Small company, big theme

How iOnctura is pursuing drug resistance

Most meaningful scientific discoveries require a context in which to develop. This could be a technology transfer office at a university, or a research and development division at a large company. However large the incubator, the individuals pushing a project forward need to be ambitious and they need to have a theme.

"Our goal is to modulate key culprits of immunosuppression in the tumour microenvironment to maximize the therapeutic potential of checkpoint inhibitors for patients," said Catherine Pickering, chief executive and co-founder of iOnctura at the company's launch in 2017.

Now seven years later iOnctura, a spin-out of Merck Ventures, the corporate venture arm of Merck KGaA, has two clinical-stage assets in its portfolio and a third in preclinical development. The lead asset, roginolisib, is a small molecule allosteric modulator of an isoform of the PI3K family of enzymes which are involved in cellular functions such as cell growth and intracellular trafficking in cancer. This product is currently being investigated in uveal melanoma. The clinical programme will soon be expanded to include a combination study with a checkpoint inhibitor in non-small cell lung cancer. Altogether, roginolisib is being explored in five indications.

A second product, cambritaxestat, is a small molecule autotaxin inhibitor that is currently being studied in combination with chemotherapy in pancreatic cancer. This product is thought to have particular relevance for highly fibrotic tumours. A third product, a small molecule inhibitor of the transforming growth factor beta (TGF-beta) signalling pathway in solid tumours, hasn't reached the clinical stage.

Propelling the company forward is an €80 million Series B financing, announced on 20 June and led by new investor Syncona Ltd. Participating in the round was the EIC Fund, the venture arm of the European Innovation Council, as well as five existing investors.

To Dr Pickering, the progress made by the company since its launch has been both taxing and exhilarating. "I got a lot of grey hairs, I have to say, along the way," she commented, in an interview on 22 July. But the result is a company with nearly €130 million in dilutive and non-dilutive financing and a lead programme on the cusp of multiple Phase 2 studies. The emotions have now tipped to exhilaration.

Dr Pickering holds a PhD in medicinal chemistry as well as a master of business administration. iOnctura's other co-founder is Lars van der Veen, a chemist. Both individuals held executive positions at Merck KGaA in the lead up to iOnctura's founding and then transitioned to the new company. Dr Pickering led global oncology and immuno-oncology licensing and business development at Merck while Dr van der Veen was director of alliance management. The co-founders consulted extensively within and outside Merck as well as with officials at Cancer Research Technology, the commercial arm of Cancer Research UK.

After much research, they settled on five assets: two from Merck and three from Cancer Research Technology. "We were tumour agnostic then, however resistance mechanisms were always at the heart of everything. It started with immune resistance mechanisms because that was the ethos of the company and then we started to look at certain non-clinical models," Dr Pickering said. The assets from Merck included one which was to become the current lead product, roginolisib. It was a small molecule in the immunology portfolio of Merck Serono, Merck's biologics subsidiary in Geneva, and was being developed for lupus, an autoimmune disease. "All of the IND (investigational new drug application) had been completed. The drug was ready; it just needed repositioning in oncology," Dr Pickering said.

Unusually, the drug is an allosteric modulator of P13K-delta, an isoform of the PI3K family of enzymes which has been known for years as a target of B cells. "But we learned very early on with our collaborators and people expert in the field that PI3K-delta is absolutely more than a target of B cells…some tumours seem to up-regulate PI3K-delta as a mechanism, as the tumour becomes more and more established," Dr Pickering said.

This was not all. A second finding was that regulatory T cells (Tregs), which are a suppressive T cell subset that help prevent autoimmune diseases but can also dampen the immune response in cancer, rely on PI3K-delta. "If you inhibit PIK-delta you can stop these Tregs in their tracks. So you can bring down Tregs and turn your tumour microenvironment into a more immune active environment rather than an immune suppressive [one]," the executive said.

According to the US National Cancer Institute, nearly all current treatments for cancer encounter resistance from tumours at some point after their administration. This could be weeks after a patient receives treatment, or even years later. The resistance mechanisms can be molecular, arising from cells within a tumour, or they can come from the tumour microenvironment. The tumour microenvironment is often cited as a source of resistance to immune checkpoint inhibitors.

The iOnctura trial of roginolisib in uveal melanoma is a monotherapy trial giving the company time to study the resistance pathway and the effects of the treatment closely. The upcoming lung cancer trial will study the drug in combination with the checkpoint inhibitor dostarlimab from GSK Plc. This is being done under a collaboration with GSK and a Swiss cancer foundation. In both the mono and combination studies, the iOnctura scientists will be studying the drug's mechanism of action closely. Roginolisib is the first allosteric modulator of PI3K-delta and has a unique binding mode which locks the enzyme into an inactive state.

This article was written by the *MedNous* editor.