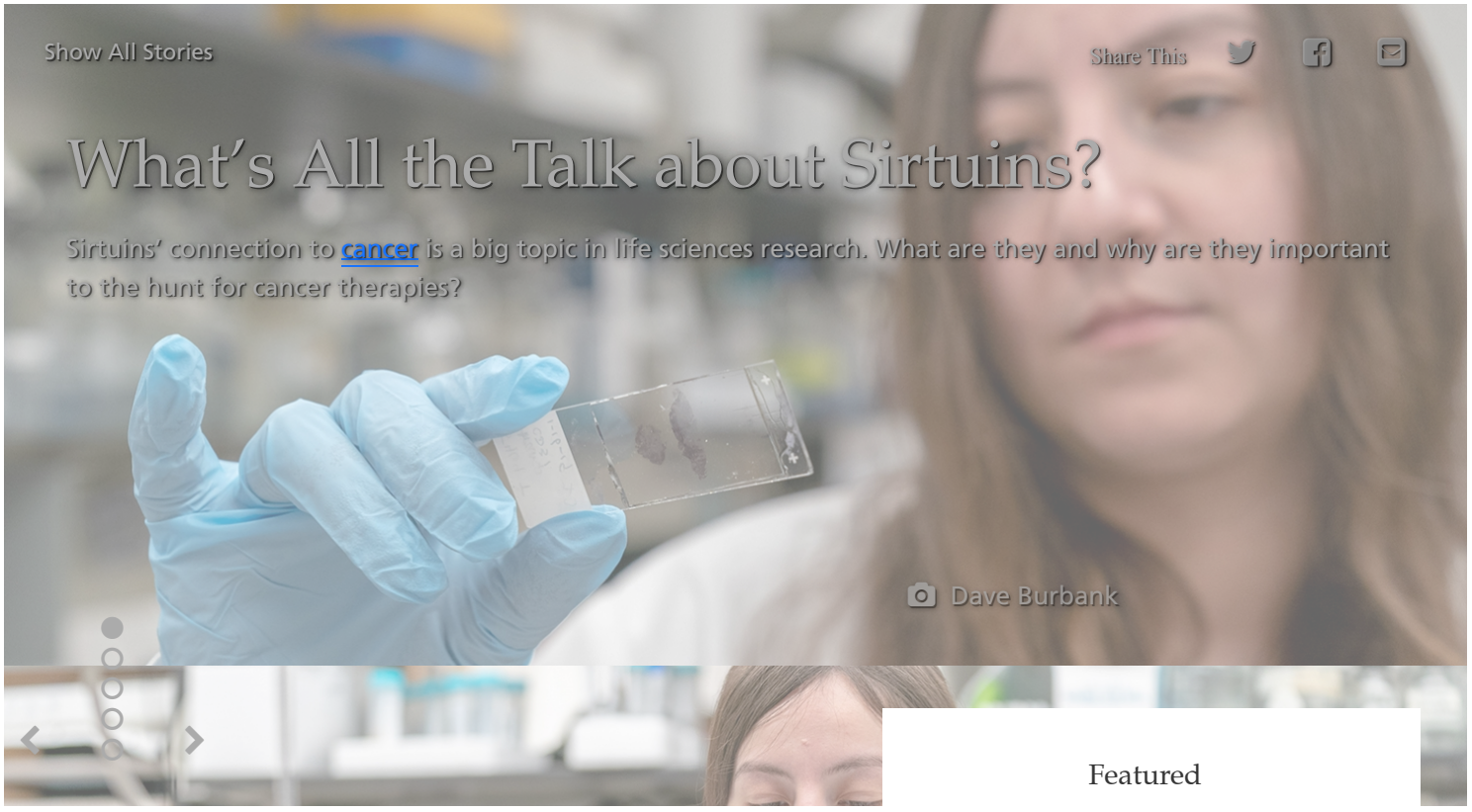
What's All the Talk about Sirtuins?

Sirtuins' connection to cancer is a big topic in life sciences research. What are they and why are they important to the hunt for cancer therapies?



by Colton Poore '20

"Genotyping mice, collecting tumors, weighing tumors, it's a lot of what I do," says Irma Fernandez—a third-year graduate student in Biochemistry, Molecular and Cell Biology at Cornell. She chuckles as she explains the routine of her important tasks as if to imply that this is not what most people do. "I work on one of the more unusual projects in my lab," Fernandez confesses.

Mirroring the uniqueness of her project, Fernandez's status as a graduate student is also distinctive. She is a joint student in the labs of Robert S. Weiss, Biomedical Sciences, and Hening Lin, Chemistry and Chemical Biology. Whereas most people work with one major principal investigator (PI) on their research, Fernandez works with two, the product of a long-standing collaboration with Weiss, Lin, and Richard A. Cerione, Molecular Medicine/Chemistry and Chemical Biology. Having dual PIs allows Fernandez to combine the biochemistry focus of the Lin lab with the molecular biology and genetics focus of the Weiss lab—her key areas of interest.

What Are Sirtuins? What Is Their Function in the Body?

Fernandez's research centers on sirtuins and their link to cancer. After genetic information is translated into a protein structure, an additional chemical group is sometimes added to the final protein to modify it. Researchers think this is a regulatory

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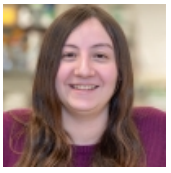

Irma Fernandez
Graduate Researcher

Highlights

mechanism in cells. Sirtuins remove the added chemical groups on the protein, which can affect the modified protein as well as other nearby proteins.

"This supports the idea that SIRT5 acts as an enhancer for tumor formation and growth."

In a cancer cell context, removing a group can either enhance or suppress tumor growth, depending on the group's identity and location. Various sirtuins are able to remove different post-translational modifications from proteins. Although there are seven sirtuins in mammals, Fernandez is particularly interested in sirtuin five (SIRT5).

Sirtuin Five, or SIRT5

"SIRT5 is interesting because we found that it is over-expressed in many cancers. In particular, it's really over-expressed in breast cancer," Fernandez says. From this initial observation, Fernandez hypothesized that the group that SIRT5 was removing from the protein was enhancing the formation and development of cancers.

This is where the mice come in. There is a specific gene, PYMT, that can be introduced into mice models to cause mammary tumor formation. Likewise, the mouse genome contains a gene that codes for the expression of SIRT5. Using lab techniques, Fernandez was able to produce mice models that were SIRT5 knockouts, meaning that those models did not express SIRT5. Those same models, however, carried the PYMT gene, meaning that they would develop breast cancer. What Fernandez and her colleagues found, though, is that the SIRT5 knockout mice lived longer, had a lower overall tumor burden, and their tumors did not metastasize as quickly as the mice that expressed SIRT5. "This supports the idea that SIRT5 acts as an enhancer for tumor formation and growth," Fernandez says.

After demonstrating this in mice models, Fernandez further confirmed the result in vitro by performing a similar experiment with cultures of cells. As in mice, she found that SIRT5 knockout cancer cells exhibited significantly less growth than cancer cells that expressed SIRT5.

"Now that I was able to show that SIRT5 does appear to enhance cancerous growth, I'm now trying to figure out how it does that—the exact mechanism behind why SIRT5 acts as a promoter for breast cancer."

Determining How SIRT5 Increases Cancer Growth and How to Stop It

In her proteomic analyses, Fernandez found one particularly likely suspect. One sequence on a protein, known as IDH2, was a top target for SIRT5 to act on. SIRT5 would remove a specific chemical group known as succinyl, which was attached to IDH2 causing it to activate.

When IDH2 is activated, it produces NADPH, an important molecule in the body. It is relevant in a cancer context because NADPH reduces the number of reactive oxygen species (ROS) in a cell. As a tumor grows three-dimensionally, it causes ROS levels to be elevated. If enough ROS are present, the cell dies, and the tumors stop growing. Tumor cells, therefore, work hard to reduce the amount of ROS in order to grow larger and potentially metastasize to other cells. SIRT5's activation of IDH2 might be the molecular mechanism that explains how breast cancer cells reprogram their metabolism and how SIRT5 supports tumor formation in breast cancer.

In addition to figuring out the mechanism behind why SIRT5 is linked to cancer, Fernandez is working with the Lin Group to test a small molecule inhibitor that prevents SIRT5 from functioning. "In humans, we can't really knockout genes in a lab the way we can with mice and bacteria. But if we can make something that can inhibit SIRT5, it might produce similar results to the experiments in mice models, where the effects of cancer were much less when they didn't express SIRT5."

Fernandez's project might someday aid in cancer therapy by turning off a gene that enhances cancerous growth. "What I've found in my experiments is that inhibiting SIRT5 has no noticeable effects in normal cells. SIRT5 knockout mice live and reproduce normally." SIRT5 may only have impact in specific contexts, including in cancer cells—meaning that creating an artificial inhibitor of SIRT5 would be extremely beneficial to cancer therapy with minimal to no side effects.

The Rewards of a Collaborative Experience

While the rest of the Weiss lab concentrates primarily on DNA damage projects, Fernandez's research has allowed her to explore new techniques for the lab. "There are some things I have had to do that no one in my lab had any experience with. For instance, I had to surgically transplant cancer cells in mice models, and no one really knew how to do that." Luckily, another PI in a completely different group, Nataszia Kurpios, Molecular Medicine, had experience with the procedure and offered to not only sit down to discuss the technique but also offered to perform a demonstration. "Cornell is very collaborative. When I first came here, I was a little intimidated, but the students and faculty here are incredibly supportive and willing to help each other out."

In addition to her research, Fernandez is involved with SACNAS (Society for the Advancement of Chicanos/Hispanics and Native Americans in Science) and is a member of the Molecular Biology and Genetics Diversity Council. She wants to recruit for more diversity in science and introduce more people to the collaborative and supportive environment that she has discovered through her research at Cornell.

"My research allows me to combine my interests in biology—enzymology, biochemistry, and immunology. And anybody should be able to have the opportunity to do that, whatever they're interested in."

After all, the world is wide, and cancer biology—though ideal for Fernandez—is only one of the near infinite mysteries of the world, all awaiting their own elucidation.

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