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Canadian Biotech CEO on the rACE2 to Neutralize COVID19 and Beyond

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"Why look at JN Nova? **This is a very good investment opportunity in a company that is largely supported by non-dilutive funding. We are developing a product that will have an impact on subsequent emerging COVID variants, and it will be developed for acute kidney injury or AKI and potentially for ARDS by inhalation. Recovery from both pathologies is dependent upon ACE2 replacement. AKI is clearly a major unmet medical need, and with financing, we will ensure the company's growth to support a full clinical proof of concept in this field and generate a major value inflection as we enter the public market." Dr. John Gillard**

CEOCFO: ***Dr. Gillard, what is the idea behind JN Nova Pharma Inc?***

Dr. Gillard: JN Nova is developing a highly potent pan-COVID therapeutic agent, with potential for acute kidney and lung protection. With my co-founder Dr. Nathan Yoganathan and our prior company, we had an excellent experience working with the National Research Council of Canada Human Health Therapeutics in biologics development. My personal objective behind forming the company was to use, I think, an extension of my life's experience as a chemist in molecular and mechanism-based therapeutic development, to address this emerging COVID19 crisis. So that is why we sought to immediately work with the NRC team to identify a molecular target, because we knew they were able to engage in molecular design, in-vitro and in vivo testing, and ultimately biomanufacturing if we were able to get funding.

We also needed to ensure that the chosen target for inhibition of the viral infection mechanism would be safe for infected patients. So at such an early point in this pandemic, it was also vital to identify translational clinicians who would help us evaluate the safety of this target and the likely patient populations who would benefit from the drug.

The plan then was to use the human ACE2 as a competitive target of the virus, to act as the molecular trap, we did this by designing an equivalent, but very smart, very potent, very high-affinity version of the human ACE2 target. Delivered, so that the virus has to bind to the trap,

not to the human ACE2 target and therefore does not infect the lungs or airways. When it became apparent that the virus also caused the loss of ACE2 when it infected people, we also wanted to help people to recover from what the virus does to our bodies, so we chose to select the drug candidates with both potent viral trapping mechanisms and systemic ACE2 replacement.

The NRC reviewed and awarded the project their internal Pandemic Response Funding status and we established the company as an independent partner, licensed the emerging technology and raised capital and major grants from the Federal Government of Canada.

We are now raising financing for the next development stage.

CEOCFO: ***Has there been much support for your efforts?***
Dr. Gillard: This project was extremely well supported by the commitment of The Human Health Therapeutics research groups of the National Research Council of Canada who have past experience in making biological products of this nature. We have 25 senior scientific members of the NRC-HHT here in Montreal and in Ottawa, Ontario, with whom we have worked in the past. They have committed their full development resources along with the bioanalytical and assay development skills of biological products, to actually get this done for us. It was complicated to have access to animal viral models and doing detailed organ toxicity in viral models in animals of COVID19 is pretty difficult. These have all been done in the NRC MSL3 facilities. Also, we are supported by the Mt Sinai Hospital Tannenbaum Research Institute and the Ottawa Hospital Research Institute kidney research department who has applied their experience in renal models, so we can measure all of the biomarkers, simply in the blood and urine that are needed for clinical trials. We have had aid from various federal government supporting agencies to get this early work done.

CEOCFO: ***Has the plan changed?***
Dr. Gillard: Not so much for our teams and a lot has been learned that supported our concept.

What we said well over a year ago is that this pandemic is going to roll out through various cycles, and we are going to see multiple phases of it as different variants escape immune protection. We have had to ensure that our approach was indeed independent of all of these changes and we have since shown that every mutant form known is fully blocked by our chosen drug candidate, and this is the way it will likely be in the future, whether future variants are really dangerous like Delta, or more widespread, like Omicron.

The second point was, why are some people so vulnerable and what can we do to block what actually makes these people so sick? What are the markers of the vulnerable groups and what happens to them?

Again, this turns out to be related to the ACE2-loss mechanism, which is induced by the viral infection. By replacing the lost ACE2 with our drug candidate, we will have a special therapeutic impact on people that have pre-conditions like cardiovascular, kidney, and diabetic conditions. These groups are very vulnerable to the loss of ACE2, in their lungs or in the

kidney, and in the case of COVID infection, those are regrettably the two clinical events that result in high mortality in the ICU. It would probably also have an effect on long-haul COVID, so there is an entire category of SARS COV-related therapeutic impacts that the drug will have.

We've also collected evidence to be convinced that the longer-term use of this therapeutic class will be for independent clinical uses in acute kidney injury and in acute respiratory distress, which can be induced by bad infections and sepsis. After COVID, that is really where we would like to take the product, clinically.

CEOCFO: ***What can you tell us about why the drug works and how it works?***
Dr. Gillard: There is a long answer to your question, but essentially, it is a replica of the human ACE2 target, which can also trap the virus, but it can also replace the lost ACE2 enzyme in the body, which is what is responsible for so much longer-term toxicity.

We intended to develop a therapeutic agent against this SARS-CoV-2 viral strain, with a view for it to be a very potent viral neutralizer in the short term, but also to maintain full activity against likely emerging mutants, as we fully anticipated would happen. And frankly, this is the way this pandemic did evolve. Viral mutations changed the susceptibility to previous immune responses and lessened the protection from vaccination and antibodies. Therefore, we wanted to have an approach that would be sufficiently powerful against all of these likely emergent strains, especially since we would need to have longer-term therapeutic applicability for a drug to be considered a therapeutic candidate. The actual target of the virus on ACE2 is in a different domain from the enzymatic domain, so our changes in the trapping domain have been made to maintain full ACE2 enzyme activity. This drug is also known as a biological, delivered with what we call an Fc-fusion protein. So we have a drug that has very distinct properties from the competition.

There is a whole range of clinically approved Fc-fusion proteins, whether we are talking about anti-arthritis drugs, or anti-cancer or immune drugs, which are the primary biological agents in therapeutic use. These drugs use this delivery approach because the Fc unit can be modified to deliver proteins and biological agents into the body with a nice distribution, specifically into some cells and organs, and also can activate the immune system. We have avoided immune stimulation and the drug has a long duration of action in the body. It will have distinct qualities in preventing acute kidney injury, or in facilitating recovery from acute kidney injury in COVID patients.

CEOCFO: ***How does your approach compare with some of the other ideas on the table?***
Dr. Gillard: In the beginning of the pandemic, the therapeutic approach was to make antibodies against the viral spike protein. Antibodies were targeted to very specific small segments of the virus spike, hence very subject to minor changes in the virus. We said that we want to use something similar to trap the viral spike protein, but not with an antibody because as we know, antibodies lose their effect. Emerging mutations in the spike protein have rendered them inactive against all versions of the virus. Also, we now know that prior immunization, which also makes

specific antibodies, is losing its effect over time because the segment that the virus is presenting to the antibodies is no longer the same as that targeted by the original vaccine. This would call for constant new vaccine generation and mass distribution again.

However, what we are doing is presenting the human ACE2 target itself, but tuned by making molecular changes, to give an extremely high affinity for the virus. The virus cannot mutate to avoid its own target, or if it does, it will have a very reduced infectivity.

We also have designed these drugs to provide this ACE2 replacement enzyme in the organs of concern. A single dose gives a 3-to 5-day enzyme replacement, whether it is the lungs or the kidney, which is really enough for the body to recover when we have dramatically reduced the virus That is the big difference from other viral trapping drugs like antibodies.

CEOCFO: ***Would you give us some examples?***
Dr. Gillard: Who else has gone out there with this approach? There have been a couple of initial approaches with unmodified ACE2 targeting, one that is continuing is by a company called Apeiron. Their approach is to deliver just the ACE2 enzyme, which is the same idea, but they did not tune it to have the extremely potent cross-mutant inhibition, and it has a short half-life which necessitated multiple daily dosing. In a way, they did not make it any more fundamentally competitive to trap the virus than the actual human lung ACE2 target. Our drug is nearly a million times more potent in trapping the virus than the natural ACE2. That is remarkably it, in terms of this concept, which is somewhat amazing because if you talk to any scientist, they will tell you that the fundamental approach by this virus is to attack ACE2 and wipe it out from the lungs, and this is a major cause of severe injury!

The other current drugs that are approved, let us take the Pfizer drug, for example, is to tackle a proteolytic enzyme that the virus needs to use to propagate itself. This is a sound approach, provided the drug reaches the virus and the enzyme is specifically inhibited without side effects to the host. This specificity is hard to achieve for viral replication, which uses very similar enzymatic processes as their host, for example, remdesivir. My first major anti-viral success was with 3TC, for treating HIV, which was remarkably effective and selective in doing this, so this is a holy grail for pure anti-virals, which is not achieved yet for COVID. Also, none of these drugs helps with replacing the lost ACE2 and preventing subsequent organ damage.

CEOCFO: ***What are your next steps? Where are you?***
Dr. Gillard: We are in biomanufacturing.
We have produced what is called the Master Cell Banks to produce these agents. We have transferred the bio-manufacturing process from our NRC partnership to our GMP biomanufacturing facility, with the anticipation of running the clinical trials towards the end of the year at this point. Biological product development, during and post COVID, has been really complicated for those that did not have access to large scale-up biomanufacturing facilities and to get access to raw materials for biomanufacturing, and so on. However, we have a truly committed

group who have brought these timelines forward and are proceeding with exceptional diligence to bring forward products for clinical trials.

We have also developed a nebulized formulation so it can be inhaled. In animal models, it works very well. It goes straight into the lung and gets high local concentrations in viral trapping. We just simply trap the virus and stop it from infecting you. There is strong initial evidence for ACE2 replacement being a significant therapeutic mechanism in acute respiratory distress (ARDS) so this is the next clinical target for the inhaled version of this class.

CEOCFO: ***What is the funding situation for JN Nova? Development is always expensive.***
Dr. Gillard: Biological development is very expensive! We have been very well supported with Federal government financing in Canada through what is called the Industrial Research Assistance Program. In this case, it is dedicated to bringing novel COVID19 therapeutics to the clinic. We have 25 people working here in Montreal and Ottawa, supporting all aspects of product development. As we produce the material, which is currently is in manufacturing, we will be ready to run clinical trials, for which we have excellent non-dilutive funding. We have good affiliations with translational clinical units here in Canada, and also with a couple of major US universities, and of course, there is a lot of interest coming from Asia. We have had several dedicated private individuals who have financed the company, along with the founders. We now have reached major milestones to engage in advanced discussions to bring through a Series A closing. That is where we are going, with a lot of interest from the US!

CEOCFO: ***Is it easy for potential investors to understand?***
Dr. Gillard: I think it initially depended on the investors' perception of the urgency vs duration of the COVID situation. Most investors saw the likely COVID product lifetime as being short and vaccination removing the need for therapeutics. Mutation and virus evolution have changed this, it is now viewed as a likely chronic disease, for which break-outs must be treated and our approach is considered well adapted for hospitalized patients as well as for inhalation treatment in non-hospitalized patients.

In addition to COVID anti-viral efficacy, our drug's mechanism is shown to be very effective in animal models of AKI, so for patients who have a renal deficiency, and have a very high probability of acute kidney injury (AKI), this is a great advantage of our product now seen by investors. Namely that in treating hospitalized COVID patients we will have a means of assessing this product to prevent exacerbated organ injury.

Therefore, I think that our knowledgeable investors are now looking at it and saying, "Yes, this is a multimillion-dollar market, this truly is a justified approach to an unmet medical need and you will demonstrate this early on, with non-dilutive funding."

Market valuations of biotech companies with potential renal treatments are high. Major drug companies are looking to in-license therapeutics for AKI if the approaches are proven and safe, and which have a mechanism that is understandable and has been measured, with predictable

biomarkers, in a proof-of-concept clinical trial. A relatively straightforward way of doing an initial clinical trial is to show this in hospitalized patients for whom prevention of acute kidney injury is to be evaluated. Patients who have renal vulnerabilities will be assessed on how their full range of renal biomarkers changes throughout treatment. Now they are very much interested in that aspect of this because to run an AKI trial independently of COVID, is complicated and expensive. To run it in conjunction with the hospital population who are at risk is a strategically smart move

We are not alone in the AKI clinical field, but acute kidney injury, which in the end leads to chronic kidney injury, which leads to dialysis and unfortunately kidney replacement, is the single biggest cost to Medicare the United States. Thirty-six billion dollars, so it is enormous, and there is really nothing, apart from mild protection, there is really nothing that is a very effective treatment. These renal issues are really, significantly evolving in emerging countries in the world, I was just in Dubai to present at the Dubai Arab Health Conference, and it is actually staggering, the degree of renal damage and renal injury that is apparent in the Emirates and India is just an example of it. Therefore, our view is that this would be an ideal product to be licensed for regional distribution for these indications.

CEOCFO: ***Sum it up for us? Why look at JN Nova?***
Dr. Gillard: This is a very good investment opportunity in a company that is largely supported by non-dilutive funding. We are developing a product that will have an impact on subsequent emerging COVID variants, and it will be developed for acute kidney injury or AKI and potentially for ARDS by inhalation. Recovery from both pathologies is dependent upon ACE2 replacement. AKI is clearly a major unmet medical need, and with financing, we will ensure the company's growth to support a full clinical proof of concept in this field and generate a major value inflection as we enter the public market.