Recent research advances and clinical trials benefiting people with Down syndrome

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ANSCHUTZ MEDICAL CAMPUS

LINDA CRNIC INSTITUTE for DOWN SYNDROME

GLOBAL DOWN SYNDROME FOUNDATION

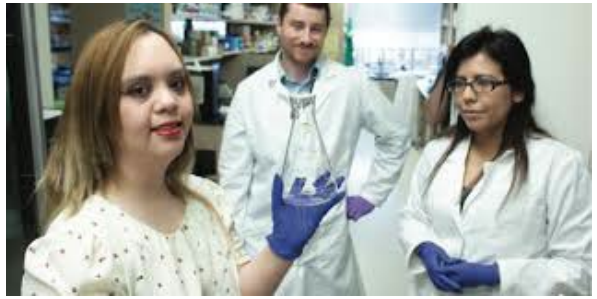
University of Colorado Anschutz Medical Campus

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

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

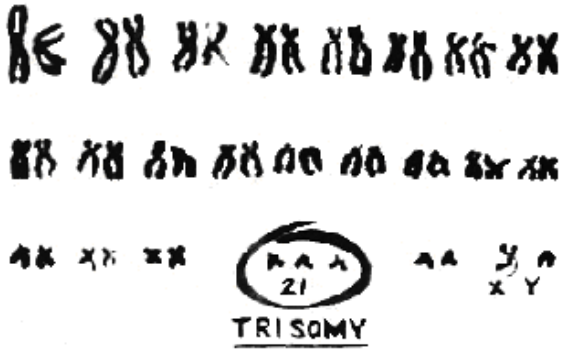
Cancer

Atherosclerosis

Hypertension

Allergies

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



Autoimmunity

Alzheimer’s

Leukemias

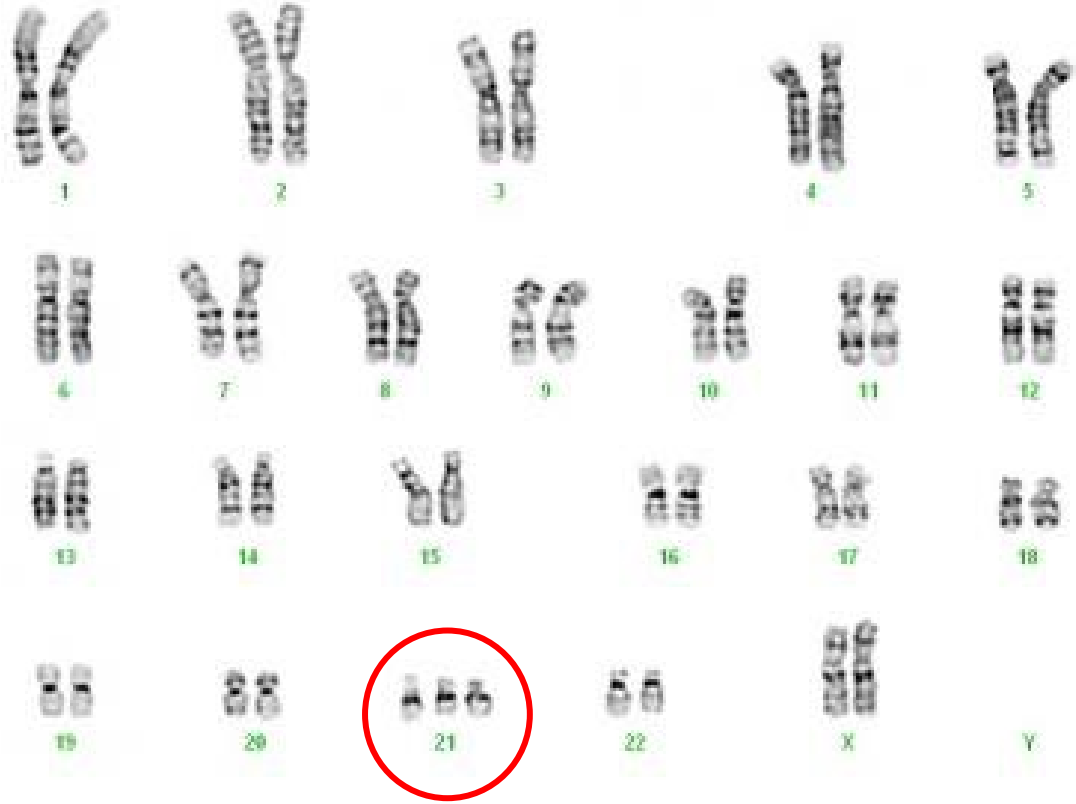
COVID-19

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?

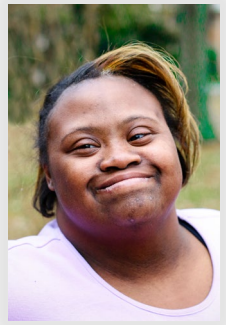
How could we counteract the undesired effects of chromosome triplication and gene overdose to benefit people with Down syndrome?

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

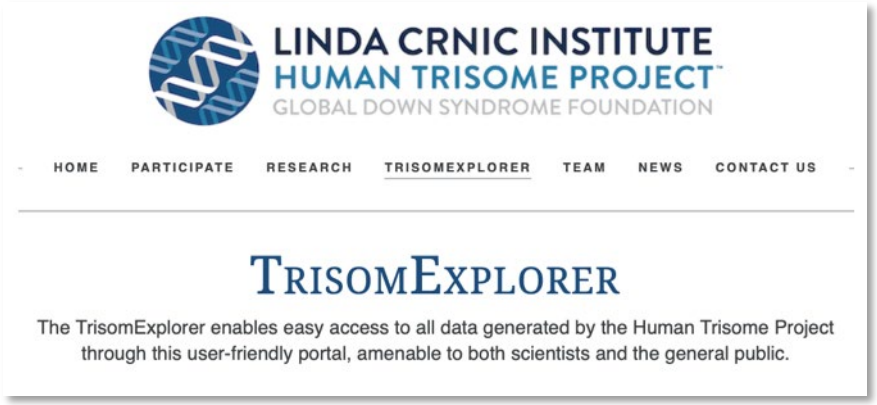
What factors define the ultimate clinical impacts of the extra chromosome?

The Crnic Institute Human Trisome Project (HTP)

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

More than **1100** participants recruited since 2016!

www.trisome.org



Thousands of datasets generated

900+ Clinical histories

500+ Metabolomes

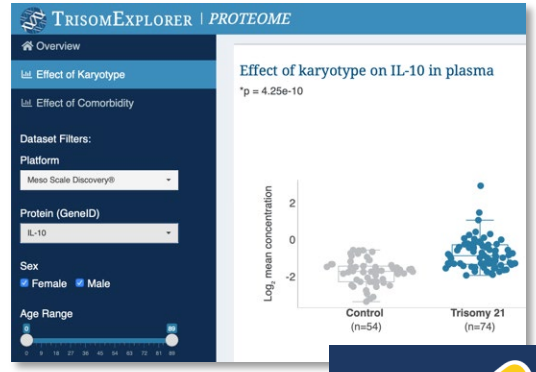
400+ Genomes

400+ Immune maps

500+ Transcriptomes

500+ Microbiomes

TRISOMEXPLORER



INCLUDE Data Hub

30+ Projects supported

20+ 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

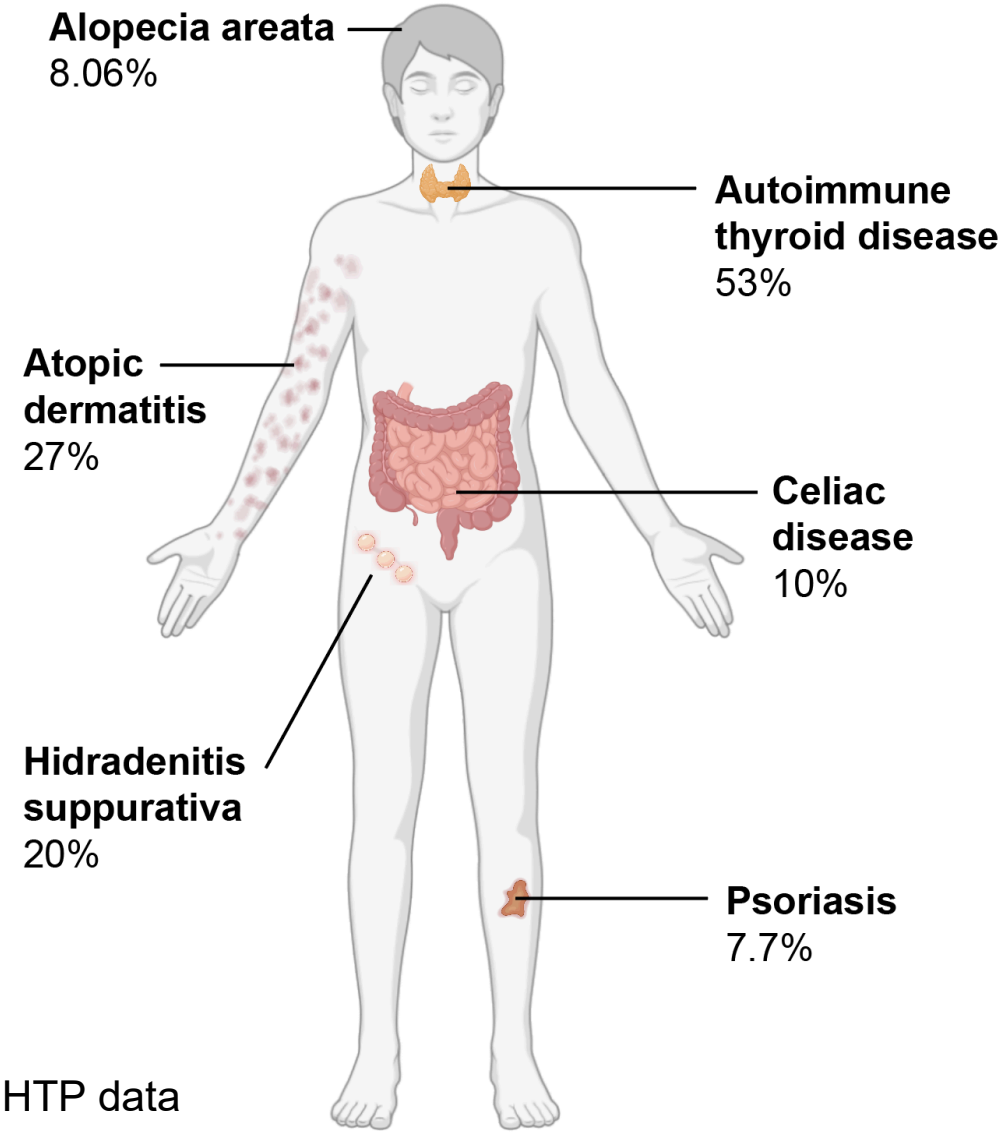
ClinicalTrials.gov Identifier: NCT04246372

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

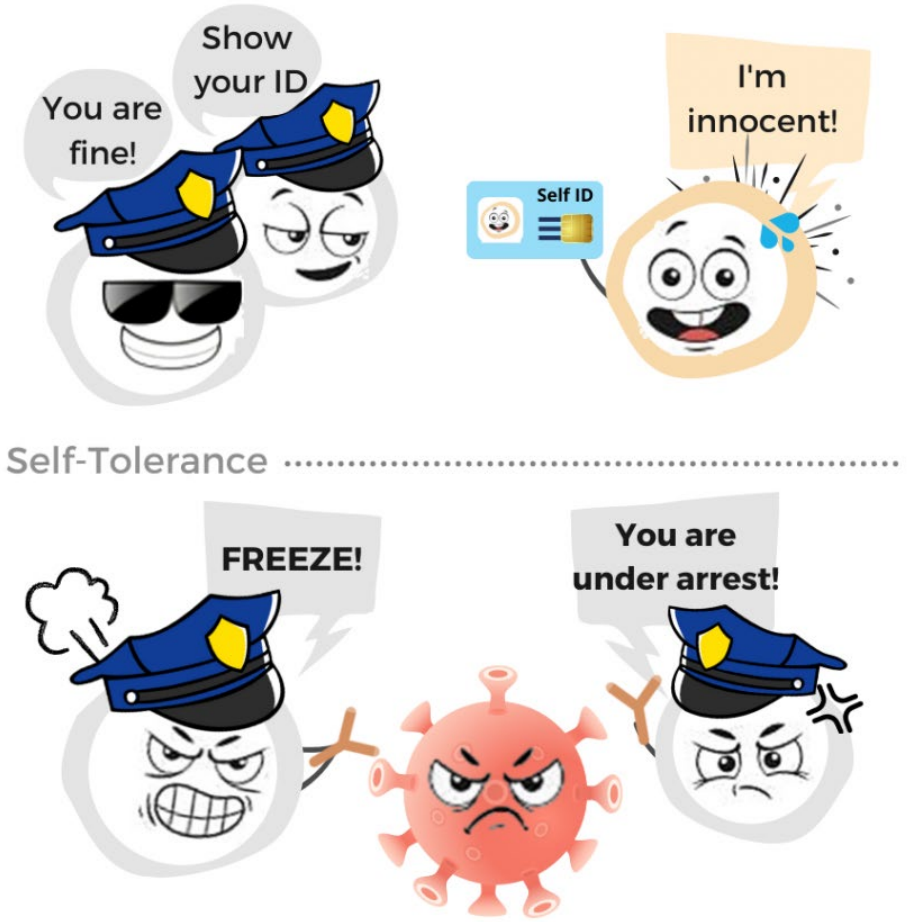
>25% adults with Down syndrome have been diagnosed with one or more autoimmune skin conditions

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

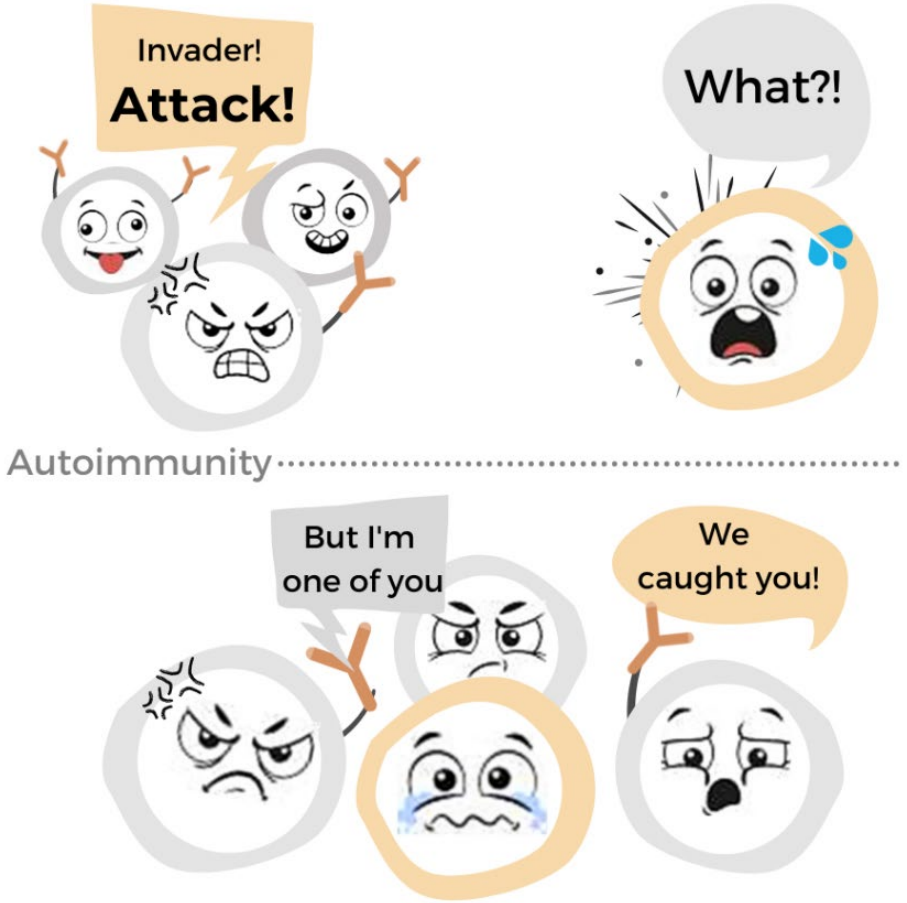
Type I diabetes, 'Down syndrome arthropathy', and other, more rare autoimmune conditions, are also more common

Autoimmunity in a nutshell:

Good: self-tolerance



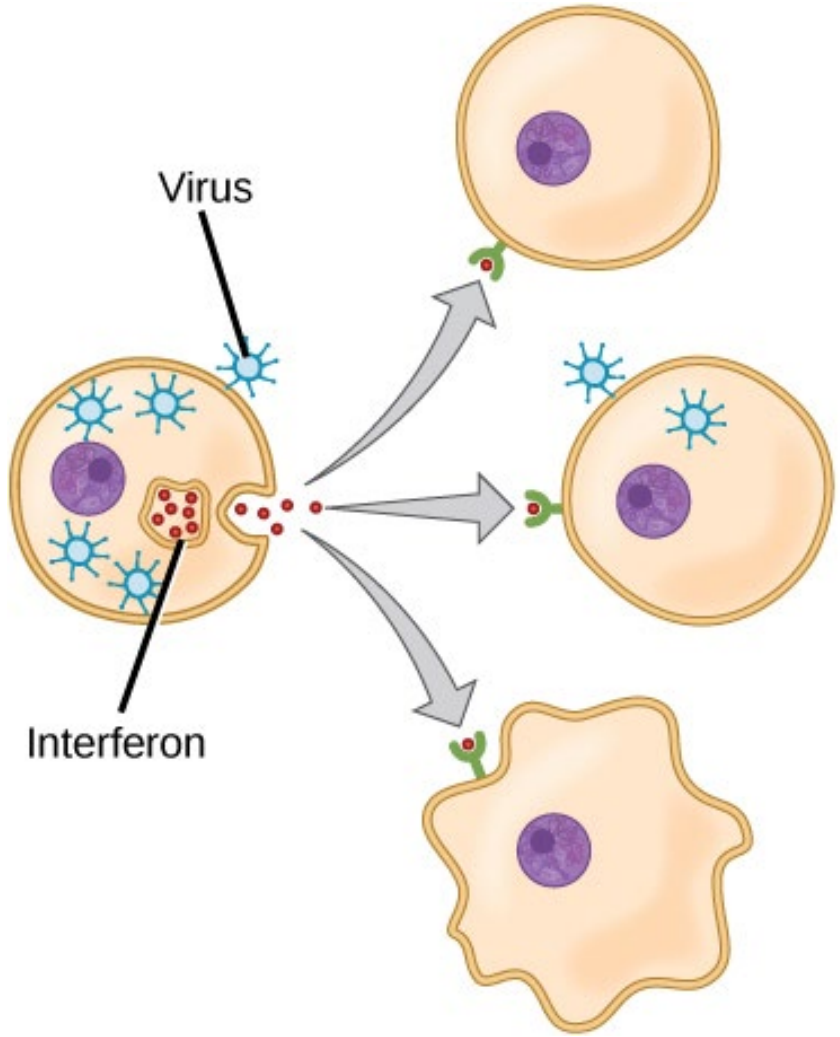
Bad: self-harm



Adapted from Advanx Health blog

People with Down syndrome have hyperactive interferon signaling

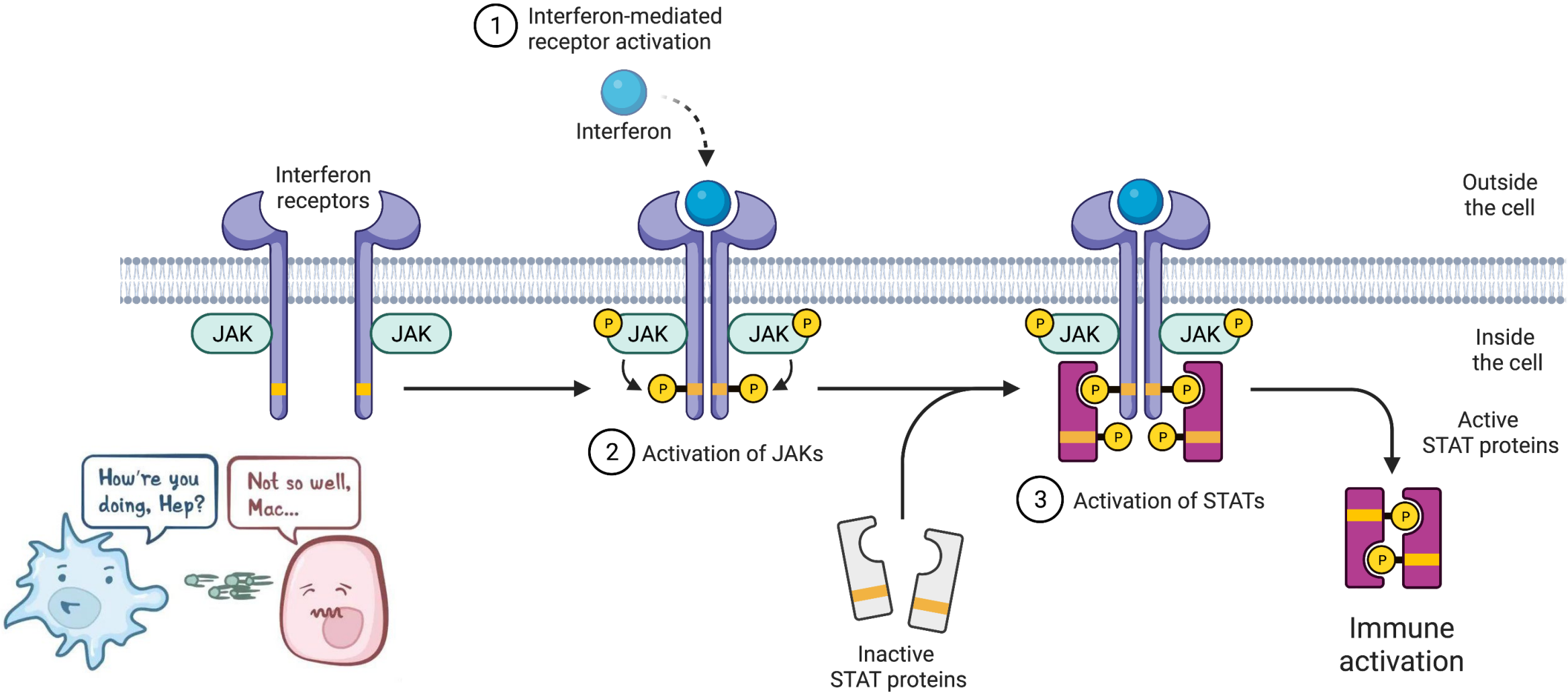
What is interferon signaling?



- 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

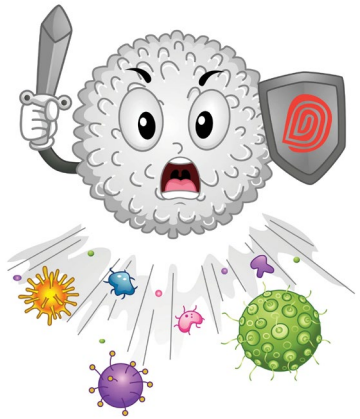


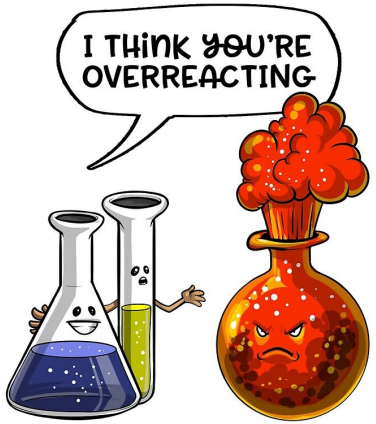
Interferon receptor ‘overdose’ is not good

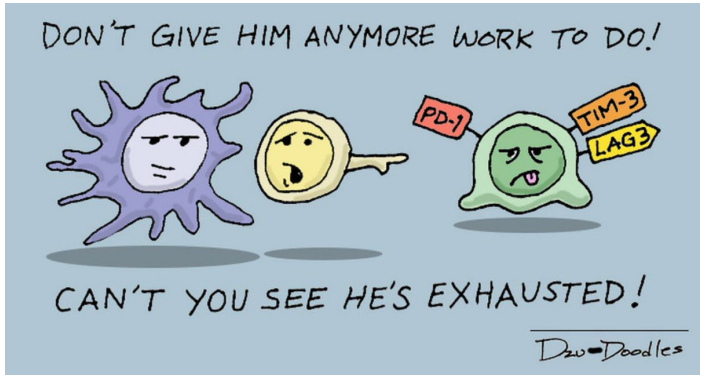
- An extra copy of the interferon receptors leads to ‘over-reaction’ throughout the immune system.

- 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…

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

Approved therapies that decrease the interferon response: JAK inhibitors

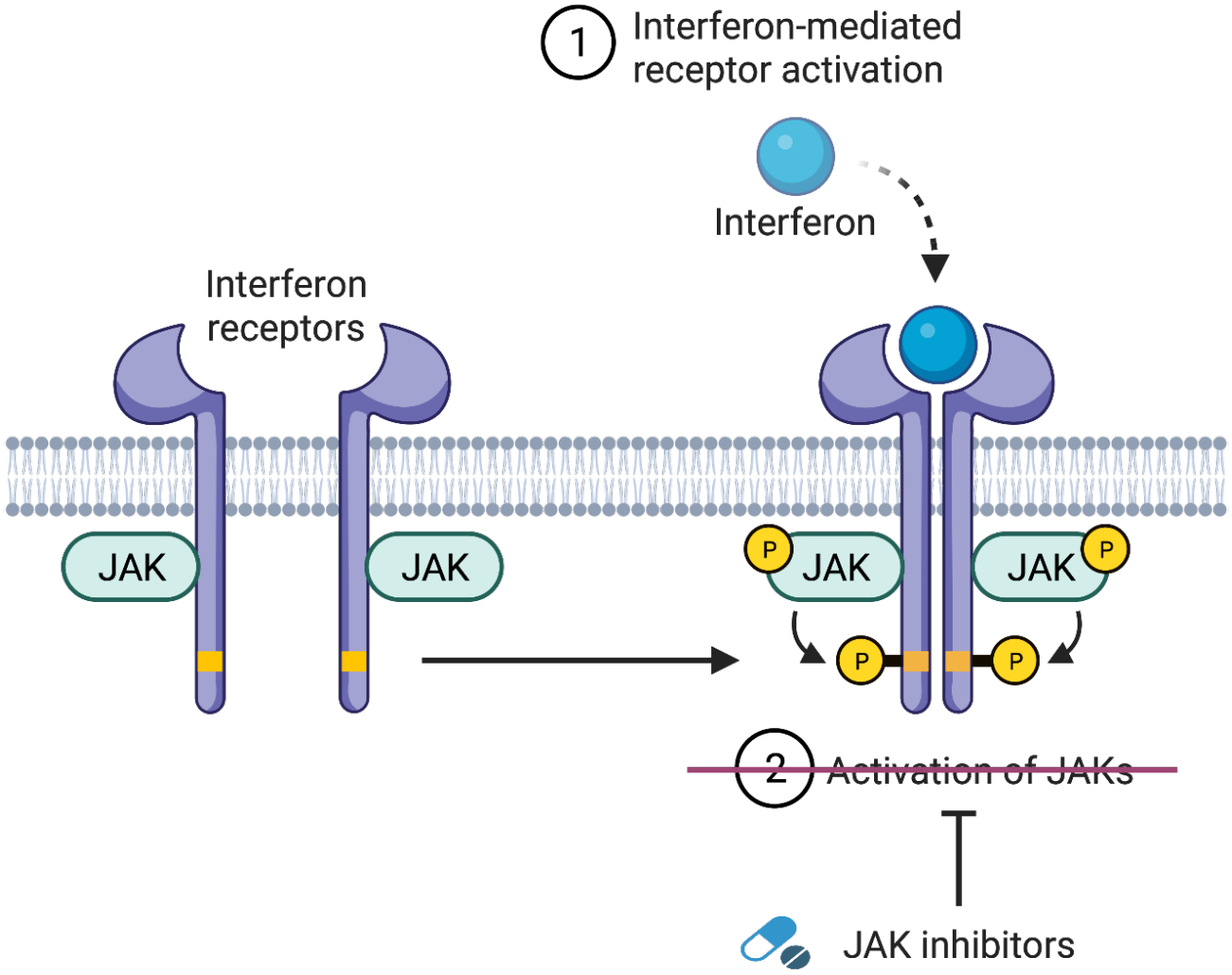
Target	JAK1/3	JAK1/2	JAK1	JAK1/2	JAK1
Rheumatoid arthritis	+	+	+		
Psoriatic arthritis	+		+		
Polyarticular course JIA	+				
Ulcerative colitis	+		+		
Atopic dermatitis			+		+
COVID-19		+			
Alopecia areata		+			
Chron's disease			+		
Polycythemia vera				+	
Ankylosing spondylitis			+		
Myelofibrosis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

Crnic Institute's 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 25% 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?

Top level results

Analysis of first 10 participants

- **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


Norris


Dunnick


Wallace


Gurnee


Rachubinski


Patel


Fidler

Benefits going well beyond skin deep!

- All participants showed normalized immune markers
- 7/7 participants with autoimmune thyroid disease displayed decreased levels of ‘autoantibodies’
- Significant improvements in measures of spatial memory, visuomotor function, and anxiety/depression scores.
- **7/10 participants continue to take the medicine with a prescription**.


Norris


Dunnick


Wallace


Gurnee


Rachubinski

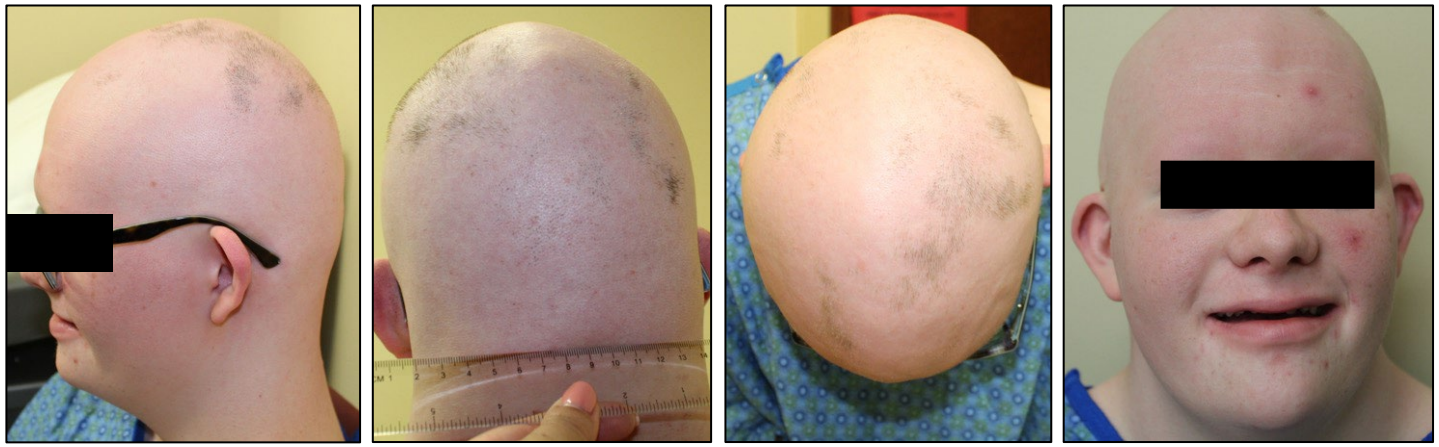

Patel


Fidler

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 all over the world 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!

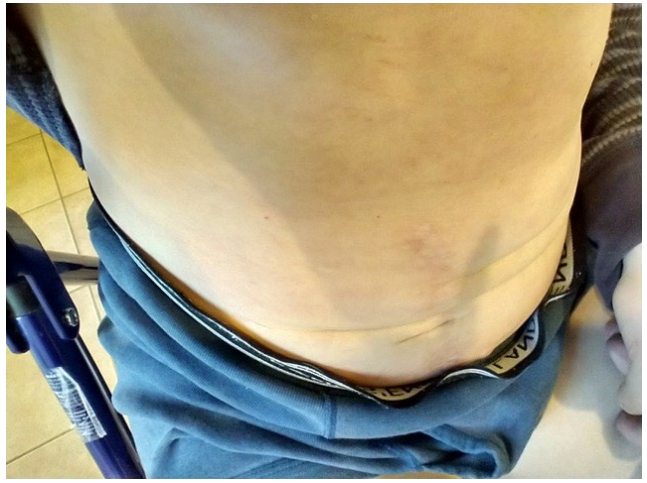
Stopping the autoimmune attack to the scalp

Male, 40 years old – Psoriatic arthritis

When a picture is worth a thousand words

Before

After

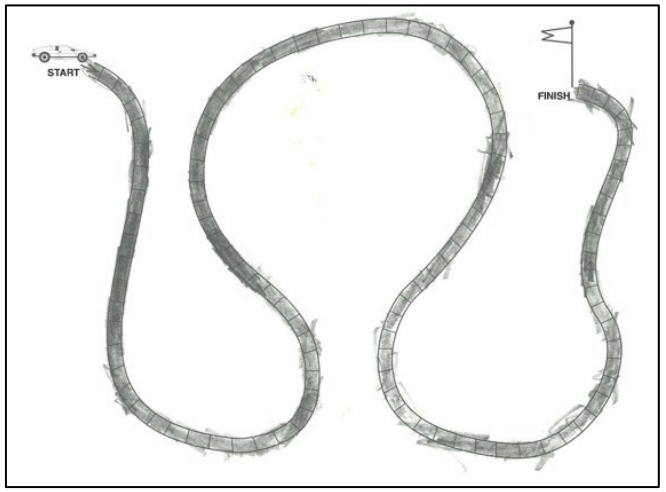
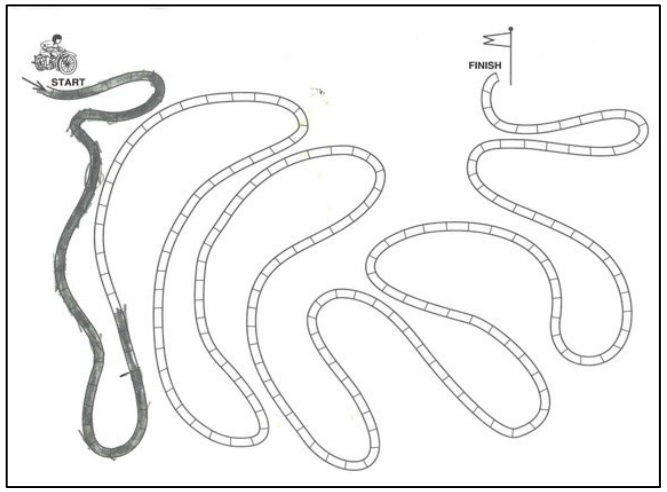
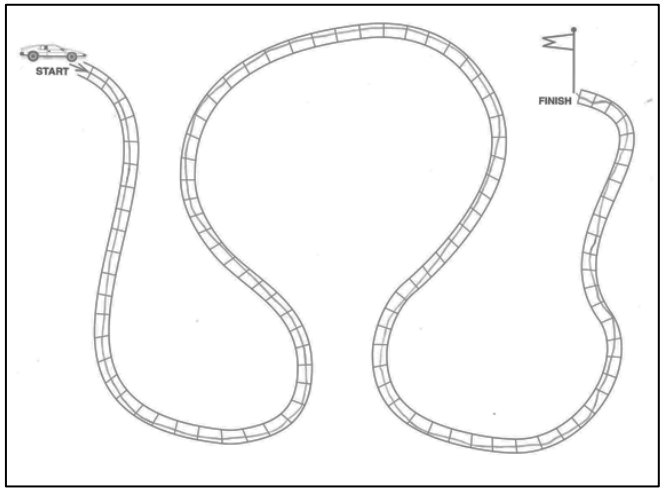
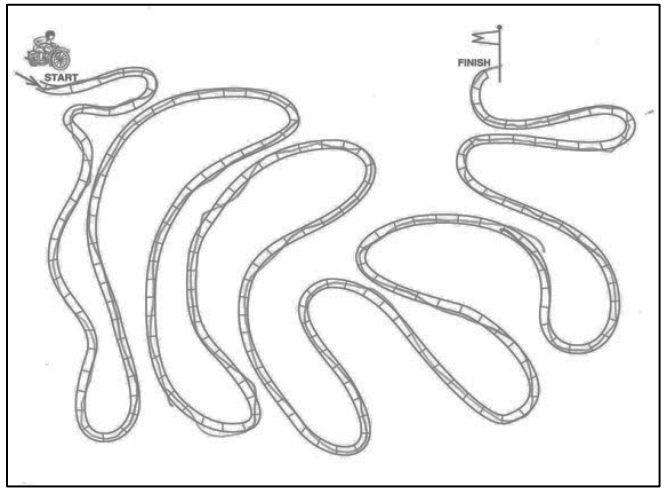


Participant monitored outside of the trial at the University of Vermont Medical Center

Female, 28 years old

History of Down syndrome Regression Disorder

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

	NEPSY II (car)	NEPSY II (motorcycle)
Before		
After		

- Before treatment, the participant was receiving electroconvulsive therapy (ECT) three times a week
- Today, the participant is not receiving ECT or any other medication except tofacitinib.
- The benefits are so obvious that participant was prescribed tofacitinib ‘off-label’ by neuroimmunologist, and both Pfizer and Medicaid agreed to pay for it.
- Participant will be presenting at this conference!

Down syndrome Regression Disorder (DSRD)

- A rare but devastating condition characterized by catatonia, loss of speech, 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), often associated with preceding immune trigger events.

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

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

Recruiting now!

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.

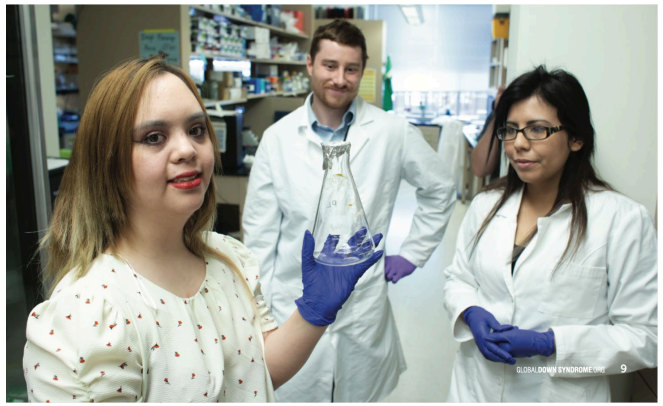
Is it safe?

Is it effective?

What is the mechanism?

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.



Learn more:

Use QR code or learn more at https://bit.ly/TofainDS

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Acknowledgements

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Lina Patel

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Lina Patel
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Laurie Ryan (NIA)
Erika Tarver (NIA)
And so many many more!

Many many collaborators at the University of Colorado

The amazing team at the Global Down Syndrome Foundation

THE INCLUDE PROJECT

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

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

NIH National Center for Advancing Translational Sciences

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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!

U.S. Representative Cathy McMorris Rodgers (R-WA) speaks while Dr. Joaquín Espinosa, Michelle Sie Whitten, and Dr. Richard Hodes look on.