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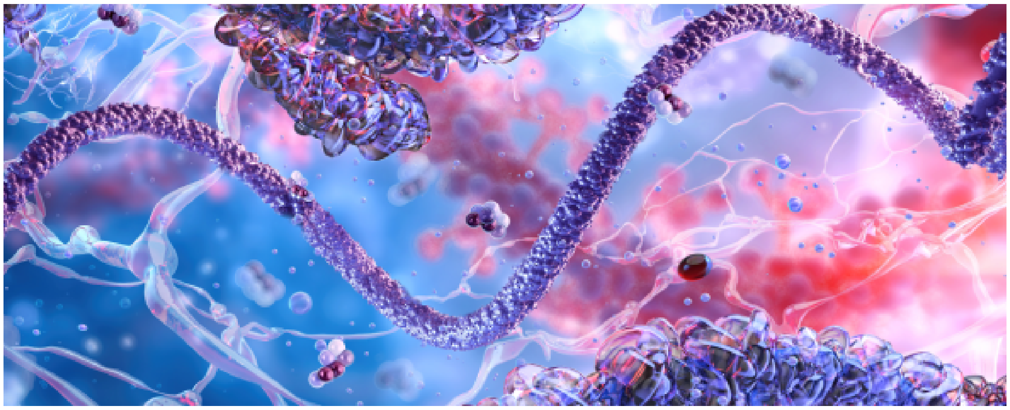
Protein Map Illuminates Hidden Drivers of Childhood Cancer



April 25, 2025

A high-resolution map of how protein organization inside the cell provides a platform for interrogating the way cancer mutations disrupt entire protein assemblies—not just individual genes. By combining spatial proteomics with pediatric tumor genome data, researchers uncovered 102 previously overlooked cancer drivers, highlighting the power of structural context in interpreting cancer genomes and identifying new therapeutic targets.

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DOI: https://doi.org/10.1158/2159-8290.CD-NW2025-0034

Publisher: American Association for Cancer Research

Article Type: News

Mutations traced to disrupted protein complexes, not just single faulty parts.

A detailed map of how proteins assemble, interact, and localize within a human cancer cell line is offering scientists a powerful new reference for exploring how cells are built—and what happens when that molecular architecture is disrupted in disease.

Using a combination of high-resolution microscopy, mass spectrometry, and machine learning algorithms, a team led by Trey Ideker, PhD, a systems biologist at the University of California, San Diego, charted the spatial organization of more than 5,100 proteins in U2OS osteosarcoma cells.

The resulting atlas—built in collaboration with bioengineer Emma Lundberg, PhD, of Stanford University in California and KTH Royal Institute of Technology in Stockholm, Sweden, and proteomicist Edward Huttlin, PhD, of Harvard Medical School in Boston, MA—revealed a rich cartography of 275 distinct molecular assemblies, ranging from small complexes composed of a few dozen proteins, such as proteasomes, to larger structures containing hundreds, such as the nucleolus (Nature [Epub 2025 Apr 9]).

According to Georg Kustatscher, PhD, a proteomics researcher at the University of Edinburgh, UK, what sets this study apart is how the diverse data types are woven together to reveal patterns and relationships that would be invisible through any single technique. “The combination is what creates new insights,” says Kustatscher, who was not involved in the research. “It’s the blueprint for how we can do this in biology.”

Notably, many of the documented assemblies had not been previously described—and proteins that consistently co-localize in these structures may form novel molecular machines with unrecognized roles, including in tumorigenesis, notes Leah Schaffer, PhD, the study’s first author and a former postdoc in Ideker’s lab. “That’s an exciting thing,” she says. “Now that we have this data-derived map of the cell that is not biased toward well-studied proteins, we can begin to find assemblies that may not have previously been known but that could be recurrently mutated across cancers.”

To explore this idea, the researchers overlaid their spatial blueprint with genome data from 772 pediatric tumors spanning 18 cancer types. They then traced how cancer-associated mutations mapped onto the protein assemblies, revealing not just scattered gene disruptions but concentrated damage to shared cellular machinery.

In total, 21 assemblies were frequently disrupted by mutations across various pediatric tumors. These included well-established oncogenic players such as the SWI–SNF chromatin remodeling complex—one of the most widely mutated protein assemblies in human cancers—as well as less familiar structures such as nuclear pores, cell junction complexes, and the NCOR-associated transcriptional repression complex.

Across these assemblies, the researchers identified 250 putative cancer proteins, all of which had been overlooked in conventional gene-by-gene cancer screens. Of these, 102 were validated as oncogenic drivers in mouse tumor models and could now serve as novel targets for future cancer therapies.

Serinus Biosciences, co-founded by Ideker in 2022, is now operationalizing that concept, employing what co-founder and CTO Maxwell Sherman, PhD, calls a “protein complex–centric approach to drug discovery.” The multimodal cell maps of protein organization generated by Ideker’s lab serve as the company’s foundation, he explains. Sherman’s team then integrates diverse orthogonal data to identify more effective therapeutic targets, with an initial focus on breast and colorectal cancers.

“That is really the power of these maps,” Sherman says.

At a more fundamental research level, notes Lundberg, the discovery of previously unrecognized drivers of cancer highlights the power of a spatial, assembly-level framework to reveal hidden mechanisms of disease and reshape how cancer genomes are interpreted. It also reinforces the idea that cancer disrupts entire protein complexes responsible for essential cellular functions, rather than targeting individual genes alone. “It helps to shape our understanding—shifting it toward thinking about mechanisms, and not genes only,” she says. **–***Elie Dolgin*