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MICROBUBBLE IN MEDICINE TO TRANSFORM DIAGNOSIS AND THERAPY

Thierry Bettinger

Welcome everybody. Today we will talk about gas Microbubble and their use for diagnostic application.

What we will try to ask today with our two guests, first with Doctor Emily White, managing director of the Focused Ultrasound Foundation, as well as Doctor Victor Jeannot, R&D program manager at Bracco, is how this bubble could be used for new indication not only in the field of imaging, but also therapy, as you will hear today.

This is Talking Images, a podcast powered by Bracco Imaging. I am Thierry Bettinger, ultrasound R&D director of Bracco in Switzerland.

So, a few words about gas Microbubbles. We are able to prepare gas Microbubbles that are stable and stabilized with an envelope either of proteins, but more frequently of lipids. They are very small; we are talking about bubbles that are the diameter of a few micrometers that corresponds to something like 1,000,000 times smaller than a meter.

They are used for various indications after administration in the vein directly, and they act as a contrast agent for ultrasound imaging, able to depict blood flow in various organs in the body.

And in that respect, they are very effective to detect perfusion defects. There are many clinical applications where the bubbles are used today in cardiology, but also in radiology, in liver, breasts and ovary.

It has been injected in more than 100 million patients and it's today currently used in the main countries in the world.

So Victor, what could you say about this technology and what is particularly exciting about it?

Victor Jeannot

What I found fascinating with this Microbubble, it's a number of applications for which you can imagine using it in the therapeutic and medical field in general.

If you look at the intrinsic properties of Microbubble, you can consider using it in several ways. You can consider to use it as a carrier to encapsulate drug or gene. You can also consider using oscillating properties to modify the biological structure within the body and you can even use its buoyancy properties to extract cell from a blood sample and to diagnose some diseases.

Thierry Bettinger

Thank you very much, and that's indeed interesting insight.

Emily, do you have anything else to add on this aspect of use of bubble for therapy application part? Because I know that this is something you've been involved in in the past.

Emily White

Hi Thierry. Thanks for the invitation to join you today. I'm thrilled to be here.

I think one of the most interesting and exciting things about Microbubbles to me is that it's not just theoretical bench research, right? This works actually in clinical trials and first in human studies. And that's something that's different than when I started at the Foundation seven years ago. It's so exciting to see it now in humans.

Thierry Bettinger

I agree with you. It's really something that we see emerging in clinic and proofs of concept are starting to be reported in various studies.

So, thank you for your insight. Victor, do you have in mind other application for the gas Microbubble, I mean we talked about buoyancy, we talked about therapeutic application and what do you have in mind?

Victor Jeannot

Yes, there are few applications which are of interest beyond what we have worked up to know.

You can use the envelope of Microbubble to put specific tags. If you combine that with the buoyancy properties of the Microbubble you can selectively bound the Microbubble to specific white blood cell which are contained in the human body.

You can extract this white blood cell, grow it and after we inject to patients to treat cancer. You can use the same approach, meaning having a tag on the surface of Microbubble to specifically target a biomarker which are expressed in some disease condition.

This is what we called ultrasound molecular imaging.

Thierry Bettinger

So, it's interesting to see how flexible these formulations are and that you can indeed tag them to make them specific for some biomarkers.

Indeed, we keep hearing molecular imaging for various imaging application, but not necessarily for ultrasound imaging. Can you describe a little bit more this molecular imaging application, what it is and how it is useful for?

Victor Jeannot

A lot of groups have reengineered Microbubble with tag to target them to specific vascular biomarker and to visualize molecular processes like inflammation or angiogenesis as example.

So, this technique is of great interest not only to diagnose, but also to follow the evolution of the diseases or the response of these diseases to a specific treatment which has been put in place. So, if we take the example of angiogenesis, for example, which is the growth of blood vessel from existing vasculature, but which is also a feature of tumor and tumor development, we can image by ultrasound molecular imaging the progression of the tumor.

Thierry Bettinger

Interesting. Having such an imaging tool for noninvasively detect expression of biomarkers in the body would definitely change the way physicians are managing their patients.

Victor Jeannot

It's true, this is a breakthrough. There are different groups now which are performing clinical research for the follow up of inflammatory diseases, but also for thyroid, breast or ovarian cancer. We can expect to have the first product coming on the market for the patients within the three to four coming years.

Thierry Bettinger

Thank you both for your insight in these different clinical uses of gas Microbubble.

In this second part of the podcast, I would like to spend time on getting more details on the use of bubble for therapeutic application. We have recorded something like more than 7000 publications in the last two decades. And very active clinical development program also going on in various territories and for drug but also gene delivery.

I know that you both, Emily and Victor, are very knowledgeable of these applications.

First to Emily and for the audience that is not necessarily familiar with this ultrasound technology. Can you tell us a bit more about therapeutic ultrasound? I mean the one without using bubble but just ultrasound alone. Is it already used in clinic and for which indications?

Emily White

Sure, I'm happy to answer those questions. Therapeutic ultrasound at its very basic is just using sound waves for therapy instead of diagnosis. By simply altering the sound wave, you can elicit all sorts of different biological effects in the body.

So, one way to think about this is as a child if you ever used a magnifying glass to burn a hole in a leaf, like you're using all of those ultrasound waves and converging them on a single point and having all of the energy take place at that single point. And the second question is "is it in the clinic?". Absolutely, it's in the clinic and it's not just in clinical trials, there are 16 companies around the world, there are 32 indications that have regulatory approval. In fact, 39 regulatory agencies have approved 369 different specific approvals. So, they're approximately about 1000 treatment sites that we know of and approvals that are already in existence and well commercialized or uterine fibroids, prostate cancer, liver and kidney tumors, bone metastases, primary bone tumors, tissue tumors and then in the neurological space, essential tremor, Parkinson's disease and psychiatric of depression and obsessive-compulsive disorder.

So, I just want to point out that of those 32 indications, they're all using just thermal ablation alone and not in combination with anything else as their main mechanism of action. So basically, we're using heat to cook the tissue to kill it. But what we're here to talk about today, I think is even more exciting in ways we can combine this therapy of using therapeutic ultrasound focused ultrasound with Microbubbles to do some amazing things in the body.

Thierry Bettinger

Thank you, Emily for this very detailed answer and your feedback.

What we'd like now to do is to leverage on this power of ultrasound and the capacity to generate some mechanical effect to further amplify this effect in a very local way, combining it with gas Microbubble and this is where we as you said, we enter in an area that we not only cook and burn some specific area of organs, but also improve the delivery of therapeutic agents such as drug or genes. Victor, what do you think as a possible added value of gas Microbubble in this really emerging technology?

Victor Jeannot

One of application which has a strong added value of combining this Microbubble with focused ultrasound it's to exploit the mechanical activity of the Microbubble to affect biological structure.

An example which highlights the possibility of that it's to use this oscillation of the Microbubble and mechanical effect to disrupt blood clots, which are affecting patients in stroke.

This can also be used to alter the permeability of some biological barrier, and in particular to some barrier which are impermeable, and which prevents the access of therapeutic drug to the brain and prevents the treatment of disease.

Thierry Bettinger

Thank you for your additional information, Victor. To give a little more sense to what you just explained, recent publication describe the possibility to exploit this technology of bubble combined with ultrasound to improve by three to six times the deposition of a drug in the brain, so it's very concrete example that the technology work and that this is already demonstrated in human patients.

Knowing your implication in this field, Emily, could you tell us which are the main clinical indications where the gas Microbubble combined with therapeutic ultrasound could play a role?

Emily White

As Victor alluded to, I think the promise for diseases in the brain is probably what holds the most potential. Lethal tumors like glioblastoma in adults or DIPG in children, even brain metastases, cancers that like to spread to the brain like breast cancer or melanoma or small cell lung cancer, all of these diseases have difficulty with chemotherapeutics having any sort of effect, and part of that is because of that blood brain barrier that Victor mentioned and that blood brain barrier in the normal course of your life is a good thing, right? You don't want to get a brain infection from a common head cold. So, you're trying to keep all the viruses out of your brain to protect that space, but when you are sick and you need to get therapeutics in there, it's a difficult transition to get those drugs there.

But not only in the neural oncology space, I think also in the neurodegenerative space, there's large promise, things like Parkinson's disease, right now, we're just treating symptoms, but maybe we could treat the disease as a whole or devastating diseases like ALS, Lou Gehrig's disease, or even Huntington's.

So, while the brain I think holds the most promise, it's not the only place where I think this is relevant. I think the oncology indications hold great promise too. Pancreatic cancer is notorious for having really thick stroma, which is very difficult for drugs to penetrate. It's just the way the tumors sort of develop, but with the aid of micro bubbles maybe we can get better penetration into pancreatic cancer and change the survivability and the outcomes.

In addition, just in general in the oncology space, if we can get the drugs where we need them and not have the drugs circulating everywhere else at high levels, maybe we can tore the toxicities that are related to hair loss or GI distress or peripheral Neuropathies, where people complain of numb fingertips or numb toe tips or the bottoms of their feet. So I think there's lots of potential everywhere from this field.

Thierry Bettinger

Thank you, Emily, for your input. I agree with you, the list of possible benefit for the patient is pretty large. The two example you gave at that retain my attention is indeed the brain and for various disorders but as well as pancreatic cancer, so strong medical needs.

I know that the Focused Ultrasound Foundation has been active for more than a decade in this field, and I'd like to give you the opportunity to give more details about the current initiatives and programs ongoing and the Foundation to support this innovative field of therapeutic ultrasound.

Emily White

Sure, happy to. Our foundation was formed in 2006 and our mission is really simple. It's to get this technology to the patients as soon as possible. So, with the time sensitive mission, we're always looking at ways in which we can try and help move the field along.

We're the largest non-governmental funder of this technology in the world, and our first decade we spent the majority of that money, about $100 million, on trying to prove if the technology will work and now we say that we've sort of switched, we have an inflexion point and now we're trying to figure out when, now that we know that it works, it will be clinically adopted and so, as the field changes, the programming of the foundation also changes.

We're constantly looking at what are the bottlenecks that are preventing this technology from moving forward and what can we do to try and help either eliminate that bottleneck or aid the field as a whole. So, a decade ago, you know, we weren't thinking about all the commercialization or the reimbursement, but now that's something that we spend lots of time and effort on.

You know, we spend a lot of time now working on the commercial sector and that's actually how I met Thierry, you, years ago as our first Partners Program and trying to work with the companies and through strategic partnerships or trying to help fundraise first in human clinical trials or other things that corporations need in addition to trying to raise patient awareness, physician training, all of those types of things.

Thierry Bettinger

Thanks, Emily. Indeed, I think the community acknowledged the strong support that the Foundation is providing to this field and this technology.
I think one last burning question, and I believe most of the audience would be really excited to hear about your answers, so sorry for putting you much pressure about that. When do you think that such a technology might be available for patient treatment and what do you see as major milestones and hurdles to see this translating to clinic and to the patient for their best management?

Emily White

So, our annual report, the state of the field just came out last week and we know that in 2022 we had 1000 treatment sites treat about 100,000 patients and it continues to go up every year. So, the technology is already here. There is some commercialization, but as I said earlier, that's all-thermal ablation.

So, I think, given the exponential growth in clinical trials in the past few years, we're going to see this research really progress on and hurdles are going to be in the regulatory space in the reim-

bursement space. Just anything that comes with commercialization of medical technology it takes time, it can be a frustrating process sometimes with regulatory guidelines.

I think the Foundation has helped to really build a sense of community and none of the companies think of each other as competitors.

It's the sort of standard of care that it is unacceptable to society that is really our competitor and what can we do to try and help everybody to move the field forward to get this to the patients? And I think 5 to 10 years we'll be having a very different conversation.

Thierry Bettinger

So, I'd like to thank both of our guests for their very meaningful and interesting contribution. I'd like to underline that Bracco is indeed investing in these applications. We see the various possible way to exploit bubble for different diagnostic, non-diagnostic and therapeutic application and this wide scope give us a lot of hope that we will see the field being completely different in few years' time thanks to this technology.

I'm Thierry Bettinger, thank you for joining us and thanks to Doctor Emily White and Doctor Victor Jeannot for contributing to this podcast.

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