News and Perspectives

Drugging the Undruggable: New Ways to Repair or Destroy Cancer's Toughest Targets

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Abstract

Treatment failure is a common challenge for conventional cancer treatments—but recent advances in drug development are opening up new treatment avenues. In this *News and Perspectives* article, JMIR Correspondent Cliff Dominy reports on promising new drug therapies that are helping to tackle previously "undruggable" tumors.

Key Takeaways

- Novel strategies have been developed to inhibit, repair, and even eliminate traditionally undruggable tumors.
- Several new drugs have been approved to treat solid tumors, providing new therapeutic options for patients with advanced-stage disease.

For patients with cancers resistant to conventional therapy, the options can be limited. Thanks to advances in biomedical technology and machine learning that are expanding and streamlining drug discovery and design, previously "undruggable" tumors are beginning to yield to innovative new therapies.

In the Beginning

It has been a quarter century since drug developers began using small molecules to directly target cancerous growths in humans. Their strategy: find the active site on a cancer-linked protein and block it. But what happens if your malignant target has a relatively flat, featureless surface that's difficult for the treatment to bind to—like cancer-associated flat proteins, including RAS and p53?

The RAS family of signaling proteins (KRAS, HRAS, and NRAS) were considered to be the poster children of undruggable cancer targets. RAS proteins regulate normal cellular growth and replication by switching between ON (telling the cell to grow and divide) and OFF (stopping that growth signal) configurations. Over time, mutations in the RAS gene can lock the RAS protein into the ON position, resulting in cancerous growth. Dysfunctional RAS proteins have been reported in many solid tumors, with KRAS mutations reported in the majority of pancreatic cancer cases.

In 2013, Kevan Shokat and colleagues were studying the role of KRAS mutations in solid tumors. They noticed that a common genetic mutation that flipped KRAS into the cancer-driving ON position, simultaneously *un*flattened the protein—offering up a single, potentially druggable, external target. Could this new site be blocked with a drug to force the mutant into its OFF position, thereby halting uncontrolled tumor growth?

Drug developers evaluated several suitable candidates, the most successful of which, Amgen's sotorasib, received accelerated Food and Drug Administration (FDA) approval in 2021 to treat advanced non–small cell lung carcinoma in tumors that carried the targeted mutation. Phase II studies showed that patients on sotorasib responded favorably to therapy, with a few participants showing no detectable lung tumors on completion of the study.

This breakthrough proved to be the tip of the iceberg, with drug developers focusing on evaluating novel therapies against other flat oncoproteins.

Sotorasib was soon followed by KRAS competitor adagrasib in 2022. In 2026, the FDA approved two more first-in-class therapeutics: daraxonrasib, a dual RAS ON/OFF controller used in pancreatic cancer treatment, and vepdegestrant, the first PROTAC (proteolysis targeting chimera) drug targeting estrogen receptors in advanced or metastatic breast cancer.

P53: Fixing the Problem

The tumor suppressor protein p53 manages cell integrity by responding to DNA damage and cellular stress signals in healthy cells, helping protect cells from becoming cancerous. Genetic mutations in its gene, *TP53*, can destabilize the resulting protein, causing uncontrolled tumor growth, which drives several human cancers—including nearly all ovarian cancers.

Ecaterina (Cathy) Dumbrava, MD, is an Associate Professor in the Department of Investigational Cancer Therapeutics at the MD Anderson Cancer Center in Houston. She explains, "All of us have p53, it's like a police officer of the cell, or guardian of the genome." When functioning normally, p53 can "jail" damaged cells by triggering cell-cycle arrest or programmed cell death. With a cancer-inducing mutation, Dumbrava says, "the police officer is corrupted... and the cell is able to just go ahead and multiply."

Like the RAS proteins, p53 has been challenging to target, in part due to its flat surface structure. A common p53 mutation known as Y220C is found within the protein's crucial DNA-binding domain. While this cancer-linked mutation makes p53's structure unstable at body temperature, compromising its tumor-suppressing action, it also creates a druggable surface pocket, making p53 targetable. Could targeting this pocket and restabilizing Y220C rescue its healthy tumor-policing function?

Researchers at PMV Pharma used 3D modeling of p53 protein to develop rezatapopt, a selective reactivator designed to restabilize the mutant p53 and restore healthy functioning. Rezatapopt is currently being evaluated in the PYNNACLE clinical trial series, with preliminary results showing promise. "The PYNNACLE study is really a testament to precision oncology," says Dumbrava, a lead investigator on the trial. In its August 2026 interim update, PMV Pharma reported an overall response rate of 46% to rezatapopt monotherapy in a sample of 76 patients with advanced ovarian cancer. Many tumors shrank within weeks of treatment initiation, with 4 patients showing complete responses—meaning, no detectable tumors—on imaging.

Vepdegestrant: Eliminating the Problem

Breast cancer is the most commonly diagnosed cancer in women and the fourth leading cause of cancer death, with the most common form, ER+/HER2-, occurring in approximately 70% of cases. Most patients receive and respond to standard treatment—inhibiting estrogen receptor function—but some 40% of patients may eventually develop treatment resistance, and some 15% may not respond to treatment from the outset. When traditional approaches fail, new approaches are needed.

To tackle the problem, scientists at Arvinas developed the PROTAC technology. PROTAC drugs don't inhibit their targets—they destroy them. Arvinas's leading PROTAC drug, vepdegestrant, was designed to flag the estrogen receptor protein for removal by the proteasome. As Erika Hamilton, MD, director of breast cancer research at the Sarah Cannon Research Institute, explains, "The proteasome is what I like to call the intracellular garbage disposal. It chews up the estrogen receptor and then... is recycled—it is free to go and work on another estrogen receptor." The advantage: one vepdegestrant molecule can remove multiple receptors, leading to greater efficacy at lower doses.

Vepdegestrant has two functional domains separated by a chemical linker. One end, the "warhead," recognizes and binds to a pocket on the estrogen receptor, while the other end tags the doomed protein with small ubiquitin proteins—a signal for the proteasome to take out the garbage.

Hamilton was the lead investigator on the phase 3 VERITAC-2 trial, which evaluated the safety and efficacy of vepdegestrant against fulvestrant, the current standard of care. For tumors that had acquired resistance to fulvestrant, the PROTAC was associated with a 42% reduced risk of tumor progression.

In May 2026, vepdegestrant became the first PROTAC-enabled technology to be approved by the FDA to treat ER+/HER2- breast tumors with mutations in the estrogen receptor gene. "What really stood out to us," Hamilton says, "was how well vepdegestrant was tolerated. It was extremely rare for patients to discontinue treatment or reduce the dose, so this was a drug that not only worked, but that patients could tolerate quite well." Another benefit: no needles. "Vepdegestrant is something people can take orally at home, which is a big win from our patients' viewpoint."

Toward a Precision Future

Solid tumors are complex moving targets, constantly reinventing themselves following a therapeutic assault in order to survive.

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>
> Ecaterina (Cathy) Dumbrava, MD

Hamilton says that the future is moving toward a more personalized therapeutic approach where, "a broad drug arsenal will ultimately allow us to treat each individual patient, and their cancer, in the most appropriate way." Dumbrava agrees, "There is hope. Things have changed so much in the past 10 to 15 years in treating cancer."

Keywords: antineoplastic agents; molecular targeted therapy; precision medicine; proteolysis-targeting chimeras; breast neoplasms; lung neoplasms; pancreatic neoplasms; ovarian neoplasms

Please cite as:

Dominy C
Drugging the Undruggable: New Ways to Repair or Destroy Cancer's Toughest Targets
J Med Internet Res 2026;28:e115394
URL: https://www.jmir.org/2026/1/e115394
doi: 10.2196/115394

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