Zoran Gatalica Interview

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1. Where did you grow up?

I was born in Bjelovar, a small town 80 kilometres east of Zagreb. Families from both my mother's and father's side lived in that region for centuries.

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

Those were happy times, and I still have very fond memories of my childhood. Carefree life in a small town had its own benefits and furthermore our town had a fantastic handball team. Our team, RK Partizan, Bjelovar had at that time won the handball championship of Yugoslavia several times, played several times in the finals of the European team championship and was even the European champion in 1972. That meant that RK Partizan was the champion of the entire world, since handball was played mainly in Europe. We youngsters were all very proud of our team and our town, and by inference we all felt quite important. The downside was that all the beautiful girls in our town were enamoured of handball players and other sportsmen; since I did not belong to that crowd, I was out of luck.

3. How did you decide to study medicine?

I made my final decision to try to enter Medical School in Zagreb during my senior year in high school, but I wasn't quite sure if that was something for me or not. I considered psychology and maybe even some other science career or engineering. At the end of the Medical School entrance exam, I wasn't even sure if I made it. I studied for the exam that summer of 1979, but there were "distractions", as any 18-year-old should have had. Eventually, and to my surprise, I was accepted. I got the news about this acceptance from my cousin while playing tennis, and still remember how I lost focus and thus the entire match against my best friend. I still regret it, even though, and for the record he was and still is a good tennis player.

4. How enjoyable were your first three preclinical years? What do you remember from those days?

I studied hard. I did well in some subjects and not so well in others, but overall, it was enjoyable. I met a beautiful girl who later became my beautiful wife. During the third year, I became a student preceptor ("demonstrator") in physiology and enjoyed quite a bit the opportunity to show off in front of my younger colleagues, while helping them learn the elements of physiology. Later on, I became a student preceptor in pathology, but it never occurred to me that I would ultimately choose pathology for my career.

5. Were the clinical years more enjoyable or more traumatic than the first three years?

I felt that I was well prepared for the clinical part of my medical school education and was eager to test what I learned in pre-clinical years. Accordingly, I enjoyed interacting with patients and instructors. It was gratifying to recognize symptoms of certain diseases in real life, and thus use the knowledge I acquired from books. For me, those years were never traumatic, and at some point I started enjoying the "easiness" of clinical years, maybe even a bit too much for my own good.

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

My favorite clinical teacher must have been Dr. Danilo Tepavčević. He had a truly encyclopaedic knowledge, but he was also quite a character. He taught us everything with incredible enthusiasm and

Figure 1. Picture with my wife, Biljana, taken on the day of her graduation from the Medical School, in front of the old entrance to the Dean's office (Stari Dekanat)

love, even when we were not able to respond to his questions as quickly as he expected it from us. He suffered from Buerger's disease and by the time I met him he was already a double amputee. That handicap, however, did not prevent him from enjoying life (he was a great opera fan) and giving his students the best education possible (and occasional flick on the wrist).

7. Were you involved in any extracurricular activities during your student years?

As mentioned before, I have worked in two departments as a preceptor to make some money. At today's exchange rate it was not much, maybe, a couple of euros per session, but for a penniless student even that was a welcome relief.
I was active also in the Foreign Medical Student Exchange program. Our organization hosted every summer several medical students from all over the world, and we spent time with them and showed them around Zagreb and Croatia. During the summer after my fourth year it was my turn to go abroad and I spent a month in the department of internal medicine of the Royal Hallamshire Hospital in Sheffield. There, for the first time I was exposed to a clinical trial. It was exciting even though I do not remember much about the details of that study. I believe it was about prostaglandins and platelets in peripheral vascular disease. I also started a couple of research projects in the Department of Physiology under the mentorship of Drs. Nikša Pokrajac and Hrvoje Banfić. One of these projects, dealing with compensatory kidney growth led to my graduation thesis ("diplomski rad"). At some point I became very skillful in operating (nephrectomizing) mice; the skill had not left me and many years later I tried to revisit the idea during my time at UTMB, applying expression array analysis to detect growth mechanisms in uni-nephrectomized mice. Did not produce any meaningful result, mostly because the methodology (mice gene expression arrays) was still in its infancy.

8. What did you do after graduation?

After the internship, I became an instructor ("asistent") in Physiology. My daily tasks included teaching medical students and working in the laboratory on my doctoral thesis. Under the mentorship of Hrvoje Banfic, we worked on the effects of epidermal growth factor on the metabolism of the phospholipids, focusing on transmembrane signaling. It was a "hot topic" and I almost, literally once burned down the lab (I forgot to switch off some open flame, it caught fire) but luckily Hrvoje caught it in time and extinguished it.

9. Why did you join Dr. Banfić in the Department of Physiology ?

As a medical student I have spent many hours working in Dr. Banfic's lab and thus it was obvious to me that he would be an ideal mentor for my doctoral thesis. At that time he had recently com-

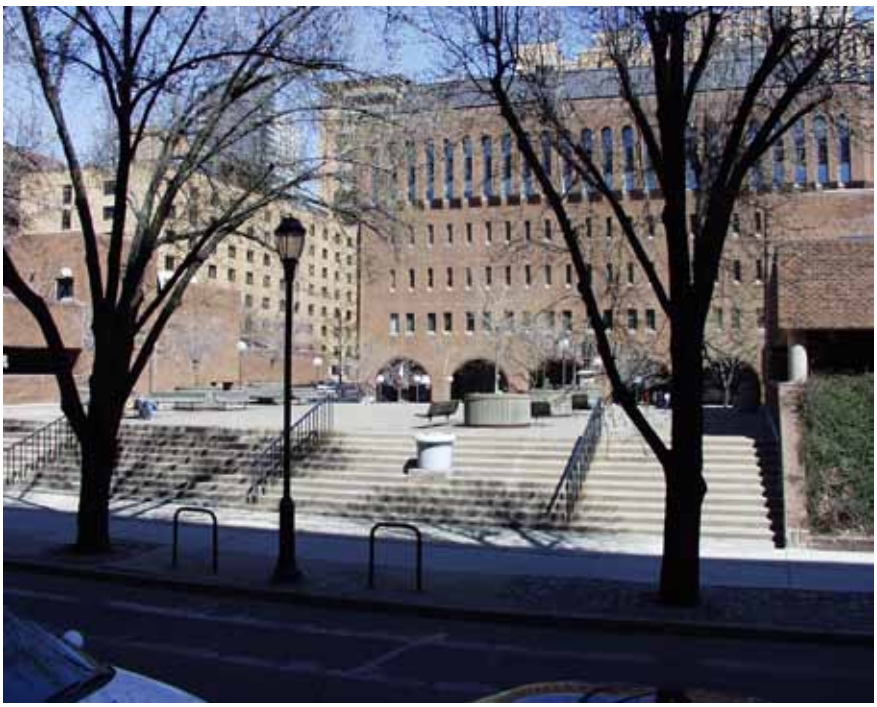
pleted his scientific doctorate and was willing to accept me and serve as my mentor. Furthermore, he had additional training at Cambridge, UK studying second messengers under Dr. Robin Irvine, one of the most influential researchers in that field at the time.

10. What did you learn from those few years spent in the Department of Physiology?

It felt like I spent much more time than the 3 years interrupted by a year of military service. Those were very important years in my postgraduate education. Among other things, I learned to design experiments and adopt assays, and to be always critical in evaluating the results before submitting them for publication. I also learned to write and evaluate scientific papers. In January of 1989, I defended my doctoral thesis entitled "The effect of epidermal growth factor on the metabolism of phospholipids in the rat renal cortical slices". Major results were published in 1988 (Gatalica Z and Banfic H. Epidermal growth factor stimulates the incorporation of phosphate into phosphatidic acid and phosphoinositides but does not affect phosphoinositide breakdown by phospholipase C in renal cortical slices. Biochimica and Biophysica Acta 1988 Mar 11;968(3):379-84).

11. Why did you move to the United States?

During my doctoral studies about the role of epidermal growth factor receptor, I interacted with Dr. Boris Mildner, who has a few years earlier studied EGFR in Philadelphia at the Wistar Institute with Dr. Barbara Knowles. Reading a paper that Boris wrote while working in the USA I saw that one of his co-authors was a certain professor at Thomas Jefferson University (TJU) in Philadelphia, by name of Ivan Damjanov, you probably know him (ha-ha!). I wrote to him and he accepted me to his lab in Philadelphia. The rest is history, that we are now recording.
My first travel across the Atlantic to Philadelphia was exciting and memorable. It coincided with the period during which the airplane company PanAm was going out of business. Thus, I missed several flights and finally arrived in Philadelphia, well behind the schedule and after midnight. Your wife Andrea and Hrvoje Vrčić, who already worked in your laboratory, picked me up in the middle of the night and took me to an apartment in Philadelphia on 13th and and Locust St. I was to share it with Hrvoje for some time. It was a cheap one but provided a lot of free entertainment. Suffice to say that the part of Philadelphia where we lived was at that time known as the "entertainment district". Several of our male and female neighbors living in the same apartment house were sex-workers.



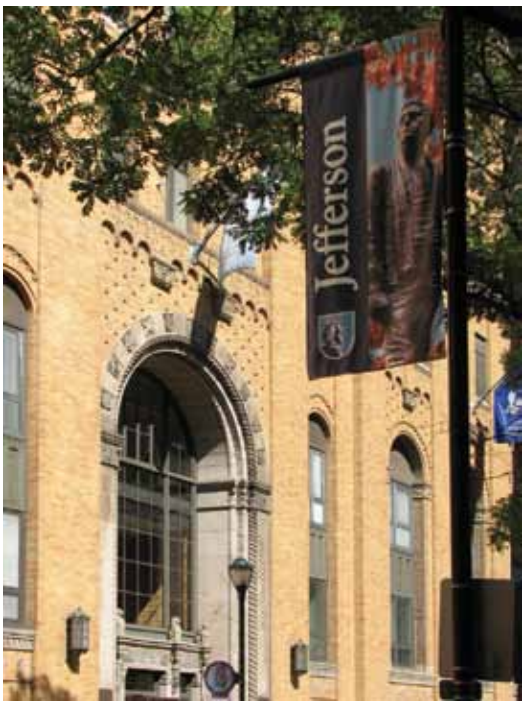


Figure 2ab. Thomas Jefferson University, Philadelphia. I started as a postdoc in 1990 and later completed my residency training in pathology in 1996.

12. How did you decide to become a pathologist?

I worked as a student preceptor in anatomic pathology in Zagreb, but did not find it too interesting. It was mostly autopsy material (too late to impact patient's life). Later on, I attended some intraoperative pathology consultations as a 5th year student at Rebro University Hospital.It was interesting, but again my heart was then in physiology and biochemistry. I thought that microscopy was a bit too subjective. After learning that in America I can specialize in both anatomic and clinical pathology, and thus practice some clinical biochemistry, cytogenetics and even molecular genetics, it clicked with me.

13. After you finished your residency training in anatomic and clinical pathologist and passed your Board examination, you worked in Galveston, Texas and thereafter in Omaha, Nebraska. How valuable were those years in academic medicine?

During the residence training I had a privilege to learn from the best pathologists including Drs. Markku Miettinen, Bong Hyun, Peter McCue and Robert Peterson, to name a few. They taught me not just diagnostic skills, but more importantly, to conduct appropriate studies and utilize various methods of investigations on tissue samples. Thus, after turning down an offer from our Chairman Dr. Emanuel Rubin to stay at TJU, and following the suggestion of Dr. Raphael Rubin, I took a job at the University of Texas Medical Branch (UTMB) in Galveston, TX, which at the time was one of the top research institutions. The head of that Department of Pathology was Dr. David Walker, one of the best-known researchers in infectious diseases. I worked in the Division of Surgical Pathology led by Dr. A. Brian West, the best mentor a junior attending could have. I also took part in research activities in experimental infectious pathology with the group led by Roberto Garofalo, who turned out to be a son of exiled Italians from Istria ("esuli Italiani"), and so we became immediate friends. At first, being in academia felt like the right decision, and I did what was expected from me writing grants, teaching students and residents, writing papers and giving lectures. In the late nineties and early two thousand, new technologies started to emerge, and I was immediately drawn to their potential for the advancement of pathology. The human genome was soon "completed" and out of this effort came eventually massively parallel sequencing better known as Next Generation Sequencing (NGS) (I am skipping a lot). With that, a number of biotechnology companies mushroomed, and thus I was drawn by the siren call of private biotechnology business.

Figure 3. Members of the Division of Surgical Pathology UTMB, Galveston 1996-97. Picture is taken in front of Keiller Building which serves as home to the Department of Pathology, UTMB's internationally known World Health Organization Collaborating Center for Tropical Diseases, and the Center for Biodefense. I am second on the left, flanked by two outstanding surgical pathology fellows, Thaira Oweity and Gbo Yuoh. In the Center of the picture is Dr. A. Brian West (gentleman with the beard) who recruited me to UTMB.

14. Is it during that time that you became interested in molecular biology?

As a first year pathology resident I encountered an interesting case of a young man dying of aortic dissection (Gatalica Z, Gibas Z, Martinez-Hernandez A. Dissecting aortic aneurysm as a complication of generalized fibromuscular dysplasia. Hum Pathol. 1992 May;23(5):586-8.). At that time a team at Dr. Darwin Prockop's lab at TJU was working on hereditary diseases of collagen, and I thought that they may be interested in helping me elucidate "funny" looking collagenous proliferations in the aorta. The researchers in that group (a team led by Drs Helena Kuivaniemi and Gerard Tromp) sequenced the entire collagen type III gene and within a month or so, we had a cause for the fibromuscular dysplasia, a hitherto disease of an unknown etiology; it was a mutation that caused the disease, and it was likely hereditary. We published the findings in Journal of Clinical Investigations (https://doi.org/10.1172/JCI116490), but the funny thing is that this paper is so difficult to find (early internet era publication) that it never got attention it deserved (and you cannot find it by doing PubMed search using my name, because not all the authors are linked and I was 18th of 24 authors). Naturally, I was immediately drawn to the genome as the primary cause of many human diseases. At UTMB I had an opportunity to continue the work on the genome, this time using microarrays (human and mouse), but my interest really picked up when I joined Creighton University in Omaha, and teamed up with Henry T. Lynch, a well know clinical geneticist, who described a syndrome that still carries his name. A couple of years later, I started to collaborate with Transgenomic, Inc., a biotechnology company in Nebraska becoming their first medical director. We worked on sequencing of tumors and produced a few good papers (and of course some duds, ha-ha) but it cemented my view on the future of pathology as fundamentally a molecular discipline.

15. You reached out from your regular University based job and started working with molecular biologists in private companies. Why?

As mentioned already, my first interaction with a biotechnology company was with Transgenomic, INC., which at the time was already publicly traded. Then I hired a young assistant Dr. Jill Hagenkord to run a molecular diagnostics lab at Creighton University which quickly became a new biotechnology venture (iKaryos; Jill was the CMO and I was a Scientific Board member along with Drs Federico Monzon, Julie Bridge and Jeffrey Kant). A can-do culture of a biotechnology business was what attracted me to switch from academia to private companies. No more writing grants for a limited budget to do what you love. Instead, I found practically limitless opportunities in the private biotechnology sector. That led me to join Caris Life Sciences (CLS). In that company I worked 9 years and during that time I co-authored over 60 publications describing various aspects of cancer genomics.

16. How useful was your work in molecular biology for your future career?

Extremely important and very useful. However, I must emphasize, my involvement was always based on collaboration and teamwork. Despite interest for molecular biology, which is the most important prerequisite, it is hard to sufficiently know (and by that I mean in minute detail) all intricacies of the technology. My contribution was mostly an ability to apply, develop and validate laboratory assays for clinical usage (laboratory developed tests, LDT). Once you have this completed, the rest is "easy", just wait for the customers to order and pay for your assays. Which brings the importance of sales and marketing to the business ventures: You can have the best tests for the most important diseases, but you'll go nowhere without investments, good sales and marketing skills.

17. How difficult was it for you to give up on your academic career and join a big company like Caris?

As mentioned above, the biggest positive change was cultural. Working in the private sector is driven by financial success, and all is tied to this. In academia we frequently forget where our salaries come from; in private sector it is very clear, and if you forget from time to time, there is somebody who will remind you of "the realities of life".

18. What is Caris?

- Caris Life Sciences is one of the largest referral laboratories for precision oncology testing. Caris acquired Molecular Profiling Institute (MPI) from Phoenix's International Genomics Consortium and the Translational Genomics Research Institute (TGen), for approximately $40 million in 2007. MPI has developed several proprietary diagnostic tests to guide disease treatment based on individual patients' genomic or proteomic profiles and, in the case of cancer patients, the molecular characteristics of their tumors. Their pioneering work was published (J Clin Oncol. 2010 Nov 20;28(33):4877-83.) just before I joined Caris, and was one of my main reasons to accept their offer. The first author of that study was Daniel von Hoff, MD, one of the most influential oncologists in the US. Dan and I continue to collaborate to this day.

19. At Caris you became Executive Medical Director of Pathology. What was your "job description", or in other words what did Caris expect from you?

I took over as medical director of a division (Molecular Profiling Institute) of Caris Life Sciences, at the time of significant changes in their business model. Within 8 months of my

employment, the company was completely reorganized and all the non-molecular business (diagnostic AP services like dermatopathology, hematopathology, GI and other services) were sold to Miraca Holdings Inc. (the total purchase price was $725 million). The sole focus of the Company was shifted to precision oncology at the sole remaining lab in Phoenix where I became the first Executive Medical Director.

20. You worked at Caris for 9 years. What did you accomplish and what are you most proud off?

Team work. An incredibly smart and dedicated people worked there. Working with such a team it was very easy to be a director.

21. Caris allowed you to do quite a bit of research, and you published many papers about your work. Which of those are your most important papers i.e., contributions to science?

My most cited paper is still an academic one (Saitoh Y, Pasricha PJ, West AB, Popnikolov NK, Gatalica Z, Watari J, Obara T, Kohgo Y, and Waxman I: Prevalence and distinctive biological features of flat colorectal adenomas in a North American population. Gastroenterology 2001; 120:1657-1665). It was a true collaborative effort between gastroenterologists (from the US and Japan) and three UTMB pathologists (Nikolay Popnikolov, then a resident in pathology, today a Professor at Indiana University, A. Brian West, a first-class GI pathologist, and myself). Therein we described the importance of proper endoscopy technique and biology of flat colorectal adenomas.

I am most proud of my little study on apocrine carcinomas of the breast which I wrote as a junior surgical pathologist (Gatalica Z: Immunohistochemical analysis of apocrine breast lesions. Consistent over-expression of androgen receptor accompanied by the loss of estrogen and progesterone receptors in apocrine metaplasia and apocrine carcinoma in situ. Pathology Research and Practice 1997; 193:753-758.). It is rarely cited (about 120 times since publication), but it was my entry into the field of breast pathology. Several years later I took Semir Vranic, MD as a graduate (PhD) student in my lab at Creighton University who got interested in the topic and we wrote a few more papers together. Later, we were recognized as the lead experts for that rare type of cancer and were invited to contribute a chapter to the World Health Organization "blue book" on breast tumors, a compendium of tumor pathology that is read all over the world.

Of the Caris papers, I particularly like our work on PD-L1 and PD-1 in cancers, specifically in tumors exhibiting high microsatellite instability (MSI-H carcinomas) (Zoran Gatalica, Carrie Snyder, Todd Maney, Anatole Ghazalpour, Daniel A. Holterman, Nianqing Xiao, Peggy Overberg, Inga Rose, Gargi D. Basu, Semir Vranic, Henry T. Lynch, Daniel D. Von Hoff, and Omid Hamid. Programmed Cell Death 1 (PD-1) and Its Ligand (PD-L1) in Common Cancers and Their Correlation with Molecular Cancer Type. Cancer Epidemiol Biomarkers Prev 2014; 23(12):2965-70.) and the application of NGS technology to the measurements of microsatellite instability (Van der Walde Ari, Spetzler David, Xiao Nick, Gatalica Zoran, Marshall John. Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients. Cancer Med. 2018 Mar;7(3):746-756); These two papers help broaden the clinical utility of immune check point inhibitors (e.g., Pembrolizumab). It seems like my most talked-about publication was on the topic of cancers of unknown primary site (Gatalica Z, Millis SZ, Vranic S, Bender R, Basu GD, Voss A, Von Hoff DD. Comprehensive tumor profiling identifies numerous biomarkers of drug response in cancers of unknown primary site: analysis of 1806 cases. Oncotarget. 2014 Dec 15;5(23):12440-7). I also have high hopes that our paper on Neurotrophic Receptor Tyrosine Kinases (NTRKs) (Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with NTRK gene fusions. Mod Pathol. 2019 Jan;32(1):147-153) will soon become my best cited work because tumors carrying these gene fusions respond to targeted therapy really well.

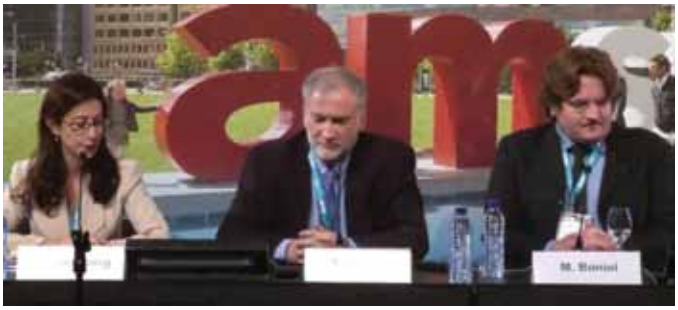


Figure 4. European Cancer Congress 2013 (ECCO-ESMO-ESTRO). Here in this picture at the news conference, I am discussing a study on the importance of molecular profiling in evaluation of cancers of unknown primary (CUP).

22. You already told us about your most cited papers. Give us some statistics please. How many citations did your papers receive so far? What is your h-index?

According to Research Gate this May, my work was cited over 12,800 times, my h-index is 60 and according to the Elsevier I am in the top 2% of world scientist based on their metrics. This last honor is certainly due to my collaborations, as almost all of the main collaborators are listed independently in the same category of scientists.

23. Your work was recognized by your peers. Thus you were invited to give many lectures and address many meetings, and travelled around the world. Which one of those events do you remember most fondly?

It must be the bi-annual meeting of the Kidney Friends, that was organized by our dear friends Ondrej Hes and Michal Michal of Pilsen, Czech Republic. Ondra prematurely died last year.

He and Michal Michal were the kindest organizers and treated everyone as their most valuable and intimate friends. This series is scientifically very important for urology specialists, and it will continue to take place in the future honoring Ondra's vision of teamwork and international collaboration.

24. Your trainee and long time collaborator, Dr. Semir Vranić, just became member of the Academy of Arts and Sciences of Bosnia and Herzegovina. Is he your most successful student and trainee or collaborator? What were the highlights of that very productive mentorship and collaboration with Dr.Vranić?

Yes, of course! Semir is by far the most successful graduate student of mine. He obtained a training grant from International Union for Cancer Research and American Cancer Society which supported his fellowship at my lab at Creighton University. From that year of hard work he and I published together 12 papers (seems to me as some sort of a record for a graduate student?). He is now an Associate Professor at the Qatar University School of Medicine in Doha. We continue to collaborate and to write papers together. Earlier this year we just submitted for publication our 59th jointly written manuscript, with 3 more projects in mind for 2023-24.

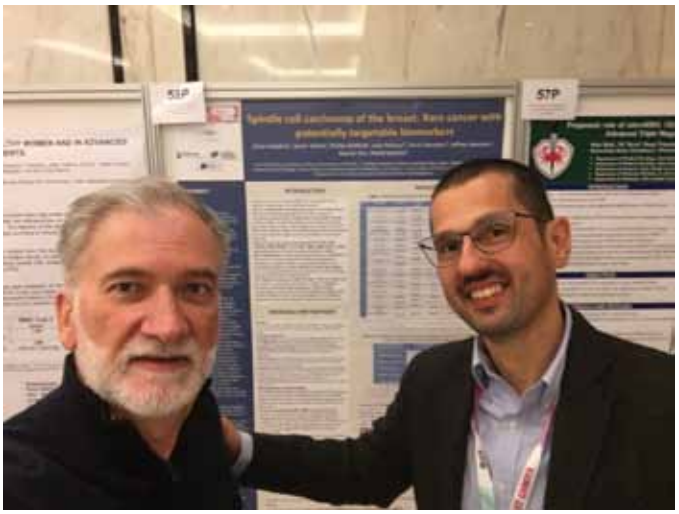


Figure 5. In front of a poster with Semir Vranić, MD, PhD, my former graduate student and long time collaborator. Photographed at the Congress of the European Society of Medical Oncology(ESMO) in Barcelona, Spain, 2019 .

25. Do you have regular contacts with your Croatian colleagues? Are you planning any joint research projects with them, conferences or publications?

Several of my classmates are now department heads and both the current and the past Dean of Medical School are my classmates. They are all wonderfully successful and have engaged me on a number of occasions. For example, I have presented research and lectured on various topics at Saltykow Memorial and Ljudevit Jurak Symposium, as well as the Croatian Oncologic Congress.

26. In your curriculum vitae you list many consultancy partnerships and advisory positions that you hold. Will you continue along that pathway or do you have other plans for the future?

I have recently retired from my position as the Director of Anatomic Pathology and the endowed James Park Dewar MD Professor at the University of Oklahoma, to pursue consultancy jobs aimed at promoting precision medicine. So, I am now consulting a couple of early start-up companies, one clinical stage privately held company and one very large publicly traded company. As you can see, it is quite a diverse group of biotechnology businesses that value my experience in the field. It wouldn't be possible to do it without first learning the ropes (in Croatian:"ispeci zanat") and for quite a long time. One, apparently, must be very patient (although patience is not my strong trait) and persistent to become recognized in however small or large a field you are working in. There are no guarantees. My young son recently asked me how does one become a consultant, because it seemed to him that this is a good position to be in. We had a long conversation, and I am not sure I fully convinced him that I have an answer for him. But it worked for me, but none of that would be possible without family support.

Figure 6. Several images from a couple of Ljudevit Jurak symposia (collage). It is always nice to meet old, and make new friends.

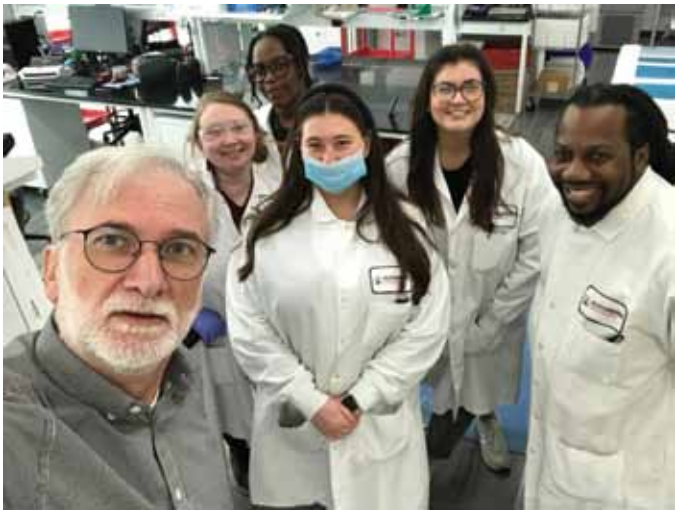


Figure 7. At Scipher Medicine clinical laboratory (located within Alexandria Center for Advanced Technologies) at Research Triangle Park, NC (March 2023)

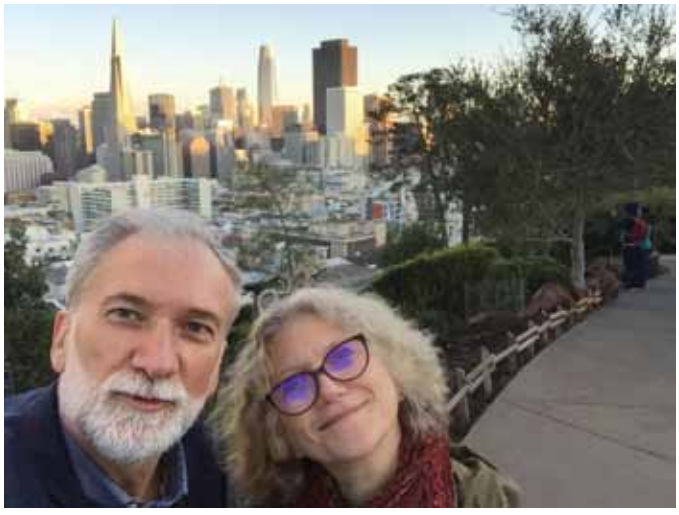


Figure 8. With Biljana in San Francisco, probably our favourite US city.