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The future of clinical neuroscience: A view from the bench

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Abstract

Here, I develop the argument that clinician-scientists crucially contribute to the translation of knowledge from basic neurosciences to understanding disease and eventually therapies. Invasive experimental approaches in humans are still limited. Therefore, the translation of insights provided by research in animals to applications in humans remains a formidable challenge and successes have been rare. In my own experience, my combined training as a clinician and as a cellular neurophysiologist have allowed me to work with animal and human models of brain function in which the neuron forms the basic unit. This has greatly facilitated me to conduct experimentation at a neuronal circuit level with the prospect of translating it to humans. I advocate, therefore, the creation of dedicated postgraduate programs in academic and clinical neurosciences to train the next generation of clinical-scientists. Such careers require a strong motivation, but will immerse trainees in a fascinating intellectual environment with a promise to contribute to fundamental insights that ultimately benefit patients.

Keywords

Medical career development, future of clinical neuroscience, basic and clinical neuroscience, clinical and scientific training, translational neuroscience, mouse model of addiction, deep brain stimulation, women in science

I consider myself a neuroscientist with a strong interest in translational research. I am also a clinical neurologist and enjoy the interactions with my patients. I lead a lab of about 20 persons. Our research aims are to characterize the neural basis of drug addiction. In our experiments, we use mouse models to study the synaptic plasticity in the basal ganglia, which drives drug-adaptive behavior.

Most of my colleagues in our Faculty of Medicine would consider my research as basic. Indeed, we are primarily concerned about genes, synapses, glutamate receptors, neural circuits, and mouse behavior. Yet our questions emerge from clinical necessities and the quest to develop novel treatment strategies. Therefore, I have recently initiated several projects in patients, in particular performing single unit recordings during deep brain stimulation surgery.

How did I get there? And what would I recommend a colleague who is at the beginning of her/his career?

I studied medicine in Lausanne and Berne in the 1980s becoming attracted by the study of the brain already during the preclinical years. I was fascinated by its utterly complicated anatomy and vividly remember Hendrik van de Loos impressive bimanual (!) drawings of the nervous system. I also liked the electrophysiological description of neuronal function, where I saw the opportunity to study the brain with the rigor of physics.

It became clear to me that I wanted to study the basics of brain function, starting with a defining phenomenon of nerve cells: the action potential. In a 3-year MD thesis (no Md-PhD program was offered at the time) with Hans Rudolf Lüscher, I learned the basics of the scientific profession: How to design and carry out experiments, to create appealing graphical representations and to describe, analyze, and submit for publication.

From my experience I conclude that immersion into research cannot be too early. This needs to start already

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Figure 1. The author in front of the neurology ward, where he works as an attending.

during medical school. At the Faculty of Medicine in Geneva, we run a program that allows students to immerse in a lab for several weeks, which is very successful. This constitutes a break from the many mandatory courses, which unfortunately make up the curriculum of most universities. In my case, I extended my studies by an additional year of internships.

Next I continued my clinical training in neurology at the Inselspital, witnessed the last months of Marco Mumenthaler reign, and started with Christian Hess, while Claudio Bassetti was my chief resident. While I enjoyed these years I was inpatient to continue my research. I felt, probably rightly so, that delaying my postdoctoral fellowship by a year of internal medicine to fulfill an important request of the neurological specialty training would lead to a big handicap (apparently discussion are underway to drop this requirement). This may have been a mistake and once in a while, it is pointed out to me that the absence of an FMH title is really a shortcoming.

In any case, I would argue that clinical medicine can only benefit from a closer proximity of physicians with a sound scientific training, particularly in a university hospital. I strongly believe that the future of academic medicine would be brighter if there was a specialized training for those who commit their career to research, yet want to keep a link to clinics.

What made me want to become an independent scientist were the 3 years of postdoctoral fellowship in the laboratory of Roger Nicoll in San Francisco. There I learned the in and out of synaptic plasticity, a putative cellular mechanism of memory in health and disease. The interactions with my fellow postdocs and students (while I was in the lab, Rachel Wilson discovered endocannabinoids as a retrograde messenger that fine-tunes synapses as part of her doctoral work) left a strong mark.

Despite an attractive offer in San Francisco, I decided to return to Switzerland, to Geneva, with my wife, a pediatric endocrinologist, and my 1-year-old son. Also, because dual career paths were best accepted in the French part of Switzerland at the time. Here, I founded my lab early 2000. Thanks to the generosity of Thedi Landis and a career development award of the SNF, I was also able to continue clinical work and to see patients.

In the following years, I decided to orient my interests toward the study of the neural basis of drug addiction. The premise was that cocaine, heroin, and nicotine had in common to cause excessive dopamine levels, which then would change transmission of glutamate and gamma-aminobutyric acid. This concept brought me back to my roots, the mechanisms of synaptic plasticity. Since then I was fortunate to secure support to assemble a group of scientists who share this fascination, while continuing to supervise interns in clinics.

In the lab, starting in 2007, we were more and more using the powerful tools of circuit neurosciences, including optogenetics, and genetically encoded activity sensors to establish links of causality between the activity of neurons and behavior in mouse models of drug addiction seemed all of a sudden possible. The arrival of Pierre Pollak in Geneva definitely had an impact on my translational thinking, because I was introduced to deep brain stimulation (DBS). I am still at awe each time we operate on a patient who is conscious while we record from his brain cells.

The last years have indeed been utterly fascinating. Specific interventions based on the cellular dissection of circuits of motivation could change the animal's behavior with much precision. Empowered with these results my thanking deepened along translational lines. Wouldn't it be cool if we could apply similar approaches in humans?

The idea of ontogenetically inspired DBS was born. After all, the proceedure initially used to treat essential tremor may also work for addiction and other psychiatric diseases. Harnessing circuit dissection in mouse models of a disease to design rational protocols that would emulate the mechanism with electrical stimulation in humans. In other words, we put mechanisms first.

The future of clinical neuroscience seems bright, if we succeed to integrate the results from molecular and cellular neuroscience to understand disease, before we attempt novel therapies.

I observe, however, that clinical colleagues often are too ambitious in their projects, which are often loosely focused around testing a novel intervention, when in fact it remains unclear what should be done in the first place. Simplifying the research protocols, progressing in small but logically connected steps may boost the efficacy of clinical research avoiding early termination of the study.

In the remaining decade until the retirement (Switzerland still has a mandatory age, but hopefully, a few years will be added, given the current discussion on social security) I believe my clinical and scientific interest will increasingly pay off. Looking back, I am very happy with my decision to move between the different language regions during medical school. Switzerland is unique, because one can immerse into a different culture while staying within the same national system.

Listing to my patients to better understand how we can help them was and still is my biggest attraction for clinics. I remember my first patient whom I saw during the 3-year internship at the Rambam Hospital in Haifa, Israel. He was an Iman, who was referred to the clinical because the followers could no longer understand him. Ephraim Bental, my supervisor, had him pull out his tongue, pointed to the fasciculation muscle and concluded that he suffered from amyotrophic lateral sclerosis. I was deeply impressed but also irritated by the little understanding of the underlying causes (and maybe even more so by the nonchalance that some colleagues dismissed this discrepancy).

To students and younger colleagues, I recommend strongly: Travel and take full advantage that medicine is a universal discipline. Students can only benefit from other cultures and will learn to put our approach into perspective. Research in medicine is a global endeavor and interacting with colleagues from all over the world is a major appeal.

As general recommendations, I would reiterate, *first*, my advocacy for a better training of more clinical scientists. The current FMH rules for specialty training do not sufficiently take such career paths into account and may actually be an obstacle in the highly competitive academic world. We definitely need more clinicians with sound scientific training. *Second*, all my mentors have been men. Training more women while creating an environment to promote careers is the lifeline for future academic research. Talented and motivated women must be encouraged to go all the way, the 'pipeline' must no longer be leaky.

In conclusion, I am well aware of the privilege of having the possibility to live my passion while receiving support from funding agencies, academic institutions, and the clinic. Training young colleagues in the lab and the hospital gives the reassurance of a bright future of clinical neuroscience. Patient suffering from neurological diseases demand it.

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