

An Important Update on Groundbreaking Clinical Trials & Research

October 3rd, 2023
Joaquin M. Espinosa



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


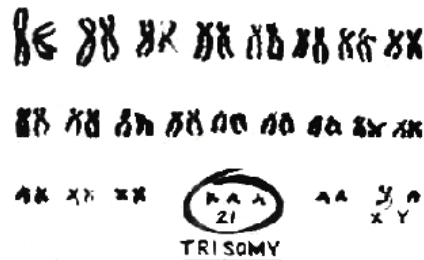


People with Down syndrome have a different 'clinical risk profile'



Cancer
Atherosclerosis
Hypertension
Allergies

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



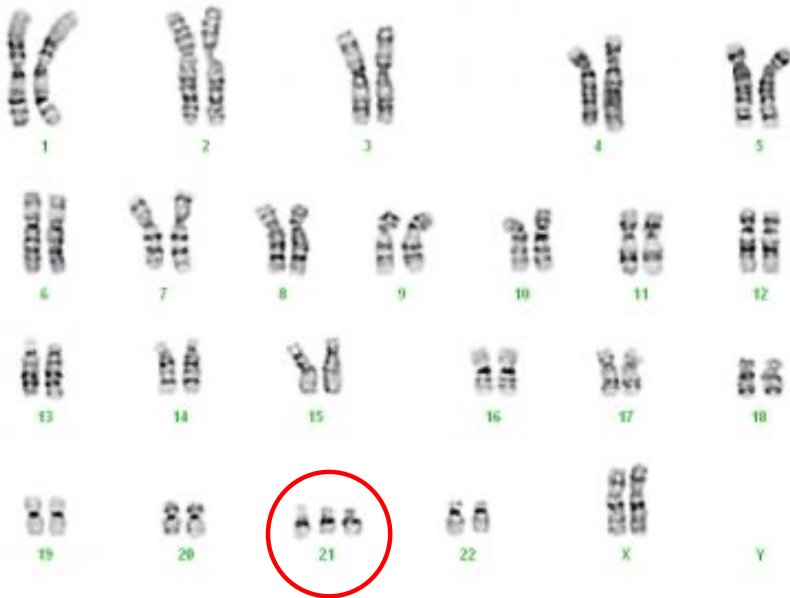
Autoimmunity
Alzheimer's
Leukemias
COVID-19

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



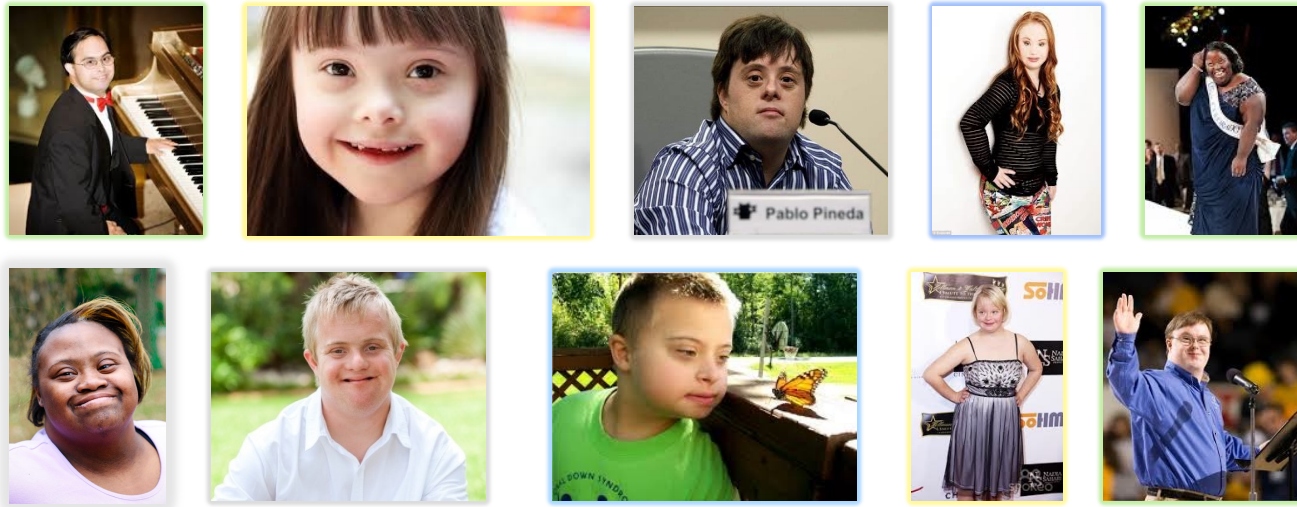
How does an extra copy of this little piece of DNA cause the developmental and clinical hallmarks of Down syndrome?

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

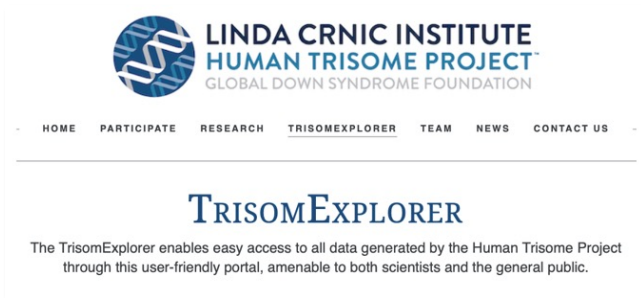
What factors define the ultimate clinical impacts of the extra chromosome?

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



1100+
Clinical histories



500+
Metabolomes



400+
Genomes



400+
Immune maps

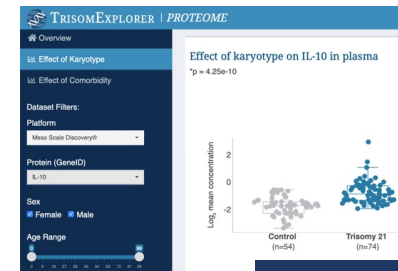


500+
Transcriptomes



500+
Microbiomes

TRISOMEXPLORER



40+ Projects supported

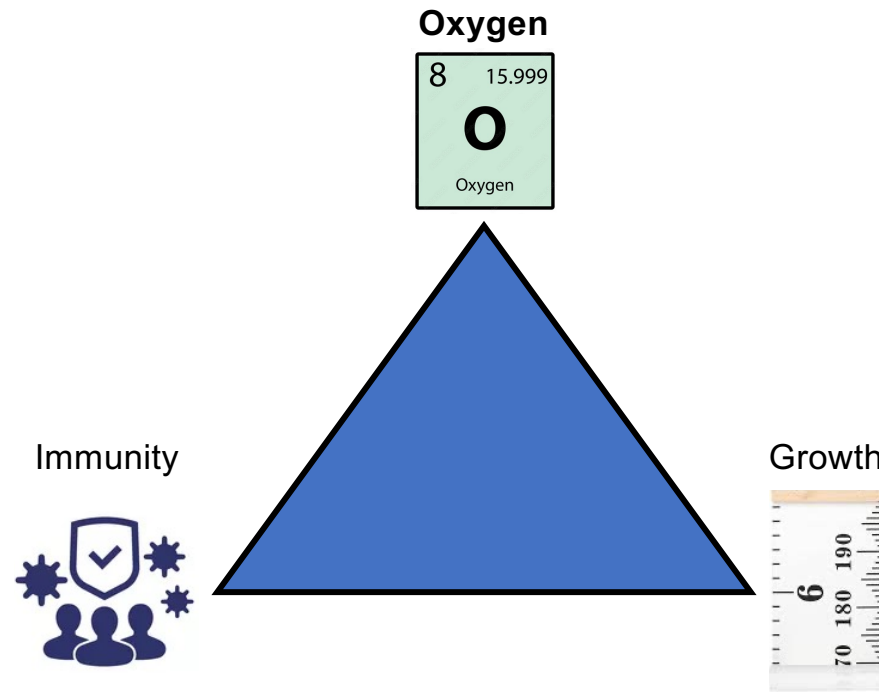


20+ Papers published / under review

People with Down syndrome love to participate in research!

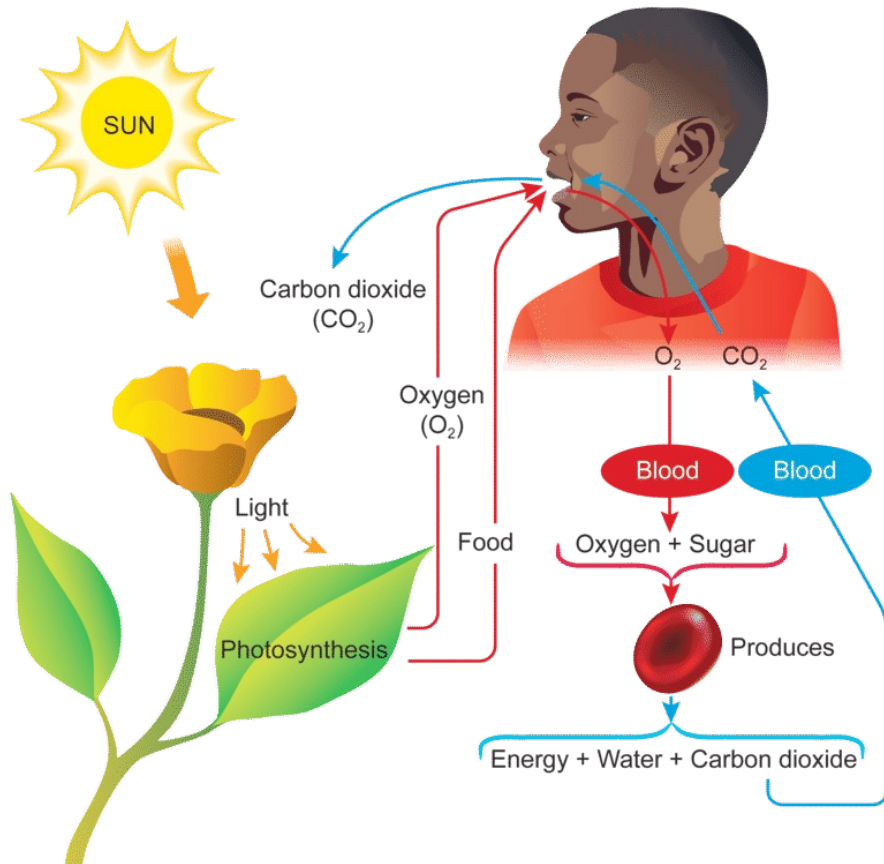
Three pillars of health:

Oxygen, growth, and immunity



Breathe, grow, and be yourself

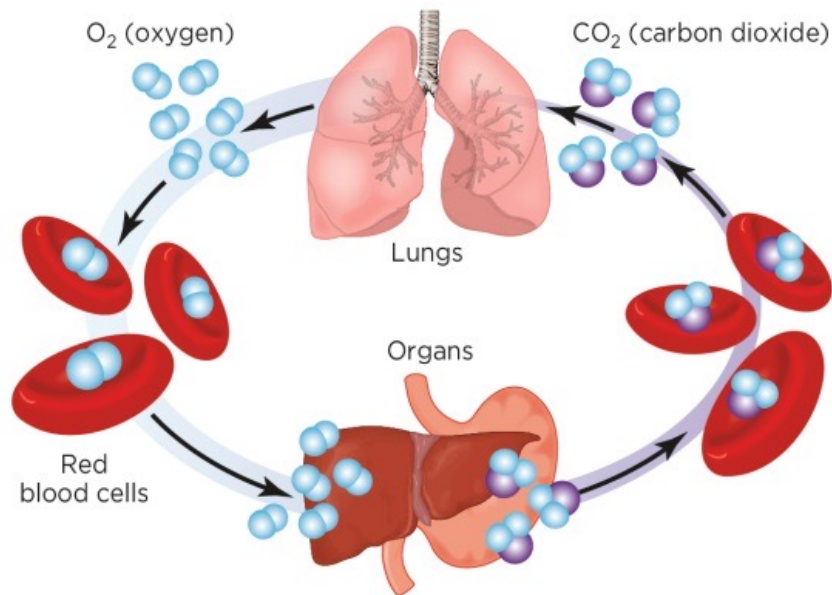
Oxygen is important



Life on Earth:

1. The Sun shines
2. Trees, plants, and algae use sunlight and carbon dioxide (CO₂) to grow and produce di-molecular oxygen (O₂)
3. We breathe in air, which is ~21% O₂, to stay alive.
4. Our cells employ the oxygen we breathe, along with a carbon source (such as sugar), to create energy.
5. We breathe out CO₂

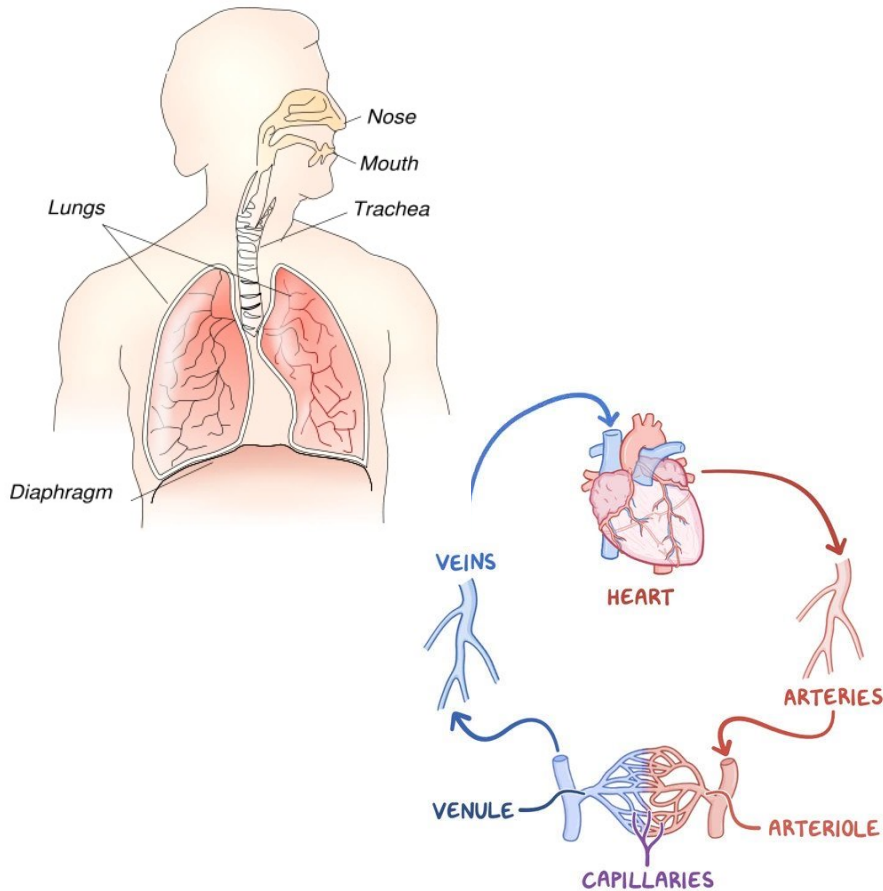
Breathing is important



Breathe in, breathe out:

1. Air goes in through our nostrils (ideally).
2. Once in the lungs, oxygen is loaded into red blood cells.
3. Red blood cells deliver oxygen to all other parts of the body.
4. Red blood cells take up the carbon dioxide (CO_2) back to the lungs.
5. We breathe out the excess CO_2 .

Other important things:



1. Air must flow freely through the 'upper respiratory tract' into the lungs.
2. Lungs must be free of other things (such as water, food) to take air.
3. The heart should pump blood efficiently in and out of the lungs.
4. The heart should pump faster when we need more oxygen (such as during exercise).
5. Red blood cells, which are the most abundant cells in the human body, should be in good shape too.







Scientific fact:

On average, individuals with Down syndrome have less oxygen in the blood

Individuals with Down syndrome display '**hypoxemia**' or '**hypoxia**'

What are 'normal' oxygen levels?

Blood oxygen saturation (SpO₂)

100 - 98	%		Normal
97 - 95	%		Insufficient Tolerable, patient hardly notices any influence
94 - 90	%		Decreased Immediate intervention (eating, exercise)
< 90	%		Critical Referral to specialist
< 80	%		Severe hypoxia Hospitalization
< 70	%		Acute danger to life

It is unusual for people with Down syndrome to display 98-100% oxygen saturation

People with Down syndrome tend to be 'hypoxemic'

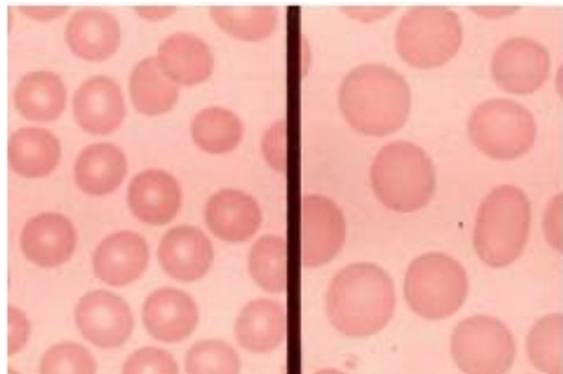


Key scientific observations:

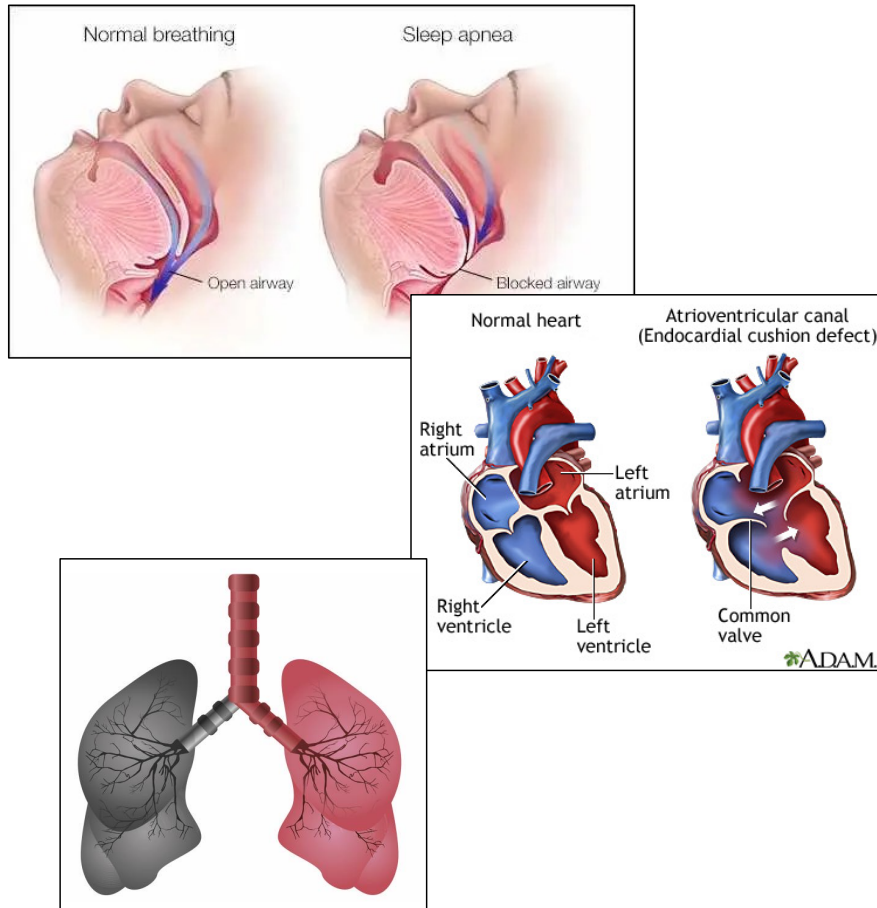
1. On average, individuals with Down syndrome have less oxygen in the blood.
2. Individuals with Down syndrome do more breaths per minute, that is, they are breathing harder.
3. People with Down syndrome are constantly making new red blood cells (a.k.a. erythropoiesis).
4. Red blood cells of people with Down syndrome are fewer in number but bigger in size, a sign of 'young' red blood cells (a.k.a. macrocytosis).

Normal

Macrocytic



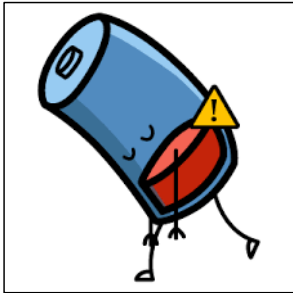
Why do persons with Down syndrome experience hypoxia?



There could be several causes:

1. Obstructive sleep apnea (OSA).
2. Inadequate heart function.
3. Decreased lung function.
4. Decreased 'adjustment' (sympathetic response).
5. Other causes.

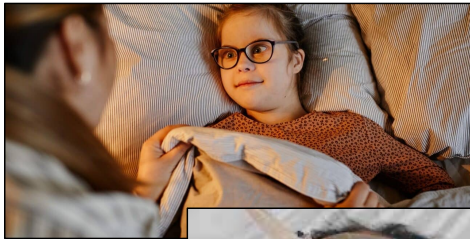
Hypoxia is no fun



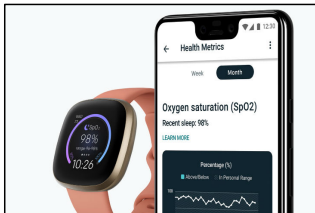
Hypoxia can lead to:

1. Decreased brain activity, including poor reflexes, decreased memory recall, decreased attention, impaired judgment, decreased motor coordination.
2. Decrease muscle work capacity, contributing to a lethargic or fatigued state.
3. If more severe, hypoxia can cause seizures and other neurological complications (e.g., **nystagmus**).
4. Over time, hypoxia could impair growth and normal organ function.

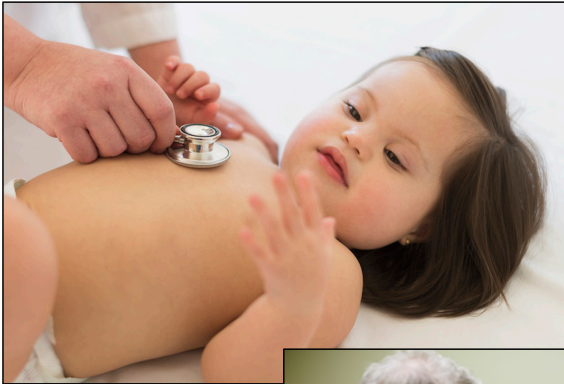
Call to action: How to help our beloved ones with Down syndrome?



- Be aware of hypoxia!
- Complete a sleep study.
- Consult with your doctor about OSA therapeutic options: tonsillectomy, adenoidectomy, CPAP, hypoglossal stimulation.
- Track oxygen levels at home: knowledge is power!



Call to action: How to help our beloved ones with Down syndrome?



Beyond congenital heart defects:

- Continue to monitor for good heart function during annual health check ups (such as electrocardiograms).
- Don't leave heart issues 'unattended'.
- Keep a healthy heart through good diet and exercise.

Call to action: How to help our beloved ones with Down syndrome?



- Watch out for ‘dysphagia’: food and water going into the lungs.
- Complete a swallow study if recommended by your doctor.
- Engage in feeding therapy as needed.
- Stay clear of lung infections!: use masks, get vaccines, and use distancing as needed
- Watch out for **vitamin D deficiency**: vitamin D is important for lung development and function

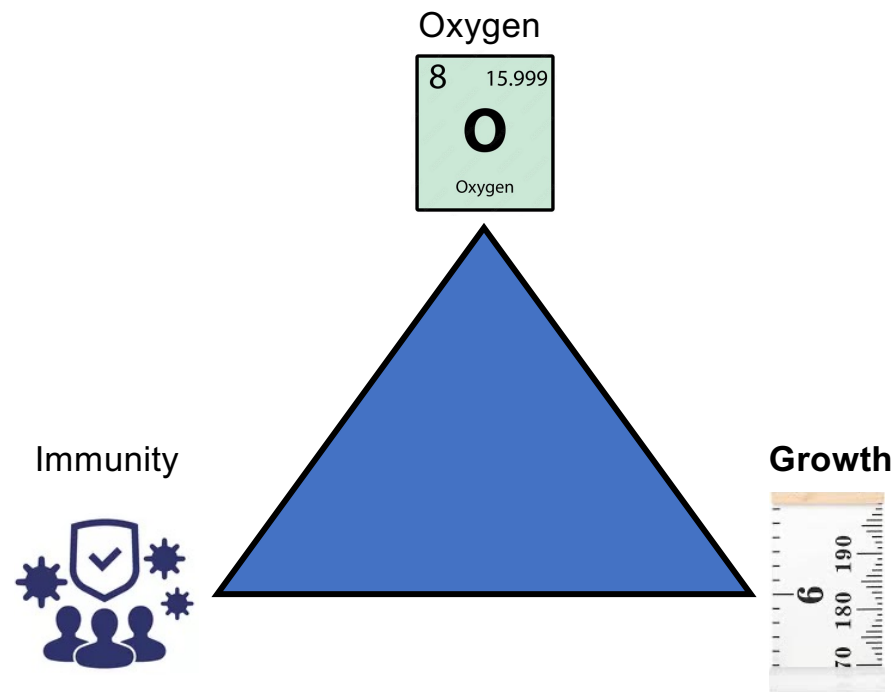
Call to action: How to help our beloved ones with Down syndrome?



- Learn to breathe properly!
- Start a yoga practice
- Walk in green spaces, get out in the Sun, and hug a tree as often as possible!
- Keep a healthy weight

Three pillars of health:

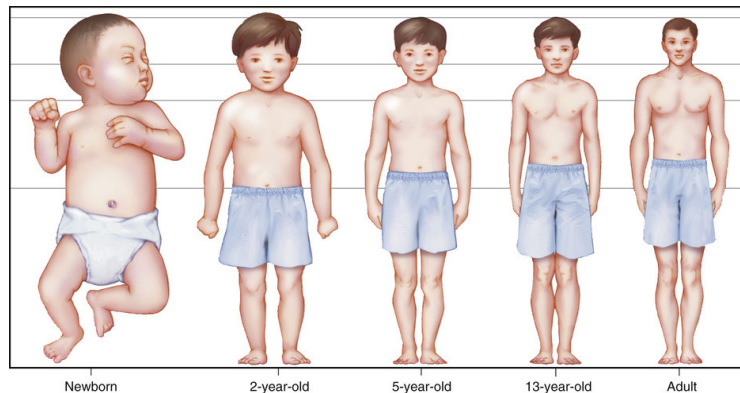
Oxygen, **growth**, and immunity



Breathe, **grow**, and be yourself

Growth and regeneration in human health

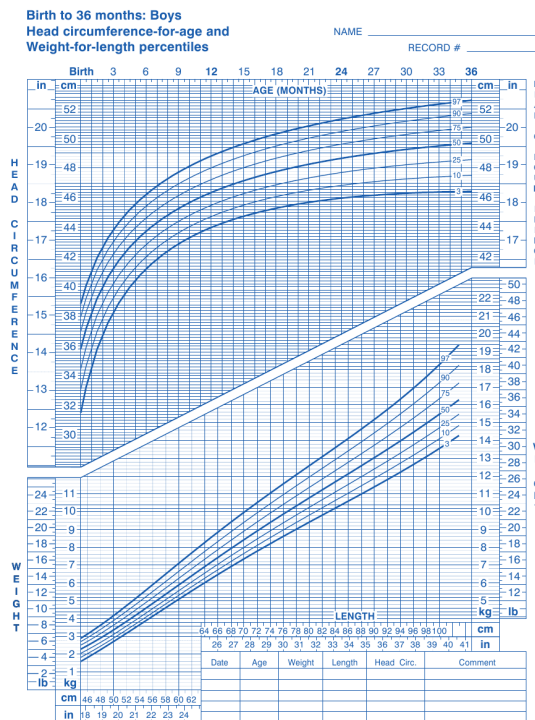
Human development involves coordinated growth of various body parts, organs and tissues



- Human development involves not only growth in size, but also increase in the number of cells and harmonic changes in the proportions of various body parts.
- Coordinated changes in body size and body composition are key for healthy human development.
- Proportional growth of muscles and bones is needed for muscle strength, psycho-neuro-motor development, social adjustment, well being, and quality of life.

Growth and regeneration in human health

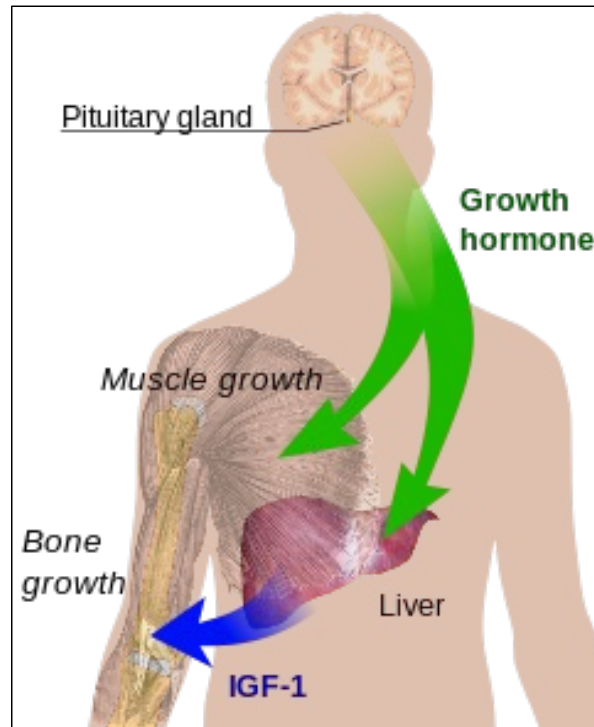
Human development involves coordinated growth of various body parts, organs and tissues



- The coordinated growth and shift in proportions during early childhood is captured by growth charts.
- Head circumference grows exponentially during the first year of life.
- Weight and height increase more linearly during early childhood.

Growth and regeneration in human health

Human development involves coordinated growth of various body parts, organs and tissues



- Human growth is driven by the pituitary growth hormone and the insulin-like growth factor 1 (IGF1).
- Growth hormone is produced by the pituitary gland, IGF1 is produced mostly (~75%) by the liver.
- Deficiencies in either growth hormone or IGF1 impair human growth and development.

Growth and Down syndrome

Persons with Down syndrome display stunted growth and differences in body proportions

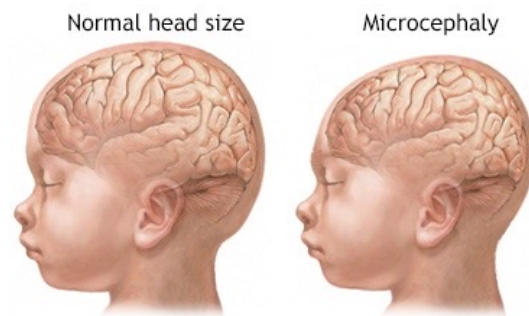


- It is estimated that persons with Down syndrome are, **on average**, 20% shorter than they would otherwise be if they did not have trisomy 21.
- Persons with Down syndrome have, on average, increased 'body mass index' (BMI), that is, more pounds per inch.

BMI formula: weight (lb) / [height (in)]² x 703

Growth and Down syndrome

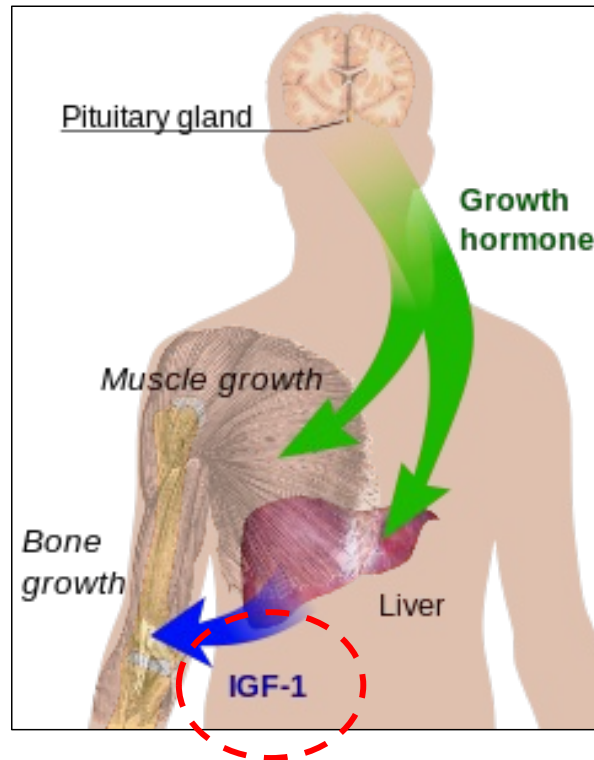
Persons with Down syndrome display smaller head circumferences and decreased brain volume



- On average, individuals with Down syndrome have decreased brain volume, with some brain regions being more affected than others.
- Decreased brain volume is likely to contribute to the neurodevelopmental differences characteristic of Down syndrome.
- **Disclaimer:** although brain size is modestly correlated with IQ, **there is much more to intelligence than just brain size!!**

Growth and Down syndrome

Why are persons with Down syndrome smaller?



On average:

Persons with Down syndrome make the right amount of growth hormone

However:

Individuals with Down syndrome make less IGF1!

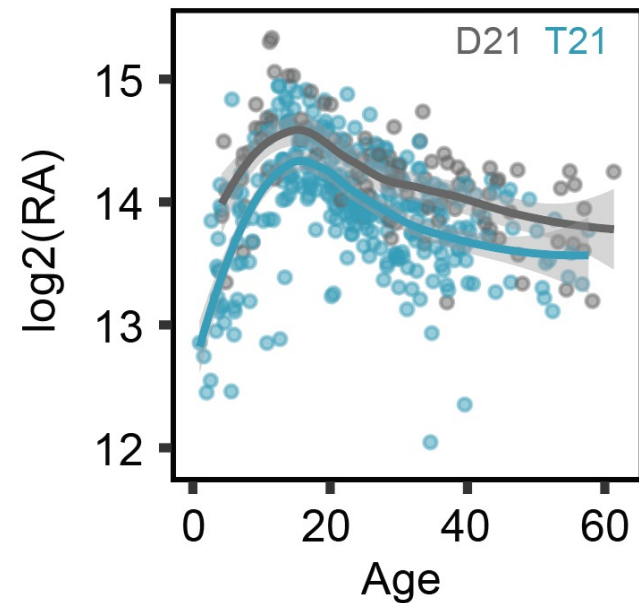
IGF1 deficiency and Down syndrome

What could be the impacts of IGF1 deficiency?



Lifelong physiological properties of IGF-I	Growth	Bone metabolism	Lipid and glucose metabolisms	Neuroprotection
	Neurogenesis and synaptogenesis	Anabolizing	Antioxidant and antiinflammatory	Antiapoptotic
	Genital development	Proliferative	Hepato- and cardioprotection	Mitochondrial protection

IGF1: Insulin-Like Growth Factor 1



D21: controls T21: trisomy 21

IGF1 deficiency and Down syndrome

What could be the impacts of IGF1 deficiency?



IGF1 deficiency could contribute to:

- Stunted growth
- Poor bone health
- Accelerated ageing
- Decreased brain health
- Alzheimer's disease

Lifelong physiological properties of IGF-I	Growth	Bone metabolism	Lipid and glucose metabolisms	Neuroprotection
	Neurogenesis and synaptogenesis	Anabolizing	Antioxidant and antiinflammatory	Antiapoptotic
	Genital development	Proliferative	Hepato- and cardioprotection	Mitochondrial protection

Disclaimer: a lot more research is needed to decipher the exact effects of IGF1 deficiency in Down syndrome.

IGF1 deficiency and Down syndrome

What could be the impacts of IGF1 deficiency?



Stunted growth in Down syndrome is associated with higher risk of:

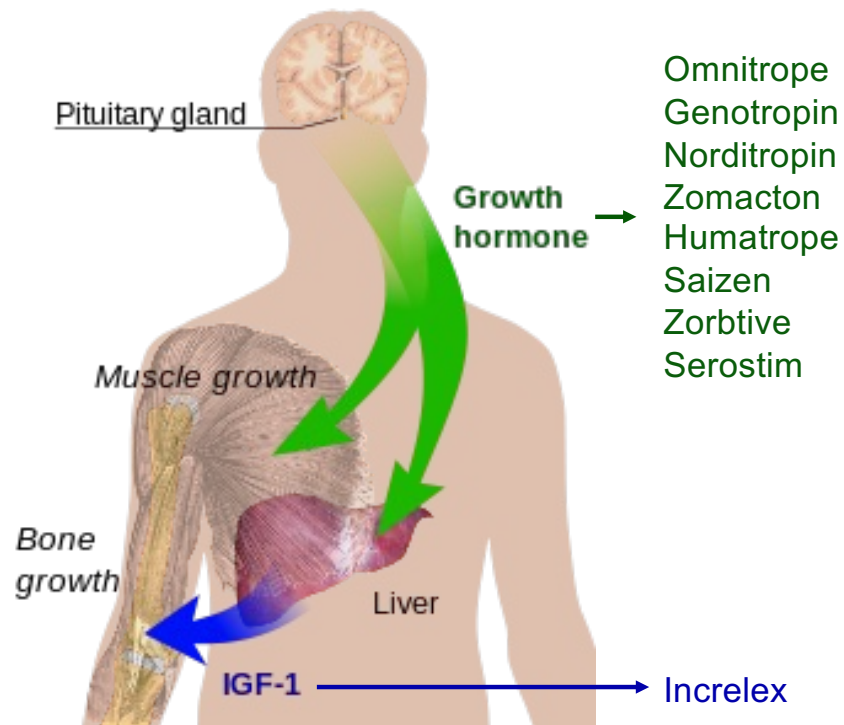
- Autism dual diagnosis
- Some forms of lung disease
- Some autoimmune disorders

One study found a significant association between stunted growth and lower intelligent quotient (IQ):

Klosowska et al, Translational Pediatrics 2022

Lifelong physiological properties of IGF-I	Growth Neurogenesis and synaptogenesis Genital development	Bone metabolism Anabolizing Proliferative	Lipid and glucose metabolisms Antioxidant and antiinflammatory Hepato- and cardioprotection	Neuroprotection Antiapoptotic Mitochondrial protection
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What could be the benefits of growth hormone therapy (or IGF1 therapy) in Down syndrome?



Both growth hormone and IGF1 exist as FDA-approved therapies for some forms of growth disorders.

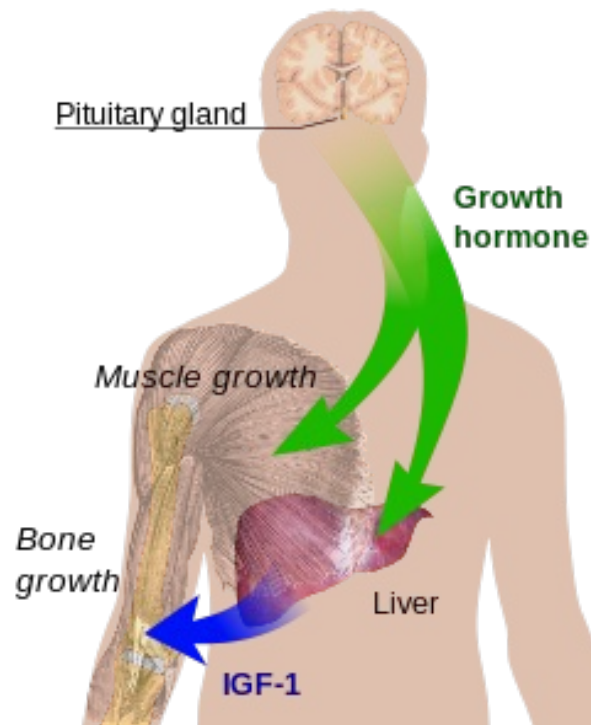
Growth hormone is approved for:

- Growth Hormone Deficiency
- Short Bowel Syndrome
- HIV-associated wasting

IGF1 is approved for:

- Severe Primary IGF1 Deficiency (SPIGFD)

What could be the benefits of growth hormone therapy (or IGF1 therapy) in Down syndrome?



- Growth hormone therapy has been tested in Down syndrome but IGF1 therapy has not been tested (to the best of our knowledge)
- Growth hormone treatment was shown to 'boost' IGF1 production in Down syndrome, thus alleviating IGF1 deficiency
- **What were the benefits (and side effects) of growth hormone treatment in persons with Down syndrome?**

What could be the benefits of growth hormone therapy (or IGF1 therapy) in Down syndrome?

GH treatment in pediatric Down syndrome: a systematic review and mini meta-analysis

David Shaki^{1,2}, Eli Hershkovitz^{1,2*}, Shai Tamam³, Arkadi Bollotin², Odeya David^{1,2}, Guy Yalovitsky², Neta Loewenthal^{1,2}, Lior Carmon^{1,2}, Dganit Walker¹, Raphael Nowak² and Alon Haim^{1,2}

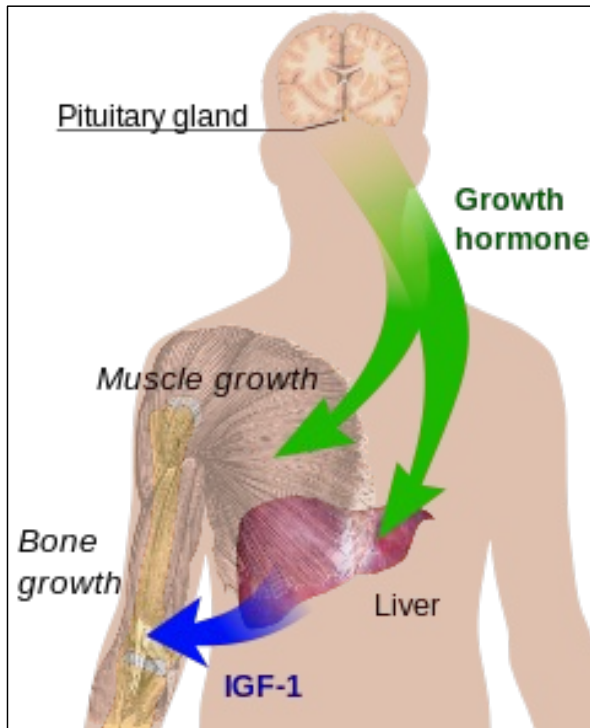
¹Pediatric Endocrinology Unit, Soroka University Medical Center, Beer Sheva, Israel, ²Faculty of Health Sciences, Ben-Gurion University, Beer Sheva, Israel, ³Library of Life Sciences and Medicine, Tel Aviv University, Tel Aviv, Israel



2022

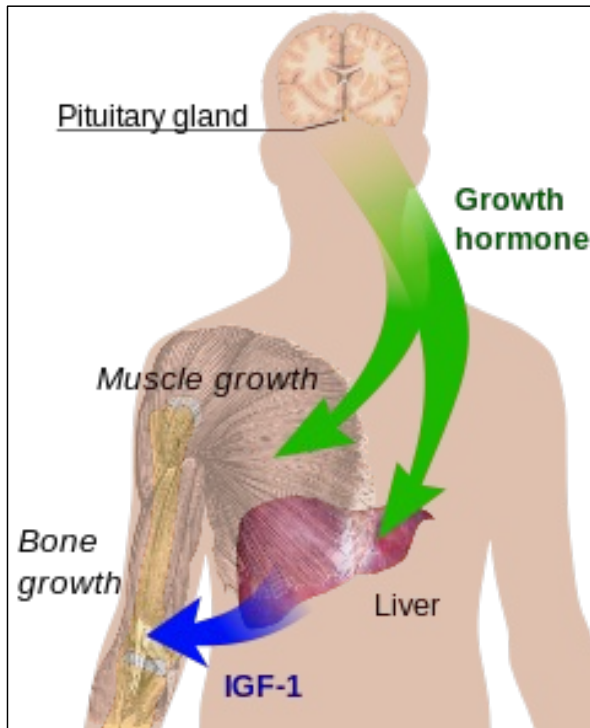
- Sixteen studies reported the medical use of growth hormone in children with Down syndrome.
- Growth hormone was found to be safe and effective for ‘short-term’ height growth.
- Other potential benefits (e.g., cognition?) remain undefined and would require more research.
- **Author’s conclusions:** “As GH treatment is safe and effective for short-term height growth, GH therapy should be considered in long-term treatment (of children with Down syndrome)”.

Calls to action



- **More research is needed!**
- Start a collective dialog about the impact of stunted growth and 'dysmorphogenesis' (i.e., abnormal formation of organs and tissues)
- Engage endocrinologists and rheumatologists in the 'medical care team' (i.e., specialists who understand growth hormone and IGF1)

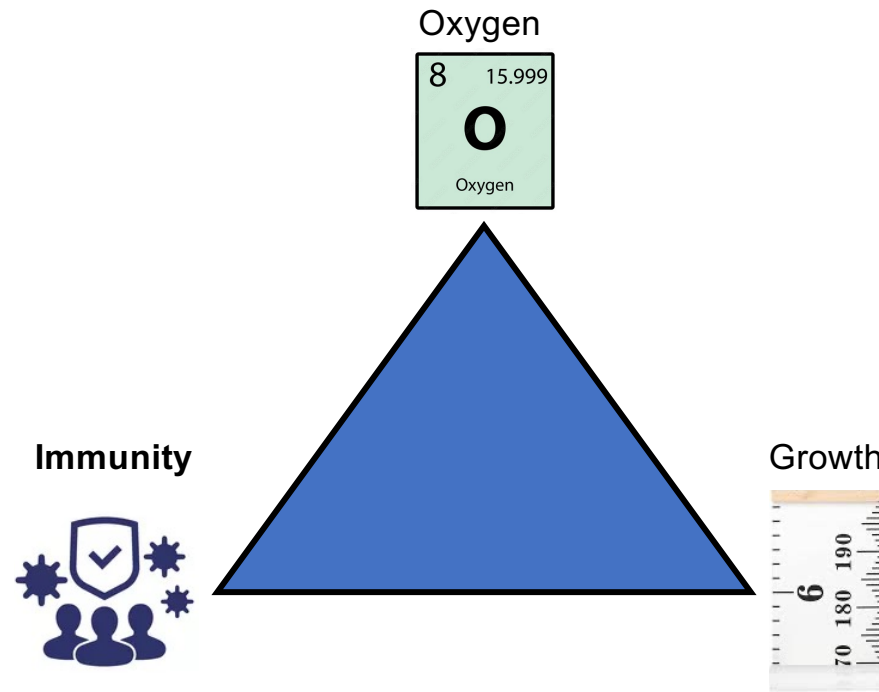
Calls to action



- **Take care of the liver!:**
- No booze
- Balanced, low fat diet, keep a healthy weight
- Watch out for signs of liver dysfunction during health check ups:
 - Alanine transaminase (ALT)
 - Aspartate transaminase (AST)
 - Alkaline phosphatase (ALP)
 - Albumin
 - Bilirubin
 - Gamma-glutamyltransferase (GGT)
 - Other tests

Three pillars of health:

Oxygen, growth, and immunity



Breathe, grow, and **be yourself**

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



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

[Recruitment Status](#) ⓘ : Recruiting

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

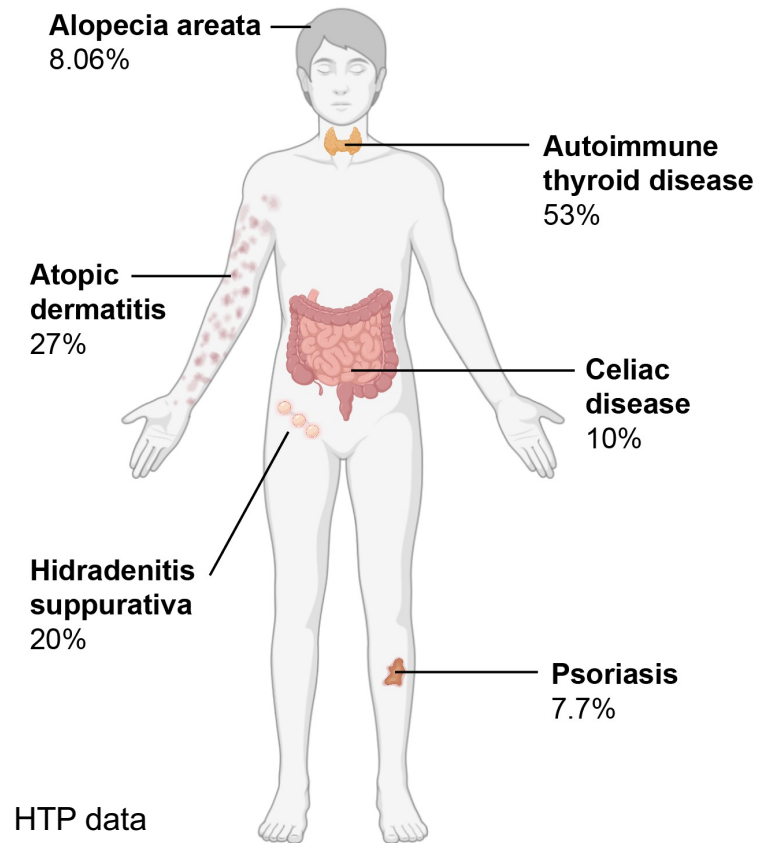
[Last Update Posted](#) ⓘ : February 16, 2021

See [Contacts and Locations](#)

U.S. National Library of Medicine

[ClinicalTrials.gov](https://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 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

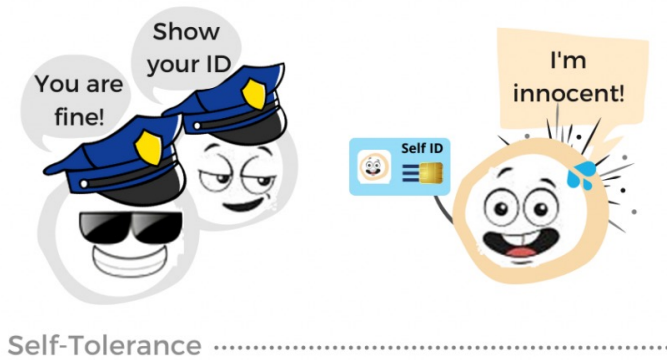
~**10%** of adults with Down syndrome have been diagnosed with celiac disease

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

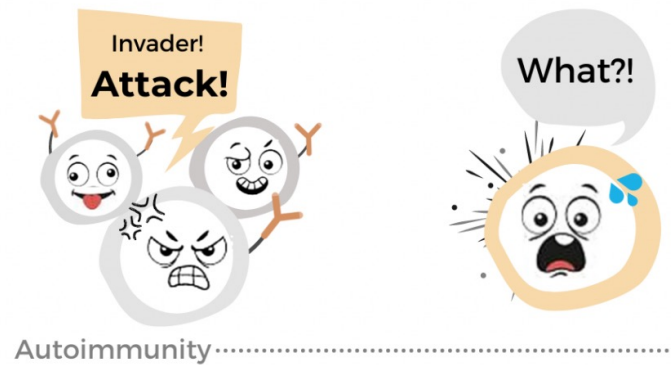
Autoimmunity in a nutshell:

Good: self-tolerance

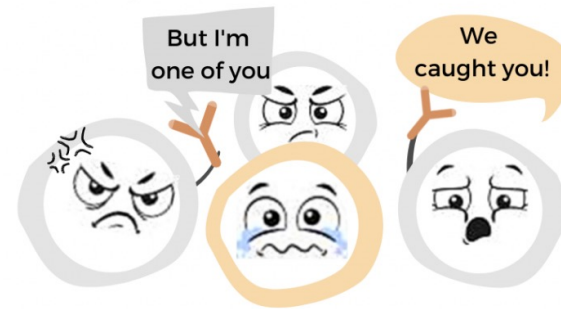
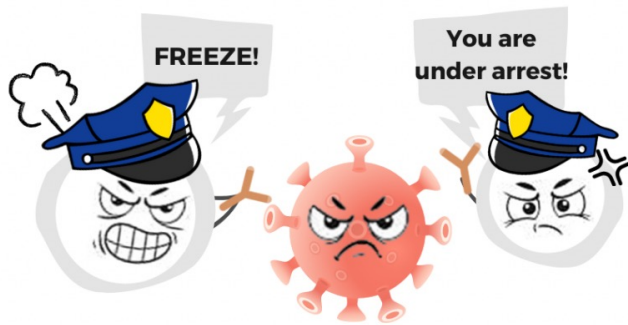
Bad: self-harm



Self-Tolerance



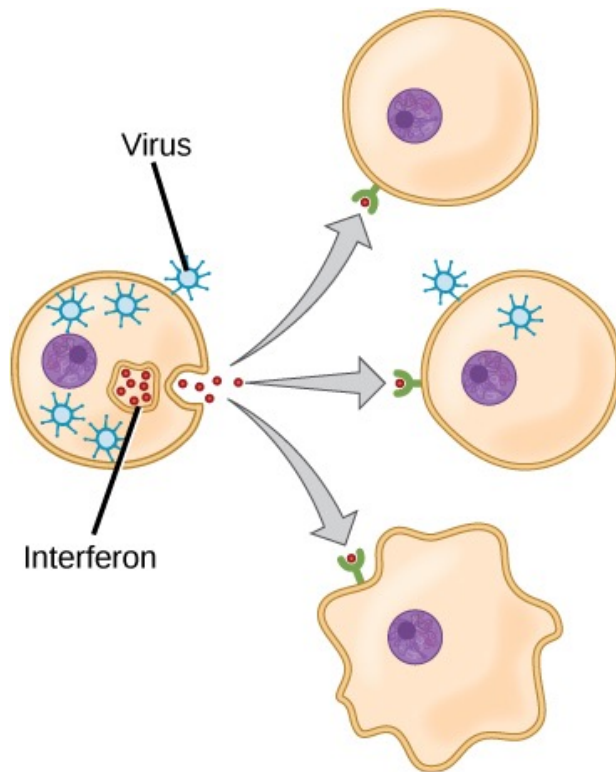
Autoimmunity



Adapted from Advanx Health blog

People with Down syndrome have hyperactive interferon signaling

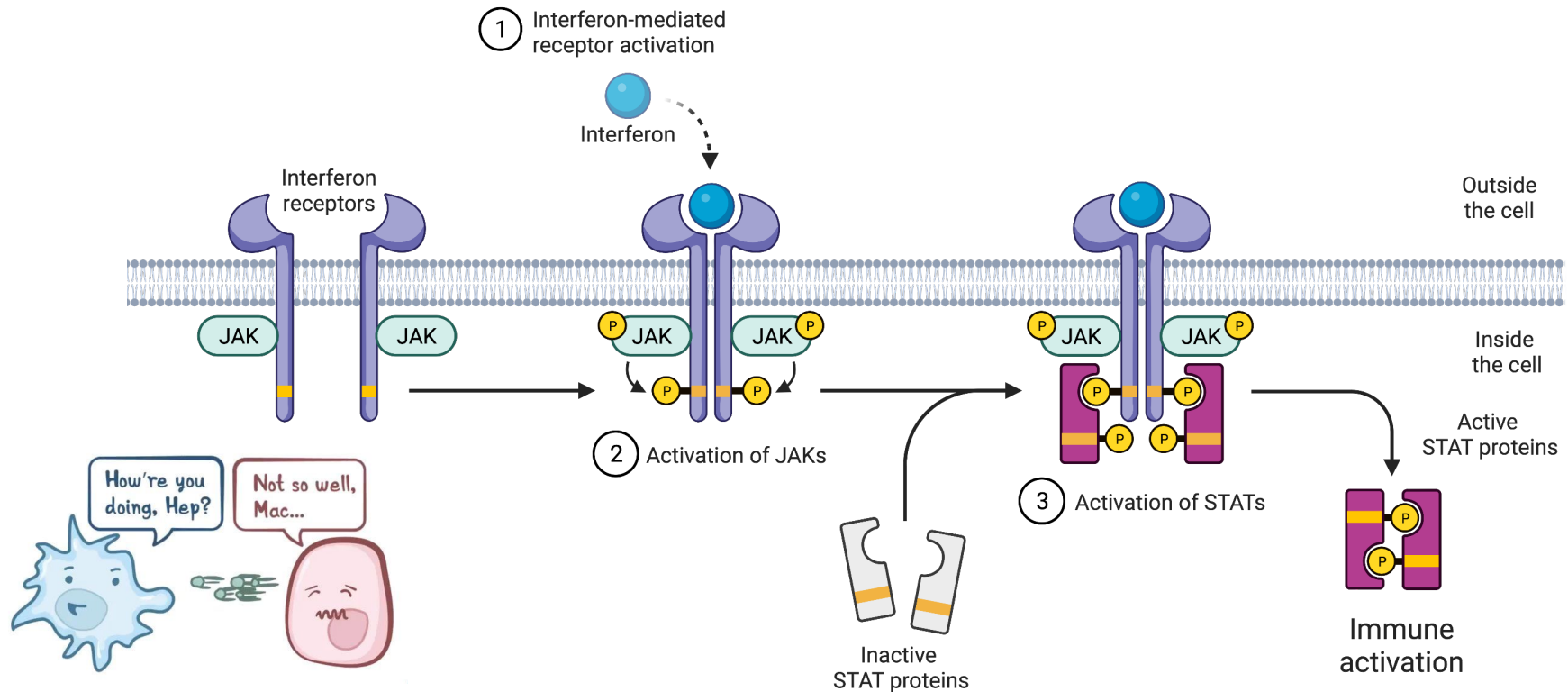
What is interferon signaling?



- 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.

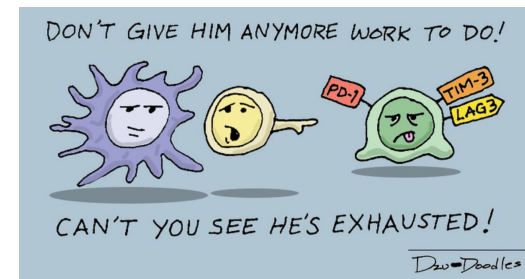
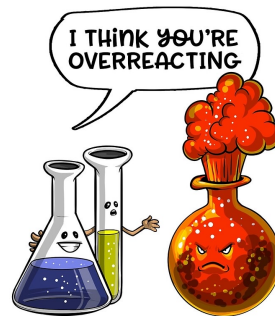
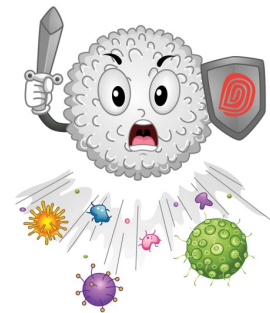
Why do people with Down syndrome have hyperactive interferon signaling?

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



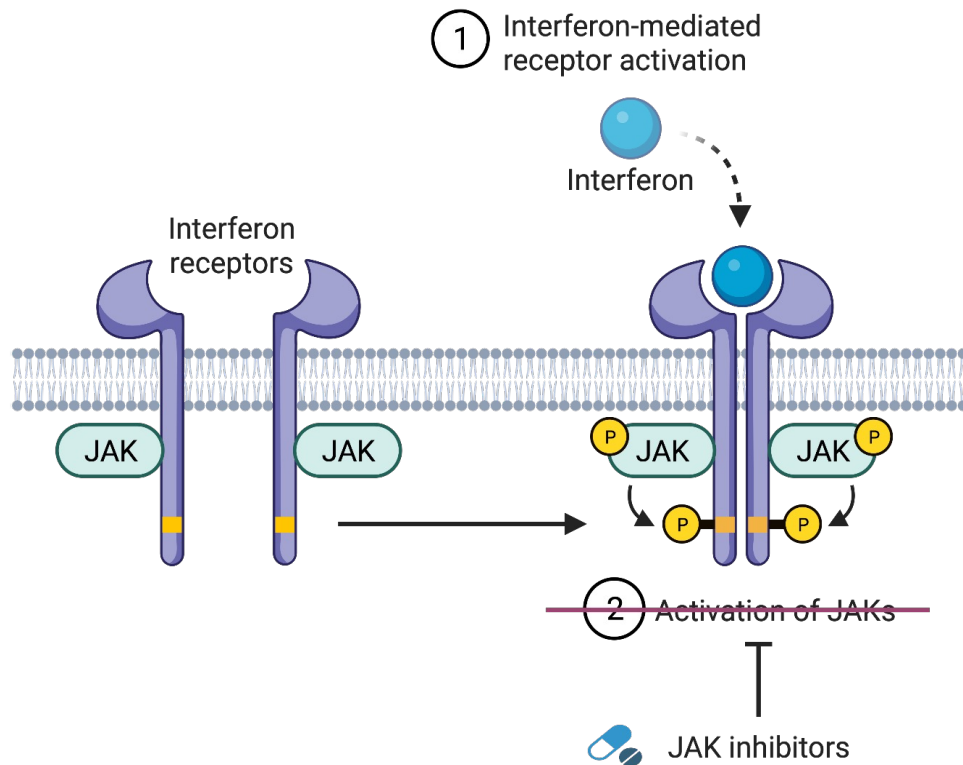
Target	JAK1/3	JAK1/2	JAK1	JAK1/2	JAK1
Rheumatoid arthritis	+	+	+		
Psoriatic arthritis	+		+		
Polyarticular course JIA	+				
Ulcerative colitis	+		+		
Atopic dermatitis			+		+
COVID-19		+			
Alopecia areata		+			
Chron's disease			+		
Polycythemia vera				+	
Ankylosing spondylitis			+		
Myelofibrosis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

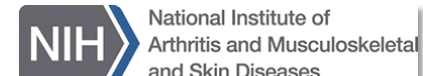
More than 25% of adults with Down syndrome have been affected by one of these conditions

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

Funded by:



THE INCLUDE PROJECT



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



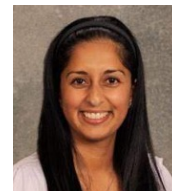
Wallace



Gurnee



Rachubinski



Patel

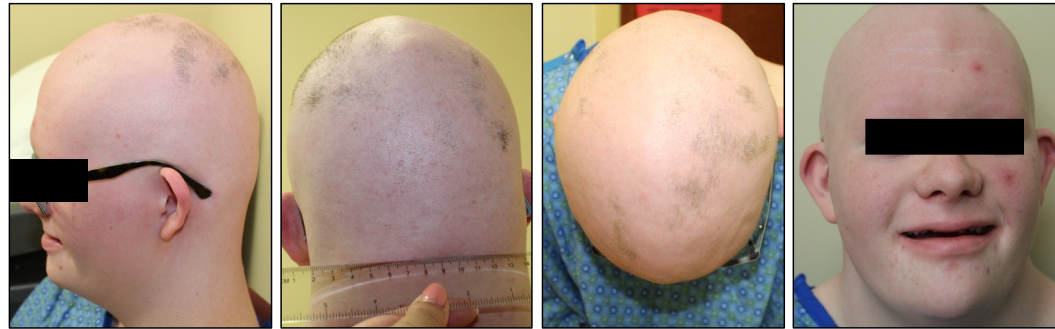


Fidler

Male, 17 years old, alopecia areata

When a picture is worth a thousand words

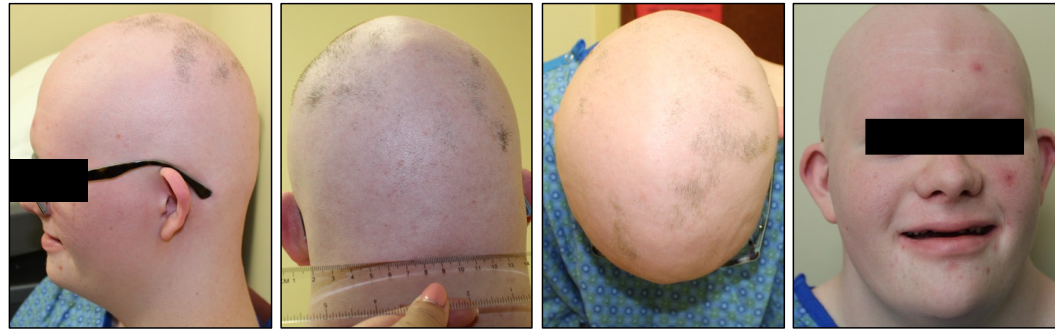
Baseline
SALT = 86



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



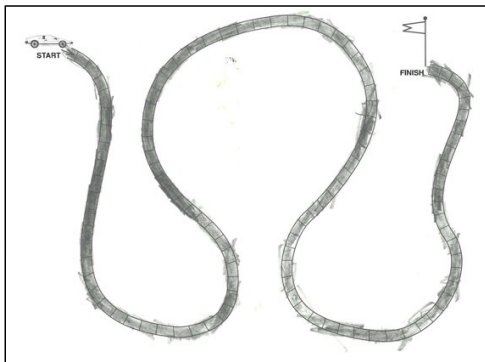
Participant monitored outside of the trial at the University of Vermont Medical Center

Female, 28 years old

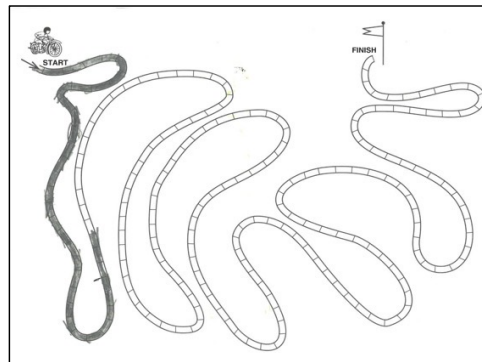
History of Down syndrome Regression Disorder

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

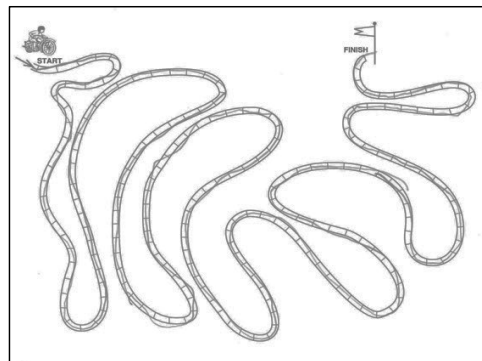
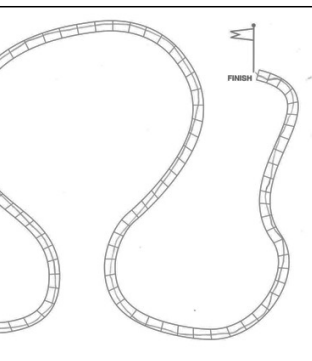
NEPSY II (car)



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.
- The benefits are so obvious that participant was prescribed tofacitinib 'off-label' by a neuroimmunologist, and both Pfizer and Medicaid agreed to pay for it.

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:



Rachubiski



Patel



Kammeyer



Galbraith

Consultants:



Sanders



Tartaglia



Charoensook

Funded by:



THE INCLUDE PROJECT



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.

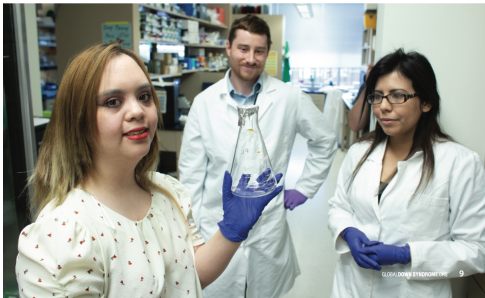
Is it safe?

Is it effective?

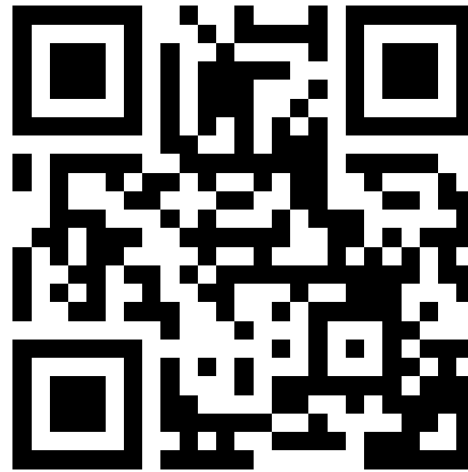
What is the mechanism?

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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Lina Patel

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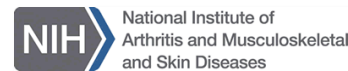
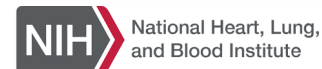
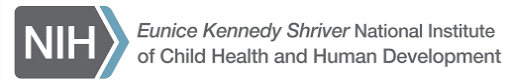
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Laurie Ryan (NIA)
Erika Tarver (NIA)

And so many many more!

THE INCLUDE PROJECT



The amazing team at the Global Down Syndrome Foundation

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!

