Rucaparib—targeting DNA repair and a patient's perpective

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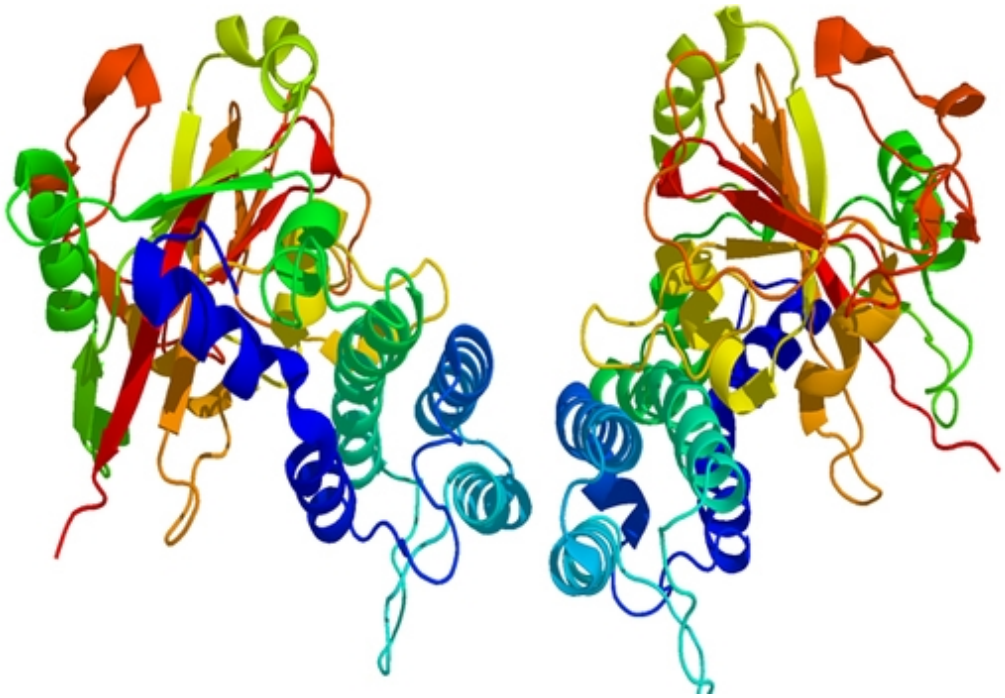

Credit: Cancer Research UK

Inhibitors of the DNA repair enzyme poly (ADP-ribose) polymerase (PARP) kill BRCA-deficient tumours, and have significant activity in single agent and combination therapy. Professor Herbie Newell, of Newcastle University (with Hilary Calvert, Nicola Curtin, Barbara Durkacz, Bernard Golding, Roger Griffin and Ruth Plummer), was part of the team responsible for making the PARP inhibitor rucaparib.

In December 2016, the FDA fast-tracked rucaparib (Rubraca) into the clinic to treat women with advanced ovarian cancer who have received two or more prior chemotherapies and whose tumours have a BRCA gene mutation. Here Herbie explains the start of the story.

"In the late 1980s, temozolomide, a DNA-methylating agent, was the drug of the moment. We reasoned that a PARP inhibitor should make temozolomide, as well as some other drugs and ionising radiation, more active by inhibiting DNA repair. There was lots of scepticism from pharma as they said a PARP inhibitor wouldn't be a standalone drug and would increase toxicity; consequently there was no major commercial interest. Nevertheless, in a collaboration between the Cancer Research Unit and the School of Chemistry, we established a drug discovery group in Newcastle in 1990 to make and test PARP inhibitors. Rucaparib was subsequently identified in collaboration with Agouron and Pfizer GRD, and is now being developed and marketed by Clovis Oncology.

The critical breakthrough for PARP inhibitors was the recognition of single agent activity in cells defective for homologous recombination repair, as found in BRCA-deficient tumours (reported independently in *Nature* in 2005 by two UK teams). With the help of the CRUK Centre for Drug Development, rucaparib went into phase 1 trials in 2003, and went on to stimulate high levels of commercial interest in PARP inhibitors in multiple companies. The FDA approved rucaparib in December 2016, having previously identified it as a breakthrough drug."

In 2003, Professor Ruth Plummer, now the chair of the New Agents Committee, wrote the prescription for the first patient in the world to be treated by rucaparib, the first ever cancer patient to be treated by a PARP inhibitor. "It was always clear we had a drug that did something. We have some patients whose scans are currently clear and have been for some years now. It's fantastic – really great. The patient from our first trial doesn't even come to clinic now – he's been discharged!"

Susan Ross: a patient's perspective on rucaparib

Susan Ross from Whitley Bay in Tyne and Wear was first diagnosed with ovarian cancer with a BRCA gene mutation 10 years ago. Here Susan explains her experience of being part of a clinical trial of rucaparib (Rubraca) at the Northern Centre for Cancer Care in Newcastle.

"Early in 2015 I was told the ovarian cancer had returned and unfortunately an operation was not possible. I was facing the prospect of having chemotherapy again. Previously I had had three rounds of chemotherapy as well as four operations, so knowing what treatment was going to entail, my heart sank. I thought 'Can I go through this again?' and 'Do I really want to go through this again?'

My consultant organised a BRCA gene mutation test, which showed I was a BRCA2 mutation carrier. I was then offered the opportunity to go on a clinical trial of this new treatment rucaparib, and I grabbed it with both hands.

My care is overseen by Dr Yvette Drew, and I attend the unit every three weeks to be monitored, and discuss any worries with the nurses and doctors. I've been taking rucaparib as part of this trial since December 2015 and it's the best I've felt in 10 years, both physically and mentally. With the help and support of all the staff, it feels like I've got my life back.

Being part of a clinical trial means I'm monitored very closely. I am so thankful for all those who have been involved in the development of rucaparib and for making this clinical trial possible. Being part of a clinical trial is an opportunity to help make a difference, help cancer patients in the future and hopefully find a cure for this awful disease. I'd do it again in an instant."

Provided by Cancer Research UK