Prospects for the prevention and treatment of respiratory virus-induced exacerbations in asthma and COPD.

Garth Rapeport
CEO Pulmocide
Asthma causation is currently believed to be the interaction of environmental triggers (the seed) and host factors (the soil).

Lemanske.
Pediatr Allergy Immunol 2002: 15: 1–6
Genetic predisposition – patients with asthma genetic predisposition may be more susceptible to severe RSV infection – alternatively those with susceptibility to RSV infection may develop asthma after RSV infection.
Virus induced bronchial inflammation – proposed mechanism
Respiratory virus infection in early childhood are generally believed to contribute to asthma causality (and are largely responsible for exacerbations).

Some differences between RSV and Rhinovirus (HRV).
Epidemiologic data provides a link between respiratory virus infection with asthma and wheezing.

- Children with a history of severe respiratory syncytial virus bronchiolitis often suffer recurrent bouts of wheeze, and almost half are diagnosed as asthmatic in the following 6 years.

- Infants who were born approximately 120 days before the peak of RSV season had the highest rate of hospitalization for wheezing illnesses.

- Infection with rhinoviruses are known to cause wheezing in infants and is a major predictor of asthma at 6 years of age (in those children).

- Current belief that that a gene (family history of asthma)-by environment (RSV bronchiolitis) interaction is necessary for the expression of disease.

- Rhinovirus most commonly associated with asthma exacerbations.
Annual cycles of emergency room presentations for asthma (AS) and chronic obstructive pulmonary disease (COPD) as multiples of the weekly mean number by week of the year, combining all events from April 2001 to March 2004 in Ontario, Canada.

Further evidence:
The Human rhinovirus challenge model in COPD patients

Symptom scores and lung function during experimental rhinovirus infection. The time course for daily symptom scores is shown for (A) total daily upper respiratory tract (URT) symptoms, (B) total daily lower respiratory symptoms, and (C) breathlessness. (D) The time course of post-bronchodilator peak expiratory flow as a percentage of baseline.
Therapeutic challenges for respiratory viral infections

1. Inflammation caused by common respiratory viruses are refractory to corticosteroids. *We do not have effective anti inflammatory agents.*

2. There are no effective antivirals for treatment of RSV and HRV.

3. Unlikely that RSV vaccine will be introduced for very young infants (0-6m) who are most liable to severe RSV infection.

4. HRV vaccine extremely unlikely.
Prevention or therapeutic intervention?
Effective management of respiratory virus infection has potential to transform treatment of asthma (and COPD). Potential approaches include vaccines, antivirals and host defence interventions.

**Antivirals**
- High level of interest in the development of RSV and HRV antivirals
- Antiviral treatment will benefit from early intervention
- Point of care diagnostic required
- Topical therapy (nasal of lung delivery) may offer safety and efficacy advantages

**Vaccines and Mabs**
- 60 RSV vaccine candidates in development
- 16 candidates are in clinical development
- Effective protection of infants may require maternal immunization to cover first 6 months
- High barriers to widespread immunization of pregnant mothers

**Host defence modulators or anti inflammatory approaches**
- Enhanced host immunity (recombinant interferon-alpha2b, IH or IN, Synairgen)
- Anti inflammatory – addresses steroid refractory inflammation
  - Respivert, RV568
Antivirals
Rhinovirus

1. Requires optimal antiviral efficacy against 160 rhinoviruses.
2. Colds are not usually life-threatening, so regulatory authorities would have a very low threshold for adverse effects (may restrict development to prevention or treatment of exacerbations in asthma and COPD).
3. No animal model. Only humans show symptoms of rhinovirus infection (may be overcome with human epithelium in ALI).

RSV

1. Antiviral discovery targets RSV A and B sub groups only
2. RSV results in life-threatening bronchiolitis so risk benefit ratio may allow some safety margins.
3. There are animal models which are semi-permissive for infection and allow in vivo testing in prophylaxis mode.
4. Human challenge model provides good system for early intervention (within 24h of volunteers becoming PCR positive). Has not been tested in RSV symptomatic subjects (later intervention).
HRV antiviral
Vapendavir (BTA798, an analog of pirodavir, Biota- Aviragen)
– HRV capsid binder

Reported a experimental rhinovirus infection study in 2009: 9-day oral treatment with 400 mg vapendavir twice a day (2 days prior to infection) significantly reduced viral load

In March 2012, Biota successfully conducted a phase II multi-center, randomized, double-blind, placebo-controlled study in mild asthmatic adults with symptomatic, naturally acquired rhinovirus infection.

Oral vapendavir (400 mg twice daily for 6 days) was associated with significantly lower symptom scores early in the illness and continuing up to 2 weeks compared with placebo. Vapendavir recipients also had higher peak expiratory flow rates on day 5, reduced overall use of asthma relief medications, and less frequent HRV RNA detection on day 3 (74% versus 91%).

Biota announced a phase IIb multicenter, randomized, double-blind, placebo-controlled dose-ranging study in laboratory-confirmed HRV-infected patients with moderate-to-severe asthma (referred to as the SPIRITUS trial) – 7 days treatment in patients who are PCR positive for HRV (480 patients) – 28 day follow up.

https://clinicaltrials.gov/ct2/show/NCT02367313
RSV hospitalizations in the USA

‘High-risk Infants’
- Pre-term, congenital heart disease, lung disease, <4 months old
- Average length of hospital stay 4 – 8 days
- High potential for ICU admission – 15 – 30% reach ICU, average LOS upto c. 10 days
- Average direct hospital costs of $15k to $28k / patient
- Increase in average cost for infant during first year of life vs infant with no history of RSV:
  - $56k (<33 weeks)
  - $30k (33 – 36 weeks)

‘Low-risk Infants’
- Healthy term infants (>4 months of age)
- Average length of hospital stay 2 – 4 days
- <10% reach ICU, with an average stay of 2.5 – 3.8 days
- Average direct hospital costs of $10k / patient
- Increase in average cost for infant during first year of life vs infant with no history of RSV: $8k

US Hospitalised Infants
<1 year old
c. 60,000 – 125,000

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RSV hospitalizations in the USA

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C. 60,000 – 125,000
RSV is located in bronchial epithelium – may be difficult to access with systemic (oral) treatments

Welliver et al. JID 2007;195:1126-36, and DeVincenzo. JID 2007;195
Evidence that RSV antiviral may offer benefit
( DeVincenzo JID 2011 )

The mean RSV viral load at days 1, 2 and 3 dichotomized by duration of hospitalization. The full line represents viral loads from patients who were hospitalized for 4 or more days. The dotted line represents specimens collected from patients who remained in hospital for less than 4 days. Error bars represent SEM of the mean. ns: not significant.

More rapid individual RSV clearance rates independently associated with shorter duration of hospitalization ( p = 0.035 )

But association doesn’t predict benefit of antiviral; depends on timing and viral dynamics
**Phase I/IIa**

Infants (up to 23 months) hospitalized with RSV LRTI

- **N=53**, 59 sites
- **Nov 14 - Dec 15 (16)**

**Expansion cohort**

**Phase I**

Infants (1-12 months) hospitalized with RSV

- **N=168**, 66 sites
- **Jul 14 - Sept 16**

**Gilead:** Presatovir (GS-5806)

**Phase 2/2B**

Adults hospitalized with RSV

- **N=200**, 82 sites
- **Jul 14 - April 2017**

**Phase 2/2B**

HSCT recipients with an acute RSV LRTI

- **N=60**, 37 sites
- **Jan 15 - March 17**

**Phase 2/2B**

HSCT recipients with an acute RSV URTI

- **N=200**, 58 sites
- **Jan 15 - March 18**

**JNJ:** JNJ-53718678

**Ablynx:** ALX-0171

**Phase 2a Adult RSV challenge**

- **N=66**
- **1 site** [UK, Retroscreen]
- **May 15 - Sept 15**

**Phase 2B**

Infants with acute RSV (UKCRN 31100?)

**Phase 2B**

Lung transplant recipients with acute RSV infection

- **N=60**, 34 sites
- **Dec 15 - Jul 17**

**ArkBio:** AK0529

**Phase 1 Healthy adults**

- **N=74**, Sites=1 [Australia]
- **Oct 14 - June 15**

**Phase 1b**

Infants (1-24 months) hospitalized with RSV

- **N=25** (1 site)
- **Sites=1** [Australia, Adelaide]
- **Sep 15 - Term in July 16 (original: Dec 16)**

**Biota/Aviragen:** BTA585

**Phase I Healthy adults**

- **N=60**, 1 site [Biota, US]
- **Aug 15 - Dec**

**Phase I Healthy adults**

- **N=48**, 1 site [Biota, US]
- **Aug 15 - Dec**

**Phase 2 RSV Challenge**

- **N=60** 1 site [Biota, UK (hVivo)]
- **March 16 - Nov 16**

**Phase 2, infants (1-24 months) hospitalized with RSV**

- **N=78** Sites=1 [Australia, Brisbane]
- **March 16 - Sept 17**

**Phase 1 Adult Taste profile study**

- **N=12**, 1 site [Nottingham (Quotient?)]
- **June 16 - July 16**

**Phase 1 Adult Cardiac Repolarization**

- **N=78**, 1 site [Arizona, US]
- **June 16 - Oct 16**

**JNJ Alios:** ALS-8176

**Nucleoside polymerase inhibitor**

**Aviragen**

**Avigen**

**Current RSV Antiviral Landscape (source: clinicaltrials.gov)**

- Inhaled, nanobody, F protein inhibitor
- Oral, F protein inhibitor
- Oral solution, F protein inhibitor
- Oral, small molecule F protein inhibitor
- FDA grant fast track status
- Study terminated (reason unknown)

**Phase 1 Adult, Taste profile study**

- **N=12**, 1 site
- **Phase 1 Adult, Cardiac Repolarization**

- **N=78**, 1 site

**Current RSV Antiviral Landscape (source: clinicaltrials.gov)**
RSV human challenge – ALS 8176 and GS 5806
## Antivirals for RSV – target profile considerations

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>• Potent antiviral therapy which is effective against both RSV-A and B strains – and can be used effectively even in patients with established infection (i.e. there is no specific treatment window)</th>
</tr>
</thead>
</table>
| Target Population | • The most likely target population will be hospitalised ‘at risk’ babies (i.e. premature, CV issues), as well as potentially full-term babies under 4 months.  
• Companion point of care diagnostic required |
| Administration | • Oral or Inhaled routes |
| Efficacy | • A key measure will be the impact on viral load, with 90% reduction in the first 24 hours (leading to limited detectable level within 24 to 36 hours)  
• It is anticipated that rapid, effective antiviral could result in a 50% reduction in length of stay  
• In patients that are admitted directly to ICU, the product could decrease time in ICU and days on a ventilator  
• The product should have an impact on the overall 1 year costs for patients, as well as future impact of wheezing / asthma |
| Safety / tolerability | • There should be no significant adverse toxicities (or drug interactions) |
Vaccines
Prospects for HRV vaccine

There are only about three strains of influenza each season, while there are usually 20-30 different types of rhinovirus circulating each season in each geographic area.

Only about 10% of those will show up again the next year.

Unlike influenza, it is impossible to predict the spectrum of rhinovirus types for an upcoming cold season.

Ideally would need to incorporate 100 different strains into one vaccine and that would take care of only the most common cold-causing virus.

More than 200 viruses can cause URTIs including some strains of influenza virus, adenoviruses, coronaviruses, enteroviruses, and respiratory syncytial virus.
RSV vaccine development also challenging
Higgins et al. / Vaccine 34 (2016) 2870–2875

RSV vaccine candidate numbers in research and development per vaccine platform

Vaccine platform RSV vaccine candidates
Live-attenuated and live-vectored 12
Protein-based 30
Whole-inactivated 1
Particle-based 15
Subunit antigens 14
Nucleic acid 4
Gene-based vectors 11 Replication competent and deficient alphavirus, adenovirus, and modified vaccinia virus Ankara (MVA) vectors encoding RSV surface antigens (including replication-competent and –deficient D.

Challenges:
Infants: presence of maternal antibody; immature immune system; susceptibility to RSV disease; safety concerns (generic)

Children: 50% of childhood hospitalizations occur after 6 months of age; maternal antibody has waned; less susceptible to severe RSV disease and more mature immune system than younger children; potential to decrease transmission to others
Challenges: clinical endpoint may be more difficult to achieve than in neonates, safety issues

Maternal: having experienced multiple previous infections may limit response to vaccination; need for substantial increase in antibody levels to protect the infant; quantify the relationship between neutralizing antibody level and degree of protection; safety concerns
Synagis reduces RSV hospitalisation and improves wheezing outcomes

Early studies of respiratory syncytial virus (RSV) prophylaxis with RSV intravenous immunoglobulin and palivizumab, an anti-RSV monoclonal antibody, done in Canada, Europe, and Japan, suggested that preventing RSV lower respiratory tract infections resulted in improvements in both wheezing respiratory outcomes and lung function measured 7–10 years later. Wenzel SE, Gibbs RL, Lehr MV, Simoes EA. Respiratory outcomes in high-risk children 7 to 10 years after prophylaxis with respiratory syncytial virus immune globulin. Am J Med 2002; 112: 527–33.


### RSV Vaccine and mAb Pipeline

#### RSV Vaccine and mAb Snapshot

<table>
<thead>
<tr>
<th>TARGET INDICATION</th>
<th>P = PEDIATRIC</th>
<th>M = MATERNAL</th>
<th>E = ELDERLY</th>
<th>T = TDD</th>
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<td>LIVE-ATTENUATED/CHIMERIC</td>
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<tr>
<td>AveVax</td>
<td>Laurence-Blumer</td>
<td>RNA Vaccine</td>
<td>Saba Vaccines</td>
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<td>Inovio</td>
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#### PHASE 1

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#### WHOLE-INACTIVATED

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#### NUCLERIC ACID

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#### GENE-BASED VECTORS

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#### COMBINATION/IMMUNOPROPYLSIS

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**Note:** Updated: July 15, 2016

Summary and conclusions

- RSV and HRV antivirals - demonstrating a significant impact on clinical measures (reduction of hospital stay, reduced ICU stay, reduced first year costs) will be key in gaining acceptance and supporting pricing arguments for new treatments
  - There is still some debate on the potential for antivirals to impact these measures in patients with established infections, where anti-inflammatory components may be important
  - Need for companion diagnostic (point of care)

- Ensuring guideline inclusion / endorsement from the American Academy of Pediatrics, which is key for payor and formulary acceptance

- Future competitive impact of RSV prophylactic vaccines, particularly for maternal immunisation. Recent data (Novavax etc) are not encouraging that a vaccine is likely in the short-medium term.
Re purposing example:
Therapeutic effects of itraconazole against HRV