MVA Platform Technology Development

IDT Info Package, 2023

Introduction to IDT Biologika

CDMO Sites

Owner

Klocke Holding GmbH
Carsten Klocke and Stefan Klocke

IDT Biologika
Dessau (Germany)

End to end manufacturing of vaccines, CGTs and biologics for clinical trials and commercial supply. EMA, FDA and ANVISA approved site.

IDT Biologika
Rockville (USA)

Manufacturing according US FDA regulations for development and manufacturing of phase I/II investigational medicinal products. Approved by US CDC
EHS/ ISO-certified.

IDT Biologika / ZENIT
Magdeburg (Germany)

Process development for viral vector and cell and gene therapy technologies up to BSL2

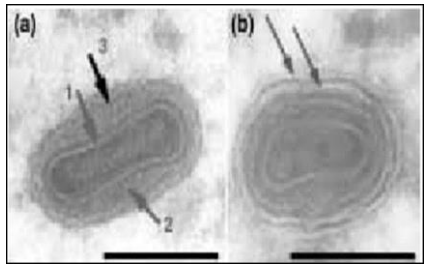
1,900
employees in 2021

€ 293 m
turnover in 2021

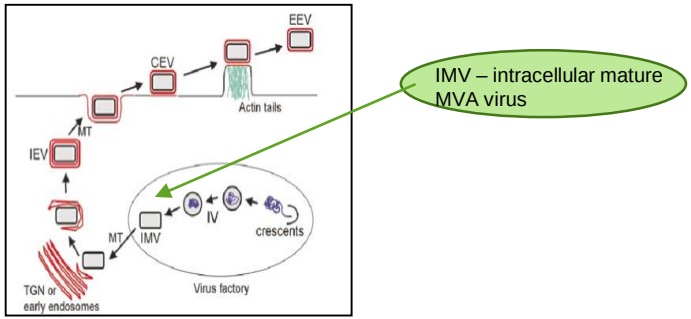
€ 550 m
invested by IDT since 1993

MVA Platform Development

- IDT started MVA vector development in 1997
- Major published projects with Oxford University, Bavarian Nordic, Geovax and Ludwig Maximilian University Munich, CEPI
- Vector vaccine candidates for Malaria, Tuberculosis, HBV, HIV, Smallpox, Filoviruses, MERS CoV, SARS CoV2
- IDT developed several technologies for manufacturing – latest DF-1 cell technology (Cell line licensed from Minnesota State University)
- Major achievement – High resolution large scale DSP technology for purification of IMV virus particles



Vaccinia- 4 virus configurations - Ref: Journal of General Virology (2002), 83, 2915-2931



MVA Manufacturing @ IDT

- Large Scale MVA Manufacturing has been established based on DF-1 cell line technology
- Upstream process is successfully established in cell stacks (16xCS40, total cell cultivation area: 40.71 m^2)
- Downstream process is based on Virus extraction, enzymatic DNA removal, and TFF, resulting in high yields (1x10E7 IU/cm^2) and consistent batch to batch quality
- Aseptic validation for BDS as well as for DP has been performed and is maintained
- Upscaling to fixed bed bioreactors is currently ongoing and will be ready to implement in 2023
  - On a development scale IDT Biologika achieved yields up to 10x higher in Univercells “Hydro” (2.4m²) fixed-bed compared to PALLs iCellis system (up to 4m²)
  - IDT Biologika successfully performed two feasibility runs on Univercells 200m² fixed-bed (“Nitro”) in the Nevoline system achieving titer yields of ≥1.0x107 IU/cm² (minimum requirement) using the IDT Biologika owned MVA-SARS-2-ST construct.
  - Further development activities were performed to streamline the approach, resulting in a robust USP process suitable for manufacturing recombinant MVA .

Development of a live recombinant vaccine against MERS CoV

Until now, IDT has provided the following MVA-MERS-S vaccines to be tested in clinical trials:

Product	Phase	Registration	Funding	Publication
MVA-MERS-S (CEF)	Ia	NCT03615911	DZIF	Koch et al., 2020; Fathi et al., 2022; Weskamm et al., 2022
MVA-MERS-S (DF-1)	**Ib**	**NCT04119440**	**CEPI**	**In preparation**
MVA-MERS-S (DF-1)	II	At planning stage with CEPI		
MVA-SARS-2-S	Ia	NCT04569383	DZIF, BMBF	**in preparation**
MVA-SARS-2-ST booster	Ib	NCT04895449	BMBF	**in preparation**
MVA-SARS-2-ST inhaled booster	I	NCT05226390	State of Lower Saxony	

- IDT successfully moved the MVA manufacturing technology from the CEF platform (chicken embryo fibroblast) to the more scalable DF-1 platform (spontaneously immortalized chicken fibroblasts).
- The clinical Phase 1a study (funded by DZIF) was using CEF derived material, while following clinical trials (either CEPI, BMBF or DZIF funded) were using DF-1 derived material.

Achievements of Phase 1a (CEF material)

Benign safety profile with only transient mild-to-moderate reactogenicity. Participants experienced no severe or serious adverse events (AE). Local reactions, headache and fatigue were the most common adverse events (AEs) and seen in 69% (18/26), 62% (16/26) and 65% (17/26)

20/23 (87%) of all vaccinees showed **seroconversion** using a MERS-CoV-S1-ELISA Binding antibody titres correlated with MERS-CoV-specific neutralizing antibodies.

Specific **T-cell responses** were detected in **20/23 (87%)** of all immunized study participants.

Safety and immunogenicity of a modified vaccinia virus Ankara vector vaccine candidate for Middle East respiratory syndrome: an open-label, phase 1 trial

Till Koch*, Christine Dahlke*, Anahita Fathi, Alexandra Kupke, Verena Krähling, Nisreen M A Okba, Sandro Halwe, Cornelius Rohde, Markus Eickmann, Asisa Volz, Thomas Hesterkamp, Alen Jambrecina, Saskia Borregaard, My L Ly, Madeleine E Zinser, Etienne Bartels, Joseph S H Poetsch, Reza Neumann, Robert Fux, Stefan Schmiedel, Ansgar W Lohse, Bart L Haagmans, Gerd Sutter, Stephan Becker, Marylyn M Addo

Summary

Background The Middle East respiratory syndrome coronavirus (MERS-CoV) causes a respiratory disease with a case fatality rate of up to 35%. Given its potential to cause a public health emergency and the absence of efficacious drugs or vaccines, MERS is one of the WHO priority diseases warranting urgent research and development of countermeasures. We aimed to assess safety and tolerability of an anti-MERS-CoV modified vaccinia virus Ankara (MVA)-based vaccine candidate that expresses the MERS-CoV spike glycoprotein, MVA-MERS-S, in healthy adults.

Methods This open-label, phase 1 trial was done at the University Medical Center Hamburg-Eppendorf (Hamburg, Germany). Participants were healthy men and women aged 18–55 years with no clinically significant health problems as determined during medical history and physical examination, a body-mass index of 18·5–30·0 kg/m² and weight of more than 50 kg at screening, and a negative pregnancy test for women. A key exclusion criterion was a previous MVA vaccination. For the prime immunisation, participants received doses of 1×10^7 plaque-forming unit (PFU; low-dose group) or 1×10^8 PFU (high-dose group) MVA-MERS-S intramuscularly. A second identical dose was administered intramuscularly as a booster immunisation 28 days after first injection. As a control group for immunogenicity analyses, blood samples were drawn at identical study timepoints from six healthy adults, who did not receive any injections. The primary objectives of the study were safety and tolerability of the two dosage levels and reactogenicity after administration. Immunogenicity was assessed as a secondary endpoint by ELISA and neutralisation tests. T-cell immunity was evaluated by interferon-γ-linked enzyme-linked immune absorbent spot assay. All participants who were vaccinated at least once were included in the safety analysis. Immunogenicity was analysed in the participants who completed 6 months of follow-up. This trial is registered with ClinicalTrials.gov, NCT03615911, and EudraCT, 2014-003195-23.

Findings From Dec 17, 2017, to June 5, 2018, 26 participants (14 in the low-dose group and 12 in the high-dose group) were enrolled and received the first dose of the vaccine according to their group allocation. Of these, 23 participants (12 in the low-dose group and 11 in the high-dose group) received a second dose of MVA-MERS-S according to their group allocation after a 28-day interval and completed follow-up. Homologous prime–boost immunisation with MVA-MERS-S revealed a benign safety profile with only transient mild-to-moderate reactogenicity. Participants had no severe or serious adverse events. 67 vaccine-related adverse events were reported in ten (71%) of 14 participants in the low-dose group, and 111 were reported in ten (83%) of 12 participants in the high-dose group. Solicited local reactions were the most common adverse events: pain was observed in 17 (65%; seven in the low-dose group vs ten in the high-dose group) participants, swelling in ten (38%; two vs eight) participants, and induration in ten (38%; one vs nine) participants. Headaches (observed in seven participants in the low-dose group vs nine in the high-dose group) and fatigue or malaise (ten vs seven participants) were the most common solicited systemic adverse events. All adverse events resolved swiftly (within 1–3 days) and without sequelae. Following booster immunisation, nine (75%) of 12 participants in the low-dose group and 11 (100%) participants in the high-dose group showed seroconversion using a MERS-CoV S1 ELISA at any timepoint during the study. Binding antibody titres correlated with MERS-CoV-specific neutralising antibodies (Spearman's correlation r=0·86 [95% CI 0·6960–0·9427], p=0·0001). MERS-CoV spike-specific T-cell responses were detected in ten (83%) of 12 immunised participants in the low-dose group and ten (91%) of 11 immunised participants in the high-dose group.

Interpretation Vaccination with MVA-MERS-S had a favourable safety profile without serious or severe adverse events. Homologous prime–boost immunisation induced humoral and cell-mediated responses against MERS-CoV. A dose-effect relationship was demonstrated for reactogenicity, but not for vaccine-induced immune responses. The data presented here support further clinical testing of MVA-MERS-S in larger cohorts to advance MERS vaccine development.

Funding German Center for Infection Research.

Achievements of Phase 1a (CEF material)

Persistence of MERS-CoV-spike-specific B cells and antibodies after late third immunization with the MVA-MERS-S vaccine

Leonie M. Weskamm,[1,2,3,*] Anahita Fathi,[1,2,3,6] Matthijs P. Raadsen,[7] Anna Z. Mykytyn,[7] Till Koch,[1,2,3,6] Michael Spohn,[8,9,10] Monika Friedrich,[1,2,3] MVA-MERS-S Study Group, Bart L. Haagmans,[7] Stephan Becker,[4,11] Gerd Sutter,[5,12] Christine Dahlke,[1,2,3,13,14,*] and Marylyn M. Addo[1,2,3,6,13]

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Increased neutralization and IgG epitope identification after MVA-MERS-S booster vaccination against Middle East respiratory syndrome

Anahita Fathi[1,2,3,4], Christine Dahlke[1,2,3], Verena Krähling[5,6], Alexandra Kupke[5,6], Nisreen M. A. Okba[7], Matthijs P. Raadsen[7], Jasmin Heidepriem[8], Marcel A. Müller[9,10], Grigori Paris[8], Susan Lassen[1,2,3], Michael Klüver[5,6], Asisa Volz[11,12], Till Koch[2,3,4], My L. Ly[1,2,3], Monika Friedrich[1,2,3], Robert Fux[13,14], Alina Tscherne[13,14], Georgia Kalodimou[13,14], Stefan Schmiedel[3,4], Victor M. Corman[9,10], Thomas Hesterkamp[15], Christian Drosten[9,10], Felix F. Loeffler[8], Bart L. Haagmans[7], Gerd Sutter[13,14], Stephan Becker[5,6] & Marylyn M. Addo[1,2,3]✉

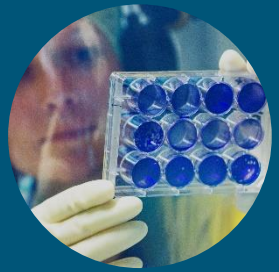
Durability and long-term persistance after MVA-MERS-S booster vaccination

Summary on MVA-MERS-S Vaccine Development

- The MVA-MERS-S Vaccine Development program was started by DZIF, and since 2018 is continued by CEPI
- IDT successfully transitioned manufacturing from CEF based platform to DF-1 based platform, leveraging synergies between MERS and SARS programs
- MVA-MERS-S (DF-1) showed excellent safety and immunogenicity profile in preclinical studies
- MVA-MERS-S (CEF) showed excellent safety and immunogenicity profile in Phase 1a
- Phase Ib (DF1 derived material) is currently ongoing and preparation for upscaling for CTM2 manufacturing are initiated
- Phase IIa (DF-1 derived material) will be conducted in an endemic area (2024/2025)
- Alignment with Saudi FDA on Emergency Use Application and Commercialization will guide next steps

Thank you for your kind attention

German Center for Infection Research



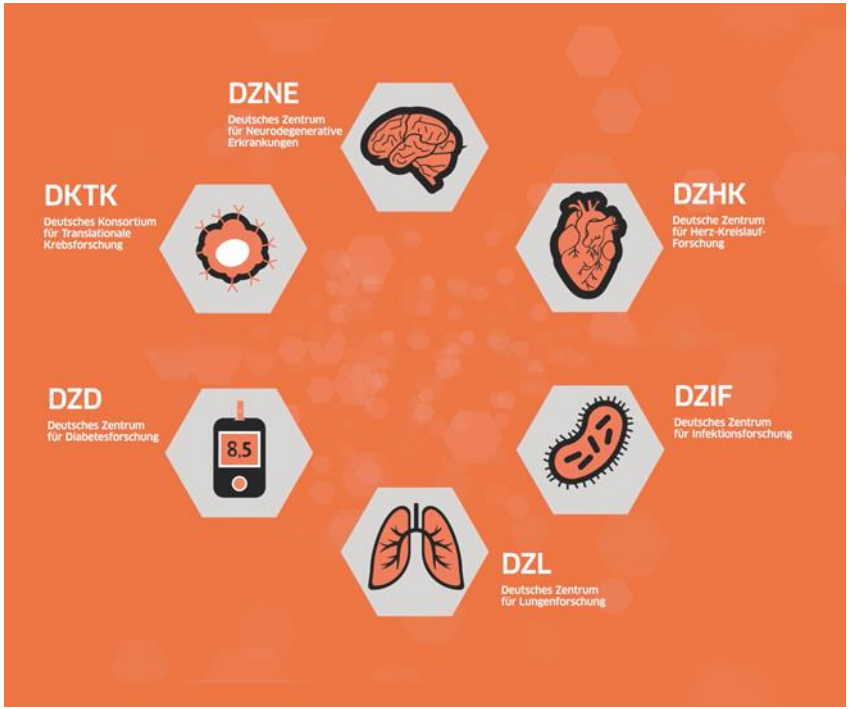
United against infections

Over **700** doctors and scientists from **35** institutions collaborate in a network,

jointly developing new approaches to prevent, diagnose and treat infectious diseases,

aiming to effectively translate research results from bench to bedside, and vice versa.

One of eight German Centers for Health Research



DZG in brief

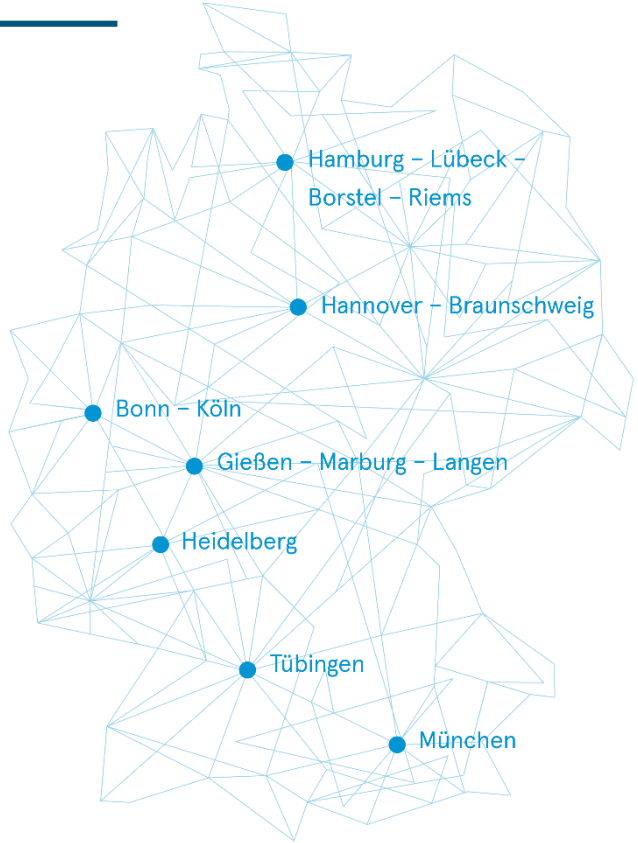
The goal: to combat major widespread diseases more effectively

The financing: The Federal Ministry of Education and Research (BMBF; 90%) and the respective states of partner sites (10%)

The near future: Two further DZG on

- Mental Health (start in 2023)
- Child and Adolescent Health

DZIF sites, member institutions and partners



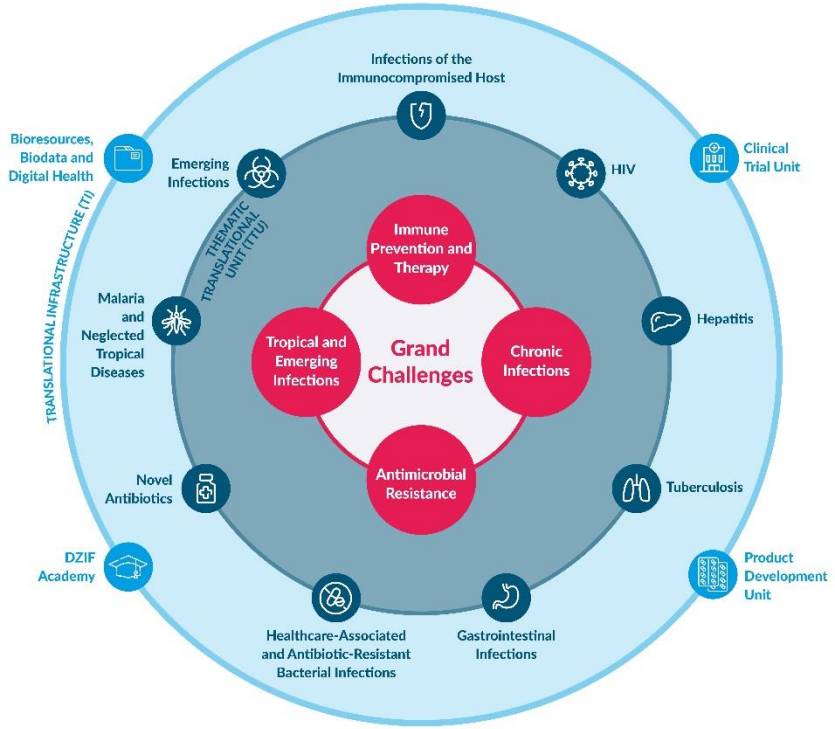
- Universities
- University hospitals
- Non-university research institutions
- Federal institutions (research sections)
  - The Federal Institute for Vaccines and Biomedicines (PEI)
  - The Federal Institute for Drugs and Medical Devices (BfArM)
  - The Robert Koch Institute (RKI)
  - The Federal Research Institute for Animal Health (FLI)

Faster towards new applications

Vision: More effective and rapid translation of scientific results to enhance health and quality of life of patients

Mission: To support scientists and clinicians in developing biomedical discoveries to novel preventive, diagnostic and therapeutic products

Focus on specific infectious disease threats connected to the GC

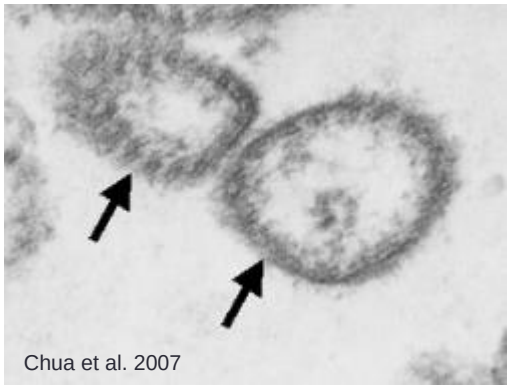


9 Research Areas

- Infection of the Immunocompromised Host
- HIV
- Hepatitis
- Tuberculosis
- Gastrointestinal Infections
- Healthcare-Associated and Antibiotic-Resistant Bacterial Infections
- Novel Antibiotics
- Malaria and Neglected Tropical Diseases
- Emerging Infections

MVA-Nipah – Vaccine Candidate

PROJECT PROPOSAL



Chua et al. 2007

MVA-Nipah Project Proposal

- **The project aims to develop a MVA-based Nipah vaccine candidate**

- For this a consortium will be built by
  - IDT, VABIOTECH, VG-CARE and DZIF (as coordinator)

- Four major milestones should be reached:

  1. Selection of MVA-Nipah Lead candidate
  2. Establishing of animal models and PoC
  3. Production of GMP material
  4. Phase I clinical study demonstrating safety and immunogenicity

Nipah Virus & Competition

Pathogen

- **Nipah virus is a bat-borne zoonotic henipavirus that causes severe infection in humans and other animals**
- Prototype member of the genus *Henipavirus* in the family *Paramyxoviridae*
- Nipah virus genome is a non segmented negative-sense, single-stranded RNA
- Particles are variable in shape (filamentous or spherical) and contain a helical nucleocapsid

Epidemiology

- First human infections were identified in Malaysia 1998
- Listed by World Health Organization (WHO) as a likely cause of future epidemic (Blue print R&D initiative)
- Frequent small outbreaks in Bangladesh since 2001 / periodically identification of Nipah virus in eastern India
- Evidence of Nipah virus in Chiropteran bats in a number of countries, including Cambodia, Ghana, Indonesia, Madagascar, the Philippines and Thailand

Disease

- Severe systemic and often fatal neurologic (encephalitis) and/or respiratory disease
- Case fatality rate estimated at 40% to 75% by WHO

Competition

- Several pre-clinical vaccine candidates and approaches
- Moderna: Phase I (with NIAID support): pre-F/G
- Auro Vaccines LLC: Phase I (HeV-sG-V): Subunit
- CEPI: Phase I: rVSV-Nipah (PHV02)

MVA-Nipah Vaccine Candidate

Approach/Biology

- Modified Vaccinia virus Ankara (MVA) is an attenuated poxvirus vaccine strain
- MVA-Nipah: MVA delivering Nipah protein (tbd)
- Strong humoral and cellular immune response
- Very good safety profile

Status

Preclinical Development
First MVA-Nipah constructs and data generated

Manufacturing
High expertise with MVA process at IDT

Consortium

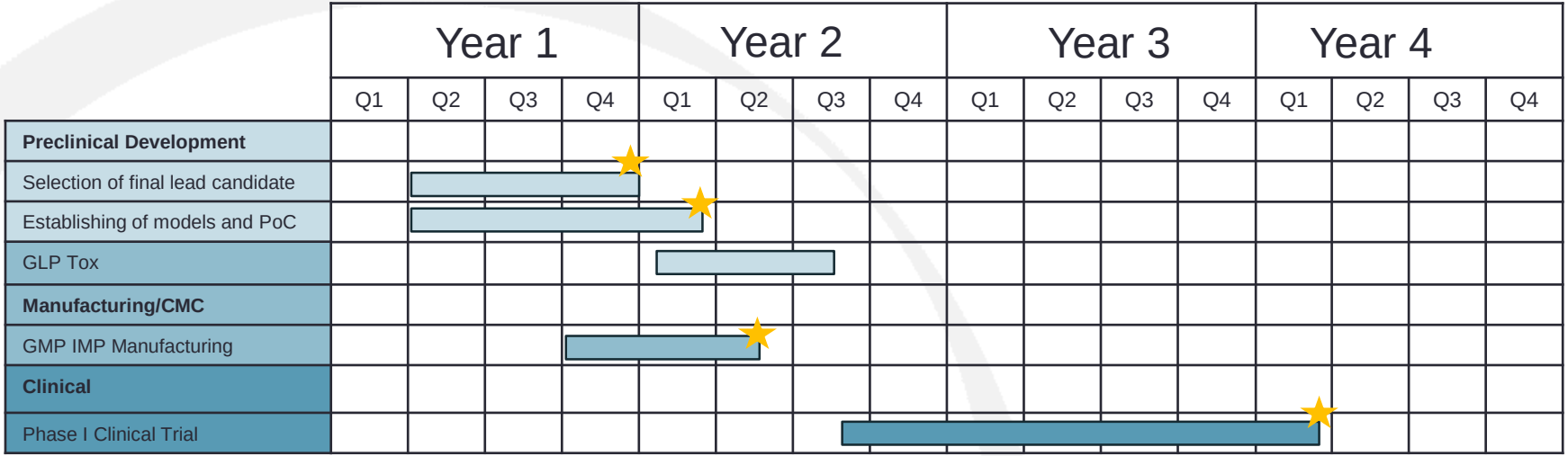
Coordinator: TPMO/DZIF
Klaus Schwamborn

Steering Committee:
Representatives of DZIF, IDT, VG-CARE

Reasons to believe

- Kalodimou et al. in 2019 show promising immunogenicity data
- Build on experience and expertise on MVA-MERS and MVA-SARS-CoV2 (CMC, dosing, schedule etc.)

MVA-Nipah Project plan* & key milestones



Future perspective

- **Phase I Clinical Trial planned for 2024/2025**

Funding

- **DZIF** – planned to fund preclinical development and manufacturing of IMP (TBC)
- **VG-CARE/BMBF** – planned to fund clinical phase I (TBC)

***Subject to available funding**

key milestones ★

MVA-Nipah - Budget

Institution/PI	Work package	High Level Cost estimation (TBC)
Gerd Sutter/Asisa Volz (DZIF)	Selection of MVA-Nipah Lead candidate	~ 0.25 M€
Stephan Becker (DZIF)	Establishing of animal models and PoC	~ 1.0 M€
Simone Kardinahl (IDT)	Production of GMP material	~ 3.0 M€
Le Huu Song Marylyn Addo (VG-CARE/DZIF)	Phase I clinical study demonstrating safety and immunogenicity	~ 1.5 M€
TBD	Epidemiological studies of Nipah virus	~ M€ (TBD)
		Total ~ 5.75 M€ + (~ 4 years)

Consortium: Structure & Responsibilities

Steering Committe (Klaus, Simone, Velavan, TBD)

IDT Simone Kardinahl **Process, Manufacturing**	**DZIF** Klaus Schwamborn **PROJECT LEAD**	**VG-CARE** Thiru Velavan **VG-CARE Coordination**
VABIOTECH Do Tuan Dat **Tech Transfer**	**DZIF** Gerd Sutter/ Asisa Volz **Lead identification**	**VG-CARE** TBD **Epidemiology**
	DZIF Stefan Becker **Animal Model**	**VG-CARE** Le Huu Song **Clinical**
	DZIF Marylyn Addo **Analysis, Clinical Support**	

Industry ⟺ **DZIF** ⟺ **VG - CARE**

THANK YOU