2017/2018

THE JOHNS HOPKINS KIMMEL CANCER CENTER

ON TARGET

The Newsmagazine of the Department of Radiation Oncology and Molecular Radiation Sciences

Honoring a Pioneer

The Moody Wharam Professorship

Moody Wharam, M.D.

New Drugs Improve Kill Effect of Radiation Therapy

Cancer cells are crafty—just ask clinician-scientist **Phuoc Tran**. In his current research, he has seen how cancer co-opts an exquisite process of human development to undergo its most lethal transformation. A process that normally directs an embryo to grow from a single cell into a fully developed human being may be the same one used by cancer cells to invade other parts of the body.

"IT IS METASTATIC DISEASE THAT PATIENTS ARE DYING FROM, AND **DECIPHERING EMT COULD BE AN IMPORTANT STEP** TOWARD HELPING THESE PATIENTS."
– PHUOC TRAN. M.D., PH.D.

This cellular guidance program is called EMT, and Tran says a cell undergoing EMT to form an embryo looks exactly the same as a rogue cancer cell as it spreads from its place of origin to a different organ in the body.

"The program isn't bad, but the timing is," explains Tran. The downstream consequences of this bad timing are the most critical event in the timeline of a cancer development, a sentinel event that often distinguishes a curable cancer from an incurable one. It is called metastasis, and it occurs when a cancer migrates to another part of the body. This is the stage that ups the ante because it usually causes cancers to become resistant to treatment.

Stopping or reversing the event is a priority of Tran's. "Local disease is often curable with standard therapies," he says. "It is metastatic disease that patients are dying from, and deciphering EMT could be an important step toward helping these patients."

EMT is a program that should be turned off and filed away after full embryo development. What reactivates it is not completely understood, but Tran suspects it is an ongoing injury to cells, such as chronic inflammation. "Cancer cells select the processes they need to survive. They don't reinvent the wheel. Everything cancer needs is already there," says Tran. "It pulls the programs it needs from our DNA and uses them to its advantage." What's more, there is a natural cellular resistance built in to EMT. It's an important safeguard that allows embryos to grow and survive, but in cancer, this resiliency makes for a resistant cancer. "A spreading cancer is like an astronaut going into space. He has special equipment to adapt and survive in a foreign environment. EMT provides survival gear to cancer cells, allowing them to travel and invade distant parts of the body, and resist external stimuli that would kill normal cells," says Tran.

To prove his theory, Tran is using a uniquely engineered mouse model that allows him to turn genes on and off. By manipulating genes, he is able to make the mice get spontaneous tumors in different organs, creating an animal research model representative of the way humans develop cancers. With this realistic model, Tran can study the role of EMT in many cancer types. By incorporating luciferase, the gene in fireflies that causes their iconic glow, into the model, Tran and team are able to make all of the genes related to EMT glow in the mice.

He has identified a plant-based drug called harmine that directly interferes with the EMT program. Now, he can test the drug in his unique animal model and other laboratory models to see if it can block EMT, and convert resistant cancers to radiation treatment and anticancer drug-responsive cancers.

EMT is not Tran's only focus, however. As a radiation oncologist, he is always searching for new ways to make cancers more sensitive to radiation therapy.

He believes he may have found one in the DDX3 gene. It is common across cancers, and if it is taken away, the cancer cannot survive.

Tran is collaborating with radiology and radiological science researcher **Venu Raman**, whose homegrown drug RK33 targets DDX3 and inhibits cancer cell growth and also their ability to repair DNA damage caused by radiation therapy. Tran is testing the effectiveness of the drug using his engineered mouse model and the Small Animal Radiation Research Platform, invented by radiation physicist John Wong. Early promising data mean the drug may be moving closer to the clinic.

The drug appears to have broad activity, already showing promise in sarcoma and lung, breast, prostate, brain and colon cancers. Tran says the next step is to gain investigational new drug approval from the FDA and funding to move the drug to clinical trials. ■

New Tool Delivers Prostate Cancer Destruction

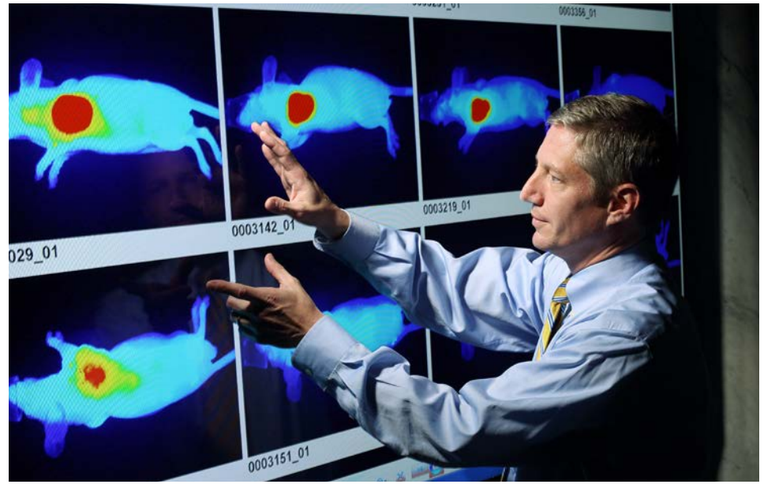
The merging of two discoveries provides a novel way to deliver cell destruction to prostate cancer. At the center of the research are two things familiar only to scientists—aptamers and siRNA.

Aptamers are small molecules that work much like antibodies to target things—like cancer—that don't belong in our bodies. They are really good at binding to other molecules. Prostate cancer expert **Shawn Lupold**, developed an aptamer that targets the prostate-specific membrane antigen (PSMA), a protein found in most prostate cancer cells.

Today, the process is automated, and Lupold can make his aptamer in two weeks, but when he first took on the project as a graduate student, it took him five years to drill down to just the right chemical formulation among many billions of molecules.

At the same time Lupold was working on his aptamer, **Theodore DeWeese**, Director of Radiation Oncology and Molecular Radiation Sciences, was working on another technology called small interfering RNAs (siRNA), which have the ability to turn off genes. Radiation therapy kills cancer cells by damaging their DNA. Some cancer cells, however, are able to repair the damage and survive, so DeWeese's plan was to use siRNA to turn off genes that help perform these repairs. Lupold's aptamer would allow him to do it selectively—causing harm only to cancer cells.

Lupold's prostate cancer-targeted aptamer was the perfect delivery vehicle for DeWeese's radiation-sensitizing siRNAs. Their final product was an aptamer that used PSMA as a chemical GPS system to guide the siRNA to prostate cancer cells where they block DNA repair mechanisms, making prostate cancer cells ultrasensitive to radiation therapy.



Shawn Lupold, Ph.D.

"It's almost as if we turned up the radiation, but we did it molecularly," says Lupold. Actually increasing the dose of radiation therapy would surely kill more cancer cells but be far too toxic to normal cells. This approach has the same effect and is safe.

Their treatment worked well in animal models, and aptamers are already FDA-approved for other medical purposes, so Lupold and DeWeese do not anticipate any safety problems. To move the therapy to clinical trials, they will need about $1 million to outsource the production of clinical-grade aptamers.

Lupold and DeWeese are also exploring aptamers as a way to safely deliver and track radiation-releasing alpha particles to painful and deadly prostate cancer cells that spread to the bone.

DeWeese says the cancer-targeting siRNA aptamers are unique to Johns Hopkins and considered the gold standard. The current version is specifically targeted to prostate cancer, but he says with an adjustment to the chemical GPS, they can be adapted to target essentially any cancer. ■

"IT'S ALMOST AS IF WE TURNED UP THE RADIATION, BUT WE DID IT MOLECULARLY. IT HAS THE SAME EFFECT AS INCREASING THE DOSE OF RADIATION—**KILLING MORE CANCER CELLS**—BUT WITHOUT TOXIC SIDE EFFECTS TO NORMAL CELLS." **– SHAWN LUPOLD, PH.D.**

Combined Radiation/ Immune Therapies

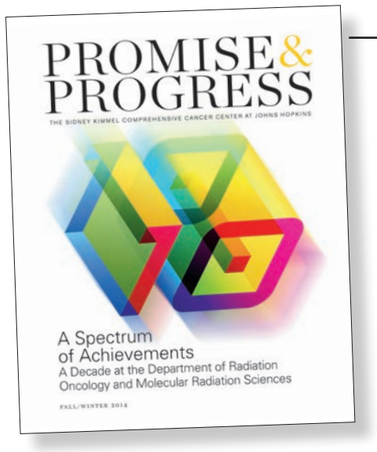
Experts from the Department of Radiation Oncology and Molecular Radiation Sciences are expanding evidence that shows targeted radiation stimulates an immune response against cancer.

As cancer cells are destroyed by radiation, they release their proteins into the bloodstream, clearly revealing their identities as cancer cells and, as a result, attracting the attention of the immune system. Conversely, however, there is growing proof that limiting radiation therapy to certain areas may also benefit the immune response to cancer.

Radiation oncology resident **Ariel Marciscano** is collaborating with experts in the Bloomberg~Kimmel Institute for Cancer Immunotherapy to study how best to treat lymph nodes surrounding tumors that potentially may harbor hidden cancer cells. Radiation therapy is typically administered to these lymph nodes, but Marciscano has found it may destroy certain white blood cells that live in the lymph nodes and are critical to the immune response.

Using the small animal radiation research platform (SARRP), invented by radiation physicist **John Wong**, Marciscano compared mouse models radiating only the tumor to models radiating the tumor and lymph nodes. His findings, featured at the annual meeting of American Society for Radiation Oncology, showed that treatment of the lymph nodes might hinder the immune response to cancer. Marciscano's research, made possible by SAARP technology, is the first of its kind and indicates a need to shift the treatment paradigm when radiation therapy is combined with immunotherapies. Learning how to administer and sequence combined treatments involving immunotherapies is critical to their effectiveness, and this study provides vital new information essential to advancing emerging immune-targeted therapies.

Ariel Marciscano, M.D.



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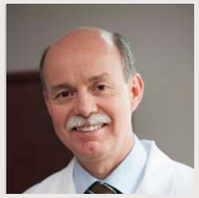


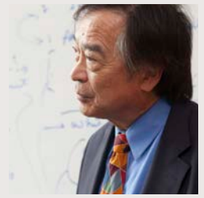
Theodore DeWeese, M.D., the Sidney Kimmel Professor and Director of Radiation Oncology and Molecular Radiation Sciences, was named vice president of interdisciplinary patient care for Johns Hopkins Medicine. He will work with other directors to develop new service lines across the Johns Hopkins system, and will build on the work he helped catalyze to form the highly successful Kimmel Cancer Center multidisciplinary clinics.

Matthew Ladra, M.D., M.P.H., assistant professor of Radiation Oncology and Molecular Radiation Sciences, was named one of *Washingtonian* magazine's 40 Under 40. The honor highlights men and women under age 40 who are "shaping local industries." The magazine calls the winners "names you should know now—because they'll be part of the conversation for years to come." Ladra was selected for running the Kimmel Cancer Center at Sibley pediatric radiation oncology program, a collaborative program with the Children's National Health System that provides radiation oncology experts and greater convenience for families who live in the national capital region.

Marikki Laiho, M.D., Ph.D., the Willard and Lillian Hackerman Professor of Radiation Oncology and Vice Chair of Research, received the prestigious Harrington Discovery Institute Scholars-Innovator Award. Laiho was chosen for her research on the RNA polymerase pathway, called POL1. It is a critical pathway mutant cancer genes use to communicate with cancer cells and recover from damage caused by radiation treatment. Laiho developed a new compound, known as BMH-21, that disrupts this communication, causing the death of cancer cells.

Ana Kiess, M.D., Ph.D., received the *Journal of Nuclear Medicine*'s Editor's Choice Award for her paper on PSMA-targeted α-particle radiopharmaceutical therapy, a new prostate cancer-targeted treatment that delivers radiation-releasing alpha particles to cancer cells that have spread throughout the body. The article also highlights the importance of micro-scale dosimetry studies to measure and better understand the amount of radiation the body receives. The journal selected the paper as one of 2016's top three basic science manuscripts.

Phuoc Tran, M.D., Ph.D., was appointed clinical director of radiation oncology. Tran also received a $1 million Movember-Prostate Cancer Foundation Challenge Award to study stereotactic radiation therapy as an immune-stimulating approach to advanced prostate cancer. In 2015, he was also selected for the ASCO Leadership Development Program. Tran's research includes a new approach to salvage radiotherapy for prostate cancer, a mainstay of treatment for men with a persistently detectable PSA or a delayed rise in PSA without evidence of cancer spread. Salvage radiotherapy alone does not always control PSA progression for men at highest risk for prostate cancer progression. Tran is studying whether adding drugs that target the androgen, or male hormone, receptors to salvage radiation therapy will better control prostate cancer and prevent cancer recurrence.



John Wong, Ph.D., director of medical physics, received two prestigious honors. He was awarded the 2017 Edith Quimby Lifetime Achievement Award of the American Association of Physicists in Medicine. In addition, the first conceptual paper on adaptive radiation therapy in *Physics in Medicine and Biology*, co-authored by Wong, was selected as one of the journal's 25 most important papers published in its 60-year history. The paper was featured in the journal's 60th anniversary collection and was among the papers celebrated at the 50th anniversary of the International Conference on the Use of Computers in Radiotherapy.

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Marie-Jo Corry

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