Scientific research in the INCLUDE era
New discoveries and clinical trials
to improve health outcomes
in Down syndrome

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LINDA CRNIC INSTITUTE
for DOWN SYNDROME

GLOBAL
DOWN SYNDROME FOUNDATION®

Children’s Hospital Colorado
Anna and John J. Sie Center for Down Syndrome

DENVER HEALTH. est. 1860 FOR LIFE’S JOURNEY

Alzheimer’s and Cognition Center
UNIVERSITY OF COLORADO ANSCHTZ MEDICAL CAMPUS

Adult Down Syndrome Clinic
The NIH INCLUDE Project
Investigating co-occurring Conditions across the Lifespan to Understand Down syndrome

Frank Stephens testifying in Congress
The NIH INCLUDE Project
What is the impact on the scientific community?

- Many new ideas from scientists across diverse disciplines
- Many new synergistic collaborations
- Strong recruitment and training of new talent
- ‘Translation’ of discoveries into clinical trials to test new therapeutic strategies
People with Down syndrome have a different ‘disease spectrum’

Cancer

Heart Disease

- Coronary Artery Disease
- Atherosclerosis
- Hypertension
- Angiopathies (e.g. diabetic retinopathies)

Alzheimer’s

Autoimmunity

Leukemia

- Autism, Seizures
- Congenital Heart Defects
- Autoimmune Disorders (e.g. T1D, Celiac Disease, Hashimoto’s, Vitiligo, Rheumatoid Arthritis) and more...

The ~6 million human beings alive today with trisomy 21 may hold solutions to many major medical conditions
Each one of them is dealing with trisomy 21 in their own unique, personal way. They are more awesome than different, yet they are **ALL** unique.

Our motto: 

*Nothing in the study of Down syndrome makes sense except in the light of Personalized Medicine*
The Crnic Institute’s Human Trisome Project

A large and detailed cohort study of people with Down syndrome

www.trisome.org

UNLEASHING THE POWER OF TRISOMY 21 TO ADVANCE BIOMEDICAL RESEARCH

HTP@ucdenver.edu
The Crnic Institute’s Human Trisome Project

A large and detailed cohort study of people with Down syndrome

Goals:

1. To enable a personalized medicine approach for the management of Down syndrome in the clinic.

2. To enable the design of novel diagnostic and therapeutic tools to improve health outcomes in Down syndrome.
Key observation from the HTP: widespread autoimmunity in Down syndrome

>60% of adults with Down syndrome have been diagnosed with one or more autoimmune conditions in their lifetime. That is >6-fold more than observed in typical people.

People with Down syndrome are affected by many autoimmune conditions.
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?
Trisomy 21 activates the Interferon response

People with Down syndrome show a hyperactive ‘Interferon response’

The Interferon response is a key aspect of the immune system that ‘interferes’ with viral infections

The Interferon response acts throughout the entire human body

Without an Interferon response, we would probably die within days of a common viral infection

Too much Interferon response is known to cause autoimmunity

People with Down syndrome are ‘fighting off’ viruses 24/7, even when there is no virus present
Trisomy 21 activates the Interferon response

4 of the 6 IFN receptors are encoded on chr21!!

People with Down syndrome show a hyperactive interferon response
Peer reviewed publications

**Trisomy 21 consistently activates the interferon response**


**Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation**

Kelly D. Sullivan, Donald Evans, Ahwan Pandey, Thomas H. Hrahia, Keith P. Smith, Neil Markham, Angela L. Rachubinski, Kristine Wolter-Warmerdam, Francis Hickey, Joaquin M. Espinosa, & Thomas Blumenthal

**Mass Cytometry Reveals Global Immune Remodeling with Multi-lineage Hypersensitivity to Type I Interferon in Down Syndrome**

Katherine A. Waugh, Paula Araya, Ahwan Pandey, Kimberly R. Jordan, Keith P. Smith, Ross E. Granrath, Sanoth Khanal, Eric T. Butcher, Belinda Enriquez Estrada, Angela L. Rachubinski, Jennifer A. McWilliams, Ross Minter, Tiana Dimasi, Kelly L. Colvin, Dmitry Baturin, Andrew T. Pham, Matthew D. Galbraith, Kyle W. Bartsch, Michael E. Yeager, Christopher C. Porter, Kelly D. Sullivan, Elena W. Hsieh, and Joaquin M. Espinosa

**Trisomy 21 activates the kynurenine pathway via increased dosage of interferon receptors**

Rani K. Powers, Rachel Culp-Hill, Michael P. Ludwig, Keith P. Smith, Katherine A. Waugh, Ross Minter, Kathryn D. Tuttle, Hannah C. Lewis, Angela L. Rachubinski, Ross E. Granrath, Maria Carmona-Iragui, Rebecca B. Wilkerson, Darcy E. Kahn, Moshilshree Joshi, Alberto Lloó, Rafael Blesa, Juan Fortea, Angelo D’Alessandro, James C. Costello, Kelly D. Sullivan, & Joaquin M. Espinosa

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

Paula Araya, Katherine A. Waugh, Kelly D. Sullivan, Niclas G. Nuñez, Emiliano Roselli, Keith P. Smith, Ross E. Granrath, Angela L. Rachubinski, Belinda Enriquez Estrada, Eric T. Butcher, Ross Minter, Kathryn D. Tuttle, Tullia C. Bruno, Mariana Maccioni, and Joaquin M. Espinosa
Is there a way to ‘normalize’ the Interferon response in people with Down syndrome?
FDA-approved therapies that decrease the Interferon response: JAK inhibitors

<table>
<thead>
<tr>
<th>Company</th>
<th>Marketed Name</th>
<th>Target</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lilly</td>
<td>olumiant® (baricitinib) tablets</td>
<td>JAK1&amp;2</td>
<td>Rheumatoid arthritis (2018)</td>
</tr>
<tr>
<td>abbvie</td>
<td>RINVOQ® (upadacitinib) tablets</td>
<td>JAK1</td>
<td>Rheumatoid arthritis (2019)</td>
</tr>
</tbody>
</table>

Also currently in clinical trials for Interferon-driven conditions more common in people with Down syndrome, including:

- Alopecia areata
- Atopic dermatitis
- Depression
- Hidradenitis suppurativa
- Juvenile idiopathic arthritis
- Leukemia
- Vitiligo
Off-label use of Tofacitinib for alopecia areata in Down syndrome
The first clinical trial for JAK inhibition in Down syndrome

• For immune-driven skin conditions:
  o Atopic dermatitis
  o Alopecia areata
  o Hidradenitis suppurativa
  o Psoriasis
  o Vitiligo

• Treated with Tofacitinib (aka Xeljanz) for 4 months
• Safety as the primary endpoint
• While also monitoring:
  o Markers of immune dysregulation in the blood
  o Impacts on other autoimmune conditions
  o Impacts on cognition and quality of life
Scientific aims of the first JAK inhibitor clinical trial in Down syndrome

**Aim 1:** Define the safety profile.
Scientific aims of the first JAK inhibitor clinical trial in Down syndrome

**Aim 1:** Define the safety profile in Down syndrome.

**Aim 2:** Determine the impact on immune dysregulation.

Many ‘inflammatory markers’ elevated in Down syndrome
Scientific aims of the first JAK inhibitor clinical trial in Down syndrome

**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.
Scientific aims of the first JAK inhibitor clinical trial in Down syndrome

**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 the impact on cognition and quality of life.

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Human Development and Family Studies  
Colorado State University
Important information

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IRB-approved and listed in Clinicaltrials.gov:
https://clinicaltrials.gov/ct2/show/NCT04246372

Important dates:

Pre-screening by phone starts in March 2020

Screening and enrollment of first 10 participants planned for between April and September 2020

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Thanks!

THE INCLUDE PROJECT

GLOBAL

All the wonderful individuals with Down syndrome and their families who participate in research