Experimental Neurotherapeutics: Surfing the Tidal Wave of New Opportunities

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The subspecialty of experimental neurotherapeutics trains neurologists in discovering and developing new treatments for neurologic diseases. Based on development of exciting new treatments for genetic and inflammatory diseases, we predict that there will be many other breakthroughs. The job market has expanded rapidly in academia, the pharmaceutical industry, government, and not-for-profit sectors; many new opportunities can be anticipated. The burgeoning opportunities in the field mandate that training address the challenges of overcoming obstacles in therapeutic discovery, implementation science, and development of affordable and equitably available treatments.

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Neurology has changed from a predominantly diagnostic specialty to one at the leading edge of novel treatment development. Despite major advances, the burden of neurological diseases continues to increase worldwide, and many new treatments are inaccessible to the population at large.[1] There is a great need for developing the next generation of clinical neuroscientists who are focused on preclinical and clinical therapeutic development, implementation science, and policy development. This article considers training and career opportunities in neurotherapeutics, challenges in the field, and potential solutions.

Historical Perspective

Experimental neurotherapeutics[2]—discovering and developing novel treatments for neurologic diseases—has emerged as a subspecialty field in neurology. In the 1980s, the need to train clinical trialists in neurology led to the first training programs in therapeutic development, clinical trial methodology, and regulatory science in the Intramural Program of the National Institute of Neurological Disorders and Stroke (NINDS) and other academic neurology departments.[2] In 1997, a subspecialty society, the American Society for Experimental Neurotherapeutics (ASENT) was established "to advance development of improved therapies for diseases of the nervous system."

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ASENT includes multidisciplinary academic investigators, industry researchers, and government agencies such as the National Institutes of Health (NIH) and the US Food and Drug Administration (FDA), as well as advocacy organizations. In 2004, the journal *Neurotherapeutics* reflected this growing subspecialty interest. Over the following 2 decades, multiple free-standing programs, including the American Neurological Association summer course for Clinical and Translational Research in the Neurosciences, the NINDS Clinical Trials Methodology Course, the NIH Course in Neurotherapeutics Discovery and Development for Academic Scientists, and multiple other academic–industry and government–industry training partnerships were developed to meet the growing demand for neurotherapeutics training. By 2022, there were nearly a dozen established clinical fellowship training programs at US, UK, and Canadian academic institutions targeting experimental neurotherapeutics.

Neurotherapeutics training programs reflect the breadth of skills needed for bench-to-bedside therapeutic development with two main types of training programs:

1. Laboratory-based programs focus on disease pathophysiology, identification of therapeutic targets using in vitro and animal models of diseases, and preclinical drug development. Programs typically train MD or PhD scientists, focus on bench or early translational methodology, and include training related to methods for biomarker discovery, drug candidate discovery and screening, central nervous system drug delivery, engineering, bioinformatics, genetics, device development, and toxicology, pharmacokinetics, and pharmacodynamics evaluation.
2. Clinical research programs focus on clinical or later-phase translational research methodology. Most trainees are MD clinical neuroscientists with a specific disease subspecialty interest. These programs can include epidemiologists, statisticians, pharmacists, and clinical psychologists as well as individuals with expertise in regulatory science. Ideal clinical research programs include an overview of core concepts of the preclinical programs related to drug discovery, knowledge of key regulatory requirements, basic clinical trial statistical tenants and designs, and exposure to early and midphase clinical trial design and development. Programs that include training on target community engagement and retention, current health policy, and neurotherapeutic cost and market value are at the forefront of the future of the field.

Depending on career goals and program focus, a neurotherapeutics trainee will vary in the exposure to the type of mentors, skills acquired, and duration of fellowship (Table). Laboratory-based training usually requires deep focus on one project, whereas clinically focused training requires trainee involvement in multiple projects at different stages of the trial "life cycle" including: identifying a putative therapeutic and developing a rationale for its study in a clinical trial; defining the natural history of the disease; developing outcome measure(s) and identifying robust clinical endpoints; preparing a statistical analysis plan; writing the protocol and operations manual; obtaining human subjects research approval; operationalizing a study team; identifying and recruiting subjects; obtaining FDA approval of Investigational New Drug or Investigational Device Exemption applications; conducting, monitoring, and managing data; data analysis; and manuscript preparation.[3,4] However, ideally, training should enable the beginning investigator to design and conduct their own clinical trial.

Meeting the Challenges of Experimental Neurotherapeutics

Training in State-of-the-Art Technology Needs to Be Harnessed to Expedite Development of Novel Neurotherapeutics

New models are needed for in vitro screening, for example, human brain organoids, disease relevant animal models, and models of the blood–brain barrier. A new federal agency, Advanced Research Projects Agency for Health (ARPA-H), is being established[5] to catalyze health breakthroughs that cannot readily be accomplished through traditional research or commercial activity. Technology developments in artificial intelligence and machine learning can be used for drug synthesis, prediction of mechanism of drug action, and toxicology. Recent advances in cell-based therapeutics, gene therapy, gene editing tools, and RNA-targeting gene therapies have put academic centers in the forefront of therapeutic development. Advances in human subjects' research technologies—such as remote monitoring, remote consent processes, telehealth platforms, versatile trial recruitment strategies, decentralized trial design, digital device innovations, and integration of real-world evidence—are also critical.[6]

Collaboration between Academia, the Pharmaceutical Industry, and Regulatory Bodies Needs to Be Fostered, with Trainees Exposed to These Multiple Domains Early in Their Career Development

Development of pharmacological agents has been the domain of the pharmaceutical industry. Costs for the development of new therapeutic agents can be >1 billion dollars.[7] In contrast, most research on disease

TABLE. Opportunity for Neurotherapeutics Coursework

Name	Organization	Duration	URL
NINDS Clinical Trials Methodology Course	University of Michigan	1 year with 1-week residential course	https://nett.umich.edu/training/ctmc
ReDI: Clinical Investigator Training Course[a]	CDER, FDA	3 days	https://www.fda.gov/drugs/news-events-human-drugs/clinical-investigator-training-course-citc-update-12072021-12082021
Training in Neurotherapeutics Discovery and Development for Academic Scientists	ASENT	3.5 days	http://ndd.ucdavis.edu/
Translational and Clinical Research Course	American Neurological Association	Annual meeting	https://myana.org/membership/postdoctoral-fellows-residents-trainees

[a]Although this course is not specific to neurotherapeutics, it often encompasses issues pertinent to the field.
Abbreviation: ASENT = American Society for Experimental Neurotherapeutics; CDER = Center for Drug Evaluation and Research; FDA = US Food and Drug Administration; NINDS = National Institute of Neurological Disorders and Stroke; ReDI = Regulatory Education for Industry.

pathophysiology, identification of therapeutic targets, and provision of patient care is done in academic centers, supported by public funding.[8,9] Collaboration between all parties to establish new and acceptable outcome measures for use in clinical trials will expedite this process.

Trainee Recruitment

Opportunities in neurotherapeutics must be communicated to potential trainees, particularly underrepresented minorities, and introduced into the medical student curriculum and neurology residency training. The many exciting breakthroughs in the treatments of genetic, inflammatory, and vascular disease predict a rapid growth in novel treatments. Neurotherapeutics can accommodate trainees interested in bench, translational, and clinical academic disciplines. Developing a diverse workforce is essential for defining the use of novel therapeutics for understudied populations.

Career Advancement

Clinical trials take many years to complete and often have a long list of investigators.[10] The current system of credit for "authorship" is archaic and does not equitably reflect the contributions of team science.[11] Making certain that team science rewards all members of the team must be part of the training of clinical trialists.[11] The most sensible approach is to avoid naming authors in favor of specifying a "study group." The precise contributions of all investigators can then be specified in the paper.

Career Opportunities in Experimental Neurotherapeutics

Academic Positions

Physician scientists are often the innovators of novel therapeutics—in both preclinical research and investigator-initiated clinical trials. Recently, because of the growing number of potential molecularly based treatments for hundreds of diseases, academic researchers have focused on "trial readiness," with an emphasis on clinical or biomarker outcome measures that would serve as the basis for establishing the benefit of treatment and securing regulatory approval. Such research frequently generates intellectual property that can help monetize careers in clinical research. Academic positions can also be supported by NIH and FDA grants, foundations, advocacy groups, philanthropy, and investigator-initiated trials supported through partnerships with the pharmaceutical industry. Challenges can occur when investigators do not have free and unrestricted access to study data—collaborative agreements with the pharmaceutical industry must address this point.

Pharmaceutical Industry

Training in experimental neurotherapeutics is the stepping stone for positions in both drug development and clinical trials. Industry neurologists often return to positions in academic departments of neurology and vice versa. Trainee experiences in industry can foster productive collaborations with longtime academicians interested in

neurotherapeutics and bring new knowledge to their departments. Industry–academic partnerships—such as the MGH–Takeda Neuroscience Fellowship—provide collaborative training bridging academic and industry neurologists that further enhances the ability to train expert experimental neurotherapeuticians.

Not-for-Profits

Experts in experimental neurotherapeutics are sought after for leadership positions in advocacy organizations or private foundations focused on discovering treatments for neurological diseases. Such individuals bring skills important for the success of meeting the needs of patients with one of the target diseases, as well as skills essential to help monetize the operations of such organizations.

Government

The NIH recruits neurologists trained in experimental neurotherapeutics as program staff. The FDA has an ever-growing need for neurologists and other clinical neuroscientists skilled in all aspects of drug discovery and clinical trials. The new agency ARPA-H will provide opportunities for therapeutic development with strict timelines.

Private Practice

Neurologists in group practices often serve as site investigators for multicenter clinical trials, both pharmaceutical and academic. An experienced business manager facilitates trial participation. Experienced practicing neurologists can also pursue investigator-initiated trials. Practices benefit by revenue generation as well as having novel treatment for patients with otherwise untreatable diseases.

Conclusions

The tidal wave of new treatments demands that more neurologists be trained in experimental neurotherapeutics. The job market is increasing rapidly, and new opportunities arise as treatments are developed for the major neurodegenerative diseases. Addressing diversity in the workforce, equity in availability and affordability, and access, and fostering the development of implementation science in neurology are all challenges that confront the field and the field's trainees.[12,13] These challenges will make experimental neurotherapeutics a growth industry in the years ahead.

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Author Contributions

L.B.R., A.B., R.C.G., and A.N. contributed to the conception and design of the study. L.B.R., A.B., R.C.G., and A.N. contributed to the acquisition and analysis of data. All authors contributed to drafting the text.

Potential Conflicts of Interest

M.M.M. is the Editor-in-Chief of *Neurotherapeutics*. T.P.S. is the President of ASENT. A.J.C. is the incoming President of ASENT. The remaining authors have nothing to report.

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