The codeptimized, intranasally delivered, live attenuated RSV vaccine MV-012-968 is well tolerated and increases RSV pre-specific IgA levels in healthy adults

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Introduction
RSV is a leading cause of infant lower respiratory tract infection and hospitalization as well as elderly pulmonary disease. There is no approved RSV vaccine. We describe here the first in human study of the live attenuated vaccine candidate MV-012-968. A derivative of the RSV A2 OF strain (Stobart, C. E. et. al. Nature 2014), MV-012-968 was designed to attenuate RSV without substantial impairment of immunogenicity, via codeptimization of NS1, NS2, and G genes. The virus was also attenuated by deletion of IR, which increased expression of the G gene. Mutation was introduced to ablate expression of secreted G protein. The wt RSV A2 F was substituted with Line1 F, which favored the meta-stable pre-fusion conformation and conferred thermostability.

Results
MV-012-968 was highly attenuated in lower/respiratory tract of cotton rats

Cotton rats (CR) were inoculated i.n. with 5x10⁵ PFU of MV-012-968 (n=4), MV-012-990 (n=4, 282-Quad, another candidate research set), wt A2L19F (n=24), and wt A2 (n=4), mock agent (Mn. Essen: Media, n=12), or no agent (n=6) on Day 1. Viral titers in nose and lungs were determined by plaque assay (n=6/group) on Day 2, 5, 7, 10. No infectious MV-012-968 was detected in nose or lung at any time point. On Day 2 and 5, CR inoculated with MV-012-968 had significantly lower viral loads in upper and lower respiratory tracts than CR inoculated with wt A2 or A2L19F (p<0.0001, two-way ANOVA, Turkey multiple comparison test).

Despite heavy attenuation, MV-012-968 elicited serum neutralizing antibodies in cotton rats comparable to levels induced by wild type RSV

CR were vaccinated (5x10⁵ PFU of text article) on Day 1, then challenged (1x10⁶ PFU of A2L19F) on Day 21. Titers of A2L19F in nose and lungs were measured by plaque assay on Day 26 (n=6/group). CR vaccinated with MV-012-968 were completely protected in lung and significantly protected in nose against challenge. Only unvaccinated animals showed detectable virus replication 5 days post challenge in nose and lung tissue (p<0.0001, one-way ANOVA, Turkey multiple comparison test).

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Efficacy in Lung (day 26)

Conclusions

MV-012-968 protected cotton rats against wt RSV challenge 26 days after vaccination

Summary

LAIV MV-012-968 has been rationally designed to attenuate RSV without compromising immunogenicity

MV-012-968 has a highly attenuated replication phenotype and provided protection against wt RSV challenge in the cotton rat model

MV-012-968 was immunogenic in cotton rats, eliciting serum Ab responses comparable to wt RSV and inducing mucosal IgA, which has been correlated with protection

MV-012-968 was well tolerated in healthy ‘sero low’ adults, with no serious or severe adverse events, and with infrequent post-vaccination adverse events that were, when present, mild and short-lived

No infectious virus was recovered from any nasal swab through Day 56 as measured by plaque assay

Serum (RSV) nAbs and pre-specific binding) and nasal mucus (pre-specific binding) Ab responses were measured through post-inoculation Day 56. As anticipated in naturally temperate adults, no change in RSV-specific serum Ab titers was observed. An increase in RSV-specific nasal IgA (2-2 fold over baseline) was detected in 6/9 recipients at the 10 PFU dosage and 3/10 recipients at the 100 PFU dosage during the 14 days following study vaccination:

Doseage of MV-012-968 (n) 10 PFU (10) 100 PFU (9)

2-fold increase in RSV pre nasal mucosal IgA (%) 2 (50.0) 6 (66.7)

Acknowledgments

We thank Christina Rostad and Christopher Stobart for generating the MV-012-968 constructs. We are grateful to Barney Graham for his advice and insights. Jason McKellan provided insights for the performance of CR IgA EUISA. We thank Charlie Kimmel and Amanda Gardiner for clinical operational support. We thank the participants in Study MV-003 who provided their valuable time and biological specimens that generated these data. This project was funded in part by a Fast Track SBIR 844441134357 and R01 AI103714 from NIAID/NAO, D.M., K.L., B.S.M., X.C., A.G., R.S., and M.L.M. are employed by Meissa Vaccines. J.B. is employed by Sigmuv BioSystems Inc., Rockville, MD

Table 1: Characteristics of pre-specific nasal IgA in healthy ‘sero low’ adults

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>10 PFU (n=10)</th>
<th>100 PFU (n=9)</th>
<th>Change (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25 (13)</td>
<td>25 (13)</td>
<td>0 (9)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>6 (60)</td>
<td>5 (55)</td>
<td>1 (15)</td>
</tr>
<tr>
<td>Race (%)</td>
<td>50 (50)</td>
<td>50 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 (5-121)</td>
<td>72 (31-121)</td>
<td>2 (49)</td>
</tr>
<tr>
<td>White Americans</td>
<td>7 (50)</td>
<td>6 (67)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>American Indian</td>
<td>3 (20)</td>
<td>2 (22)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (25)</td>
<td>5 (56)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Non Hispanic</td>
<td>0 (0)</td>
<td>4 (44)</td>
<td>4 (44)</td>
</tr>
</tbody>
</table>

Serum samples were taken on Day 42 from CR vaccinated on Day 1 with 5x10⁵ PFU of MV-012-968 (n=18). Samples were pooled (n=3 animals/pool) and serum nAb titers against reporter expression MV-120 and A2L19F determined via miunulocclusion. Percent neutralization was calculated: [100% plates at cut-point dilution/n x plates%100]. ECD and confidence intervals (CI) were determined by non-linear fit. Despite high levels of attenuation, MV-012-968 produced levels of serum nAb comparable to wt RSV