The most advanced version of Jonas's tool—a cylinder about the size of a grain of rice—can be loaded with up to 48 drugs, or combinations of drugs. With a standard biopsy needle, researchers inject the device into the tumor, where the drugs are released. The drugs are spaced far enough apart on the device that compounds in adjacent reservoirs will not seep into the same region of the tumor tissue. After 24 hours, the implant is removed, along with a bit of the surrounding tissue, with a larger-core needle. By staining the tumor samples with antibodies to cell death or proliferation markers, researchers can determine how well each drug worked.

A future version of this tool could potentially test more than 48 drugs without major changes to its size or design. Practically speaking, though, "it's probably easier to put two devices into one tumor to test 96 drug combinations," Jonas says.

The MIT team tested its technology in mouse models of human prostate, breast, and skin cancers (Sci Transl Med 2015;7:284ra57). In one set of animals, the researchers measured tumor cell apoptosis in response to drugs loaded into the implanted device. These local cellular readouts correlated with tumor cell responses in a separate cohort of animals treated systemically with the same drugs.

Plans are under way to test the device this summer in patients with breast cancer, to show that the local molecular readouts, such as expression of cell death or proliferation markers, correlate with clinically relevant markers such as tumor shrinkage and long-term survival, Jonas says.

The Presage team, working with scientists at Fred Hutchinson Cancer Research Center in Seattle, developed a hand-held injection device with eight needles (Sci Transl Med 2015;7:284ra58). Doctors can use this device, called CIVO, much as they would administer a flu shot, Klinghoffer explains.

Guided by ultrasound imaging, the physician positions the device over the length of the tumor and pushes a lever to deliver up to eight drugs. Part of the tumor is removed 1 to 3 days later for analysis by immunohistochemical assays and high-resolution imaging. These analyses could help doctors choose the best drug for the patient.

The scientists have used CIVO successfully in mice engrafted with human tumors and in dogs with naturally occurring cancer. The team also tested CIVO in people with lymphoma. The mouse experiments showed that localized tumor responses predicted responses to the same drugs given systemically, and the research in dogs and people found no serious side effects with the microinjection procedure.

In a related commentary, R. Charles Coombes, MD, PhD, professor of medical oncology at Imperial College London, UK, writes, "These techniques offer a possible alternative to the 'hit and miss' way of using anticancer drugs in patients that has unfortunately become accepted practice" (Sci Transl Med 2015;7:284ps10). ■

Genomic Marker Predicts Response to PD-1 Inhibitor

A phase II study has identified the first genomic marker, mismatch repair (MMR) deficiency, to predict response to PD-1 blockade in colorectal and other cancers. Researchers presented the findings at the American Society of Clinical Oncology Annual Meeting in Chicago, IL, on May 30. Initial data from the study were published concurrently in *The New England Journal of Medicine* (N Engl J Med 2015 May 30 [Epub ahead of print]).

Researchers hypothesized that because tumors with MMR deficiency have a faulty DNA repair system and generally harbor hundreds—even thousands—of mutations, they might be more susceptible to augmentation of the immune system with a PD-1 inhibitor, explained Dung T. Le, MD, an assistant professor of oncology at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine in Baltimore, MD, who presented the findings. This is because each mutation has the potential to encode a mutant protein that might be recognized as an antigen by the immune system.

To test their theory, researchers turned to patients with colorectal cancer, whose tumors are often sequenced to check for defects in any of four mismatch-repair genes—*MLH1*, *MSH2*, *MSH6*, and *PSM2*—characteristic of hereditary Lynch syndrome. They recruited 25 patients with MMR-deficient and 25 patients with MMR-proficient colorectal cancers. In addition, they recruited 21 patients with other types of tumors that exhibited MMR deficiency.

Patients in all three cohorts had previously treated metastatic cancer, and all received the anti–PD-1 antibody pembrolizumab (Keytruda; Merck), given intravenously at a dose of 10 mg/kg every 2 weeks. In patients with colorectal cancer, the tumor marker carcinoembryonic antigen (CEA) was measured before and during the trial.

Le reported that 62% of the patients with MMR-deficient colorectal cancer experienced tumor shrinkage compared with 0% of those with MMR-proficient disease. The disease control rates, which account for both tumor shrinkage and stable disease, were 92% and 16% respectively.

In the group of other MMR-deficient cancers, the overall response rate (ORR) was 60% and the disease control rate was 70%. Patients with MMR-deficient non-colorectal cancers responded much like those with MMR-deficient colorectal tumors: The ORR was 60% and the disease control rate was 70%. This group included patients with advanced endometrial cancer and several types of advanced gastrointestinal cancers.

"The responses were durable in a treatment-refractory patient population, and many of these responses are ongoing for over a year," said Le.

Reductions in CEA levels occurred quickly in the MMR-deficient group, usually within a few weeks of starting treatment. That's an indication that "the T cells were sitting there and that they were inhibited," said Le. "They were waiting to be released." In contrast, CEA levels increased in patients with MMR-proficient tumors.

Of note, MMR-deficient tumors had an average of 1,782 mutations; MMR-proficient tumors had just 73. Having a higher number of mutations was linked to a better response. However, some patients with MMR-deficient tumors didn't respond to pembrolizumab, which may mean that "those

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Dung T. Le, MD, discusses the use of mismatch repair deficiency to predict response to PD-1 blockade in colorectal and other cancers.

patients may not have a mutation that the immune system can recognize," explained Le, adding that researchers plan to further assess the MMR-deficient non-responders.

Although MMR deficiency can occur in many cancer types, including those in the uterus, stomach, biliary tract, pancreas, ovaries, prostate, and small intestine, in addition to colorectal cancer, Le said it is too early to recommend that all patients with cancer be tested for it. Researchers first need to confirm their findings in a larger group of patients. "This was a small study," she said. ■

Study May Yield Breakthrough for DIPG

A recent study suggests that a drug approved for the treatment of multiple myeloma may hold promise for treating diffuse intrinsic pontine glioma (DIPG), a pediatric brain tumor that currently has no effective treatment.

Researchers screened 16 human DIPG cell lines against a panel of 83 promising targeted agents and chemotherapies approved for pediatric brain tumors. The multihistone deacetylase inhibitor panobinostat (Farydak; Novartis) was selected for further study based on its efficacy in 12 of the 16 cell lines.

When the researchers injected the drug into mice implanted with DIPG tumors, they found that it slowed tumor growth. The findings set the stage for a phase I clinical trial of panobinostat, slated to begin by the end of this year (Nat Med 2015;21:555–9).

"This disease is the leading cause of brain tumor death in children, and we've made zero progress in treating it over the past several decades," says the study's senior author Michelle Monje, MD, PhD, a pediatric neuro-oncologist and assistant professor of neurology at Stanford University School of Medicine in Palo Alto, CA. "It's exciting that we have preclinical data that suggests a therapy."

Observing that DIPG cells eventually developed resistance to panobinostat, the researchers also experimented with a combination of panobinostat and GSK-J4 (GlaxoSmithKline), a development-stage demethylase inhibitor that has shown some potential for treating DIPG. They discovered that the two drugs work synergistically to counteract known mechanisms of epigenetic dysfunction in DIPG cells.

Panobinostat's potential as a therapeutic agent is consistent with earlier research showing that about 80% of DIPG tumors harbor recurrent K27M mutations in genes encoding histone H3 that prevent trimethylation, causing broad epigenetic dysregulation, says Monje. By inhibiting histone deacetylase, investigators expected panobinostat to increase acetylation, but they were surprised to discover that it also restored methylation and normalized gene expression.

DIPG has been difficult to study because tumors are enmeshed in the brain stem, cannot be removed, and are not typically biopsied. However, 5 years ago, Monje established the first cell culture of DIPG from an autopsy sample. Similar efforts to obtain tumor tissue for research have led to the development of additional DIPG cell cultures in Monje's lab and in several other labs internationally.

"In the past we would take adult glioblastoma tumors and test those cells for targets, but we now understand that the mutations found in DIPG are not the same as those found in adult tumors," says Mark Kieran, MD, PhD, clinical director, Brain Tumor Center, Dana-Farber/Boston Children's Cancer and Blood Disorders Center in Boston, MA, who was not involved with the study. "What makes this study so unique is that it uses the appropriate targeted cells from actual DIPG patients and shows that, *in vitro*, panobinostat can turn off tumor cell proliferation and, *in vivo*, it can cross into the brain and turn off tumor growth."

Kieran cautioned that many questions remain about panobinostat's potential in DIPG. For example, while systemic administration of the drug showed effectiveness in mice used in the study, it is not known whether it will cross the blood–brain barrier in children. Monje's team used convection-enhanced delivery to directly infuse panobinostat into the brain stem in mice, but that method has not yet been approved for humans.

"That one drug is suddenly going to knock out DIPG is unlikely, but for a disease where we've seen no progress in 50 years, this paper is an enormous advance in our understanding," says Kieran. "For the first time, we have at least some idea of how to start moving forward." ■

New Options for EGFR-Mutant Lung Cancer

Two new drugs that target the most common cause of acquired resistance to earlier EGFR inhibitors may offer a much-needed treatment option for patients with EGFR-mutated non–small cell lung cancer (NSCLC), according to findings from early-phase clinical trials.

AZD9291 (AstraZeneca) and rociletinib (Clovis Oncology) are third-generation EGFR tyrosine kinase inhibitors that are active against the T790M *EGFR* mutation, the most common mechanism of resistance in patients whose tumors progress after treatment with first-generation EGFR inhibitors, such as erlotinib (Tarceva; OSI Pharmaceuticals) and gefitinib (Iressa; AstraZeneca). In separate trials, AZD9291 and rociletinib were associated with response rates of 61% and 59%, respectively, among T790M-positive patients resistant to first-generation EGFR inhibitors, compared with 21% and 29% among patients without the mutation (N Engl J Med 2015;372:1689–99; N Engl J Med 2015;372:1700–9).