THE FRONT ROW
at Scripps Research

Close encounters: Designing drugs that recruit the cell's own machinery to fight cancer and beyond

Michael Erb, PhD
Associate Professor, Department of Chemistry

ABOUT THE LECTURE

Many devastating diseases are driven by proteins that conventional drugs can't easily reach. In his Front Row lecture, Scripps Research professor Michael Erb explained how his group is developing proximity-based drugs, including molecular glues, that bring specific molecules together inside cells. Rather than simply blocking a protein's activity, proximity-based drugs recruit the cell's own machinery to remove disease-driving proteins or redirect other cellular pathways. Erb discussed how this strategy could help scientists pursue cancer targets that have long resisted traditional treatments.

TOP TAKEAWAY POINTS

- Conventional drugs depend on proteins having the right shape, as many targeted therapies work by fitting into small pockets on proteins. This strategy has produced important cancer medicines—including kinase inhibitors, which block enzymes that help cancer cells grow and survive. However, many disease-driving proteins don't have usable pockets. These "undruggable" proteins are often crucial for cancer cell survival, which is why scientists need new ways to reach them.

- Molecular glues offer a different approach to drug discovery. Instead of blocking one protein directly, a molecular glue brings two things together inside a cell that wouldn't normally meet. That forced contact gives the cell new instructions. In some cases, the glue recruits the cell's protein-disposal machinery, causing a harmful protein to be tagged and destroyed. This approach can rewire biology by changing which molecules interact inside the cell.

- Some existing drugs have revealed the unique potential of molecular glues. For example, rapamycin works by helping one protein influence another, while thalidomide was found to recruit Cereblon (part of the cell's protein-disposal system) to destroy otherwise undruggable proteins that help multiple myeloma cells survive. Both drugs have helped scientists understand that small molecules can bring proteins together to change cell behavior.

- Erb is developing ways to find molecular glues more deliberately. A major challenge is that it's hard to predict which small molecule will bind one protein and recruit the right partner. Erb's strategy is to start with a molecule that already binds a target protein, then make many close chemical relatives and search for the rare one that also recruits cellular machinery. Through this approach, Erb has identified a small molecule called dHTC1 that degrades ENL (a leukemia-linked protein) and showed promising results in a preclinical model.

- Proximity-based drugs may eventually do more than destroy proteins. Erb described experimental compounds that bring unexpected proteins to damaged DNA repair sites. These compounds appeared especially harmful to cancer cells with BRCA2 gene defects, which are associated with breast and ovarian cancer. They may also work against cancer cells that resist PARP inhibitors: drugs that interfere with DNA repair in certain tumors. These new strategies in proximity pharmacology are part of a larger effort to build better drugs for combination therapies that may someday offer cures for cancers that are currently difficult to treat.

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