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Nuclear-penetrating, DNA-binding antibodies as cancer therapies

Melbourne-based Patrys has developed the Deoxymab platform, a unique technology able to produce antibodies that not only target and penetrate cancer cells, but bind to their DNA and block their repair enzymes, halting further progression.

Antibodies have been used as anticancer drugs for more than 20 years and have revolutionized cancer therapy with their ability to bind to specific targets. Most conventional antibodies cannot enter cells, and thus can only target markers on the cell surface, resulting in a wide range of inaccessible intracellular targets. In addition, few cell-surface markers are completely cancer-specific, leading to side effects when antibodies attack healthy cells.

Patrys, a Melbourne-based biotech company, is overcoming these limitations by developing cell-penetrating antibodies (Deoxymabs), a completely new antibody-based technology that targets tumors, penetrates cells, binds to DNA and blocks DNA repair. "Deoxymabs are a very different sort of antibody as they don't bind to proteins on the cell surface but instead are taken up into cells where they inhibit targets that other antibodies can't reach—this is absolutely unique," explained Patrys CEO James Campbell. "No one else is developing this sort of cell-penetrating antibody as a cancer therapy."

Patrys's first-in-class lead candidate to emerge from the Deoxymab platform is PAT-DX1, a lupus autoantibody that has been humanized and optimized for efficacy, manufacturability and novelty (and modified to ensure no risk of lupus-like side effects). PAT-DX1 exploits the fact that, although all cells have mechanisms to repair damaged DNA, these DNA damage response (DDR) processes are defective in many cancer cells. Simultaneously, as tumors grow and undergo cycles of proliferation and cell death, they constantly release DNA, resulting in a 'cloud' of DNA fragments in their vicinity.

How does PAT-DX1 target cancer cells?

PAT-DX1 targets tumors because it is attracted to and preferentially accumulates near the mass of extracellular DNA released from dead and dying tumor cells. The antibody binds to the DNA fragments and is transported across the plasma membrane into the cell via a nucleoside transporter. (Acting as molecular tractors, transporters are used by cells to salvage nucleosides and other useful molecules from the extracellular environment.) PAT-DX1 then penetrates the cell nucleus where it binds to sites of damaged nuclear DNA, inhibiting DDR processes (**Fig. 1**). The degree of inhibition is modest and insufficient to kill normal cells with robust DNA repair machinery. But because the DDR processes of cancer cells are already defective, the additive effect of PAT-DX1 is fatal.

Patrys's technology brings together all the advantages of antibodies—including specificity and safety—with those of DDR therapies, such as PARP inhibitors, that target DDR deficiencies, explained Campbell. "PAT-DX1 is at the convergence of these two transformative anticancer technologies, providing the advantages of PARP inhibitors without the problematic side-effect profile of many small molecules," he said.

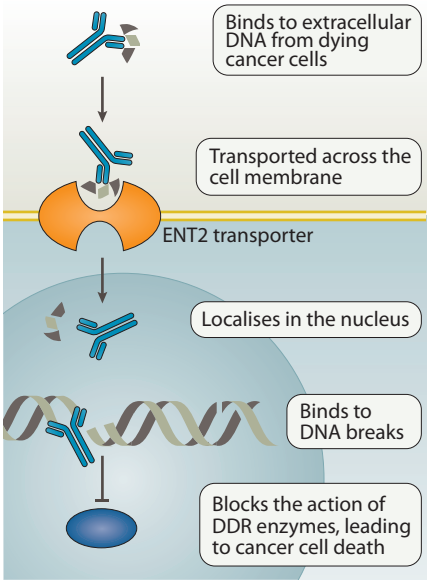

Fig. 1 | PAT-DX1 in action. The antibody binds to the DNA fragments of dying tumor cells and is transported across the plasma membrane into the nucleus of the cell by a nucleoside transporter. PAT-DX1 then penetrates the nucleus and binds to damaged nuclear DNA, inhibiting DNA damage response (DDR) processes.

Selectively toxic to cancer cells, especially those that have deficiencies in DNA repair, PAT-DX1 is well-suited to the treatment of a wide range of malignancies, such as gliomas, melanomas, pancreatic, prostate, breast and ovarian cancers. Currently, Patrys is focused on the use of PAT-DX1 for cancers with PTEN and BRCA2 mutations that are currently difficult to treat, specifically glioblastoma and triple-negative breast cancer—two significantly underserved therapeutic indications.

It is the versatility of PAT-DX1 that lends itself to several possible development paths. In addition to its role as a single tumor-killing agent, PAT-DX1 sensitizes cancer cells to other DNA-damaging treatments, enhancing the efficacy of radiation therapy and some chemotherapies. Furthermore, Patrys can link PAT-DX1 to nanoparticles loaded with standard chemotherapeutic agents or other drugs for the targeted delivery of anticancer medications and imaging agents.

Promising results

The company is progressing PAT-DX1, and a nanoparticle-conjugated form, toward the clinic. Results from preclinical studies in a range of animal models of cancer, including triple-negative breast cancer and glioblastoma, are very positive. PAT-DX1 has been shown to significantly improve survival in an animal model of glioblastoma, work synergistically with the approved PARP inhibitor olaparib to kill glioblastoma stem cells and, when linked to nanoparticles, significantly increase the efficacy of chemotherapy. Clinical trials of PAT-DX1 are planned to begin in 2020.

Reflecting the unique capabilities of the Deoxymab platform, the impressive data announced over the past year and several new intellectual property filings, Patrys has performed strongly in 2018, raising more than $7 million so far. The company has also built an impressive team of academic partnerships, counting Yale University and Harvard's Beth Israel Deaconess Medical Center in the USA and the Walter and Eliza Hall Institute and Garvan Institute in Australia among its collaborators. With a wide range of potential applications for Deoxymab technology, Patrys is open to discussions on how best to exploit the platform's multiple uses.

"The scope of this platform technology is significant," said Campbell. "We're progressing a technology that not only has potential as a single agent, but also as an adjunct to increase the efficacy of existing chemo- and radiotherapies. The potential to improve patient outcomes is, we believe, substantial."

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