A New Treatment Strategy for Synovial Sarcoma

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First author Yao Yu, PhD, (right) presented the study at the 2025 American Association for Cancer Research conference. She is pictured here with senior author Ling Cai, PhD, (middle) and lab colleague Arum Kim, PhD.

Synovial sarcoma is a rare, aggressive soft tissue cancer with few effective treatment options, which means patients often have a poor prognosis. Now researchers at Duke University School of Medicine have found a weakness in the disease, suggesting a possible new treatment.

Nearly all people with synovial sarcoma have a particular disruption in the regulation of genes — a specific gene fusion called SS18::SSX. This fusion creates a unique protein that changes the function of certain gene-regulating complexes, promoting cancer.

In a study published April 23, 2025 in the journal Science Advances, researchers led by Greg Wang, PhD, professor of pharmacology and cancer biology, and Ling Cai, PhD, assistant professor of pathology, discovered a way to disrupt this hallmark g mutation.

Using cancer cell line data, chemical tools, and genomics and molecular biology, the team discovered that a protein called WDR5 interacts with the SS18::SSX protein at cancer-related genes, promoting changes that support cancer growth.

The results are “surprising and exciting at the same time,” Wang said. “The findings demonstrate that there exists a disease cell dependency on the WDR5 complex, which can provide a therapeutic window — killing cancer while not affecting normal cells.”

In studies in cell lines and in mice, the scientists, including first author Yao Yu, PhD, a postdoctoral associate in the Wang lab, found that if they used a small molecule to degrade WDR5, they could suppress the cancer-promoting activities of SS18::SSX. This method also led to changes that activated p53, a cancer-suppressing protein.

The small molecule that they used in the study — MS67 — is a proteolysis targeting chimera (PROTAC), a class of drugs that has emerged as a promising therapeutic strategy in recent years, Wang said. At least a dozen drugs in this class are now in clinical trials for several types of cancer.

“Targeting WDR5 by our lead PROTAC compound, in our opinion, will be promising in treating the genetically defined synovial sarcoma: those with the SS18::SSX fusion,” Wang said.

His lab and those of collaborators hope to partner with clinical researchers and pharmaceutical industry partners to pursue this strategy.

Other Duke authors included postdoctoral associate Bo Pan, PhD.

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