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FOR IMMEDIATE RELEASE

A genetic inheritance from Neanderthals holds therapeutic promise for a 21st century pandemic

Montreal, July 8, 2021 - Earlier this year, a team of researchers with the Lady Davis Institute (LDI) at the Jewish General Hospital (JGH) and the Biobanque Quebec COVID-19 discovered that people who had elevated levels of the protein OAS1 experienced less severe illness and lower rates of mortality when infected with COVID-19. In a paper published in *Nature Medicine*, they posited that small molecules capable of boosting OAS1 warranted further study for their effect in triggering the body's immune response against the virus.

Now, an international OAS1 Consortium, called CONTEST, including scientists from Canada, the United States, the United Kingdom, and Sweden, has teamed up with Toronto-based Cyclica, the partner of choice for data-driven drug discovery, to identify likely drug candidates that could be given to patients soon after testing positive so as to forestall serious symptoms, hospitalization, intensive care, and death.

"Despite efforts to vaccinate against COVID-19, the pandemic continues to take a fearsome toll around the world," said Dr. Brent Richards, a senior investigator at the LDI's Centre for Clinical Epidemiology and Professor of Medicine, Human Genetics, Epidemiology and Biostatistics at McGill University and one of the leaders of CONTEST. "Consequently, it remains critical that we develop treatments to alleviate the terrible disease burden it inflicts on individual patients and precarious health care systems. Our consortium is dedicated to pursuing the promise of OAS1 on this front."

As part of its COVID Stimulus Program, which includes over 20 COVID-19 related in kind projects, launched in March 2020, Cyclica is providing its services to the CONTEST Consortium pro bono. Applying its artificial intelligence drug discovery platforms, Cyclica assimilates data relevant to the OAS1 protein to search for existing, but not obvious, drugs and identifying those with potential to trigger its production, thereby improving the patient's immune response to the SARS-CoV2 virus. This method of drug discovery has the advantages of being efficient and economical because it repurposes small molecules that have already been discovered and are, thus, that much closer to clinical approval.

“Given Cyclica’s commitment to progressing research within the COVID-19 community, the collaboration with Dr. Richards is an effort we are very keen to support in hopes of continuing to advance knowledge within the coronavirus space, as well as additional virus and disease areas” indicates Dr. Vern De Biasi, Cyclica’s Chief Partnership Officer.

“The protective effect of elevated OAS1 was particularly large,” points out Dr. Sirui Zhou, a post-doctoral fellow at the LDI and first author of the paper, “such that we observed a 50% decrease in the odds of very severe COVID-19 per standard deviation increase in OAS1 circulating levels.”

OAS1 likely emerged in people of European ancestry through interbreeding with Neanderthals tens of thousands of years ago. Evolutionary pressure slowly increased the prevalence of this form of OAS1, such that it is now detectable in more than 30% of people of European descent. It is likely that this protein has served as protection against earlier pandemics, and may now prove significant for reducing the suffering caused by the current one.

Researchers in Dr. Richards’ lab made the discovery by analyzing proteins detectable in peripheral blood as a potential target. The challenge lay in determining which proteins play a causal role in disease progression, since their levels may also be influenced by COVID-19 itself or other confounding factors. Recent advances in proteomic technology - that is, the capacity to isolate and measure hundreds of circulating proteins at once - combined with genetic analyses through Mendelian randomization (MR) makes possible the delicate work of untangling which proteins affected COVID-19 adverse outcomes, rather than vice versa. The research has now reached the stage where AI can unravel the further mystery of how to activate protective immune functions that will ward off COVID-19.

From genetic determinants of 931 circulating proteins, Dr. Zhou found that increase in OAS1 levels was associated with reduced COVID-19 death or ventilation, hospitalization, and susceptibility in up to 14,134 COVID-19 cases and 1.2 million controls. The results were consistent in multiple sensitivity analyses. They proceeded to measure OAS1 levels in 504 patients with different COVID-19 outcomes from the Biobanque Québec COVID-19, and found that increased OAS1 levels in post-infection patients were associated with protection against very severe COVID-19, hospitalization, and susceptibility.

With global vaccination levels unlikely to result in herd immunity any time soon, and case counts recently surpassing 180 million including 3.8 million deaths, the search for effective treatments will remain a public health priority.

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