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Revolutionary Clotting Factor Producing Gene Therapy for Treating Hemophilia

Tony Materna
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CEOCFO: *Mr. Materna, what is the concept behind Haplomics?*
Mr. Materna: Haplomics is a genetic engineering company. The first disease on which we are focused is hemophilia, specifically developing better therapies for treating hemophilia and potentially coming up with a cure.

CEOCFO: *Why hemophilia first?*
Mr. Materna: Our scientific founder Dr. Tom Howard's initial discoveries were in the area of hemophilia. He realized that there were variations between different people on the F8 gene which controls the production of the clotting factor that the body needs to stop bleeding. These differences between people on that gene explains one of the big mysteries in treating hemophilia, which is that about a third of the people who suffer from hemophilia and get a clotting factor product as a treatment develop an immune reaction against it, which renders it useless. Doctors have been mystified as to why that was happening and now we think we know why. It is because of these variations in the gene. You are basically giving people clotting factor that doesn't match their own. Many patient's immune systems see that difference as foreign and dangerous and trigger an antibody immune response which attacks the therapeutic clotting factor and inhibits its function. Dr. Howard's discoveries also are serendipitous because treating hemophilia is a $5+ billion industry in the US alone.

CEOCFO: *Where are you in the process today as far as reviewing, discovering, testing?*
Mr. Materna: We are an early stage company with a long pedigree. The company was actually incorporated in 2005, primarily as a holding company for Dr. Howard's patents, of which we have developed a fairly extensive patent portfolio with seven different patent families, and more to come shortly. When I came on board, two years ago, we went from a holding company to an operational drug development company. Most of what we are doing currently is pre-clinical research and development. We are testing things out and basically working to accumulate sufficient data that we will be able to take to the FDA and say we now have enough data that we should try this out on some real patients. We believe we could be ready for Phase I/II clinical trials as soon as two years.

CEOCFO: *Is this your first venture into the health area?*
Mr. Materna: It is for me. I am a serial entrepreneur. I have been involved in six other companies in the high tech sector, two of which have gone on to be hundred million dollar concerns. One had a hundred million dollar IPO and one was an acquisition. However, this is my first venture in the life sciences. I have a degree in mechanical engineering from UC Berkeley. What I have learned is that genetic engineering and mechanical engineering actually have a lot in common. They are both pretty much straight engineering. We work with genetic 'guide RNA' and enzyme 'cutters' and molecular 'repair vehicles' that all latch into place on the DNA double helix. The concepts seem to resonate with me very well, so I have enjoyed coming up to speed on them.

CEOCFO: *Why was Haplomics compelling for you?*
Mr. Materna: To use genetic engineering to modify the genes of people who are ill and cure them is almost science fiction. In fact, it was science fiction until not long ago. So for me, it just was something new. In my career I have never repeated an industry when starting a new company. People often ask, "How could you spend three or five years becoming an expert in this industry and not stay in it?" but I find it boring to do it again. I have always found that in going into a new area I bring a lot of experience and knowledge that sounds fresh to people in that industry, and I often find that I can be very disruptive. I think of things in ways that have not been traditionally done and it has been beneficial to my entrepreneurial career. I believe the same thing is going on here. We can be very disruptive to the way business has been done in hemophilia for thirty years, which could be hugely beneficial to the patient community. Things like less immunogenic clotting therapies and a cure. That would be disruptive to the $12 billion global clotting factor industry.

CEOCFO: ***Would you give us an example of what you have brought to the table that has made a change for Haplomics?***
Mr. Materna: I would say that the first thing is that I am very aggressive and impatient for progress. The company had existed largely as a holding company for developing patents and ideas and it had an academic sort of pace to it and there were not any strong attempts to commercialize. Less than a month after coming on board I heard, over a dinner conversation between two of our scientists, that they actually thought they could pull off this gene repair. That night I kicked off our current development project, in which we are trying to demonstrate *in vitro*, in a dish, that we actually can take cells from a patient, genetically repair them, and the cells in the dish will start producing clotting factor. We want to introduce those repaired cells back into the patient in large numbers, so that they can make enough clotting factor themselves. They'd be cured. That night, when I heard the scientist discussing this possibility I said, "You guys can actually do this?" And they said, "Well, we think so." I said, "How long would it take? How much money do we need?" After they told me I said, "We are starting tomorrow!" I immediately understood the potential of it and we have been driving towards it ever since. This is our big thing. It is not the only thing we do, but it is the big one.

"They see a hot young biotech company entering clinical trials and they pay a premium to make it their own."- Tony Materna

CEOCFO: ***How do you repair the gene?***
Mr. Materna: Hemophilia is a bleeding disorder where people's blood does not clot. Everyone thinks the problem is that you will get cut and you will bleed out. That is certainly possible, but that is not the real danger. With hemophilia patients the danger is internal bleeding; getting bumps, bruises, and what are called spontaneous bleeds, which happens in all of us all the time, but we have sufficient clotting factor to trigger what is called the clotting cascade. It shuts off small internal bleeds immediately, so we never notice. However, if you do not have clotting factor then nothing shuts off the bleed and you have a painful, crippling and sometimes life threatening problem. The common area of concern for a severe hemophilia patient is the joints. We are big, heavy mammals and when we move around we always are breaking capillaries in our knees, for example. If you cannot stop the bleeding you have uncontrolled bleeds in joints, which become swollen, painful, and damaged. There are other issues too, and of course, the biggest problem is if you get a bleed inside your cranium, which will kill you like a stroke. It is a never ending battle for patients and their families.

Hemophilia is a genetic disorder caused by a mutation that can occur on the F8 gene, which is responsible for making clotting protein. It is almost always inherited. It mostly affects males. About one in 5,000 male births will be a boy with hemophilia. Mothers can be carriers, but it is rare for women to actually suffer from it. It is possible to acquire hemophilia if you do not already have it, but again, it is very rare. There are at least two thousand different mutations that cause it, but there is one mutation in particular that causes almost half of all severe hemophilia. It is called the Intron 22 Inversion. While it sounds complicated, it is actually pretty simple. The mutation occurs in the part of the gene that makes clotting factor; when about eighty percent of the gene splits and flips during the conception process. It leaves about twenty percent of itself behind and it is now facing the wrong direction and is missing its tail end piece. That results in the incomplete production of clotting factor protein, and this protein can't escape out of the cell into the blood stream where it's needed.

To repair this defect we are using some very exciting new gene editing tools called CRISPR/Cas9. This gene cutting and editing system was discovered about three years ago by scientists at both MIT and Berkeley. It comes from the same immune system that bacteria use to cut up and neutralize attacking viruses. These scientists figured out a way to use that mechanism to do gene editing more efficiently than what had been tried before. Using this technique you can go into a piece of DNA and you can cut it at the exact spot that you want and then insert genetic material at that spot, using a process called homologous repair, which basically is seamless gene editing.

In our application of this technique, we plan to draw blood from a hemophilia patient and isolate a particular type of cell that the body uses to produce clotting factor. This type of cell is called an endothelial cell. Endothelial cells line all of the blood vessels in your body at the location where clotting factor is inserted into your blood stream. In hemophilia, these cells are defective because they have a problem with the F8 gene. We will draw out those endothelial cells, isolate them, and insert some different genetic constructs we've made. The first construct we use has an enzyme in it which will cut the DNA at the site of the mutation. We actually do what is called a double stranded break, where we cut the helix in two places. Then, floating nearby we have what we call a 'repair vehicle', which is a piece of DNA that we want to insert and, using some other techniques, they lock up precisely in the right orientation and the mutation is repaired. We have demonstrated this on live cells over the last year; both the cutting and the insertion. We have fine-tuned our technique and

are at this moment, in our lab as we are talking, attempting to do the repair on endothelial cells from actual hemophilia patients. We are hoping that in the next three months we will be able to make a pretty substantial announcement.

CEOCFO: ***The basic premise of how hemophilia is caused; is that universally accepted so that it is just the method to fix it that is in question?***
Mr. Materna: The mechanism for the cause of hemophilia has been very well studied. It is caused by a lack of functional clotting factor. The clotting factor is either not made or is made in a defective way because of a genetic problem. There are many different types of mutations. We will eventually get around to fixing all of them, but we went for the one that would help the most people the soonest, the Intron 22 Inversion. As it happens, our particular technique of repairing this missing tail end of the gene actually picks up a half dozen other mutations that are also located in that spot. Therefore, our current technique actually will end up curing closer to fifty three percent of people with severe hemophilia.

CEOCFO: ***For lack of a better way to put it; once you make the replacement how long is it going to work, could it possibly be permanent? What do you expect or what have you seen?***
Mr. Materna: That is a good question! Once we have done the repair outside the patient and we have separated out the cells that are successfully repaired, we then multiply those up to millions of cells. Then we reintroduce them back into the patient. It could be as simple as just infusing the repaired cells into the patient's blood stream and letting them float around until they engraft, which is basically the repaired cells lodging someplace that they are happy with and continuing to live and function and put out the missing clotting factor. The real trick for us is to find out what is the best way of doing the re-introduction of the repaired cells. This is what we need to figure out next with some special mice we have bred. We have genetically engineered these mice so they have exactly the same Intron 22 Inversion defect as the human patients; we call them 'humanized mice,' because they have human hemophilia. We also know that endothelial cells tend to be very long lived, so we have reason to be optimistic.

We believe that if we can get enough repaired cells engrafted in the patient and they produce enough clotting factor, we can get to the point that these people will stop having the spontaneous internal bleeds that cause so much pain and damage. We may even get their clotting factor high enough so that they can have a normal life and not have to repeatedly infuse their veins with commercial clotting factor; perhaps even high enough so that if they are young boys they can participate in sports! We have a dozen different ways to try and probably two or three will work. We need to find the one that is the optimal.

CEOCFO: ***Different diseases are in and out of favor with the investment community and even with the medical community's attention. Where does hemophilia stand? Are people interested?***
Mr. Materna: Many diseases do go lagging because not enough people have them to give big pharma companies the financial incentive to try to treat or cure them. Hemophilia is interesting in that regard, from a business perspective, because it is both considered a rare disease and a fantastically expensive one to treat. About 20,000 people in the United States have hemophilia and about 400,000 worldwide, and only a quarter of the worldwide patients receive treatment. Therefore, it is a small number of patients. However, clotting factor used to treat hemophilia is extremely expensive. The estimated annual treatment cost in the United States is about $250,000 per patient and that is if you are just a normal patient. If you develop this immune response that I was talking about, where your body essential rejects normal clotting factor, then you have to go to a different treatment regime which can run over one million dollars a year. I had lunch with a guy whose annual treatment cost is ten million dollars a year and he is not even the most expensive. Therefore, there is over $5 billion in sales of clotting factor in the United States and about $12 billion dollars worldwide. It is a very big business. There are about five or six major pharmaceutical companies who sell clotting factor that each have billion dollars revenue streams here in the US and worldwide. As a result, we have gotten interest from the life sciences venture capital community because anything that we do is probably going to be a billion dollar product. They sense that it has a big upside.

CEOCFO: ***You mentioned there are some other things on the back burner?***
Mr. Materna: Yes. Besides the gene repair, which of course is the big one, we also have ideas on how to improve existing therapies and existing clotting factor products to make them less immunogenic to the patient. If patients have an immune response, it is very hard to get rid of it. There are some existing techniques for doing that, but they do not work in about half the patients with the immune response. Therefore, we have some ideas on things we can do, such as using 'tolerizing' peptides to calm their immune system down again, so that they can again receive the clotting factor therapy. Those are two other areas. I should add that in each of these three areas of our research and development efforts, the gene repair, a new less immunogenic clotting factor, and tolerizing the immune system, Haplomics has received Phase I grants from the National Institutes of Health to study them further. We also have some upcoming ideas on diagnostics.

We understand the immune response sufficiently so that we think we can develop diagnostic tools that will predict ahead of time who is going to develop which immune reaction. If you could test people before hand and prevent giving them one of the therapies that would in their particular case cause the immune reaction, you would have what is a hot subject here in the early part of the twenty first century, which is personalized medicine. Personalized medicine is all about understanding someone's genetic heritage and tailoring medications to that heritage. We think that our diagnostic would not only will apply to hemophilia, but could also be useful for analyzing a broad range of protein therapeutics that might trigger an immune response, which, by-the-way, is the number one reason that they fail their multi-hundred million dollar Phase III clinical trials. It is because they cause unintended immune responses in a small percentage of the patients and the FDA just will not tolerate that.

CEOCFO: ***Are you currently seeking funding or partnerships?***
Mr. Materna: We are. I am working to finish a three hundred thousand dollar angel investment round to finish off our genetic repair effort. Then in the Spring, Q2 2016, after we have made our announcement, we are looking to do an eight to ten million dollars Series A round to fund our work with the humanized mice. There also is a colony of dogs that have a natural version of the Intron 22 Inversion. We are going to try and cure the mice and then cure the dogs and we figure if we can cure a small mammal and then a large mammal then we will be ready to go to the FDA. We believe, for our investors, that we could actually have a fairly quick exit, because we know that when we get into Phase I/Phase II clinical trials we will likely be acquired by a big pharma company, to the tune of two to four hundred million dollars, perhaps more. That's what the big pharma companies are doing these days. They see a hot young biotech company entering clinical trials and they pay a premium to make it their own.

CEOCFO: ***Why take note of Haplomics, Inc today?***
Mr. Materna: People should be looking at Haplomics today because we are working at the very frontiers of what will be probably one of the dominant technologies of the twenty first century, which is gene engineering and gene repair. Our techniques could be applicable to a broad range of other diseases, basically any genetic disease where our body is not producing something it should for a genetic reason. We will be able to go in there and get it to start doing so. There is a long list of illnesses that fit that category, some more rare and some common. From just our products now, each have a billion dollar pipeline potential and we actually could be in clinical trials in two to three years. From an investment point of view it would be a pretty quick exit and could mean a fifty, to even a one hundred to one, return on capital.

Interview conducted by: Lynn Fosse, Senior Editor, CEOCFO Magazine

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Haplomics

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