Scientific research in the INCLUDE era

New discoveries and clinical trials to improve heath outcomes in Down syndrome

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GLOBAL DOWN SYNDROME FOUNDATION

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DENVER HEALTH est. 1860 FOR LIFE'S JOURNEY

Adult Down Syndrome Clinic

Alzheimer's and Cognition Center
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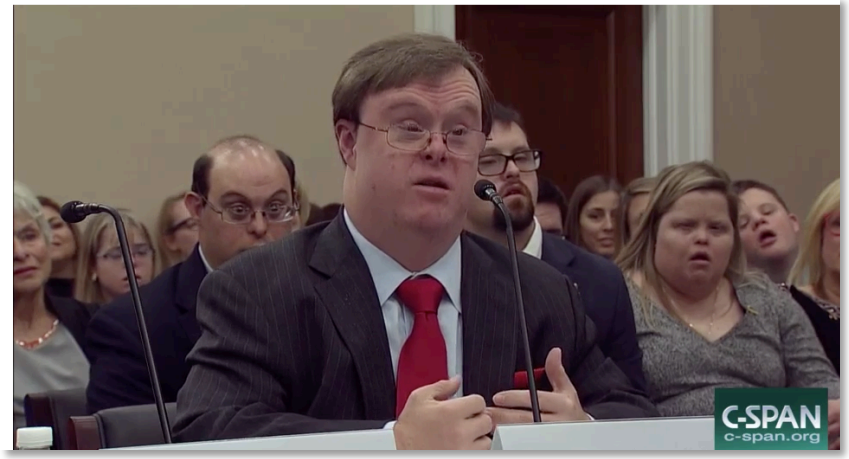
The NIH INCLUDE Project

Investigating co-occurring **C**onditions across the **L**ifespan to **U**nderstand Down syndrom**E**

NIH National Institutes of Health

Turning Discovery Into Health

THE INCLUDE PROJECT



Frank Stephens testifying in Congress

The NIH INCLUDE Project
What is the impact on the scientific community?

- Many new ideas from scientists across diverse disciplines
- Many new synergistic collaborations
- Strong recruitment and training of new talent
- ‘Translation’ of discoveries into clinical trials to test new therapeutic strategies

People with Down syndrome have a different ‘disease spectrum’

Cancer

Heart Disease

Coronary Artery Disease
Atherosclerosis
Hypertension
Angiopathies
(e.g. diabetic retinopathies)

Alzheimer’s

Autoimmunity

Leukemia

Autism, Seizures, Congenital Heart Defects
Autoimmune Disorders (e.g. T1D, Celiac Disease, Hashimoto’s, Vitiligo, Rheumatoid Arthritis) and more…

The ~6 million human beings alive today with trisomy 21 may hold solutions to many major medical conditions

Each one of them is dealing with trisomy 21 in their own unique, personal way

They are more awesome than different,
yet they are **ALL** unique









Our motto:

Nothing in the study of Down syndrome makes sense except in the light of Personalized Medicine

The Crnic Institute's Human Trisome Project

A large and detailed cohort study of people with Down syndrome

www.trisome.org

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The Crnic Institute's Human Trisome Project

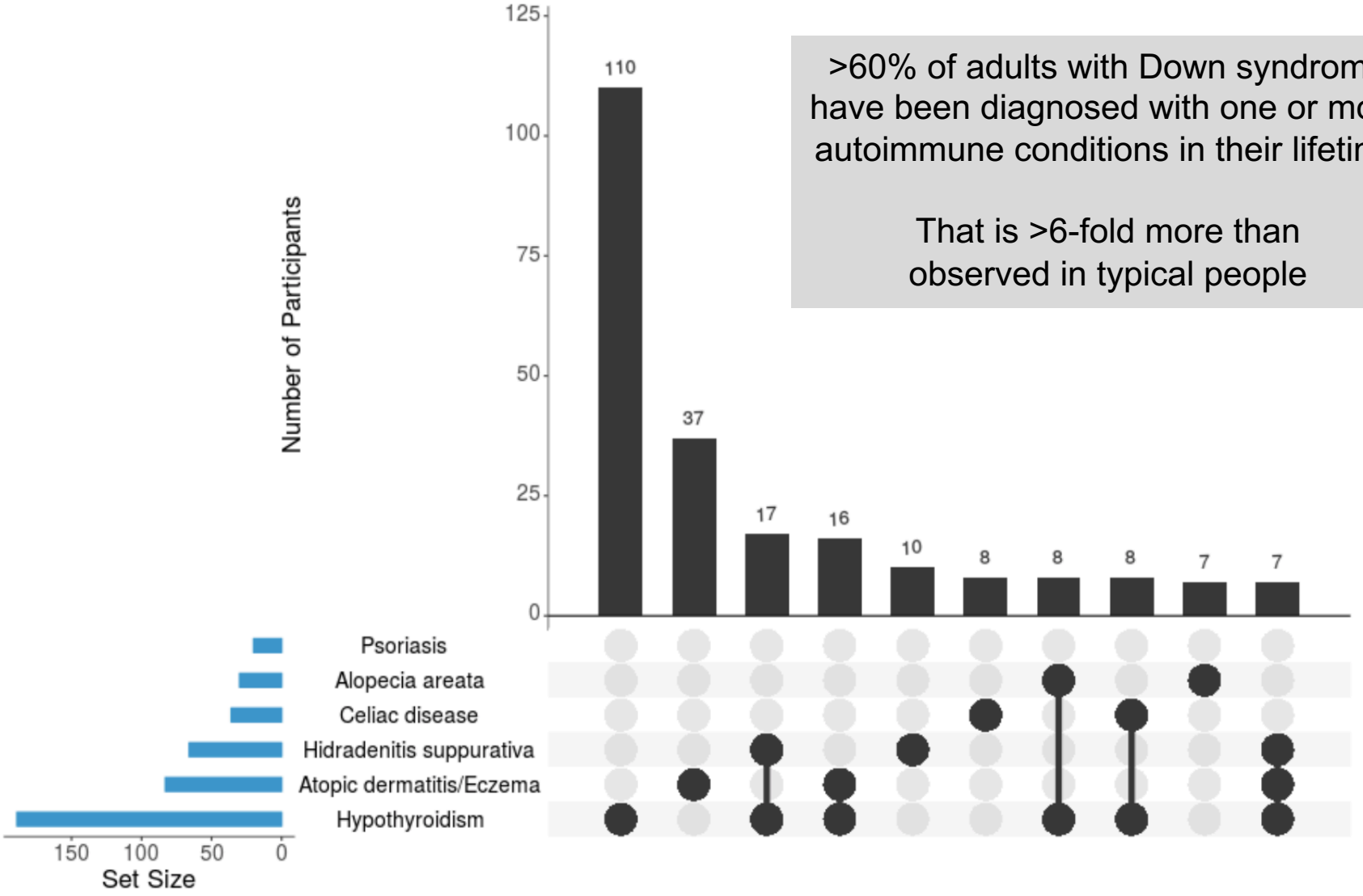
A large and detailed cohort study of people with Down syndrome

Goals:

1. To enable a personalized medicine approach for the management of Down syndrome in the clinic.

2. To enable the design of novel diagnostic and therapeutic tools to improve health outcomes in Down syndrome.

Key observation from the HTP: widespread autoimmunity in Down syndrome



>60% of adults with Down syndrome have been diagnosed with one or more autoimmune conditions in their lifetime

That is >6-fold more than observed in typical people

People with Down syndrome are affected by many autoimmune conditions

Key observation: widespread autoimmunity in Down syndrome

The immune system of people with Down syndrome is ‘dysregulated’

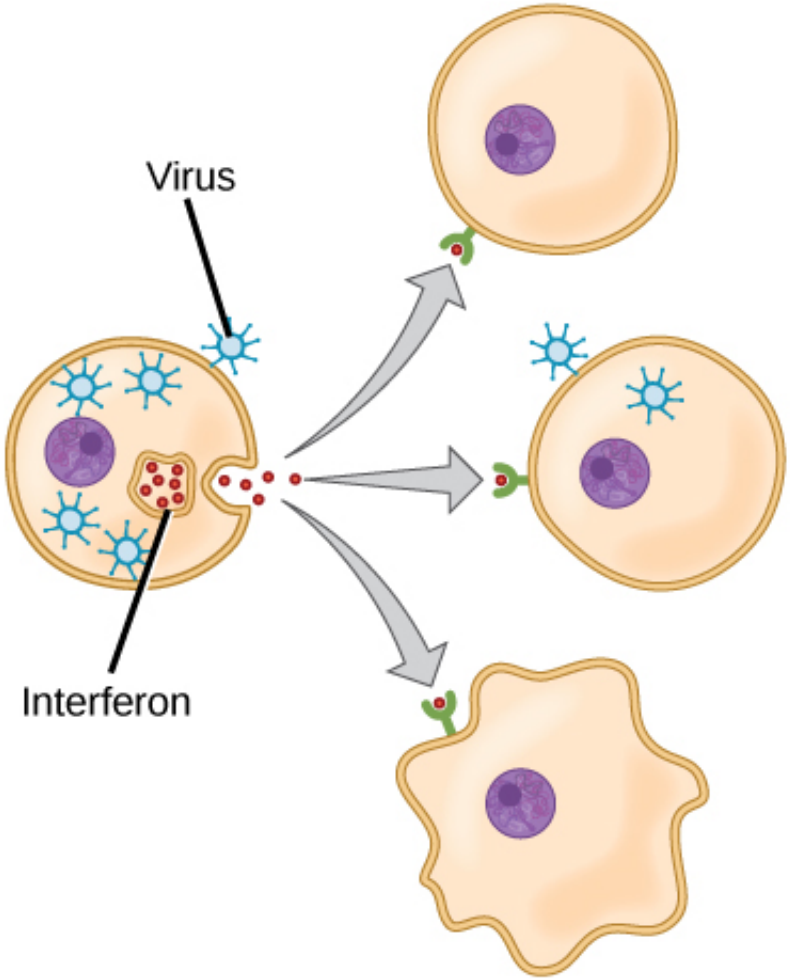
The immune system of people with Down syndrome is mistakenly attacking healthy tissues, such as the thyroid gland, the skin, and the intestines.

What other tissues may be undergoing inappropriate ‘immune attack’?

What explains this immune dysregulation in Down syndrome?

Is there a way to stop this autoimmune attack?

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

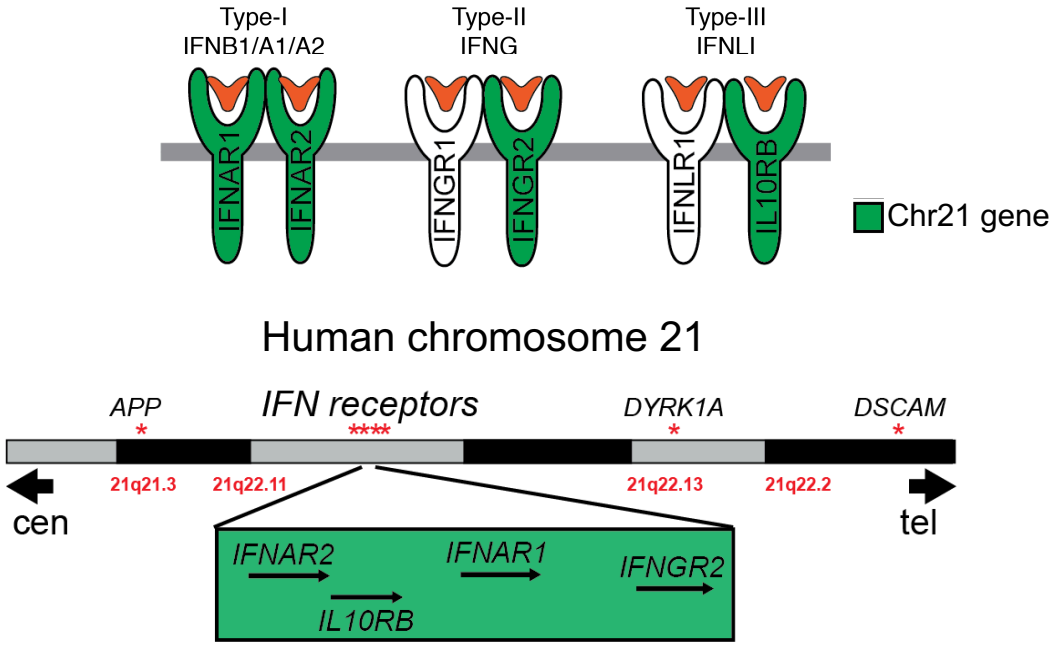
Without an Interferon response, we would probably die within days of a common viral infection

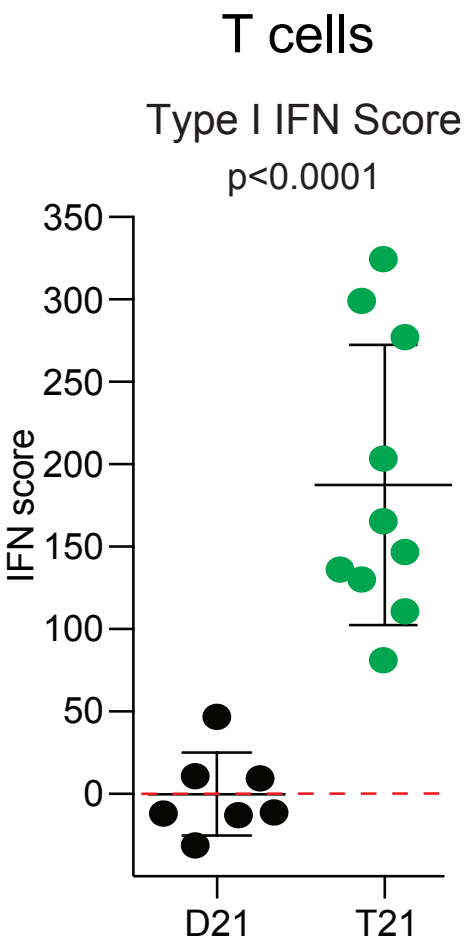
Too much Interferon response is known to cause autoimmunity

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!!





People with Down syndrome show a hyperactive interferon response

Peer reviewed publications

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]*

eLIFE elifesciences.org

2016

Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation

Kelly D. Sullivan[1,2], Donald Evans[1], Ahwan Pandey[1,2], Thomas H. Hraha[3], Keith P. Smith[1], Neil Markham[1], Angela L. Rachubinski[4], Kristine Wolter-Warmerdam[5], Francis Hickey[5], Joaquin M. Espinosa[1,2,6] & Thomas Blumenthal[1,6,7]

SCIENTIFIC REPORTS

2017

Mass Cytometry Reveals Global Immune Remodeling with Multi-lineage Hypersensitivity to Type I Interferon in Down Syndrome

Katherine A. Waugh,[1] Paula Araya,[1] Ahwan Pandey,[1,2,3] Kimberly R. Jordan,[4] Keith P. Smith,[1] Ross E. Granrath,[1] Santosh Khanal,[2] Eric T. Butcher,[1] Belinda Enriquez Estrada,[1] Angela L. Rachubinski,[1,5] Jennifer A. McWilliams,[4] Ross Minter,[1] Tiana Dimasi,[1] Kelley L. Colvin,[1,5,6] Dmitry Baturin,[7] Andrew T. Pham,[1] Matthew D. Galbraith,[2] Kyle W. Bartsch,[1] Michael E. Yeager,[1,5,6] Christopher C. Porter,[8] Kelly D. Sullivan,[1,2,5] Elena W. Hsieh,[1,4,5] and Joaquin M. Espinosa[1,2,3,9,*]

Cell Reports

F1000Prime RECOMMENDED

2019

Trisomy 21 activates the kynurenine pathway via increased dosage of interferon receptors

Rani K. Powers[1,2,3], Rachel Culp-Hill[4], Michael P. Ludwig[1,3], Keith P. Smith[1], Katherine A. Waugh[1], Ross Minter[1], Kathryn D. Tuttle[1], Hannah C. Lewis[1], Angela L. Rachubinski[1,5], Ross E. Granrath[1], María Carmona-Iragui[6,7], Rebecca B. Wilkerson[4], Darcy E. Kahn[1], Molishree Joshi[8], Alberto Lleó[6], Rafael Blesa[6], Juan Fortea[6,7], Angelo D'Alessandro[1,4], James C. Costello[2,3], Kelly D. Sullivan[1,3,5,8]* & Joaquin M. Espinosa[1,3,8,9]*

nature COMMUNICATIONS

2019

Trisomy 21 dysregulates T cell lineages toward an autoimmunity-prone state associated with interferon hyperactivity

Paula Araya[a,b], Katherine A. Waugh[a], Kelly D. Sullivan[a,c,d], Nicolás G. Núñez[b,1], Emiliano Roselli[b], Keith P. Smith[a], Ross E. Granrath[a], Angela L. Rachubinski[a,d], Belinda Enriquez Estrada[a], Eric T. Butcher[a], Ross Minter[a], Kathryn D. Tuttle[a], Tullia C. Bruno[e,f], Mariana Maccioni[b,2], and Joaquín M. Espinosa[a,c,g,2]

PNAS Proceedings of the National Academy of Sciences of the United States of America

2019

Is there a way to ‘normalize’ the Interferon response in people with Down syndrome?

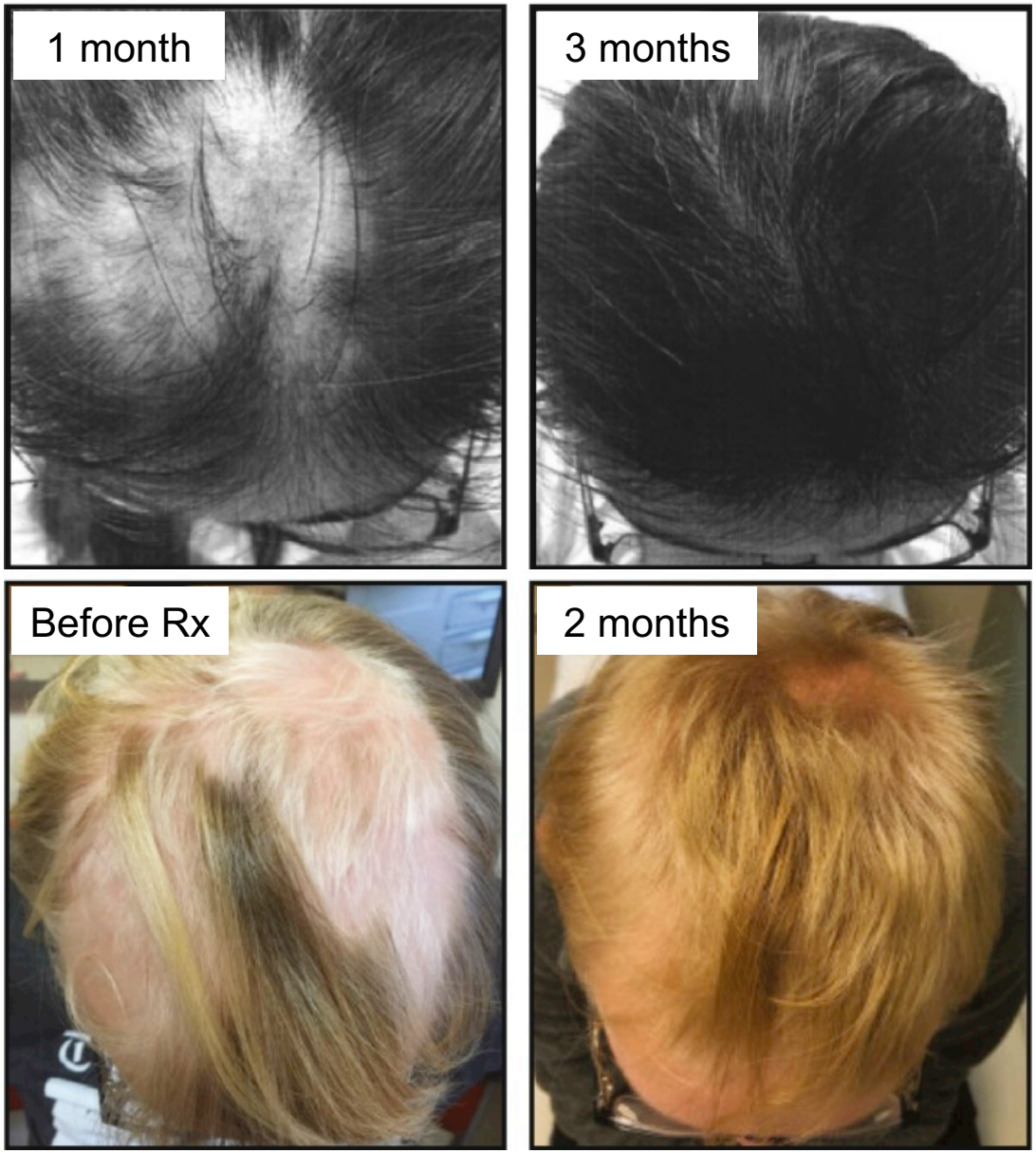
FDA-approved therapies that decrease the Interferon response: JAK inhibitors

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

Also currently in clinical trials for Interferon-driven conditions more common in people with Down syndrome, including:

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

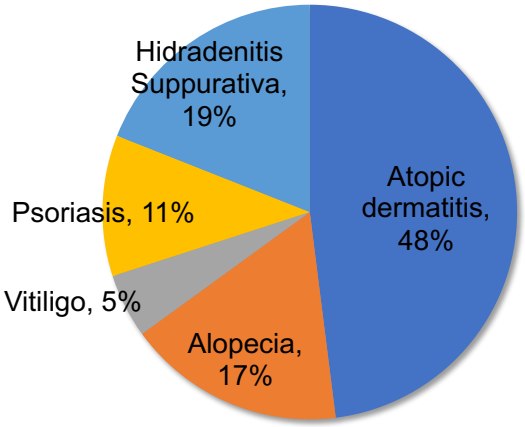
Off-label use of Tofacitinib for alopecia areata in Down syndrome



XELJANZ®
(tofacitinib)

The first clinical trial for JAK inhibition in Down syndrome

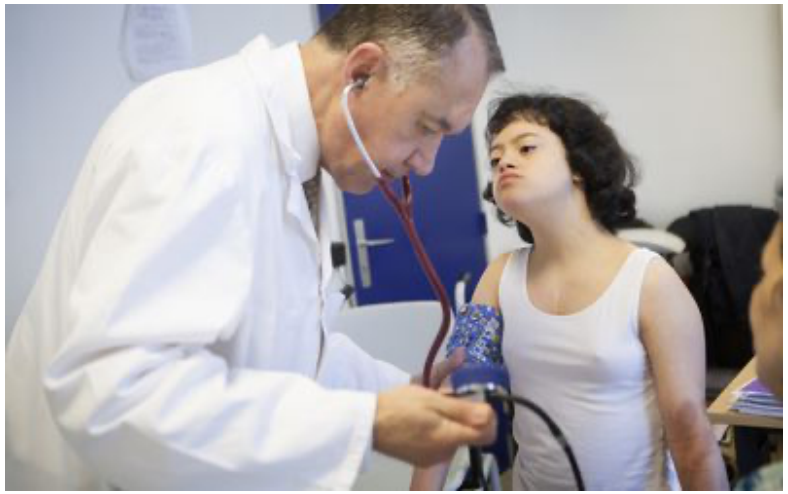
- For immune-driven skin conditions:
  - *Atopic dermatitis*
  - *Alopecia areata*
  - *Hidradenitis suppurativa*
  - *Psoriasis*
  - *Vitiligo*
- Treated with Tofacitinib (aka Xeljanz) for 4 months
- Safety as the primary endpoint
- While also monitoring:
  - *Markers of immune dysregulation in the blood*
  - *Impacts on other autoimmune conditions*
  - *Impacts on cognition and quality of life*



XELJANZ® [tofacitinib]

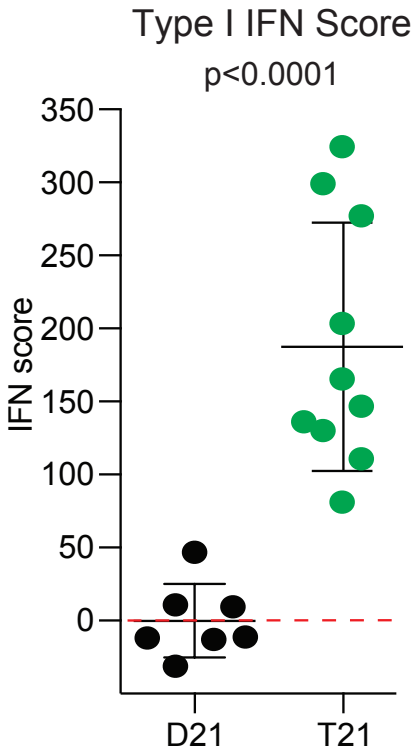
Scientific aims of the first JAK inhibitor clinical trial in Down syndrome

Aim 1: Define the safety profile.

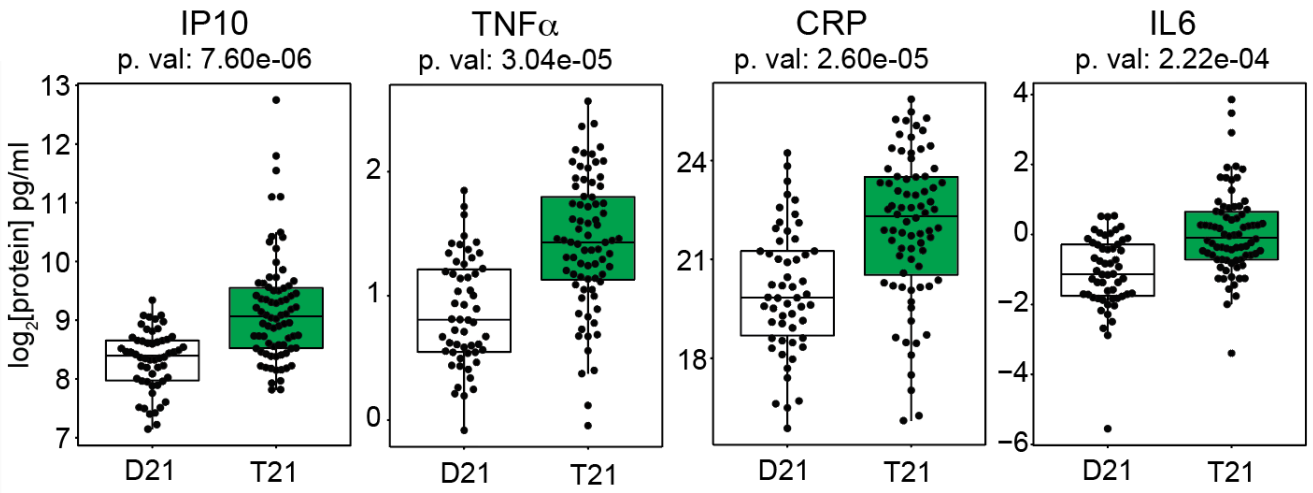


Scientific aims of the first JAK inhibitor clinical trial in Down syndrome

Aim 1: Define the safety profile in Down syndrome.
Aim 2: Determine the impact on immune dysregulation.

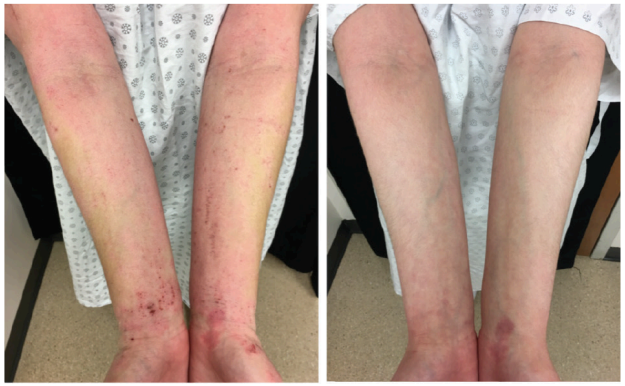


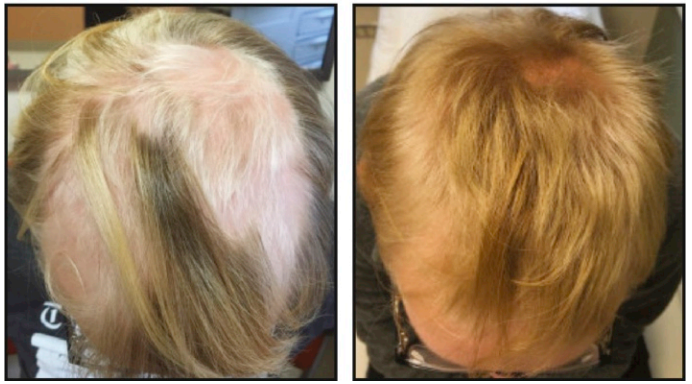
Many 'inflammatory markers' elevated in Down syndrome



Scientific aims of the first JAK inhibitor clinical trial in Down syndrome

Aim 1: Define the safety profile in Down syndrome.
Aim 2: Determine the impact on immune dysregulation.
Aim 3: Define the impact on immune skin conditions.





Area of Involvement: Each body region has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

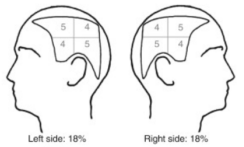
0	None
1	Mild
2	Moderate
3	Severe

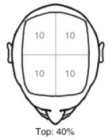
- ✓ Take an average of the severity across the involved area.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)

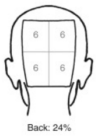
Scoring table:

Body region	Erythema (0-3)	Edema/ Papula-tion (0-3)	Excoria-tion (0-3)	Lichenifi-cation (0-3)	Region score (0-6)	Multiplier	Region subtotal
Head/neck	(+	+	+	)	X	X 0.1	
Trunk	(+	+	+	)	X	X 0.3	
Upper extremities	(+	+	+	)	X	X 0.2	
Lower extremities	(+	+	+	)	X	X 0.4	
Final Score (sum of subtotals)							

Quadrant	Percentage Involved	Multiplier	Subtotal
Left side		0.18	
Right side		0.18	
Top		0.40	
Back		0.24	
		Total	







Scientific aims of the first JAK inhibitor clinical trial in Down syndrome

Aim 1: Define the safety profile in Down syndrome.
Aim 2: Determine the impact on immune dysregulation.
Aim 3: Define the impact on immune skin conditions.
Aim 4: Characterize the impact on cognition and quality of life.

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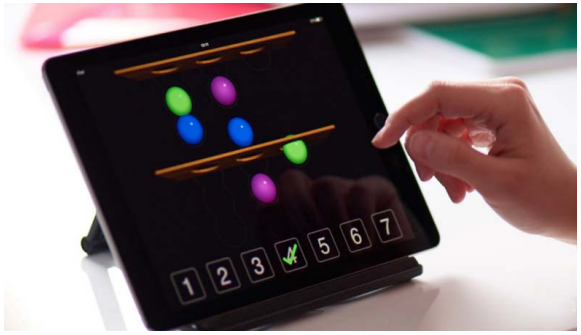

Important information

Funded by the **National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)** through the **INCLUDE Project**

IRB-approved and listed in Clinicaltrials.gov:
https://clinicaltrials.gov/ct2/show/NCT04246372

Important dates:

Pre-screening by phone starts in March 2020

Screening and enrollment of first 10 participants planned for between April and September 2020

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Thanks!

THE INCLUDE PROJECT

All the wonderful individuals with Down syndrome and their families who participate in research