Setting the pace in radiopharmaceutical development

Radiotherapy has a long history, going back more than 100 years to the discovery of X-rays in 1895 by Wilhelm Conrad Röntgen, a German mechanical engineer and physicist. Marie Curie, born in Poland and educated in France, invented a technique for isolating radioactive isotopes. This led to the discovery in 1898 of the elements polonium and radium and set in motion the development of radiotherapy, an entirely new class of medicines.

External beam radiotherapy and brachytherapy are two types of radiotherapy. More recently, scientific and investor attention has focused on targeted radionuclide therapy where a radioactive chemical is linked to a cell-targeting molecule, injected into the body and directed against cancer cells.

A confluence of events has led to a growing focus on the radionuclide sector. One is scientific interest in precision therapies, or therapies that can successfully target proteins controlling cancer cell growth. The other is the need for effective diagnostics to identify these proteins and guide physicians on which patients to treat.

Biotech companies in multiple geographies are starting to put all of this together. One of these players is Ariceum Therapeutics GmbH of Germany. Ariceum is neither a university spin-out, nor a rebranded pharmaceutical company. It belongs to a group of companies funded by venture capital on the basis of assets that address a major investment theme.

In an interview, Manfred Rüdiger, the chief executive, explained how the company got started and what its priorities are for the future. "What makes radiopharmaceuticals so attractive for many, is that you use the same compound for imaging and therapy, at least the targeting moiety of the compound is identical," he said. The name given to products with this dual capacity is theranostic, which combines the words for therapeutic and diagnostic.

The two procedures work in lockstep. Thus, patients can be screened, but only those with a confirmed disease will be treated. "What also makes it attractive for healthcare payers is that the imaging is relatively cheap," Dr Rüdiger said.

Ariceum was co-founded in 2021 by EQT Life Sciences and HealthCap, respectively private equity and venture capital groups based in Sweden. The investment theme was radiopharmaceuticals and the assets were patents and data from preclinical and clinical studies of a radionuclide therapy called 177Lu satoreotide tetraxetan. This is a peptide receptor radionuclide therapy targeting the somatostatin type 2 receptor which is overexpressed in many cancers including hard-to-treat small cell lung cancer, high-grade neuroendocrine tumours and neuroblastoma.

Satoreotide was originally developed by Ipsen SA of France which took a strategic decision in late 2021 to divest the assets. In separate transactions, these assets were transferred to Ariceum and to a company in Canada. EQT and HealthCap prepared for the transfer by completing a €25 million Series A financing for the company in June 2022. In April of this year, Ariceum received a further €22.75 million A round extension bringing the total financing to date up to €47.75 million. The most recent financing was co-led by new investors Andera Partners and Earlybird Venture Capital.

Ariceum is working on three parallel strategies: to set up manufacturing capacity, broaden its tool box of technologies, and advance satoreotide in the clinic. Satoreotide is expected to face competition from Lutathera, a marketed product from Novartis which also targets the somatostatin receptor.

The manufacturing step was initiated in October 2022 with an agreement between Ariceum and AmbioPharm Inc, a contract development and manufacturing organisation in the US, to supply peptide conjugates for use in clinical trials. The conjugates will be radio-labelled for targeted tumour diagnosis and therapy. "The challenges on manufacturing, logistics, storage and supply [are] the biggest things that people need to work on," Dr Rüdiger said, adding that there are some similarities between radiopharmaceuticals and cell therapies which have a very short shelf-life. Owing to the decay of the radioactive substance, the active drug will need to be manufactured on site in a hospital, or in manufacturing hubs that supply hospitals.

Ariceum's tool box is the sum of all of the technologies the company needs now or may need in the future. It consists of peptide variations, linker variations, chelator variations and different isotopes.

On 11 May, Ariceum announced a collaboration with the Belgian pharma company UCB SA that will enlarge this tool box. The two companies will identify and develop radiopharmaceuticals for the treatment of solid tumours and immune-related diseases. UCB will give Ariceum access to its technology for discovering synthetic macrocyclic peptides, while Ariceum will share its expertise in radiochemistry and labelling technology.

Whilst all this is happening, Ariceum is advancing satoreotide in the clinic for neuroendocrine tumours and small-cell lung cancer, both aggressive tumours. The choice of aggressive tumours was strategic because the company believes it has a molecule that can outperform Lutathera in certain settings. "Conceptually we have the better compound," the executive asserted. This is because satoreotide is an antagonist of the somatostatin receptor while Lutathera is an agonist. As an antagonist satoreotide binds to the target receptor and stays on the surface of the cancer cells for longer. By contrast, the agonist gets internalised quickly in a process known as ligand-induced endocytosis.

"When you do the measurements, it really doesn't matter whether you do it in cell culture or in animals or in humans, roughly four times more radioactivity ends up in the tumour when you use the antagonist as compared to the agonist," the executive said.

The difference matters if the candidate drug is intended to target aggressive tumours.

This article was prepared by the *MedNous* editor on the basis of a literature search and an interview with Manfred Rüdiger.

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