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Breaking the Mold: Partnering with the National Institutes of Health Intramural Research Program to Accelerate PhD Training

Katie Soucy,[1]
Rick M. Fairhurst,[1]
Geoffrey M. Lynn,[1]
Kevin Fomalont,[1]
Thomas A. Wynn,[1] and
Richard M. Siegel[2,*]

Immunology is an increasingly interdisciplinary field. Here we describe a new model for interinstitutional graduate training as partnerships between complementary laboratories. This collaborative model reduces time to graduation without compromising productivity or alumni outcomes. We offer our experience with one such program and thoughts on the ingredients for their success.

Despite tremendous recent advances in technology, communications, and the translation of basic scientific discoveries into new diagnostics and therapies for human diseases, graduate training in immunology and other areas of biomedical research in the United States has remained remarkably unchanged since the early 20th century, with coursework and laboratory rotations taking up much of the first 2 years, and a single mentor shepherding the student through a research project over 3 or more subsequent years. The time to graduation still averages more than 6 years in the biomedical sciences field (http://www.nsf.gov/statistics/2016/nsf16300/), with uncertain benefit of this extended time to research productivity and career advancement.

Partnering with the National Institutes of Health Intramural Research Program for PhD Training

The Intramural Research Program (http://irp.nih.gov/) of the National Institutes of Health (NIH), with its main campus in Bethesda, Maryland, comprises nearly 1000 laboratories conducting research across a wide spectrum of biomedical sciences, and places a strong emphasis on translational research powered by the NIH Clinical Center. Despite these strengths and a cadre of world-class scientists, the NIH does not confer graduate degrees, and until the late 1990s no formal mechanism existed for graduate students to train at the NIH. In 1999, during Harold Varmus' tenure as the NIH Director, he and Michael Gottesman, the NIH Deputy Director for Intramural Research, founded the NIH Graduate Partnerships Program (GPP; https://www.training.nih.gov/programs/gpp), which established PhD training programs as partnerships between the NIH and select universities.

More than a dozen different PhD partnership programs, using two main training models, have been developed under the aegis of the NIH GPP. In several programs, including the NIH–University of Pennsylvania GPP in immunology (http://www.med.upenn.edu/immun/NIHPartnership.shtml), students pursue PhD coursework and rotations at the partner institution and do their PhD thesis work under the supervision of a principal investigator at the NIH. The second, which we discuss in depth here, is a novel model where students design a PhD project with two research supervisors, one at the NIH and one at the partner institution, and conduct an equal amount of research in each laboratory. This model works particularly well with European PhD (or DPhil) programs, in which students have no required coursework or rotations, and commit early to their research supervisors and project. This format allows for 2 years of research in each of the partner laboratories within a 4-year timeline.

The origin of dual-mentored PhD training at the NIH goes back to 2001, when Michael Lenardo, an immunologist at the NIH, partnered with John Bell and Andrew McMichael at the University of Oxford, and Keith Peters at the University of Cambridge to incept the NIH–Oxford–Cambridge Scholars Program (NIH–OxCam Program, http://oxcam.gpp.nih.gov/), which has since trained more than 200 graduate students. The NIH–OxCam Program is not limited to a specific discipline, but its students often choose to study immunology and infectious diseases, building on particular strengths at these institutions. In a hybrid of American and European PhD training models, the program selects students in March, before they have committed to a pair of co-mentors, and then helps them over the next 4 months to match with a university partner and mentor with the guidance of an NIH-based 'Class Dean' and visits to the two partner universities. Advised by their two co-mentors, students write a thesis project proposal in August and then officially matriculate at Oxford or Cambridge in October. In designing their training plans, students consider which aspects of their research they will conduct at each site and draft a timeline that typically comprises two large blocks of time (e.g., 1.5–2 years) at each institution, which are often punctuated by shorter trips to the partner laboratory. Other NIH–European PhD partnerships (https://www.training.nih.gov/programs/gpp/institutionalpartnerships/longform) have followed a similar model.

The strengths of patient-based translational research at the NIH and partner institutions have made the NIH partnership PhD training very attractive to MD/PhD students, and since 2006, the NIH MD/PhD Partnership Training Program (http://mdphd.gpp.nih.gov/) has enabled combined-degree students to obtain their PhD training in an NIH GPP. More than 80 MD/PhD students have now obtained their PhDs in this way, mostly in the NIH–OxCam Program.

The Power of Partnership: Outcomes from Dual-Mentored PhD Training

Putting together mentor pairs with complementary expertise is critical to leveraging the power of dual-mentored PhD training. Successful pairings often combine common interests with discrete areas of expertise. Examples of such pairings include one of us (T.A.W.) with expertise in the immunological mechanisms underlying fibrosis at the NIH, and Professor Ludovic Vallier with expertise in stem cell biology at the University of Cambridge. With this mentorship pair, Trey Gieseck studied how hepatocytes derived from induced pluripotent stem cells can be used to reverse organ fibrosis and facilitate organ regeneration, publishing four first-author and two coauthored papers on this work [1–6]. This project is now being continued by another student, demonstrating that PhD partnership projects can generate continuing collaborations. Another one of us (R.M.F.) with expertise in malaria pathogenesis and immunity at the NIH co-mentored Jessica Hostetler with Professor Julian Rayner, a senior group leader at the Wellcome Trust Sanger Institute with expertise in genetic techniques, to study malaria parasites. Jessica identified novel candidate vaccines for malaria caused by *Plasmodium vivax*, a relatively neglected pathogen, advancing our understanding of *P. vivax* pathogenesis and immunity [7–10]. To better illustrate the challenges and rewards of dual-mentored partnership PhD training from a student perspective, Geoffrey Lynn writes about his experience in vaccine research at the NIH and University of Oxford (Box 1).

Box 1. In His Own Words: Bridging Continents and Disciplines, Geoffrey Lynn's Experience in a Dual-Mentored PhD Program

Geoffrey Lynn completed his PhD research under the mentorship of Robert Seder, an immunologist at the NIH Vaccine Research Center, and Len Seymour, a gene therapy and vaccine design expert at the University of Oxford. In his PhD work he developed and characterized a novel vaccine adjuvant incorporating Toll-like receptor agonists into a synthetic polymer and published his findings in Nature Biotechnology [12]. He is currently a postdoctoral research fellow at the NIH, and plans to complete his MD degree at Johns Hopkins University in 2019.

My first task as a student in the NIH–OxCam Program was to propose a thesis project that I would complete in my two labs. The uncertainty surrounding the potential outcome of this proposition was simultaneously intimidating and exhilarating: for the first time in my education I would have a hand at writing my own future.

After 2 months of planning, my two mentors and I agreed on my project: I would develop vaccines for infectious diseases using polymers chemically synthesized at the University of Oxford, which I would then test for efficacy in animal models in the Vaccine Research Center at the NIH. The initial idea was to combine the specializations of two departments. Within months, however, the scope of my project expanded to eventually involve five departments in three countries. I worked with Karel Ulbrich at the Institute of Macromolecular Chemistry in Prague, Czech Republic, to learn advanced chemistry methods to synthesize polymers. I then used these polymers as scaffolds for attaching small molecule immunostimulants, which I synthesized in the Imaging Probe Development Center at the NIH, to generate vaccine adjuvants for safety and efficacy testing at the University of Oxford and the NIH Vaccine Research Center. Following rapid progress in polymer synthesis, I also collaborated with Olivier Lantz at Institut Curie in Paris to develop therapeutic cancer vaccines. The reason for my travels between departments and institutions was to increase my overall efficiency. I went to the specific lab that specialized in whatever technique or chemical synthesis method I needed to perform. In the open structure of the NIH–OxCam Program, I was physically unrestricted by geography and mentally unconfined by a predetermined program of study.

A major strength of the NIH–OxCam Program was that it enabled me to be a powerful conduit for information sharing between scientific nodes. Chemistry departments got access to knowledge and model systems that were previously inaccessible, and immunologists got new vaccines and chemical tools that directly resulted from this crosstalk. Our collaborative network continues to expand and is yielding new scientific insights as well as promising therapies.

The overarching result for me personally was that my own maturation as a scientist was accelerated. The program necessitated that I bridge departments and disciplines, and in so doing I had to quickly gain confidence in leading my own project. The broader implication is that my training countered the tendency toward scientific isolationism fortified by institutional and departmental boundaries. In offering a new paradigm for graduate student education, the NIH–OxCam Program is breaking down barriers and empowering students to be the conduits that link the world's scientific nodes.

Despite the challenges of navigating two laboratories and institutional environments, we have found that the expected 4-year timeline of the program shapes the students' expectations early on, leading more than 75% of students to submit their thesis within 5 years, with a median time to degree of 4.3 years for NIH–OxCam graduate students, more than 2 years lower than the median of 6.5 years for traditional biomedical graduate students in the United States. While this may cause concerns that students may publish fewer papers from their PhD work, this has not been the case. Students have published an average more of more than four research papers from their PhD work, two as first author. These papers have also been quite impactful. From 2002 to 2014, first-author publications have been collectively cited 9142 times, averaging 61 citations per publication (https://oxcam.gpp.nih.gov/research/overviews.asp). Communicating clear expectations for the training timeline and productivity to students has helped enable their successes.

For many of these students, the accelerated timeline of PhD training has continued in the progression of their academic

careers. Although the average age to the first NIH R01 grant is now around 42 years (http://grants.nih.gov/grants/new_investigators/), NIH–OxCam PhD program alumni have received R01 funding for the first time by an average age of 33 years. A notable example is alumnus Paul Tesar, a former NIH–Oxford PhD student and recipient of an R01 grant at age 34, who attributes much of his early success to his graduate partnership training and the early research independence he experienced while developing a new type of mouse stem cell [11]. Awards won by NIH–OxCam Program alumni include a MacArthur 'Genius' Grant and National Science Foundation CAREER Award to Danielle Bassett within 5 years of completing her PhD.

Successes and Challenges of Partnership PhD Training at the NIH: A View from 15 Years Out

After supervising numerous trainees and administering the NIH–OxCam Program, we believe that the dual-mentored PhD paradigm has had great success, but also some challenges over the past 15 years. Keeping the leaders and administrations of partner institutions united on the program's goals and funding structure requires continuous efforts. Funding some aspects of graduate training within the NIH, a US government institution, has also posed some challenges. Fortunately, private charities, including the Foundation for Advanced Education in the Sciences (https://faes.org/), and the International Biomedical Research Alliance (http://biomedalliance.org/) have been enormously helpful in funding and organizing housing, meetings, and leadership training opportunities that the Federal Government cannot provide.

Working with two mentors on two continents requires students to be effective communicators and self-starting, independent learners–qualities we try to identify during the admissions process. Some students we encounter during interviews, while extremely qualified academically, seem better suited for traditional PhD or MD/PhD programs. From informational teleconferences and the interview visit to the NIH, students usually receive sufficient information to self-select the program based on their abilities, leading to a very high matriculation rate of accepted students (average 65–75%). This selectivity has not come at the expense of diversity, as 40% of students come from public universities, 48% are women, and 10% self-identify with underrepresented minority backgrounds. Remarkably, despite the absence of laboratory rotations, the proportion of students needing to change mentors for lack of a good match is extremely low. For students well-suited to dual-mentored PhD training, the creativity they use to design interdisciplinary research projects, the communication they need to keep their mentors aligned with their research goals, and the empowerment they feel when taking ownership of their project are strengths that make the dual-mentored partnership approach a very attractive paradigm for 21st-century graduate training in immunology specifically and biomedical research generally. For MD/PhD students in particular, having one more clinical and one more basic science-oriented mentor can be particularly beneficial. Beyond the NIH, other research institutes that do not confer PhD degrees are increasingly partnering with universities, and may look to our experiences with dual-mentored NIH partnership training for guidance. For students in traditional PhD programs, participating in internal or external collaborations as part of their PhD training may be a way to experience some of the features of a dual-mentored PhD experience, and should be encouraged.

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[1]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA
[2]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892, USA

*Correspondence: SiegelR@mail.nih.gov (R.M. Siegel).

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