The development of RegaVax(Corona) a potent single dose COVID-19 vaccine candidate

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To the attention of Dhr 5.1.2e & Dhr 5.1.2e . 5.1.2e

RegaVax(corona) August 18st 2020

CONTEXT An emergency response to the rapidly evolving COVID-19 pandemic urges the development of potent and fast-acting vaccines to contain SARS-CoV-2. Generally, live-attenuated vaccines (LAV), such as the yellow fever virus vaccine YF17D, elicit high potency (>95% seroconversion in vaccinated individuals and result typically in life-long protection). For YFV17D, this protection is already reached within a very short period of time (~10 days). We are the only team, worldwide, that uses the yellow fever vaccine as a vector to develop a potent COVID19 vaccine that provides complete protection against infection in an animal model following one single shot.

THE PLATFORM TECHNOLOGY At KU Leuven we developed a platform technology to design and produce live-attenuated recombinant vaccines vectored by the original yellow fever (YF17D) vaccine. As such the YF vaccine serves as a vehicle (i.e. vector) for the foreign antigen (i.e. part to which immune response/antibodies are developed) to trigger an immune response towards this antigen. The plug-and-play technology has been validated using a series of targets and model antigens such as rabies, Zika, Ebola and Lassa (inserted in the YF backbone). We name this technology tentatively the **RegaVax** platform [e.g. RegaVax(zika); RegaVax(rabies)....] All constructs proved highly immunogenic (triggering antibodies towards the respective pathogen) and safe in several animal models (mice, hamsters). The rabies vaccine candidate efficiently protects mice against lethal challenge with both the rabies and the yellow fever virus *(such studies still to be carried out for the Ebola and Lassa vaccine candidates).* RegaVax(zika) fully protects against lethal Zika and yellow fever infection in a mouse model [PMID: 32116148]. Moreover, it completely prevented congenital malformations in mice following direct intraplacental challenge of pregnant mothers [PMID: 30564463]. It also results rapidly in high titers of neutralizing antibodies in non-human primates and protection from Zika virus challenge (data not shown, but available upon request). This platform has now been employed to develop a vaccine candidate against SARS-CoV-2.

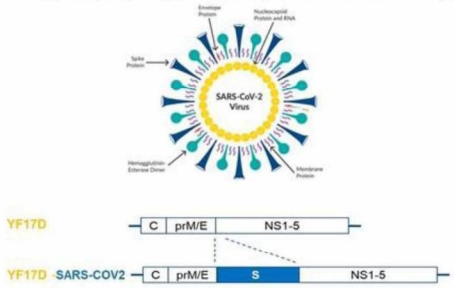
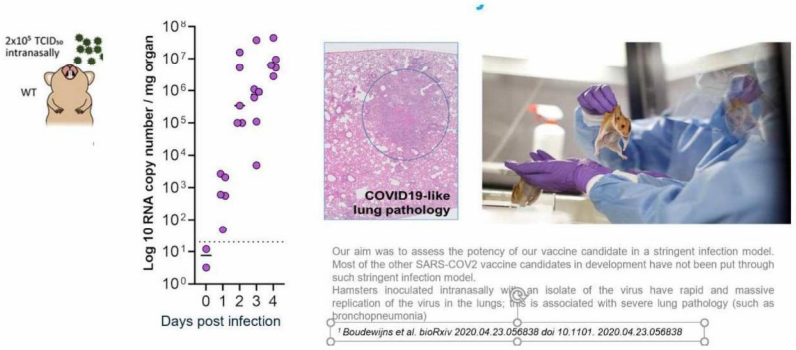


Fig 1. The genetic sequence of the spike protein (blue) of SARS-CoV-2 is inserted in the genetic sequence of the yellow fever vaccine YF17D

RegaVax(CORONA) [or YF17D/SARS-COV-2, short **YF-S0**] In January 2020 we employed the RegaVax technology to engineer within a time span of a couple of weeks prototype vaccine candidates against SARS-COV2. Soon after the genetic code of this novel pathogen was available, we cloned (variants of) the Spike protein ('S') of the SARS-CoV-2 into the YF17D backbone following a pre-established procedure. Several constructs were engineered that replicate in cell cultures and that produce the SARS-CoV-2 Spike (S). From the 8 vaccine candidates engineered, two proved most efficient in inducing an immune response in mice. Next, the efficacy of the vaccine candidate against virus infection was studied. Since mice did not appear to be a good SARS-COV2 infection model, we established a robust hamster infection model (Boudewijns et al., 2020). Intranasal infection of hamsters with SARS-CoV-2 results in high viral loads in lungs and severe lung pathology. Disease evolution is monitored by µCT of the lungs under high biosafety level 3+ (BSL3+) conditions. This model allows to evaluate immunogenicity and efficacy of the vaccine candidates.

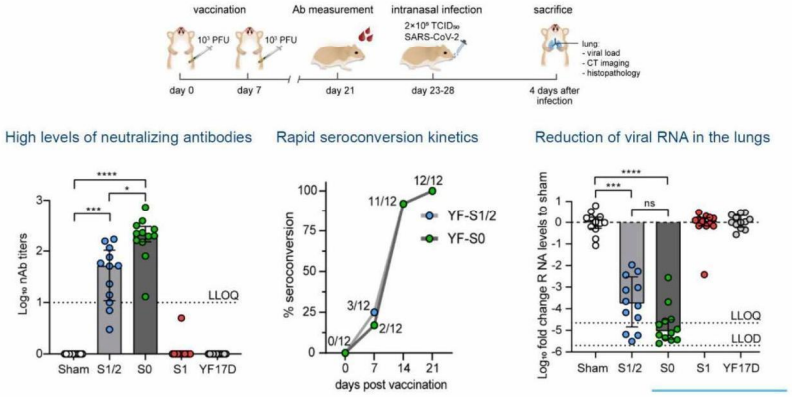
RegaVax(corona) August 18st 2020

Fig 2 A SARS-COV2 hamster infection model to allow testing of vaccine efficacy



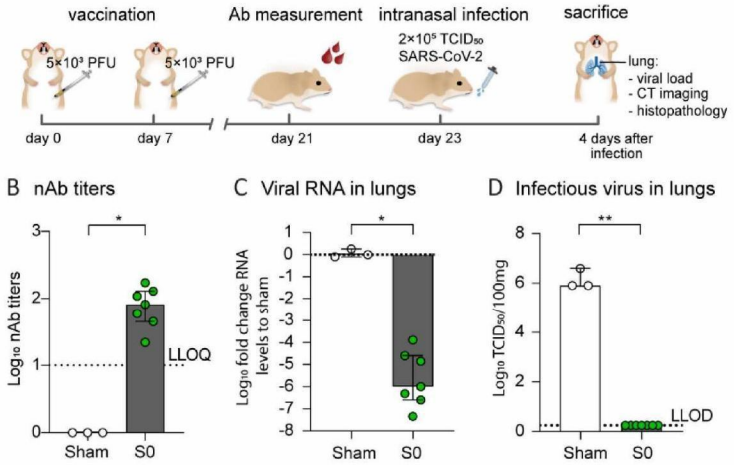
Our vaccine candidate induces consistently SARS-CoV-2 specific IgG as well as neutralizing Ab (nAb) in vaccinated hamsters. Moreover, it confers spectacular protection against aggressive infection. No or nearly no virus (RT-qPCR, virus titration) could be detected in the lungs of vaccinated animals (~500.000 fold reduction). The lungs of vaccinated hamsters that had been infected were near to normal, this in marked contrast to the control vaccinated animals. These data and the data shown below, as well as a large additional datapackage have been submitted for publication in a top peer reviewed international journal. It is currently available on the preprint server biorxiv (Sanchez-Filipe et al., 2020) (under review in Nature) www.biorxiv.org/content/10.1101/2020.07.08.193045v1

Fig 3A. RegaVax(corona) efficiently protects hamsters against SARS-COV2 infection



Hamsters were vaccinated (two doses of either construct S1 or the irrelevant RegaVax(rabies) vaccine). Three weeks later animals were inoculated intranasally with SARS-COV2 and infectious viral titers in the lungs were determined 4 days later (at the time of peak viral replication in control animals). ***Vaccine construct YF-S0*** *proved most efficient and results in most animals in sterilizing protection (note that the y-axis is on a logarithmic scale)*

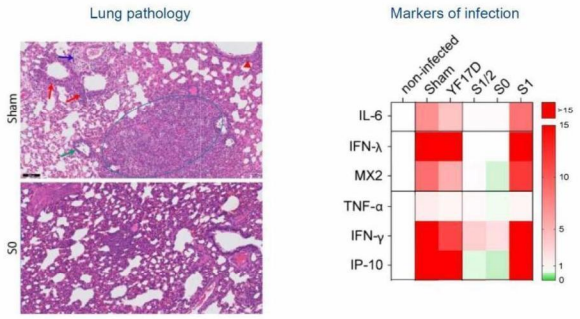
Fig 3B RegaVax(corona) efficiently protects hamsters against SARS-COV2 infection



Repeat experiment : Hamsters were vaccinated with two doses of construct YF-S0 or sham (control). Three weeks later animals were inoculated intranasally with SARS-COV2 and infectious viral titers in the lungs were determined 4 days later (at the time of peak viral replication in control animals).

Moreover, the vaccine candidate also prevents efficiently the transmission of the virus from infected to uninfected sentinels that are housed together in the same cage (either when only the sentinels were vaccinated or when both groups were vaccinated) (data not shown but available upon request).

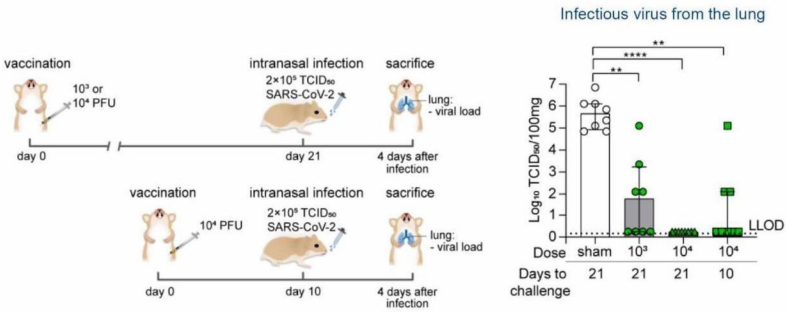
Fig 4 RegaVax(corona) efficiently protects hamsters against lung disease and markers of infection.



RegaVax(corona) protects lungs of infected hamsters against lung disease. Left panel, histological sections through the lungs of infected animals that had been vaccinated with sham or with YF-S0. Control animals developed typical COVID disease, YF-S0 vaccinated animals not. In the right hand panel increase in cytokine and other biomarkers were monitored. A heatmap is presented (the more intensive the color, the higher the levels of the marker). Construct YF-S0 caused a near to normalization of these makers that are typical for infection.

Vaccines against SARS-COV2 should ideally result rapidly and already after one single injection in protection against infection. We observed that RegaVax(corona) Already 10 days after one single injection of the vaccine, most hamsters were efficiently protected against intranasal virus infection. This is in line with the characteristics of the parent yellow fever vaccine that results already after one dose rapidly in a protective activity.

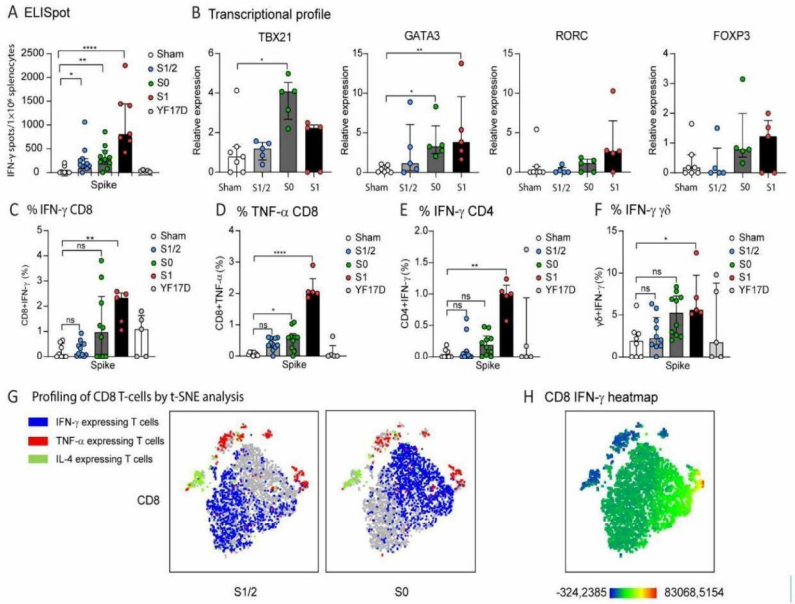
Fig 5 One single dose of RegaVax(corona) protects against SARS-CoV2 lung infection, in some hamsters already within 10 days after vaccination.



Hamsters were vaccinated with one single dose of RegaVax(corona) and were infected 10 of 21 days later. When vaccinated with a dose of 10⁴ PFU all animals that were challenged 21 days after vaccine had no longer infectious virus detectable in the lungs. Remarkably, most of the animals that were already challenged 10 days after the single dose vaccination had no longer detectable virus in their lungs.

It is becoming more and more clear from studies in man that the neutralizing antibody titers against SARS-CoV2 are decreasing rapidly. We have not yet been able to study the longevity and boostability of RegaVax(corona). However, given that the titers of neutralizing antibodies that are induced are high, it can be expected that it takes also longer of those to drop below levels that would no longer protect. Importantly, RegaVax(corona) results in an excellent and vigorous immune response; this akin to the parent YFV17D vaccine.

Fig 6 RegaVax(corona) results in an optimal and vigorous cell mediated immune response



RegaVax(corona) induces a vigorous cellular mediated immune response (for details, please see the Sanchez-Filipe et al., 2020)

THE PATH FORWARD Of the many vaccine candidates in development against SARS-COV2, RegaVax(corona) is, to the best of our knowledge, the only one that uses the yellow fever vaccine as a vector. Based on the evidence provided above and a large additional dataset (see Sanchez-Filipe et al., 2020) demonstrating immunogenicity (humoral and cellular) and efficacy and safety in preclinical models, it is concluded that RegaVax(corona) holds great promise to contribute to the global effort to combat the pandemic. Hamster data suggest that RegaVax(corona) will result, following one single dose in, possibly long-lasting, protective activity. Such characteristics are of utmost importance in a pandemic situation.

Obviously a number of vaccines from (large) pharma are being developed at a stunning speed and are currently already in clinical development and thus more advanced than ours [the reason for which is that these parties started the GMP production very early and at (financial) risk before having a full view on efficacy in preclinical models]. However, of the 120 or more vaccine candidates in some stage of development, ours is the only one that is based on the yellow fever vaccine as a vector. Most of the other vaccines can be grouped because they are based on the same technological approach. This bring the risk that if one vaccine within a certain class fails, that the entire class or at least a vast number of vaccine candidates, may fail. Since RegaVax is the only COVID-vaccine candidate based on the yellow fever vaccine, it offers an important and very much needed diversification to the landscape of SARS-CoV2 vaccine candidates. Moreover, and as outlined above, it's unique characteristics (single dose potency, excellent humoral and cellular immunity and likely also longevity) make it a particularly promising candidate in the battle against this pandemic virus.

We have stipulated the path forward to (pre-)clinical development (manufacturing, regulatory, etc.) with the aim to fast track for Phase 1/2a clinical testing in human volunteers as early as Q4/2020-Q1/2021. The phase 1 study will be carried out at the University hospitals of the University of Leuven. A competent CDMO (contract development and manufacturing organization) for the manufacturing of our vaccine Batavia www.bataviabiosciences.com/viral-vaccines/ has been identified. This CDMO will develop high-quality (GMP) material for pre-clinical safety and toxicity studies and the clinical trials. Scientific Technical Advice (STA) has been obtained in July 2from the Belgian and German regulatory authorities (FAGG and PEI). The meeting minutes are currently being reviewed by these organizations. During the STA meeting we also asked questions regarding the GMO aspect for the development of SARS-CoV2 vaccine. Both organizations agreed that our vaccine candidate may be considered as a class 1 pathogen, hence no particular problems are to be expected. It should be mentioned that the EU parliament adopted mid July 2020 new guidelines regarding aspects of GMO during manufacturing of SARS-CoV2 vaccine candidates. These guidelines will largely facilitate the further development of certain coronavirus vaccines, including ours.

The Phase 2a study will be multi-center and multi-country, using the Belgian Clinical Network, with University hospitals in Flanders and Wallonia as well as hospitals abroad. The plan is to consider such studies to be carried out with, but not limited to, the EUHA alliance (European University Hospital Alliance www.euhalliance.eu), to which for example also Erasmus MC belongs. The study will include 1340 subjects and will include a dose ranging study in different age groups, an additional safety study and immunogenicity studies.

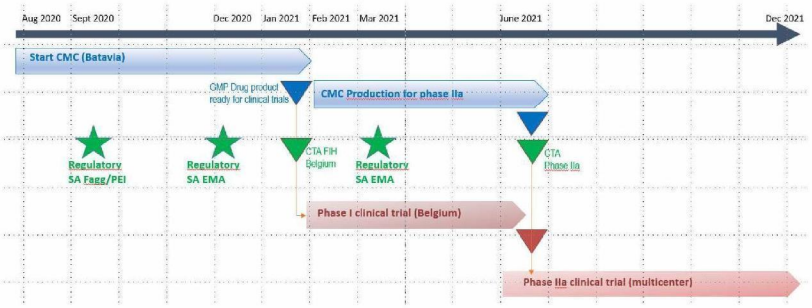


Figure: RegaVax overall development roadmap

So far the development of the technology has almost entirely been done with internal KU Leuven funding and donations of the public to the University for COVID-research. KU Leuven now needs additional funding to enable the further fast-track development of this unique and promising candidate. Moreover, the development of the coronavirus vaccine will also pave the way for the development of other vaccine candidates based on the RegaVax technology (information package available upon request).

A SPECIAL PURPOSE VEHICLE

To rapidly advance the development of RegaVax(corona), we will setup a dedicated legal entity under the form of a BV-SRL, a special purpose vehicle (SPV). This will allow to act quickly in terms of key decisions and in function of the very tight timelines which are needed not to lose momentum. The SPV will hold a license on the core IP of the project (with KU Leuven as Licensor)

A SEASONED AND DEDICATED MANAGEMENT TEAM

Mrs. 5.1.2e 5.1.2e 5.1.2e as acting CEO will lead the SPV. Esthel is an industry veteran which has ample experience in the commercialization of vaccine products. She joined GSK as Franchise head for the pediatric vaccines portfolio, where she was responsible for commercialization and late stage development of pediatric vaccines such as the rotavirus vaccine, meningitis vaccines, Infanrix hexa, the polio vaccine, MMR, MMRV and the hepatitis portfolio. In her Governmental Affairs role she worked on GSK's malaria vaccine and constructed a network with governmental and non-governmental organizations, such as USAID, DFID, NORAD, GAVI and UNICEF as well as with financial organizations such as the European Investment Bank (EIB) and the World Bank. For Pfizer she marketed and commercialized the meningitis portfolio in Europe and Australia, with adaptation of the vaccinology calendars for infants and adolescents in most of the EU countries and Australia. **Dr. Pierre Vandepapelière** will (initially) combine the function of Chief Scientific Officer (CSO) and Chief Medical Officer (CMO). He is MD, PhD with over 20 years of experience in the biopharma industry, including the clinical development of complex programs from preclinical to phase 3 and registration. He has among others expertise in vaccines and biological drugs. He has experience as leadership at GSK as well as managing small Biotech. He has global experience in pharmaceutical development: clinical, regulatory affairs (Europe, North America, Asia), business development, marketing, safety, medical affairs, pre-clinical, interactions with non-governmental organizations, other pharmaceutical and

biotech companies, investors, key opinion leaders, clinical investigators and contract research organizations. Next to Mrs. 5.1.2e and Dr. 5.1.2e a C-level entrepreneurial team will be recruited, including a CMC and CFO profile, with extensive experience in the vaccine field. Meanwhile, financial management will be managed by KU Leuven R&D (www.kuleuven.be/lrd). This KU Leuven Technology Transfer Office has long-standing experience with a wide spectrum of Tech Transfer and the set-up of spin-off companies (https://lrd.kuleuven.be/en/spinoff). KU Leuven has a portfolio of 135 spin-off companies.

The operational team will be supported by a very experienced and engaged **scientific advisory board (SAB)**, including **Prof. Dr.** 5.1.2e 5.1.2e who is professor of Virology at the Rega Institute for Medical Research at the KU Leuven and in whose laboratory (www.antivirals.be) the RegaVax-technology has been developed. He published ~500 scientific papers and is past-president of the International Society for Antiviral Research (www.isar-icar.com). He is co-founder of the KU Leuven spin-off company Okapi Sciences which had already 5 years after incorporation a successful exit (www.lrd.kuleuven.be/spinoff/cases/okapi-sciences). Several discoveries of the Neyts-lab have been licensed to the pharmaceutical industry, for example a class of highly potent dengue inhibitors that is now in clinical development at Janssen Pharmaceutica. **Dr.** 5.1.2e who is the scientific leader of the RegaVax project in the Neyts-lab; he is an expert in molecular virology and vaccinology and co-inventor of the technology, **Prof. Dr.** 5.1.2e 5.1.2e director of the Leuven University Vaccinology Center (LUVAC) she is an MD who has a long-standing expertise in coordinating major vaccine clinical trials at the Leuven University Hospitals (UZ Leuven). **Prof. Dr.** 5.1.2e is a medical doctor and clinical microbiologist at UZ Leuven (UZ Leuven) and associate professor at KU Leuven; he has an extensive expertise in international health and global health diplomacy; he was a member of the Belgian GEES (Group of Experts for the Exit-Strategy) and has been the spokesperson for the Belgian inter-federal crisis center during the acute phase of the COVID-19 outbreak ; **Dr.** 5.1.2e 5.1.2e who is an expert on yellow fever vaccination, he is Vice President Corporate Societal Responsibility at UCB, Former Associate Vice President and Director Global Strategic Pharmacovigilance at Sanofi Pasteur (producer of the YFV vaccine), former Vice President and Head Global Clinical Safety and Pharmacovigilance (UCB). For manufacturing two expert consultants will be involved, i.e. **Dr.** 5.1.2e 5.1.2e (former VP Head of R&D China @ GSK) and **Dr.** 5.1.2e former VP Head on New Product Development @ GSK. For regulatory affairs expert advisors include 5.1.2e 5.1.2e President of the International Alliance for Biological Standardization, **Dr.** 5.1.2e associate professor at the University of Namur and formerly (for 16 years) senior clinical assessor at FAMPH/FAGG and **Dr** 5.1.2e 5.1.2e former senior manager technical regulatory affairs at GSK; currently Director of Operations at the European Vaccine Initiative (EVI; www.euvaccine.eu). There will also be intensive interactions (as has been in the past, with EVI). The management and SAB will be governed by a governance board which will be -amongst others- composed of leading experts in the vaccine and biopharmaceutics business (TBD).

THE INVESTMENT NEEDED.

An investment is needed to reach an important value inflexion milestone, being the completion of a Phase I-IIa study. KU Leuven made 5 M€ available in July 2020 to secure the contract with the CDMO Batavia Biosciences (www.bataviabiosciences.com) to initiate the GMP production for the clinical studies. A term sheet is currently also being installed with the Wallonia based CDMO Univercells (www.univercells.com) who will be able to produce substantial volumes (100's millions of doses) of the vaccine at later stages (phase III and commercial) and this to secure sufficient vaccine production capacity in the future (thus on top of what will be produced by Batavia).

The pre-financing of KU Leuven of 5 M€ at its own risk allows to stay on track for now. To keep the momentum, we are currently preparing the setup of the SPV and secure the needed funding from both public and private investors in two tranches. A first tranche of 50M€ is needed as soon as possible but at the latest in November 2020, to fund activities for the first year of operations. This entails the chemistry and manufacturing of the drug substance and drug products for Phase 1/2a clinical trials and the conduct of initial phase of the clinical trials Phase 1/2a.

The project has been presented to Belgian's prime minister Mrs Sophie Wilmès and experts in the cabinet of the prime minister including Mr Nicolas de Callatay; there was an interest to explore avenues forward. As a result, there are now intensive interaction, with FPIM (the Belgian Federal Holding and Investment Company www.sfpi-fpim.be/en) via Mrs Goedele Ertveldt and Mrs Céline Vaessen; there is true enthusiasm and willingness to make a substantial investment, up to 10M€ possible. FPIM centrally manages the federal government's shareholdings, cooperates with the government on specific projects and pursues its own investment policy in the interests of the Belgian economy.

There have been multiple interactions with the cabinet of Flemish minister Mrs Hilde Crevits, in particular with M 5.1.2e A path forward is being stipulated whereby it is currently being exploited to make a substantial investment by PMV's (Participatie Maatschappij Vlaanderen). The vaccine has also been presented to Walloon minister-president Mr Elio Di Rupo who expressed an interest and suggested further discussions. Finally, after discussions with 5.1.2e and 5.1.2e 5.1.2e EU policy officers at DG Health who are responsible for SARS-CoV2 vaccine related matter; avenues for support from the European Investment Bank (EIB) will be explored. A substantial support by the various governments should allow to secure at least 10% private investment in the SPV in the first tranche.

<u>With the current letter/document we want to further explore whether a co-investment of the Dutch government would be possible</u>. Such investment could be made to support the process development and GMP production process at Batavia and also to support phase II clinical studies in Dutch hospitals. The costs of Batavia to allow phase I/II studies have been estimated at 6 M€ and the cost of phase II clinical trials in Dutch study centers are estimated at 1.5M€. Hence, in such scenario, a total investment by the Dutch Government of 7.5 M€ would be envisaged.

A fast decision and commitment of the respective governmental parties in the first tranche of 50 M€ in the SPV is urgently needed to maintain the fast-track development of RegaVax. KU Leuven LRD has a very successful track record in creating start-ups (over 130), very often venture capital (VC) backed companies. From our extensive experience with a wide investor network we know that raising VC money is an intensive and time-consuming process with due diligence that may take several months. There is currently no time for such efforts. We therefore believe that a predominant governmental

support is currently the only realistic way forward for this first tranche. It will allow to conduct the first in human (FIH) trials and engage with a more mature project in active fund-raising discussions with several private investors, financial and corporate VC funds to secure the second tranche. Hence investment participation of the respective Governments in the second tranche are expected to be much lower. Whereas in the first tranche investments from governments & EU should be dominant, this would be reversed in the second tranche.

In addition, the SPV will obviously also strive to apply for available non-dilutive financial resources such as from CEPI, the Bill & Melinda Gates foundation (BMGF) and other funding bodies. 5.1.2e 5.1.2e and team have a long-standing success rate in obtaining substantial funding from organizations such as the Wellcome Trust, the BMGF and several others.

Once a phase I study has been positively concluded, and a multicenter phase IIa has been completed, the SPV will be in an optimal position to either securing funding for late stage development and large-scale production or establish a partnership with a large pharmaceutical company (to conduct the Phase III studies).

KU Leuven will contribute a worldwide exclusive royalty-free transferable license to the granted mother patent and the COVID-19 patent applications (covering various vaccine constructs with coronavirus spike protein inserted) in the field of beta-coronaviridae for human medical applications and a license to the know-how. KU Leuven will also contribute the results of the preclinical research (*in vivo* POC study), financed at risk by KU Leuven to the SPV.

As public governmental funding is considered, it is important to take state support regulations into consideration. Such regulations state that public organizations cannot provide a substantial commercial advantage to certain organizations and hence any transaction needs to be market conform. It is important to mention that the European Commission (EC) has significantly relaxed the regulations for subsidizing COVID-19 related projects, which might also be a source for additional funding of the SPV structure further down the road.

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