Halting cancer by halting DNA repair

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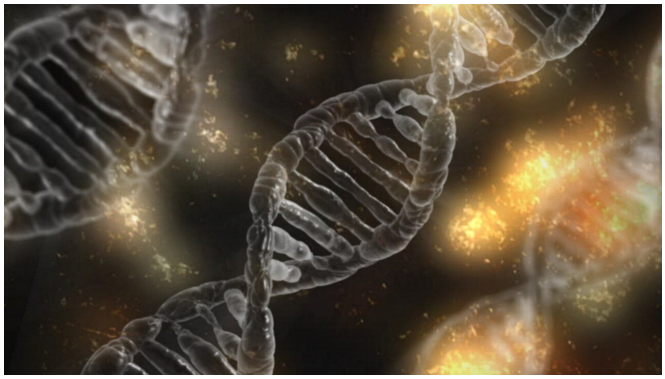

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PARP inhibitors are rapidly transforming the treatment of ovarian, breast, prostate and other types of cancer. To develop these drugs, researchers supported by Cancer Research UK had to decipher how blocking DNA repair could expose a weak point in the biology of cancer cells.

In the early 1990s, Steve Jackson seemed to have his career all planned out. Freshly recruited to the University of Cambridge as a group leader at the Gurdon Institute, he was going to keep doing what he'd done so successfully as a postdoc—study the fundamentals of gene transcription. But then came an experiment that changed everything.

His lab's first graduate student, Tanya Gottlieb, was given the task of investigating the function of an enzyme Jackson had "stumbled across" during his postdoc. This enzyme was activated when it bound to DNA, but Gottlieb and Jackson discovered that it wasn't activated by DNA alone—it was stimulated by DNA breakages.

The finding swept Jackson into the emerging field of DNA repair, and, from there, into cancer research.

Jackson soon hit upon an idea—could inhibiting DNA repair enzymes aid in killing cancerous cells? The thinking is counterintuitive. Within the cells of a human body, DNA is constantly breaking—remarkably, the genome of each cell sustains around 100,000 ruptures a day. By restoring the integrity of broken DNA—and, so, preventing mutations—the body's DNA repair mechanisms protect us from cancer. Blocking repair would, therefore, seem to be a highly dangerous thing to do.

However, Jackson drew on the fact that chemo- and radiotherapy are partly predicated on the increased susceptibility of rapidly dividing cancer cells to DNA damage. Moreover, such therapies massively activate DNA repair systems, and the cancer cells that survive such treatments rely heavily on these systems. It seemed plausible, therefore, that suppressing DNA repair might make existing cancer therapies more effective.

Two hundred miles north of Cambridge, researchers at Newcastle University were working on the same concept. They were focusing specifically on a previously discovered DNA repair enzyme called PARP. This protein binds to, and is activated by, single-stranded breaks in DNA, synthesizing a chain of ADP-ribose molecules that recruit the enzymatic machinery that will repair that breakage. Based on a growing body of academic work, the Newcastle team believed that a PARP inhibitor administered alongside either chemotherapy or ionizing radiation would help destroy tumors.

Soon, Jackson's attention also turned to PARP and, in parallel, these two research groups pushed forward drug discovery programs that led to the clinical approval of PARP inhibitors for cancer treatment.

The drug born of Jackson's research is olaparib, which is marketed as Lynparza by AstraZeneca. The Newcastle team developed rucaparib, initially developed by Agouron Pharmaceuticals and now sold as Rubraca by Clovis Oncology. After the promise of these two pioneering medicines became

apparent, two other drugs—niraparib and talazoparib—were developed by other pharmaceutical companies.

To get here, however, the Cambridge and Newcastle groups had to overcome a problem: no matter how appealing their idea was in theory, pharmaceutical companies were too wary of the dangers of interfering with DNA repair to invest heavily in this approach.

Each group succeeded through partnering with The Cancer Research Campaign—one of the two charities that merged to form Cancer Research UK (CRUK) in 2002. The charity was willing to invest in the type of risky, blue skies research that makes big pharma nervous.

Independently, the two groups made a vital discovery that led them to fully realize the potential of PARP inhibitors. In collaboration with other academic groups (including Alan Ashworth's team at the Institute of Cancer Research in London, which is part-funded by CRUK), they found that PARP inhibitors can target a particular weakness of cancers driven by mutations in BRCA genes.

Currently, PARP inhibitors are approved for treating BRCA-mutation-associated ovarian, breast, Fallopian tube, pancreatic and prostate cancers as second-line and, increasingly, as first-line treatments. It is also becoming increasingly clear that olaparib and rucaparib are effective in treating certain forms of BRCA-mutation-negative cancers, and research is ongoing to further explore such promising opportunities.

Today, over 30,000 patients have been treated with olaparib and that number is growing rapidly. Jackson is therefore able to say that his basic research—and his drive to commercialize it—has saved and extended people's lives. Looking back, he says of his relationship with the Newcastle group that "some friendly competition is a good thing—you know you're in an exciting place when there's competition."

"But," he adds purposefully, "this isn't about two antagonistic groups. It's all about academic groups translating their science to make the world a better place."

Newcastle and the idea of a sensitizer

Ruth Plummer is a consultant medical oncologist at Newcastle University. In 2003, she wrote the first ever prescription for a patient to receive a drug designed to suppress DNA repair.

That moment came eight years after Plummer had joined the Newcastle team and got excited by the promise of their nascent PARP inhibitor project. It was an appointment that marked a turnaround in her career. Plummer had done a Ph.D. in neuroscience while completing her medical degree, but she clicked with cancer specialist Hilary Calvert, the head of Newcastle's clinical trials unit, and she felt strongly that "in oncology, things were changing—or had the potential to change."

Research into PARP at Newcastle, Plummer says, was inspired largely by a 1980 paper showing that cells in a dish treated with a DNA-damaging agent died in greater numbers if PARP was simultaneously inhibited than in the absence of PARP inhibition.

The compound used in that paper was a weak inhibitor of PARP with no prospects of becoming a clinically useful drug. But it was good enough to conduct experiments that supported the hypothesis that more cancer cells died if PARP was inhibited during chemo- or radiotherapy.

The Newcastle team looked to The Cancer Research Campaign for support and together they searched around to see if anyone was developing drugs that blocked PARP. They weren't.

Therefore, The Cancer Research Campaign funded Newcastle's initial work and then financed the creation of a Drug Discovery Unit there. That unit was led by Herbie Newell and Calvert, and included an in-house medicinal chemistry team, headed by Bernard Golding and Roger Griffin, which developed a panel of promising PARP inhibitors.

The emergence of these compounds led to a partnership with Agouron Pharmaceuticals, a small San Diego biotech startup specializing in early drug

development. In 1999, as Plummer and colleagues pushed toward a first test of these drug in patients, a subsidiary of Pfizer bought Agouron Pharmaceuticals. The Cancer Research Campaign commercial team had a crucial role in this acquisition and in shepherding the drugs toward clinical testing. They led negotiations and after the deal they continued to work with Pfizer in various ways, including the management of patents.

Despite these investments from Pfizer, however, there were still cold feet about the drug's safety when time came to run the first PARP inhibitor clinical trial. So, the Center for Drug Development at the newly forged CRUK—established to take risky projects through early phase clinical research—stepped in to sponsor the trial.

This trial, which began in 2003, tested rucaparib in combination with a chemotherapeutic agent in patients with various tumors including late-stage melanoma. The hope was that inhibiting PARP would heighten the effects of chemotherapy. But, as with any Phase 1 trial, the priority was to determine if rucaparib was safe and tolerated by patients. By examining biopsies of the patients' tumors, Plummer also wanted to confirm that the drug was able to get into human tumors and inhibit PARP there.

"We were very cautious when we went into the clinic," Plummer says. "We thought it would be alright, but nobody had done it… We built a big safety factor into the trial." Dosing started low and she was also open and clear with the patients about both the risks involved and the wider goals. "I did what I do in clinical practice all the time," she says. "I told the patients, 'We hope we might have a new and better drug, but we don't know.'"

The study showed that the drug was, indeed, safe and—as Plummer puts it—"that it does what it says on the tin." The question was now how best to use it.

Frustratingly, it became apparent that although a PARP inhibitor was fairly safe when used alone, it was difficult to use in combination with another chemotherapy agent, as together the two drugs caused serious side-effects at doses below those needed for cancer treatment. Furthermore, in this first trial, the gains in slowing tumor growth were inconsistent and only weak to moderate, and overall survival did not improve.

However, while this clinical work proceeded, two pivotal meetings—one in a seminar room, one in a bar—changed everything.

BRCA to the Future

In the early 2000s, at a conference in Oxford, Jackson had a late-night conversation with Ashworth, who was then working at the Institute of Cancer Research in London. Jackson had by then helped develop an effective PARP inhibitor. Ashworth was an expert on BRCA-mutation-associated cancers. Their chat led to a groundbreaking experiment.

Jackson had sought an industrial partner to explore his idea that blocking repair enzymes would help treat cancer.

However, as had happened with the Newcastle team, the big drug companies Jackson spoke to weren't interested; the risk was perceived as too great. So, with the support of the University of Cambridge, Jackson turned to The Cancer Research Campaign to help him spin out his own company.

In addition to working with the university's Technical Transfer Office to file patents, the charity provided seed funding and support to Jackson, and in December 1997 KuDOS Pharmaceuticals was born. The founders then worked together to secure significant venture capital funding, so that by mid-1999 the company was up and running.

Using the Jackson lab's biological expertise and the various assays it had developed, KuDOS quickly identified promising molecules for inhibiting PARP and other repair enzymes. Jackson says KuDOS's early reasoning was similar to Newcastle's—that PARP inhibition might sensitize cancer cells to existing DNA-targeting therapies. However, his thinking was also strongly shaped by the concept of synthetic lethality.

As Jackson explains, many fundamental cellular functions are achieved by two or more pathways working towards essentially the same endpoint. Such functional overlap makes biological systems robust to genetic or drug-induced disruption of a single pathway. This means that disrupting one of the functionally overlapping pathways often has no obvious effect on a cell. But if all the pathways are halted, the cell dies.

Jackson speculated that this principle would apply to drugs disrupting the vital task of DNA repair, which involves multiple partially overlapping pathways. After all, PARP inhibitors were relatively safe—evidence that inhibiting this specific DNA repair pathway alone didn't have overtly deleterious effects on human cells. But what if two pathways were disrupted?

That night in Oxford, Ashworth told Jackson about his work on BRCA mutations. Inheriting a faulty copy of either BRCA1 or BRCA2 drastically increases a person's risk of developing cancer, particularly breast or ovarian—although disease only occurs when cells undergo mutations that compromise or delete the patient's remaining functional copy of BRCA1 or BRCA2.

BRCA1 and BRCA2 encode DNA repair proteins that help repair double-stranded breaks. Jackson and Ashworth speculated that cells lacking a functional BRCA-dependent repair pathway might be relying more heavily on PARP-mediated DNA repair to survive. These cells might therefore be killed by a drug that took out this second pathway.

The two scientists realized they had perfectly complementary resources: Ashworth had cell lines lacking BRCA genes and Jackson had PARP inhibitors. A powerful collaboration was immediately struck, and straight after the conference Jackson and his colleagues at KuDOS had the drugs sent to Ashworth's lab.

Plummer recalls a near identical exchange at Newcastle. Thomas Helleday, who was then at Sheffield University, visited Newcastle to give a seminar about his work on BRCA genes and used essentially the same logic to lay out the case for why cells lacking BRCA1 or BRCA2 might be killed by a PARP inhibitor. Nicola Curtin, the leader of Newcastle's drug development biology program, immediately offered Helleday the drugs he needed to test the idea.

The two sets of collaborators were aware of each other's research but worked independently. First using cultured cells, then using tumors lacking BRCA genes grafted into mice, both groups found that their PARP inhibitor given at certain doses killed cells without a BRCA gene, whereas cells containing either one or two copies of that BRCA gene survived.

These research findings suggested that PARP inhibitors—at least for certain patients with certain cancers—might achieve that goal. The two groups agreed to submit their work nearly simultaneously and their papers came out back-to-back in the 14 April 2005 issue of *Nature*.

Into the clinic

"Within six weeks of the papers coming out we'd gone back to CRUK," Plummer says, "requesting support to test rucaparib in patients with BRCA mutations."

The trial was quickly agreed, although some delays meant it didn't commence until 2007. Excitingly, Plummer saw the tumor of the second patient she treated shrink.

KuDOS's Phase 1 clinical trial of olaparib started in mid-2005 and then was taken forth by AstraZeneca, which acquired KuDOS in December that year. That trial involved 60 patients with late-stage breast, ovarian or prostate cancer—22 of whom were carriers of BRCA1 or BRCA2 mutations. The drug was found to be safe in all patients. Much more strikingly, olaparib clearly reduced tumor size in around half of the BRCA mutation carriers—especially in people with ovarian cancer.

Jackson recalls vividly KuDOS's development director, Peter Harris, announcing at a board meeting that one of the first treated patients had a dramatic reduction in tumor size, calling it "a real eureka moment."

Subsequent work homed in on BRCA mutation carriers and on ovarian cancer, with Phase 2 and 3 trials confirming the effectiveness of olaparib and rucaparib against these tumors. In December 2014, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved olaparib for treating ovarian cancer in carriers of BRCA1 or BRCA2 mutations who've previously undergone chemotherapy. Two years later, the FDA gave rucaparib accelerated approval for similar indications.

Other pharmaceutical companies developed different PARP inhibitors, two of which have now been FDA-approved. Zejula (niraparib), developed by Tesaro, was approved for ovarian and Fallopian tube cancers in 2017. Talzenna (talazoparib), developed by Pfizer, was approved in 2018 for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated HER2-mutation-negative locally advanced or metastatic breast cancer.

In December 2019 and June 2020, respectively, the FDA and EMA approved olaparib for BRCA1- and BRCA2-mutated metastatic pancreatic cancers, and in May 2020 the FDA approved olaparib for BRCA1- and BRCA2-deficient metastatic prostate cancers.

Jackson is excited by the use of PARP inhibitors as first-line treatments. In his office, he brings up on screen the Kaplan-Meier curves from three successive trials of olaparib for BRCA-mutation-associated ovarian cancer. As the drug was given earlier and earlier to patients, the further apart the survival curves of the drug and placebo groups became. Pointing to the third one, he beams, "that includes cures!"

Plummer says she too has several patients she treated with PARP inhibitors who have gone into complete remission. "Not many," she says, "but it can happen and that is fantastic."

Where to now?

As clinicians increasingly refine the use of PARP inhibitors in patients with inherited BRCA mutations, there is also a drive to identify people who don't carry germline BRCA mutations but whose cancers might also be sensitive to PARP inhibitors. These include tumors with somatic loss of BRCA gene function and tumors that don't lack BRCA function but which have deficits in this DNA repair pathway via some other means—a concept termed "BRCAness."

An important research focus now is therefore to develop better biomarkers and other tests for identifying tumors that will be sensitive to PARP inhibitors. And that includes discovering signals that might say if a cancer from a BRCA1 or BRCA2 mutation carrier will be resistant to this drug class.

Plummer is also currently running trials to test whether combining a PARP inhibitor with cancer immunotherapy is useful. These were inspired by work from other groups showing that blocking PARP can increase the immunogenicity of tumor cells and, so, enhance the effectiveness of the rapidly evolving immunotherapy approach to cancer .

Jackson remains focused on discovery science, while forever seeking ways in which his work might inform clinical medicine. Among numerous projects in his lab, he's particularly interested in the mechanisms of resistance to PARP inhibitors, and how they might be overcome. "Resistance to one drug can give you sensitivity to another drug," he says. That potential second drug might target another aspect of DNA repair, he says, noting that two of his old colleagues at KuDOS, Niall Martin and Graeme Smith, now lead a company called Artios Pharma, which is developing such drugs. "But that's all for the future," he says.

Provided by Cancer Research UK