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Sylvester Grant Funds Early-Stage Prostate Cancer Study

Researchers are investigating ways to make immunotherapies more effective.

Sylvester Comprehensive Cancer at the University of Miami Miller School of Medicine has awarded a $50,000 Tumor Biology Intra-Programmatic Pilot Award to Himanshu Arora, Ph.D., assistant professor of research at the Desai Sethi Urology Institute, and Fangliang Zhang, Ph.D., associate professor of research in the Department of Molecular and Cellular Pharmacology, to overcome immune resistance in high-grade prostate cancer.

Himanshu Arora, Ph.D.

These awards give Sylvester scientists seed funding to pursue high-risk, high-reward research. In this case, Drs. Arora and Zhang will be studying two protein modifications – arginylation and nitrosylation – and how they impact prostate cancer's response to immunotherapy.

"High-grade prostate cancer has a high mortality rate and does not usually respond to most current therapies," said Dr. Zhang. "We believe that, by investigating these posttranslational modifications, we can unleash the immune system's therapeutic possibilities."

Even after proteins are first synthesized, they are often incomplete. Many undergo some form of posttranslational

modification, during which additional molecules are added to adjust protein function.

Fangliang Zhang, Ph.D.

Arginylation modifies proteins by adding the amino acid arginine, which can reduce a molecule's lifespan. Nitrosylation adds nitric oxide (NO) and is associated with cell signaling.

"I was researching how nitrosylation can influence the later stages of prostate cancer, and Fangliang was looking at arginylation," said Dr. Arora. "We were having coffee one day, talking about what we were doing, and realized how these research angles complement each other. We can work together on it and eventually go for an NIH grant."

Overcoming Resistance to Checkpoint Inhibitors

While immunotherapies called checkpoint inhibitors have been quite effective for different cancer types, they have not been particularly promising in prostate cancer. Arginylation and nitrosylation may both play a role in overcoming this resistance. Dr. Arora's research has shown that NO production is reduced in prostate tumors, which may be one way prostate tumors invalidate the body's immune response.

The current research is focused on the CSF1R protein and how it influences the tumor microenvironment to foster cancer growth and resist the immune system. CSF1R resists inhibition (by CSF1R blockade) in prostate cancer; however, nitrosylating the protein may support effective inhibition, which could invigorate immunotherapies and help immune cells attack

tumors.

This process may also require the protein ATE1, which plays a known role in prostate cancer development. ATE1 arginylates proteins and may also help rescue CSF1R signaling and restore the immune response.

Seed funding programs play an important role in the research ecosystem. Scientists can face a catch-22 when applying for NIH grants. They need evidence in order to get the grant, but they need the grant in order to gather the evidence. The Tumor Biology Intra-Programmatic Pilot Award gives them initial support to gather the data they need to pursue additional funding and move important work forward.

“The Pilot Award is essential to help us fill in a few gaps in our knowledge,” said Dr. Arora. “This study will help us further develop models to validate how coordination between nitrosylation and arginylation can potentially sensitize tumor microenvironments and make them responsive to immunotherapies.”

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