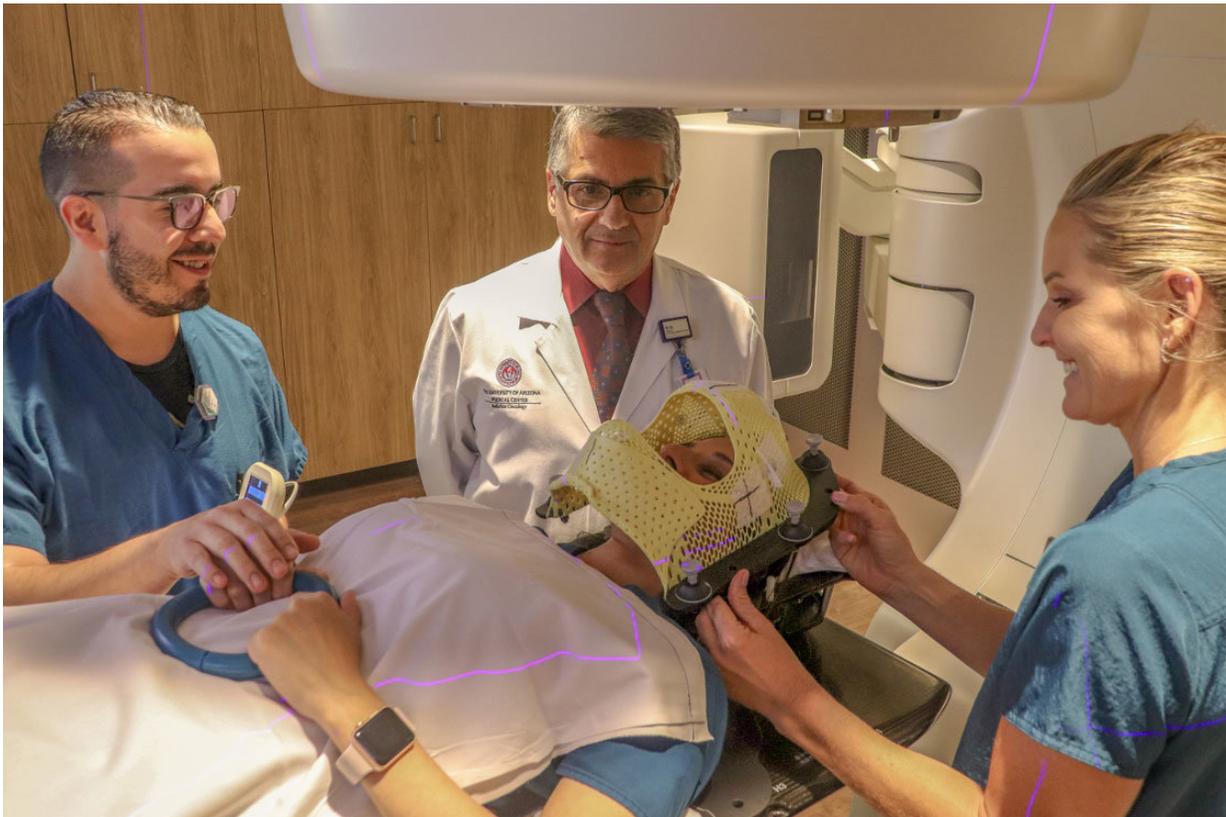


Team uncovers promising lead in genetic approach to treating glioblastoma

November 29 2018, by Anna C. Christensen



Baldassarre Stea, MD, PhD, (center), treats brain tumors with DNA-damaging radiation. Credit: Anna C. Christensen

Glioblastoma, a deadly brain cancer that has grabbed headlines for claiming the lives of Sens. Edward Kennedy and John McCain, could be

"tricked" into sparing more of its victims.

A team of University of Arizona researchers who looked for genetic differences between glioblastoma cells from long- and short-term survivors discovered that those who survived longer had a protein that might be targeted to increase survival in all glioblastoma [patients](#). The results were presented this month at the Society for Neuro-Oncology conference in New Orleans. This work is in its early stages, and the researchers say they are many years and millions of dollars away from potential translation into treatments for patients.

"Glioblastoma essentially is incurable," said Baldassarre "Dino" Stea, MD, Ph.D., head of the UA College of Medicine—Tucson Department of Radiation Oncology. "In the past 15 years, only one drug—temozolomide—has been invented, whereas the rest of the cancer field is zooming forward."

With surgery, followed by chemotherapy and radiation, adults with glioblastoma survive for an average of 11-15 months. Some succumb sooner, while others outlive their initial prognosis by months or even years.

"I was curious to know how genes are differentially expressed in patients who live longer," said Michael Hammer, Ph.D., co-director of the UA Cancer Center Genomics Shared Resource and research scientist with the UA BIO5 Institute. "If we can identify a pathway in the tumor that we might be able to target, we can try to make the short-lived patients look more like the long-lived patients."

Drs. Stea and Hammer helped discover that long-term survivors manufacture a protein called WIF-1 in relative abundance. The team first searched for "signaling pathways," a collection of genes that control cellular function under normal circumstances but can go awry to cause

cancer.

"The Wnt signaling pathway popped up as the most important pathway to limit the survival chances of glioblastoma patients," Dr. Hammer said. This pathway normally is involved with tissue maintenance but can fuel tumor growth if it becomes overactive. Long-term survivors appeared to rely on genes that suppress the function of the Wnt signaling pathway.

"We had a pile of genes and looked for an overrepresentation of these genes compared to a random set of genes," Dr. Hammer said. "We found that, in patients who survived longer than average, certain genes were tamping down Wnt signaling."

After sifting through 800 [genes](#) in 23 glioblastoma samples, the team identified the WIF-1 gene, which manufactures the WIF-1 protein, as an important inhibitor of the Wnt pathway and a strong predictor of long-term survival.

"The Wnt pathway is deranged, and WIF-1 is the police. Cancer grows when there aren't enough police to keep the deranged person in check," Dr. Stea said. "Some people are endowed with more WIF-1 and survive longer."

While testing for the WIF-1 gene someday may help oncologists predict which patients will survive longer, a greater hope is that this work will lead to a drug that targets glioblastoma tumors with more precision than standard treatment.

"We hope to create a drug to suppress the Wnt pathway so that everybody survives longer," Dr. Stea said. "It would be the pot of gold at the end of the rainbow."

Dr. Stea believes new approaches are essential to extend survival for

glioblastoma patients.

"I think we have reached the apex of what the surgeon can do, and have achieved the most we can with radiation," he said. "The cure will not come from more radiation or more surgery—glioblastoma is a genetic problem that we have to solve genetically."

One way to enlist human genetics in the fight against glioblastoma is to enhance the effects of radiation, which kills cancer cells by damaging their DNA. Glioblastomas have a special ability to repair this DNA damage, diminishing radiation's effectiveness.

"I'm poking holes in the DNA of glioblastoma cells, and the Wnt pathway goes back and helps to repair the damage," Dr. Stea said, referring to his work as a radiation oncologist. "It's like I'm exploding a bridge so the enemy cannot cross, but overnight they rebuild the bridge."

By taking cues from WIF-1, scientists might be able to weaken [glioblastoma](#)'s ability to repair radiation-damaged DNA.

"The Wnt pathway activates DNA repair. If we can suppress Wnt, we also suppress DNA repair. When we mimic that in the lab by adding WIF-1 protein to [glioblastoma cells](#), they become more sensitive to radiation," said Eric Weterings, Ph.D., assistant professor at the UA College of Medicine—Tucson Department of Radiation Oncology, who also contributed to the study.

"Right now, I can only give so much radiation. If we exceed that threshold, we're more likely to damage the brain," Dr. Stea added. "We have a hint that WIF-1 can help radiation do a better job, compounding its cancer-killing effect."

This preliminary research was fueled in part by a gift from one of Dr.

Stea's [glioblastoma patients](#), who is a long-term survivor at three-and-a-half years. He hoped researchers could learn from long-lived patients like himself. Many times, grateful patients help fund UA Cancer Center research.

"He is happy to be alive and very generous, so he made a gift," Dr. Stea said. "That's how the program got going."

To expand upon their findings, the team currently is applying for grants to continue their research.

"We didn't have a huge sample population, so these results could be a fluke—but they are statistically significant," Dr. Stea said. "The next step is to validate with hundreds of patients and then to perform further studies with inhibitors of the Wnt [pathway](#)."

"It's a step forward," Dr. Weterings added. "In the future, this work might give us a larger and yet more specific arsenal of options to treat this disease."

The team already is collaborating with Tech Launch Arizona, filing a provisional patent application on the gene signature for a companion diagnostic and possible [radiation](#) sensitizer.

Provided by University of Arizona

Citation: Team uncovers promising lead in genetic approach to treating glioblastoma (2018, November 29) retrieved 19 September 2024 from <https://medicalxpress.com/news/2018-11-team-uncovers-genetic-approach-glioblastoma.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.