

An Important Clinical Trial for People with Down Syndrome

Insights into Inflammation, Autoimmune Conditions, Quality of Life and More

December 8, 2021



LINDA CRNIC INSTITUTE
for **DOWN SYNDROME**



Adult Down
Syndrome Clinic

Mission

Significantly improve the lives of all people with Down syndrome through advanced biomedical research

Vision

Provide the world's first fully integrated institute for Down syndrome with the highest quality basic, translational and clinical research, clinical trials, therapeutic development, medical care, education and advocacy in the pursuit of the mission.

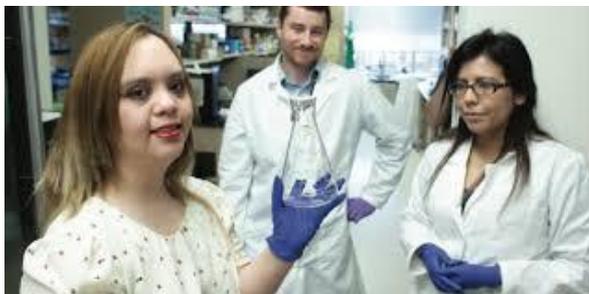
A network of affiliate organizations

Working together
to improve the
lives of people
with Down
syndrome.



The Crnic Institute is the largest, most well funded center for Down syndrome research in the world

60+ research teams



200+ scientists



#1 in NIH funding



170+ scientific publications
since 2012

THE INCLUDE PROJECT



The Crnic Institute is a leader in clinical research in Down syndrome

The Crnic Institute's Human Trisome Project (HTP) is a deep study of people with Down syndrome, a true discovery accelerator leading to multiple scientific breakthroughs



LINDA CRNIC INSTITUTE
HUMAN TRISOME PROJECT™
GLOBAL DOWN SYNDROME FOUNDATION

Discoveries enabled by the Human Trisome Project have illuminated the key role of immune dysregulation, leading to a new clinical trial

Before treatment

2 months

7 months



Tofacitinib for Immune Skin Conditions in Down Syndrome

ClinicalTrials.gov Identifier: NCT04246372

Recruitment Status ⓘ : Recruiting
First Posted ⓘ : January 29, 2020
Last Update Posted ⓘ : October 28, 2020
See [Contacts and Locations](#)

Active and recruiting

Funded by:

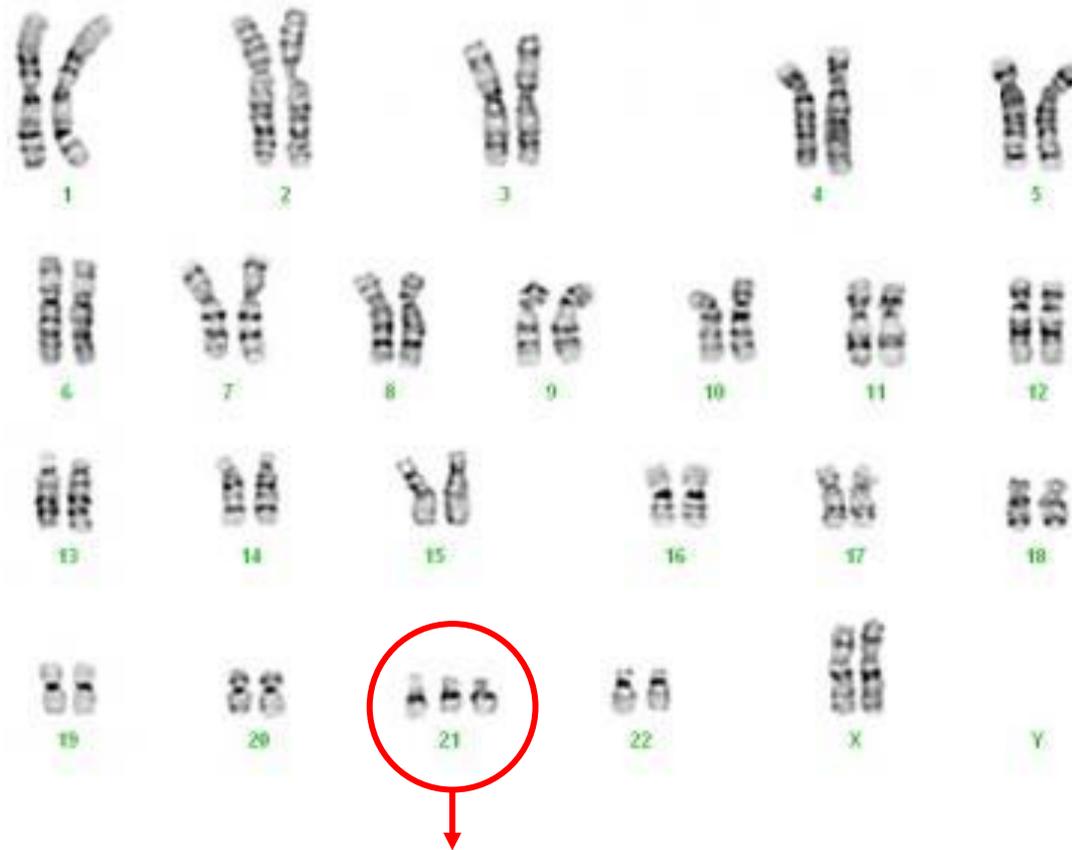
THE INCLUDE PROJECT

People with Down syndrome have a different 'disease spectrum'



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

An extra copy of chromosome 21 modulates the appearance and severity of major medical conditions



How does a mere 50% increase in this little piece of DNA causes the developmental and clinical hallmarks of Down syndrome?

Serving people with Down syndrome through advanced biomedical research leading to better medical care



How to facilitate and accelerate this process time and time again for researchers in Colorado, across the USA, and around the world?

- Pilot funding for new projects
- Access to deidentified human biospecimens (biobank)
- Free access to experimental models (e.g. mouse models of DS)
- Easy access to and facilitated analysis of data (TrisomExplorer Portal)
- Membership in a highly collaborative community (Crnic Supergroup)
- Administrative and logistical support all along the 'pipeline'

An example of translational science: from petri dish to clinical trial in four years



2016



2020

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 Smith¹, 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*}



Tofacitinib for Immune Skin Conditions in Down Syndrome

ClinicalTrials.gov Identifier: NCT04246372

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[First Posted](#) ⓘ : January 29, 2020

[Last Update Posted](#) ⓘ : February 16, 2021

See [Contacts and Locations](#)

 U.S. National Library of Medicine

ClinicalTrials.gov

Key observation: widespread autoimmunity in Down syndrome

>**60%** of adults with Down syndrome have been diagnosed with at least one autoimmune condition

~**50%** of people with Down syndrome display hypothyroidism, attributed to autoimmune thyroid disease (AITD)

~**25%** adults with Down syndrome have been diagnosed with one or more autoimmune skin conditions

~**10%** of adults with Down syndrome have been diagnosed with celiac disease

Type I diabetes, 'Down syndrome arthropathy', and other, more rare autoimmune conditions, are also more common



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.

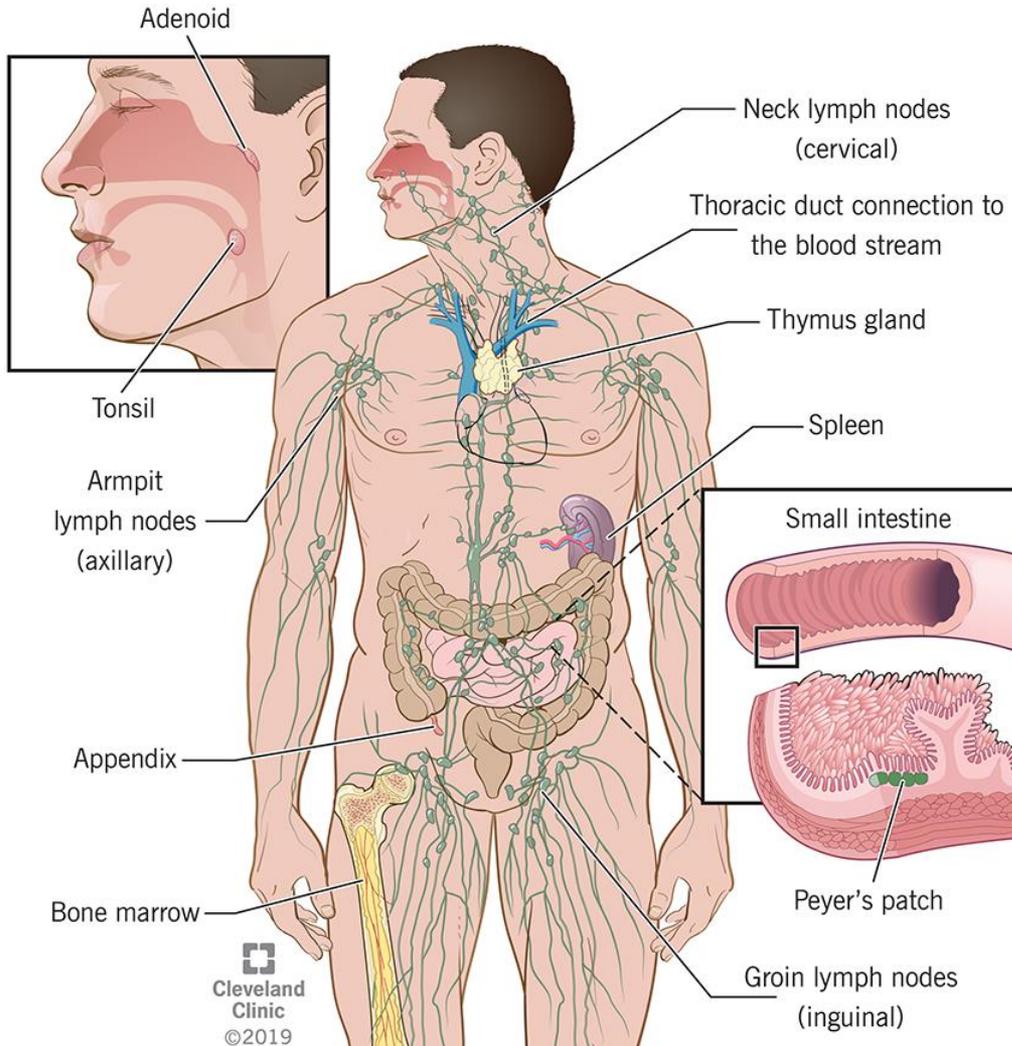
What other tissues may be undergoing inappropriate ‘immune attack’?

What explains this immune dysregulation in Down syndrome?

Is there a way to stop this autoimmune attack?



What is the immune system?



The immune system is a large network of organs, white blood cells, proteins (e.g. antibodies, cytokines) and chemicals.

This system works together to protect us from foreign invaders (bacteria, viruses, parasites, and fungi) that cause infection, illness and disease.

The immune system acts throughout the human body.

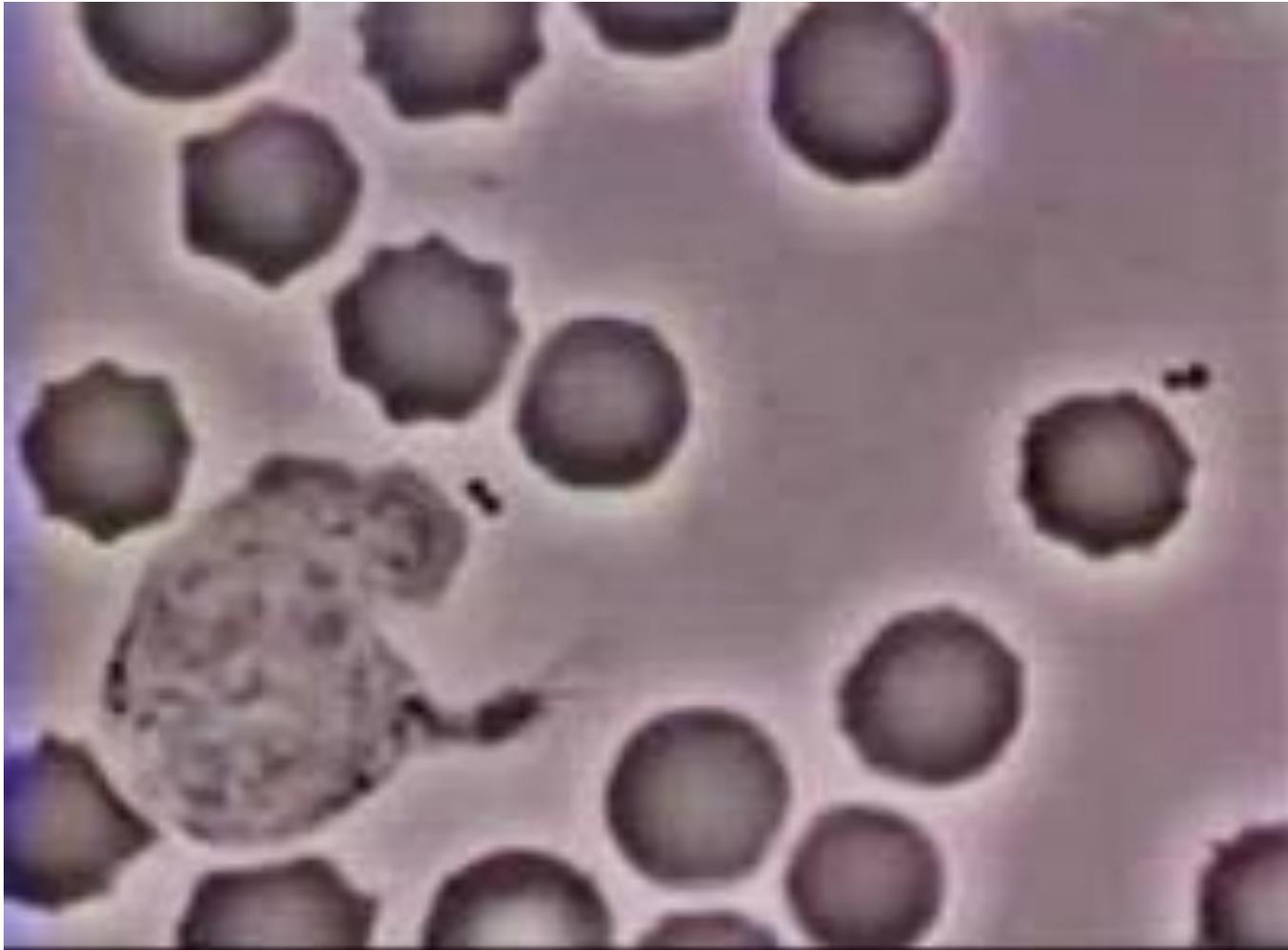
**The immune system has two main branches:
the innate and the adaptive immune systems**

**Innate and adaptive immune cells work together
to fight off invaders**



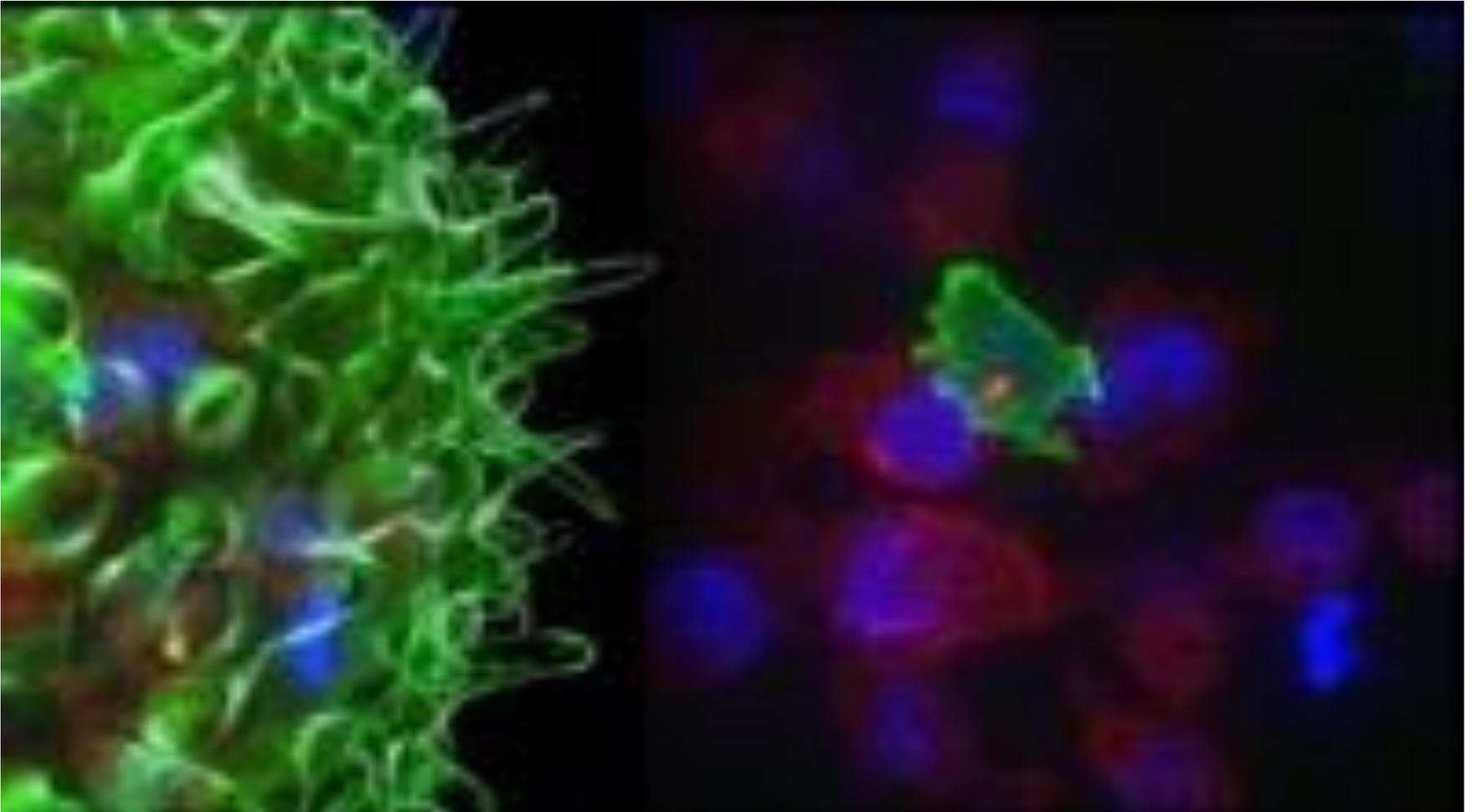
The immune system works for us 24/7

In this movie, we can see an innate immune cell known as a 'neutrophil' chasing after and eventually 'eating' a bacteria



The immune system works for us 24/7

In this movie, we can see a type of immune cell known as killer T cell, or 'cytotoxic CD8+ T cell', attacking cancer cells

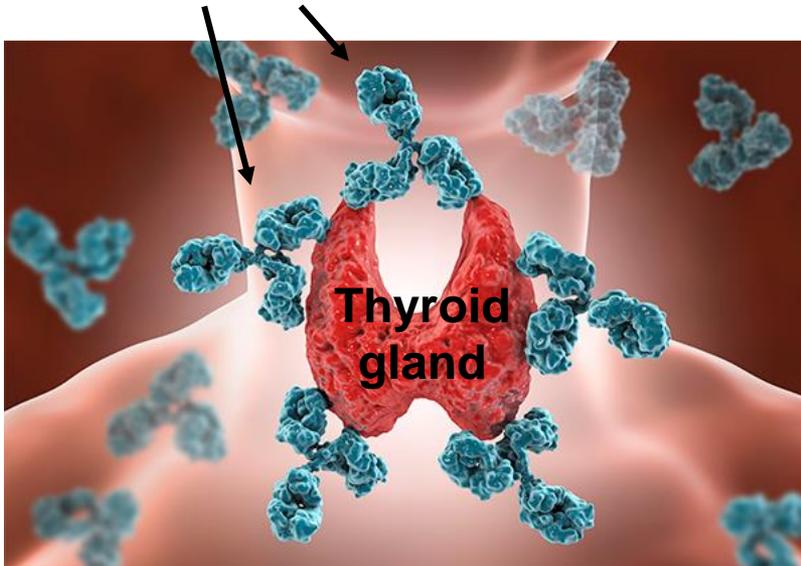


Autoimmunity:

When the immune system mistakenly attacks a healthy part of the body

Autoimmune diseases are driven by 'autoreactive' T cells and/or 'autoantibodies'

Autoantibodies



Examples:

Autoantibodies against the thyroid gland will cause autoimmune thyroid disease.

Autoreactive T cells attacking the hair follicles will cause alopecia areata.

Research Questions

Why is the immune system of people with Down syndrome making more mistakes?

What drives the presence of more autoreactive T cells and autoantibodies in Down syndrome?

The culprit: the Interferon response

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 Smith¹, 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 Evans³, Ahwan Pandey^{1,2}, Thomas H. Hraha³, Keith P. Smith¹, Neil Markham¹, Angela L. Rachubinski⁴, Kristine Wolter-Warmerdam⁵, Francis Hickey⁵, 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-Hill⁴, Michael P. Ludwig^{1,3}, Keith P. Smith¹, Katherine A. Waugh¹, Ross Minter¹, Kathryn D. Tuttle¹, Hannah C. Lewis¹, Angela L. Rachubinski^{1,5}, Ross E. Granrath¹, Maria Carmona-Iragui^{6,7}, Rebecca B. Wilkerson⁴, Darcy E. Kahn¹, Molishree Joshi⁸, Alberto Lleó⁶, Rafael Blesa⁶, 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*}



2019

PNAS

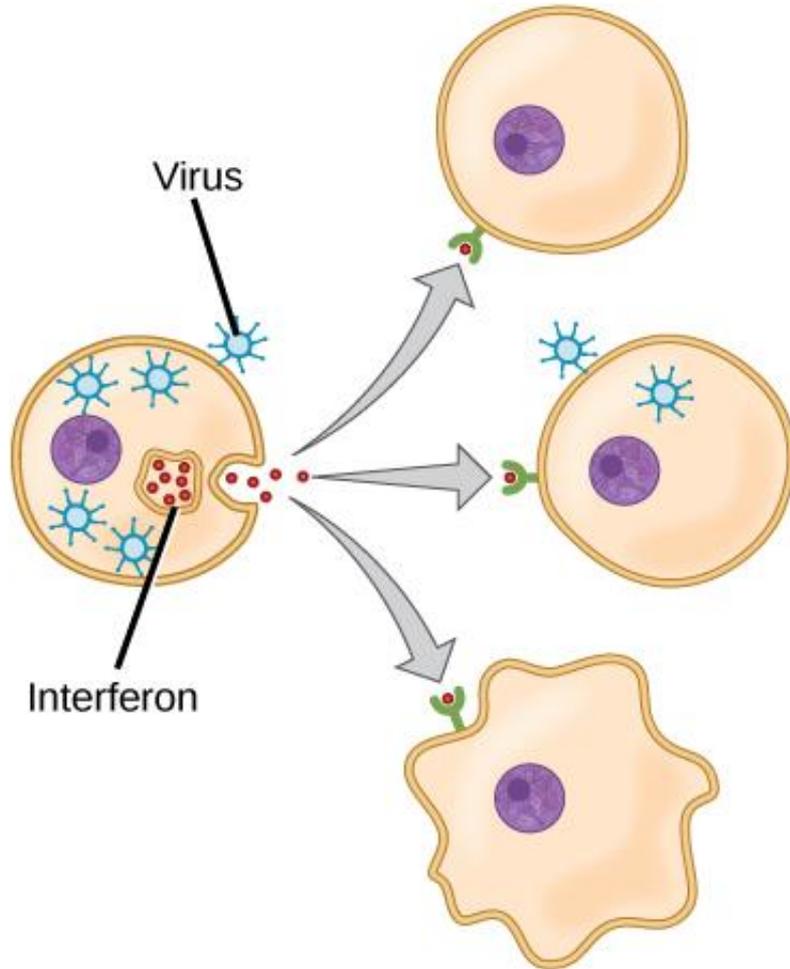
Proceedings of the
National Academy of Sciences
of the United States of America

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 Joaquin M. Espinosa^{a,c,g,2}

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

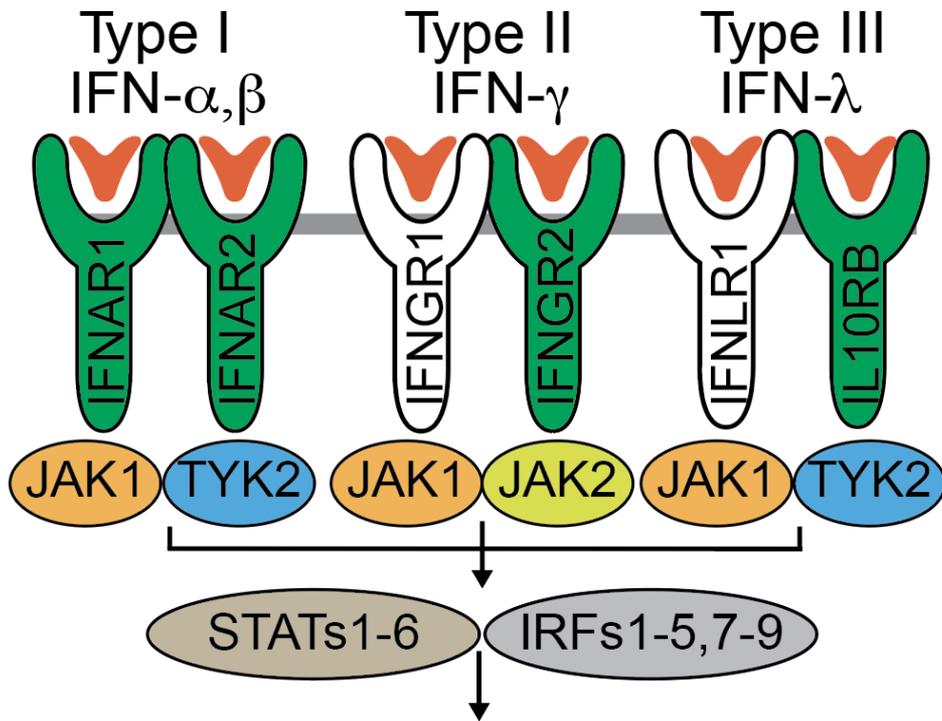
The Interferon response acts throughout the entire human body

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

Too much Interferon response is known to cause autoimmunity and other health issues.

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

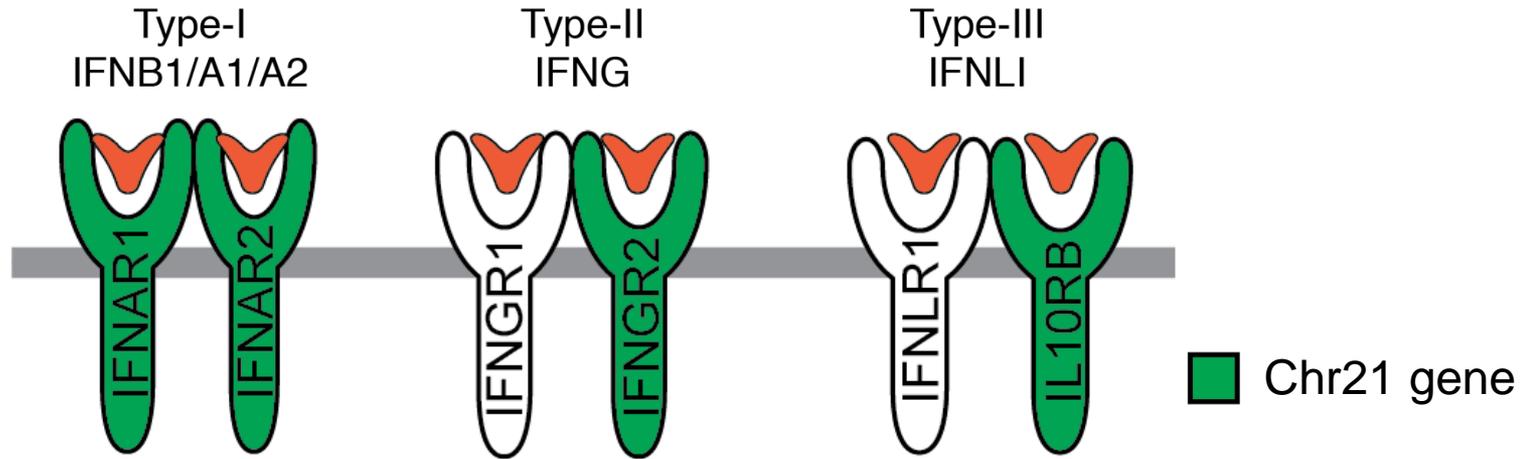
Interferon, Interferon, Interferon



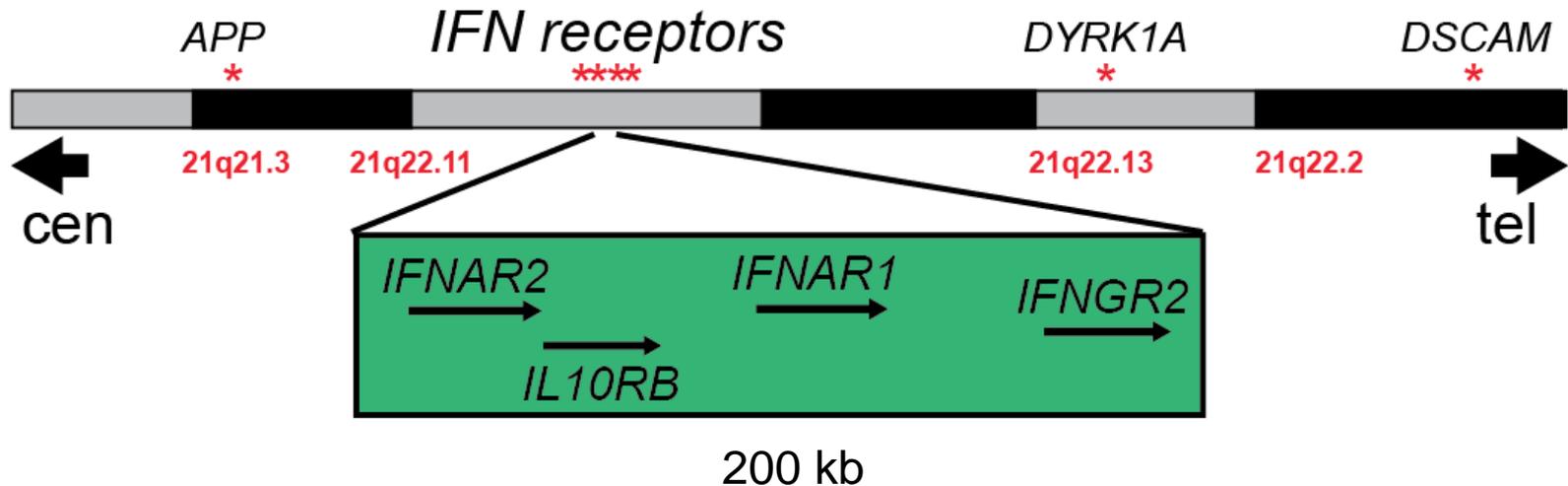
Transcription of Interferon Stimulated Genes
Immune Activation, Antiviral Response

- There are three major types of IFN signaling, involving different ligands and receptors
- All interferon signaling require the JAK1 enzyme to function
- Interferon signaling mounts the antiviral response

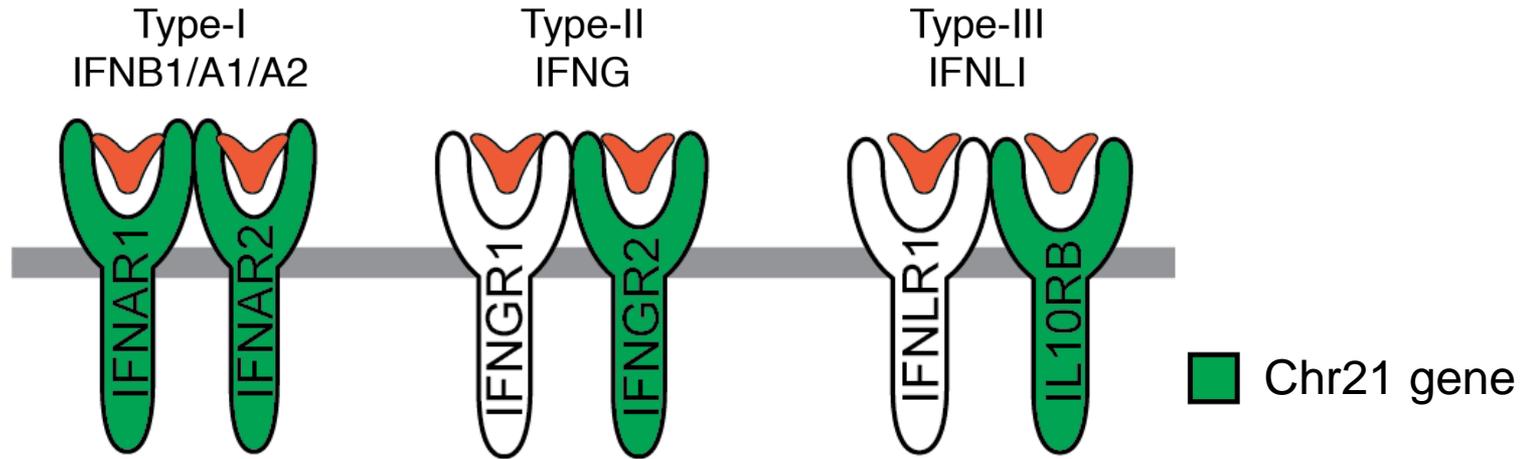
4 of the 6 IFN receptors are encoded on chr21!!



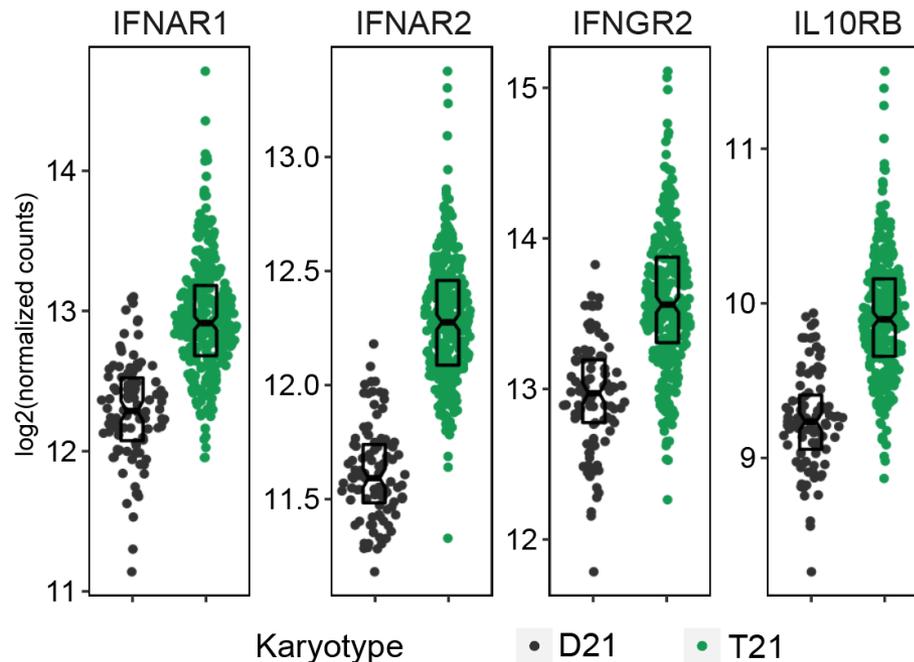
Human chromosome 21



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



Measurement of IFN receptors in the bloodstream of research participants:

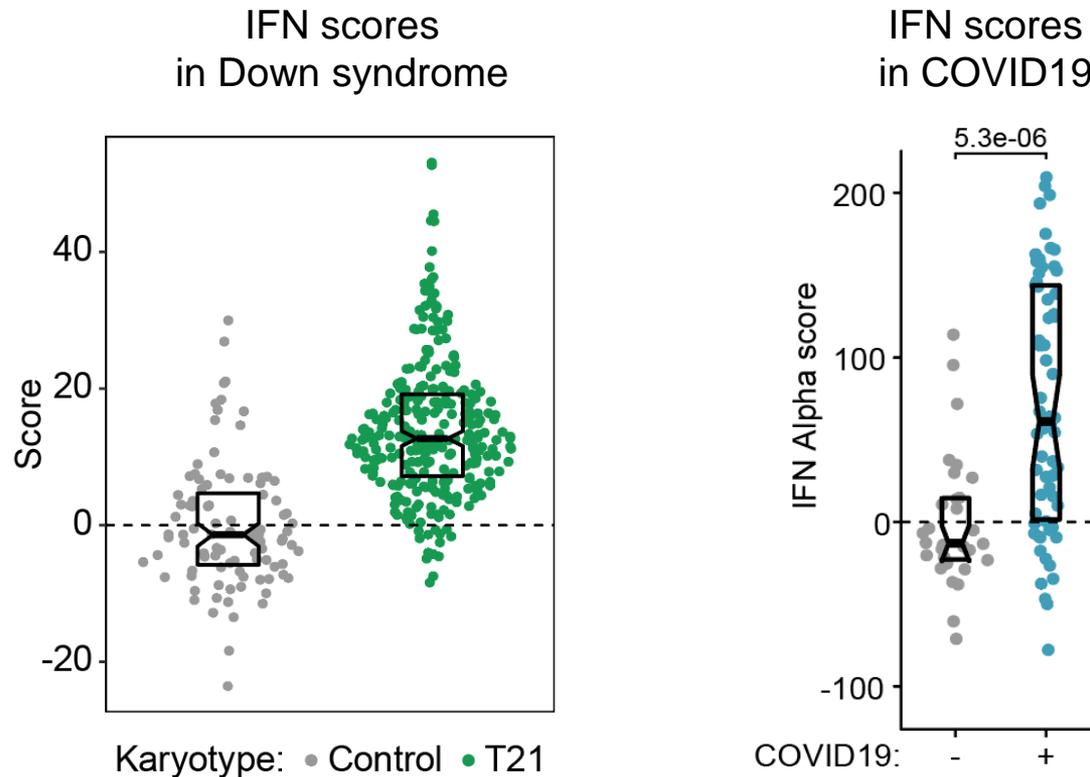


Receptor 'overdose' is not good

- An extra copy of the Interferon receptors leads to 'over-reaction' throughout the immune system.
- Interferon hyperactivity is a known risk factor for autoimmunity in the typical population.
- Interferon hyperactivity could have other harmful effects, such as increased complications from viral infections (e.g. RSV, COVID-19).
- Chronic Interferon hyperactivity could lead to premature ageing and exhaustion of the immune system later in life.

Interferon hyperactivity in Down syndrome across the lifespan

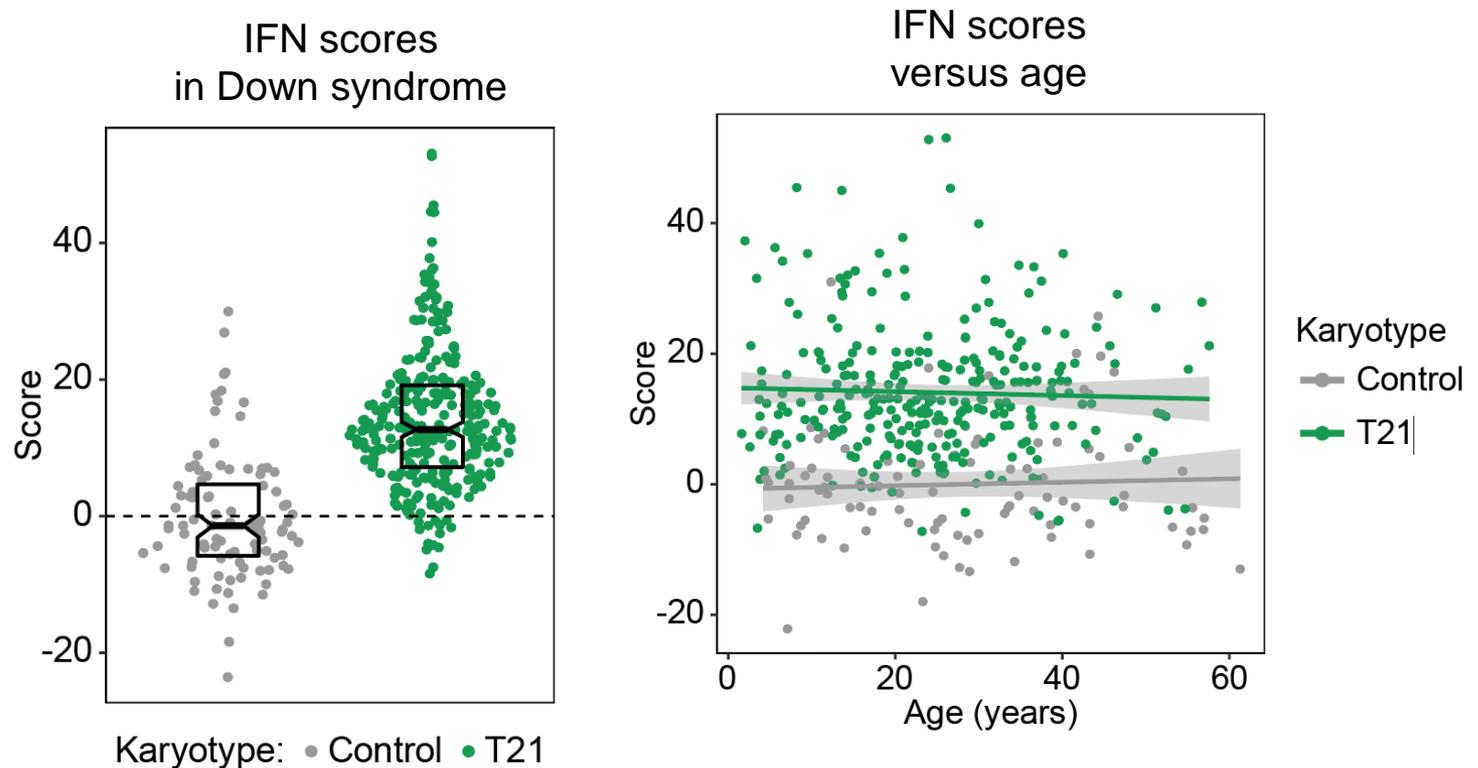
Interferon (IFN) scores are elevated **at baseline** in Down syndrome



The blood of people with Down syndrome looks like is fighting a viral infection **all the time...**

Interferon hyperactivity in Down syndrome across the lifespan

Interferon hyperactivity is observed at all ages



The blood of people with Down syndrome looks like is fighting a viral infection **all the time...**

Would drugs that block Interferon signaling improve health outcomes in Down syndrome?

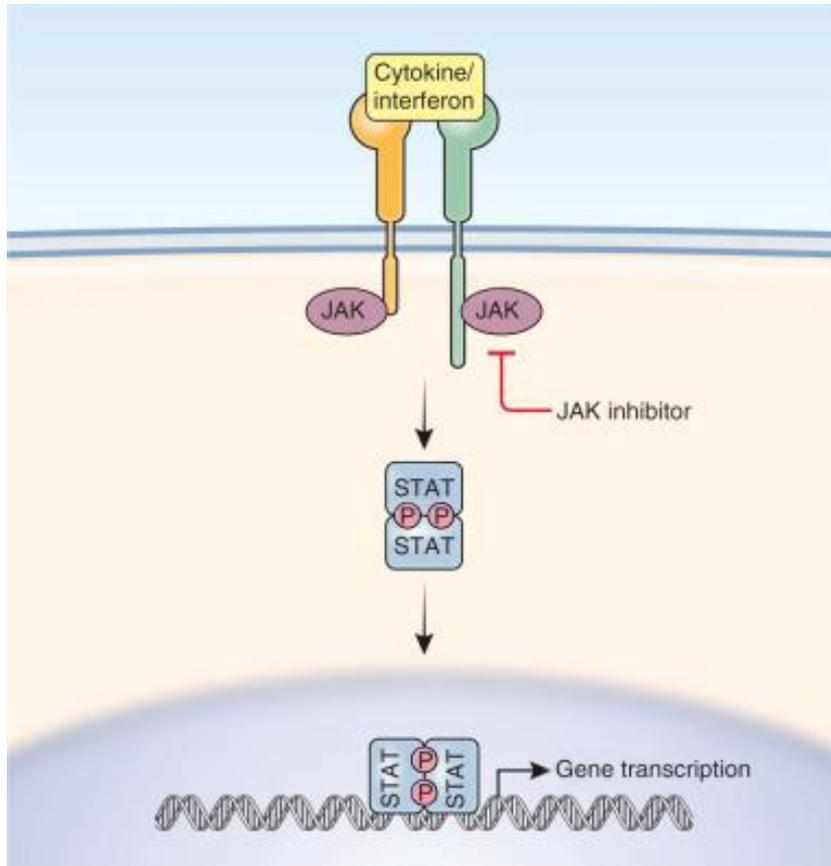
FDA-approved therapies that decrease the Interferon response: JAK inhibitors

Company	Marketed Name	Target	Indication
	Jakafi [®] ruxolitinib (tablets)	JAK1&2	Myelofibrosis (2011), polycythemia vera (2011), GVHD (2019)
	XELJANZ [®] [tofacitinib]	JAK1&3	Rheumatoid arthritis (2012), psoriatic arthritis (2017), ulcerative colitis (2018), polyarticular JIA (2020)
	olumiant [®] (baricitinib) tablets	JAK1&2	Rheumatoid arthritis (2018)
	 RINVOQ [™] upadacitinib 15mg tablets	JAK1	Rheumatoid arthritis (2019)

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

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

JAK inhibitors could attenuate the ill effects of interferon receptor overdose

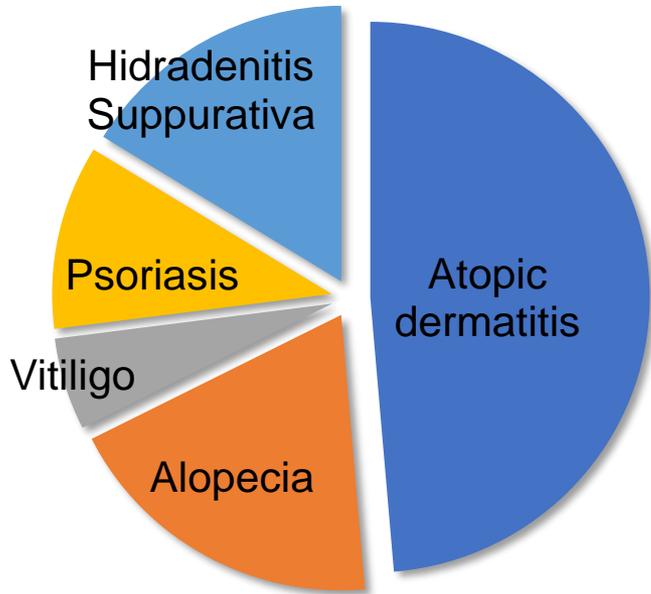


JAK inhibitors are small molecules designed to inhibit the JAK enzymes acting 'downstream' of the interferon receptors.

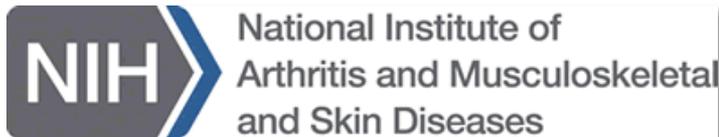
JAK inhibitors are taken daily orally as pills and have a short 'half life' in the body.

The action of JAK inhibitors is fully reversible, as they are rapidly cleared from the human body within hours.

Crnic Institute's clinical trial for JAK inhibition in Down syndrome



THE INCLUDE PROJECT



Targeting five autoimmune skin conditions in one trial

All five conditions are more prevalent in Down syndrome

~25% of adults with Down syndrome have been affected at some point by one of these conditions

4-9 months of treatment with an FDA-approved JAK inhibitor: Tofacitinib (Xeljanz)

Study Objectives and Design

- Individuals with Down syndrome ages 12 - 50
- Phase II, single arm, open-label
- 16-week treatment with Tofacitinib
 - 2-week optional follow-up for those not on Extension Arm
 - 24-week Extension Arm
- Moderate-to-severe skin condition:
 - Psoriasis
 - Hidradenitis suppurativa
 - Vitiligo
 - Atopic dermatitis
 - Alopecia areata (affecting at least 25% of scalp)

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 impact on cognition and quality of life.

Top level figures as of December 8, 2021

- Pre-screened 65 participants
- Screened 20 participants
- All 13 'eligible' participants were enrolled
- 12/13 participants completed the main arm of 16 weeks
- 1/13 to complete the main arm before the end of the calendar year
- Interim analysis was triggered when the 10th participant completed the 'main arm'

Top level results

- **Zero** serious adverse events
- 6/6 participants with alopecia areata experienced hair regrowth, to varying degrees
- 2/2 participants with atopic dermatitis saw complete remission
- 1/1 participant with psoriasis saw complete remission
- 2/5 participants showed improvements in hidradenitis suppurativa

Top level results

Benefits going well beyond skin deep!

- 9/10 participants showed decreased in their interferon scores
- 7/7 participants with clinically significant anti-thyroid autoimmunity displayed decreased levels of autoantibodies

Top level results

Tantalizing results, but more data is needed...

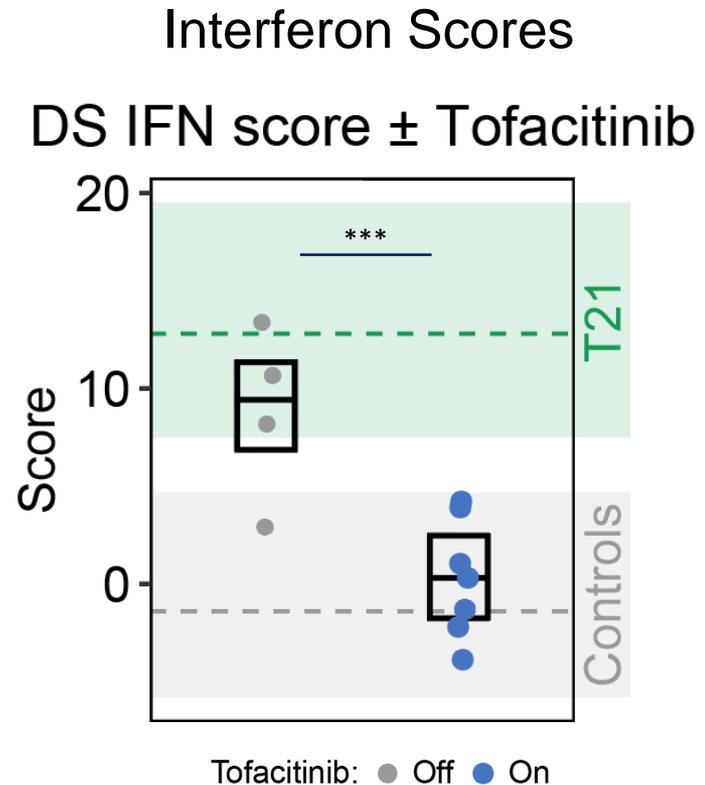
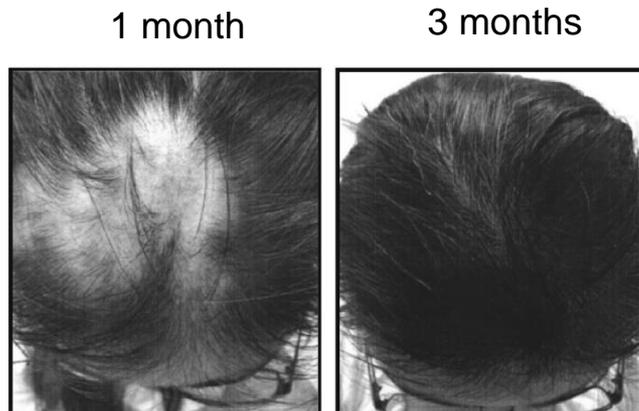
At $n=10$, we detected a significant improvement in:

- One measure of spatial memory
- One measure of visuomotor function
- Anxiety/depression scores

Tofacitinib normalizes interferon activity

Female, 22-24 years old at time of blood draws, taking Tofacitinib 'on and off' since 2016 for alopecia areata

Participant provided 10 research blood draws while being **on** and **off** Tofacitinib.



JAK inhibition 'normalizes' IFN scores, bringing them down to the range observed in the general population

TOFA0022 – Male, 17 years old, AA

When a picture is worth a thousand words

Baseline
SALT = 86



TOFA0022 – Male, 17 years old, AA

When a picture is worth a thousand words

Baseline
SALT = 86



Week 16
SALT = 4

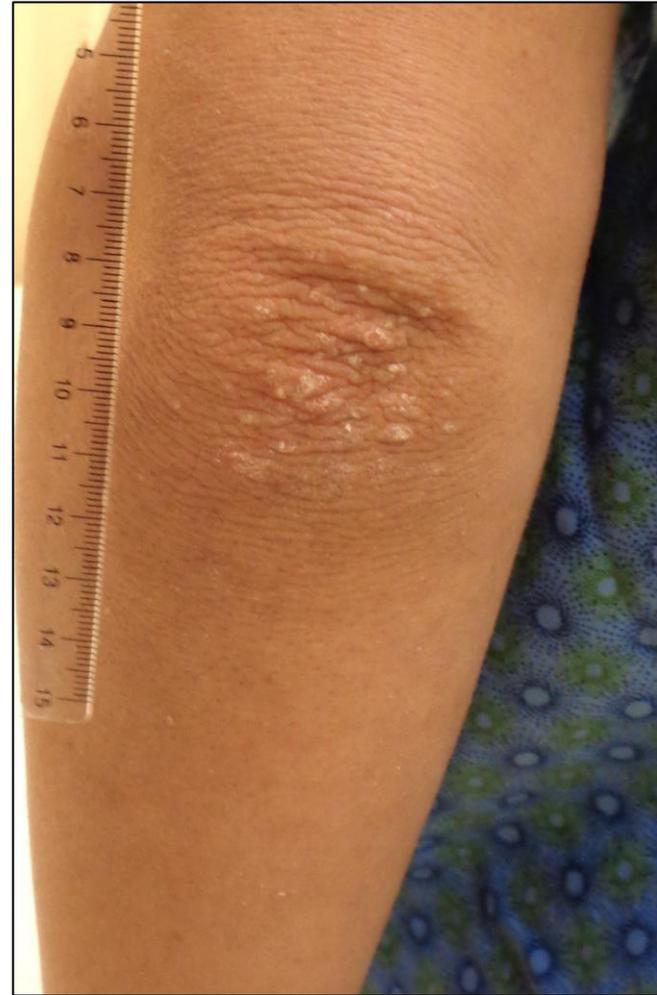


Participant referred to as 'Ed Sheeran' by the research team

Significant improvement in psoriasis



Screening



Week 16

Significant improvement in psoriasis



Screening



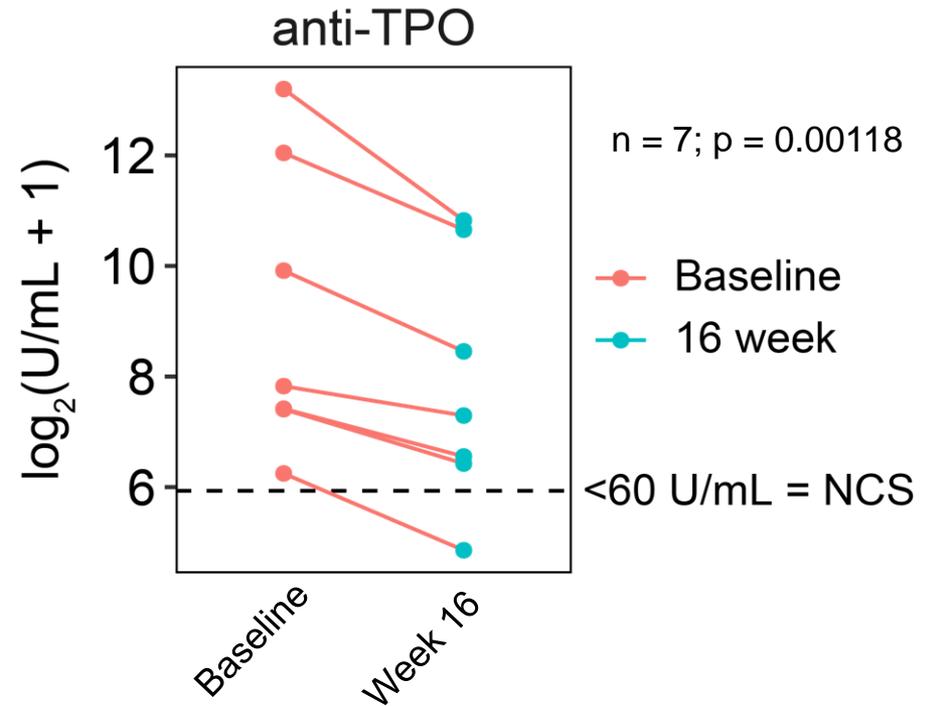
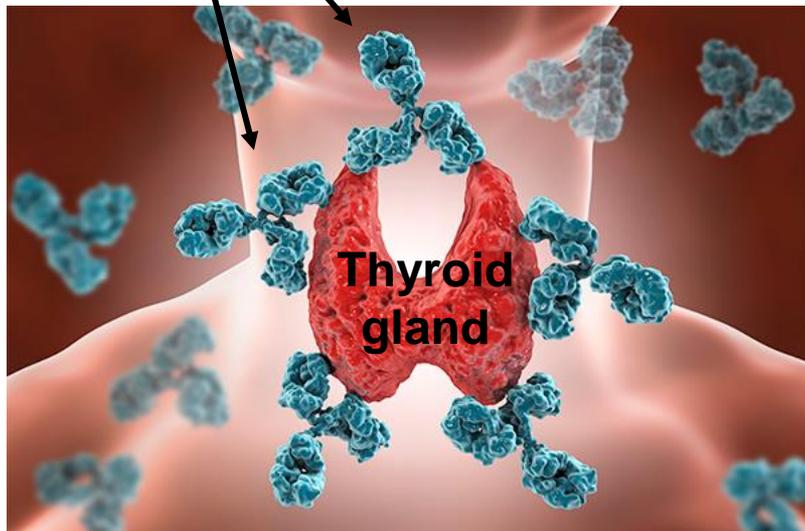
Week 16

Significant decrease in the autoimmune attack to the thyroid gland

Autoimmune thyroid disease is the most common autoimmune condition in Down syndrome

All 7 participants with 'clinically significant' anti-TPO antibodies displayed decreases in autoantibody levels

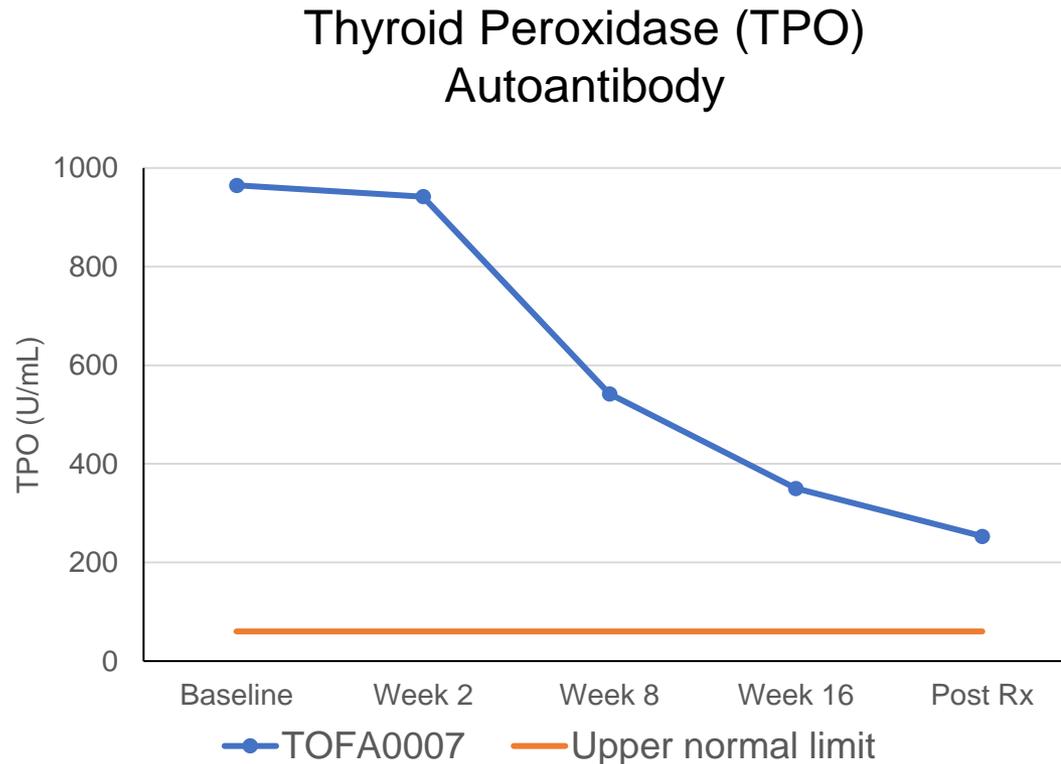
Autoantibodies



Values above 60U/mL are 'clinically significant'

Benefits going beyond skin deep

Remarkable decrease in autoantibodies attacking the thyroid gland upon treatment with Tofacitinib



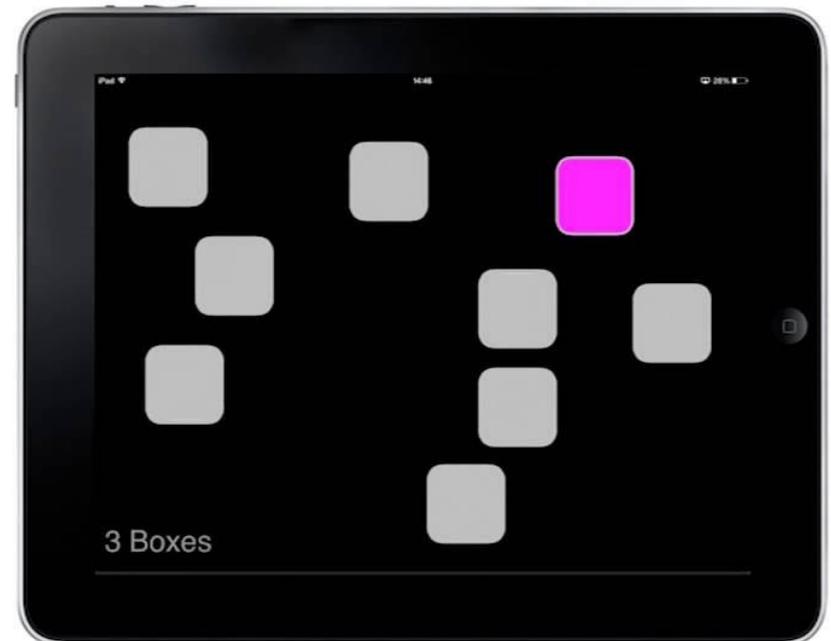
Autoimmune thyroid disease is the most prevalent autoimmune condition in Down Syndrome

Significant improvement in one measure of spatial memory

The CANTAB Spatial Span test

Participants are asked to remember the sequence in which boxes shown in the tablet are 'lit up'

Result: significant improvement in the **Forward Reach Score**, that is, the longest sequence problem successfully reached (but not passed) by the subject.



Significant improvement in one measure of visuomotor function

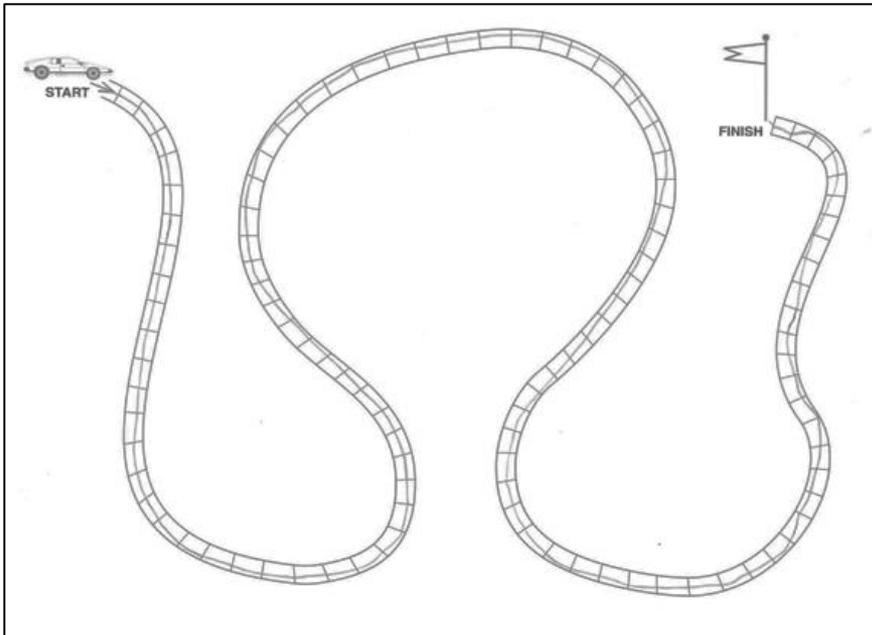
The NEPSY II test

Participants are asked to 'track' the path with a pencil

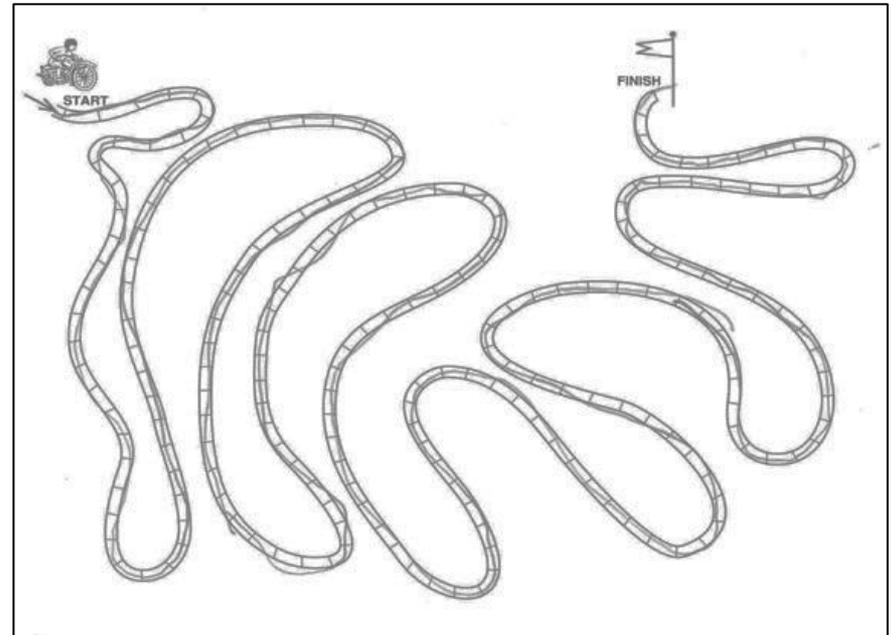
The task is videorecorded and analyzed for errors and time to completion

Result: significant decrease in the total number of errors

Car



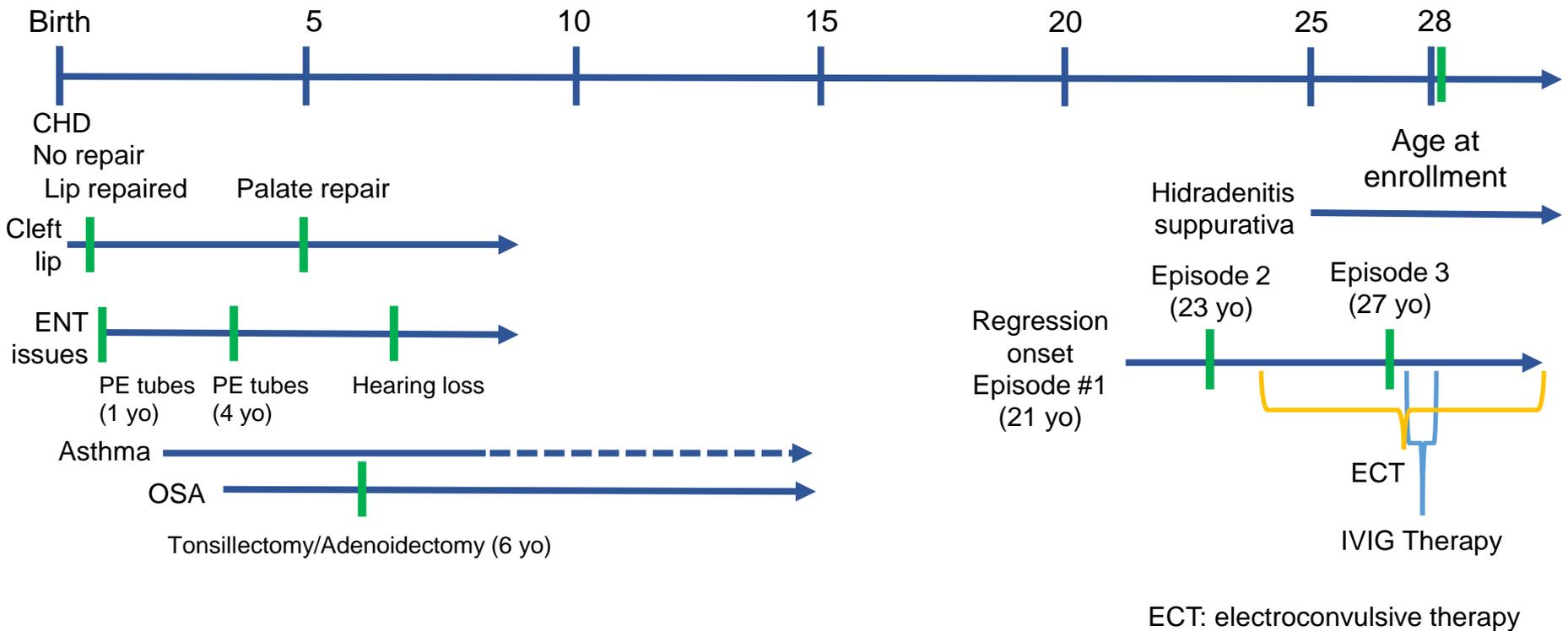
Motorcycle



TOFA0001 – Female, 28 years old

Hidradenitis suppurativa

Medical History



Potential autoimmune encephalitis diagnosis at age 27

Down Syndrome Regression Disorder (DSRD)

- A rare but devastating condition characterized by sub-acute onset of catatonia, mutism, depersonalization, loss of ability to perform activities of daily living, hallucinations, delusions, and aggression.
- A subset of DSRD cases are associated with neurodiagnostic abnormalities indicative of immune dysregulation affecting the central nervous system (CNS), often associated with preceding immune trigger events.
- Is DSRD an autoimmune condition, akin to autoimmune encephalitis?

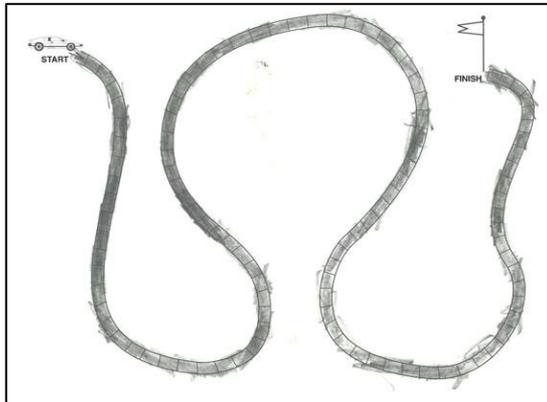
TOFA0001 – Female, 28 years old

Down Syndrome Regression Disorder

Improvement in 13 out of 16 cognitive tests performed!

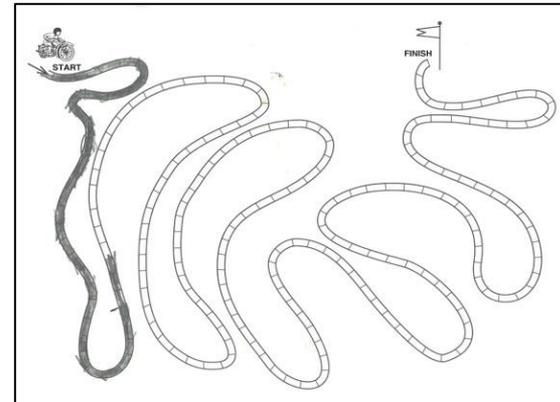
ECT frequency was decreased from 3 times a week
down to once a week or every other week

NEPSY II (car)

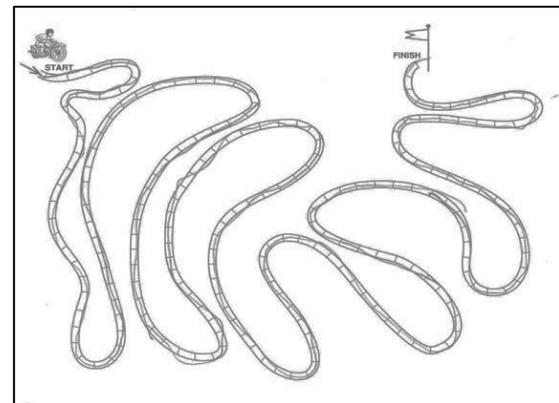
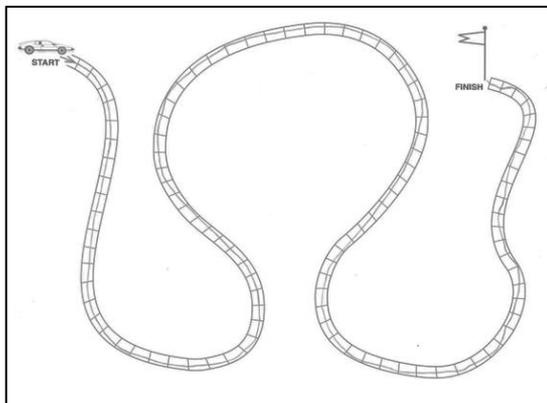


Baseline

NEPSY II (motorcycle)



Week 16



Clinical trial for mechanistic investigation of DSRD therapies

Specific Aims:

1. To define the relative safety profile of Lorazepam, IVIG, and Tofacitinib in DSRD.
2. To compare the efficacy of Lorazepam, IVIG, and Tofacitinib in DSRD.
3. To investigate potential mechanisms underlying DSRD and its response to therapies.

Multi-site collaboration between the Crnic Institute, Children's Hospital Colorado, and Children's Hospital Los Angeles.



Santoro
Neuroimmunology



Sannar
Psychiatry



Patel
Psychology



Kammeyer
Neuroimmunology



Sanders
Neurology



Rachubisnki
Crnic



Espinosa
Crnic (contact PI)

Coming in 2022...

Improving medical care for people with Down syndrome, one family at the time

Hi Joaquin and Belinda,

I just received an update today that the patient we were working on together (XXXXX YYYYYY) is doing remarkably better after starting tofacitinib. He's only been on it for about 6-8 weeks but his severe psoriasis is apparently now completely resolved and his CRP has decreased from >100 to 14. His arthritis is also considerably better and he is working out on his stationary bike again, something he has not done in over 3 years. XXXXX's mother, ZZZZ, was absolutely beside herself with joy when I spoke with her.

I am working on getting some before and after photos and will be seeing him in a couple weeks. We should work on getting follow-up blood work to you.

Thanks so much for all your help with this. Truly inspiring to see your work translated in to such an effective therapy.

Happy Thanksgiving,

Ralph

Ralph C. Budd, M.D.

University Distinguished Professor of Medicine and Microbiology & Molecular Genetics
Director, Vermont Center for Immunology & Infectious Diseases (VCIID)
The University of Vermont College of Medicine, Burlington, VT 05405-0068

Conclusions

- The first phase of clinical trial was successfully completed despite COVID-19.
- So far, the intervention is deemed safe.
- Skin pathology is clearly improved, with alopecia areata, psoriasis and atopic dermatitis showing the best responses.
- Other autoimmune conditions, such as autoimmune thyroid disease, may also benefit from this intervention as well.
- Tantalizing preliminary results justify the investigation of potential improvements in neurological function.

Important information

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



THE INCLUDE PROJECT

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Linda Crnic Institute for Down Syndrome

School of Medicine

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Home > Get Involved > Participate in a Study

- Participate in a Study
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- Join Our Team
- Contact Us

Participate in a Study

Are you someone with Down syndrome who is currently in participating in research? Learn more about studies that are currently accepting participants here.

Research on tofacitinib to treat immune skin conditions in people with Down syndrome

The purpose of this research is to determine whether tofacitinib is a safe and effective treatment for immune skin conditions in people with Down syndrome, and to further our understanding of the immune system in Down syndrome.

Adults with Down syndrome between the age of 12 and 60 years may be eligible to participate if they have an active immune skin condition. For example: eczema or atopic dermatitis, alopecia areata,



DSresearch@cuanschutz.edu

A team effort!

Clinical and Translational Sciences Program @ Crnic

Amanda Hill

Angela Rachubinski

Belinda Enriquez Estrada

Kayleigh Worek

Tyler Smith

Keith Smith

Ross Granrath

Rylie Meyer

Hannah Lyford

Ella Britton

Dermatology team

Dr. David Norris

Dr. Cory Dunnick

Dr. Liz Wallace

Dr. Emily Gurnee

Data Sciences Program @ Crnic

Dr. Matt Galbraith

Jessica Shaw

Neetha Eduthan

Kohl Kinning

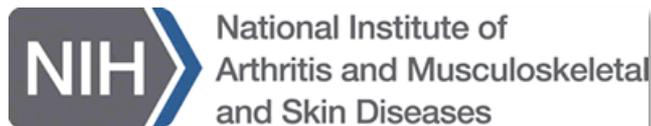
Administrative support

Monica Lintz

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The wonderful participants and their families!



THE INCLUDE PROJECT



Thanks to GLOBAL, today is a new age in Down syndrome research, with new NIH funding opportunities, new cohort studies, new clinical trials, and new big data science efforts. The future is bright!

