John Marchica:

Welcome to Health Care Rounds. I'm your host, John Marchica, CEO of Darwin Research Group and faculty associate at the Arizona State University, College of Health Solutions. Here, we explore the vast and rapidly evolving healthcare ecosystem with leaders across the spectrum of healthcare delivery. Our goal is to promote ideas that advance the quadruple aim including improving the patient experience, improving the health of populations, lowering the cost of care and attaining joy in work. Please send your questions, comments, or ideas for Health Care Rounds to podcast@darwinresearch.com. And if you like what you hear, please don't forget to rate and review us wherever you get your podcasts. Let's get started.

Kim Asciutto:

Today, John speaks to Dr. Noam Emanuel. He has over 26 years of research and development, marketing and management experience in biotechnology projects, including development of drug delivery systems and immunology. His extensive expertise includes immunotherapy, vaccines, immunodiagnostics, systemic and local drug delivery and medical devices. Dr. Emanuel has a number of approved patents in the field of drug delivery and diagnostics. He is a co-founder of PolyPid and served as its CEO during the company's first three years. He received his PhD from the Faculty of Medicine at the Hebrew University of Jerusalem.

John Marchica:

Let's just get started.

Dr. Noam Emanuel:

Okay. Go ahead.

John Marchica:

Before we get into PolyPid a little bit later, just start us off and tell us a little bit about your background.

Dr. Noam Emanuel:

Okay. Okay. About myself? I'm not used to talk about myself much. I'll do my best. Okay. First of all, yes, as said, my name is Noam Emanuel. My background is PhD degree from the Faculty Medicine Hebrew University in Jerusalem, and I accomplished studies. It was 2000... sorry, 1996, 25 years ago. And then my studies was around actually anticancer liposomes. I was in the lab with the Doxil, if you know the Doxil anti-cancer liposomes.

John Marchica:

Yes.

Dr. Noam Emanuel:

With the doxorubicin, so I was at vet lab at the time. It was registered in the FDA at the time. It was a big celebration. And then over the years I was in the biotech companies, experienced immunodiagnostic vaccine, systemic drug delivery, local drug delivery, also immunotherapy. And yeah, that's my experience over the 25 years, over 100 patents, most of them granted or allowed, almost everything in

drug delivery, some in diagnostics. And also, I'm the co-founder of PolyPid in the '90... 2009, sorry. And I was the CEO over the first three years, and now I'm the chief scientist of PolyPid.

John Marchica:

And your PhD is in what area?

Dr. Noam Emanuel:

I started immunologist actually, and I came to the lab as immunologist but very quickly I understood that what is really interesting here is drug delivery and can use actually immunology and my knowledge in antibodies to actually target the liposome, the tumors. So from that point onward, I was fully dedicated to drug delivery system, targeted drug delivery.

John Marchica:

It sounds like my other day job. No, I'm just kidding. Just kidding.

Dr. Noam Emanuel:

It's okay.

John Marchica:

So in our pre-interview, we talked a lot about surgical site infections and here in the US, CMS has focused a lot on SSIs and healthcare-acquired infections. And I know that it's been a major priority for health systems for many years, so talk to me about surgical SSIs and the magnitude of the problem.

Dr. Noam Emanuel:

Yeah. Okay. So first of all, what is SSI? I think we need to understand, SSI stands for surgical site infection. That means it's closely related and, of course, resulted from surgical incision. Actually, we have bacteria everywhere, on our skin, in the environment, inside our body, outside of our body. We cannot avoid that on one hand. On the other, there is traumatic event that can be by accident, also by surgery, and then bacteria can be introduced into areas where it should not be. And then, when it catched that infection, that's what we call SSI. Now, it can be superficial, involve only the skin, and subcutaneous, but also the deep involving, of course, the fascia, muscle layers, fat, et cetera, and then become very, very severe. And, of course, there are combination of both. So as we understand, infection in general is not something nice, and infection due to surgery is even worse actually.

So that also can generate a lot of morbidity. And of course, etra surgeries, readmission, and of course, mortality and a lot of costs. So if we like, we can go into the cost, but first of all, the dimension. Just to understand the dimension of SSI weights, minimally invasive surgeries can go up to 9% of infection. And if it goes in colorectal surgery, in open surgery, it can go to even 15% infections of the patients. And open surgeries with comorbidities can go up to 30% of the patient. And that, of course, include obesity, diabetes, COPD, all of these type of comorbidities. And in open heart surgery, it's less, about 4% to 8%, but then comes mortality that can be even 40% of the deep infections. So that's very, very severe. In... Yeah. Go ahead.

John Marchica:

No, I was just going to say that's extremely high rate.

Dr. Noam Emanuel:

Yeah, absolutely because some infection is very severe and extremely costly. I will go into that again later, but just to say also that in orthopedic, in trauma surgery, it can go to almost 20% infection. So, that's really a very significant morbidity. And as I said, very, very intensive in terms of cost, hospitalization and all that. So the impact of SSI is on the patient, of course, on the surgeon, but also on the hospital. On the patient, as I said, morbidity, mortality, hospitalization, typically between seven to 11 days in the hospital, additional IV antibiotics. Revision surgery is increasing in the use of antibiotics that can generate kidney failures, GI infection like Clostridium infections. And, of course, even the risk of a resistant bacteria.

Now, for the surgeon, now you can imagine that the surgeon is working hours on a patient, very successful operation, and now a small bacteria will destroy everything. So first of all, frustration, then reputation. And now it's also reported. Financial, in some hospital, there is a various, even annual bonus can be heard. And of course that's a very significant for the hospital itself. First of all, of course, mostly economic. That's the direct impact, first of all. We all know the reimbursement by the DRG. So here, the abdominal surgery will cost $20,000, open heart surgery SSI will cost even $100,000, and orthopedic can go to about $75,000. That's very significant and on the shoulder of the hospital. Now, there's also in addition, the CMS winking, what we call in the Medicare that can be very significant and then medical payment can be of use in 1% annually for the worst SSI offenders. It's the bottom 25% of the hospitals. And of course, reputation, patients are shopping, shopping around for the best hospital. And of course, infection rate is not something to admire as you know. So altogether it's not so great.

John Marchica:

Yeah. I was surprised. I thought that we had had, I don't want to say completely under control, but we had had this problem much more under control these days. And I was surprised at the magnitude that you were talking about just now and what's related to that is the issue of antibiotic resistance. And I've been hearing about it since I got started in healthcare with at it more than two decades ago. And so my question is with, especially as a scientist, with all the remarkable breakthroughs from pharma that we've seen in the vaccine world with COVID, right? Just this amazing transformation in a year, why has pharma not met this challenge of antibiotic resistance?

Dr. Noam Emanuel:

Yeah. First of all, yeah, it's very frustrating situation. Actually antibiotics is, together with a nuclear power, is the two majors I would say invention during the last century, I would say. Without antibiotics, we cannot imagine, more than a medicine without antibiotics. That's for sure. Now, what this tool is working properly, everything is great. We can fight bacteria that, as I said, is everywhere on our skin, inside the body, outside the body, environment. But when it's not working, that's a disaster. Now, antibiotic resistant bacteria is a natural mechanism, bacteria is resisting everything that try to pose in or to kill it, if it's a fungal or everything, the environment. So, bacteria need to find ways to survive. And that's why it can fight anything that try to kill it, including antibiotics. That's one of the mechanisms now.

So, that's a natural process. As much as we use antibiotics or anything else to kill bacteria, the more resistant bacteria will appear. And now, that means that when we use this tool again, again, again, and very intensively, that means on the other hand that we are actually creating more and more

resistant bacteria and the power of the tool is reduced. As long as we're using that. That means we all the time need to find a new ways, and new molecules, and new mechanisms to attack bacteria in order to kill it efficiently. Now we are using antibiotics everywhere. As we know, we use that for prevention, we use before surgery. We use that for treatment, empirical antimicrobial treatment. That's also very, very common in agriculture. So we cannot avoid using antibiotics. That's part of the game. And as said immediately after antimicrobial resistant emerge.

Now, if we want to invent new mechanisms and new antibiotics, again and again, that means to develop a new drug. And as we know, developing a new drug is very, very costly, high risk process, very long process, about 10 years, about 1 billion and even more. And now at the end of the day, antibiotic is relatively not very expensive. So the cost of the antibiotics cannot cover the use. And actually the development process that is so expensive on one hand and on the other, resistant bacteria cannot [inaudible 00:13:23] very, very, very rapidly to a new antibiotics, that pushed the industry out of the game. And now there's very few new antibiotics that are developed and approved by the agencies. And that's a big failure in the system.

John Marchica:

I hear what you're saying and basically it's a simple ROI, right? I mean, it makes... It's certainly more, I don't want to use the word profitable, but it makes more sense these days to go after rare diseases or certain areas where you can charge more and recoup your investment. And I'm just wondering, is the failure at the policy level. In other words, could the FDA and I'm really getting out of my league here, but I'm just thinking out loud, could the FDA perhaps offer, orphan drug status to a super-powered antibiotic that would only be used in certain cases. And so therefore you could maybe charge more for that to recoup your investment, but at least to be able to have a stable of antibiotics, that could be the last resort that might encourage pharma to invest that extra dollar and to bring your product to market if it were more protected. Does that make sense?

Dr. Noam Emanuel:

Sure. But in reality, everybody aware that resistant bacteria is there and the risk is growing rapidly and they will come that people will think twice and even 10 times before they will go to surgery, just because the risk of infection. That's all known, but still the situation and the industry and in the field is a such that the big pharma is out of the game, only small companies going in, and then very often failed marketing and earning money for the effort, for the risk that they can. And that's the situation. Now, they can encourage, of course, the regulators [inaudible 00:15:41] countries can encourage the development of new antibiotics by different means, but still it doesn't work perfectly. And the situation is such that now very few antibiotics are registered and only very, very few is going to be registered over the next few years. And that's create the big failure.

Now, as I read the different mechanism people are suggesting to solve the problem. One of them is to pay not per use, but per availability of the drug and the new mechanism when you wait to pay for the companies. I don't know if it works or not, but as we know now, the situation is such that it takes years to develop new antibiotics. It takes huge risk. And for now, at least the big pharma is out of the game. That's the situation today. Now, with the COVID-19 situation, the situation become even worse because now people are boring patients, COVID patient, with antibiotics and AMR, antimicrobial resistant bacteria, is emerging quickly and the disaster, Mayo care also at this field. And now the time leg needed to develop new solutions is too, too far to answer the question.

John Marchica:

Sure, sure. So I want to get into PolyPid. How does surgeons typically deal with SSI prevention today and what is the solution that the PolyPid is offering?

Dr. Noam Emanuel:

Okay, actually, the problem is ancient. From the beginning of medicine, we have bacteria, we have to fight bacteria, we have to fight infections. So physicians are taking many measurements to fight infection. First of all, they use gloves. They use air conditioning, they use sterile tools, sterile environment. They try to reduce the number of bacteria on their skin, not taking many measurements, but on top of that, they need to use also antibiotics.

Now, with the use of antibiotics, what is very common is to use systemic antibiotics. And with systemic antibiotics, what they do is they administrate IV, typically IV antibiotics between half an hour to one hour before surgery. One dose of antibiotic typically wide range antibiotic, cephalosporins are very, very common. And with that actually that's the most important part of what they do beside all the physical measurements and the disinfection of the area. And when antibiotic administrate it via the systemic, via the bloodstream, only a very small portion of them [inaudible 00:18:55] reach the actual site, the incision. And that is the only means they have in order to prevent the infection. As I said, earlier, infection are there, SSI is there in spite of all, what use in spite of all the means taken, all the measurements and also in front of the antibiotic they are using. So that's what people do today.

Now, what we can offer, what we think is right to do is use antibiotics locally. And that's very important because as I said earlier, the systemic antibiotic cannot penetrate well into the site, into the incision. And when the knife goes down, as we said, actually bloodstream stopped and there is a hematoma at the site. And that means you cannot load more and more antibiotic into the site, no matter how much your load from the systemic, it doesn't go into the site over several days. And sometimes even two weeks in terms of, in the case of bones, for instance. So that's leave a very significant depth for the bacteria to growth in the site. In the end incision, remember that the antibiotic penetrate just before surgery will last only for a very short time, let's say several hours, one day, no more than that. And then the bacteria can grow and create SSI.

So the situation today is that systemic antibiotic is the major solution. I would say basically the only solution in putting inside incision to prevent SSI beside all the other means. And what we offer is actually local delivery means the most logical. We believe that the logical way to do things right, is to load them directly where it's needed, nothing to the circulation whereas most of that will be lost, over 90% will be lost just for safety issues, not for efficacy. If you load that into the site, you can generate a very significant high concentration only locally without systemic exposure. And that's exactly what you'd want to do. You want to get the greatest, the maximum effect locally without systemic exposure, as much as possible. That's the base of our solution, local delivery rationale, local delivery. That will actually be very, very effective locally, but with no finger print in the circulation.

John Marchica:

So, I know that you're in clinical trials at this point. What exactly you say, the solution is local, but what exactly is... Describe the technology, I guess, and in terms that I can understand that you're working on and that you're now I believe in phase 3 trials.

Dr. Noam Emanuel:

Yeah. Yes, PolyPid is now in phase 3 trials, actually three phase 3 trial, two of them in abdominal surgery, one in prevention of sternal infection in open heart surgeries. And that's what we do today. And the technology we named the technology PLEX and that's term for Polymer-Lipid Encapsulation matriX. And that sounds complicated. But basically what we do is taking polymers and taking lipids, all known to the art and very safe and create a very unique matrix that is very, very condensed. And it's a less of polymers and lipid, polymer and lipids, one after the other alternate layers about four nanometers between them. Where the drug will be encapsulated within the layers within each one of the layers. Typically you will have in the PLEX a solution about 5,000 to 10,000 layers, like that. Now, the water is coming from the outside and actually disintegrate only the outer layer. Only the outer layer that touch the water.

Body water, body temperature is sufficient to disintegrate only the outer layer, and then release the drug into the environment. Now, a new layer will be exposed to the same condition and now like that again, and again, layer by layer. It will release the drug into the environment, into the incision. In the case of SSI, it will be also similar in, let's say, anticancer agent in cancer, you will have constant supply of the API of the drug into the site, one layer after the other. Now, very importantly, water cannot penetrate through the layers. Deeper into the layer, it will touch on the surface. That means that the drug within the layer deep in the layers will be fully secured for the environment. And that's very critical because the environment is very hostile to the... For the drugs.

If you want to keep a while, the site over weeks and even months, if needed, it means that you need to protect your drug reservoir within the body of a very prolong time. That means you have to actually protect that in anhydrous environment. And that's very unique to the PlEX technology. It can protect the drug over the days and weeks if needed according to plan. And now we can tune the release weight and the release duration. You can tune the release weight in order to control the local exposure. And you can control also the duration by actually controlling the number of layers you're using and the degradation of the outer layer. So together you have a very strong tool to actually control the exposure locally of the drug to the needed site. That's the PLEX technology, very short, as short as I can.

John Marchica:

Well, it's fascinating. It's fascinating. So the just briefly, what are the three clinical trials that you have in phase 3?

Dr. Noam Emanuel:

Okay. One as said is in the sternum is now a little bit slowly in going slowly. [inaudible 00:25:29] because of their priorities, but the two majors are two phase 3 studies in colorectal resection, abdominal surgeries. And that's a very major unmet need because here the infection can come. The bacteria can come from the outside, but also from the inside, from the bowel, because you have colorectal resection. So, infection rate is very, very significant. Can go up to as said almost 30% of the patient, especially if they have comorbidities, especially if it's open surgeries. So, these two studies are in colorectal resection surgeries. And what we do is actually treating the patient, it's double arm, of course, a blinded study control. And now we are loading to half of the patient the D-PLEX 100, it's a PLEX-based solution with antibiotics. And with that way, it prevent, we're trying to prevent the SSI inside the incision. It's multinational, of course, and a multicenter studies.

John Marchica:

It's amazing. It's amazing. One thing that I was thinking of, and I know this is somewhat apples to apples or apples to oranges, excuse me, comparison. But we worked with a client several years ago that had a very promising technology for ear infections. And when there would be ear surgeries and when they'd have to go in and kids who had chronic ear infections and the typical way that the people would handle that as exactly as you described antibiotics before surgery, and then a follow up of antibiotics, and they had a technology where during the surgery, they could drop this into the ear. And then there would be a sort of a sustained release over a 10-day period if I remember correctly. And so the logic was there, the efficacy was there, but the company largely failed.

I mean, the last time I looked at their annual report, they had something like a couple of hundred thousand dollars in annual sales. And one of the reasons why I think, and I'm not privy to their, and exactly what happened. I don't know that anybody really knows, but I think a lot of it had to do with pricing and that they were making an HDR argument that preventing readmissions, and then it was more cost-effective to go their route that ultimately there would be a significant benefit so they could charge more. And so I'm wondering, as I said, this is apples to oranges comparison, especially when you think about the issues of mortality issues and things like that. But have you thought about, as you bring this to commercialization, assuming that the clinical trials prove to be effective and safe, have you thought about these kinds of pricing issues and being accepted into these large US health systems that use tens of millions of dollars of antibiotics every day? Have you thought about that?

Dr. Noam Emanuel:

Oh, we're trying our best to first of all, to bring benefits to patients-

John Marchica:

Of course.

Dr. Noam Emanuel:

To hospitals. Yeah. That's for sure. And we know that the situation now in SSI is not stable means all the time it's increased, no matter what people do, MDRs are there. I didn't mention that earlier, but resistant bacteria is very significant because we know a challenge, but we show with our solution that we can overcome resistant bacteria including bacteria that is resistant to our antibiotics. And that's very important because what we want to get here is a solution that will be very, very wide solution for different indication in different surgeries. And now when you go to prevention, it's not treatment, it's prevention. What you try to do here is, is to avoid infection regardless the type of bacteria you are going to encounter any bacteria should be affected and now resistant bacteria is included and some of the bacteria will be resistant to antibiotics, what to do? When now, that's life.

And now we showed that the high concentration of it for a long period is very effective and so effective that can kill resistant bacteria, including to the antibiotic we are using. What I'm saying here, that we believe that our solution will not be on the very effective in general, but will be served for many different indications. Not only for one very specific. And we believe that a wide indication is what this product should be aimed. And with that we believe we can cover the most important areas in SSI, not only one small, tiny indication, but all the big open surgeries, the high morbidity surgeries, the surgeries with higher infection rate, that open surgeries.

And there is a huge unmet need. That's not only a very small niche. We are talking about open heart surgeries. We're talking about abdominal surgeries that are very common and there are so many

millions of events around the medicine that needs such a solution. So although we start with a colorectal resection, that is a segment in abdominal surgery, actually that's the most aggressive and what we call proof of concept in the most extreme situation, just to say that this solution can be served to basically almost any indication. And with that we believe that we can cover a significant markets. And with that our fate would be different than what you said earlier.

John Marchica:

So last question, what's the end game? In other words, will you be commercializing the technology. Will you be licensing the technology to say an antibiotic manufacturer. How do you plan to get this to market?

Dr. Noam Emanuel:

From the beginning, it was 2006. As we started, we had a very important decision. We made a very important decision. We are not creating a platform and serve as a platform for other to use it. We're not the taxi drivers for other drugs.

John Marchica:

Right.

Dr. Noam Emanuel:

We are going to create solutions. We are going for solution. We are going to be a pharma company. We are going to find a way to develop a drug that will solve a real problem. That's what we did. We started from the beginning. We concentrated in infection quite from the beginning. We found ourself into the SSI, a very, very important and wide field, as we said earlier. And we developed everything from the beginning to the end, including that GMP factory we have in Israel, a 1000 meters square state of the art. So we know to manufacture, we know to develop, we have our own clinical studies, and now we have in New Jersey, also offices, office, and office that will serve for a marketing, the product in the US, all without forces.

Of course, in the Far East Europe, we'll use other vendors and other companies to market the product, and ask for them to be independent. So from the beginning to the end, we have a platform, but we are not using this platform, not offering this platform to everybody, but we want to be part of the big game as a pharma company. Now, if a company offer us who will be to partner on an API together with our platform. That's great. Of course, we're going to do that. And of course we are not only concentrating infection. Now, infection is there is the forms, but immediately after come cancer and with anticancer agents, the same ID locally, no systemic exposure or minimal with very, very high local effect, even against resistant cancer says to chemotherapy the same ID. So the second generation of PLEX will be anticancer agents. And then we'll come other things later on.

So we believe that we are going to be a pharma company from the beginning to the end, and of course, collaborations is great with other companies. But what we believe is that drug and drug delivery equal in importancy means, without drug delivery, good drug delivery, many drug would not work properly. If you want to increase the efficacy and safety, you need a very good way or means introduce and it's equal in importancy.

John Marchica:

Well, it has been fascinating. I think your company is so interesting. I enjoyed our previous conversation as well as today. And I'm glad that... And the chance to have this discussion, I think that people are also going to find this technology fascinating. If they want to learn more about your organization, what is the URL?

Dr. Noam Emanuel:

It's a [inaudible 00:36:13] that and we have our PolyPid website. They can learn as much we can expose and those calls publications and scientific others and yeah, maybe podcast [inaudible 00:36:29] is also another mean. So thank you very much.

John Marchica:

Yeah. Well, thank you again. And let's keep in touch. Seriously, let's keep in touch.

Dr. Noam Emanuel:

Thank you.

John Marchica:

I'd like to see how you progress.

Dr. Noam Emanuel:

Thank you very much, John. Thank you very much for the time and having me. Looking forward next time with many news.

John Marchica:

That's right. Well, take care.

Dr. Noam Emanuel:

Thank you very much. Have a great day. Bye-bye.

Kimmy Asciutto:

From all of us at Darwin Research Group, thanks for listening. Health Care Rounds is produced and engineered by me, Kim Asciutto. Theme music by John Marchica. Darwin Research Group provides advanced market intelligence and in depth customer insights to healthcare executives, our strategic focus is on healthcare delivery systems and the global shift toward value-based care. Find us @darwinresearch.com. See you next round.