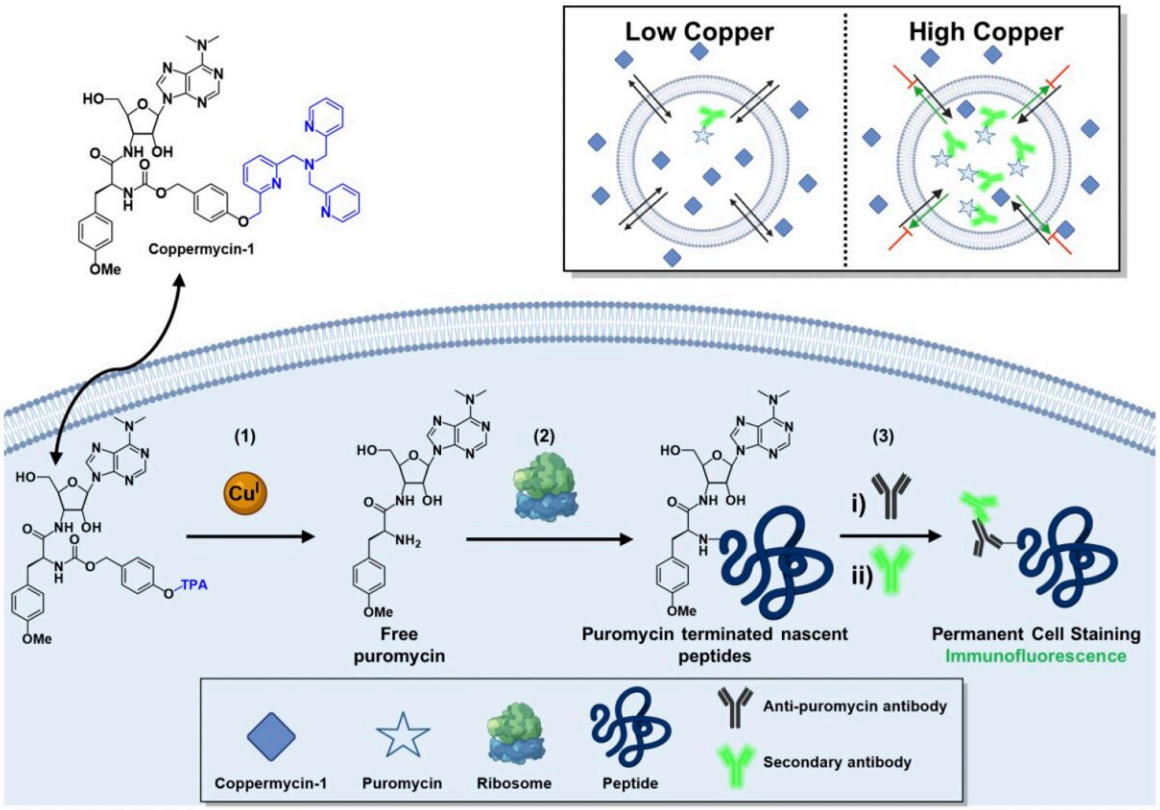
Copper-detection tool discovers possible chelation target for lung cancer

January 22 2025, by Wendy Plump



Schematic detailing the design strategy for the histochemical activity-based sensing of labile Cu(I) pools. Credit: Chang Lab

The Chang Lab at Princeton Chemistry continues in its mission to elucidate the role of metal nutrients in human biology: last year, iron;

this year, copper. The lab's first paper of 2025 showcases its development of a revelatory sensing probe for the detection of copper in human cells and then wields it to uncover how copper may be regulating cell growth in lung cancer.

Researchers also offer a possible treatment modality in which copper chelation shows promising results in certain lung cancers where cells have two related phenomena: a heightened transcription factor responding to oxidative stress and a diminished level of bioavailable copper.

Their collaborative paper, "A histochemical approach to activity-based copper sensing reveals cuproplasia-dependent vulnerabilities in cancer," was published this week in the *Proceedings of the National Academy of Sciences*. It follows on the heels of a companion July 2024 paper focusing on iron.

In this latest work, the lab's histochemical, activity-based sensing probe was deployed on a panel of human tumor cell lines from the National Cancer Institute to identify cell types with elevated levels of copper. Copper is essential to health. But copper imbalances have long been implicated in cancer cell growth and other disease states. The goldilocks balance in all mammals is so vulnerable to disruption that tools to track and assess the onset of copper-dependent cell growth, or cuproplasia, are in high demand.

"Copper is one of the most important metal nutrients for health. It's consumed in the diet, so it's really nature versus nurture because every cell in every organism in every kingdom of life needs it," said Christopher Chang, the Edward and Virginia Taylor Professor of Bioorganic Chemistry.

"When you think about diseases as complicated as cancer, you really

want to understand the fundamentals of what causes an individual cell or collection of cells to live or die. And then you want to bring it back to something that you would use to block or kill that excess growth.

"What we need are more sophisticated biomarkers, and that's the direction we've taken with this technology. We wanted a method that you could inject in many cell types in parallel, or inject in tissue, and then isolate cancer cells of different types and see which ones had a large or small dependence on cuproplasia."

The research was carried out with chief collaborators Marco Messina at the University of Delaware and Gina DeNicola at the H. Lee Moffitt Cancer Center and Research Institute in Florida.

Connecting copper with antioxidants

The paper describes a direct link between copper and a transcription factor called nuclear factor-erythroid 2-related factor 2 (NRF2). A buildup of free radical damage in cells leads to what scientists call the antioxidant response, where NRF2 is activated and it promotes gene expression to make proteins that will combat that oxidative insult.

The Chang Lab's work steps into this arena, bridging sensing and catalysis to map the regions where this is happening.

"Heightened levels of copper in cells are known to produce oxidative stress," said Aidan Pezacki, co-lead author of the paper and graduate student in the Chang Lab.

"So, we would expect cancers with a high demand for copper-dependent cell growth to also have higher levels of oxidative stress. Since NRF2 is directly responsible for combating oxidative stress, we thought it might be involved in regulating copper levels, as well."

Specific lung cancers are known to have very high amounts of NRF2. Researchers were therefore able to make a connection between higher levels of NRF2 and lower levels of copper that were consequently vulnerable to copper chelation. Chelation therapy allows scientists to "grab hold of" and withhold metal nutrients, thus depriving cell growth of an important fuel.

"We took these NCI cell lines and treated them with a copper chelator and then compared cells with either low or high NRF2," added Pezacki. "What we found was that all the cells with higher NRF2 have higher rates of cell death when we treated with the copper chelator.

"We suspect that the NRF2 is sequestering copper and then the chelator depletes the cells of copper even further, and this dual deprivation doesn't keep up with the cell's need for the nutrient. That makes copper chelation a potentially viable therapeutic strategy in cancers where the metal is already scarce and tightly regulated."

Chang emphasized that results have yet to move into human tissue.

"This is a proof-of-concept study for profiling metal vulnerabilities in lung cancer. It's also a platform that we think could be generally applied to not only cancer but the broader process of cell growth," said Chang.

"All diseases, ultimately, are a question of too much or too little cell growth or cell death. And that's the elemental balance we're tracking with this research and the basic science we're interested in here. It's part of solving the larger puzzle that goes along with decoding how diet, environment, and lifestyle can shape and determine disease states."

The paper was authored by Marco Messina, Laura Torrente, Aidan Pezacki, Hanna Humpel, Erin Li, Sophia Miller, Odette Verdejo-Torres, Teresita Padilla-Benavides, Donita Brady, David Killilea, Alison Killilea,

Martina Ralle, Nathan Ward, Jun Ohata, Gina DeNicola, and Christopher Chang.

More information: Marco S. Messina et al, A histochemical approach to activity-based copper sensing reveals cuproplasia-dependent vulnerabilities in cancer, *Proceedings of the National Academy of Sciences* (2025). DOI: 10.1073/pnas.2412816122

Provided by Princeton University