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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, CARE 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 focus areas: 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 to provide fast therapeutic options to patients suffering from COVID-19 (drug repositioning). Multiple drugs were identified, although previously identified by others. Other drugs were identified as active in cell culture, but 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. A great deal of enzyme, assays, structures, and mode of action have been determined and published, to feed drug discovery. CARE has also produced a collection of clones, reagents, and protocols available to the scientific community.

The small molecule drug discovery efforts 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 in an infectious animal model has been obtained for three of the programs. CARE has indeed validated several animals models, including mouse, syrian hamster and non-human primate models.

CARE has delivered three well-characterized potent monoclonal antibodies, CH-P5C3, CH-P2G3 and CH-P4-J15, isolated from human donor B cells, with different epitopes. The three antibodies showed complete prophylactic protection in hamsters or non-human primates challenged with SARS-CoV-2 virus. CARE transitioned from identifying emergency track neutralizing antibodies with potency against SARS-CoV-2 to developing preparedness track neutralizing antibodies with broader activity against Sarbecoviruses and/or betacoronaviruses, with a dual strategy, i.e. to 1) screen for broadly active anti-coronavirus monospecific antibodies and 2) evaluate bispecific antibodies that would synergize in neutralizing potency and breadth by binding two conserved epitopes on the Spike protein. CARE successfully identified broadly active neutralizing antibodies against different coronavirus subfamilies, and characterization is underway. Although there has been no significant breakthrough to date with the bispecific antibodies, efforts continue with our extensive toolbox and antibodies clones reported in the literature.

OMICS experiments are ongoing to evaluate the physiopathology of SARS-CoV-2 infection and CARE is now validating hits identified by pharmacological or genetic approaches. 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 established a complete Clinical Trial Platform infrastructure 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 coronavirus 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 to provide know-how and independent evaluation of external hits. The joint efforts 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 greatly facilitate 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, also to prepare for potential future coronavirus outbreaks. The availability of a potent, broad-spectrum anti-coronavirus drug will allow treatment of patients (such as individuals with 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.