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.

Institut Pasteur
Microbes and Infection 15 (2013) 625–629
www.elsevier.com/locate/micinf

Review

Middle East respiratory syndrome coronavirus (MERS-CoV): challenges in identifying its source and controlling its spread

Lu Lu [a], Qi Liu [a], Lanying Du [b], Shibo Jiang [a,b,*]

[a] *Key Laboratory of Medical Molecular Virology of Ministries of Education and Health, Shanghai Medical College, Fudan University, Shanghai 200032, China*
[b] *Lindsley F. Kimball Research Institute, New York Blood Center, 310 East 67th Street, New York, NY, USA*

Received 9 June 2013; accepted 10 June 2013
Available online 19 June 2013

Abstract

Middle East respiratory syndrome coronavirus (MERS-CoV), a novel human coronavirus that caused outbreaks of a SARS-like illness in the Middle East, is now considered a threat to global public health. This review discusses the challenges in identifying the source of this fatal virus and developing effective and safe anti-MERS-CoV vaccines and therapeutics in order to control its spread and to combat any future pandemic.

Keywords: Coronavirus; MERS-CoV; SARS-CoV; Source; Vaccine; Therapeutics

1. Introduction

On 20 September 2012, Dr. Ali Moh Zaki, a virologist at Dr. Fakeeh Hospital, Jeddah, Saudi Arabia, first reported on the Program for Monitoring Emerging Diseases (ProMED-mail) that a novel coronavirus (nCoV) had been isolated from the lungs of a 60-year-old male patient with acute pneumonia and acute renal failure [1]. On 23 September 2012, the World Health Organization (WHO) was informed by the United Kingdom (UK) of a 49-year-old male Qatari national who had a travel history to Saudi Arabia and Qatar and showed symptoms of nCoV infection [2]. In November 2012, the virus was identified as a novel betacoronavirus, the closest relative of the bat coronaviruses HKU4 and HKU5, by Dr. Ron Fouchier's group at the Erasmus Medical Center in Rotterdam, the Netherlands, and thus termed "hCoV-EMC" [3]. In May 2013, this virus was renamed as the Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses [4], and the term was then adopted by WHO [5].

By 7 June 2013, WHO had been informed of 55 confirmed cases, including 31 deaths (a case fatality rate of 56%), from four countries in the Middle East (Saudi Arabia, Jordan, Qatar, and the United Arab Emirates), three countries in Europe (France, Italy, and the United Kingdom), and one country in Africa (Tunisia) (Table 1) [5]. Some of the patients reported in Europe were originally infected during their travel in the Middle East and became ill after their return to Europe, while others who had not been to the Middle East, but had been in close contact with laboratory-confirmed or probable cases, became infected because of limited person-to-person transmission. So far, eight MERS-CoV clusters have been reported. The largest cluster was linked to one healthcare facility in Al-Ahsa, Saudi Arabia, consisting of 25 patients and including 14 deaths. Two of these patients are healthcare providers who were infected after caring for patients with MERS-CoV infection [5,6]. This evidence strongly suggests human-to-human transmission involving different modes, such as droplet and contact transmission, although the efficiency of

* Corresponding author. Key Laboratory of Medical Molecular Virology of Ministries of Education and Health, Shanghai Medical College, Fudan University, Shanghai 200032, China. Tel.: +86 21 54237673; fax: +86 21 54237465.
E-mail address: shibojiang@fudan.edu.cn (S. Jiang).

1286-4579/$ - see front matter
http://dx.doi.org/10.1016/j.micinf.2013.06.003

Table 1
The cumulative number of MERS cases and deaths as of 6 June 2013 [5].

Countries	Cases	Deaths
Middle East	45	28
Saudi Arabia	40	25
Jordan	2	2
Qatar	2	0
United Arab Emirates (UAE)	1	1
Europe	8	3
United Kingdom (UK)	3	2
France	2	1
Italy	3	0
Africa	2	0
Tunisia	2	0
Total	55	31

human-to-human transmission of MERS-CoV is lower than severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) [6]. However, MERS-CoV may gain increased human-to-human transmissibility after its further adaptation and evolution in humans or as-yet unknown intermediate hosts, eventually causing a global pandemic like the one caused by SARS-CoV in 2003 [7–10].

On 27 May 2013 at the Sixty-sixth World Health Assembly, Geneva, Switzerland, Dr. Margaret Chan, the Director-General of WHO, pointed out that "the novel coronavirus is a threat to the entire world" because we still do not know where the virus hides in nature or how people become infected [11].

On 5 June 2013, the Obama administration designated MERS-CoV a threat to public health and national security and gave officials the authority to fast-track the approval of tests and treatments for MERS-CoV [12]. Dr. Kathleen Sebelius, the Secretary of the Department of Health and Human Services of the United States, made the designation, allowing the U.S. Food and Drug Administration (FDA) to quickly approve products after accepting an "emergency use application (EUA)" [13].

In mid-October of this year, more than two million Muslims will undertake the Hajj, an annual pilgrimage to Mecca, and they will remain in a confined geographical area over a five-day period. Medical authorities in Saudi Arabia have taken immediate steps to implement control measures over fears of a potential MERS-CoV pandemic resulting from this event, including the advisement to wear face masks in overcrowded areas [14].

Therefore, while researchers need to take appropriate steps now to identify the source of MERS-CoV, track down its intermediate host(s), and develop strategies for controlling its spread, these goals also bring a number of challenges.

2. Challenge in identifying the source of MERS-CoV

The first challenge confronting researchers is identifying the source of MERS-CoV. Genetically, we know that this virus is closely related to *Tylonycteris* bat CoV HKU4 (Ty-BatCoV HKU4) and *Pipistrellus* bat CoV HKU5 (Pi-BatCoV HKU5) in bats from Hong Kong. However, the molecular clock analysis suggests that these bat viruses are unlikely the direct ancestor of MERS-CoV [15].

MERS-CoV uses the evolutionarily conserved dipeptidyl peptidase 4 (DPP4) as its functional receptor [16], enters into the target cell via plasma or endosomal membrane fusion, and replicates in the host cell in a similar way as SARS-CoV does [17] (Fig. 1). It can infect various mammalian cell lines, such as primate, porcine, bat and rabbit cells [18], suggesting that MERS-CoV may have broad species tropism. It was reported that some MERS-CoV cases, as noted above, had a history of contact with animals, such as camels and goats [19], suggesting that MERS-CoV may have jumped from bats to these animals before infecting humans. However, its animal reservoir and intermediate hosts still have not been identified, which has significantly hindered the development of strategies to control this emerging infectious disease and combat the potential pandemic of MERS.

3. Challenge in designing MERS vaccines

To control MERS, we must develop an effective and safe vaccine, which constitutes a second challenge to researchers. However, the problems encountered in the development of SARS vaccines should be revisited before the MERS vaccines are designed. Some of the inactivated virus-based, DNA-based and viral vector-based vaccine candidates could induce Th2-mediated immunopathology or immunoenhancing pathology [20–24], raising concerns about the safety of the SARS vaccines.

Our previous studies have shown that the SARS vaccine candidates based on the receptor-binding domain (RBD) in the S1 subunit of the SARS-CoV spike protein is more effective and safer than the above-mentioned vaccine candidates [17,25,26]. By comparing the sequences of spike proteins of SARS-CoV and MERS-CoV, we predicted that a 286-amino acid fragment (residues 377–662) in the S1 subunit of MERS-CoV contains its RBD [27]. We strongly believe that the RBD in the MERS-CoV spike protein is therefore an important target for developing MERS vaccines.

Most recently, Chan et al. reported that the sera of some convalescent SARS patients contained antibodies that could cross-react or cross-neutralize MERS-CoV [28]. This raises a hope that people with histories of SARS-CoV infection might not be susceptible to MERS-CoV infection. However, our study demonstrated that the epitopes eliciting the cross-reactive antibodies may not be located in the RBD of SARS-CoV S protein [29]. Thus, it is doubtful whether these antibodies really have a role in cross-protection against MERS-CoV.

4. Challenge in developing anti-MERS therapy

To date, no effective antiviral therapeutics against MERS-CoV have been discovered. Clinical management is mainly supportive, placing emphasis on organ support for respiratory and renal failure. In cases of acute respiratory failure, the use of extracorporeal membrane oxygenation (ECMO) is expected to improve survival rates significantly [30].

Several nonspecific antiviral drugs, such as ribavirin, lopinavir, and type I IFN, have been used for treating SARS,

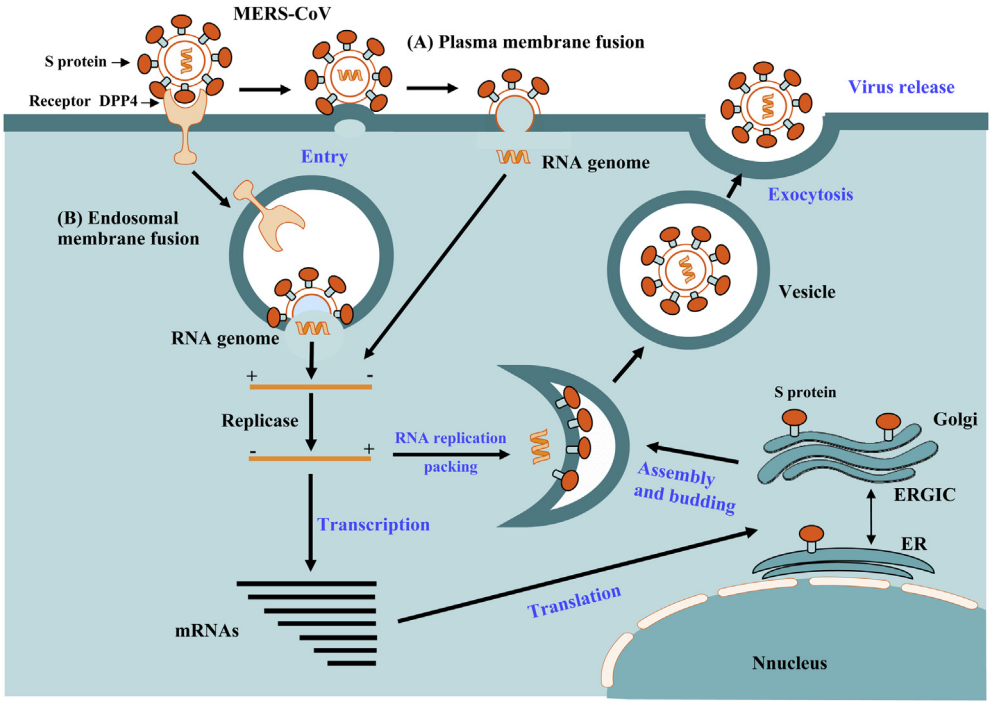

Fig. 1. The life cycle of MERS-CoV. MERS-CoV first binds, via its S protein, to the receptor DPP4 on the target cell [16], and then releases its RNA genome, through plasma or endosomal membrane fusion, into the target cell. After transcription and translation, the new genomic RNA and viral proteins are then assembled into virions, which are transported via vesicles and released out of the host cell, in a way similar to SARS-CoV [17].

although their actual efficacy in these patients is still unclear [31,32]. IFN-α was shown to inhibit *in vitro* MERS-CoV replication in cells [33], but it is unknown whether it works *in vivo*.

It has been thought that cytokine storm, a potentially fatal immune reaction characterized by the massive release of proinflammatory cytokines, is responsible for the deaths of patients infected by highly pathogenic avian influenza A (H5N1) virus or SARS-CoV [34,35]. Therefore, immunosuppressant or immunomodulatory drugs, which diminish inflammation during infection, are expected to have therapeutic benefit [36]. However, whether or not the immunosuppressant drugs should be used for treating MERS patients is debatable. First, no report has yet shown that cytokine storms are indeed responsible for the deaths of MERS patients. Second, cell host response to infection with MERS-CoV is much different from that to SARS-CoV infection [37]. Yuen and colleagues believed that corticosteroid should not be considered for treating MERS, particularly since patients with severe pneumonia and respiratory failure could be supported by ECMO until the cytokine storm is over [38].

Similar to HIV and SARS-CoV, MERS-CoV enters the target cells through its S2 protein-mediated membrane fusion (Fig. 1). Therefore, the S2 subunit of the MERS-CoV S protein may serve as a target for developing MERS-CoV fusion inhibitors. In the early 1990s, Jiang et al. [39] and Wild et al. [40] found that the peptides SJ-2176 and T20 derived from the HIV-1 gp41 HR2 domain had potent anti-HIV-1 activity. In 2003, T20 was approved by the U.S. FDA for treatment of HIV-infected patients who fail to respond to the current antiretroviral drugs [41,42]. In 2004, Jiang and colleagues identified an anti-SARS-CoV peptide (CP-1) from the SARS-CoV S protein S2 subunit of the HR2 domain [43]. Similar approaches could also be used to identify anti-MERS-CoV peptides. Different from the T20-based HIV/AIDS treatment regimen, which needs long-term injection [44], the MERS-CoV fusion inhibitor-based therapy would only require a regimen of a few days at the onset of MERS-CoV infection to save patients' lives.

5. Conclusion

In conclusion, MERS-CoV, which originally caused outbreaks of a SARS-like illness in the Middle East, is now considered a threat to global public health. While its human-to-human transmission is so far limited, serious concerns over its pandemic potential have been raised. Therefore, researchers must take immediate steps to identify the source of this fatal virus and develop effective and safe anti-MERS-CoV vaccines and therapeutics in order to control its spread and to combat any future pandemic.

References

[1] A.M. Zaki, Novel Cornavirus – Saudi Arabia: Human Isolate, http://www.promedmail.org/direct.php?id=20120920.1302733 (accessed 09.06.13).
[2] WHO, Novel Coronavirus Infection in the United Kingdom, http://www.who.int/csr/don/2012_09_23/en/index.html (accessed 09.06.13).
[3] A.M. Zaki, S. van Boheemen, T.M. Bestebroer, A.D.M.E. Osterhaus, R.A.M. Fouchier, Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia, N. Engl. J. Med. 367 (2012) 1814–1820.

[4] R.J. de Groot, S.C. Baker, R.S. Baric, C.S. Brown, C. Drosten, L. Enjuanes, R.A. Fouchier, M. Galiano, A.E. Gorbalenya, Z. Memish, S. Perlman, L.L. Poon, E.J. Snijder, G.M. Stephens, P.C. Woo, A.M. Zaki, M. Zambon, J. Ziebuhr, Middle East respiratory syndrome coronavirus (MERS-CoV); announcement of the coronavirus study group, J. Virol. (15 May 2013). (Epub ahead of print).

[5] WHO, Novel Coronavirus Infection – Update (Middle East Respiratory Syndrome-coronavirus), http://www.who.int/csr/don/2013_06_07/en/index.html (accessed 09.06.13).

[6] Centers for Disease Control and Prevention, Update, Case Definitions, and Guidance – MERS Update, http://www.cdc.gov/coronavirus/mers/case-def.html (accessed 09.06.13).

[7] J.S.M. Peiris, S.T. Lai, L.L.M. Poon, Y. Guan, L.Y.C. Yam, W. Lim, J. Nicholls, W.K.S. Yee, W.W. Yan, M.T. Cheung, V.C.C. Cheng, K.H. Chan, D.N.C. Tsang, R.W.H. Yung, T.K. Ng, K.Y. Yuen, Coronavirus as a possible cause of severe acute respiratory syndrome, Lancet 361 (2003) 1319–1325.

[8] N.S. Zhong, B.J. Zheng, Y.M. Li, L.L.M. Poon, Z.H. Xie, K.H. Chan, P.H. Li, S.Y. Tan, Q. Chang, J.P. Xie, X.Q. Liu, J. Xu, D.X. Li, K.Y. Yuen, J.S.M. Peiris, Y. Guan, Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003, Lancet 362 (2003) 1353–1358.

[9] C. Drosten, S. Gunther, W. Preiser, W.S. van der, H.R. Brodt, S. Becker, H. Rabenau, M. Panning, L. Kolesnikova, R.A. Fouchier, A. Berger, A.M. Burguiere, J. Cinatl, M. Eickmann, N. Escriou, K. Grywna, S. Kramme, J.C. Manuguerra, S. Muller, V. Rickerts, M. Sturmer, S. Vieth, H.D. Klenk, A.D. Osterhaus, H. Schmitz, H.W. Doerr, Identification of a novel coronavirus in patients with severe acute respiratory syndrome, N. Engl. J. Med. 348 (2003) 1967–1976.

[10] P.A. Rota, M.S. Oberste, S.S. Monroe, W.A. Nix, R. Campagnoli, J.P. Icenogle, S. Penaranda, B. Bankamp, K. Maher, M.H. Chen, S.X. Tong, A. Tamin, L. Lowe, M. Frace, J.L. Derisi, Q. Chen, D. Wang, D.D. Erdman, T.C.T. Peret, C. Burns, T.G. Ksiazek, P.E. Rollin, A. Sanchez, S. Liffick, B. Holloway, J. Limor, K. McCaustland, M. Olsen-Rasmussen, R. Fouchier, S. Gunther, A.D.M.E. Osterhaus, C. Drosten, M.A. Pallansch, L.J. Anderson, W.J. Bellini, Characterization of a novel coronavirus associated with severe acute respiratory syndrome, Science 300 (2003) 1394–1399.

[11] M. Chan, WHO Director-General Praises the World Health Assembly for its Work, http://www.who.int/dg/speeches/2013/world_health_assembly_20130527/en/index.html (accessed 09.06.13).

[12] M.R. Wilson, Administration Declares Mideast Flu a Potential Public Health Emergency, http://thehill.com/blogs/healthwatch/public-global-health/303441-administration-declares-mideast-flu-a-public-health-emergency#ixzz2VLnzfH16 (accessed 09.06.13).

[13] Department of Health and Human Services, Determination and Declaration Regarding emergency Use of in Vitro Diagnostics for Detection of Middle East Respiratory Syndrome Coronavirus (MERS-CoV), http://www.gpo.gov/fdsys/pkg/FR-2013-06-05/html/2013-13333.htm (accessed 09.06.13).

[14] E. Tanquintic-Misa, Saudi Arabia Moves to Control MERS-CoV before Mecca Hajj Pilgrimage Season (6 June 2013). (Ref Type: Report), http://www.ibtimes.co.uk/articles/475277/20130606/saudi-mers-cov-mecca-hajj.htm.

[15] S.K. Lau, K.S. Li, A.K. Tsang, C.S. Lam, S. Ahmed, H. Chen, K.H. Chan, P.C. Woo, K.Y. Yuen, Genetic characterization of betacoronavirus lineage C viruses in bats revealed marked sequence divergence in the spike protein of Pipistrellus bat coronavirus HKU5 in Japanese pipistrelle: implications on the origin of the novel Middle East respiratory syndrome coronavirus, J. Virol. (29 May 2013). (Epub ahead of print).

[16] V.S. Raj, H. Mou, S.L. Smits, D.H. Dekkers, M.A. Muller, R. Dijkman, D. Muth, J.A. Demmers, A. Zaki, R.A. Fouchier, V. Thiel, C. Drosten, P.J. Rottier, A.D. Osterhaus, B.J. Bosch, B.L. Haagmans, Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC, Nature 495 (2013) 251–254.

[17] L. Du, Y. He, Y. Zhou, S. Liu, B.J. Zheng, S. Jiang, The spike protein of SARS-CoV: a target for vaccine and therapeutic development, Nat. Rev. Microbiol. 7 (2009) 226–236.

[18] J.F. Chan, K.H. Chan, G.K. Choi, K.K. To, H. Tse, J.P. Cai, M.L. Yeung, V.C. Cheng, H. Chen, X.Y. Che, S.K. Lau, P.C. Woo, K.Y. Yuen, Differential cell line susceptibility to the emerging novel human betacoronavirus 2c EMC/2012: implications for disease pathogenesis and clinical manifestation, J. Infect. Dis. 207 (2013) 1743–1752.

[19] U. Buchholz, M.A. Muller, A. Nitsche, A. Sanewski, N. Wevering, T. Bauer-Balci, F. Bonin, C. Drosten, B. Schweiger, T. Wolff, D. Muth, B. Meyer, S. Buda, G. Krause, L. Schaade, W. Haas, Contact investigation of a case of human novel coronavirus infection treated in a German hospital, October–November 2012, Euro. Surveill. 18 (2013). pii: 20406.

[20] D. Deming, T. Sheahan, M. Heise, B. Yount, N. Davis, A. Sims, M. Suthar, J. Harkema, A. Whitmore, R. Pickles, A. West, E. Donaldson, K. Curtis, R. Johnston, R. Baric, Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants, PLoS Med. 3 (2006) e525.

[21] F. Yasui, C. Kai, M. Kitabatake, S. Inoue, M. Yoneda, S. Yokochi, R. Kase, S. Sekiguchi, K. Morita, T. Hishima, H. Suzuki, K. Karamatsu, Y. Yasutomi, H. Shida, M. Kidokoro, K. Mizuno, K. Matsushima, M. Kohara, Prior immunization with severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) nucleocapsid protein causes severe pneumonia in mice infected with SARS-CoV, J. Immunol. 181 (2008) 6337–6348.

[22] M. Bolles, D. Deming, K. Long, S. Agnihothram, A. Whitmore, M. Ferris, W. Funkhouser, L. Gralinski, A. Totura, M. Heise, R.S. Baric, A double-inactivated SARS-CoV vaccine provides incomplete protection in mice and induces increased eosinophilic pro-inflammatory pulmonary response upon challenge, J. Virol. 85 (23) (2011) 12201–12215.

[23] C.T. Tseng, E. Sbrana, N. Iwata-Yoshikawa, P.C. Newman, T. Garron, R.L. Atmar, C.J. Peters, R.B. Couch, Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus, PLoS One 7 (2012) e35421.

[24] M. Jaume, M.S. Yip, Y.W. Kam, C.Y. Cheung, F. Kien, A. Roberts, P.H. Li, I. Dutry, N. Escriou, M. Daeron, R. Bruzzone, K. Subbarao, J.S. Peiris, B. Nal, R. Altmeyer, SARS CoV subunit vaccine: antibody-mediated neutralisation and enhancement, Hong Kong Med. J. 18 (Suppl. 2) (2012) 31–36.

[25] Y. He, H. Lu, P. Siddiqui, Y. Zhou, S. Jiang, Receptor-binding domain of severe acute respiratory syndrome coronavirus spike protein contains multiple conformation-dependent epitopes that induce highly potent neutralizing antibodies, J. Immunol. 174 (2005) 4908–4915.

[26] S. Jiang, M.E. Bottazzi, L. Du, S. Lustigman, C.T. Tseng, E. Curti, K. Jones, B. Zhan, P.J. Hotez, Roadmap to developing a recombinant coronavirus S protein receptor-binding domain vaccine for severe acute respiratory syndrome, Expert Rev. Vaccines 11 (2012) 1405–1413.

[27] S. Jiang, L. Lu, L. Du, A.K. Debnath, A predicted receptor-binding and critical neutralizing domain in S protein of the novel human coronavirus HCoV-EMC, J. Infect. 66 (2013) 464–466.

[28] K.H. Chan, J.F. Chan, H. Tse, H. Chen, C.C. Lau, J.P. Cai, A.K. Tsang, X. Xiao, K.K. To, S.K. Lau, P.C. Woo, B.J. Zheng, M. Wang, K.Y. Yuen, Cross-reactive antibodies in convalescent SARS patients' sera against the emerging novel human coronavirus EMC (2012) by both immunofluorescent and neutralizing antibody tests, J. Infect. (10 Apr 2013), http://dx.doi.org/10.1016/j.jinf.2013.03.015. (Epub ahead of print), pii: S0163-4453(13)00071-6.

[29] L. Du, C. Ma, S. Jiang, Antibodies induced by receptor-binding domain in spike protein of SARS-CoV do not cross-neutralize the novel human coronavirus hCoV-EMC, J. Infect. (16 May 2013). (Epub ahead of print).

[30] T.V. Brogan, R.R. Thiagarajan, P.T. Rycus, R.H. Bartlett, S.L. Bratton, Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database, Intensive Care Med. 35 (2009) 2105–2114.

[31] L.J. Stockman, R. Bellamy, P. Garner, SARS: systematic review of treatment effects, PLoS Med. 3 (2006) e343.

[32] V.C. Cheng, S.K. Lau, P.C. Woo, K.Y. Yuen, Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection, Clin. Microbiol. Rev. 20 (2007) 660–694.

[33] E. Kindler, H.R. Jonsdottir, D. Muth, O.J. Hamming, R. Hartmann, R. Rodriguez, R. Geffers, R.A. Fouchier, C. Drosten, M.A. Muller, R. Dijkman, V. Thiel, Efficient replication of the novel human

betacoronavirus EMC on primary human epithelium highlights its zoonotic potential, mBio 4 (2013) e00611–e00612.
[34] M.T. Osterholm, Preparing for the next pandemic, N. Engl. J. Med. 352 (2005) 1839–1842.
[35] K.J. Huang, I.J. Su, M. Theron, Y.C. Wu, S.K. Lai, C.C. Liu, H.Y. Lei, An interferon-gamma-related cytokine storm in SARS patients, J. Med. Virol. 75 (2005) 185–194.
[36] J.R. Tisoncik, M.J. Korth, C.P. Simmons, J. Farrar, T.R. Martin, M.G. Katze, Into the eye of the cytokine storm, Microbiol. Mol. Biol. Rev. 76 (2012) 16–32.
[37] L. Josset, V.D. Menachery, L.E. Gralinski, S. Agnihothram, P. Sova, V.S. Carter, B.L. Yount, R.L. Graham, R.S. Baric, M.G. Katze, Cell host response to infection with novel human coronavirus EMC predicts potential antivirals and important differences with SARS coronavirus, mBio 4 (2013).
[38] J.F. Chan, K.S. Li, K.K. To, V.C. Cheng, H. Chen, K.Y. Yuen, Is the discovery of the novel human betacoronavirus 2c EMC/2012 (HCoV-EMC) the beginning of another SARS-like pandemic? J. Infect. 65 (2012) 477–489.
[39] S. Jiang, K. Lin, N. Strick, A.R. Neurath, HIV-1 inhibition by a peptide, Nature 365 (1993) 113.
[40] C.T. Wild, D.C. Shugars, T.K. Greenwell, C.B. McDanal, T.J. Matthews, Peptides corresponding to a predictive alpha-helical domain of human immunodeficiency virus type 1 gp41 are potent inhibitors of virus infection, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 9770–9774.
[41] J.M. Kilby, J.J. Eron, Novel therapies based on mechanisms of HIV-1 cell entry, N. Engl. J. Med. 348 (2003) 2228–2238.
[42] J.P. Lalezari, K. Henry, M. O'Hearn, J.S. Montaner, P.J. Piliero, B. Trottier, S. Walmsley, C. Cohen, D.R. Kuritzkes, J.J. Eron Jr., J. Chung, R. DeMasi, L. Donatacci, C. Drobnes, J. Delehanty, M. Salgo, Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America, N. Engl. J. Med. 348 (2003) 2175–2185.
[43] S. Liu, G. Xiao, Y. Chen, Y. He, J. Niu, C.R. Escalante, H. Xiong, J. Farmar, A.K. Debnath, P. Tien, S. Jiang, Interaction between heptad repeat 1 and 2 regions in spike protein of SARS-associated coronavirus: implications for virus fusogenic mechanism and identification of fusion inhibitors, Lancet 363 (2004) 938–947.
[44] S. Liu, S. Wu, S. Jiang, HIV entry inhibitors targeting gp41: from polypeptides to small-molecule compounds, Curr. Pharm. Des. 13 (2007) 143–162.