Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

MERS – A cautionary tale

Since the initial outbreak of Severe Acute Respiratory Syndrome (SARS) a decade ago, scientists have gained some ground in rapidly sharing resources and information [1], as indicated in 2013 by the fast and efficient reaction to the H7N9 bird flu by governments, scientific institutes and the media [2,3]. However, since Middle East Respiratory Syndrome (MERS) was first reported in Saudi Arabia in mid-2012, the same scientific enthusiasm shown for H7N9 had already begun to wane, with even less interest shown by Big Pharma.

MERS coronavirus (MERS-CoV) was identified as a member of the C lineage betacoronaviruses, closely related to the bat coronaviruses HKU4 and HKU5 [4]. As a classic example of interspecies transmission, MERS-CoV can be transmitted to humans *via* animal reservoirs, probably dromedary camels, as well as close person-to-person contact [5,6]. Transmissibility, coupled with the high structural similarity to SARS-CoV, which infected 8273 and killed 700 people in 2002–2003, initially sparked concerns about the pandemic potential of MERS, with the World Health Organization (WHO) classifying it as a "threat to the entire world" [7]. Like SARS-CoV, MERS-CoV causes respiratory distress and multiple organ failure with a high fatality rate close to 35%. To date, about 1300 laboratory-confirmed cases, including 455 related deaths, have been reported to WHO (http://www.who.int/csr/don/12-june-2015-mers-korea/en/), but targeted and effective therapeutics remain to be elucidated, indicating a much slower response to this potential pandemic than reaction to the H7N9 bird flu.

The biggest Ebola epidemic of all time struck Western Africa in December 2013. Its spread was effectively halted only a few months ago after claiming over 11,000 deaths. However, after monopolizing media attention at the height of public concern, initial interest quickly faded, and none of the major pharmaceutical companies seemed willing to invest in significant R&D based on these alarming statistics.

Meanwhile, MERS, which had been mostly sheltered from media attention, made its way back into the headlines by its arrival in May 2015 in South Korea, where it has caused the biggest outbreak outside of Saudi Arabia, with 128 confirmed cases and 14 deaths, including the third generation descendant of MERS cases (http://www.like-news.us/?i713521-Korea-is-now-the-third-generation-descendant-of-the-first-cases-of-MERS-has-caused-14-deaths), resulting in an understandable state of panic. Over two thousand schools were closed, more than 3800 people were asked to self-quarantine in Seoul, and 70 individuals are under quarantine at Osan Air Base after a service member tested positive for MERS. The panic also spread to China after a Korean man with MERS-CoV infection traveled to Hong Kong and Guangdong Province. As a direct consequence, calls for an acceleration in the development of efficient countermeasures are resurfacing.

Fortunately, laboratories doing basic research in this area had not lost their focus during the last few years, and have continued their battle against the most threatening viral infections of this day and age, including HIV, SARS-CoV, and the H7N9 and Ebola viruses. Their work may lead us towards potential solutions to prevent MERS-CoV infection.

The MERS-CoV virus forces its way into human cells by binding to its receptor, dipeptidyl peptidase-4 (DPP4) protein, on the epithelial cell surface of the respiratory tract *via* the receptor-binding domain (RBD) in the S1 subunit of its spike (S) protein [8]. The S2 subunit then changes its conformation and partially inserts into the target cell, drawing viral and host cell surfaces closer in order to permit plasma membrane fusion. This conformational change requires the formation of a fusion core by two heptad repeat regions (HR1 and HR2) of the S2 subunit.

Based on their studies on viral fusion/entry inhibitors against HIV-1 [9] and SARS-CoV [10], Shibo Jiang and colleagues at Fudan University were able to quickly design a peptide (HR2P) imitating the HR2 region of the MERS-CoV S protein. In cell culture, HR2P can efficiently interfere with the fusion process and thus block viral entry and replication [11]. In collaboration with the team of Stanley Perlman at the University of Iowa, who developed a mouse model expressing human DPP4 (hDPP4) for MERS-CoV infection [12], the same researchers demonstrated that intranasal administration of HR2P-M2, an analogous peptide of HR2P with improved stability, solubility and antiviral activity, into hDPP4-transduced mice resulted in their protection from MERS-CoV challenge [13]. It is thus expected that HR2P-M2 peptide in a nasal spray formulation could be used to protect high-risk populations, including family members of MERS patients, healthcare workers and others who have had or will have close contact with MERS patients.

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As further demonstrated by Jiang's group, combining HR2P-M2 peptide with m336, an RBD-specific human neutralizing monoclonal antibody (mAb) having potent neutralizing activity against MERS-CoV infection *in vitro* and *in vivo*, resulted in a strong synergistic effect against MERS-CoV infection [14,15]. They therefore proposed that combinatorial use of the HR2P-M2 peptide intranasally and the m336 mAb intravenously could be used to treat MERS patients [15].

Development of an effective and safe vaccine is the ultimate goal to control or eradicate an emerging virus, such as the smallpox virus. Based on their previous experience in developing RBD-based SARS vaccines [16–18], the researchers have also designed a subunit MERS vaccine candidate consisting of an optimized fragment of MERS-CoV S protein RBD and a human IgG Fc, S377-588-Fc [19,20]. This vaccine candidate elicited highly potent neutralizing antibody responses, which protected hDPP4-transduced mice from MERS-CoV challenge, suggesting promise for its further development as an effective and safe MERS vaccine [21] (Fig. 1).

Nevertheless, the realization of an efficient prophylactic or therapeutic agent requires testing in preclinical and clinical studies. This, of course, requires a sustained level of investment by both government and pharmaceutical industries that is beyond the capacity of academic institutions. Yet, gaining this level of commitment has proven to be a delicate business in the unpredictable vaccine market. For instance, in 2009, millions of unused H1N1 vaccines had to be destroyed because the epidemic turned out to be milder than expected. Public outrage ended the careers of several European health ministers. However, public opinion could have just as easily shifted if the opposite scenario had taken place. Similarly, interest in the Ebola virus – known since 1976 – and sincere efforts to produce a vaccine for it only spiked after it had already killed thousands of people, devastating the economies of fragile Western African countries for at least a decade [22].

In sum, despite the outstanding progress made in the fields of monitoring, modeling and predicting viral spread, an undeniable fortuity factor remains when it comes to nascent pandemics. No one can guarantee if, how and when the virus will mutate, or what dangerous abilities it might acquire [6]. This precautionary truth remains and should outweigh economic risk, fickle public opinion, and unfounded rumors on the internet.

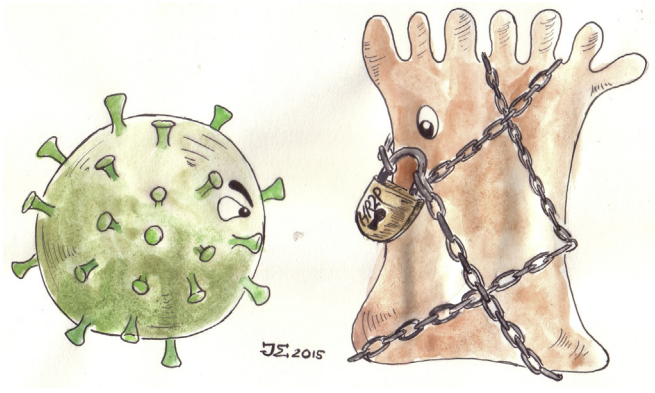

Fig. 1. Strategies that interfere with binding of MERS coronavirus to receptors on human epithelial cells should block infection.

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