Overview of Funded Research on MERS-CoV

Middle East Respiratory Syndrome – Coronavirus (MERS-CoV)

October 2015

GLOBAL RESEARCH COLLABORATION FOR INFECTIOUS DISEASE PREPAREDNESS

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1. EU FUNDED RESEARCH (OCTOBER 2015)

Of the projects described below, only SILVER has currently made a tangible and significant contribution to MERS research. E-com@EU has used MERS as an example for risk perception, success and failures of communication strategies in epidemics. VIROGENESIS is a very new H2020 project on virus discovery that will work on many different viruses, MERS just being one example of many. PREPARE is an important project on the clinical management of patients in the case of emerging epidemics in Europe, but it has not worked yet on MERS since there is not currently an epidemic in Europe.

- **SILVER [1] (Small-molecule Inhibitor Leads Versus Emerging and neglected RNA viruses)** is a drug design program to face emerging diseases caused by RNA viruses. Around the end of 2012, the SILVER project activated its outbreak pipeline to address the emerging MERS‐coronavirus, for which neither vaccination nor antiviral therapy was available. During the final two years of the SILVER project, nine SILVER partners with different backgrounds and expertise (virology, bioinformatics, enzymology, structural biology, and medicinal chemistry) collaborated closely on the characterization of the new virus, the development of a MERS‐CoV toolbox, and the identification and development of inhibitory compounds and strategies.

  Despite the inherently unpredictable nature/timing of this outbreak and the fact that the origin (virus family wise) of new agents cannot be anticipated, and despite the obvious difficulties of running an outbreak pipeline in nine different locations, it can be concluded that SILVER's response was timely and meaningful. Although antiviral drug development in general remains a time-consuming process, solid leads for further anti-coronavirus research were obtained, trans-European collaborations were initiated and strengthened, and SILVER contributed to creating a better starting position to combat this and future zoonotic coronavirus outbreaks.

[1] https://www.silver-europe.com/ - FP7 funded project - start: 2010-10-01; end: 2015-03-31 - EU contribution: € 12.000.000

- **E-com@eu**[2] **(Effective Communication in Outbreak Management: development of an evidence-based tool for Europe).** Literature reviews were completed on risk perception.The success and failures of communication strategies implemented by institutions such as the ECDC and the CDC during the H1N1 pandemic were analyzed, as well as epidemiological characteristics of past and current outbreaks (H1N1, MERS) as disease models to create a simulation.

- **VIROGENESIS** [3] **(Virus discovery and epidemic tracing from high throughput metagenomic sequencing).** Next-generation sequencing (NGS) analysis pipelines are rapidly becoming part of the routine repertoire of research, clinical and public health laboratories in the public sector and private industry. Middle East Respiratory Syndrome-coronavirus (MERS-CoV) is only one example of the many recent virus discoveries made through analysis of NGS data. Yet, only a small part of the several millions of short-length sequence fragments generated by NGS machineries, many of which are expected to be of viral origin, can be analyzed with current methods in bioinformatics. Even for well-known (pathogenic) viruses, proper epidemiological analyses are becoming more and more difficult due to the lack of bioinformatics tools that can handle the large and growing size of datasets.

  The VIROGENESIS consortium will overcome the most pressing bioinformatics obstacles to making full use of NGS by developing a software platform for end-users with tools underpinned by novel algorithms, models and bioinformatics methods. The speed and flexibility of the tools will make it possible to run analyses on a daily basis for a variety of subjects, including diagnostics, phylogeography, phylodynamics and transmission of drug resistance. The tools will be piloted and incorporated in the many available bioinformatics pipelines and software programs used in the field. We will make our tools available in a modular, free and open source software platform that offers opportunities to small and medium enterprises (SMEs) to further exploit this market. The VIROGENESIS consortium brings together leading European academic institutions, SMEs, bioinformatics developers, and virology end-users who initiated this project in response to a clear interest from EMBL, NCBI and the Global Microbial Identifier (GMI) platform.

- **PREPARE4 (Platform foR European Preparedness Against (Re-)emerging Epidemics)** will implement ‘inter-epidemic’ large-scale clinical studies, patient-oriented pathogenesis studies and develop novel diagnostics. In addition PREPARE, develops and tests pre-emptive solutions to bottlenecks that prevent rapid clinical research responses in the face of new infectious disease threats. The project has the goal of mounting a rapid, coordinated deployment of Europe’s clinical investigators, within 48 hours of a severe infectious disease outbreak in Europe. PREPARE is holding regular and, if needed, ad-hoc meetings of its 'Outbreak Research Mode Committee', which decides about different research response modes and subsequent actions within PREPARE. This includes the option of rapidly launching clinical trials in the case of new

[2] http://ecomeu.info/ - FP7 funded project – start: 2012-02-01; end: 2016-01-31 – EU contribution: € 1 999 607
[3] http://www.kuleuven.be/english/research/EU/p/horizon2020/sc/sc1/Virogenesis - Horizon 2020 funded project - start: 01/06/2015; end: 31/05/2018 – EU contribution: € 2.995.968
[4] PREPARE - FP7 funded project - start: 2014-02-01; end: 2019-01-31 – EU contribution: € 23 992 375

epidemics. For MERS-CoV infections, PREPARE has been in 'Outbreak Research Mobilisation' Mode (the second of 3 escalations) from 16 May 2014 until 11 November 2014 and continues now to be in 'Outbreak Research Preparation' mode (the first escalation), but has so far not decided to launch any clinical trials on MERS-CoV.

- **ZAPI[5] (Zoonosis Anticipation and Preparedness Initiative)** aims to develop a universal platform for the rapid antigenic characterization of pathogens, and the design and surge production of vaccines and neutralizing reagents against emerging pathogens, in particular viruses. This platform will build on close collaborative partnerships between human and veterinary medical institutions, governmental regulatory agencies, expert academic groups and industrial partners. In addition, this platform aims at ensuring a fast track for the timely registration and implementation of the control tools as soon as possible after pathogen emergence. ZAPI will deliver proof-of-concept by focusing on three viruses, representative of currently emerging infectious pathogens: Schmallenberg virus (SBV), MERS-CoV and Rift Valley fever virus (RVFV). The development and application of the proposed platform for intervention strategies against these three viruses will demonstrate its potential as a broadly applicable and synergistic approach for the rapid characterization and development of control tools against future emerging viruses.

2. GERMANY FUNDED RESEARCH (AUGUST 2015)

Funded by BMBF (German Federal Ministry for Education and Research) - DZIF (German Center for Infection Research)

Outbreaks of emerging pathogens appear suddenly and rapid response is crucial to contain the spread of the disease. Actions must be taken both to raise the awareness of the public health sector, and to develop strategies to speed up biomedical research and production of candidate vaccines and therapeutics. The mission of the Thematic Translational Unit Emerging Infections is to establish a research infrastructure that contributes to rapid containment of emerging infections and to mitigate the consequences of such outbreaks for the public. To fulfil this mission, the Thematic Translational Unit Emerging Infections shall link expert individuals and research groups within three areas covering the entire response chain: pathogen detection, diagnostics, and clinical management; emergency vaccines; and broad-range antivirals.

The activity of the Thematic Translational Unit Emerging Infections will:

- Improve our ability to rapidly detect unknown pathogens and deploy diagnostics for novel pathogens
- Link DZIF partner hospitals to develop and agree on standardized treatment plans for emerging disease entities
- Shorten the time to availability of novel vaccines against emerging infectious agents by developing vaccine platform technology for rapid implementation of novel pathogen

[5] Total budget: 22 385 918 € (IMI funding: 9 508 688 €, EFPIA in-kind: 9 875 000€); start date: 01/03/2015 – end date: 29/02/2020.

Examples of Other MERS Related Projects

The development of diagnostic tools together with industrial partners for detection of MERS CoV, Novel Coronavirus Detection.

Prof. Dr. Christian Drosten, Rheinische Friedrich-Wilhelms-Universität Bonn. For more information refer to this link: http://www.virology-bonn.de/index.php?id=40

- A preclinical bridging study on MVA-MERS-S, an experimental prophylactic vaccine against the Middle East Respiratory Virus Syndrome
- GMP Manufacture and Phase I clinical investigation of MVA-MERS-S, an experimental prophylactic vaccine against the Middle East Respiratory Virus Syndrome

Prof. Dr. Gerd Sutter, Ludwig-Maximilians-Universität München; 2014–2017, Related Press Release:

http://www.dzif.de/en/news_media_centre/news_press_releases/view/detail/artikel/coronaviruses_getting_to_a_vaccine_as_fast_as_possible/

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Funded by DFG (German Science Foundation)

Coronaviruses as a paradigm for the transmission interface between wildlife, livestock and humans

Professor Dr. Christian Drosten, Rheinische Friedrich-Wilhelms-Universität Bonn
Funded since 2014

Project Description

The importance of coronavirus (CoV) host switching and the zoonotic or epidemic potential of CoV has been underlined by the emergence of a novel CoV in the Arabian Peninsula in 2012, known as the MERS-CoV. In this project we investigate the complex process of coronavirus host switching, integrating various disciplines such as animal ecology, epidemiology, as well as molecular virology and innate immunity research. The objectives in the second working period reflect the new possibilities created by Ghanaian veterinarians entering the team, as well as the pressing need for more insight into reservoirs and origins of MERS-CoV. We continue our investigations of diversity and evolution of CoV in small mammals, working beyond bats in the second working period. We add as a new component the importance of livestock as potential intermediary hosts through virus and antibody testing in livestock.

Molecular biology investigations will continue to address the issues of receptor-mediated cell entry and evasion of the target cell´s interferon defence. In the area of training and capacity building, we

will continue to provide field training in ecological methodology on site, and add an additional emphasis on practical skills in molecular biology by intensified training abroad. The overall goal of the project is to provide a much better insight into the various stages of viral emergence and to interlink research capacities between the disciplines of ecology and virology, and between investigators in Germany and Ghana.

Surface glycoproteins of two bat paramyxoviruses: functional characterization and importance for host switch

Professor Dr. Georg Herrler, Stiftung Tierärztliche Hochschule Hannover, Institut für Virologie
Funded since 2014

Project Description

In recent years, bats have been recognized as a major reservoir for a number of viruses. From time to time, viruses succeed in crossing the species barriers and cause infections that may be lethal for the affected humans or animals. Examples are the coronaviruses responsible for the severe acute respiratory syndrome (SARS) or the Middle East respiratory syndrome (MERS), or the Nipah virus within the family Paramyxoviridae, genus Henipavirus.
Attempts to detect viral nucleic acid in bats have been quite successful; however, to isolate infectious virus from bats is still a challenging task. So far, there is not a single report about a successful isolation of a coronavirus from bats. In this case, the limiting factor appears to be the interaction of the viruses with receptors on the cell surface. As far as paramyxoviruses are concerned, there were a few successful virus isolations, though the total number is rather low. This makes it difficult to evaluate the zoonotic potential of the viruses and the danger for man and animals. However, there have been two interesting findings recently that allow us to analyze the tropism of bat viruses in more detail and thus to get a better knowledge about these infectious agents. Nipah-like henipaviruses have been isolated only in South East Asia. However, genomic RNA has been detected also in African bats.
We have shown for the first time that the surface glycoproteins of an African henipavirus (G and F) have biological activities. Their ability to induce the formation of syncytia, i.e. multinucleated giant cells, shows that these glycoproteins have a functional receptor-binding as well as fusion activity. In the proposed project, we will analyze the biological activities of G and F as well as their ability to mediate infection in more detail. This knowledge will provide a basis for the successful isolation of an African henipavirus.The detection of genomic RNA from paramyxoviruses in bats revealed the presence of a virus that is closely related to mumps virus. With the surface glycoproteins (HN and F) of this mumps-like bat virus we were also able to induce syncytia formation.
Similar to the above mentioned African henipavirus, we will analyze the biological activities of the two glycoproteins in more detail. In this case, we will provide the basis for a mutational analysis of the human mumps virus that will reveal which amino acid exchanges are crucial for the transition of the human virus to the bat virus.

3. JAPAN FUNDED RESEARCH (OCTOBER 2015)

AMED funded research on Middle East Respiratory Syndrome – Coronavirus (MERS-CoV)

In response to the MERS outbreak in South Korea in May 2015, AMED provided additional funds to ongoing MERS research projects to accelerate their outcomes.

The following are about the Japanese research projects that are currently focused on MERS-CoV:

1. **Detection of Middle East respiratory syndrome coronavirus using reverse transcription loop-mediated isothermal amplification (RT-LAMP).**
   Dr. Shutoku Matsuyama, Department of Virology III, National Institute of Infectious Diseases, Tokyo, Japan et al.
   Dr. Matsuyama is a team member of *Dr. Tsutomu Kageyama* (Influenza Virus Research Center, National Institute of Infectious Diseases, Tokyo, Japan), who is a leader of the AMED project 'Research and development of detection systems for influenza virus, measles virus, rubella virus, MERS-CoV, and other respiratory viruses'.

   Their study developed a novel RT-LAMP (Reverse Transcription-Loop-mediated isothermal amplification) assay for detecting MERS-CoV using primer sets targeting a conserved nucleocapsid protein region. The RT-LAMP assay was capable of detecting as few as 3.4 copies of MERS-CoV RNA, and was highly specific, with no cross-reaction to other respiratory viruses. Pilot experiments to detect MERS-CoV from medium containing pharyngeal swabs inoculated with pre-titrated viruses were also performed. The RT-LAMP assay exhibited sensitivity similar to that of MERS-CoV real-time RT-PCR. (referred to *Virology Journal2014 Aug 8, 11:139. K. Shirato, S. Matsuyama et al.*). For the 2015 year, the research team plans to improve the conventional RT-LAMP method.

2. **Middle East respiratory syndrome coronavirus infection mediated by the transmembrane serine protease TMPRSS2.**
   Dr. Kazuya Shirato, Department of Virology III, National Institute of Infectious Diseases, Tokyo, Japan, et al.
   Dr. Kazuya Shirato is a member of the team of Dr. Makoto Takeda, Department of Virology III, National Institute of Infectious Diseases, Tokyo, Japan. They are working on the AMED project 'Research and Development of Novel Diagnosis and Innovative Treatment for Middle East Respiratory Syndrome and Emerging Influenza'.

   The Middle East respiratory syndrome coronavirus (MERS-CoV) utilizes host proteases for virus entry into lung cells. In their study, they established Vero cells constitutively expressing type II transmembrane serine protease (Vero-TMPRSS2 cells) (Shirogane et al., 2008 J Virol 82:8942-6) that showed large syncytia by MERS-CoV infection.

By using Vero-TMPRSS2 cells and other cell lines derived from lung assay system, they found as follows:

1. Vero-TMPRSS2 cells have extreme high susceptibility for MERS-CoV in contrast to non-TMPRSS2 expressing parental Vero cells.
2. MERS-CoV employs both the cell surface and the endosomal pathway to infect Vero-TMPRSS2 cells.
3. A single treatment with camostat (TMPRSS2 serine protease inhibitor) is sufficient to block MERS-CoV entry into a well-differentiated lung-derived cell line.(referred to *Journal of Virology* 2013 Dec; 87(23): 12552-12561, K. Shirato, S. Matsuyama et al.)

For the 2015 year, the research team plans to create the model animals to develop new ways to diagnose MERS in the laboratory and to understand the molecular basis of the MERS pathogenic expression.

4. U.S. GOVERNMENT FUNDED RESEARCH (SEPTEMBER 2015)

Activities on Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

Although progress has been achieved in understanding the basic biology of MERS-CoV, preclinical development and research on potential MERS-CoV medical countermeasures (MCMs) remains preliminary and significant work is likely to be required before any MCMs will be ready for human clinical trials. Limited funding is available through the National Institute of Allergy and Infectious Diseases (NIAID) and the Biomedical Advanced Research and Development Authority (BARDA) for the preclinical and clinical development for MERS-CoV MCMs. Animal model development had also steadily advanced with the availability of transgenic mouse models, described below, for early product candidate screening and modeling of human-like pathogenesis. However, candidate medical products were only marginally advanced between June, 2014 and April, 2015 (the date of the last in-depth assessment), and this was largely based on efforts that had already been funded by NIH, or were undertaken by industry at their own expense.

Major factors hindering progress in the pre-clinical development of MERS-CoV MCMs are the lack of established animal models for human disease from MERS-CoV infection, limited availability of non-human primates (e.g. common marmosets), and limited funding for preclinical development of MERS-CoV MCMs. While some progress has been made in addressing these gaps, more work is needed to facilitate the availability of potential MERS-CoV MCMs for human clinical trials.

- **April 2015 Medical Countermeasures Assessment:** The Office of the Assistant Secretary for Preparedness and Response convened a meeting in early April 2015 of subject matter experts and external stakeholders to review the current status of information on candidate products for prophylaxis, diagnosis or treatment of human disease. This meeting was timely in light of the subsequent outbreak of MERS-CoV in South Korea and ongoing outbreaks in Saudi Arabia and

Jordan. A report was developed, based on the framework of an earlier review and assessment conducted in June, 2014.

The major recommendations of the assessment are enumerated below:

1. Standardize use of animal models for studying disease pathogenesis and for evaluation of potential medical countermeasures.
2. Establish a clinical specimen and assay validation panel working group to develop a strategy for point of care MERS-CoV diagnostics and prioritize the creation of validation panels for use by commercial partners in MERS-CoV diagnostic development.
3. Ensure that there are sufficient laboratory populations of non-human primates needed to support preclinical research, with a priority on initiating studies of therapeutics.
4. Accelerate product development of the most promising currently available therapeutic candidates, to include an immunotherapy and a small molecule antiviral drug compound.
5. Prioritize studies to further the scientific understanding and control of MERS-CoV disease in humans and animals, including vaccination studies in camels.
6. Develop a standardized clinical trial protocol and partner with an effective clinical trials network within the Gulf Coast Countries (GCC) to assist in evaluating safety and effectiveness of therapeutic candidates.

- **Animal Models:** Studies have demonstrated that a number of small animals commonly used as laboratory animal models (e.g. mice, hamsters, ferrets) are not susceptible to MERS-CoV. As a result multiple approaches are being taken to develop small animal models including but not limited to testing of nontraditional species (e.g. mink), passage of virus in animals, engineering of animal models through rational design (e.g. transgenic animals that express human DPP4, the MERS-CoV receptor), etc. NHP models that are under development include rhesus macaques and common marmosets. Major gaps for the NHP models include characterization of the different MERS-CoV strains, determining and standardizing the optimal viral challenge dose, volume, route of exposure, and the ability for sequential sampling in marmosets and determining clinical relevant symptoms. Overall, common marmosets appear to be better suited than rhesus macaques for therapeutic studies designed to target severe disease given the slightly slower onset of illness and the longer duration and severity of disease. However, the limited supply and availability of common marmosets in the U.S. is currently a major barrier to the development of MERS-CoV MCMs. Large animal models in development include camels and camelids such as alpacas. These models may be important to help understand the virology and immunology of MERS-CoV infection in dromedary camels. See Appendix 1 for more details.

- **In-vitro Diagnostics:** The CDC submitted a request for Emergency Use Authorization (EUA) of an in-vitro diagnostic on May 29, 2013 with data to support the performance of their molecular assay to detect the MERS-CoV virus in several sample types. On June 5, 2013, FDA granted an EUA for use of the test by trained technicians in qualified laboratories for testing symptomatic patients. On June 10, 2014 the EUA was expanded to include the ability to test asymptomatic contacts after a US returning traveler case. This assay has been made available to multiple public

health, U.S. Department of Defense (DoD), and World Health Organization (WHO) laboratories worldwide but is limited in terms of being able to scale up reagents to support a possible surge in the numbers of infected cases. The lack of FDA-cleared commercial assays is likely due to the limited availability of samples from infected and recovered patients. A USG working group has been formed to develop panels of specimens that could be sourced, stored and made available to diagnostic assay developers to help validate the performance of their devices and support an EUA. This model has been used previously to generate panels of difficult to source specimens for Ebola virus diagnostic test developers. Funding such a project will be a major challenge that needs to be explored.

- **Therapeutics:** There are no candidate products that have been specifically evaluated for treatment of MERS-CoV patients in well controlled clinical studies. Potential therapeutics for MERS-CoV patients include approved drugs with non-specific properties such as immunomodulators (e.g. corticosteroids, intravenous immunoglobulin, interferons), approved small molecule drugs for other diseases that are being screened for specific activity against MERS-CoV, small molecule drugs with broad antiviral activity, and new therapies (immunotherapeutics, other inhibitors) with specific activity against MERS-CoV. Appendix 2 provides an overview of the known MERS-CoV therapeutics pipeline. A limited number of preclinical studies in MERS-CoV-infected humanized mice and NHPs with candidate therapeutics have been performed, with more planned. BARDA has established an Interagency Agreement (IAA) with Rocky Mountain Labs (RML) that provides for the testing of therapeutic candidates for prophylaxis and efficacy in RML's published marmoset model. Under this IAA, BARDA will support a prophylaxis study in September and has lined up additional MERS candidates (both antibody-based and small molecules) to test, pending the availability of marmosets.

  BARDA and FDA participated in the September 9-10, 2015 MERS-CoV Research Initiatives Workshop, sponsored by the College of Public Health and Health Informatics and King Saud bin Abdulaziz University for Health Sciences, in Riyadh, Saudi Arabia. The workshop included a robust discussion of clinical trial design, including the potential for using a common master protocol to evaluate candidate therapeutics. Representatives of five companies presented updates on the status of their respective MERS-CoV therapeutic candidates in anticipation of potential clinical trials.

  The goals of the meeting were to:
  - Engender national and international research collaboration across sectors and disciplines relevant to MERS-CoV;
  - Identify specific promising therapeutics to consider for evaluation in the context of appropriately staged clinical research leading to clinical trials in KSA;
  - Develop action-oriented research recommendations to fill gaps in knowledge in the prevention and clinical care of patients with MERS-CoV

Participants in the meeting agreed that:

- A research infrastructure should employ an adaptive design that allows either efficient sequential or parallel evaluation of treatments, in comparison to a concurrent control group, ideally taking the form of a randomized, blinded (to the intervention) clinical trial.
- While much has already been done, further work towards these evaluations should commence immediately, including collaborative national and international intellectual, scientific, logistical, regulatory and financial support.

Meeting participants also identified research gaps related to the natural history, epidemiology, zoonotic transmission, and diagnosis of MERS-CoV as well as the development of animal models.

- **Vaccines:** NIAID, academic investigators, and several companies have initiated the development of MERS-CoV candidate vaccines. Appendix 3 provides an overview of the known MERS-CoV human and animal vaccine pipeline. Most vaccine development approaches are still in pre-IND evaluation in animal models. They have generally targeted the spike protein of MERS-CoV and are recombinant subunit, DNA or virus particle vector vaccines. At least four vaccine candidates have demonstrated immunogenicity in mice using the MERS-CoV Spike (S) protein as an immunogen, through subunit and/or DNA vaccine platforms.

  The Vaccine Research Center (VRC), NIAID, is evaluating two approaches based on the S protein, an S DNA prime-S1 subunit protein boost regimen and an S1 subunit protein prime-S1 subunit protein boost. Favorable immunogenicity data (generation of high quality neutralizing antibody) have been generated in mice and in NHP (rhesus macaque) systems, the latter system showing radiological efficacy after virus challenge. The DNA prime-protein boost approach elicited responses to a larger number of epitopes, a more favorable T cell response and better protection.

  One live-attenuated MERS-CoV candidate vaccine is in early development. Preliminary studies for several MERS-CoV vaccine candidates have been initiated and demonstrate immunogenicity and two have progressed to NHP challenge. One vaccine company (Inovio) is preparing to submit an IND and anticipates start of a Phase 1 study in 2015. Additionally, a number of MERS-CoV vaccine candidates are being developed with extramural funding/support from NIAID/DMID. These include vaccines based on recombinant S protein receptor binding domain, adenovirus-vectored S protein vaccines and work aimed at developing a modified live vaccine (MLV).

  One such MLV deletes an essential gene (E) and is consequently attenuated, being able to undergo only a single cycle of infection in the host yet providing appropriate immune stimulation theoretically. These extramural projects are all at a very early stage of development. To further support vaccine development, VRC/NIAID has developed serological assays (including a panel of 8 pseudotyped lentivirus reporters for assessing neutralizing antibodies) and reagents (including neutralizing murine mAbs with specificities to multiple regions of the S protein).

Animal Models in Development

Organization	Species	Notes
The University of Iowa	Mouse expressing human DPP4 (from Adenovirus 5 vector)	Transient and localized expression of DPP4. Mild infection. Funding support provided by NIAID.
University of Texas Medical Branch-Galveston	Mouse Knock-in of human DPP4, constitutive promoter	Expression of DPP-4 throughout the animal (including brain). Relentless weight loss and death within days post infection. Virus in the brain.
Regeneron	Mouse Knock-in of human DPP4, natural promoter	Stable expression of human DPP4 under a natural promotor (e.g. limited to the lung). Viral replication and lung pathology observed. Possible lethal phenotype, no virus in the brain.
Utah State University and Icahn School of Medicine	2 x transgenic mouse models	MCM evaluation. Funding support provided by NIAID.
Rocky Mountain Laboratories, NIAID Integrated Research Facility, NIAID	Rhesus Macaque	Macaque DPP4 receptor binds MERS. Infection causes acute localized to widespread pneumonia with transient clinical disease. Similar to mild /moderate human MERS-CoV cases. Advanced medical imaging being used to chart and better characterize disease development as well as to measure potential benefit of MCM. Multiple virus isolates being evaluated. Similar to mild/moderate human MERS-CoV cases.
Rocky Mountain Laboratories, NIAID Integrated Research Facility, NIAID	Marmoset	Marmoset DPP4 receptor binds MERS naturally. Multiple routes of infection used. Similar to more severe human MERS-CoV cases. Lethality is ~2(Advanced medical imaging being used to chart and better characterize disease development as well as to measure potential benefit of MCM. Multiple virus isolates being evaluated. Disease course was more severe than rhesus but no deaths were observed with either isolate tested.
Rocky Mountain Laboratories, NIAID	Dromedary Camels	Infection studies in a small number of dromedary camels are underway in a large animal BSL3 facility in the U.S.
Lab of Infectious Diseases, NIAID	Rabbit	Transient infection, no clinical signs, passaging 4-5 times. Possible enhancement of disease seen upon second challenge.
AutoImmune Technologies	Mink	Mink epithelial are permissive to MERS-CoV infection. DMID grant.

Therapeutics in Development

a) MERS-CoV Small Molecule and Biologics Treatment Candidates

Organization	Drug	Target	MERS Activity	Notes
Rocky Mountain Laboratories	Ribavirin + IFN	Polymerase + Immunomodulator	Active in Rhesus macaques	Approved for Hepatitis C virus. Compassionate use for MERS
University of Hong Kong/Bayer	Interferon B1b	Immunomodulator	Active in cell culture	
Hemispherix Biopharma	Alferon N	Immunomodulator	Active in cell culture	Approved for HPV
Romark Laboratories	Nitazoxanide	Host functions	Active in cell culture	Approved for Cryptospordia and Giardia, not active in all labs
AbbVie	Lopinavir	Protease	Active in cell culture	Approved for HIV
BioCryst Pharmaceuticals	BCX4430	Polymerase	Active in cell culture	
University of Missouri	SSYA10-001	Helicase	Active in cell culture	
Small Business Grant	DPP4 Decoy	Spike/Binding	Binding assay	Funding support provided by NIAID.
Small Business Grant	Peptide Inhibitors	Spike/Fusion	Binding assay	Funding support provided by NIAID.
Loyola University, Chicago, Stritch School of Medicine	Protease Inhibitors	MERS PLpro MERS 3CLpro	Active in cell culture	Funding support provided by NIAID.
Various	FDA Approved Drug Screen Chloroquine and chlorpromazine appear promising	Multiple targets	Active in cell Culture. Chloroquine and chlorpromazine also active in the mouse model	Multiple screening efforts. Funding support for some projects provided by NIAID.
Planet Biotechnology	DPP4-Fc	DPP4-Fc chimera that mimics the MERS-CoV receptor	Active in cell culture	Produced in tobacco

b) MERS-CoV Immunotherapeutic Treatment Candidates

Organization	Drug	Development Status
	IVIG	In clinic
Kingdom of Saudi Arabia	Convalescent serum	Clinical trials active, not recruiting[6]
NCI	M336, M337, M338	Live MERS-CoV neutralization; NHP studies
University of Hong Kong	MERS-4, MERS-27	Live MERS neutralization
Dana Farber Institute	3B11, 1F8, 3A1, 80R	Live MERS neutralization; NHP studies
University of Minnesota	Mersmab1	Live MERS neutralization
Regeneron	REGN3015, REGN3048	VLP neutralization, efficacy in humanized mice; testing in NHP in July; IND-enabling preclinical tox studies ongoing
Juntendo University	2F9 and YS110	VLP neutralization
Adimab	Anti-Spike	VLP-neutralization
Integrated Biotherpeutics	Anti-Spike	VLP neutralization
Sanford Research	Polyclonal	Mouse and NHP studies; IND enabling preclinical toxicology; Vialed product

Vaccines in Development

a) MERS-CoV Human Vaccine Candidates

Organization (Vaccine type)	Preclinical Immunogenicity (species)	Preclinical Efficacy (challenge model)	Scale-up Capability/Timing
Novavax (S protein trimer in 40 nm particle; adjuvanted likely)	Mouse-immunogenicity shown (Camel studies being planned)		Yes/≈6 months for manufacture Ph I vaccine
NIAID/VRC (Two candidate vaccine approaches: DNA S prime-S1 protein boost and S1 prime-S1 boost)	Mouse and NHP-immunogenicity shown	NHP (macaque-radiological efficacy shown) (Camel and marmoset studies planned)	Yes, at NIAID

[6] https://clinicaltrials.gov/ct2/show/NCT02190799

Organization (Vaccine type)	Preclinical Immunogenicity (species)	Preclinical Efficacy (challenge model)	Scale-up Capability/Timing
Inovio (DNA expressing S; electroporation device)	Mouse, NHP and camel immunogenicity shown	NHP (viremia, lung pathology and survival)	Yes, via GMP affiliate.
Greffex (full S expressing, fully deleted Adeno packaging vector; RBD constructs being developed)	Mouse immunogenicity shown		
NIAID Supported Extramural Projects (Adeno vector, Recombinant Spike, Live attenuated)	Platform development and mouse immunogenicity	Mouse model development to evaluate vaccine efficacy	
New York Blood Center (Receptor-binding domain (RBD)-based MERS subunit vaccine)	Immunogenicity and Protective efficacy in a mouse model, including via nasal delivery	BALB/c mice	

b) MERS-CoV Camel Vaccine Candidates

Organization	Vaccine Type	Camelid Vaccination Studies (PI)
USG/academic institution consortium	S protein nano-particle /Matrix C adjuvant (baculovirus expressed)	Camel vaccination without active challenge, in Saudi Arabia, Egypt, Qatar, and Mongolia; projected start July 2014
USG/academic institution consortium	Inactivated whole virus	See above
Rocky Mountain Laboratories, NIAID	S protein subunit vaccine/Advax adjuvant (baculovirus expressed)	Camel and alpaca vaccination-challenge studies at CSU started in June 2014; analysis in progress
Erasmus University	MVA vectored S protein	In progress, in Qatar, using a camel infection model
Novavax A.B. (Sweden)	S nanoparticles with Matrix C adjuvant	In discussions with KSA Department of Agriculture