NO ONE GETS BETTER WITH PARKINSON'S DISEASE:

UNTIL NOW

Dopamine Reduction Therapy to Conquer Parkinson's

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A NOVEL APPROACH TO TREATING PARKINSON'S DISEASE

Parkinson's disease is currently understood as a deficiency of dopamine in the brain cells that control movement. Our research shows exactly the opposite: that Parkinson's disease is an *excess* of dopamine inside those brain cells. There are strong, consistent data showing that reducing dopamine reverses the pathology of the disease. An already available drug, RB-190, has been shown to reduce the levels of dopamine by inhibiting the key enzyme for its synthesis (by blocking an enzyme called tyrosine hydroxylase). Because RB-190 is an FDA approved drug, we can build on existing data and start a clinical trial for Parkinson's disease at mid-stage saving time, effort and money. The FDA confirmed that the next step in development would be a mid-stage (Phase 2A) clinical trial.

When I started to study ways to treat Parkinson's, I saw similarities to my experience investigating the once standard of care for heart failure. For that disease, standard practice was to treat patients suffering from worsening symptoms using with increasing amounts of catecholamines (e.g., adrenaline, noradrenaline). They responded positively at first, but in time the medicines caused their condition to deteriorate. This counter-productive response led me to consider whether *less adrenaline* and not more might be the proper treatment. Further investigation proved that hypothesis right: Beta Blockers—which block the action of adrenaline, protecting the heart from its toxicity and slow the beating of the heart—were then developed and are now the standard treatment. I and my colleagues had turned the standard of care for cardiovascular disease upside down.

This experience gave me the courage to question the current strategy of giving Parkinson's patients ever increasing amounts of the dopamine precursor levodopa. Just as for heart failure, our analysis suggests the appropriate treatment for Parkinson's is the opposite of the present standard of care—lowering the amount of dopamine and not increasing its amount or activity.

There has been a regrettable lack of progress in treating Parkinson's disease – in fact, there have been no new approaches to treating the disease since the 1960s. And no existing treatment slows, stops or reverses the inevitable worsening of the disease. Our novel approach represents an incredible opportunity for patients and their families as well as investors.

A Personal Motivation

As my buddy Ivan dwindled due to his Parkinson's disease, his doctors increased the dose of his dopaminergic medicines, and then added more medicines to increase the activity of dopamine in his brain. But doing so did not slow his decline. I asked, "if Parkinson's is a disease of dopamine deficiency, then why isn't Ivan experiencing any benefit from these treatments?" There was no scientific answer that made sense to me, so I sought to understand why this was so.

The first step was to measure the amount of dopamine in the brains of Parkinson's patients. The traditional method is to measure dopamine in the brain tissue; however, the level of dopamine in brain tissue does not directly relate to the function or dysfunction of the brain cells that control movement. We chose instead to determine the dopamine level inside the brain cells themselves.

We determined that the amount of dopamine inside the brain cells that control movement is much higher in Parkinson's disease, meaning that these brain cells known as dopaminergic neurons *experience Parkinson's as a state of dopamine excess*, which is toxic to these brain cells. We discovered that Parkinson's is a disease of dopamine excess (and therefore, toxicity). This is in direct opposition to the standard teaching.

What Does the Science Teach?

In the 1960s, data were published that showed that brain tissue levels of dopamine were markedly reduced in brains of people who died with Parkinson's. To test the effects of increasing dopamine, patients were treated with levodopa, which the body converts into dopamine. This treatment resulted in almost immediate improvement in movement. Based on subsequent clinical studies, the treatment became the standard of care, with the first drug approved by the FDA in 1970.

This is the standard of care for Parkinson's disease today. And over the last five decades, we've learned that these dopaminergic therapies do reduce symptoms, but they do not address the underlying disease. People do improve when given these drugs, and while the drugs are superior to a placebo, the improvement is typically 6-9 months and likely requires increases in doses of the medicines to maintain the improvement. To date, no randomized, placebo-controlled clinical trial has been conducted for longer than 9 months, so the actual duration of benefit is not known.

In parallel with these clinical studies, laboratory data show that the level of dopamine most relevant to movement function and dysfunction is not the tissue level, as reported in the 1960s, but rather, the intracellular (and more specifically cytosolic) level of dopamine – the amount inside these dopaminergic neurons. Too little dopamine inside the neurons means that these cells cannot send messages to other cells which is necessary to initiate and control movement. And too much dopamine inside the neurons leads to toxic effects, meaning that these dopaminergic neurons will become dysfunctional and over time, die off. So too much dopamine in these neurons also means that these cells cannot send messages to the other cells which is

necessary to initiate and control movement. In a person with Parkinson's, symptoms would be similar if dopamine were too low or too high within the neurons, which means we need to know the dopamine levels –this information can't be inferred from the usual clinical tests.

THE BREAKTHROUGHS

We discovered that the amount of dopamine free inside the dopaminergic neurons is high. And it is not a little bit high. It's very high. The Figure shows the level is 87% higher than normal in the caudate region of the brain and 361% higher in the putamen, the two areas that control movement). This may be why dopaminergic therapies don't "fix" the disease – there is already too much dopamine in these brain cells. (In a separate White Paper, we discuss how drugs such as levodopa still work, at least for a while, which is important to understand given the data showing that reducing dopamine is advantageous.)

A common mistake in biology is to declare victory after discovering a new mechanism of disease. Many times, those scientists learned later that the discovery was an epiphenomenon and not a causative or treatable target. This is why the laboratory data with RB-190 are so exciting and important.

Peer-reviewed publications establish the effects of RB-190 (alpha-methyl-p-tyrosine) as it reduces levels of dopamine. In each of these publications (which used a total of 8 laboratory models of disease) this dopamine reduction therapy reverses each measure of disease pathology that was measured (see figure below), including levels of oxidative stress, deposition of alpha-synuclein, rate of neuron death – including by blocking three biologic pathways causing cell death by apoptosis – preserving brain structure, restoring movement and prolonging survival. None of these studies showed any negative effects.

RB-190 tested in nine publications using eight models of PD: RB-190 reverses disease pathology in every model.

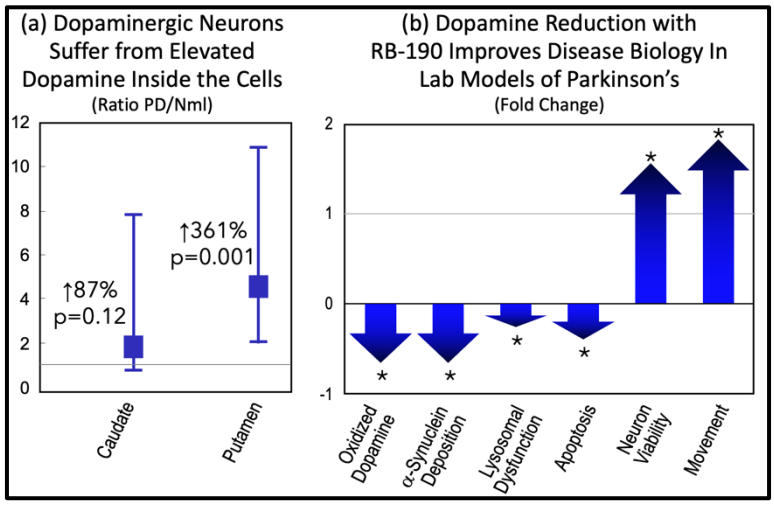

Figure. (a) In each brain region responsible for movement, the intracellular level of Parkinson's is elevated. These levels represent the free dopamine that is not sequestered in the vesicles that exerts toxic effects on the brain cells. (b) The benefits of dopamine reduction with RB-190 in reversing pathology of the disease are represented in summary.

In several diseases, the literature teaches that the short-term and long-term effects can differ – and at times be opposite. Drugs helpful initially can be toxic later, and those with side effects when administered can save lives in the long run. The disparate short-term and long-term effects of dopaminergic therapies represents an opportunity. By understanding the risk of

reducing dopamine, we were able to show the FDA a plan to minimize risk short-term. And based on the science referenced here, we can optimize the dosing regimen to see long-term benefit, which we anticipate as early as 3-4 months within initiation of therapy with RB-190.

What does this mean exactly? Current therapies are inadequate. In part that may be explained by our discovery that dopaminergic neurons experience the disease as a state of dopamine excess, and therefore toxicity. Dopamine reduction therapy with RB-190 is shown in multiple laboratory models to reverse disease pathology.

Formal engagement with the FDA via pre-IND and Type C meetings confirms that the next step in the development of RB-190 as a treatment for Parkinson's is a mid-stage (Phase 2A) clinical trial, which now requires FDA approval of an IND (investigational new drug) application.

THE TACTICS FOR DEVELOPMENT OF RB-190

Right Brain Bio was formed to develop and commercialize RB-190 for treatment of Parkinson's disease, and with our expertise, we can do so in a time and cash efficient program.

RB-190 is a repurposed drug, which means that it was previously developed for a different use. In the case of RB-190, Merck developed it for treatment of high blood pressure caused by a rare cancer that produces high levels of dopamine. This tumor is so rare that RB-190 would have earned orphan drug status if that term existed back then. Following its approval in 1979, the drug's use for over 4 decades has not revealed any new safety issues, which is reassuring when investigating its use in Parkinson's because many drugs fail in development because of surprising safety problems. And this experience with extensive use of the drug means that safety problems are not a significant worry for RB-190.

The FDA embraces the value of such prior data when developing drugs and so a separate approval pathway allows the developer of a repurposed drug to use the existing data. This is why Right Brain Bio does not need to launch a preclinical program in order to launch a clinical trial. And this is why Right Brain Bio can skip Phase 1 and move directly to Phase 2 clinical development. The time and cash savings for this development pathway (a repurposed drug using the FDA's 505(b)(2) path) are huge.

And repurposed drugs can be highly successful. Two repurposed drugs were recently approved for new neurologic indications – Austedo and Ingrezza – and each earned more than $1B within a few years. Thus, as a repurposed drug, RB-190 is cheaper and faster to develop with the opportunity to generate huge revenue.

Right Brain Bio employs a disciplined, stepwise development path built on a solid foundation. That foundation consists of the low-cost work to prepare RB-190 and Right Brain Bio for launch of the initial clinical trial, including the discoveries, the granting of the key patent, engagement with the FDA, recruitment of a first-rate Scientific Advisory Board, identification of investigative sites and determination of a drug manufacturer.

The next key landmark is clinical proof of concept to validate the laboratory proof of concept data already published. Our discussions with experts showed we needed to demonstrate

tolerability of the drug. If the current understanding of the disease is correct (and Right Brain Bio's is wrong) then people with Parkinson's would not tolerate taking this drug (RB-190). Thus we can quickly justify our claim for the potential of RB-190 by administering it to a small number of Parkinson's patients and seeing whether patients will tolerate this novel dosing strategy proposed to the FDA.

The clinical trial we propose will require less than 20 people be treated with the drug for a period of not more than 3-4 months.

IMPORTANT PRECAUTIONS

Important: No one with Parkinson's or a clinician treating the disease who reviews our approach should attempt to seek the commercially available version of RB-190. That commercial drug is only available in doses that are very likely to be too high to be safe to use in people with Parkinson's and their use appears likely to cause such worsening that a Parkinson's patient could find themselves hospitalized and/or in an akinetic state. Do not use the commercially available version of the drug.

Right Brain Bio has proposed a dosing regimen to the FDA that data suggest to be safe, but are not proven to be safe. The FDA did not reject this approach. The use of RB-190 in any form should only be considered within a clinical trial, which we've designed and vetted. With funding, we will submit this protocol to the FDA for its approval to begin the initial clinical trial. The efficiency of developing a repurposed drug is amplified by inside knowledge of regulatory processes, advantages of lean teams and defined triggers for advanced work such as reformulation and IP expansion.

DISCLAIMER

This document represents the interpretation and synthesis of data and clinical phenomena to illustrate the scientific rationale for development of RB-190 as a treatment for Parkinson's Disease. None of this information is reviewed by the FDA or any other legal authority and is intended as an introduction for Right Brain Bio's proposed investigations. None of this information should be used as justification for treating any people with Parkinson's, particularly given the likely risks when treated with available dose strengths of alpha-methyl-p-tyrosine. Right Brain Bio does not accept any responsibility for use of this information for any clinical decision making, whether direct or indirectly related to the materials within.

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