Stopping the autoimmune attack in Down syndrome: new breakthroughs and clinical trials

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LINDA CRNIC INSTITUTE
for DOWN SYNDROME

GLOBAL
DOWN SYNDROME FOUNDATION

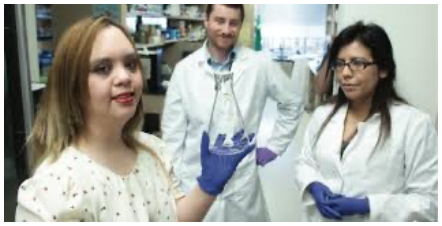
University of Colorado
Anschutz Medical Campus

INCLUDE
Data Coordinating Center

The Crnic Institute is the largest center for Down syndrome research in the world

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

60+ research teams



200+ scientists

200+ scientific publications since 2012

GLOBAL DOWN SYNDROME FOUNDATION

University of Colorado Anschutz Medical Campus

People with Down syndrome have a different ‘clinical risk profile’

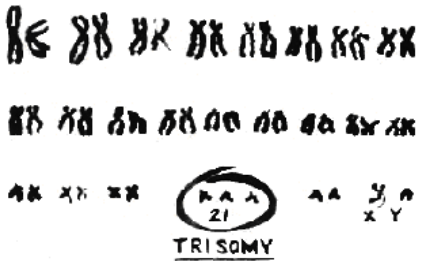
Cancer

Atherosclerosis

Hypertension

Allergies

Common (but variable) traits:
Stunted growth
Neurodevelopmental delays
Early aging



Autoimmunity

Alzheimer’s

Leukemias

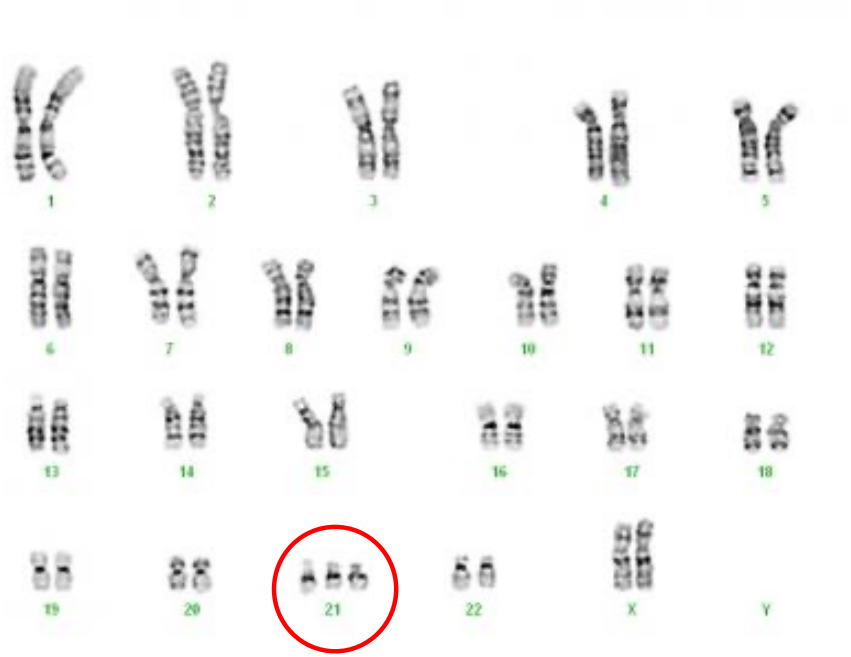
COVID-19

Congenital heart disease, autism spectrum disorders, seizures disorders, and more…

To help people with Down syndrome live longer and healthier lives, we must study the **co-occurring conditions** of Down syndrome

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

Human chromosomes: the karyotype



How does an extra copy of this little piece of DNA cause the developmental and clinical hallmarks of Down syndrome?

Which exact genes (out of ~200) encoded on chromosome 21 cause the various features of Down syndrome?

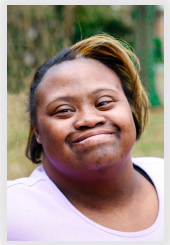
How could we counteract the undesired effects of chromosome triplication and gene overdose to benefit people with Down syndrome?

Diversity = Discoveries

Persons with Down syndrome will teach us how to help them









They are dealing with the trisomy in their own unique personal way

Not two of them are the same, each of them can teach us something new

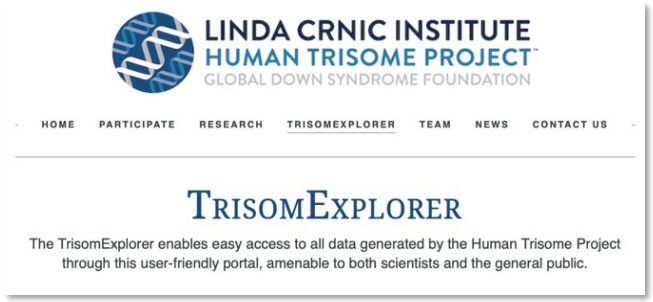
What factors define the ultimate clinical impacts of the extra chromosome?

The Human Trisome Project (HTP)

A large and diverse cohort study with deep clinical data,
a multidimensional biobank, and a public researcher portal

1300 participants recruited since 2016!

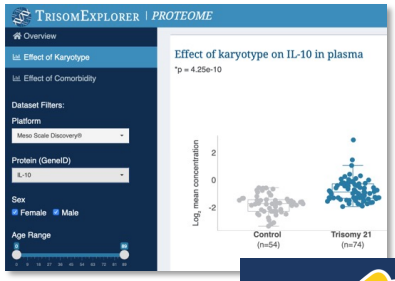
www.trisome.org



Thousands of datasets generated

- **1300** Clinical histories
- **500+** Metabolomes
- **500+** Genomes
- **400+** Immune maps
- **500+** Transcriptomes
- **500+** Microbiomes

TRISOMEXPLORER



INCLUDE Data Hub

40+ Projects supported

25+ Papers published / under review

People with Down syndrome love to participate in research!

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

Idea

Basic Research
- Identify Target

Pre-Clinical Research
- Validate Target
- Develop Therapeutic

Clinical Trials
- Test Safety
- Test Efficacy

Regulatory Approval & Medical Care

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 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

Tofacitinib for Immune Skin Conditions in Down Syndrome

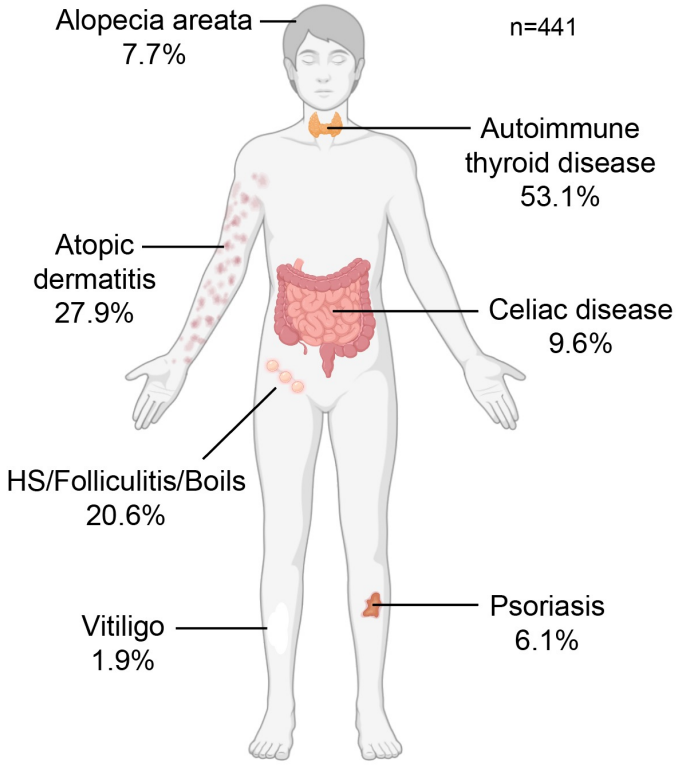
ClinicalTrials.gov Identifier: NCT04246372

Recruitment Status : Recruiting
First Posted : January 29, 2020
Last Update Posted : February 16, 2021

See Contacts and Locations

NIH U.S. National Library of Medicine ClinicalTrials.gov

Key observation: widespread autoimmunity in Down syndrome



HTP data

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

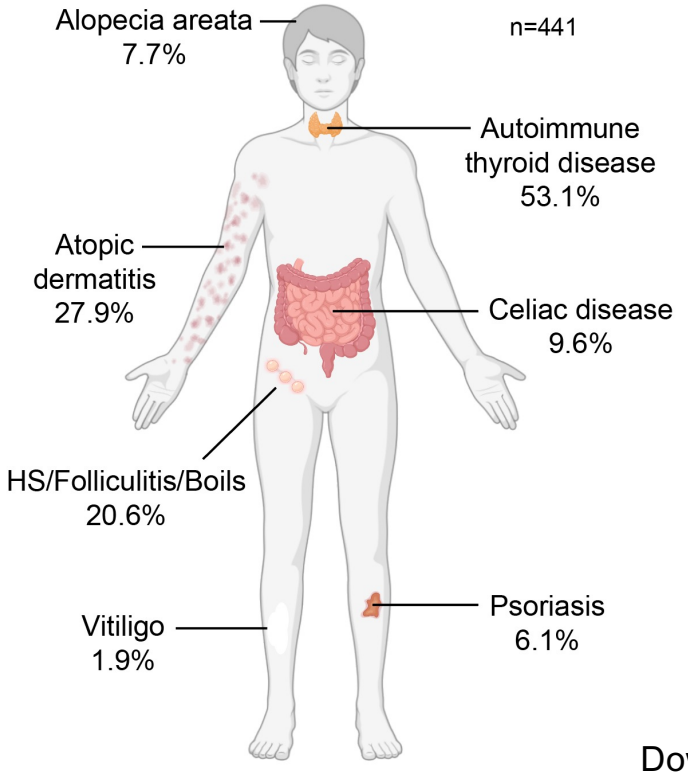
>50% of people with Down syndrome have autoimmune thyroid disease (AITD), leading to **hyper**thyroidism or **hypo**thyroidism

>35% 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

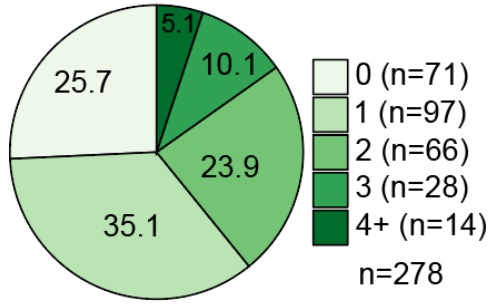
Type I diabetes, ‘Down syndrome arthropathy’, and other, more rare autoimmune conditions, are also more common

Key observation: widespread autoimmunity in Down syndrome

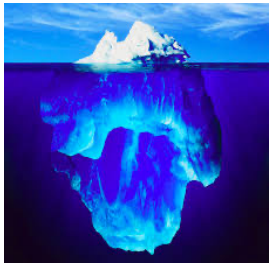


HTP data

Adults:



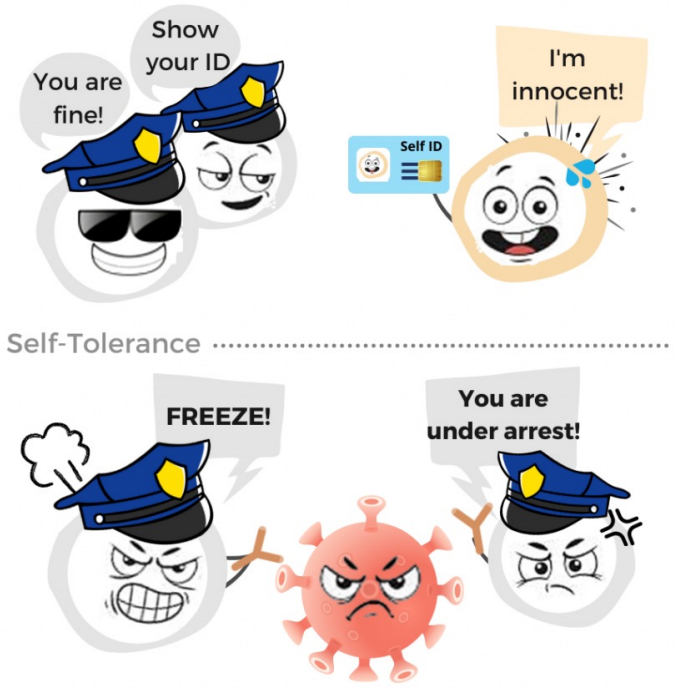
Is this just
the 'tip of the iceberg'?



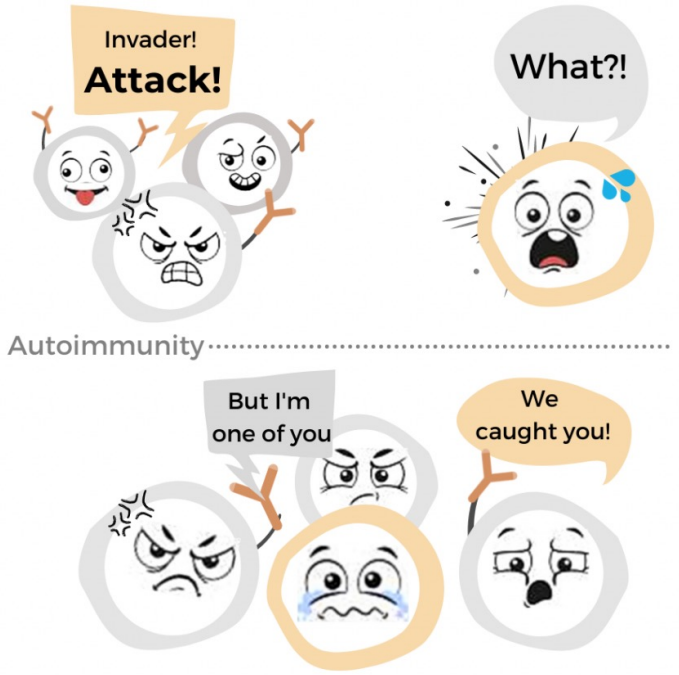
Down syndrome = Multiorgan Autoimmunity of Pediatric Onset Syndrome

Autoimmunity in a nutshell:

Good: self-tolerance



Bad: self-harm



Adapted from Advanx Health blog

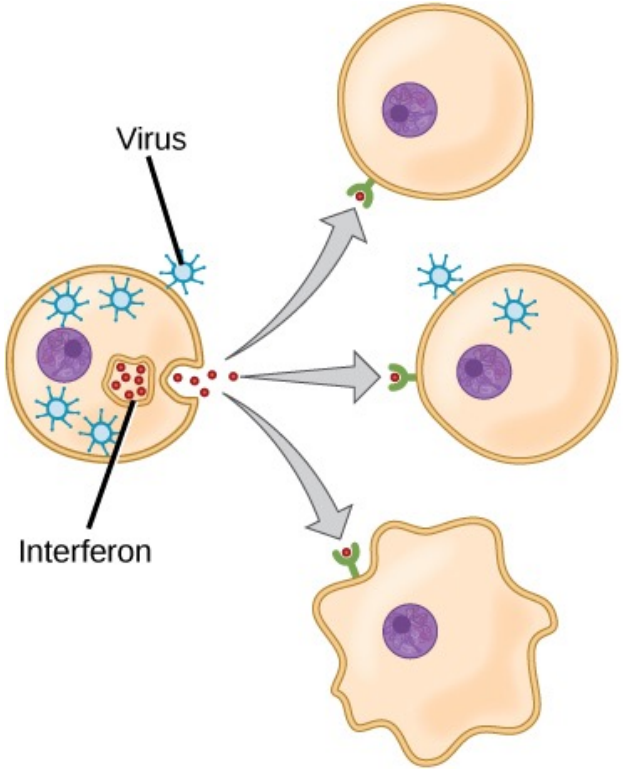
Down syndrome is:

(select all that apply)

- ❑ A chromosomal abnormality
- ❑ An intellectual and development disability
- ❑ An immune disorder

People with Down syndrome have hyperactive interferon signaling

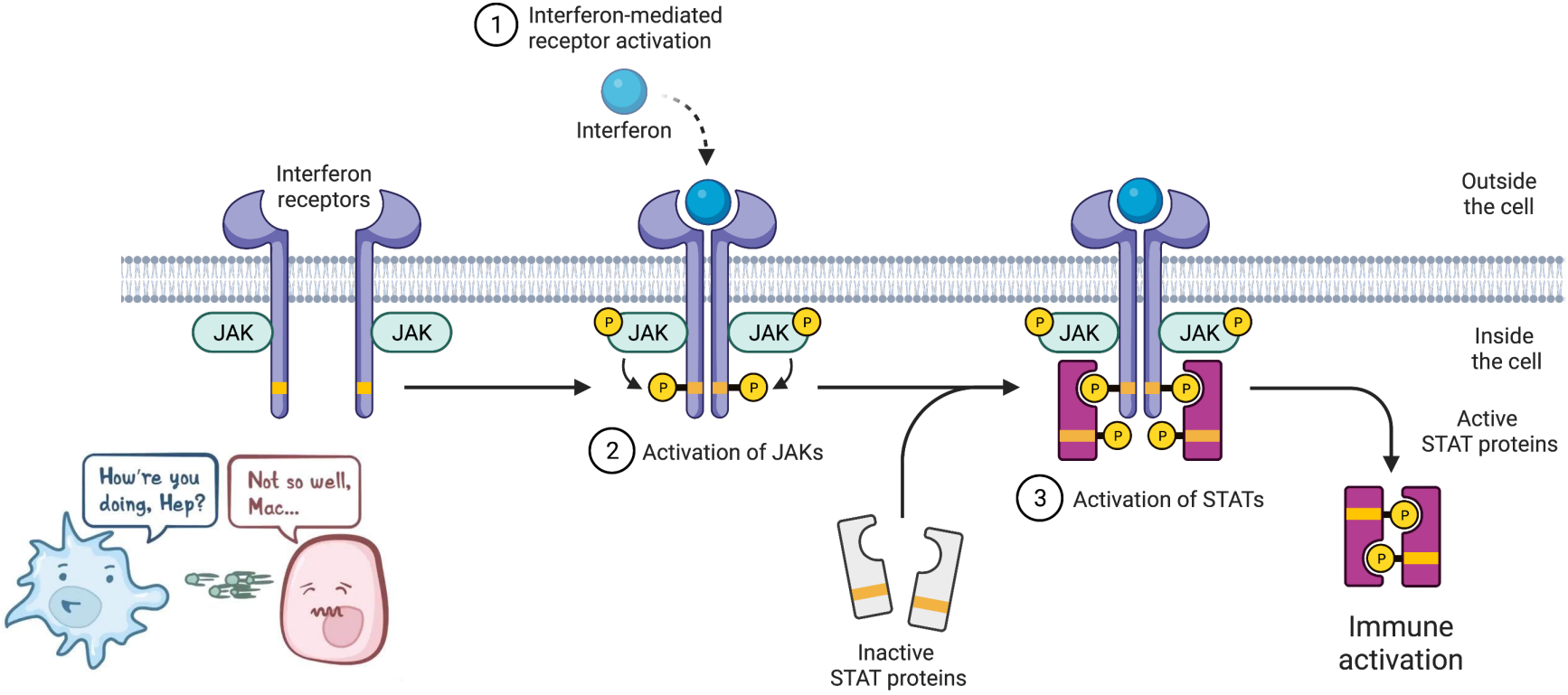
What is interferon signaling?



- Interferon signaling is an important part of the immune system involved in the anti-viral defense.
- Interferons are ‘cytokines’ that activate many different types of immune cells.
- Interferon hyperactivity is a known risk factor for autoimmunity.

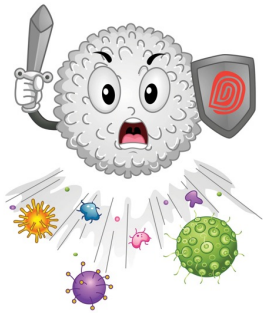
Why do people with Down syndrome have hyperactive interferon signaling?

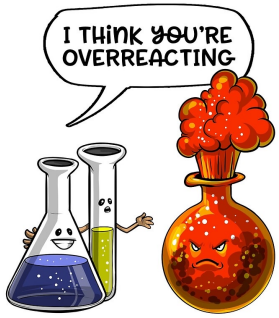
The interferon receptors are encoded on chromosome 21!
People with Down syndrome ‘over-produce’ interferon receptors

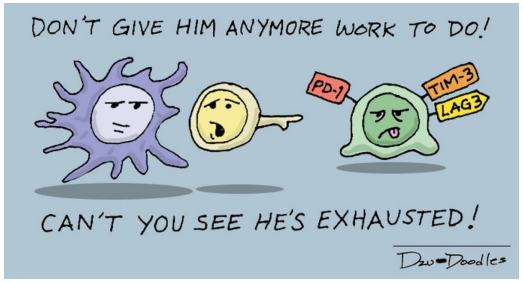


Interferon receptor ‘overdose’ is not good

- An extra copy of the interferon receptors leads to ‘over-reaction’ throughout the immune system.
- Interferon hyperactivity can cause the immune system to make mistakes and attack healthy tissues.
- Chronic interferon hyperactivity could lead to exhaustion of the immune system later in life.



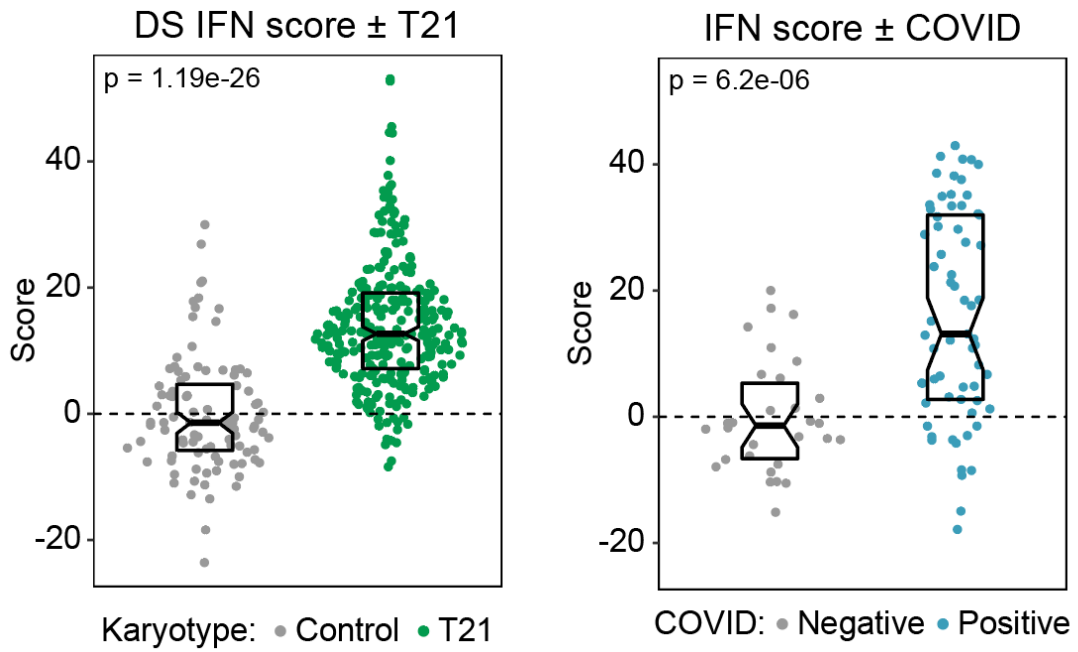




Too much of a good thing sometimes is bad…

Massive elevation of the interferon response in Down syndrome

Interferon scores are commonly used to monitor the degree of interferon activity



Interferon hyperactivity is similar to that observed during a COVID-19 infection

Would drugs that decrease the interferon response improve the health of persons with Down syndrome?

Approved therapies that decrease the interferon response: JAK inhibitors

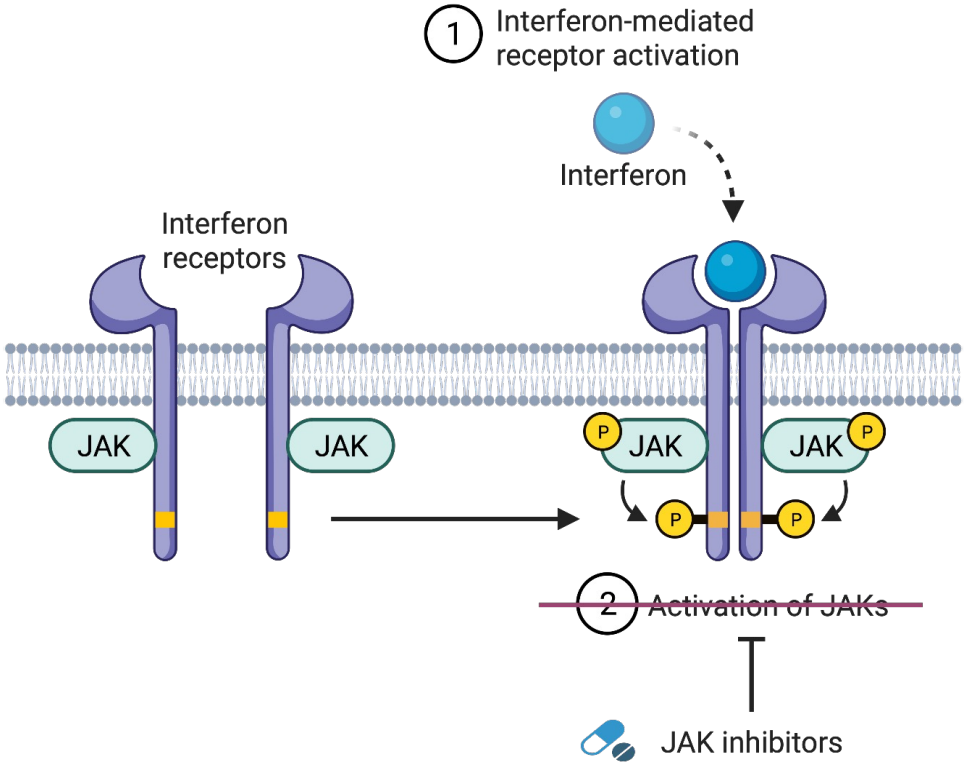
Target	JAK1/3	JAK1/2	JAK1	JAK1/2	JAK1
Rheumatoid arthritis	+	+	+		
Psoriatic arthritis	+		+		
Polyarticular course JIA	+				
Ulcerative colitis	+		+		
Atopic dermatitis			+		+
COVID-19		+			
Alopecia areata		+			
Chron's disease			+		
Polycythemia vera				+	
Ankylosing spondylitis			+		
Myelofibrosis				+	
GVHD				+	
Axial spondylarthritis			+		

There are many JAK inhibitors approved for 13 different indications!

These medicines are used by rheumatologists, dermatologists, gastroenterologists, hematologists and more!

Could JAK inhibitors 'normalize' the immune system in Down syndrome?

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.

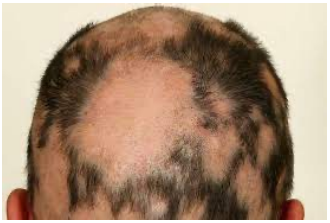
JAK inhibitors are taken daily orally as pills and have a short ‘half-life’ in the body.

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

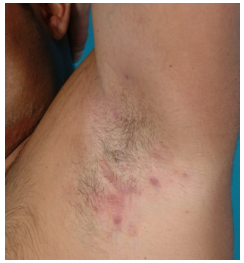
First clinical trial for JAK inhibition in Down syndrome

Treating five autoimmune skin conditions in one trial

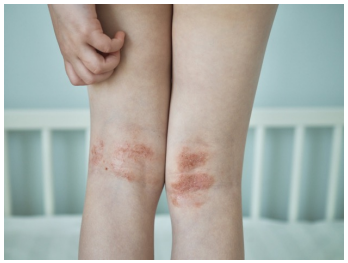
Alopecia areata (patchy hair loss)



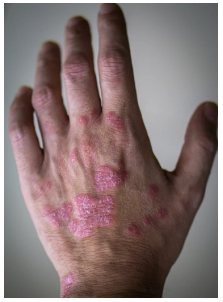
Hidradenitis suppurativa (boils)



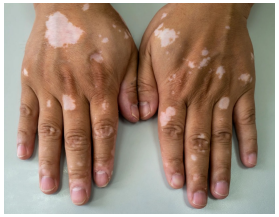
Atopic dermatitis (eczema)



Psoriasis



Vitiligo



All five conditions are more common in people with Down syndrome

More than 35% of adults with Down syndrome have been affected by one of these conditions

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

Funded by: NIH THE INCLUDE PROJECT NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

Study Objectives and Design

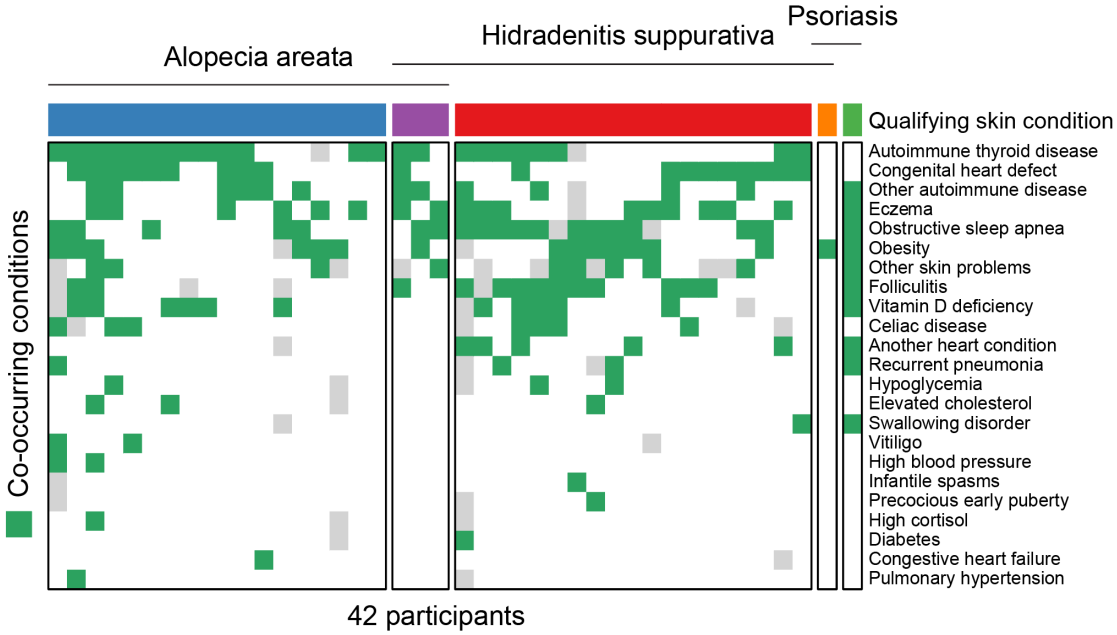
- Individuals with Down syndrome ages 12 – 50
- Everyone receives the medicine
- Travel and lodging expenses are covered

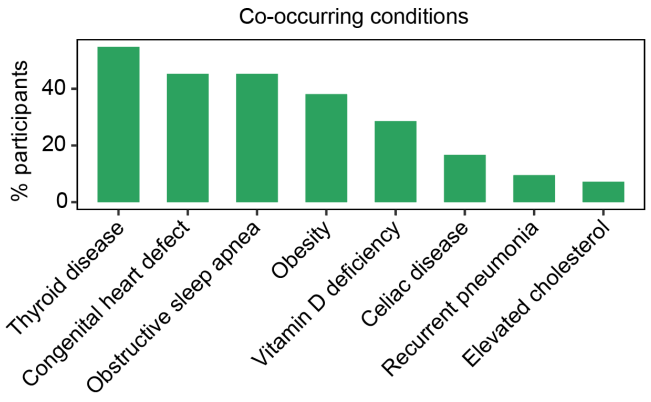
Goal 1: Define the **safety** profile in Down syndrome.
Goal 2: Determine the impact on **immune dysregulation**.
Goal 3: Define the impact on **immune skin conditions**.
Goal 4: Characterize impact on **cognition and quality of life**.

Is it safe?
Is it effective?
What are all the possible benefits of normalizing the immune system?

Clinical trials in Down syndrome: a labor of love

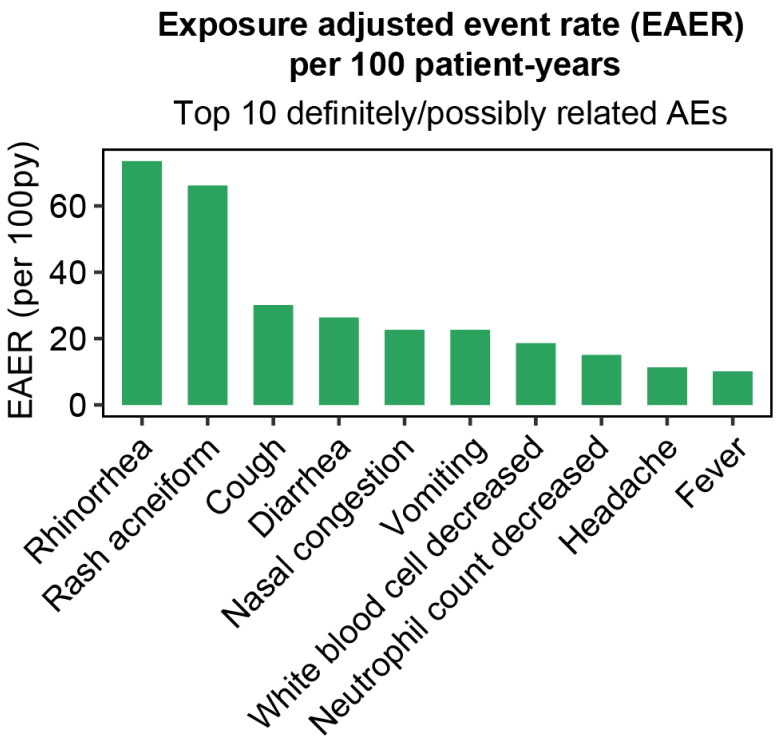
A population with massive medical complexity





The importance of tailored exclusion and inclusion criteria and monitoring protocols

Defining the safety profile of JAK inhibition in Down syndrome



Key findings:

Every 100 patient years:

~70 runny noses
~60 skin rashes
~30 coughs
~25 diarrheas
~20 cases of vomiting
10-20 events of lower white blood cell counts

Without a placebo arm, it is impossible to define whether these rates are lower or higher than expected.

Safety endpoint: met!

Concomitant medications considerations

- JAK inhibitor risks include thrombosis
- Estrogen-containing oral contraceptive pills (OCPs) also increase the risk of thrombosis

One Serious Adverse Event (SAE) reported:

- Blood clots
- Participant was taking OCPs
- Participant withdrawn; has fully recovered.
- Plans to resume tofacitinib as clinical care; OCP use discontinued

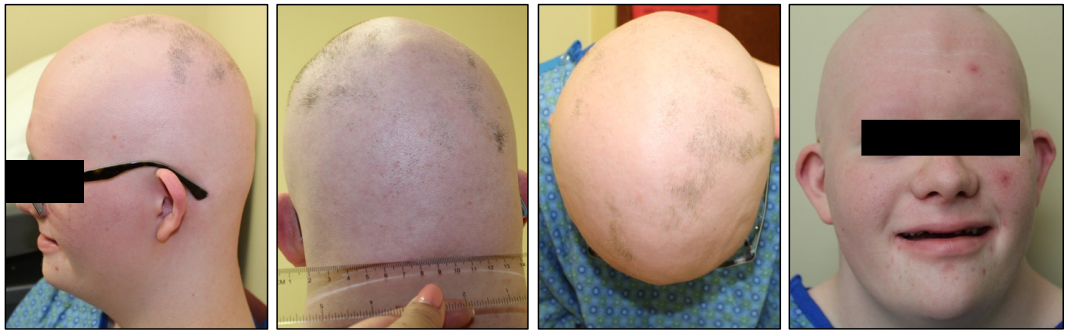
Clear improvements in skin pathology

- **14 of 18** participants saw improvements in alopecia areata
- **11 of 19** participants saw improvements in hidradenitis suppurativa
- **6 of 7** participants with co-occurring atopic dermatitis saw improvements
- **3 of 4** participants with psoriasis saw improvements
- **>60% of participants pursue a clinical prescription to continue treatment after the trial**

Male, 17 years old, alopecia areata

When a picture is worth a thousand words

Baseline
SALT = 86

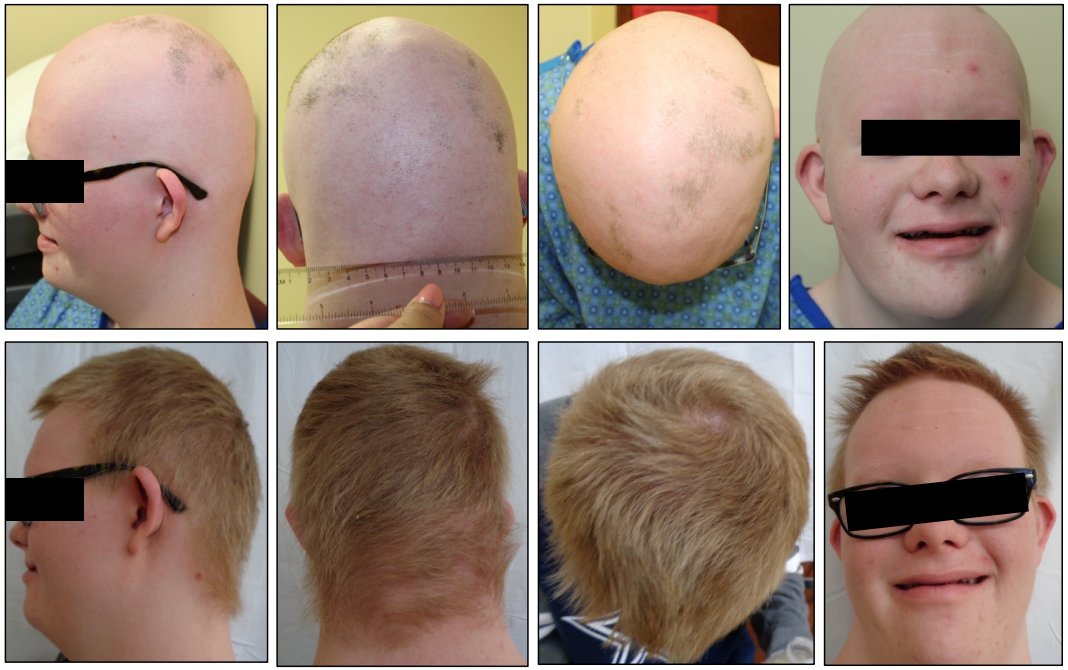


Male, 17 years old, alopecia areata

When a picture is worth a thousand words

Baseline
SALT = 86

Week 16
SALT = 4

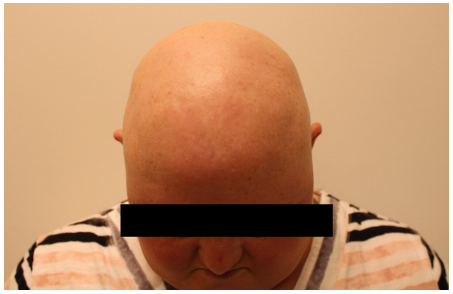


Participant referred known as ‘Ed Sheeran’ to the research team

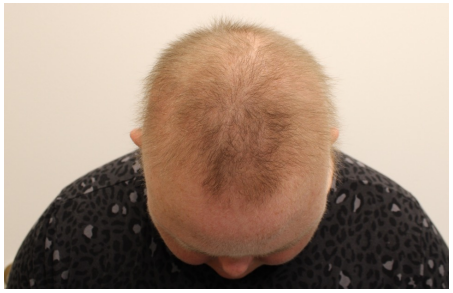
Participants travel from far away to participate

When a picture is worth a thousand words

Before

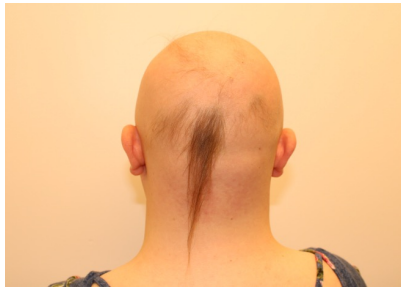


4 months

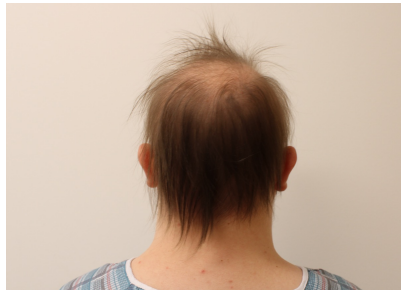


Female, 30 years old
from Australia!

Before



9 months

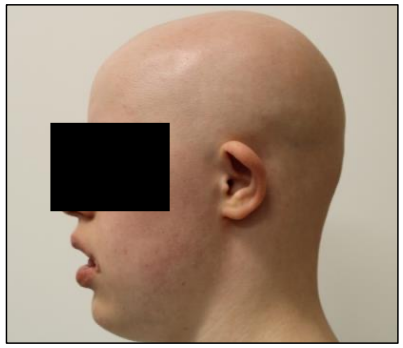
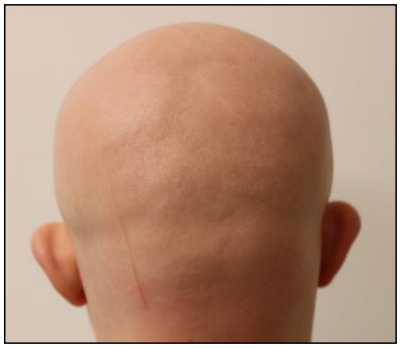
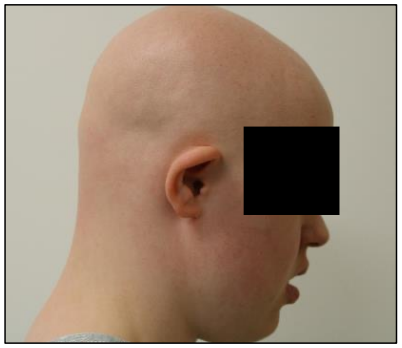


Female, 26 years old
from Texas!

Stopping the autoimmune attack to the scalp

Female, 17 years old, alopecia areata

Baseline
SALT = 100

Week 16
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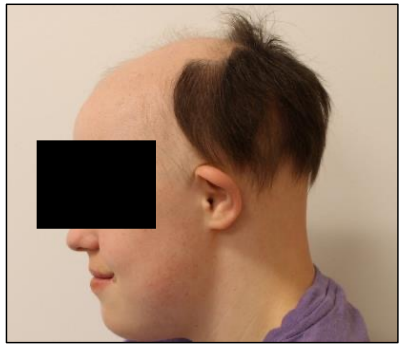
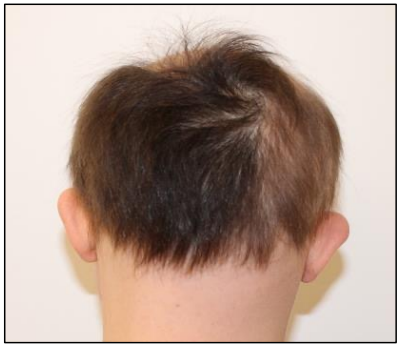
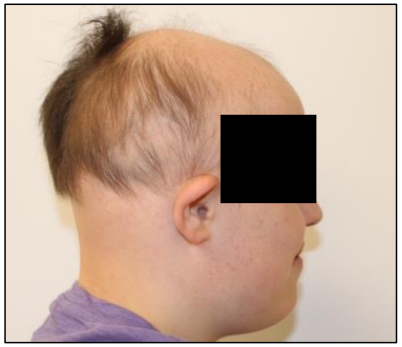
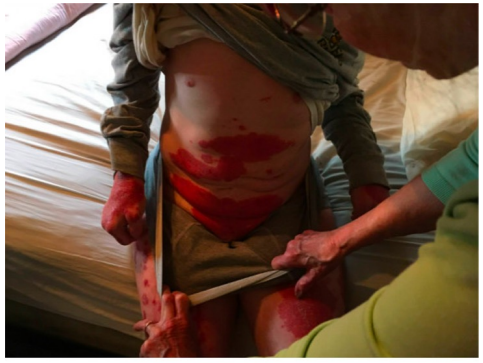




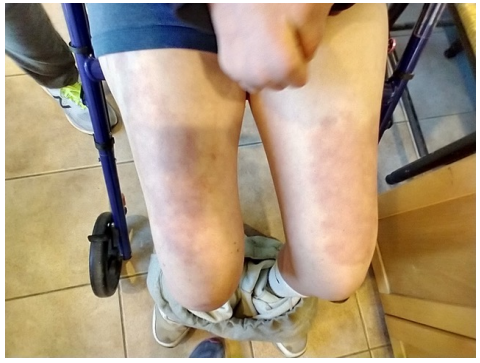
Male, 40 years old – Psoriatic arthritis

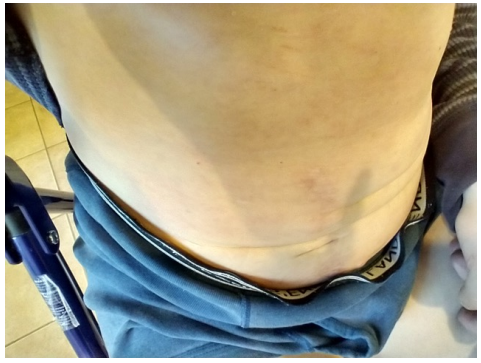
When a picture is worth a thousand words

Before



After





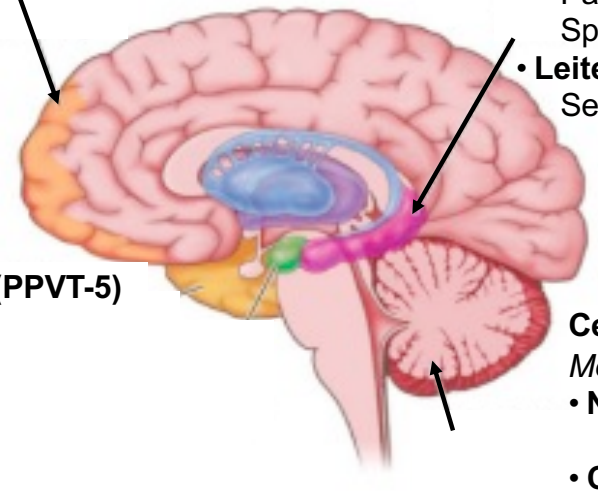
Participant monitored outside of the trial at the University of Vermont Medical Center

Characterizing effects on cognition and quality of life

Diverse cognitive tests to assess different domains of neurological function

Prefrontal Cortex
Working memory and executive function
- **Leiter 3**
  - Forward/Reverse Memory
  - Attention Sustained
  - Nonverbal Stroop

- **Kaufman Brief Intelligence Test (KBIT-2)**
  - Overall Development
- **Peabody Picture Vocabulary (PPVT-5)**
  - Expressive Vocabulary



Hippocampus
Episodic and spatial memory
- **CANTAB**
  - Paired Associate Learning
  - Spatial Span
- **Leiter 3**
  - Sequential Order

Cerebellum
Motor Control
- **NEPSY II**
  - Visuomotor
- **CANTAB**
  - Reaction Time Interval

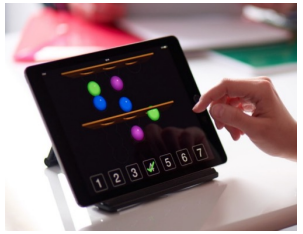
What is the impact of chronic inflammation on brain function?

Characterizing effects on cognition and quality of life

Improvements in:

- Self-reported scores of positive affect, general cognitive function, and anxiety. (PROMIS toolkit).
- Episodic and spatial memory (CANTAB test battery).

Patient-Reported Outcomes
Measurements Information Systems



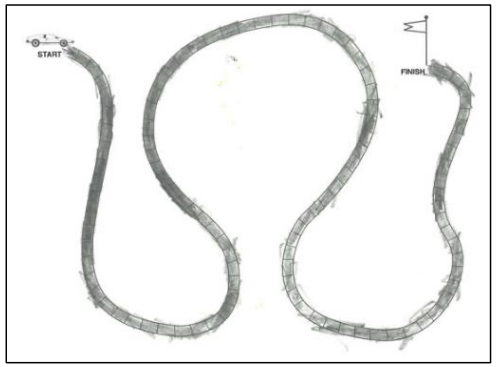
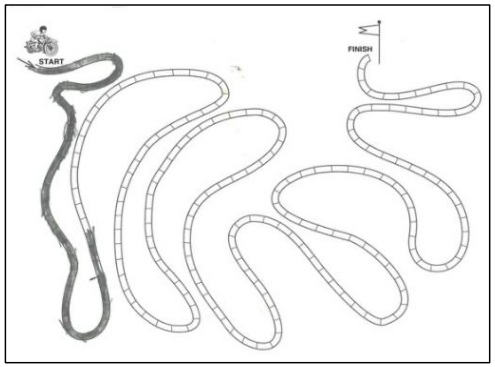
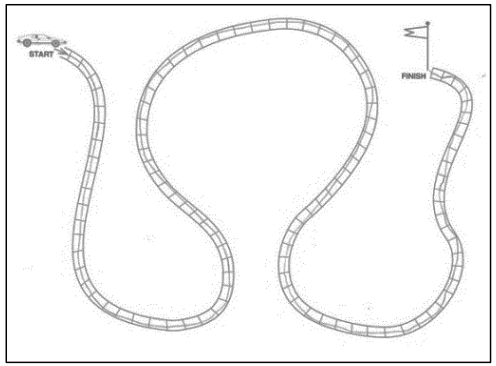
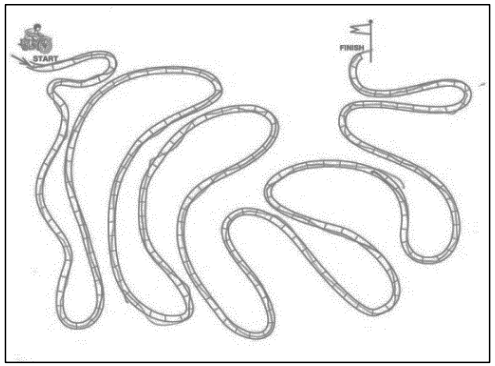
Cambridge Neuropsychological
Test Automated Battery

Disclaimer: we do not have a placebo control arm!

Female, 28 years old

History of Down syndrome Regression Disorder

Clear improvement in visuomotor function as measured by the NEPSY II test

	NEPSY II (car)	NEPSY II (motorcycle)
Baseline		
Week 16		

- Before treatment, the participant was receiving electroconvulsive therapy (ECT) three times a week
- The benefits were so obvious that participant was prescribed tofacitinib ‘off-label’ by her neuroimmunologist, and both Pfizer and Medicaid agreed to pay for it.

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 signs of immune dysregulation affecting the central nervous system (CNS).

- Is DSRD an autoimmune condition, akin to autoimmune encephalitis?

Short Communication

JAK inhibition in Down Syndrome Regression Disorder

Angela L. Rachubinski [a,b,*], Lina R. Patel [a], Elise M. Sannar [c], Ryan M. Kammeyer [d], Jessica Sanders [b], Belinda A. Enriquez-Estrada [a], Kayleigh R. Worek [a], Deborah J. Fidler [e], Jonathan D. Santoro [f,g], Joaquin M. Espinosa [a,h,*]

Journal of Neuroimmunology

August 2024

When the families drive the research

Story behind the design of the first randomized clinical trial for Down Syndrome Regression Disorder

Well+Being

A mystery illness stole their kids' personalities. These moms fought for answers.

Their children's decline was dramatic, with patients losing function in days or weeks, including the ability to talk, move or take care of themselves.

May 12, 2024

The Washington Post

Clinical trial for mechanistic investigation of therapies for Down Syndrome Regression Disorder

A collaboration between the Crnic Institute, Children's Hospital Colorado, and Children's Hospital Los Angeles.

Principal Investigators:

Santoro

Sannar

Espinosa

Co-Investigators:

Rachubisnki

Patel

Kammeyer

Galbraith

Consultants:

Sanders

Tartaglia

Charoensook

Funded by: NIH THE INCLUDE PROJECT NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Clinical trial for mechanistic investigation of therapies for Down syndrome Regression Disorder

Three goals:

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.

Is it safe? Is it effective? What is the mechanism?

A Phase II, three-arm, open-label, research intensive trial

Lorazepam
Brand name: Ativan
Benzodiazepine

IVIG
Brand name: Gammagard
Intravenous Immune Globulin

Tofacitinib
Brand name: Xeljanz
JAK inhibitor

All three medicines studied in this trial are already FDA-approved for **other** medical conditions

The power of ‘drug repurposing’: this study benefits from extensive available data for all three drugs

Open label: participants will know which medicine they are taking

No placebo arm, but instead ‘a delayed treatment group’ for comparison

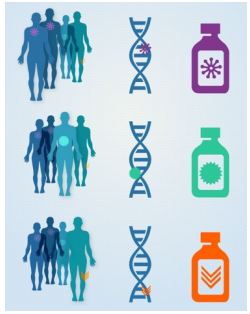
Why compare these three medicines?

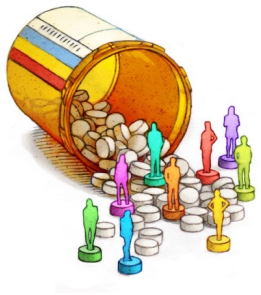
Who would benefit the most from which medicine?

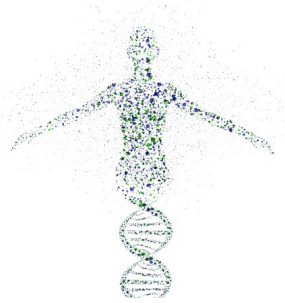
What are the diagnostic characteristics that could predict a good response?

Are there ‘biomarkers’ in the blood or cerebrospinal fluid that could match each participant to their best therapeutic option?

Developing a personalized medicine approach for the treatment of DSRD

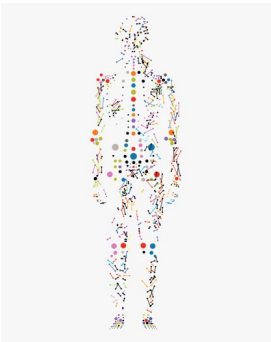






A research-intensive clinical trial

- Blood samples and cerebrospinal fluid samples will be collected for deep analysis using cutting-edge technologies.
- Each participant will undergo significant testing to monitor for potential improvements in diverse areas of brain function.
- A multidisciplinary team with expertise in psychiatry, neurology, psychology, immunology, genetics, and molecular biology will analyze the data.



Summary of Study Design

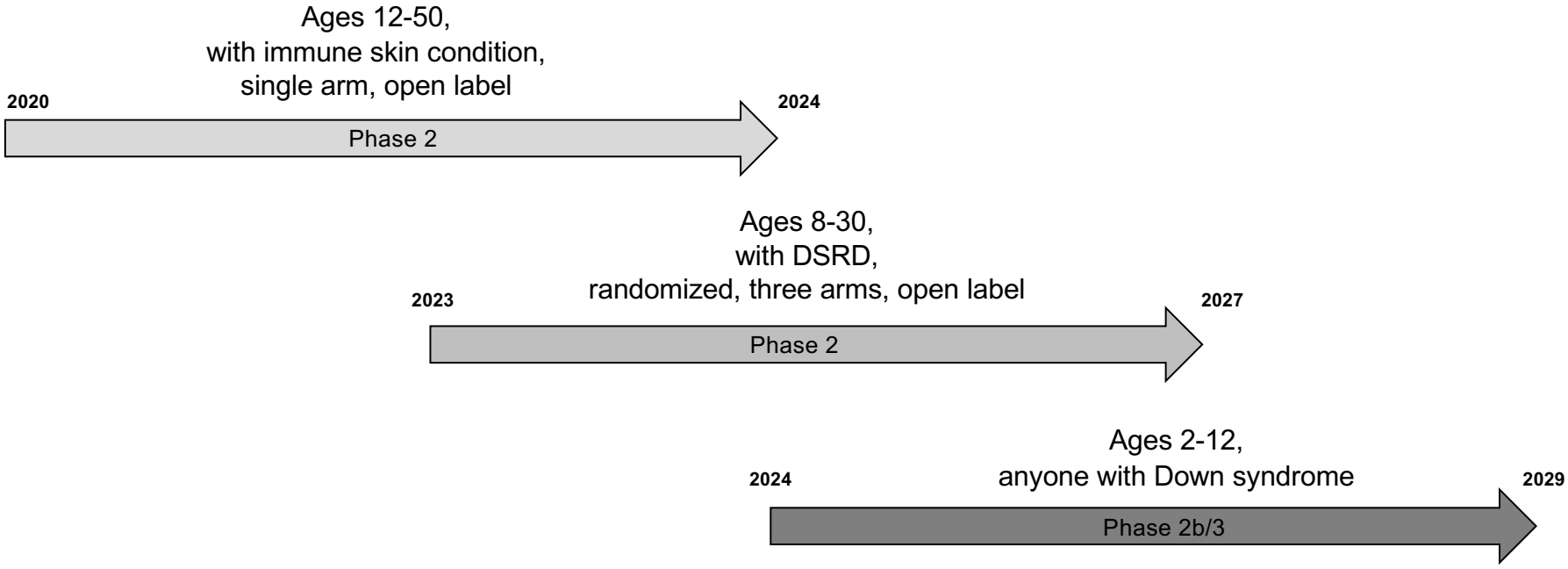
- Individuals with possible or probable Down Syndrome Regression Disorder
- Ages 8-30 years old
- Two sites with 30 participants each
- 60 participants total / 20 on each treatment
- 12 weeks (3 months) of treatment with one medicine

Anschutz Medical Campus/ Children's Hospital Colorado

Children's Hospital Los Angeles

Translating discoveries into clinical trials:

With safety as the top priority, testing JAK inhibition at earlier ages:



MISSION-1:
Modulating the **I**mmune **S**ystem in Down **S**yndrome
for **I**mproved **O**utcomes and **N**eurodevelopment

Clinical trial for pediatric JAK inhibition in Down syndrome

- Ages 2-12, Down syndrome
- No requirement for qualifying co-occurring conditions
- 6 months of JAK inhibition (tofacitinib), dosed by weight
- Inclusion and exclusion criteria as per standards in pediatric rheumatology
- Two arms: JAK inhibitor versus ‘standard of care’



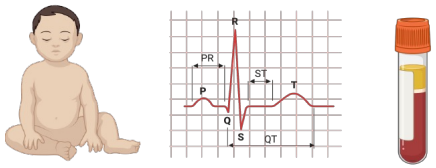

Initial phase funded by: the **Anschutz Acceleration Initiative** and the **Anna and John J. Sie Foundation**

Clinical trial for pediatric JAK inhibition in Down syndrome

Aim 1
Safety profile and clinical benefits

Adverse event monitoring

Health assessment and clinical labs



Leads:
Fuhlbrigge, Bloom, Tarshish

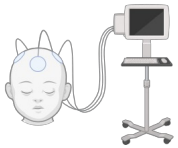
Aim 2
Effects on neurodevelopment and neurological health

Cognitive function

Language

Social development

Neurological health



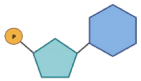
Leads:
Fidler, Patel, Kammeyer

Aim 3
Effects on pathophysiology

Transcriptome

Proteome

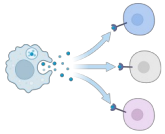
Metabolome



Neurodegeneration + neuroinflammation

Autoantibodies

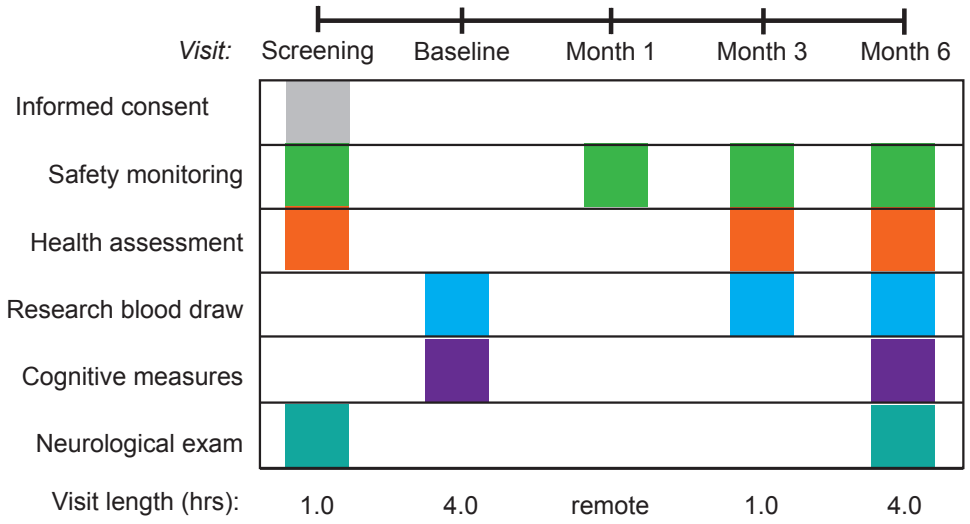
Immune system



Leads:
Human Trisome Project team

Clinical trial for pediatric JAK inhibition in Down syndrome

Six months of treatment, standard follow up as per rheumatology guidelines



A multidimensional investigation of the effects of JAK inhibition

Initial phase funded by: the **Anschutz Acceleration Initiative** and the **Anna and John J. Sie Foundation**

Paving the way for a Phase III clinical trial

10+ JAK inhibitors approved globally

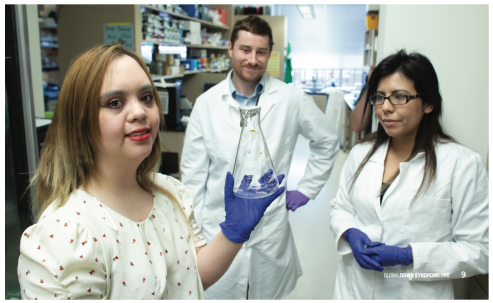
*2 of them approved for 2 years and older

Tofacitinib comes off patent in the next 14 months!

The first generic JAK inhibitors may be on the horizon…

Conclusions

- Dysregulation of the immune system can cause many health issues in Down syndrome.
- Normalizing the immune system could improve the health and quality of life of persons with Down syndrome.
- Persons with Down syndrome participating in research projects are enabling transformative discoveries that help all people with Down syndrome.



Reach out to learn more!

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Lyndy Bush
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THE INCLUDE PROJECT

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NIH National Heart, Lung, and Blood Institute

NIH National Institute of Allergy and Infectious Diseases

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

GLOBAL DOWN SYNDROME FOUNDATION®

ANNA & JOHN J. SIE FOUNDATION

NIH National Center for Advancing Translational Sciences

NIH National Institute on Aging

NIH National Institute on Deafness and Other Communication Disorders
Advancing the science of communication to improve lives

School of Medicine
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

INCLUDE Data Coordinating Center

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The research participants and their families

Michelle Sie Whitten and the amazing team at the Global Down Syndrome Foundation