Commentary: Øystein Rekdal

A strategy for raising response rates to immunotherapy

There are huge challenges to be addressed in oncology in the coming years, one of which is the low response rate by many cancer patients to current immunotherapy drugs. At our Norwegian company Lytix Biopharma AS we have been studying this problem for some time and have come up with a candidate immunotherapy which we believe could mobilise the body's own defences against cancer, but in a different way than existing drugs.

Central to our approach is the discovery of a naturally occurring peptide that forms the first line of defence for humans against microbes. We have discovered that some of these peptides can also have an effect against cancer. Called LTX-315, our molecule draws on more than 30 years of research at Tromsø University which is located above the Arctic Circle in Norway. It was here that our scientists first identified the host defence peptide bovine lactoferricin (LFcinB) as a molecule of interest in the natural world. They have subsequently been designing antimicrobial and anticancer properties for this peptide.

Our researchers found that the peptide had a 10-fold higher activity against bacteria than the parent protein, lactoferrin. After reading an article about the anticancer effects of lactoferrin, we wondered whether the peptide fragment might have a stronger activity against cancer cells. After testing the peptide in an animal cancer model, we discovered – to our great surprise – that it did. The solid tumours in the animal models disappeared within a few days.

We were also able to re-challenge the animal model with cancer cells and to our even greater surprise, the tumour did not return after we had treated the animals from the same cancer. Not only had we found a molecule that was able to kill the cancer, it was also able to induce a vaccination effect. This was the starting point for the next stage of research. We began to make different derivatives of the molecule to see which elements of the peptide were critical for the anti-cancer activity. This is how we arrived at LTX-315.

We reduced the size of the molecule from 25 amino acids to nine amino acids, including one that is chemically modified. The molecule is easily manufactured, increasing our confidence in its eventual use in humans. We chose LTX-315 from hundreds of analogues and tested it against 50 cancer cell lines. We found that it has an acceptable specificity for cancer cells versus healthy cells and is able to kill chemo-resistant cancer cells.

After being directly injected into a tumour, LTX-315 works by breaking down the cell and causing the cancer cell membrane and intracellular compartments to disintegrate. Like bacteria, cancer cells have negatively charged targets that protrude from their cell membranes. These attract the peptide through electrostatic interactions. It's these negatively charged targets that allow LTX-315 to distinguish between tumours and healthy tissues.

Once it has penetrated the cell membrane, LTX-315 causes the destruction of the machinery inside the cancer cell that is essential for its survival – specifically the mitochondria that supply its energy. It ends up in almost in an explosion of the cancer cell – accompanied by a release of molecules that are able to activate the immune system, since as the mitochondria are destroyed, this causes the release of bacteria-like 'danger signals' that invoke the immune system to attack the tumour. They create tension so the immune system wakes up and becomes alert.

Mitochondria are thought to originate from a bacteria, which may explain why they are targeted by our cationic molecules.

A solid tumour often contains many different cancer cells with different mutations, which makes it very challenging to completely eradicate a cancer. Since mitochondria have their own DNA, the exposure of mutated proteins encoding both nuclear DNA and mitochondria DNA from cells killed by LTX-315 could potentially result in a broader immune response towards the tumour and increase the probability that a broader immune response could be activated to conquer the cancer.

The mutated proteins or tumour antigens that are released are only found on the surface of the tumours – including those that may be residing elsewhere on the body after spreading, or metastasising, from the original cancer. This leads to the metastasised tumours becoming vulnerable to attack as the body learns to recognise these tumour-specific antigens.

The unique mode of action of our molecule is patent protected in the US in combination with chemotherapy and with anti-CTLA-4 checkpoint inhibitors. LTX-315 has already been granted patent protection in Europe, Australia, New Zealand, China, South Korea and Russia.

Overall, we have strong patent protection in major markets including the US and Europe up to 2035.

Interim data from our Phase 2 ATLAS-IT-05 study in combination with Merck & Co's Keytruda (pembrolizumab) in stage III-IV melanoma patients refractory to treatment with PD-1/PD-L1 inhibitors has shown a stabilisation in this heavily pre-treated and late-stage patient population with a disease control rate in approximately half of the patients for up to one year following the start of treatment and one patient with a partial response.

This is just the beginning. The patients we are treating have failed on multiple lines of therapy and their immune system is already very depleted. We like to use the analogy of a car: if you try and start the engine with a flat battery, then you are unlikely to get very far. But if the battery is fully charged, you can begin your journey. We think LTX-315 will work best in earlier stage patients who have had fewer treatments, where the immune system is still functioning.

This article was written by Øystein Rekdal, PhD, CEO of Lytix Biopharma AS.