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Interview

Olivier Litzka from Andera Partners on VC and how the biotech industry is working its way out of the trenches.

Targeted radiotherapy powered by Biotech

Clinical studies: CTIS
The new EU study portal is well-meant, but disappointing

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Industry growth is hampered by a lack of qualified personnel

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COVER STORY

Targeting cancer with Radio-Biotech

Radiopharmaceuticals have turned into a hot commodity when it comes to M&A financing and deals. Targeted therapies that employ high-energy attachments linked to antibodies, small molecules or peptides promise fewer side effects and a localised attack on the tumour. Novartis initially cracked open the door with an innovation from France. Now investors are trying to play catch-up, and startups have seen a surge in demand. The companies involved are both toolmakers and those digging for radioactive gold.

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Targeting cancer with Radio-Biotech

ONCOLOGY Steel, rays, poison ... those are the traditional medical approaches to treating cancer. Surgery, radiology and chemotherapy – or a combination thereof – have been the weapons of choice for oncologists for decades. Targeted radiotherapy is a newer molecular variant designed to maximise damage to the tumour and minimise damage to surrounding tissue. Now the success of approved radiopharmaceuticals has caught the attention of investors and Big Pharma.

The big idea behind radiopharmaceuticals is to combine the strengths of two kinds of cancer treatments – radiology and targeted therapies. In simple terms, it involves attaching radioactive isotopes to a molecule, then irradiating cancer cells with a high degree of specificity and selectivity by matching those molecules to known targets.

Funding is piling up

Headlines about deals in the pharma industry make it clear that global interest in radiopharmaceuticals is growing, and some major deals in the area stand out. The value of the global radiopharmaceutical industry was estimated at around US$5bn in 2017, and could grow to US$15bn in the coming years in the United States alone, according to industry experts.

Investments in the sector are correspondingly large. Novartis AG alone has spent around US$6bn on acquisitions, and is currently regarded as the global leader in the field. The Swiss multinational entered it in 2017/2018 with its US$3.9bn purchase of French company Advanced Accelerator Applications SA and its then-hopeful Lutathera, which addresses gastroenteropancreatic neuroendocrine tumours (GEP-NETs). With its approval in 2018, Lutathera became a major role model in the radio space, and has since been viewed as a door-opener. Later in 2018 Novartis spent a further US$2.1bn to acquire Endocyte Inc., integrating Pluvicto (177Lu-PSMA-617), which uses lutetium (^{177}Lu) – a beta-emitter targeting prostate-specific membrane antigen (PSMA). It received approval in 2022.

Although the pandemic posed major challenges, more deals followed soon. In June 2021, Bayer AG acquired Noria Therapeutics Inc. and PSMA Therapeutics Inc. The aim was to develop a prostate cancer treatment that uses a small molecule to deliver radioactive therapy to cells carrying PSMA markers. However, little has been heard to date about this me-too prostate product. Last year Eli Lilly also acquired Point Biopharma Global for US$ 1.4bn after a small bidding war for the two therapeutic programmes. They target metastatic castration-resistant prostate cancer and also GEP-NETs – other me-toos – but the deal included production facilities as a sweetener.

RayzeBio has also recently made headlines. Founded in California (US) in 2020, the company raised around US$418m in four venture capital rounds before going public on the NASDAQ last September with a gigantic IPO totalling US$311m. Its lead therapeutic candidate uses the same molecule as Novartis' Lutathera to also target GEP-NETs, but swaps out lutetium-177 for actinium-225 – an isotope that emits more destructive alpha particles. It's capable of delivering hundreds of times the energy in a much smaller radius, one only a few cells in depth. Just three months later, in December 2023, Bristol Myers Squibb acquired RayzeBio for US$4.1bn, topping off a massive buying spree. In just a few months in the second half of 2023, BMS spent around US$24bn on business development and acquisitions.

Narrow focus on targets

These examples show that the focus of development was essentially on prostate cancer and special forms of neuroendocrine tumours. Similarly, the target molecules are limited to two main focuses of interest: PSMA and somatostatin receptor 2 (SSTR2), which are overexpressed in GEP-NETs and extensive-stage small-cell lung cancer (ES-SCLC). New targets like Fibroblast Activation Protein (FAP) are also slowly getting some limelight, however, as indicated by an in-licensing deal of two FAP-targeting peptides from German biotech company 3BP with Novartis. 3BP (Berlin) is receiving an initial payment of US$40m, and

may see US$425m in development, regulatory and commercial milestone payments.

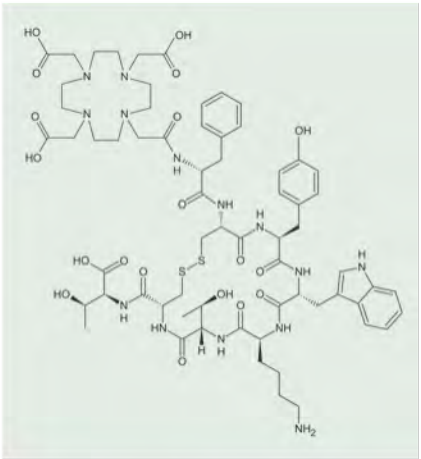
Newcomers ramp up the pace

The action around other startups is also heating up. European-American company ARTBIO (Oslo, London, Basel and Cambridge/US) raised an oversubscribed and scaled-up US$90m Series A financing with investors Third Rock Ventures, F-prime Capital and Omega in December to advance its pipeline and the development of isotope technology for a new class of alpha radiation therapies. In Germany, the newly founded company Ariceum Therapeutics (Berlin) doubled its Series A financing round in spring last year from the end of 2022 to around €48m, with new investors Andera Partners and Earlybird Venture Capital joining existing investors HealthCap, Pureos Bioventures and the billion-dollar fund EQT Life Sciences.

Also in 2023 – and again in the private sector – a substantial financing round totalling around US$250m was publicised for Munich-based company ITM Isotope Technologies. The company, which for research purposes is based near the nuclear power plant at the Technical University of Munich, has continuously raised funds. Little wonder then that the rumour mill has churned out speculation about an imminent IPO. So far, however, one has not materialised, probably due to the lack of a good window.

Production partnerships ...

The field of players in targeted radiotherapy can be broken down into companies that either come from the production of radioisotopes and have mastered the production processes there, those that are suppliers for other radiopharma developers or, like Munich-based ITM, those that have even developed and marketed their own 'isotope generator' for clinical use in imaging anywhere in the world. The global reach of ITM, which has 400 employees, is already quite considerable. Geographically, its activities



A door-opener for radiopharmatherapy was the formal prospective, randomised controlled study of a peptide-isotope chelator developed by Advanced Accelerator Applications SA (France). DOTATATE (DOTATATE,[1] DOTA-octreotate, oxodotreotide, DOTA-(Tyr3)-octreotate,[2] and DOTA-0-Tyr3-Octreotate) is eight amino acids long, with a covalently-bonded DOTA bifunctional chelator.

range from China to Canada and the US, where it was recently granted a manufacturing licence for radioisotopes.

Another company in the segment is Berlin-based Eckert & Ziegler AG, which is very broadly positioned in the radiology product world. It reports a rise in demand for supplies for radiopharmaceutical drug development, alongside many cooperation agreements with international companies. For example, the firm has signed a comprehensive supply contract for therapeutic radioisotopes with Nucleus Radiopharma, a joint venture between the Mayo clinic network (US) and venture capital company Eclipse. Eckert & Ziegler will be the core supplier of high quality lutetium-177 (Lu-177) and actinium-225 (Ac-225), both in non-carrier added form. Eckert & Ziegler will also support the startup ARTBIO in realising the manufacture and supply of its therapies using its proprietary AlphaDirect™ Lead-212 (Pb-212) isolation technology. The partnership aims to accelerate the development of lead-212-based alpha-emitting radioligand therapies, starting with the clinical development of ARTBIO's lead product AB001 for the treatment of – again – prostate cancer. In addition to the US, which the ARTBIO manufacturing process will specifically be developed for, Eckert & Ziegler's global service network for contract manufacturing includes production facilities in Berlin (Germany) and Jintan (China). Competitor ITM also has long-standing manufacturing partnerships in China in place.

Besides the small but growing interest in lead isotopes, supply generally remains focused on lutetium-177 and actinium-225, which are commonly-used radioactive substances in cancer treatment. They respectively emit alpha (Ac-225) and beta (Lu-177) particles to destroy tumour cells. While Lu-177-based drugs have been approved for various indications and are seeing increasing demand worldwide, dozens of clinical trials are underway for both radioisotopes. According to market experts, demand for Ac-225 will increase significantly over the next decade, but a bottleneck at the moment continues to be a lack of GMP quality control. It remains the biggest challenge of all, especially in the academic environment – but more on that in a moment.

... and the hunt for targets

Another group of companies are the gold diggers, and concentrating more on identifying suitable target molecules and selecting the appropriate transporter molecule for the radiating cargo. This field is developing particularly dynamically as VC investors have come sniffing about since the approvals of Pluvicto and Lutathera. Interestingly, startups like these – with an eye for target, active ingredient and linked radioactive isotope – can almost be described as 'next-generation ventures', because they're being built by researchers and developers who were either trained in early successful radiopharmaceutical development projects at large pharma companies, or were involved in early pioneering companies that have since been taken over. Now being poached and hired in new startups because of their experience, they could help bring their expertise to bear in the sector in a more agile

and faster way than they could working for Big Pharma.

In the case of ARTBIO, industry veterans Philippe Dasse and Daniel Rossetto were respectively hired as Chief Technical Officer Head and Senior Vice President of Supply Chain and External Manufacturing at the same time as the Series A deal was finalised. Dasse was most recently Head of Technical Operations for Radioligand Therapies at Novartis Oncology. Prior to that, he was the first employee of Advanced Accelerator Applications back in 2002, and went on to assume increasing responsibility for managing all technical operations until his departure. Rossetto also came from Novartis, where he was most recently Global Head of Supply Chain at the newly-acquired AAA specialty unit. In this role, Rossetto led a diverse team that built a fast and flexible internal and external supply network to deliver the clinical and commercial radioligand therapy (RLT) portfolio, including Pluvicto, to prostate cancer patients.

The German capital calls

Berlin-based Ariceum was able to convince investors like Pureos Bioventures, EQT LifeSciences and Andera Partners by also bringing together a team with relevant experience. CEO Manfred Rüdiger has a track record in several positions at various biotech companies, while Germo Gericke contributes radioligand expertise. Gericke has a long history at Novartis, was involved in the scene from the very beginning, and in part helped to shape it. He speaks of a 'renaissance of radiotherapy', because early projects – when the sector first began finding its feet years ago – were unsuccessful. Even so, he says, they had lessons to teach. "It was only with Pluvicto and Lutathera that the door really opened," Gericke told EUROPEAN BIOTECHNOLOGY. But experts in the field still have a lot to discover. Setbacks can and will occur, and there is still a steep learning curve ahead. After 15 years with Novartis and helping to integrate Endocyte and AAA, Gericke joined Ariceum in 2023.

Ariceum does not see itself as a classic one-trick-pony startup, or as a specialist in one or the other isotope, but rather as a strategic anchor – a strong European radiopharmaceutical company that aims to combine and advance the best approaches with the most effective isotopes, regardless of fixed isotope or target molecule expertise. That's why the newly-founded firm acquired Theragnostics Ltd so quickly after setting up shop itself. Theranostics has its own unique approach to the target molecule and the desired mode of action on the tumour cell. There, an isotope (Auger) is used that emits locally in the nanometer range and is bound to a known PARP inhibitor (DNA repair enzyme). The approach was so convincing for Ariceum's inves-

tors that they simply bought Theranostics and kept on the expert team involved in its design and development.

Both Gericke and Manfred Rüdiger compare the current state of the radiopharmaceuticals field with the course that checkpoint inhibitors took. There, initial successes triggered a wave of imitators, and the ideas for their use and combination expanded enormously in the years that followed. That led to the emergence of today's state of play, which has not only provided new insights into the immune system but also successes in treatment. Both see the gold rush in targeted radiopharmaceuticals in a similar light. Currently, companies that have mastered or have a grip on supply chains in isotope production are being snapped up or financed. At the same time, many firms are still focussing on the known target molecules PSMA or SSTR2, and are trying out new isotopes or light variants of them. On the surface, the spectrum of indications is therefore still very limited. But that's changing as investors grow more willing to take risks, not least because the known field of prostate cancer's target PSMA and GEP-NETS, along with SSTR2, has already been mostly ploughed and cultivated.

Linking diagnostics and therapy

In what are called 'theranostics', a somewhat overused if catchy buzzword, the diagnostic approach is directly combined with the therapeutic application via the same active ingredient molecule. In diagnosis, a small amount of radioactivity is first used to scan a patient with positron emission tomography (PET) – frequently in combination with CT for anatomic allocation – to determine the degree of expression of a target in the tissue. If the attached diagnostic isotope is then swapped out for an emitter that can damage the cancer tissue, the diagnostic molecule can at least theoretically become a radioactive therapeutic agent. .

That's a big 'if', however. The switch from diagnostic to therapeutic agent is not always a slam-dunk. Requirements for diagnostics and therapeutics are not identical. What they have in common is high affinity, specific binding and stability in plasma. But there are also differences in terms of goals. Diagnostics should only remain in the body for a short time, in order to keep a patient's exposure to radiation as low as possible. This can also mean that they only remain a relatively short period of time (a few hours) on the tumour. Therapeutic agents, on the other hand, should remain on/in the tumour for as long as possible (several days for Lu177 & Ac225) in order to be able to develop their effect as intensively as possible during the decrease in intensity determined by their radioisotopic half-life.

In reality, the carrier molecules can be identical (DOTA-TATE with Ga68 and Lu177) or can differ slightly (for instance with Ga68-PSMA-11 and Lu177-PSMA-617). Sometimes, however, the change of isotope from Dx to Tx alters the carrier molecule so much that it has to be 'reinvented' from scratch, a situation that has posed big problems for some companies in the past.

The challenge of toxicity

A diagnostic agent does not have to be as selective as a therapeutic, because the radiation exposure for healthy tissue is lower, while temporary accumulations of the agent in the blood, kidney or liver don't generally pose a problem for the organism. However, the accumu-

Radiolabeling (I) in ITM Isotope Technologies SE facilities. The company is headquartered close to the nuclear power plant at the Technical University of Munich.

Picture: © ITM Isotope Technologies SE

The right emitter of choice

Alpha is the largest particle with the least penetrative power. With a short particle range and high linear energy transfer, alpha-emitting radionuclides demonstrate high cell-killing efficiencies.

Beta-emitting radioisotopes have the longest particle pathlength (≤12 mm) and lowest linear energy transfer (LET) (0.2 keV/µm), supporting their effectiveness in medium to large tumors. Although the long particle range is advantageous in evenly distributing radiation dose in heterogeneous tumors, it can also result in the irradiation of healthy tissue surrounding the tumor site.

Auger electrons have high LET (4–26 keV/µm) but a limited path length of 2–500 nm that restricts their efficacy to single cells, thus requiring the radionuclide to cross the cell membrane and reach the nucleus.. ■

lation of high radiation exposure in the liver or kidneys is a major challenge for radiotherapeutic agents.

This is where the different variants of active-substance molecules come into play. Antibodies have a longer blood half-life, and peptides are retained in the kidneys in order to be recovered in their individual building blocks from amino acids. In this process, the residence time of the radioisotope in these organs and possible collateral damage to these tissues is a balancing act. Exploring organ-specific radiation levels may seem secondary when initially treating a condition like a diseased prostate gland. But the collateral enrichment of radioactivity in the spleen or bone marrow is an issue. So the balancing act doesn't just involve finding a good target molecule on the surface of cancer cells in the solid tumour tissue. Nowadays, every radiopharmaceutical's degradation and excretion pathways must also be taken into account. Each variant cargo molecule has different advantages and disadvantages, and they can be evaluated.

Another topic is specificity. PSMA for example is also expressed and accumulates in the lacrimal and salivary glands, nasal mucosa, liver, spleen, kidneys, intestines and bladder. The choice of the best isotope in terms of benefit-risk assessment therefore has to be taken very seriously, because hitting the prostate tumour hard and repeatedly will also eventually severely damage or destroy those other tissues as well.

Tissue toxicity has therefore stood in the way of the rapid expansion of radiopharmaceutical treatments, and any application has to be proven safe as a top priority.

Grey areas of application

That led the pharmaceutical industry as a whole to initially turn its back on the field, and its potential was mostly further developed in academia. More recently, this has led to a very lightly regulated area of application for radiopharmaceuticals as "compassionate use", a kind of last straw for the cancer patients concerned.

For other classes of therapeutic agents, it would have been unthinkable that, as in the case of Pluvicto, around 2,000 patients had already been treated 'compassionately' with the compound before the start of the first clinical trial. Viewed critically, one could say that those thousands of patients were treated as guinea pigs.

But at least the results were positive, and provided insights into how radiopharmaceuticals can lead to noticeable treatment success in patients. Pluvicto showed an impressive response in the authorisation-relevant study. Still, some industry experts say the lack of regulation has led to a kind of 'Wild West' of drug development in the sector.

Pragmatic regulation needed

Germo Gericke is also critical of the fact that regulation is not keeping pace with developments. He says that compassionate use is undermining a commercial market environment, which in turn unsettles investors and lulls reimbursers from health insurance companies into a false estimate of prices and what development actually costs. Another issue is that whereas drug development is harmonised in Europe with the EMA as a central authority, this is not the case for federal offices for radiation protection. Although calls for more regulation and harmonisation are not exactly typical for the pharma industry, this is an issue in radiation protection, and the fragmentation of rules slows European development. The FDA and even its Chinese counterpart, the CFDA, have on the other hand set pragmatic, scientific regulatory requirements, and these have an effect on innovation.

Industry vs. Academia

Industry experts have yet another concern – the home-brew tradition of some clinicians in providing isotope ligands for imaging or even therapy through special labs located in the pharmacies of some university hospitals. They only cover established markers or targets, and rarely take an innovative turn. But clinicians in academia

Radiolabeling (II): a manipulator in the process cell

don't want to give up established procedures. In the context of the reform of the European Union Pharmaceutical Framework, the manufacturing of nuclear medicinal compounds is under review and will see new regulation. The pharma industry in radioligand diagnostics and therapeutics has serious doubts that home-brewed compounds make a relevant and qualitatively equivalent contribution to patient care and urges that GMP manufacturing must become the standard. The unspeakable argument by some academic associations that patients deserve individualised treatment in this context has to be dispelled.

Radiopharmaceuticals are regulated as drugs and need to be developed and manufactured with the same level of care as other classes of therapeutics (e.g. biologics, small molecules, cell therapies, vaccines). Also, they will only be approved by FDA or EMA based on well-run clinical trials providing a clear understanding of efficacy versus side-effects in well-defined patient populations. With the expansion of radioligand therapy, many questions about both radiobiology and the interaction with the immune system will be answered, and only a clear regulatory framework can help pave the way for better medicine.

With the growing success of radiopharmaceuticals, a broad spectrum of specialized CDMOs is evolving across the world, larger pharma companies will have manufacturing facilities of their own. The homebrew era has to come to an end. ■

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Pictures: © ITM isotope technologies SE