Take A Deep Breath: Lung Infection and Cognition in Down Syndrome

Michael E. Yeager
Pediatrics/Cardiology; Bioengineering
Disclosure

Our lab has received funding from the following:

- Jerome LeJeune Foundation
- Jayden DeLuca Foundation
- Celgene, Inc.
- American Heart Association
- Linda Crnic Institute for Down Syndrome
Disclosure
Morbidity and Mortality in Persons with Down Syndrome Manifests Predominantly as Infectious Lung Disease


<table>
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<td></td>
<td>&lt;1 year</td>
<td>1 year</td>
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<td>Dementia</td>
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<td>1.4</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
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<td>6.8</td>
<td>3.8</td>
<td>5.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Malignancies, all</td>
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<td>5.7</td>
<td>1.9</td>
<td>5.3</td>
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<td>Leukemia</td>
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<td>4.3</td>
<td>1.9</td>
<td>3.3</td>
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</tr>
<tr>
<td>Solid tumors</td>
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<td>1.4</td>
<td>0.0</td>
<td>2.0</td>
<td>0.0</td>
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<tr>
<td>Other congenital malformations</td>
<td>14.9</td>
<td>1.6</td>
<td>11.4</td>
<td>1.8</td>
<td>17.1</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>175</td>
<td>370</td>
<td>105</td>
<td>394</td>
<td>70</td>
</tr>
</tbody>
</table>

In DS, is the problem the lung, the immune system, or both?
Infectious lung disease accounts for 54% of hospital admissions for persons with DS

Average length of admission is 2-3 times longer than those without DS

Persons with DS have increased frequency of respiratory tract infection (62 fold higher rate)

Increased risk for acute respiratory distress syndrome
   16 fold, 8 fold, 335 fold more likely to be hospitalized, intubated, or to die, respectively

Infectious respiratory disease accounts for more deaths in DS than any other medical condition; 12 times more likely to die than typical population
Lung Health is Front and Center for Persons with DS and Their Families

Ever Made A Croup Tent At Home? I Did Every Year From 1983-2004

So What’s the Mission, the Goal?

1. Awareness! Persons with DS, autoimmunity, & lung disease
2. Learning how Trisomy 21 leads to respiratory & autoimmune diseases will help those with DS and those without DS

Folks with DS will feel better-physically & mentally
Post-Influenza Pneumonia

Lessons from the Flu:

Changes in Immune Cell Function in Postinfluenza Bacterial Pneumonia

Flu usually not lethal, bacterial “super”infection often is (>50% of deaths)

Associated with high levels of interferons (types I and II), IL-10, TGF-beta

Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice

Arash Shahangian,1,2 Edward K. Chow,3 Xiaoli Tian,4 Jason R. Kang,† Amir Ghaffari,1,2 Su Y. Liu,† John A. Belperio,4 Genhong Cheng,1,5 and Jane C. Deng‡

1Department of Microbiology, Immunology and Molecular Genetics, and Medical Scientist Training Program, David Geffen School of Medicine, UCLA, Los Angeles, California, USA. 2G.W. Hooper Foundation, UCSF, San Francisco, California, USA. 3Division of Pulmonary and Critical Care Medicine and Molecular Biology Institute, David Geffen School of Medicine, UCLA, Los Angeles, California, USA. 4Department of Laboratory Medicine, University of Washington, Seattle, Washington, USA. 5Clinical Laboratory of Immunology and Pathology, Royal Children's Hospital, Melbourne, Australia.

Influenza-related complications continue to be a major cause of mortality worldwide. Due to unclear mechanisms, a substantial number of influenza-related deaths result from bacterial superinfections, particularly secondary pneumococcal pneumonia. Here, we report what we believe to be a novel mechanism by which influenza-induced type I IFNs sensitize hosts to secondary bacterial infections. Influenza-infected mice deficient for type I IFN-α/β receptor signaling (Ifnar−/− mice) had improved survival and clearance of secondary Streptococcus pneumoniae infection from the lungs and blood, as compared with similarly infected wild-type animals. The less effective response in wild-type mice seemed to be attributable to impaired production of neutrophil chemoattractants KC (also known as Cxcl1) and Mip2 (also known as Cxcl2) following secondary challenge with S. pneumoniae. This resulted in inadequate neutrophil responses during the early phase of host defense against secondary bacterial infection. Indeed, influenza-infected wild-type mice cleared secondary pneumococcal pneumonia after pulmonary administration of exogenous KC and Mip2, whereas neutralization of Cxc2, the common receptor for KC and Mip2, reversed the protective phenotype observed in Ifnar−/− mice. These data may underscore the importance of the type I IFN inhibitory pathway on CXC chemokine production. Collectively, these findings highlight what we believe to be a novel mechanism by which the antiviral response to influenza sensitizes hosts to secondary bacterial pneumonia.

Important Mediator of the Enhanced Susceptibility to Bacterial Pneumonia after Influenza Infection

Karita S. Sluijs,§* Leontine J. R. van Elden,¶ Monique Nijhuis,¶ Rob Schuurman,¶ Claudine Florquin,¶ Michel Goldman¶ Henk M. Jansen,¶ René Lutter,‡ and John A. Belperio,

*Department of Immunology, Netherlands Cancer Institute, Amsterdam, The Netherlands. ‡Division of Pulmonary and Critical Care Medicine and Molecular Biology Institute, David Geffen School of Medicine, UCLA, Los Angeles, California, USA. §Medical Scientist Training Program, David Geffen School of Medicine, UCLA, Los Angeles, California, USA. ¶Medical Research Council Centre for Influenza Viral Infections, Institute of Virology, University of Amsterdam, Amsterdam, The Netherlands.

Influenza pneumonia is a serious disease, and it is becoming increasingly prevalent due to antibiotic resistance and underlying chronic health conditions. We established a mouse model to study the role of IL-10 in host defense against Streptococcus pneumoniae infection. C57BL/6 mice were intranasally inoculated with 10 median tissue culture infectious doses of influenza virus (A/Puerto Rico/8/34 or PBS) on day 0. By day 14 mice had regained their normal body weight and had cleared influenza virus from the lungs, as determined by real-time quantitative PCR. On day 14 after viral infection, mice were challenged intranasally with S. pneumoniae (serotype 3) intranasally. Mice recovered from influenza infection were highly susceptible to secondary pneumococcal pneumonia, which was reflected by a 100% lethality on day 3 after bacterial infection, whereas control mice had a 3% and 83% lethality on day 6 after pneumococcal infection. Furthermore, 1000-fold higher bacterial counts with S. pneumoniae and, particularly, 50-fold higher pulmonary levels of IL-10 were observed in mice with secondary pneumococcal infection in control mice. Treatment with an anti-IL-10 mAb 1 h before bacterial inoculation resulted in a marked reduction in lethality and markedly reduced lethality during secondary bacterial pneumonia compared with those in IgG1 isotype control mice. This reduced susceptibility to secondary bacterial pneumonia is at least in part caused by excessive IL-10 production and reduced neutrophil function in the lungs. The Journal of Immunology, 2004, 172: 7603–7609.
Hypothesis

In persons with DS, the lung is in a chronic state of susceptibility to severe *S. pneumoniae* pneumonia that phenocopies post-viral infection in non-DS individuals.

Strong Inference

Interferonopathy

Toll-like receptors

Immune suppression IL-10/TGF-beta

Respiratory commensal bacteria

Trisomy 21 consistently activates the interferon response

Kelly D Sullivan¹,²,³,⁴*, Hannah C Lewis¹,², Amanda A Hill¹,², Ahwan Pandey¹,²,³,⁴, Leisa P Jackson¹,³,⁴, Joseph M Cabral¹,³,⁴, Keith P Smith¹, L Alexander Liggett¹,⁵, Eliana B Gomez¹,³,⁴, Matthew D Galbraith¹,²,³,⁴, James DeGregori¹,⁵,⁶,⁷,⁸,⁹, Joaquin M Espinosa¹,²,³,⁴*

J. theor. Biol. 86, 603–606

Letter to the Editor

Interferon Action and Chromosome 21 Trisomy
Hypothesis

In persons with DS, the lung is in a chronic state of susceptibility to severe *S. pneumoniae* pneumonia that phenocopies post-viral infection in non-DS individuals.
Hypothesis

In persons with DS, the lung is in a chronic state of susceptibility to infections, phenocopying post-viral infection in non-DS individuals. This state can lead to severe respiratory syncytial virus bronchiolitis, a frequent cause of hospitalization in DS children (10,26–28). Also, an increased risk of hospitalization, endotracheal intubation, and death due to influenza A virus infection was reported in DS (29). In addition, we found an increased proinflammatory cytokine response to live influenza A virus in children with DS, which might contribute to an increased severity of their clinical course of this infection (30). Bacterial pathogens, both Gram positive and Gram negative, can also cause lower RTIs in children. However, nothing

Increased production of interleukin-10 in children with Down syndrome upon ex vivo stimulation with Streptococcus pneumoniae

Chantal J.M. Broers¹, Reinoud J.B.J. Gemke¹, Servaas A. Marre²,³, Michel E. Weijerman¹ and Anne Marceline van Furth⁴

BACKGROUND: Children with Down syndrome (DS) have an increased susceptibility to infections, due to altered humoral and/or cellular immunity. The aim of the study was to determine the cytokine production in whole blood of children with DS upon stimulation with heat-killed Streptococcus pneumoniae and lipopolysaccharide (LPS), in comparison with their healthy siblings.

METHODS: Whole blood of 61 children with DS and 57 of their healthy siblings was stimulated with 200 ng/ml LPS and 4 x 10⁵ colony-forming units/ml S. pneumoniae during 6, 24, and 48 h. Concentrations of pro- and anti-inflammatory cytokines, tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, IL-12p70, and IL-10 were determined at all time points.

RESULTS: Children with DS show an increased IL-10 production upon stimulation with S. pneumoniae compared to their healthy siblings. At most time points, no significant differences were seen in cytokine production upon stimulation with LPS.

CONCLUSION: Children with DS may be prone to a severe course of pneumococcal pneumonia, because of an increased anti-inflammatory response.
Hypothesis

In persons with DS, the lung is in a chronic state of susceptibility to severe S. pneumoniae pneumonia that phenocopies post-infectious sequelae.
Post-Influenza-Like Lung in Down Syndrome?

Post-influenza, non-DS

- Fulminant Remodeling
- Platelet Activating Factor Receptor (PAFR)
- IFN signaling increase
- IL-10 signaling increase
- TLR down
- Immune cell dysfunction

DS

- ?
Post-Influenza-Like Lung in Down Syndrome?

**Organ**

- Subpleural cysts
- Pulmonary hypoplasia
- Congenital heart defects

**Tissue**

Fig. 9  Tracheal rings. Axial CT of the chest in a 23-month-old boy with Down syndrome shows a circular configuration of the trachea (arrow). This along with the small caliber of the trachea is consistent with a diagnosis of complete tracheal rings.

**Cells**

Fig. 3  Tetralogy of Fallot and esophageal atresia/tracheoesophageal fistula. Anteroposterior chest radiograph in a newborn boy shows that the heart has a boot-shaped contour with an upturned apex compatible with a diagnosis of tetralogy of Fallot. A nasoenteric tube is coiled in the upper esophageal pouch (arrow), consistent with esophageal atresia. The presence of bowel gas (arrowhead) in the upper abdomen confirms the presence of a tracheoesophageal fistula. There are also 13 pairs of ribs.

We need to explore mouse models of DS more fully for these...
Post-Influenza-Like Lung in Down Syndrome?

**Organ**
- Saline
- *S. pneumoniae polysacc*

**Tissue**

**Cells**
- Control
- Dp(10)
- Dp(16)

- Lung Remodeling Score
- Control
- Dp(10)
- Dp(16)

- Green = CD15
- Blue = DAPI (nuclei)

- Hematoxylin & Eosin

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**B**

- Green = CD15
- Blue = DAPI (nuclei)

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**C**

- Control
- Dp(10)
- Dp(16)
- DS
Increased PAFR facilitates increased S. pneumoniae adhesion

Involvement of the platelet-activating factor receptor in host defense against *Streptococcus pneumoniae* during postinfluenza pneumonia

Koenraad F. van der Shuijs,
Leontine J. R. van Elden,
Monique Nijhuis,
Rob Schuurman,
Sandrine Florquin,
Takao Shimizu,
Satoshi Ishii,
Henk M. Jansen,
Rene´ Lutter, and Tom van der Poll

Laboratory of Experimental Internal Medicine; Department of Pulmonology; Laboratory of Experimental Immunology; Department of Pathology, Academic Medical Center, University of Amsterdam, Amsterdam; Eijkman-Winkler Institute, Department of Virology, University Medical Center, Utrecht, The Netherlands; Department of Biochemistry and Molecular Biology, Faculty of Medicine, The University of Tokyo; and CREST of Japan Science and Technology Corporation, Tokyo, Japan

**Post-Influenza-Like Lung in Down Syndrome?**

**Organ**

**Tissue**

**Cells**

**TLR2**

**TLR4**

**PAFR**

**Bactin**

**Ctl**

**Dp16**

**Fig. 1.** Overview of the different PRRs involved in recognition of S. pneumoniae. Cell wall components and possibly PLY of extracellular bacteria are recognized by TLR2 and -4 respectively. Moreover, S. pneumoniae is internalized by phagocytic cells and subsequently degraded in phagosomes leading to the release of bacterial peptidoglycan and nucleic acids. While unmethylated CpG-containing DNA is sensed by TLR9 within the endosomes, other bacterial components might gain access to the cytosol possibly dependent on PLY-mediated membrane disruption. For example, pneumococcal peptidoglycan fragments are detected by NOD2 within the cytosol. Moreover, pneumococcal DNA is detected by AIM2 and by an additional still not identified cytosolic PRR. TLRs as well as NOD2 subsequently stimulate the production of NF-kB-dependent cytokines including TNFα, IL-6, KC and pro-IL-1β. While functional TNFα, IL-6 and KC are released after translation, the production of IL-1β requires a second signal. This is provided by the NLRP3 and the AIM2 inflammasomes activated by PLY and bacterial DNA, respectively, which mediate cleavage of pro-IL-1β into mature IL-1β. Sensing of S. pneumoniae DNA by the yet-to-be-identified cytosolic DNA sensor activates the adaptor STING and the transcription factor IFN3, and stimulates type I IFNs responses.
Post-Influenza-Like Lung in Down Syndrome?

**Organ**

**Tissue**

Lung stains

**Cells**

Human

Peripheral blood

Fibroblasts

PB/BALF

Lung Cells

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### Migration

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<thead>
<tr>
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<th>Ctl</th>
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### Phagocytosis

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### CD11b+/CD14+/CD206+

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### CD11b+/CD15+/CD163+

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<td>n=11</td>
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* AAM, LDG, Fibrocytes, Pro-collagen
Cell/Individual particle tracking Icy
Post-Influenza-Like Lung in Down Syndrome?

Organ

Low density granulocyte migration, relative to control

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<tr>
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<th>Control</th>
<th>Dp(10)</th>
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<td>0.0</td>
<td>1.0</td>
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Tissue

Lung stains

Human

Peripheral blood

Fibroblasts

Cells

Dp16

PB/BALF

Lung Cells

Migration

Relative Migration Distance In response to MCP-1, 18 hours

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<th>Dp16</th>
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<tr>
<td>0</td>
<td>50</td>
<td>20</td>
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Phagocytosis

% CD14+ Phagocytosing

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<td>0</td>
<td>55% decrease</td>
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* Significant difference
Post-Influenza-Like Lung in Down Syndrome?

Post-influenza, non-DS

- Fulminant Remodeling
- PAFR
- IFN signaling increase
- IL-10 signaling increase
- TLR down
- Immune cell dysfunction

DS
Is there A Link Between Lung Disease and Cognition in Down Syndrome?

R. H. J. Versteegen, †H. B. M. van Gameren-Oosterom, †M. Fekkes, †E. Dusseldorp, †E. de Vries* and J. P. van Wouw†

*Department of Pediatrics, Jeroen Bosch Hospital, ‘s-Hertogenbosch, the Netherlands, and †Department of Child Health, Netherlands Organisation for Applied Scientific Research TNO, Leiden, the Netherlands

Accepted for publication 24 April 2012

Significant impact of recurrent respiratory tract infections in children with Down syndrome

Table 1. Patient characteristics and additional morbidity of 8-year-old Down syndrome population in relation to parent-reported presence of recurrent respiratory tract infections

<table>
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<tr>
<th>Additional morbidity</th>
<th>RRTI †</th>
<th>RRTI ‡</th>
<th>Total</th>
<th>Chi-squared test</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Other morbidity, not specified</td>
<td>43 (29)</td>
<td>38 (22)</td>
<td>81 (25)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
<td>3 (1)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>19 (13)</td>
<td>20 (11)</td>
<td>39 (12)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Eye disease</td>
<td>77 (52)</td>
<td>81 (46)</td>
<td>158 (49)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>28 (19)</td>
<td>6 (3)</td>
<td>34 (10)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>*There was no significant difference in age between both groups determined by a t-test.</td>
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<tr>
<td>†Percentage out of all children attending regular education.</td>
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<td></td>
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<tr>
<td>‡Parental reported morbidity.</td>
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RRTI †, children with respiratory tract infections; RRTI ‡, children without respiratory tract infections; NS, not significant.
Is there A Link Between Lung Disease and Cognition in Down Syndrome?

Table 2. Results of multiple regression analyses for scale scores of the McCarthy Scales of Children’s Abilities (MSCA) of 8-year-old Down syndrome children with and without parent-reported recurrent respiratory tract infections (RRTI)

<table>
<thead>
<tr>
<th>Scale</th>
<th>RRTI&lt;sup&gt;+&lt;/sup&gt;</th>
<th>RRTI&lt;sup&gt;-&lt;/sup&gt;</th>
<th>Regression coefficient† (β)</th>
<th>Effect size‡ (f&lt;sup&gt;2&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 130)</td>
<td>Male (n = 75)</td>
<td>Female (n = 55)</td>
<td>Male (n = 140)</td>
</tr>
<tr>
<td>Verbal</td>
<td>33.06 (19.13)$§</td>
<td>29.64 (19.96)</td>
<td>40.68 (16.18)</td>
<td>37.09 (15.72)</td>
</tr>
<tr>
<td>Perceptual performance</td>
<td>26.76 (16.58)</td>
<td>21.80 (15.84)</td>
<td>32.34 (14.90)</td>
<td>28.83 (14.87)</td>
</tr>
<tr>
<td>Quantitative</td>
<td>9.44 (6.80)</td>
<td>7.86 (6.46)</td>
<td>12.22 (6.57)</td>
<td>10.46 (6.75)</td>
</tr>
<tr>
<td>Memory</td>
<td>10.74 (7.77)</td>
<td>9.27 (7.69)</td>
<td>13.94 (7.37)</td>
<td>11.77 (6.31)</td>
</tr>
<tr>
<td>Motor</td>
<td>23.23 (12.57)</td>
<td>20.03 (12.64)</td>
<td>27.67 (11.78)</td>
<td>24.99 (11.51)</td>
</tr>
<tr>
<td>General cognitive score</td>
<td>69.30 (40.25)</td>
<td>59.36 (40.22)</td>
<td>85.24 (34.43)</td>
<td>76.35 (33.60)</td>
</tr>
<tr>
<td>Developmental age</td>
<td>3 years 8 months (10.91)</td>
<td>3 years 6 months (10.53)</td>
<td>4 years 3 months (10.53)</td>
<td>3 years 11 months (10.66)</td>
</tr>
</tbody>
</table>

Lower scores indicate more impaired development.
*P < 0.05; **P < 0.01; ***P < 0.001.
†β = unstandardized regression coefficient of the effect of RRTI, correcting for the effect of socio-economic status, childcare attendance, being breastfed, age and gender; (‡Effect size (f<sup>2</sup>): small effect (0.01–0.10), moderate effect (0.10–0.33) and large effect (>0.33).
§Mean scores are presented with standard deviation between brackets.
RRTI<sup>+</sup>, children with recurrent respiratory tract infections; RRTI<sup>-</sup>, children without recurrent respiratory tract infections.

Key messages

- Children with Down syndrome are known to be at increased risk of recurrent respiratory tract infections.
- In 8-year-old children with Down syndrome, parental report of recurrent respiratory infections was associated with more delayed development, increased risk of behavioural problems and lower health-related quality of life.
Lung Disease & Cognition: Tantalizing Clues

Cognitive Assays in Dp16 mice

**Distance Moved**

- **Ctl Lung**
  - 0 cm
  - 2000 cm
  - 4000 cm
  - 6000 cm
  - 2000 cm

- **Ts Lung**
  - 4000 cm
  - 6000 cm
  - 8000 cm
  - 2000 cm

**Velocity**

- **Ctl Lung**
  - 5 cm/s
  - 10 cm/s
  - 15 cm/s

- **Ts Lung**
  - 10 cm/s
  - 15 cm/s
  - 20 cm/s

* denotes significant difference between conditions.

Do lower learning and memory scores correlate to inflammatory cytokines?

Do repeat lung infections worsen cognitive score?

**TNFalpha**

- **Ctl Lung**
  - 20 pg/mg tissue
  - 40 pg/mg tissue
  - 60 pg/mg tissue

- **Ts Lung**
  - 60 pg/mg tissue
  - 40 pg/mg tissue
  - 20 pg/mg tissue

**IL-1b**

- **Ctl Lung**
  - 10 pg/mg tissue
  - 20 pg/mg tissue
  - 30 pg/mg tissue

- **Ts Lung**
  - 60 pg/mg tissue
  - 40 pg/mg tissue
  - 20 pg/mg tissue

* denotes significant difference between conditions.
Take Home Messages

Individuals with DS are significantly challenged by infectious lung disease
  Post-influenza state of susceptibility to severe bacterial lung infection
  Chronic respiratory infection linked to myositis/myopathy, myocarditis, CNS inflammation

Infectious lung disease likely impacts cognition
  Reducing burden in DS would greatly improve QOL
  Reducing burden in DS may preserve cognition

The future is BRIGHT!! Great things have happened, and MUCH more is on the way
  ex: Amniotic fluid stem cells “trained” to patch congenital heart defects-submit July 23rd
  ex: Autoimmunity and Lung Disease
Many Thanks
Kelley Colvin
Persons with DS and their families
Support
Global
Sie Center
Crnic Institute
Funding