of Dana-Farber Cancer Institute in Boston, MA, who wasn’t connected to the study. But if larger studies prove definitive, he says, the ADC will be a useful addition to breast cancer treatment. “It’s not a home run, but a substantial number of patients seem to benefit.” —Mitch Leslie

Researchers Reveal Another KRAS Inhibitor

Although researchers have long thought that RAS proteins were undruggable, two KRAS\textsuperscript{G12C} inhibitors are now in phase I clinical trials. A recent study presents a third molecule, Boehringer Ingelheim’s BI-2852, which targets a different pocket on KRAS and might work against all KRAS mutations, not just KRAS\textsuperscript{G12C} (Proc Natl Acad Sci USA 2019;116:15823–9).

Members of the RAS family are mutated in about 20% of cancers, making them prime therapeutic targets. KRAS, for instance, is one of the most commonly altered oncogenes, with mutations occurring in up to 96% of pancreatic cancers and 54% of colorectal cancers. However, scientists have only recently identified pockets on RAS proteins into which a drug might fit. Thus far, one inhibitor, Amgen’s AMG 510, has shown a favorable safety profile and partial responses in patients with non–small cell lung cancer, colorectal cancer, and appendix cancer (Cancer Discov 2019;9:988–9).

Pursuing other possibilities, Darryl McConnell, PhD, of Boehringer Ingelheim in Vienna, Austria, and colleagues homed in on a second pocket, known as switch I/II, which lies at the junction of two regions that RAS uses to signal and drive cell proliferation. The pocket is small, shallow, and contains slippery polar amino acids, making it extremely challenging for chemists to find molecules that stick tightly, he says. When the researchers ran a conventional screen on 1.7 million compounds, they didn’t uncover any promising hits, which “shows that classical approaches don’t work on RAS,” says McConnell. He and his colleagues turned to an alternative approach that involves testing molecular fragments, some of which were pieces of the compounds they had assessed previously. These smaller pieces can fit snugly into the pocket and don’t clash with the protein as full-sized molecules do, explains McConnell. Two screens on 15,600 fragments, performed with collaborator Stephen Fesik, PhD, of Vanderbilt University in Nashville, TN, revealed 55 that bound weakly to the switch I/II pocket. Guided by X-ray crystallography, the team progressively tweaked the structure of their molecules to improve binding and produced one that attaches tightly to the inactive and active forms of the protein.

Switching on KRAS leads to phosphorylation of ERK, a change the researchers used as an indicator of KRAS activity. They found that in culture, the inhibitor almost completely blocked ERK phosphorylation in KRAS-mutated lung cancer cells and cured their proliferation. The new molecule is not yet a drug, McConnell says, but it is a good starting point for one. Its potency and specificity are what need to be improved.

Both inhibitors in clinical trials target the KRAS\textsuperscript{G12C} mutation, which occurs in a minority of KRAS-mutated cancers, notes Luke Gilbert, PhD, of the University of California, San Francisco, who wasn’t connected to the study. “What this paper suggests is that there are inhibitors that could target other types of RAS-mutant proteins.” He says it’s also encouraging that the molecule binds to active and inactive KRAS, which may help prevent resistance.

“The discovery ‘adds to the tools we have for understanding how to block RAS,’” says John O’Bryan, PhD, of the Medical University of South Carolina in Charleston, who also wasn’t connected to the research. But developing the molecule into a drug will require much more work, he says. For instance, researchers will have to assess its pharmacology in cells and animals, test whether it works against cells other than lung cancer cells, and show that it causes tumor regression. “The question is whether we can move this compound forward to develop a potent RAS inhibitor for use in the clinic,” he says. —Mitch Leslie

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The first two cancer biosimilars are now being sold in the United States: bevacizumab-awwb (Mvasi; Amgen/Allergan), a biosimilar of the angiogenesis inhibitor bevacizumab (Avastin; Genentech), and trastuzumab-anns (Kanjinti; Amgen/Allergan), a biosimilar of the HER2-targeted agent trastuzumab (Herceptin; Genentech). They cost about 12% to 13% less than their reference products.

Researchers concluded that Janssen’s erdafitinib (Balversa) may be effective for patients with locally advanced or metastatic urothelial carcinoma who have an FGFR3 or FGFR2 mutation and have not responded to platinum-containing chemotherapy (N Engl J Med 2019;381:338–48). In the phase II BLC2001 trial, 99 patients had an objective response rate of 40% and a median overall survival of 13.8 months.

AbbVie announced that it acquired the biopharmaceutical company Mavupharma for an undisclosed amount. The deal will give AbbVie access to Mavupharma’s pipeline of cancer therapies, which target the STING immune pathway—including MAVU-104, a small-molecule inhibitor of ENPP1.

Germline BRCA2 mutations may be associated with an increased risk of NHL in children and adolescents (JAMA Oncol 2019 Jul 25 [Epub ahead of print]). Researchers analyzed whole-genome sequencing data from 1,380 survivors of Hodgkin lymphoma and NHL, and 59,345 healthy controls. They found that the 565 survivors of NHL were significantly more likely to have BRCA2 mutations than healthy controls.

The World Health Organization added 12 cancer drugs to its list of essential medicines, including the PD-1 inhibitors pembrolizumab (Keytruda; Merck) and nivolumab (Opdivo; Bristol-Myers Squibb) for advanced melanoma (https://www.who.int/medicines/en/).

The Biden Cancer Initiative has suspended operations indefinitely in response to former Vice President Joe Biden’s presidential run. Biden started the nonprofit 2 years ago after the creation of the federally funded Beau Biden Cancer Moonshot. The organization facilitated collaboration among researchers, companies, and patient groups.