PAUL-MARTINI-STIFTUNG

Symposium der Paul-Martini-Stiftung (PMS) am 2. März 2021

im Rahmen des 6th German Pharm-Tox Summits

Kontakt:
Dr. Siegfried Throm
Telefon 030 20604-300
info@paul-martini-stiftung.de

„Herausforderungen bei der Entwicklung und Produktion von Impfstoffen gegen COVID-19"

PD Dr. Bestehorn/VKliPha und **Dr. Siegfried Throm**/Geschäftsführendes Vorstandsmitglied der PMS und Geschäftsführer Forschung, Entwicklung, Innovation (FEI) im vfa begrüßen die 250 via livestream Teilnehmenden zu diesem von der PMS unterstützten Symposium; dieses findet wegen der Corona-Pandemie rein virtuell statt.
Throm stellt die vom vfa getragene PMS kurz vor.

Dr. Siegfried Throm / Geschäftsführer FEI im vfa referiert zu **"Herausforderungen bei der Entwicklung von mRNA-Impfstoffen".** Er gibt zunächst einen Überblick über den Stand der Entwicklung von COVID-19 Impfstoffen (182 in präklinischer, 73 in klinischer Entwicklung, davon 3 in der EU zugelassen und 3 im Zulassungsverfahren), die 3 wichtigsten COVID-Impfstofftypen (Protein/Vektorvirus/mRNA-Impfstoffe) und deren Verteilung in der klinischen und präklinischen Pipeline. Danach geht er auf die wichtigsten Vorteile von mRNA-Impfstoffen ein und stellt die Schritte bei der Entwicklung des weltweit ersten, in 10 Monaten zur Zulassung gebrachten mRNA-Impfstoffs von BioNTech/Pfizer vor. Aus 20 Impfstoff-Kandidaten nach dem präklinischen Screening wurden zunächst vier in die klinische Phase gebracht, wovon einer, BNT162b2, mit rund 44.000 Teilnehmenden in einer Zulassungsstudie getestet wurde. Dabei wurden alle primären Endpunkte erreicht: Die Schutzwirkung vor symptomatischen COVID-Erkrankungen betrug 95 %, auch bei älteren Personen, bei guter Verträglichkeit. Ähnliche Ergebnisse wurden auch mit dem zweiten bisher zugelassenen mRNA-Impfstoff von Moderna erzielt. Zusammenfassend liegen die Chancen von mRNA-Impfstoffen im raschen Impfstoff-Design, der schnellen Produktion ohne Tiermaterialien und Viren, der Nicht-Integration der mRNA in die Zell-DNA sowie darin, dass für diese Impfstoffe kein Adjuvans benötigt wird. Herausforderungen bestehen in der Empfindlichkeit der mRNA gegen Ribonukleasen, der Notwendigkeit von Tiefkühllagerung (-20 bis -70 °C) und der "Verpackung" der mRNA in dafür geeignete Lipidnanopartikel. Eine besondere Herausforderung war auch die Durchführung der Zulassungs-

Hausvogteiplatz 13
10117 Berlin
www.paul-martini-stiftung.de

studie unter Corona-Bedingungen in 5 Ländern auf 4 Kontinenten in nur 3 Monaten.
Diese erstmalige erfolgreiche Entwicklung lässt hoffen, dass mRNA-Impfstoffe auch gegen andere Infektionskrankheiten wie Tuberkulose, HIV und Malaria entwickelt werden können.

Dr. Ralf Wagner / Head Section Viral Vaccines/PEI informs on **"Regulatory Challenges and requirements for the approval of mRNA COVID 19 vaccines".**

He begins with the objectives (fast approvals of effective and safe COVID 19 vaccines) and the "Regulatory requirements and flexibilities for COVID 19 vaccines"

I. Quality requirements for COVID 19 vaccines: Here he gives an overview on model specifications for mRNA drug substances and mRNA vaccines with all the parameters which have to be tested and complied with before batch release.
II. Pre/Non-clinical aspects: In 2020 international regulatory agencies have agreed that prior to phase IIb/III studies no GLP repeat dose toxicity studies would have to be completed with COVID 19 vaccine candidates. Yet, there has to be relevant immunogenicity data and the potential risks of disease enhancement (Antibody-Dependent Enhancement, ADE and Enhanced Respiratory Disease, ERD) have to be addressed.
III. Specific requirements for clinical studies: For phase I/IIa studies healthy younger persons should be recruited to the beginning and according to a staggered approach later on persons with comorbidities and of older age. Aims of clinical development are the characterisation of immunogenicity, generation of safety data (follow-up for at least 2 months and long-term follow-up for 2 years after the second dose) and generation of efficacy data the latter being extremely challenging and complex under COVID pandemic conditions.

Finally Ralf Wagner presented four future regulatory perspectives:
Adaption of vaccine to protect against circulating SARS-CoV-2 variants. (The European Medicines Agency (EMA) has just published its reflection paper with guidance for vaccine manufacturers on the required data.)
Ongoing and long-term safety evaluation on the basis of data from ongoing clinical trials and pharmacovigilance investigations.
Long-term efficacy/immunogenicity evaluation on the basis of data from ongoing effectiveness studies and immune titers.
Conversion of the conditional approvals to regular marketing authorisations.

Dr. Jean Lang / **Associate Vice President R&D Sanofi Pasteur**
informs on
"Challenges in the development of protein-based vaccines."

To demonstrate the pressure to develop COVID vaccines he presents up-to-date figures for COVID cases in various countries; worldwide 2.5 m people have died with or due to a SARS-CoV-2 infection. Antibody responses to such an infection vary considerably from patient to patient. He then gives an overview on the various vaccine platforms (RNA, DNA, recombinant protein, vectoral, inactivated and live attenuated vaccines) which are all used. Sanofi is pursuing two COVID vaccine projects:

1. a recombinant protein vaccine in cooperation with the US Biomedical Advanced Research and Development Authority (BARDA). This vaccine is produced with baculoviruses in insect cells and uses an adjuvant from the cooperation partner GSK.
2. an mRNA vaccine in cooperation with Translate Bio.

He then explains what is done to fasten development without compromising quality, safety and efficacy and he shows the 8 steps necessary to manufacture the protein vaccine – beginning with the production of the DNA template followed by the production of the antigen till the final vaccine with the adjuvant. Manufacturing will take place at 6 sites in the US and 5 in the EU. Advance purchase agreements have been concluded primarily with the US, UK, the EU and the COVAX (COVID-19 Vaccines Global Access) Facility, an initiative i.a. of the World Health Organisation, GAVI (Global Alliance for Vaccines and Immunisation) and CEPI (Coalition for Epidemic Preparedness Innovations) to secure supply of COVID vaccines for low- and middle-income countries. Sanofi is also providing manufacturing capacities for the BioNTech/ Pfizer and the J&J vaccine. New variants (UK, South Africa, Brazil e.g.) pose current and future challenges.
Sanofi's protein vaccine will be tested in phase III trials in Q2 and might get first (emergency) approvals in Q4 2021.

Dr. Christine Dahlke / Senior Post Doc UKE and Project Manager/Deutsches Zentrum für Infektionsforschung (DZIF), Hamburg speaks about
"The development of a viral vector vaccine against COVID-19: First-In-Human trial testing MVA-SARS-2-S".

She begins with an overview on epidemics and pandemics which shows that these are happening more and more frequently (MERS, SARS, ZIKA, Ebola, SARS-CoV-2). In the past reactive strategies have been applied with the result that specific remedies could only be developed after the outbreak had surpassed its height. What is needed is a proactive strategy which would allow a head start at the beginning of an epidemic. To enable this CEPI has been founded in 2016 and WHO has developed a list of prioritized pathogens which might trigger the next

major epidemic. This list contains i.a. Ebola, Lassa, Zika, MERS and "Disease X" – which is now COVID-19.
To be better prepared a plug and play approach should be used. The DZIF is developing an approach on the basis of a non-replicating viral vector vaccine: MVA (Modified Vaccinia Ankara) which had been used as a smallpox vaccine from 1968 – 1985. And since 1992 there have been numerous further experiences with this vector virus as it was used in trials to develop vaccines against HIV, tuberculosis, Ebola and Zika. Therefore, a lot of safety data for this vector virus is already available.
An MVA-based vaccine candidate against MERS was developed in 2013 and had been tested in dromedary camels, showing protection against MERS-CoV. In 2017 a first-in-human study showed a favorable safety profile, and a boost immunization induced humoral and cell-mediated responses against MERS. A later boost immunization effected a strong and long-lasting antibody response. Therefore, an MVA based SARS-CoV-2 vaccine seems to be a good choice. It is developed together with DZIF colleagues from Munich and Marburg. In a phase I study with 30 participants dosed on day 0 and day 28 safety data has been satisfying. Yet, immunogenicity has been lower than expected. Therefore, modified constructs are in development and will be tested in the near future.

Berlin, 10. März 2021