
LEGENDS IN UROLOGY

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I would like to express humble gratitude to the Legends in Urology Section of *The Canadian Journal of Urology* for allowing me, a basic and translational scientist, to share my scientific journey over time that has allowed me to improve the outcomes for prostate cancer patients, globally. The moniker legend seems inappropriate for a person who stands on the shoulders of so many talented physicians and scientists for my own achievements; however, it is highly flattering to be included in this very esteemed group of former recipients.

The Early Years

Born in St. Louis, I was privileged to have a wonderful public school experience, which launched my curiosity and passion for mathematics, biology, chemistry and physics. My elder second cousin, Samuel D. Soule, MD, a legend of OBGYN at Washington University, not only gave birth to me and my brother Edward but also unsuccessfully recruited me to medical school! I chose graduate school. We lost our mother soon after high school graduation, which caused me to learn fast how to be self-sufficient. In fact, the summer job between each undergraduate year with the largest global veterinary pharmaceutical and biologics company, Norden Laboratories, taught me the elements of infectious diseases. In search of graduate schools with renowned programs in microbiology and immunology, I was drawn to Baylor College of Medicine. At the time, this institution had the largest and most diverse molecular virology program on earth. I spent the next 4 years in Houston learning about the wonders of human viruses of all shapes, sizes and nucleic acid as well as epidemiology and infection control. Intense is an understatement. Dr. Janet Butel, the discoverer of the SV40 T antigen became my first amazing mentor. Dr. Butel taught her students how to think, reason and solve dauntingly complex problems – especially on our feet. Without a doubt, and with tremendous gratitude for Dr. Butel – I have carried these acquired skills throughout my career.

The Formative Years – From Houston to La Jolla

My research fellowship at Scripps Clinic under the mentorship of molecular pathologist Thomas Edgington, MD, began my growth and appreciation for the diversity of human diseases that are diagnosed under a microscope. This fellowship prepared me for two jobs in industry. The first was an infectious disease diagnostic company that honed analytical skills. The second, that I am very proud of, was Corvas International. As the first scientist hired into this startup, we translated laboratory findings into clinical therapies for diverse cardiovascular unmet medical needs. Learning how to interact and collaborate with elite academic clinical and scientific investigators as well as working with industry and investors was an invaluable experience.

The Prostate Cancer Foundation Experience

In 1997 I received a call from Michael Milken about a position at what was then called CaP CURE. This led to a visit to his offices where I experienced his power of nature. His vision of curing prostate cancer by funding research was clear and laser-focused. In a word, I was “seduced” into becoming the first Chief Science Officer of the Prostate Cancer Foundation. Mike Milken is a philanthropist and very successful financier. His major success was the democratization of capital for people with innovative business ideas. When diagnosed in 1993 with prostate cancer, he applied his business brilliance to find a solution to his health problem which he knew would benefit so many men and their families. But this was not the beginning of his medical research philanthropy. In the past Mike had already funded Bert Vogelstein’s, cancer genetics research at Johns Hopkins University, Dennis Slamon’s

research on HER2/neu in breast cancer that led to trastuzumab and Larry Einhorn's research that led to successful medical therapy for testis cancer. Mike recognized the brilliance in these three-early career physician-scientists, and many others – a fact that he propagates throughout his brilliant philanthropic career.

The organization was still in its first incarnation having been well led by my mentor, friend and urologist extraordinaire Dr. Stuart Holden. Dr. Holden patiently taught me the major unmet medical needs of advanced prostate cancer patients and in 1997 there were many. At that time, the Foundation was directing a large genetics program, a clinical trials consortium, and was funding small, individual investigator research awards. In retrospect, the brilliance of Dr. Holden to initiate these programs jump started a moribund field. We attracted the best and the brightest and initiated patient-centric programs to move basic science into the clinic.

In 2007, the Foundation hired Jonathan W. Simons, MD as CEO. For me, this transition in leadership was an epiphany. Having known Dr. Simons for many years as a world-class physician-scientist scholar, his leadership transformed the Foundation and allowed me to practice science at the highest level of significance. Put simply, our fingerprints are on every FDA-approved treatment for advanced prostate cancer. Our early funding was critical. For example, seeding many chemotherapy projects in our therapy consortium led to the finding that prostate cancer is sensitive to taxane chemotherapy. Our early support of survivorship studies on the adverse effects of androgen deprivation therapy led to the finding that bisphosphonates protected against skeletal-related events. This led to the development of zoledronic acid and RANK ligand medications. More recently, and of great pride, was funding of studies showing that abiraterone acetate is an intracrine androgen antagonist and that androgen receptor is amplified and mutated in castration-resistant disease which led to the synthesis and development of enzalutamide. The use of abiraterone and enzalutamide earlier in potentially lethal prostate cancer is now known to extend life and delay the onset of medically complex metastatic disease.

One of the great joys is the annual selection of Prostate Cancer Foundation Young Investigators. This highly talented cohort of physicians and scientists represents the next generation of hope for patients. Its more than just money – we support their careers with workshops, mentoring, career guidance and give the great visibility in the research and donor communities. At times I feel like a shepherd of sorts for many of these fine young people.

More recently, in collaboration with Stand Up 2 Cancer and AACR, we funded two Prostate Cancer Dream Teams. These Dream Teams were selected in a brutally competitive manner and were multi-institutional. The International Dream Team included University of Michigan, Memorial Sloan Kettering Cancer Center, Dana-Farber Cancer Institute, University of Washington and was led by Drs. Arul Chinnaiyan and Charles Sawyers. The West Coast Dream Team brought together University of California-Los Angeles, University of California-San Francisco, Oregon Health and Science University and the University of British Columbia with leadership from Drs. Small and Witte. The landscape of genomic alterations published by the International Dream Team was a benchmark milestone in the field and revealed genomic findings that will lead to the next generation of therapeutic targets for lethal prostate cancer. In the near term, discovery of unanticipated high incidence of DNA repair genes led to the rapid development of PARP inhibitors, a new class of life-prolonging medication for advanced prostate cancer. The West Coast Dream Team is focusing on genomic alterations responsible for treatment resistance. In the near term this team has discovered mechanism(s) of resistance to PARP inhibitors, the newest class of medication for advanced prostate cancer in registrational trials, globally.

The role of research to improve outcomes for cancer patients is accelerating at an unprecedented rate and is enabled by cancer genomics and improved imaging and diagnostics. Research achievements enrich a person's professional life and takes them out of their silo. The surgeon-scientist in 2017 and beyond has opportunity and responsibility to engage in research for the betterment of their patients. After decades of over-diagnosis and overtreatment, urologists have at their side multiparametric MR to better diagnose and target biopsies in primary prostate cancer as well as emerging PET imaging protocols that will more accurately stage patients. Although both methods are being used generally, the true performance characteristics are not well calibrated. In fact, images generated outside of institutes of great excellence are often inaccurate and potentially misleading and degrade care. It's the responsibility and opportunity especially for young surgeon-scientists to perform research that will standardize these methods, and others, which in turn has the potential to greatly improve outcomes for your patients by directing

appropriate therapy – not too much and not too little! Surgeon-scientists also can play a powerful research role in medical interventions for primary metastatic prostate cancer. With the migration of oral medications to earlier and earlier prostate cancer, this new class of emerging cohort will first present in your clinic. There is great value to partnering with medical oncologists for the management of these patients – but you see them first and have a responsibility to their best management. Research! Research! Research!

Finally, I am extremely proud of the Annual PCF Scientific Retreat. This invitation-only meeting combines the best and brightest minds from academia, pharmaceutical industry, government and non-pharma industry in a very interactive forum. Physicians and scientists with interests in urology, medical oncology, pathology, radiation oncology, nuclear medicine, radiology, survivorship, bioinformaticians, biology, immunology, cell biology, pharmacology, genomic/genetic science, mathematics – from within and outside the prostate cancer community – all attend and contribute. Many consider this the top prostate cancer meeting in the world. From my prospective, the goal is to expose attendees to problems and concepts that they simply could not hear anywhere else in the world. The number of collaborations that are sparked at this meeting are innumerable. The diversity of the attendees causes increased creative thought in all. We call this the ultimate knowledge exchange and indeed the Retreat represents an annual opportunity to advance research and to set a challenging funding strategy for the Foundation.

All said and considered, I believe my greatest achievement is convening and socializing the field of prostate cancer research. After all, without the people we have nothing. Bringing together diverse people to solve major problems has become my most treasured area of expertise. Creating a community where people feel safe and are motivated to present unpublished data is a privilege. And promoting the careers and work of others without expectation of personal gain brings the biggest smile to my face. It is all about results and progress for patients. The human capital we have aggregated is powerful and I believe unprecedented driver of longer and better lives for all prostate cancer patients.

While I am personally and exceptionally proud of the accomplishments of the Prostate Cancer Foundation team, we all stand on the shoulders of Mike Milken who has guided, motivated and given so much of his own time and treasure to the effort – tirelessly and without compromise. I am thankful to Mike for granting me the opportunity and resources to impact research for patients for two decades but the work is not finished. We do not intend to rest until all men with advanced prostate cancer survive and thrive.

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