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 IC₅₀) 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.

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The authors declare no conflict of interest.

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