resistance and the prothrombotic effects of anti-platelet factor 4/heparin antibody induction on vein graft failure assessed 6 months after surgery using state-of-the-art multidetector CT coronary angiography. The study is nearly two-thirds of the way towards its goal of enrolling 350 patients from 3 national and 2 international institutions. To fund this study, Dr. Smith was able to secure over $1 million in financial support from several pharmaceutical companies as well as substantial non-financial support from the Johns Hopkins Clinical Research Center. It is anticipated that the infrastructure developed for this observational study will lead to a follow-up interventional study that would incorporate novel strategies developed in Dr. Smith's laboratory for preventing early vein graft failure.

Mentorship. In the course of his research activities, Dr. Smith has provided direct mentorship to six clinical cardiology fellows, two surgery residents, two post-doctoral fellows from Vascular Surgery and Hematology and three medical students. Drs. Alex Brown and Edward Siegal were Four Schools Physician-Scientist Program scholars and Dr. James Waters was a surgical resident funded both by a National Research Service Award and by the Lester Foundation who spent dedicated time in Dr. Smith's laboratory. While most of his mentees remain in clinical training, three have gone on to faculty appointments at the University of Kansas City, University of Pennsylvania and the University of Oslo.

Clinical service. In addition to his research pursuits, Dr. Smith is an active interventional cardiologist who devotes approximately 40% of his time to clinical duties. This includes 14 weeks in the cardiac catheterization laboratory, weekly primary angioplasty call

coverage at both Johns Hopkins Hospital and Bayview Medical Center, and one half day a week seeing patients in clinic.

External recognition. Dr. Smith's research efforts have earned him both national and international recognition. He has recently been named for a three-year tenure to the American Heart Association Bioengineering and Biotechnology 1 National Peer Review Study Section and will be chairing a session at the upcoming 2006 American College of Cardiology Annual Scientific Sessions. He has been invited to speak about his research at numerous meetings including plenary talks at the International Society for Heart Research and at a symposium on Genetic and Cell Therapies for Cardiovascular Disease sponsored by the Mayo Clinic. In addition to these national events, he was an invited speaker at the 4th International Congress on Vascular and Endovascular Surgery in Tokyo, Japan and at the Beijing Institute for Heart, Lung and Blood Vessel Disease. He has also spoken on the topic of gene therapy for heart disease in Berlin, Germany.

Summary. Dr. Smith is a rarity in cardiology: he has excelled at fundamental and clinical research, landing an R01 in the highly-competitive present funding climate, while maintaining an active interventional practice. His work is original and creative. Dr. Smith has served as a model for numerous young trainees. By any measure (grants, publications, societies and speaking invitations), he has achieved significant national and international recognition. It is with the highest enthusiasm that I initiate and support Michael Smith's promotion.

Yours sincerely,
Chair, Department of Medicine