Nenad Bogdanović Interview

Damjanov, Ivan; Pećina, Marko

Source / Izvornik: **Rad Hrvatske akademije znanosti i umjetnosti. Medicinske znanosti, 2023, 556, 140 - 151**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:489188

Nenad Bogdanović Interview

Nenad Bogdanovic MD, PhD
Professor in Geriatric Medicine
Karolinska Institutet
Department for Neurobiology, Caring Science and Society - NVS
Division of Clinical Geriatrics
NEO,
and
Senior Consultant
Geriatric and Neurogeriatric
Theme Inflammation and Aging
ME Aging R94
Department for Cognitive Disorders
M52
Karolinska University Hospital

e –mail: nenad.bogdanovic@ki.se

1. How did you decide to study medicine?

This is a very good question which is difficult to answer by simple saying that was a natural way or family heritage. Neither my mother nor my father were in the medical profession. My granduncle was a well-known doctor in Šibenik, known for his work on improving the health in our town during the first half of 20th century. He was a big joker and I admired him while I was a little boy. I liked to visit him and play with various instruments especially with the old x-rays machine he had hidden in the small room at the end of the corridor of his house. My granduncle died of a malignancy induced by x-rays since body protection at that time was very weak.

My interest in biology I can trace to my high school years and my biology courses I took in the 2nd Zagreb Gymnasium. I liked biology in general but my hobby was hunting and dissecting frogs and engaging in similar pastimes. Culminating my biology related activities was a treatise about the development of cardiovascular systems in vertebrates that I wrote by the time of my graduation. It was a demanding task since nobody around me could help me write it and there was nobody with whom I could discuss those topics. I was reading some biology books recommended by my teacher but nobody taught me how to write a scientific paper or an essay, how important it is to quote the literature appropriately and how to prepare a list of references at the end of the paper. I wanted to impress my teacher and did not include any references into my writing, thus trying to show off how well I know this scientific issue. Thinking about all this today I feel a bit ashamed about my ignorance and naivete. Nevertheless it was obviously an experience that I will never forget. I even asked my sister, who is an academic painter, to make a few drawings for me. These were definitely better than my text.

During my high school years my best friend (he is my wedding witness) got me interested in car engines. Building and dismantling motors became a consuming passion of mine. My favourite entertainment was removing the engine from Citroen 2CV that I could take out from the car in about 3 hours. That were the days. During the summer vacation I liked observing, studying the action and dealing with the motors of small fishing boats. TOMOS 4 was the very first outboard motor that fascinated me, followed by Seagull, VOLVO Penta and Fariman. I used to ride motorboats at sea even if the weather conditions were not optimal. Not once I did encounter very bad weather conditions at the sea but luckily without serious consequences. Weather conditions perplexed me ever since and even today I pay attention to the changes of the weather and follow carefully the weather forecasts.

During that period of my life I was also preoccupied intensely with basketball. In 1968 Yugoslavia was the basketball world champion and that was an impetus for us teenagers to start playing the game for good. Together with a gang of friends I joined Medveščak, a team that was in second division. I liked that since it was a really a combination of sport and social gathering. Our sport and social events taught me how to share good and bad with my close friends. It was a lesson for the rest of my life.

From what I have said so far, you can see that by the end of high school there were three things that were important for my future life: biology/anatomy, motors and weather. I had to decide what to study and choose between Medicine, Physics or Engineering. What should I be, I had to decide. A doctor, an engineer or a meteorologist? The simplest answer was to try to enrol in all three faculties at the same time. Since I had passed the entrance examination for all three faculties, I decided to try do study course at the same time in parallel and make the final decision of what to become for later on. Thus in September 1972 I first started attending the physics lecture and then one month later entered into the medical school. The pivotal moment were the first anatomy lectures, and the feelings that overwhelmed me upon entering the anatomy museum and having the first look at the complexity of the human body. From that moment I was sure that I want to spend my life studying the structure

and function of the human body. The anatomy course was so intensive that I did not want to continue with physics and even did not attend any lectures at the Faculty of Engineering. I was very sure that my future lies in medicine without actually knowing what future will bring to me. I continue with sport but to a lesser extent. Gradually I stopped playing basketball and started with tennis since the Medical School owned several tennis playgrounds in the vicinity of the main campus.

Did I have any ideals, conviction or beliefs by that time? Probably not fully formed but I definitely wanted to follow in the steps of my parents. They were my idols and I wanted to find a balance between their characters, on one side may father and on the other my mother. My father was a Supreme Court judge in Zagreb with a PhD degree in jurisdiction and a huge knowledge of jurisprudence knowledge acquired before WWII. His ideals were to devote his life fighting for justice, freedom from the influence of authorities, with an emphasis on strong personal identity and endless work for the right causes and legal duties. My mother was a caring and very social person, an ardent educator, tolerant to the maximum in all respects, ready in any time to share everything with everybody. That was a way how our family was functioning as an ideal unit. Both of them were helping everybody and never ever accepted any reward for that. The anecdote but absurd situation was when somebody left a bag (I don't know what was in that bag) in front of our door. My father came outraged and has sent my mother find that person and force him to take the "present" back.

Following the example of my parents I refused to be part of any group, political or religious or any other, or to yield to the pressure of such groups. Like my parents I have been trying to be progressive, to have empathy towards others irrespective of their background or origin. I was always impressed by those whose actions were based on knowledge and honesty, and had inherent personal values. That was and still is my *modus vivendi.*

Figure 1. 40 years of generation, Zagreb, The Croatian Medical Association, 1976

2. Did you enjoy your student days in Zagreb?

I did enjoy greatly those days. I met a bunch of new friends with some of whom I still have close contacts even though we live in different parts of the world. Those friendships are very important to me and I consider them to be among the most valuable "gifts" my Medical School gave me for life.
During my medical school years I was very active in student groups, including the student club called Koma. That was the place where we used to meet and share our problems as well as to take action at the faculty assembly to improve our student condition. Those days students were not considered to be partners or important factors in shaping our own educational process. The entire faculty was structured as a pyramid defined by hierarchy headed by the dean, a cadre of powerful chairmen and a wide base composed of the aching faculty. The students were practically not included in that power structure and our student's budget was negligibly small in that time.
One of the main goals of our student organization was to produce teaching material in form of transcripts of lectures for those subjects where our professors were was not able or not willing to write a textbook, or translate a text from a foreign language. The typical example was pathophysiology where we did not have any official literature but rather machine written short texts that was provided after we have heard each lecture. We were working day and night to get enough copies for the entire class using two Gestetners mimeographs which used to be always out of function after a few hours of printing. The copy machines were the accessible in the main administration offices but could not be used by us students.
The second important activity was improvement of teaching and education via a student teaching committee led by us and Dr. Branko Richter, the Professor of parasitology. His contribution to our studies during the first 3-4 years was immeasurable.

Figure 2. With NIKON microscope, I did have the most advanced one, 2001

I became involved in scientific work already at the second year when I joined the neuroanatomy group of Professor Kostović, which later expanded into the Croatian Institute for Brain Research. Thus I learned the basic principles of science and how to start thinking like a scientist. With that initial experience I was able to form a students' scientific committee that tried to attract students to enter science. We also organized small local scientific conferences and annual conferences for medical and dental faculties in the region. At the time, I became the student representative on the Scientific-teaching Council of our Medical School, where we accomplished what was considered to be impossible up to then. Thus in 1981 during the inauguration and of the leadership bodies of the Medical School, I led the student group requesting the right for students to nominate their own candidate for the position of educational vice dean. In response to that unexpected and unsettling situation for the new dean, the leadership of student organization has been replaced by the novices chosen by the faculty as trustworthy, and the entire "rebelian" student organization has been placed under the full «control» of the faculty administration. As an example our year budget was same as a cupboard that new student leaders got after the replacement.

3. What were your favourite subjects and which professors you still remember?

My favourite subject was anatomy and especially neuroanatomy that was taught by professor Kostović. He was my idol and became my scientific mentor after I had completed my medical studies. The second subject was clinical neurology. Dr. Stevo Knežević, the professor of neurology played a pivotal role in attracting me to clinical neurosciences. I was determined to pursue a professional and scientific career due to the combination of neuroanatomy and neurology I had studied under the guidance of these two professors.

4. As a student did you do some research or had some serious extracurricular interests?

After my examination of neuroanatomy I joined the Kostović lab. He just arrived from USA and continued working on human brain development which he began in America. Thus I became part of a very propulsive and world-renowned research group involved in the study of foetal brain development. It was a time when I was hard working trying to finish my student obligations on one side and scientific tasks formulated by Dr. Kostović on the other. I spent enormous periods of time drawing the neurons by camera lucida system, and endlessly examining the microscopic sections of the brain. I tried to get the 3D image of dynamic foetal brain in time and space and that was extremely demanding but the results of my efforts from those days I am seeing even today. I still remember fondly that my first scientific question was how to understand the development of *induseum griseum*.

Figure 3. 2004 with Nobel laureate in medicine Richard Axel Columbia NY

Figure 4. Professor Bengt Winblad

5. While you were studying in 1980s there were not too many neuroscientist in Zagreb, or am I wrong? How did you decide to enter neuroscience not knowing exactly what you would like to study?

At that time Ivica Kostovic was the leading neuroscientist in the field of neuroanatomy especially developmental brain anatomy. After his arrival from USA and his historic description of the subplate layer the neuroanatomy in Zagreb had got the enormous push and I was lucky to join the group at the very beginning. Kostović did have a strong connection with well known Croatian neuroscientists abroad who had provided an important scientific support like Paško Rakić, Krešimir Krnjević and Ante Padjen. It seemed that the neuroscience in Croatia has a good future. The scientific results published over the last few decades prove that the optimistic prediction was actually correct.

6. You entered science through neuroanatomy, and your first papers dealt with morphology of the foetal brain. Do you think that this was a good way to begin your future studies of the brain and its diseases?

I think that the most of my papers dealt with morphology, starting with several works on human development followed by animal models of cholinergic depletion to the clinic-morphological work on neurodegenerative disorders. Was that the good way I don't know but that was a way that I extremely liked and had shaped my position today, I do think successfully

7. Did you have any role models? Or in other words, did you have a clear idea what it meant to be a neuroscientist?

I did not have an idea what does it mean to be neuroscientist. I found that work with the brain was so cool and interesting. When this passion continued I gradually became a full fledged neuroscientist. Even as a clinician today I am neuroscientist since I am thinking as a basic and clinical researcher while I am meeting patients. Probably that I did have several role models, starting with Ivica Kostović and Stevo Knežević, followed by Bengt Winblad who was my mentor in the world of neurodegeneration here at Karolinska Institute in Sweden.

8. Did you dream of becoming a basic scientist, a future clinician or you always intended to combine science with clinics?

I do think that I always wanted to combine both basic and clinical work. Even after 10 years in basic neuroscience, being student demonstrator and assistant professor in anatomy and neuroanatomy, I felt that I needed to apply my knowledge in a clinical setting and in direct contact with patients. This way I feel that I am applying my knowledge of neuroanatomy and basic neuroscience to everyday clinical praxis of neurology.

9. Did your plans change after you moved to Sweden?

Sweden gave me the possibility to utilize my knowledge as a neuroscientist and neurologist in the entire new field of neurodegeneration that I could not find in that time in Zagreb. I am very much aware that my plans had expanded in non-presidential manner that I could not even dream 33 years ago

10. Was the move to Sweden one of those crucial events that changed your worldview for ever?

Definitely that is true. The circumstance that led to my move to Sweden was almost anecdotal. I was completing my neurology training for the New University Hospital that Zagreb which was supposed to become the modern state-of-the-art hospital and it was then under construction. I felt that I want to put into practice in that hospital my to great loves at that time, neuroanatomy and neurology. I wished to have some kind of conference or meeting that leading basic and clinical neuro researchers put their brains together. I was too young without so many connection in the world and I decided purposely to convince my clinical mentor Knežević and basic science mentor Kostović to organise a conference and invite the leading people in the field to come to Zagreb. I had tried to be the executive organiser and to do my best to get my dream realized. That was a very demanding task. When I did present my idea to Knežević he rejected it and the same happened when I presented this idea to Kostović. The reason why they did not like the idea I could not understand. Reflecting about those events today I think that they did not want to combine different fields where they are not confident and this type of combined field in the field of neurodevelopment and neurodegeneration was not common in the scientific society at that time.

Figure 5. Brain Net Europe meeting in Budapest 2005

I found myself in very uncomfortable situation, but I said to myself to try to use the trick which did work on the end of the day. I had approached to Kostović and said that Knežević is very interested in the conference and that we have a unique opportunity for brainstorming between scientists in these two areas of neuroscience. The same arguments I presented to Knežević, and finally they both agreed and the conference took place in Dubrovnik 1990. I was so happy that I decided to do my best to have the conference succeed.

Those days there were no companies organising scientific conferences so we had to do everything ourselves. Kostović had invited the leading developmental neuroscientists (Rakić, Mishkin, Braak, etc) and Knežević invited the leading authorities on neurodegenerative diseases, such as Winblad, Reisberg, DeLeon and several others. The conference was a great success, the book of the proceeding was published, and memories of the event lingered for many years thereafter in the minds of many participants. 30 years after conference took place, I meet many of them and most still remembered fondly the meeting in Dubrovnik. That meeting was part of my destiny, since there in Dubrovnik I met my future mentor Professor Winblad, I met his at the airport and drove him to the hotel. During that ride we discussed many topics of common interest. I consider it as the beginning of a long-lasting friendship. At the end of the meeting he invited me to Sweden. He was, namely, developing a new research and clinical centre and thus he suggested that I could be of a big help to him in his effort with my a basic science and clinical experience. At the same time he told me that I could master new research elements of clinical and preclinical treatment of neurodegenerative diseases, which would then help me establish my own neurology-neuroscience practice in Zagreb in the New Hospital. That was our original plan and rest is history.

11. How difficult was it for you to leave Zagreb and move to Sweden?

Theoretically it was not. After I received the invitation, my entire family moved to Sweden with the idea to stay there for 1-2 years. We were very enthusiastic by thinking how the new department in the new hospital in Zagreb would be opened soon. But the situation had changed after one year. Hospital was stopped to build, and 200 doctors got fired without any plan to be employed somewhere else in the health system. Those were very difficult times, since I and my wife lost our jobs and were practically in the street with our first child. But Sweden wanted us to stay and offered me to continue my (our) work. That was difficult but at

Figure 6. With Prof Knezevic a clinical mentor 2005

Figure 7. Krnjevic, Rakic, Kostovic, giants of Croatian neuroscience, Zadar 2005

Figure 8. At my clinical department 2006

that moment it was a survival move. The major difficulties were to leave my parents and my sister, Zagreb as a my town, friends and colleagues, almost my entire life behind. I was not worried about work in Sweden, I already had a project and scientific tasks but the environment all around us was totally new for me and my family

12. To a young Croatian physician contemplating a move to Sweden what advice would you give on how to survive the first few months or years in that Scandinavian country?

Very simple advice if they are aiming to work. Important is to come with extra knowledge and skills at hand and a clear idea what you want to accomplish. Scandinavian countries are very focused and practically oriented and are able to recognize if they are getting extra value for their money. They are willing to help with everything from the beginning regarding even the needs for rest of the family and children. The quicker you are in the system, the more valuable you are for the host. When I had arrived, I did have a working permit from the first day, kindergarten and flat fixed for the family, and all that helped of course.

13. What were your major professional challenges in Stockholm?

Entering into a new research and medical system was not so difficult, but it was quite challenging to master the local language and to understand the work and legal differences. The knowledge that you bring from your own country is an asset but how to apply it might not be so simple. Adjusting to the new work conditions and local routine should be grasped as quickly as possible. The daily work in the clinical setting in Sweden may differ considerably from the work one did in Croatia, but one must adjust. In the clinical setting there is a big difference than in Croatia. Relation between workers and leaders is extremely professional and respectful. I knew all my rights from the very beginning. I do think that is a common professional behaviour at least here in Sweden.

14. Did you join a group or did your start working with a senior scientist?

After arriving to Karolinska Institute I had joined the group where senior scientist was my mentor, but the group also included 3 additional scientists of my rank and 2 technicians

15. How long did it take you to establish your own research lab and form a research group?

Since arrived as a young scientist I had to enter a PhD program after one year. During that time, I could not establish the group but completing my PhD program I was given the opportunity to form my own neuromorphology lab and brain bank. A technician and a PhD student were also assigned to me to help me with my research. In parallel I did start working at the clinic but keeping my 50% preclinical research position.

16. Was there a critical moment when you realized that you „finally made it“ in Stockholm?

A critical moment of that kind occurred during the first year of my stay in Sweden. It was not an earth-shaking event but I still

remember my outburst of joy and happiness after I successfully completed an immunostaining for demonstrating the enzyme cholintransferase in tissue sections. I was working on neurosurgical stereological lesions of nucleus Meynert performed to deplete the cholinergic innervation of the brain. That was an animal model for pharmacological treatment of cognitive impairment, which a very popular topic at that time. I got this task due to my skills in neuroanatomy and morphology as well as I learned psychological testing of experimental animals. One of procedures that I still had to master was immunostaining. The technician in the group where I had started was considered to be an expert and was responsible for the immunostaining. She could not get staining done after endless number of trials and it was considered to be impossible to perform. Then I suggested some modifications of the staining protocol, based on my previous experience in Zagreb. I knew that this enzyme is very sensitive and the proper fixation and tissue preparation is crucial for immunostaining. I decided to do everything by myself hoping that I will get a result. It was a very stressful moment but I was highly motivated to succeed. At the end I managed to complete the immunostaining. I was so overwhelmed with emotions that I started to cry in my small room, but then I pulled myself together, and then came out and showed the results to the rest of my group. I knew that I am going to change my position in the group and from a visitor become a respectful and fully accepted member. After that I did have much more freedom especially after the missteps in the immunostaining protocol had been changed. That technician responsible for the immunostaining was later included in my own group and today we are best professional colleagues. For me this event showed how important it is bring knowledge and useful working skills from your native country, especially if you have skills that the host may not have.

Figure 9. In front of Karolinska Hospital 2006

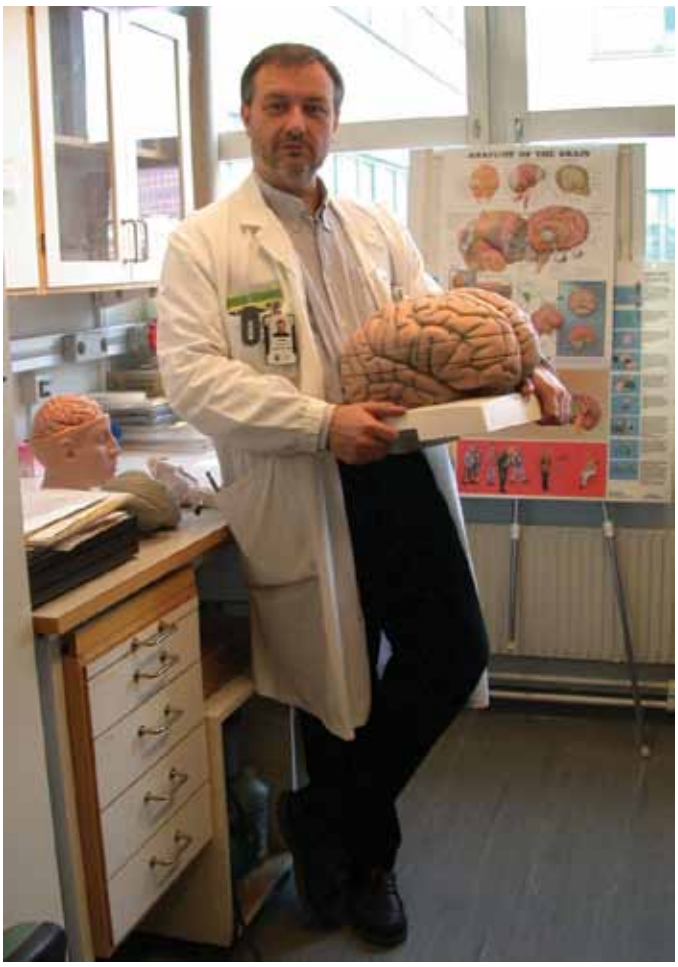

Figure 10. Clinician in the lab 2006

17. By nature are you a patient easy-going person or an impatient one who wants to have thing happen all at once, or as soon as possible?

Definitely not an easy going person. As a clinician and a senior physician I must be disciplined, plan ahead of time and stick to established protocols. I cannot improvise and I cannot postpone any assessment or plans for the patient care since so many persons are affected by my decisions. I try to resolve any issue during my working hours, and if possible never leave anything for later. The same applies to my preclinical research. But as any other human being I do make subjective estimates for some future events and actions, hoping that these problems could be resolved in near future. Accordingly, I am trying not to be a robot and remain flexible.

18. In a previous interview of yours that you gave to the Croatian magazine NACIONAL there is mention of a scientific award nick-named „little Nobel". When did you receive it, what for and what did it mean to you?

Ah that is a construct of the Croatian journalist. In 2004 I have been awarded by the highest pedagogic prize at the Karolinska Institute called Master of education. Students in Stockholm use to give this prize for their teachers who have excelled at education. I did get it for my teaching of neurology based on a combined clinical neurology neuroanatomy approach. To this end I would make a presentation of the clinical findings and then provide neuroanatomy material to supplement the clinical data. Students liked this multifaceted approach in which we juxtaposed clinical neurology with the dissection of the brain and neuropathology, combining morphology, functional anatomy and clinical symptoms. In real life situations the students were discussing clinical symptomatology by pointing out the anatomical regions on the fixed brains in the autopsy room. That was a pretty new and innovative approach at the Karolinska Institute and the students appreciated my efforts to integrate several aspects of neurosciences. Since the presentation of the student award coincides with the Nobel prize award, and since the Nobel laureate in medicine is present at the student festivities (I have a photo with him) the student prize was nicknamed "Little Nobel". The Swedish correspondent for Croatian news agency HINA did send short notice about it to Zagreb, but I do not know all the details about it. The prize that I received from students is mostly given to teachers involved in graduate education. I like teaching and thus I teach postgraduate courses in geriatric medicine, PhD courses in neurodegeneration, different courses for psychologist, nurses and courses for the Swedish medical doctors in training who are resident in neurology, geriatric, general and internal medicine. Moreover I do some lecturing for Croatian medical doctors regarding geriatric medicine.

19. From your curriculum vitae it seems that you have numerous functions and titles. I simply could not believe that a single person can do all that at the same time. Could you tell us how do you juggle all these responsibilities, assignments and tasks?

Ha ha ha I don't know which parallel functions you referring to, but it is true that I hold several active posts which are coordinated one with another, and thus quite manageable. Nevertheless, I work 12 hrs per day and most often I am on top of it, and finish on time my daily duties. For details about my private life you can ask my wife and she will tell you a few stories about her "absentee husband".

20. Which one of your papers do you consider to be your most important contribution to science?

I like to list three papers:
1. Volume and number of neurons of the human hippocampal formation in normal aging and Alzheimer's disease. G Šimić, I Kostović, B Winblad, N Bogdanović. Journal of Comparative Neurology 379 (4), 482-494, 1997
2. Bogdanovic N, Corder B, Lannfelt L, Winblad B. APOE polymorphism and clinical duration determine regional neuropathology in Swedish APP 670/671 mutation carriers: implication for the late onset Alzheimers's disease. J Cell Mol Med, 6(2):199-214, 2002
3. Environmental enrichment and the brain AH Mohammed, SW Zhu, S Darmopil, J Hjerling-Leffler, P Ernfors, Winblad B, Diamond MC, Eriksson PS and Bogdanovic N. Progress in Brain Research 138, 109-133, 2002
The first paper deals with the total number of neurons in the hippocampus. It is one of the only two papers in the world literature dealing with this problem. The method that was applied called stereology and we used it to estimate the total number of neurons in the structure. This paper was cited 609 times and is my most citated paper despite the field is very narrow.
The second paper deals with the clinics and neuropathology findings in the brains of patients who had the Swedish mutation. It is the first publication in the world dealing with this disease and discusses the gene-gene interaction in the clinical context.
The third paper as a big review deals with an environmental influences and plasticity of the morphology of the brain and we have stressed there the possible unique features of the Einstein brain

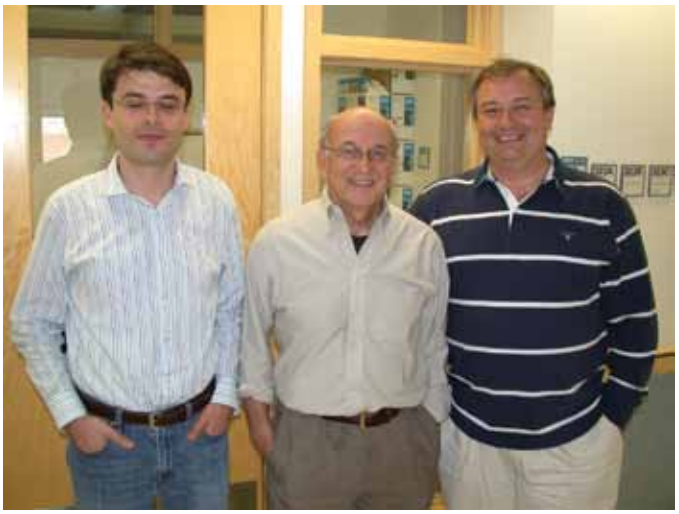

Figure 11. With Rakic and Sestan at Yale 2011

Figure 12. Explaining the brain to the patient, 2016 Oslo

Figure 13. Getting 1 mil dollars from mr Thon in Oslo 2017

21. Some of your papers are experimental, and some are clinical. Furthermore you are the discoverer of two Alzheimer disease mutations, Swedish and Arctic; I do not know how one would classify the papers dealing with such data. The question for you is as follows: How do you balance laboratory research and clinical investigations and all other activities that are hard to classify?

A shift in my research from classical preclinical experimental models to the clinical-pathological approach occurred a few years ago. As I have mentioned before, I was working 50% of my time as a clinician and 50% running the morphology lab and brain bank, which was collecting brains. In parallel with my clinical position I was also a consultant neuropathologist for 15 hrs per months assessing the the pathologic changes in post-mortem brains. The Swedish Ministry of Health has recognised my expertise in the field and awarded me this very unique position to analyse the postmortem brains from clinical cases that passed through my clinic. I was able to see all correct or mistaken diagnoses. In Sweden I did around 964 neuropathological autopsies with entire procedure of taking out the brain, preparing the tissue blocks for formalin fixation and frozen material. I was reading the slides and report the diagnoses, as very few neuroscientists do today. However, I feel that I should follow in the steps of the great neurologists/neuropathologists of previous times, including Alzheimer, Nissl, Fisher, Pick and several others. Concerning Swedish and Arctic mutations, I met those families as member of our team but I also did the first autopsies of patients with those unique mutations. Both mutations had led to the development of common mice models of AD. The work on the Arctic mutation 20 years ago enabled us to get the foundation for developing the first successful antibody against Alzheimer that were registered by FDA in January 2023 that got the name Lecanemab (Brand Name in the U.S.: LEQEMBI™)

22. You are best known internationally for your work on Alzheimer disease, and many of your publications deal with this topic. Maybe you could summarize in a few sentences your contributions to the genetics, clinical aspects and cell pathology of Alzheimer disease.

Most of my papers deal with the questions regarding Alzheimer neurodegeneration but I did also work on frontotemporal dementias, Lewy-body dementias, vascular and other neurologic diseases. To understand Alzheimer disease, we have to understand how it differs from other dementias. As I said previously understanding the genetics and unique morphological features of those two mutations that we discovered helped us to better understand presentation of the hallmarks of Alzheimer, amyloid plaques and tangles. The Arctic mutation has shown that pathology never reached the most advanced form of plaques but produces most toxic forms of protofibrils that are in focus

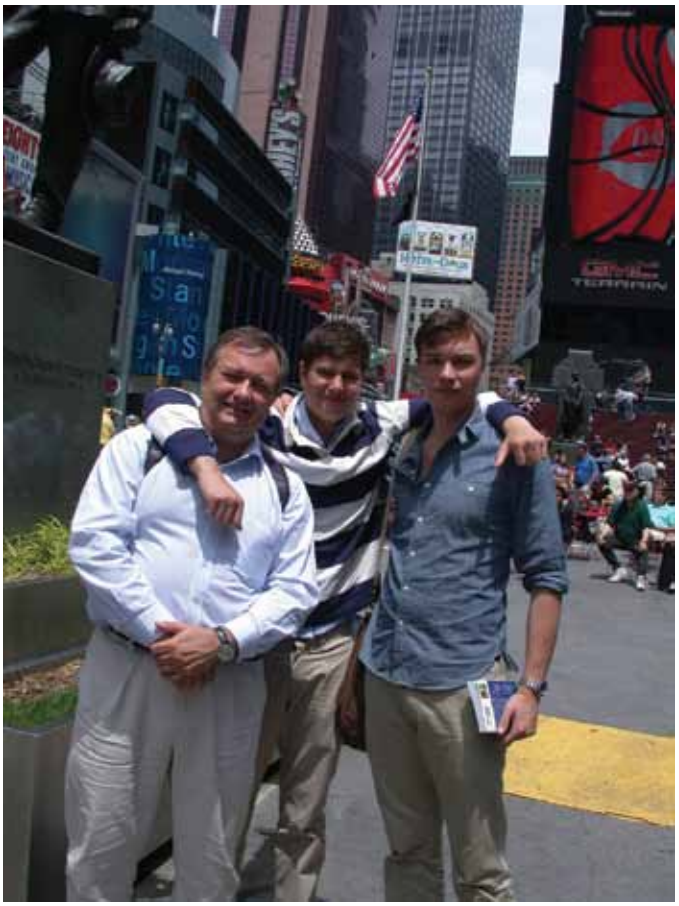

Figure 14. With my sons in Big Apple where I had a company HQ 2011

of antibodies currently registered this January by FDA. APOE lipoprotein, is coded by a gene that is one of the greatest risk genes for the Alzheimer disease in the elderly. In our Nature paper (*Nature Medicine,* 4:1182-4, 1998) we have stressed how APOE is involved in other diseases like HIV, as a contributing factor for cognitive impairment. My work on Swedish mutation and APOE has shown that gene to gene interaction can shape the clinical and morphological features even in mutation brains as mentioned earlier. Some of pioneer work I did on cholesterol function in the Alzheimer disease brain where astrocytes seem to be mostly involved (Neurosci Lett. 13;314(1-2):45-48, 2001). Other pioneering work was done showing the difference in intraneuronal amyloid concentration among the Alzheimer brain neurons regardless of mutation or idiopathic cause of the disease (Neuroreport. 2008, Jul 16;19(11):1085). At the clinical side of my research, I was always interested with the unusual clinical features and possibilities to test those differences, thus non-classical clinical presentation of the Fronto temporal Lobe dementias (Neuropathology. 2011 Jun;31(3):271-9, AJNR Am J Neuroradiol. 2009;30(6):1233-9), speech disorders and its testing (Cortex. 2007;43(5):60715, Folia Phoniatr Logop. 2009;61(5):269-274, Brain and Language, 79(2):333-339,2001, Logopedics Phoniatrics Vocology 2008 10:1-10)
Generally speaking, I have tried to be provocative in my work, trying to broad the field and challenging the established views. Was I successful or not I am not able to judge now.
Beside my clinical work I did some international education in the field of clinical development and organisation of the neurodegeneration department. The latest example was my engagement in Clinical Hospital Luohu in Shenzhen China where I spent some time during the 2018 and 2019 just before Corona pandemic. I did educate colleagues how to approach clinically to neurodegenerative diseases and what is the most important for diff diagnostic – I did established my small policlinic work and had some dozen patient that I did follow up.

23. You are actively working with drug companies on developing new drugs for the treatment of Alzheimer disease. How far did you get to reaching that goal?

I was actively working with 2 companies Wyeth and Pfizer on developing the anti-amyloid antibodies. It was 11 years ago when entire development of AD drugs failed due to several unfortunate factors. One of the specifically important reasons for this failure was that the clinical diagnosis of AD was established only on the clinical criteria. This means that doctors relied solely on identifying symptoms and signs of Alzheimer's disease without confirming the physical changes in the brain that typically accompany the disease. This approach resulted in misdiagnosis of patients, as other conditions with similar symptoms might have been mistaken for AD. Diagnosis of AD without the use of biomarkers or imaging techniques is no longer considered sufficient, as it can lead to incorrect diagnosis and inappropriate treatment. In USA use of biomarkers was not common and thus 30 % of wrong diagnosed patients were entered in the clinical trials in Phase 3. The results were disastrous for this field of drug development. We in Europe were using biomarkers for AD but we did not have a chance to continue the work since the drug company Pfizer had decided to terminate the program. Consecutively FDA had changed the rules how to perform clinical trials for AD. Overall, the changes in clinical trial rules and approaches to diagnosing AD have improved the accuracy and effectiveness of treatments for this devastating disease. However, there is still much work to be done to better understand the underlying biology of AD and develop more effective therapies for patients.

24. You have three patents to you name. Did these patents produce any tangible results so far?

Those 3 patents are as follows:
1) Apparatus for determining the volume of solid body and it's in real-time measurement, 2009. It has been in use while we

Figure 15. With my wife at the summer holidays 2015

Figure 16. In the depth of glacier at Spitsbergen islands

were working for 10 years on the project BrainNet Europe on the standardization of neuropathological protocols sponsored by Europe Committee. The main purpose was to standardise the method of measuring the shrinkage of the tissue. I personally did not have any financial benefit from this patent.

2) Method for purifying amyloid plaques, 2005.
3) Disease marker for AD and its use. 2003. This patent was related to the purification of the amyloid protein in the brain and its use as a biomarker. Both patents are part of the 10 years research collaborative project between Karolinska Institute and the Japanese company Sumitomo which is the ultimate owner of the patent.

25. You are interacting with scientists from other Scandinavian countries and are part of two European consortia for the study of the brain. Did some of your papers result from collaborative studies with scientist from other countries?

- BrainNet Europe is the project of EU granted for the period of 10 years to 20 different brain banks. Scientists, clinicians and neuropathologists in these banks worked together for many almost 10 years and have published more than dozen articles related to the standardization and harmonisation of the protocols related to utilisation of the brain tissue and characterisation of the pathological proteins.
- EUGMS is the European geriatric medicine Society the coordinated body for the all countries that have geriatric medicine as a specialisation. I am a member of the executive board and project COST (European Cooperation in Science and Technology) that is a funding organisation for research and innovation networks. That specifically aims to introduce the geriatric medicine specialisation in the south-east European countries. Croatia is a part of the project and I represent both Sweden and Croatia in attempt to build up geriatric medical services in my homeland. I am a specialist in geriatric medicine and have been licensed in Croatia as a first geriatrician. I am member of the geriatric working group of Ministry of Health in Croatia as an expert regarding establishing of geriatric medicine.

26. Perusing the list of you publications I see some names indicating that some of your collaborators are from our region here. Do you have any active projects with neuroscientists from the old country?

I am a visiting professor at the Medical faculty in Zagreb. I tach a postgraduate course at the Croatian Institute for Brain Research and I am an external mentor for PhD candidates at the Institute working on the ischemic perinatal brain lesions in animal models. I have an additional active collaboration with some scientist from the Institute more related to the specific experiments and articles that were published jointly. I am also involved in an active project on blood biomarkers for Parkinson and Alzheimer disease that is going on in collaboration with the neurology department at the University Hospital Rijeka.

Figure 17. At neurology clinic in China Shenzhen 2019

Figure 18. Patient in China 2019

27. Which projects preoccupy you currently the most and what are your short term and long term plans?

At Karolinska Institute and Karolinska University Hospital I am working on a project related to the characterization of amyloid fibrillar forms in the blood. We are using a sophisticated fluorescence techniques trying to develop it as a technique for the detection of future biomarkers. For that project me and my collaborators were highly awarded by Thon foundation from Norway and from diverse Swedish scientific and governmental foundations bodies (see photos)
The second project aims to improve the accuracy of dementia diagnoses in very old people who do not have amyloid proteins in their brain, but were previously misdiagnosed with Alzheimer's disease. The study will involve a comprehensive clinical assessment of individuals with suspected dementia, including cognitive testing, imaging studies, and other diagnostic assessments.
The researchers will use the latest diagnostic criteria for all types of dementia and will focus on identifying features that distinguish between different types of dementia, including Alzheimer's, vascular, frontotemporal, and Lewy body dementia. They will also examine the clinical course of the disease, including the progression of symptoms, response to treatment, and impact on quality of life. This project has significant implications for patient care, as accurate diagnosis is critical for appropriate treatment and care planning for individuals with dementia.
The third project: I am planning and excited to return to Boston University and continue important work, on von Economo neurons in monkey brains that I started many years ago with Prof Helen Barbas but due to my endless duties in Sweden the project was laying at the bottom of my desk. Specifically, these von Economo neurons have been implicated in the social and emotional processing of information, and studying them in monkeys can shed light on their functional significance in the human brain.

28. Do you have any plans for some collaborative projects with Croatian scientists?

I am keeping the long project with Rijeka, and COST program via EUGMS where the main aim is to establish geriatric medicine in the region using all possible country specific educational and professional contacts.

29. Any message for our younger colleagues considering to follow in your footsteps and move abroad?

My advice is to master certain techniques and skills while you are still in Croatia. Also try to establish contacts with colleagues from other parts of the world by publishing in international journals, attending congresses, making poster presentations, using different EU programs for student exchange, define you research interest together with mentor, get a PhD or post-doc position in Croatia or abroad. If you go abroad try to come back to Croatia and build up scientific infrastructure and initiate the national and international projects helping country to enter international family of scientist and putting Croatia higher at the scientific map. That privilege to be accepted back in the country of origin is the most valuable step in forming the new scientific environment and usually it is highly appreciated. I deeply regret that I did not get an offer and chance to come back earlier and share my experience with experts in Croatia.

Figure 19. With Queen Silvia at the grant award ceremony 2023.