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Now & Next with Jubilant Biosys: We talk with Michael Gallatin, Ph.D., president and co-founder of Mavupharma (Mavu)

***Saurabh Kapure**, Vice President, Business Development, USA for Jubilant Biosys, recently sat down with **Michael Gallatin, Ph.D.**, president and co-founder of Mavupharma (Mavu), the drug discovery and development company, to discuss some of the latest developments in the industry and at Mavu. They chatted for about an hour. During that time, Dr. Gallatin shared his thoughts about Mavupharma, his role at the company, the evolution of biopharma, drug discovery, development, and the road ahead for the industry with Saurabh. The following Q&A, which has been lightly edited for clarity and length, are some key excerpts from their conversation.*
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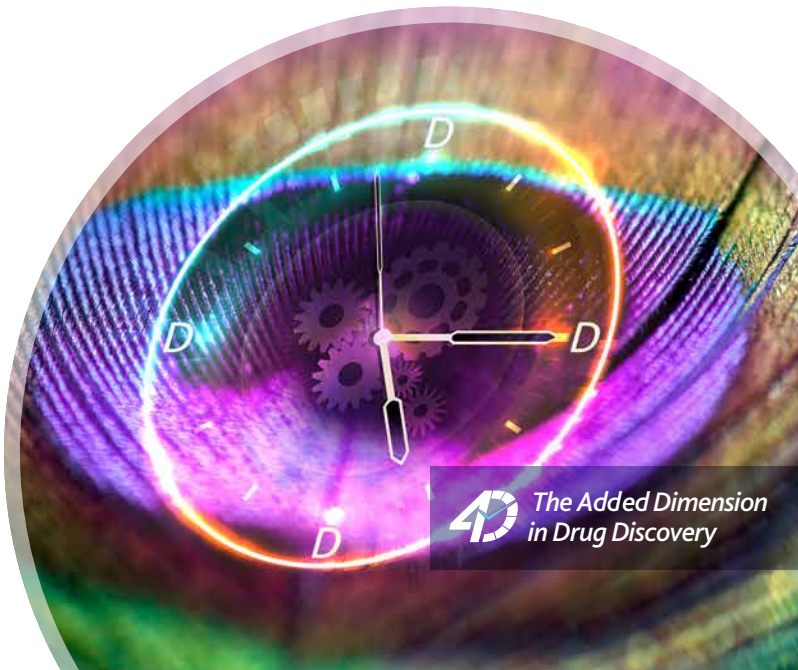

Jubilant (Q): What does Mavupharma do, and why does it do it?

Mike Gallatin (A): Mavupharma is part of a revolution in how medicine looks at, and approaches, treating cancer, both today and for the future.

We're working on harnessing the body's own immune system to fight cancer – more specifically, on modulating how the immune system is activated in preventing some of the things cancer cells do that allow them to cloak or camouflage themselves and then negatively impact the immune system. If we can remove or minimize those elements, the body's immune system will recognize cancer cells more effectively and eliminate them.

In more formal terms, Mavupharma is a drug discovery and development company. We're focused on novel approaches to selectively targeting the STING pathway, and leveraging the body's innate immune system to treat cancer and infectious diseases. One of our key differentiators is that we're developing orally bioavailable, non-nucleotide modulators of the STING pathway in order to treat cancer and infectious diseases. This is largely new territory in our field, but it's built on decades of rigorous research, experimentation and work. By the way, "STING," which I've now referred to twice, stands for "Stimulator of Interferon Genes."

Q: STING is "stimulator of interferon genes."Can you say more about what that means and why it's important?

A: To understand STING and its role, first we need to briefly discuss something called, "immune checkpoints." Interestingly, this last year, the Nobel Prize was awarded to a scientist named Jim Allison (who happens to be a friend of mine) for the concept of "immune checkpoints."

Q: What are "immune checkpoints?"

A: Immune checkpoints are things that are in the immune system that prevent it from going haywire and having autoimmunity, where the immune system attacks healthy tissues.

The discovery here was that tumor cells have figured out a way to use these checkpoints to their advantage, to evade the immune system.

You can think of immune checkpoints, and the dynamics around them, metaphorically. It's like you have a platoon of soldiers here and a platoon of enemy soldiers just over there, but the latter, the enemy soldiers, are so well camouflaged that the first platoon can't see them. If you could just remove or reduce their camouflage, the enemy platoon would be seen, identified and eliminated immediately by the first platoon. As simple as this sounds, it represents a major sea-change in how we treat cancer today.

Q: Why is this important, why is it a "sea-change"?

A: Pharma companies have been developing drugs that work to block these checkpoints and facilitate the elimination of cancer cells. When these drugs work, they can work spectacularly well and actually produce cures – and I mean real cures. In the same way that you would clear bacteria, you can now clear certain tumors. It's remarkable.

Unfortunately, this approach only works in maybe 12% to 15% of all cancer patients. (There are some cancers, like melanoma, where they work markedly better, say up to 30% or so, but even that leaves a lot of room for improvement).

Still, think of blocking immune checkpoints as one part of a triad that's required to be in place in order to effectively fight a cancer. In terms of this triad, the way it works is first you have to eliminate the checkpoint; then, the tumor has to express something that the adaptive part of the immune system, i.e., T effector cells, will be able to recognize; finally, part three of the triad is you have to activate what's called "the innate immune system."

Q: What is "the innate immune system?"

A: The innate immune system which couples with the adaptive side to mount a more effective anti-tumor response, are cells that can exist within the tumor or immune cells. They chew up the tumor a bit and then essentially shoot up a bright flare and say to the rest of the immune system, i.e., the T-cell side, "Hey, you guys need to pay attention and come in here because there's something that needs to be eliminated!"

Now we can circle back to that other key aspect I mentioned earlier, "STING." Again, STING stands for "stimulator of interferon genes." It is actually a physical entity, a protein. As the name implies, once STING is activated, it mobilizes a whole cascade of downstream events that involve the expression of so-called Type 1 interferons. The Type 1 interferons then go on to trigger a bunch of other things that help to prime, amplify and recruit T-cells that are effective against the tumor. It's an incredibly interesting and elegant process.

Q: How does it work, how does STING get activated?

A: Simply put, the way STING gets activated is that upstream, there's an enzyme called cGAS which exists in all cells and essentially is a censor. cGAS detects pieces of DNA inside the cell that shouldn't be there, including detecting tumor DNA fragments inside of the cell. If a macrophage engulfs a tumor cell and chews it up and gets these DNA fragments from the tumor, that can activate cGAS, that synthesizes cGAMP which then binds to and triggers STING with the attendant downstream immune amplifications.

Q: So, where is all this going?

A: Just a little more context and it will be clearer. In the last few years, some in the pharma industry have been working on drugs we refer to as "direct agonists." These are drugs that bind directly to statin and they activate statin. Because of the physical properties of these drugs, the agonists have to be injected directly into a tumor and that represents a number of challenges. Two of the key ones are:

- First, it's incredibly challenging to get the dose right. If you get too much activation, it has a negative effect on the patient's immune system, and you don't get systemic memory clearance of the tumor and other lesions throughout the body.

- Next, it's just not practical to inject all the lesions that might exist in a patient's body and since the lesions are not all identical, sometimes you'll get protection against one lesion, but not against all the other metastatic lesions.

So, there are big challenges both from the scientific as well as from the potential commercial perspective. I mean, how practical is that?

Q: What does this have to do with Mavupharma?

A: When we started Mavupharma, we had an idea for what we refer to as a "conditional agonist of STING." That is something which would only work to activate STING in the tumor, and would do so in all of the tumor lesions. The way we accomplished that is by inhibiting an enzyme called ENPP-1. ENPP-1 is part of a class of enzymes called "phosphodiesteras- es" which, in this context, essentially chew up second messen- gers, e.g., cyclic GMP, cyclic AMP, and in the case of ENPP-1, the dinucleotide, cyclic GAMP. When ENPP-1 does that, it dampens the immune response, which, in the context of the anti-tumor response, is not a good thing. What is a good thing, however, is to inhibit ENPP-1.

One of the truly exciting things we've been able to do at Mavupharma is to make drugs that bind to and inhibit ENPP-1, and in so doing, block its ability to chew up cyclic GAMP. Because of that, effectively we're raising the level of the immune system response.

In fact, we've been able to develop an oral drug to accomplish this. This is really significant and different – and it really sets us apart because most other STING drugs need to be injected directly into a cancer tumor and that's neither efficient, nor very practical.

Revisiting your lead-off question, "What does Mavupharma do?" A more concise description of Mavupharma I can give now is that we have developed conditional agonists of the STING pathway that only act in the context of a tumor, and in particular, a tumor that's been treated with radiation or some other agent, or one that's been treated with one

of the checkpoint inhibitors I mentioned before. Our drugs don't activate the immune system systemically to cause toxicities. They only activate in the tumor itself. And now we can even give these drugs as a pill, orally. We don't have to inject the tumor.

That was one of the big hurdles we had to overcome. And we did just that with Jubilant Biosys.

By the way, I want to be clear that this is not yet in clinical trials. We've done it successfully in a variety of animal subjects, and human trials are forthcoming.

Q: Why did you name the company "Mavupharma?" What does Mavupharma mean, if anything? How did you develop the name?

A: There's a funny anecdote behind the name of our company. When we started the company, I was intent on calling it "Hornet" – you know, STING, hornet.... But we wanted to remain in deep stealth mode and not let our industry know what we were working on. So, we decided to pick something that most people, or companies, in our orbit wouldn't figure out, that is if they thought about it at all.

Our chief chemist, Joshua Dingo, who is from Kenya, by way of Columbia University, Genentech and a bunch of other places, inspired me to look up the Swahili word for "hornet." It was "mavu." In Swahili, "mavu" means "hornet," hence the connection with STING. And "Mavupharma" was born! We usually use "Mavu" in conversation; it's shorter and is still meaningful.

Q: How large is the market you are potentially addressing with this?

A: Of course, this is a forward-looking statement, but if only 12% to 15% of all cancers respond to current checkpoint therapy, there's obviously a huge amount of white space to be filled. There's another 75%, or so, of cancers that, in theory, would respond to the checkpoint therapy if you had this other element of the immune triad present. So, it's potentially an enormous market.

Of course, as we discussed, not all cancers are going to show that synergy, but the bottom line is we have orally available, systemically acting, conditional agonists of the STING pathway—which is just huge.

Q: Tell us about your background and your role at Mavupharma, as co-founder and president.

A: As you just said, I'm President of Mavupharma, and co-founder, along with my colleague, Greg Dietsch, who is co-founder and Chief Scientific Officer. The genesis of Mavupharma, and the idea for our approach, were conceived and started with Greg and me.

I'm an immunologist and have been in immuno-oncology for more than 30 years. I was on the faculty at Fred Hutchinson Cancer Research Center and before that was a Fellow at Stanford, focused on immunology/inflammation and oncology. I've also held various senior executive and research positions at the big pharma companies and others.

Dr. George Rathmann, one of the fathers of the biotechnology industry, recruited me to ICOS Corp, which he co-founded. Before that, George was the founder of Amgen, and responsible for developing two of the ground breaking drugs of the biotech industry — Epogen and Neupogen. At ICOS, I was one of the founding scientists, serving as Vice President and Scientific Director, and responsible for the discovery, preclinical research, medicinal chemistry and process chemistry groups including those that generated and supported the worldwide registration and launch of Cialis, another successful drug in the pharma industry, as well as working on a number of drugs involved with oncology.

I'm currently also a senior advisor on the Frazier Healthcare Partners Life Sciences team—Frazier, an investor in Mavupharma, led a $20 million Series A financing in 2017— and on the Board of Directors of Mavupharma, due to my relationship with Frazier Health.

During this period of time, but even more so in the last 10 and now five years, pharma has experienced a dramatic acceleration of progress – it's really a revolution in how we look at and approach treating cancer. It's remarkable, and humbling, but also exhilarating, to be even a small part of this.

The other thing is while I am an immunologist, my remits, starting with running research at ICOS, have encompassed the management of all aspects of drug discovery and development up through clinical entry. So, I essentially oversee the entire process from the first discovery of lead compounds through their optimization into a profile that will be clinically and commercially attractive. To do that I also oversee the discovery chemistry, drug metabolism, toxicology, manufacturing, and a lot of business development aspects. I'm constantly talking to potential strategic partners, typically large pharma that have an interest in our area commercially, as many of them do. And I'm quite involved in all aspects of Mavupharma's business, which includes our relationships with CRO's, such as Jubilant Biosys with whom we've been collaborating for several years now and doing so successfully in a semi-virtual manner.

Q: Can you say more about this style of working?

A: Mavupharma has offices in Kirkland, Washington and San Diego, CA. We have a ton of academic collaborations with universities across the U.S., as well as CROs in India and elsewhere.

Our primary CRO, the one which has really been central to the success of our company, is Jubilant Biosys. They are headquartered and have major facilities in India, plus the U.S. and Europe.

In terms of technical capabilities, Jubilant are extremely competent in medicinal chemistry, in drug metabolism, toxicology, structural biology, biology, all the aspects that one needs for the projects and work we do at Mavupharma.

They are both our intellectual and strategic partners. It's not a case of "Here's your contract, CRO, now go run your tox study and send us the report when you're done."

Jubilant functions as a fully integrated part of our project team. One of the things that really distinguishes them as a partner for us is they are extremely good at communicating. Sounds basic, but it isn't, and it's absolutely critical to the success of our work at Mavu.

From the start of our work together, we've had a deepening consultative relationship with Jubilant, as well as tactical with weekly and bi-weekly calls, video conferences and check-ins at any time day or night we require. It doesn't matter whether we're interacting with their office in Washington state, which is our own time zone, or talking to their folks 6,000 miles away in Bengaluru, India. They over-service, and they constantly innovate. We have tremendous respect for their intellectual contributions, capabilities and service.

In reality, working this way with Jubilant represented a whole new business model – one that works really well for an organization like ours. It's a model that directly impacts the point of capital and time efficiency.

Fundamental to a lot of our development work at Mavu is an iterative process. The cycle time for that iteration is absolutely critical to how long it takes to get from early discovery to something that's ready to go in a clinic. I can tell you, categorically, that the combination style team that we use— very experienced pharma drug discoverers in-house at Mavu, plus the Jubilant team – can do things faster and at less cost, making the iterative cycle is quicker. And on a strategic level, we are not hindered as are a lot of large organizations are, and so able to move more quickly. One case, for example, took us probably about a year and a half to go from the starting gate to having a very new drug compound ready to be considered as a clinical candidate. That kind of velocity is just not the norm in our field. That's super-fast, especially on an unprecedented target, as ours was (unlike making a copycat beta blocker or similar). I'd be very surprised if that timeline could be achieved in the classic large pharma environment, an everything-in-house setting. This is how you prevail and win. I'm very enthusiastic about this model going forward.

Q: How long have you been working with Jubilant?

A: We've been working with Jubilant since 2016 and ramped up very quickly.

Q: What range of Jubilant services have you used?

A: A sweeping range of services. To name just a few of them: medicinal chemistry, structural biology, x-ray crystallography, computational chemistry, drug metabolism, pilot toxicology, screening toxicology in multiple species, cell biology (they have excellent immunology folks, by the way).

Early on, Mavu had some tough nuts to crack—the biology was pretty novel and we had to pound on that a few months to figure it out. We succeeded and that is in no small part because we had the bare capabilities. We designed a lot of the experiments, and then with Jubilant, had someone to reliably execute them.

Q: What does success in your work look like to you? When can you say, "Hey, this was a success," or "our vision is being fulfilled?"

A: Ultimately, I would define success for the idea that Greg and I had as success in the clinic treating cancer patients who a year or two before would not have been responsive to treatment. That's the ultimate success. That's the ultimate goal, right? There really is no other success.

Success as it relates to our collaboration with Jubilant, I can define from multiple perspectives. One of the most important though is the creation of a specific clinical candidate compound or compounds that have met all the criteria of potency, selectivity, pharmacokinetics, toxicology, manufacturability, etc., to go for and enter the clinic to test the hypothesis. And we have reached that milestone. So, as far as Jubilant's contributions are concerned, to date they have more than checked the box of success in our work together.

Q: After being in this this industry for more than 30 years, are you still excited by it?

A: I am excited by it every day. It's interesting you should bring that up. I'm actually much more enthusiastic now then I was 10 years ago. I think we're finally beginning to see that the power of all these tools we have in our industry, whether it's CRISPR or something else, as my old boss George Rathmann used to say, we're going to be living in the age of miracles.

I think that's really true. Ten years from now, maybe even five, I'm confident there are going to be a lot of diseases, cancers in particular, that were previously thought of as incurable, we'll look at as essentially either fully cured or as chronic, manageable diseases. Of course, that can't happen fast enough, but I think that is going to be the case.

Q: That's a remarkable vision and description of future reality that's actually starting to take shape now. It's particularly inspiring to realize that it's occurring in real life. Thanks for sharing your time and your thinking.

A: It's been fun talking to you. Thank you.