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INFECTIOUS DISEASES

Cattle engineered to produce human antibodies against coronavirus

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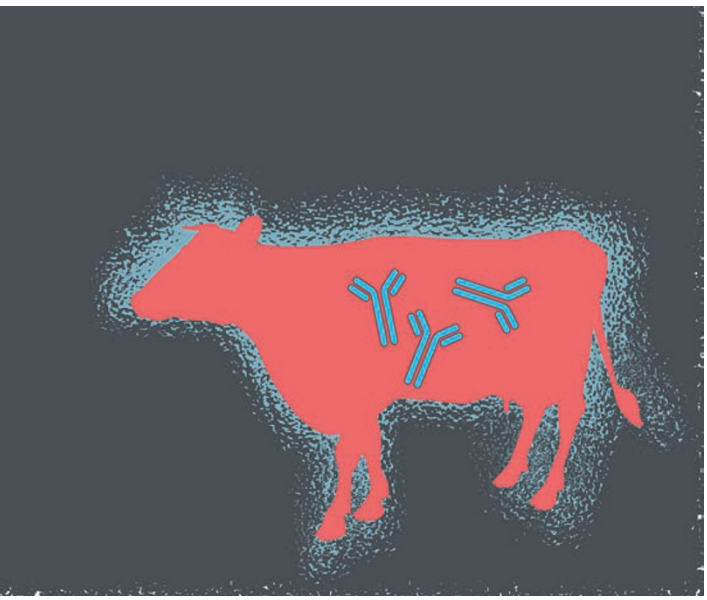
Passive immunotherapy — for example, using specific antibodies — may represent a good possible treatment strategy against Middle East respiratory syndrome coronavirus (MERS-CoV). However, producing large-enough quantities of such antibodies is economically and logistically challenging. In a new study, Luke *et al.* use transchromosomic (Tc) bovines to produce human anti-MERS-CoV antibodies that show efficacy *in vitro* and in a mouse model of MERS-CoV infection.

The authors used cattle that lack bovine immunoglobulin (Ig) genes and instead carry a human artificial chromosome bearing the genes encoding human Ig heavy chain and κ-light chain proteins, with a bias for producing IgG1 subclass antibodies. Following vaccination, these animals can each produce 150–600 g of human polyclonal IgG antibodies per month.



S.Harris/NPG

Next, the authors created two different MERS-CoV vaccines: a whole-killed Jordan strain virion vaccine (WKVV) and an Al-Hasa strain spike protein nanoparticle vaccine (SPNV). Tc bovines were vaccinated every 21–28 days on five occasions (V1–V5) with WKVV or SPNV. Two human polyclonal IgG products — named SAB-300 or SAB-301, respectively — were purified from the hyperimmune plasma collected from the animals after V2, V3, V4 and V5. *In vitro*, pre-treatment of Jordan strain MERS-CoV with SAB-300 or SAB-301 before culturing with Vero E6 kidney epithelial cells markedly reduced virus-induced cytopathy, implying that these antibodies neutralize MERS-CoV.

Antibody-dependent enhancement of infection — whereby antibodies facilitate the entry of viruses into cells that do not carry the usual entry receptor for the virus — has been suggested to occur following the use of some anti-CoV vaccines. Here, the authors treated Jordan strain MERS-CoV with SAB-300 or SAB-301 before incubating the virus with Raji cells — human B cells that lack dipeptidyl peptidase 4 (DPP4; the MERS-CoV entry receptor) and that therefore are not permissive to MERS-CoV. Levels of MERS-CoV-specific RNA transcripts in the Raji cells 48 hours later were not increased by pre-treatment with either SAB-300 or SAB-301, implying that these treatments do not facilitate virus entry into these cells.

Although mice do not typically express DPP4 and so are resistant to MERS-CoV infection, transduction of mice with a human DPP4-expressing adenovirus (Ad-hDPP4 mice) confers susceptibility. The authors intraperitoneally injected Ad-hDPP4 mice with SAB-301 or a control human IgG and, 12 hours later, intranasally infected them with MERS-CoV. By day 5 post-infection, viral titers in the lung of SAB-301-treated mice, but not of controls, were below the limit of detection. SAB-301 treatment of Ad-hDPP4 mice 24 hours after MERS-CoV exposure also reduced lung viral titers 5 days later to below the limit of detection. Thus, a single treatment of SAB-301 can be effective either prophylactically or after exposure to MERS-CoV.

This study demonstrates how large quantities of human MERS-CoV-neutralizing antibodies can be rapidly produced in Tc bovines, thus providing a possible strategy for the development of passive immunotherapies against coronaviruses or other new and emerging infectious diseases.

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ORIGINAL ARTICLE Luke, T. *et al.* Human polyclonal immunoglobulin G from transchromosomic bovines inhibits MERS-CoV *in vivo*. *Sci. Transl Med.* **8**, 326ra21 (2016)
FURTHER READING Zumla, A. *et al.* Coronaviruses — drug discovery and therapeutic options. *Nat. Rev. Drug Discov.* http://dx.doi.org/10.1038/nrd.2015.37 (2016)

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