

Q&A with Randy Milby, CEO of Hillstream BioPharma Inc. revolutionizing drug delivery by Encapsulating Drugs in Nanoparticles small enough to be taken up by the Leaky Vasculature of the Tumor Cell improving the Efficacy while reducing Side Effects of Cancer Therapeutics



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“We are taking established drugs and putting them in a nanoparticle to improve the side effect profile and increase efficacy.” - Randy Milby

CEOCFO: *Mr. Milby, the first thing I see on the Hillstream BioPharma, Inc site is “Enhancing the Safety and Efficacy of Cancer Therapeutics.” How are you doing that?*

Mr. Milby: Hillstream BioPharma is improving efficacy and diminishing the side effects of first line drugs by encapsulating them in a nanoparticle. These nanoparticles then circulate through the bloodstream but the size of the nanoparticle is critical. That is because the nanoparticle is one hundred to one hundred and fifty nanometers and that is the size that can be taken up by leaky vasculature of the tumor cell. Therefore, you now have drugs that are encapsulated and they get taken up by the tumor and the drug is actually released inside the tumor. This enables you to increase the efficacy and decrease the side effects.

CEOCFO: *What does “taken up by the tumor” mean? What is happening in the body?*

Mr. Milby: That is a great question. A tumor needs a lot of blood supply, but the new blood vessels created by the growing tumor are often abnormally formed and referred to as “leaky”. Therefore, nanoparticles of optimal size can exit the vasculature and flow into the tumor. The interesting aspect of this is that it is the acidity inside the tumor that eats away, dissolves if you will; that polymeric coating and releases the drug inside the tumor.

CEOCFO: *What gave you the idea this would work?*

Mr. Milby: I licensed this nanoparticle technology from NanoProteagen. There are many different drugs encapsulated with nanoparticles, however, part of the issue is that many are not taken up by the tumor, as I just described it. In this case we radio labeled our formulation. We showed it in a mouse model our nanoparticles were actually taken up by a tumor.

CEOCFO: *Are there particular types of cancer or types of tumors that are better suited for this or is it somewhat across the board?*

Mr. Milby: It is somewhat across the board, although we are very focused initially. The first drug that we are utilizing is Bortezomib. The brand name Velcade® is utilized first line for the treatment of multiple myeloma, but prolonged dosing can be limited side effects, notably peripheral neuropathy. This drug has been out on the market since 2003, therefore the safety and efficacy are well known, and the nanoparticle has the potential to improve one or both. Peripheral neuropathy, in laymen's terms, is that tingling and somewhat painful feeling that you get when your arm or leg falls asleep. It can be very painful and debilitating for patients. It is very difficult for them to even do things like even buttoning a shirt. Therefore, we wanted to put the drugs in the nanoparticles and alleviate that type of side effect. Improving this side effect profile in myeloma is the first target indication because it can have an important impact on patient's lives and may lead to increase efficacy through reducing interruptions in therapy or potentially greater uptake in tumor cell.

CEOCFO: *Where are you in the process?*

Mr. Milby: Right now, we are finishing up some preclinical work. We intend to meet with the FDA for our pre IND meeting in the fourth quarter of this year. We are completing two more preclinical animal studies.. Have the pre IND discussion and our plan is to initiate phase 1/2 studies in 2019.

CEOCFO: *What did you learn from the testing so far?*

Mr. Milby: We have learned that, first the nanoparticle can be manufactured at the optimal size for tumor uptake. We have seen that we can put a higher concentration of drug in our mouse model verses Velcade or Bortezomib alone without the same dose limiting toxicities. Therefore, we have been able to demonstrate that you can have a higher payload, which goes back to my comment that it is being taken up by the tumor and released primarily in the tumor and not in the rest of the body. Our goal is to demonstrate the benefit of nanoparticle to improve safety, with a secondary eye on improving overall efficacy. Because we have demonstrated increases in maximal dosing, there is a future opportunity for using this approach in solid tumors.

CEOCFO: *What have you learned from past experiences about bringing drugs to market?*

Mr. Milby: We do this to help patients and it takes longer than you would want it to take, but it is important to be methodical and improve patient outcomes.. You can take a drug that is already established with a solid efficacy profile, decrease the side effects which may also increase the efficacy, but at the very least improve the overall safety and patient's lives as they undergo cancer treatment.

CEOCFO: *What is your funding situation? Are you seeking investment or partnerships?*

Mr. Milby: This is a private company. It has been self-funded through friends and family at this point. We have been talking with potential investors, but I wanted to have this additional data to share with them which solidifies the rationale, dosing, and establishes an important milestone for and IND and the clinical development program... We will go out and start talking with potential investors in this quarter and next quarter.

CEOCFO: *How did you decide where to start first and what type of tumor?*

Mr. Milby: That is a good question. We actually went from looking at efficacious drugs and side effects of different drugs in areas where we felt the technology could make a meaningful difference in patient outcomes. The reason Bortezomib was chosen, as I mentioned, was because it is a very effective drug, but peripheral neuropathy is a frequently occurring and potential debilitating side effect which can limit its use.

CEOCFO: *What if anything has been the response from members of the medical community that have seen what you are doing?*

Mr. Milby: The response is very positive, because oncologists are already using bortezomib first line, but they struggle with the side effects. These are drugs that are already on the market from a regulatory path point of view, which allows us to utilize the 505 (b)(2) Regulatory Path for our nanoparticle formulations. Because bortezomib is a foundation of care, if Hillstream can establish a novel formulation that decreases the side effects and increases the efficacy, from their point of view this is great for treating patients with multiple myeloma!

CEOCFO: *What, if any, challenges are there in the nano encapsulation process?*

Mr. Milby: Generally, for most nanoparticles it is just getting the sizing correct. This is a polymer nanoparticle. It has taken a little bit longer than we would like, but we have made tremendous progress in the last several months in our process and pre-clinical data. When you start to manufacture at commercial scale it is critical to have consistent particles and we are confident that we have resolved that.

CEOCFO: *Are there many competing ideas to what you are doing?*

Mr. Milby: As I mentioned earlier, there are other drugs in nanoparticles. There are not that currently any with bortezomib, or in multiple myeloma. However, to your point about nanoparticles, I would not say there are many companies, but there are companies going for nanoparticles and using nanoparticles for the very same reason we are. I would say that goes back to if you can get these drugs to the patients and lessen the side effects, then I think that we are doing the patients a great service.

CEOCFO: *Are there any potential side effects of the nanoparticles that you have seen and heard about or are looking for?*

Mr. Milby: So far we have not seen anything of significance. When we advance beyond the mouse model that is when we take it into some of the Phase I studies with the FDA. We will be looking to see where the nanoparticles get taken up in humans. What we see now in animal and in vitro models it gets taken up in the tumor cell. Right now we have not seen it, but to your point, we are always looking at the overall safety.

CEOCFO: *You are working with HSB-407. What is HSB-408?*

Mr. Milby: That is the Oxaliplatin drug with a proprietary nanoparticle delivery. Similar to our rationale with bortezomib, we believe there is an opportunity to improve the delivery and safety with oxaliplatin in colorectal cancer. To date, we have not done a lot of work on this one, but we have licensed the right. We are really focused on the Bortezomib nanoparticle first. My philosophy is to stay focused and get the first one both from the animal data point of view and through the FDA pre-IND

discussion, clinical development and approval. Then we can go on to the second drug. However, let us keep everyone focused at this point.

CEOCFO: *There is so much to look at in health. Why should people pay attention to Hillstream BioPharma, Inc?*

Mr. Milby: That is a great question. There are many interesting opportunities out there, but I think one of the interesting things for Hillstream BioPharma Inc. is that by encapsulating these known leading drugs we decrease the side effects and potentially increase the efficacy. As you know, in oncology, treatment is combination therapy, because one drug does not necessarily do everything, therefore, by making important improvements, we maintain the standard of care and extend opportunities that may have not been achievable with the safety or dosing profile in the existing form. For the investors, if you have a company improving upon existing leading medications, which can limit the timeframe for development and overall investment in order to bring novel and improved treatments to patients in serious conditions where the market needs remain high. Therefore, our goal is to maintain nanoparticle bortezomib as a standard of care in combination therapies for the treatment of multiple myeloma which we believe is an important and rewarding opportunity.

CEOCFO: *What if anything might someone miss or misunderstand when they first look at Hillstream BioPharma?*

Mr. Milby: What we are building this company on is not immuno-oncology at this point. We are not using some of the newer therapies. However, we are taking established drugs and putting them in a nanoparticle to improve the side effect profile and increase efficacy. It is not as sexy as some of the new therapies, but leading oncologists and researcher are excited and believe it is important to helping their patients and believe there may be additional applications pending our dosing, safety, and efficacy assessments. One of the things that we have seen, based upon these nanoparticles, is that it inhibits the resistance that builds up for some drug therapies by incorporating it inside the nanoparticle. Those are things that the investor should be watching for from Hillstream BioPharma, because the tumor is very smart, so if you can prevent the patient from developing a resistance to the drug initially, the patient can stay on the therapy longer without the debilitating side effects and therefore the efficacy increases in cancers where we still have substantial room for improvement.

