demonstrates not only that biomaterials can be of sufficient quality to carry out useful photochemistry, but that in some ways they may be more advantageous in biological applications. Most traditional nanoparticle syntheses require organic capping ligands to control the particle shape. These ligands present a barrier to charge transfer between the semiconductor and the catalyst, often requiring electron tunneling (33). The ligand-free approach taken here may help to establish a favorable interface between the bacteria and the semiconductor, resulting in improved efficiencies. Additionally, metal chalcogenides such as CdS have had limited application because of oxidative photodegradation; the ability of bacteria to precipitate metal chalcogenides from the products of photodissolution (Cd²⁺ and oxidized sulfur complex ions) suggests a potential regenerative pathway to circumvent the debilitated photoinstability through a precipitative self-regeneration.

The M. thermoacetica–CdS system displays behavior that may help it to exceed the utility of natural photosynthesis. First, the quantum yield increased with higher M. thermoacetica–CdS concentrations. The ability to tune the effective light flux per bacterium by changing the concentration of the suspension is a considerable advantage over similar light management practices in natural photosynthesis that are achieved through genetic engineering of chloroplast expression (28). Second, the catabolic energy loss observed during dark cycles in natural photosynthesis was absent in our hybrid system, which may be an innate feature of the Wood–Ljungdahl pathway, in which acetic acid is a waste product of normal respiration. Additionally, many plants and algae tend to store a large portion of their photosynthetic products as biomass, which requires extensive processing to produce useful chemicals. In contrast, the M. thermoacetica–CdS system directs ~90% of photosynthetic products toward acetic acid, reducing the cost of diversifying to other chemical products.

This system could be improved by substituting Cys oxidation with a more beneficial oxidation reaction, such as oxygen evolution, wastewater oxidation for water purification, or oxidative biomass conversion (29, 30). Expanding the material library available through biologically induced precipitation will increase the capacity for light absorption and raise the upper limit on semiconductor–bacteria photosynthetic efficiency. The availability of genetic engineering tools for M. thermoacetica (31), as well as the introduction of electrochemical and nanoparticle precipitation behavior in model bacteria such as Escherichia coli (32, 33), suggests a potential role for synthetic biology in rationally designing such hybrid organisms.

Beyond the development of advanced solar-to-chemical synthesis platforms, this hybrid organism also has potential as a tool to study biological systems. The native integration of semiconductor nanoparticles with bacterial metabolic processes provides a distinctive optical tag for the study of microbial behavior, such as semiconductor–bacteria electron transfer (34, 35), by providing a sensitive, noninvasive, nonchemical probe.
The identification of dipeptidyl peptidase 4 (DPP4) component for vaccines against CoV infections. Therefore, strict implementation of quarantine and isolation measures, as well as the development of candidate vaccines and antivirals, is urgently needed.

The spike protein is considered to be a key component for vaccines against CoV infections. The identification of dipeptidyl peptidase 4 (DPP4) as the MERS-CoV receptor (17) has facilitated the subsequent characterization of the receptor binding domain in the S1 region of the MERS-CoV spike protein (18, 19). When tested as a vaccine in mice, full-length spike protein of MERS-CoV expressed by modified vaccinia virus Ankara (MVA-S) induced high levels of circulating antibodies that neutralize MERS-CoV and limited lower respiratory tract replication in animals transduced with the human receptor DPP4 and inoculated with MVA (20, 21). MVA, a highly attenuated strain of vaccinia virus, serves as one of the most advanced platforms for human vaccine development. In dromedary camels, MERS-CoV replication is mainly restricted to the upper respiratory tract (22). Therefore, we inoculated four dromedary camels twice at a 4-week interval, with 2 × 10^8 plaque-forming units (PFU) MVA-S delivered intranasally in one nostril using a mucosal atomization device. Upon challenge, the MVA-S vaccine developed detectable serum neutralizing MERS-CoV-specific antibody titers (Fig. 1A). No MERS-CoV–specific antibodies were detected in sera of the PBS- or MVA-wt–immunized control animals. The specificity of the antibody response was confirmed by enzyme-linked immunosorbent assay, using recombinant S1 protein (fig. S1). In addition, low levels of MERS-CoV-neutralizing antibodies (virus neutralization titer of 1:20 to 1:40) were detected 3 weeks after the boost immunization in the nasal swabs of three animals (Fig. 1B). Because a MVA-vector vaccine was used, antibodies neutralizing MVA were also detected (Fig. 1C); these antibodies cross-neutralized camelpox virus (Fig. 1D). Camelpox virus infections occur frequently in dromedaries and cause severe disease that can be prevented by vaccines based on attenuated camelpox viruses (24).

Three weeks after the boost immunization, all dromedary camels were inoculated with 10^7 median tissue culture infectious dose (TCID50) of MERS-CoV via the intranasal route, using a mucosal atomization device. Upon challenge, the animals showed only mild clinical signs, which were mainly limited to a relatively small rise in body temperature in control-vaccinated animals 1 day after challenge (fig. S2). In addition, some dry mucus was observed in one of the nostrils of most animals after day 4, but from days 8 to 10 onward, all control-vaccinated animals exhibited a runny nose that was not observed in MVA-S–vaccinated animals (Fig. 2, A and B). Previous studies have shown that both experimentally and naturally infected dromedary camels may show nasal discharge after MERS-CoV infection (15, 22). We next tested nasal respiratory tract samples for the presence of infectious virus. Whereas MERS-CoV was found at high titers in all four control-vaccinated animals, mean viral titers in the animals that received the MVA-S vaccine were significantly reduced (Fig. 2C). At 4 days post-inoculation (dpi), an increase in MERS-CoV RNA level was noted in the MVA-S–vaccinated animals (Fig. 2D). At 6 dpi, one of the MVA-S–vaccinated animals excreted low levels of infectious virus (10^3 TCID50/ml) (Fig. 2C). Sequencing of the spike gene of this virus showed no amino acid changes in the receptor binding domain (fig. S3), which suggests that this virus did not emerge as
Fig. 2. Clinical signs and MERS-CoV excretion in nasal swabs of dromedary camels vaccinated with MVA-S vaccine. (A and B) Two MVA-S–vaccinated (A) and two control-vaccinated dromedary camels (B) were analyzed for the presence of mucus excretion 8 to 10 days after MERS-CoV challenge. (C and D) Detection of infectious MERS-CoV (C) and MERS-CoV RNA (D) at different time points after challenge in nasal swabs of dromedary camels vaccinated with MVA-S (white bars) or MVA-wt or PBS (black bars). Dashed lines depict the detection limit of the assays. Error bars represent mean values ± SEM; *P < 0.05; n = 4 animals per group. GE, genome equivalents.

Fig. 3. Detection of MERS-CoV in tissues of vaccinated dromedary camels. (A and B) Levels of MERS-CoV viral RNA (A) and infectious virus (B) were determined in tissue homogenates from MVA-S–vaccinated (green and black bars) or control-vaccinated (red and blue bars) camels 4 days after challenge.
a result of escape from vaccine-induced antibodies (Fig. 2C). Rather, the observation that this animal had no detectable MERS-CoV antibody response in the nasal swab at time of challenge may indicate that, for unknown reasons, priming with the MVA-S vaccine was less effective in this animal compared with the other vaccinated animals. Antibodies to MERS-CoV rapidly increased 8 dpi in control-vaccinated animals (fig. S4), consistent with the absence of infectious virus in the nasal swabs at that time (Fig. 2C). Low levels of viral RNA, but no infectious virus, were detected in nasal swabs after MERS-CoV challenge (fig. S5), but not in any of the sera tested.

To analyze pathological changes and viral replication in organs of the animals, we euthanized two animals per group and performed necropsies at 4 and 14 dpi. Gross pathology showed no substantial changes in the organs of any of the animals. However, at 4 dpi MERS-CoV RNA transcripts were detected in several organs of the control-vaccinated animals (Fig. 3A), although infectious virus particles were restricted to noses and tracheas (Fig. 3B). In the absence of infectious MERS-CoV, relatively high levels of viral RNA have also been observed in tissues of experimentally infected rhesus macaques and rabbits (25, 26). In contrast, infectious MERS-CoV particles were found at low levels in the noses of animals that had received the MVA-S vaccine (Fig. 3B). At 14 dpi, only viral RNA was detected, mainly in control-vaccinated animals (fig. S6).

Differences in upper respiratory tract viral replication between vaccinated groups were confirmed by MERS-CoV in situ hybridization (ISH) and immunohistochemistry (IHC). At 4 dpi, only a few cells in the nasal epithelium of MVA-S-vaccinated dromedaries stained positive for MERS-CoV RNA by ISH, as compared with cells from control-vaccinated animals (Fig. 4, A and B). Viral replication in the control-vaccinated animals was consistent with histopathological analyses showing multifocal moderate rhinitis with multifocal epithelial necrosis, as well as lymphocytic and neutrophilic exocytosis (Fig. 4C). In the nasal submucosa, we observed edema and infiltrates with lymphocytes, neutrophils, plasma cells, and macrophages. In the trachea and bronchi, we noted infiltration in the lamina propria, as well as a multifocal mild tracheitis and bronchitis with epithelial necrosis and lymphocytic and neutrophilic exocytosis. In the lymph nodes and the tonsils, we detected follicular hyperplasia. Marked MERS-CoV antigen expression in the nasal epithelium was associated with the nasal lesions (Fig. 4C). Through the use of ISH, the presence of MERS-CoV RNA in the nasal cavity was confirmed in cells similar to those that scored positive by IHC (Fig. 4C). Furthermore, a few epithelial cells in the trachea and bronchi and those covering the palatum molle—as well as large stellate cells (consistent with dendritic cells) in the lymphoid tissue of the palatum molle, tonsils, and tracheal and cervical lymph nodes—were found to be positive for viral antigen by IHC (fig. S7). In contrast, in MVA-S-vaccinated animals the rhinitis was accompanied by less submucosal edema with antigen expression in some nasal cells (Fig. 4C). Eosinophilic granulocytes were not observed in the lungs of MVA-S-vaccinated animals challenged with MERS-CoV. In one MVA-S-vaccinated animal, viral antigen expression was found in a few dendritic-like cells in the lymphoid tissue of the palatum molle, tonsils, and tracheal and cervical lymph nodes, as well as in the gut-associated lymphoid tissue of the duodenum (table S1). At 14 dpi, we observed multifocal mild rhinitis, tracheitis, and bronchitis and follicular hyperplasia in the lymphoid tissue of control- and MVA-S-vaccinated animals. In the lungs of almost all animals, we detected multifocal mild infiltration of neutrophils, histiocytes, and lymphocytes that was not associated with viral antigen expression. In the other extrarrespiratory tissues examined, we found no substantial morphological changes or viral antigen expression. Overall, these results indicate that vaccination of dromedary camels with MVA-S induces protective immunity resulting in reduction of excreted infectious MERS-CoV, without evidence for antibody-dependent enhancement of viral replication, as seen in feline CoV infection (27). Given the potential transient nature of mucosal immune responses, follow-up studies are needed to determine the longevity of the responses induced by the MVA-S vaccine, with respect to protection as well as antibody-dependent enhancement of viral replication when antibody levels are waning. In addition, dosing of the vaccine and alternative methods of administration must be explored in more detail before this candidate vaccine will be useful in the field.

Protective immunity to CoV’s is orchestrated by antibody and cellular immune responses. Investigations in mice have already provided evidence that inoculation with MERS-CoV spike protein–based candidate vaccines, monoclonal antibodies directed against the spike protein, or dromedary immune serum induces protective immunity against lower respiratory tract MERS-CoV infection (28–30). In dromedary camels, a DNA vaccine encoding the spike protein induced MERS-CoV neutralizing antibody responses that were similar to antibody levels in animals inoculated with the MVA-S vaccine, but no challenge experiments were performed (31). However, studies in the field also indicated that MERS-CoV–seropositive dromedaries may carry MERS-CoV viral RNA in their nasal excretions (8, 15, 16). Thus, sterilizing immunity
Co-circulation of three camel coronavirus species and recombination of MERS-CoVs in Saudi Arabia

Jamal S. M. Sabir,1 Tommy T-Y. Lam,2,3,4 Mohamed M. M. Ahmed,1,6,7 Lifeng Li,3,4,5 Yongyi Shen,3,4 Salah E. M. Abo-Aba,1 Muhammad I. Qureshi,1 Mohamed Abu-Zeid,1,7 Yu Zhang,2,3,4,5 Mohammad A. Khiyami,4 Nyud S. Alharbi,6,7,8 Najih H. Hajrah,9 Meshaal J. Sabir,1,7 Mohammed H. Z. Mutwakil,1 Saleh A. Kabili,1 Faten A. S. Alsulaimany,7 Abdullah Y. Obaid,9 Boping Zhou,2 David K. Smith,6 Edward C. Holmes,5 Huachen Zhu,2,3,4 Faten A. S. Alsulaimany, Jamal S. M. Sabir,1 Abdullah Y. Obaid,9 Boping Zhou,2 David K. Smith,6 Edward C. Holmes,5 Huachen Zhu,2,3,4

Outbreaks of Middle East respiratory syndrome (MERS) raise questions about the prevalence and evolution of the MERS coronavirus (CoV) in its animal reservoir. Our surveillance in Saudi Arabia in 2014 and 2015 showed that viruses of the MERS-CoV species and a human CoV 229E–related lineage co-circulated at high prevalence, with frequent co-infections in the upper respiratory tract of dromedary camels. Including a betacoronavirus 1 species, we found that dromedary camels share three CoV species with humans. Several MERS-CoV lineages were present in camels, including a recombinant lineage that has been dominant since December 2014 and that led to the human outbreaks in 2015. Camels therefore serve as an important reservoir for the maintenance and diversification of the MERS-CoVs and are the source of human infections with this virus.

Major outbreaks of Middle East respiratory syndrome (MERS) have been repeatedly reported in the Arabian Peninsula since 2012 and recently in South Korea (1,2)–3, revealing concerns about potential changes in the mode of MERS coronavirus (CoV) transmission. Although increasing evidence suggests that dromedary camels are the most likely source of human infections (4–14), the prevalence and evolution of the MERS-CoV in this animal and the route of virus transmission to humans are not well defined, and little is known of other CoV species that may circulate in camels and how they might influence CoV ecology.

We conducted surveillance for CoVs in dromedary camels in Saudi Arabia, the country most affected by MERS, from May 2014 to April 2015. Initially, paired nasal and rectal swabs were collected from camels at slaughterhouses, farms, and wholesale markets in Jeddah and Riyadh. Because rectal swabs were negative for MERS-CoVs (tables S1 and S2), only nasal swabs were subsequently collected at these sites and in Taif (15). Of the 1309 camels tested, 25.3% were positive for CoV, as established by reverse transcription polymerase chain reaction (RT-PCR) and confirmed by Sanger sequencing. The majority of the CoV-positive camels

1Biotechnology Research Group, Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia.
2State Key Laboratory of Emerging Infectious Diseases (The University of Hong Kong–Sherzer Branch), Shenzhen Third People’s Hospital, Shenzhen, China.
3Shantou University—The University of Hong Kong Joint Institute of Virology, Shantou University, Shantou, China.
4Centre of Influenza Research and State Key Laboratory of Emerging Infectious Diseases, School of Public Health, The University of Hong Kong, Hong Kong Special Administrative Region, China.
5Marie Bashir Institute for Infectious Diseases and Biosecurity, Charles Perkins Centre, School of Biological Sciences and Sydney Medical School, The University of Sydney, Sydney, New South Wales 2006, Australia.
6Department of Nucleic Acids Research, Genetic Engineering and Biotechnology Research Institute, City for Scientific Research and Technology Applications, Borg El Arab, Post Office Box 21934, Alexandria, Egypt.
7Microbial Genetics Department, Genetic Engineering and Biotechnology Division, National Research Center, Dokki, Giza, Egypt.
8King Abdulaziz City for Science and Technology, Riyadh 11442, Saudi Arabia.
9Department of Chemistry, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia.

*These authors contributed equally to this work.
†Corresponding author. E-mail: zhuchh@hhu.hk (H.Z.); yguan@hhu.hk (Y.G.)
An orthopoxvirus-based vaccine reduces virus excretion after MERS-CoV infection in dromedary camels


Science 351 (6268), 77-81.
DOI: 10.1126/science.aad1283 originally published online December 17, 2015

Coronaviruses in the Middle East

Middle East respiratory syndrome coronavirus (MERS-CoV) causes severe acute respiratory illness and kills about a third of people infected. The virus is common in dromedary camels, which can be a source of human infections. In a survey for MERS-CoV in over 1300 Saudi Arabian camels, Sabir et al. found that dromedaries share three coronavirus species with humans. Diverse MERS lineages in camels have caused human infections, which suggests that transfer among host species occurs quite easily. Haagmans et al. made a MERS-CoV vaccine for use in camels, using poxvirus as a vehicle. The vaccine significantly reduced virus excretion, which should help reduce the potential for transmission to humans, and conferred cross-immunity to camelpox infections.

Science, this issue p. 81, p. 77