

## Accepted Manuscript

Title: Host-directed therapies for improving poor treatment outcomes associated with the middle east respiratory syndrome coronavirus infections

Author: Alimuddin Zumla Esam I. Azhar Yaseen Arabi  
Badriah Alotaibi Martin Rao Brian McCloskey Eskild  
Petersen Markus Maeurer



PII: S1201-9712(15)00215-5  
DOI: <http://dx.doi.org/doi:10.1016/j.ijid.2015.09.005>  
Reference: IJID 2427

To appear in: *International Journal of Infectious Diseases*

Please cite this article as: Zumla A, Azhar EI, Arabi Y, Alotaibi B, Rao M, McCloskey B, Petersen E, Maeurer M, Host-directed therapies for improving poor treatment outcomes associated with the middle east respiratory syndrome coronavirus infections, *International Journal of Infectious Diseases* (2015), <http://dx.doi.org/10.1016/j.ijid.2015.09.005>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

## Host-Directed Therapies for Improving Poor Treatment Outcomes Associated with the Middle East Respiratory Syndrome Coronavirus Infections

### AUTHORS:

Alimuddin Zumla<sup>1,2</sup>, Esam I Azhar<sup>2</sup>, Yaseen Arabi<sup>3</sup>, Badriah Alotaibi<sup>4</sup>, Martin Rao<sup>5</sup>, Brian McCloskey<sup>6</sup>, Eskild Petersen<sup>7</sup> and Markus Maeurer<sup>5\*</sup>

All authors contributed equally

### INSTITUTIONAL AFFILIATIONS:

**Alimuddin Zumla** FRCP. Email: [a.zumla@ucl.ac.uk](mailto:a.zumla@ucl.ac.uk): <sup>1</sup>Division of Infection and Immunity, University College London, and NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, United Kingdom, and <sup>2</sup>Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia

**Esam I Azhar** PhD. Email: [eazhar@kau.edu.sa](mailto:eazhar@kau.edu.sa): <sup>2</sup>Special Infectious Agents Unit, King Fahd Medical Research Centre, and Medical Laboratory Technology Department, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.

**Yaseen Arabi**, FCCP. Email: [arabi@ngha.med.sa](mailto:arabi@ngha.med.sa): <sup>3</sup>Intensive Care Department, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, 11426, Kingdom of Saudi Arabia

**Badriah Alotaibi** MPH. Email: [otaibi\\_b1@yahoo.com](mailto:otaibi_b1@yahoo.com) <sup>4</sup>Global Center for Mass Gatherings Medicine, Ministry of Health, Riyadh, Kingdom of Saudi Arabia.

**Markus Maeurer** FRCP. Email: [Markus.Maeurer@ki.se](mailto:Markus.Maeurer@ki.se): **Martin Rao** PhD Email: [martin.rao@ki.se](mailto:martin.rao@ki.se) <sup>5</sup>Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, and Centre for Allogeneic Stem Cell Transplantation, Karolinska University Hospital Huddinge, Stockholm, Sweden.

**Brian McCloskey** FFPH. Email: [Brian.McCloskey@phe.gov.uk](mailto:Brian.McCloskey@phe.gov.uk) <sup>6</sup>Global Health Department, Public Health England, London, United Kingdom

**Eskild Petersen** MD. Email: [eskildp@dadlnet.dk](mailto:eskildp@dadlnet.dk): <sup>7</sup>Department of Infectious Diseases and Clinical Microbiology, Aarhus University Hospital Skejby, Aarhus, Denmark

**Keywords:** MERS, MERS-CoV, mortality, treatment, host-directed therapy, respiratory infection, ARDS,

### *\*Correspondence:*

**Professor Markus Maeurer** PhD.FRCP Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, and 2 Centre for Allogeneic Stem Cell Transplantation, Karolinska University Hospital Huddinge, Stockholm, Sweden. **Email:** [Markus.Maeurer@ki.se](mailto:Markus.Maeurer@ki.se)

### Abstract

Three years after its first discovery in Jeddah Saudi Arabia, the novel zoonotic pathogen of humans, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) continues to be a major threat to global health security [1]. Sporadic community acquired cases of MERS continue to be reported from the Middle East. The recent nosocomial outbreaks in hospitals in Seoul, Korea and at the National Guard Hospital in Riyadh, Saudi Arabia indicate the epidemic potential of MERS-CoV. Currently there are no effective anti-MERS-CoV anti-viral agents or therapeutics and MERS is associated with a high mortality rate (40%) in hospitalised patients. A large proportion of MERS patients who die have a range of pulmonary pathology ranging from pneumonia to adult respiratory distress syndrome with multi-organ failure, compounded by co-morbidities, reflecting a precarious balance of interactions between the host-immune system and MERS-CoV. Whilst we wait for new MERS-CoV specific drugs, therapeutics and vaccines to be developed, there is a need to advance a range of Host-Directed Therapies. A range of HDTs are available, including commonly used drugs with good safety profiles, which could augment host innate and adaptive immune mechanisms to MERS-CoV, modulate excessive inflammation and reduce lung tissue destruction. We discuss the rationale and potential of using Host-Directed Therapies for improving the poor treatment outcomes associated with MERS. Carefully designed randomized controlled trials will be needed to determine whether HDTs could benefit patients with MERS. The recurrent outbreaks of MERS-CoV infections at hospitals in the Middle East present unique opportunities to conduct randomized clinical trials. The time has come for a more coordinated global response to MERS and a multidisciplinary global MERS-CoV response group is required to take forward priority research agendas.

## **INTRODUCTION AND BACKGROUND**

The past two decades has seen the emergence and spread of novel viral respiratory tract pathogens of humans, such as severe acute respiratory syndrome coronavirus (SARS-CoV), H7N9 avian strain of influenza A virus, swine influenza A H1N1, and Middle East respiratory syndrome coronavirus (MERS-CoV), for which no specific treatment options are available and carry a high morbidity and mortality rate [1, 2, 3, 4, 5]. MERS-CoV was first reported from Jeddah in September 2012 when it was isolated from a Saudi patient who died of a severe respiratory illness and multi-organ failure [6]. Since then community and hospital acquired MERS cases have been reported from twenty-nine countries from the Middle East, Africa, Europe, North America and Asia [7]. Three years since its first discovery, many fundamental questions regarding the epidemiology, pathogenesis, immune responses and optimal treatment regimens of MERS-CoV remain unanswered [8, 9, 10]. MERS-CoV continues to be of global concern as illustrated by recent nosocomial outbreaks at the National Guard Hospital in Riyadh, Saudi Arabia [11, 12, 13] and at hospitals in Seoul, Republic of Korea [14, 15, 16]. The Korean outbreak which resulted in 186 confirmed MERS cases with 35 deaths arose from a Korean traveler who imported MERS-CoV from the Middle

East [17]. As of 21 August 2015, there have been 1432 laboratory confirmed cases of human infection with 507 deaths (40% mortality) [18].

### **CURRENT DEFICIENCIES OF MERS-CoV TREATMENT**

Current clinical management of seriously ill MERS patients is fraught with difficulties [19, 20]. There are no MERS-CoV-specific anti-viral, other therapeutic or immune based treatments approved for treating patients. Thus supportive care is the main stay of treatment and is focused on prevention of complications, particularly organ failure, ARDS, and secondary bacterial infections [21]. Due to the high mortality in hospitalized MERS cases, empiric treatment has been tried on an ad hoc patient basis. Reports of the empiric individual or combination use of steroids, interferons (IFN- $\alpha$  and IFN- $\beta$ ), other generic anti-viral drugs have been tried have been used to treat MERS patients with no significant effects on clinical outcome [22, 23, 24, 25, 26, 27, 28]. There have been no controlled randomized clinical trials of any treatment intervention performed to date. The use of convalescence plasma, monoclonal antibodies and mycophenolic acid are further options available and require evaluation in controlled clinical trials. There are several anti-MERS-CoV drugs in development but to date no anti-MERS-CoV therapeutics have been developed or approved by regulatory authorities. The unacceptable high mortality rate associated with MERS-CoV and its epidemic potential, indicates an urgent need for development of newer anti-MERS-CoV drugs, vaccines and alternate treatment approaches [29, 30].

### **MERS-CoV PATHOGENESIS AND HOST IMMUNE RESPONSES**

Infection with MERS-CoV presents as a spectrum of clinical manifestations from asymptomatic, mild to severe disease which progresses to multi-organ failure and death. A large proportion of patients infected with MERS-CoV are either asymptomatic or have mild illness and complete recovery occurs due to effective innate and acquired immune responses which eradicates the infection [31]. No comprehensive immunopathogenesis studies have been conducted to date. The protective and deleterious human response to MERS-CoV remains to be determined. Pneumonia and multi-organ involvement is a common feature in patients with MERS [32]. The high mortality seen in MERS-CoV could be attributed to acute lung injury, development of acute respiratory distress syndrome (ARDS) [33]. ARDS is associated with leaky alveolar-capillary interfaces with pulmonary oedema, hypoxia, polymorphonuclear leucocytic or lymphocytic cells with upregulation of pro-inflammatory cytokines and gamma interferon and an aberrant immune response, which results in further tissue damage and deterioration of lung function. Sixty percent of MERS patients with acute lung injury or ARDS either recover after receiving intensive care and 40% of MERS patients succumb to the disease [34].

A large majority of patients who die due to infection with MERS-CoV may have some form of immunosuppression due to old age or having co-morbid conditions (diabetes, chronic lung, renal, cardiac

or liver disease or have an underlying immunosuppressive condition) [35]. It appears that the outcome of MERS patients may represent a precarious balance of both host- and MERS-CoV-induced immune signaling events [36]. It is not known whether mortality is a reflection of an ineffective host response to MERS-CoV or whether an aberrant host immune response contributes to pathogenesis and poor prognosis. Interventions that could manipulate this host-pathogen relationship via modulation of the host response to MERS-CoV infection may help improve mortality rates in patients with MERS [37]. For instance, genome analysis suggest that immune signaling modulation may affect outcome [38], and adenosine deaminase may prevent MERS-CoV entry into host cells [39]. A range of Host-Directed Therapies (HDTs) have the potential for improving the treatment outcomes of severe lung infections [40].

### HOST-DIRECTED THERAPIES FOR MERS

The general principles of using HDTs are to augment anti-MERS-CoV protective immune mechanisms, modulate destructive immune-mediated inflammatory responses, and protect tissues from inflammatory damage. A range of HDT interventions are available [41, 42] which require evaluation for treatment of patients with MERS:

- 1) 'Repurposed' commonly used drugs with excellent safety profiles include those being used for lowering cholesterol, diabetes, arthritis, antibiotics, epilepsy and cancer, which can modulate autophagy, promote other immune effector mechanisms, antimicrobial peptide production and repair of damaged tissues,
- 2) Micronutrient products with immune-modulatory effects,
- 3) Cellular therapy using mesenchymal stromal cells obtained from patient's own bone marrow to reduce aberrant inflammation, regenerating tissues and inducing anti-MERS-CoV immune responses.

**Repurposed drugs:** Several commonly available products with a longstanding safety record which are readily available and require evaluation as treatments for severe MERS, and for which open label clinical trials should be considered [43]. Statins have shown potential for treatment of influenza [44] and other diseases with lung injury [45]. They induce autophagy and maturation of phagosome and have anti-inflammatory effects through peroxisome proliferator-activated receptor- $\gamma$  and transforming growth factor- $\beta$ . Non-steroidal anti-inflammatory drugs such as Indomethacin, Ibuprofen and Acetylsalicylic acid inhibit cyclooxygenase and reduce inflammation and tissue pathology [46]; overt inflammatory immune responses, have been curbed using etoposide in patients with severe influenza infection [47], which may in part be due to differential susceptibility of Treg (regulatory T-cells)[48]. The diabetes drug Metformin increases mitochondrial ROS production and enhances macrophage autophagy [49]. Several cancer drugs such as Gleevec (Imatinib)-a tyrosine kinase inhibitor, activate autophagy and reduce inflammatory responses [50]. Doxycycline has potential for protection against destruction and degradation of tissue collagen and other structural proteins through its matrix metallo proteinase (MMP) inhibitor effect [51]. A

recent study describes a library of 290 compounds screened for antiviral activity against MERS-CoV and severe acute respiratory syndrome coronavirus (SARS-CoV). Of these 27 compounds with activity against both MERS-CoV and SARS-CoV were identified [52]. These compounds include inhibitors of dopamine receptor used as anti-psychotic drugs and inhibitors of estrogen receptors used for cancer treatment.

***Autologous bone-marrow derived stromal cells:*** Mesenchymal stromal cells (MSCs) derived from the patient's own bone marrow may have the potential to modulate aberrant immune responses through their anti-inflammatory and tissue-repairing effects for severe viral and bacterial infections of the lung (Refs). The use of adjunct therapy using MSCs derived from the patient's own bone marrow and expanded *ex vivo* before re-infusion, is currently under evaluation for range of infectious and non-communicable diseases and should be evaluated for improving treatment outcome of MERS-CoV in hospitalized cases, with very encouraging and life-saving results in the MSCs treatment of patients with ARDS [53].

#### **ADVANCING HOST-DIRECTED THERAPIES FOR MERS**

Repurposed drugs have well-defined safety and pharmacokinetic profiles their individual evaluations through controlled clinical trials are required to define their effectiveness in treatment of severe cases of MERS and patients with co-morbidities. Treatment outcome measures would be effect on mortality, lung function, and long term sequelae, immune responses, and resolution of lung inflammation and tissue regeneration. To achieve optimal treatment several variables need to be explored when trialing these agents including patient's age, the presence of co-morbid illness, the extent of disease and the timing of the intervention. Carefully designed randomized controlled trials will be needed to determine whether HDTs could benefit patients with MERS, and optimally these studies. HDT trials in MERS could benefit from experience in managing life-threatening clinical situations, where overt inflammation caused by a 'cytokine storm' in the context of T-cell based therapies of malignant diseases, can be controlled. Highly activated T-cells are not responsive to glucocorticosteroids [54, 55, 56], and yet may respond to newer drugs, such as anti-TNF reagents (e.g. etanercept), anti-IL-6 and anti-IL-1beta [57].

Many fundamental questions regarding MERS epidemiology, pathogenesis, protective immune responses, viral kinetics, and optimal treatment remain unanswered three years into its first discovery. A MERS-CoV response group is required and the recurrent outbreaks of MERS-CoV infections at hospitals present unique challenges for control of MERS-CoV and at the same time provides an opportunity to conduct randomized clinical trials and answer priority research questions. The time has come for a more coordinated global response to take forward important priority epidemiological, translational clinical and basic science research forward. The establishment of clinical trials capability within a global consortia

will develop infrastructure and build local capacity to take forward further evaluations of new drugs, therapeutics and vaccines

## References

- 1 World Health Organization. Middle East respiratory syndrome coronavirus (MERS-CoV). <http://www.who.int/emergencies/mers-cov/en>. [accessed on 16 August 2015]
- 2 Chan JF, Lau SK, To KK, Cheng VC, Woo PC, Yuen KY. Middle East respiratory syndrome coronavirus: another zoonotic betacoronavirus causing SARS-like disease. *Clinical Microbiology Reviews*. 2015;28:465-522.
- 3 Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, Nicholls J, Yee WK, Yan WW, Cheung MT, Cheng VC, Chan KH, Tsang DN, Yung RW, Ng TK, Yuen KY; SARS study group. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet*. 2003;361:1319-25.
- 4 Bui C, Bethmont A, Chughtai AA, Gardner L, Sarkar S, Hassan S, Seale H, MacIntyre CR. A Systematic Review of the Comparative Epidemiology of Avian and Human Influenza A H5N1 and H7N9 - Lessons and Unanswered Questions. *Transbound Emerg Dis* 2015 Jan 29. doi: 10.1111/tbed.12327. [Epub ahead of print]
- 5 Rider TH, Zook CE, Boettcher TL, Wick ST, Pancoast JS, Zusman BD. Broad-spectrum antiviral therapeutics. *PloS one*. 2011;6(7):e22572.
- 6 Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012;367:1814-20.
- 7 <http://www.who.int/emergencies/mers-cov/en/>. [accessed 6 September, 2015]
- 8 van den Brand JM, Smits SL, Haagmans BL. Pathogenesis of Middle East respiratory syndrome coronavirus. *J Pathol*. 2015 Jan;235(2):175-84. doi: 10.1002/path.4458. Review.
- 9 World Health Organization. Middle East Respiratory Syndrome coronavirus (MERS-CoV) – Saudi Arabia. <http://www.who.int/csr/don/12-august-2015-mers-saudi-arabia/en>. [accessed on 6 September 2015]
- 10 WHO MERS-CoV Research Group. State of Knowledge and Data Gaps of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Humans. *PLoS currents*. 2013;5.
- 11 Assiri A, McGeer A, Perl TM, Price CS, Al Rabeeah AA, Cummings DA, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. *The New England journal of medicine*. 2013;369(5):407-16.
- 12 Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, Al-Rabiah FA, Al-Hajjar S, Al-Barrak A, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *The Lancet infectious diseases*. 2013;13(9):752-61.

- 13 Saad M, Omrani AS, Baig K, Bahloul A, Elzein F, Matin MA, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Intl J Infect Dis* 2014;29:301-6.
- 14 Lee SS, Wong NS. Probable transmission chains of Middle East respiratory syndrome coronavirus and the multiple generations of secondary infection in South Korea. *Int J Infect Dis* 2015;38:65-7.
- 15 Hui DS, Perlman S, Zumla A. Spread of MERS to South Korea and China. *The lancet Respiratory medicine*. 2015;3:509-10.
- 16 Petersen E, Hui DS, Perlman S, Zumla A. Middle East Respiratory Syndrome- advancing the public health and research agenda on MERS- lessons from the South Korea outbreak. *Int J Infect Dis* 2015;36:54-5
- 17 Mizumoto K, Saitoh M, Chowell G, Miyamatsu Y, Nishiura H. Estimating the risk of Middle East respiratory syndrome (MERS) death during the course of the outbreak in the Republic of Korea, 2015. *Int J Infect Dis* 2015;39:7-9
- 18  
WHO/MERS/Clinical/15.1.[http://apps.who.int/iris/bitstream/10665/178529/1/WHO\\_MERS\\_Clinical\\_15.1\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/178529/1/WHO_MERS_Clinical_15.1_eng.pdf) Accessed 23rd August 2015
- 19 WHO Report: Clinical management of severe acute respiratory infections when MERS coronavirus is suspected: What to do and what not to do Interim guidance 2015WHO/MERS/Clinical/15
- 20 Hui DS, Memish ZA, Zumla A. Severe acute respiratory syndrome vs. the Middle East respiratory syndrome. *Current opinion in pulmonary medicine*. 2014;20(3):233-41.
- 21 WHO Report: Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected. Interim guidance. Updated 2 July 2015
- 22 Al-Tawfiq JA, Momattin H, Dib J, Memish ZA. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. *Intl J Infect Dis* 2014;20:42-6.
- 23 Chan JF, Chan KH, Kao RY, To KK, Zheng BJ, Li CP, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. *The Journal of infection*. 2013;67(6):606-16.
- 24 Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis* 2014;14:1090-5.
- 25 Shalhoub S, Farahat F, Al-Jiffri A, Simhairi R, Shamma O, Siddiqi N, et al. IFN-alpha2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *Journal Antimicrob Chemother* 2015;70:2129-32.
- 26 Spanakis N, Tsiodras S, Haagmans BL, Raj VS, Pontikis K, Koutsoukou A, et al. Virological and serological analysis of a recent Middle East respiratory syndrome coronavirus infection case on a triple combination antiviral regimen. *International journal of antimicrobial agents*. 2014.



- 27 Falzarano D, de Wit E, Martellaro C, Callison J, Munster VJ, Feldmann H. Inhibition of novel beta coronavirus replication by a combination of interferon-alpha2b and ribavirin. *Scientific reports*. 2013;3:1686.
- 28 Khalid M, Al Rabiah F, Khan B, Al Mobeireek A, Butt TS, Al Mutairy E. Ribavirin and interferon (IFN)-alpha-2b as primary and preventive treatment for Middle East respiratory syndrome coronavirus (MERS-CoV): a preliminary report of two cases. *Antivir Ther* 2015;20:87-91
- 29 Lurie N, Maniolo T, Patterson AP, Collins F, Frieden T: Research as a part of the public health emergency response. *N Engl J Med* 2013;368:1251–5.
- 30 Hui DS, Zumla A. Advancing priority research on the Middle East respiratory syndrome coronavirus. *The Journal of infectious diseases*. 2014;209(2):173-6.
- 31 Memish ZA, Zumla AI, Al-Hakeem RF, Al-Rabeeah AA, Stephens GM. Family cluster of Middle East respiratory syndrome coronavirus infections. *The New England journal of medicine*. 2013;368:2487-94.
- 32 Zumla A, Hui DS, Perlman S. Middle East respiratory syndrome. *Lancet*. 2015 Jun 3. [Epub ahead of print] Review.
- 33 Smits SL, van den Brand JM, de Lang A, Leijten LM, van Ijcken WF, van Amerongen G, Osterhaus AD, Andeweg AC, Haagmans BL. Distinct severe acute respiratory syndrome coronavirus-induced acute lung injury pathways in two different nonhuman primate species. *J Virol*. 2011;85:4234-45.
- 34 Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, Ghabashi A, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Annals of internal medicine*. 2014;160(6):389-97.
- 35 Memish ZA, Cotten M, Watson SJ, Kellam P, Zumla A, Alhakeem RF, Assiri A, Rabeeah AA, Al-Tawfiq JA. Community case clusters of Middle East respiratory syndrome coronavirus in Hafr Al-Batin, Kingdom of Saudi Arabia: a descriptive genomic study. *Int J Infect Dis* 2014;23:63-8.
- 36 Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer journal* 2014; 20:119-22.
- 37 Zumla A, Memish ZA, Maeurer M, Bates M, Mwaba P, Al-Tawfiq JA, Denning DW, Hayden FG, Hui DS. Emerging novel and antimicrobial-resistant respiratory tract infections: new drug development and therapeutic options. *Lancet Infect Dis* 2014;14:1136-49.
- 38 Kindrachuk J, Ork B, Hart BJ, Mazur S, Holbrook MR, Frieman MB, et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. *Antimicrob Agent Chemother* 2015;59:1088-99.
- 39 Raj VS, Smits SL, Provacia LB, van den Brand JM, Wiersma L, Ouwendijk WJ, et al. Adenosine deaminase acts as a natural antagonist for dipeptidyl peptidase 4-mediated entry of the Middle East respiratory syndrome coronavirus. *J Virology* 2014;88:1834-8.

- 40 Dyll J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, Johnson RF, Olinger GG Jr, Jahrling PB, Laidlaw M, Johansen LM, Lear-Rooney CM, Glass PJ, Hensley LE, Frieman MB. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection respiratory syndrome coronavirus infection. *Antimicrob Agents Chemother* 2014;58:4885-93.
- 41 Zumla A, Chakaya J, Hoelscher M, Ntoumi F, Rustomjee R, Vilaplana C, Yeboah-Manu D, Rasolof V, Munderi P, Singh N, Aklillu E, Padayatchi N, Macete E, Kapata N, Mulenga M, Kibiki G, Mfinanga S, Nyirenda T, Maboko L, Garcia-Basteiro A, Rakotosamimanana N, Bates M, Mwaba P, Reither K, Gagneux S, Edwards S, Mfinanga E, Abdulla S, Cardona PJ, Russell JB, Gant V, Noursadeghi M, Elkington P, Bonnet M, Menendez C, Dieye TN, Diarra B, Maiga A, Aseffa A, Parida S, Wejse C, Petersen E, Kaleebu P, Oliver M, Craig G, Corrah T, Tientcheu L, Antonio M, Rao M, McHugh TD, Sheikh A, Ippolito G, Ramjee G, Kaufmann SH, Churchyard G, Steyn A, Grobusch M, Sanne I, Martinson N, Madansein R, Wilkinson RJ, Mayosi B, Schito M, Wallis RS, Maeurer M. [Towards host-directed therapies for tuberculosis](#). *Nat Rev Drug Discov*. 2015 Aug;14(8):511-2. doi: 10.1038/nrd4696. Epub 2015 Jul 17.
- 42 Zumla A, Maeurer M; Host-Directed Therapies Network (HDT-NET) Consortium; Host-Directed Therapies Network HDT-NET Consortium. Host-Directed Therapies for tackling Multi-Drug Resistant TB - learning from the Pasteur-Bechamp debates. *Clin Infect Dis*. 2015 Jul 28. pii: civ631. [Epub ahead of print]
- 43 Dyll J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. *Antimicrob Agent Chemother* 2014;58:4885-93.
- 44 Fedson DS: Treating influenza with statins and other immunomodulatory agents. *Antiviral Res* 2013;99:417-35.
- 45 Singla S, Jacobson JR. Statins as a novel therapeutic strategy in acute lung injury. *Pulm Circ* 2012;2:397-406.
- 46 Dinarello C: Anti-inflammatory agents: present and future. *Cell* 2010;140:935-50.
- 47 Henter JI, Palmkvist-Kaijser K, Holzgraefe B, Bryceson YT, Palmer K. Cytotoxic therapy for severe swine flu A/H1N1. *Lancet* 2010;376: 2116
- 48 Zhao J, Cao Y, Lei Z, Yang Z, Zhang B, Huang B. Selective depletion of CD4+CD25+Foxp3+ regulatory T cells by low-dose cyclophosphamide is explained by reduced intracellular ATP levels. *Cancer Res* 2010;70:4850-8.
- 49 Zmijewski JW, Lorne E, Zhao X, Tsuruta Y, Sha Y, Liu G, Siegal GP, Abraham E. Mitochondrial respiratory complex I regulates neutrophil activation and severity of lung injury. *Am J Respir Crit Care Med*. 2008;178:168-79.
- 50 Rizzo AN, Aman J, van Nieuw Amerongen GP, Dudek SM. Targeting Abl kinases to regulate vascular leak during sepsis and acute respiratory distress syndrome. *Arterioscler Thromb Vasc Biol*. 2015;35:1071-9

- 
- 51 Goktolga U, Cavkaytar S, Altinbas SK, Tapisiz OL, Tapisiz A, Erdem O. Effect of the non-specific matrix metalloproteinase inhibitor Doxycycline on endometriotic implants in an experimental rat model. *Exp Ther Med*. 2015;9:1813-8
- 52 de Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, van Nieuwkoop S, Bestebroer TM, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agent Chemother* 2014;58 :4875-84.
- 53 Wilson JG, Liu KD, Zhuo H, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. *The Lancet Resp Med* 2015;3:24-32.
- 54 Siemieniuk RA, Meade MO, Alonso-Coello P, Briel M, Evaniew N, Prasad M, Alexander PE, Fei Y, Vandvik PO, Loeb M, Guyatt GH. Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. *Ann Intern Med*. 2015 Aug 11. doi: 10.7326/M15-0715.
- 55 Hinrichs CS, Palmer DC, Rosenberg SA, Restifo NP. Glucocorticoids do not inhibit antitumor activity of activated CD8+ T cells. *J Immunother* 2005;28:517-24.
- 56 Li LB, Goleva E, Hall CF, Ou LS, Leung DY. Superantigen-induced corticosteroid resistance of human T cells occurs through activation of the mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (MEK-ERK) pathway. *J Allergy Clin Immunol* 2004;114:1059-69.
- 57 Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J* 2014;20:119-22