

# Immune modulation in Down syndrome and COVID-19

**Joaquín M. Espinosa, PhD**

Executive Director

Linda Crnic Institute for Down Syndrome

Professor of Pharmacology

University of Colorado School of Medicine

Anschutz Medical Campus



School of Medicine  
UNIVERSITY OF COLORADO  
ANSCHUTZ MEDICAL CAMPUS



LINDA CRNIC INSTITUTE  
*for* **DOWN SYNDROME**



**GLOBAL**  
DOWN SYNDROME FOUNDATION\*



Children's Hospital Colorado  
\* Anna and John J. Sie Center for Down Syndrome



**DENVER**  
**HEALTH.**  
— est. 1860 —  
FOR LIFE'S JOURNEY



Alzheimer's and Cognition Center  
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

**What do Down syndrome and  
COVID19 have in common?**

**Can the study of Down syndrome  
help us understand COVID19 and vice versa?**

**Both conditions involve 'hyperinflammation'**

**Similar immune-modulatory strategies  
could potentially benefit both,  
individuals with Down syndrome  
and COVID19 patients**

# What is a cytokine storm?

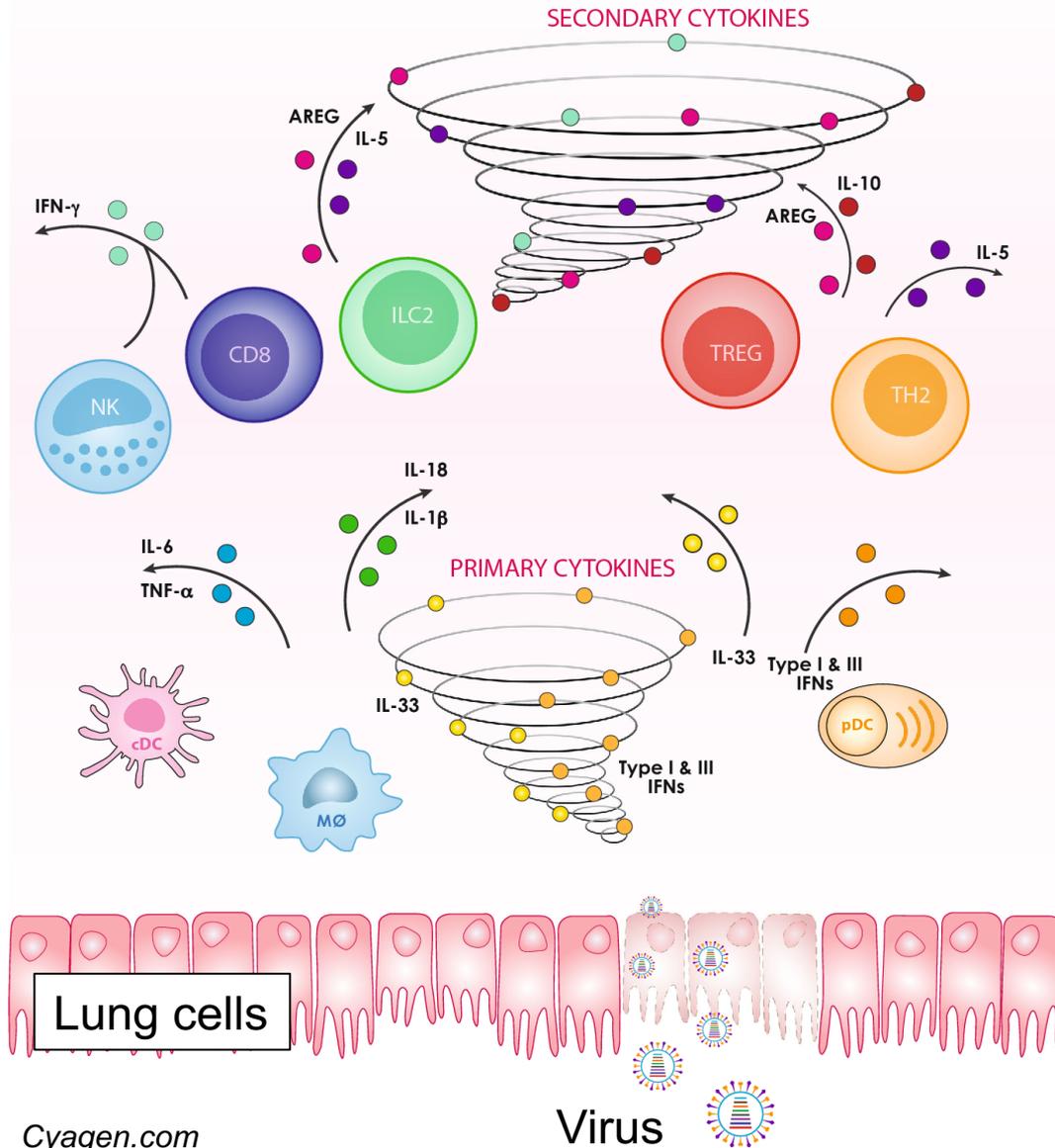
A cytokine storm refers to an over-reaction of the immune system, leading to high levels of inflammatory proteins known as 'cytokines'

This overload of cytokines can damage organs such as the lung, heart, kidneys and liver, eventually leading to organ failure.

The cytokine storm caused by the SARS-CoV-2 virus is associated with the severity of COVID19 symptoms



# Cytokine storms during lung viral infections



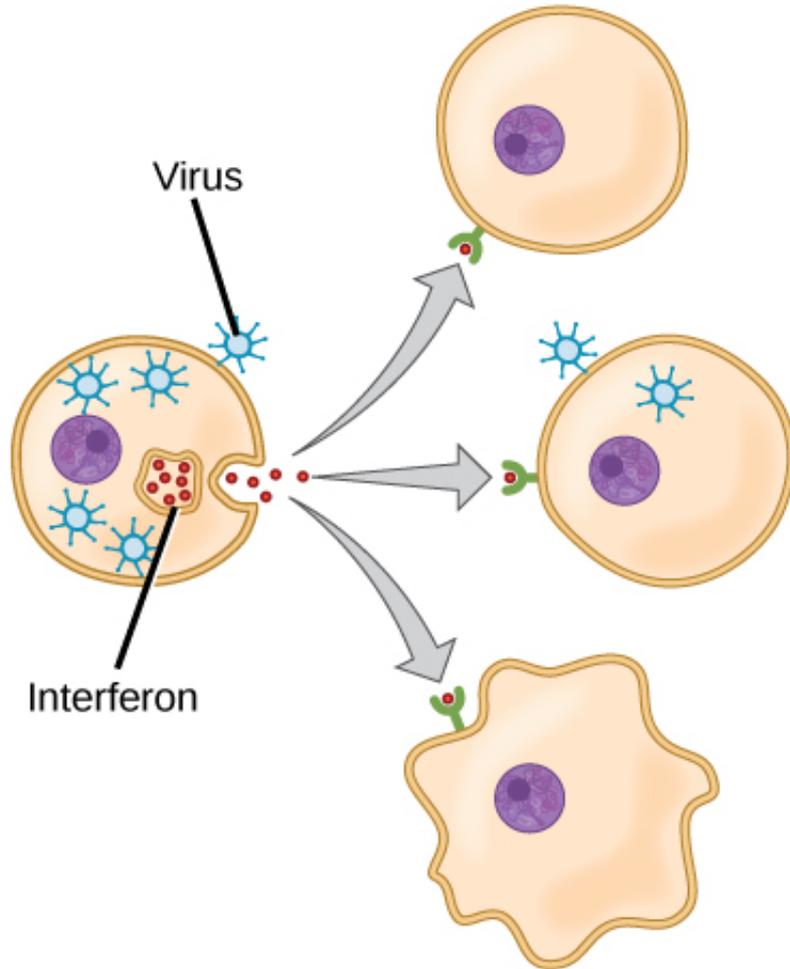
Lung epithelial cells are 'first responders', producing 'primary cytokines' such as Type I and III Interferons (IFNs).

A first wave of immune activation involves immune cells known as macrophages and dendritic cells (DCs), which produce other primary cytokines, such as IL-6, TNF- $\alpha$ , and IL-1 $\beta$ .

A second wave of immune activation involves additional immune cells, such as NK cells and various types of T cells (CD8, helpers, Tregs), which in turn produce yet more cytokines, such as IFN- $\gamma$ , IL-10, and others.

Eventually, dozens of cytokines are induced.

# Trisomy 21 activates the Interferon response



People with Down syndrome show a hyperactive 'Interferon response'

The Interferon response is a key aspect of the immune system that 'interferes' with viral infections

The Interferon response acts throughout the entire human body

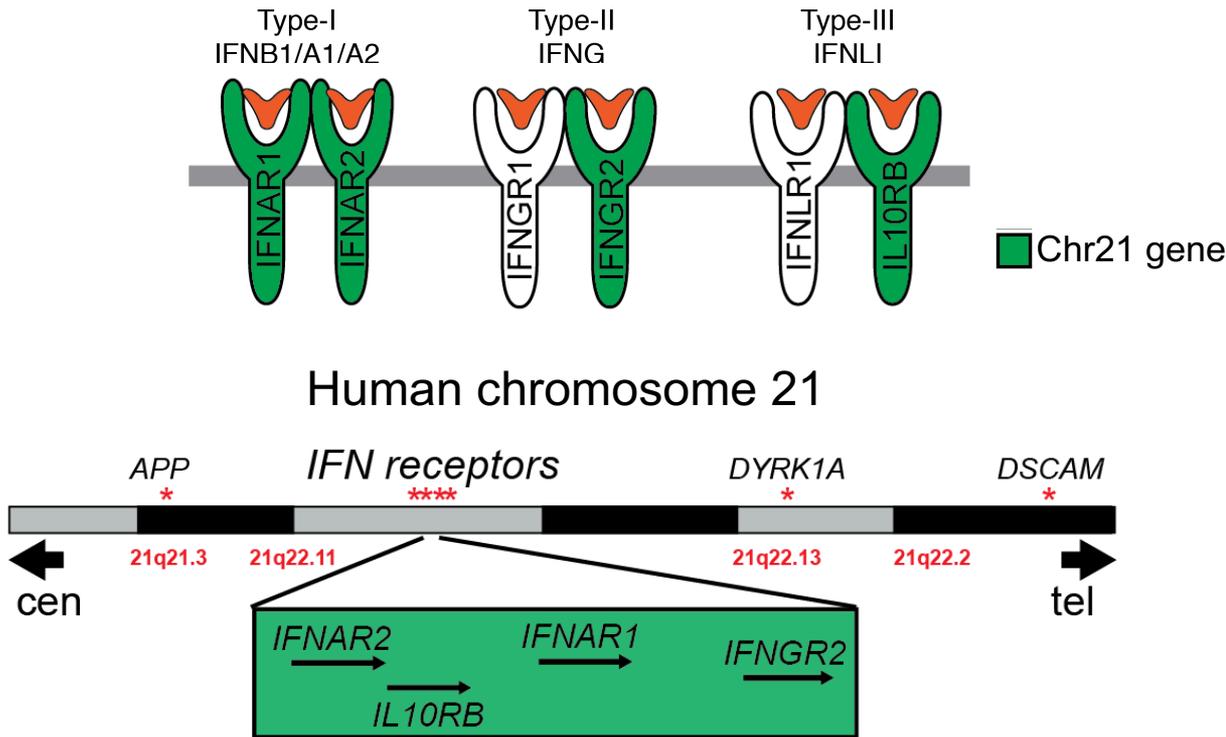
Without an Interferon response, we would probably die within days of a common viral infection

Too much Interferon response is known to cause autoimmunity which is more common in Down syndrome

People with Down syndrome are *'fighting off'* viruses 24/7, even when there is no virus present

# Trisomy 21 activates the Interferon response

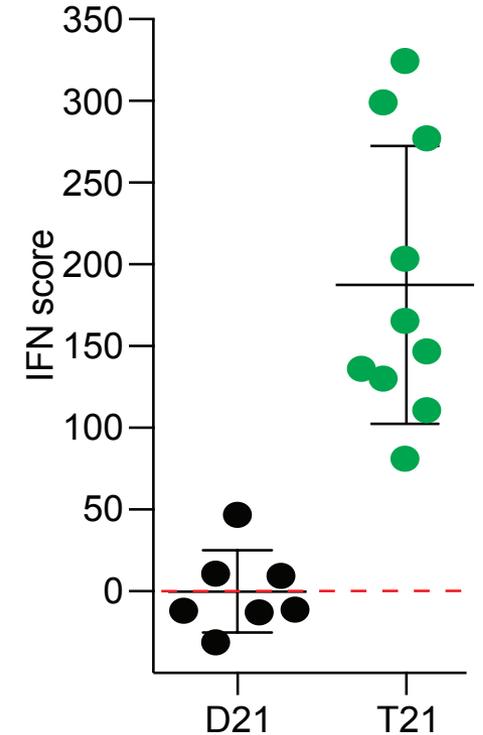
4 of the 6 IFN receptors are encoded on chr21!!



T cells

Type I IFN Score

$p < 0.0001$



D21: typical people  
T21: trisomy 21

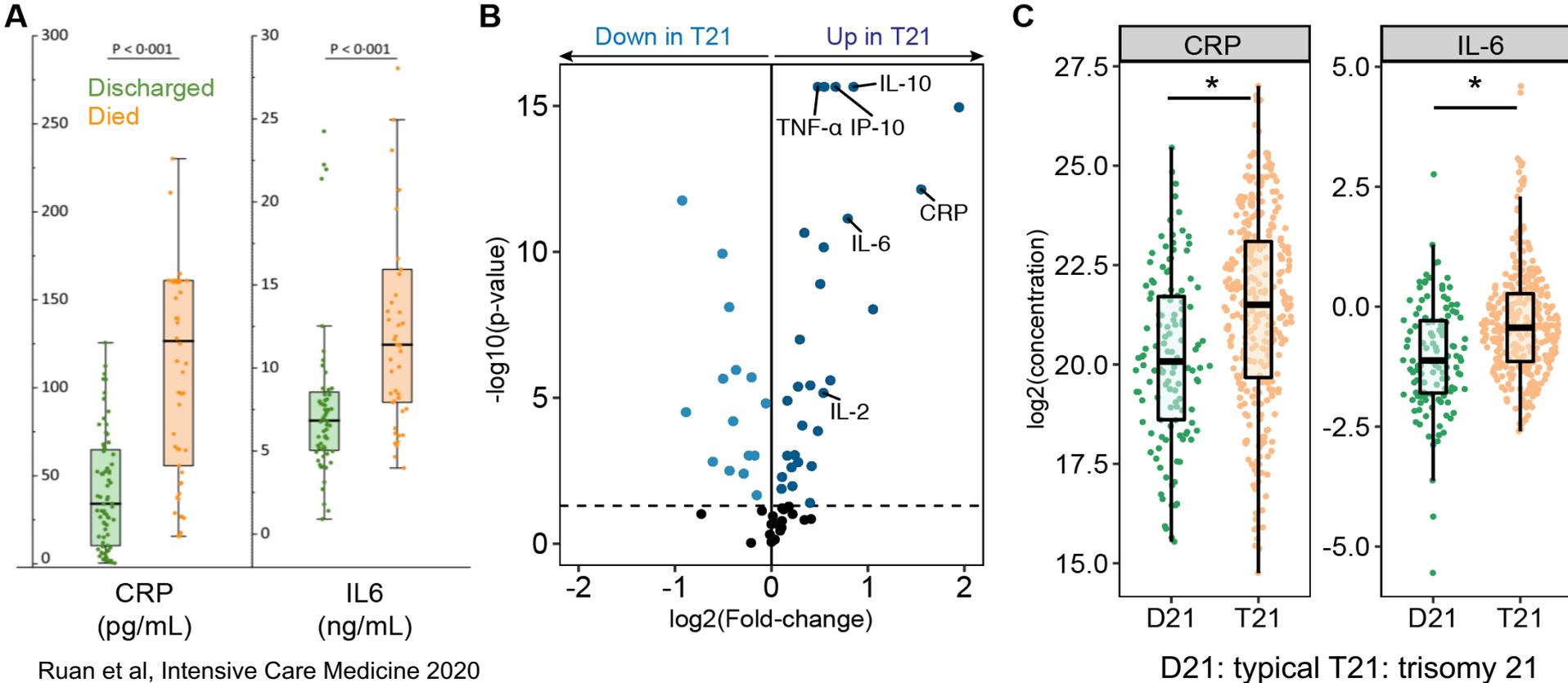
People with Down syndrome show a hyperactive interferon response

# Hyperinflammation is associated with both COVID-19 severity and trisomy 21

Cytokine measurements

COVID19 patients

Healthy individuals with trisomy 21

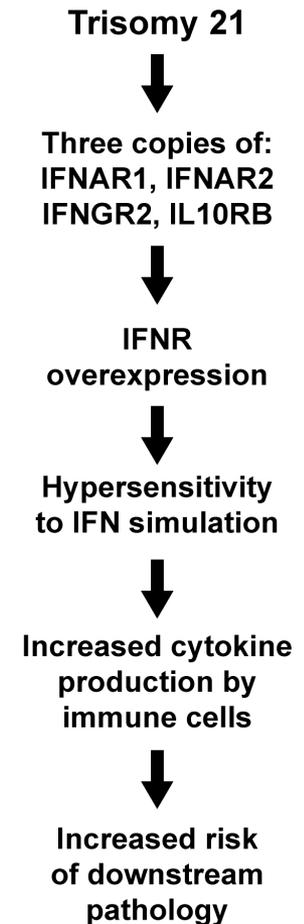
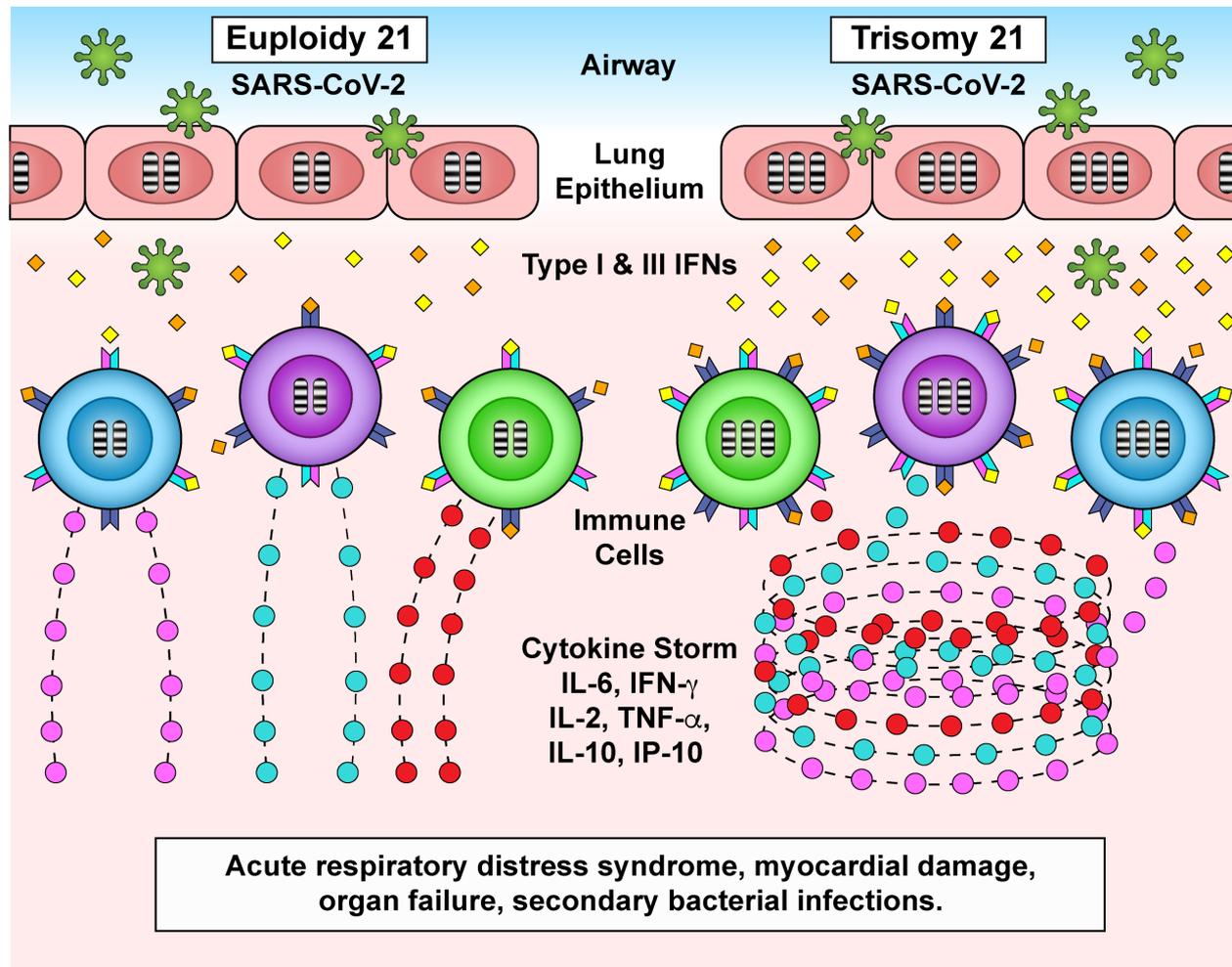


The cytokines associated with high risk of COVID19 are elevated in Down syndrome

Healthy individuals with Down syndrome display a 'mild cytokine storm'

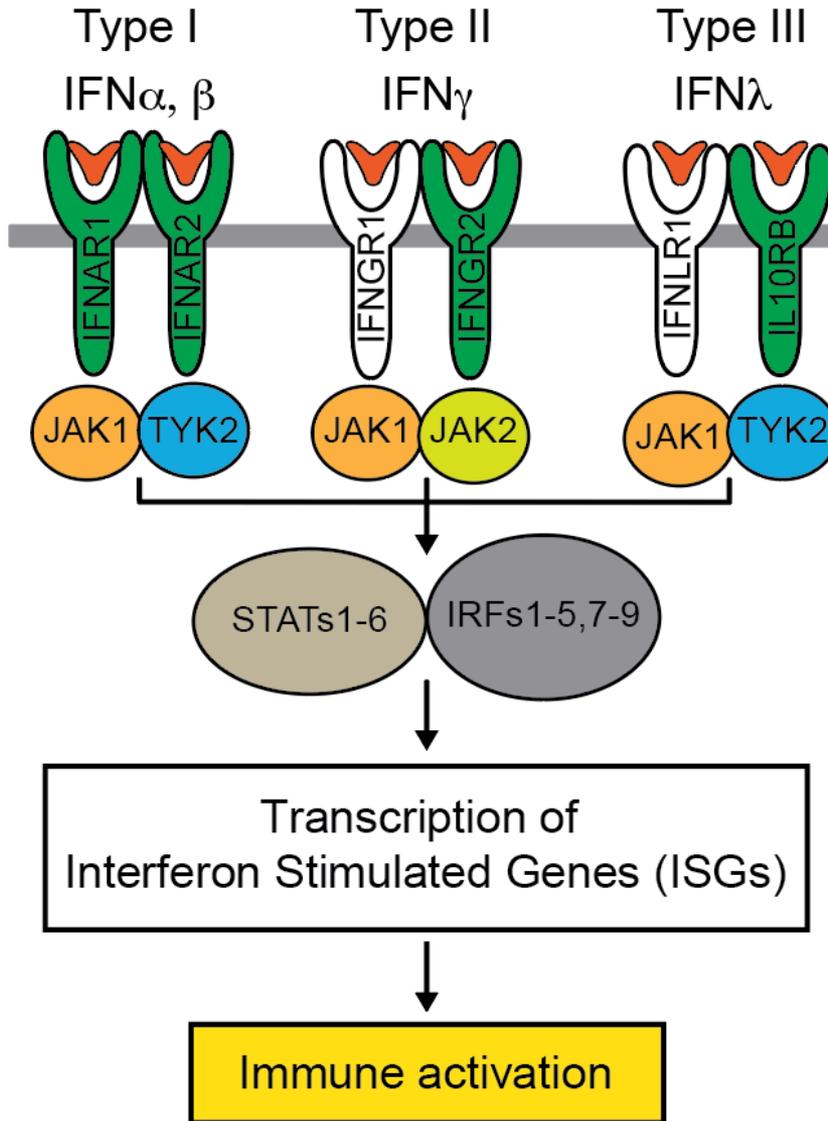
# Is Interferon hyperactivity good or bad during COVID19 in Down syndrome?: **It's bad**

Increased IFN activity is likely to cause stronger cytokine storms, with increased risk of downstream pathology



**Is there a way to tone down the hyperinflammation observed in both COVID19 and Down syndrome?**

# Three types of IFN signaling



All three types of IFN signaling employ 'JAK kinases' for signal transduction.

JAK1 is required for all three types of IFN signaling.

# FDA-approved JAK inhibitors tone down the Interferon response

Company	Marketed Name	Target	Indication
	<b>Jakafi</b> <sup>®</sup> ruxolitinib (tablets)	JAK1&2	Myelofibrosis (2011), polycythemia vera (2011), GVHD (2019)
	<b>XELJANZ</b> <sup>®</sup> [tofacitinib]	JAK1&3	Rheumatoid arthritis (2012), psoriatic arthritis (2017), ulcerative colitis (2018)
	<b>olumiant.</b> (baricitinib) tablets	JAK1&2	Rheumatoid arthritis (2018)
	 <b>RINVOQ</b> <sup>™</sup> upadacitinib 15mg tablets	JAK1	Rheumatoid arthritis (2019)

Also tested in clinical trials for :

- Alopecia areata
- Atopic dermatitis
- Depression
- Hidradenitis suppurativa
- Juvenile idiopathic arthritis
- Leukemia
- Psoriasis
- Vitiligo

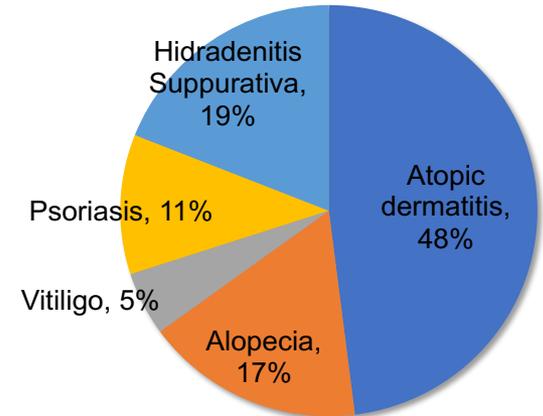
# Using JAK inhibitors to treat alopecia areata in Down syndrome



# The first clinical trial for JAK inhibition in Down syndrome

- For immune-driven skin conditions:

- *Atopic dermatitis*
- *Alopecia areata*
- *Hidradenitis suppurativa*
- *Psoriasis*
- *Vitiligo*



- Treated with the JAK inhibitor Tofacitinib for 4 months
- Safety as the primary endpoint
- While also monitoring:
  - *Markers of immune dysregulation in the blood*
  - *Impacts on other autoimmune conditions*
  - *Impacts on cognition and quality of life*

# JAK inhibition in COVID-19



**Novartis announces plan to initiate clinical study of Jakavi® in severe COVID-19 patients and establish international compassionate use program**

April 2, 2020



• HOME / • INVESTORS / • LILLY BEGINS CLINICAL TESTING OF THERAPIES FOR COVID-19

## Lilly Begins Clinical Testing of Therapies for COVID-19

04/10/2020

- Baricitinib Research Commences in NIH-led Adaptive COVID-19 Treatment Trial

Download PDF



Pfizer's COVID-19 push: antiviral candidate identified as anti-inflammatory Xeljanz starts trial

Several clinical trials, including NIAID's ACTT, are now testing JAK inhibition in COVID-19

# Conclusions

Individuals with Down syndrome display immune dysregulation that could increase the risk of developing more severe symptoms during COVID19.

Toning down the immune system can have therapeutic benefits in both Down syndrome and COVID19.

Individuals with Down syndrome and COVID19 should be monitored more closely for signs of hyperinflammation.

Individuals with Down syndrome should be included in ongoing clinical trials testing the safety and efficacy of JAK inhibitors and other immune-modulatory strategies in COVID19.

# Credits

## **Crnic Institute: Kelly Sullivan**

Katie Tuttle

Ross Minter

Kate Waugh

Paula Araya

Dayna Tracy

Jessica Baxter

Michael Ludwig

Keith Smith

Angela Rachubinski

Amanda Hill

Belinda E. Estrada

Ross Granrath

Kayleigh Worek

Matthew Galbraith

Jessica Shaw

Kohl Kinning

Kyle Bartsch

## **The Global Down Syndrome Foundation Team**

## **Department of Pharmacology:**

Moli Joshi

Huy Duc

Maddie laird

Zdenek Andrysik

Heather Bender

Maria Szwarc

Roubina Tatavosian

Emily Adam

## **The Crnic Admin Team:**

Monica Lintz

Lyndy Bush

## **Key Collaborators:**

Sunita Sharma

Fernando Holguin

Beth Tamburini

Matt Burchill

David Orlicky

Eric Schmidt

Tom Campbell

David Norris

Cory Dunnick

Lenny Maroun

## **Funding:**



**THE INCLUDE PROJECT**

