

PROMOTION RECOMMENDATION  
THE UNIVERSITY OF MICHIGAN  
MEDICAL SCHOOL  
DEPARTMENT OF OPHTHALMOLOGY AND VISUAL SCIENCES  
DEPARTMENT OF PATHOLOGY

Rajesh Rao, M.D., assistant professor of ophthalmology and visual sciences, Department of Ophthalmology and Visual Sciences, and assistant professor of pathology, Department of Pathology, Medical School, is recommended for promotion to associate professor of ophthalmology and visual sciences, with tenure, Department of Ophthalmology and Visual Sciences, and associate professor of pathology, without tenure, Department of Pathology, Medical School.

Academic Degrees:

M.D.	2007	Yale University School of Medicine
B.S.	2000	University of Wisconsin, Madison

Professional Record:

2013-present	Assistant Professor of Ophthalmology and Visual Sciences, University of Michigan
2013-present	Assistant Professor of Pathology, University of Michigan
2011-2013	Instructor of Ophthalmology and Visual Sciences, Washington University

Summary of Evaluation:

Teaching: Dr. Rao has a passion and aptitude for teaching all levels of learners from undergraduate students, graduate students, residents, fellows, allied health providers, to practicing health care providers on a local to national, and even international level. He is routinely invited to major conferences to give lectures on specific topics for various national and international organizations such as the American Academy of Ophthalmology, Macula Society, and Association for Research in Vision and Ophthalmology. He has also been invited as a visiting professor to national and international institutions. In addition, Dr. Rao is a leader in social media in our profession, with one of the highest number of followers among all faculty internationally in his specialty area of retinal diseases. He has mentored surgical and medical retinal fellows, ophthalmology residents, medical students, graduate students and undergraduate students. His mentorship has resulted in numerous publications in peer-reviewed journals for the learners who work with him. He is currently the only physician-scientist at Kellogg who is a thesis mentor for UM PIBS graduate students. Since 2014, Dr. Rao has been involved with the Ophthalmology 733 course for graduate students and, since 2015, the Ophthalmology Resident Review Course. In 2018, his involvement with the Biological Sciences PIBS 503 Graduate course began. In all three courses, he has been responsible for content creation for didactic learning. Dr. Rao has a major social media presence on Twitter, Instagram, and LinkedIn.

Research: Since 2013, Dr. Rao has focused his epigenetic laboratory research on two themes: ocular cancers and stem cell biology. He has a multifaceted research program that has fundamentally altered the understanding of stem cell-to-retina cell fate determination and molecular (epi)genetics of ocular cancer. Specifically, he and his lab use stem cell biology, genomics, and epigenetics as languages to better understand how the retina forms, so they can learn new ways to generate the retinal cells that die in disease, with the hope of regenerating cells through cell or drug therapies. They also use these

technologies to make new insights into how eye/orbit cancers develop and to determine whether they harbor the genetics that make them vulnerable to molecularly targeted therapies.

Building on Dr. Rao's early seminal work at Harvard defining the "white space" of how epigenetic proteins known as histone methyltransferases (HMTs) regulate mammalian eye development and human eye disease, his work at Michigan demonstrated that pharmacologic EZH2 inhibitors (FDA approved for other cancers) could potentially be repurposed as the first rationally based therapeutic for infantile ocular cancers. His work is notable because there are no biologically targeted treatments for retinoblastoma, medulloepithelioma, and orbital basal cell carcinoma. Through collaborative work with Scott Tomlins, M.D., Ph.D. (UM), they have elucidated the targetable cancer genome across several types of ocular cancers that cause significant mortality and morbidity. Together with Dr. Tomlins, Dr. Noah Brown, and Dr. Bryan Betz in the Department of Pathology, he pioneered the use of liquid biopsies for NGS and PCR-based diagnostics for a difficult-to-diagnose, but lethal, cancer known as vitreoretinal lymphoma. Retinal surgeons around the country reach out to him for assistance in the diagnosis of these difficult cases by sending him their surgical samples. Today M-Labs is working with Dr. Rao to "market" this service for a wider population of ophthalmologists across the US. No other investigator has defined the targetable cancer genome of so many ocular cancers in so short a period (2016-2020).

Dr. Rao's second research theme relates to epigenetics, stem cell biology, and development. His research lab revealed for the first time how the aberrant loss of epigenetic silencing (by *Ezh2* deletion) during fetal retinal development leads to derepression of ectopic gene activity (*Six1* upregulation) and delayed photoreceptor degeneration, which causes adult-onset vision loss. Specifically, they found that the timing of *WDR5* expression regulates the neuroectoderm (retina) versus mesoderm (heart, blood) fate decision through effects on chromatin accessibility and *p53*(9). Their work introduces the transformative idea that the interplay of ubiquitous chromatin modifiers and TFs at a critical developmental window triggers retinogenesis. This work altered key concepts related to congenital retinal defects in *p53*-associated syndromes, the use of *p53* mutant human pluripotent stem cell-derived retinal cells for transplants, and potential off-target effects of 'therapeutic' *WDR5* inhibitors, which is being developed in a \$1 billion program.

Dr. Rao is a consummate collaborator. His collaboration with Drs. Sally Temple and Jeff Stern at the Neural Stem Cell Institute (New York), consists of planning a stem cell therapy trial for patients with macular degeneration in 2021. Dr. Rao will be the site surgeon, and this trial would be the first stem cell retinal transplantation clinical trial in the state of Michigan, and the first-in-human study using a unique adult stem cell source: retinal pigment epithelial stem cell. In addition to his basic science projects, Dr. Rao is very involved in clinical research that relates to non-invasive, multimodal, and enhanced-depth imaging of the retina. He uses enhanced-depth imaging OCT to image structures deep in the retina, the choroid and sclera, and image unique features of deep lesions in the choroid, many for the first time, such as choroidal macrovessels, sclerochoroidal calcification, metastases, neurofibromas in neurofibromatosis type I, and hypopigmentation in Waardenburg syndrome. His team was the first to perform wide field imaging of the far retinal periphery in living humans. His imaging work helps clinicians distinguish a variety of similarly appearing benign and malignant or pathological conditions that occur at the retino-choroidal-scleral interfaces.

Dr. Rao has published 82 peer-reviewed papers (66 since his 2013 appointment), five non-peer-reviewed publications, two books, two book chapters, and 60 abstracts. His work is in top journals including *Ophthalmology*, *Nature*, *Molecular Cell*, and *New England Journal of Medicine*. He has been invited to give presentations at major national and international conferences including the Retina

Society, Macula Society (the youngest member ever inducted), and the Association for Research in Vision and Ophthalmology (ARVO).

Dr. Rao has gained national and international recognition as an expert in epigenetic regulation of retinal development and disease and applications of stem cells for blinding diseases such as age-related macular degeneration and eye cancers. Dr. Rao has received over \$3.675 million in competitively awarded research support from the NIH, Research to Prevent Blindness, Alcon Research Institute, Knights Templar Eye Foundation, and the E. Matilda Ziegler Foundation. His work has been funded by 13 grants—including a newly awarded R01 where he is one of fewer than 15 retinal surgeons nationwide with an NIH R01 grant! He has been honored with several national and international awards such as the NEI/NIH Challenge to Identify Audacious Goals in Vision Research and Blindness Rehabilitation (2013), and the Young Physician Scientist Award from the American Society for Clinical Investigation (2017).

Recent and Significant Publications:

Li Q, Mao F, Zhou B, Huang Y, Zou Z, denDekker AD, Xu J, Hou S, Liu J, Dou Y, Rao RC: p53 Integrates Temporal WDR5 Inputs during Neuroectoderm and Mesoderm Differentiation of Mouse Embryonic Stem Cells. *Cell Rep* 30(2): 465-480.e6, 2020. PM31940490

Cani AK, Hovelson DH, Demirci H, Johnson MW, Tomlins SA, Rao RC: Next generation sequencing of vitreoretinal lymphomas from small-volume intraocular liquid biopsies: new routes to targeted therapies. *Oncotarget* 8(5): 7989-7998, 2017. PM28002793

Rao RC, Chan MP, Andrews CA, Kahana A: EZH2, Proliferation Rate, and Aggressive Tumor Subtypes in Cutaneous Basal Cell Carcinoma. *JAMA Oncol* 2(7): 962-963, 2016. PM27054919

Yan N, Cheng L, Cho K, Malik MT, Xiao L, Guo C, Yu H, Zhu R, Rao RC\*, Chen DF\* \*Co-corresponding authors: Postnatal onset of retinal degeneration by loss of embryonic Ezh2 repression of Six1. *Sci Rep* 6: 33887, 2016. PM27677711

Khan M, Walters LL, Li Q, Thomas DG, Miller JM, Zhang Q, Sciallis AP, Liu Y, Dlouhy BJ, Fort PE, Archer SM, Demirci H, Dou Y, Rao RC: Characterization and pharmacologic targeting of EZH2, a fetal retinal protein, and epigenetic regulator, in human retinoblastoma. [Used as Cover Image of November 2015 issue] *Lab Invest* 95(11): 1278-1290, 2015. PM26280220

Service: Dr. Rao provides exceptional clinical care to his patients on the Retina and Uveitis Service at the Kellogg Eye Center. Dr. Rao is an expert in the diagnosis, management, and surgical treatment of the retina and vitreous as well as ocular trauma, surgical management of complex retinal detachment, and ocular oncology. He provides safe and innovative medical and surgical care to his patients.

Dr. Rao works collaboratively at the University of Michigan with colleagues in the Department of Pathology, the Center of Organogenesis, Stem Cells and Regenerative Medicine, and the Comprehensive Cancer Center. He also serves as a vital link to our clinical, teaching, and research program at the Ann Arbor VA. In addition, Dr. Rao has served on the selection committee for the Ophthalmology Residency Committee (four years), the Medical and Vitreoretinal Fellowship selection committee (seven years), and as an interviewer for the Molecular and Cellular Pathology, PIBS Ph.D. program. At the university level, he recently served a three-year term as a medical school representative to the Faculty Senate Assembly.

On the national level, Dr. Rao is serving on the National Eye Institute's (NIH) strategic planning group and has been elected to several major societies such as the Macula Society, the Retina Society, and the American Association of Ophthalmic Oncologists and Pathologists. Dr. Rao has and is currently serving as a reviewer for several top tier journals such as *Retina*, *JAMA Ophthalmology*, *British Journal of Ophthalmology*, *Ophthalmology*, and *Cancer Research*. He has been a reviewer for many study sections including the NEI R01 study sections, France Ministry of Health, and the Department of Veterans Affairs.

External Reviewers:

Reviewer A: "...he has shown to be a dedicated teacher and mentor to medical students, residents and fellows...multiple visiting professor speaking opportunities that show his recognition among his peers...is highly regarded by his peers and senior colleagues alike due to his intellectual capacity, fund of knowledge, work ethic, scientific curiosity and scholarship. His professional work has shown to be impeccable and he strives for excellence in every project he proposes...he is an excellent vitreoretinal surgeon and clinician."

Reviewer B: "In sum, this is an outstanding original paper from the Rao lab with great impact on the field of mammalian embryonic development and novel roles for WDR5 and TP53...impressive list of over 80 original manuscripts that is way ahead of his peers...his experience was nationally recognized as he was asked to serve as a panel member of the newest NEI Strategic Plan...Dr. Rao clearly reached an *international* recognition in his field of research due to high quality and originality of his research and his ability to both write high profile original papers and invited interviews. Dr. Rao has an extensive support from non-NIH funds...The RPB award is highly competitive, given to approximately six most promising rising stars in vision research per year. The Ziegler Foundation award is also highly competitive...a research application RO1EY030989...has been funded for 5 years...Together, this is an extraordinary grant support. The Department of Ophthalmology and Visual Sciences is very fortunate to have Dr. Rao among the faculty."

Reviewer C: "...Dr. Rao is in an extremely small group of individuals to be both a) members of the Retina Society (and other esteemed clinical societies) and b) have received an R01 grant for laboratory research...Dr. Rao has recently been awarded an R01 to study...while also being able to successfully repair complex vitreoretinal conditions in the operating room is already sufficient, in my opinion, to elevate him to the next level in the academic ladder...his 82 peer-reviewed publications, 2 book chapter, and 2 books reveals an astonishing diversity of themes...Dr. Rao's time management skills and dedication to continued learning must certainly be off the charts. Dr. Rao's careful identification of several new key targets has a very strong potential for the development of new diagnostics and new therapies...he is the recipient of an impressive number of grants...is highly active in teaching and mentoring both in the clinic and the laboratory."

Reviewer D: "...possesses all of the qualities necessary for promotion with tenure...would easily achieve that level and distinction here...extensive clinical and basic science teaching...mentored dozens of medical students, residents, clinical and research fellows and post docs...depth of knowledge in the clinical environment as well as the basic research environment is truly a gift and the impacts he is making in both of these areas are invaluable...excelled with regard to scholarship and research...over 80 peer reviewed publications as well as significant NIH funding...invited and peer reviewed presentations and publications is exceptional for an individual in his eight year on faculty...volunteer service in important national and international organizations...national and international reputation and has allowed him to make an impact throughout the world...exceptional specialist in the area of retinal diseases as well as ocular oncology...made an impact on the retina


service at the University of Michigan and because of the research background that he brings to the clinic; he is one of only a handful of specialists in this area who excel in the clinical arena as well...brings great prestige to the University of Michigan Department of Ophthalmology and is also an individual who would be easily recruited to that level at many fine institutions across the country..."

Reviewer E: "...tremendous trajectory from the start of his young career and has excelled at all levels: scholarship, clinical care, and education...nationally...stellar reputation as a kind, capable, and forward-thinking clinician...manages complex cases of retinal detachments...long tenure demonstrates equipoise, great leadership and enthusiasm for his trainees...national and international reputation for producing a high quality of innovative research...imparting education to others...enthusiastic about the future of clinician scientists...progressed through what the National Institutes of Health would applaud as a committed, true clinician scientist trajectory...perfect ascension to the role of independently funded clinician scientist at the Assistant Professor level!...truly outstanding work at the Assistant Professor level...sought out clinical-mentor amongst his residents and retina fellows... critical recruitment piece for incoming residents and fellows ... nationally and internationally Dr.Rao is clearly a bright and rising star...clearly has tremendous qualifications to advance to the Associate Professor with Tenure position..."

Reviewer F: "I consider him a leader in our field and deserving of promotion. Dr. Rao has quickly gained an international reputation as a skilled ophthalmic clinician and researcher. He has been remarkably productive...been continuously funded since setting up his lab at the Kellogg Eye Institute in 2013...The breadth of his research interests are remarkable... He is a great example of a physician who can manage to integrate a busy clinical practice while continuing to pass along his acquired knowledge to his peers and students of every level. Given his level of productivity, I am certain he would be promoted were he a faculty member [here]."

Summary of Recommendation:

Dr. Rao has shown excellence and productivity in his clinical work, teaching, research, and service and is already a sought after and recognized national and even international authority in his field. With his enthusiasm, limitless energy, and determination, combined with his skills and expertise, he will continue to be an innovator and leader in the international setting in the years to come. We enthusiastically recommend Rajesh Rao, M.D. for promotion to associate professor of ophthalmology and visual sciences, with tenure, Department of Ophthalmology and Visual Sciences, and associate professor of pathology, without tenure, Department of Pathology, Medical School.



Marschall S. Runge, M.D., Ph.D.  
Executive Vice President for Medical Affairs  
Dean, Medical School

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