Nanobiotix - Accelerating the Future of Nanotherapeutics | December 16, 2024

Laurent Lévy:

Good morning, good afternoon, everyone. I'm Laurent Lévy, CEO of Nanobiotix and happy to welcome you here to present you our company and what we see for the future in term of development of new therapeutics to bring that to millions of patients. Before getting into the meat of this meeting, which is about the new platform Nanobiotix is developing, just want to step back and come back to the fundamentals we've been using to develop our different product and platform in the company.

For the past decades, we've been able to develop three platform for different purposes. One in oncology, one for the CNS disorder, and one would see multipurpose. All those platforms, they have something in common. They're not purely based on biology or chemistry. They're based on physics and why that? The whole idea of Nanobiotix was to think about the question, can we bring the physics at the subcellular level to bring new mode of action into patient to help them? And that's what we've been doing with the different platform we are developing today.

What's the advantage of this? There's something fundamental with physics is that the mode action that you can produce with it will be much less influenced by the viability of biology and therefore you can have product or approaches that could be shared by millions of many patients. And it has been the motto for years at Nano to develop only product that are first in class and that can be used in many patients to help all those patients.

And today we're going to talk about Curadigm, but before that, I would like to come back to the priority of the company, which is to bring to life and to bring to market our first in class radio enhancer, NBTXR3. The idea with this product is really to address one of the largest and top markets in oncology, and we do that with Johnson & Johnson, which is the partner we've been choosing for more than a year now, and we've licensed our first product to them.

So what do we think about when we say oncology? We're thinking at a particular aspect of oncology, and as you can see on this slide, we're looking at interventional oncology, but more precisely a patient at the time of diagnosis. What is clear with the numbers you can see is most of the patient having a cancer at the time of diagnosis, they have a local problem. Only a small part of them have metastasis. As you can see also, most of the pharma and the biotech, they try to tackle this problem of metastatic patient and there's not much development, not much research done to how can we help this patient when they are still at the early stage of the disease and when they have a local disease. Because if you can do so, that's where you will have probably the biggest impact in oncology, and that's where we focus our attention. That's where we focus the first development for the company.

And talking about local control or talking about local disease, there is one tool that is widely used in oncology, which is radiation therapy. As you can see here, it's a patient getting radiation. More than 60% of all cancer patients are getting radiation. All the big cancer like breast cancer, lung cancer, prostate, they all use in the vast majority radiation therapy. Nevertheless, you have some limitation with this tool and the limitation is due to the fact that when you try to irradiate a tumor, you also have to irradiate surrounding healthy tissue, therefore you are limited by the dose you can deliver in the tumor versus the side effects you will create. That's what led us to develop a unique drug, which is called NBTXR3, and now JNJ1900, which is a product that has been designed based on crystalline inorganic nanoparticle.

So some tiny objects that are small enough to go into the cell and when they are into the cell, thanks to the specific design of this nanocrystal, they are able to absorb the energy of radiation therapy. So after a single injection, those particles will diffuse and the tumor will penetrate the cell, the patient will get the

normal radiation, and the particle will absorb the energy and will create a high quantity of damage around them.

So it's a physical modification that will lead to the destruction of the cell. The way we want to apply that is the following. For many patients, there is a need of better local control. So we have this injection in the tumor that we irradiate and then we provide better local control to patients. There is a subsequent biological consequence of that, which is the physical destruction of the cell will trigger also a priming immune response that could be useful for the treatment of the primary tumor, but also for systemic disease.

So as you can see here, we have a product based on the physical modification that triggers some biological consequences that could help a lot of patient getting radiation. And here what you see is the first pass to get there. We have a large number of clinical trial ongoing, including two late stage program, one in lung cancer, stage three, one in head and neck for any patient [inaudible 00:05:35] to cisplatin. And we intend to develop this product with our partner J&J for the larger number of patients to reach as many patients as possible. So just in a nutshell, what we intend to do with this first product and this collaboration is really addressing and helping the maximum of patient in oncology. That's why we've been signing in the recent past a $2.5 billion deal in [inaudible 00:06:02] plus royalties. And when you look at just the two first indications we want to target like lung cancer stage three and head and neck, it's around 100,000 patients we could help per year only in US and EU5.

That's potentially a big market. And associated to that, we also will have a substantial amount of [inaudible 00:06:23] that will lead us to financial sustainability and will allow us to continue to develop. And when I think about continuing developing things, the next big step for us is to develop this new platform, Curadigm, this platform that should lead to many new first-in-class products. And here what we are doing is really the idea that we can transform the way we design drug and the way we apply them. And this could be applicable for many products that you see every day, like RNA, DNA best product, oncology, virus, and many more. Just to give you a glimpse about what this technology is and what is the potential, I'm going to turn another mic to Matthew, our head for the platform Curadigm that is going to explain what it is, how it works, and then we'll go back together for panel discussion. Matthieu?

Matthieu Germain:

Thank you Laurent for the introduction. I'm going to introduce Curadigm platform. And to start this introduction, I would like to mention a fact. If we look at the therapeutic landscape, especially at the innovative therapeutic, it's very dispersed in term of nature of therapeutic agent, ranging from lipid based, polymer based nanomedicine loaded with small molecule nucleic acid, viruses, inorganic nanoparticle, recombinant nanoprotein, and so on. But all this nature of therapeutic shared a common challenge. When you want to deliver by intravenous route of an administration treatment, they will need to reach their target at a subcellular level. Meaning to reach target, they will have to overcome different barrier. The first one being at the organ level, then one in the right organ, they will need to address the specific cell population and then reach their target at the subcellular level.

At each barrier, you will have off target loses of your product and degradation of the therapeutic agent. And if we look more specifically at the first barrier, the organ level, an analysis has been performed and shown that for nanoparticle in oncology, the median accumulation of the nanoparticle in the tumor is less than 1%. Of course, it's better than a small molecule injected as such, but still there is some roof for improvement in the field.

Why such a low amount accumulated in the target tissue? The first main challenge at this organ level for a therapeutic agent is a liver. The liver is the main organ of the reticular endothelial system, a system

which is dedicated to the clearance of endogenous waste such as cellular debris, dead cell, and so on, but also exogenous materials such as pathogens. Why? How does it work? The liver has a specific structure allowing to decrease the blood flow within this organ, maximizing the interaction with specific cells which are dedicated to recognize and clear endogenous cellular debris, external pathogens, but also a large part of therapeutic agent, including the one I was mentioning previously. And at the end, if we want to illustrate the impact of the liver, if we take a mouse and we inject a fluorescent nanoparticle to mimic a therapeutic agent. As you can see on this picture of this mouse, as soon as you inject intravenously the nanoparticle, all the fluorescence is localized within the liver. There is no more fluorescent in the rest of the body of the animal, meaning everything is in the liver and a very tiny portion of the dose will be able to reach the target.

Why? Where does it come from? The situation is coming from a combination of different physicochemical attributes, size, [inaudible 00:10:47] charge, hardness and shape, and this specific combination of these parameters will drive the recognition by the liver cells involved in the clearance of therapeutics, and all the therapeutic agent I was mentioning at the beginning of the presentation at this combination of parameters leading to the internalization by the liver.

This is why we decided leveraging on this knowledge to design this concept developed by Curadigm, which could be summarized in one sentence. It's really to prime the body to receive the treatment. By priming, I mean we design a nanoparticle, which is called a nanoprimer, which is dedicated to be intravenously administered just before the therapeutic agent. The nanoprimer will reach the liver and it'll occupy transiently the cells involved in the clearance of the therapeutic agent, meaning that when in a second time you inject intravenously the therapeutic agent, there is less recognition by the liver. You increase systemic viability of the therapeutic agent, allowing an higher accumulation of this therapeutic within the target tissue, which could be a tumor if we're talking about oncology or another organ of tissue, if we are talking about another therapeutic [inaudible 00:12:09].

So if we come back to a mouse injected with a fluorescent nanoparticle, let's take another mouse and we treat this mouse with the nanoprimer first and then we inject the fluorescent nanoparticle. As you can see, even one hour administration of the fluorescent nanoparticle, you can still see the whole body of the animal, which is still fluorescent, meaning that the nanoparticle continue to circulate within the blood and is available for subsequent accumulation in the target tissue to deliver the treatment more efficiently.

Of course, this approach has already been tried using different approaches in the past. The first approach which has been developed was the use of conventional liposome. Conventional liposome mean they use the same liposome that is used to deliver the treatment within the tumor to ensure the pre-treatment of the liver. You cannot ensure both aspects. You cannot deliver with the same object the therapeutic within a tumor, and at the same time occupies the liver, meaning that the effect is moderate and you will need to use a high dose of the liposome, potentially bringing toxicity.

Second approach is the use of lipid emulsion, which is used for parenteral nutrition. The approach is to deliver in the patient body a high dose of lipid, an emulsion of lipid, but this emulsion lead to a high polydispersity of the lipid nanoparticle, different composition in fatty acid, and so on, meaning that you will also need a very high dose to generate a moderate effect and potentially bringing toxicity.

Then finally, the third approach is to use a small molecule to decrease clearance by the liver. So this approach use molecules such as clodronat, which is toxic for the [inaudible 00:14:14] cells in the liver, meaning you will kill these [inaudible 00:14:17] cells, so there is less clearance by the liver, but you are the toxicity of the small molecule. This is why we really think we've got key differentiating factors with the nanoprimer. Why? This nanoprimer is a lipid based nanoparticle and the mode of action is related really to the physicochemical parameters of the nanoparticle of the nanoprimer itself. There is no API,

no small molecule encapsulated in the nanoprimer. We optimize the physical physicochemical properties of the nanoprimer to ensure the specific interaction with the cells involved in the clearance of the therapeutic agent. The effect is transient because the nanoprimer is biodegradable and-

Matthieu Germain:

... the effect is transient because the nanoprimer is biodegradable, and as soon as the nanoprimer is eliminated by the liver, the liver will come back to its physiological function, trapping again the remaining therapeutic agent. And of course we checked preliminary safety with the nanoprimer and the first result confirmed that we are safe with our nanoprimer.

The beauty of this concept resides also in the fact that you could, with the nanoprimer answer different need of the therapeutic agent. If we come back to the fact that the therapeutic agent, the major part is loose or could bring some toxicity, and only a small portion will deliver the efficacy, we can see it in different way. The first one, oh, sorry, a product could be limited by the lack of efficacy. In this case, when you combine the nanoprimer, you can increase efficacy of the treatment for same dose administered. But for some of our product, you are not limited by the efficacy, but you are limited by the toxicity of the therapeutic agent.

So when you combine the nanoprimer with this product here, you can preserve the same efficacy, but for a lower dose administered of the product and a lower toxicity.

Also, our nanoprimer is a strong opportunity to be a game changer in the way some treatment are administered to the patient. For this, let's use an example. RNA-based therapeutics. This treatment are very efficient. Everybody's aware of the impact of RNA-based therapeutics for COVID action. There is approved product for liver-related diseases. But when it come to use this RNA therapeutics by IV route of administration for extrahepatic delivery, it's still a challenge for this kind of nature of therapeutics. And we really think then the nanoprimer could unleash the power of RNA-based therapeutics.

And to demonstrate the impact of the nanoprimer on RNA-based therapeutics, we had the opportunity during our collaboration with the Langer Lab in MIT to evaluate the impact of the nanoprimer on the accumulation and bioavailability of small interfering RNA loaded in lipid nanoparticle developed by the Langer Lab.

On this graph, you've got the impact of the nanoprimer on the accumulation of the siRNA in the liver on the mouse model. And what you can see is that when we add the nanoprimer to the treatment, we decrease by 40% the accumulation of the siRNA within the liver and it's correlated with an improvement of the blood bioavailability of the siRNA in the systemic circulation of eightfold. So clearly we increase the blood, the systemic bioavailability of therapeutic agent with the nanoprimer.

At the end, what we want to obtain is an improvement of the efficacy of the treatment. For this during another collaboration, we combined the nanoprimer with an siRNA-based therapeutic agent, siRNA loaded lipid nanoparticles during a tumor growth delay experiment on mice model. We use a triple negative breast cancer tumor model and we follow the tumor growth during the experiment, depending on the treatment administered to the animal.

On this graph, the yellow curve correspond to the response obtained with the therapeutic agent alone at the defined dose. You can see we obtained a tumor growth delay inhibition of 36%. When we add the nanoprimer, you obtain the pink curve, and this for same dose of the therapeutic agent administered, we increase the tumor growth inhibition to 80%. So clearly we significantly increase the efficacy of the treatment when we add the nanoprimer.

We also evaluate the impact of the nanoprimer on the efficacy of small molecule-loaded nanomedicine. For this we used irinotecan loaded liposome. We first evaluate the impact of the nanoprimer on the

tumor accumulation of the drug loaded in the liposome CPT-11, the prodrug, and the active metabolite, SN-38. We evaluate the impact of the nanoprimer on the colorectal tumor cancer in mice model. And what we obtain is that when we add the nanoprimer, we increase by three to four fold the accumulation of the drug in the tumor, and we make the correlation between the tumor accumulation and the efficacy of the treatment generated with irinotecan loaded liposome.

For this, we perform a tumor growth delay experiment, and what we obtain is that the red curve corresponds to the response tumor growth with the irinotecan loaded liposome alone at a defined dose. The blue curve corresponds to the same dose of irinotecan loaded liposome but with the pretreatment of the nanoprimer. As you can see, we significantly increase the efficacy of the treatment with the nanoprimer, and we generate similar efficacy result by combining the nanoprimer with the real Onivyde, which is approved in the treatment of pancreatic cancer.

Finally, a last example of what we could achieve with the nanoprimer by combining it with a recombinant protein, asparaginase. Asparaginase is used in the treatment of acute leukemia. The mode of action of asparagine is localized within the blood. This recombinant protein will degrade asparagine. Asparagine, which cannot be synthesized by the tumor cell at the opposite of healthy cells. So by depleting asparagine you will kill the tumor cells. So blood bioavailability of the recombinant protein is very important.

But the half-life of this recombinant protein is also very short. So we perform an experiment to evaluate the impact of the nanoprimer on the systemic bioavailability of asparaginase on mice model. And what we obtain is that when we add the nanoprimer, we increase by threefold on the darker curve, so bioavailability of the asparaginase. This is a great opportunity to improve the duration of the effect of this recombinant protein, potentially decreasing the number of injection required for the treatment and potentially decreasing associated toxicity.

Now to finish, let's come back to the therapeutic agent. If you look at the therapeutic agent, you will see that you will have to ensure different function to deliver the treatment in a single nano-object. You will have to take care of course of the systemic bioavailability, which is a very big portion to ensure to deliver the treatment. But you will have also to ensure drug loading, tissue targeting, cell uptake, endosomal eescape, drug release, and so on. So a large number of function to be regrouped in a single object. You cannot ensure an optimization of each function. There is a notion of compromise in the design of the therapeutics.

And here the nanoprimer could really be a game changer because we could rethink the design of the therapeutics because this nanoprimer will ensure the systemic bioavailability, meaning it will remove the function of bioavailability from the therapeutics to the nanoprimer so you create a space to improve existing function such as endosomal escape, for example. Or you can create a new function in the therapeutics itself. So clearly dissociating the function in two independent objects is a strong opportunity to boost all the function of the therapeutics and deliver more efficiently the treatment to the patient.

And now I'm going to leave the floor to Laurent to give you an overview of the business opportunity associated to this nanoprimer.

Laurent Lévy:

Thank you, Matthieu. As you have seen, this is a new concept that will bring many opportunities, many potential product development. And we're starting at Nanobiotix to think about how can we use that not only for our own purpose internal development, but also to help the industry out there.

When you look at the first approach we could go for, you have many approved product that could benefit from this. By improving the benefit-risk ratio they exhibit in some indication could get to label expansion or improvement of safety of this product. You have so many other product under development that could be benefiting for this new approach, making it more efficient. Or it could be for late-stage product, but for preclinical product too.

And if you think about the industry, about the past, about the number of product that have failed, not because of a lack of efficacy but because some hepatotoxicity. So that's also here a big area where this product can revive some of the product and make them use for the benefit of patient.

When you look at those three first buckets, you already have many things to do, and that's probably where we are going to start looking at partners or looking at licensing of this technology to help the industry to get better or larger number of product.

What we're going to do also is developing our own platform that will provide product for Nanobiotix to develop. And here we're going to focus on what Curadigm platform can bring that you cannot do without. It's very important, Matthieu was mentioning RNA-based delivery product. If you had this Curadigm nanoprimer into the game, then you'll be able to deliver RNA IV. And that's opening a new field for this type of product. It's true for RNA, but it's true for many other approaches. And the history of medicine is full of product that could not be developed because of this barrier. With Curadigm, the possibility to overcome this barrier allowed Nano to be able to develop many products for its own benefit based on this platform.

But we will have time later to talk about that. And what I would like to do now is to introduce some of our colleagues and discuss about this technology and open the panel for discussion.

For this panel, I would like to welcome two members. I will first introduce Dr. Margaret Liu, which is a seasoned scientific and entrepreneur that is starting now working with us at Nanobiotix as a new [inaudible 00:26:53] of the Supervisory board and soon-to-come fully board member. And we've been having a long discussion with Margaret about this technology and how this could help patients and how this could help industry. That's the reason why I invited her to participate to this panel for her to be able to share her thinking and how does she see what we try to develop with Curadigm.

On the other side of the screen, you can see Dr. Jeff Bockman, which we've been working with for quite a long time now on different projects, trying to help to shape this industry with new product. And Jeff has also helped us to animate many panels in oncology in different setup for different technology. And we thought that it's always good to have an external view on what we do and some challenge that Jeff always bring into the game.

So thank you for being here. And Jeff, if you want to start shooting question and asking things and challenges, free to go.

Jeff Bockman:

All right, great. Well, it's an honor to be participating, moderating once again. Yes, it's been a long time well, Laurent, going back to early days of Nanobiotix and excited to hear Dr. Liu's comments. Very, very honored and esteemed guest.

So let's just start off at the highest level here, given the slides that have just been presented, kind of giving an overview of Curadigm and this platform. So this nanoprimer approach, how would you say it's differentiated from other approaches in the industry that are designed to improve bioavailability, whether bioavailability of small molecules, large molecules, et cetera. I poise that to you first, Laurent.

Laurent Lévy:

Well, I think what Matthieu did present at the end of his presentation is the key thing. Most of the product we are developing in our industry, we're thinking about one object, one object that will do everything. And when we start doing so, it's the science of compromise. And you do those compromises even before injecting this product into a patient. And we know how important bioavailability is, but also efficacy and many parameters that are embedded in one object.

So as soon as you start releasing one of the constraints, that's where you are opening many doors and many opportunities. So I think that's a beginning of a new story for our industry to start developing new type of treatment that are not only based on one thing doing everything but maybe different approaches to fulfill different function that is needed by the patients.

Jeff Bockman:

Great. So I think one thing I'm curious about is that clearly there are various approaches that address some of these various elements that have been talked about that can compromise ...

Jeff Bockman:

... about that can compromise, let's say, the therapeutic window for drugs. And there's use of Bitannivir, for example, to block liver metabolism and increase the drug levels in certain cases. And of course, there are all sorts of delivery platforms which are designed to address some of these issues of increasing accessibility. Maybe you can just talk a little about, either you, Laurent or Matthew, about how the nanoprimer is either an alternative to those or may actually be useful in combination with some of those other approaches, whether those are physical approaches like a pump or subcutaneous device or something, or some of the currently used drug approaches to modulate activity.

Matthieu Germain:

I could start if you want. I think we could identify synergies between nanoprimer and some of our approaches to optimize the delivery of therapeutic agent because the nanoprimer will lead with liver viability by decreasing the liver clearance. But after this, biodistribution typically remained related to the physicochemical property of the therapeutic agent. There is a lot of different approaches designed to optimize the therapeutic agent to enhance the delivery within a target in specific tissue organs. So really there is synergies between these approaches to deliver more efficiently the treatment and after it, to come back to what Laurent was mentioning, really to rethink the design of the therapeutics when you add the nanoprimer to this treatment. So I can see it really as a synergy, especially in the nanomedicine field, to have a better degree of different cargo, small molecule nucleic acid. And so definitely.

Jeff Bockman:

Margaret, did you have any comments at this point?

Margaret:

Oh, I think that those are really the key things, but I did want to add something slightly different that's complementary to what you're mentioning, which is that using the nanoprimer means that one can still add on other targeting moieties to whatever you're delivering. So it is good in that it helps to get rid of the nonspecificity of the uptake in the liver, but at the same time, it doesn't preclude anyone from developing other rationales, other parts of the molecules for targeting, targeting a receptor on a tumor cell, for example. So it's a very synergistic approach that can really help to augment then whatever additional approaches people are using for designing targeting specifically. And I think that that's one of the advantages. It's a little different issue than what you mentioned, but I think it's important to point

out that you can still then have this synergy of using additional targeting rather than this just being the one thing that you do, which is to decrease the hepatic delivery.

Jeff Bockman:

Great. Yeah, thank you. So curious about the residency or half-life or how long that nanoprimer remains in the body. And then I do have a related question to that, which had been touched on the slides, but I'd like to probe a little bit more in terms of the effects on the therapeutic window, but maybe you can just take the first point first.

Matthieu Germain:

Yeah, sure. This is a very important question. It's related to the duration of the effect of the nanoprimer, also the residency of this nanoprimer in the body. Clearly if we go step by step, I mean as soon as you inject the nanoprimer, accumulation within the liver is very short. I mean it's very quickly accumulated in the liver due to the physical chemical properties of this nanoprimer. And now right after accumulation, you will have an interaction with specific receptors on macrophages on toll-like cell. Then the nanoprimer will be internalized in the endosomal-lysosomal pathway and since this is a lipid based, on the particle, it'll be metabolized by the phospholipase in this lysosome.

And it's related to the duration of the effect of the nanoprimer because the time for the cell to ensure the metabolization of the nanoprimer, it will slow down the rate of internalization of the therapeutic agent within this pathway. And as soon as the nanoprimer is fully metabolized, the effect is no more present and the liver will come back to its physiological function. The duration of the effect is about 24 hour, the time for the cell surface metabolization. So this is a time of residency of a nanoprimer within the body.

Jeff Bockman:

So I'm just curious whether this concept of a nanoprimer is kind of a monolithic type of entity or whether there are variations on a theme that you have for that nanoprimer that might be applicable for different indications and uses.

Matthieu Germain:

Yes, definitely. This is very important aspect. The initial version of the nanoprimer is really focused, if I may say, on the reticuloendothelial system in the liver for cells and liver sinusoidal endothelial cells. But yes, we are exploring extension of the concept, allowing a broader application of the concept, targeting some other cells within the liver and potentially a different declination of this nanoprimer. But this is something ongoing. We've got some IP to secure before entering more in details of this new version of the nanoprimer. So I hope we'll have new result to share later on.

Jeff Bockman:

Great. Great. Thank you. So kind of curious about what you can say about the translation of the preclinical results, which mostly you've shown are in cancer models, how you anticipate or what evidence or clues you have about that translatability into humans as you anticipate going into some type of a first in human study?

Laurent Lévy:

Well, I think as you know, there's a big difference between animal model and human, especially when we look at some targeted molecule. We designed the model to respond to a molecule and the model works and it's different when it's in human. Here I think there is a different level of correlation we can think about because every mammalian have a system with a liver. Of course, they are different, there's different volume, different synergies and things, but still the concept is the same. At some point, the liver will capture some of the subject.

And we know from the literature and all the clinical trial that have been done that some of the objects that Mathew has mentioned in the presentation, they are captured by the liver in human. So if we can just go to the first step of this process, which is to bring an object that will mimic the object you want to avoid to be captured by the liver within the translation between an animal and a human is very high. Now, of course, we'll have to adjust a number of parameters like concentration, et cetera, et cetera, but the concept itself should be highly transferable to a human being.

Jeff Bockman:

And I want to ask a follow-on question, and it may be to both of you, but also be curious for Margaret perhaps to weigh in. So I think when you just think about this in the presentation, the first thing you say is, "Wow, it's very cool." You can increase the activity. You certainly talked about the ability to conceivably address the safety tolerability by reason of increased activity for the same dose or maybe even able to lower the dose. But certainly there are on-target off tissue toxicities that one might presume with just greater circulation time could still result in problems. And I'm thinking really through a cancer lens at the moment. Can you comment on that at all and to what degree you think that is or is not relevant?

Matthieu Germain:

Yeah, I can answer this question. Of course, yes, off-target toxicity is very important since with the nanoprimer, we'll modulate the systemic viability, we'll have to ensure that we preserve the bio-distribution. We had the opportunity to evaluate on some of the product we combine with the nanoprimer, especially on liposome, what was the impact of the nanoprimer on the bio-distribution profile of the therapeutics and what we obtained is that typically we increase the accumulation within the tumor by three to four fold due to the enhanced permeability and retention effect in this tissue. And for the healthy organs, I mean the bio-distribution remained quite similar compared to the one without the nanoprimer. There's still a small portion in some secondary organ of the reticuloendothelial system which contain macrophages and so on. So we are focused with the nanoprimer on the liver, but the increase is quite small, if I may say. It's 1.5 fold compared to the therapeutics alone.

So it doesn't really change the bio-distribution profile and off-target toxicity of the therapeutics. And if I may jump also on a very important aspect regarding the safety, there is a safety of the nanoprimer itself also, which is very important because we cannot have any sign of toxicity due to the nanoprimer since we are not a therapeutic agent as itself. And we have the opportunity to explore preliminary safety with the nanoprimer performing in vitro and in vivo experiment. And in vitro, we didn't observe any sign of cellular toxicity, even with maximized dose of the primer. No immunological toxicity. I mean there is no activation of the complement, no modification of the cytokine/interleukins expression profile on human blood.

So typically the first result are very good. And they have been confirmed by an evaluation performed by the NCL, Nanotechnology Characterization Lab in US, which is an organization dedicated to promote nanomedicine development. And they generated the same result, confirming the safety of the nanoprimer and in vivo on rodent model, we didn't observe any variation in them in hepatic enzyme

such as AST, ALT, hematobiological parameters, and so on. No sign of toxicity. Of course, we'll move on in deeper exploration of the preclinical safety package. But first results are very encouraging from this side.

Jeff Bockman:

And this may be something that you'll be doing down the road and certainly would need to be thinking about. And that is... Since certainly oncology, we're mostly talking about combination therapies, you would need to be thinking in a more holistic way about the impact on the regimen of the multiple agents. There might be some small molecule cytotoxics, there might be a biologic antibody, something else, and all of those are conceivably going to be affected depending on the timing and the regimen and when the nanoprimer gets used.

Matthieu Germain:

Yes. But the good point also, you see here that the nanoprimer is really focused on reticuloendothelial system, Kupffer and the liver sinusoidal endothelial cells. So if you have a co-treatment involving a small molecule injected as such, the metabolism pathway is going to be through the cytochrome, within the hepatocyte. And the nanoprimer is not dedicated to interact with cytochrome metabolization pathway. So we want impact the metabolization of the small molecule. It's very dissociated. So this is a good point also for multi-therapy treatment.

Jeff Bockman:

Yeah, that's a good point of clarification for everyone I think. Thank you. Margaret, any comments, thoughts?

Margaret:

Well, I just wanted to add that I think that when one thinks about it... Fortunately there are tools to determine what the impact is. So you do your normal pharmacokinetics, for example, during the administration of a drug. And what may happen is the effects will be distinguished both by longer presence of your drug potentially, because you don't have all of this absorption in the liver. And that may differ then as well, depending on what the entity is. So for example, mRNA molecules need to be formulated in lipid nanoparticles precisely because they're so easily degradable. And so besides the issue of being able now not to get stuck in the liver, you have the issue of you have more in the circulation, but the persistence then may differ between a molecule like that or a virus, which may target other cell types, for example, if you're delivering some kind of virus as your vector for killing cells. So the issue is that you can measure the impact depending on what the entity is that you're delivering because you'll have this primary effect of not being trapped by the liver, but then...

Margaret:

... of not being trapped by the liver, but then each entity that you're looking at has its own particular targeting and pharmacokinetics and other ways of binding that may take it to the tumor or to other cells, et cetera. But these are all things that get evaluated anyway for each product. And so the tools exist in order to determine exactly what the impact is that might affect dosing or even regimens.

Jeff Bockman:

Great. Thank you, Margaret. Laurent-

Matthieu Germain:

Maybe if I can add.

Jeff Bockman:

Please.

Matthieu Germain:

During the talk with Margaret, it was remind me a bell as there is also an important aspect of the Nanoprimer, the mechanism is transient as we were discussing. And clearly I think this is an advantage regarding the safety aspect also. If you looked at current nanomedicine, everybody is using PEGylation to extend the systemic viability of the robotic agent. But at the end, let's take an example, Doxil, typically. Doxil has been generated to decrease the cardiotoxicity of doxorubicin by encapsulating the drug within the PEGylated liposome. The PEGylation means that you will keep your therapeutic agent in the blood for something like a week, and at the end you will have a modification of the biodistribution in over tissue, in the extremity and the feet and in the hand, bringing a new limiting toxicity.

So you replace toxicity by another one. With the Nanoprimer, the improvement of the systemic viability is transient. I was mentioning approximately 24 hour. That's enough to accumulate your therapeutic agent in a tumor typically, but that's short enough also to prevent accumulation in other tissue due to a very extended circulation time. So I think we have an advantage from this side also.

Jeff Bockman:

Great, great. And then actually we'll come back to that shortly I think. But Laurent, just to pull us a little bit out of the weeds for a moment. How is the company thinking of developing Curadigm mean from a corporate development, BD standpoint? Bring it forward on your own, doing partnership, partnerships, plural, and that may tie back to the issue of different applications of even the Nanoprimer, let alone any follow on Nanoprimers, but Laurent?

Laurent Lévy:

Laurent think with this concept, what we do is two things. First, we could solve some of the problem of our industry today, problem that people have developing some of the drugs. So we think here there's a big opportunity to develop partnerships with different type of partner or different type of application with different type of product. And that will be definitely part of the job we're going to do. We already have a good number of MTAs that have been signed and product being tested in many combination. That's part of the job. The other part is really building in-house our own platform and products so we can have the ownership of a full product, the Nanoprimer plus the other to develop that and to bring that to human and as fast as possible in our development to market. So that will be the mixed business model we're going to use. And this is needed because there's a lot of applications. So we can do everything, that's for sure. And so finding partners, validating the technology, developing with us, increasing the use of this product for patient will be the right path.

Jeff Bockman:

So in fact, you've just alluded to it is, although the presentation does focus on oncology, clearly the applications are beyond that. Can you speak a bit to that, either Laurent or Mathieu?

Laurent Lévy:

Well, I think the application are not necessarily linked to a therapeutic area, obviously, but more to the type of object we develop. So if you just take RNA as the example, it can be used in many indications if you took drug delivery system that's the same. There are many products that exhibit that kind of physical chemical quality that we can help. So yes, it's going way beyond oncology. Nevertheless, the company has already developed knowledge in oncology and that should be logical for us to continue in this field at least for a while.

Jeff Bockman:

So this has all the appearances of being quite transformative. I'm just curious what type of reaction you've had from anyone externally that you might've spoken with, whether early partners or financial folks or others in terms of how they're viewing this?

Laurent Lévy:

Well, I think we have had different type of things. What is sure is, because as I said, it does solve some of the well-known problem of our industry, there is a natural, "Okay, it has value." That's the first thing, and it's interesting. And after it's different, so how does this work? How do you sell that? How do you reimburse this? How do you develop it? Is it a combo? Is it two different product? So they're natural question when you develop something new, but we have an answer for all that. And I think in a broad view we found mainly if not only people that think there is a big opportunity here, but it's the beginning, so we need to push and to make that happen.

Jeff Bockman:

Yep. So given the diverse applicability across therapeutic areas, specific diseases, different types of therapies, how are you thinking of prioritizing? You mentioned oncology obviously as leveraging the resident knowledge from Nanobiotix's work, but how are you thinking about diversifying or de-risking or increasing the optionality given that this can be applied to areas that are well validated that involve, as you said, RNA or nanoparticles like some of the gene therapy or related areas or vaccines that are in nanoparticles and others that are, let's say, not so well validated, including still sadly as a lapsed virologist, oncolytic viruses and other places. So how are you weighing that? And I'm sure Margaret would like to comment as well, but I'll start with you Laurent.

Laurent Lévy:

So in term of priorities in the company, we have a well-defined pathway to develop our own product and platform. So that's something we will disclose later on next year, but we have a clear pathway moving forward. On the other side from the BD perspective, that will be more based on the partner's need. As I mentioned, we have different MTAs ongoing, different tests with this product. It's a lot in oncology, but not only, so we will see how did things move forward and we'll go step by step.

Jeff Bockman:

All right. Any comments there, Margaret, in terms of applicability?

Margaret:

Well, I think that oncology is an obvious place to start because there's been so much focus on how do you take treatments from intratumoral injection to intravenous injection, because of the issues of not all tumors are accessible or the challenge. And so having something that could be given intravenously for oncology, whether it's a drug or whether it is a virus that can kill the tumor cells is a very obvious and I

think a big opportunity as a first step. What I think is really important though is that other arenas, let's say gene therapy for inherited disorders, where right now the viral vectors that are used for delivery have to be given in huge numbers. The thing about that is this to me seems like an area that really is ripe for exploring. But what it will take is it'll take people in those areas to recognize that instead of just focusing on how do you make a vector? What's the payload?

How do we manufacture enough of this to say, "Oh, this is actually the same issue that confronts oncologists every day"? And so it's important then to get people in other arenas to recognize that this same type of technology is really addressing a similar problem, which is if you're losing a lot of your vector to someplace like the liver, you have less vector that's going to the intended target to make your therapeutic product, regardless of what that therapeutic product is, whether it's for treating cancer or whether it's treating an inherited disorder. So I think that one of the keys is actually just to get people who are in these other fields to think outside of the box that they've been working in, which has been payload and maybe stabilization of the vector or manufacturing, which of course can be a challenge when people are manufacturing viral vectors, and some people have accomplished the numbers, but I think that that's the issue is having people understand the value for other arenas as well as for cancer.

Jeff Bockman:

Absolutely. And I think of course, just from personal experience, having started in the dark side of industry at a biotech working on delivery of ribozymes and other agents and working with nanoparticles, and 30 years on, people still trying to optimize lipid nanoparticles or related LNPs that will avoid the liver for delivering the active to places other than the liver where you want to go still does remain a challenge. And this does look like a very transformative approach that at least to some degree, and maybe to a significant degree, might obviate some of those limitations. So I'm curious then, Laurent, what's next for Curadigm?

Laurent Lévy:

Well, I think we have a lot to do when you see the potential of this. As I said, there's a big path for us. Now the team is focusing on developing our own product based on this platform. That's something we'll be able to talk about second half of next year. I think for the first part of next year we'll be able to show some new data coming out from these Nanoprimers and how we could apply that in some of the situation that could be very beneficial to patient. But we'll make an update to the rest of the world and the market soon to explain how we're going to develop that, and more importantly, what's coming in term of news flow about this technology.

Jeff Bockman:

Absolutely. And of course there still are three which started this story many years ago with nanobiotics.

Laurent Lévy:

Right. And there's a lot to do here too. There's a big collaboration with our partner, J&J and we need to make sure that this is a success and we can bring this product to market.

Jeff Bockman:

Great. Any further comments from any of you? I think we've covered a lot of ground today. So Laurent, we've had a great discussion, clearly a tremendously interesting and quite potentially broadly utilizable transformative, if we may say, and we've used that platform technology that you have here in Curadigm. So how would you summarize the benefits, the potential, the so what if you will, for Nanoprimer? So

Laurent Lévy:

For us, it's like the continuation of nanobiotics story. We've been always looking at how nanophysics could help patient and preferably millions of patients. So that's a good step too for us. This technology offers many opportunities that we're going to explore step by step, having BD activities, but also having internal activities developing our own product and we're going to start delivering that to the patients. So there's a lot to do, but we think we have a unique opportunity to change the face of the industry with this, but that's where we're going to go.

Jeff Bockman:

Great. Well, I want to thank everyone for the time today. Thank you for those overviews, Mathieu and Laurent. Thank you for your comments, Margaret. Thanks everyone.

Laurent Lévy:

Thank you everyone.

Matthieu Germain:

Thanks everyone.

Margaret:

Bye.