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A new Cancer Target brings new Cancer Hope

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CEOCFO: ***Dr. Weickert, what is the vision behind Pacylex Pharmaceuticals?***
Dr. Weickert: Pacylex is developing a new first in class therapeutic to hit a new target in cancer. A researcher at the University of Alberta named Dr. Luc Berthiaume discovered a connection between a biological process called myristoylation and certain cancers, particularly blood cancers, like leukemia, lymphoma and myeloma. He also found that a drug that suppresses the process of myristoylation has a disproportionate impact on those leukemia, lymphoma and myeloma cell lines, killing them while sparing normal cells.

Additional research by Pacylex showed that in animal models, where you transplant tumor tissue into mice, you can completely regress or eliminate those tumors by administering an NMT inhibitor, NMT stands for N-myristoyltransferase inhibitor, called PCLX001 into those animals. In some cases, complete tumor regression or elimination was seen, with as few as five doses of the drug. This is what the company is now moving towards clinical study as a potential new dramatic therapeutic that could eliminate the cancers rather than simply suppressing their growth.

CEOCFO: ***What is myristoylation?***
Dr. Weickert: Myristoylation is a biological process of adding a small fourteen carbon fatty acid to the amino-terminus of roughly six hundred proteins in the body that are responsible for controlling normal growth and metabolism; what we call homeostasis. The myristoylation process is critical for certain regulatory complexes involved in certain cancers, like the B cell receptor complex, which is involved in modifying proliferation and pro-survival signaling in leukemia and lymphoma.

The B cell receptor complex has two different myristoylated proteins and when you inhibit myristoylation you completely disrupt the function of this complex; you eliminate the modification of a handful of these important pro-survival and proliferation factors. As a result, the cancer cells go into what they call apoptosis, or programmed cell death; those cancer cells basically become self-destructive. They commit suicide in a matter of hours to days.

CEOCFO: ***Why does the drug work? What is happening in the body?***
Dr. Weickert: Because of the importance of this B cell receptor complex in allowing the survival and growth of tumor cells in these hematologic malignancies, they are exquisitely sensitive to the drug. However, there is another factor. One of the two human enzymes involved in myristoylation; they are called NMT1 and NMT2, so it is pretty simple, one of those two enzymes is actually down regulated in these specific cancers, making the cancers even more sensitive than normal cells to an inhibitor of the remaining enzyme. Thus, you are getting and effect equivalent to what you call,

"selective lethality", by administering a drug to which the cancer cells are an order of magnitude or more sensitive than normal cells are.

CEOCFO: ***What are you working on right now? Where are you in the process?***
Dr. Weickert: We are currently preparing to file the regulatory authorization document called a Clinical Trial Authorization to initiate clinical studies at three sites in Canada. The company Pacylex is a Canadian company headquartered in Edmonton, Alberta and our three clinical sites are at the Cross Cancer Institute in Edmonton, Princess Margaret Hospital in Toronto and the BC Cancer Agency in Vancouver. Those three sites are expected to begin clinical trials sometime early in 2021. We are expecting to file for authorization to begin those studies by the end of this year.

CEOCFO: ***What is special about trial sites you mentioned?***
Dr. Weickert: These are three of the most prominent, if not "the" most prominent cancer institutes in Canada. They have an extraordinary number of patients and they have extraordinarily well qualified oncologists through which we can conduct the studies. We have principal investigators at all three sites that are primed to begin enrolling patients as soon as we have the authorization to do so.

In addition, our Chief Medical Officer, John Mackey, is a practicing oncologist and happens to be the Director of Clinical Trials unit at the Cross Cancer Institute in Edmonton. This means that he cannot be the principal investigator for the study, so we actually have a different principal investigator who has been recruited to actually perform and conduct the study at the Cross Cancer Institute. However, these are really marquee institutions within Canada.

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CEOCFO: ***What has been the response from medical people who are aware of what you have developed?***
Dr. Weickert: Medical people find it extraordinarily exciting to have a new mechanism and a new first in class therapy. In cancer, most of the therapeutic evolution that has taken place over the last five or six decades has been combination therapy. However, combinations only work when they are working through orthogonal mechanisms; mechanisms that are different at the root of how they affect the cells. Finding a new orthogonal mechanism that could potentially combine with other mechanisms to yield a better outcome for patients is a pretty exiting outcome.

We have physicians, not only in Canada, but also in the United States and in England that are standing by to conduct clinical studies of their own as soon as we have the authorization to do so. We have researchers at the MD Anderson Cancer Center in Houston, Texas and also at the University of Birmingham, who have access to a huge number of potential patients and they are both eager to begin conducting a study in acute myeloid leukemia, which we intend to start probably mid next year.

CEOCFO: ***You have been personally involved in a number of companies over the years. What attracted you to take on Pacylex? What do you understand about the whole process of development, dealing with the regulatory authorities and all of the pieces that go into it that will help smooth the way?***
Dr. Weickert: Those are two really good questions and I am going to separate them completely. The reason why I am exciting about Pacylex is that I have a long-standing interest in what I call life science diamonds in the rough. What these are to me are genuine medical breakthroughs, but they happen outside of the main stream ecosystem. For example, if this discovery was made at Harvard of Stanford or MIT, those institutions have a network that would immediately know how to help that new breakthrough reach investigators, investors, pharmaceutical companies and so on. However, sometimes when these new breakthroughs arise at places like the University of Alberta in Edmonton there is no infrastructure there, there is no ecosystem there that can help support those developments, and many times, real genuine medical breakthroughs do not make it because they cannot get the traction they need to get all the way through into the clinic and then through those clinical studies. Those are real losses! A great example of this is gastric ulcers. We know the two physicians in Australia who received the Nobel Prize for discovering that gastric ulcers were caused by *Helicobacter pylori*. However, what most people do not know is that there was a Greek physician named John Lykoudis,

who in the 1950's and 1960's treated 30,000 Greeks with gastric ulcers, using an antibiotic cocktail of his own invention, in order to cure them of their ulcers. He got a patent in Greece in 1961, but JAMA (The Journal of the American Medical Association) refused to publish his results and the Greek medical authorities fined him for malpractice. Because he was a Greek practicing physician, no one took him seriously and his innovation, which could have started treating people back at the beginning of the 1960s, was ignored and we did not start treating gastric ulcer patients with antibiotics and curing them until the turn of the millennia.

The second part of your question is what experience do I bring from the development and regulatory side that helps me understand what we have to navigate to get this product developed. I have been working in drug development for over twenty-eight years. The first fifteen years where with public pharma; companies with a lot of resources and a lot of experience in the team. What I have done in the last thirteen plus years is I have taken that experience out to startups, where that experience is not present from day one. In fact, most academic startup teams do not have significant drug development experience in their founding team. Therefore, I am bringing, not just the understanding of the business and the strategy and the engagement for investors and strategic partners, but I am also bringing an understanding of how to develop drugs. I have been the global project manager for oncology drugs, anti-infective drugs and other therapies earlier in my public pharma career.

I have an intimate knowledge of all the development steps from pre-clinical testing all the way through Phase III and NDA filing. I understand what the regulatory burdens are and what you need to show for an IND, for an end of Phase II meeting and for an NDA. However as well, in understand some of the advantages of certain regulatory filings like an Orphan Drug designation or a Fast Track designation, which can give you opportunities to engage with regulatory authorities more frequently and more openly than you would normally do with a drug in development. Also, things like Fast Track gives you a faster registration review. Orphan designation gives you a longer period of market exclusivity. I understand the different regulatory pieces necessary to optimize the development of a clinical asset.

CEOCFO: ***What have you recognized that you might not have known early on how to navigate the system?***
Dr. Weickert: There are many things that come around again and again. For example, not necessarily with Pacylex, but with another company I am helping, the priority review vouchers are an important regulatory tool for encouraging the development of compounds that treat diseases that would ordinarily be ignored from most large pharma companies, because the market is too small or it is mostly in the developing world. However, a priority review voucher is a tool that allows a company to get approval in six months or less. Normal approval takes roughly a year. That is the target for the FDA. Now, in a product in a very competitive landscape, where there are multiple companies trying to get their products on the market; going from a twelve month to a six-month review can be an enormous advantage of getting there first and getting your product launched first.

Pharma companies are willing to pay up to roughly one hundred million on average right now for a priority review voucher. In some cases, they have gone for over three hundred million. Therefore, a company's ability to obtain a priority review voucher can yield an early financial return for that company for a product that ordinarily would not get a return that fast. That can become a really useful tool. As I said, this does not apply to Pacylex, but that has come up with another one of my companies recently, where that priority review voucher might be a material asset for that business, because they have a product that is well fitted to potentially obtaining one if they decide to select that indication as one of their initial indications.

There are few things that are completely new, but there is stuff that comes up again and again. However, on the new side of the priority review voucher, just last month that expired for diseases that are impacting children, so there had been a priority review voucher program for certain childhood conditions and that has gone away. Now it is only still in effect for certain tropical and rare diseases. That is a recent change that is quite material for a number of companies and their potential products.

CEOCFO: ***What, if anything, has changed for Pacylex under the COVID environment?***
Dr. Weickert: We do not have face to face meetings anymore. Surprisingly little has changed in terms of our ability to continue to execute towards the clinical trials that I mentioned, except that when India, where we are making our drug substance, was shut down for several months in the early stages of pandemic, the ability to manufacture our drug was

also shut down. Therefore, we experienced a several month delay in our ability to obtain the drug necessary to create the capsules that would be used in the clinical studies.

CEOCFO: *What is your funding situation today at Pacylex?*
Dr. Weickert: Pacylex closed a seed round in February of roughly five million Canadian dollars. We are currently in the midst of a Series A, looking for twelve and one half million (US dollars). We do have some leads and are in negotiations with some companies. We also have some strategic interest, but we do not yet have a deal finished. Therefore, we are still doing our best to highlight the company and we are presenting at a number of conferences, most recently at the BIO Investors Conference last month, and in addition, the recent publication in Nature Communications of the research results on lymphoma, allow us a nice new opportunity to engage with people who have seen those published results.

CEOCFO: *Is cancer of interest to investors today?*
Dr. Weickert: Oncology has been very hot for a long time. In the last five years, there has probably been more investment in oncology than any other therapeutic area and it remains very attractive to investors. Although, because of the investment and the attractiveness, it is a very crowded space. There are an awful lot of companies working in that same space, but it is still very attractive.

Even the recent pandemic has not dimmed interesting in oncology, but it certainly has highlighted infectious disease as a neglected therapeutic area that perhaps deserves more interest from investors, as well as obviously, the interest it is getting from the governments that are attempting to support it. Yet, oncology is a very, very appealing area and one of the things that drives that is that there have been more transactions in oncology by large pharmaceutical companies than pretty much every other therapeutic area put together. Therefore, if that is what pharma is buying, that is what investors are going to be supporting.

CEOCFO: *What was unexpected in your finds so far?*
Dr. Weickert: The only thing that I would say that we have obtained since I joined the company almost three years ago, that we did not have plenty of evidence about before, is the toxicology results. Those are essential for going into the clinic. We have elaborated on and embellished the other results we already had, we have not learned necessarily, fundamentally new things. What we learned in the toxicology that surprised me the most was that dogs, one of the two species we used, do not have not have a very close homolog to one of the NMT enzymes in humans. When you are working in animal species you are using them as a surrogate for what you are likely to see in people.

What we learned in the tox study is that dogs, unlike every other species we looked at; mice, rats, pigs, monkeys, humans; those species are all ninety-four to ninety eight percent homologous in one of the two enzymes, NMT2. Dogs are only seventy eight percent homologous. That means that dogs, although they are a normal species that we use for preparation to do an oncology study or most clinical studies, and they are a species that the FDA agreed would be an appropriate species for us to use; much to our surprise they are very different with one of those two NMT enzymes. That was completely unexpected. The data was available somewhere, but we did not know that information going in, so that was a shock. You expect species to be closer when you are using them as a model system.

CEOCFO: *There are so many new ideas to evaluate. Why pay attention to Pacylex Pharmaceuticals?*
Dr. Weickert: There are some features about this drug that I have not described that are really important to think about. One is that this drug is oral, so you just take it as a pill once a day. That is really appealing. Patients can be medicating at home; they do not have to come into an infusion center like many cancer patients do. Number two; it is a drug that is very potent. In our in vitro assays it is ten times as potent as Dasatinib and Ibrutinib. These are two multibillion-dollar leukemia and lymphoma drugs that are on the market now. It is a great place to start, at ten times their potency.

Another really critical thing is that because we are working through a new mechanism of action, we have the potential to synergize with other drugs. Oftentimes, when you look at the crowded oncology field you think, "There is so much competition out there!" However, in our case we look at that crowded field and say, "Look at how many potential partners we have." We could potentially work with almost every drug out there, because we work through a different mechanism of action than they do.

The last really important thing is that this is tumor killing. We are not just inhibiting the growth of the tumor like many drugs do. We are actually triggering apoptosis, a programmed cell death in the tumors. As a result, this drug has the potential to achieve complete durable remissions in patients, even as a mono therapy, and it is exciting to have a potential mechanism that would produce a dramatic improvement in the care and the outcomes for patients.