

## **MARSEILLE-BASED TASKFORCE ANNOUNCES THE RESULTS OF EXPLORE COVID-19 TRANSLATIONAL STUDY**

- **This research study led to a better understanding of the immune mechanics at work in COVID-19 and provides insight into the cytokine storm in severe patients**
- **Based on the results, Hôpitaux Universitaires de Marseille AP-HM is conducting a randomized, double-blind Phase II clinical trial study to evaluate the safety and efficacy of Innate Pharma's anti-C5aR antibody, avdoralimab, in COVID-19 patients with severe pneumonia**

**Marseille, France, May 8 2020** - Marseille Immunopole (MI) and a group of Marseille-based hospitals, including the emergency, intensive care and internal medicine units at La Timone, North and Laveran Hospitals and the MI/AP-HM immunoprofiling platform at La Timone Hospital, along with the biotech company Innate Pharma, unveiled the results of the EXPLORE COVID-19 exploratory translational study, which were published today on the open access platform, [Research Square](#). The goal of this research project was to gain valuable new translational insights on the immune response in COVID-19 patients and identify potential immunotherapy approaches that could help to fight the viral infection.

### **Immunology of COVID-19**

The immune system plays a dual role in COVID-19. Once our white blood cells have identified the virus, they activate, eliminating it within a few days before returning to their normal state. This sequence is found in all patients, the vast majority of whom have few or no symptoms. However, in 15% of the cases, this phase is followed by an immune storm causing a hyper-inflammation of the lungs. This deterioration of the lungs results in the patient experiencing respiratory discomfort, which can lead to acute respiratory distress syndrome (ARDS).

To date, the immune mechanisms involved in both phases of the disease are still not fully understood and no treatment has been shown to be effective against COVID-19, particularly in the severe forms that cause most deaths.

### **EXPLORE COVID-19 results**

By analyzing the immune response in 82 patients at different stages of the disease (pauci-symptomatic, with pneumonia and ARDS), the researchers were able to clarify some of the immune dynamics at work. First, they confirmed that lymphopenia (a decrease in the level of white blood cells that affects T, B and NK cells) increases with the severity of the disease. They also identified immune brakes induced by SARS-CoV-2, namely CD39, PD-1 and NKG2A. The latter data supports ongoing and potentially upcoming clinical trials with the corresponding immune checkpoint inhibitors at early stages of COVID-19.

Interestingly, researchers also reported that the blood level of C5a, a highly inflammatory peptide of the complement cascade, increased with the severity of the disease. The myeloid cells in the deep lung of severe patients overexpressed the C5a receptor C5aR1. This is in line with the well-known key role of the C5a/C5aR pathway in the overproduction of pro-inflammatory cytokines such as IL-6,

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TNF $\alpha$  and others, called cytokine storm, reported in several viral infections (SARS-Cov-1, H1N1, H5N1...) but also, as shown by the researchers, in COVID-19.

Supported by the results of this study, Innate Pharma recently announced the start of a randomized, double-blind Phase II clinical trial, named FORCE<sup>1</sup>, evaluating the safety and efficacy of its anti-C5aR antibody, avdoralimab (IPH5401), in COVID-19 patients with severe pneumonia.

*"This study demonstrated that during viral infections, the immune mechanisms that allow the body to naturally stop the inflammatory phase can get out of control and become deleterious,"* underlined **Pr. Eric VIVIER**, Professor at AP-HM – Aix-Marseille University – Centre d'Immunologie de Marseille-Luminy, Chief Scientific Officer at Innate Pharma and Coordinator of Marseille Immunopole. *"We also observed high levels of circulating C5a and over-activation of the C5a/C5aR-dependent myeloid pathway, which is believed to contribute to inflammation in the lungs. Thus, once activated by COVID-19, C5a/C5aR causes the attraction and activation of neutrophils and macrophages, contributing to the cytokine storm in COVID-19-related pneumonia. It is this harmful mechanism that we are now trying to block with the anti-C5aR antibody in the current FORCE Phase II trial."*

*"In this longitudinal study, we analyzed 40 parameters that reflect the immune response to SARS-CoV-2. We were able to measure the involvement of lymphoid cells, myeloid cells and various immune checkpoints in the two phases of COVID-19 and identify potential therapeutic approaches"* explained **Dr. Frédéric VELY**, Assistant-Professor in Immunology at Aix-Marseille University, Head of the MI/AP-HM immunoprofiling platform at la Timone (AP-HM). *"Thus, beyond anti-C5aR, immunotherapy antibodies blocking CD39, PD-1 and NKG2A receptors, already developed in cancer, could stimulate the action of T and/or NK lymphocytes in the early stages of the disease."*

*"We now know that COVID-19 is a systemic disease that affects multiple organs and tissues, but respiratory distress remains the main problem facing emergency and critical-care teams"* said **Dr. Julien CARVELLI**, Intensive care physician at la Timone (AP-HM). *"To give the lungs time to rebuild, we use a ventilator oxygen or even an artificial respirator, but the process is long, it can lead to after-effects and can sometimes be insufficient. More than ever, we need a treatment that allows us to reduce the duration of mechanical ventilation and save lives."*

*"These results are important because they enrich our knowledge of the pathophysiology of these syndromes and open the way to randomized, double-blind, placebo-controlled clinical trials"* added **Emilie GARRIDO-PRADALIER**, Director of Health Research at AP-HM *"Beyond this scientific and medical adventure, EXPLORE COVID-19 is also a human story. To mobilize quickly, deliver efficiently, but also rigorously, we need talent but also a lot of commitment and solidarity. These qualities are the strength of the Marseille Immunopole collective."*

Innate Pharma funded the EXPLORE COVID-19 study, which was conducted at its labs in Marseille-Luminy as well as at the MI/AP-HM immunoprofiling platform at la Timone (AP-HM), under the leadership of Dr Frédéric VELY.

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<sup>1</sup>FORCE: **FOR** COVID-19 **E**limination

### Identification of immune checkpoints in COVID-19 | [DOI:10.21203/rs.3.rs-27340/v1](https://doi.org/10.21203/rs.3.rs-27340/v1)

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### Hôpitaux Universitaires de Marseille-AP-HM

With 4 hospitals and 3,400 beds, Hôpitaux Universitaires de Marseille – AP-HM is the third University Hospital Center in France. It is also the first employer in the region, with over 12,000 employees and almost 2,000 physicians. Its missions are treatment, teaching, research as well as prevention and health education. Its establishments offer a full range of medical specialties, from local health care to advanced treatments for rare and complex pathologies, for adults and children. Its medical and health care teams are committed to providing care that combines excellence with proximity, easily accessible to all.

**More on: [AP-HM website](#) and [@aphm actu](#)**

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### **Marseille Immunopôle**

The French immunology cluster MI federates researchers, clinicians, engineers and industrials who work in the research and development of immunotherapy antibodies against cancers and inflammatory diseases and new diagnostic solutions in immuno-oncology.

MI brings together a unique continuum of excellence ranging from targets discovery to the clinical development of drug candidates and diagnostic tests: Aix-Marseille University (AMU), CNRS, Inserm, 10 research & technology centers, 3 hospitals of Hôpitaux Universitaires de Marseille – AP-HM, the Paoli-Calmettes Institute, Eurobiomed, biotech and industrials, first and foremost, the French leaders of immuno-oncology Innate Pharma and HaliuDx. Supported by all the public authorities and innovation actors of the territory, the Departmental Committee of the French League against Cancer, the Public Investment Bank and the Commissariat General for Investment, MI headquarters are located at the Timone Hospital in Marseille.

**More on: [MI website](#) and [@Immunopole](#)**

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### **French Army Military Hospital in charge of doctor training**

The Laveran Hospital was inaugurated on 7 November 1963. Its name pays tribute to Alphonse Laveran, an illustrious military physician who discovered the parasite responsible for malaria in 1880. He was awarded the Nobel Prize for Medicine in 1907. Initially built to complete the military hospital equipment of the region and as a convalescent hospital for patients evacuated from external theaters of operations, it very quickly became the Army Training Hospital (HIA) in September 1966.

The Laveran Hospital has a total of 221 beds and 885 staff, including 540 military personnel. In 2019, it recorded more than 43,000 consultations, 25,770 emergency department visits, 1,300 medical and surgical hospitalizations and 2,870 on-call SMUR services. Reference hospital for the French Foreign Legion, Laveran has only 24% of militaries among its patients.

**More on: [French Defence Health Service website](#) and [@HopitalLaveran](#)**

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