

**Abstract**

SARS-CoV-2 infection results mostly in virus clearance. However, it can cause an acute respiratory disease known as COVID-19 with non-defined treatment. COVID-19-associated hyperinflammation leads to lung inflammation, systemic sepsis and death. We have treated >300 patients with immunosuppressants, mostly tocilizumab (IL-6R blocker), but also with baricitinib or anakinra, and observed reduced lung distress and reduced deaths. Importantly, one-time tocilizumab delivery was more effective when administered before severe respiration insufficiency and in patients of <70 years of age. The data suggest that patients with severe disease develop an age-dependent abnormal pro-inflammatory response, and that improvement of the anti-inflammatory therapy is needed. Our objective is to optimize treatments by identifying efficient immunosuppressants, in combination with immunological status analyses at different patient ages. Such analyses will identify patients at risk and predict the earliest point for intervention before the attainment of critical disease and treatments lose efficiency. We have designed a translational study to measure immunological parameters, focusing on T cells (activated/regulatory), monocytes (M1 /M2) and cytokines levels at distinct disease stages and upon treatment with different immunosuppressants. These data could identify new molecular and cellular therapeutic targets, provide mechanistic insight into the etiology of hyperinflammation, and optimize treatments.

## Scientific and technical feasibility

**What are the scientific fundamentals underlying your idea? Have you performed a proof of concept validation?**

The main objective of our project is to optimize immunosuppressant therapy for the hyperinflammatory profile of COVID-19 patients through a translational study that combines immunosuppressant-based treatment of patients with analysis of relevant immunological parameters.

- There is solid evidence from Chinese COVID-19 patients for hyperinflammation and sepsis development associated with the disease (Fei Zhou et al., 2020. *The Lancet*. doi:10.1016/S0140-6736(20)30566-3). Therefore, the main idea of our project is based on the concept that anti-inflammatory therapy would lead to reduced inflammation and patient mortality.
- We provide proof of concept for the effectiveness of immunosuppressant therapy in reducing admission to ICU and mortality of COVID-19 patients. This is shown by an open prospective cohort clinical study that included 600 patients and in which 213 were treated with tocilizumab and showed statistically significant improvement in patient survival (In an open study tocilizumab treatment reduces mortality and ICU admission in COVID-19 Patients; in preparation for publication). Data from this study showed statistically significant increased effectiveness of tocilizumab treatment: 1) when initiated in less severe disease stages, and 2) in <70 years old patients. These data urge for immunological analysis in order to define the concepts behind these findings, and thus optimize immunosuppressant treatments and intervention time points.

**Describe how the Project's Leader knowledge and experience in field of the Asset(s) would contribute to the success of the Project. Discuss it in the context of the composition and the relevancy of the rest of the team members**

The Project Leader is Professor of Medicine at the UAH and Head of Service at HUPA (Hospital Príncipe de Asturias). Dr. Alvarez de Mon is currently in charge of treating > 1000 COVID-19 patients and all the clinical treatments described in this proposal were performed under his immediate supervision. He is also collaborating with other hospitals, including the IFEMA Center for COVID-19 patients and the Ramon y Cajal Hospital. He is the coordinator of two collaborative projects by the Community of Madrid "Translational Medicine in Inflammation and Cancer (the last awarded in 2018) together with the other two principal investigators of the project, Professor Carlos Martinez-A (CNB/CSIC) and Dr. Dimitrios Balomenos (Group Leader, CNB/CSIC). The three investigators have common interests in the control of inflammation in disease, and have publications in common, including recent articles on the mechanism of the M1/M2 macrophage regulation in *The Journal of Clinical Investigation* (Rackov et al., 2016. *J Clin Invest*. <https://doi.org/10.1172/JCI83404>), and in *Frontiers in Immunology* (Front Immunol, 10.3389/fimmu.2017.00493). The two Principal Investigators at CNB/CSIC will be responsible for the immunological analyses of the patients, while the Project Leader will be responsible for the treatment of patients with immunosuppressants. The three investigators are co-authors of a manuscript in preparation on the therapeutic effect of tocilizumab on COVID-19 patients.

**Has your Asset(s) been under evaluation by other funding programmes prior to this call (an object of research grants or other innovation or acceleration programmes)? Please detail the most relevant ones.**

The same team has submitted a project proposal to the Instituto de Salud Carlos III call on "Projects in investigation of SARS-CoV-2 and the COVID-19 disease", which is under evaluation. The project was oriented toward more general aspects of immunomodulatory treatments for COVID-19, as at the time of submission we did not have the current data that associate the therapeutic effect of the immunosuppressant tocilizumab to less severe stages of disease or to the age of the patients.

## Transferability and Market Potential

**According to the stage of development of the Asset(s), what are the identified needs and determinants that currently condition its successful progression to the commercialization phases?**

COVID-19 treatment remains elusive. Our data of an open clinical study showed that treatment of patients with the immunosuppressant tocilizumab resulted in increased patient recuperation (manuscript in preparation), indicating that treatment of hyperinflammation with immunosuppressants is a viable therapeutic option. Better recovery results were obtained when treatment was administered before severe disease, and in patients of <70 years of age.

□ Although the data show positive results, we need more detailed analyses in order to design accurate therapeutic approaches. As the disease is new, the immune status of COVID-19 patients remains unknown and we need to generate immunological data in order to advance with our objective and optimize immunosuppressant treatments. It is determinant to analyze the immunological status at different disease stages, which are presently identified on the basis on pneumonia status and oxygen saturation, in order to further characterize and redefine these disease stages. This will assist in identifying patients that are at risk for hyperinflammation, and to define the earliest and time point for intervention without compromising the immune response of the patient to the virus. Furthermore, treatment with different immunosuppressants is planned, and the immunological analyses during and after treatments. We will also establish the dose of treatments and adjust them for the elder population due to their increased inflammation.

**Who are your end-users? What is the market segment and the market size you are addressing?**

Our main objective is to optimize COVID-19 immunosuppressant-based treatments using approved immunosuppressants (such as tocilizumab, anakinra, baricitinib) in order to optimize immunosuppressant treatments, using immunological analysis of the patients. Our project is tailored to detect COVID-19 patients at risk for hyperinflammation, predict the earliest point for immunosuppressant treatment and identify most suitable immunosuppressant-based treatments.

□ Therefore our results will be directed to the scientific and medical communities in order to improve COVID-19 treatments worldwide. The market segments that will be benefitted by our work are the manufacturers of immunosuppressant drugs. As our analysis might identify new targets for treatment, companies that we have established collaboration with could be also involved. Overall, the success of our work will have an impact at the medical and socioeconomic levels. The ultimate beneficiaries will obviously be the patients and the society

## Societal relevance and potential impact

**What is the unmet need you aim to address and why is it timely and relevant? What potential impact will your solution have?**

Effective treatment of COVID-19 remains elusive and therapeutic proposals range from boosting the immune response to reducing inflammation. A vaccine is a long-term solution and it might not give the expected results. Due to the extent of the pandemic, treatments are in urgent need. One of the major complications of COVID-19 is the development of hyperinflammation that is manifested as cytokine storm that leads to death.

Our major aim is to establish anti-inflammatory treatments for COVID-19 patients and reduce their mortality. Our first data from >300 patients treated with immunosuppressants, mostly tocilizumab (IL-6R blocker), show statistically increased survival of patients.

We propose a translational study to measure immunological parameters in combination with immunosuppressant treatments to optimize anti-inflammatory therapeutic approaches. This optimization could lead to increased cure rates, and also target older COVID-19 patients. Improving the recovery of COVID-19 patients and their survival will have a great impact in controlling the COVID-19 pandemic. Such progress will have important socio-economic effects. If the proposed treatments would prove efficacious, deaths would be considerably reduced. This would greatly lessen the social alarm and could ease the severe precautions that different States have adopted in order to contain the pandemic. The relevance of the proposal would be even greater if the pandemic persists or if it revives in next fall/winter.

**What are the available solutions that currently address the specific problem you aim to solve? What is the innovation of your solution? Who will be the main beneficiaries of your solution?**

The time frame of starting anti-inflammatory therapy is critical, as if applied early it could compromise the immune response against the virus and if applied late it would not be effective. Our innovative idea is that definition of the precise point for an early immunosuppressant will be a crucial in optimizing therapeutic effects for COVID-19 patients. We hypothesize that the patient's immunological parameters will reveal the earliest time point for anti-inflammatory treatment application for COVID-19-associated sepsis without compromising the immune response. Indeed, our data from >200 patients show that patients treated with tocilizumab at an earlier stage of the disease, display statistically significant increased survival, as compared to treated patients with severe disease. We propose to measure cytokine profiles, T cells (activated CD4+ vs regulatory) or monocytes and the determination of their phenotype, state of activation and the ratio of M1/M2. This analysis will lead to the best definition of the stages of the disease and facilitate the optimization of immunosuppressant-based treatments. As older patients (>70 years old) are more resistant to improvement after immunosuppressant treatment, our analysis could point to more intense or different treatments for those patients. We believe that our work will generate knowledge that can be applied in designing efficacious treatments for COVID-19 and result in beneficial socioeconomic outcomes.

Team

<b>Team Member</b>	<b>Name</b>
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