Title	No evidence for a superior platform to develop therapeutic antibodies rapidly in response to MERS-CoV and other emerging viruses
Author(s)	Dimiters S, D; Jiang, SB; Ying, TL; Tseng, KCT; Zhang, LQ; Yuen, KY
Citation	Proceedings of the National Academy of Sciences, 2015, v. 112 n. 37, p. E5115
Issued Date	2015
URL	http://hdl.handle.net/10722/220053
Rights	Proceedings of the National Academy of Sciences. Copyright © National Academy of Sciences.; This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

No evidence for a superior platform to develop therapeutic antibodies rapidly in response to MERS-CoV and other emerging viruses

Pascal et al. (1) generated mAbs using a platform called VelocImmune and evaluated their potency against the Middle East respiratory syndrome coronavirus (MERS-CoV) in vitro side by side with mAbs previously reported and in a mouse model developed by using VelociGene technology. The authors concluded that "Traditional approaches for development of antibodies are poorly suited to combating the emergence of novel pathogens. . .and that this study forms the basis for a rapid response to address the public threat resulting from emerging coronaviruses or other pathogens that pose a serious threat to human health in the future."

To support the superiority of their approach, as implied by this statement, the authors cited human mAbs previously published by three groups (2–4) and compared some of them with their own REGN3051 and REGN3048, which they found to be "more effective neutralizers than previously isolated MERS-CoV monoclonal antibodies." They also report that their antibodies "are >1 log better inhibitors compared with other published antibodies developed with conventional approaches." However, they did not evaluate the exceptionally potent (picomolar IC_{50}) mAbs from one group (2) and used only published sequences, but not mAbs, provided by the investigators from the other groups (3, 4). Thus, effects that could affect potency, including those resulting from posttranslational modifications, are excluded. They also claim that the VelocImmune platform can rapidly ("within several weeks") identify potent mAbs. However, using phage display for panning of a very large human antibody library, Ying et al. (2) identified the exceptionally potent mAb m336 in a week.

According to the authors, their mouse model of MERS-CoV infection was established by replacing the mouse gene encoding a receptor targeted by the virus (DPP4) with its human counterpart, such that "this humanized DPP4 in vivo model of MERS-CoV infection recapitulates pathological sequelae that are seen in MERS-CoV infection of humans." To our knowledge, currently, there is no animal model that can recapitulate pathology of human MERS-CoV infections in humans; therefore, it follows from this statement that their model is superior to others, which is not based on evidence. Because a full understanding of MERS pathogenesis and pathology in humans is uncertain, claiming that their model recapitulates pathological sequelae in humans, especially in the absence of morbidity and mortality, seems premature and unjustifiable. Moreover, a marmoset model (5) may be the most relevant model of MERS-CoV infection and disease. It is not cited in the text, although the reference for it is given in the bibliography.

Finally, in the title of the article, the authors claim that their antibodies are fully human. However, only the germ-line antibodies inserted in the mouse genome are fully human. Because the maturation of those antibodies is in mice and the tolerance checkpoints are by mouse proteins in a mouse environment, the somatic mutations could lead to cross-reactivity of their antibodies with human tissues and immunogenicity, and therefore to undesirable adverse events and safety concerns.

Taken together, the data do not provide evidence that their platform of developing mAbs, as well as models of infection and disease, is superior.

Dimiter S. Dimitrov[a,1], Shibo Jiang[b,1], Tianlei Ying[b], Chien-Te K. Tseng[c], Linqi Zhang[d], and Kwok-yung Yuen[e]

[a]Protein Interactions Group, Laboratory of Experimental Immunology, Cancer and Inflammation Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Frederick, MD 21702-12011; [b]Key Laboratory of Medical Molecular Virology of Ministries of Education and Health, Shanghai Medical College and Institute of Medical Microbiology, Fudan University, Shanghai 20032, China; [c]Departments of Microbiology and Immunology, University of Texas Medical Branch, Galveston, TX 77555; [d]Comprehensive AIDS Research Center, Research Center for Public Health, School of Medicine, Tsinghua University, Beijing 100084, China; and [e]State Key Laboratory of Emerging Infectious Diseases, Department of Microbiology, Research Centre of Infection and Immunology, Carol Yu Centre for Infection, The University of Hong Kong, Hong Kong Special Administrative Region of the People's Republic of China

1 Pascal KE, et al. (2015) Pre- and postexposure efficacy of fully human antibodies against Spike protein in a novel humanized mouse model of MERS-CoV infection. *Proc Natl Acad Sci USA* 112(28): 8738–8743.
2 Ying T, et al. (2014) Exceptionally potent neutralization of Middle East respiratory syndrome coronavirus by human monoclonal antibodies. *J Virol* 88:7796–7805.
3 Jiang L, et al. (2014) Potent neutralization of MERS-CoV by human neutralizing monoclonal antibodies to the viral spike glycoprotein. *Sci Transl Med* 6(234):234ra59.
4 Tang XC, et al. (2014) Identification of human neutralizing antibodies against MERS-CoV and their role in virus adaptive evolution. *Proc Natl Acad Sci USA* 111(19):E2018–E2026.
5 Falzarano D, et al. (2014) Infection with MERS-CoV causes lethal pneumonia in the common marmoset. *PLoS Pathog* 10(8):e1004250.

Author contributions: D.S.D. and S.J. designed research; and D.S.D., S.J., T.Y., C.-T.K.T., L.Z., and K.-y.Y. wrote the paper.

The authors declare no conflict of interest.

[1]To whom correspondence may be addressed. Email: dimiter.dimitrov@nih.gov or shibojiang@fudan.edu.cn.