cells under siege, Cas is deployed against invaders, usually bacteriophages. A Cas enzyme is a masterly gene-cutting engine. It uses two bound RNAs—guide and tracer strands—that are central to their activity. Cas innately interacts with DNA and generates clean double-stranded breaks at loci specified by the guide RNA. In June 2012, Doudna and Emmanuelle Charpentier, a microbiologist at Umea University in Sweden, set the scientific community aflutter when they reported in the journal Science how they transformed the bacterial defense strategy into a new way to modify genes by hand. A member of Doudna’s team also figured out how to combine the activity of two of nature’s CRISPR RNAs into a single-guide strand.

Doudna received the 2014 Lurie Prize in Biomedical Sciences awarded by the Foundation for the National Institutes of Health. Last fall, she and Charpentier each won a $3 million Breakthrough Prize for their CRISPR research. The honor was funded by several big names in technology, including the founders of Facebook, Google, and the DNA company 23andMe.

**Targeted Therapy Makes Inroads in Medulloblastoma**

By Charlie Schmidt

Children with medulloblastoma, a rare brain cancer, face a challenging prognosis. Standard treatments have boosted 5-year survival rates beyond 80%, but depending on a child’s age, side effects—especially from radiation to the brain and spinal cord—can be devastating. Younger children, with their rapidly developing nervous systems, can wind up with substantial cognitive deficits that make it difficult for them to live independently as adults. Scientists are therefore highly motivated to develop more targeted therapies that could limit the need for radiation—or at least delay it until a child becomes old enough to tolerate treatment without a major drop in IQ.

Last July, investigators reported considerable progress toward that goal. In two concurrent phase II clinical trials, treatment with a targeted drug called vismodegib, which is approved already for basal cell carcinomas of the skin, shrank or eliminated tumors in four of 43 treated patients for 2 months or more. And in 13 patients, vismodegib stopped tumor growth for 17 months. Other gene-modifying technologies have never generated the excitement surrounding CRISPR. Zinc finger nucleases can achieve double-stranded DNA breaks, as can transcription activator-like effector nucleases. But some biologists have complained that both types of nucleases can be finicky. Neither possesses the reliability or simplicity of CRISPR–Cas9, said MIT’s Zhang.

His institution holds the only U.S. patent on CRISPR–Cas9 technology. The University of California and the Broad Institute of MIT and Harvard University are embroiled in an intellectual property dispute over which was first to develop the gene-editing system. Zhang insists the method emerged in his laboratory, not Doudna’s. Corn said there is no question that Doudna and Charpentier were first.

Vakoc credits his graduate student, Junwei Shi, as the catalyst behind his lab’s move to CRISPR–Cas9 last year. Their research allowed them to “rediscover” six key targets already known in acute myelogenous leukemia. With CRISPR–Cas9 it took about 2 weeks to uncover what had taken scientists using conventional methods 60 years to find. Vakoc won the prestigious Outstanding Achievement in Cancer Research Award from the American Association for Cancer Research earlier this year. He and other investigators marvel at how quickly they now produce mouse models.

“Mouse models can be made very quickly with this technology, so for cancer research CRISPR is really transformative,” Corn said. “In a variety of cancers there are all kinds of passenger mutations. But there are also driver mutations and you may want to show how they proliferate. With genome editing you can very rapidly test mutations and ask whether they are a cause of the cancer,” said Corn, a former cancer researcher at Genentech.

He said the work under way at CSHL by Vakoc and colleagues is important because it shows how CRISPR–Cas9 helps produce answers expeditiously when investigating the genome.

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updated: The following PDQ summaries were recently alternative medicine. The summaries are peer-reviewed, evidence-based and comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:

**PDQ (Physician Data Query)** is the National Cancer Institute's source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:

**The PDQ Childhood Central Nervous System Germ Cell Tumor Treatment** summary was revised to include results of the Children’s Oncology Group study ACNS0122. This study evaluated neoadjuvant chemotherapy followed by radiation therapy for children with localized non-germinomatous germ cell tumors. The neoadjuvant chemotherapy regimen consisted of carboplatin/etoposide alternating with ifosfamide/etoposide. At the completion of induction chemotherapy, responding patients received 36 Gy of craniocarpal radiation, with 54 Gy to the tumor bed. On the basis of central review of response to induction chemotherapy, 87% of patients showed either a partial response (PR) or a complete response (CR). For the 102 eligible patients in the study, 5-year event-free survival (EFS) was 84% ± 4%, and overall survival (OS) was 93% ± 3%. At 3 years, EFS was 90% ± 4%.

**Alternative Targets**

Meanwhile, scientists are investigating ways to inhibit the downstream proteins. In 2014, Cho and colleagues published findings in *Nature Medicine* showing that a small molecule called JQL inhibits the activity of bromo and extra C-terminal (BET) proteins that, in turn, regulate the transcription of SOFU and GLI. Developed initially to block transcription of the myc oncogene, previously thought to be untreatable, BET inhibitors such as JQL are now eagerly sought in drug development. JQL targets a BET protein called BRD4. Cho’s research shows that in addition to blocking myc in multiple myeloma, JQL interferes with SHH signaling downstream of smoothened. Cho said that JQL or a different BET inhibitor might overcome resistance to vismodegib, both in the half of SHH patients with primary resistance to smoothened inhibition and in others who inevitably become resistant to it. “What we’re really trying to do is hit the most downstream proteins such as GLI, which is responsible for the entire SHH transcriptional output,” Cho said. “This is a novel way of targeting cancer in general. Instead of hitting kinases and upstream components, you target the transcriptional machinery. JQL is essentially an epigenetic drug.”

Marcel Kool, Ph.D., senior scientist in the division of pediatric neurooncology at the German Cancer Research Center in Heidelberg, said phase II results with vismodegib offer crucial evidence that targeted therapy can work in medulloblastoma. But the drug has its drawbacks, he said, including potential side effects in the bones that could be problematic, especially for young children. Moreover, vismodegib doesn’t work in patients with p53 mutations, he said, who tend to have highly aggressive tumors.

Scott Pomeroy, M.D., Ph.D., neurologist-in-chief at Boston Children’s Hospital, says a promising approach could be to combine smoothened inhibitors with other targeted therapies, including BET and PI3 kinase inhibitors. Pomeroy said toxic effects associated with drugs that act on gene transcription could be worrisome “since they could affect not just genes in the SHH pathway but many other genes as well.” He added, “We’re only now beginning to learn how well tolerated they are.”

One significant limitation to clinical research in SHH medulloblastoma is that fewer than 150 new cases occur per year. According to Pomeroy, investigators are exploring the potential for multinational clinical trials that can recruit cases from throughout Europe and North America. Researchers held recent meetings in Boston and Heidelberg, he said, to “strategize and come up with shared approaches. We need to increase numbers and get these trials done faster and more efficiently.”

“The challenge with SHH medulloblastoma, he added, is that since current treatments save lives, parents tend to be reluctant to gamble with an experimental therapy. “People ask, ‘When is all this new research going to pay off?’” he said. “And the answer is that it’s paying off now, but not in a single step. We can’t turn off the radiation machines yet—as we gain success with targeted treatments, we can peel back on radiation and chemotherapy, but this is going to be a sequential process.”

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