Research & Clinical Trials Aimed at Elongating Life & Improving Health Outcomes in Down syndrome

June 23th, 2022

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School of Medicine
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

LINDA CRNIC INSTITUTE for DOWN SYNDROME

GLOBAL DOWN SYNDROME FOUNDATION

University of Colorado Anschutz Medical Campus

Children's Hospital Colorado

uchealth

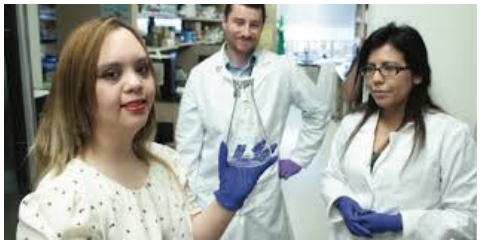
A network of affiliate organizations

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

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

180+ scientific publications since 2012

GLOBAL DOWN SYNDROME FOUNDATION®

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People with Down syndrome have a different ‘disease spectrum’

Cancer

Atherosclerosis

Hypertension

Allergies

Autoimmunity

COVID-19

Alzheimer’s

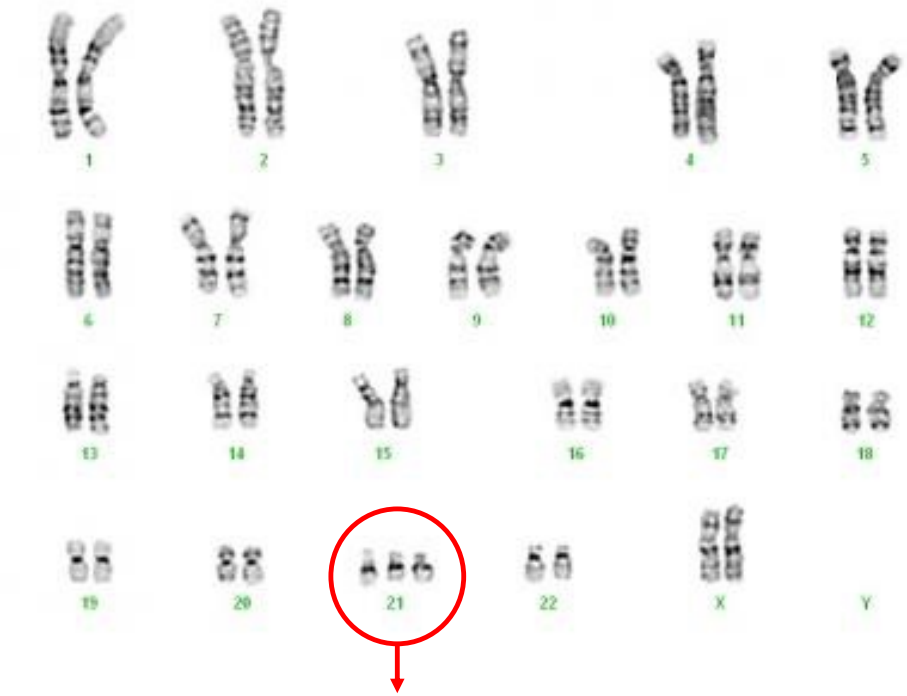
Leukemia

Autism, Seizures, Congenital Heart Defects and more…

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

How does an extra copy of chromosome 21 exert these effects?

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?

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

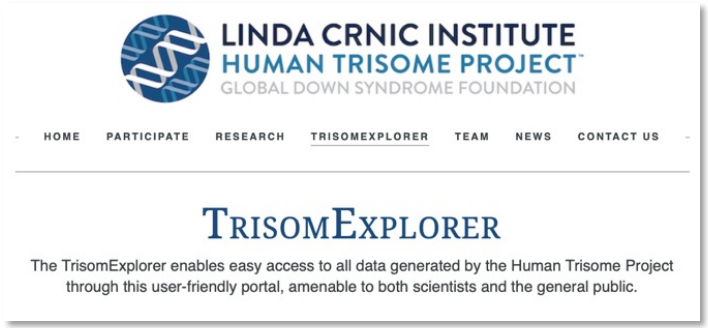
NIH U.S. National Library of Medicine
ClinicalTrials.gov

The Crnic Institute Human Trisome Project (HTP)

A large and detailed cohort study with deep clinical metadata, a multidimensional biobank, and a public researcher portal

More than **800** participants recruited since 2016!

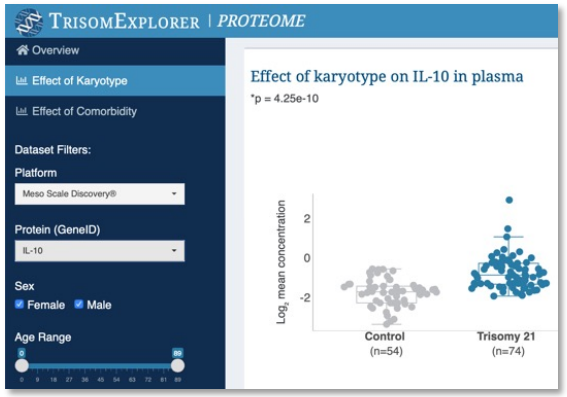
www.trisome.org



Hundreds of datasets generated

- **700+** Clinical histories
- **500+** Metabolomes
- **400+** Transcriptomes
- **400+** Immune maps
- **500+** Cytokine profiles
- **500+** Microbiomes

TRISOMEXPLORER



30+ Projects supported

20+ Papers published / under review

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?





The likely culprit: a hyperactive 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 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

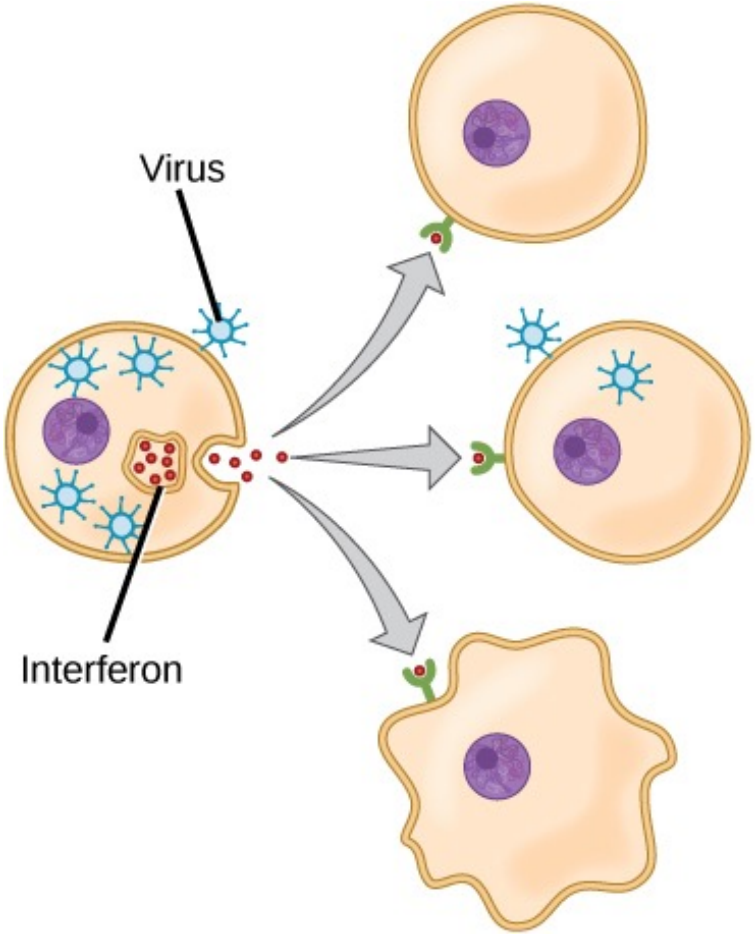
Trisomy 21 dysregulates T cell lineages toward an autoimmunity-prone state associated with interferon hyperactivity

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

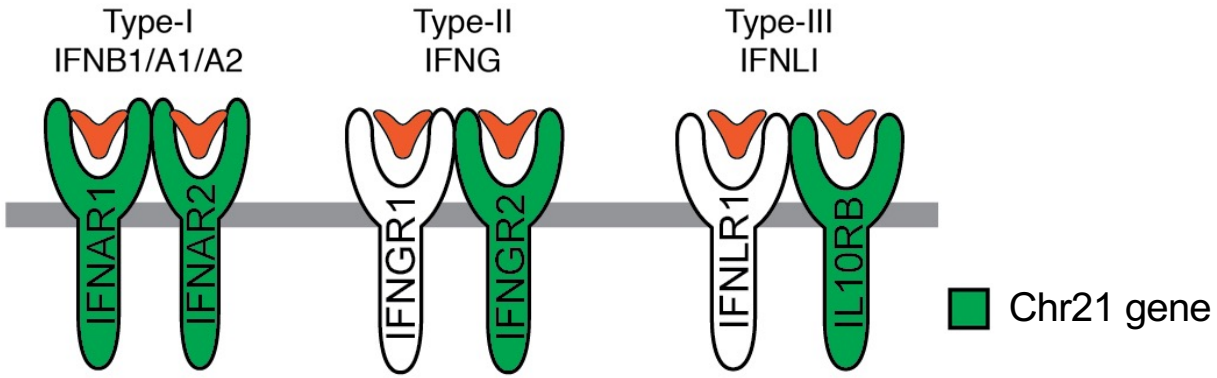
2019

What is interferon signaling?

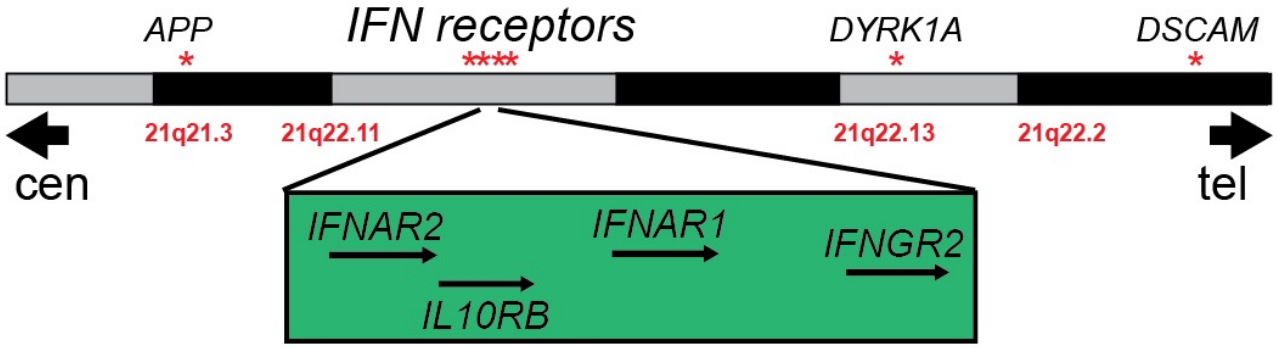


- Interferon signaling is an important part of the immune system involved in the anti-viral defense
- Interferon signaling activates many different types of immune cells
- Interferon hyperactivity is a known risk factor for autoimmunity

What drives interferon hyperactivity in Down syndrome?
4 of the 6 interferon receptors are encoded on chr21!!!



Human chromosome 21



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 general 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.

Too much of a good thing sometimes is bad…

Would drugs that decrease interferon signaling improve health outcomes in Down syndrome?

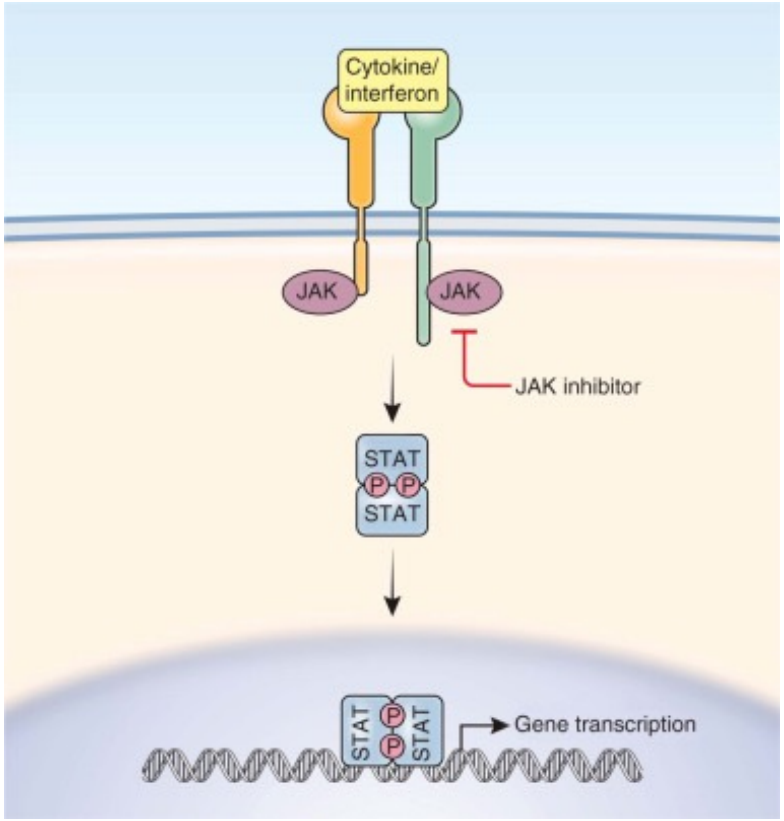
FDA-approved therapies that decrease the interferon response: JAK inhibitors

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), polyarticular JIA (2020)
Lilly	olumiant® (baricitinib) tablets	JAK1&2	Rheumatoid arthritis (2018), COVID-19 (2022)
abbvie	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

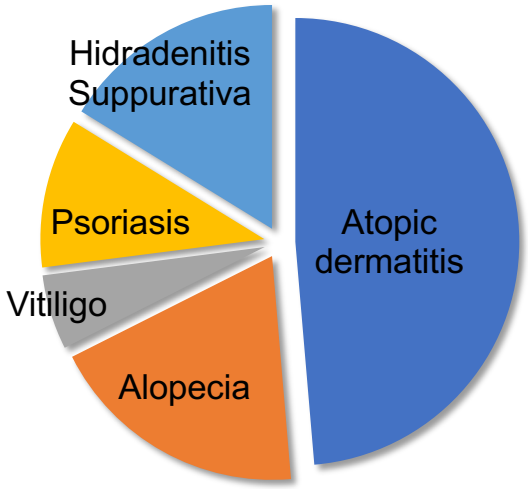


JAK inhibitors are small molecules designed to inhibit the JAK enzymes acting ‘downstream’ of the interferon receptors.

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



NIH

THE INCLUDE PROJECT

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

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
  - Optional 24-week Extension Arm
- Moderate-to-severe autoimmune skin condition:
  - Psoriasis
  - Vitiligo
  - Alopecia areata (affecting at least 25% of scalp)
  - Hidradenitis suppurativa
  - Atopic dermatitis

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 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


Dr. David Norris


Dr. Cory Dunnick


Dr. Elizabeth Wallace


Dr. Emily Gurnee


Dr. Lina Patel


Dr. Debbie Fidler

Top level results

Benefits going well beyond skin deep!

- All participants showed normalized immune markers
- 7/7 participants with clinically significant anti-thyroid autoimmunity displayed decreased levels of autoantibodies
- Significant improvements in one measure of spatial memory, one measure of visuomotor function, and anxiety/depression scores…


Dr. David Norris


Dr. Cory Dunnick


Dr. Elizabeth Wallace


Dr. Emily Gurnee

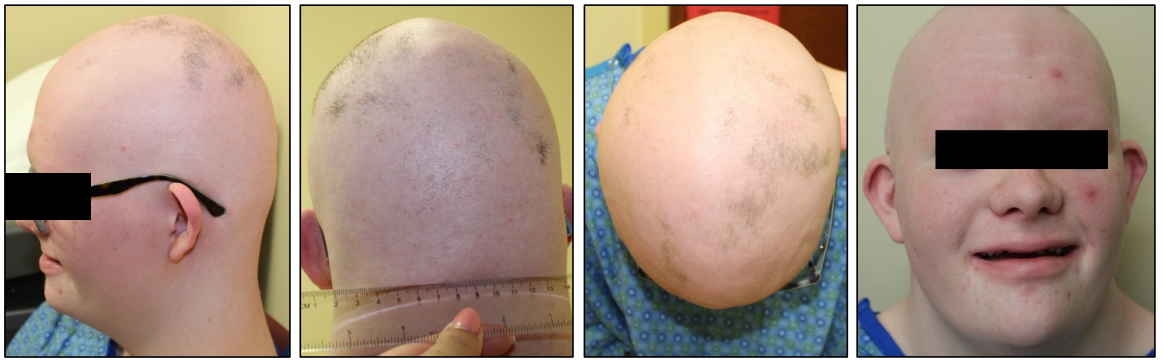

Dr. Lina Patel


Dr. Debbie Fidler

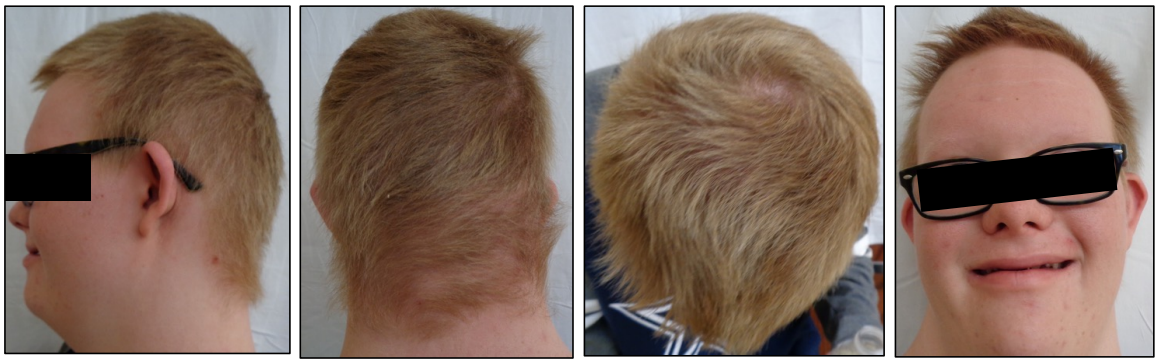
Male, 17 years old, alopecia areata

When a picture is worth a thousand words

Baseline
SALT = 86



Week 16
SALT = 4

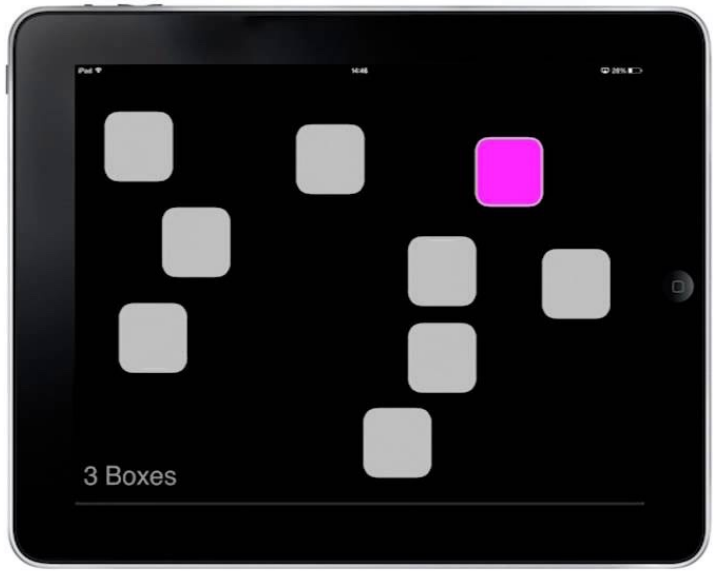


Observed improvement in one measure of spatial memory

The CANTAB Spatial Span test

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

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



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?

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

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 2023…

Conclusions

- The pilot phase of clinical trial was successfully completed.
- 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.
- **7/12 participants are now taking the medicine with a prescription**

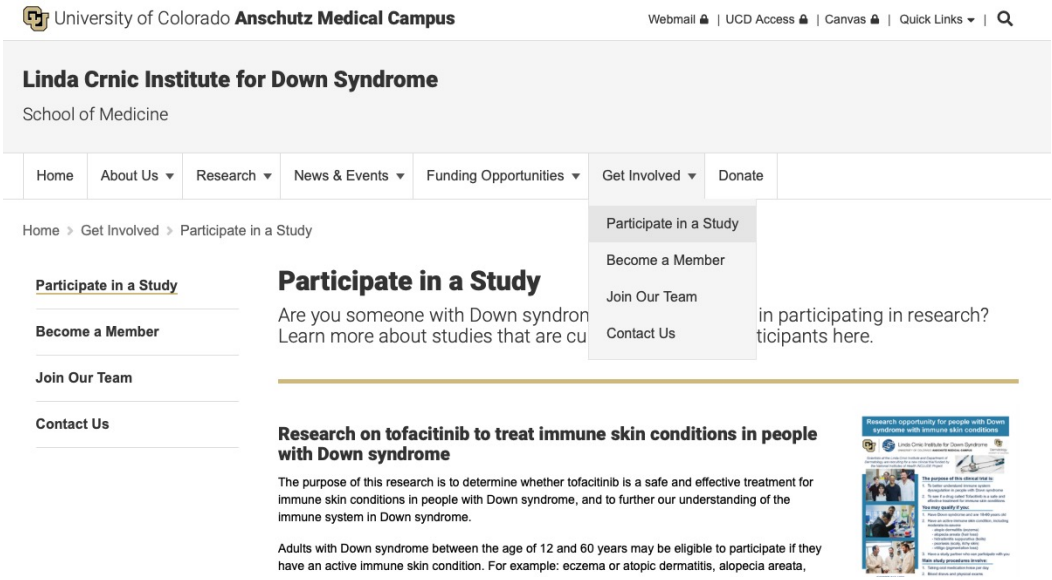
Important information

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

National Institute of Arthritis and Musculoskeletal and Skin Diseases

THE INCLUDE PROJECT

Search: crnicinstitute.org



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	Belinna Guerra
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	Lyndy Bush	Chelsea Donohue	Anne Fiala

The wonderful participants and their families!

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

THE INCLUDE PROJECT

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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!