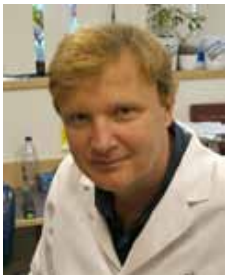
Dimitri Krainc Interview



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1. Where did you grow up?

I grew up in Celje, Slovenia

2. What do you remember from your high school days?

The curriculum was very hard, and the professors were tough! I was a good student, but more interested in sports and girls. But the good news is that I found my wife there, and that I played lots of basketball.

3. How did you decide to study medicine?

The original plan was to be become a professional basketball player, but that did not work out—fortunately. I thought medicine was an opportunity to work with people, something that I liked more than working with "machines", and to learn some interesting biology about human body, and maybe even help cure some bad diseases one day. It was a combination of reasons. The decision to study medicine was also partly done by exclusion of things I did not want to study--and after removing those, very few options were left. I use this approach in general—first decide what I don't want to do (Figure 1).

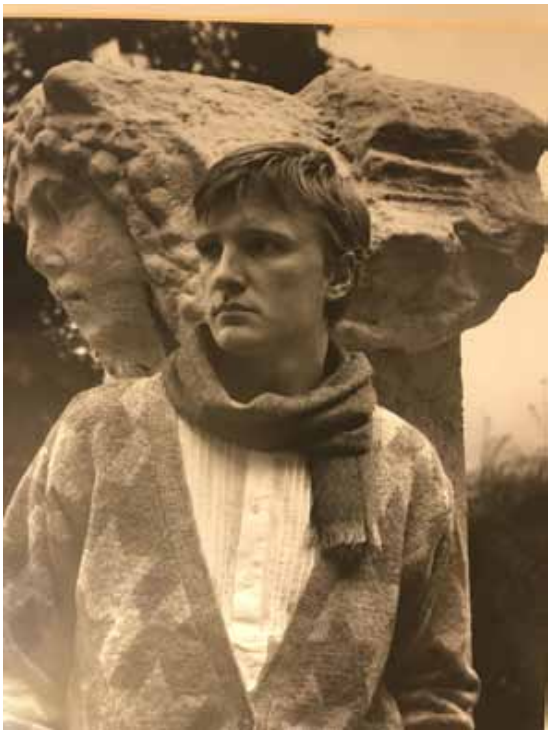

Figure 1. As a youngster who did not care much about medicine

4. How enjoyable were the first three preclinical years of your studies? Who were your favorite professors?

My first year of medicine I completed in Ljubljana, but my mother who was born and raised in Zagreb convinced me to switch to medical school in Zagreb, and so I started my second year at the University of Zagreb School of Medicine. It was the best decision of my life! I would have never reached this point in my career were it not for that move to Zagreb.
I also loved my professors in Zagreb—almost all of them. They were "old school" teachers—kind, helpful,and scholarly. I had many favorites, like Professors Pokrajac, Čulo, Durst-Živković, Lacković.

5. Which were your favorite subjects and favorite professors in the clinics?

I was less happy with the clinical education because it was too theoretical with limited practical teaching.
I remember fondly professor Labar who was very smart and thoughtful as a clinician. He was also very supportive of young people and cared a lot about us students. There were many others who were excellent clinicians, of course.

6. Did you have any role models during your medical school years?

Not really.

7. Did you engage in any extracurricular activities and what did you do during your free time?

I worked in the lab of Professor Lacković. He was great, he truly loved science and cared about helping young people become successful. He created a nice environment in his group with many wonderful colleagues that were encouraging and supportive. I credit him for helping me start my research career. I enjoyed interacting with other scientists in the lab, discussing neuroscience with the them, and attending interesting lectures and meetings (Figure2).

Figure 2. As a medical student attending the First Yugoslav Neurobiology Conference entitled " Neurotransmitters in Health and Disease",Zagreb ,1986.

8. Did you have concrete plans on what to do after graduation?

I went to US during medical school, for a summer project with dr. Norton Neff who used to be a colleague of prof Lacković at NIH and after graduation I returned to his lab.

9. When did you decide to become a neurologist?

During medical school when I saw some terrible neurological disorders and developed a desire to understand them and maybe contribute to finding a cure for them. I also liked the fact that clinical neurology was like building a puzzle during history and exam—like detective work that I enjoyed.

10. Did you try to find a job in Zagreb after graduation and how did you decide to move to Boston?

I completed my internship at KBC Rebro, then went to work with dr. Neff for a short time to complete my project that I started as a medical student, and then went to Harvard where I stayed for 22 years.

11. What do you remember from your training period at the Massachusetts General Hospital in Boston?

It was a wonderful experience. I was surrounded with some of the best clinicians who taught me all the secrets of clinical neurology that still serve me well today. I also had great research mentors and was able to elevate my research work to new heights during that time. The overall culture there was very scholarly, collaborative and pleasant—contrary to common perceptions about Harvard.

12. Was this your first encounter with basic neurosciences?

No! It was with prof Lacković and then Norton Neff

13. Did you ever consider giving up clinical work with patients and devoting yourself to entirely to basic science research?

I did not. I loved both very much and could not give up any of them.

14. Did you have a mentor who influenced you more than all others of your teachers?

Dr. Lacković in Croatia(Figure 3) and Dr.Anne Young in the US. Anne Young was the first woman department chair at MGH/Harvard and she made major contributions to neuroscience with her studies of basal ganglia in neurology. She was also president of American Neurological Association. I am especially happy to hold the same position now.

Figure 3. Professor Zdravko Lacković my first mentor

15. How did you become interested in molecular biology?

It was at Harvard where I experienced molecular biology first hand in the department of molecular biology where the faculty co-authored the famous "red book" entitled—Protocols in Molecular Biology.

16. What did you do after you completed your training and became a Board certified neurologist?

I started my lab at Harvard, published my first paper as lab PI (in Science) and continued working as clinical neurologist.

17. Could you cite that paper and say what was it all about?

Here is the full citation of that paper:
Dunah AW, Jeong H., Griffin A., Kim MJ, Standaert DG, Hersch SM, Mouradian MM, Young AB, Tanese N. and **Krainc D**. Sp1 and TAF130 transcriptional activity disrupted in early Huntington's Disease**.** ***Science***, 2002.
We found that the glutamine expansion in huntingtin disrupts specific transcriptional programs in neurons. These data suggested that the deregulated gene expression may be an early step in HD pathogenesis as a result of interference by the soluble forms of mutant huntingtin. Our work also indicated that one of the primary and direct effects of mutant huntingtin on transcription is via specific repressor mechanisms, whereas other effects of huntingtin on transcription may be compensatory or secondary.

18. How long did it take you to establish your own laboratory and get your first research grants?

About 2 years after the completion of my neurology residency at MGH.

19. You are now Chair of a University Department. How long did it take you to reach that position?

I was faculty member at MGH/Harvard for 11 years before I became chairman at Northwestern.
I came to Northwestern in 2013 and very soon became an active member of our Medical School and Medical Center. In this photograph I am with my good friend and collaborator Dr. Andrew Parsa (Figure 4), the Chair of the Department of Neurosurgery. He came to Northwestern at the same time like me, but unfortunately he die a few years thereafter from a heart infarct.

20. Coud you list your major duties at Northwestern University School of Medicine in Chicago?

I run my lab, direct a Center for Neurogenetics, and run a very large clinical department with more than 200 faculty and a total of 300 other staff members. I also lead a relatively large research team and run a well funded basic science neurobiology laboratory (Figure 5).

Figure 4. With Dr. Andrew Parsa, Chair of neurosurgery

Figure 5. My research team at the Northwestern University in Chicago

21. How would you define yourself? A neurologist who does basic science research or a basic scientist who also does neurology? In other words, how do you balance your hospital work and patient care with basic science research?

A neurologist who does basic science. At Harvard I got the job primarily because of my clinical performance, coupled with research, of course. Those who are good scientists but lousy clinicians do not get a job there nor at Northwestern. Feinberg School of Medicine at the Northwestern Medical Center is primarily a medical institution and I am first and foremost a physician, who treats patients together with the rest of the medical staff and my physician colleagues (Figure 6).

Figure 6. With two other Chairs at Northwestern University. Dr. Leonidas C. Platanias, Chair of the Cancer Center (left) and Dr. Serdar Bulun, Chair of the Department of Obstetrics and Gynecology.

22. Among the key words on the list of your basic research papers there are many that I would not know how to define. Let's take just two of those: dysfunctional organelles or deregulated gene transcription. Could you give us a brief definition and explain why are these concepts important.

The overarching goal of my laboratory has been to define key molecular pathways in the pathogenesis of neurodegeneration with a goal of identifying targets for therapeutic development. Using genetic causes of disease as a guide, we have focused on pathogenic mechanisms that occur across different neurodegenerative disorders such as accumulation and deficient degradation of aggregation-prone proteins and organelle dysfunction. Importantly, we examined an interesting clinical link between Parkinson's disease and Gaucher disease that is caused by mutations within the GBA1 gene that codes for glucocerebrosidase (GCase). We found that mutations in GBA1 lead to hypoactive lysosomal GCase resulting in accumulation of glucosylceramide that stabilizes a-synuclein oligomers that were shown to be toxic to neurons. We also made a surprising observation that accumulation of a-synuclein can lead to inhibition of normal GCase. Specifically, a-synuclein interferes with ER to Golgi trafficking of GCase which in turn leads to decreased GCase activity, lysosomal dysfunction and more accumulation of a-synuclein. The bidirectional effects of a-synuclein and GCase forms a positive feedback loop that, after a threshold, leads to self-propagating disease (**Mazzulli et al, *Cell*, 2011**). This key study was the first to demonstrate that wild-type GCase was decreased in idiopathic PD, a finding that was later confirmed by several other groups. This work was extended by the analysis of dopaminergic neurons derived from patients with idiopathic and various forms of familial PD, where our group identified a time-dependent pathological cascade that included mitochondrial oxidant stress, accumulation of oxidized dopamine and neuromelanin, deficiency of GCase, lysosomal dysfunction and α-synuclein accumulation. Importantly, this toxic cascade was **observed only in human**, but not in mouse PD neurons, at least in part due to species-specific differences in dopamine metabolism and formation of neuromelanin that is present only in human neurons. Increasing dopamine synthesis or α-synuclein levels in mouse midbrain neurons partially recapitulated pathological phenotypes observed in human neurons (**Burbulla et al, *Science*, 2017**). These findings highlighted the importance of studying human neurons in PD and at least in part explain why animal models of PD do not exhibit degeneration of DA neurons that is observed in PD patients.

In addition to identifying a functional convergence of mitochondrial and lysosomal dysfunction in PD, we recently identified the formation of direct mitochondria-lysosome membrane contacts that mark sites for lysosomal regulation of mitochondrial networks, while conversely, mitochondrial contacts regulate lysosomal dynamics (**Wong et al, *Nature*, 2018**), providing a

new angle to studies of these organelles in neurodegenerative diseases including PD.
Based on the above findings, we developed small molecule activators (**Zheng et al, *J. Med Chem,* 2016 and *JACS*, 2018**) of mutant and wild-type GCase that improved enzyme activity in sporadic PD, as well as multiple genetic forms of PD (e.g. LRRK2, Parkin, DJ-1, GBA1), suggesting that activation of wild-type GCase is sufficient to ameliorate lysosomal dysfunction and accumulation of oxidized dopamine, glucosylceramide and alpha-synuclein in various forms of PD as a therapeutic target (**Burbulla et al, *Science* 2017, *Science Translational Medicine*, 2019**).

23. In 2021 you received a 9 million-8 year research grant (https://news.feinberg.northwestern.edu/2021/05/07/krainc-to-receive-9-million-8-year-nih-grant/). What does your proposal entail and what do you expect to accomplish in your studies.

The goal of our research is to identify modifiers of penetrance in many genetics forms of Parkinson's' disease (since most genes are not fully penetrant). Targeting such modifying pathways may help with more comprehensive therapeutic development of neurodegenerative disease.

24. You have numerous patents to your name. Furthermore you are the principal founding scientist of biotech companies Lysosomal Therapeutics and Vanqua Bio and also serves as Venture Partner at OrbiMed. Why did you establish these companies?

I am listed as the inventor on 31 patents in the field of neurodegenerative disorders, primarily Huntington's and Parkinson's disease, 4 of which have been licensed to companies. I founded a biotech company, LTI, focused on Parkinson's disease that signed a $600M partnership with Allergen before their acquisition by AbbVie. Most notably, we developed allosteric activators of lysosomal glucocerebrosidase (GCase) encoded by the gene GBA1 that is linked to Parkinson's disease (US-10934270—quinazoline compounds for modulating GCase activity). These activators were developed based on our discovery of the role of GCase in synucleinopathies published in *Cell* in 2011 and represent the first example of targeted therapy for neurodegenerative disease. These GCase activators were licensed to Vanqua Bio, which I founded.

25. Outside of your University you are also active in national medical societies. This year you became President of the American Neurological Association. Congratulations! Which aspect of your work or personality prompted your peers to elect you to that position?

I was elected by my peers in recognition of my research discoveries and leadership of the department that my staff and I elevated into one of the top neurology departments in the US..

26. You serve on the Editorial Boards of several journals. Which one of these is the highest ranked journal?

Journal of Clinical Investigation

27. In our interviews we like to include some statistics. What is your h-index? How many citations did your papers receive so far?

My h-index is 94 and my papers received over 48 000 citations so far.
https://scholar.google.com/citations?user=64hgxAUAAAAJ&hl=en

28. What is your favorite paper?

Mazzulli JR, Xu YH, Sun Y, Knight AL, McLean PJ, Caldwell GA, Sidransky E, Grabowski GA, Krainc D. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell. 2011;146(1):37-52.
It was cited over 1300 times

29. You are member of several Academies and have also received several other honors and awards. Which one of these do you value the most?

Membership in the US National Academy of Medicine that is part of the national Academies of Science, Medicine and Engineering and is considered the highest honors in our field.

30. Are you still in contact with your Croatian colleagues? Are you planning any joint research projects with them, conferences or publications?

I did a sabbatical in Zagreb about 20 years ago when I served as chair of neurology in KBC Rebro. At that time I developed a Center for genomics at MF Zagreb and trained dr. Fran Borovečki to run it after I retuned back to US. The Center is still active and I consider this my most important contribution to my alma mater.

31. Any messages for the medical students and your junior colleagues in Croatia?

Try to become really skilled in your craft and if you have to leave Croatia to receive additional training, please make sure you return home. Croatia needs you.