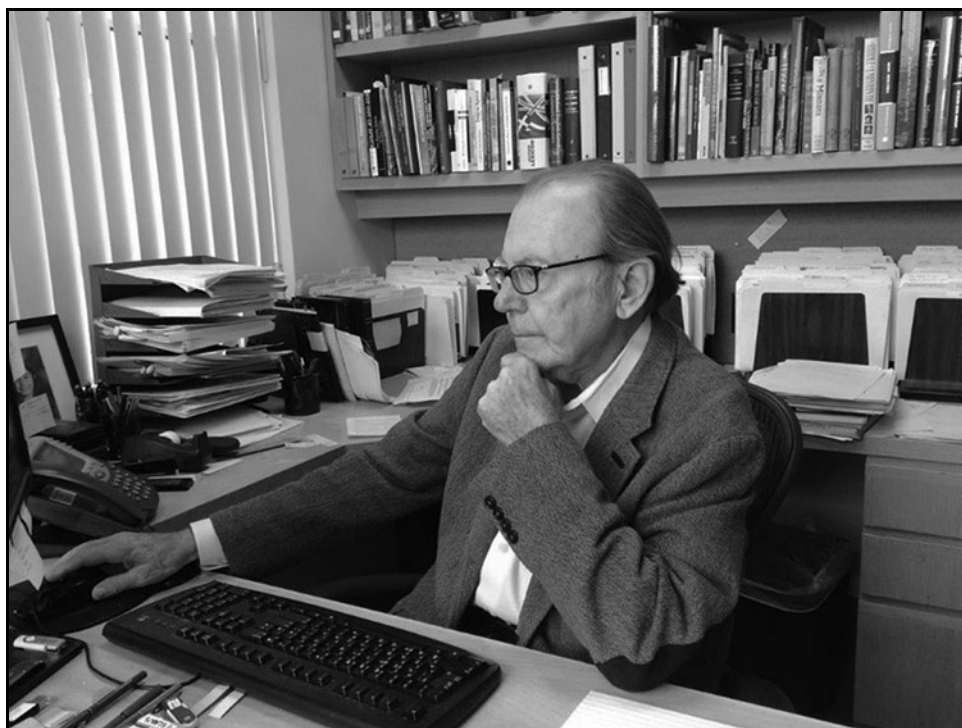


A Tribute to George Stamatoyannopoulos

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ODE TO GEORGE

AT THE OUTSET, I wish to express my deep sense of appreciation and gratitude to George Stamatoyannopoulos for his farsightedness in launching the American Society of Gene (and Cell) Therapy, the first annual meeting of which was held in Seattle, Washington, in 1998. I vividly recall the moving inaugural Presidential Address that George gave, emphasizing the role the young generation of scientists should play in the future success of the Society. Here, I would like to narrate two distinct reminiscences and stories about George.

My first story dates back to circa 1990, when I first reached out to George soon after we described the generation of an AAV2-parvovirus B19 hybrid virus¹ in the hopes of using it as a vector to deliver

the β -globin gene. The general idea at the time was to achieve site-specific integration by AAV2 (a landmark discovery by Dr. Kenneth I. Berns and his colleagues)² and erythroid progenitor cell-restricted expression from the parvovirus B19 promoter.³⁻⁵ While our studies with the AAV2-B19- β -globin vector were underway, Art Nienhuis and Jude Samulski joined forces and reported AAV2 vector-mediated γ -globin gene transfer and expression in human K562 erythroleukemia cells at the RNA level.⁶ George was not only extremely gracious in sharing his β -globin expression cassette, but his laboratory also performed β -globin gene expression in human K562 cells at the RNA as well as at the protein level.

Assuming that George was a Member of the National Academy of Sciences, I asked him whether

he could contribute our manuscript to *PNAS* as well, to which he responded wryly, “They don’t let Greeks and Indians into the Academy.” In any event, our coauthored article was eventually published in *Gene Therapy* in 1996,⁷ of which I remain immensely proud two decades later.

In retrospect, the use of AAV2 (the only available serotype vector available at the time) was not ideal since AAV2 transduces murine hematopoietic stem/progenitor cells (HSPCs) poorly. Thus, despite our sustained efforts,^{8–11} the use of a murine model to demonstrate the feasibility of AAV2 vectors for the potential gene therapy of hemoglobinopathies did not succeed. It wasn’t until 2013 when we identified AAV6 as the most efficient serotype for transducing human HSPCs,^{12,13} and it is my fervent hope that the optimized AAV6-B19- β -globin vector will prove to be a useful alternative for the potential gene therapy of human hemoglobinopathies in the not-too-distant future, based on recent success with AAV6 vectors and human HSPCs.^{14–16}

My second story about George is somewhat more personal. I would occasionally run into George at the annual meetings of the ASGCT, but in 2011, when George saw me, he immediately blurted out, “You have gained 15 pounds.” I was astonished as to how precisely he was able to guess the extent of my weight gain. Needless to add that George’s comment motivated me to shed those extra 15 lbs [plus 5 more!] over the ensuing 2 years, for which I will remain eternally grateful to him, because that weight loss was instrumental in reversing my prediabetic diagnosis.

I saw George again at the ASGCT meeting in 2015 in New Orleans, and he told me that he just turned 81 years young. I told him that my wish was to look half as good as he does when—and if—I turn 81.

In sum, the fact that, despite overwhelming odds, I have continued to pursue AAV vector-mediated β -globin gene delivery more than a quarter of a century after I first reached out to George is a very small token of my deep sense of appreciation, as well as the utmost respect and awe in which I hold George.

Long live George!

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PRAISE FOR GEORGE STAMATOYANNOPOULOS

It is an honor and privilege to participate in this Festschrift issue to acknowledge George Stamatoyannopoulos, who we commonly refer to as George Stam.

Back in 1992, after several visits to Seattle, Dr. Stam took a chance and offered me a faculty position in his Division of Medical Genetics as part of the Markey Molecular Medicine Center at the University of Washington. This came at a time when my scientific colleagues were telling me I had enough sense to stay away from gene therapy because it was not real science. The initial contact was not easy. I had written and called several times in 1991/1992, but I literally had to pull him aside at an evening reception at the American Society of Human Genetics to get his ear. George had many redeeming qualities as a mentor. His willingness and ability to rip apart my grants (fortunately prior to submission) was invaluable. He would say, “Young man, the science is great, but presentation is key to getting a good score.” I still remember the hours I spent going through his handwritten notes, as in those days word processing programs were relatively archaic. I sometimes wondered if there were a few Greek terms thrown in to see if I was paying attention. Nevertheless, these lessons were vital for me and helped me advance my own career. George liked to solicit the views of others, but he was tough. I remember discussing an important topic during my first faculty meeting. After much debate, he turned to me and said, “Young man, what do you think?” I replied, “I think we have heard both sides and I am ready to vote.” George paused and chuckled, “Vote? In my many years as division head—we never vote.”

George would come and discuss his frustration on how the American Society for Human Genetics failed to devote much time to gene therapy topics at the annual meeting. I still remember George walking into my office to ask my opinion and discuss his idea for starting what is now the American Society for Gene (and Cell) Therapy (see doi:10.1038/mt.2010.11 and doi:10.1038/sj.mt.6300284 for historical perspective). Of course, being a new assistant professor, I had no idea how one goes about starting a society, but it sounded like a great idea. I was fortunate to see and learn the steps and processes required for such a major undertaking. George kept with it and the rest, as we say, is history. I appreciate that he selected me to be on the Society’s founding Board of Directors. Those who have more recently joined the gene therapy com-

munity may not fully appreciate what George did to get the Society on its feet and keep it going, even during the field's darker days. The payoff has been great because the Society has been so important in bringing together diverse scientific, medical, manufacturing, and regulatory communities from across the globe. I am grateful to what George taught me, and our community is indebted to his contributions to our field. Almost 25 years later, I look forward to seeing George and hearing the greeting, "Young man."

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THE GODFATHER OF OUR FIELD

Modern science is a multinational and collaborative endeavor. As one of the many Greek "scientific immigrants," I made the journey from the lab of Professor Aglaia Athanassiadou to doctoral studies in the George Dickson's lab, where I was also mentored by Professor Nick Anagnou. Both professors Athanassiadou and Anagnou themselves had sojourned elsewhere for many years before returning to Greece. It was during this period that I encountered the work of Professor George Stamatoyannopoulos, the eminent Greek "scientific immigrant" who has had such an impact on gene/cell therapy via his research, not least through founding the American Society of Gene & Cell Therapy (ASGCT). With more than 2,000 members in the United States and worldwide, ASGCT is the largest association of individuals involved in genetic and cellular therapeutics.

Professor Stamatoyannopoulos received his MD from the University of Athens and his doctorate of science degree from the University of Athens, before his own "scientific migration" to the United States. Professor Stam, as he is more widely known to the community (and because Stamatoyannopoulos can often be a mouthful to non-Greek speakers!), has more than 400 research publications and thousands of citations. He has been the founder of multiple biotech companies and is widely acknowledged as a leader in the field of hemoglobinopathies. For over four decades his research has focused on the delineation of the cellular and molecular processes by which hemoglobin switches from fetal to adult form during development. His research is currently focusing on the control of human globin genes during development and differentiation, the development of treatments for sickle cell disease, the development of

somatic gene therapy for β chain hemoglobinopathies (together with Dr. Lila Yannaki in Thessaloniki), the identification and delineation of regulatory elements of the human genome (together with his son, John Stamatoyannopoulos, who is also an eminent scientist), and the investigation of molecular genetics of Bronze Age populations inhabiting the Aegean basin in Greece and in the Balkans. George has been the recipient of several prestigious honors and awards, the latest being this very Festschrift.

I first met George at an ASGCT congress in Washington DC that I attended with my wife Nadia, a nonscientist. We were both impressed by two things: his vast and equally extensive and deep scientific and nonscientific knowledge (including history and philosophy), and his devotion of time and limitless encouragement and mentorship to the younger generation. When I finished my talk in 2014 at another conference held in Patras, Greece (where his earth-shattering data were preceded by a real earthquake!), I still remember George congratulating me (to his long-time friend and colleague at the University of Washington, Professor Thalia Papayianopoulou) with the line, "The kid is progressing well." I am proud to be one of many of George's "scientific kids" and delighted and honored to have met him in my "scientific migrant" life. I will always keep him in the highest esteem! For all of us "relatively speaking" younger scientists/members of the gene/cell therapy societies, I think Professor George Stamatoyannopoulos is rightfully acknowledged as the scientific godfather of the gene and cell therapy field for Greek (and other) scientists.

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GEORGE STAMATOYANNOPOULOS AND THE PREVENTION OF THALASSEMIA: THE EXPERIENCE OF CYPRUS

The concept of the possible prevention of thalassemia was first put forward by Ida Bianco and Enzo Silvestroni in 1955 when they suggested to Italian health authorities the establishment of a center for

the study of “microcytemia,” which would include free medical care for patients and the establishment of large-scale screening and preventive counseling programs. This suggestion required investigation on the social, legal, and cultural level if it was to become a practical policy for the limitation of new affected births. Prenatal diagnosis was not an option in those days, so the result of screening and counseling could only be avoidance of marriage between carriers. This would predictably meet with resistance even by at-risk couples, and the people had to be asked whether such a program would be acceptable. Such an enquiry was not undertaken until the 1960s when George Stamatoyannopoulos stepped in.

He chose a village in Greece in the Arta region, known to have a high carrier rate for beta thalassemia, where he first went to screen the population and to counsel them concerning the risk of marriage between carriers. He suggested avoidance of such marriages and returned a year later to see the result. He noted that there was no marriage avoidance on the basis of genetic risk. These results were published in 1974 in *Excerpta Medica*.

His next stop was Cyprus in 1972, another high prevalence area. In the early 1970s, the treatment of thalassemia was accepted to be regular blood transfusion and iron chelation using desferrioxamine. The dose of the drug was not well defined, and the government was providing 12 (500 mg) vials per month to each patient. It was however known that many patients and doctors were using increasing doses, and that demands on hospital admissions and blood donations were increasing dramatically. The Ministry of Health requested a World Health Organization (WHO) consultancy and George Stamatoyannopoulos was selected. By this time, WHO expert groups were also suggesting screening of couples to identify carriers and prenatal diagnosis, “provided they are willing to have the affected pregnancy termination.”¹⁷ The results of his consultancy were presented and adopted by the Ministry immediately. A summary was published in the *British Medical Journal*.¹⁸ In his discussion he states: “This small Mediterranean nation is thus burdened with one of the highest frequencies of thalassaemia genes in man. The local public health service has to face the problems of a severe disease whose management is completely inadequate, whose cure is not in sight, and whose prenatal diagnosis is unavailable.”

The actions taken in Cyprus following his report are well known, have resulted in the minimization of new births, and as a result existing patients were given the best possible resources to survive. If there was no prevention, the increasing number of pa-

tients would have had little chance, even for an adequate supply of blood.

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THE BRILLIANT GEORGE STAMATOYANNOPOULOS

Writing about Dr. George Stamatoyannopoulos is quite a challenge—what at first glance may appear as hyperbole is none other than an accurate reflection of an enormous personality and an equally enormous body of work.

George was already internationally known in the early 1960s when he moved from Greece to Seattle, where he pursued a brilliant academic career as professor of medicine, pathology, and genome sciences and director of the Markey Molecular Medicine Center at the University of Washington, producing more than 400 original publications. His research led to the discovery and understanding of the molecular mechanisms of red blood cell production during human ontogeny and made an essential contribution toward the elucidation of the genetic basis of thalassemia and hemoglobinopathies at large. He has been a pioneer worldwide in the ever-growing field of gene therapy; his unique vision was instrumental for the development and implementation of innovative approaches for preclinical models of gene therapy and the establishment of the American Society of Gene Therapy, where he became the first president.

George is a father figure to his team members, whom he inspires for the best. He has a strong personality and rare human qualities. He is a born leader and a true visionary with a capacity to transform his ideas to plans and actions, an original thinker, impressively effective, demanding with both himself and his colleagues, and a rationalist who is also rich in emotions, always eager to assist and offer. George is especially fond of the younger generation and has never forgotten his roots.

Dr. Stamatoyannopoulos is a legend for the members of the Hellenic Society of Gene Therapy and Regenerative Medicine (HSGTRM), the members of the Hellenic Society of Haematology, and the Greek patients with thalassemia. Many members of both societies, including three of seven board members of the HSGTRM (Drs. Anagnou,

Vasilopoulos, and Yannaki), have had the privilege to be trained by George in his department, but perhaps more importantly, received his mentorship throughout their professional life.

The Hellenic Society of Gene Therapy and Regenerative Medicine is organizing its inaugural meeting, including an International Symposium on the Advances of Gene Therapy, in Thessaloniki, Greece on September 23–24, 2016. Dr. Stamatoyannopoulos is the president of the Scientific Committee and is working enthusiastically toward preparing an outstanding program.

On a personal note, George is my mentor, especially in matters of organizing and developing new units and scientific events, a valuable advisor and friend. Among other things, he guided me through the establishment and operation of the Gene and Cell Therapy Centre at the George Papanicolaou Hospital in Thessaloniki, he trained our scientific personnel in his department, and is continuously collaborating with us in pioneering studies on gene therapy of thalassemia and beyond.

Overall, I sincerely believe that the terms charismatic and outstanding are apt for his personality and achievements. George, on behalf of the Hellenic Society of Gene Therapy and Regenerative Medicine, may you live long and share with us your many gifts!

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AN INSPIRATION

Dr. Stamatoyannopoulos is a long-term collaborator with the Gene and Cell Therapy Center (Dr. Yannaki's lab) of the George Papanicolaou Hospital in Thessaloniki, Greece, with which I am affiliated. I've known Dr. Stamatoyannopoulos since 2005, when I started working at the Center. In 2006, I was blessed to receive a year's training in gene therapy techniques in his laboratory in Seattle and work under his direct supervision. I still remember his warm welcome and his effort to encourage every small scientific step I was taking forward. Although I was only a BSc holder at the time, he showed a remarkable trust in my research capabilities that further awakened my interest in gene therapy. Until now, he remains a close mentor

and strong supporter of the research we are conducting in Dr. Yannaki's lab. Importantly, despite his outstanding scientific contributions, beyond any doubt Dr. Stamatoyannopoulos remains very humane and kind. In short, I dare to regard Dr. Stamatoyannopoulos as my continuous source of inspiration, and I am proud to be one of the many Greek researchers who were given the chance to meet and work with him.

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GEORGE STAMATOYANNOPOULOS: THE MENTOR, THE FATHER, AND THE PROUD GREEK

The mentor. I have been blessed to have George Stamatoyannopoulos as a mentor for the past 18 years. My encounter with Dr. Stam had an outsized impact on the path my career and my life took after I met him in 1998, early after obtaining my Greek board certification in hematology. I have had the considerable privilege of being supervised by him during my first steps in gene therapy and closely interacting with his personal authenticity, passionate commitment to research, and selfless work ethic. At that time, I had also the privilege to witness some of his legendary verbal fights over scientific matters with Thalia, his loveliest and toughest competitor ever, that were generating a unique learning atmosphere in the lab. Upon my return to Greece, George has been instrumental in helping me to set up a gene and cell therapy program at the G. Papanicolaou Hospital in Thessaloniki, and since then, a long-standing collaboration between the two institutions has been established, translated in two clinical trials and studies on the optimization of mobilization and graft sources for thalassemia gene therapy. Our mentor–mentee interaction continues up to now, and I often seek his advice on critical scientific questions or dilemmas. I am and I will be eternally grateful for his mentorship!

Among diseases, thalassemia syndromes have always been his scientific passion and life-long challenge. He likes to narrate how enthusiastically and with true devotion in the late 1950s, he, a young doctor during his military service, used to fill a small wooden chest (*kaselaki* in Greek) and visit by bus or on foot, in some instances, remote

mountainous and difficult-to-access villages in the Greek mainland and islands in order to take blood samples and study families with hereditary traits. At those times, he managed, with as little as a *kaselaki* but with extreme motivation and deep thinking, to pioneer the population genetics of red cell enzymopathies and hemoglobinopathies.

What is not a very well-known aspect of his personality is his inexhaustible love of history and collection of invaluable rare editions of ancient historical books. In order to combine his childhood dream of becoming a historian with his passionate curiosity, he is currently investigating the genetics of the Bronze Age population of Minoans and Mycenaeans and the genetics of the populations of Greece and the Balkan peninsula. To pursue this goal, in his 80s and more than 50 years after his first campaigns in the Greek countryside, he, himself, visited rural Greece once more from one side to the other.

The father. George has been a father figure in my life, offering guidance the times I felt lost and overwhelmed and teaching me lessons that impacted my life. In times of tragedy, his wise words and paradigms retrieved from Greek legends and history have softened the soul pain and created meaning.

The proud Greek. George, although being a world citizen for more than 50 years, never forgot his Greek origin and the unique history and legacy of his staggeringly beautiful mother country. He is emotionally suffering for the proud, but powerless, Greece these last years that Greece has been hurting under austerity.

Now in his eighties, George keeps scientifically active and motivated like when I first met him. I can see that he is still carrying his *kaselaki* of his first youth with the research passion and the endeavor to pursue it to the best of his ability and above all obstacles. He is an inspired and inspiring academic leader and a real intellectual whose scientific productivity and intellectual vigor advances with his aging, as a natural consequence. In his words, "The career of the real intellectuals never reaches a sunset. It simply ends abruptly with their death."

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A TRIBUTE TO GEORGE

I sat outside a conference room at the American Society of Hematology meeting and was greeted by George. In a Greek accent, "Zon, how are those fish doing?" I told him that the mutants we had were great, but it will be very difficult to clone the genes. "Zon, the only way you will ever get this done is if Harold Varmus (the NIH director) wants a zebrafish genome project." I knew this was a brilliant idea, and the next day, I called Harold and asked for his advice. He thought it was a great idea, and that started the Trans-NIH Zebrafish Genome Initiative. Without George, there would be no zebrafish genome project.

When I started the International Society for Stem Cell Research (ISSCR), I called one person, George. Given what he did for the Gene Therapy Society, he would have the right advice. I was so excited when he showed up at the ISSCR meetings. He has always been so supportive.

These stories illustrate how far-reaching George's contributions to society have been. Thanks, George, for being you!!

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PROFESSOR STAMATOYANNOPOULOS AND CYPRUS

When George Stamatoyannopoulos first cast his scientific eye over the island of Cyprus, most authors of this short praise had not even been conceived. The resulting study, published in 1973, truly put "thalassemia in Cyprus," both alpha and beta, on the map, establishing our small country as exceptionally afflicted by the disease and, at the same time, as a potential role model for its control and management.

Much has changed since, facilitated by fundamental insights into the hemoglobin switching gained, animal models developed, and scientific attention focused on thalassemia by the now eminent Professor Stam. Cyprus has the most effective

thalassemia control program worldwide, keeping annual births of thalasseemics below 5% of the expected birth rate. Mandatory premarital testing, prenatal molecular diagnosis, preimplantation genetic diagnosis, and, soon, noninvasive prenatal diagnosis contribute to giving at-risk couples a choice of whether or not to carry an affected pregnancy to term. Disease management, helped by the dedicated national Thalassemia Centre and by improvements in iron chelation and blood supply and safety, has enabled patients to live ever longer, ever fuller lives, with birth rates from thalasseemic women even surpassing those in the population at large. The high carrier rate is still there, but the stigma, as thalassemia is still called in local everyday language, has lost its sting. In answer to a quizzical note posed by George and his coauthors, some 40 years later we can confidently say that “prospective genetic counseling applied at the level of populations has beneficial effects” indeed.

George and his immediate associates (or, should we say, disciples) continue to be productive collaborators and coauthors in local and international projects, be it in the chemical induction of γ -globin as a drug therapy for β -globinopathies, in the application of lentiviral gene therapy for β -thalassemia, or by the inclusion of Cypriots in George's effort to map the distribution of Hellenic DNA around the globe. George continues to look forward, and we keep looking forward to his next visit to Cyprus!

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