Innate-adaptive immunity duo as a regimen for conferring rapid-sustained-broad protection against pathogens

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A litany of demands for better vaccines

Problem: Current vaccines confer protection in a slow motion.
Solution: Develop a drug-vaccine duo (DVD) by activating a protective innate-adaptive immunity duo.

Problem: Current vaccines do not confer broad protection.
Solution: Develop a universal vaccine component within a DVD context.

Problem: Current injectable vaccines are associated with pain; fear; medical license; syringe needle disposal; and systemic inflammation.
Solution: Develop noninvasive vaccines by delivering vaccines to the interface between the body and environment (e.g., oral vaccine; nasal vaccine; skin-patch vaccine).
Ad5-vectored influenza vaccine

Influenza virus

- Growth varies from strain to strain
- Some strains are lethal
- Prone to reassortment/mutation events
- Low-titer production in eggs

Ad5 vector encoding influenza HA

- More consistent growth rates
- Benign vectors
- No reassortment events
- High-titer production in cultured cells
- A new RCA-free Ad5 can be generated by the AdHigh system within one month
Prophylactic influenza therapy by Ad5-vectored drug-vaccine duo

Lung histopathology 19 days post-influenza virus infection (2X)

Normal; no PR8

Pre-exposure to AdE; PR8 challenge

No Ad5 pre-exposure; PR8 challenge

Pre-exposure to AdNC.H1.1; PR8 challenge

Ad5-vectored drug-vaccine duo induces rapid-sustained protection against influenza – a vaccine more than just a vaccine

Influenza drugs

**Class I: M2 ion channel blockers – impaired by drug resistance**

- Amantadine
- Rimantadine

**Class II: Neuraminidase inhibitors – impaired or to be impaired by drug resistance**

- Oseltamivir (Tamiflu)
- Zanamivir (Relenza)
- Peramivir

To bypass drug resistance: Taking the way a licensed drug as we know how it works, then doing the exact opposite.

**Class III: Induction of an anti-influenza state – may not induce drug resistance**

- Adenovirus-vectored drug-vaccine duo (DVD)
Ad5-vectored nasal influenza vaccine protected ferrets against the A/VN/1203/04 (H5N1) avian influenza virus

Ferrets were immunized i.n. on Day 0; and challenged with A/VN/1203/04 at a dose of 10 FLD\textsubscript{50} (10\textsuperscript{2} EID\textsubscript{50}) at SRI on Day 56. HA, Ad encoding HA1+HA2; HA1, Ad encoding HA1; E10, 10\textsuperscript{10} vp; HI, GMT of serum HI titers on Day 51.
Human Phase I clinical trial of an Ad5-vectored nasal avian influenza vaccine

Study design

- Ad<sub>5</sub>VN1203/04.H5 vector encodes HA1+HA2 of the A/VN/1203/04 (H5N1) avian influenza virus
- Randomized, double-blind, placebo-controlled, single-site study
- Three cohorts at an escalating dose of 10<sup>8</sup>, 10<sup>9</sup>, and 10<sup>10</sup> vp
- Administered by nasal spray
- Two doses on Days 0 and 28
- Total of 48 healthy volunteers, aged 19 – 49
- Sixteen human subjects per dose cohort, including 4 placebo controls per cohort
- RCA free, cell culture based manufacturing in PER.C6 suspension cells in serum-free medium at SAFC
- Human clinical trial was performed by Dr. Scott Parker at UAB
# Rationale to develop an Ad5-vectored nasal influenza vaccine

<table>
<thead>
<tr>
<th></th>
<th>Licensed TIV</th>
<th>Licensed LAIV (FluMist)</th>
<th>Ad5-vectored nasal influenza vaccine</th>
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<tbody>
<tr>
<td>IFV required</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Egg required</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Mode of administration</td>
<td>Intramuscular injection</td>
<td>Nasal spray</td>
<td>Nasal spray</td>
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<tr>
<td>Replication postvaccination</td>
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<td>No</td>
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<tr>
<td>Reassortment</td>
<td>No</td>
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<tr>
<td>Antiviral co-administration</td>
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<td>No</td>
<td>Yes</td>
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<tr>
<td>Nearly-immediate protection</td>
<td>No</td>
<td>Yes (animal model)</td>
<td>Yes (animal model)</td>
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<tr>
<td>Systemic inflammation</td>
<td>Yes</td>
<td>No</td>
<td>No (conceivably)</td>
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Inflammation induced by noninvasive vaccination tends to be benign