A pan-cancer strategy

Developing radionuclide PARP inhibitors

Poly (ADP-ribose) polymerase (PARP) is a validated cancer target with approved PARP inhibitors (PARPi) for the treatment of several cancers. Currently four PARP inhibitors have been authorised in the US. As small molecules they block a biological pathway, in this case the ability of cancer cells to repair themselves. But it is also possible to use these same PARP inhibitors as vehicles to deliver radioisotopes to cancer cells and destroy them. In this article, we discuss how our company, Theragnostics Ltd, is using radiopharmaceuticals to exploit this growing field of cancer research.

PARP is an enzyme that normal cells use to repair damaged DNA which can occur by accident during cell growth. It is activated when bound to damaged DNA in the nucleus, and as a result the natural substrate, NAD+ or an inhibitor of PARP (PARPi), can only bind to *active* PARP. When PARP is not bound to damaged DNA, it is *inactive*, and the binding site is blocked. Therefore, while PARP is expressed ubiquitously in the body, most of it is in an inactive form. Where there is 'normal' DNA damage repair, it is tightly regulated and at very low levels.

However, in cancers, there are very high levels of DNA damage, causing the cancer cell to overexpress PARP to keep up with the DNA repair in an unregulated manner. Therefore, PARP inhibitors block, by 'trapping' PARP on the damaged DNA, the ability of cancer cells to repair themselves and they die. But there are other molecules, such as BRCA, that can also repair damaged DNA, so PARP inhibitors work best when these pathways are genetically mutated, leading to a loss of function of BRCA.

As a result, conventional drug PARP inhibitors were initially approved in patients with BRCA mutant cancers whereby the combination of PARP inhibition with a germline BRCA mutation leads to 'synthetic lethality,' that is, blocking the cancer's ability to repair damaged DNA. There have been reports of PARP inhibitor resistance over time, but it is important to note that this is not related to PARP itself but rather to the reversion of BRCA function, that is, the cancer cell regains the ability to repair DNA via the BRCA pathway.

Theragnostics has tagged a PARP inhibitor with a medical radioisotope, creating a diagnostic or therapeutic radiopharmaceutical. It is essential to understand that radiopharmaceuticals are typically administered in tiny 'nanomolar' concentrations with only picomolar to femtomolar concentrations of molecule labelled with the radioisotope. As a result, there is no pharmacologic effect on the PARP inhibitor itself; it is merely being used as a vehicle to deliver the radioisotope to the cancer cell.

This enables Theragnostics to use the same targeting molecule to perform SPECT or PET imaging or radionuclide therapy using either an alpha, beta or Auger therapeutic radioisotope. This gives the cancer clinician the powerful ability to image, treat and re-image the response to radionuclide treatment, whereby the same molecule can be used as a diagnostic and therapy. Theragnostics has licensed the PARPi molecules providing global freedom to operate.

The imaging diagnostic PARP inhibitor, which has been tagged with the PET isotope F-18, has been in two Phase 1 clinical studies at Memorial Sloan Kettering Cancer Center. One was in head and neck cancer and the other in cancers of the brain. These studies showed that, in a total of 18 patients, F-18 PARPi was safe. Because the patients were imaged prior to surgery, it was possible to correlate the uptake and retention in primary and metastatic lesions in the PET image with PARP1 histopathology of surgical samples. Such uptake has been observed in head and neck cancer, metastatic renal carcinoma, metastatic melanoma and glioblastoma. Although these were Phase 1 safety studies, the PET uptake in the cancer lesions correlates with the amount of PARP1 expressed in the tumour as measured by histopathology.

Importantly, pharmacokinetic analysis of F-18 PARPi demonstrates that it is not retained in normal tissues, has a biodistribution reflective of blood clearance and is rapidly eliminated via the liver into the gut.

This indicates that there is little or no radiopharmaceutical PARP inhibitor binding to PARP in normal tissue. It only binds to active PARP in cancerous tissue. This is because the chance of F-18 PARPi encountering active PARP in cancer is so much higher than in normal tissue, a term referred to as the 'tumour to background' ratio. This bodes well for the development of a radionuclide PARPi therapy.

Theragnostics is focused on the development of a radionuclide PARPi therapy by tagging the PARPi with Iodine-123 which emits an Auger electron. An Auger electron is a very high energy emission which is highly lethal over very short distances – less than the diameter of a nucleus (<100nm) – but imparts little or no energy over the greater length of the diameter of a cell.

Given that active PARP is already situated on the damaged DNA (within 10 nm) an Auger isotope is perfectly matched to the location of the target, thereby maximising the cancer cell kill while minimising toxicity to normal tissue, delivering a large therapeutic index. To date, I-123 PARPi has demonstrated non-clinical efficacy in an orthotopic model of glioblastoma whereby a very low radioactive dose administered directly to the tumour demonstrated significant survival.

Conclusion

The business case for radionuclide PARPi is enormous. It is in essence a pan-cancer target and the number of possible therapeutic indications is vast compared to traditional cancer therapeutics.

This article was written by Dr Greg Mullen, chief executive officer of Theragnostics Ltd.

