Pathogenesis and impact of respiratory viruses

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Respiratory Infection and the Impact of Pulmonary Immunity on Lung Health and Disease

Joseph P. Mizgerd

Global Burden of Disease
(DALYs lost in 2004, worldwide)

- Acute Lung Infection
- Neoplasms
- Diarrheal Diseases
- Depression
- Ischemic Heart Disease
- HIV / AIDS
- Cerebrovascular Disease
- Tuberculosis
- Malaria
- COPD
- Diabetes Mellitus
- Asthma
- Alzheimer / dementias

Deaths due to infection or lung disease (US, 2005)
Influenza vs respiratory syncytial virus

**Influenza**

- No re-infection by same strain
- Imperfect vaccines:
  - Vaccine-induced immunity rapidly wanes
  - Mainly homotypic immunity
  - Annual vaccination required

**RSV**

- Recurrent re-infection with similar strains
- No vaccine
  - Poor immunogenicity
  - Vaccine-enhanced disease
  - Very active research field

Human
RSV bronchiolitis
RSV interference with host immune response

Non-structural proteins
• NS1 disrupts IRF3 binding to the IFNβ promoter
• NS2 protein binds RIG-I, blocking innate signalling
• NS1/2 enhance degradation of STAT2, terminating innate response
• NS1/2 inhibits cDC maturation, inhibiting APC functions

Surface glycoproteins
• G protein binds to CX3CR1 on pDC/cilliated cells
• Secreted G acts as a decoy for antibody
• F binds to TLR4, possibly causing innate desensitisation

Internal proteins
• N disrupts the synapse between CD4 and CD8 cells

Global burden of RSV in children under 5 years of age

Mortality
- 118,200-149,400 deaths children <5 years; 13-22% of all ALRI mortality <5 years due to RSV
- 48-50% out of hospital
- 4-7 months median age at RSV-related death
- OR 6.5:5 of death for infants with pneumothorax
- OR 119.4:4 of death for infants with sepsis
- 70% children who died had comorbidity in HICs

Hospitalisation
- Incidence <1 year is 3 times greater for preterm than term infants
- 45% hospitalisations occur <6 months of age
- 79% of hospitalised children previously healthy

Global incidence RSV LRTI
- 28% LRTI due to RSV
- 3.2 million RSV LRTI requiring hospitalisation

Lancet Infect Dis 2018; 18: e295-311
Published Online
June 15, 2018
http://dx.doi.org/10.1016/S1473-3099(18)30292-5
The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates


Live-attenuated or chimeric
- RSV D46/NS2/NI/ΔM2-2-HindIII phase 1
- RSV LID ΔM2-2 1030s phase 1
- RSV D46 cpΔM2-2 phase 1
- RSV cpM2 phase 1
- RSV ΔNS2Δ1313 I1314L phase 1
- MEDI-559
- MEDI-534
- Ad26.RSV.preF phase 1/2+3
- MVA-BN RSV phase 2
- VXA-RSVf phase 1
- DPX-RSV-SH phase 1
- MEDI-7510

Monoclonal antibodies
- REGN-2222
- MEDI8897 phase 2

Particle-based
- RSV F nanoparticle phase 1/2/3+
- SynGEM development halted

Vector-based
- RSV001
- ChAd155-RSV phase 2
- MVA-BN RSV phase 2
- VXA-RSVf phase 1
- GSK RSV F development halted

Subunit
- DS-Cav1 phase 1
- Novartis F-protein
- MEDI-7510

Published Online
June 15, 2018
http://dx.doi.org/10.1016/S1473-3099(18)30292-5
Age and RSV disease

Protective and harmful immunity to RSV infection Annu Rev Immunol 35, 501–32
Respiratory Syncytial Virus, Airway Inflammation, and FEV₁ Decline in Patients with Chronic Obstructive Pulmonary Disease

Tom M. A. Wilkinson, Gavin C. Donaldson, Sebastian L. Johnston, Peter J. M. Openshaw, and Jadwiga A. Wedzicha

- 88 COPD patients (from East London)
- Prospective study, 14-month duration
- Daily diary cards
- Sputum samples every 3 months
  - 272 samples collected
    - Quantitative microbiology
    - RSV by qualitative PCR
- 34 patients were RSV negative throughout (RSV free)
- 42 patients had RSV detected in one or more samples, but not all sputa (intermittent RSV)
- 12 patients were RSV positive in all their samples (‘persistent’ RSV)

FEV₁ = forced expiratory volume in 1 second

FEV₁, decline vs baseline (mL/year)

No RSV

Intermittent RSV

Persistent RSV
Macavity's a Mystery Cat: he's called the Hidden Paw—
For he's the master criminal who can defy the Law.
He's the bafflement of Scotland Yard, the Flying Squad's despair:
For when they reach the scene of crime—Macavity's not there!
Antiviral B cell and T cell immunity in the lungs

Christopher Chiu & Peter J Openshaw

- Activating effects
- Augmenting vaccination
- Too much immunity
- Immunopathology
- Too much virus
- Lack of ‘danger’
- Regulatory effects
- Immune tolerance of infection

VOLUME 16  NUMBER 1  JANUARY 2015  NATURE IMMUNOLOGY
RSV load and immune mediator levels in nasal mucosal lining fluid

- 55 infants with bronchiolitis, one hospital, 2016/17 season.
- 30 were RSV infected:
  - 18 ‘moderate’ (ward care)
  - 12 mechanically ventilated ‘severe’

Up to 13 samples per patient
Compared to moderately ill children, those with severe RSV bronchiolitis have:

- **Lower** nasal viral loads
- **Reduced**, IP-10/CXCL10, CCL5 and IFNγ levels

Gene expression in mucosal samples at enrolment

Compared to moderately ill children, those with severe bronchiolitis have:

increased MUC5AC and IL17A
The relationship between viral load and interferon breaks down in severe disease, where mucus production mediates airway plugging and respiratory failure.

**Infantile viral lung infection**

*Pathogenesis progresses through stages*

- **Mild** (Community)
- **Moderate** (Hospitalised)
- **Severe** (Respiratory Failure)
Infant study group

St Mary’s Hospital
Cally Feather
Marwa Ghazaly
Farhana Abdulla
Simon Nadel

Kaz Ito
Matthew Coates
Lyndsey Cass
Garth Rapeport

Imperial College London
Ryan Thwaites
Trevor Hansel

Charing Cross
Alison Cox
Panos Pantelidis
Pinglawathee Madona
David Muir
Experimental infection of human volunteers

Meta Roestenber, Marie-Astrid Hoogerwerf, Daniela M Ferreira, Benjamin Mordmüller, Maria Yazdanbakhsh

Lancet Infect Dis 2018
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June 8, 2018
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Studies that intentionally infect people with disease-causing bugs are on the rise
By Joe Cebula | May 18, 2018, 3:04 AM
£3m, 4 yr MRC-funded network to:

Support, develop and advocate the use of Human Infection Challenge, to...

• Improve understanding of infections and the diseases they cause
• Enhance the development of new/better vaccines/treatments for LMIC infections

The network

www.hic-vac.org
## Network Management Board

<table>
<thead>
<tr>
<th>Name</th>
<th>Surname</th>
<th>Institution</th>
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<tbody>
<tr>
<td>Peter</td>
<td>Openshaw</td>
<td>Imperial College London <em>(Director)</em></td>
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<tr>
<td>Andrew</td>
<td>Pollard</td>
<td>University of Oxford <em>(Deputy Director)</em></td>
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<td>Stephen</td>
<td>Gordon</td>
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<tr>
<td>Cherry</td>
<td>Kang</td>
<td>Translational Health Science and Technology Institute, India</td>
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<tr>
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<td>Ferreira</td>
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<td>Robert</td>
<td>Read</td>
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<td>John</td>
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<td>Imperial College London</td>
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Human challenge network focus:

S. pneumoniae

S. typhi/paratyphi

Malaria

M. tuberculosis

HIV

Hepatitis

Polio

Pseudomonas

Shigella

Group B strep

N. meningitidis

Cholera

R. typhi

Rotavirus

H. influenzae

Gonorrhea

Lassa

B. pertussis

HSV

Schistosoma

RSV

Coronavirus

S. aureus

Leishmania

Rhinovirus

Hookworm

Group A strep

Influenza
UK Members (n=114)
Non-UK Members: n=77
Membership

Total members September, 2018: 191, 25% LMIC

1. **Investigators (74)**: Independent current HIC studies
2. **Associates (69)**: Work with Investigators (Postdoc etc.)
3. **Affiliates (48)**: Others interested in HIC studies

What we provide:

- Eligibility to apply for HIC-Vac funding
- Invitations to meetings and events
- Profile on website – networking and collaborations
- HIC-Vac mailing list for network notices
Inoculation of volunteers with RSV

- Healthy, aged 18 – 55 years
- Intranasal $10^4$ pfu RSV A Memphis 37
- Keep in seclusion from D-1 to D10
- Intensive daily sampling
- Follow-up:
  - day 14 (airway)
  - day 28 (airway and blood)

Dr Max Habibi
and Chris Chiu
RSV infection of adult volunteers

Quarantine and daily nasal sampling

Nasal curettage

Day 0  3  10  14

Nasal sampling

RSV M37 inoculation

Net viral replication

Net immune control

Eclipse phase

Shedding phase

Daily viral load log_{10} copies mL

Day post-inoculation 2  4  6  8  10  12  14
Symptoms & viral load: comparing RSV and flu

Pre-selected for seronegativity

Influenza

Not pre-selected for seronegativity

RSV
Outcome of RSV inoculation in 61 adults

- **RSV inoculation N=61**
  - 44% No infection N=27
  - 56% Viral infection N=34
    - 32% No symptoms N=11
    - 68% Common cold symptoms N=23

Graph shows mean daily total URT symptom score over time for infected and uninfected individuals.
The silent phase is vital in understanding outcome.

Host shows a response: virus defeated
Host mediators suppressed: virus succeeds
The infection challenge team

Chris Chiu
Maximillian Habibi
Agnieszka Jozwik
Aleks Guvenel
Hannah Jarvis
Onn Min Kon
Jai Dhariwal
Annemarie Sykes
Mark Almond
Ernie Wong
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Hiromi Uzu
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Belen Trujillo-Torralbo

Alessandro Sette
Bjoern Peters
John Sidney

Rafi Ahmed
Jens W quemert
Xander de Haan

Thank you