CANCER DRUGS: TARGETING UNDRUGGABLE PROTEINS

BY YANA PETRI

Many of us know someone who has been affected by cancer. At first glance, current cancer statistics look grim: the average American has about a 40% lifetime risk of developing cancer and a 20% chance of dying from it.[1] Yet there is reason to be optimistic. In the past decade, scientists have tremendously advanced our understanding of underlying causes of cancer, while also developing novel drugs that may potentially deliver safer and more robust cancer treatments than conventional FDA-approved small-molecule inhibitors.

Many prominent scientists in the field of drug discovery, including Brent Stockwell, a chemical biologist at Columbia University in New York, believe that the challenge of coming up with new cancer treatments lies in undruggable disease-causing proteins.[2,3] These mutated or aberrantly regulated proteins are considered extremely difficult to target with available drug discovery technologies.[3] A poster child of undruggable proteins is mutated K-Ras, which is responsible for about one-third of all cancers.[3]

Ras protein family members (K-Ras, N-Ras, and H-Ras) have been studied for more than thirty years and are thought to play a crucial role in the regulation of cell proliferation, differentiation, and survival, by signaling through a number of downstream pathways.[4] The signaling function of Ras proteins is tightly controlled by the cell through a mechanism that resembles a light switch. In healthy cells, Ras proteins cycle between a GDP-bound state—when the growth signal is off—and a GTP-bound state—when the growth signal is on.[3] The transition between these two states is in part regulated by binding of GTPase-activating proteins (GAPs). These vigilant regulators convert GTP to GDP and make sure that the cell growth signaling function of Ras proteins gets turned off in a timely manner. Mutations in genes that code for the structure of Ras proteins can interfere with GAP binding. This causes Ras proteins to get stuck in a permanently activated "on" state, which ultimately leads to uncontrolled proliferation of Ras-mutant cells.[4] Scientists are not yet sure what causes mutations in Ras genes, but the evidence that these mutations contribute to cancer is indisputable.[3]

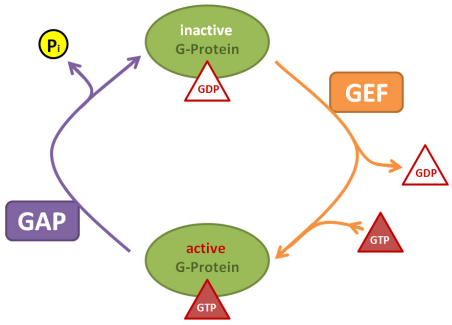

Figure 1. Ras (a type of G-protein) cycle that shows the GDP-bound "off" state and GTP-bound "on" state.

But what makes K-Ras and other undruggable proteins so elusive? Most small-molecule drugs are inhibitors: they work by binding to a protein and physically blocking its function.[3] It is helpful to think of a drug as a key and of the protein as a lock. In order to bind, the drug must fit snugly into a pocket on the surface of a protein. In fact, the presence of well-defined pockets is the hallmark of druggable proteins.[2] Undruggable proteins like K-Ras are quite different—they do not have obvious binding pockets. Some are annoyingly smooth; some are floppy and disordered. Others like to form strong interactions with nearby proteins and evade small molecules that attempt to separate them. Astonishingly, about 90% of all proteins are considered undruggable.[5] Because of this challenge, drugs that were approved by the FDA before 2009 collectively interacted with just 2% of all proteins in human cells.[5]

With these considerations in mind, what is the future of cancer drug discovery? Kevan Shokat and Craig Crews—two leading researchers in chemical biology—have emphasized the need for creative chemical approaches to developing novel cancer drugs. And while it is unclear which approach will ultimately cure cancer, one thing is certain: novel inhibitors and proteolysis targeting chimeras (PROTAC) are beginning to generate a lot of excitement in the field.

In 2013, Shokat and his team discovered that a specific type of mutant K-Ras, K-Ras(G12C), has a druggable surface pocket that was not apparent in previous crystallographic studies.[7] To come up with a starting structure of a novel K-Ras inhibitor, the scientists screened a library of small molecules against K-Ras and used mass spectroscopy to identify compounds that were able to bind to the newly discovered pocket. Next, they obtained a 3D crystal structure of K-Ras bound to the most promising compound. Based on this structural data, Shokat and his team optimized the lead compound and came up with a first novel inhibitor of K-Ras.

Many follow-up studies came out after Shokat's discovery, but some researchers doubted that the new pocket would be druggable in living organisms. However, in 2018, Yi Liu and others reported that tumors indeed decreased in mice that were treated with the new K-Ras inhibitors.[8] This study served as a key step towards starting clinical trials with patients who have a specific K-Ras mutation.[8] In parallel to Shokat, Crews developed another strategy to target undruggable proteins. His lab came up with "smart" small molecules—proteolysis-targeting chimeras, or PROTACs for short—that can entirely destroy proteins instead of just blocking their function.[9]

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The mechanism through which PROTACs induce protein degradation is beautiful and simple. PROTACs consist of three components: the "head," which binds the cancer-causing protein, the linker, and the "tail," which binds another protein called E3 ligase.[9] The E3 ligase attaches ubiquitin to the cancer-causing protein, which acts as a signal for the activation of the natural cellular quality-control machinery. In this mechanism, cancer-causing proteins tagged with a ubiquitin chain are recognized by the proteasome, which literally rips them to pieces.

PROTACs have many advantages over traditional inhibitors. They have long-lasting effects, are likely safer, and do not induce drug resistance.[9] However, their biggest benefit lies in the ability to truly "drug the undruggable." Because PROTACs can in theory bind anywhere on the cancer-causing protein—for instance, to a surface pocket that is not involved in protein function—all cancer-causing proteins, including those that don't have drug-binding pockets, have the potential to be destroyed.

PROTACs are already poised to enter the mainstream. A couple of years ago, Crews launched a startup called Arvinas,

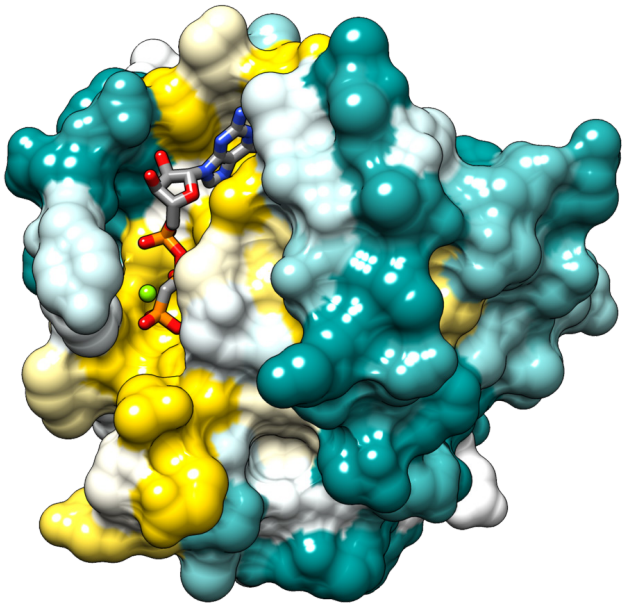

Figure 2. Surface structure of K-Ras analogue H-Ras bound to GDP. Shokat's team discovered a new pocket on its surface that was not apparent in previous crystallographic studies.[7]

"...not a single drug has been FDA-approved against mutant protein K-Ras, which is responsible for about one third of all cancers."

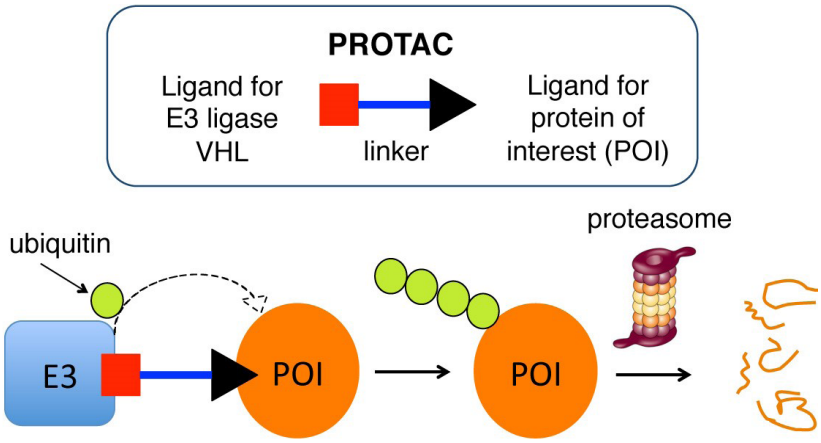

Figure 3. Schematic of how PROTACs degrade cancer-causing proteins.

which openly announced its plans to take PROTACs into clinical trials in the near future. Several labs have also recently used PROTACs to degrade a challenging protein target named BRD4, which is important in the onset of leukemia.[10]

Stephen Hawking once said: "I believe things cannot make themselves impossible." Indeed, it is up to us to create new technologies that render the term "undruggable" obsolete. While this vision currently lies just out of reach, such advances in drug development allow us to imagine a not-too-distant future of personalized medicine in which patients can be cured by taking drugs that target the unique mutations that underlie their cancer.

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IMAGE REFERENCES

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