

Steven Zivko Pavletic Interview

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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 and the present issues 60-61 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
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Steven Živko Pavletić Interview



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1. How did you decide to study medicine?

This is a complicated question with a simple answer – I had to make my choice. The classical “gymnasium” type high school provided me with excellent general education but with only one path forward which was to decide about the graduate school. It was probably a mix of multiple interests, affection for working with people, and the family environment I grew with both parents biologists who opened for me the world of life and natural sciences. So, in the fall of 1974 I applied to medical school at the Zagreb university and my life path took a direction I never regretted.

2. What were your favorite subjects in the preclinical years of your studies?

Funnily to say, but the most daunting, most challenging, most demanding, and stressful course was human anatomy which was in the end the one which resulted with most impactful and colorful memories on the medical school years. It is probably because it was all first, first real serious medical subject, first colloquia, first exams, first encounter with human mortality and the glorious construct of human body. Legacies of Drago Perović and Jelena Krmpotić were felt everywhere, and professors, instructors, and colleagues all were great and inspiring. It became a matter of honor and duty for me to take on the teaching next generations and after passing the anatomy exam in 1976 I served as a student assistant at the Anatomy Department in Zagreb.

3. Who were your favorite professors?

There are many. All left their trace and impact on my career. My experience is skewed, and personal and singling ones would do great injustice to others. I am incredibly proud and grateful to my medical school for the education, love for medicine and dedication to clinical sciences which armed me so well for the next stages in my life.

4. Any memorable events from those days? Any anecdotes that you like to tell to your students and trainees?

The whole medical school experience is joyful and memorable despite very hard work and so many beautiful sunny weekends and long nights spent at the desk studying. My goal was always to get all exams done by July 15 so I could enjoy the summer months doing other things than medicine – that was one of best decisions in my life and time no one could ever have given me back.

5. Which clinical subjects and professors impressed you the most? Any stories about them?

Since you are pressing me :-)) - The immunology group at the Department of Physiology was just fabulous. Again, singling out specific names does so much injustice to anyone I might forget. I call them Zagreb Immunology School - professors Allegretti, Culo, Dekaris, Marušić, Taradi, Silobrčić, Vitale, Malenica, Boranić, Kaštelan and many others. It all collectively provided foundations and competitive advantage for the excellence and great achievements in the realm of organ and tissues transplantation in Croatia. During the strict clinical years in medical school which I can place in the period 1977-1979 my most memorable experiences relate to working with Professor Dr. Ivan Kuvačić on studying hematologic derangements during the pregnancy which laid foundations for my subsequent interest in hematology.

6. How did you study for the clinical examinations?

Studying for clinical examinations was the easiest and most enjoyable part of medical school. This is probably truth for most medical students. Just lots of reading but also lots of hands on at the bedside talking to real patients who all have been typically very grateful and friendly to us students. My favorite and most memorable clinical subject was internal medicine propaedeutics – introduction to internal medicine world which amazed me and served so well for the rest of my career. My most memorable clinical exam was the internal medicine which took place at the site of renowned Institute for Diabetes “Vuk Vrhovac” with the legendary professor Zdenko Škrabalo and his at that time junior associate professor Mate Granić. It was an exam for which I prepared by far the most of all clinical examinations.

7. How did you decide to become an oncologist?

Your questions are pointed so well since oncology is leaning inseparably on internal medicine. I always tell my fellows trainees – one cannot be a good oncologist unless you are already a great internist. By the same analogy – one cannot be a great clinical investigator unless you are already a superb oncologist. During my first job at the Center for Medical Sciences of the Zagreb University Medical Center (KBC) in 1980-1984 I had an opportunity to visit the famous National Cancer Institute in Milan and was able to meet in person with the director and the breast cancer surgeon Professor Umberto Veronesi. During those visits I also got to know Professor Alberto Costa who directed newly

founded European School of Oncology which goal was to promote multidisciplinary oncology education across Europe. These inspiring events were driving my subsequent quest to apply the new field of medical oncology to Croatia. It took me couple years to find the fertile ground for these ideas which I found in 1986 when as the internal medicine resident joined Professor Boris Labar at the Division of Oncology, Clinical Hospital Center Rebro. What followed was an amazing life-long collaboration and focus to find cures for hematologic cancers.

8. What were your first experiences in the hospital after graduation?

My first real hospital work experiences are linked to the period of 1985-1988 when I was an internal medicine resident at the Clinical Hospital Center Rebro. I enjoyed and absorbed each hospital rotation. I was waiting for this since my graduation from medical school in 1979. In those days it was very difficult to get a job as a resident in any medical specialty straight out of medical school. There was a mandatory requirement two years in primary care after graduation and those jobs were also very difficult to find. I was fortunate to be selected for the Center for Medical Sciences, KBC Rebro which was nascent under direction of Dr Goran Piljac. There I was able to fulfill this 2-year requirement under auspices of occupational medicine. There was also one obligatory year 1983-1984 I had to serve in the military. So finally in 1985 I was able to do what I have been so eagerly waiting for – to start a specialization in clinical medicine. First 18 months at KBC Rebro was a period of soul searching and I spent gratifying months with two groups – one was Division of Gastroenterology where at the time Professor Boris Vucelic returned to from the United States and taught me state of the art which served me very well in my subsequent career in dealing with gastrointestinal and liver complications in patients with graft-versus-host disease (GVHD). The other was time spent at the Division of Clinical Immunology with Professor Zvonimir Horvat which experiences served me exceptionally well to learn about autoimmune disease and what dysregulated lymphocytes and immune system can do to the patient.

9. How did you come to America?

During my years as the internal medicine resident and especially after joining Professor Labar’s group in 1986 it became clear that America, specifically United States, was a place where most important advances in clinical medicine come from. America is also



Figure 1. Steven Živko Pavletić and Boris Labar at the Department for bone marrow transplantation at the Clinical Hospital Center Rebro, 1986.

where medical oncology specialty started and the home of clinical bone marrow transplantation. There was a need for my own continuing subspecialty education. Also, Zagreb hematology center needed international integration and recognition if we wanted to grow to the world class excellence. These two tendencies were well met by Professor Boris Labar who was then a new Division of Hematology chief. Boris embraced me and entrusted me boldly while I was only a second-year internal medicine resident and we decided to join hands and embark on organizing the first international meeting “New Trends in the Treatment of Acute Leukemia” held in 1987 in Dubrovnik under the auspices of the European School of Oncology in Milan. Therefore, Dubrovnik was again a very special place in our history, this time for Croatian hematology. Credit goes also to my colleagues Drs Mirando Mrsić, Damir Nemet, Vinko Bogdanić, Ranka Serventi and oth-

ers for continuing these meetings tradition including during the Croatian War of Independence when this conference was held temporarily in Zagreb and Brijuni until 1998 when it returned back to the free Croatian Dubrovnik. During the 2nd conference in 1989 I was approached by Professor Dean Buckner of Seattle, who invited me to join their team for a combined clinical and research bone marrow transplant fellowship. In 1990 Professor E. Donnall Thomas of Seattle received Nobel Prize for Medicine specifically for the development of clinical allogeneic bone marrow transplantation. It was hard to resist excitement seeing with my own eyes big crowds of people and journalist that October day in front of the old Fred Hutchinson Cancer Research Center.

10. How did the practice of medicine in the US differ from the medical practice in Croatia those days?

Arriving to US from Croatia in January 1990 felt as if coming from a different planet. Deep differences existed between the societies, levels of economic development, political and financial systems and between the health care systems. This was also the time before internet and cell phones and when traveling and access to latest publications were much more restricted primarily due to financial constraints. Also, this was the time when the level of English literacy was very low among medical professionals in Croatia which was oppositely proportional to the widespread level of smoking cigarettes in the hospitals by physicians and staff. All these are unthinkable today when my junior colleagues come and visit from Croatia with impeccable English and all seamlessly blend instantly into the daily US clinical routine. Of importance, they put me to serve on clinical transplant service at the Fred Hutchinson Cancer Research Center three weeks after I arrived at Seattle in 1990. It became immediately obvious to me in which areas our medical training in Zagreb was good and where we were deficient. In anything what related to hematology and bone marrow transplant I was able to immediately excel and participate in. Similarly, was when it came to the areas of internal medicine such as gastroenterology, hepatology, clinical immunology, endocrinology, nephrology, cardiology. Areas where our internal medicine training was deficient at that time were pulmonology, critical care medicine, neurology, infectious disease, and anything what relates to “hands on” procedures.

11. What were the salient moments during your fellowship at the Fred Hutchinson Cancer Center of the University of Washington in Seattle?

There are many. It was a whole new world experience. The most important is the realization of how the clinical research is integrated into day-to-day medical care. This is not only about the differences in resources but about values system, dedication, and organization of the work. The other is the high level of independence and responsibilities expected from residents, and fellows



Figure 2. Steven Živko Pavletić, one of the presenters at the 1998 meeting entitled New Trends in the Treatment of Acute Leukemia. The meeting was held at the newly renovated Hotel Excelsior in Dubrovnik.

when it comes to medical practice. Other differences include the central role of the clinical pharmacist on the unit, existence of “mid-level practitioners” such as physician assistants, high proficiency and independence by nursing staff and the existence of research nurses at center of clinical research protocols implementation. These are all are major differences that still exist between US and European academic medical centers.

When it comes to specific salient moments – I can mention two from the very early days in Seattle. First is my first night on call when I was still jet lagged. A very sick intensive care patient on ventilator and hemodialysis support experienced cardiac arrest. I already mentioned my limited expertise with the critical care medicine I had in Croatia at that time. Thanks God the nurses knew what to do! – enough said and never repeated. I decided in a moment to become the best intensive care doctor medicine has ever seen! We also did experience a first ever in history respiratory syncytial virus in hospital spread among transplant patients in February of 1990 which was memorable and does resonate too nowadays.

Finally, it is to be noted that my fellowship also included two years of laboratory work on a tumor immunology project with my former mentor Alex Fefer who became famous on conducting first identical twin transplants for leukemia. I had zero laboratory research experience when I started my fellowship and naturally it was a challenge. I am glad in the end we published a well referenced paper on the potential role of interleukin-7 in immunotherapy. (Pavletic Z, Benyunes MC, Thompson JA, Lindgren CG, Massumoto C, Alderson MR, Buckner CD, Fefer

A. Induction by interleukin-7 of lymphokine-activated killer activity in lymphocytes from autologous and syngeneic marrow transplant recipients before and after systemic interleukin-2 therapy. *Exp Hematol.* 1993 Sep;21(10):1371-8. PMID: 8359237.)

12. What did you accomplish during those Fellowship years?

In the US I did two fellowships. First was the bone marrow transplant fellowship in Seattle at the Fred Hutchinson Cancer Research Center and the University of Washington. This fellowship at one of the top US academic medical centers taught me how to integrate clinical research in clinical medicine and back. This stay in Seattle also allowed me to train at the best place in the world for the area of my academic interests. The knowledge, contacts, mentors, and peers I got to know carried me further through the rest of my career. Second fellowship was at the University of Nebraska Medical Center in Omaha in Medical Oncology. This fellowship allowed me to become a trained oncologist and learn about all cancers beyond hematologic malignancies. Years of my US training 1990-1997 prepared me well for what was to come next.

13. Why did you choose hematology? Did you have role models or important mentors?

As they say, in life, you follow your heart, do the hard work and follow the opportunities which start coming your way. From my medical school I had that natural intention to help people and hopefully play a role in moving the progress forward. Initially as the medical student the research path led me to the field of pathology of pregnancy which encapsulated some of the most challenging complex entities in medicine. It is also a field which allowed me to share with people some of their most joyful and scary moments in life and ultimately being able to help. My first original paper was “Changes of the blood picture in pregnancy” published in “*Medicinar*” with my mentor Dr. Ivan Kuvacic. As my interests have shifted toward the oncology, I was looking for the best opportunities during my internal medicine residency at the Clinical Hospital Center Rebro. At the time the Rebro team under leadership of Dr Boris Labar and Dr Vinko Bogdanić started doing some of the fist allogeneic bone marrow transplants for leukemia in that part of the world. Being selected to join that team in 1986 was defining moment for my career. I also had an opportunity to graduate in 1988 from one of the first classes of the new hematology postgraduate training while in Zagreb. Some other hematologist mentors at the time I want to give credit to include Drs Damir Nemet, Zvonimir Čepelja, and Branko Jakšić. I need to mention also one of the greatest hematologists of all the times, my mentor at the University of Nebraska Medical Center, Professor James Armitage. He taught me about hematology, lymphoma, transplantation and how to organize successful academic leadership.



Figure 3. C. Dean Buckner, collaborator of the Nobel Prize winner ED Thomas at the Fred Hutchinson Cancer Research Center, University of Washington in Seattle, WA. He invited Živko Pavletić to move to Seattle and take a position within his Department.

14. From Seattle you moved to University of Nebraska Medical Center, Omaha, Nebraska where you became Director of the Allogeneic Stem Cell Transplantation. What did this new job offer you that you did not have in Seattle?

When I moved to Omaha, at the University of Nebraska in 1992 this bone marrow transplant center was in the zenith of one of the most important paradigms shifts in the history of bone marrow transplants. Namely until 1992, about 25 years into modern bone marrow transplants history, the central dogma was that the “real” pluripotent hematopoietic stem cells could be obtained only from the bone marrow. This belief has been proven wrong through the works of Drs Anne Kessinger and James Armitage at the University of Nebraska Medical Center in Omaha who first in the US started using successful transplants from cells obtained through peripheral blood veins instead from the bone marrow harvests. Multiple advantages are associated with such approach which include faster recovery of hematopoiesis after transplant, shorter hospital stays and no need for general anesthesia since now blood cells could be collected through the veins by a procedure called leukapheresis. Such transplants were initially performed for obtaining autologous hematopoietic stem cells from lymphoma patients and around 1995 it became also routine for collecting stem cells from allogeneic healthy donors. When I became senior faculty and later the allogeneic program director in Omaha that center was one of the few world centers experienced in using allogeneic peripheral blood for transplantation. These experiences surpassed at the time the experiences of the center in Seattle and opened unprecedented opportunities for my professional development. The successes of this new approach to transplantation did not come without a cost as it was noted that such patients were at higher risk of developing a late post-transplant immunological complication called chronic GVHD, which became focus area of my academic research in years to come.



Figure 4. Steven Živko Pavlečić and Georgia Vogelsang of the Johns Hopkins University, Baltimore, MD. The two of them were instrumental in starting an NIH program dealing with the chronic GVHD.

15. What did you accomplish in Omaha, Nebraska?

My ten years in Omaha from 1992-2002 were the most important formative years in preparations for what was to become my career at the National Cancer Institute, National Institutes of Health. I became very proficient and comfortable in managing the most complicated medical conditions including critically ill, post-transplant and cancer patients. Also, I was able to participate in some most exciting clinical research developments in the field of cell transplantation at the time. My American academic publications productivity truly took off after I joined faculty in Omaha. Some pioneering papers from that time include first publications of the experiences with using allogeneic peripheral blood stem cells for patients with leukemia and lymphoma, also first reports of autologous and allogeneic stem cell transplants for chronic lymphocytic leukemia. We also started successfully one of the few transplant programs for patients with autoimmune diseases including rheumatoid arthritis and multiple sclerosis. The 10-year stay in American Midwest was also a very gratifying experience from my personal and family point of view. An excellent medical center, affluent city with the famous investor Warren Buffett on the helm of philanthropy, two medical schools and great people. There is also an impressive Croatian Cultural Center to be found in Omaha with the Croatian flag visible high in the middle of the cornfields. When one crosses the Nebraska border with the car the state slogan says, “Welcome to Nebraska – Good life”.

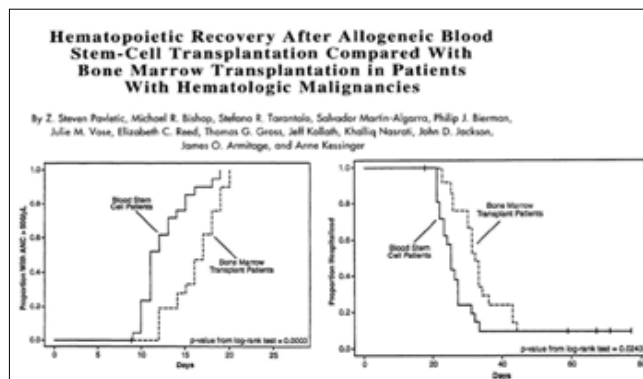


Figure 5. Key paper about the transplantation of peripheral blood derived stem cells was published in the Journal of Clinical Oncology.

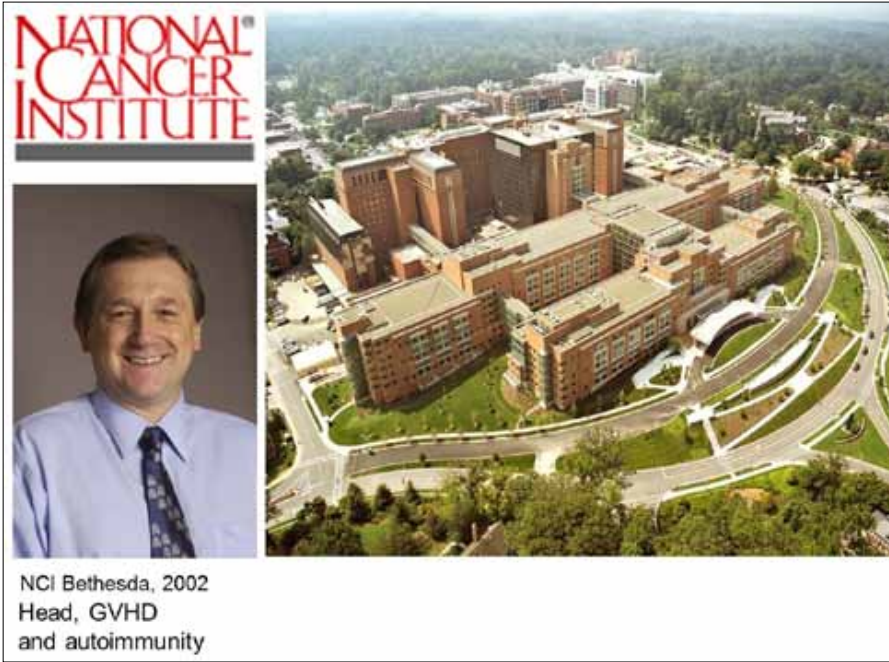


Figure 6. Steven Živko Pavlečić at the NCI, where he became Director of the Department for the study of the GVHD and autoimmune diseases.

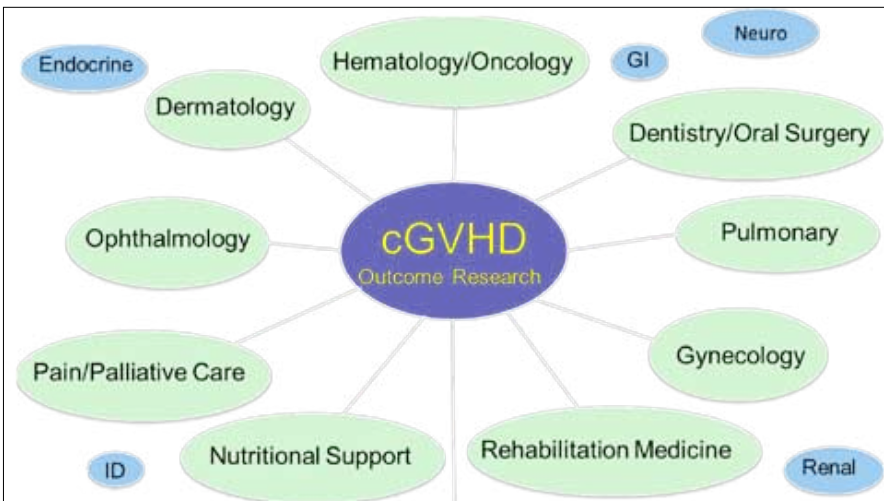


Figure 7. Multidisciplinary model for the study of the chronic GVHD as developed by the research group at the NIH.



Figure 8. Director of the NCI John Niederhuber presenting the Director's Award to Steven Živko Pavlečić, who earned it for his work on the chronic GVHD.

16. As a non-American how did you become a member of the most prestigious American Alpha-Omega-Alpha Society?

This is an award dearest to my heart as it transcends my connection both with America and with medicine. Alpha Omega Alpha Honor Medical Society (ΑΩΑ) is an honor society in the field of medicine and has active chapters in more than 130 accredited medical schools in the United States. Most new members are top 10 percentile students elected in their final year of medical school, but distinguished teachers, faculty members, residents, and alumni can also be exceptionally inducted into the society. All elections are held at local Chapters. The ΑΩΑ motto is, "Be Worthy to Serve the Suffering." I was elected in 1993 as the internal medicine resident as the only one in the class. Out of about 4000 members inducted to ΑΩΑ each year, and it is almost unheard of to be elected as non-American medical schools graduate. Therefore, I take it as very special and unique recognition both to me and to my medical school in Zagreb alma mater. It is the reminder on how in America everything is possible and "sky is not the limit".

17. How did you decide to move to the National Cancer Institute, Bethesda, Maryland?

This move came as a natural evolution in my career. It is useful to know that National Cancer Institute (NCI) is the largest institute out of 27 institutes at the National Institutes of Health (NIH) which is a 45-billion-dollar agency of the US government dedicated to funding of the biomedical research. I consider NIH the best American invention which was instrumental in initiating most advances in medicine over last 60 years. NCI has also an independent funding status among the NIH due to the National Cancer Act that defines a special commitment of the US government to addressing cancer as the major public health problem. Each NIH institute has an "extramural" and an "intramural" portion. The "extramural" programs consume about 85% of the NIH budget which goes for funding of the biomedical research across the US through the competitive peer reviewed grants review mechanism. The "intramural" program of each NIH institute is located at the NIH center in Bethesda, Maryland in



Figure 9. The meeting of the Society Croatian Hour [Hrvatska ura (HURA)], which was founded in 2010 by Steven Živko Pavlečić. The participants – starting from the left: Jadranka Stević, don Dubravko Turalija, Helena Skračić, Filip Pirs, Vice Skračić, Katija Jeličić, Steven Živko Pavlečić, Masenjka Katić, Juraj Radić, Tanja Holtzapfle, Kate Suryan, Ankica Pavlić, Branka Slavica, and Margareta Habazin.



Figure 10. Steven Živko Pavletić and Boris Labar at the meeting held in Dubrovnik in 2011 under the title New Trends in the Treatment of Acute Leukemia. Their collaboration began many years earlier, and continues with good results.

the suburbs of the Washington DC. NIH clinical center is the largest hospital in the world which is completely dedicated to medical research. This is not a very big hospital, maybe 200-250 beds with a large outpatient clinic. For a patient to receive medical care at the NIH Clinical Center it is a requirement to be enrolled on a clinical research protocol. However, if a patient is eligible and gets enrolled on a clinical protocol at the NIH, from that point all costs of medical treatments are paid for by the US government. In sum, it is the best place in the world to practice academic clinical research devoid of commercial pressures. There are no excuses for failure and the only marching order is to do something great what will make the difference in patient's lives. In 1999 intramural NCI decided to establish a new bone marrow transplant clinical program and as part of that series of recruitments in 2001 I received the invitation to join the team. For me it was an opportunity impossible to resist to. Moving family from Omaha to Washington DC area was not easy but, as I often tell my junior associates – each move is worth the effort if is a good move. In 2002 I took the job at the NCI in Bethesda NIH Clinical Center where I am still working today.

18. Did the leaders of NCI recruit you for a special function or were you allowed to define your own agenda?

This was a mutual agreement driven by my own academic interests and the new center needs for experienced bone marrow transplant faculty who could assume leadership positions in the new program. Accordingly, I was appointed to lead the newly formed section for Graft-versus-Host disease and autoimmunity.

19. In 2003 you established the trans-NIH multi-institute clinical research program in chronic graft-versus-host disease (GVHD)? How was this research program conceived?

The establishment of the inter-institute NIH chronic GVHD study group in 2003 is one of the great examples of why the NIH intramural research program exists. The goal of the intramural NIH research program is to address difficult problems in medicine which the extramural academic medical community is having hard time to address. Typically, such problems include rare disease, complex disease or disease which need urgent attention. In 2003 allogeneic hematopoietic stem cell transplantation became a well-established form of curative immunotherapy for hematologic cancers. Numbers of transplants have been steadily growing and due to improving safety of these procedures increasing number of patients have become long term survivors. About 50% of them developed new disease in medicine, chronic iatrogenic induced cGVHD. This autoimmune complication is mediated by the newly transplanted donor derived immune system which is attacking the transplant recipient. Patients develop chronic symptoms in multiple organs including skin, eyes, oral mucosa, lungs, genitalia, gastrointestinal tract, liver, joints and fascia. Such symptoms are chronic and disabling and severely affect patients quality of life and cause excess mortality. Patients are cured from leukemia and then must suffer from a new disease instead. In 2003 there were no new therapies being developed for cGVHD, there was limited understanding of disease biology, there were no standard criteria for diagnosis or response assessments and there were no Food and Drug Administration approved therapies. It was obvious that something better was supposed to be done to address cGVHD and the intramural NIH and NCI with multidisciplinary clinical and laboratory research expertise was the ideal place for starting such program.

20. Your interest in GVHD led you to become the Chair of the 2005, 2014 and 2020 NIH chronic GVHD consensus projects. What did you accomplish in that position?

Series of the three NIH consensus conferences set the stage for prospective preclinical and clinical research focused on cGVHD. We brought all stakeholders at the table representing both the US and international transplant community. These projects are a textbook model example of how to approach addressing a new disease in medicine. The first conference held in 2005 at the NIH was an expert opinion driven and provided standardized definitions for cGVHD diagnosis, staging, histopathology, supportive care, biomarkers development, therapy response criteria, and the design of clinical trials. Prospective studies which followed led to the 2014 conference which was evidence-based and provided refinements and revisions of the original criteria. These advances set the stage for the clinical translation and the first in history US Food and Drug Administration approval of novel

agents for cGVHD in 2017 (ibrutinib, a BTK and ITK inhibitor). Two subsequent approvals followed in 2021 (*belumosudil*, a ROCK2 inhibitor and *ruxolitinib* a JAK1/2 inhibitor). These approvals would not have been possible without the methodical work and leadership which started in 2003 at the NIH. The most recent cGVHD NIH consensus conference held in 2020 as a three-day virtual event put forward new concepts for prevention and therapy which may ultimately lead to effective personalized treatments and elimination of this devastating problem in cancer survivors. The 18 original papers published by the NIH consensus conferences since 2005 became some of the most referenced in the transplant literature.



Figure 11. The April 2022 meeting of the American–Croatian Forum, which was attended by Steven Živko Pavlečić, President and founder of ACAP (Association of Croatian American Professionals) and the principal force behind the Croatian Healthcare Tourism Initiative. The participants of the meeting (from the left): Don Markušić, Jena Havidich, Goran Krstačić, Živko Pavlečić, Mirjana Semenčić-Rutko, and Mašenjka Katić.

21. Thereafter you became the Chair of the American Society of Hematology Immunotherapy Task Force. What did this task force have on its agenda?

This was a gratifying and interesting experiment both for American Society of Hematology (ASH) and me personally. Around 2017 we witnessed the explosion of data and information about genetic mutations in leukemia patients. Understanding of which of those mutations are important and which could be potentially used as diagnostic tools or novel therapeutic targets, was lagging. To rapidly address these new challenges ASH decided to

form the precision medicine task force to which I was invited to participate. In contrast to usual term limits on the standard committees invited experts on such task force had an open mandate to set the agenda. Very soon into these discussions a decision was made to form an offshoot task force to focus on equally rapidly emerging field of genetically engineered T cell therapies for hematologic cancers (CAR T). Dr. Sophie Paczesny of Indiana University and myself were appointed as co-chairs. Several initiatives came to fruition because of this effort, including newly organized resources for patient referrals, organization of the first ASH summit in immunotherapies and thematic publications in leading hematology journals. My favorite accomplishment was the participation in the development of the new ASTCT consensus guidelines for CAR T toxicities (cytokine release syndrome and neurotoxicity) which was published in 2019 and is currently one of top referenced and accessed papers in the hematopoietic stem cell transplant literature. (Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, Maus MV, Park JH, Mead E, Pavletic S, Go WY, Eldjrou L, Gardner RA, Frey N, Curran KJ, Peggs K, Pasquini M, DiPersio JF, van den Brink MRM, Komanduri KV, Grupp SA, Neelapu SS. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant.* 2019 Apr;25(4):625–638. doi: 10.1016/j.bbmt.2018.12.758. Epub 2018 Dec 25. PMID: 30592986.) The success of Task Force for Immunotherapies prompted ASH in 2020 to transform this newly formed ad hoc group into a regular standing subcommittee.

22. What are your current major responsibilities at the NCI?

I serve as the GVHD and Late Effects section chief and continue to direct the NIH chronic GVHD trans-institute study group. In 2020 I was also appointed as the clinical director of a new NIH intramural myeloid malignancy program with primary goal to focus on myelodysplastic syndrome which is a type of a common bone marrow cancer for which there are no curative treatments besides allogeneic hematopoietic stem cell transplant. The bulk of my time is spent by being the principal investigator on numerous new therapies clinical protocols for chronic GVHD and for myelodysplastic syndromes. These engagements include work with patients, administrative and teaching responsibilities, mentoring trainees and numerous collaborative and publications initiatives.

23. Lets discuss some statistics: How many papers, including review articles and book chapters or books did you publish? How many times have your papers been cited according to the Science Citation Index? What is your h-index?

I cannot give you a precise answer, but the best short answer would be as follows: I have some 250 primary publications in addition to approximately 50 review articles. Google Scholar reports



Figure 12. The 2017 meeting at the building of the Croatian Academy of Sciences and Arts included Stella Fatović-Ferenčić, Marko Pećina, Živko Pavletić, Adriana Jadranka Pavletić, and Pavao Rudan.

that my h-index is 75. For more details interested readers could find the current details about my publications on <https://scholar.google.com/citations?user=Q39FQWcAAAAJ&hl=en>

24. What is your most important, or for that matter most favorite, paper?

The paper I am most fond of is: Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. *Biol Blood Marrow Transplant.* 2006 Mar;12(3):252-66. doi: 10.1016/j.bbmt.2006.01.008. PMID: 16503494. This is the first ever paper which comprehensively outlined the concept of therapy response criteria in chronic GVHD clinical trials. The subsequent iteration in 2014 laid the foundation for first in history FDA drug approvals in 2017 and 2021.

25. You have been honored and have received several awards for your contributions to hematology and clinical medicine. Which ones of these mean the most to you?

The meaning of the election to the Alpha Omega Alpha Honor medical society in 1993 was discussed earlier. The recognition I am affectionate about is the election to the Croatian Academy of Sciences and Arts as a corresponding member in 2018. I am very fond of this fundamental Croatian institution and see its enormous potential in the environment of rapidly evolving societal and technological challenges we are facing today. The 2006 NCI Director's award for the accomplishments with the NIH chronic GVHD consensus project through the national and

international effort as also a very special recognition. Finally, an award I am very proud of is The Clinical Research Foundation 2022 finalists for the Top 10 US Clinical Research Achievement Awards. This award is special since it is given to the whole NIH chronic GVHD team for the paper of a novel therapy for patients with refractory sclerotic cGVHD. Development of Pomalidomide in the Treatment of Chronic Graft-Versus-Host Disease, published in *Blood* in 2021. Curtis LM, Ostojic A, Venzon DJ, Holtzman NG, Pirsil F, Kuzmina ZJ, Baird K, Rose JJ, Cowen EW, Mays JW, Mitchell SA, Parsons-Wandell L, Joe GO, Comis LE, Berger A, Pusic I, Peer CJ, Figg WD, Cao L, Gale RP, Hakim FT, Pavletic SZ. A randomized phase 2 trial of pomalidomide in subjects failing prior therapy for chronic graft-versus-host disease. *Blood.* 2021 Feb 18;137(7):896-907. doi: 10.1182/blood.2020006892. PMID: 32976576; PMCID: PMC7918188.

26. You have collaborated with numerous Croatian physicians and mentored many of them. Could you summarize these activities for us and single out the most important or consequential ones.

During my time in the US these activities become particularly abundant after my arrival to the NCI in 2002. Since that time about 30 Croatian hematologists and some related specialties spent time with me at the NCI for trainings and study visits of various durations from several weeks to up to one year. One of the first and I am very proud of is Dr. Iskra Pusić who worked with me both in Omaha Nebraska and at the NCI, she is now the professor at Washington University in St Louis and the leader in the field of chronic GVHD.

Most consequential once have been a series of numerous visits by the Zagreb faculty which started with one-year fellowships at the NCI by Dr Dražen Pulanić in 2009 and Dr Lana Grković-Desnica in 2010. These culminated in 2013 with the formation of the Zagreb chronic GVHD team which without hesitation I can call now as one of top two chronic GVHD multidisciplinary clinical teams in Europe. This experience validates the model of such interactions between diaspora and homeland experts. This example provides a proof of principle for establishing such continuous circuits of sustainable circulation of knowledge and

people. Today's means of communication undoubtedly allow this. The Zagreb chronic GVHD team proved to be successful in all metrics for the academic success which include international grants, high impact publications and clinical research productivity and excellence.

There are two names of exceptionally brilliant junior people whom I spent time with during my years in US. These individuals sparked like shooting stars, made a lasting impact on their environments and standards of medical practices in Croatia and are now unfortunately not anymore with us. First is Dr. Marin Nola who can be credited for the renaissance of the lymphoma hematopathology diagnostics in Croatia. The other is Dr. Davorika Dušek an exceptionally talented young specialist in infectious disease who left us in the fall of 2020 as one of the many unsung medical personnel victims of the COVID pandemic. We miss them direly as they legacy continues.



Figure 13. The 2017 meeting at the Croatian Museum of Medicine and Pharmacy of the Croatian Academy of Sciences and Arts included the following: Silvijia Brkić Midžić, museum consultant and Director of the Museum, Marko Pečina, Stella Fatović-Ferenčić, Steven Živko Pavletić, and Adriana Jadranka Pavletić.

27. As the current President and a cofounder of the Association of the Croatian American Professionals, you have promoted the collaboration between the physicians in the US Croatian diaspora and physicians and other scientists in the mother country. What did you manage to accomplish so far? Do you have any plans for the future?

Association of the Croatian American Professionals (ACAP) is the newest organization of the US Croatian diaspora which was founded in 2014. It grew from just 35 members in 2015 to 2300 in the fall of 2022. ACAP as a non-political and non-religious non-profit organization which brings together newer generations of Croatian American professional diaspora. All ACAP members are high achievers and leaders in their respective areas of endeavors from medicine, science, public policy, arts, finances, law, and education. Medicine comprises almost 20% of the US economy and many top experts, academicians and health care professionals have also Croatian roots. Our goal has been to bring together this critical mass and put in service of growing collaborations on projects with Croatian counterparts in the areas of education, transfer of technology and knowledge, professional development of our members and improving the health and wellbeing of people in Croatia. The 7th ACAP annual conference will take place for the first-time outside US, in Zagreb on July 5-9, 2023. One motto of the conference will be “*Croatia a country for healthy living*”.



Figure 14. Pickleball, a new sport presented in 2017 to the members of the Croatian Academy of Sciences and Arts, including Marko Pečina and Vjekoslav Jerolimov.

28. I read an article that you are involved in promoting Croatian medical tourism. How far did you get so far?

The topic of medical tourism has been a central part of ACAP activities as it relates to focus on medicine and medical sciences. We use term medical tourism broadly and when applied to Croatia we consider a broad spectrum of topics which reach from development of better care for cancer patients and physicians education,



Figure 15. Steven Živko Pavletić receiving the 2022 award as one of the authors of the 10 best clinical research articles published in the USA in the previous year. In this photograph, he is seen with Harry P. Selkerom, President of the Clinical Research Forum and Chair of the Clinical Health Forum, as well as Dean of the Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA.

to development of nursing homes, health resorts, retirement communities and medical wellness. In 2018 ACAP formed the *Medical Tourism Committee at the Embassy of Croatia in Washington DC*, a multidisciplinary group of 40 experts who continue to work on these topics. We came quite far in the areas of collaborating with the Croatian ministries of health and tourism and in June 2022 we signed a collaborative agreement with the *Kvarner Cluster of medical tourism* to promote jointly an evidence-based pilot project in lifestyle medicine and medical wellness at sites in Opatija and Crikvenica to be implemented in November 2022.

29. Do you have any hobbies?

I am a passionate pickleball recreational player. My wife Adriana and I started playing pickleball in 2014 when there was only one club in the area where we live in Maryland, Montgomery County. Nowadays pickleball is by far a fastest growing sport in America with more than five million players. There are numerous places to play indoors and outdoors. Pickleball is a sport invented in America, in Seattle in 1960s and is played on the court exact sizes as the badminton court. It gained however increased popularity over last 5-10 years and it boomed especially during the COVID pandemic. Many celebrities and former tennis players play pickleball today. It could be described as a ping pong on a small tennis court, it is played usually in doubles, with paddles and plastic wiffle balls. It is a sport easy to learn, socially interactive and friendly. It is highly recommended for recreation, and it will likely become part of year around tourism offerings.

30. Do you have any advice for the current medical students in Croatia?

Get the best education you can get – and then do something with it.



Figure 16. The multidisciplinary team from Zagreb formed to study and treat the cGVHD. In the photograph (taken in 2017) – standing (from the left): Lucija Jurišić, Dina Ljubas Kelečić, Antonija Babić, Tamara Vukić, Marinka Mnavak-Stripetić, Radovan Vrhovac, Zlatko Giljević, Romana Čević, Nina Šaban, Zinaida Perić, Ervina Bilić, Ernest Bilić, Sanja Mazić, Ante Vulić, and Toni Matić. Sitting (from the left): Lejla Kurić, Ranka Serventi Seiwert, Steven Živko Pavletić, Lana Desnica, and Dražen Pulanić.