Clinical Trials for Immune Therapies in Down Syndrome: New Results and Upcoming Studies

August 27, 2026
DS-Connect® Webinar

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LINDA CRNIC INSTITUTE for DOWN SYNDROME

GLOBAL DOWN SYNDROME FOUNDATION

INCLUDE Data Coordinating Center

INCLUDE DS-Biorepository

DS-Connect® The Down Syndrome Registry

Quiz time!

Which of the following **genetic conditions** have available therapies approved by the Food and Drug Administration (FDA)?

- ❑ Rett syndrome
- ❑ Prader Willi syndrome
- ❑ Spinal Muscular Atrophy
- ❑ Tuberous Sclerosis
- ❑ Friedreich Ataxia
- ❑ Cerebral adrenoleukodystrophy
- ❑ CLN2 disease (Batten disease)
- ❑ Down syndrome

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- ✓ Friedreich Ataxia
- ✓ Cerebral adrenoleukodystrophy
- ✓ CLN2 disease (Batten disease)
- ❖ ~~Down syndrome~~

Answer:
all but one…

Quiz time!

Which of the following **genetic conditions** has the highest prevalence in the human population?

- ❑ Rett syndrome
- ❑ Prader Willi syndrome
- ❑ Spinal Muscular Atrophy
- ❑ Tuberous Sclerosis
- ❑ Friedreich Ataxia
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- ❑ Down syndrome

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- ❑ Tuberous Sclerosis
- ❑ Friedreich Ataxia
- ❑ Cerebral adrenoleukodystrophy
- ❑ CLN2 disease (Batten disease)
- ✓ **Down syndrome**

Answer:
Down syndrome!

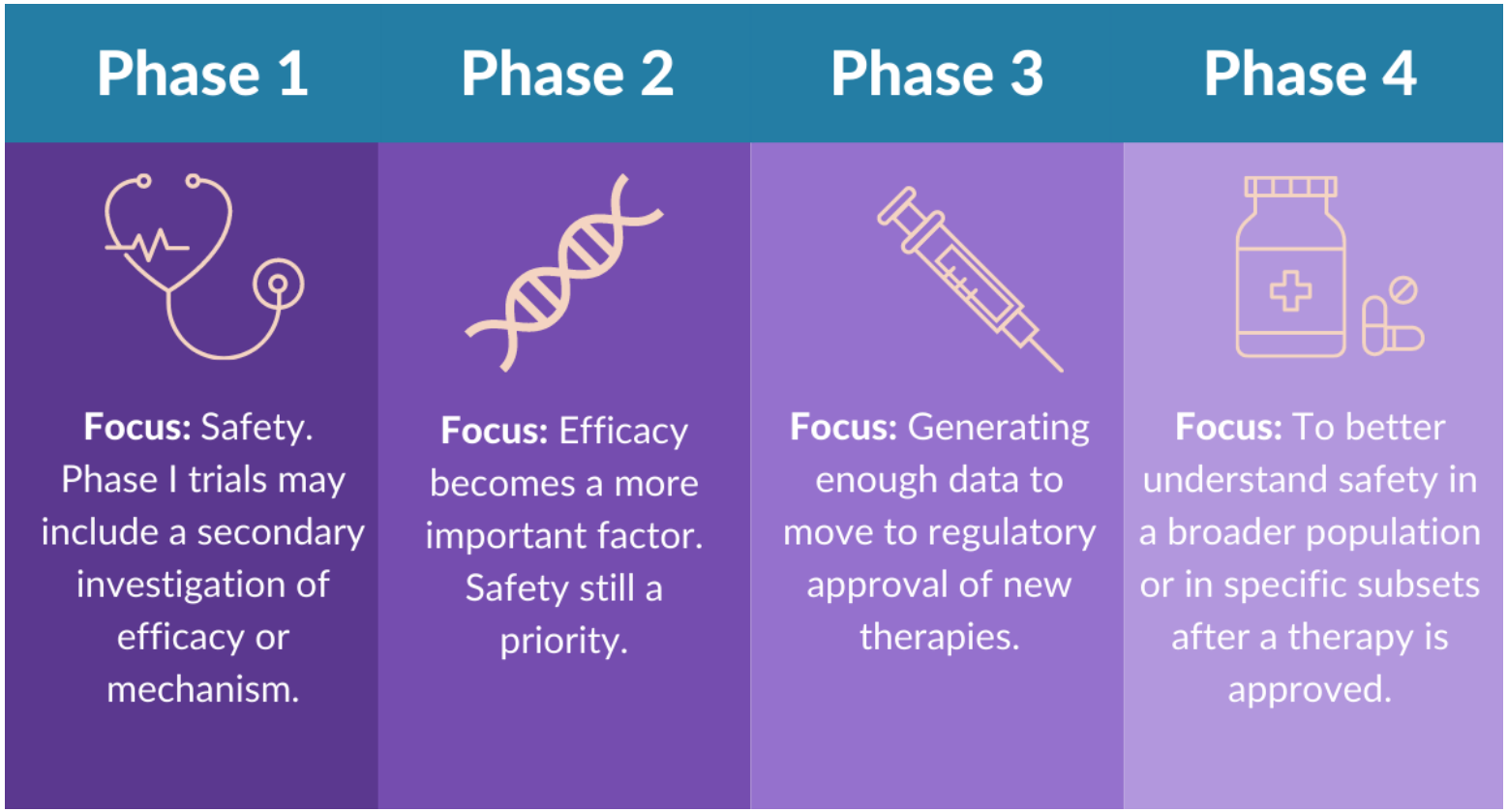
Question:

What does it take for a medicine to receive FDA approval for treatment of a genetic condition?

Answer:

A phase 3 clinical trial with positive results

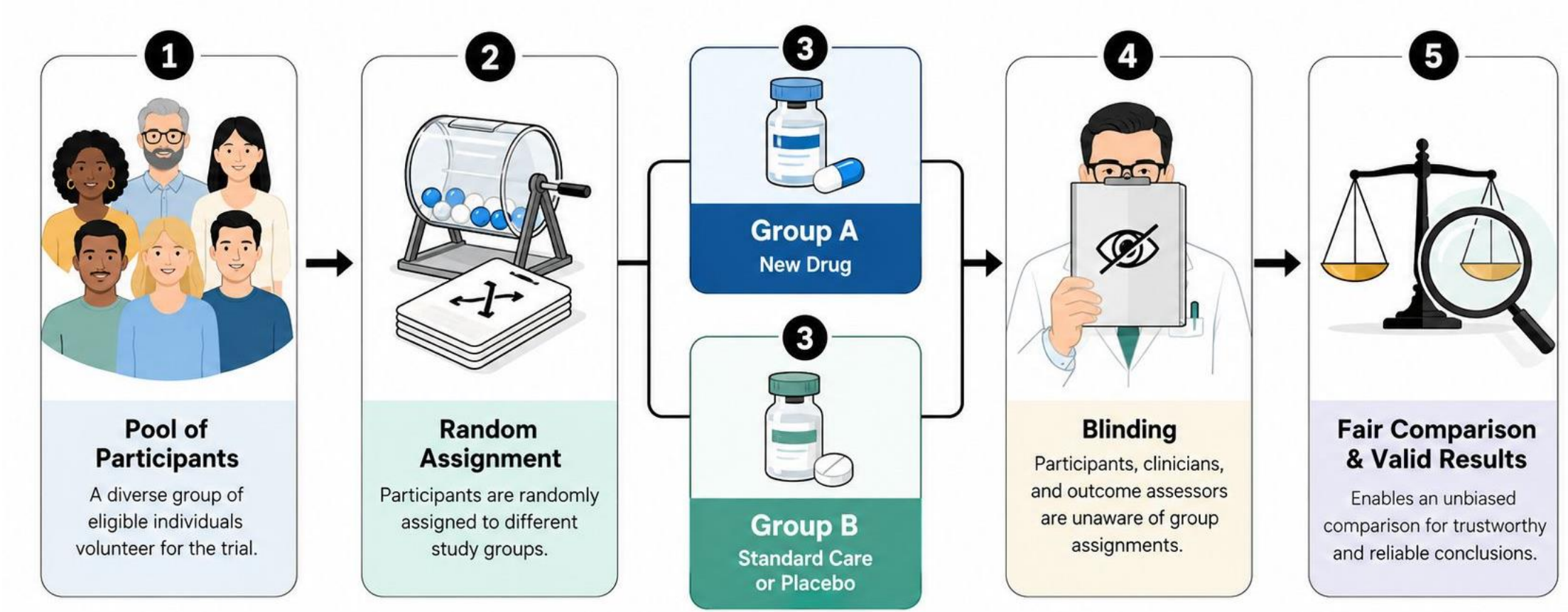
Clinical trials 101



For every 100 medicines that enter Phase 1 clinical trials, fewer than 10 will received regulatory approval

Phase 3 clinical trials: the gold standard

Randomized, placebo-controlled, double blind



https://honcology.com/blog/phase-3-clinical-trial

Quiz time!

How many **Phase 3 clinical trials** have been **completed** to define the therapeutic value of medicines in Down syndrome?

- ❑ 1
- ❑ 2-5
- ❑ 5-10
- ❑ 10-20
- ❑ 20-30
- ❑ More than 30

Quiz time!

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- ❑ 2-5
- ❑ 5-10
- ❑ 10-20
- ❑ 20-30
- ❑ More than 30

Answer: 1

Results: Negative

Efficacy Assessment of Systematic Treatment With Folinic Acid and Thyroid Hormone on Psychomotor Development of Down Syndrome Young Children (ACTHYF)

ClinicalTrials.gov ID NCT01576705

Sponsor Institut Jerome Lejeune

Information provided by Institut Jerome Lejeune (Responsible Party)

Last Update Posted 2020-05-13

Quiz time!

How many **Phase 3 clinical trials** are currently **enrolling** to define the therapeutic value of medicines in Down syndrome?

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- ❑ 2-5
- ❑ 5-10
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- ❑ 1
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- ❑ 10-20
- ❑ 20-30
- ❑ More than 30

Answer:

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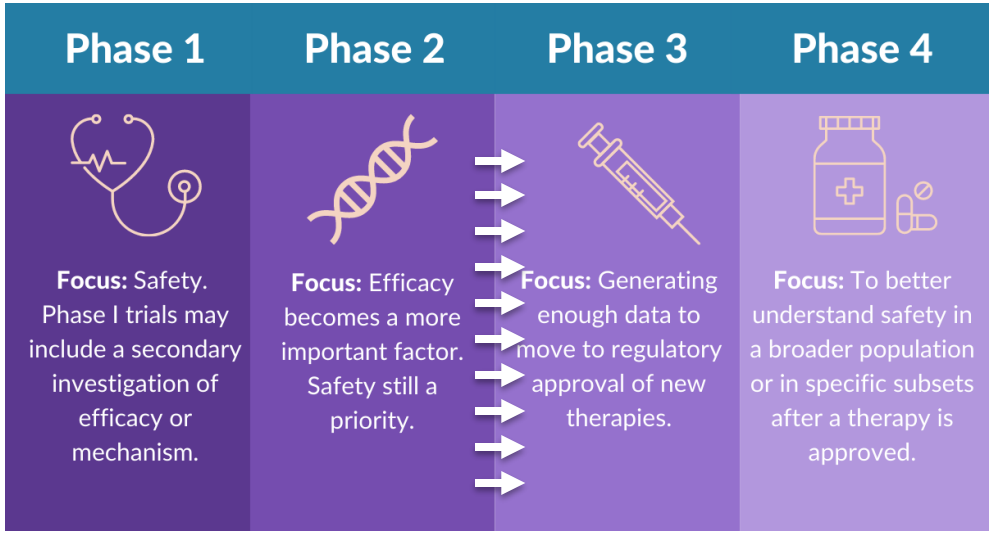
The times are changing…:

Today, there are more Phase 2 clinical trials enrolling people with Down syndrome than ever before!!!



2017: an inflexion point

Congressional hearing on Down syndrome research

U.S.A. House of Representatives

October 25th, 2017

Michelle Sie Whitten, Dr. Joaquin Espinosa, Dr. William Mobley, Frank Stephens

Frank Stephens:
'I am a man with Down syndrome, and my life is worth living'

Dr. Francis Collins, Frank Stephens

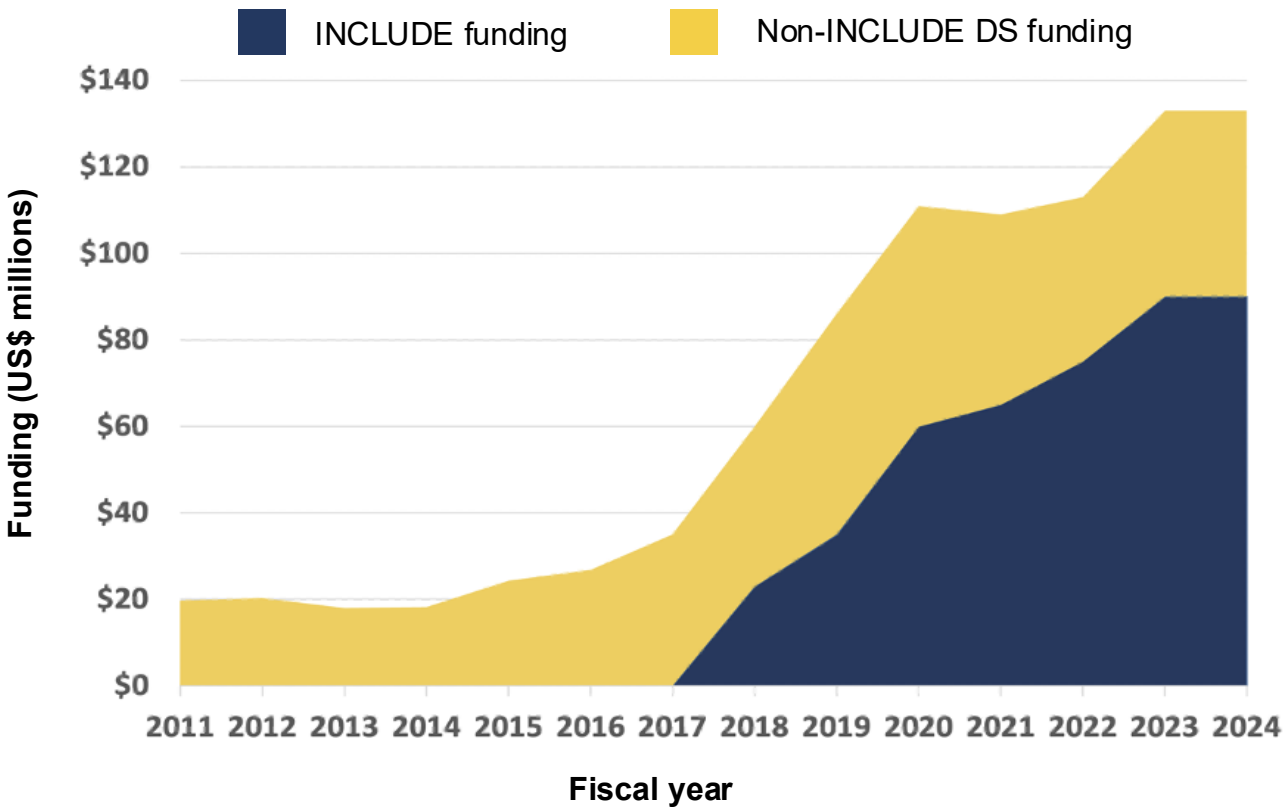
A productive collaboration between self-advocates, members of Congress, the GLOBAL Down Syndrome Foundation, scientists, and NIH officers, leading to creation of the NIH INCLUDE Project

2018: NIH launches the INCLUDE Project

INvestigation of **C**o-occurring conditions across the **L**ifespan to **U**nderstand **D**own syndrom**E**

$548M of INCLUDE funding so far…

NIH funding for Down syndrome research



*Figures up to 2024, not up to date

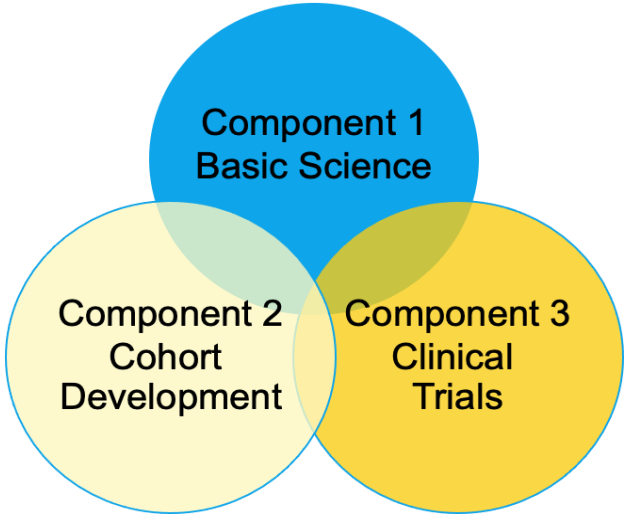
THE INCLUDE PROJECT

19 NIH Institutes participating

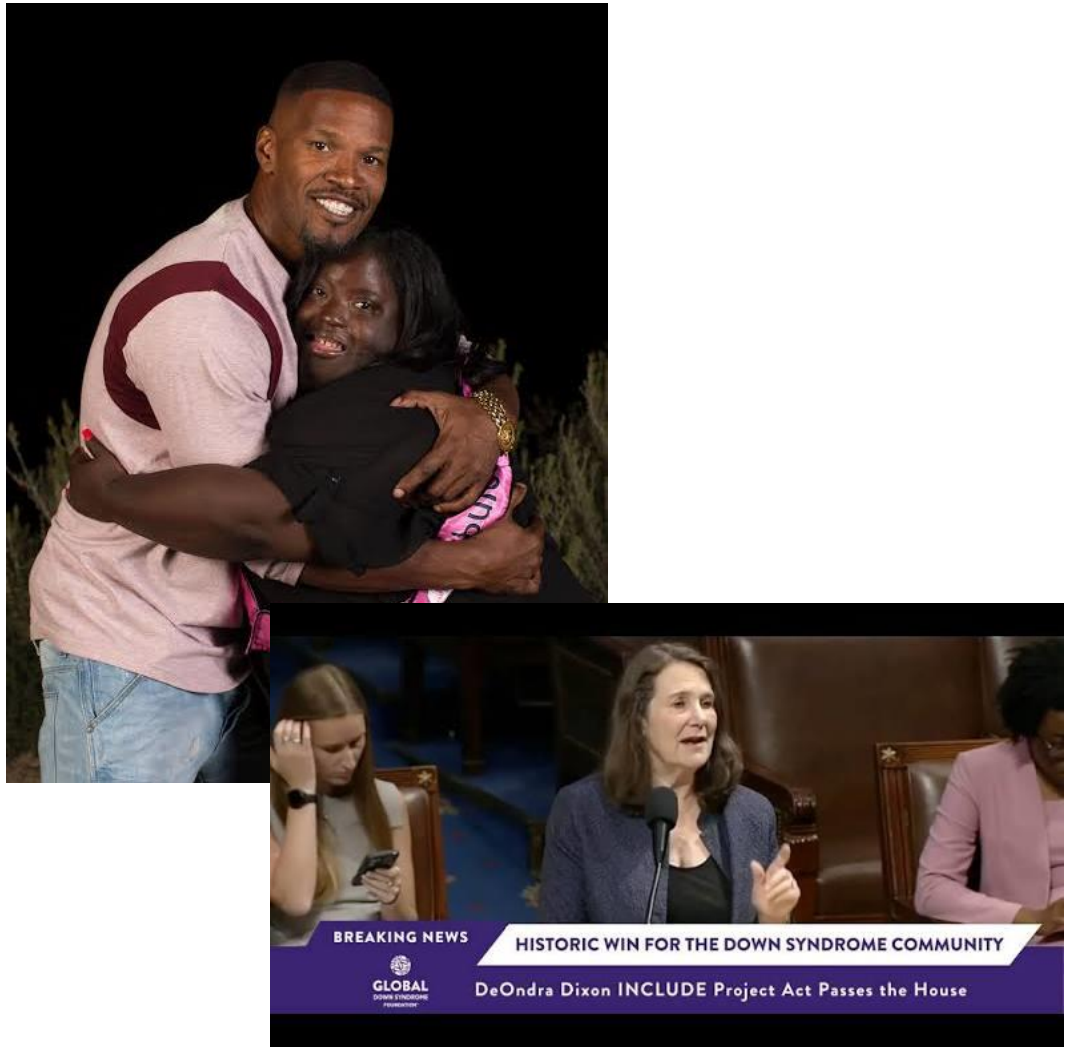
412 Projects funded

26 Clinical trials

600+ Scientific publications



DeOndra Dixon INCLUDE Project Act



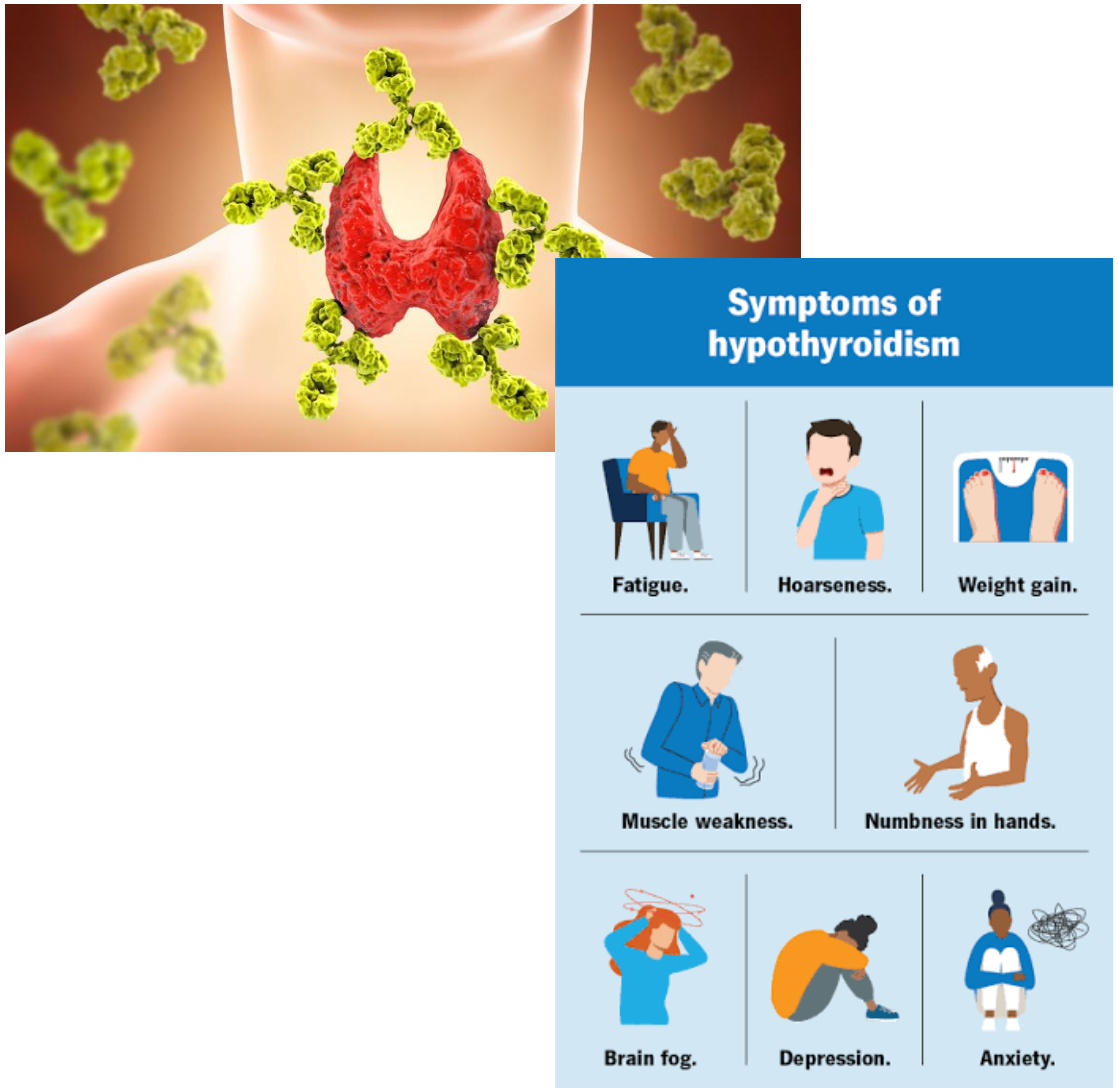
New legislation just passed the House and Senate that would make the INCLUDE Project funding more stable from year to year.

Named in memory of DeOndra, Jamie Foxx's sister, who passed away a few years ago.

A remarkable advocacy achievement by the GLOBAL Down Syndrome Foundation.

The first approved medicine for Down syndrome could be an immune therapy

Autoimmune thyroid disease



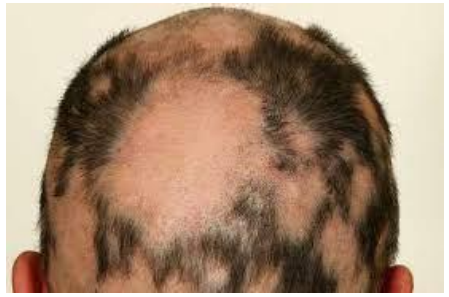
>50% of adults with Down syndrome have been diagnosed with autoimmune thyroid disease:

- Hypothyroidism
- Hyperthyroidism
- Hashimoto's disease
- Grave's disease

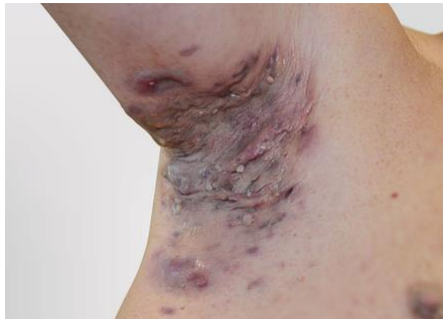
Thyroid medications are probably the most common medications used in Down syndrome

Immune skin diseases

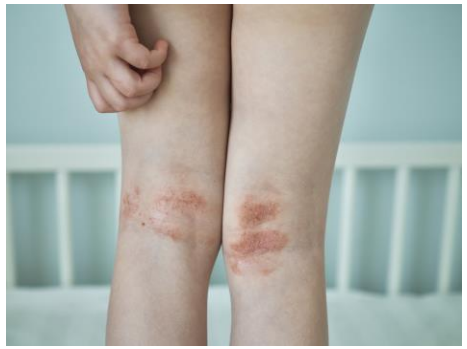
Alopecia areata (patchy hair loss)



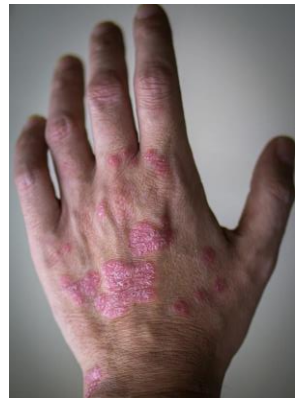
Hidradenitis suppurativa (boils)



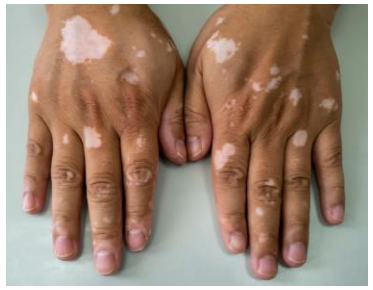
Atopic dermatitis (eczema)



Psoriasis



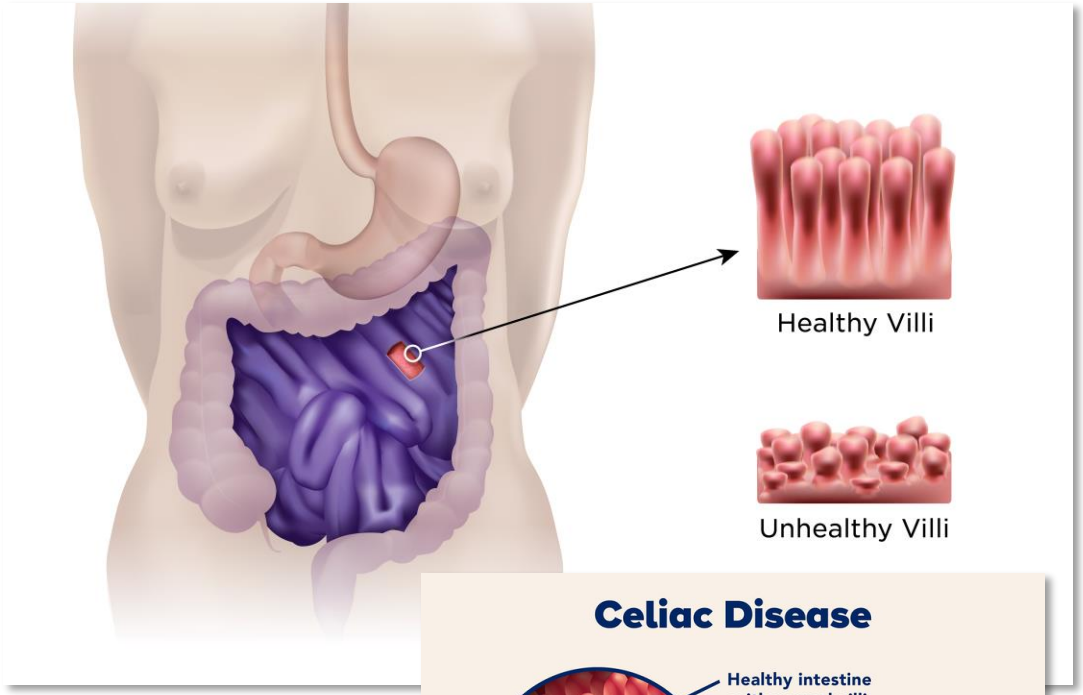
Vitiligo

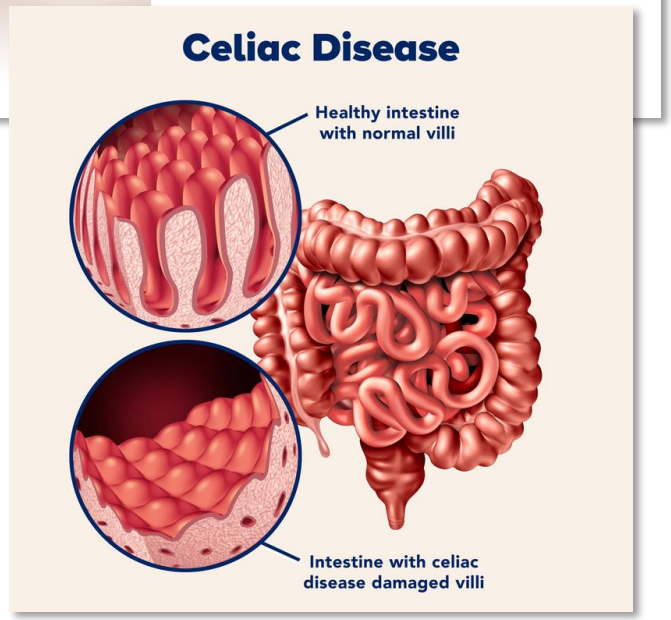


And other immune-driven skin diseases

>35% of adults with Down syndrome have been diagnosed with one or more of these immune skin conditions

Celiac disease



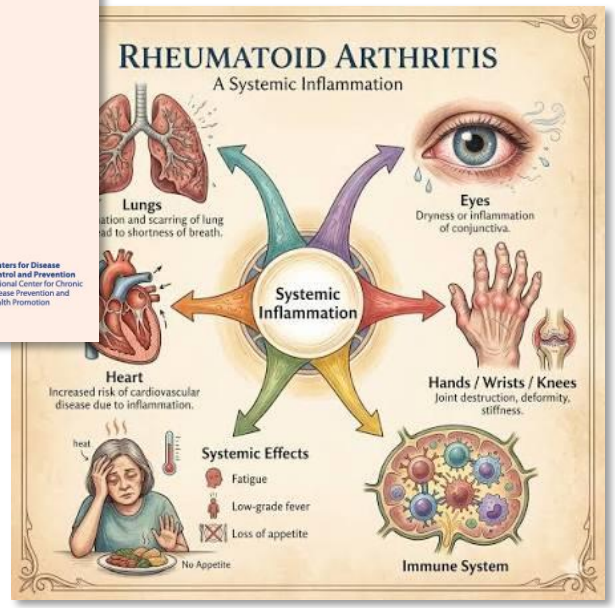


~10% of adults with Down syndrome have been diagnosed with celiac disease:

- Gluten intolerance
- Digestive issues
- Nutritional deficiencies
- Skin problems
- Bone and joint pain
- Neurological symptoms
- Mouth and dental issues

Celiac disease is likely under-reported in Down syndrome

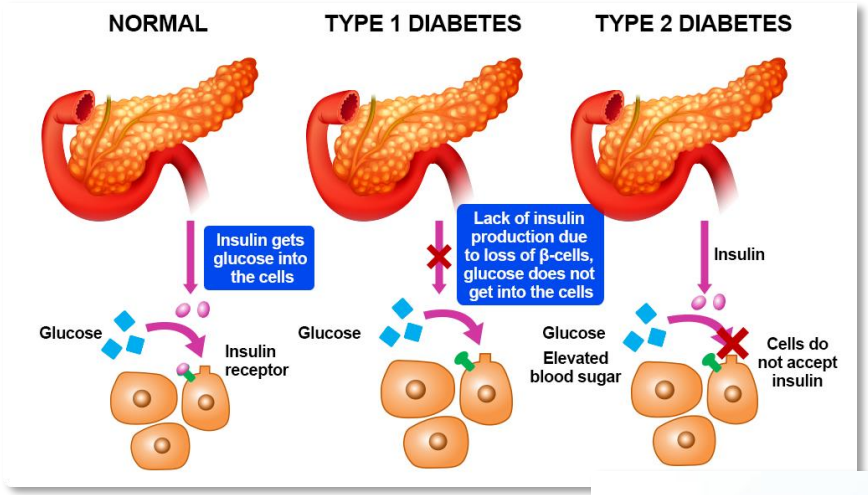
Down syndrome arthropathy (i.e., arthritis)

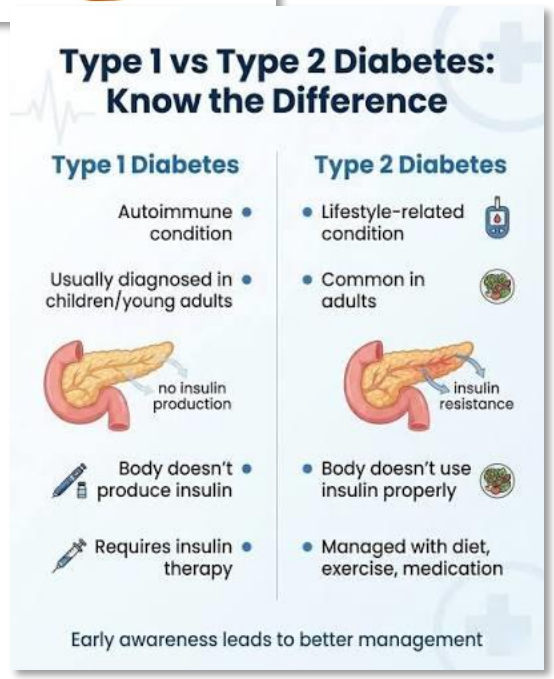


People with Down syndrome are at risk of a form of inflammatory joint disease known as ‘Down syndrome arthropathy’, which may show as:

- Rheumatoid arthritis
- Juvenile arthritis
- Psoriatic arthritis
- Other forms of arthritis

Type I diabetes





Type I diabetes is more common in Down syndrome:

- Autoimmune disease
- Lack of insulin production
- Early onset (pediatric, juvenile)
- Requires insulin therapy

Symptoms:

- Extreme thirst, frequent urination, unexplained weight loss, severe fatigue, blurred vision, numbness or tingling in the hands or feet, slow-healing cuts or frequent infections.

Severe complications from lung infections

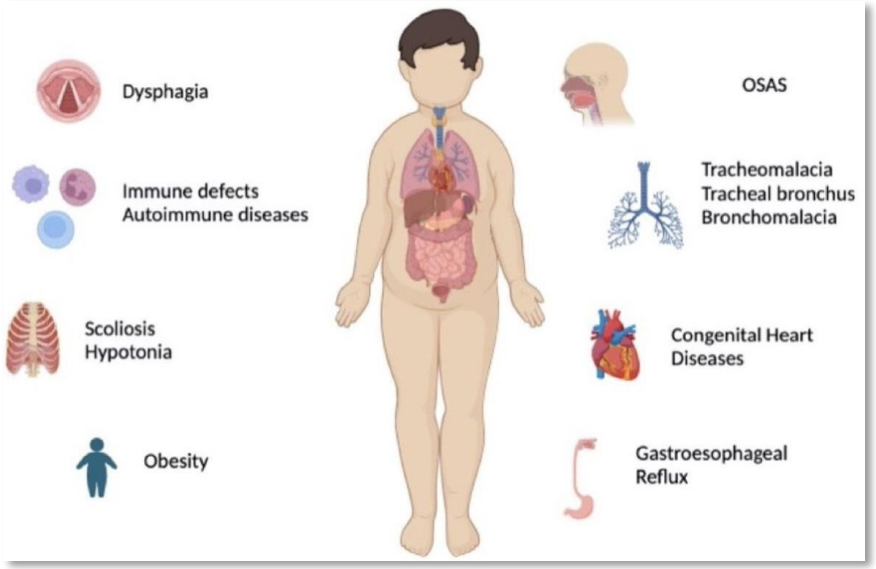
Children and adults with Down syndrome are more likely to be hospitalized upon lung infections:

- Respiratory Syncytial Virus (RSV)
- Flu
- COVID-19
- Bacterial pneumonia
- Others…

Lung infections are among the leading causes of mortality across the lifespan in Down syndrome

Recurrent infections

Risk factors for recurring infections in DS

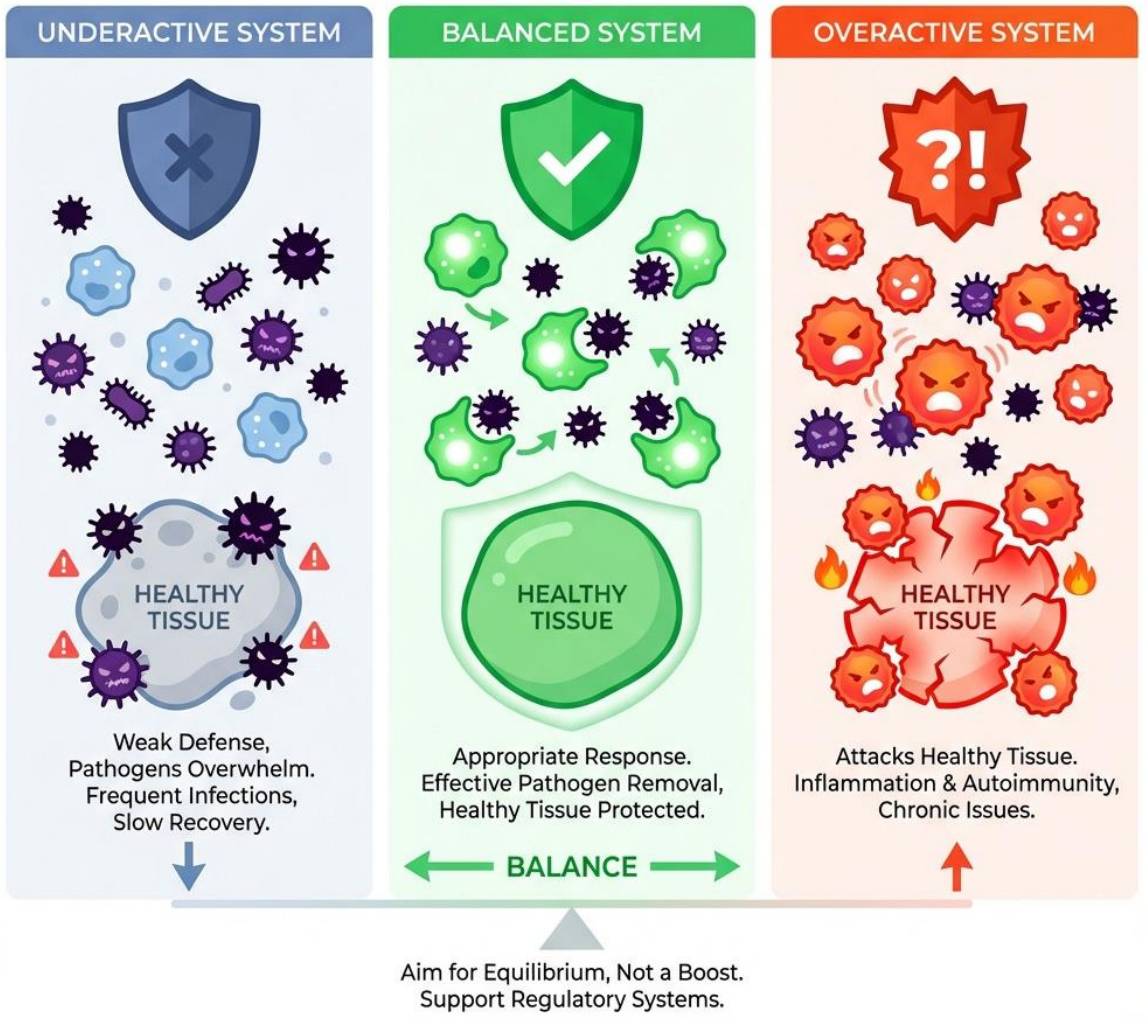


Children and adults with Down syndrome are more likely to experience recurrent infections that do not resolve quickly:

- Lung infections
- Ear infections
- Skin infections
- Gut infections
- Others…

These observations point to an unusual form of ‘immunodeficiency’.

People with Down syndrome have a highly dysregulated immune system



In Down syndrome, the immune system displays signs of both:

Overactivity:

- Autoimmune disorders
- Severe complications from infections

Underactivity:

- Recurrent infections
- Slow recovery

Could all these immune issues be addressed with a single medicine?

The 10-year journey of a discovery: from petri dish to advanced clinical trials

Idea

Basic Research
- Identify Target

Pre-Clinical Research
- Validate Target
- Develop Therapeutic

Clinical Trials
- Test Safety
- Test Efficacy

Regulatory Approval & Medical Care

2016 → 2020-2024 → 2023-2026 → 2026…

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

First trial **completed**

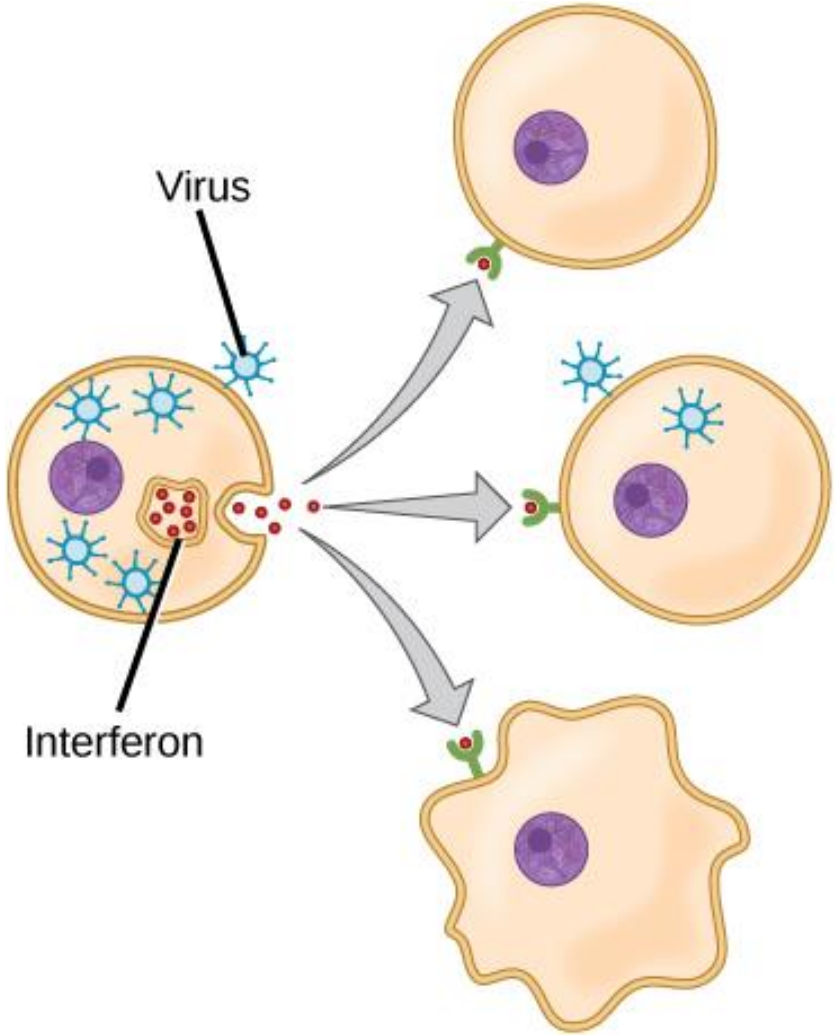
Second trial **completed**

Third trial: **currently recruiting**

Working together, we could witness the approval of the first immune therapy for Down syndrome in the next few years

People with Down syndrome have hyperactive interferon signaling

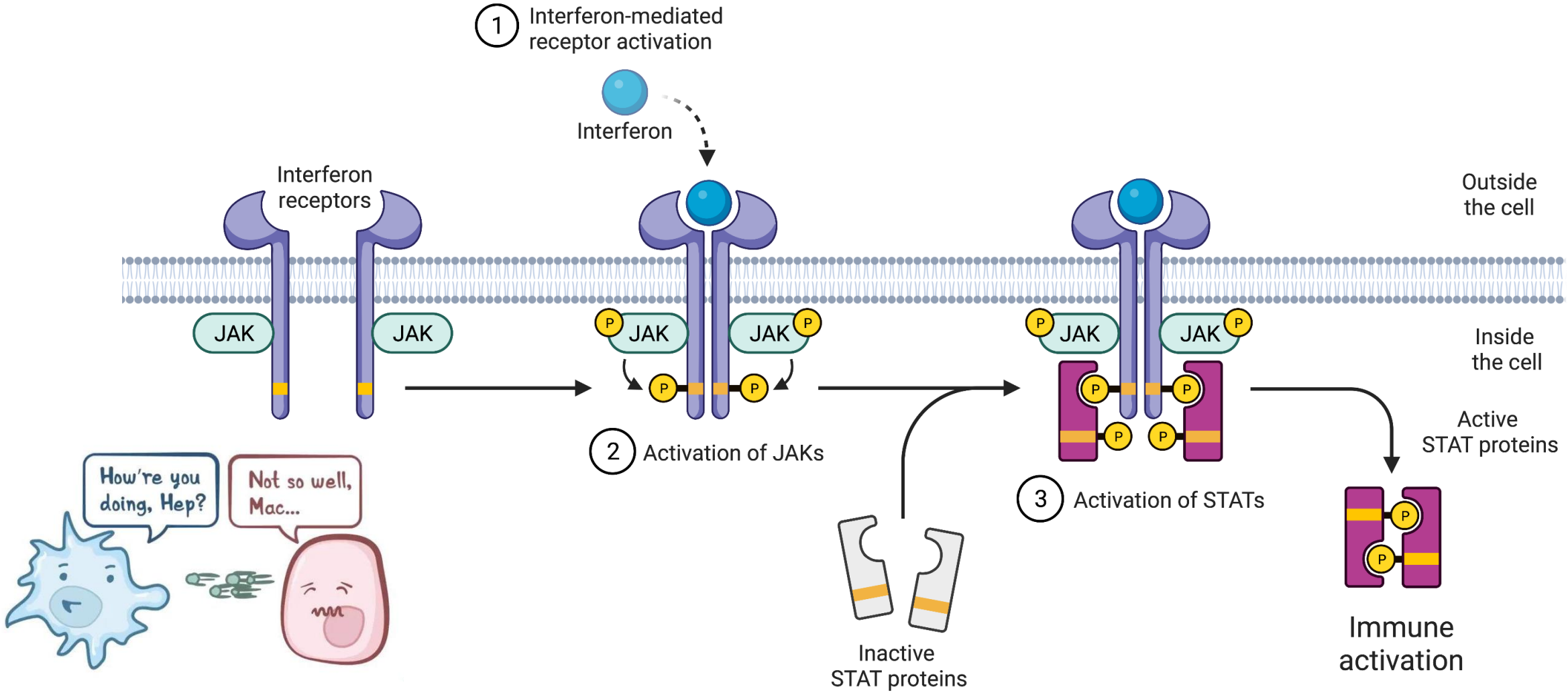
What is interferon signaling?



- 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 causes autoinflammation and 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

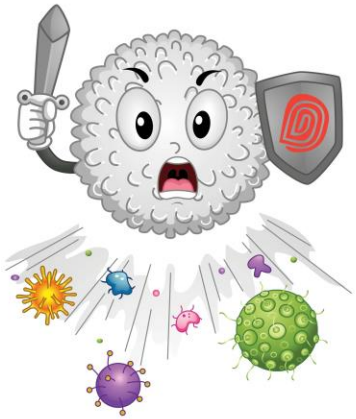


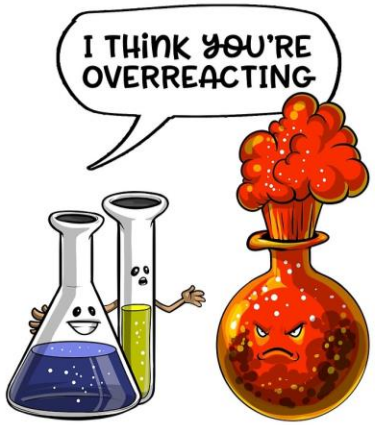
Interferon receptor ‘overdose’ is not good

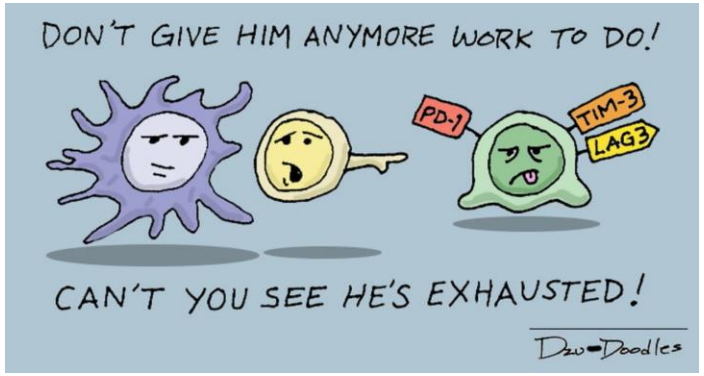
- An extra copy of the interferon receptors leads to ‘over-reaction’ throughout the immune system.

- Interferon hyperactivity can cause the immune system to make mistakes and attack healthy tissues (i.e., autoimmunity).

- 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

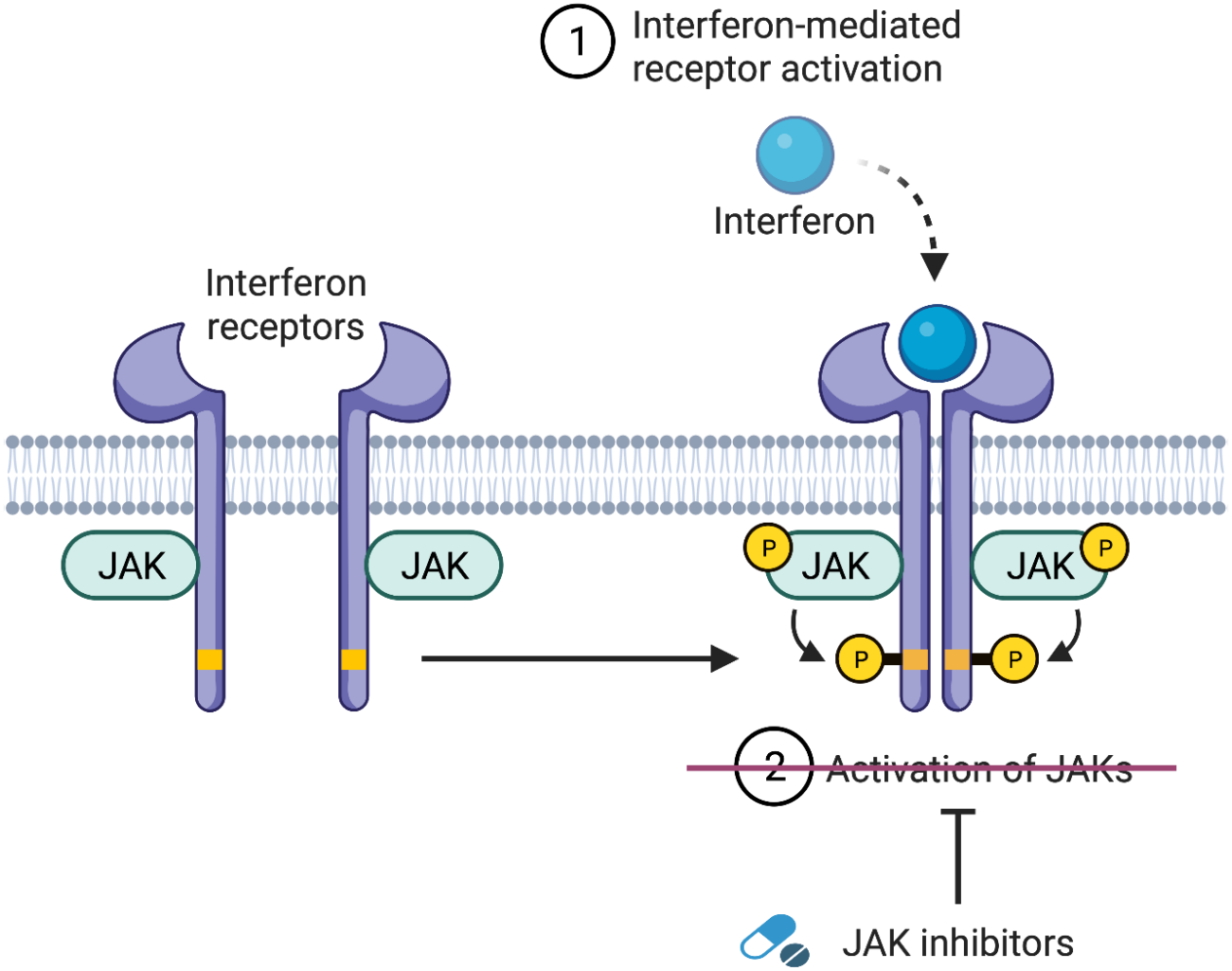
Target	JAK1/3	JAK1/2	JAK1	JAK1/2	JAK1
Rheumatoid arthritis	+	+	+		
Psoriatic arthritis	+		+		
Polyarticular course JIA	+				
Ulcerative colitis	+		+		
Atopic dermatitis			+		+
COVID-19		+			
Alopecia areata		+			
Chron's disease			+		
Polycythemia vera				+	
Ankylosing spondylitis			+		
Myelofibrosis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

There are 10+ JAK inhibitors approved for 20+ 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.

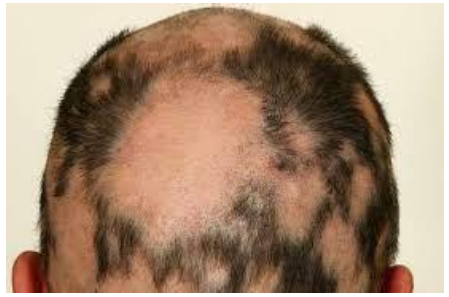
JAK inhibitors are taken daily orally as pills or liquid and have a short ‘half-life’ in the body.

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

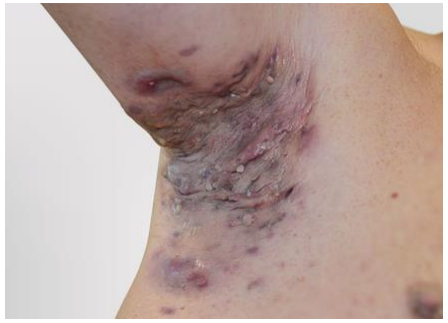
First clinical trial for JAK inhibition in Down syndrome

Treating five autoimmune skin conditions in one trial

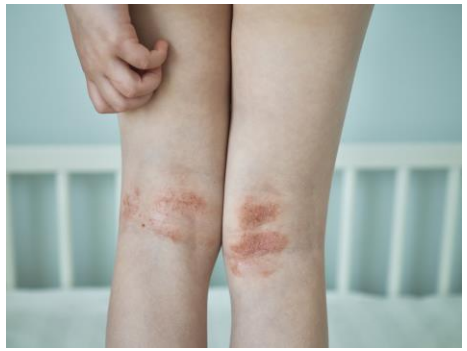
Alopecia areata (patchy hair loss)



Hidradenitis suppurativa (boils)

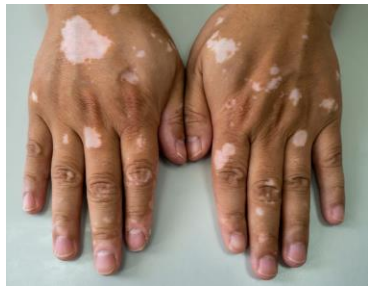


Atopic dermatitis (eczema)



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

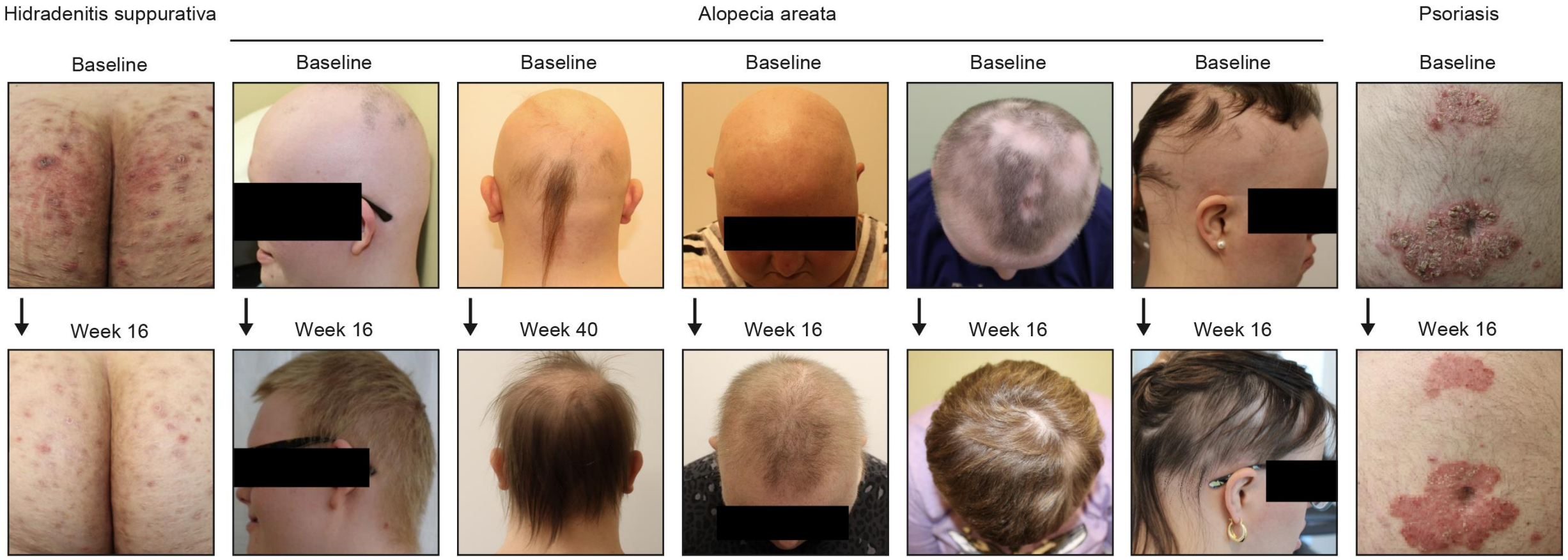
4-9 months of treatment with the FDA-approved JAK inhibitor Tofacitinib (Xeljanz)

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

JAK inhibition is safe in Down syndrome

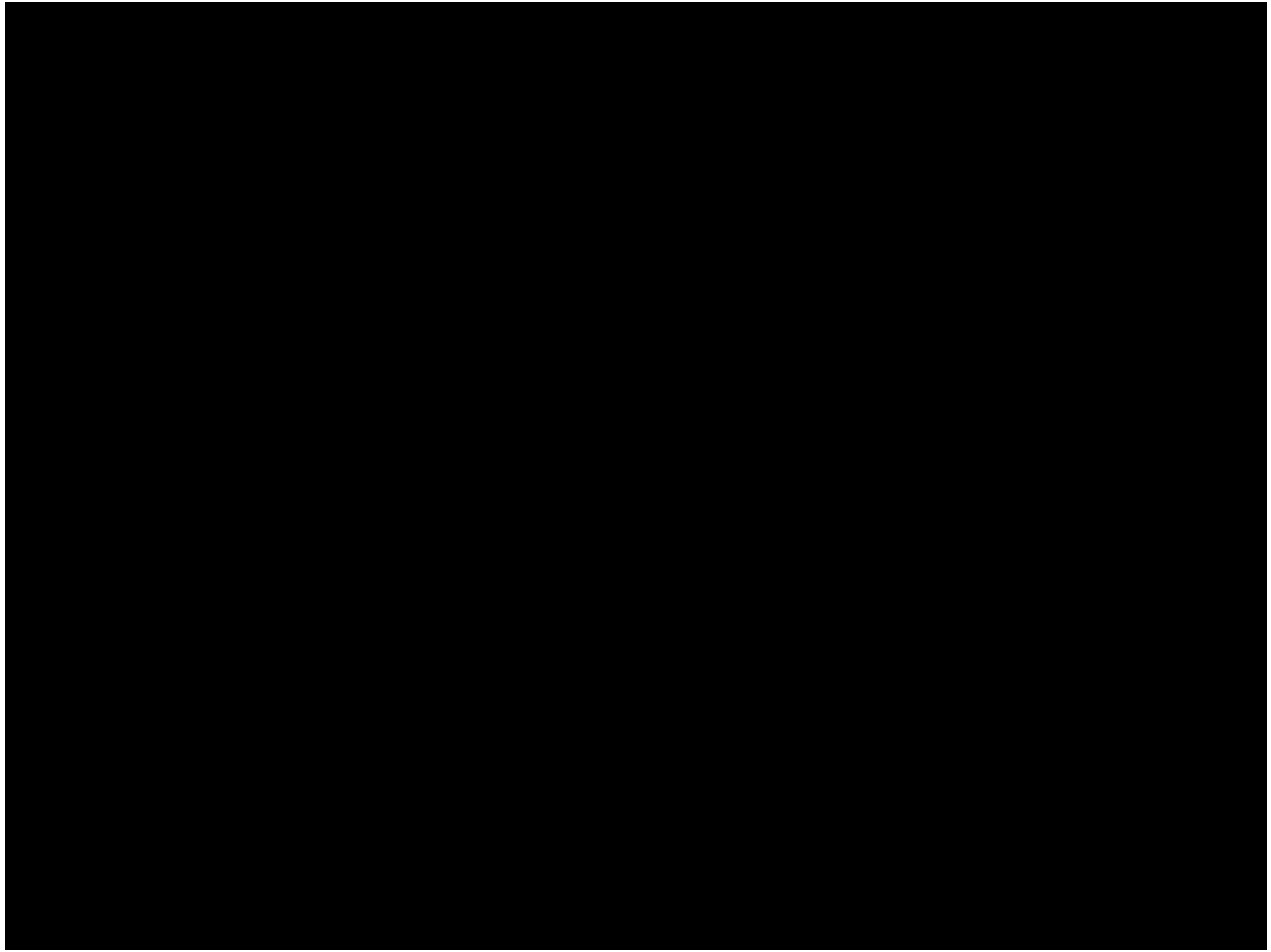
- Safety profile similar to that observed in the general population.
- Among 47 participants enrolled in the first trial, only one participant was discontinued from the medication.
- Even though 10 participants were infected by COVID19, none of them needed to be hospitalized or discontinued from the medicine.
- More than half of participants continued to received the medicine after the trial and have been on the medicine for many years.

JAK inhibitors can be used safely in Down syndrome to treat many different immune skin conditions



Since the start of the trial in 2020, JAK inhibitors have been approved for alopecia areata, psoriasis, and atopic dermatitis

Benefits of JAK inhibitors go much deeper than the skin…



Down Syndrome Regression Disorder (DSRD)

- A devastating condition characterized by rapid 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?

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,*]

2024

Journal of Neuroimmunology

Evidence of blood–brain barrier dysfunction and CSF immunoglobulin synthesis in Down Syndrome Regression Disorder

Jonathan D. Santoro[1,2], Neetha Paul Eduthan[3], Mellad M. Khoshnood[1,2], Saba Jafarpour[1,2], Natalie K. Boyd[1], Benjamin N. Vogel[1], Lina Nguyen[1], Lilia Kazerooni[1], Eleanor Britton[3], Hannah R. Lyford[3], Matthew D. Galbraith[3,4], Angela L. Rachubinski[3,5] & Joaquin M. Espinosa[3,4]

2025

ANNALS of Clinical and Translational Neurology

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.

A multidisciplinary collaboration between neuroimmunologists, psychiatrists, psychologists, and biologists.


Santoro


Sannar


Rachubinski


Patel


Kammeyer


Galbraith

Plus a wonderful team of clinical coordinators,
clinical research managers, psychometrists, nurses, and data scientists

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

Completed!

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.

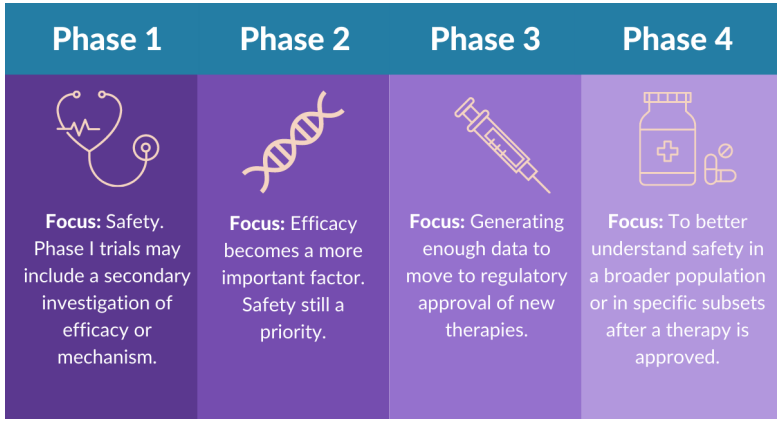
Is it safe?

Is it effective?

What is the mechanism?

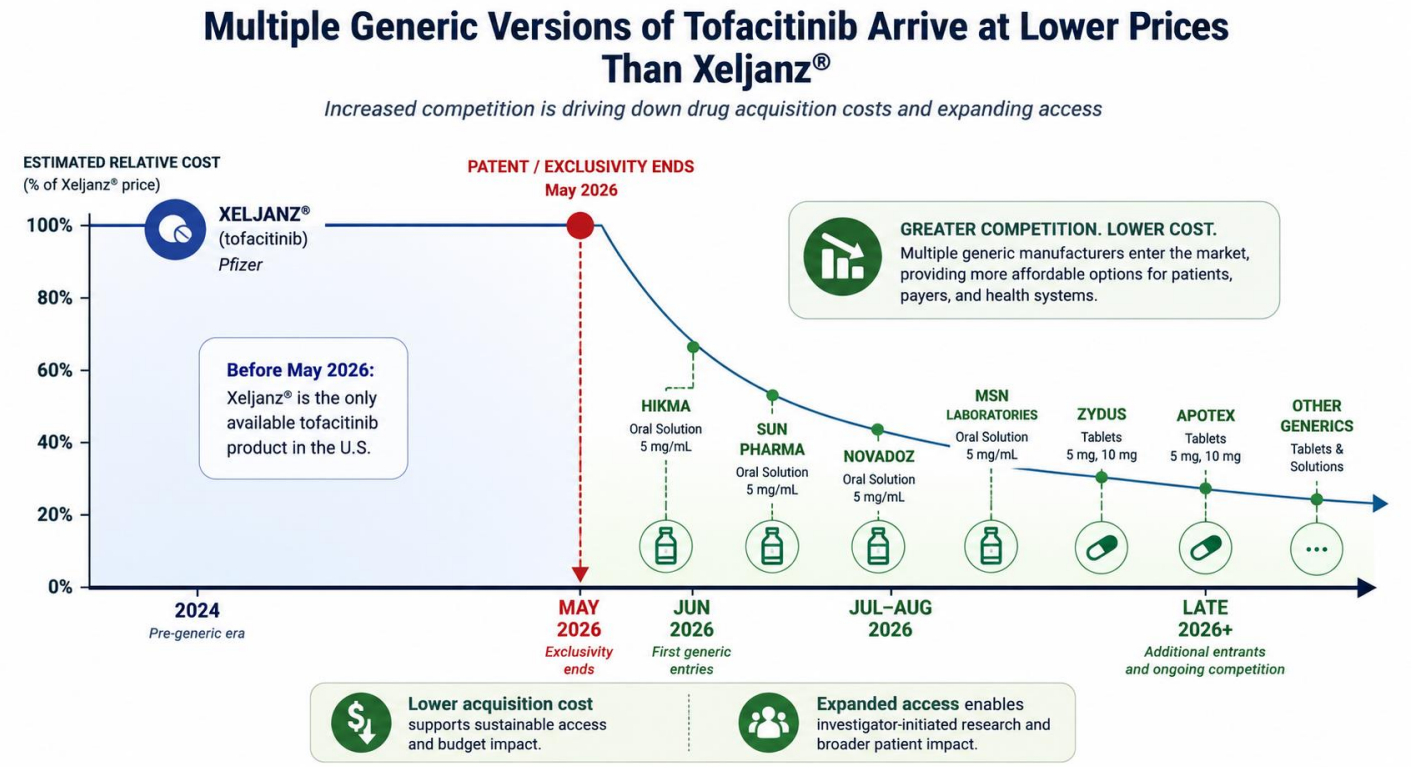
Immune therapies in DSRD

- All three medicines were found safe and beneficial, with strong inter-individual variability.
- Participants receiving immune therapies displayed more statistically significant improvements.
- **Phase 3 clinical trials for the two immune medicines (tofacitinib and IVIG) are now under planning, stay tuned…**



Generic tofacitinib: a game changer

In 2026, multiple generic versions of the JAK inhibitor tofacitinib were released in the USA



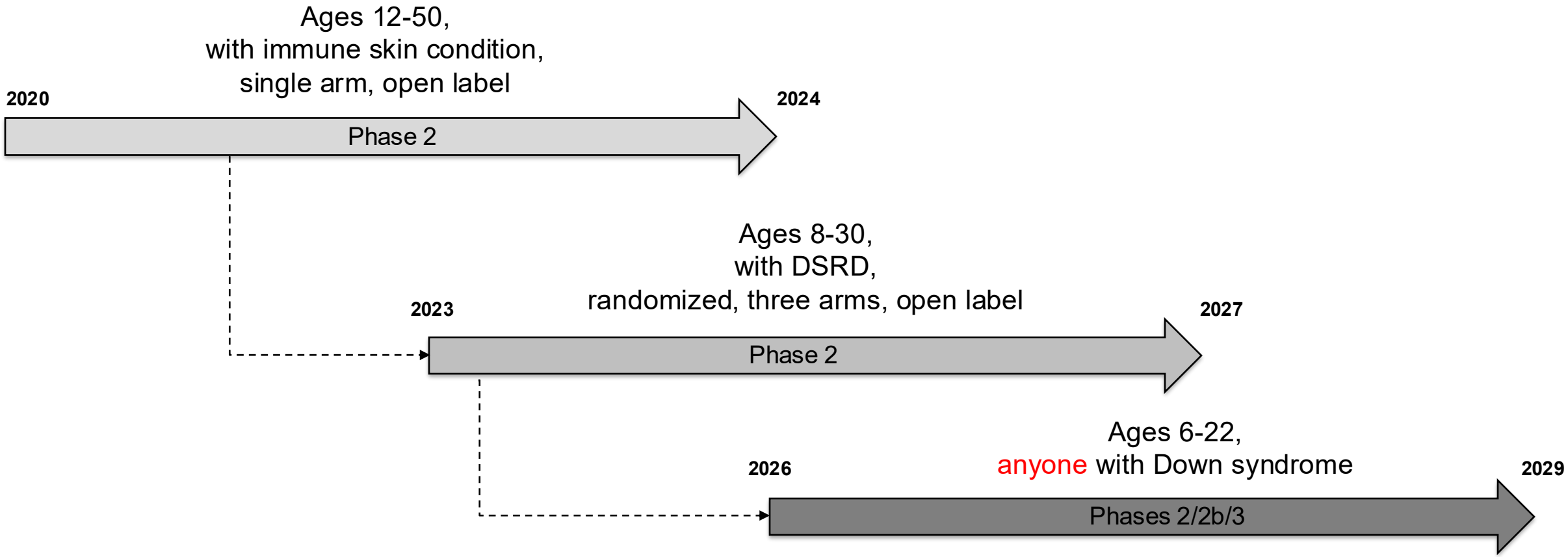
The monthly cost for tofacitinib treatment has dropped from:

~$6,000 per month down to:

~$300 per month (oral solution)
~$25-60 per month (tablets)

Investigating all the potential benefits of JAK inhibition :

Third clinical trial is now open to **anyone** with Down syndrome

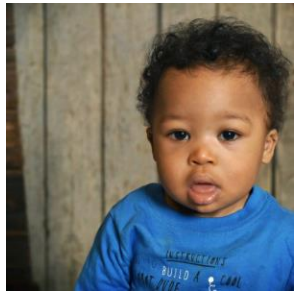


MISSION-1:
Modulating the **I**mmune **S**ystem in Down **S**yndrome
for **I**mproved **O**utcomes and **N**eurodevelopment

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

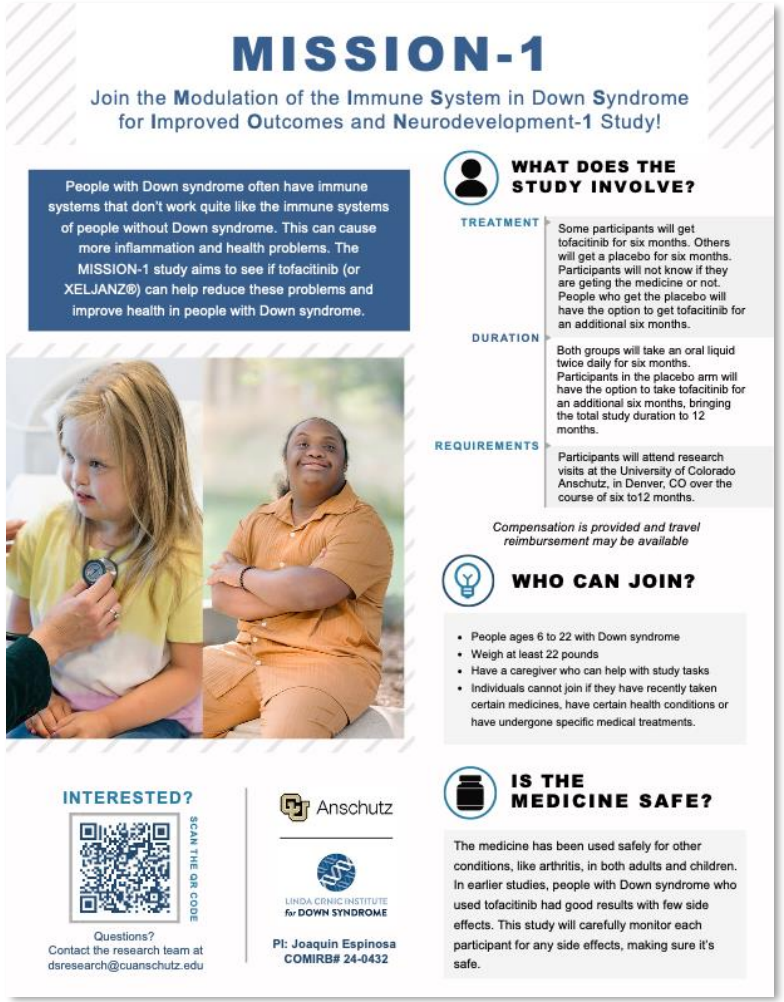
- Phase 2b, ages 6 to 22, Down syndrome
- No need for a co-occurring condition
- Randomized, double blind, placebo controlled
- 6 months of tofacitinib or placebo, 6 months open-label extension
- Primary endpoints: **global pediatric health** and **neurodevelopmental outcomes**.
- **First six participants already enrolled!**

What would be the effects of early immunomodulation in Down syndrome?

Funded by the **Anschutz Acceleration Initiative** and the **GLOBAL Down Syndrome Foundation**

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



MISSION-1

Join the Modulation of the Immune System in Down Syndrome for Improved Outcomes and Neurodevelopment-1 Study!

People with Down syndrome often have immune systems that don't work quite like the immune systems of people without Down syndrome. This can cause more inflammation and health problems. The MISSION-1 study aims to see if tofacitinib (or XELJANZ®) can help reduce these problems and improve health in people with Down syndrome.

WHAT DOES THE STUDY INVOLVE?

TREATMENT
Some participants will get tofacitinib for six months. Others will get a placebo for six months. Participants will not know if they are geting the medicine or not. People who get the placebo will have the option to get tofacitinib for an additional six months.

DURATION
Both groups will take an oral liquid twice daily for six months. Participants in the placebo arm will have the option to take tofacitinib for an additional six months, bringing the total study duration to 12 months.

REQUIREMENTS
Participants will attend research visits at the University of Colorado Anschutz, in Denver, CO over the course of six to12 months.

Compensation is provided and travel reimbursement may be available

WHO CAN JOIN?

- People ages 6 to 22 with Down syndrome
- Weigh at least 22 pounds
- Have a caregiver who can help with study tasks
- Individuals cannot join if they have recently taken certain medicines, have certain health conditions or have undergone specific medical treatments.

IS THE MEDICINE SAFE?

The medicine has been used safely for other conditions, like arthritis, in both adults and children. In earlier studies, people with Down syndrome who used tofacitinib had good results with few side effects. This study will carefully monitor each participant for any side effects, making sure it's safe.

INTERESTED?

SCAN THE QR CODE

Questions?
Contact the research team at
dsresearch@cuanschutz.edu

Anschutz

LINDA CRNIC INSTITUTE for DOWN SYNDROME

PI: Joaquin Espinosa
COMIRB# 24-0432

INTERESTED?

SCAN THE QR CODE

Questions?
Contact the research team at
dsresearch@cuanschutz.edu

Study team

A collaboration among pediatric neurologists, rheumatologists, neuroimmunologists, psychologists and biologists.


Baumer


Fuhlbrigge


Bloom


Tarshish


Sriram


Kammeyer


Patel


Fidler


Rachubinski


Chelales


Brecl


Cameron

And many more team members!!!!

Our new job:

IMMUNE-DS

Integrative **M**ultidisciplinary **M**atrix for Imm**une** Therapies in **D**own **S**yndrome

A nationwide collaboration to enable participation in clinical trials for immune therapies in Down syndrome across the USA

IMMUNE-DS

Conclusions

- JAK inhibition is a valid strategy to lower the burden of autoimmunity and autoinflammation in Down syndrome, with potential for multidimensional benefits.

- Testing of JAK inhibitors is justified for a variety of clinical endpoints in this population, including immune skin disorders, autoimmune thyroid disease, celiac disease, Down syndrome arthropathy, type I diabetes, and other immune-driven conditions common in this population.

- Beyond co-occurring conditions, JAK inhibition may provide benefits for overall health, development, and aging in Down syndrome.

Credits

First and foremost, the self-advocates and their families

THE INCLUDE PROJECT

NIH National Institute of Allergy and Infectious Diseases

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

NIH National Heart, Lung, and Blood Institute

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIH National Center for Advancing Translational Sciences

GLOBAL DOWN SYNDROME FOUNDATION®

ANNA & JOHN J. SIE FOUNDATION

THE ANSCHUTZ FOUNDATION

EVERYONE involved in this effort:

- Researchers, from basic scientists to clinical researchers
- Physician scientists
- Data scientists
- Clinical coordinators and their managers
- Administrative staff
- Outreach and communications staff
- NIH officers
- IRBs
- DSMB members
- Donors

Special thanks to Michelle Sie Whitten and the team at the Global Down Syndrome Foundation