HUMAN
VACCINES
PROJECT
EUROPE

Minister of Health, Welfare and Sports and Deputy Prime Minister
Mr. H. de Jonge,
Parnassusplein 5, 2511 VX Den Haag

Amsterdam / New York, 24 June 2020

Your Excellency, dear Deputy Prime Minister De Jonge,

The development of a COVID-19 vaccine is an urgent global priority and has highlighted major shortcomings in our pandemic preparedness as well as major gaps in our understanding of human immunity. In particular, it has highlighted challenges in protecting vulnerable populations such as older adults and those living in lower and middle income countries (LIMCs) that make up substantial proportions of national and global populations. Such populations often have impaired or declining immune systems, greater disease susceptibility and burdens, as well as poorer responses to vaccination. Protecting these populations is key to rapidly ending this pandemic, preparing for the next, and improving vaccine development for a wide range of diseases.

In the light of the COVID-19 pandemic, the *Human Vaccines Project* has launched two major initiatives focused on addressing the key challenge of enhancing how we protect vulnerable populations. These initiatives include:

1. The establishment of a *European Immunomics Platform (attachment 1)*, starting with the countries that are partners in the Inclusive Vaccines Alliance. This platform will be directly linked to the global *Human Immunomics Initiative* a joint collaboration between the Human Vaccines Project and the *Harvard Chan School of Public Health (attachment 2)*. The Netherlands is at the core of this initiative, because for its program of work 2 out of the 3 identified cohorts are Dutch cohorts (Lifelines, Rotterdam Studies).
2. The *COVID Vaccine Initiative* which is focused on ensuring that COVID-19 vaccines are effective and accessible for vulnerable populations in LIMC's *(attachment 3)*.

Together these initiatives will establish the basis for the next generation of vaccines capable of protecting vulnerable populations, including novel strategies for enhancing the effectiveness of COVID-19 vaccines should first generation vaccines fail to effectively protect these key populations groups. These initiatives leverage an approach pioneered by the Human Vaccines Project to define the principles of effective immunity through intensive clinical vaccines studies that make use of advances of systems biology and Artificial Intelligence and Machine Learning (AI and ML). Importantly, they also establish the Netherlands as the European Hub under a worldwide effort to better understand and harness human immunity by leveraging and linking the considerable scientific capacity across the country.

Such initiatives are highly complementary to the efforts to develop and test COVID-19 vaccines in healthy populations, as well as efforts by GAVI and WHO to prepare of the deployment of a COVID-19 vaccine.

We are asking your support for these two recent initiatives launched by the Human Vaccines Project.

Yours sincerely,

5.1.2e 5.1.2e
5.1.2e 5.1.2e

Human Vaccines Project

Stichting Human Vaccines Project Europe | Brakersweg 53 | 1901 XX Castricum | The Netherlands
5.1.2e www.humanvaccinesproject.org

HUMAN
VACCINES
PROJECT
EUROPE

Background:
Traditionally, vaccine have worked best in healthy young adults and children, and have been less effective in populations that have less robust, challenged or declining immune systems. In particular, vaccines against respiratory diseases such as influenza have had poor effectiveness in populations such as adults over the age of 65. It is not yet clear how well first and second generation COVID-19 vaccines will perform in these populations.

This challenge is rooted in a limited understanding of human immunology, particularly across diverse populations. In older adults (especially over the age of 65), age-related declines of immunity (known as immunosenescence) are associated with significant increases in the risk of a wide range of infections and a decline in effective responses to vaccination. For populations in LIMICs a range or environment factors (and perhaps genetic variation) can limit the effectiveness of vaccines, and include nutritional status, concomitant infections, environmental exposures, microbiome variation and other factors. Systems biology analyses of developing world populations have shown stressed immune signatures marked by high levels of inflammation more similar to aged populations. High levels of HIV or chronic TB infections may further complicate responses. The initiatives below would seek to define the signatures of protection for these key population groups, as well as vaccination strategies that would be tailored to address the immunological challenges of each group.

Ad 1: Human Immunomics Initiative (HII) and creating a European Immunomics Platform

Earlier this year the Human Vaccines Project and the Harvard T.H. Chan School of Public Health announced a major new collaboration to determine the principles of effective immunity in older adults called the Human Immunomics Initiative (HII). Focused on one of the fastest growing demographics globally, the HII seeks to accelerate the development of vaccines and immunotherapies that are effective in older adults which have a substantial disease risk and burden as evidenced by the recent COVID-19 pandemic. Under the HII and the Amsterdam-based Stichting Human Vaccines Project Europe, foundational studies will be conducted in the Netherlands leveraging world class longitudinal cohorts and immunological expertise across the country. Under a global scientific plan which seeks to study immunity in globally diverse older adults, the Netherlands would serve as the primary scientific hub for further European studies linking to North American via connections to Harvard, and planned studies in Asia.

During the life course, immune memory against vaccine-preventable childhood infections conferred by childhood vaccination wanes below protective levels, in particular after midlife. The result is that at old age respiratory diseases like influenza, pneumococcal pneumonia and whooping cough resurface. Not only does immune memory decreases at old age, but the ability of older individuals to respond effectively to vaccination also declines. The only way to identify the universality of this age-dependent effect on immune responsiveness is to study the immune responsiveness in community-based life course cohort studies. This research will be crucial for developing effective and safe vaccines against COVID-19 and other public health threats.

Fundamental to the approach and program of work of HII, is to differentiate between chronological and biological age. Using blood-based biomarkers for liver, kidney, metabolism, immune system, as well as brain- function, Wu and Goudsmit recently developed an algorithm for "biosystems-age" that was demonstrated to predict risk of mortality and morbidities including stroke, diabetes, cancer, coronary heart disease, and COPD in a cohort of community based individuals aged ≥55 years (Rotterdam Study) (manuscript in preparation).

HUMAN
VACCINES
PROJECT
EUROPE

Immune aging is part of biological aging. Like other systems, changes in immune functioning over lifetime are likely less dictated by chronological age than by individual trajectories that are determined by individual baselines and genetic and environmental interactions. Measuring changes in cell-subset frequencies in healthy adults of different ages followed longitudinally, Alpert et al. found that trajectories of immune aging better described a person's immune status than chronological age and to predict all-cause mortality beyond well-established risk factors.

Immune aging involves all compartments of the immune system. Advances in systems biology, bioinformatics, and artificial intelligence now enable to study the immune system and other systems of the human body holistically. HII will take a holistic systems biology approach to develop algorithms for biological age and immune age and to decode the mechanisms and rules of effective immunity at old age.

Scientific Program:
Recruitment of study cohorts is time and resource consuming. Instead HII will make use of existing large-scale population cohorts that follow subjects longitudinally for health outcomes and that collect and bio-bank specimen such as blood samples at different moment in time. These cohorts provide access to well-phenotyped populations whilst offering opportunities for additional research. HII has identified three cohorts for its program of work listed below, and it in discussions for engagement with an additional cohort in Asia:

1. The first to develop and optimize its research tools (Lifelines, Netherlands);
2. The second to develop models of immunity in relation to health status in an aging population (Rotterdam Study, Netherlands);
3. The third to recruit subjects for vaccine trials to confirm developed models of effective immunity participants (Framingham Study, USA).

The Netherlands, through HVP, proposes to take the lead in expanding the Human Immunomics Initiative across a number pof European countries resulting in a European Immunomics Platform and create creating a European network. We have already reached out to leading German (Helmholtz Centre for Infection Research), French (Cohorte Constances) and Italian (InLiMes) research centers specialized in community-based cohort studies. who would be very supportive of the creation of such a platform with the mission to execute long-term studies in elderly populations. Deciphering vaccine responsiveness and immune ageing (including COVID-19 vaccines, once licensed) would be crucial to respond effectively to current and future pandemics and global health threats.

Requested Budget: EUR **2.817.500** *(attachment 4)*

HUMAN VACCINES PROJECT EUROPE

Ad 2: The COVID Vaccine Initiative (CVI) works in two interconnected areas.
Protecting Vulnerable Populations: The CVI will a) Define the course of COVID-19 disease in aging populations and LMICs, defining signatures of protection in natural infection, and prepare clinical sites to rapidly execute COVID-19 vaccine studies; and b) Evaluate the safety, host response and efficacy of experimental COVID-19 vaccines in aging populations and LMICs, facilitating global licensure and deployment. This will provide the framework for prioritizing and improving COVID-19 vaccines and fill a critical gap in scientific knowledge required to address other diseases such as influenza, and future pandemics.
Translating Science to Policy: The CVI will ensure the development of evidence-based policy for COVID-19 vaccines. It will create a series of briefing to ensure that the major R&D challenges impeding the development of safe and effective COVID-19 vaccines for vulnerable populations are addressed, and will also serve as a neutral forum for dissemination and synthesis of critical information and data relevant to accelerating vaccine development and deployment.

The specific niche of HVP's COVID Vaccine Initiative is a population focus on aging adults and those living in LMICs, to undertake our comprehensive and integrated systems biology approach to 1) Identify biomarkers at baseline (Pre-immunization) which can differentiate and predict vaccine responders from non-responders; and 2) Determine correlates of protection, and whether baseline is predictive of outcome for protective efficacy.

Vaccine Developers may partner with HVP's COVID Vaccine Initiative in clinical development and-or laboratory assessment of ongoing clinical trials:

Clinical Trials in Aging Populations and Those Living in LMICs: In this model, HVP would work with the vaccine developer to design and conduct Phase 1/2 trials in vulnerable population groups, for evaluation of the safety, reactogenicity and immunogenicity of the COVID-19 vaccine candidates and facilitate Phase 3 efficacy trials in LMICs. Costing for clinical trials to be developed.

Laboratory Studies from Clinical Trials Samples Obtained from Vaccine Developers: HVP would evaluate pre- and post-immunization samples for assessment of host responses (immune and systems biological responses (**Table 1 below).** The HVP network has a suite of advanced data integration, AI and machine learning tools enabling biomarker identification and predictive signatures for responders vs. non-responders to candidate vaccines (Tsang JS et al 2020).

Collectively, these studies will help define 1) Predictive biomarkers and correlates of protection in vulnerable populations; 2) Strategies for optimization of vaccine platform specific immunity, which will be advantageous for vaccine developers utilizing their platforms for vaccine development across diseases, and 3) Expediting clinical strategies for efficacy testing in vulnerable population groups and regulatory strategies for licensure.

Requested budget: **EUR 85.000.000 (USD 96.1M)**