Journal of Infection and Public Health (2016) 9, 231—235

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# Rapid generation of a human monoclonal antibody to combat Middle East respiratory syndrome

**Davide Corti**[a,*], **Nadia Passini**[a], **Antonio Lanzavecchia**[b,c], **Maria Zambon**[d]

[a] *Humabs BioMed SA, 6500 Bellinzona, Switzerland*
[b] *Immune Regulation Unit, Institute for Research in Biomedicine, Università della Svizzera Italiana, 6500 Bellinzona, Switzerland*
[c] *Institute of Microbiology, Eidgenössische Technische Hochschule Zurich, 8093 Zurich, Switzerland*
[d] *Microbiology Services Colindale, Public Health England, London NW9 5HT, United Kingdom*

Received 21 March 2016; accepted 3 April 2016

**Summary** The last century has witnessed the emergence of several previously unknown viruses as life-threatening human pathogens. Several examples include HIV, Ebola, Lujo, and, most recently, the Middle East respiratory syndrome (MERS) and Ebola. In this study, we describe a method for the swift generation of a human-derived monoclonal antibody, known as LCA60, as a treatment for MERS infections. LCA60 antibody was generated using the Cellclone Technology from the immortalized B cells of a human donor recovering from MERS. Only four months were required from the initial screening of B cells to the development of a stable CHO cell line suitable for the production of clinical grade antibody, thereby delineating a rapid pathway for the development of antiviral therapies against emerging viruses. Currently, the LCA60 antibody is being considered for clinical development, which includes prophylaxis in individuals at risk and a treatment for severe MERS-CoV infections.
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* Corresponding author.
*E-mail address:* davide.corti@humabs.ch (D. Corti).

http://dx.doi.org/10.1016/j.jiph.2016.04.003
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MERS is a highly lethal pulmonary infection [1] caused by a previously unidentified coronavirus (CoV), which is thought to infect Dromedary camels [2]. MERS first surfaced in April 2012, when the virus was rapidly identified by two independent groups. MERS also belongs to a novel subgroup of the C betacoronavirus [3,4] (Fig. 1). MERS-CoV spread to 26 countries, causing episodes of infection over the last three years. As of April 14, 2016, a total of 1741 cases and 675 deaths were reported to WHO, of which were mostly from Saudi Arabia. Most cases of human infection are not transmitted by direct contacts with camels but can occur through direct contact with MERS patients in hospitals [5]. Indeed, healthcare exposure seems to play a key role in the spread of MERS-CoV outbreaks.

Treating viruses is still a challenge in modern medicine. The most effective measure to combat viral diseases is preventive vaccines. However, as observed with the latest Ebola outbreak, vaccines cannot be developed and applied sufficiently rapidly to contain acute outbreaks. Given the danger of newly emerging viruses, novel strategies need to be developed to generate rapidly effective treatments. Interestingly, antibody-based treatments are one of the most promising approaches for the treatment and prevention of viral diseases. Emil V. Behring and Kitasato Shibasaburō pioneered the use of a passive antibody therapy in the early 1890s, when they showed that hyperimmune sera of animal origin could protect against diphtheria and tetanus. Serum therapy for other infections followed and was substituted only when antibiotics were discovered in the 1940s. Unfortunately, the use of polyclonal animal sera is associated with several side effects, including hypersensitivity reactions and serum sickness, that results from the administration of large amounts of animal proteins. These problems led to the replacement of animal sera with human hyperimmune immunoglobulin preparations, such as those used to prevent or treat or prevent cytomegalovirus, varicella zoster virus, hepatitis B virus and respiratory syncytial virus (RSV) infections in high risk populations. Importantly, Respigam, the hyperimmune immunoglobulin product against RSV, was replaced in 1998 by Synagis, the first monoclonal antiviral antibody on the market. Clinical studies showed that in patients with severe pneumonia caused by viral infections, the convalescent sera conferred a therapeutic benefit when administered to patients with severe infections during the Spanish influenza, pneumonia from 1918 to 1919, SARS-CoV in 2003, H5N1 influenza A in 2006, H1N1 influenza A virus in 2009 and, most recently, during the Ebola outbreak [6]. There have been attempts to collect therapeutic antibodies from the serum of recovering MERS patients as well as people living with these patients or health worker contacts. However, it was recently discovered that antibody titers in convalescent plasma are too low to produce a therapeutic effect (communication from Dr. Yaseen Arabi during the MERS-CoV Research Initiative Workshop held on 9—10 September 2015 in Riyadh).

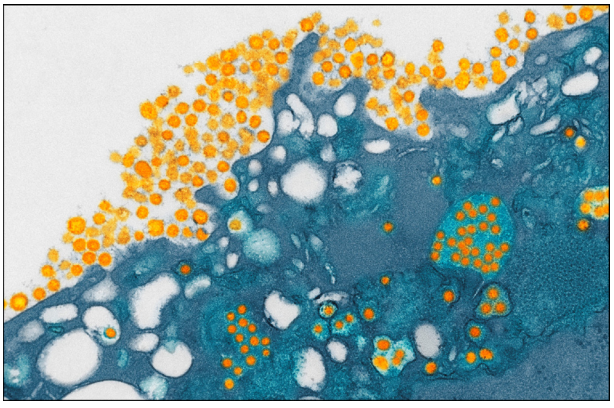

**Figure 1** Colored transmission electron micrograph of MERS coronavirus particles (orange) budding from a host cell (blue).
Credit: Public Health England/Science Photo Library.

Thus, monoclonal antibodies are an ideal alternative to hyperimmune sera or hyperimmune immunoglobulin preparations. They can be produced by immortalizing memory B cells with Epstein—Barr virus (EBV) or by fusing a B cell with an appropriate partner cell to produce hybridomas. These methods have a very low efficiency, so alternative strategies have been developed. Such alternatives include the humanization of murine monoclonal antibodies through protein engineering, the selection of human antibodies from phage display libraries as well as the immunization of transgenic mice carrying human immunoglobulin loci combined with the production of monoclonal antibodies using the hybridoma technology. Although these methods have led to the development of several therapeutic monoclonal antibodies against cytokines or surface antigens, their impact on infectious disease therapy has been less successful. There are several advantages to using human memory B cells for the production of monoclonal antibodies: (i) antibodies are fully human, (ii) memory B cells are readily accessible in blood and persist for a lifetime, (iii) there is low or no risk of cross-reactivity against self-antigens, (iv) the human immune response is directed against the virulent pathogen, (v) functional assays can be used to isolate antibodies based on their function (''agnostic approach'') with no need to use molecular targets

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