GLOBAL
DOWN SYNDROME FOUNDATION®

Take a Deep Breath: Lung Infection & Cognition in Down Syndrome

Global Down Syndrome Foundation's Webinar Series

Welcome by: Michelle Whitten,
Presentation by: Dr. Michael Yeager

Tuesday, January 29th, 2019

Global Down Syndrome Foundation
A Unique Affiliate Model!

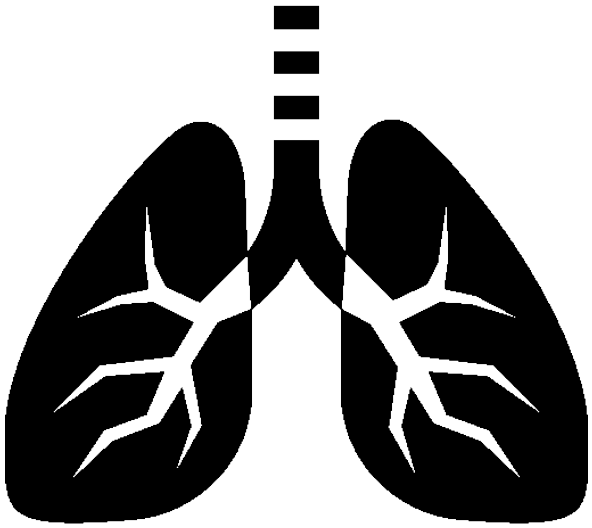
The Global Down Syndrome Foundation is part of a network of affiliate organizations that work closely together on a daily basis to deliver on our mission, vision, values, and goals:

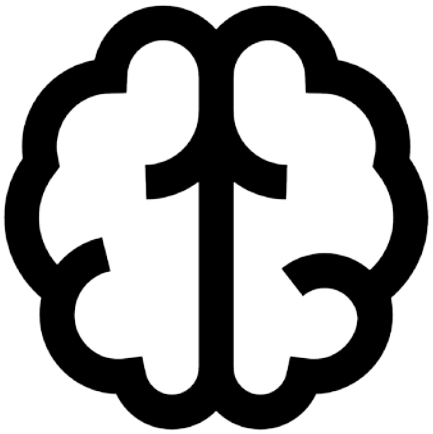
Global & Affiliates

- **Global:** was established as a 501(c)3 in 2009 and is "Dedicated to significantly improving the lives of people with Down syndrome through Research, Medical Care, Education, and Advocacy"

- **Affiliates are:**
  - Established with a lead gift from Anna & John J. Sie Foundation
  - Must work closely together to benefit people with Down syndrome
  - Must be self-sustaining financially

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





Michael E. Yeager
Pediatrics-Cardiology; Bioengineering

LINDA CRNIC INSTITUTE for DOWN SYNDROME

Disclosure

Our lab has received funding from the following:

- **American Heart Association**
- **Celgene, Inc.**
- **Global Down Syndrome Foundation**
- **Jayden DeLuca Foundation**
- **Jerome LeJeune Foundation**
- **Linda Crnic Institute for Down Syndrome**

Disclosure

My younger sister, Ms. Amy Yeager

Morbidity and Mortality in Persons with Down Syndrome Manifests Predominantly as Infectious Lung Disease

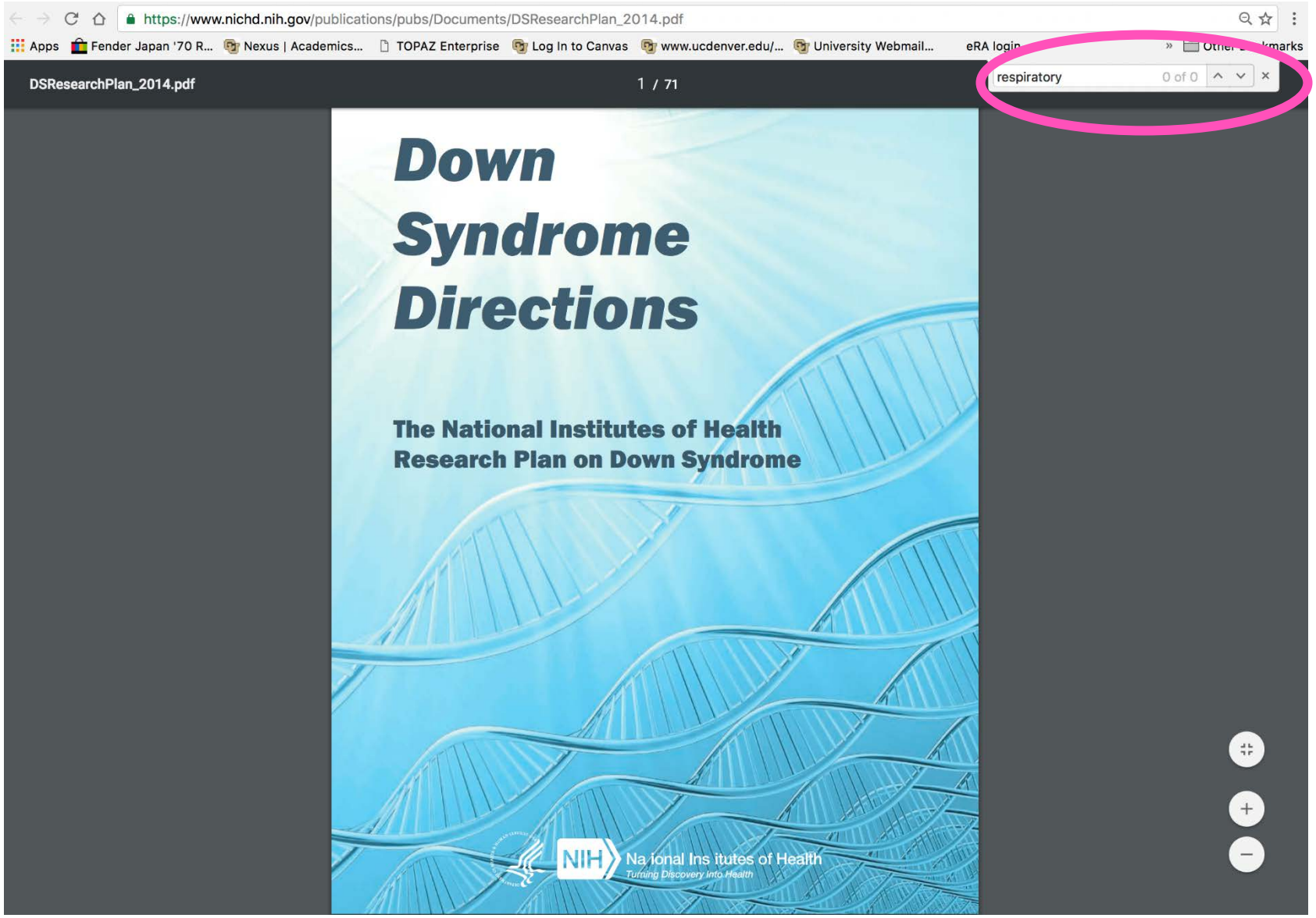
TABLE II. Main and Contributing Causes of Death (%) Over Three Time Periods (1969–1979, 1980–1990, and 1991–2003) in Individuals With Down Syndrome, Divided into Two Age Groups (<1 year, 1-year) and Levels of Significance for Changes Between the Periods 1969–1979 and 1991–2003 (Percentages Will not Add to 100% Since Each Individual Can Have Multiple Diagnoses)

	P1		P2		P3			P1 vs. P3	
	1969–1979		1980–1990		1991–2003		1969–2003	*P*<	*P*<
Age	**<1 year**	**1 year**	**<1 year**	**1 year**	**<1 year**	**1 year**	**All**	**<1 year**	**1 year**
Infectious diseases (incl. pneumonia)	38.3	54.3	27.6	52.0	30.0	57.1	51.2	NS	NS
Pneumonia	31.0	44.0	7.6	41.7	7.1	48.7	40.9	0.001	NS
Congenital heart malformations	74.3	34.6	75.2	26.1	51.4	11.3	29.4	0.001	0.001
Circulatory disease	2.3	17.3	16.2	20.6	35.7	33.3	24	0.001	0.001
Dementia	0.0	0.3	0.0	6.6	0.0	23.3	11.2		0.001
Epilepsy/seizures	0.0	5.9	1.0	9.1	1.4	15.3	9.6	NS	0.001
Atherosclerosis/ischemic heart disease	0.0	6.8	0.0	7.6	0.0	9.7	6.9		NS
Central nervous system disease	0.0	3.2	1.0	7.1	1.4	7.6	5.4	NS	0.004
Gastrointestinal disease	3.4	6.8	3.8	5.6	5.7	4.8	5.2	NS	NS
Malignancies, all	1.7	5.7	1.9	5.3	0.0	2.9	3.7	NS	0.032
Leukemia	1.7	4.3	1.9	3.3	0.0	1.1	2.2	NS	0.001
Solid tumors	0.0	1.4	0.0	2.0	0.0	1.8	1.5		NS
Other congenital malformations	14.9	1.6	11.4	1.8	17.1	0.6	3.5	NS	NS
Number of deaths	175	370	105	394	70	816	1,930		

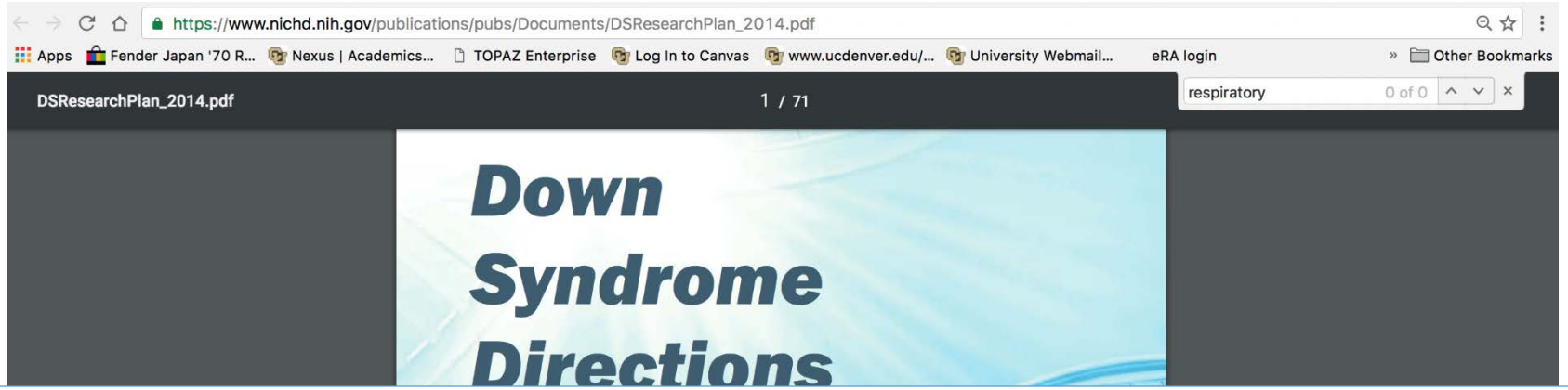
In DS, is the problem the lung, the immune system, or both?

Englund et al, Am J Med Gen 2013

The Lung is Overlooked in DS



The Lung is Overlooked in DS



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,[1] Amir Ghaffari,[1,2] Su Y. Liu,[1,2] John A. Belperio,[4] Genhong Cheng,[1,5] and Jane C. Deng[4]

[1]Department of Microbiology, Immunology and Molecular Genetics, and [2]Medical Scientist Training Program, David Geffen School of Medicine, UCLA, Los Angeles, California, USA. [3]G.W. Hooper Foundation, UCSF, San Francisco, California, USA. [4]Division of Pulmonary and Critical Care Medicine and [5]Molecular Biology Institute, David Geffen School of Medicine, UCLA, Los Angeles, California, USA.

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 Cxcr2, 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.

portant Mediator of the Enhanced Susceptibility al Pneumonia after Influenza Infection

luijs,*†‡ Leontine J. R. van Elden,¶ Monique Nijhuis,¶ Rob Schuurman,¶ drine Florquin,§ Michel Goldman,‖ Henk M. Jansen,† René Lutter,†‡ and

monia is a serious complication during and shortly after influenza infection. We established a mouse pneumococcal pneumonia and evaluated the role of IL-10 in host defense against *Streptococcus* om influenza infection. C57BL/6 mice were intranasally inoculated with 10 median tissue culture (A/PR/8/34) or PBS (control) on day 0. By day 14 mice had regained their normal body weight and om the lungs, as determined by real-time quantitative PCR. On day 14 after viral infection, mice *oniae* (serotype 3) intranasally. Mice recovered from influenza infection were highly susceptible to eumonia, as reflected by a 100% lethality on day 3 after bacterial infection, whereas control mice and 83% lethality on day 6 after pneumococcal infection. Furthermore, 1000-fold higher bacterial with *S. pneumoniae* and, particularly, 50-fold higher pulmonary levels of IL-10 were observed in in control mice. Treatment with an anti-IL-10 mAb 1 h before bacterial inoculation resulted in nd markedly reduced lethality during secondary bacterial pneumonia compared with those in IgG1 ild self-limiting influenza A infection renders normal immunocompetent mice highly susceptible to pneumococcal pneumonia. This increased 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.

Observed in DS?

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

eLIFE
elifesciences.org

SHORT REPORT

Trisomy 21 consistently activates the interferon response

Kelly D Sullivan[1,2,3,4*], Hannah C Lewis[1,2], Amanda A Hill[1,2], Ahwan Pandey[1,2,3,4], Leisa P Jackson[1,3,4], Joseph M Cabral[1,3,4], Keith P Smith[1], L Alexander Liggett[1,5], Eliana B Gomez[1,3,4], Matthew D Galbraith[1,2,3,4], James DeGregori[1,5,6,7,8,9], Joaquín M Espinosa[1,2,3,4*]

Toll-like receptors

Immune suppression IL-10/TGF-beta

Respiratory commensal bacteria

J. theor. Biol. **86,** 603–606

LETTER TO THE EDITOR

Interferon Action and Chromosome 21 Trisomy

Hypothesis

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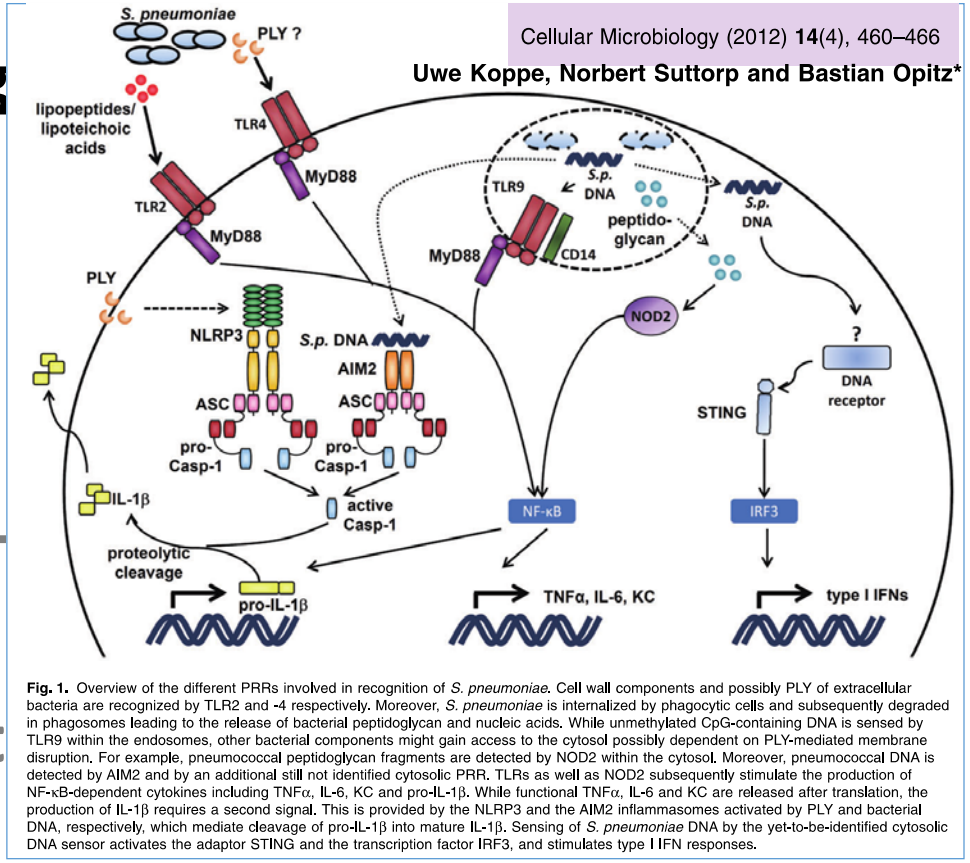
Strong

Interferonopathy

Toll-like receptors

Immune suppression IL-10/T

Respiratory commensal bact



Cellular Microbiology (2012) **14**(4), 460–466

Uwe Koppe, Norbert Suttorp and Bastian Opitz*

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-κB-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 IRF3, and stimulates type I IFN responses.

Hypothesis

In persons with DS, the lung is in a chronic state of susceptibility t

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Interferonopathy

Toll-like receptors

Immune suppressi

Respiratory comm

2014

nature publishing group

Clinical Investigation | **Articles**

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

Chantal J.M. Broers[1], Reinoud J.B.J. Gemke[1], Servaas A. Morré[2,3], Michel E. Weijerman[1] and Anne Marceline van Furth[4]

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 4×10^7 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.

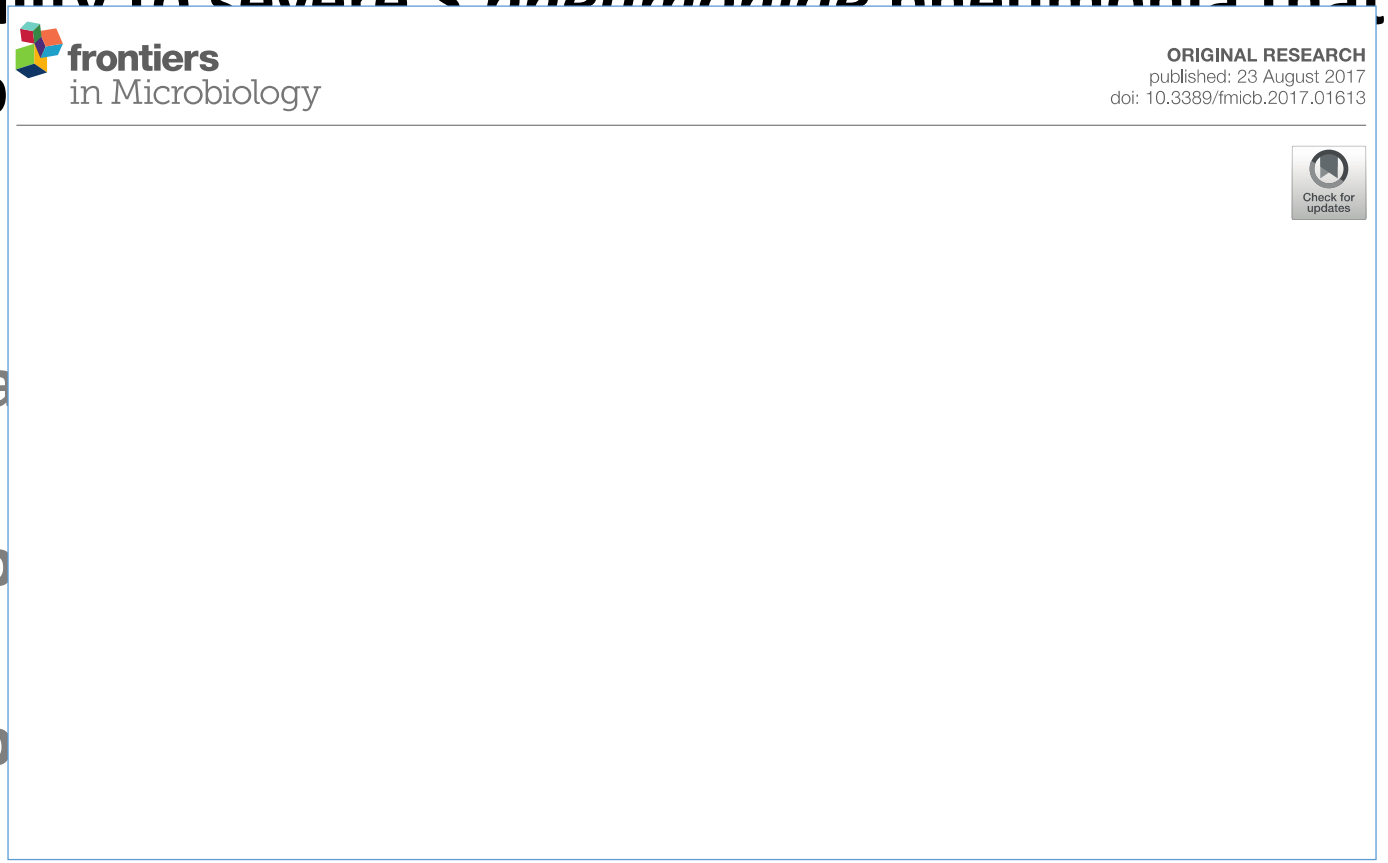
RESULTS: Children with DS show an increased IL-10 production upon stimulation with *S. pneumoniae* compared to their healthy siblings. At most time points, no significant differences were seen in cytokine production upon stimulation with LPS.

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

and the adaptive immunity are reported in DS, for example, mannan-binding lectin deficiency (13), a high number of pro-inflammatory $CD14^{dim}CD16^{+}$ monocytes (14), changes in T- and B-lymphocyte counts (15–17), early aging of the immune system (18,19), an intrinsic defect of T and B lymphocytes (16,20,21), IgG2 and IgG4 subclass deficiencies (16,17,21–24), impaired antibody response to pneumococcal vaccine (25), and diminished invariant natural killer T cells (14,17) and regulatory T cells (17). These lower RTIs in DS children are most often caused by viral pathogens, such as respiratory syncytial virus. This 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

Hypothesis

In persons with DS, the lung is in a chronic state of susceptibility to severe *S. pneumoniae* pneumonia that phenocop



Interferonopa

Toll-like recep

Immune supp

Respiratory commensal bacteria is different

Post-Influenza-Like Lung in Down Syndrome?

Post-influenza, non-DS		DS
✓	Fulminant Remodeling	?
✓	Platelet Activating Factor Receptor (PAFR)	?
✓	IFN signaling increase	✓
✓	IL-10 signaling increase	?
✓	TLR down	?
✓	Immune cell dysfunction	✓

Post-Influenza-Like Lung in Down Syndrome?

Organ

Subpleural cysts

Pulmonary hypoplasia

Congenital heart defects

Tissue

Cells

Fig. 5 Respiratory syncytial virus bronchiolitis. Anteroposterior radiograph of the chest in a 14-month-old girl with Down syndrome shows symmetrical hyperinflation of the lungs, streaky perihilar opacities and other focal right upper lobe opacities. The girl was diagnosed with respiratory syncytial virus (RSV) bronchiolitis

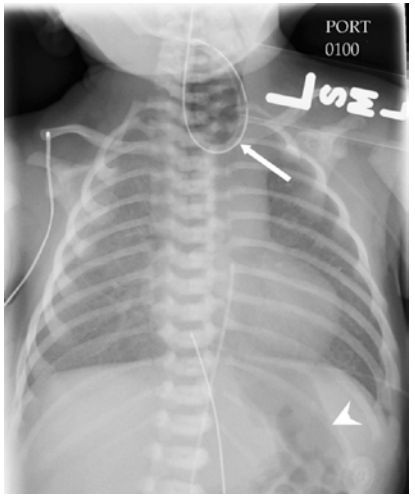


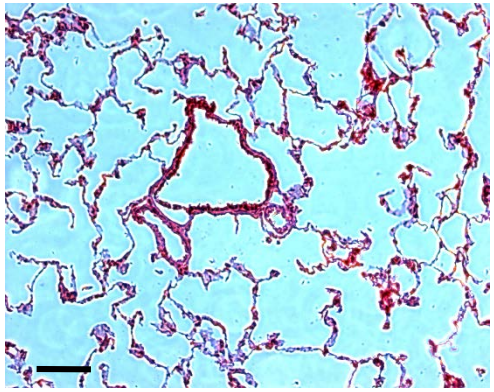
Fig. 3 Tetralogy of Fallot and esophageal atresia/tracheoesophageal fistula. Anteroposterior chest radiograph in a newborn boy shows that the heart has a boot-shaped contour with an upturned apex compatible with a diagnosis of tetralogy of Fallot. A nasoenteric tube is coiled in the upper esophageal 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

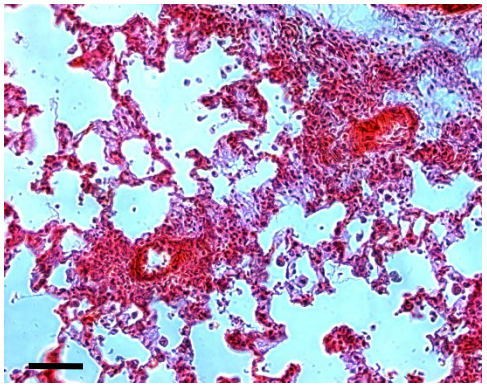
Radhakrishnan et al, Pediatr Radiol 2014

Post-Influenza-Like Lung in Down Syndrome?

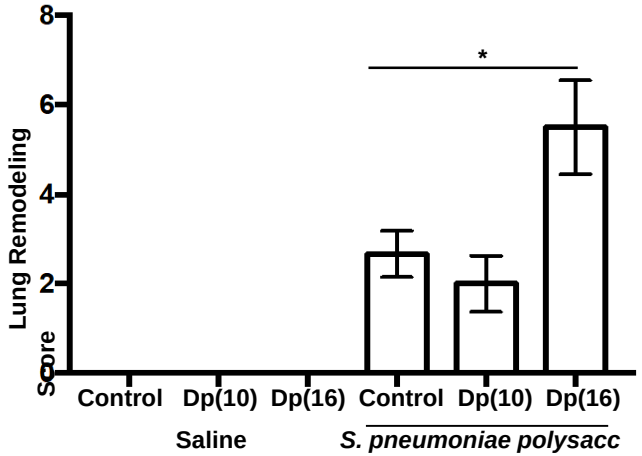
Organ | **Tissue** | **Cells**



Saline



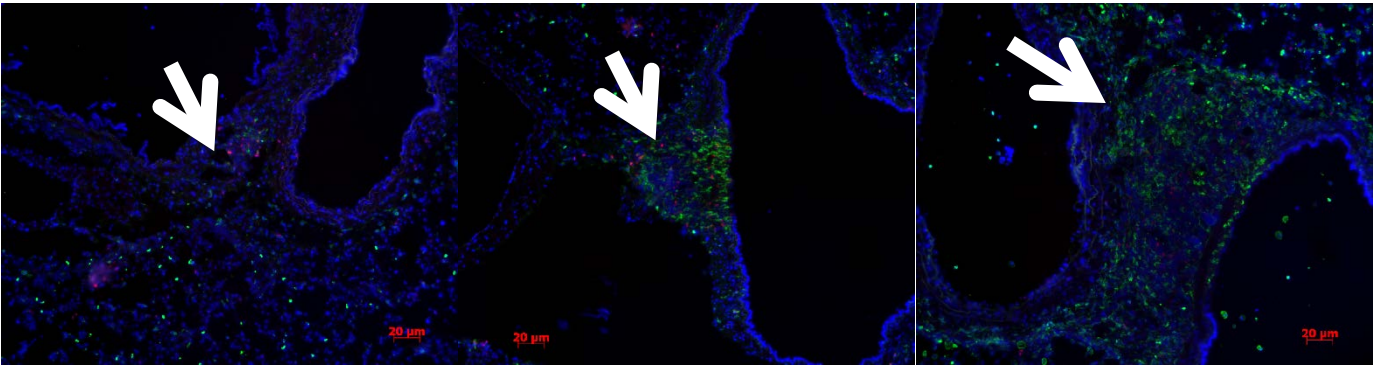
S. pneumoniae polysacc

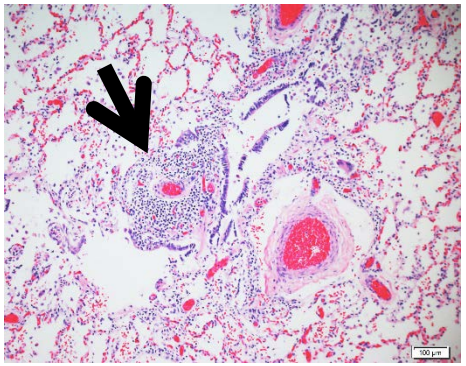


B

Green = CD15 Blue = DAPI (nuclei)

Hematoxylin & Eosin





Control Dp(10) Dp(16) DS

C

Post-Influenza-Like Lung in Down Syndrome?

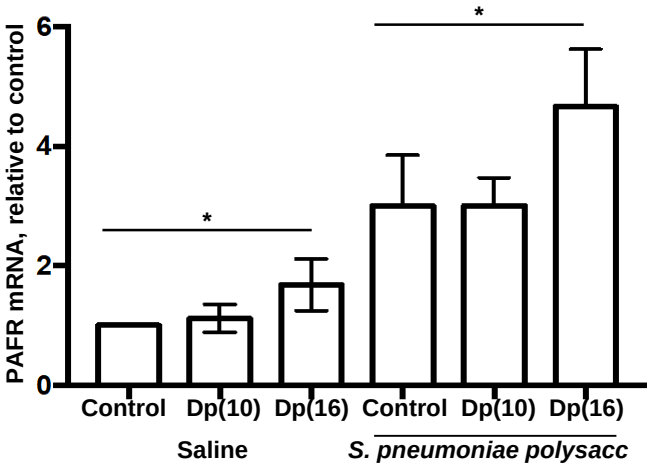
Organ | **Tissue** | Cells

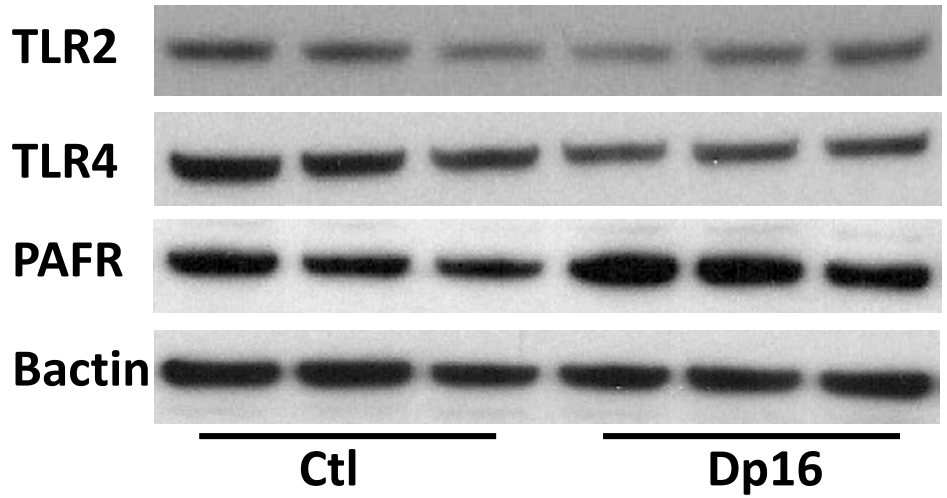
Increased PAFR facilitates increased S. pneumo adhesion

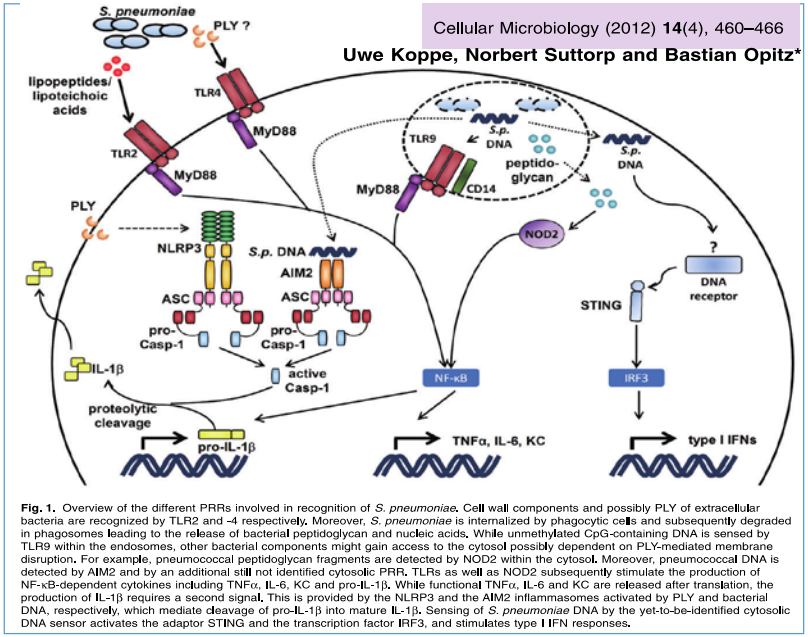
Involvement of the platelet-activating factor receptor in host defense against *Streptococcus pneumoniae* during postinfluenza pneumonia

Koenraad F. van der Sluijs,[1,2,3] Leontine J. R. van Elden,[4] Monique Nijhuis,[4] Rob Schuurman,[4] Sandrine Florquin,[5] Takao Shimizu,[6] Satoshi Ishii,[7] Henk M. Jansen,[2] René Lutter,[2,3] and Tom van der Poll[1]

[1]*Laboratory of Experimental Internal Medicine,* [2]*Department of Pulmonology,* [3]*Laboratory of Experimental Immunology,* [5]*Department of Pathology, Academic Medical Center, University of Amsterdam, Amsterdam;* [4]*Eijkman-Winkler Institute, Department of Virology, University Medical Center, Utrecht, The Netherlands;* [6]*Department of Biochemistry and Molecular Biology, Faculty of Medicine, The University of Tokyo; and* [7]*CREST of Japan Science and Technology Corporation, Tokyo, Japan*







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Post-Influenza-Like Lung in Down Syndrome?

Organ

Tissue
Lung stains

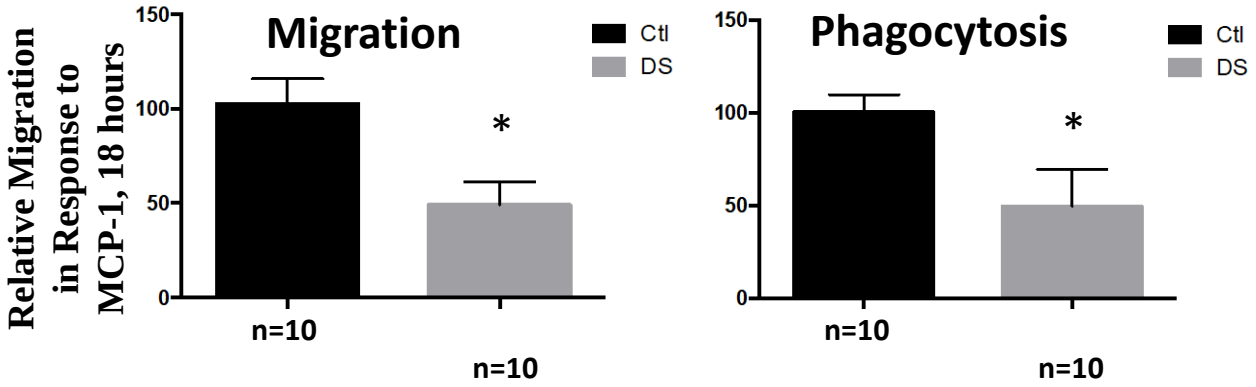
Cells

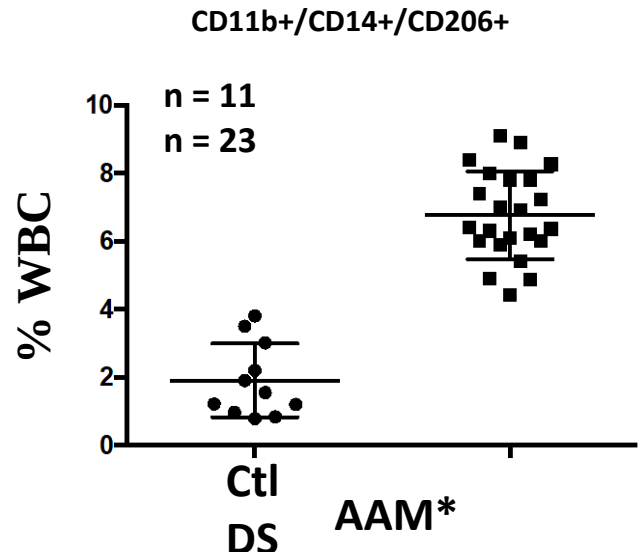
Human
Peripheral blood

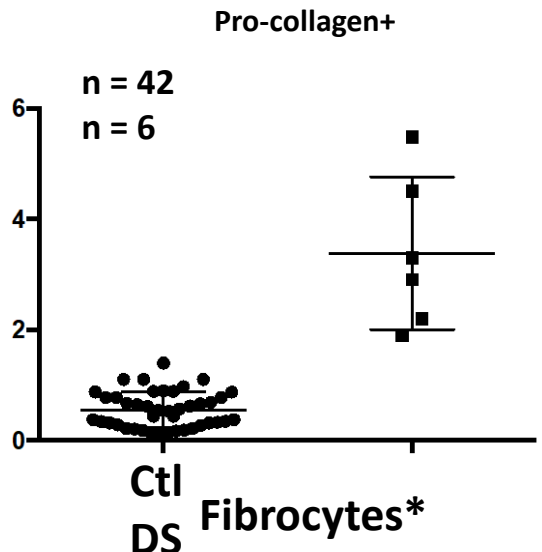
Fibroblasts

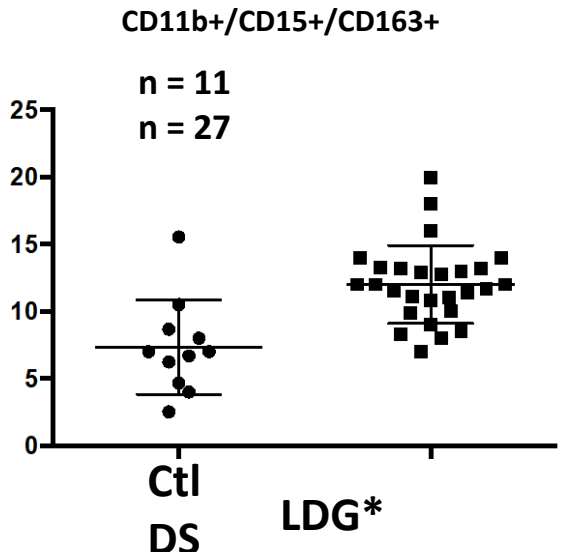
Dp16
PB/BALF

Lung Cells

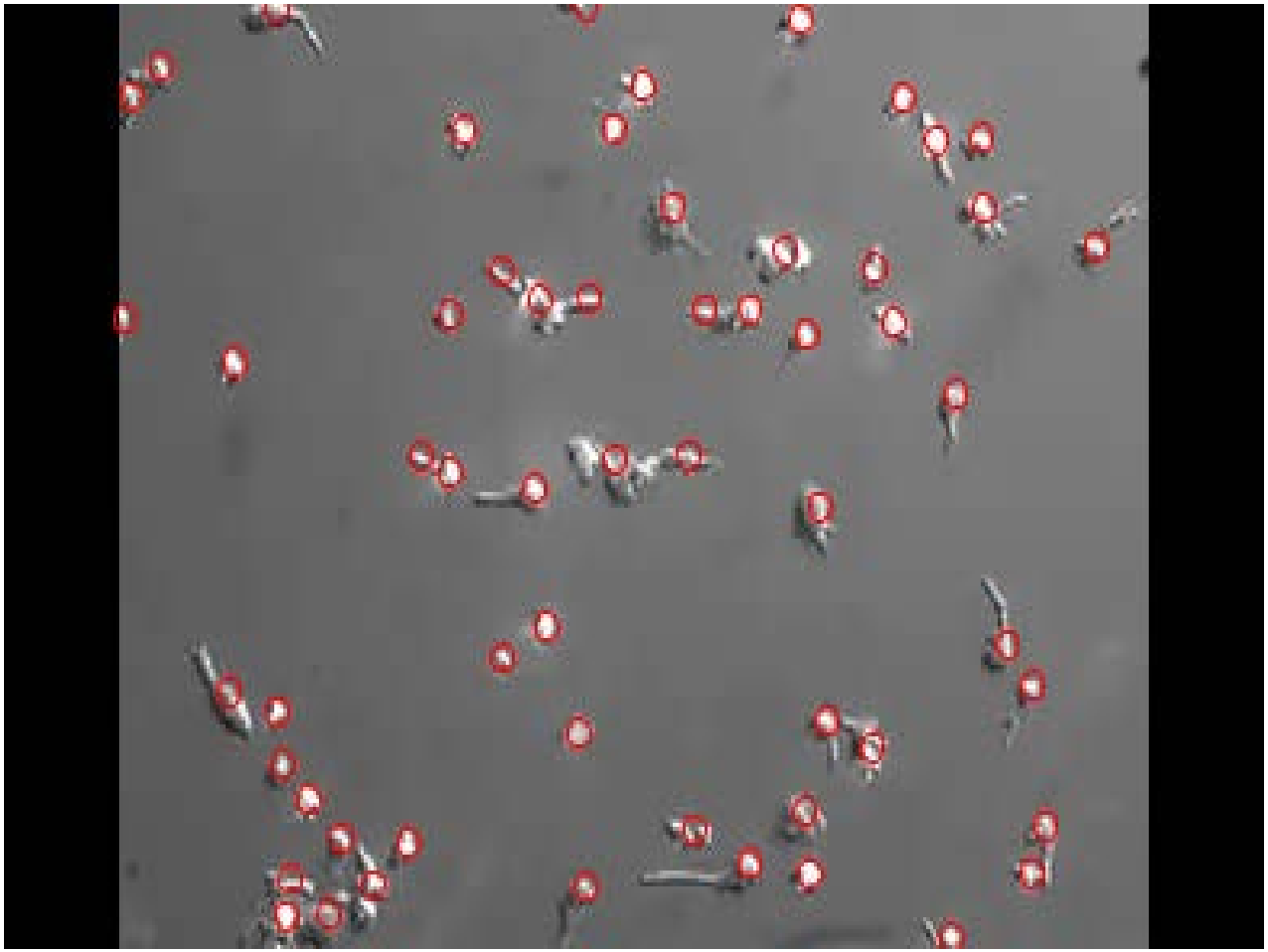








Cell/Individual particle tracking Icy



Post-Influenza-Like Lung in Down Syndrome?

Organ

Tissue

Lung stains

Cells

Human

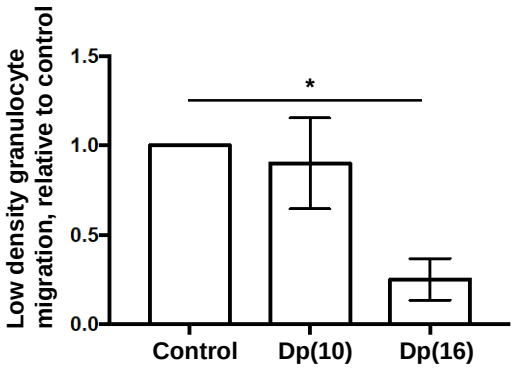
Peripheral blood

Fibroblasts

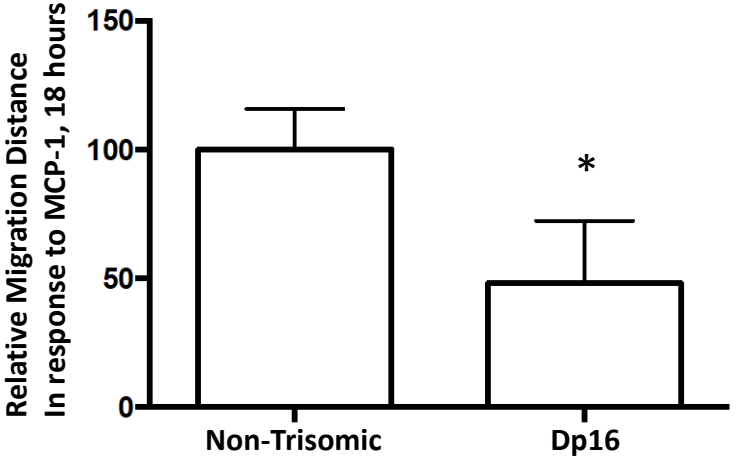
Dp16

PB/BALF

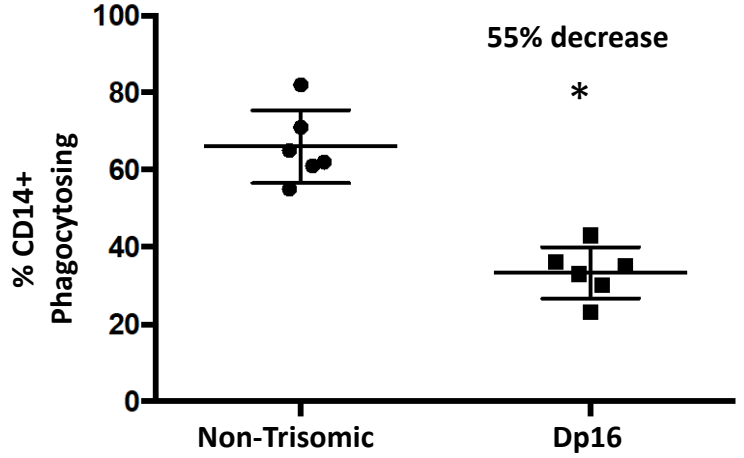
Lung Cells



Migration



Phagocytosis



Post-Influenza-Like Lung in Down Syndrome?

Post-influenza, non-DS		DS
✓	Fulminant Remodeling	✓
✓	PAFR	✓
✓	IFN signaling increase	✓
✓	IL-10 signaling increase	✓
✓	TLR down	✓
✓	Immune cell dysfunction	✓

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

Child: care, health and development

Original Article

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

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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 (RRTI)

	RRTI⁺	RRTI⁻	Total	Chi-squared test
	n (%)	*n* (%)	*n* (%)	*P*-value
Male	85 (57)	84 (48)	169 (51)	NS
Female	64 (43)	92 (52)	156 (49)	
Age at inclusion* (mean, range and SD in years)	8.14 (7.8–8.8) ± 0.14	8.15 (7.8–9.1) ± 0.16	8.14 (7.8–9.1) ± 0.15	
School attendance				
Ever attended regular education	99 (30)	142 (44)	241 (74)	0.003
Regular education attendance at inclusion	65 (2[illegible])	[illegible] (28)	[illegible] (4[illegible])	NS
Pre-school (*normally age 4–5 years*)	21 (32)†	11 (12)	31 (20)	0.018
First grade (*normally age 6 years*)	33 (51)†	62 (67)	95 (61)	0.010
Second grade (*normally age 7 years*)	11 (7)†	[illegible] (21)	[illegible] (1[illegible])	NS
Level of parental education				
Primary or secondary education	24 (7)	31 (10)	55 (17)	NS
Higher secondary education	55 (17)	63 (19)	118 (36)	NS
University education	70 (22)	82 (25)	152 (47)	NS
Being breastfed (>1 month)	57 (18)	60 (18)	117 (36)	NS
Siblings	140 (43)	170 (52)	310 (95)	NS
Childcare (age <4 years)	142 (44)	160 (49)	302 (93)	NS
Additional morbidity‡				
Congenital heart disease	73 (49)	64 (36)	137 (42)	0.022
Diagnosis of asthma	28 (19)	6 (3)	34 (10)	<0.001
Gastrointestinal disease	26 (17)	19 (11)	45 (14)	NS
Eye disease	77 (52)	81 (46)	158 (49)	NS
Impaired hearing	66 (44)	32 (18)	98 (30)	<0.001
Thyroid dysfunction	19 (13)	20 (11)	39 (12)	NS
Diabetes mellitus	1 (<1)	2 (1)	3 (1)	NS
Other morbidity, not specified	43 (29)	38 (22)	81 (25)	NS

*There was no significant difference in age between both groups determined by a *t*-test.
†Percentage out of all children attending regular education.
‡Parental reported morbidity.
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)

	RRTI⁺		RRTI⁻		Regression coefficient† (β)	Effect size‡ (f^2)
	Total (n = 130)	Male (n = 75) Female (n = 55)	Total (n = 140)	Male (n = 69) Female (n = 71)		
Verbal	33.06 (19.13)§	29.64 (19.96) 37.47 (17.18)	40.68 (16.18)	37.09 (15.72) 44.11 (16.08)	−7.33**	0.04
Perceptual performance	26.76 (16.58)	21.80 (15.84) 33.33 (15.43)	32.34 (14.90)	28.83 (14.87) 35.93 (14.20)	−5.67**	0.03
Quantitative	9.44 (6.80)	7.86 (6.46) 11.44 (6.75)	12.22 (6.57)	10.46 (6.75) 13.93 (5.99)	−2.61**	0.04
Memory	10.74 (7.77)	9.27 (7.69) 12.64 (7.53)	13.94 (7.37)	11.77 (6.31 16.10 (7.77)	−3.12**	0.04
Motor	23.23 (12.57)	20.03 (12.64) 27.47 (11.32)	27.67 (11.78)	24.99 (11.51) 30.25 (11.62)	−4.63**	0.04
General cognitive score	69.30 (40.25)	59.36 (40.22) 82.29 (36.84)	85.24 (34.43)	76.35 (33.60)	−15.59**	0.04
Developmental age (SD in months)	3 years 8 months (10.91)	3 years 6 months (10.53) 3 years 11 months (10.66)	4 y (			

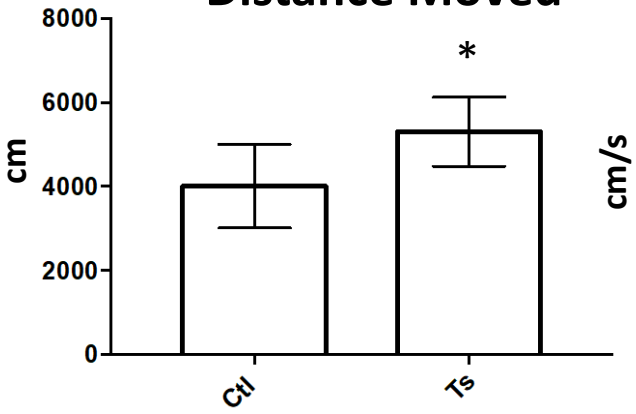
Lower scores indicate more impaired development.
*P < 0.05; **P < 0.01; ***P < 0.001.
†β = unstandardized regression coefficient of the effect of RRTI, correcting f
(>1 month), siblings, gender, congenital heart defect, diagnosis of asthma, gast
‡Effect size (f^2): small effect (0.01–0.10), moderate effect (0.10–0.33) and large
§Mean scores are presented with standard deviation between brackets.
RRTI⁺, children with recurrent respiratory tract infections; RRTI⁻, children witho

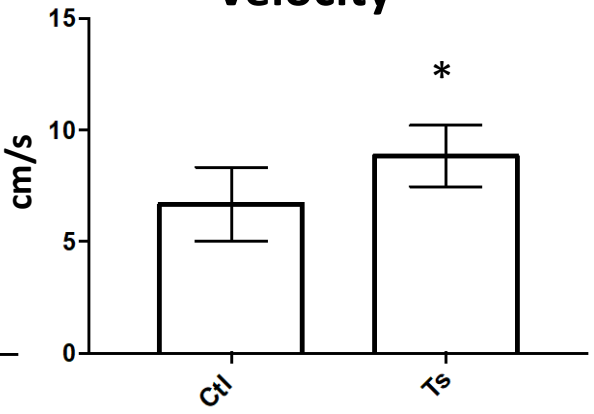
Key messages

- 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

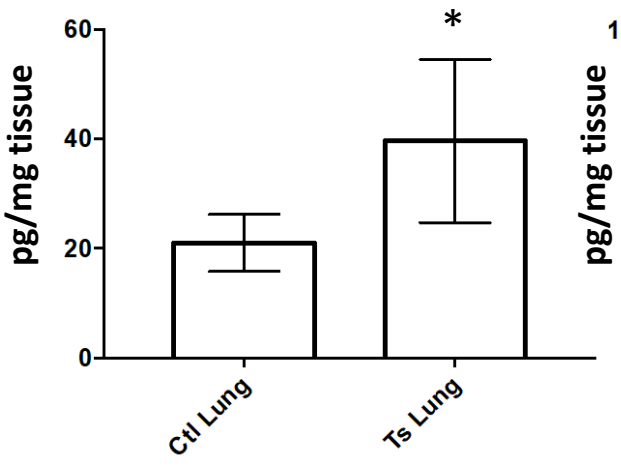
Cognitive Assays in Dp16 mice

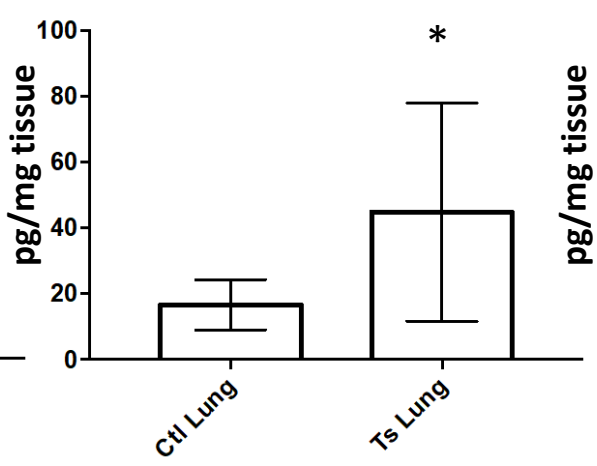


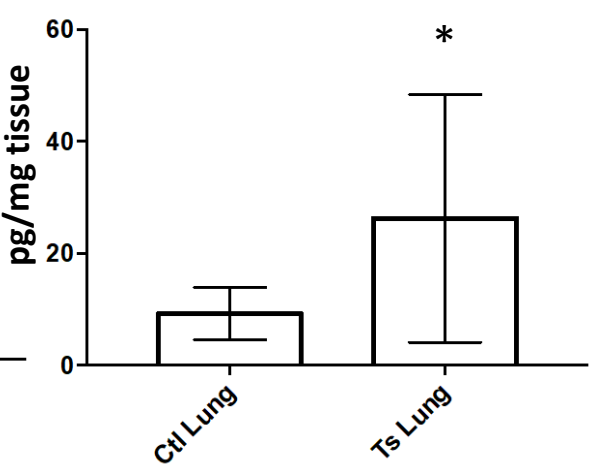


Do lower learning and memory scores correlate to inflammatory cytokines?

Do repeat lung infections worsen cognitive score?







Take Home Messages

Individuals with DS are significantly challenged by infectious lung disease

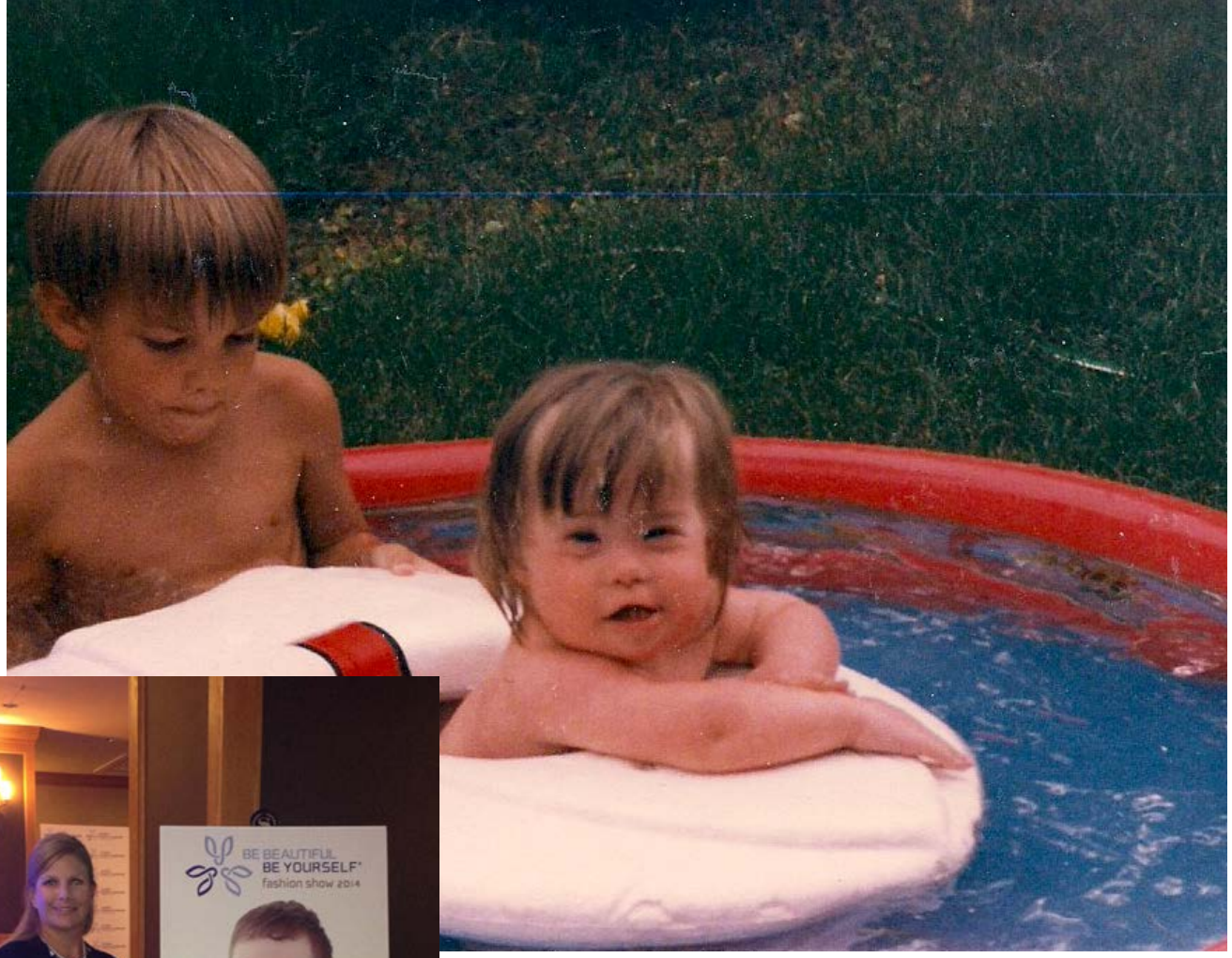
- **Post-influenza state of susceptibility to severe bacterial lung infection**
- **Chronic respiratory infection linked to myositis/myopathy, myocarditis, CNS inflammation**

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

LINDA CRNIC INSTITUTE for DOWN SYNDROME

FONDATION Jérôme Lejeune chercher, soigner, défendre

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