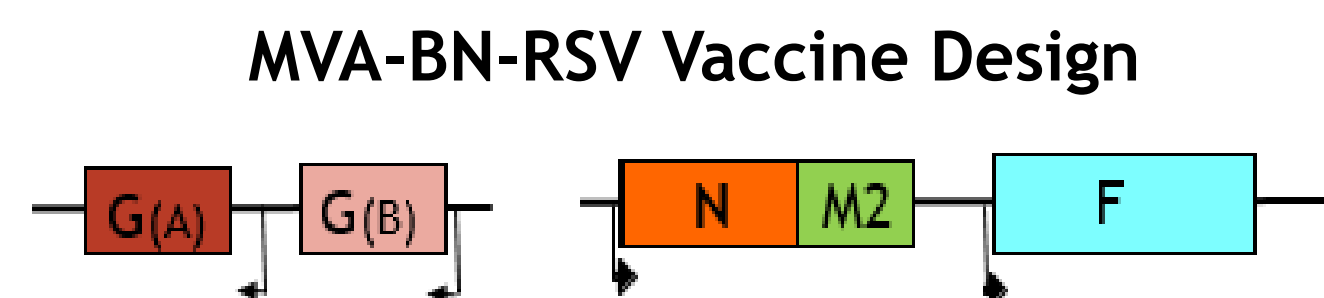


A NOVEL MULTI-INSERT MVA-BN BASED RSV VACCINE PROVIDES IMPROVED PROTECTION IN MICE AND COTTON RATS

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BACKGROUND



RSV can cause severe respiratory tract infections not only in infants, but also in older adults. No licensed vaccine against RSV is currently available. Recent attempts relying solely on the RSV fusion- (F) protein failed. We designed MVA based RSV vaccines that express either RSV F only, or additional RSV antigens and evaluated the role of these RSV antigens in vaccine efficacy.

The lead candidate MVA-BN-RSV is depicted above.

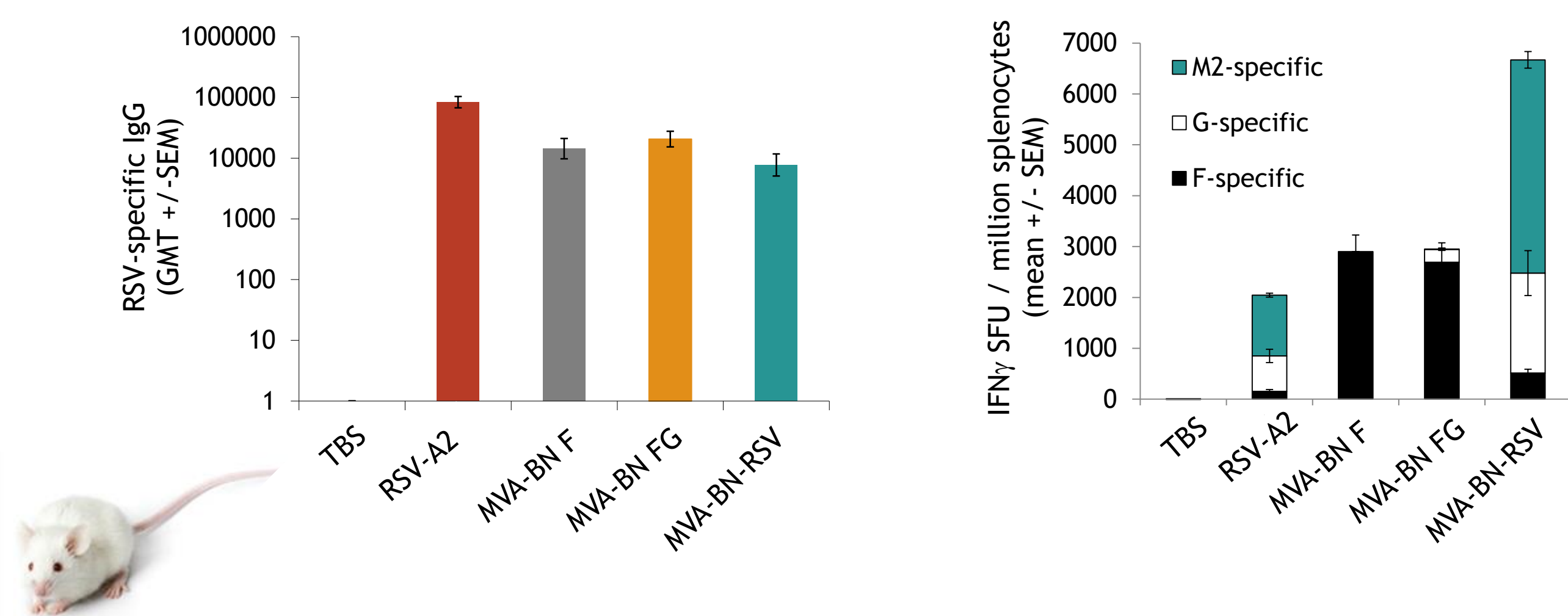
METHODS

BALB/c mice or cotton rats were vaccinated on Days 0 & 21 with 1×10^8 TCID₅₀ of MVA-BN based constructs expressing either RSV F only, RSV F and G (A subtype), or RSV F, G (A & B subtype), N and M2, i.e. MVA-BN-RSV. RSV-A2 was used as a positive control, Tris buffered saline (TBS, non-vaccinated) as negative control.

Two weeks later, animals were intranasally infected with RSV A2 and viral load was determined by plaque assay or RT-qPCR 4 days post infection. Enhanced respiratory disease induced by FI-RSV was evaluated in terms of IL-5 and eosinophils. The expression of pre-F versus post-F by HeLa cells infected with recombinant MVA-BN was determined by flow cytometry.

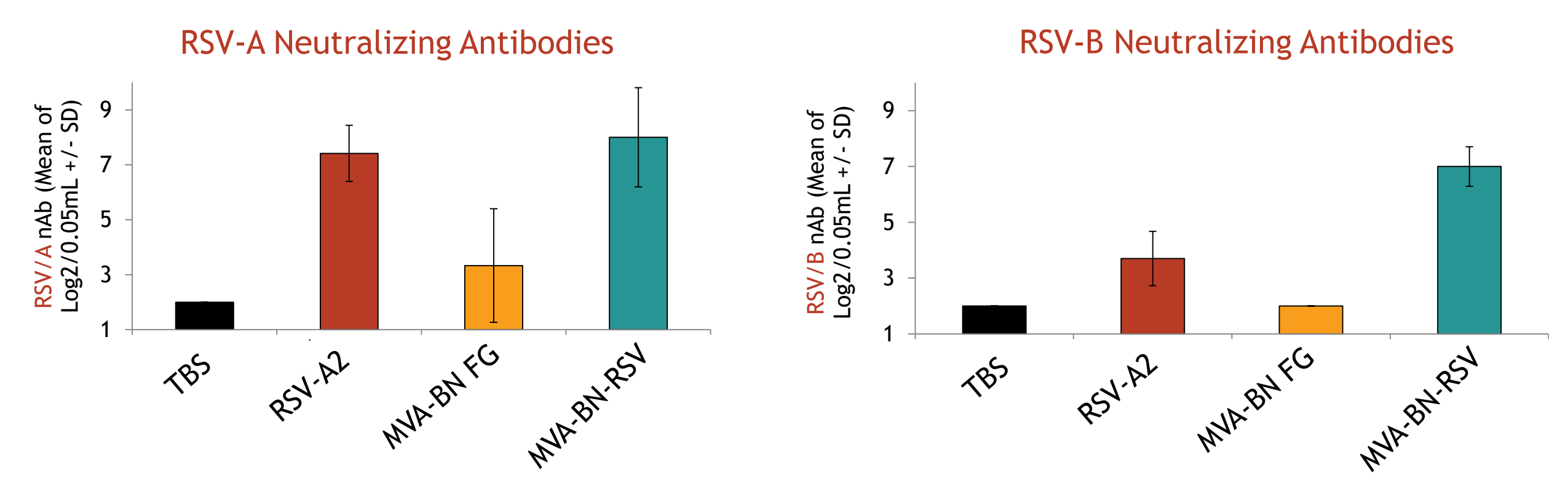
MVA-BN based RSV vaccines are immunogenic in mice

- All constructs induced comparable levels of antibodies, including neutralizing antibodies (latter not shown)
- The addition of more RSV antigens increased the magnitude of T cell responses, especially against internal proteins, while mimicking the composition of RSV-A2



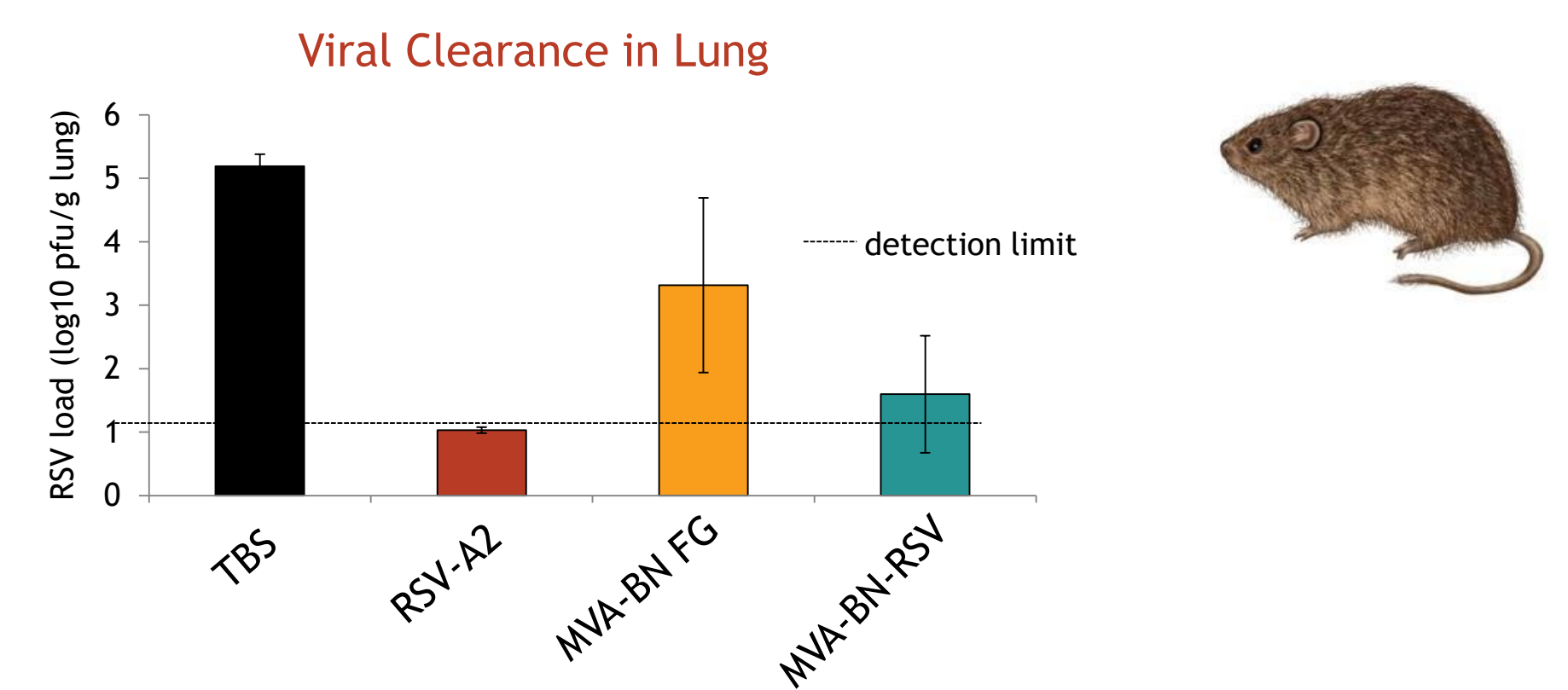
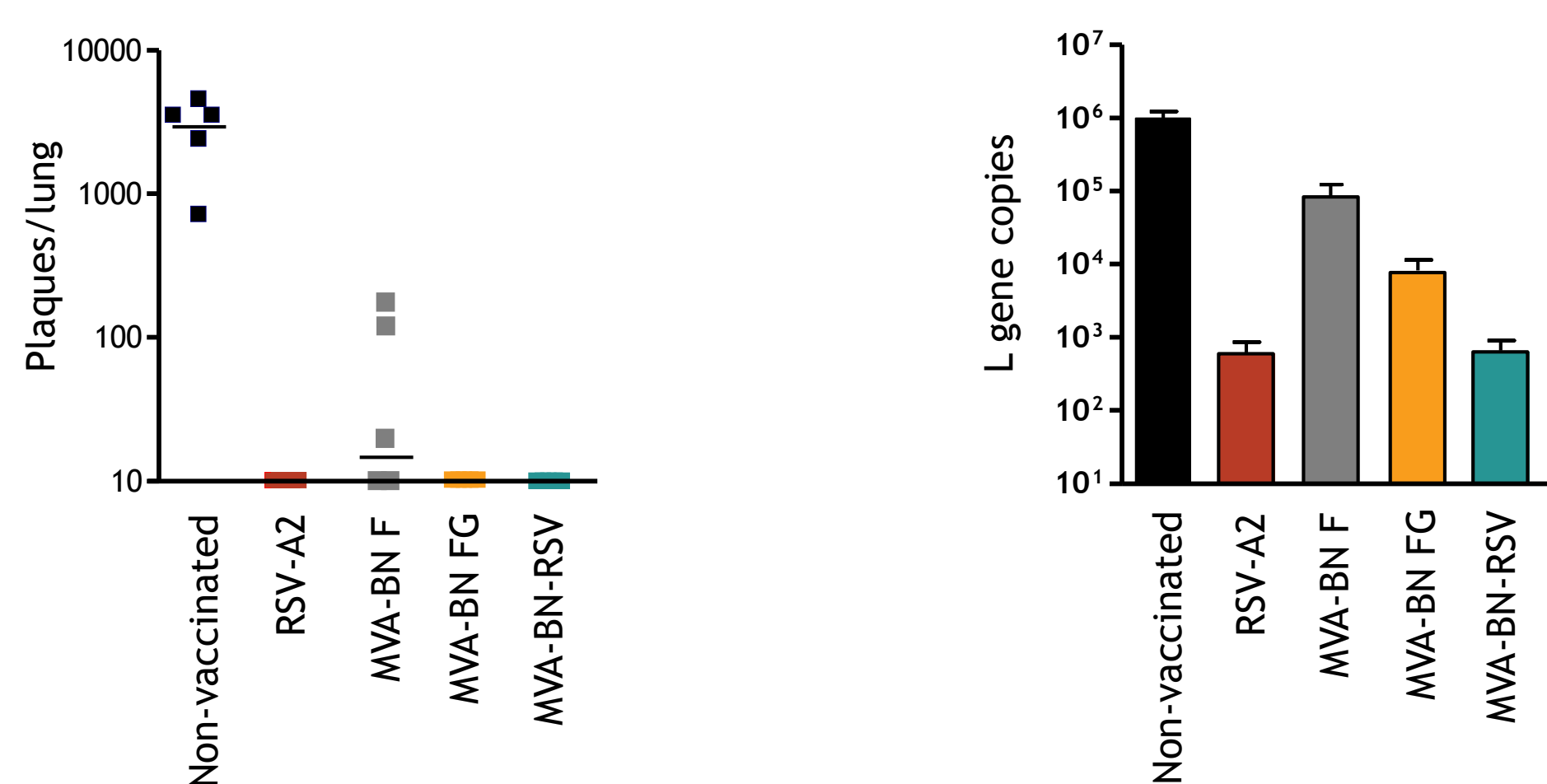
Additional RSV antigens increase vaccine efficacy in cotton rats

- Additional RSV antigens in MVA-BN-RSV led to higher levels of RSV-A and RSV-B neutralizing antibodies
- RSV-A neutralizing antibodies were comparable to those induced by RSV-A2, while RSV-B neutralizing antibodies were increased, indicating a benefit of the B subtype G protein encoded by MVA-BN-RSV
- Protective efficacy was increased by additional RSV antigens and comparable to that afforded by the RSV-A2 control



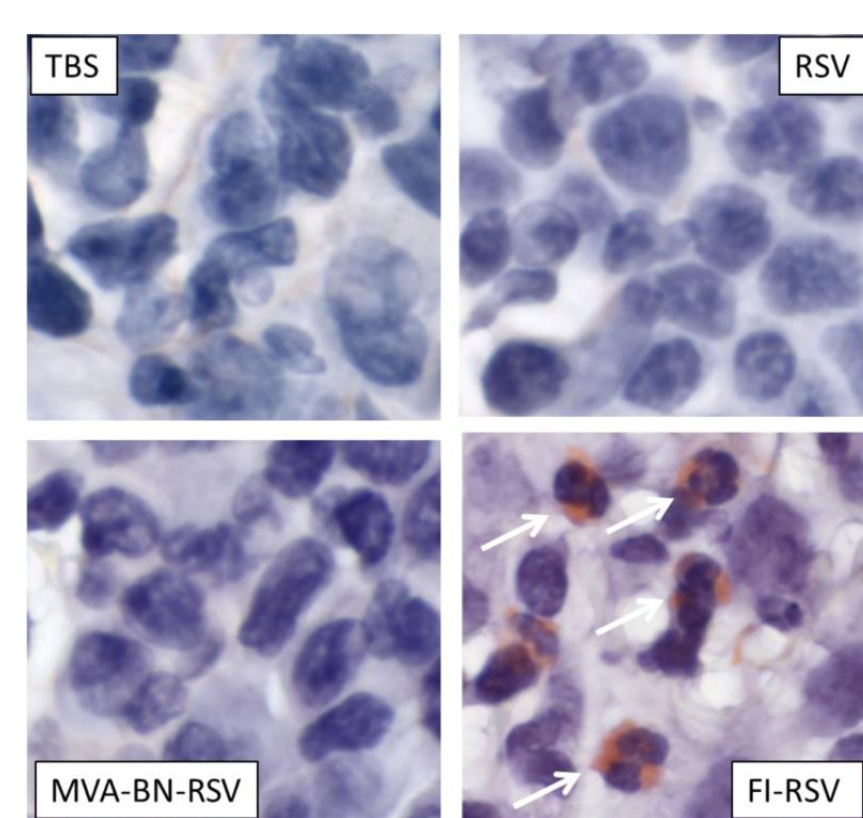
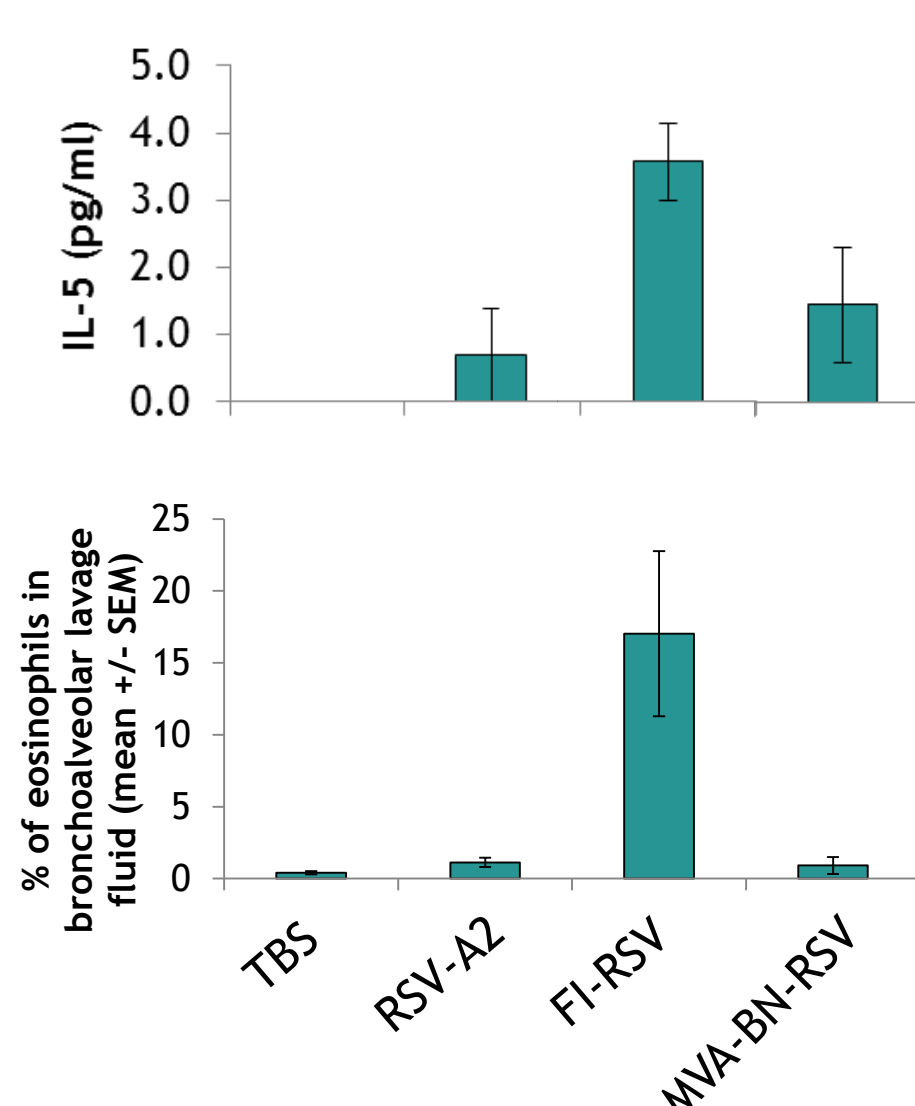
Additional RSV antigens increase vaccine efficacy in mice

- Infectious RSV was still detectable in 3 of 5 mice vaccinated with MVA-BN-F, whereas the addition of G led to total clearance in lung
- Improved efficacy with the expression of additional antigens in the sensitive RT-qPCR
- Protection afforded by MVA-BN-RSV was comparable to that induced by RSV exposure

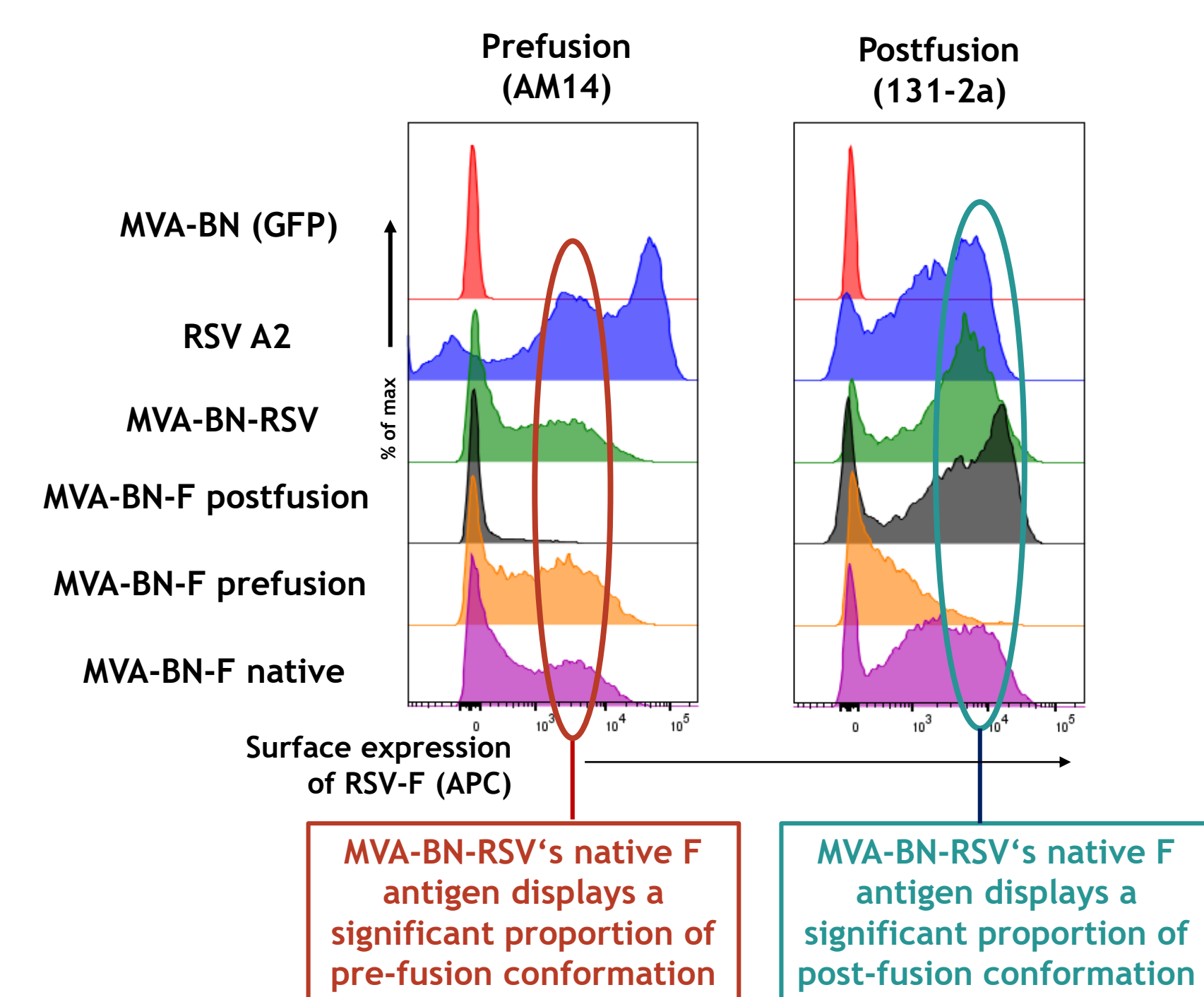


MVA-BN-RSV does not induce enhanced respiratory disease

- In contrast to formalin inactivated (FI) RSV, MVA-BN-RSV does not induce elevated serum IL-5 or eosinophil infiltration in the lung evaluated by cytopsin and histology 4 days after RSV infection.



MVA-BN-RSV's native F antigen displays both pre- and post-F conformations



CONCLUSIONS

- Expression of multiple RSV antigens increased the immunogenicity and efficacy of an MVA based RSV vaccine compared to the expression of F alone
- Limited efficacy of the F-only construct is not due to a lack of the pre-F conformation as shown by the presence of both pre- and post-F in MVA-BN-F infected cells
- MVA-BN-RSV encoding F, G and M2/N was shown to be as immunogenic and efficacious as RSV in two different animal challenge models, without inducing enhanced disease
- Phase 1 and 2 clinical trials recently confirmed the favorable safety profile and immunogenicity of MVA-BN-RSV

Acknowledgements
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