Can a Tiny Protein be the Key to Reopening the World?

GOR DIAN KNOT
Is there an Alexandrian solution for the COVID-19 Gordian Knot currently entangling the world’s economy and public health? Can modulating a tiny protein be the key?

HOW YOUR IMMUNE SYSTEM WORKS
The human immune system is still the best defense against infectious disease. Our immune system relies upon a specialized set of proteins called Cytokines, Chemokines, and RANTES to regulate the body’s defense against invasion. These proteins work in concert to protect the human body against disease or other potentially damaging foreign elements. Chemokines, a small Cytokine, are messenger proteins that mark invading cells for attack. RANTES is a specialized Chemokine that acts as a ‘magnet protein’ recruiting and directing leukocytes (white blood cells) in the immune response. When the immune system is in balance (homeostasis), the system is an efficient alien cell killing machine. In a portion of the population, however, external forces such as a virus can destabilize the immune system. When this occurs, the immune system can become hyperactive attacking both viral and healthy cells in a phenomenon called cytokine release syndrome or cytokine storm syndrome (CRS/CSS).

IMMUNE SYSTEM RUN AMOK
It is generally recognized that CRS/CSS is the primary cause of severe morbidity and death in patients with COVID-19. The easiest way to understand CRS/CSS is that your entire body becomes engulfed in a nuclear war against itself. CRS/CSS leads to rapid escalation of inflammation throughout the body. It has been theorized that many different cytokines are induced in CRS/CSS, so blocking just one type of Cytokine is insufficient. Clinical research recently published in pre-release form, however, indicates that the RANTES protein is the primary control mechanism for CRS/CSS in COVID-19. The research by CytoDyn, Inc. and IncellDx, Inc. suggests that disrupting the alliance between RANTES and CCR5 (a binding protein on the surface of white blood cells) that occurs in COVID-19 patients can resolve unchecked inflammation, restore immune homeostasis, and reduce the COVID-19 plasma viral load. RANTES levels were observed to be highly elevated in COVID-19 patients and were fundamentally driving the COVID-19 disease process. This finding should come as no surprise. Overactive RANTES is of broad clinical importance in an array of human diseases including AIDS, cancer, acute respiratory distress syndrome, atherosclerosis, asthma, transplantation, as well as autoimmune diseases such as arthritis, blood clots, diabetes, stroke, pulmonary disease, and kidney inflammation/failure. It is well documented that the primary cause of disease severity and death in influenza patients are the proteins whose imbalance results in CRS/CSS.

COVID CRASH AND BURN
In mild/moderate Covid-19 patients, CRS/CSS may manifest over time. The joint research indicated that RANTES can increase from three to five times homeostasis levels very
quickly. This clinical finding is consistent with physician reports. Physicians commonly describe patients that incur the “COVID Cliff or COVID Crash”. Patients experience a sudden and immediate clinical deterioration that hits days or weeks into a COVID-19 infection. Sometimes the crash hits with such force, that some patients die before getting to the hospital. Patients may have a fever and tightness in the chest for a week or two and not appear to be worsening, then rapidly deteriorate in a matter of hours.

FROM VIRUS TO AN IMMUNE SYSTEM DISEASE
The research indicates that the changes are brought on by the expression of RANTES. The initial virologic phase, sometimes asymptomatic, suddenly erupts in an uncontrolled response which leads to immune chaos, immune suppression, and more Cytokines. At this point, COVID-19 has changed from a viral disease to an immune system disease for which anti-viral drugs may have limited efficacy. This is true for both adults and pediatric patients suffering Kawasaki’s Disease-like symptoms.

NEW TREATMENT IN CLINICAL TRIALS
There is emerging experimental clinical evidence around a potential treatment to block and control the adverse effects of elevated RANTES. Ten critically ill COVID-19 patients at New York’s Montefiore Medical Center received a drug called Leronlimab (produced by CytoDyn) under an FDA-approved emergency investigational new drug (EIND) request. Leronlimab is an investigational drug in Phase 2b/3 development for HIV treatment. The patients were confirmed SARS-CoV-2 positive patients with significant pre-existing co-morbidities, some transplant recipients, and were receiving intensive care treatment including mechanical ventilation, supplemental oxygen for ARDS, or Extracorporeal Membrane Oxygenation (ECMO). Consistent with previous reports of severe COVID-19 disease, these patients also showed evidence of lymphopenia with liver and kidney damage. Despite the loss of 5 patients, all patients treated with Leronlimab experienced a return to more normal immune activity and a reduction in viral load.

Research is continuing. Leronlimab has completed a Phase 2 double blinded, placebo controlled, randomized study for the treatment of COVID-19 for mild to moderate patients. Safety information has been released by CytoDyn. Unblinded efficacy data is currently being analyzed.

OUTSTANDING SAFETY PROFILE
The Leronlimab treatment arm in the Phase 2 trial experienced a nearly absurd 58.4% reduction severe adverse events (SAEs) compared to the placebo arm. (21.4% or 6 SAEs in 28 Patients in the placebo arm versus only 8.9% or 5 SAEs in 56 Patients in the Leronlimab arm.) This is difficult to put into context. Doing nothing created 2.4 times the SAEs than patients receiving Leronlimab.

MECHANISM OF ACTION
How does Leronlimab work? Mechanism of Action (MOA) refers to the specific biochemical interaction by which a drug substance produces its pharmacological effect. With Leronlimab, blood assays created and patented by IncellDx can specifically identify and measure the specific molecular targets to which the drug binds. In the case of Leronlimab, it intercepts the binding action between the protein RANTES and its complementary protein CCR5. IncellDx’s clinical diagnostics can measure the immune system manifestations and viral loads of COVID-19 in
infected patients. These diagnostics provide physicians with two essential bits of information: (1) which patients are highly likely to fall victim to the COVID Cliff and (2) which patients are experiencing a COVID Cliff. *Both bits provide critical insight into the management and treatment of COVID-19.*

**MEASURING THE MOA**
Patients treated with Leronlimab under the FDA’s EIND program experienced reversed hyper-immune activation, inflammation, and immunosuppression. In addition, the resulting RANTES modulation was also responsible for reductions in COVID-19 plasma virus. *The effect was like an anti-viral drug, but the actual operation was a control mechanism placed on the human immune system.*

**TREATMENT TRIFECTA**
Modulating RANTES with Leronlimab restored the immune system to homeostasis and decreased the viral burden. *The result is a COVID-19 trifecta.* Leronlimab was shown, through IncellDx’s testing protocol, to (1) calm the Cytokine Storm, (2) return the immune system to homeostasis, and (3) reduce the viral load.

**IS THERE HOPE?**
So, does a tiny protein no larger than 7.8 kilodynes hold the key to reopening the world? Infection and antibody testing will be helpful in building public confidence, but not sufficient to completely allay public anxiety. Vaccination will have the most effect on public confidence. Unfortunately, any vaccines are still at least 6-12 months away. The ultimate anxiety around Covid-19 is severity and the risk of death, particularly for citizens in the most vulnerable population groups. A laboratory test and treatment option that, in advance, can be used to identify, protect, and possibly direct how to treat this vulnerable population can significantly bridge the public confidence gap between where the world is today, and where it can be with a successful vaccine. *Understanding the role of the tiny RANTES protein and Leronlimab (which modulates its activity) in the treatment of COVID-19 could mean that a diagnosis is no longer a death sentence.*

*Conflict of Interest Disclosure. I am a shareholder of CYDY.*