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**Speaker:** The *BioWorld Insider Podcast*.

**Lynn Yoffee:** This is the *BioWorld Insider Podcast*. I'm Lynn Yoffee, *BioWorld's* publisher. Radiopharmaceuticals have been used for a long time for diagnostics, but radiopharma therapies are entering a new era. They are becoming widely accepted as a key tool in the oncology armamentarium. They have the potential to provide patients with a big bump in efficacy, with fewer side effects and less damage to healthy tissues. *BioWorld* just launched a seven-part series taking a deep dive into this evolving technology as a disruptor in the cancer treatment space. Today, *BioWorld* staff writer, Lee Landenberger, talks with another BioWorld staff writer, Tmara Sami, the lead writer for our series. Over to you, Lee.

**Lee Landenberger:** Thanks, Lynn. Radiopharmaceuticals have entered a new fast pace era indeed, and the chronology begins a long time ago, 1895. Three years later, Marie and Pierre Curie discover radium rays. Then in the 1950s, there was just the one therapy that was iodine, and that was the only one until the early 2000s. A lot has happened in the past 20 years, and Tamra spent the past few weeks looking into all this. Tamra, those years have been particularly strong. Can you give me a capsule summary of why there's been so much advancement in the past couple of decades?

**Tamra Sami:** Sure, Lee. Thanks for having me. I think the global interest really took off after some big deals in the space, was around the same time that Bayer Xofigo was approved in 2013 by the FDA, and that was for prostate cancer patients with bone metastases. Around the same time then, Novartis spent about six billion in acquisitions. Acquired Endocyte for two billion, and with that, inherited Pluvicto, which uses lutetium. That was for prostate specific membrane antigen prostate cancer.

That really opened up the space into a wide patient population. I think more than anything, the deal dollars is what really sparked interest globally. Then Bayer also made another big acquisition shortly after that, moving into another prostate cancer space. Since then, since 2016, approvals have picked up and FDA has greenlighted more imaging agents, which tie into the therapeutic side. It's a point-and-shoot model. They're now moving into the therapeutic space. There's a lot in the pipeline right now.

**Lee:** When you look at the technology and the big corporate players involved like Novartis, when you're looking at the technology, what is it? Is it the technology that's become so advanced and the larger companies are snapping up those that are developing it?

**Tamra:** That's part of it, but it's really merging chemotherapy and radiation therapy. With this age of personalised medicine, now we're targeting things and we're much more specific. Now, we're taking nuclear medicine and we're attaching these radioactive elements onto these radioligands, which are able to target the cancer more specifically. The ones that are really taking off, they're called theranostics or it's a point-and-shoot model, where first, they take a small amount of radioactivity and image a patient, so then they're able to target that exact point on the tumor where it lights up. That's why it's called point and shoot.

Somebody else said, I think it was Steven Chester with Isotope Technology, he says, "You see what you treat and you treat what you see early on in drug development." As the radio isotope accumulates at the tumor site, it decays and releases that radiation. Then the other thing is, these things have a pretty short half-life then the radioactive material just putters out. The main thing is that now we're able to target the tumor site directly without damaging the tissue around it.

Then the other thing that this also offers is it offers the opportunity to speed up dosing optimisation because you're looking at it, you're tracking it through imaging, you can see where it's being taken up, you can see where it's being distributed, so that maybe down the road, they won't have to do the dose ascending studies in quite the same way because they can see what the tumor's taking up and provides it additional information there.

**Lee:** Those are the big corporate players and that's what they're doing. I read in the series that there are certain countries, and it looked like the European countries are the leaders in the radiopharma space. Why is it that they're ahead of everyone else?

**Tamra:** There's a couple of things that make it interesting. Actually, Australia is also one of the leaders. Australia and Germany and Belgium, and then a couple of people that we spoke to said France as well. Australia is interesting because Australia is sometimes a test market because of its small population. Often, innovative therapies players will go into Australia first and test a therapy. The main reason, it all has to do with supply, Lee. Germany has a large supply, and so those companies that were able to really tamp down the supply chain are pretty much leading the industry right now.

Novartis is one of the biggest players, but it has been riddled with supply issues. There's a couple of companies that seem to have an edge. Isotope Technologies in Munich has a leading edge and it's got monopoly on supply. A lot of these players early on saw that, and so they bought up the supply chain to tamp that down. They appear to be the leaders in the space right now. Australia's Helix is one of them.

**Lee:** You're talking about supply challenges, but the United States seems to lag behind.

**Tamra:** The United States is lagging behind. It's interesting because on the one hand, Canada has a large supply. There have been supply shortages in Canada, though. Shortages of the raw material for the isotopes have caused some problems. Another problem is also that these therapies have very short half-lives. Some of them are only active for like six or eight hours. If you are manufacturing in Germany, you can't really ship that because it's only going to be alive for six hours. You have to be close to your supply chain. It's an interesting space when you think about these are nuclear medicines and they really arose from nuclear weapons that were made back in the 1940s with uranium.

A group called the Manhattan Project figured out that plutonium gave higher yielding weapons and that was more effective. In the 1980s, there was a campaign to extract what was thorium-229 from that stockpile of a uranium. That was pretty much split into two batches. One batch stayed in the US and the other batch went to Germany. That's pretty much the entire global supply of Actinium right now.

Then Lutetium had similar issues. They're produced in a nuclear reactor and there's a limited number of nuclear reactors. In like 2008 to 2010, there was a global shortage of several main isotope-producing centers in Canada and the Netherlands causing delays to patient treatments. Then recently, with Novartis, it had some issues with supply and had stopped treating patients because of those similar issues.

Another wrench in the system, and the United States should be able to do this better than Europe, is the regulatory red tape. You're not just being regulated by say, the FDA. You're being regulated by the nuclear regulator when it comes to transporting this radioactive material. You've got clinical regulations. You've got these layers of regulations.

Now, in Europe, you're crossing countries and you can't ship the material from country to country. Say, if you're a supplier in Germany, you can ship to the United States, but you can't really ship across other European countries, which seems a bit nuts. It's making for a very difficult space to enter, and so the supply issue seems to be everything in this space, more so than in any other space that I've seen.

**Lee:** Let me ask you another question. I was curious, earlier on, you mentioned how there's a shorter half-life for these treatments, and that means being a patient is a different experience than it used to be. Shorter half-lives, less damage to tissue. Can you give me an idea of what it's like being one of these patients now as maybe compared to a few years ago?

**Tamra:** For example, with iodine, as a patient, if you came in to be treated, you would have to isolate for 48 hours in a solitary room because everything was radioactive. Your waste material was radioactive. That doesn't seem to be the case anymore. The patient's waste material is still a bit radioactive, but it's not a cause for concern anymore. From the companies that we've spoken with, this is an area where simply companies like Bayer and Novartis being in this space have pretty much trained the clinicians. Clinics are are well versed in how to handle these new types of radioactive material.

They have to get a license from the Nuclear Regulatory Council and there's enough of them in academic medical centers that deal with these that, they have services that deal with the radioactive material. It's not really an issue for the patient anymore. They don't have to isolate. They pretty much get treated and may have to hang out in a room for usually just a few hours and then go on home. I was hearing stories of patients that had to be isolated in another room in their home, and that was more in the old days with iodine but that's not really not the case anymore. We've learned a lot about how to deal with this.

**Lee:** Are these treatments more effective?

**Tamra:** Iodine was very effective but it had also carried a lot of damage. We've gotten better at targeting just in the age of personalised medicine, we're better at targeting specific biomarkers and specific proteins. As is the case generally in treating cancer, we're getting more specific. These radioactive ligands targeted cancer therapies will just target that particular protein. We think that they'll be more effective particularly with metastatic cancer. Not only they be more effective but they'll also cause less damage. At least that's the great hope. We haven't seen enough approved yet to be sure but it's looking pretty good from the people I've spoken with.

**Lee:** We've come a long way in the past 20 years and I'm curious, do you have an idea of what the future looks like with this technology?

**Tamra:** From the people that we've spoken with, it's another tool in the oncology toolbox and it seems the direction is getting more and more specific, get it early and that really is the cure. Diagnose it early, find it. Patients will still have surgery to take out a tumor but now we'll be able to monitor it continuously. We have the right target, the right ligand. If it starts to spread, it becomes easier to treat. With metastatic disease, when surgery isn't an option, these radiotherapies are going to really help instead of external beam radiation where you just kill everything around you, and chemotherapy that has a myriad of side effects, this really could be a strong tool in the toolbox to help these patients.

**Lee:** Got it. Thanks Tamra This series is fascinating. I urge everybody to read it. It's running this week in *BioWorld* and it'll be up on our site for a while. Thank you for all you did and great job.

**Tamra:** Thanks, Lee.

**Lee:** Lynn, back to you.

**Lynn:** Thankyou Tamra and Lee for these insights. For our listeners who would like to learn more about this topic check out *BioWorld*'s multi-part special report, radiopharmaceuticals the next big disruptor. As always, *BioWorld* will continue to keep you informed of all the most important scientific clinical and business updates.

That's our show for today. If you need to track the development of drugs, turn to bioworld.com. Follow us on Twitter and you can email us at newsdesk@bioworld.com. Also, if you're enjoying this podcast, don't forget to subscribe. Thanks for joining us.

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