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Next Generation Targeted Cancer Therapies - The Cellectar Story!

CureTalks launches its new series featuring biotech companies at the cutting edge of innovation and breakthrough research with the purpose of bringing their contributions to the fore and informing the patient community. This talk series will be hosted by Gary Petersen, our Myeloma talk cohost, panel member and editor of myelomasurvival.com.

We kickstart the series with Cellectar, a clinical stage biopharmaceutical company focused on the discovery, development of drugs for the treatment of cancer.

Cellectar, has a targeted universal drug conjugate with a potential to be used for many cancers. This drug conjugate, CLR131 was granted Orphan Drug designation for the treatment of multiple myeloma by both the U.S. and the European Commission and is currently being evaluated in a Phase 2 and Phase 1 studies. The drug conjugate works by delivering a radioactive, toxic compound directly to tumor cells, while limiting exposure to healthy cells.

Gary Petersen talks to James Caruso, CEO and Jarrod Longcor of Cellectar Biosciences about product development, clinical trials, special challenges of a small biotech in the current investment environment and some of the innovative products in the pipeline.

Full Transcript:

Gary Peterson: Hi, this is Gary Peterson and welcome to Cure Talks with Gary. We will be talking about the new breakthrough research in therapies with the CEOs and Senior-level Management of companies. The first set of this series is Next Generation Targeting Cancer Therapies with Cellectar Pharmaceuticals. So, we welcome you all. Small biotech has been the Genesis of every approved class of drugs for myeloma and all new myeloma classes of drugs have had at least two FDA designations, like orphan drug or fast track. Specifically, that just means that the FDA is looking at them, feels that these drugs are really anointed. It has great drugs for these orphan diseases. Myeloma for example, has eight such drugs that dual designations and six of those are from small pharma. So, small pharma likes Cellectar has for such designations for Orphan diseases. And as a new class of drug with application across many cancers. I am so pleased to be able to discuss this lifesaving development of Cellectar with senior level management. We are honoured to have Cellectar CEO and President James Caruso as well as the Chief Business Officer Jarrod Longcor. So, welcome to both of you. I'd like to break this into two parts. The first of which is just a general outline of Cellectar, and I'd like to do that with James Caruso. James, would you please provide a background and history of the company and how your organization can do so much with so little?

James Caruso: Those my pleasure Gary. First and foremost, thank you very much for allowing us to participate in your program. You do great work, and I'm sure it's very rewarding for you and is very helpful for your audience. So, thank you for the opportunity to be here with you today. Cellectar bioscience has a very interesting story. Currently today we're located in Florham Park, New Jersey. However, the company

originated in the Midwest and our base technology that Jarrod will talk to in greater detail and I'm sure your audience is very interested in learning more about our delivery platform to targeted mechanism that makes it or proprietary technology make it different.

This technology came from the University of Michigan and then researchers and academics transitioned to the University of Madison, Wisconsin, and that's where Cellectar Biosciences was found and originated. Interestingly, this technology, this targeted mechanism. was designed for the delivery of Diagnostic and Optical Imaging agents. So, with the delivery vehicle these researchers and scientists were adding fluorescent Imaging agents and diagnostic agents for PET Scan etc and the delivery vehicle time and time again, regardless of the types of payloads added demonstrated a preferential delivery to cancer cells, cancer stem cells in the past decisions spearing healthy tissue. Now, the company was doing some great research, but unfortunately was failing financially and as a result was close to shutting its doors, going bankrupt. When Jared and I first came to the company, we took a real hard look at the technology and what we realized was this technology could better serve in patient's and better deliver on the growth and success of the company if it was redeployed. Not a focus on Diagnostic and Optical Imaging agents, we said let's take oncology therapeutic payloads, add them to this delivery vehicle and now we can treat cancer patients.

And so, the company at the time Gary had very little money as I mentioned was going bankrupt and we were able to gobble together some financing and some capital and we were able to reposition reposition the company very quickly when we pivoted towards the treatment of cancer. And we started in the heme malignancy space if you will and we wanted to focus on an area that we knew we could accelerate through the clinic and really help patients and that was when these orphan and ultra-orphan spaces that really made a lot of sense for us, on a lot of different levels. And fast forward five years later that's where the company is currently set. So, we survived over those five years. It's been a very challenging journey, but we're really now on the cusp of transformation, most importantly for patients as we launch into pivotal trials in the fourth quarter of this year as Jarrod will talk to. Our data looks really really good and it was really good and very difficult to treat the patient population.

So, we have the opportunity to do some really good with CLR 131, which is booming gasps. Now you also mentioned, and I think this is important, with your P&L, the size of your P&L, how has the team done so much with so real. And I will say just like anything Gary, first and foremost, it's about your people. We just have the great team here at Cellectar. Highly dedicated and highly committed in our battle against cancer. Personal experiences that fuel, either with family or friends, that fuel this dedication and this commitment. And as an organization, in our low level the productivity is very high recorded, a reason for that is, we work double time in terms of working on CLR 131 getting this to a clinic and hopefully providing a compound or drug that can help patients. On the functional side of that, we've installed we call a collaborative and outsourcing model and what this Outsourcing model has allowed us to do is it's really kind of limited our infrastructure and the day-to-day costs of running the company and we've outsourced quality third-party vendors a lot of work and what this allows us to do Gary is much much more with much much less because we don't sit on this heavy infrastructure and day-to-day cost. With the collaborative Outsourcing model has allowed us to do is really invest our limited capital and resources in projects, in areas that we believe can really advance our research. So, as I mentioned, it's a small team, we are highly productive, we manage the P&L very very tightly. It's as thin of a P&L statement as you're going to see and thanks to the team, we get significant bang for a dollar.

Gary Peterson: Well, seems and you would expound on that what are the additional challenges that confront a small biotech company versus a huge biotech company like Johnson & Johnson, Pfizer or others such as that? What are the specific challenges you have, one of which was like you mentioned I was putting together the resources in order to move things forward?

James Caruso: That's a great question. And it's a fair question as well, I mean, I've had the opportunity to work both in large multinational pharmaceutical companies as well as in three or four small biotech companies as well. So, I'm familiar with both business models and they are significantly different right. In these larger companies to access the resources is obviously not an issue. They contain significant infrastructure. They can sustain significant investment in research and development and maintain 30, 40, 50

thousand employees as a result. And for smaller biotech companies and we have low double digits, we have to do a lot more with a lot less. And for us it's access to capital financing, which is why when we do the very thoughtful and strategic in terms of our investments and finances. We then have to take that money and be so judicious in terms of how we invest that capital to ensure that we can optimize those resources and advance our clinical development as far as we possibly can. I think it's also really interesting because of those large scale, the multinational pharmaceutical companies there're a lot of mistakes that are made and they're transparent to the public because they're so big and have so many resources.

Where in smaller companies, we have to be razor-sharp day in day out because we can't afford to make mistakes because these mistakes or unfortunately the mishaps, can have an impact in the near term and in the future plan. So, we work without a safety net which makes it very very challenging and so that's why you need a team that is totally dedicated and committed to get these types of projects and these types of work done and completed. I would say the other, there's a lot of differences here, but the other one that I think your audience would be appreciative of it's just the scale and the size of the infrastructure associated with these large multinational pharmaceutical companies. So, they have dozens and dozens of developed products and developing. Typically dozens of products that are commercialized on market generate revenue and if one or two or three or four or five or six fail in the clinic, it's really at the end of the day non material because they can backfill with additional products that are in development. The same is true commercially, sometimes it's a forecast and if those forecasts are not reached for a particular asset or compound, there's dozens of others that can fill that gap. With smaller biotech companies, typically don't have this massive R&D budget and you typically don't have dozens of products or any product on the market.

And so, your revenue is generated through financing and what we've done to try to distinguish Cellectar Biosciences from other like small biotech in size is we really try to mitigate risk. And said another way, we've kind of spread the field here with CLR 131 or our lead asset. And what we've done is we focused in on multiple b-cell malignancies. It was like a basketball coach have had really nice data in multiple myeloma subsets. We have got really nice data in waldenstrom's another ultra-orphan disease as well as DLBCL and other NHL Non-Hodgkins Lymphoma of cancers or indications. And so, what we wanted to do Gary was not focus just on vindication which were unsuccessful, patients potentially may not benefit from what we believe are real feature benefits of CLR 131. It was really unique product profile elements that make this compound unique versus on market existing products, but we also wanted to create opportunity where if we were unsuccessful in one year, we had multiple other indications that potential bring this product to market.

Gary Peterson: Yeah. I've got one more question. I'd like to ask before we move on. I want to give Jarrod an opportunity to discuss the product a little bit as well. But now one of the things that I've seen and you were talking about it is that just being able to fund the company and how you do that and I've had my eye on looking at some of the things that happened in the capital markets. But it is kind of tough as you've made people's eyes glaze over because when I talk about it, but if you can talk to the audience without getting a glassy-eyed about how does uncontrolled predatory stocks, a short sales affect your company's ability to expedite product development? Obviously, you could do more if you had more.

James Caruso: Absolutely, Gary. One of the things I do best is I have eyes glass over. So, I'll be responding to this. I think all small cap companies are spot on, right. You are really subject to the mortgage, your stock price is really your currency, you don't have commercial revenue, you respond to the clinical development of your assets from the sale of your stock. And so, to your point, in the small cap space you could have individuals that may short the stock and those types of activities may have a negative impact on the growth of your stock and it is a significant issue. At Cellectar we are working on the clinical development of CLR 131 because we know if we can deliver the product to market that can help patients, that will transform the company and also potentially transform the life of the patient, their families, and potentially the communities that they live in.

Gary Peterson: When are you going to probably have a phase 3 trial for Cellectar and based on my research if you get into a phase 3 trial with an orphan drug, you have at least 75 % chance of FDA approval. So, to me I just do not understand, like your stock is valued much less now than it was at your initial IPO. However, you're closer to the finish line and ever, you're on the two-yard line you're about to put the ball

over and people still don't see that, and it just blows my mind. It's mathematics, and a little bit of probability theory but in any event, I appreciate you and all the things that you do and all the things that small biotechs' do. Because without small biotech, without IMiD's without proteasome Inhibitors, without monoclonal antibodies, I'd be dead. So, thank you. Now, I'd like to move on right now if you don't mind, I'd like to go on to Jarrod. Jarrod, I'm just so happy to see you again. I saw you at ASH and I stopped by at your point with James is that I talked with both Jarrod and I can't remember the other person, but she was involved mostly with the presentations. I guess that the at ASH and they were just Stellar people. So, you do have a great team behind you and my conversation is now with you just shows they've got great leadership as well. So, Jared I'm intrigued by the mechanism of action for CLR 131 and can you explain what that action is specifically?

Jarrod Longcor: Absolutely Gary, my pleasure. So, I'm going to actually cause everybody's eyes to glaze over because that's what I do best. I'm very talented at that. So, I'm going to try and simplify this as much as I possibly can to keep it sort of not too technical. But simply speaking the way you can think about CLR 131 is essentially like an antibody drug conjugate. We've got a radio eye attached to one side of it and then we specifically target to tumour cells with our proprietary delivery vehicle known as a phospholipid ether. Now, how does that actually work? How do we successfully Target using a phospholipid to a tumour cell? So, as many people in your audience may know tumour cells actually have a significant metabolic need. These needs are increased due to their division of the cell. They have increased need for energy. So, ATP and they have increased need for signaling molecules besides, having the phospholipid membrane increase. In that hospices all cells, when they make ATP have sort of two mechanisms that they use, normal cells and cancer cells use the same two mechanisms. One is called glycolysis where the breakdown of glucose to create ATP any other is called the beta oxidative pathway, which is the breakdown a long chain fatty acids and phospholipids to create ATP. In normal tissue that ratio of glucose or glycolysis to beta osteopathy is like 80 to 90% on glycolysis and 10 to 20% on the beta osteopathy.

In tumour cells that shifts and becomes more of a 50-50 to 40-60. So, there's a lot more utilization of the beta osteopathy. In addition to that the tumour cells need for those additional signaling molecules and for extra lipid membrane potential requires them to actually modify their cell surface. That modification allows them to actually pull in these molecules out of the bloodstream, these phospholipids and long chain fatty acids right out of the bloodstream and the way they do this is they create specialized, localized regions on the cell membrane known as lipid rafts. And these lipid rafts form and they exist for upwards of 10 days. And that's exactly what we bind to. So, we think of an antibody drug conjugate when they bind one antibody to one epitope. What we do is we bind a lot of molecules to a single lipid rafts and these lipid rafts, it's not like there's just one on a tumour cell surface, there are hundreds and what we've seen is that universal across for many of these tumour cells. So, that's about the simplest way I can describe it.

Gary Peterson: Okay. Now you said normal cells also have that but, in less quantity, right? So, are they also affected?

Jarrod Longcor: Yeah. So, normal cells do have it but what changes this in a normal cell, these lipid rafts will form and dissipate in about 2 nanoseconds so very short period of time. And then they are in very low copy number. So, in the orders of 10 to 20 sort of lipid rafts on the cell surface at any time. When you look at a tumour cell as I mentioned these lipid rafts are stabilized for up to 10 days. So, they exist there one rule to is there for seven to ten days on average and then what you see is that the copy number or the amount of lipid rafts on a self-service are more in hundreds of thousands as compared to 10-20. And so that's totally the change, that's what gives us the ability to get so much more drug into the tumour cells and get so much more targeting out of this as opposed to some other technologies.

Gary Peterson: So, it's like battleship. More battleships you have out there more likely it would hit one.

Jarrod Longcor: There you go. That's a good analogy. I used to always tell people, we've sort of engineer probably, people use talk about the Trojan Horse approach with cancer. And I think this is about as close to a true Trojan Horse. The tumour cells can't help, they have to take up these long-chain fatty acids and what we have is essentially a long chain fatty acid mimetic. And the tumour cells suck us in like a vacuum cleaner

not knowing what we're bringing with us. And once we're in then we do our business and we kill the tumour cells from within.

Gary Peterson: Okay. What are the newest drugs available for blood cancer is a monoclonal antibody, but this has to target a specific antigen like cd38, PCMA and why is your method of targeting cancer not require a specific antigen and I think you kind of said that but I think adjunct to that would be, do all cancer cell in a why your seems to will cross boundaries. So, do all cancer cells have the same need for the rafts and sink those little suckers?

Jarrod Longcor: Like Battleship. Yeah. So, what I'd say is, the reality is as you said it before with regard to antibodies and the benefits that patients see but we will get an antibody comparing to a phospholipid either. Antibodies as you said target a specific antigen and let's take cd38. Cd38 is expressed on multiple myeloma cells but it's not expressed in all of the cells and it's not overexpressed in a hundred percent of patients. In fact, if you look at daratumumab, which is an anti CD38 antibody, it works on about 30% of the patients. Why? Because the antigen the CD38 is overexpressed in about 30% of patients. And in the inside of that 30% of patients it may be overexpressed only on the 50% of the tumour cells that are actually in that patient. So, we never get to 100% of the cells being targeted.

To your question when it comes to lipid rafts, in every tumour type we have looked and every type of tumour arena we've looked, we see that the lipid rafts are conserved whether that be in cancer stem cells, whether that be in the primary tumour were in metastatic tissue. We've been able to find that not only lipid rafts present but they're over expressed at a high abundance. They are always there and it's always plenty of them. And this is what we see we've been able to target cells what we call circulating tumour cells. These are cells that get into tumour cells, that get into the bloodstream or actually can see new metastasis. We're actually able to target those, we are able to target what's called micro metastasis, very small collection of tumour cells. Often as ____ and so we will work to see if we can cover a lot of those tumour cell cycle, its life cycle. So, cancer stem cell to a primary tissue to metastatic tissue those antigens that are expressed along that way change over the course of time. This is why you what you see is patients develop resistance to treatments because what you're targeting changes and the cancer is trying to survive despite the challenges, you're giving it. In the case of these lipid rafts, they never get rid of them. They are constituently present because of this need for the energy source, and that's what we're taking advantage and how we're getting it.

Gary Peterson: So, you are cutting off the electricity?

Jarrod Longcor: Basically, eventually that's what we end up doing. We shut them down.

Gary Peterson: Okay. So, many new drugs have been approved like Selinexor ____, Daratumumab, Elotuzumab all of which as a single agent really don't have much activity whatsoever. Yet, fractional dosing for CLR 131, which is I guess you get to give it twice over a period of time has a fifty percent response rate in heavily pre-treated patients. Now to me that's remarkable. And why is this such a secret to the myeloma patient and for all of oncology for that matter. Is that another example of size matters?

Jarrod Longcor: Yeah, great question. I think size does make a difference to some extent here. I'll start with let's start with the first one you mentioned. They're selling XOR and Karyopharm. I think if we look back at when Karyopharm was first getting going, and they were in Phase 1 and early Phase 2 studies. They might not have been as well known or understood in there and sell an XOR, the compound itself may not been widely known. I think as they got later in that development into late Phase 2 into their pivotal study phase 3 study, then they gathered more awareness. And they also at that point they became a larger company to your question to Jim before they got to a point where their market cap was bigger, and they were starting now running 2-3 studies at a time.

When you go to and that's where size really matters in this goes to what Jim was saying earlier, when you look at a large pharma like a J&J, this is where size really does matter. When they're developing daratumumab they're not running one study in multiple myeloma. They're running a half dozen or dozen

studies looking at it in combination looking at it at different dosing paradigm looking at it and subpopulations in a ____ study. What does that do? That increases their awareness across not only they keep paying the clinicians out there, but also patients hear more about it. Because they come across all these studies and they get a better sense of what's going on. In our case as Jim mentioned for small company, we have very small P&L, very targeted P&L, we happen to know where we're going and we have to be very judicious and targeted in our studies because we just don't have a billion dollars to spend today to spread out like that. And I think that's where the awareness comes down.

I think right now, we're putting out that data that Phase 2 data that you're referring to with nearly a 50 percent response rate in approximately, coming out of 53 patients across to dose and groups and that's meaningful data. And I think that starts to raise our awareness and people are going to start and have started to take notice of Cellectar and CLR131 and I think that's going to increase now as we continue down the road.

Gary Peterson: Well, thank you. For many solid tumours the best treatments which historically been to cut it out because that kind of gets rid of it if it's a solid tumour and then to radiate it, to kill the remaining tumour cells around where the cancer was growing. However, your drug carries a radioisotope which will circulate in the blood and I know what it's recessive safe, but I'm wondering now, how do you ensure that the patient will not turn into the next Spider-Man?

Jarrod Longcor: If I could, I would. But joking aside and I will agree with you. Yes, the literature does say that targeted radio therapeutics of this type what they are called radio conjugates or what have you been very sick. They've been used for a long time, several decades with some of the more recent ones and there is older literature that talks about early days with radio therapeutics being injected. The secret with our drug though with CLR131 is again is that up take the how much drug do we actually get to the tumour. When you infuse the drug less than one percent of that amount of drug that's infused into the patient actually gets into the tumour. In our case we see up to 40% of our infused drug in the tumour at the end of the day. Why does that happen? We accumulate into the tumour cell over the course of a very short window. We start fighting, within five minutes of the infusion, you can start to see CLR131 or any one of our pre-clinical programs.

You can see those molecules start to accumulate into the tumour cells in that very early window and that continues over the next course of days. What happens is now taken to your point, if you take a hundred percent of what we injected into the patient 40% of it gets into the tumour that only leaves you maybe even 60% still circulated for a short period of time and then that's excreted relatively quickly. So, there's a relatively low probability, a low amount circulating in the patient at any given time in addition to that and I know I'm going to go on a little bit here. In addition, that we actually inject a very low dose in comparison to other treatments. If you look at something like what is used in the Pediatric Arenas a compound called MIBG I-131 which is iodine-131 attached to a different delivery of MoAb modality. We can deliver 16 times the amount of drug to the tumour that that drug delivers. That means we give 16 times less to get the same results. So, where they're giving a thousand molecularly dose. We can give 80 molecularly dose and get the same results. That difference means there's much less radiation impacting any of the body.

The real beauty in this is when you move beyond just what I'm saying, but you look at our clinical data and our safety profile, that's where you really see this play out. We don't see what's called off target effects. We're not damaging the healthy tissue when we're circulating. We don't see any changes in the liver enzymes that people, that you monitor for liver impact. You don't see any kidney damage being caused by it, no heart damages, no cardiovascular. Nothing in the lungs, nothing in the bloodstream. What you do see is on target as you mentioned before in your multiple myeloma suffer. In multiple myeloma, where do we go? We're going to the bone marrow to get after the tumour cells, we get in there we get into the tumour cells. What do we see? We see cytopenias or decreases in certain blood counts associated with the drug. That's a non-target effect because our drug is getting right in there at the tumour in the bone marrow, and it would be right next to potentially stem cells that will produce your thrombocytes, your erythrocytes, those cell types in your bloodstream and they'll be depleted a little bit. And what we've seen is that at any dose that we have given that's all we see, and we don't see, there's been no dose limiting toxicity associated with those at this point.

Gary Peterson: Well, fantastic. I appreciate that. My next question had to do with how it differs from antibody drug conjugates, which you've already talked a little bit about that, unless you want to expound on that. Right now, that happens to be one of the big things. I mean five years ago, there's maybe 3 clinical trials at ASH for antibody drug conjugates and it's exploded. It's like 150 or 200 now. So, I mean it's just exploded, and it sounds to me like you've got something well as shown to be as effective or far more effective than some of those that have come out. So, I'm just wondering what the difference is? What makes yours so much more effective yet invisible to a lot of people.

Jarrod Longcor: I think again that the idea is we get so much more drug into the tumour than an antibody drug conjugate can. When you do an antibody drug conjugate, and this is sort of this really get into some of the secrets also of antibody drug conjugates. So, remembering that the antibody binds through a single epitope. It's a one-to-one ratio antibody to epitope. This is why, antibody drug conjugates they try to attach 4-8 chemical to molecule that's actually doing the work to that antibody. They attach a larger number to it to get more drug into the tumour. So, at any given time because of that one to one ratio, it's the only way they can increase the concentration. The greatest challenge with antibody drug conjugates is once they get into the tumour cell, they are taken into what's called a lysosome.

It's a sub compartment inside the tumour cell that the drug then has to get back out of and then get to what you want to target. The beauty with what we do is again when we bind to the lipid raft, it's not a one-to-one ratio. We can put 50 molecules or 100 molecules on any lithograph and get internalized as a large group. This is why we see so much higher delivery. On the other side of that, we don't go to the lysosome because of what the mechanism by which we enter the cell, we go directly into the cytoplasm. So, we won't have to get outside of another compartment to do what we need to do. We're directly where we want to be and the way we track inside the cells, we go right to where the nucleus, in and around the nuclear area.

This allows us to where the radioisotope that's where you want to be because you want to deliver it as close to the DNA as possible to break it apart, which is one why we're so different than some of these other small molecule plays when we attach small molecules, it allows us to have greater control over what we attached, how we release it and that we can bring things into the tumour cell that until now could never have been used in an antibody drug conjugate play. So, I wouldn't say we have competitive advantages over certain things with antibody drug conjugates. But each of these has a place in the treatment paradigm for patients because certain things will work better at certain places.

Gary Peterson: Can you please provide us with what you feel is the future of your platform and cancer therapy? For example, what we've always seen was when you move it, instead of and stage and we appreciate that. We all myeloma patients, when we have tried everything, we would like to think that there's one more thing. We're so happy that Selinexor has been approved because it gives us another chance at life. I see CLR131, the same thing but more effective, and so you give us another last chance at life, but we also know that when you move these drugs too earlier in the course of the disease, look at Daratumumab, almost no single agent activity, but you move it further back into when more towards newly diagnosed, it really works. So, where do you see your drug going?

Jarrod Longcor: Yeah, absolutely. I actually see us sort of straddle and my mind and what do I mean by that. We can work in the late stage disease setting as you described to be in that more challenging to treat patient population. But in addition to that, I think you can easily see this compound because of the limited adverse events that we do see what it will pair up nicely in combination, which is what they're commonly using these days in early lines of treatment first line, second Line, triplids, doublids. Some people talking about quadlids. But looking at that paradigm, I can easily see us combined with some of the compounds that are already approved. We would work very synergistically with some of those with CLR131, but the other nice part about our drug, some diseases can develop some radio resistance, but if you can get enough radioisotopes into those tumour cells, you're still going to break up enough DNA to kill the tumour.

And so, if a patient takes CLR131 in first line, in combination with something and then they progress they could still come back and using CLR131 and seventh line. And still have an effective meaningful benefit for the drug in both ends of that and that's why I think of it as sort of straddle. In Multiple Myeloma, in the case

where Jim mentioned earlier Waldenstrom's Macroglobulinemia, a closely related disease to multiple myeloma, we are looking in that space. We have wonderful response rates, right now we're focused in the later line approval process. But again, I see us being utilized in early lines with that. I think you mentioned sort of in the broad scheme of things. We've also got this drug CLR131, we're developing for paediatric indications. Paediatric brain tumours is a host of soft tissue sarcomas and it's what we see, and we were sharing some interesting information earlier today on this what we see is, exactly what we've been seeing in multiple myeloma. We're seeing that we track to the tumour, we get after it and it's about getting to the to the right doses and being able to help the children.

Gary Peterson: Well, that's outstanding and obviously I have got my own focus and happens to be like cancers but the things that I think it's a childhood Cancer, 72% of those happen to be rare cancers, so and nobody wants to work on them because they are so rare. And so, I'm just so pleased to hear that you guys are performing in that space and you have so many drugs for so many of those paediatric cancer. So, thank you so much. Well, that was my last question and just thank you so much for being part of this new series. To me, I don't know why you're such a big secret. I mean you guys are providing, potentially game changer when you think a lot of drugs that have been approved for late trying of treatment are 5, 10, 25, 30% at a high-end.

And you guys are at 50% on your fractional dosing is just plain remarkable. So, James and Jared thank you so much for all that you do and the fight that you has put up just to stay in business and to deliver these things because you guys are really the ones that can save a life. You've done it for millions of myeloma patients. And I mean that the small biotech companies because now one drug – velcade was a little small company in the very beginning before it got bought up by Takeda. Cellectar was a 10-million-dollar company losing _ left and right when they picked up thalidomide which was sitting on the shelf in some English lab and used it for leprosy to begin with that and now, they were sold for ninety billion dollars. Well, obviously Paul biotech is where it all begins and it's happening the same way with myeloma, that 6 out of 8 being small biotech. So, I don't want to see you guys go away. I want to see all succeed, get your drugs to market and give us and children the new last chance at life. So, thank you.

James Caruso: Thank you very much, Gary.

Jarrod Longcor: Thank you very much.

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