

## ESSAY - INTERVIEWS

### MOST ILLUSTRIOUS ALUMNI OF THE SCHOOL OF MEDICINE, UNIVERSITY OF ZAGREB, ZAGREB, CROATIA

Dear Readers,

In the issue 544=52-53 of our periodical, RAD HAZU – Medical Sciences, we introduced a new feature entitled *ESSAY – INTERVIEWS „Corresponding Members of Croatian Academy of Sciences and Arts, Department of Medical Sciences“*. For the issues 54-55,56-57,58-59,60-61,62-63 and the present issues 64-65 of our journal we decided to expand the scope of that series and include interviews with other internationally known alumni of the School of Medicine, University of Zagreb, Zagreb, so that we could profile even those alumni who are not Corresponding Members of the Croatian Academy of Sciences and Arts. This change of venue required us to change also the title of this series of interviews, and rename it in Latin **Illustrissimi alumni Facultatis Medicae Zagabiensis**. The same interviews, translated into Croatian will be published on the electronic web site of the Medical Faculty **mef.hr**.

**Dr. Ivan Damjanov**, Emeritus Professor of Pathology, The University of Kansas School of Medicine, Kansas City, USA, who is also a Corresponding Member of the Croatian Academy of Sciences and Arts agreed to continue conducting these interviews. Like the initial interviews those in the present volume are produced under the same Latin title in cooperation with the editors of “mef.hr”, the official website of the School of Medicine, University of Zagreb. The preface to the initial series of interviews is reprinted here for historical reasons and to show that the main goals and intentions for this series remain the same despite the changes of the title of the series. In the issues 58-59 there is one exception because Ivan Damjanov-Interview was conducted by Marko Pećina.

*Marko Pećina*

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The preface in the Issue 544=52-53

The present series was conceived as a set of informally recorded conversations with the best-known and internationally recognized graduates of the School of Medicine, University of Zagreb. The English version of these interviews is now being published by HAZU to make them accessible to a wider readership, including all those who do not understand or read Croatian.

The primary goal of this series of dialogues in RAD HAZU is to present and recognize the outstanding alumni of the School of Medicine University of Zagreb, Zagreb, Croatia. We hope that our readers will enjoy reading about the memorable events in the lives of these physician-scientists, their achievements, and scientific contributions that made them famous worldwide.

The emphasis of these discourses will be on the human side of science and medicine. Our goal was to give the interviewees a chance to reminisce about their trials and tribulations as well the happiness and fun they experienced in their lives. In other words, the objective of the interviews is and will be to give our esteemed interlocutors an opportunity to tell their life story in their own words and show us “how they did it” while still keeping their personal and professional lives in balance.

Finally, it’s a good time to remind you, our readers, of the Latin saying “*verba volant scripta manent*”, which justifies publishing so many written words that otherwise would have been forgotten. By producing these pieces, our purpose was to preserve the informal records of the lives and work of featured physician-scientists; and by transforming their verbal testimonials into written documents, leave a permanent trace of their activities for future generations in the archives of HAZU.

*Marko Pećina  
Ivan Damjanov*

## Ana Barač Interview



Ana Barač, MD, PhD, FACC, FAHA  
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### 1. Where were you born and where did you grow up?

I was born and grew up Split. It was the time of “staro splitsko rođilište” and Split as an industrial port in 70-ies and 80-ies, so well depicted in the novels of the Split writers. Years later, living and having a family in the U.S., I found myself reading the “Knjiga o jugu”, by Jurica Pavičić, a legend of Dalmatian and Mediterranean literature, and reflecting how birthplace shaped who I became and what I long for. And Tisja Kljaković Braić’s 2015 novel “U malu je uša Đava” sent me right back to Splitska Riva in the eighties, with a fantastic laugh and a reminder how these memories influenced my perspective of career and life.

### 2. What were you favorite subjects in high school?

The high school years were the formative ones, in particular when it comes to discovering interest in science, and I remember them fondly. I went to splitski MIOC, the class of 1998-1992, at the time of one of the re-reforms of the high school education in what was then Yugoslavia. That meant that the curriculum emphasis was still on math, physics, and informatics, however, human sciences classes were reintroduced, and we had Latin, philosophy, sociology, and an option for an additional language. Our class took French, and I loved languages including Latin and Italian which I took outside of school. It is hard to pick the favorite subject! MIOC is known for math and physics which were a highlight and thought in an environment of extremely talented students. In retrospect, biology inspired my curiosity the most and ended up guiding my next decision.



*Figure 1. Professors and students of my high school 1992 class from MIOC in Split, 30 years after graduation.*

### 3. How did you decide to study medicine?

Leaving high school, I wanted to study molecular biology which meant going to Zagreb. No one in my family was in biology or medicine so I spoke to friends, older students, and professors about the experiences. The entry exam was in the fall of 1992, and included biology, chemistry, and physics, I believe. I applied for Medical School and Molecular biology which was with Faculty of Science (Prirodoslovno-matematički fakultet) and was limited to 30 students making it very competitive. The results of the exams were posted on the doors of the Faculty of Science – in Zvonimirova for Molecular Biology and in Šalata for Medicine- it is funny how vivid these memories before the online test results are! It was also before the cell phones so I was by myself in Zagreb, in front of the posted lists on the door, having to make a decision between the two programs. I remembered the conversations with senior colleagues about the career options, who told me that several successful Croatian scientists doing molecular biology abroad were alumni of the School of Medicine and that molecular tools were very relevant and for medicine. So I decided to go into medicine to pursue biomedical science.



*Figure 2. This photograph was taken during my Anatomy course in the Fall of 1992. We are standing in front of the Institute of Anatomy of the Medical Faculty, University of Zagreb. Dr. Ksenija Kos, our clinical assistant for anatomy is in the center, I am in the back row, second from the left, and among my colleagues are several close friends till today, including Dr. Sonja Badovinac and Dr. Lana Bijelić.*

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

The second year was my absolute favorite with neuroscience, physiology, and pharmacology, opening the new world of mechanisms, why and how the organs functioned. And if I need to choose one favorite subject it would be the pathophysiology class in the third year, linking the mechanisms to the disease processes. It was logical and scientific. More than the individual professors, I remember working with clinical assistants (“demonstratori”), in particular in pathophysiology, who made me want to become an assistant in pathophysiology as well. I was trying to get to my dream of learning molecular science and truly cherished getting the opportunity to work in a laboratory of pharmacology, led by Professor Zdravko Lacković and, at time senior staff members, Professor Vlado Trkulja and Professor Melita Šalković. That was my first true exposure to basic science publications, literature review, laboratory techniques and running experiments. And it was eye opening: so much to do and learn.



*Figure 3. As a student I received the Rector's award in 1995.*



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

My memories of clinics are more blurry, but internal medicine was my favorite subject. And among subspecialties, cardiovascular disease and hematology including blood malignancies were the most fascinating. Both disciplines were dynamic in the late nineties, with new tools such as cardiac imaging and echocardiography blooming, and new treatment approaches transforming the prognosis. I remember reading about it and wishing that our clinical training was more connected to these advances and patient care.

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

Maybe because my path was somewhat unconventional, I remember these years as a pursuit for maximum learning, of both basic and clinical science, without having a role-model in either of the worlds. I became interested in wanting to bridge them, translating interest in mechanisms into clinical world, which in the 90ies and early 2000s was difficult in Zagreb.



*Figure 4. In 1998 I received my MD degree. Professor Ana Marušić banded me the diploma.*

**7. Did you have time for any extracurricular activities and what did you do during your free time?**

I loved spending time with friends and going to Kinoteka/movies, Zagrebačko kazalište mladih (ZKM), and other theater and art performances. I remember gloomy weather and so many coffee gatherings.

**8. I was told that your GPA at graduation was a perfect 5/5. Is that why you received The University Rector's Award?**

This must be corrected, my GPA was 4.9, in the top percentiles but not perfect 5. I received the University Rector's Award in the third year for the GPA and for the scientific project that I did in the pharmacology laboratory. I was proud of the achievement and grateful to Professor Lackovic for the opportunity.

**9. What did you do after graduation?**

I stayed on with the Pharmacology (Katedra farmakologije) as a scientific assistant (znanstveni novak) and enrolled in Postgraduate studies in Biomedicine. My clinical interest was internal medicine and cardiovascular disease but the system of applying and entering the residency program (specijalizacije) at that time was plagued with problems. It was sad to see many of the most qualified students with the highest GPAs having to leave to pursue clinical training. And it felt a bit as a slap in the face when my application for internship positions, including volunteer ones, were rejected at Zagreb and Split hospitals. On the positive side, I could still work in the laboratory and be involved with the students and the Medical school.

**10. After two years at the Clinical Hospital in Zagreb you found your way to the research laboratory of Dr. Ivan Đikić in Sweden. How did that happen? Was that a valuable experience?**

In October of 1998, the fall after my graduation, I attended the First International Conference on Signal Transduction in Dubrovnik, organized by Dr Ivan Đikić. That was the conference that changed my life. Among the star-studded faculty was the Nobel Prize laureate Dr. Edmond Fischer and it felt that the entire world of cell signaling was there, ready to teach and show us the future. I knew that was what I wanted to do next. I approached Dr Đikić about the opportunity of getting experience in his laboratory and he encouraged me to apply for grants that could cover the trip and stay in Uppsala, Sweden. Options for funding were limited because the postwar Croatia was not yet part of many of the scientific conventions, however after a couple of failures in 1999 I got the scholarship from Swedish Institute, followed by the fellowship of the Federation of European Biochemical Societies (FEBS) in 2000. This allowed

me to spend a year, from summer of 1999 to summer of 2000 with Dr. Đikić's lab in the Ludwig Institute for Cancer Research in Uppsala, Sweden. It was the most incredible experience with full immersion into modern molecular signaling, focused on G-protein coupled receptors (GPCRs) and their interactions with other kinases. I absolutely loved working in the lab and learning from other post-docs, students, and investigators. It was one of the most memorable years of my life and it culminated with the presentation at 2<sup>nd</sup> International Conference of Signal Transduction, held in Dubrovnik in May of 2000. I still have the poster that I proudly presented at that meeting together with all the lab colleagues: it was an incredible feeling to be part of the scientific community. One of the people who came to my poster was Dr Silvio Gutkind, a scientist from the National Institutes of Health (NIH) and expert in GPCR signaling, who was invited faculty at the meeting.

**11. Thereafter you came to the US through the Fogarty International Fellowship Program. Why did you choose that pathway? How important was that fellowship for you future career?**

I wanted to continue the work in molecular signaling and after talking to Dr. Gutkind the conference in Dubrovnik, he invited me to interview for a position in his laboratory at the NIH. I was awarded a Fogarty International Fellowship which funds international fellows for work at the NIH campus in Bethesda, Maryland. Because medical degree in the US is at the level of graduate school, this was a post-doctoral position and advanced molecular biology experience from Sweden was critical. This was a large laboratory including many fellows from around the world, Italy, Spain, Argentina, Mexico, Thailand, Japan, France, and India: we were all together, all studying different aspects of GPCR signaling. I shared the apartment with one of my colleagues from Zagreb Medical School, Dr Ivana Munitić, whose passion was immunology and who today leads an immunology laboratory and teaches biomedicine at University of Rijeka. The NIH is a unique place with many Institutes dedicated to the investigations spanning essentially entire biomedicine, live on the same campus. Our laboratory was focused on basic science, but I also interacted and collaborate with the colleagues working in clinical areas. And it was these collaborations that proved the most important for my next step in career. Entering my 3<sup>rd</sup> year of the fellowship at the NIH I wanted to move towards clinical models as the next step. This was the time when molecular signaling was coming full force into the clinical care, in particular in oncology, and the same molecules that we were studying in the lab, were becoming druggable targets. I decided to pursue residency in the US, and matched in the Internal Medicine Program of Georgetown University and Washington Hospital Center located in Washington DC, about 10 miles away from the NIH campus.



*Figure 5. In 2006 I received the Saul Zukerman, M.D., Humanitarianism in Medicine Award from the Department of Medicine at Washington Hospital Center, in Washington, D.C. It was an honor to be handed this award by the Chair of Medicine, Dr. Leonard Wartofsky (standing on the right of the photograph), who remains my mentor and a role-model.*



*Figure 6. My dear mentor, Professor Ivan Đikić. We have continued to collaborate even after I moved to clinical world, and I consider him a forever mentor. Professor Đikić received in 2006. an award from the American Association for Cancer Research (ACCR) for outstanding research achievements. This photograph is from the Annual ACCR dinner of held in Washington, DC, where he was honored with the Award. I am sitting between Dr. Đikić (to the left of me) and my husband Dr. Federico Asch. Tanja Rudež, award winning Croatian science writer is standing behind me.*

12. During all that time you were also a postgraduate student working on your PhD degree at the University of Split. How did you manage all that? Did you fly to Split to defend your thesis? Who was your thesis advisor?

The path to PhD started in Sweden, in the laboratory of Professor Đikić where I started the work on the G-protein coupled receptor signaling, and it continued in the laboratory of Dr. Gutkind at the National Institutes of Health, with Dr. Đikić staying on as my PhD thesis advisor. After 4 years in the laboratory, in 2003 I started clinical training which put the thesis writing on hold, but it allowed me to initiate new projects on endothelial dysfunction. It was fortunate that my residency was at Washington Hospital Center in Washington DC, so I could work with my clinical research mentors and colleagues Dr. Julio Panza and Dr. Umberto Campia. Most importantly, I am truly grateful to the University of Split that allowed me to become the part of its biomedical postgraduate program and defend the PhD thesis there in the fall of 2008. It was an honor and privilege to have Professor Đikić as advisor and the thesis board (Povjerenstvo) chaired by the Akademik Stjepan Gamulin, and with professor Željko Dujčić and professor Mladen Boban participating.

13. With a solid background in science you finished thereafter your clinical training at MedStar Washington Hospital Center and MedStar Georgetown University Hospital, Washington DC. Was that a critical period of your life that made you decide to become a clinician scientist?

You are right, it was during the clinical training when the “aha, that is what my calling is” moment occurred. I was in the cardiac imaging laboratory, looking at the echocardiographic images of the heart and asking why it became dilated, changed, weakened, and what the trigger was. The answer must be at the molecular level, and I felt that we as a medical community were empowered by all the advances in the basic science world. At the same time there were many new layers and questions that opened: how do we study this in the reality of the clinical world? Who are the patients who will develop heart failure and how can be predict and prevent it?



**14. Did you ever consider giving up clinical work with patients and devoting yourself to exclusively to basic science research? Or “was it in your stars” to become a hybrid basic research scientist-physician?**

Yes, and I have considered it many times. When I started medical school and when I went to Sweden, I thought that basic science research held all the answers and was my life path. And even starting residency I had thought I would go back to the bench full time. What I did not know is how important patient care would become to me: the ability to be there and help one person at a time, the relationships with the patient and their families. It was not only a privilege and deeply human experience, to take care of patients, it also became the driver of my research questions. At the same time, this meant that I could not dedicate enough time to pursue having a basic science laboratory, I had to give that up. But I feel fortunate that I can collaborate with basic science researchers and work on bridging the gap between basic science and clinical needs.

**15. You are one of pioneers and leaders of a new subspecialty of cardiology, called cardio-oncology. What is that? Could you also describe for us how did you become a cardio-oncologist. For those who want to learn more about your specialty, maybe you could give us a link to one of your on line presentations about cardio-oncology.**

Cardio-oncology story is a very personal one. As a cardiology fellow, I became interested in anthracycline-related cardiomyopathy and around that time a basic science paper was published about the deleterious effects of BRCA1/2 mutation on the hearts of mice exposed to doxorubicin. Women carrying the BRCA1/2 mutations very often develop breast cancer and are treated with anthracycline-based chemotherapy, however, it was not known whether they may be at higher risk for anthracycline-related cardiomyopathy due to their mutation. We designed a case-control study to enroll women BRCA1/2 carriers who received doxorubicin as part of the treatment for breast cancer and compare them with similarly treated women with history of breast cancer who were not BRCA1/2 carriers. We invited the study participants for a clinical visit and echocardiogram and the main endpoints were echocardiographic parameters of cardiac function including global longitudinal strain. For this study, I received funding from the Georgetown’s Lombardi Comprehensive Cancer Center, however, it was difficult to enroll patients as I was not part of the oncology clinical care. That is where the idea of cardio-oncology clinic came from: it became clear that the cardiovascular needs of oncology patients were broad and that we needed clinical setting to address the needs as well as to be better able to conduct research. Our study was negative, there were no significant differences in the echocardiograms of women with and without BRCA1/2 mutations (<https://pubmed.ncbi.nlm.nih.gov/26749359/>), but I felt that it was learning through this project that was critical in training as a specialist in cardio-oncology.

Cardio-oncology spans across the intersections between the cardiovascular disease and cancer; including shared risk factors, growing prevalence of both diseases in aging population, and cardiovascular side effects of cancer therapies. In clinical practice, we define it as cardiovascular care of patients with cancer and survivors and if I need to choose one paper, it would be the Journal of American College publication from 2015 (<https://www.jacc.org/doi/10.1016/j.jacc.2015.04.059>). There are many fun stories, including the one about the very name of the specialty which was/is also called onco-cardiology, that lie behind this manuscript. It was conceived around 2012 with group of cardiologists in the American College of Cardiology when we formed a working group and performed an environmental survey of cardio-oncology practices in the US. We sent a questionnaire to cardiology division chairs asking about their institutional practices, whether they had specialists, and what they perceived as the gaps in care. The results were interesting: majority identified lack of guidelines in this field as an important barrier, together with the lack of resources and funding for specialized training. Fast forward to 2023, we now have many major society documents, as well as guidelines, addressing different aspects of cardiovascular care in this patient population. We have international conferences as well as two dedicated journals (JACC Cardio-Oncology and Cardio-Oncology Journal) that provide resources and also play an important role in the growth of the field.

Regarding the online presentations, I would love to share one at the ACC.2019 Scientific Sessions (<https://www.youtube.com/watch?v=p11sMuqA4t4>) where I was interviewed by Dr. Giselle Suero-Abreu, at that time a medicine resident (and a “FIT (fellows in training) Roving reporter”) that illustrates the importance of the role of mentorship and professional community building and about the opportunities in training in cardio-oncology.

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**16. Your current title is D’Aniello Chair and Director of Cardio-Oncology, at Inova Schar Cancer and Inova Schar Heart and Vascular Institute. Why did you accept that position? Could you describe for us what your duties are at this Institute?**

Inova is a large health care system located in Northern Virginia and geographically forms part of what is called DMV (District of Columbia-Maryland-Virginia) metropolitan area. The invitation to join Inova came with a task to create a true link between two large service lines, Inova Schar Cancer Institute (ISCI) and Inova Schar Heart and Vascular (ISHV). The position of the D’Aniello Chair was created with the philanthropic support of the D’Aniello family which enabled us to create a unique environment that bridges clinical care and research beyond traditional

structures of separate cardiology and oncology departments. For example, I report to the Presidents of the ISHV and to the President of the ISCI, and work closely with cardiologists and oncologists, on both clinical and research projects. That is one of the reasons I accepted this position: I was challenged with developing new models of care needed for the maturing field.

**17. Do you still work in a research laboratory and do you see patients?**

I see patients for cardiovascular needs throughout the cancer treatment continuum. This means addressing cardiovascular risk factors, identifying need for cardiopreventive strategies prior to cancer treatment, monitoring, and management during treatment as well as visits during cancer survivorship. I also read imaging studies in the echocardiographic laboratory and the

cardiac magnetic resonance laboratory. And I participate in clinical research which involves collaboration with the laboratories, in particular for biomarker studies.

**18. You have an impressive bibliography. Could you give us some numbers, please.**

**How many original scientific papers published in refereed journal did you write? How often were they cited? What is your h-index?**

This is very kind of you to say but I want to point out that numbers of papers and citations get skewed depending on the field. The National Library of Medicine resources have become my go to place to update bibliography (<https://www.ncbi.nlm.nih.gov/myncbi/ana.barac.2/bibliography/public/>) Of 162 publications in peer reviewed scientific journals, about 105 are original



*Figure 7. Presentation on Global Cardio-Oncology Society Annual meeting in Madrid, October 2023. (Barac at the podium with colleagues from cardiac imaging, including (from right to left) Dr. Charlotte Manisty from Barts College in London, Dr. Dinesh Thavendiranathan from University of Toronto, Dr. Marielle Scherrer-Crosbie from University of Pennsylvania, and Dr. Lauren Baldassare from Yale University, discussing cardiac magnetic resonance (CMR) in cardio-oncology.*



research and more than 50 are clinical documents, state of the art reviews, and editorials. For the citations, Research Gate website gives a number of 9843 citations with h-score of 44.

**19. What is your most often cited paper? Is it also the paper that you like the most and consider to be your most important contribution to science?**

I was part of the Expert consensus document on Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy developed in collaboration between the American Society of Echocardiography and the European Association of Cardiovascular Imaging which was published in 2014 and at more than 1400 citations it is probably the most cited manuscript that that I co-authored. I say probably because papers on clinical guidance often receive high number of citations, however their relevance may significantly decrease when there is rapid growth of the field. Indeed, in 2023 this paper is rather outdated and in need of a major update. A more recent consensus paper that I think is important to the field is the International Society of Cardio-Oncology statement on the definitions of cardiovascular toxicities of cancer therapies (<https://pubmed.ncbi.nlm.nih.gov/34904661/>) which was published in late 2021 and within less than 2 years has more than 180 citations.

**20. In addition to a list of original papers you list 58 scientific reviews and editorials in refereed journals. Most if not all of these you wrote by invitation, or am I wrong? As the saying goes “if an editor is looking for somebody to write a review or an editorial for his/her journal he/she should invite the busiest person he/she knows.” You obviously like to write! Isn't that true? How did you find time to write all these papers?**

I am not a fast writer although I keep hoping to become one! I remain inspired by the innovation and good science, and I believe that the editorials and scientific reviews are a way to give back to the community. In clinical world, they often convey a message on “where does this research fit in clinical practice” and I think it is important to pause and think about that. So, I prioritize that time.

**21. You gave more than 140 invited lectures. What accounts for so many invitations? Which one of these was the most memorable one?**

I believe that the reason for the invitations is the rapid growth of cardio-oncology which was driven in part by the explosion of novel cancer treatments, many of which have cardiovascular effects. I cherish the opportunity to present as it gives me a chance to learn from the audiences and learn about different perspectives and ways of asking questions or organizing clinical practice.

Most importantly, it allows me to meet new colleagues, clinicians, scientists, investigators, and trainees, which is very special. It is very hard to single out the most memorable presentation, I would love to mention the recent invited presentation to Karolinska University Hospital in Stockholm, Sweden, where I was invited to present on cardiovascular effects of the immune checkpoint inhibitors, which is one form of cancer immunotherapy. I was invited by my dear colleague Professor Marcus Carlsson who leads the Karolinska Institute’s cardiac imaging clinical and research laboratory. It was inspiring to meet with cardiology and oncology colleagues as well as discuss research projects with imaging fellows and trainees on how to move the field forward. It was also very special to visit Sweden, after more than 20 years of leaving Uppsala.



*Figure 8. American College of Cardiology Live Course on Advancing Cardiovascular Care of the Oncology Patient Heart House, Washington DC, April 2023. Course Co-Directors Dr. Ana Barać (first from the left) and Dr. Bonnie Ky (fourth from the left), vice-chair Dr Richard Cheng (3rd from the left) and program committee members.*

**22. How much interest is there for cardio-oncology in the medical community and the lay public world-wide? Equally among the cardiologists and the oncologists?**

I believe that there has been an increased awareness of cardiovascular effects of cancer treatments as well as of the importance of cardiovascular disease as a cause of morbidity and mortality in cancer survivors. There are many positive aspects that we need to recognize: first, that we are witnessing much improved cancer survivorship with many people living longer with and/or surviving cancer. Many cancer-targeted and immunotherapies have dramatically improved prognosis and we have discovered that they are also playing a role in cardiovascular homeostasis. An example are vascular endothelial growth factor (VEGF) inhibitors which very often can cause hypertension as an on-target effect, but can rarely cause heart failure and ischemic effects. There has been a growing interest in cardiology community to better understand these phenomena as well as to develop approaches to treat these patients.

**23. You also serve on the editorial boards of several medical journals. Maybe you could list some of them.**

I have served on the Editorial board of the Journal of the American College of Cardiology (JACC) since 2008, and I also served as an Associate Editor for the inaugural years of the JACC sister-journal, JACC Cardio-Oncology. It was a privilege to be part of a creation of a new journal and work with the great colleague and friend, Dr. Bonnie Ky from University of Pennsylvania, as the Editor in Chief. Journal represents constant work and constant learning.

**24. You also serve and as an *ad hoc* reviewer for many leading scientific journals. You list 37 journals for which you have reviewed one or more papers. Is it that you just cannot say “no” when they invite you or do you think that this is expected of you and only a part of your professional duty; a voluntary contribution to the international biomedical community?**

Yes, there is a sense of commitment and the need to give back to the community through constructive review. Receiving a well meant and well written critique can be powerful, and when we do good job as reviewers and editors and investigators, we make the field stronger. That said, I do say “no” today quite often as time restraints have grown together with more requests coming in.

**25. After the Rector’s Award which you received as a medical student in Zagreb, did you receive any other honors and awards?**

Several awards were very special in my career. The Swedish Institute Award and the Federation of the European Biochemical Society Award in 1999 provided me with the funds to spend

time in Dr. Đikić’s laboratory. During my clinical residency I received the Saul Zukerman, M.D. Humanitarianism in Medicine Award, which is given each year to Washington Hospital Center resident who exhibited compassionate and human care. This was the most special award as it was voted by the peers and faculty, and handed to me by our then Chairman of Medicine, Professor Leonard Wartofsky, whom I consider a lifelong mentor and role model.

**26. You are on the teaching staff of several Universities. Do you teach medical students or give practice related CME lectures to practicing physicians?**

I am on teaching staff at Georgetown University where I mentor students in research.

**27. How much do you travel for business or pleasure?**

I travel for work approximately once a month, for conferences and meetings. This sometimes includes international travel which is fun and it allows me to meet and stay in touch with inspirational colleagues and friends. Most of my personal travel is to see family, in Croatia and in Argentina. My husband’s family lives in Buenos Aires and the decision to stay in Washington DC also had to do with the fact that it has an international airport with good connections to Split and Buenos Aires.

**28. Do you have any hobbies, or to say it otherwise, do you have enough time for hobbies and your family?**

There is no such thing as enough time: it is a constant balancing act! My husband and I have a 15 year-old daughter Lara who travels each and every summer to Croatia to see her cousins and stay with her “nona” (my mom), and in winter goes to see cousins in Buenos Aires and be with “abuela” (my husband’s mom). This means that the time to travel and stay in touch with the family always stays on top of the priorities, and here in Washington DC it is about seeing and being with friends. We have both lived here for more than 20 years now and have been fortunate to be surrounded by great friends.

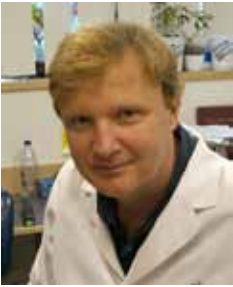
**29. Any messages for the medical students and your junior colleagues in Croatia?**

Follow your passion and never give up.





## Dimitri Krainc Interview



Dimitri Krainc, MD, PhD,  
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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 them, and attending interesting lectures and meetings (Figure 2).



*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. Could 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. Plataniotis, 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  $\alpha$ -synuclein oligomers that were shown to be toxic to neurons. We also made a surprising observation that accumulation of  $\alpha$ -synuclein can lead to inhibition of normal GCase. Specifically,  $\alpha$ -synuclein interferes with ER to Golgi trafficking of GCase which in turn leads to decreased GCase activity, lysosomal dysfunction and more accumulation of  $\alpha$ -synuclein. The bidirectional effects of  $\alpha$ -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  $\alpha$ -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  $\alpha$ -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 Allergan 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  $\alpha$ -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 returned 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.