Clinical and translational research benefiting people with Down syndrome

A multidisciplinary collaborative effort enabled by the CCTSI

January 13th, 2022
Joaquin M. Espinosa, PhD
The Crnic Institute is the largest, most well funded center for Down syndrome research in the world

60+ research teams
200+ scientists

#1 in NIH funding

170+ scientific publications since 2012
Crnic Institute Membership – Top Metrics

- 65 active faculty members
- 20 different departments
- 40+ trainees at the graduate and post-doctoral levels

The largest center for Down syndrome research in the world
In the last four years alone, Crnic faculty members have secured >$60M of NIH funding for Down syndrome research

- 48 awards from 9 different NIH Institutes
- 32 Principal Investigators across the CU system
- 12 R01s or Transformative R01s
- 23 Supplements or Competitive Revisions
- 4 R21s
- 2 R61s (clinical trials)
- 7 other miscellaneous types of awards
A supplement to the CCTSI UL1 to accelerate clinical translational research in Down syndrome

Ronald Sokol, MD
Professor, Pediatrics-Gastroenterology, Hepatology & Nutrition
Director, Colorado Clinical and Translational Sciences Institute

Supplement to NCATS UL1: *Accelerating Clinical Research on Down Syndrome at the CCTSI and Beyond*

$775,742  2019-2020

What exactly was done with these funds?
The Crnic Institute’s Human Trisome Project (HTP)

A pan-omics cohort study with deep clinical metadata, a multidimensional biobank, and a public researcher portal

UL1 supplement funded -omics data generation and portal development

www.trisome.org

Hundreds of datasets generated

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

30+ Projects supported

15+ Papers published / under review
An example of translational science enabled by the HTP and supported by the CCTSI:
from petri dish to clinical trial in 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

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
People with Down syndrome have a different ‘disease spectrum’

- Cancer
- Atherosclerosis
- Hypertension
- Allergies

- Autoimmunity
- COVID19
- 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?
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
The likely culprit: a hyperactive interferon response

Trisomy 21 consistently activates the interferon response


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


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, Santosh Khana, Eric T. Butcher, Belinda Enriquez Estrada, Angela L. Rachubinski, Jennifer A. McWilliams, Ross Mintzer, Tania Dimassi, Kelley L. Colvin, Dmitry Batulin, Andrew T. Pham, Matthew D. Galbraith, Kyle W. Bartosh, Michael E. Yeager, Christopher C. Forte, Kelly D. Sullivan, Elena W. Ishio, and Joaquin M. Espinosa.

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


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

What is interferon signaling?

• Interferon signaling is an important part of the innate immune system

• Interferon activates many different types of immune cells

• Interferon signaling shuts down RNA and protein synthesis

• Interferon hyperactivity is a known risk factor for autoimmunity
There are three major types of IFN signaling, involving different ligands and receptors.

All interferon signaling requires the JAK1 kinase to function.

Interferon signaling mounts the antiviral response.

Mutations that lead to chronic IFN overproduction cause ‘interferonopathies’, a group of monogenic disorders that share key phenotypes with Down syndrome.
4 of the 6 interferon receptors are encoded on chr21!!

Human chromosome 21

- **APP**
- **IFN receptors**
- **DYRK1A**
- **DSCAM**

Genes:
- **IFNAR2**
- **IFNAR1**
- **IFNGR2**
- **IL10RB**

Chromosome 21 gene positions:
- **21q21.3**
- **21q22.11**
- **21q22.13**
- **21q22.2**

200 kb
IFN receptor overexpression and ISG induction in Down syndrome

All four IFNRs are overexpressed in immune cells with trisomy 21

Dozens of downstream IFN-stimulated genes (ISGs) are also elevated in Down syndrome (e.g., IFI27, IFIT1B)

Funded by the UL1 supplement
The blood of people with Down syndrome looks like it is fighting a viral infection all the time…

IFN scores and many inflammatory cytokines are elevated at baseline in Down syndrome.

Transcriptional IFN scores

Cytokine profiling

Funded by the UL1 supplement
Would drugs that attenuate interferon signaling improve health outcomes in 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)</td>
<td>JAK1</td>
<td>Rheumatoid arthritis (2019)</td>
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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
A clinical trial for JAK inhibition in Down syndrome

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
  - Hidradenitis suppurativa
  - Vitiligo
  - Atopic dermatitis
  - Alopecia areata (affecting at least 25% of scalp)

**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.
Study Objectives and Design

R61 pilot phase:
- ~2.5 years
- Complete treatment for 10 participants
- Interim analysis

R33 phase:
- Three years
- Full analysis of 40 completed participants
Study Design

A lot of work!!

Major logistical support from the CCTSI, all activities take place at the CTRC…
Running a clinical trial for an immunosuppressive agent in a very vulnerable population in the COVID19 era…

COVID19 delayed activities by 6 months, but we eventually surpassed the recruitment target…
Top level figures as of January 13, 2022

• Pre-screened 65 participants
• Screened 20 participants
• All 13 ‘eligible’ participants were enrolled and completed the main 16-week treatment arm
• Interim analysis was triggered when the 10th participant completed the ‘main arm’ in October 2021
Top level results

• **Zero** serious adverse events

• 7/7 participants with alopecia areata experienced hair regrowth, to varying degrees

• 3/3 participants with atopic dermatitis saw complete remission

• 1/1 participant with psoriasis saw complete remission

• 3/6 participants showed improvements in hidradenitis suppurativa
Top level results

Benefits going well beyond skin deep!

- 9/10 participants showed decreased interferon scores

- 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…
Female, 22-24 years old at time of blood draws, taking Tofacitinib ‘on and off’ since 2016 for alopecia areata. Participant provided 11 research blood draws while being off and on Tofacitinib.

JAK inhibition ‘normalizes’ IFN scores, bringing them down to the range observed in the general population.
Tofacitinib resolves autoimmune skin pathology

When a picture is worth a thousand words

17 year old male, alopecia areata

Baseline
SALT = 86

Screening

28 year old male, psoriatic arthritis

Week 16
SALT = 4

Participant known as ‘Ed Sheeran’ to the research team
Significant decrease in the autoimmune attack to the thyroid gland

Autoimmune thyroid disease is the most common autoimmune condition in Down syndrome

All 7 participants with ‘clinically significant’ anti-TPO antibodies displayed decreases in autoantibody levels

Values above 60U/mL are ‘clinically significant’

$n = 7$
$p = 0.00118$
Significant 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: significant improvement in the Forward Reach Score, that is, the longest sequence problem successfully reached (but not passed) by the subject.
Significant improvement in one measure of visuomotor function

The NEPSY II test

Participants are asked to ‘track’ the path with a pencil

The task is videorecorded and analyzed for errors and time to completion

**Result:** significant decrease in the total number of errors
Conclusions

• The pilot phase of clinical trial was successfully completed despite COVID19.

• 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.
What can people with Down syndrome teach us about COVID19?

• Trisomy 21 increases risk of mortality from COVID19 by 10-fold

• The Human Trisome Project platform was rapidly repurposed to launch the COVIDome Project, which has enabled several important discoveries and publications about COVID19 pathophysiology

• Long term use of JAK inhibitors cuts down risk of COVID19 in-hospital mortality by half:

Long-term use of immunosuppressive medicines and in-hospital COVID-19 outcomes: a retrospective cohort study using data from the National COVID Cohort Collaborative

Kathleen M. Andersen, Benjamin A. Bates, Emaan S. Rashidi, Amy L. Olex, Roslyn B. Mannon, Rena C. Patel, Jasvinder Singh, Jing Sun, Paul G. Auswaert, Derek K. Ng, Jodi B. Segal, Brian T. Garibaldi, Hemalakumar B. Mehta, G. Caleb Alexander, on behalf of the National COVID Cohort Collaborative Consortium

Resubmission under review
Accelerating translational research in COVID19 via the COVIDome Project

Matched multi-omics datasets completed for ~300 research participants

**Experimental approach**

- Whole blood RNA → Transcriptome
- Plasma → Proteomics, Cytokines, Metabolomics
- PBMCs → Mass Cytometry
- RBCs → Metabolomics

Demographic and Clinical Data

COVIDome Dataset

COVIDome Explorer

covidome.org

Samples received in July 2020, portal launched in November 2020, paper published in August 2021

1400+ users across 60+ countries and counting…

Dr. Thomas Flaig
Vice Chancellor for Research
Q&A