

A parainfluenza virus vector expressing the respiratory syncytial virus (RSV) prefusion F protein is more effective than RSV for boosting a primary immunization with RSV

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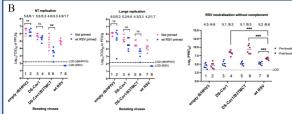
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Background.

Live pediatric RSV vaccines for intransal immunization are being developed based on attenuated RSV, or based on recombinant chimeric bovine/human parainfluenza virus type 3 (rB/HPIV3) expressing the RSV F protein. This rB/HPIV3-expressed RSV F protein has been engineered for increased stability in the highly immunogenic prefusion (pref DS-Cav) conformation, with or without replacement of its transmembrane and cytoplasmic tail domains (TMCT) with their counterparts of the bovine parainfluenza virus type 3 (BPIV3) F protein to direct incorporation into the vector virion for increased immunogenicity. In previous studies to evaluate prime-boost regimens of liveattenuated RSV, replication and immunogenicity of the second dose were strongly inhibited by the immune response to the primary dose. Infection of the rB/HPIV3/RSV-preF vectors does not rely on RSV F, and should not be substantially inhibited by preexisting immunity to RSV, suggesting that rB/HPIV3/RSV-preF vectors may be suitable to boost immunity following primary immunization with live-attenuated RSV vaccine.

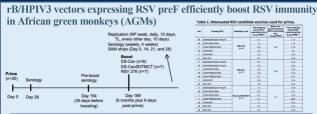
RSV and B/HPIV3/RSV-preF vector boost regimens in hamsters





- A. Hamsters were primed intranasally with wt RSV (groups A D) or remained un-primed (groups E H). 6 weeks later, the primed and un-primed groups were boosted intranasally with the indicated viruses:
 - · B/HPIV3 empty vector control,
 - DS-Cav1 (rB/HPIV3/DS-Cav1, expressing RSV F with greatly increased stability in the pre-F
 conformation due to the DS-Cav1 mutations).
 - DS-Cav1/B3TMCT (rB/HPIV3/DS-Cav1/B3TMCT, expressing RSV F with DS-Cav1 mutations plus replacement of its transmembrane/cytoplasmic tail (TMCT) domains with those of the BPIV3 F protein to achieve efficient incorporation into the vector virion), or
 - wt RSV

B. Both rB/HPIV3/RSV F vectors, when used as a boost in RSV primed hamsters, replicated more efficiently and induced significantly higher RSV-neutralizing serum antibody titers than a wt RSV boost.



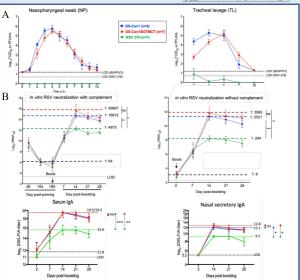


Figure 2. Twenty AGMs were primed intranasally with one of five different RSV vaccine candidates (Table 1). As shown in the time line, about 6 months later, animals received an intranasal boost of RSV 276 (a live RSV vaccine candidate with M2-2 deletion) or B/HPIV3-vectored RSV Pref (rB/HPIV3/DS-Cav1 or rB/HPIV3/DS-Cav1 or r

(A) B/HPIV3 vectors expressing RSV preF replicated in the respiratory tract of AGMs previously immunized with live-attenuated RSV, and (B) induced significantly greater increases in RSV-neutralizing antibody iters than live-attenuated RSV 276. Notably, boosting with B/HPIV3 vectors induced high-quality serum RSV-neutralizing antibodies, detectable in neutralization assays without added complement, as well as increases in mucosal IgA titers.

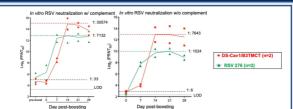


Figure 3. Boost immunization of AGMs at 15 months post-prime. AGMs received a single intranasal immunization with live-attenuated RSV (RSV 276), and after 15 months were boosted with the indicated virus (RSV 276, green, or B/HPIV3/DS-Cav1/B3TMCT, red) via the same route. rB/HPIV3/DS-Cav1/B3TMCT boost induced greater increases in serum RSV-neutralizing antibody titers than boosting with RSV 276.

Mothode

Primary immunization of hamsters and AGMs was performed intranasally with RSV (wt RSV in the hamster model; live-attenuated vaccine candidates in AGMs), followed by secondary immunization with RSV or with the indicated rB/HPIV3-RSV-preF vector. Replication of the boost virus in the upper and lower respiratory tract was evaluated. Serum and nasal secretions were collected to measure the serum RSV neutralizing antibody titers and levels of RSV F-specific serum and nasal secretory IgA.

Results.

In hamsters that received a primary intranasal dose of RSV, a secondary dose –6 weeks later with RSV was completely restricted for producing infectious virus, but induced a significant increase in serum RSV plaque-reduction neutralizing antibody titer (RSV-PRNT). Boosting instead with an rB/HPIV3/RSV-preF vector resulted in efficient replication and induced significantly higher RSV-PRNTs than RSV. In AGMs that received a primary intranasal immunization with a live-attenuated RSV vaccine, a booster infection with RSV vaccine –6 or ~15 months later was highly restricted, whereas booster infections with the vectors was less restricted. Compared to RSV, boosts with the vectors induced 7- to 15-fold higher titers of RSV-specific serum antibodies with high neutralizing activity, as well as significantly higher titers of RSV-specific serum and nasal secretory IgA.

Conclusions.

These data suggest that heterologous RSV prime - B/HPIV3/RSV-F vector boost strategies allow for efficient replication of the B/HPIV3 vector in RSV immune animals, resulting in greater increases in mucosal and systemic RSV immunity. These results support clinical development of this approach.

Citation

Bo Liang, Yumiko Matsuoka Cyril Le Nouën, Xueqiao Liu, Richard Herbert, Joanna Swerczek, Celia Santos, Monica Paneru, Peter L. Collins, Ursula J. Buchholz, Shirin Munir. A parainfluenza virus vector expressing the respiratory syncytial virus (RSV) prefusion F protein is more effective than RSV for boosting a primary immunization with RSV. J Virol, 2020 Oct 28: JVI.01512-20. PMID: 331 15876.

Competing Interests B.L., P.L.C., U.J.B., and S.M. are conventors on a patent for the development of PIV3-vectored bivalent vaccines against R8V and HPIV3. P.L.C. and U.J.B. are also coinventors on patent applications for the development of various attenuated versions of R8V for use spediarity vaccine.