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Issue: October 16, 2023

Disease-Modifying Mechanisms in the Brain and GI Tract with Risvodetinib for the Treatment of Parkinson's Disease and Related Disorders

Dr. Milton Werner
President/CEO

Inhibikase Therapeutics
https://www.inhibikase.com/

Contact:
Milton H. Werner, PhD
678-392-3419
mhwerner@inhibikase.com

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Interview conducted by:
Lynn Fosse, Senior Editor
CEOCFO Magazine

"Treating major CNS disease, which encompasses Alzheimer's, Parkinson's, ALS, etcetera, has been a 100% failure business for forty years. We persevere because our outcomes are very strong." Dr. Milton Werner

CEOCFO: ***Dr. Werner, what is the concept behind Inhibikase Therapeutics?***
Dr. Werner: Inhibikase was built to transform how we develop and establish utility for new medications to treat major CNS (Central Nervous System) disease in neurodegeneration. The way we have gone about that is by modeling human disease in detail, discovering the underlying biochemistry driving that disease. That led to the discovery of a series of targets that would have relevancy to how the disease works in a human being. We could validate in these models that those targeted pharmaceuticals are effective at halting and reversing the course of neurodegeneration in a living organism, which is a stark contrast from virtually every other company over the last forty years.

CEOCFO: ***Why? Has this approach not been tried before?***
Dr. Werner: I come from a long history of cutting-edge science. I am not trying to toot my own horn, but that is just my history in science. I have worked at the cutting-edge across cancer, and human development. I have always looked to find ways to solve problems. Since I grew up in the 1970s in Los Angeles, I am a 'TV' scientist, meaning I like to see what it is I am doing. This feeds into why I have gone about trying to identify how a process works before I try to modify it. However, that was not feasible in Parkinson's disease in the past.

It is not as if Inhibikase discovered all the tools necessary to model human Parkinson's, which is our primary focus. We have been able to make use of the tools created by many others and to collaborate with people who made those discoveries to bring to the table our tools in medicinal chemistry, pharmacology, and how to conduct modeling studies in a relevant way to human treatment. That combination of our efforts and skill set along with many others has pushed our knowledge forward, without being concerned for how long it will take or how complicated it could become; it just had to be done. That is one of the strengths of small companies in biotech: we are able and willing to take on the basic science initiatives to make new medications become more successful.

The problem has been that efforts of this kind were far less detailed and far less robust in the past, in part because they did not yield new medicines in the past. People didn't understand why they would spend three or four years doing all this if it was not giving us a better chance of success for patients. I would argue that now our chance of creating workable therapeutics is very high because we have done so well in reproducing human disease in animals where we can take everything apart and figure out how it works. That is where we think we are.

CEOCFO: ***Would you give us an example of what you found through your process that might have surprised you?***
Dr. Werner: My history in science goes back in time. I began as a student at UC Berkeley. A colleague of mine, Mark Kelly, who had trained elsewhere and was also at UC Berkeley doing some work, was one of the first people to put forward the concept of a "misfolded protein disease". Diseases like Parkinson's or Alzheimer's have these protein aggregates which we often refer to as plaques, and the idea was that these plaques only showed up in disease, so we needed to just figure out how to get rid of them. My mindset was that there was no guarantee that those misfolded proteins, or plaques, were actually causing disease, so we had to figure that out first.

It was not until 2015 that Inhibikase, as a company, formally got involved. We got involved because we made discoveries in certain medications that inhibit signaling enzymes like c-Abl and that we could model diseases like Parkinson's. We then demonstrated that the role of this plaque or misfolded protein is completely different than what people previously thought. People thought plaques cause disease, but our work showed that, at least in Parkinson's, plaques did not cause disease at all. Rather, plaques initiate a disease process that led to the identification of all the protein factors inside the affected neurons in the brain that are degrading in Parkinson's; similar discoveries have been made for how different neurons degrade in Alzheimer's. Those discoveries identified the targets. Had we not gone about attacking the problem this way, we'd would have nowhere to go. That was a transformative moment.

We performed what by today's standards is a relatively simple experiment; we introduced a defect into the brain of a mouse that mimicked the defect of Parkinson's in a human. Once introduced, we just stood there and waited for the disease to emerge. Because it is a slowly progressive disease, we watched the disease develop over time. We

watched the mice get sick and, because we could analyze the brains of different mice as a function of time, we could figure out what was changing over time. We saw protein plaques form that showed that although they are necessary to start the disease, they do not actually cause disease themselves. It requires the presence of an enzyme on the inside of the neuron to recognize that the plaque protein is present. That enzyme is called the Abelson tyrosine kinase or c-Abl, and it is really c-Abl that is driving all of the downstream events that degraded neurons in the mouse brain. Since we had already created medicines that could target c-Abl for other neurological reasons, we had this alignment between our medications and the efforts of us and others who developed ways to model disease. It was the 'ah-ha moment' and we knew exactly what to do. Within a few months of testing, we could show that we could fix a mouse that has Parkinson's.

CEOCFO: ***What did you see that made you realize plaque was not the cause?***

Dr. Werner: By the time we got involved formally as a company, there had been two sets of failed experiments, not because they were not thought through by two large pharma companies, but they were using antibodies to target these plaques in Alzheimer's. One was from Eli Lilly and Company; one was from Roche. Both companies were trying to remove plaque, which we know that in early clinical studies plaque removal did not result in a clinical benefit. Then in the middle of the 2010s, these companies reported the readout of five or ten-year prophylactic studies in geographically isolated communities in the world with a high frequency or high prevalence of Alzheimer's disease. They thought that they could treat them with plaque removal antibodies and that they should be able to prevent the population of people who are involved in a trial from getting the disease. Much to everyone's dismay, that was not what happened. Those antibody therapies had almost no effect. Therefore, we, as a company, decided to focus on the biochemistry of the disease to understand what role the plaque protein is playing.

We knew that the tools existed to introduce the lesion or Parkinsonism into one half of the brain and leave the other half of the brain in individual animals alone, so each animal had its own internal control. That was an important technical accomplishment because it showed that we do not have to imagine that every animal is exactly the same as every other animal, and certainly people are not. Instead, we could watch what happens in one side of the brain relative to the other side, and then in those experiments we could watch the changes in real time and know that they are meaningful in every animal. We watched the movement of these plaque proteins from outside the affected neurons to the inside and we saw biochemically that this enzyme, c-Abl, was amped up and activated. That particularly revealing because that enzyme plays a role in biology that is fundamental. If you are an embryo or a fetus, c-Abl is used as the primary signaling molecule for growth and differentiation. It drives unspecialized cells to initiate specialization, like to form nerves or organs or bone, etcetera. Once the organism is fully developed, including human beings, c-Abl plays different role, a protective one. In a mature cell or tissue or organ, c-Abl is there to recognize or sense abnormality. Whenever it senses an abnormality, c-

Abl sets off a cascade that is unique to the type of cell that it's in, turning on a program to kill that cell because our organs have many more cells than it needs to function. Abl's role is to kill the unnecessary things and to prevent toxicity from spreading, so in models of Parkinson's, that occurs by removing the neurons that might have acquired something toxic, like a protein plaque.

When we saw that Abl was the thing that was so important to the process, that allowed us to trace targets of Abl downstream that disrupt the biochemistry of normal neurons that are affected in Parkinson's, and then characterize them all. We then could use various medical or pharmaceutical agents to block different aspects to these pathways and show they have a predicted outcome. That was revealing. We were able to model the human disease well enough to have predictive outcomes from therapies given to animals. In our case which was unique, we could treat the animals well into their disease course at the same dose we would give to a human being to accomplish the same goal and change the course of the disease. That is rare; usually you cannot do that in an animal and you have to give them much more of the drug because of the way pharmacology in animals work versus a human, as they are much smaller than us. In this case that was well matched so that we could mimic the human therapy in these lower organisms.

CEOCFO: ***You mentioned tools you developed; what have you figured out that is allowing you to get so much further than others?***

Dr. Werner: It comes in two ways. On the medicinal chemistry side, we are working in an area, the Abelson Tyrosine Kinases, which have been the targets of cancer in therapies since the early 1990s. The first personalized medicine, in fact, was an inhibitor of an Abelson kinase. That drug was called GLEEVEC® (imatinib mesylate). It was built by recognizing and targeting a mutation in an Abelson kinase that caused a blood cancer; the inhibitor could 'fix' the mutation and suppress the cancerous outcome. The problem was that the Abl family is composed of enzymes and those enzymes are so similar in their active site that it is hard to have a drug select for a subset of those members of the family. Because you cannot select just the ones that you want to target for a therapeutic purpose, you can get many more toxicities and side-effects from a new drug than you intended. Those off-target effects limit the size of the patient population you can treat. If a thousand people have a fatal cancer and you are going to give them very bad side-effect to suppress that cancer, well that is probably ok. However, you cannot give that same side effect to a million people because the risks are too great.

We used our visualization approach, which is called RAMP™. It is a medicinal chemistry approach that learns from prior experience that we have had in the industry. You can think of it like an AI (Artificial Intelligence) influenced approach, even though it is not that sophisticated. RAMP could recognize how to discriminate the differences between members of the same enzyme family. We then had a test to evaluate whether we target just a subset of the Abl family by looking at how the molecule is broken down in a living organism, what's called its metabolism. We predicted the drug should have a good safety profile if we could predict how it is being broken down in the body, but it is rare

to be able to design the safety of a drug into a new chemical entity. Here we sort of did that, and it turned out to be much more successful than we could have ever imagined. We predicted what the side effect profile might be like and how to improve it and then it turned out the drug was even better. RAMP™ is one of the major tools we implemented.

The other major tool was our willingness to do the brute force research science. Because I could never find anybody to pay for it, I used my background as an academic scientist and former professor at the Rockefeller University in New York City to go to the typical funding agencies like the National Institutes of Health, and put in a grant saying what I would like to do and why. We received our first grant in 2009 and subsequently went back and asked for a lot more money over a period of years. Ultimately, we ended up receiving $12 million from The National Institutes of Health, with additional funds coming from the Michael J. Fox Foundation, and several other public funding agencies. That is how we were able to do this kind of risky science because it was not tied to an investor dollar or to an equity sale, where there are far more restrictions on your ability to dream out loud and pursue the hard science. That was very helpful for us.

CEOCFO: ***Would you tell us about the orphan drug destination from the FDA?***

Dr. Werner: That is a recent accomplishment from early October. We work in Parkinson's broadly, although Parkinson's disease has many variations. Parkinson's disease afflicts about 1 million to 1.2 million US citizens, and about 90,000 new cases a year are thought to be diagnosed. It is growing at about 4.5% to 5% a year and the population is ageing. There are many forms of Parkinson's-related disease, some more focused on cognitive defects such as Dementia with Lewy bodies (DLB), where Lewy bodies is sort of the descriptor of the Parkinsonian plaque protein. There is another, rarer disease called Multiple System Atrophy or MSA. MSA falls into the set of diseases that are known as orphan diseases. That has a formal definition in the US law as well as the EU. If there are less than 200,000 prevalent cases, the commercial market is quite small, so that limits what a developer could earn from developing a product and recovering the costs. To justify the expense of research and development to provide some benefits to the manufacturer who is developing those therapies, the orphan drug designation was created. It provides some regulatory and commercial advantages if the drug is ultimately approved.

In this case, the same drug we use for Parkinson's disease has applicability in MSA. Why is that? Well, we developed models with our colleagues in MSA, which is a very distinct disease from Parkinson's, and showed that the same mechanisms may be present in most diseases, which was unexpected. We could show that when we give our drug Risvodetinib, also known as IkT-148009, we could modify that disease. When we had all of that data, even though that was in the preclinical setting, we opened an Investigational New Drug application known as an IND, with the US FDA. We are currently doing the same thing in Europe, although that process is not as far along. That gives us the regulatory access to starting trials in humans. It also may be of interest from a

subset of pharmaceutical companies to help pay for some of these trials. However, we do not have such partnerships established yet.

CEOCFO: ***Are you looking for partnerships today?***
Dr. Werner: We are involved in a lot of business development discussion. We think we have cracked open the door to gain access to an area of medicine that has been intractable to treatment. While Parkinson's disease has a lot of medications that can handle symptoms, none of those medications slow down the progression of the disease or reverse its course and we are interested only in reversing its course. There are plenty of symptomatic solutions. In our case, we are seeking collaboration with larger companies as we have developed a set of molecules that are quite unique.

We are now at Phase 2 in Parkinson's and if we raise the resources, we will plan to run a Phase 2 program in MSA. MSA has a real advantage as an orphan disease with a smaller market, while Parkinson's is a very large market so it is a much bigger trial. In MSA, since there are no beneficial treatments, the number of trials and the size of those trials are reduced since we do not have to show a benefit over existing medications. MSA is also very aggressive so measuring a treatment benefit is easier. A more aggressive rate of disease allows us to have a larger measurement window to see the effect of a new drug. We are looking aggressively for partnerships in MSA because it is in many ways an easier trial to run in a patient population that is much more at risk. If we are right in MSA, we believe we will be right in Parkinson's disease. However, it is going to take longer in Parkinson's disease to prove that.

CEOCFO: ***Are your methods and tools something you might want to share independently, or is it important to keep them proprietary?***
Dr. Werner: Our medicinal chemistry approach is a proprietary approach for us. It is less sophisticated than it sounds. It is experiential and instinct-driven and based on knowledge that we already have from the studies of many other people and organizations. There are several companies that have taken different approaches to inhibiting the c-Abl enzymes. One of those companies has a collaboration to apply our knowledge to some things they developed to see if their molecules have utility that could compliment what we are doing with Risvodetinib. Those experiments are just underway.

The other aspects of what we are doing in the areas of modeling disease we accomplish by collaborating with a lot of people. We sort of bridge between academic and for-profit businesses. I am the type that is willing to do just about anything to solve a problem the fastest way possible because there has been no progress in this field for decades.

CEOCFO: ***Why should the medical and investment communities pay attention?***
Dr. Werner: Inhibikase is a small company. It is suffering the woes of the public marketplace like every other small company like us. We are quite unique and our trial work has thus far been very promising. Our understanding of the mechanism disease of Parkinsonism is without precedent in our view. We are recognized by our medical and academic peers and we publish at the highest level. Investors have

underappreciated that because the patience level is limited. People expect to see outsized returns in twelve months or less in today's marketplace. That has been true since the downturn of the market that began in 2021. We have been caught up in that slide and have seen an incredible amount of volatility in the market. Despite this, we continue to grow our value proposition and productivity as a company. While there is a fundamental disconnect between medical outcomes and accomplishments and market valuations, we are continuing to execute on our programs and believe that the market will recognize this value as we further validate our very promising programs in the clinic.

Treating major CNS disease, which encompasses Alzheimer's, Parkinson's, ALS, etcetera, has been a 100% failure business for forty years. We persevere because our outcomes are very strong. They are without almost any precedence in the medical community and the pharmaceutical industry, and people are looking to see if there will be a positive clinical benefit. That is the big barrier. There has been one actual success, LEQEMBI™ for Alzheimer's disease, that was recently approved even though it has a modest benefit and unclear if that benefit will improve over time. However, LEQUEMBI™ met a clinical trial significance standard, the first to have done so, after many failed experiments. The failures in this area of medicine are not because the companies were thinking poorly or acting badly. Many companies have and continue to do robust work and still fail; everyone has.

That is where the challenge comes from the investment side, it is whether you can hang in for two or three years. This is one of the reasons we are looking to partner on the MSA work, which could have a six-month trial and have an outcome that could be quite compelling. If it is compelling because of the rate of the disease and greater ease at seeing a benefit, that means we could see a future with a success in formal Parkinson's disease, because the mechanisms are so closely linked in our minds between MSA and Parkinson's. An outcome in this area is just what everybody is chasing. Once you start to see more than one company having these outcomes, that is when you are going to see the valuation recoveries at least within the companies that are working in major CNS disease. Until then, you have to come up with every way you can to survive. Fortunately, we have a strong cash position and have access to non-diluted capital through federal contracts and grants in ways that many other companies do not. That makes Inhibikase a stronger company and hopefully we will be able to support our activities until we reach those important medical milestones.