Editorial

The Clinician-Scientist in Vision Science: A Rare and Endangered Species

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The history of the clinician-scientist is nearly as long as the history of hypothesis-driven science. William Harvey, a contemporary of Galileo in the 16^{th} and early 17^{th} centuries, was the English physician who first elucidated the circulatory system and could be considered the first modern clinician-scientist. In the ensuing half millennium, many of the seminal advances in medicine have come from medical doctors performing research: Edward Jenner and the smallpox vaccination; Robert Koch and the discovery of tuberculosis; Alexander Fleming and the discovery of antibiotics; Jonas Salk and the development of the polio vaccine; and Michael Brown and Joseph Goldstein and the linkage of cholesterol to atherosclerosis, to name only a very few. While the granting of the Nobel Prize for Medicine or Physiology is a complicated process (and not all outstanding work is so recognized), it is a proxy marker for scientific work of great value to medicine. Of the 77 US-trained recipients of this prize through 2015, 46 held the MD degree (including two MD/PhDs).

Within ophthalmology and vision science, clinician-scientists have also made many of the fundamental contributions that shape how we practice today. Adolf Weber, Ludwig Laqueur, and Albrecht von Graefe were all 19^{th} century German ophthalmologists who discovered the association of intraocular pressure with glaucomatous neuropathy and developed medical and surgical treatments to lower pressure that survive in modified forms to this day. The intraocular lens was developed by Harold Ridley, a mid-century British ophthalmologist, and the phacoemulsification technique used to perform cataract surgery was invented by Charles Kelman, an American ophthalmologist. In more recent times, the development of argon lasers for treatment of retinal disease by Francis L'Esperance, the discovery of vascular endothelial growth factor (VEGF) by Judas Folkmann leading to the development of anti-VEGF drugs by Napoleone Ferrera and colleagues, and the first approved gene therapy for hereditary disease developed by Jean Bennett, Al Maguire, and Samuel Jacobson are also the work of physician scientists. This just scratches the surface of accomplishments in our field by trained physicians performing research in eye disease.

It can be argued that physician-scientists have been successful in advancing our field thanks to their unique perspective. By understanding both the state-of-the-art in medical research and the nature of the unsolved clinical problems that are need be addressed, the clinician-scientist is uniquely positioned to advance the field. The US National Institutes of Health (NIH) has recognized the importance of the physician-scientist and has created a series of federally funded training programs to ensure a continuous pipeline of new clinician-scientists. This includes the Medical Scientist Training Program (MSTP), a training program leading to dual MD and PhD degrees over approximately seven to nine years of training for students interested in medical research, as well as the K08, K12, and K23 physician-scientist training grants. The latter are grants for trained clinicians (MD, OD, MD/PhD, or OD/PhD) to perform mentored postdoctoral training for up to five years, with substantial protected time (at least 50%). Several foundations, particularly Research to Prevent Blindness and Foundation Fighting Blindness, are also highly committed to supporting the career development of physician-scientists in vision science and provide support grants for individuals throughout their career trajectory.

For the individual who follows the full career path as a clinician scientist, the course to independent research is a long one. Graduate and postgraduate training typically includes four years of medical school, four years of graduate school, one year of internship, three years of ophthalmology residency, one to two years of clinical fellowship, and up to five years of postdoctoral training on a K- award. Thus the clinician-scientist trains nearly 20 years after college before pursuing a fully independent research career. The arrival at independence in the United States is typically marked by successful application for an NIH Research Program Grant (RPG), most typically an R01 award, which supports much of the fundamental and applied

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research in ophthalmology in the United States today. The National Eye Institute (NEI) currently budgets nearly $500 million annually to support approximately 1200 RPGs. Although the R01 cannot mark the impact of research, it is a useful proxy for individuals doing research deemed worthy by peers. Functionally it is also a marker of a successful laboratory, because it is very difficult to maintain an active research program (outside sponsored pharmaceutical studies) without NIH support.

So how do clinician-scientists fare in this domain? In this issue of *Translational Vision Science & Technology* (*TVST*), Liu et al.[1] examine the success of vision science clinician-scientists since 1962 to the present in obtaining and maintaining federal research support. Overall, they identify 386 clinicians who received NEI R01 funding since 1985. The proportion of these clinicians who also hold a PhD has been increasing, from about 8% before 1985 to 43% since 2015. Most of this research has been bench-based (there are other funding categories for clinical trials besides R01). The demographics of the clinician-scientist is also evolving, with the proportion of women increasing from 6% before 1985 to 31% today. Previous studies conducted over the period of 1996 to 2010 showed that the success rate for NEI K-awardees receiving their first R01 was ~48%.[2] The current study was most interested in the fate of these individuals—did they maintain a productive research career? There have been 175 clinician-scientist R01 awardees since 1995. Overall, 110 have received a second NEI R01 at some point in their career for a total of ~63%. However, it was noted that only about 4% appeared to have maintained continuous funding, with 50% having not received additional R01 funding 10 years after first R01 received.

These data, taken at face value, are concerning. The investment the US Department of Health and Human Services makes in clinician-scientists is large. The clinician-scientist with an MSTP-funded MD/PhD combination degree who completes a residency and a K-award will have been funded by the US government for more than 15 years, with total funding for their education exceeding $1 million. If 96% of these individuals in vision science fail to maintain a continuously funded research program, it would appear the system is failing. However, there are a number of details in the current work that need to be resolved before the alarm should be sounded. First, there is no control group of PhD scientists for comparison—how many investigators in general in the NEI move smoothly to second R01? Overall, the current success rate of established investigators at NEI in renewing grants is about 40%, as is the success rate of "at-risk" investigators who would have no NIH funding if their grant is unsuccessful (Michael Steinmetz, PhD, NEI, personal communication). Based on this, the overall 60% success rate for clinician scientists achieving multiple R01s over time may not be markedly different than the overall success rate for all investigators at NEI; these should be compared in detail using identical methodology. Second, there are additional details in terms of timely renewal that are critical. Many awardees will request no-cost extensions of their awards while they apply for new grants. It is not clear from the current study how many clinician-scientists maintained their awards and re-funded after no-cost extension. Importantly, the current study did not look at non-R01 funding mechanisms, including R03, R21, U10, R24, SBIR, and STTR grants. Some of these (particularly the R24) are much larger grants than the R01 and would be a mark of success for an investigator; in other cases a smaller grant such as R21 could be used to develop a new idea that leads to subsequent R01. SBIR and STTR are grants to small businesses and might be pursued by individuals seeking to translate their work to the clinic. Additionally, grants in institutes outside the NEI were not considered; some vision research is funded by other institutes such as the National Institute of Aging, the National Institutes of Diabetes and Digestive and Kidney Disease, the National Institute of Neurological Disorders and Stroke, and the National Institute of General Medical Sciences (NIGMS). And many investigators will have their more mature work supported by other sources including foundation grants, philanthropy, and industrial partnerships.

(My own story is contained within the data in the current work and is one reason I am concerned this work does not completely capture the success of the K-award system at NEI. I completed my MD and PhD via MSTP in 1994 and completed an NEI K08 in 2004. I was fortunate to have my first NEI R01 funded at the conclusion of the K-award and have been fortunate to be continuously funded by NIH since. However, in the current work I appear as a "failure"; after my first NEI R01 ended in 2008, I did not receive another such award until 2012. However, during the time between NEI R01s, I received an R01 from NIGMS, an R03 from NEI, and was Principal Investigator on an SBIR grant from NEI, none of which would have been counted in the current work).

Although the direness of the clinician-scientist's status within vision science may be debated, without question there are concerns about the viability of this career path. Since 1995, the US has produced about 10,000 ophthalmologists (and a larger number of optometrists). With only 175 clinician-scientists receiving federal funding, this suggests that less than 2% of our graduates are pursuing successful careers in research. The representation of clinician-scientists on NIH study sections, who score grants to guide funding decisions, is low on some critical study sections. For instance, the clinician-scientist interested in pursuing basic vision science would likely have grants assigned to the "Biology of the Visual System" study section. This group currently has 16 standing members, only one of whom has a medical degree. Absence of a clinician's viewpoint may lead to poor scoring of clinically-relevant basic research. Relative to their clinically-active colleagues, clinician-scientists are generally paid less, due in part to the NIH "cap" on covered salary which sits below the mean starting compensation of the typical ophthalmology assistant professor according to the American Association of Medical Colleges. This leads to financial incentive to abandon research for clinical practice if grant funding becomes scarce. Conversely, the clinician-scientist's salary is generally substantially higher than the PhD scientist's, and so more of their grant will be needed to cover their own compensation. (For a typical R01, the difference in salary support for a given effort could be enough to cover the majority of stipend for a graduate student or postdoctoral fellow, putting the clinician-scientist's laboratory at a disadvantage). Relative to the basic scientist, the clinician-scientist's time may be in higher demand, and shifting needs for clinical coverage or resident and clinical fellow training may encroach on protected research time. And finally, there is the real threat to the clinician-scientist that funding gaps will need to be bridged through increased clinical service. Taking on more clinical duties is far easier than giving them up, because established patient practices need to be distributed to other individuals.

The work by Liu et al.[1] in the current issue of *TVST* puts the spotlight on the fate of clinician-scientists in vision science in the United States and appropriately calls attention to whether conditions are favorable for their success. NIH-wide data on the funding success of MD, PhD, and MD/PhD applicants has been performed, and shows nearly equivalent success between groups (https://nexus.od.nih.gov/all/2012/04/27/does-your-degree-matter/). I am not aware that similar analysis has been done within the NEI specifically. With new leadership starting at the NEI of the NIH, the timing is excellent for NEI to re-evaluate its programs, assess the current needs for clinician-scientists in eye research, and devise mechanisms for their support.

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