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**VO:** The BioWorld Insider Podcast.

**Lynn Yoffee:** This is the BioWorld Insider Podcast. I'm Lynn Yoffee, BioWorld's publisher. It's that time of year again. We're wrapping up 2022 and preparing for 2023 on today's episode. In the past year, we've seen quite a few changes in the industry driven by new science, by dips in the global economy, and the ripple effects of COVID. We saw a fall in biotech stock values and fundraisings, fewer FDA approvals, SPACs fell by the wayside, and new RNA modalities were introduced, just to name a few.

Today, BioWorld staff writer, Lee Landenberger is talking to four CEOs, the visionaries of companies that are producing new science and insights into drug development. Karen Zaderej, the CEO of Axogen, Sean Bohen, the CEO of Olema Oncology, Rob Ross, the CEO of Surface Oncology, and Rob Etherington, the CEO of Clene Nanomedicine have all joined us to take stock of what happened this year and to look ahead. Over to you, Lee.

**Lee Landenberger:** Thanks, Lynn, and thank you, everyone, for being here. We have folks gathered from all over the world, and it's a pleasure to have you with us. This past year has been really interesting. We've all watched it. Karen Zaderej, I wanted to ask you first, you're the CEO of Axogen, which is in Alachua, Florida. Your company just completed a successful phase three study of its peripheral nerve repair product called Avance. Karen, one of the big trends of the past year that has affected your company is staffing at hospitals. I wonder if you'd tell me about that. What was it like in the past year and do you see any change coming in 2023?

**Karen Zaderej:** Yes, it has been an interesting few years, I think for everyone. One of the big outcomes from the COVID pandemic has been the quitting and early retirement of a lot of the staff that really keeps hospitals and healthcare systems rolling. It has been a real challenge for the hospital systems. It's gotten better, I would have to say, in the last few quarters, but as I talk to hospital CEOs, they are saying that this is a multi-year recovery.

We've always known that there was a large number of baby boomers who were going to retire, but in COVID, many of them decided to retire a little bit early so that's left a gap. The other transitions that nurses and technicians and other staffers have done have left a gap in being able to provide care, which has created a lack of predictability and higher costs for hospitals so that labor costs have jumped up tremendously with travel nurses and also the inefficiency of many other procedure areas which are really important for hospitals to make their bottom line.

As we look ahead, I think hospitals will continue to bring in nurses to help reduce their travel nurse costs but at this point, they haven't been able to really do a lot to increase their capacity. The capacity piece will be the item that will be several years for them to bring up capacity so that they have the flexibility to do overtime so that they can bring back some departments that, frankly, they may have decided to close just because they couldn't reliably keep them open. That it is not something that will be a one-year trend. It will probably be a few years before it's done, but getting better each year.

**Lee:** I'm curious about your company. How did hospital trends affect you and what have you got coming up in 2023?

**Karen:** Well, we are a surgical repair, so it is our Avance Nerve Graft is placed surgically, so any staffing issue that is impacting the ability to run ORs and emergency departments are things that we see an effect on. Our product is used in, nerves are injured in lots of different ways, but they're injured in trauma. If you don't have a reliable emergency department that can be staffed appropriately, then hospitals at time are having to shut down those emergency departments on a temporary basis. That changes referral patterns, it changes care pathways and so that was highly disruptive.

Today, I think we reliably have the emergency department open, but we now have to have the capacity in the operating room to consistently do the procedures. Trauma is getting done today, but another area that we have is breast reconstruction, allowing the return of sensory function for women who have a reconstructed breast following a mastectomy. That procedure is an extremely long procedure, and from a capacity standpoint, hospitals are having a hard time working off the backlog of patients who have been unable to get this care so, at this point, surgeons are scheduling out as much as six months or more for those patients to get their reconstruction done.

As we look ahead, well, I do think the staffing is levelling out, so that will be good. We are seeing now much more predictability in our business, so we're able to get the procedures completed. We're continuing with our submission of our biologics license application that will be completed and submitted in late 2023. We're also completing out a new biologics processing center which we should be transitioning into in early 2023. That, along with several other clinical data components, make 2023 an exciting year for us.

**Lee:** Interesting. Sean Bohen, the CEO of Olema, I wanted to ask you about trends. Also, your company, Olema, is developing therapies for treating women's cancers. Your lead candidate is an oral small molecule with a dual activity as a complete estrogen receptor antagonist and a selective ER degrader and you're in a phase 2 study for treating breast cancer. Can you talk about what you saw for your company in the past year and what big-picture trends you might see coming up in 2023?

**Sean Bohen:** Yes, thank you. I welcome a chance to discuss that. Yes, OB1250 is, as you discussed, is a complete estrogen receptor antagonist and a CERD. In phase 2, as a monotherapy, and phase 1B in combination with CDK46 inhibitors, palbociclib and ribociclib, and as well as Alpolicib, which is a PI3 kinase alpha inhibitor. Over the course of the past year, I think what we have seen is obviously a bit of a capital crunch for many companies in the industry.

You mentioned earlier valuations and the sort of nosedive that they've taken over the year. We at Olema are extremely fortunate to have been very robust in raising capital in 2020, so we have a nice long runway into the second half of 2024 with our cash on hand. As you saw, many, many companies had to make some very difficult choices around cutting staff, cutting programs, or raising capital at significant dilution.

Again, that did not affect us, but I think it does have a drag on the industry as a whole when we see that trend happening. The problem with that is that with that availability of capital, you slow down or lose programs that may have resulted in meaningful improvements in therapy for patients in need. Obviously, for us, that's cancer patients, but this trend and this capital crunch in 2022 affected all companies, or at least all therapeutic areas.

Going forward to 2023, I think what's interesting to me is, and I think many observers if you look at the industry coverage, there was relatively little M&A and partnering between biotech and pharma in 2022, I think, compared to the expectation that many observers had. I think that expectation had two components to it. One was need in large pharmaceutical companies. Some observers have said that their analysis shows that large pharma will lose, between now and the end of this decade, 2030, $200 billion in revenue from loss of exclusivities.

Even if that's a slight overestimate, that's an extraordinary amount of revenue lost. Also in that time period, you can't have your early pipeline recover that. I think people expected more partnering and M&A to occur in 2022, particularly with valuations having fallen. That didn't happen. I think it's going to be very interesting to see if 2023 is a year when, one, the larger pharmaceutical companies realize that their own pipelines are not going to be able to fully replenish this revenue. Two, also, companies are perhaps more eager to seek a partner rather than to seek capital from the equity markets.

**Lee:** Yes, I wanted to ask you about your approach for fundraising in this coming year. Do you have to, because things have changed so dramatically, do you have to change the way you do any of that fundraising?

**Sean:** I think for many companies, the idea of using the equity markets as a source of additional capital is much less attractive than it was say a year ago. That's just because with valuations lower, any funding from equity markets is going to be much more dilutive than it would've been at higher valuations. That then, kind of consistent with what I said about partnering, that then makes strategic capital, so things like partnerships with large pharmaceutical companies, royalty agreements, basically gaining capital by giving some portion of future revenue, potential revenue as a royalty to a potential partner. Those avenues become more attractive when you run into a situation where valuations are decreased.

**Lee:** Got it. Thanks, Sean. We have two Robs on the panel today. Rob Ross, the CEO of Surface Oncology. Surface has a phase 2 study going on for its antibody against IL-27 in treating non-small cell lung cancer. Rob Ross, I'm curious about how everything went for your company in the past year and what you see, not only for your company but big picture as well for 2023.

**Rob Ross:** Happy to answer that, Lee, and thanks for having me on. I'd start by saying that I very much agree with the groundwork that Sean just laid for all of us in the small biotech space, certainly in the oncology space. Basically equity funding has fully dried up and has forced us to prioritize and be creative. Moreover, there's definitely a risk-off broader environment, both from an investor perspective as well as from a potential strategic partnership perspective where there is a real interest in seeing more mature data, later data, in order for people to make those more significant investments, either in equity or with a broader strategic partnership.

That's really forced us, just as Sean said, that's really forced us and many others in the field to really focus on the programs that we think are going to drive the most value to patients and also to the company in the near term. For us, that allowed us to really hone our portfolio to this anti-IL-27 antibody SRF388, which is a first-in-class program that is within the broader spectrum of immuno-oncology. Attempting to create anti-tumor immunity, so getting the immune system to attack and eliminate the cancer. SRF388 for us is in phase 2 trials in lung cancer and in liver cancer with what we think will be really compelling readouts in the middle of next year. We as a company were able to really focus on SRF388 as our lead program and use that to hopefully catalyze both investor and strategic interest.

More broadly, I'd also make the link between the way Karen started and then also where Sean went. We've definitely seen an increase in costs of clinical trials. Hospitals are not just struggling on the care delivery side, they're also struggling on the clinical trials infrastructure side. I don't think this is limited just to the United States. I think we're seeing this broadly both from early retirements, and in the context of COVID, people just deciding that this wasn't a space they wanted to continue their career in. We're seeing clinical trials office be fully backlogged, IRBs be backlogged, and site startup times taking much, much longer than usual.

For those of us, I think not just in oncology, but certainly, in oncology who are really focused on clinical trial data in order to drive value and in order to demonstrate that these drugs are helping patients, it's been an additional headwind, an additional hurdle that's forced everyone in the field to really focus their resources to what they think is most compelling.

**Lee:** How do you go about making decisions like that? You just got to wait until you're confronted with the problem and find a workaround, and have you had to do a lot of that in the past year?

**Rob:** Yes. We, as a company, we started from the very beginning as a multifaceted immuno-oncology product company. We didn't start with an underlying platform, rather, we at the very beginning of the company went after multiple novel targets in the immuno-oncology space. We partnered many of those programs in order to continue to finance the company. When we went into 2022, we had multiple programs in the clinic. We were able to use the clinical data in order to determine which we thought was the most promising program and that was the SRF388 program. By having more shots early on and more clinical data generation early on, it allowed us to really focus on the program that we thought was most likely to generate benefit to patients.

I'd definitely echo what Sean said before. There's certainly value in prioritization. Having said that, that also means that there are likely good programs and good molecules that could potentially be useful that get set aside or paused. We had to do that with one of our programs that we announced quite recently for no-- There was no particular problem with the programs, no problem with the molecule, but we just didn't have the finances to do the clinical trials necessary across our total clinical portfolio and we had to focus.

Now, we hope with strong data, we'll be able to go back and reinvest in that other program as well but what we are seeing at Surface is certainly replicated throughout our industry that there are other programs that may benefit patients that right now are being paused or deprioritized or just stopped.

**Lee:** Thanks, Rob. Rob Etherington who's the CEO of Clene Nanomedicine. I wanted to ask you if because you're also in the clinic, your company is developing treatments for neurodegenerative disease, you target energetic failure which is said to be an underlying cause of many neurological diseases, and you just reported some phase 2 data for treating multiple sclerosis. Can you give us a quick recap for what happened in 2022 and what you see as maybe larger forces coming out for 2023?

**Rob Etherington:** Certainly. I think Karen, Rob, and Sean before me have all spoken nicely to these themes and they are indeed some challenges for biotech in our case. In our case, just briefly, Clene is indeed developing a nanotherapeutic that patients drink orally, and we have completed in the last year clinical studies in both ALS and in MS, and the challenges that Rob just mentioned with respect to good programs needing funding to take safe drugs down efficacy paths remains a challenge for I think all of the small and arguably, even mid medium-sized companies.

In our case, we did finish the visionary study. We showed there that we could improve function on top of standard-of-care MS drugs. That is a tremendous market need. Multiple sclerosis is pretty well treated with the disease-modifying drugs, a whole number of prescriptive medicines that tamp down the body's immune system so the patients stop relapsing into their MS disease, but despite that, patients still remain functionally compromised. The way they think cognitively in some cases, but definitely, the way they move, the way they walk with small motor control as well as just basically a walk gait, and then of course vision is compromised still.

Our asset was able to improve that function. What remains now is that we prepare a phase 3 study and the points that have been raised previous to me are indeed the case. To go into the equity markets is a particular challenge. Like others have mentioned, to lean into strategic M&A, strategic opportunities with respect to licensing and or geography cells is one opportunity.

In Clene's case, we also leaned heavily on our board who completed recently a registered direct investment into Clene which we are able to do without a bank and without any discount or warrant coverage. From a dilutive perspective, that helped immensely, and we've also been pleased Clene over the last year has partnered with both the states in which we operate as well as the government for grants and for loans which we've been relatively successful at giving us runway. That's what this present environment has forced companies like all of ours to do and that is to be creative, to find ways to fund our programs so that we can continue making the progress that, frankly, these diseases require.

**Lee:** Talk to me about the science. I'm willing to bet you keep an eye on technology constantly. Were there any big changes you saw in 2022 for your company, and/or maybe there's something coming up in the coming year?

**Rob Etherington:** In our case, what we focus on is nanotherapeutics, that is to say super small molecules, in our case, a crystal built around gold. That is, yes, regular gold that serves as a new class of drug to improve, as you noted earlier, cellular energy production and its utilization. Mechanistically, what's happening is our asset is levering physics and biology, less so small molecule. Our asset's not built around a small molecule. By targeting energy metabolism, we can protect neuronal health. There is a lot of progress that is happening across multiple disease states of novel modalities to solve some of these vaccine problems.

Oncology concerns and neurodegenerative concerns remain pretty much top of mind for all of us. Now that we've thankfully resolved some of these cardiovascular concerns that were in earlier decades, very compromising, and other diseases, patients are living longer, but there's many areas that that aging patient population still compromises them immensely.

Speaking to one thing Karen said as well as Sean, the COVID pandemic we're still even though many of us have moved on from COVID to a degree, the aftereffects of it still affect us immensely. In Clene's case, we were doing an MS study when multiple sclerosis patients who had their immune system tamped down purposely to affect their disease, the last place they wanted to go into was a clinic. Then when they went to those clinics, there was these long lines and less staffing as has been noted by Karen and Sean.

The challenge Clene had is we even struggled to complete that study and ended up opening it up with only half enrollment. That was an impact that '22 still gave us. It is my hope that as we come into '23 and beyond, we can continue to get to a new normal or even back, hopefully, to the old normal so that we can get the clinical studies completed that we require to complete.

**Lee:** It's funny, I was listening to everyone's responses and I thought, COVID doesn't seem to be a player, but it's hard to take it out of the equation, isn't it?

**Rob Etherington:** Yes, obviously we have headlines in China, so COVID still remains relevant, but it's not as much of an issue as it was.

**Lee:** Thank you, everyone, for your views and your opinions. Karen Zaderej, the CEO of Axogen, thank you for joining us today along with Sean Bohen, the CEO of Olema Oncology, and the two Robs, Rob Ross, the CEO of Surface Oncology, and Rob Etherington, the CEO of Clene Nanomedicine. We want to wish you all the best of luck in the coming year. Thank you. Lynn, back to you.

**Lynn:** Thanks, everyone. This was a terrific snapshot of what is happening at each of your companies, and it's a great reflection on what's going on in the industry in general. I am clinging to the word that Karen used earlier, which is predictability. I certainly hope that in 2023 we see more predictability so that you can move these important therapeutics onward and to patients who desperately need them.

Thanks, everyone. In addition to these insights, BioWorld will be publishing our usual top stories and trends roundup for a deeper look back into 2022, setting the stage for 2023. 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 email us at newsdesk@BioWorld.com. If you're enjoying the podcast, don't forget to subscribe. Thanks for joining us.

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