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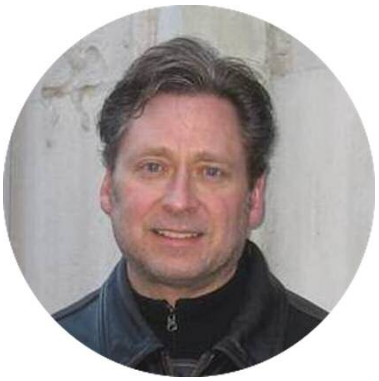
Ciclofilin Offers Hope in the Treatment of Hepatitis B Virus



Dr. Robert T. Foster
CEO
Ciclofilin Pharmaceuticals Inc.

CEOCFO: *Dr. Foster, what is the idea behind Ciclofilin Pharmaceuticals?*
Dr. Foster: The idea that we are pursuing is looking for a functional cure for Hepatitis B virus infected patients. If you look at the Hepatitis world, we have been able to effectively treat some of the viral liver diseases, most recently Hepatitis C. However, there is still no cure for Hepatitis B. So, the race for a cure is on. Chronic hepatitis B affects somewhere between three hundred and fifty million to four hundred million people worldwide. In fact, probably about one in three people, at some point in time, have been infected with the Hepatitis B virus. It is obviously a big problem. If you look at the mortality rate of Hepatitis B virus infected patients, about six hundred thousand to one million people die annually from this disease and its consequences. Again, there is no treatment. In a nutshell, our company is looking for a viable treatment. We are looking for a day where HBV patients can be cured and live free of liver disease.

CEOCFO: *Would you tell us about Cyclophilin?*
Dr. Foster: Cyclophilin is a host protein that has important properties, including enzymatic properties. In other words, you and I have Cyclophilin throughout our bodies. It is a ubiquitous protein. There are various types of Cyclophilins in humans, called "isoforms". Specifically, in the case of Hepatitis B, we are targeting something called Cyclophilin A. Cyclophilin A is one of these host proteins that is involved in viral replication. There are a number of steps involved in the viral life cycle. The virus targets the liver and, as such, has to first enter the liver cell, called a hepatocyte. Once it gains access to the inside of the cell it has to replicate and then eventually find its way outside of the liver cell, where the virus can then spread to other cells. Cyclophilins are involved in helping the virus to replicate. Viruses are either extremely smart or perhaps extremely lazy. Owing to this, they essentially hijack the host to be able to create progeny. By piggybacking onto the host they can ensure their propagation. Again, Cyclophilins in general are involved quite a bit in the viral life cycle. Therefore, if we can create a drug that targets cyclophilins, and inhibit the activity of these proteins, we should be able to inhibit the virus's ability to get into the cell, to replicate, and to find its way out. That is our mission; we are down-regulating cyclophilin activity involved in HBV infection.

CEOCFO: What have you figured out so far?
Dr. Foster: So far we have taken a fairly old drug called cyclosporine, which has been on the market in North American since the 1980s. Cyclosporine was primarily used as a drug following organ transplantation. In organ transplantation we suppress the immune system so that we turn down the body's ability to reject the newly implanted organ. Our current approach to HBV treatment involves taking cyclosporine and removing the immunosuppression. As such, we have created a drug in our company that has no ability to suppress the immune system. On the other hand, we have turned up the ability of this cyclosporine-based modification to bind a protein called, cyclophilin. Therefore, we have taken an old drug and have retooled it to bind and inhibit cyclophilin. By creating the drug in this manner we have targeted cyclophilins to specifically interfere with the Hepatitis B virus; Hepatitis B just being one of the many indications medically that are implicated with these cyclophilins.

CEOCFO: *Will the process be faster with the FDA because you started with a drug that was used before or does the restructuring start you at ground zero?*
Dr. Foster: The drug is considered to be a new chemical entity, so in a way it is a ground zero drug because it is brand new. I guess the distinct advantage that we have is that by knowing that it is like a new version of an older drug we can at least anticipate, from a pharmacologic point of view, where the efficacy and the safety issues can exist with these drugs.

Therefore, based on thirty plus years of experience with cyclosporine and based on the fact that we have in depth knowledge of what we have done with this drug, we have a very high degree of confidence that this drug will not display any sort of untoward side effects that are not anticipated. The single biggest side effect with cyclosporine for treating organ rejection is its toxicity to the kidneys. However, we have circumvented this problem by stripping out the immunosuppression. It seems the previously known kidney toxicity was related to the immunosuppressive properties and biological targets. We anticipate the FDA will treat our novel molecule the same as a new drug product.

CEOCFO: ***Where are you in the process of development today?***
Dr. Foster: We are very early in once sense because we have created a new drug. In another sense, however, we are not early. This latter point relates to the fact that our team has about two decades of experience working in the field. I've been working on cyclosporins for over 25 years. We have also previously created a cyclosporine-based drug that is now in late-stage clinical trials for another indication. Therefore, in that way I would say that we are well experienced and we have been working on these types of products for a long time. However, this particular product, which we call CPI-431-32, is quite new. We identified CPI-431-32 as our lead compound just over a year ago and we are taking it through its preclinical studies. Prior to advancing to trials in humans, we need to fully understand how our drug works from a safety standpoint, from an efficacy standpoint and to tease all of the different pharmacological activities related to his drug. We are working with a great group of people in our organization and with the Scripps Research Institute to better understand all aspects of our drug. Taken all together, we expect that it will take another eighteen to twenty-four months before we can begin testing humans in the clinic.

"From a human perspective I think what we have is potentially part of a cure for Hepatitis B." - Dr. Robert T. Foster

CEOCFO: ***Have you done some animal testing already?***
Dr. Foster: We have. We have completed a study in the transgenic Hepatitis B virus model. That was done recently with the NIH, the National Institutes of Health in the US. We showed that our drug has the ability to inhibit replication of the virus and that is specifically replication within the liver. The drug worked very well in this transgenic model. We have also conducted a study in Tokyo, Japan with a company called Stelic. That company has been doing a lot of work on fibrosis and cirrhosis of the liver. As I mentioned at the outset of this interview, Hepatitis B patients often progress to liver disease and quite a number of patients will eventually succumb to the effects of chronic Hepatitis B infection. Those effects can include liver fibrosis, liver cirrhosis and ultimately hepatocellular carcinoma, also called liver cancer. Therefore, in collaboration with the Japanese company, we looked specifically at whether or not our drug reduces fibrosis scores. And, in fact, our drug did exactly that. We saw an average fifty five percent reduction of the fibrosis score, which was statistically significant.

CEOCFO: ***What other approaches are there or have there been towards Hepatitis B? How is your approach different?***
Dr. Foster: Products are currently on the market for treatment of Hepatitis B chronically infected patients. One product is called Pegylated Interferon. Interferons stimulate the immune system; they give it a boost. However, interferon administration has been associated with numerous side effects. It is also given by injection, usually once a week. The other class of drugs used is called nucleoside or nucleotide analogs, of which five are on the market. They inhibit reverse transcription, so they interfere with the replication of virus. This class is therefore involved in the reverse transcription of DNA to RNA. This is the known mode of action for these drugs. However, there are a lot of things these drugs cannot do. For example, they cannot cure chronic HBV. Therefore, patients need to take these drugs for life. If the patient stops taking the NUC, the viral loads increase. We do our best to treat HBV patients with these drugs, but much work needs to be done to find a functional cure. Therefore, there are a number of companies investigating newer approaches to treating Hepatitis B. There are quite a variety of companies looking for new treatments. One thing that we are trying to do as a group of companies is reduce something called Surface Antigen, which are particles produced by the virus that can act as "decoys" to the immune system. High amounts of Surface Antigen can overwhelm the immune system and result in immune system exhaustion. It is expected that if we can reduce the Surface Antigen, we may be able to regain innate immunity. As expected, therefore, there are companies looking at ways of reducing Surface Antigen. There are also companies using RNA interference. They are trying to interfere with the way that RNA can produce proteins. This technology holds promise, but like so many new technologies, there can be drawbacks. The RNA interference treatments are given by injection and formulation of these products can be challenging. Our drug, on the other hand, is orally administered, which is generally more acceptable to patients. Our drug is a multi-modal or has effects on multiple pathways that work to interfere with a number of steps in the HBV life cycle. Ultimately, we anticipate that our drug will form part of the combination or cocktail of drugs used to offer a functional cure of chronic HBV. Hepatitis C virus treatment

similarly uses a drug combination, as the virus needs to be targeted in more than one way. Many companies are working on novel technologies but, for the most part, these technologies are early.

CEOCFO: ***How far will your current funding take you?***
Dr. Foster: Our current funding has probably taken us to about as far as it can go. Therefore, there is a shift that is taking us from early laboratory experiments in-house as well as with the Scripps Institute and the NIH, moving us now into financing strategy. For the next short while, we will concentrate on strategic discussions with venture funds and also possibly with pharma and biotech, as appropriate.

CEOCFO: ***Are investors showing an interest in Hepatitis B these days?***
Dr. Foster: Yes. Hepatitis B is probably one of the hottest therapeutic areas now. The virus is much more virulent that HIV and can lead to liver cancer. Liver cancer is the third most deadly form of cancer. Prior to the interest in HBV, much of the industry was focused on the treatment of Hepatitis C and that was where many research dollars were invested. However, we have now effectively cured Hepatitis C, so now the focus is on Hepatitis B; the next big thing.

CEOCFO: ***Why pay attention to Ciclofilin Pharmaceuticals today?***
Dr. Foster: We are highly confident that we have a good drug. From a human perspective I think what we have is potentially part of a cure for Hepatitis B. Therefore, I think we have a product that represents an important advance in healthcare that should positively impact patient life. That is speaking from the perspective of human health and quality of life. There is also a point of view from an investor. Given the pressing need for novel HBV therapies and given what has already happened in HCV therapy, companies working in this space, even at our early stage, do not typically stay small with small market valuations. If our product proves to be as good as we think it is, there is a good chance for a significant upswing in the value of our company. There is also the potential of licensing and acquisition. Liver disease is currently a very interesting field to watch.

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

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