

Emerging Subspecialties in Neurology: Fellowship in experimental therapeutics of neurologic disease

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Fellowships in experimental therapeutics are one solution to the challenge of developing the next generation of clinical researchers in the neurologic sciences. Through didactic teaching, mentoring, clinical research experience, hands-on training in trial design and execution, and preparation in grant writing, fellowships in experimental therapeutics prepare new investigators for clinical research careers in academic medicine or industry.

BACKGROUND This is an exciting time in medicine. There are rapid advances in our understanding of pathologic mechanisms of disease, in conjunction with an amazing potential to alter the course of disease by targeting the fundamental molecular changes that cause disease. Advances in treatment are possible in all areas of neurology—from cerebrovascular disease, epilepsy, and neuromuscular disorders, to hereditary and degenerative disorders such as Huntington disease, Parkinson disease, and Alzheimer disease. Clinician scientists are needed to help translate these rapid advances in basic sciences into improvements in patient health.

Even with this unprecedented growth in opportunities, the number of college graduates applying to medical school has been relatively flat, and too few medical graduates pursue a clinical research career. Despite attempts to increase the attractiveness of clinical research by instituting government-funded clinical research training awards, the average age at first independent federal grant (R01) for an MD is 44 years, significantly older than 2 decades before.^{1,2}

Concerns about the dwindling number of physician scientists have led the NIH and Association of American Medical Colleges (AAMC) to develop initiatives to address this gap.^{3–6} The 2002 NIH Roadmap Initiative aimed to bridge the gap between pathophysiologic advances and clinical care. The AAMC released a report in 2006 calling for medical schools and teaching hospitals to incorporate courses in clinical and translational research into medical stu-

dent and residency training.⁷ Ensuring an adequate future workforce is one of the major challenges facing the national clinical research enterprise.²

There are a variety of postresidency training options available for individuals interested in a career in clinical research in the neurologic sciences. Many universities offer Masters of Science in Clinical Research, Masters in Public Health, or certificates of completion. These programs are typically didactic in nature, offering courses in biostatistics, epidemiology, pharmacology, ethics of human research, grant writing, and clinical trial design. The NIH has developed grant programs targeted at individual investigators: the K23/K08 awards are designed to help young investigators early in their career to develop mentored clinical research proposals with the goal of independence; transitional awards such as the K12 program are specifically designed to transition young investigators to a K23, K08, or early R-series award. Many professional organizations and disease foundations offer competitive clinical research training grants which offer salary support and variable amounts of protected time for mentor-driven research projects, typically for 1–2 years. Some examples include the American Academy of Neurology's Clinical Research Training Fellowship, the Muscular Dystrophy Association's Clinical Research Training Grant, The Parkinson's Disease Foundation Fellowship for Clinical Neurologists, and the Epilepsy Foundation's Research and Training Fellowships for Clinicians.

TRAINING PROGRAMS IN EXPERIMENTAL THERAPEUTICS Experimental therapeutics, the process of translating basic science discoveries into novel therapeutic approaches for patients, is one aspect of clinical research training that has yet to receive much targeted attention in neurology. Experimental therapeutics has long been considered part of training in pharmacology and oncology where there is a post-fellowship path for clinical trial training. The Ohio

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State University has a Fellowship in Clinical Pharmacology open to licensed physicians interested in a career in clinical pharmacology and clinical trials (<http://www.clinpharm.osu.edu/fellowshipprogram/index.cfm>). There are no ACGME-accredited fellowship training programs in experimental therapeutics. The American Academy of Neurology online searchable fellowship directory (<http://www.aan.com/education/fellowships/>) identifies many programs with experimental therapeutics listed as a primary or secondary topic of the fellowship (table).

Training opportunities outside of degree and fellowship programs also exist in neurology. The National Institute of Neurological Disorders and Stroke-sponsored Clinical Trial Methods Course in Neurology is a 1-week intensive training in core principles of clinical trial design and conduct for fellows and young investigators. The program focuses on mentored development of a clinical trial protocol.

FELLOWSHIPS IN EXPERIMENTAL THERAPEUTICS IN NEUROLOGY

Two experimental therapeutics training programs in neurology serve as complementary models for future clinical research training programs. The University of Rochester Medical Center's Fellowship in Experimental Therapeutics of Neurological Diseases (URMC Program, <http://www.urmc.rochester.edu/neurology/training/experimental-therapeutics.cfm>) trains fellows for careers as clinical neuroscientists involved in both clinical and translational research. The UCB Fellowship in Neurology and Clinical Drug Development represents a collaboration between UCB Biosciences, University of North Carolina Eshelman School of Pharmacy, Duke University, and the Hamner Institutes for Health Sciences (UCB program, <http://www.pharmacy.unc.edu/programs/fellowships/ucb-fellowship-in-neurology-and-clinical-drug-development>) and prepares fellows for careers in pharmaceutical medicine. Both programs are postresidency training for MDs or MD, PhDs who have completed their training in internal medicine or pediatrics and clinical neurosciences. The UCB program accepts 1 fellow per year for 2 years of training. The URMC program accepts 2–4 trainees per year for periods of 2–3 years. Fellows are trained in the design, implementation, analysis, reporting, and ethics of clinical trials, cost benefit analysis, and outcomes research.

Both programs provide both preceptorial and didactic teaching, but with slightly different emphasis. In both programs fellows participate in coursework in biostatistics, data analysis and computing, and ethics in research, which can be expanded into a formal Master's degree program (MPH, MS-CI, MS-Tr). The UCB program has a larger emphasis on pharmacology, with courses in pharmacokinetics, dynamics, or genetics, and molecular biology and drug metabolism. The URMC program has developed 3 seminar programs to complement formal coursework: 1) Working Group on Clinical Trials, 2) Mechanisms of Disease and Therapeutic Development Workshop, and 3) Mellow Fellows. The twice-monthly Working Group Seminars provide an interactive forum for Neurology, Biostatistics, and Community and Preventive Medicine junior and senior faculty to discuss planned or in progress clinical trials, pilot data, and ideas for future studies. This forum is complemented by Mellow Fellows, an informal research-social meeting held monthly designed to provide fellows an opportunity to brainstorm new ideas with experienced investigators, biostatisticians, and each other. The Mechanisms of Disease Workshop focuses on the molecular underpinnings and basic science advances that may lead to therapeutic interventions.

Table Fellowships in neurology offering experimental therapeutics training^a

Primary topic	Institution name
AIDS	Beth Israel Deaconess Medical Center
Autonomic disorders	Clinical Neurocardiology Section, DIR, NINDS, NIH
Basic research	UMDNJ–New Jersey Medical School
Behavioral neurology	University of Rochester
Cerebrovascular disease/stroke	University of Rochester Medical Center
	Medical University of South Carolina
Epilepsy	University of Pittsburgh
	University of Rochester Medical Center
Experimental therapeutics of neurologic disorders	University of Rochester Medical Center
Memory disorders	University of Alabama at Birmingham
Movement disorders	University of Rochester Medical Center
	Duke University Medical Center
	Johns Hopkins School of Medicine
	Rush University Medical Center
	Oregon Health Sciences University & Portland VA Medical Center
	Medical College of Georgia
	The University of Maryland
	Cleveland Clinic Foundation
	Massachusetts General Hospital
	Columbia University Medical Center
	University of Chicago
	University of Florida Center for Movement Disorders and Neurorestoration–McKnight Brain Institute
	Baylor College of Medicine
Multiple sclerosis	University of Rochester Medical Center
Neuro-ophthalmology	University of Rochester
Neuromuscular disorders	University of Rochester Medical Center

^a Data compiled from AAN Fellowship online directory.

Both programs are flexible and tailored to a great degree on the needs of the fellow. In both programs the first year is largely comprised of coursework and designing and implementing fellow-initiated research projects.

During the first year fellows in the UCB program participate in brief exposures to various aspects of drug development at UCB Biosciences complemented by fellow-initiated research projects at Duke, UNC, or the Hamner. The UCB Biosciences experience expands to an intensive (4 days/week), hands-on participation in all aspects of drug development during the second year. This directly builds upon core knowledge in developing, reviewing, and composing protocols and regulatory submissions, and fellows magnify understanding of the process of execution of phase I–III clinical trials, including site selection, start-up, and monitoring, as well as issues of human subjects protection and recruitment.

The heart of the URMC program is its formal one-on-one mentoring program. The preceptorial team always includes a clinical neuroscientist and biostatistician. A basic neuroscientist and other clinical neuroscientists are often involved. The trainee and mentors work together to develop a long-term plan for training that includes development of one or more hypothesis-driven clinical research projects. The team meets regularly, typically on a weekly basis, to review and discuss the progress of the project. As it is not typically feasible to conceive, develop, and execute a clinical trial from beginning to completion during the fellowship period, each trainee is invited to participate in ongoing clinical trials at various stages of execution in order to directly learn about the process of drug development. Trainee roles have included medical monitor, steering committee member, subinvestigator, and writing group member, among others. Direct experience is a critical component of the educational program.

TRACK RECORD Programs such as the UCB program and URMC program have served as a launching pad for careers in academic medicine focused on experimental therapeutics. From URMC's 48 past trainees alone, graduates have acquired over 70 extramural grants, including 17 NIH R awardees and 15 NIH K awardees.

DISCUSSION There are many options open to the postresidency neurologist interested in clinical research. These include federally funded competitive programs, masters programs in clinical or translational research, and grants funded through subspecialty or professional

organizations. Many fellowships offer training in a variety of aspects of clinical research as part of their subspecialty training. The URMC program and UCB program are 2 of a growing number of programs that focus on experimental therapeutics and opportunities for direct clinical trial experience. Trainees spend the majority of the fellowship program either working directly with industry or paired with a mentor with experience in their field of interest. This opportunity combined with didactic fundamentals and the skill set for securing funding prepares new investigators for an academic career in clinical neuroscience.

AUTHOR CONTRIBUTIONS

J. Statland: drafting/revising the manuscript, acquisition of data. R. Griggs: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision, obtaining funding. E. Augustine: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

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