James Bradner (left) who worked at the Dana-Farber Cancer Institute in Boston, Massachusetts, with Jun Qi who synthesized the JQ1 compound.

CHEMICAL PROBES

A shared toolbox

In a pioneering move, the compound JQ1 was released to the community for free. The impact that this has had on research and development is slowly coming into focus.

BY ANDREW R. SCOTT

In 2010, a young New England firefighter lay dying from a rare and aggressive form of cancer. The disease, NUT midline carcinoma, had taken hold in his left lung and spread widely. A chest tube, inserted to offer some comfort, continually drained fluid containing cancer cells. When doctors explained the research potential of these cells, the man readily agreed to donate them to scientists at the Brigham and Women's Hospital and at the Dana-Farber Cancer Institute, both in Boston, Massachusetts. This gift was one of the key steps in a pioneering development in open innovation that now serves as a model for drug researchers worldwide.

James Bradner's group at Dana-Farber had a molecule that they hoped might make these

cells "forget they were cancer", as Bradner puts it. Sure enough, on exposure to this molecule the cells seemed to return to normal. And when the cancer cells were grown in mice — a model of the firefighter's disease — and the animals were treated with the molecule, the tumours began to shrink (P. Filippakopoulos *et al.* *Nature* **468**, 1067–1073; 2010).

Sadly, this result could not save the firefighter, but Bradner's decision to broadly release the compound through an open-source model of drug discovery has spawned a raft of patents and clinical trials of a new class of drugs: bromodomain inhibitors.

The molecule that affected the firefighter's cancer cells so dramatically was JQ1, named after the chemist who made the original compound, Jun Qi. JQ1 was not intended to be a drug; limitations in its solubility and half-life

mean that it probably never will be. Rather, JQ1 is a chemical probe — a small molecule that interacts with a target protein to allow the activity of that protein to be investigated in the cell.

JQ1 binds to a pocket-shaped region found in many proteins, called a bromodomain. This structure detects a small molecular signal attached to the histone proteins that parcel up DNA into chromatin. When the signal, which Bradner describes as "a molecular post-it note", is recognized by the bromodomain, it can stimulate the protein to begin a series of interactions that results in the activation of genes involved in sustaining cell growth and activity. But in some diseases, including cancer, cells interpret this signal as an instruction to grow and divide out of control. The development of compounds to stop

this errant bromodomain signalling could be a focus for therapy, and, as Bradner saw it, JQ1 had the potential to kick-start the process.

OUT IN THE OPEN

When JQ1's effect on the firefighter's cancer cells was first discovered, the conventional approach would have been to keep everything secret, explains Bradner, who took up the role of president of Novartis Institutes for BioMedical Research, based in Cambridge, Massachusetts, in March. Secrecy was the standard approach — all the details were kept hidden until either the prototype drug had been turned into an active pharmaceutical compound or efforts had come to a standstill. "But we did just the opposite," says Bradner. In what he describes as a "social experiment", he and his laboratory released all the information they had on JQ1. Not only that, but they also promised to supply unlimited quantities of JQ1 to any researcher who wanted it, for free and without restriction on use.

Bradner believes that this approach has greatly accelerated drug development in the field of bromodomain inhibition. His lab has sent samples of JQ1 to more than 400 laboratories worldwide, both in academia and industry, and there has been a clear increase in research activity around the bromodomain proteins it targets, leading to more than 100 filed patents (see 'Driving innovation'). These patents are not for JQ1 itself, but for other molecules that target bromodomains — the development of many of these was guided by the use of JQ1 as a research tool. Some of the structures of these drug candidates are similar to JQ1, but others are completely unrelated. Bradner is convinced that, had he not adopted the open approach, there might be only one, or at most two, bromodomain inhibitors in clinical trials, including his own, TEN-010. Instead, he knows of eight agents under development for the treatment of cancer alone.

"Normally the process of obtaining agreement to use these valuable reagents can be long and complex," says physician-scientist Ross Levine at the Memorial Sloan Kettering Cancer Center in New York. Being able to obtain probes such as JQ1 through open-access agreements has, he says, greatly assisted his research.

Researchers who attempted to assess the impact of JQ1 came to a similar verdict (Z. Arshad *et al. Expert Opin. Drug Discov.* 11, 321–332; 2016). They found that the open release of JQ1 increased innovation in the broader field of bromodomain inhibition — evidence, they said, that an open-access approach can improve the efficiency and lower the cost of both drug discovery and commercialization.

THE WIDER VIEW

Clinical trials are now under way on the use of bromodomain inhibitors to treat some of the most common cancers, including lymphomas, leukaemias, multiple myelomas and solid

DRIVING INNOVATION

More patents have been filed related to bromodomains, the target for the JQ1 chemical probe, than for similar drug-discovery targets for which the probes were not made openly available.

tumours (such as cancers of the pancreas and prostate). Development of all these molecules has benefited from data gleaned from the availability of the molecular probe.

And cancer is not the only target. The open release of JQ1 is also proving to be a boon for research into various neurodegenerative disorders such as Alzheimer's disease, as well as inflammation and viral infection.

JQ1 is just one molecule, however. How much of a trendsetter it will prove to be remains to be seen. Structural biologist Wen Hwa Lee at the University of Oxford, UK, says that although the progress made with bromodomains is a sign of the value of open access, the wider impact of open innovation remains limited. "It is such a new concept," he says. "Having been told all their careers that they have to protect their data, many scientists can find it hard to get their heads around the idea of openly sharing."

Still, developers of other chemical probes are aiming to replicate the JQ1 success story. As part of the drive to increase the ease of access to many more probes, an alliance of researchers, with the endorsement of three life-sciences research organizations — the Structural Genomics Consortium (to which Lee belongs), the Institute of Cancer Research in London and the Broad Institute of Harvard and Massachusetts Institute of Technology in Cambridge, Massachusetts — have been leading an effort funded by the UK's Wellcome Trust to collate data on chemical probes and allow researchers to obtain supplies of these molecules. In late 2015, the group launched chemicalprobes.org, an online portal to freely share probe data. Anyone can submit a probe for publication on the site, although each submission is subjected to peer review — designed to address past problems with poor-quality probes that generated misleading research results. As of March 2016, the portal hosted more than 100 probes targeted against 10 key

families of proteins, including bromodomains. Many of these probes are already being used to guide researchers towards new drugs for clinical trials.

COMMERCIAL INTEREST

Sharing chemical probes doesn't just appeal to academics — the practice is catching the attention of drug companies too. Mark Bunnage, a medicinal chemist at biopharmaceutical company Pfizer, believes that JQ1 has had "a profound impact" on basic research that has allowed the search for new drugs. As well as making use of the probe itself, Pfizer has also begun to release more information about its own molecular tools. Many of the company's chemical probes are available through vendors such as life-sciences company Sigma Aldrich. Pfizer also collaborates with the Structural Genomics Consortium to create new probes, a number of which have been included on the chemical probes portal. "This is a big change of mindset," says Bunnage. "Open-innovation approaches are definitely helping companies and academics to work together to advance the discovery and development of medicines." He hopes that the increase in collaboration in the earliest stages may reduce the number of prospective drugs that fail during phase II clinical trials.

The key to collaboration between academia and life-sciences companies is the sharing of chemical probes so that a protein or other biomolecule can be identified as a drug target early. This accelerates the basic science and allows market dynamics to kick in to incentivize the development of specific drugs. "Everyone can eventually try to develop the best drug to interact with each target," says Bunnage. Lee agrees that for open-research platforms such as the chemical probes portal to be part of a successful economic model, there comes a point at which barriers of confidentiality must come down. At some stage drug companies, driven by their requirement to make profits, must be free to develop their candidate drugs confidentially. Negotiating the transition from open to closed innovation may be a difficult process with high stakes. "Where the pre-competitive line lies must be explored by the partners involved and may also depend on the disease area and its needs," says Lee (see page S56).

The path that Bradner's career has taken since his decision to release JQ1 into the wild demonstrates that openness and commercial interests are not mutually exclusive. Tensha Therapeutics, a start-up he founded in 2011 to develop drug-like bromodomain inhibitors, was acquired by pharmaceutical company Roche in early 2016 in a deal worth around US\$500 million. Clearly, acting in the interests of open science need not preclude commercial success. ■

Andrew R. Scott is a science writer based in Perth, UK.