Agents of Change

In the lab of chemist Jim Heath, Caltech's Elizabeth W. Gilloon Professor and professor of chemistry, researchers are working to develop new capture agents for cancer—chemicals that could bind to a particular cancer biomarker, allowing the protein to be identified and studied more easily. The goal is to replace antibodies, the current gold standard for capture agents, with something cheaper and more stable.

The biomarkers that the researchers want to target are hundreds of amino acids long. Yet it is often the case that a single mutation within that sequence is enough to cause cancer. So graduate student Kaycie Butler Deyle (PhD '14) and her colleagues have been trying to zoom in on just the chunk of protein where a mutation is known to occur. For example, Deyle focused on a point mutation on the protein AKT1, where the amino acid E at position 17 is known to change to amino acid K, allowing the protein to stay attached to a cell membrane four times longer than usual—a signal that tells the cell to continue to grow, triggering cancer.

In the lab, she first synthesized the chunk of AKT1 that holds the mutation. Then she needed to come up with a chemical that could grab and hold onto that five-amino-acid-long chunk.

To figure out what that chemical might be, she used something called click chemistry, which relies on the ability of two types of molecules, or click handles, to click together when near one another. Typically this requires the incorporation of a copper catalyst, but the Heath lab came up with a new approach. Deyle first inserted one of the click handles two amino acids away from the mutation in her synthesized chunk of AKT1. Then she screened a million-member library to find a short sequence of amino acids with the other click handle attached that would bind to the AKT1 and click together with the first handle. That sequence of amino acids makes up a new capture agent for AKT1. "Essentially, we use the cancer protein to catalyze the formation of its own capture agent," Deyle says.

Next, Deyle attached a cell-penetrating peptide to her capture agent, and she used a dye to spy on its progress, making sure that the agent was getting through. It was. "Even in cells, our capture agent is still really selective for the mutation," Deyle notes.

With that work in hand, the researchers began trying to block the action of the mutant protein completely. What they've found is that an expanded version of their capture agent can successfully stop the mutant protein from binding to the cell membrane.

Thus far, the work has only been done on the benchtop. The next step will be to try it in cells. "We hope this is a route to a unique therapeutic for cancer," Deyle says. *—KF*