A virus changed my life

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ABSTRACT **The E. E. Just Award commemorates the great African-American cell biologist Dr. Ernest Everett Just, who was a successful pioneer in an era of systemic exclusion of minorities in science and academia. Receiving this award is not only an honor but a recognition of my long-standing commitment to helping Persons Excluded due to Ethnicity or Race (PEERS) to achieve success in biomedical careers. As a proud member of this group, I have devoted most of my career to training underrepresented undergraduate and graduate students to pursue scientific careers. My early work as a molecular immunologist focused on the search for enzymes involved in antigen–receptor gene recombination, as well as the characterization of nuclear factors involved in recombination and the transcriptional regulation of the murine recombination-activating genes. Over the past two decades, my research has focused on discovering and evaluating novel anticancer agents that can be used to treat various cancer types.**

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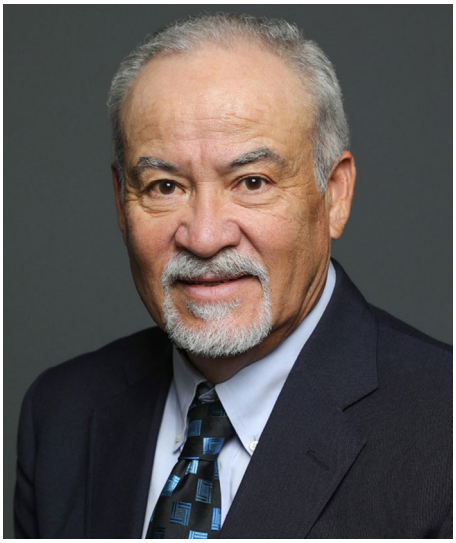
BINATIONAL BEGINNINGS

Both my mother and I were born in the border town of El Paso, Texas, a few miles from the Rio Grande, which separates the United States from Mexico. My mother married a Mexican national who was a judge and could not live in the United States, which required my parents to live across the border. Although I spent most of my early years in Mexican schools, I decided to enroll as a sophomore in a U. S. high school. My grades suffered the first year because I had to learn how to speak and write in English from scratch. However, I overcame these difficulties and finished my senior year with honors in English, one of my proudest accomplishments. At the time, Jacques Cousteau was famous for his documentary series "The Undersea World of Jacques Cousteau." I was so captivated by the series that I wanted to become a marine biologist and enrolled at the University of Texas at El Paso (UTEP) as a biology major. My father was disappointed with my academic plans and threatened to cut me off financially unless I enrolled in a worthwhile major. I told him that I would find a way to pay for my career, and that is what I did. Fortunately, I found the way to pay for school by obtaining training grants and fellowships that cleared the path to my career.



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WAS IT LUCK OR DESTINY?

The summer after my sophomore year at UTEP, I found an advertisement for summer research positions funded by the National Institutes of Health (NIH) Minority Biomedical Research Support (MBRS) program. I applied and was offered a position in Dr. Eppie Rael's laboratory, the only Hispanic biology faculty member at UTEP. His research involved using rattlesnake venom to search for novel enzymes, and he also taught the undergraduate immunology course. While

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Abbreviations used: BS, Bachelor of Science; GFP, green fluorescent protein; H2B, Histone 2B; MARC, maximizing access to research careers; MBRS, minority biomedical research support; MS, Master of Science; NIH, National Institutes of Health; PEERS, persons excluded due to ethnicity or race; RISE, Research Initiative for Student Enhancement; SACNAS, Society for the Advancement of Chicanos/Hispanics and Native Americans in Science Tex-Mex, Texan-Mexican; UCB, University of California at Berkely; UCLA, University of California at Los Angeles; UCSD, University of California at San Diego; UTEP, University of Texas at El Paso.

FIGURE 1: Connecting with two good Tex–Mex friends, Frank Talamantes (middle) and Eloy Rodrigues (right), at a 2005 national conference.

taking his course, I was amazed how little we knew about the immune system. I fell in love with the topic and decided I would become an immunologist. While pursuing an MS degree with Dr. Rael, I applied for a National Science Foundation predoctoral fellowship with the hope of obtaining a PhD and was lucky enough to get one. At the time, Texas was not a very inviting place to get an education, so I applied to only two California schools, UC San Diego (UCSD) and UC Berkeley (UCB). I received a quick acceptance from UCSD, and I was about to accept the offer when I received a call from Olivia Martinez, a graduate student at UCB. Olivia told me that the UCB admissions committee really wanted me to join them in their Immunology PhD program. Olivia, now a Stanford University professor, not only was responsible for recruiting me to UCB but also helped me survive my first semester.

THE CLONING WARS

In 1982, I joined a molecular immunology group at UCB because I wanted to learn how to clone genes and study their function. I joined the lab of Dr. Hitoshi Sakano, who had been a key player in the laboratory of Nobel Prize winner Dr. Susumu Tonegawa in the cloning of antibody genes. I became an excellent "Gene Jockey," and my first manuscript described the cloning and characterization of abnormal gene recombination events in B-cell tumors (Aguilera *et al.*, 1985). I also discovered a nuclease activity in myeloma cell extracts that cleaved the G-rich motifs required for immunoglobulin class switching recombination (Aguilera *et al.*, 1985). After obtaining my PhD, I received a UC President's Postdoctoral Fellowship under Dr. Sakano and was later appointed to my first faculty position at the University of California, Los Angeles (UCLA). My lab purified the nuclease that I had discovered as a graduate student, and we eventually obtained several peptide sequences that led to the cloning of the nuclease gene and resulted in my first patent (Lyon *et al.*, 1996, 2000; Lyon and Aguilera, 1997). We subsequently cloned the nuclease gene from several organisms and obtained active recombinant protein, which allowed us to determine its protein structure in 2017 (Evans *et al.*, 2002; Evans and Aguilera, 2003; Varela-Ramirez *et al.*, 2017). Interestingly, knockdown of this enzyme in *Drosophila* resulted in impaired immune function, which led to the discovery of another nuclease, which we named stress-induced DNase (SID) since it is activated by infection and chemical stress (Seong *et al.*, 2006, 2014).

THE VIRUS THAT CHANGED MY LIFE

In my mid-40s, I contracted chickenpox and felt that I was going to die. This event made me rethink my career, and I decided to move back home and close to family. By serendipity, my former BS and MS mentor (Dr. Rael) had become chair of the UTEP Biology Department and invited me to come back to help him reshape the department and bring in NIH training grants. At the time, I was the Program Director of the Maximizing Access to Research Careers (MARC) program at UCLA and had significant experience in writing these types of grants. In 2002, I moved to UTEP to become a full professor and director of the biological sciences graduate program. Soon after my arrival, I obtained funding for the NIH MBRS Research Initiative for Student Enhancement (RISE) program, which has been continuously funded since 2004 and has trained more than 300 minority undergraduates and 53 PhD students. Although this grant mechanism ended in 2022, we recently obtained funding to continue these programs under new U-RISE (T34) and G-RISE (T32) grants. I am proud to say that after 20 years, we increased the UTEP biology PhD program from 10 to more than 100 PhD students, with the majority being of Hispanic origin. During my career, my laboratory has trained 51 undergraduates (75% minority), of which 21 completed PhDs (plus nine in progress) and nine are currently in faculty positions. In addition, I have mentored/trained 14 PhD and seven MS students, with six in faculty positions and the majority belonging to minority groups. Mentoring and training students has brought me joy over the years and is one of the things I will miss most when I retire.

HENRIETTA LACKS' (HELA) CELLS AND MY SCIENTIFIC RENAISSANCE

In 2004, I was asked by a UTEP chemistry faculty member whether I knew of a simple way to screen thousands of compounds for anticancer activity, and my dismissive response was that I had no idea. That night, I awoke with an answer by using a human cancer cell line that I had acquired years earlier. The cell line was HeLa H2B-GFP, which allows the detection of live cell nuclei using simple fluorescence microscopy (Kanda *et al.*, 1998). Using these cells, we could screen for the loss of GFP signal once cell nuclei were fragmented during cell death (Montoya *et al.*, 2004; Aguilera *et al.*, 2006). This simple assay led to the development of a screening assay that allowed us to detect cytotoxic agents on a wide variety of cancer cell lines (Aguilera *et al.*, 2006; Lema *et al.*, 2011). As director of our Cellular Characterization Core and Biorepository facility of the Border Biomedical Research Center, which is funded by Research Centers at Minority Institutions, I was able to build a "state-of-the-art" drug-screening facility to continue searching for anticancer agents. Using this facility, we discovered several novel compounds with potent activity against a variety of cancer cell lines (Santiago-Vazquez *et al.*, 2014; Gutierrez *et al.*, 2019, 2022). Our group also determined that a known antimalarial drug has potent anticancer activity and is a topoisomerase II inhibitor (Villanueva *et al.*, 2018, 2021).

This discovery led to several international patents and the creation of a local biotechnology company that has initiated clinical trials in Africa, where the drug is approved for use against malaria.

FINDING MENTORS AND FRIENDS

It was not easy finding mentors along my career. I sought out mentors who had a similar upbringing and were successful in their academic careers. However, it was easier to find friends than mentors, and I was fortunate to make long-lasting friendships with three Tex–Mex faculty members who were also UC faculty. Two of these friends/mentors, Dr. Frank Talamantes (1943–2018) and Dr. Eloy Rodriguez, were also E. E. Just awardees, and both devoted a significant part of their careers to increasing minority representation in biomedical fields (see Figure 1). I met them as an undergraduate while attending my first Society for the Advancement of Chicanos/Hispanics and Native Americans in Science (SACNAS) meeting, and we worked alongside other long-time members to make SACNAS the successful organization it is today. My other friend, Dr. Elma Gonzalez, was a professor at UCLA and recruited me to that campus as a faculty member. Elma and I worked together for many years as codirectors of the very successful MARC training program at UCLA. I am indebted to these and other great friends and mentors for their support over my academic career. I should mention that I am very proud of my daughters, Kristina and Elizabeth Aguilera, who also hold PhDs in biomedical fields and have found success in their careers. I would like to finish by saying that we owe it to our students/trainees to be better mentors and encourage them to continue toward a productive academic/research career.

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