OPEN AMBITION

Jay Bradner believes that cancer can be defeated through control of epigenetics — and he is not shy about spreading the word.

BY AMY MAXMEN

Jay Bradner has a knack for getting the word out online. You can follow him on Twitter; you can become one of more than 400,000 online viewers of the TEDx talk he gave in Boston, Massachusetts, last year; you can see the three-dimensional structure of a cancer-drug prototype created in his laboratory and you can e-mail him to request a sample of the compound.

Bradner, a physician and chemical biologist at the Dana-Farber Cancer Institute in Boston, makes defeating cancer sound easy — one just has to play tricks on its memory. "With all the things cancer is trying to do to kill our patient, how does it remember it is cancer?" he asked his rapt TEDx audience. Bradner says that the answer lies in epigenetics, the programmes that manage the genome.

DNA serves as the basic blueprint for all cellular activity, and DNA mutations have long been known to have a role in cancer. But much of a cell's identity is determined by modifications to chromatin, which comprises DNA and the proteins that bind and package it. Epigenetic instructions, in the form of chemical marks that cling to chromatin, tell cells how to interpret the underlying genetic sequence, defining a cell's identity as, say, blood or muscle.

Findings over the past ten years have strongly implicated dysregulation of epigenetic instructions in cancer, where growth-driving genes express like crazy and genes that keep cell division in check are silenced. Bradner's aim is to create a drug that can rewrite those instructions so that cancer cells forget what they are and cease their deadly proliferation.

Bradner thinks that this epigenetic approach could strike down one of cancer's most treacherous drivers, the DNA-binding protein Myc. Myc is involved in up to 70% of cancers but is generally considered 'undruggable', because the active parts of its structure are not accessible to the kinds of small-molecule drugs that chemists generally create. "Myc is one of those things that people dream of targeting," says Dash Dhanak, head of cancer epigenetics at GlaxoSmithKline (GSK) in Collegeville, Pennsylvania.

Just as audacious is Bradner's commitment to making his reagents available and his ideas accessible to scientists and laypeople alike, a rare attitude in the highly competitive world of drug discovery. Researchers in Bradner's lab have developed a compound that interferes with Myc by manipulating epigenetic instructions, and he has sent it out to hundreds of collaborators worldwide. "That's not common in practice," says Bradner, "but from first principles, it's the right thing to do."

Detractors may scoff at Bradner's flashy approach, but those who have followed his career say that there is substance to go with the style. "Jay has figured out translational science," says Stuart Schreiber, director of chemical biology at the Broad Institute in Cambridge, Massachusetts, and Bradner's former postdoctoral adviser. "He's really just good at making important discoveries while staying connected to their clinical potential."

In 1992, while Bradner was an undergraduate at Harvard University, also in Cambridge, he took a chemistry class taught by Schreiber on small-molecule discovery. By the time he graduated, Bradner knew that he wanted to apply the methods he had learned to cancer-drug development. He headed west to Illinois, to study the disease at the Pritzker School of Medicine at the University of Chicago.

MARKED FOR DEATH

In 1999, Bradner returned to Massachusetts for a clinical residency at Brigham and Women's Hospital in Boston, and in 2004 he joined Schreiber's lab as a postdoctoral researcher. Schreiber's team was researching chemical compounds that override normal epigenetic control of gene expression by modulating chromatin. Such control systems generally involve three types of protein: 'writers', 'readers' and 'erasers' (see 'Rewriting memory'). Writers attach chemical marks, such as methyl groups (to DNA) or acetyl groups (to the histone proteins that DNA wraps around); readers bind to these marks and influence gene expression; erasers remove the marks. The marks serve as instructions that are passed down as cells divide, providing a sort of cellular memory to ensure that skin cells, for example, beget other skin cells. Epigenetics has become one of the hottest areas of biological research.

Schreiber and his group had long been looking at histone deacetylases (HDACs), eraser proteins that remove acetyl groups from histones. Some chromatin regions in cancer cells contain fewer acetyl groups than those in normal cells, and drugs called HDAC inhibitors increase acetylation. Since 2006, two such drugs — vorinostat and romidepsin — have been approved by the US Food and Drug Administration to treat cutaneous T-cell lymphoma, a rare immune-cell cancer that affects the skin. The drugs generated excitement among cancer researchers, but because they block many types of HDAC — in both healthy and cancerous cells — they can be toxic. Several trials for other cancers turned up disappointing results.

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Bradner experienced the let-down of the HDAC inhibitors first-hand in 2008, soon after starting his own lab. Chris French, a pathologist at Brigham and Women's Hospital, consulted with Bradner about a ten-year-old boy he was treating for a rare and aggressive cancer called NUT midline carcinoma (NMC), which typically kills patients within a year of diagnosis. French, an expert on NMC, diagnosed the disease after cardiac surgeons had opened the boy's chest and found a tumour the size of a baseball in his heart. Chemotherapy was not an option, as it would have hampered his recovery from surgery. Bradner and French discussed other treatments.

French had shown in 2003 that NMC is caused by a fusion of two genes[1]: *BRD4*, which encodes a reader protein, and a previously unknown gene called *NUT*. This fusion encodes a mutant protein, NUT–BRD4, which seems to act as a reader, spurring errant gene expression and forcing cells to lose their identity and become cancerous. No inhibitors of reader proteins were available then, but French and Bradner knew that vorinostat increased histone acetylation. Perhaps, they thought, if acetylation were increased, NUT–BRD4 would be so busy 'reading' elsewhere that it would overlook the region that was causing cells to become cancerous. Bradner calls the concept "the chemical equivalent of a smokescreen".

It was thin reasoning, but Bradner and French agreed that the emergency at hand warranted an experiment. They tried the drug on cancer cells extracted from the boy, and the cells seemed to forget their cancerous marching orders, reverting from round, proliferating cells into flat, skin-like cells. This gave them the confidence to try treating the boy. The tumour seemed to respond after five weeks, but the toxicity proved too high. "It was taking him four hours to swallow three pills because he kept vomiting them back up," French says. The boy stopped the treatment and died not long afterwards.

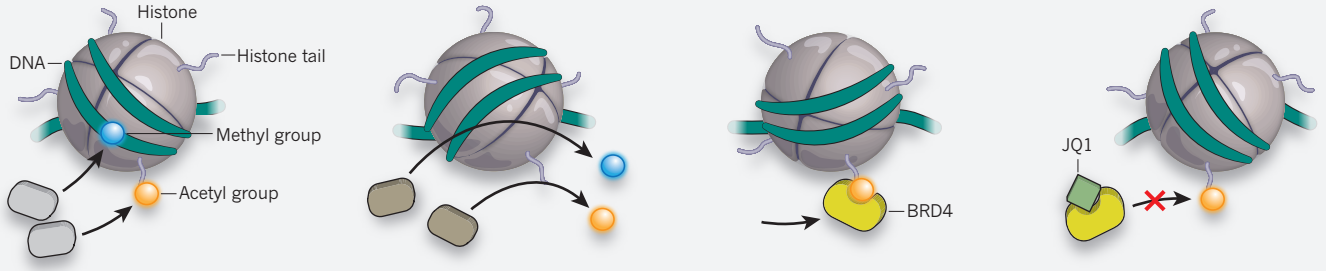
Bradner dwelled on the case, especially on BRD4, a little-studied protein that now seemed to be capable of causing cancer. Disparate lines of study suggested that BRD4 might be linked to the expression of Myc, a target most drug developers had abandoned. If Bradner could defuse BRD4, perhaps he could bring down one of cancer's most notorious dragons.

In 2009, Bradner happened upon a patent from Mitsubishi Tanabe Pharma in Osaka, Japan, for a diazepine-based compound that inhibited BRD4 by blocking its bromodomain, the region that recognizes acetyl groups on histones. Diazepines on the market, such as the anxiety medication alprazolam (Xanax), have only weak interactions with the bromodomain.

DANA SMITH

REWRITING MEMORY

Three types of protein — writers, erasers and readers — orchestrate epigenetic instructions, the chemical modifications that regulate gene expression. Researchers think that compounds that manipulate these proteins could stop cancer cells from proliferating.



Writers add chemical marks to the DNA or to the histone proteins that DNA wraps around.

Erasers remove the marks. Several drugs approved for cancer inhibit eraser proteins.

Readers, such as BRD4, bind to these marks to influence gene expression.

JQ1 blocks BRD4 from reading acetyl groups on histones and could halt progression of some cancers.

"You'd be in a coma by the time you inhibited BRD4," Bradner says. So he began searching for molecules that were similar in structure but more potent. Jun Qi, a researcher in Bradner's lab, synthesized more than 400 diazepines in search of a candidate.

By the end of 2009, they had one. Named JQ1 after Qi, the compound slips into a groove of BRD4, preventing it from binding to acetylated histones and activating genes. With JQ1, the researchers hoped to tease apart which genes BRD4 switches on — and whether any of them cause cancer.

RESEARCH PROMISE

In March 2010, French introduced Bradner to another patient with NMC, a 29-year-old firefighter from Connecticut. Chemotherapy and romidepsin treatment had failed. Bradner asked the man if he could use his cells for research, pledging that the work would help to find cures. The man agreed. He died that July, but his cells made it possible to test JQ1. The compound stopped the cancer cells from dividing and transformed them into non-cancerous cells, both in culture and in mice[2].

It takes years for promising molecules to lead to clinically useful drugs. Had drug-company researchers discovered JQ1, a single team would have forged ahead, probably in secret, to develop the compound. But Bradner decided that the quickest path to the clinic was to do the research openly, with as many collaborators as possible. Since January 2011, Bradner's team has shipped JQ1 to more than 250 labs worldwide. Work on the molecule has produced at least ten publications in top journals.

One of these publications[3], a collaboration between Bradner and Constantine Mitsiades, a cancer biologist at Dana-Farber, bolstered BRD4's connection to Myc. Mitsiades had found that multiple-myeloma cells express high levels of Myc and BRD4, but without a compound to target either of them, it was difficult to learn much more. With Bradner, he found that JQ1 reduced expression of Myc and its target genes and stopped myeloma cells from dividing in mice[3].

Chris Vakoc, a cancer biologist at Cold Spring Harbor Laboratory in New York, was studying the role of BRD4 in leukaemia when he first learned of JQ1. He phoned Bradner immediately. "The next day he sent us a huge amount of the compound," Vakoc says. In Vakoc's hands, JQ1 stopped cancer-cell proliferation in mice with leukaemia and significantly extended their lifespans[4]. JQ1 has also been used to study infectious diseases such as those caused by Epstein-Barr virus[5] and HIV[6].

"In 20 years, my lab could not accomplish all of the research that has unfolded on JQ1 in one year through this open approach," says Bradner. With US$15 million in venture capital from HealthCare Ventures of Cambridge, Massachusetts, Bradner has launched Tensha Therapeutics, a biotechnology company focused on bromodomain inhibition. The Cambridge-based biotech is now screening JQ1 derivatives to learn which are likely to have the fewest side effects — an essential early step in drug development.

Bradner is impatient, however, and is always on the lookout for drugs already in development that would be safe to use in NMC. In 2010, scientists at GSK published a study on an inhibitor of BRD4 and related molecules for treating sepsis[7]. Bradner asked the GSK researchers to try one of their compounds in patients with NMC at Dana-Farber. (Dhanak says that the company had been quietly working on BRD4 inhibitors since French's *NUT–BRD4* paper in 2003.) GSK agreed.

The first attempt was in March this year, when oncologists at Dana-Farber used the company's BRD4 inhibitor GSK525762 to treat a 23-year-old engineering graduate student with NMC. The patient died about three weeks into the treatment. French says he suspects that the dose was too low and that combining the drug with HDAC inhibitors or other epigenetic drugs could yield better results. Dhanak says that GSK might test combinations in the near future.

Any clinical trial for NMC is bound to move slowly — the disease is aggressive, and only 90 cases have been diagnosed in the past decade. To raise awareness of NMC and make it easier for patients to enrol in trials, in 2011 Bradner and his colleagues created an international NMC registry (http://www.nmcregistry.org). It seems to be working. "We were concerned we'd have a problem finding patients, and now, through social media, the patients are finding us," Bradner says.

MAKING GOOD

Not all scientists share Bradner's optimism. "Epigenetics is the new horizon, but when you get down to it, the fact is that people are just mucking around with it and finding interesting effects," says Gerard Evan, a cancer biologist who studies epigenetic signalling at the University of Cambridge, UK. Epigenetics affects many cellular functions, and researchers are only beginning to learn how it influences cell memory.

Whatever the outcome, some see hopeful signs in Bradner's open approach. Dhanak says that he welcomes it. "People like Jay have been tremendous in pushing forward the frontiers," he says.

What Bradner wants most is to fulfil his pledge to the firefighter who died from NMC. "His gift of that rare tumour, given at a time when he was beyond all conceivable treatment, was a powerful experience," Bradner says. If bromodomain inhibition fails, Bradner will apply the same open-source strategy to another target. "More and more, I feel it is so important to impact patients' suffering from cancer, and it doesn't matter whether that's with our molecules or someone else's," he says. ■

Amy Maxmen *writes for* Nature *from New York City.*

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