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Edward D. Miller, Jr. M.D.
Dean of the Medical Faculty
CEO, Johns Hopkins Medicine
100 School of Medicine Administration

Re: Promotion of Dr. Peter Espenshade to the rank of Full Professor

Dear Dr. Miller,

It is with great enthusiasm that I nominate Dr. Peter Espenshade for promotion to the rank of full professor, full time, in the Department of Cell Biology. His current rank is Associate Professor at Johns Hopkins School of Medicine, and he holds a primary appointment in the Department of Cell Biology and is a member of the Center for Metabolism and Obesity Research. Dr. Espenshade has developed an extensive track-record of scholarship demonstrated by a significant publication record of high quality primary research and review publications; he has demonstrated leadership in his primary field of regulation of cholesterol homeostasis and within Hopkins; and he has proven his commitment to the education of graduate and medical students.

By discovering that cells use their cholesterol homeostasis network to sense environmental oxygen, Dr. Espenshade created a new field of research. He is the international leader in this area. He and his students and fellows have elucidated the mechanisms that allow cells to adjust to hypoxia. These seminal studies will have broad implications for health and disease including the regulation of cell growth within tumors and the control of parasitic infections in the brain.

INTRODUCTION

Dr. Espenshade received his Bachelor of Arts degree from Princeton University in 1990, where graduated summa cum laude and Phi Beta Kappa from the Department of Molecular Biology. He received his PhD from Massachusetts Institute of Technology in 1998. With support from a National Science Foundation fellowship, he performed thesis work on the formation of transport vesicles at the endoplasmic reticulum in the lab of Dr. Chris Kaiser, currently Director of NIGMS. Dr. Espenshade completed his postdoctoral training with Nobel laureates Dr. Michael Brown and Joseph Goldstein at University of Texas, Southwestern Medical Center, where an NIH postdoctoral fellowship and a Burroughs Wellcome Fund Career Award supported his research. During his postdoctoral studies, Dr. Espenshade described the mechanism by which cells control the activity of the sterol regulatory binding protein (SREBP) transcription factor to regulate cellular cholesterol homeostasis. Based on his outstanding record of research accomplishments, Dr. Espenshade was recruited to the Department of Cell Biology as an Assistant Professor in 2002. Dr. Espenshade was promoted to the rank of Associate Professor in 2008.

RESEARCH SCHOLARSHIP

Dr. Peter Espenshade has spent the past 14 years investigating how cells measure the supply of essential molecules and adapt their physiology to changes in this supply. This work began with the studies in mammalian cells on regulation of cholesterol homeostasis and has expanded to include questions of how cells adapt to hypoxia. Throughout his work, Dr. Espenshade has demonstrated the ability to incorporate multiple model systems and experimental techniques as necessary to answer the question at hand. Currently, his laboratory carries out biochemical and genetic analyses in four fungal organisms, in mammalian tissue culture, and in mouse knockout animals.

Dr. Espenshade's research on regulation of cholesterol homeostasis and hypoxic adaptation has focused on sterol regulatory element-binding proteins (SREBPs), transcription factors which originate in the membrane of the endoplasmic reticulum and end up in the nucleus. There they activate a large number of genes, including those required for the synthesis and uptake of cholesterol and fatty acids. These events are highly regulated: When cells require sterols, SREBPs are proteolytically processed and the released transcription factor domain enters the nucleus and stimulates transcription. Elevated levels of cholesterol inhibit transcription of these target genes by a mechanism of feedback regulation that blocks cleavage of SREBP. Dr. Espenshade demonstrated that sterols control the proteolysis of SREBP by regulating its transport from the endoplasmic reticulum to the Golgi apparatus, where cleavage actually occurs. He reported these discoveries in a series of highly cited papers published in *Cell*. He found that, in the absence of sterols, a protein called SREBP cleavage-activating protein (Scap) binds to SREBP and escorts it to the Golgi apparatus, where it is cleaved by active Site-1 and Site-2 proteases residing there. In the presence of sterols, SREBP/Scap fails to enter transport vesicles and remains in the endoplasmic reticulum in its inactive form. He also helped to identify and characterize another resident endoplasmic reticulum protein Insig that binds to Scap in the presence of sterols and helps retain it.

At Johns Hopkins, Dr. Espenshade combined expertise from his graduate and postdoctoral research to use the fission yeast *Schizosaccharomyces pombe* as a model system and discovery tool for understanding mechanisms of molecular sensing with a focus on cholesterol sensing. Dr. Espenshade found that *S. pombe*, but not the budding yeast *Saccharomyces cerevisiae*, contains orthologs of SREBP, Scap, and Insig: *sre1*, *scp1*, and *ins1*, respectively. He demonstrated that *S. pombe* Scp1 senses sterols and regulates cleavage of Sre1 through a mechanism similar to way that Scap controls SREBP cleavage in mammalian cells. The development of this system opened the SREBP pathway to sophisticated genetic analysis.

In a 2005 paper in *Cell*, Dr. Espenshade reported the seminal discovery that Sre1 is not only involved in cholesterol sensing but is also a hypoxic transcription factor that activates genes required for adaptation to a low oxygen environment. Sterol synthesis requires oxygen and Sre1/Scp1 sense reduced sterols as an indirect measure of low oxygen levels. This is only the third oxygen-sensing pathway described in eukaryotes. The Sre1 pathway is distinct from the hypoxia inducible factor (HIF) oxygen-sensing pathway discovered by Greg Semenza here at Hopkins. Dr. Espenshade performed a global analysis of anaerobic gene expression in *S. pombe* and demonstrated that Sre1 is a principal activator of anaerobic gene transcription. This hypoxic function of SREBP-like proteins is broadly conserved. They are required for virulence of the clinically important, fungal pathogens *Cryptococcus neoformans* and *Aspergillus fumigatus*. Thus, the fungal SREBP pathways represent a promising antifungal drug target and Dr.

Espenshade's lab is pursuing screens for chemical inhibitors of the pathway.

Excitingly, recent unpublished data from Dr. Espenshade's lab demonstrate that human SREBP is similarly activated by hypoxia. Regulation of SREBP by oxygen likely plays a role in the growth of hypoxic solid tumors, and Dr. Espenshade is currently collaborating with Dr. Anirban Maitra, a Professor of Pathology in Sol Goldman Pancreatic Cancer Research Center, to evaluate the SREBP pathway as a target for treatment of pancreatic ductal adenocarcinoma.

Detailed studies of the fission yeast SREBP pathway resulted in a number of other major discoveries. Fission yeast lacks sequence homologs of the mammalian Site-2 protease required to release SREBP from the membrane and allow nuclear localization. Taking advantage of yeast genetics, Dr. Espenshade found that the proteolytic activation step requires a new Golgi-localized E3 ligase complex, the Dsc (defective for SREBP cleavage) complex, which contains 5 subunits. Data suggest that Sre1 is transported to the Golgi, ubiquitinated and incompletely proteolyzed by the 26S proteasome. Interestingly, the Golgi Dsc E3 ligase is homologous to mammalian ER membrane E3 ligases, such as gp78 and Hrd1, involved in ER protein quality control. Thus, the Golgi Dsc E3 ligase may be the first components to function in control of Golgi proteostasis. Structure-function studies of the Dsc E3 ligase and the role of the proteasome in this process will provide critical insight into mechanisms of protein quality control and the ubiquitin-proteasome system.

Once cleaved from the membrane, the active Sre1 transcription factor is additionally regulated by oxygen-dependent control of its DNA binding activity through a novel oxygen-sensing prolyl-4 hydroxylase Ofd1 and its direct inhibitor Nro1. While this system shares similarities with regulation of mammalian hypoxia inducible factor (HIF), the mammalian ortholog of Ofd1 (OGFOD1) is an uncharacterized enzyme. Dr. Espenshade is now investigating the physiological role of this new oxygen sensor using cultured cells and mouse genetics.

Studies of the fission yeast Insig ortholog, called Ins1, revealed that Ins1 does not regulate SREBP as in mammalian cells. Whereas mammalian Insig regulates cholesterol homeostasis by both controlling activity of SREBP and sterol-dependent degradation of the rate-limiting sterol biosynthetic enzyme HMG-CoA reductase, yeast Ins1 controls HMG-CoA reductase activity by a non-degradative mechanism. Ins1 is required for inhibitory phosphorylation of the HMG-CoA reductase active site. This negative regulatory mechanism controls sterol synthesis in response to glucose supply and represents a new paradigm for control of this key rate-limiting enzyme.

Finally, characterization of SREBP target genes in fission yeast identified a heme-binding protein Dap1 as a positive regulator of cytochrome P450 enzymes and required for ergosterol synthesis. Studies of the mammalian Dap1 ortholog, PGRMC1, demonstrated that PGRMC1 is also required for cholesterol synthesis by regulating activity of Cyp51A1, lanosterol demethylase. PGRMC1 binds to a broad range of cytochrome P450 enzymes, including the principal drug-metabolizing enzyme Cyp3A4, and likely provides a mechanism for acute, post-translational regulation of these clinically important enzymes. Knockout mouse experiments are in progress to examine the function of PGRMC1 in mammalian systemic cholesterol homeostasis.

Dr. Espenshade has exploited the strengths of both fungal and mammalian systems to make paradigm-shifting discoveries. By working between these two systems, he has and will continue to advance our understanding of how cells control the levels of lipids in their membranes and

how cells adapt to changes in oxygen supply. This foundational knowledge is critical to research into the pathophysiology of cardiovascular disease and cancer.

TEACHING SCHOLARSHIP

Dr. Espenshade has a strong record of accomplishment in teaching and mentoring graduate students during their thesis research. To date, five PhD students have completed their training with Dr. Espenshade and five more are in training. His students' accomplishments are routinely recognized by fellowship funding and research awards such as Young Investigator Day awards and meeting poster awards. All five PhD graduates are currently pursuing postdoctoral training at top labs. In addition, Dr. Espenshade also mentored eleven rotation students that pursued thesis research in other labs. Dr. Espenshade currently mentors four postdoctoral fellows. The one former postdoctoral fellow Dr. Sehgal is a senior scientist at Alnylam Pharmaceuticals, a highly regarded RNAi therapeutics company.

Dr. Espenshade is also an active participant in classroom graduate education of both medical and PhD students. From 2005-2009, he was an instructor in the Organ Systems Histology course for second year medical students. This course was eliminated in the new Genes to Society curriculum and Dr. Espenshade is now an instructor in the Cell Physiology course taught as part of the Scientific Foundations of Medicine to first-year medical students. He also continues to help teach Renal Histology to second-year medical students. Dr. Espenshade gives annual lectures in two graduate courses and has served as Course Director for the BCMB graduate program course, Cell Structure and Dynamics, since 2009. This course has an enrollment of >100 students and is one of several core courses taken by students in all School of Medicine graduate programs. Under his leadership, student satisfaction has increased as judged by course evaluations.

Dr. Espenshade also participated in four Continuing Medical Education courses directed by Dr. Peter Kwiterovich from 2005-2009. His interactions with Dr. Kwiterovich led to them coauthoring a book chapter in "The Johns Hopkins Textbook of Dyslipidemia."

ORGANIZATIONAL AND ADMINISTRATIVE ACTIVITIES

Dr. Espenshade has recently assumed an administrative role as Associate Director of the Scientific Foundations of Medicine portion of the first-year Genes to Society curriculum for the medical students. This role reflects his interest and commitment to improving education at the School of Medicine. Dr. Espenshade works to improve education through service on the Committee on MA/PhD Programs which develops School policy for graduate programs and as a member of the Institute for Basic Biomedical Sciences Vision Committee for Graduate Education which is tasked with developing a vision for the future of graduate education. The University has noticed his leadership skills, and he was selected to attend the 2009 JHMI Leadership Development Program.

Within the Department of Cell Biology, Dr. Espenshade has chaired the Hay Graduate Fellowship Selection Committee, which is annually responsible for soliciting, evaluating and awarding two graduate fellowships to departmental graduate students.

CITIZENSHIP/COMMITMENT TO JOHNS HOPKINS

Dr. Espenshade's commitment to the University is demonstrated by his service to graduate education. Dr. Espenshade is an active participant in the Biochemistry, Cellular and Molecular Biology (BCMB) and the Cellular and Molecular Medicine (CMM) PhD training programs. His service to these and other programs occurs at multiple levels including administration of graduate board oral exams (52 exams), membership on thesis committees (21 committees), and admissions interviews (84 interviews). Dr. Espenshade served as a member of the CMM Admissions Committee for two years and organized the BCMB program annual off-site retreat for two years.

Dr. Espenshade has served on numerous School of Medicine committees including the Young Investigator's Day Award selection committee and search committees for Director of the IBBS Center for Chemoprotection and for faculty in the IBBS Center for Metabolism and Obesity Research.

NATIONAL/INTERNATIONAL RECOGNITION

Dr. Espenshade's research accomplishments have been recognized by awards at multiple stages of his career. He received both predoctoral and postdoctoral fellowships to support his training. Awards that supported Dr. Espenshade's research at Johns Hopkins include the Burroughs Wellcome Fund Career Award in the Biomedical Sciences in 2001 to support the transition from postdoctoral training to a faculty position ($403,348 direct costs); the Burroughs Wellcome Fund Investigator in Pathogenesis of Infectious Disease ($450,000 direct costs); and the American Heart Association Established Investigator Award ($500,000 direct costs). In addition, he was a finalist for the Keck Foundation's 2004 Distinguished Young Scholars in Medical Research Program ($10,000 direct costs) and the Howard Hughes Medical Institute's 2009 Early Career Investigator Award. **This year, Dr. Espenshade received the 2012 Avanti Young Investigator Award in Lipid Research from the American Society for Biochemistry and Molecular Biology (ASBMB), which includes a $2,000 prize and a plenary award lecture at the 2012 ASBMB meeting.**

Dr. Espenshade's research has consistently been funded through grants from the National Institutes of Health. He renewed his R01 on its first submission and successfully competed for an ARRA Supplement to this grant. In addition, Dr. Espenshade received two R21 grants.

Dr. Espenshade is a nationally and internationally recognized leader in the field of lipid metabolism as evidenced by his membership on the NIH's Integrative Nutrition and Metabolic Processes study section since 2009. He has also served as an ad hoc reviewer for several international funding agencies. He has authored 9 reviews and book chapters by invitation.

Dr. Espenshade frequently presents his research findings through invitations to speak at international and national meetings (16 since 2006). In addition, he is frequently invited to speak in university departmental seminar series across the nation (32 seminars since 2006).

Finally, Dr. Espenshade's reputation is evidenced through the attempts at recruitment by other institutions. In 2008, Dr. Espenshade was recruited by the Burnham Medical Research Institute in La Jolla, California to set up research program in their newly formed Diabetes and Obesity Research Center in Orlando, Florida. Shortly, after his retention, Dr. Espenshade was asked to

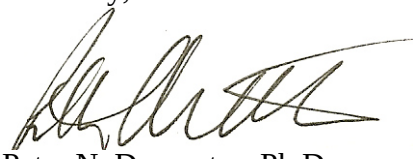
be a lead candidate in the search for the Chair of the Department of Cell Biology and Physiology at Washington University School of Medicine in St. Louis.

SUMMARY STATEMENT

Dr. Espenshade's future potential and value to Johns Hopkins School of Medicine seem almost limitless. Going forward, he undoubtedly will bring continued accolades and provide intellectual property, educational excellence, and administrative leadership to the institution. He epitomizes the Hopkins model for hiring where a small investment in a young, promising post-doctoral fellow provides a tremendous return in the future. I have no doubt that Dr. Espenshade will win a prestigious award, become a Department Director or a Dean, or launch a successful start-up at some point in the future. I am committed to Dr. Espenshade's future at Johns Hopkins and intend to do everything I can to promote his career here.

In conclusion, I am respectfully requesting your favorable consideration of my nomination of Dr. Espenshade for promotion to Full Professor in the Department of Cell Biology. I have the utmost regard for his scholarship and integrity and give him my highest possible recommendation. I am happy to answer any questions or provide any further required information.

Sincerely,



Peter N. Devreotes, Ph.D.
Professor and Director