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When it comes to cancer, there’s power in a good partner

Combinations of drugs could hold the key to overcoming some of the biggest challenges in lung and other cancers.

By Kevin Jiang | Dec 06, 2021

Few challenges are as daunting in scale and scope as the search for new treatments for cancer. As scientists push forward, it is clear that combinations of drugs could help overcome some of the biggest obstacles in oncology. Take, for example, lung cancer.

“The field of lung cancer has seen incredible breakthroughs, thanks to our ever-increasing scientific understanding of its biology,” says Anna Farago, a medical oncologist specializing in lung cancer and a clinical researcher at Novartis. “But it's a diverse disease with different subtypes that each require unique strategies to address. Many subtypes of lung cancer have few or no effective treatments, and it’s essential that we push to create new and better options for patients.”

At Novartis, researchers are tackling lung cancer on many fronts. This includes efforts to create long-sought treatments for one of the most common genetic drivers of cancer, especially in the lung, involving a form of a protein known as KRAS.

Such medicines, however, may need help to aid their effectiveness. So Novartis teams developed a specialized drug with the potential to be a partner not only for drugs against KRAS, but also for many other cancer drugs. How? By confronting one of the yet-unsolved cruxes in oncology: drug resistance.

The monumental challenge of lung cancer

The iconic rock formation El Capitan towers some 3 000 feet (about 914 meters) above the floor of Yosemite Valley, California, in the US. Adventurers from around the world scale its imposing granite walls every day. Yet, a little over 60 years ago, most thought it impossible to climb.

In a way, the story is similar for scientists working on lung cancer treatments. The disease is formidable – more people lose their lives to lung cancer each year than to any other cancer – and it was once considered untreatable. Like the trailblazers who charted the first routes up El Capitan, researchers worked over the decades to understand the disease, establishing new routes for medicines along the way. Their efforts spurred a wave of therapies that have transformed treatment for many types of lung cancer. Other types, however, still have few treatment options.

Obstacles along the route

One of the most exigent forms of lung cancer involves the protein KRAS,[1] a critical signaler of growth inside the cell. When mutated, this protein becomes stuck in an “on” state, forcing the cell to grow out of control. For nearly 40 years, efforts to turn off malfunctioning KRAS failed. Recently, however, scientists discovered new ways to target a certain mutated form of KRAS.[2]

Researchers, including at Novartis, created compounds that can latch onto KRAS in brief windows when the protein flickers off, and keep it off to halt cell growth. But these drugs face a major obstacle: Cells have many copies of KRAS and constantly produce more, which can limit the drugs’ effectiveness.

Facing El Capitan, even world-class climbers need a partner, supporting each other and contributing their individual strengths to the challenge at hand. The same principle can apply to drugs. At Novartis, scientists are testing a compound with the potential to be such a partner.

To coordinate cell growth, a complex network of proteins relay signals to and from KRAS. One of the critical proteins in this network is called SHP2.

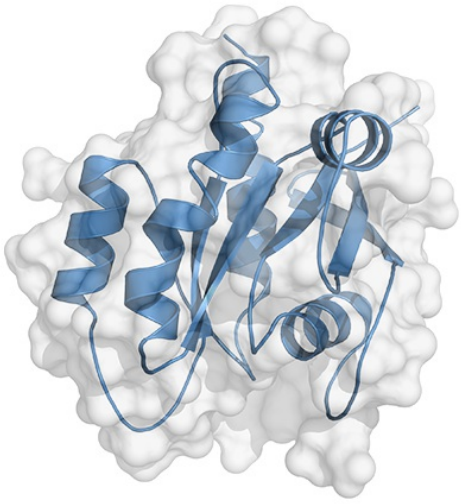
Like a light switch, SHP2 helps turn the KRAS molecule from off to on. So Novartis teams developed an SHP2 inhibitor, which is designed to gum up the switch's machinery by gluing parts of it together. Inhibiting SHP2 can cause the cell to have more “off” KRAS molecules, which could give drugs that target KRAS in this state a better chance to be effective.

Because of this synergy, researchers hope the combination of these medicines can help turn off as many KRAS molecules as possible, to stop cancer cells with certain KRAS mutations from growing. This approach is currently being studied in multiple clinical trials, and it will take time to gauge its safety and effectiveness in patients.

A partner for the climb

There may also be broader benefits for SHP2 inhibitors.

“One of the central challenges with many advanced cancers is that, eventually, resistance to therapies can develop,” says Susan Moody, a medical oncologist and clinical researcher at Novartis. “Cancer cells figure out ways around drugs, so we need to figure out how to stop them.”



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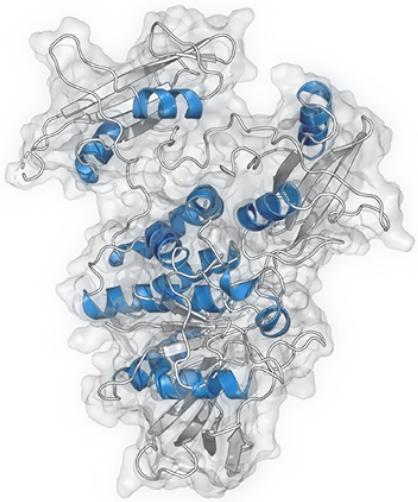

SHP2

KRAS proteins are a key signaler of cell growth, and can become stuck “on” in some cancers. SHP2 proteins play a central role in turning KRAS on.

The exact drivers of drug resistance are still hard to pinpoint. However, there is evidence, particularly in lung cancer, that many mutations linked to the development of drug resistance somehow activate or reactivate KRAS. If SHP2 is disabled, cells could have a harder time turning KRAS on, which may potentially slow or stymie drug resistance.

To this end, Novartis teams are engaged in numerous clinical trials, simultaneously testing an SHP2 inhibitor in combination with many other drugs for different types of lung and other cancers.

“We think that inhibiting SHP2, a signaling node upon which many growth signals converge, may be a way to head off several different resistance mechanisms at once,” says Moody. “We’re excited to study it in combination with other drugs, to see if this approach has the potential to help address drug resistance in certain cancers.”

More than 60 years ago, a team of adventurers took 45 days, spread out over 18 months, to make the first ascent of El Capitan. Today, the fastest pair of climbers reached the top in under two hours.

Scientists are still working to surmount the many obstacles involved in treating cancer. But as El Capitan shows, with effort, ingenuity and teamwork, overcoming seemingly impossible challenges might just be a matter of time.

Novartis researchers are exploring combinations of drugs to help overcome some of oncology’s biggest challenges.

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Reference:

1. Mutations to KRAS are one of the most frequent drivers of non-small cell lung cancer, the most common type of lung cancer.
2. The most common mutated form of KRAS is called G12C. Recent scientific advances enabled drugs that can target KRAS G12C to potentially help patients with this genetic subtype of lung cancer. Such drugs also have broader potential, as KRAS G12C is known to drive colorectal, pancreatic and many other cancers.

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