A Quarter Century of Lifesaving Discoveries in Prostate Cancer

Pacific Northwest Prostate Cancer SPORE insights have not only transformed patient care and understanding of prostate cancer biology but also supported drug discovery worldwide.

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Today, a patient diagnosed with advanced prostate cancer has options. Doctors can offer a suite of androgen-suppressing drugs to extend his life. There are genetic tests that can show whether he's a candidate for more-targeted treatments. These tests can also reveal whether his family members are at higher risk for prostate and other types of cancer. This was not always the case.

And many of these breakthroughs have been made possible by 25 years of transformative prostate research performed by scientists in the Pacific Northwest Prostate Cancer Specialized Program of Research Excellence. The National Cancer Institute created the SPORE program to strengthen ties between bench and bedside and hasten the flow of breakthroughs and insights between them.

"Twenty-five years of continued funding is a testament to the consistently excellent science conducted by PNW Prostate Cancer SPORE researchers," said Fred Hutch Cancer Center prostate cancer expert Peter Nelson, MD, who heads the PNW Prostate Cancer SPORE. "Our scientists have made practice-changing breakthroughs and widened the scope of treatment and screening options available to prostate cancer patients."

Headquartered at Fred Hutch, the PNW Prostate Cancer SPORE brings together forward-thinking prostate cancer researchers at Fred Hutch, the University of Washington, Oregon Health & Science University and the University of British Columbia. In late 2023, the international team garnered a fifth renewal, guaranteeing 30 years of continuous funding for innovative prostate cancer research.

Over that quarter century, SPORE science has untangled important prostate tumor biology, helped fuel the development of more powerful drugs, improved screening and brought precision oncology to prostate cancer.

To ensure an even better future for prostate cancer patients, the fifth round of SPORE projects builds on these successes and tackles new challenges.

“The latest round of funding will allow us to bring new precision oncology approaches and immunotherapy to the patients who need it most,” said Nelson, who holds the Stuart and Molly Sloan Precision Oncology Institute Endowed Chair and directs the Stuart and Molly Sloan Precision Oncology Institute.

SPORE: focusing on translation

When the National Cancer Institute initiated SPORE awards in 1992, the program signaled a new approach to cancer research.

“There was recognition that there was a lot of basic research and a lot of clinical research being done, but that those domains weren’t really talking to each other,” Nelson said. “Basic discoveries still took a long time to get it into the clinic. And if somebody made a clinical observation that seemed very interesting, it took a long time to then understand it mechanistically.”

The PNW Prostate Cancer SPORE is one of eight prostate cancer SPORE centers in the U.S. Each SPORE focuses on a particular tumor type and each includes three to five research projects with high translational potential. SPORE awards also support the construction and maintenance of the not-so-flashy but all-important scientific infrastructure — like administration, tissue banks and analytical cores — that make breakthroughs possible.

SPORE grants also include funding opportunities for early-career researchers, helping innovative investigators lay a strong foundation for future translational breakthroughs.

The PNW Prostate Cancer SPORE also includes a panel of patient advocates who help educate cancer patients about the current horizons in cancer research and help cancer researchers better understand patient needs.

“It became very important to recognize the patient voice in the research process,” said Nelson, who has always blended prostate cancer-focused research with care of prostate cancer patients.

Patient advocates can weigh in on research questions and directions and help educate other patients about the state of prostate cancer research.

“One of my passions is making sure patients and patient advocates are appropriately involved in decision-making. For patients, that’s in terms of decisions about their own treatment. For patient advocates, that’s about research priorities and practices,” said Marty Chakoian, a prostate cancer survivor who heads the PNW Prostate Cancer SPORE patient advocate committee. “I’m really grateful to Pete Nelson and the whole SPORE team for how they have included us.”

Chakoian, who also leads a Seattle-area support group, is enthusiastic about working with his patient advocate colleagues.

“I wouldn’t wish prostate cancer on anyone,” he says, “but mine has introduced me to some pretty

wonderful people.”

He and fellow PNW Prostate Cancer SPORE patient advocates meet bi-monthly to learn about (and weigh in on) SPORE projects and their progress.

“Even if a particular project doesn’t apply to me personally, I’m glad to know there are smart researchers working really hard to move treatments forward,” Chakoian said.

This includes early-career investigators who are laying the foundation of their research careers. By offering funding for new prostate cancer researchers and novel pilot projects, SPORE grants help build cancer research’s next generation of scientists.

This allows the SPORE to support more than its official four projects, and allows research to grow in creative new directions.

“The SPORE keeps breeding more science,” said Fred Hutch and UW medical oncologist Jessica Hawley, MD, MS.

Once an institution secures a SPORE, it can’t rest on its laurels: Every five years, a SPORE must report impressive progress to secure the next five years of funding. Only projects that make progress toward the clinic get carried forward; those that don’t pan out are replaced by promising new ideas.

PNW Prostate Cancer SPORE

Only SPORE centers with a consistent track record of excellence get renewed. The PNW Prostate Cancer SPORE has been continuously funded since its inception in 1999.

“At that point in time, there probably wasn’t a single therapy shown to help men [with advanced prostate cancer] live longer, other than testosterone suppression,” Nelson said. “That was the standard of care — and still is — for more than 70 years. But other than that, there were no life-prolonging treatments [for metastatic cancer]. So it was a pretty desperate time.”

On top of this, advanced tumors can evolve ways to resist treatments that lower androgens, requiring new approaches to halt prostate cancer growth. These are termed metastatic, “castration-resistant” prostate tumors.

To improve prognosis, understand treatment resistance and develop new therapies, scientists needed a deeper understanding of prostate cancer biology. The first SPORE projects focused on identifying the molecules that influenced the risk of developing prostate cancer, drove prostate cancer progression, shaped its responses to treatment and distinguished different prostate cancer subtypes.

“The success of the PNW Prostate Cancer SPORE is due in a large part to the vision of the original

principal investigators," Nelson said.

UW urologist Paul Lange, MD, now Chair Emeritus of UW's Department of Urology, and Fred Hutch epidemiologist and professor emerita Janet Stanford, PhD, MPH, recognized how important collaboration would be to leverage the different strengths of the research institutions in the Pacific Northwest.

"Thanks to their foundation and foresight, we remain on the leading edge of translationally focused prostate cancer research," Nelson said. "It's more powerful to collaborate: Having the manpower, the resources, and the ideas from many investigators lets you innovate and promote the most impactful research and treatment."

From the beginning, the international team spread a wide scientific net.

"Prostate cancer can be tackled from many perspectives, including prevention, understanding risk, improving screening and developing new therapies," Nelson said. "There's enough expertise in the PNW Prostate Cancer SPORE to cover a very wide swath of research."

Transforming patient care

The deep understanding of prostate cancer biology made possible by the SPORE's international team has changed treatment guidelines. These insights ushered in more targeted treatments and helped oncologists begin to understand how prostate tumors evolve to resist treatment.

In 2016, Nelson and SPORE collaborators Heather Cheng, MD, PhD, and Colin Pritchard, MD, PhD, showed that men with advanced prostate cancer were five times more likely than men in the general population to have inherited mutations in DNA-repair genes like BRCA1 and BRCA2.

The finding was unexpected, but transformative for patients and their families.

It highlighted the role that inherited mutations may play in cancer development and the importance of genetic screening for prostate cancer patients and their family members. A patient's siblings may also have inherited the same mutation, and they may have passed it to their own children. If a man tests positive for such a mutation, his family members have critical information they can use to assess their own risk. If they also test positive, the family members can opt for more aggressive screening strategies designed to catch prostate (and breast, ovarian and pancreatic) cancers early.

To improve genetic screening for men with advanced prostate cancer, Cheng, with UW colleague Bruce Montgomery, MD, initiated the GENTleMEN study (GENetic Testing for MEN with prostate cancer).

"[We set up this study] to remove barriers and improve access [to genetic testing and precision oncology] throughout the state of Washington," Cheng said of the five-year study, which began in

2017.

The study offered men with metastatic prostate cancer an internet-based way to access genetic testing. Participants who tested positive for certain inherited mutations had access to genetic counseling through Fred Hutch and could share their results with their family members and oncologists.

Cheng and the team demonstrated that their approach connected men to important genetic testing, and identified strategies that could help make the approach more feasible for more prostate cancer patients.

By 2020, the National Comprehensive Cancer Network (NCCN) guidelines incorporated new recommendations: that oncologists offer genetic testing to men with metastatic, lymph node-positive, or high-risk localized prostate cancer.

They followed GENTleMEN with the GIFTS (Genetic Information to Inform Treatment and Screening) study. GIFTS drew on Stanford's studies of inherited prostate cancer, and the NCI's Surveillance, Epidemiology, and End Results registry to proactively identify men in Washington state who might benefit from genetic testing.

But their initial results were "sobering," Cheng said.

They found that only 11% of people contacted were receiving the genetic testing recommended by the NCCN. The SPORE team increased that to 44% by mailing men saliva testing kits and a questionnaire about their family history and knowledge of genetics. GIFTS also helped them better understand the barriers to obtaining NCCN-recommended testing.

Such genetic testing can also help improve treatment for men with these mutations.

"This project led us to understand that some prostate cancers are very vulnerable to certain types of drugs that are involved in DNA repair," Nelson said. "The clinical tests that identify which patients would benefit from platinum-based drugs and PARP inhibitors were developed through SPORE-supported research."

Use of these drugs result in DNA damage that cells with defective DNA-repair enzymes can't overcome. The SPORE's findings provided a biological explanation for why some men's tumors responded to these therapies, and made it possible to better identify patients whose tumors are most likely to respond. In 2020, the first PARP inhibitor was approved to treat metastatic prostate cancer that's resistant to androgen-suppressing drugs.

"Another major outcome of PNW Prostate Cancer SPORE research involved contributions to the understanding of androgen metabolism," Nelson said. "Multiple drugs were built on foundational work in understanding the signaling of the androgen receptor."

These include the modern crop of androgen receptor-targeting drugs, like abiraterone and

enzalutamide, that have dramatically extended life expectancy for men with advanced prostate cancer.

Funding from the SPORE also allowed scientists to amass a deep and diverse archive of prostate tumor tissue samples. This biorepository was established by UW Professor Emeritus Robert Vessella, PhD. The resource allowed SPORE team members, including UW urologic oncologist Colm Morrissey, PhD, and UW Professor Emeritus and pathologist Lawrence True, MD, to see how prostate cancer evolves to drug resistant subtypes.

While more powerful androgen-suppressing drugs improve lifespan, they can also push prostate tumors in new directions. Previously rare types of prostate cancer, which can thrive without the androgen receptor, have become more common.

“One of the challenges of treating this treatment-resistant version of prostate cancer that appears is that you don’t know when it’s going to happen,” said Morrissey, who co-directs the SPORE’s Biospecimen and Pathology Core.

The tissue repository that Morrissey oversees contains tumors from men at every stage of prostate cancer as well as after treatment. The Biospecimen Core also made possible a suite of patient-derived xenograft (or PDX) models developed by UW prostate cancer expert Eva Corey, PhD.

In PDX models, bits of human tumor tissue, taken during tumor-removal surgery, are implanted into mice. This helps give scientists a better understanding of how tumors grow and respond to potential treatments under conditions that better approximate their original conditions than a 2D tissue culture dish ever could.

“These are used by investigators around the world to develop insights, in understanding prostate cancer, and in drug development,” Nelson said. “Many of the major drugs that we now use were tested at some stage using these PDX models that are supported by the SPORE.”

In addition to the Biospecimen core, the PNW Prostate SPORE supports a Biostatistics resource led by Fred Hutch biostatistician Ruth Etzioni, PhD, Fred Hutch senior statistical analyst Roman Gulati and Fred Hutch computational biologist Gavin Ha, PhD.

“The rigorous design and analysis of research experiments and clinical trials is essential to ensure that study outcomes are statistically sound and reproducible,” Nelson said.

In addition to providing expertise to all SPORE projects, Etzioni and Ha have developed new methods that have provided insights into optimal prostate cancer screening for black men at highest risk for prostate cancer, and non-invasive approaches for using blood-based assays for determining molecular subtypes of advanced prostate cancer.

Building a better future for prostate cancer patients

PNW Prostate Cancer SPORE investigators remain at the forefront of patient-focused prostate cancer research. Four major research projects and three supporting core resources, which build on prior results to forge innovative new directions, comprise the current five-year renewal.

“Project 1 addresses major challenges and opportunities in cancer prevention and early detection,” Nelson said. “Though prostate cancer can be deadly, a large number of prostate cancers are very slow growing and will never cause a problem. How do you screen people appropriately in a risk-based strategy to identify those cancers that really need to be treated?”

Cheng’s latest project, which builds on the GENTleMEN and GIFTS studies, addresses this need. She and Fred Hutch cancer epidemiologist Burcu Darst, PhD, are co-leading the extension of GIFTS, designed to understand how different categories of mutations work together to influence prostate cancer risk.

“One of the key questions of prostate cancer risk is who will get aggressive disease,” Darst said.

Inherited mutations in genes like BRCA2 strongly influence prostate cancer risk, but they’re relatively rare (about 90% of men with advanced prostate cancer don’t have such a mutation). But there are plenty of common variants scattered throughout our DNA that raise or lower our cancer risk just a tiny bit.

But all of these tiny influences can add up. Scientists can sum up these minuscule risks to get a single number, called a polygenic risk score, that sheds light on a patient’s risk of developing a certain trait. Darst has developed a polygenic risk score that helps predict a patient’s risk of developing prostate cancer. Layering it onto the risk information from rare inherited DNA-repair variants further improves prediction, she said.

“When you combine the polygenic risk score with the rare variants, you get a much better predictor for prostate cancer and aggressive prostate cancer,” Darst said.

And furthering their efforts to improve screening and recommendations for people with known inherited risk factors (but no cancer diagnosis), Cheng and UW Chief of Urological Oncology Dan Lin, MD, continue to lead the PATROL study. PATROL aims to define novel biomarkers for early detection of prostate cancer, including prostate imaging and age-adjusted PSA levels.

“Project 2 addresses another challenge: How can you increase cures of localized prostate cancer?” Nelson said. “We have a project to better identify and understand the molecular subtypes of aggressive localized prostate cancer, and test methods to attack these tumors effectively.”

Led by UBC’s Martin Gleave, MD, and Amina Zoubiedi, PhD, the Genomic Umbrella Neoadjuvant Study aims to understand how prostate tumors shift between subtypes, and how to leverage this to develop treatments that are more effective and more targeted.

“The third major area we’re addressing is, how do you treat very advanced prostate cancer more effectively?” Nelson said.

One project, helmed by Nelson and Fred Hutch oncologist Mike Schweizer, MD, seeks to turn prostate cancer’s strength — the androgen receptor that fuels prostate tumor growth and survival — into a weakness. Excess androgen receptor activity can promote DNA damage; in cells with broken DNA-repair mechanisms, this is a potentially deadly vulnerability.

“We’re taking the novel approach of ‘overdriving’ the androgen receptor as a target in prostate cancer, to augment the DNA damage of chemotherapy,” Nelson said. “We have some specificity to engage DNA-damage response mechanisms to kill these tumor cells.”

SPORE scientists are also working to bring the power of cellular immunotherapy to bear on advanced, treatment-resistant prostate cancer. They will integrate genetically engineered immune cells — a Fred Hutch specialty — with unexpected findings from OHSU PNW Prostate Cancer SPORE member Amy Moran, PhD.

Moran showed that androgens blunt the activity of immune cells called T cells, and that androgen-deprivation therapy helps improve their function. In a new clinical trial, the team is testing whether enzalutamide, a next-gen androgen-suppressing drug, will enhance the activity of T cells engineered to target prostate cancer cells.

The T cells carry a lab-designed molecule called a chimeric antigen receptor, or CAR, that helps them home in on cells with a specific target. John Lee, MD, PhD, a PNW Prostate Cancer SPORE affiliate faculty member who recently moved to the University of California, Los Angeles, developed a CAR against STEAP1, a molecule on many prostate tumor cells.

Though other CAR T cells have been tested — and fizzled — against prostate cancer, SPORE scientists are excited about Lee’s CAR. Buoyed by impressive preclinical results, the anti-STEAP1 CAR entered the NCI Experimental Therapeutics pipeline, which fast-tracks the most promising new cancer therapies. Lee’s strategy enables a long-lasting, self-multiplying type of T cell, called a central memory T cell, to hunt down cancer cells.

“The idea is to create an army of central memory T cells to fight the cancer,” said Hawley, who is Principal Investigator of the clinical trial, in collaboration with Fred Hutch’s Immunotherapy Integrated Research Center, led by immunotherapy expert Lawrence Fong, MD. Positive results from clinical tests of a bi-specific antibody (another type of immunotherapy) against STEAP1 further support their optimism, she said.

Building on decades of success, the PNW Prostate Cancer SPORE team has set its sights on a new horizon in prostate cancer: cure. Prostate cancer has long proved an elusive and tough adversary, but the field is invigorated by new (if cautious) optimism, Nelson said.

“Our longstanding goals have been for men with prostate cancer to live longer and to live better,” he said. “We believe that through understanding risk, improving early detection strategies and

applying new treatment methods, we can achieve cures.”

Sabrina Richards, a staff writer at Fred Hutchinson Cancer Center, has written about scientific research and the environment for The Scientist and OnEarth Magazine. She has a PhD in immunology from the University of Washington, an MA in journalism and an advanced certificate from the Science, Health and Environmental Reporting Program at New York University. Reach her at srichar2@fredhutch.org.

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