Cancer Metastasis is Target of New Research Initiative

Researchers at the UC San Francisco want to better understand why some cancers metastasize and how they might be more effectively treated.

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Six UC San Francisco researchers have won an Endeavor Award to build a new research collaborative at the University focused on decoding the "rulebook" of metastatic cancer as a pathway to new treatments. The Mark Foundation for Cancer Research established the awards to support research challenges that are too far-reaching for a single lab to address.

"For these big biological problems, collaboration is essential – you need it to make breakthroughs," said Jeroen Roose, PhD, professor and vice chair in the UCSF Department of Anatomy. "If you can build a collective of six or 10 or 20 different groups with different disciplines you obtain insights that you would never get from one individual lab doing independent research."

The model for the six-lab collaborative that is receiving the Endeavor award can be found in the UCSF Bakar ImmunoX Initiative, which Roose cofounded in 2018 to foster collaboration between scientists in diverse disciplines toward a more wholistic understanding of the human immune system. Now the Endeavor-funded team aims to use a similarly collaborative approach to better understand why some cancers metastasize and how they might be more effectively treated.

Metastasis occurs when cancer cells spread from a primary tumor and form cancer clusters in different parts of the body. Metastasis accounts for almost 90 percent of cancer-related deaths, and metastatic tumors are tenaciously resistant to treatment because they exhibit significant genetic variation compared to primary tumors.

"We want to understand the how, where, why and with whom metastatic cells disseminate and proliferate," said Andrei Goga, MD, PhD, professor in the UCSF Department of Cell and Tissue Biology and the Department of Medicine, who will co-lead the initiative with Roose. "Most importantly, since metastasis is the greatest challenge facing patients with cancer, we want to discover how to deconstruct these complex metastatic tumors to provide new and better therapies for patients."

Studying Metastasis From Several Different Angles

The researchers will study metastasis from several different angles. First, they aim to understand

the diversity of human metastatic cancer by studying tumor-specific traits in organoids – 3D balls of cells grown in the lab from metastatic tumor tissue samples. They will also study host-specific traits, that is, the interactions between metastatic cancers and surrounding cells in hopes of identifying factors in the tumor microenvironment that may foster metastasis. The goal is to build a "rulebook" for metastasis that will help the researchers develop a numerical value for what they call the metastatic fitness of a given primary tumor, which could help predict the risk factors for metastasis and possibly head it off with new targeted therapies.

"Metastasis is kind of a perfect storm," said Roose. "We know that cancer cells leave tumors all the time, but only rarely do they metastasize. If we understood the rulebook of metastasis, we could look at a patient's cancer and be able to predict when or how their particular tumor is going to metastasize. It would be an amazing breakthrough."

This breakthrough will only be possible because of the collaborative model of this research, Goga and Roose believe, with different labs based in different bioscience disciplines attacking the biology of metastasis from different angles.

Roose's team will focus on cancer and the immune system, while Goga's interests are focused on cancer metabolism and therapeutics. Valerie M. Weaver, PhD, director of the UCSF Center for Bioengineering and Tissue Regeneration, will study cancer biomechanics – the idea that the physical forces in a tumor's environment affect cancer cells' behavior. Sarah Knox, PhD, an assistant professor of cell and tissue biology, will study multicellular interactions between nerve cells and tumors that may play a role in driving metastasis. Jayanta Debnath, MD, PhD, a professor of pathology, will study autophagy, one of the body's processes for eliminating damaged cellular components, and its relationship with cancer formation. Eric Collisson, MD, associate professor of medicine, will bring to bear his lab's expertise in cancer genetics.

"Typically, it is metastasis that causes the demise of cancer patients, so it is crucial that we better understand the process and figure out ways to intervene," said Michele Cleary, PhD, CEO of The Mark Foundation. "Andrei Goga, Jeroen Roose, and others have assembled a powerhouse team at UCSF with diverse expertise, tools, and insights to explore metastasis in a very in-depth way. Their goal of identifying new biological targets for metastasis that lead us to new therapies would truly be a game changer for patients."

Combining Different Disciplines

Like the UCSF ImmunoX program, one of the foundational aspects of this research is in combining different disciplines and building organizational procedures that allow all the scientists to access the same data and use the same samples and generated organoids.

Typically, individual labs develop sample-handling and data procedures that benefit that lab. For instance, they may not have any incentive to preserve biological samples once their research is finished. By unifying many labs with shared funding, resources and facilities, all the researchers have incentive to develop common procedures that benefit their colleagues. This model, similar to one developed by the UCSF CoLabs Initiative, greatly increases the speed of research and ensures

greater consistency in results.

Roose hopes that the metastasis research program launched by the Endeavor Award will eventually form the foundation for a new collaborative tumor research initiative like the ImmunoX Initiative. The program would be anchored at UCSF's historic Parnassus Heights campus, radiating out to other sites, and Roose and Goga hope that it could be a keystone initiative.

"Focal programs like ImmunoX, the UCSF Diabetes Center and others in the works are driving innovation and the future identity of Parnassus Heights," said Roose. "We hope that a future program aimed at cancer metastasis will be one of them."

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