Career Pathways: Albert Lo, MD, PhD

"Al has done a lot of different things." This is how Dr. Carolee Weinstein introduced me as the incoming ASNR President (2018-2021), succeeding her term. I thought to myself, "what an interesting and true description." I asked myself, "Why is that? Why did others have such a linear path? Did my colleagues perceive me to be unfocused, or not having a clear career trajectory?" Introspectively and retrospectively, my career path made perfect sense to me, and I will share why I made the choices I did and what I learned along the way. I could not have predicted, nor planned, where I ended up from where I started, but maybe my career journey will help some of you as you make career decisions and navigate your own paths.

Cataloging academic and professional positions in a CV is a simple way to look at a career, but it doesn't tell the whole story. For me, the simple list starts with Assistant Professor of Neurology at Yale University. My subsequent positions include: Associate Professor of Neurology, Engineering, Public Health at Brown University, and Associate Director for the Veterans Affairs Rehabilitation Research and Development (VARRD) Centers of Excellence for Neurorestoration and Neurotechnology at the Providence VA Medical Center; Vice President, Neurodegeneration, and Head of Neuroinflammation and Neuromuscular Neurology at Eli Lilly and Company; and Senior VP, and Head of Clinical Translation and Clinical Development at Kisbee Therapeutics.

To understand the more detailed story, we'll need to examine the chapters of my career as I see them, with five so far, based on major career transitions to different institutions or to new research areas. In each chapter, I learned new things and gained valuable experience as my career evolved.

<u>Chapter 1: Launching My Independent Career in Academic Neurology</u>
Chapter one starts after my neurology residency training in Yale Neurology with a funded VARRD Career Development Merit Award (similar to an early career NIH K01 Career Development Award). In this stage, I became reacquainted with individual-level research in a traditional laboratory setting. The research focused on neuroprotection for progressive multiple sclerosis (MS), working with experimental autoimmune encephalomyelitis (EAE) animal models and then translating our findings into clinical trials. The EAE models are a standard pre-clinical model for studying MS-like neuroinflammation, demyelination, and neurodegeneration, but they were not yet established in our lab, which I had to get up and running. At the same time, I was learning to perform Neurology Attending duties in a MS clinic and in the broader Neurology clinical service. Advancing my research and clinical skills was a delicate balance, but both were tremendously rewarding.

In Chapter 1, I learned how much I liked integrating my basic science background with clinical training and working towards the clinical translation of my research. I discovered that I preferred translational clinical research over basic science discovery in the laboratory or clinical investigations alone. (This translational space, biased toward the clinical end, was the best fit for me — both in terms of my preferences and expertise, and this was reinforced over time).

Chapter 2: Moving Down the Translational Pipeline from Preclinical Models to Clinical Trials

Chapter two provided me with the opportunity to engage in the science of clinical trials as a principal investigator (PI) testing neurorehabilitation robots (the Lokomat and MIT-Manus). The work aimed to evaluate robotic devices designed to improve motor outcomes for individuals with multiple sclerosis or stroke. We aimed to test our hypotheses in the definitive structure of randomized clinical trials, which was not common at the time for neurorehabilitation interventions. Through these studies, I was able to work with cutting-edge neurorehabilitation robot technology and start to think about how, by establishing the efficacy of these technology-based interventions in clinical trials, our studies could build the evidence base needed to support broad adoption into rehabilitation clinical care. At the same time, I was further developing my clinical skills and clinical understanding of neurodegeneration through working with patients with stroke, MS, traumatic brain injury, amyotrophic lateral sclerosis (ALS), and other neurological conditions.

During Chapter 2, I grew from an individual research contributor to working collaboratively at a highly-functioning team level. I learned that, although we cannot control the outcomes of clinical trials, the trial team can control the quality of methodological design and implementation (even in the case of using a novel two comparison groups design, as well as a novel modular rehabilitation robot intervention). I learned that because there were so few published multi-site randomized clinical trials in neurorehabilitation, there weren't any examples or history to draw from. I recognized the need for, and the appreciated the generosity of, mentors (both those in more senior roles and peer-to-peer mentors) to solve scientific questions, such as how to structure "usual care." Fortuitously, the best examples of neurorehabilitation trials were being conducted by ASNR members (such as Bruce Dobkins for the SCILT trial and Steve Wolf for the EXCITE trial). I believe the creativity of the design and quality of implementation played a large part in the editors of *The New England Journal of Medicine* accepting our study as the first rehabilitation trial the journal had ever published, as communicated to me by the editors.

Chapter 3: Expanding into Broader Interdisciplinary Neuroscience Research and Academic Leadership Roles

In Chapter three, I moved academically to Brown University, where I had new research opportunities spanning other disciplines involved in neurodegeneration research at a high level. I collaborated with neuroscientists, epidemiologists, and biomedical engineers. I also had the opportunity to advance academically into more leadership roles at the VARRD Center of Excellence at Providence VA Medical Center. Scientifically, the most significant new activity was diving deeper into understanding the epidemiological consequences of MS disability as the PI for the Rhode Island Multiple Sclerosis Study. This study had a specific focus on how people

experienced disability and employment based on the stage of their MS progression. Further, because the study was a field-based medical record abstraction study, although labor intensive, it generated a richer and adjudicated dataset that eventually provided orthogonal data on a state-level to the National Multiple Sclerosis Societies' extensive re-estimation of MS prevalence in the U.S.

As I made my way through Chapter 3, I experienced building my own lab and building an integrated center for MS care, rehabilitation, and research (the Mandell Multiple Sclerosis Center, Hartford CT). I learned how to manage a research center of excellence and how to navigate the academic promotion process. I probably said "yes" to too many activities during this Chapter, which was a lesson on the pitfalls of being over-extended.

Chapter 4: Developing Therapeutics for Neurodegeneration in the Pharmaceutical Industry

After 15 years in academic neurology, I began Chapter four when I transitioned into industry to develop new drugs for neurodegeneration at Eli Lilly and Company. Prior to my move, I fundamentally recognized the limits of what could be achieved with rehabilitation and devices alone. A biological agent that could stop neurodegeneration — or even more aspirationally, an agent to mediate repair and regeneration — would greatly facilitate meaningful restoration of neurological function. At Lilly, I worked in early phase clinical drug development, which bridges the initial drug discovery work to first-in-human phase I trials, but really focuses on the human clinical trial aspect. If a compound's safety and potentially biomarker data were supportive from the discovery work, then I led the design of a phase II proof-of-concept clinical trial and implementation, and I oversaw the study conduct throughout the course of the trial. At Lilly, the neurodegeneration work was largely focused in Alzheimer's disease, where Lilly had strong long-time commitments. Although I had seen Alzheimer's patients in my clinical practice, the science and clinical research was a new area for me to learn about and quick gain proficiency.

During this chapter, my role also evolved from leading the development of single compounds (which still involved large global teams) to driving the development of multiple compounds, and then eventually leading the emerging ALS pipeline and developing the strategy for Lilly. While at Lilly, I was fortunate to see a rare industry success for Alzheimer's disease neurodegeneration when the donanemab phase II trial was successful in meeting its primary endpoint. I was the clinical lead for donanemab up to the phase III programs. Given the depth of failures in the field to date, this study carried high risk and high expectations. Conducting the donanemab (anti-amyloid antibody) along with the zagotenemab (anti-tau anti-body) phase II clinical trials was particularly difficult because the peak of the COVID-19 pandemic emerged after the studies were already ongoing, and we had to develop new robust COVID mitigation plans essentially immediately and globally, for study participants potentially locked-out of research clinic visits and for potential loss to follow-up. While I was at Lilly, I was also the clinical lead for a number of other clinical trials (e.g. for BACE inhibitors and anti-Tau antibody treatments for Alzheimer's disease) and nearly a dozen other molecules for various targets, where I invested just as much energy and learned a tremendous amount. However, just as in academics, the successful trials and experiments receive the most attention.

In Chapter 4, I learned the industry perspective on research into Alzheimer's disease neurodegeneration, how to negotiate through numerous clinical development processes, the ins and outs of corporate governance, managing global pharmaceutical clinical trials via an organizational structure where individuals report to multiple managers. I learned how to lead pipeline strategy and achieve my own career development and promotion in a corporate environment. I became President of ASNR during this Chapter of my career, and the COVID pandemic also affected how we wanted to adapt our yearly conference as well as the importance of our educational initiative to provide content virtually throughout the year. COVID was just another unexpected twist as we at ASNR were navigating how to implement new strategies as an independent organization.

Chapter 5: Innovation and Drug Development in a Biotech Start-up

That brings us to Chapter 5. I joined a Biotech start-up in June of 2023 after spending eight years in large Pharma (while I was there, Lilly moved up from about the 12th largest to become the largest pharma corporation in the world). This meant going from a global corporation of 35,000 people based out of Indiana to joining a company with less than 35 people in Kendell Square in Cambridge, MA. Biotech is a world of novel, high-impact science, where an individual has a larger scope of work, conducted in a smaller company within the context of an entrepreneurial and VC-funded environment.

Presently, I am learning about entrepreneurial drug development, which means working on fewer molecules than in large pharma, but they are the ones that I choose based on the company that I join. Readers may wonder why I made the change. Conceptually, I was intrigued by working at the completely other end of drug development from large pharma, and that is a small biotech startup. In this role I have the opportunity to engage more broadly and deeply with the science, and I have greater influence and decision-making influence on which clinical indications have the greatest need and make the most sense based on mechanism, as well as the clinical development operations, regulatory aspects, and commercial strategy for these molecules. I can personally hire the team for my group, and I represent the medical and clinical strategy and design of the company for the board of directors, in investor interactions, and with academic collaborators.

At Kisbee, our scientific approach is acting on the lipid network biology in the nervous system using recombinant apolipoprotein E (APOE), which has known protective variants (such as APOE Christchurch, which has gain significant attention in the news) in addition to risk mutations for the development of AD and Vascular dementia. This is fascinating biology that I have not worked on previously; and lipid trafficking, distribution, and clearance is highly relevant to the cells and tissues of the nervous system for repair and restoration. As a result, I am really excited to see this therapy brought to the clinic. The senior scientific founders are experienced and accomplished serial entrepreneurs (Dr. Stuart Schreiber and Dr. Ben Cravatt), and the leadership team has substantial relevant skills and experience. If I didn't take this opportunity to move into biotech, what would I be waiting for? I only have so much productive career time left, and It was time to take this shot.

Balancing Behind the Scenes: A Dual-Career Home Life

The above describes my “career path” from my point of view. The happy complexity of my path is just one example of how to develop one’s own career in the context of a two-career relationship. This topic is often not discussed in these narratives. In my life, my spouse and I have focused on how to best navigate careers for both of us to optimize our work and home lives. My wife has her own well-recognized career in academic leadership. My Chapter 3, which included moving to Brown University, coincided with her being recruited to the Provost Office at Harvard University. She has since founded her own educational technology start-up company, after stepping down as VP for Academic Affairs at Brown (Brown recruited her from Harvard). So, although this story is told from my perspective, it is really only half of the story which is composed of two careers.

Coming back to how this essay started with Carolee’s introductory statement, sometimes it makes sense to do a lot of different things to subserve the purpose of a career. My purpose is to solve problems for people with neurodegeneration. In short, how can I help make the lives of people with acute neurological injury or chronic neurodegeneration better? With this guiding the “why” of my career, the “how” became secondary, and I was willing to be adaptable to pursue and fulfill this one goal based on the opportunities that arose and where I thought I could best apply my background and learn. This often meant difficult choices or challenges: Do I stay in basic science or move more clinically? How can I learn the skills for a new role? Do I need to move to another institution? What opportunities do I say "yes” to? And just as importantly, what opportunities do I say “no” to?

My career transitions and path were not by my own design (I probably could not think of something so interesting). But believing in my purpose, combined with the willingness to take risks and adapt, enabled me to move forward and discover what work was most gratifying to me. The result is a career with some twists and turns, and throughout this journey, I have learned skills and have appreciated all the experiences that allowed me to grow. I will have to see what happens after Chapter 5. On one hand, there may not be a Chapter 6, as I have witnessed a lot of colleagues and friends die during COVID, so I need to be content and make the most of each Chapter, and not take my future career or life for granted. However, if I am afforded another chapter or two, then, I am sure it will be something different that I haven’t planned for, but the new challenges keep life exciting, fun, and fulfilling. My wife has always thought of the possibility for a life even outside the U.S., and I can’t wait to see how we author the next chapters of our life.

Acknowledgements: Building a Career is a Collaborative Effort, Involving Help and Mentorship from Many Others

A footnote of appreciation: I have had many influential mentors (either as senior mentors or peer-to-peer) in my life in medical school at Wake Forest University and while on the Medical School faculty at Yale and Brown. In addition, VA Rehabilitation Research and Development was an organization that provided continuity throughout my academic life. In the context of this article, I wanted to highlight ASNR members. I joined ASNR two years after completing neurology residency training. I thought it was absolutely the best organization to be a part of to

better understand the neuroscience underlying neurorehabilitation and repair. As I was starting my career, I learned an incredible amount about neurorehabilitation trials when there was very little data, and many of the people doing these pioneering studies were ANSR Members. I want to acknowledge with great appreciation, the research guidance I have received from my fellow ASNR Members, including Dr. David Good, Dr. Bruce Dobkins, Dr. George Wittenberg, Dr. Steve Wolf, Dr. Carolee Weinstein, Dr. Tom Carmichael, Dr. Steve Cramer, Dr. John Krakauer, and Dr. David Reinkensmyer, as well as Dr. Marie McNeely for her persistence, patience, and assistance in developing this particular career narrative for the ASNR series. There are too many more who I haven't mentioned here, but you know who you are.

These individuals and numerous others have been instrumental colleagues, collaborators, and supporters in my life as I have traversed the varied Chapters of my career.