DDR therapeutics and synthetic lethality – a precise way to kill cancer cells

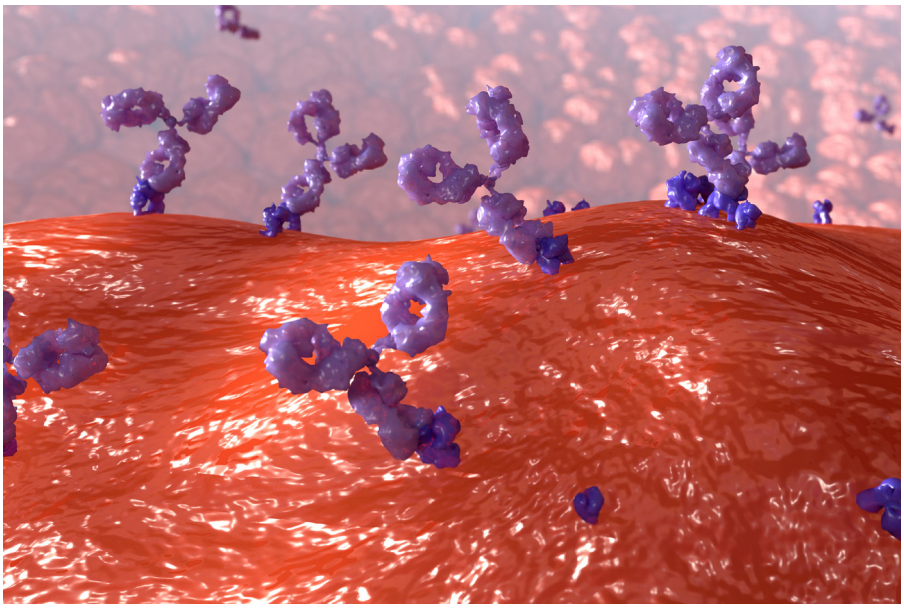
By Patrys CEO and MD, Dr James Campbell

Investors often ask me about the DNA Damage Response (DDR) mechanism and how Patrys' lead asset PAT-DX1 exploits this pathway to preferentially kill cancer cells.

In simple terms, PAT-DX1 blocks DNA repair and we've now seen in animal models that it kills cancer cells with a range of DDR gene mutations such as BRCA2 and PTEN – and importantly it does not kill cells without those mutations.

So why is this exciting?
PAT-DX1 is unique because it is the only antibody to have shown innate efficacy as a single agent via the synthetic lethality model, which is explained later in this article. PAT-DX1, unlike other antibodies and 98% of small molecules, is also able to cross the blood brain barrier – the all-important ticket to killing cancer cells in the central nervous system.

The potential for DDR therapeutics to become a game changer in cancer treatment is well explained by AstraZeneca (see here), which has elevated DDR to one of its focus pillars of oncology treatment – it has, they say, potential for delivering "more selective, better tolerated medicines to improve survival in multiple cancers."



Patrys' lead asset PAT-DX1 exploits the DNA Damage Response (DDR) mechanism to preferentially kill cancer cells.

At Patrys, we couldn't agree more. Here's a closer look at the science of DDR for context.

Firstly, we need to understand that in a healthy person many thousands of events of DNA damage occur every day – think radiation exposure from sunlight or exposure to toxins. As DNA damage impairs the ability of the body to function normally, our bodies have an elegant system of repair mechanisms to identify and fix DNA damage.

The DDR mechanism consists of more than 450 proteins that work to identify and rectify damage to the genome. There are several different types of DNA damage, ranging from small breaks in one strand of the DNA helix through to double strand breaks and even replication errors.

patrys

The five different classes of DNA damage have resulted in the evolution of five major DDR pathways.

As cancer cells emerge, they develop changes in a variety of cell functions that result in abnormal cell growth and potential to spread to other parts of the body. As part of the transformation, most cancer cells lose some of their DDR machinery and the ability to repair DNA damage in at least one of the five major pathways.

Even though cells are optimised to use specific DDR pathways, there is a degree of redundancy involved, meaning that a cancer cell with a fault in one DDR pathway will use the other pathways to try to fix arising DNA damage. This reminds me of the Apollo 13 mission, and how mission control came up with the improvisation of using the square CO2 scrubber filters from the lunar lander in place of the round filters needed in the command module. It wasn't perfect, but it worked.

So with the ability to use less than perfect tools to patch up DNA damage, cancer cells can continue to thrive and proliferate. But this is when things get really interesting.

Researchers asked what would happen if they were able to block the back-up DDR system from working – could it kill the cancer cells?

The logic was that if one DDR pathway is not working because of a biological reason (the genes for the pathway were turned off during the process of becoming a cancer cell), blocking an additional pathway by therapeutic means should deactivate the whole DDR system in the cancer cells and lead to cancer cell death.

Researchers asked what would happen if they were able to block the back-up DDR system from working – could it kill the cancer cells?

This therapeutic approach is known as synthetic lethality and has the advantage that it is the combination of two DDR pathways not working that is lethal, and that normal cells with intact DDR systems should not be killed by the DDR therapeutic. Presto.

The first instance of a DDR therapeutic being approved by the FDA was for the Astra Zeneca drug olaparib, which inhibits an enzyme called PARP that is central to repairing single strand DNA breaks. Olaparib was approved in 2014 in ovarian cancer patients with mutations to the BRCA1 or BRCA2 genes, which encode proteins involved in double strand DNA breaks (i.e. a different DDR pathway).

Olaparib has progressed to be approved in multiple indications, including breast and pancreatic cancers, and its sales exceeded US$1.2B in 2019. Three other PARP inhibitors have been approved by the major regulatory authorities and others are in clinical development, confirming that this novel approach offers new hope and significant benefit to selected groups of cancer patients. With PAT-DX1, Patrys is in the enviable position of developing a novel therapeutic that combines the established safety and toxicology advantages of antibody therapeutics with the power of synthetic lethality.

So to redefine my earlier Apollo 13 comparison to cancer cells, exploiting synthetic lethality as a therapeutic approach means more people will survive cancer, much like those astronauts did on an impossible mission to the Moon. **That's good news.**

If you'd like to learn more about Patrys' work in this space visit **Patrys.com**

patrys