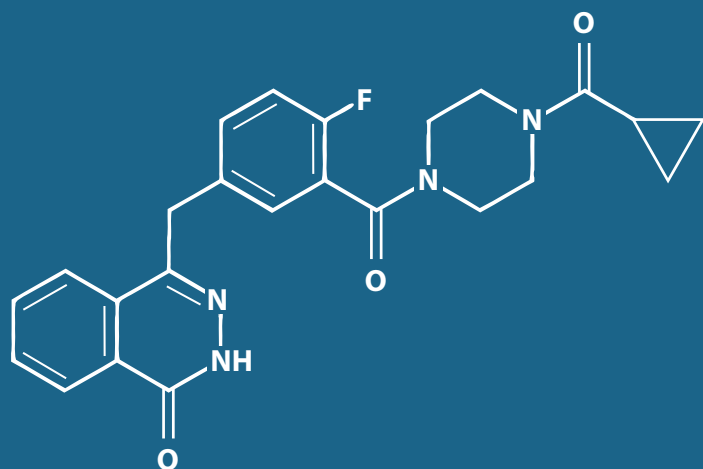


Fighting Cancer: Bench to Bedside

Treating cancer continues to challenge researchers around the world. Early stage research by Prof. Jackson's laboratory at the Wellcome Trust/Cancer Research UK Gurdon Institute in Cambridge into how DNA damage is repaired has provided further insight into how cancers arise. This research, which was largely funded by Cancer Research UK, led to the discovery of new potential targets for cancer therapies. Olaparib, a novel drug developed by Prof Jackson and colleagues, has successfully passed clinical trials and is currently available for the treatment of certain ovarian cancers.



As you settle in to read this article, behind the scenes, your cells are sustaining DNA damage from UV light, nicotine, by-products of internal chemical reactions and more. By the time you finish reading, this will amount to approximately 35 incidences of DNA damage in **each** of your 37 trillion cells. That's 10,000 hits per cell per day!

DNA is our genetic blueprint and sustaining that much damage would result in millions of mutations over our lifetimes which could have serious deleterious effects on us and our future generations. However, the number of mutations passed on to the next generation is approximated to be as few as 150. Our DNA integrity is maintained by the DNA damage response, a complex network of molecular patrols, acting as a 'Search, Signal and Repair Team'. Prof. Steve Jackson's laboratory studies these pathways with the aim of understanding how DNA is repaired at the molecular level.

DNA damage can lead to cancer and understanding the repair pathways is an important step in helping us understand how cancers occur. Prof. Jackson and colleagues have shown that some cancers have mutations in one of their DNA repair pathways, allowing them to mutate rapidly. This 'genetic instability' can lead to cells growing out of control, giving rise to tumours. Interestingly, the Jackson lab found that these cancer cells are actually more sensitive to cancer therapies that cause DNA damage such as ionizing radiation. This is because the cancer cells are now short of one DNA repair pathway and struggle to repair the excess damage from the treatment.

Based on these findings, Prof. Jackson founded the spin-out company KuDOS Pharmaceuticals Ltd. with the aim of translating these early research findings into therapies. A major breakthrough came in 2005 when Prof. Jackson and colleagues at the Gurdon Institute and KuDOS demonstrated that artificially inhibiting a key DNA repair enzyme called



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My colleagues and I are very pleased to see that our basic academic research has led to outcomes that are now enhancing the lives of many patients.



PARP (poly ADP-ribose polymerase) was lethal in cells that already had another repair pathway disrupted. This led to the pioneering concept of 'synthetic lethality' whereby two genes that are not lethal when mutated individually cause cell death if they are mutated in combination within the same cell.

In other words, cells need to get from a 'DNA damaged' state to a 'DNA repaired' state in order to survive. They can do this through route A or route B. In cancer cells that already have route A disrupted (mutated), route B is used to repair the DNA. However, if route B is also inhibited artificially by a novel therapy, the cancer cell cannot be 'repaired' and dies. This method of treatment also results in fewer and milder side effects as it selectively targets cancer cells over healthy ones.

To translate the synthetic lethality concept into the clinical setting, Prof. Jackson's research focused on cancers which already have a mutation in the DNA repair genes BRCA1/2, found in certain breast and ovarian cancers. KuDOS Pharmaceuticals identified olaparib, a PARP inhibitor which was further developed by AstraZeneca after they acquired KuDOS. Olaparib (formulated as Lynparza™) is now an approved drug in over 40 countries. In December 2015 it was approved for use by the NHS in the treatment of ovarian cancers with BRCA1/2 mutations. This is a major achievement as it is anticipated to benefit 400 women per year in the UK alone.

Olaparib has established a new cancer therapy strategy, synthetic lethality, and represents the world's first marketed drug targeting the DNA repair enzyme, PARP, as well as the first cancer medicine worldwide that targets inherited cancer predisposition. It is currently undergoing over 30 clinical trials targeting a range of cancers with BRCA1/2 mutations,

spanning breast, colorectal and pancreatic cancer in the hopes of identifying further applications. Recent clinical trial results highlighted that up to 30% of advanced prostate cancers may respond to olaparib. These findings were so promising that the US FDA (Food and Drug Administration) designated olaparib a 'Breakthrough Therapy' in 2016 for the treatment of certain metastatic prostate cancers, enabling expedited approval in this area of high unmet clinical need.

The work at KuDOS and in Prof. Jackson's lab has also led to widespread, important changes in the pharmaceutical industry's approach to cancer treatment. Numerous companies have adopted the synthetic lethality strategy, leading to more research and treatments in the pipeline. Moreover, many inhibitors identified by Prof. Jackson's research have been sold by agreement for research purposes and are distributed by biotechnology companies, enabling scientists around the world to build on this knowledge.

Looking ahead

Prof. Jackson's latest research involves understanding how tags called 'ubiquitin' and the enzymes which add and remove these tags affect the activity of DNA repair proteins. This research, in combination with the pioneering synthetic lethality concept, has led to the founding of MISSION Therapeutics Ltd. whose aim is to identify new inhibitors against enzymes which remove ubiquitin tags to target cancer, inflammation and neurodegeneration. Current work at MISSION Therapeutics includes identifying targets, screening potential therapeutic compounds and validating them in the hope that more will follow olaparib in the transition from bench to bedside and benefit patients.

Written by Marwah Hassan



For more information...

www.gurdon.cam.ac.uk/research/jackson

<http://missiontherapeutics.com>

www.bio.cam.ac.uk/impact