IMI2 Project ID 101005077

Publishable Summary

Periodic Reporting 1

April 2020- March 2021

The CARE project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 101005077. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and BILL & MELINDA GATES FOUNDATION, GLOBAL HEALTH DRUG DISCOVERY INSTITUTE, UNIVERSITY OF DUNDEE.

Summary of the context and overall objectives of the action

The Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) pandemic has emerged as the largest global health threat to humanity in this century. The wide spectrum of clinical symptoms, disease severity in high risk individuals, transmission efficiency and high mortality, raised an immediate urgency for vaccines and therapeutics. The need for the control of the pandemic is reinforced by the emergence of viral variants of concern.

CARE has developed an insight-driven research approach that simultaneously addresses the therapeutic needs of patients with COVID-19 now, while also considering the needs of future patients, by initiating research to discover and develop new treatments to protect against SARS-CoV-2 and other coronavirus threats.

In this context, the CARE consortium aims to foster synergies between research, industry and the clinic to accelerate the development of effective therapies and improve evidence-based patient management. We are one project with two areas of focus: rapid emergency response as well as on long-term preparedness for future outbreaks. Our goal is apply these learnings to the current COVID-19 emergency response through drug repositioning, and current and/or future coronavirus outbreaks by broad-spectrum small-molecule drug discovery and/or virus-neutralizing antibody discovery. To achieve this, a collection of repurposed drugs, focused libraries and small molecule libraries will be screened against SARS-CoV-2, other emerging SARS-CoV-2 variants of concern and related coronavirus genera in phenotypic or target-based assays. A focused medicinal chemistry campaign will identify small-molecule hits. In parallel, virus-neutralizing monoclonal antibodies will be generated and further characterized. Lead candidates will be evaluated in preclinical studies and advanced into Phase 1 and Phase 2 clinical trials in humans. Finally, immune markers will be identified contributing to the host immune responses to SARS-CoV-2 infections, and the correlation with clinical and virological outcomes will be determined.

Work performed from the beginning of the action to the end of the period covered by the report and main results achieved so far

The immediate efforts of the CARE consortium were focused on identifying existing drugs or molecules in advanced clinical development to provide a fast therapeutic options to patients suffering from COVID-19 (drug repositioning). During this exercise multiple drugs were identified, which were also identified by others. Some other drugs proved to be active in cell culture as well, however, none was found suitable for clinical deployment.

In parallel, by performing large screening campaigns in novel phenotypic (infected-cell) assays and target-based (on several essential enzymes) assays, novel molecules were identified with broad-spectrum anti-coronavirus activity in a bid to develop additional putative therapeutic options in the battle against SARS-CoV-2, and by extension future coronavirus outbreaks. For the target-based assays, CARE devoted efforts to obtain the widest set of SARS-CoV2 proteins, before extension to other CoVs. Protocol and clones have been established and are now available for the public and private scientific community. Although still at an early stage, promising hit matter on different known and

yet unidentified targets has been discovered and progressed via medicinal chemistry, with the intent to develop the most potent and promising ones up to Phase 2a. The close collaboration between the different teams significantly increases the chance of identifying broad spectrum potent anti-coronavirus drugs.

Multipartner drug discovery for anti-SARS-CoV-2 neutralising antibodies has been initiated. A single antibody agent for prophylactic usage in high risk patients has been identified, in vivo proof of concept generated and a profile against the variants of concern established. Further large molecule discovery to generate differentiated combination treatments for therapeutic treatment is ongoing. Continual monitoring of the competitive environment, and adjustment of the antibody discovery strategy is important to ensure that non-redundant therapeutic options are followed in the light of multiple therapeutic antibodies that have received emergency use authorizations in Europe.

In the first period, the CARE consortium focused on the set-up and optimization of experimental models of the different OMICs approaches (transcriptomics, proteomics and metabolomics) to evaluate the physiopathology of SARS-CoV-2 infection. Most of the experiments are now underway. Nonetheless, the first analyses of the samples from French and Swiss COVID-19 cohorts highlight neutrophil activation as a hallmark of severe disease and CD177 assessment as a reliable prognostic marker for routine care. Animal models were established and validated. It includes two mouse models, a syrian hamster model and a non-human primate model. The description of the models are available in CARE public deliverables. A clinical platform is also in implemention for Phase 1 and Phase 2 clinical trials.

Assembled in record time, the CARE consortium has not lost the momentum and established connections with other organizations, IMI-initiatives, and key regulatory players to best respond to the public emergency health caused by the SARS-CoV-2 pandemic. With the work rapidly progressing, the organizational infrastructure was laid to secure adaptability, coordination and relevance of the work in development.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the action so far)

The CARE newtwork of public-private collaborating teams enables the implementation of infrastructure fostering the discovery and development of candidates to respond to the curent and potential future cornavirus pandemics. Novel screening capabilities on SARS-CoV2 targets have been established generating hits suitable for further development into drugs. Expertise on SARS-CoV2 targets extends beyond CARE partners to provide know-how and independent evaluation of external hits. The joint efforts of teams from private as well as public organizations allowed the application of a variety of different approaches to identify potential starting points for hit-to-lead campaigns. Multiple private and academic organizations are working together to integrate data on the efficacy, pharmacokinetics and safety of compounds in animal models and to identify potential immediate assets of value for the current outbreak and for future outbreaks. Apart from providing a basis for the conduct of Phase 1 and Phase 2 clinical trials trials, the clinical trial platform will be made accessible to outside entities including academic institutions,

private companies and patients with an interest in conducting and participating in COVID-19 trials.

The collaboration between the different teams from private and public organizations can be taken as an example for joint drug development for other future health emergencies.

It is now recognized that antiviral drugs will be needed during and after the SARS-CoV-2 pandemic, as well as to prepare for potential future coronavirus outbreak. The availability of a potent, broad-spectrum anti-coronavirus drug will allow treatment of patients (such as transplant patients or individuals with other immune system deficiency) that cannot be vaccinated, as well as rapid deployment after the detection of a spill-over event or outbreak with a new coronavirus. As such, chemotherapeutical containment will be instrumental in halting the current SARS-CoV-2 pandemic, and preventing the social-economic burden of the next one.