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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 to control 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, its variants of concern 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 and long-term preparedness for future outbreaks. Our goal is to 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 CARE were focused on identifying existing drugs or molecules in advanced clinical development to provide fast therapeutic options to patients suffering from COVID-19 (drug repositioning). Multiple drugs were identified, which were also identified by others. Other drugs proved to be active in cell culture as well, however, none was found suitable for clinical deployment. In parallel, large screening campaigns in novel phenotypic (infected-cell) assays and target-based (on several essential enzymes) assays were conducted, totalling >1.5 millions compounds screened. During the screening process, profiling assays in translation models were set up and tools were built for target deconvolution of the hits. A great deal of enzyme, assays, structures, and mode of action have been determined and published, to feed drug discovery. Moreover, CARE has produced a collection of clones, reagents, and protocols widely available to the scientific community dedicated to molecular/structural work on SARS-CoV2 enzymes and proteins.

The small molecule drug discovery efforts performed within CARE have led to the identification of several antiviral compound series with innovative mechanism of action which can form the basis of preventive or therapeutic interventions against coronaviruses. A selection of compound series is being developed towards candidate drugs and proof-of-concept animal models has been obtained for two programs. CARE has indeed validated several animals models, including mouse, syrian hamster and non-human primate models.

CARE has delivered two well-characterized potent monoclonal antibodies, CH-P5C3 and CH-P2G3, isolated from human donor B cells. Both antibodies showed complete prophylactic protection in hamsters challenged with SARS-CoV-2 virus. The epitopes for CH-P5C3 and CH-P2G3 do not overlap, thereby allowing both antibodies to bind to the Spike protein simultaneously and greatly reducing the risk of escape mutants. CARE is now developing neutralizing antibodies with broader activity against Sarbecoviruses and/or more broadly against betacoronaviruses by evaluating bispecific antibodies that would synergise in neutralizing potency and breadth in binding two conserved epitopes on the Spike protein. Several of these bispecific antibodies have potential improvements in potency and/or breadth against recent variants including BQ.1.1.

OMICS experiments are ongoing to evaluate the physiopathology of SARS-CoV-2 infection. This will complement the analyses of the samples from French and Swiss COVID-19 cohorts which highlighted neutrophil activation as a hallmark of severe disease, and characterized a "core signature" of gene expression in convalescent severe COVID-19 patients and a gene expression profile associated with thrombosis in these subjects.

CARE has establish a complete Clinical Trial Platform infrastructure and site network for the design and conduct of clinical trials targeting COVID-19. The platform covers different aspects to speed up the setup and conduct of a clinical trial. The clinical trial platform also offers services that may be of interest to outside stakeholders looking for a clinical trial network with a specific expertise in COVID-19.

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 network of public-private collaborating teams enables the implementation of infrastructure fostering the discovery and development of candidates to respond to the current and potential future cornavirus pandemics. The delivery of novel screening capabilities on SARS-CoV-2 targets have been established generating hits suitable for further development into drugs. Expertise on SARS-CoV-2 targets extends beyond CARE partners to provide know-how and independent evaluation of external hits. The joint efforts of teams from private and public organizations allowed the application of a variety of different approaches to identify potential starting points for hit-to-lead campaigns. Detailed structural and functional data also document the hits and lead, greatly facilitating the hit-to-lead process. 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 and future outbreak. Apart from providing a basis for the conduct of clinical 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 after the SARS-CoV-2 pandemic, and to prepare for potential future coronavirus outbreaks. 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 deficiencies) 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, therapeutical containment will be instrumental in halting the current SARS-CoV-2 pandemic, and preventing the social-economic burden of the next one.