Insights from the Human Trisome Project: Immune Dysregulation, Alzheimer’s Disease and Down Syndrome

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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)

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.

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**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™ (HTP)

UNLEASHING THE POWER OF TRISOMY 21 TO ADVANCE BIOMEDICAL RESEARCH

The largest and most comprehensive study of its kind, The Human Trisome Project will help us understand why individuals with Down syndrome (trisomy 21) are protected from some medical conditions, such as cancer, while highly predisposed to others, such as Alzheimer's disease.

This research will serve first and foremost the population with Down syndrome, but also the millions of individuals without Down syndrome who are affected by the many medical conditions modulated by trisomy 21.

www.trisome.org
Project goals

1. To enable a Precision Medicine approach to Down syndrome.
2. To define how trisomy 21 causes a novel disease spectrum.
3. To develop novel diagnostic and therapeutic tools that will benefit those with trisomy 21, and also millions of typical individuals.
Project goals – short term

1. To massively accelerate the pace of Down syndrome research.
2. To complete a comprehensive cohort study of a population of individuals with trisomy 21.
3. To create a large, user-friendly public database for Down syndrome research.
4. To create a comprehensive biobank of biological samples for future Down syndrome research.
A deep study of people with trisomy 21
The Human Trisome Project
Unleashing the Power of Three

A deep study of people with trisomy 21

Metabolome
Metabolites (e.g. sugars, lipids, aminoacids, neurotransmitters)

Microbiome
Our ‘other genome’

Immune Maps
Characterizing the blood and the immune system with exquisite detail
All this information from a single blood draw and a mouth swab!

524 participants to date!

HTP00001

October 2016

HTP00300

September 2017

HTP00500

January 2019
A massive discovery accelerator

>15,000 Blood sample aliquots banked

20+ Research projects currently supported

8 Publications already enabled

6 Additional manuscripts in preparation
Any cool results yet?
Everywhere we look, it is clear that trisomy 21 causes increased Interferon signaling

Trisomy 21 consistently activates the interferon response

Kelly D Sullivan¹,²,³,⁴*, Hannah C Lewis¹,², Amanda A Hill¹,², Ahwan Pandey¹,²,³,⁴, Leisa P Jackson¹,³,⁴, Joseph M Cabral¹,³,⁴, Keith P Smith¹, L Alexander Liggett¹,⁵, Eliana B Gomez¹,³,⁴, Matthew D Galbraith¹,²,³,⁴, James DeGregori¹,⁵,⁶,⁷,⁸,⁹, Joaquin M Espinosa¹,²,³,⁴*

2016

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

Kelly D. Sullivan¹,², Donald Evans¹, Ahwan Pandey¹,², Thomas H. Hrahæ³, Keith P. Smith¹, Neil Markham¹, Angela L. Rachubinski¹, Kristine Wolter-Warmerdam³, Francis Hickey³, Joaquín M. Espinosa¹,²,⁶ & Thomas Blumenthal¹,⁴,⁷

2017

Trisomy 21 induces the kynurenine pathway via increased dosage of interferon receptor genes


doi: https://doi.org/10.1101/403642

This article is a preprint and has not been peer-reviewed [what does this mean?].

2019
What is interferon signaling?

- Interferon signaling is an important part of the immune system.
- Interferons activate many different types of immune cells.
- Interferon signaling is important to fight off viruses and tumors.
4 of the 6 IFN receptors are encoded on chr21!!

Human chromosome 21

APP *  IFN receptors *** DYRK1A *  DSCAM *

21q21.3  21q22.11  21q22.13  21q22.2

cen       tel

IFNAR2  IFNAR1  IFNGR2

IL10RB

200 kb
Immune cells in charge of fighting viruses and tumors are much more active!

T cells are key players in the anti-viral and anti-tumor response

T cells with trisomy 21 show much elevated ‘Interferon scores’, a sign of hyperactivation

This hyperactive state could drive autoimmune disorders

D21: typical control
T21: participant with trisomy 21
When too much of a good thing can be bad

Cells from people with Down syndrome are ‘hypersensitive’ to Interferons.

The immune system of people with Down syndrome is ‘supercharged’, which may have both beneficial and harmful effects.

Some aspects of the immune system may be stronger (e.g. anti-tumoral activities), other aspects would be exhausted (antibacterial defenses).
What would be the impact of a chronic Interferon response?
Understanding Down syndrome as an immune disorder

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

Kelly D. Sullivan\textsuperscript{1,2}, Donald Evans\textsuperscript{1}, Ahwan Pandey\textsuperscript{1,2}, Thomas H. Hraha\textsuperscript{3}, Keith P. Smith\textsuperscript{1}, Neil Markham\textsuperscript{1}, Angela L. Rachubinski\textsuperscript{4}, Kristine Wolter-Warmerdam\textsuperscript{5}, Francis Hickey\textsuperscript{5}, Joaquin M. Espinosa\textsuperscript{1,2,6} & Thomas Blumenthal\textsuperscript{1,6,7}
People with Down syndrome show much elevated levels of ‘inflammatory markers’

129 subjects, 75 with trisomy 21

- **IP10**
  - p. val: 7.60e-06

- **TNFα**
  - p. val: 3.04e-05

- **CRP**
  - p. val: 2.60e-05

- **IL6**
  - p. val: 2.22e-04

Each of these inflammatory markers is induced by Interferon signaling.

Each of these has been positively correlated with risk and/or progression of Alzheimer’s disease in the typical population.
What could be the impact of hyperactive Interferon on the brain?
People with Down syndrome display elevated levels of neurotoxic metabolites.

Plasma metabolomics measuring 91 metabolites
120 participants, 72 with trisomy 21

Quinolinic acid
adj. p = 4.7e-6

Log2 adjusted intensity
Quinolinic acid, the inescapable neurotoxin

- Quinolinic acid is a very ‘neurotoxic’ metabolite capable of inducing the death of neurons.
- Circulating levels of Quinolinic acid were associated with lower cognition in older adults with Alzheimer’s in the typical population.
- Quinolinic acid is a potent convulsant involved in the etiology of epilepsy and seizures, conditions that often accompany Alzheimer’s disease.

Quinolinic acid, the inescapable neurotoxin

Gilles J. Guillemín¹,²
People with Down syndrome display activation of the ‘kynurenine pathway’

This metabolic pathway is activated by Interferon, leading to conversion of the amino acid tryptophan into quinolinic acid.

The IDO1 enzyme is much elevated in the blood of people with Down syndrome.
Can drugs that block the Interferon response have therapeutic benefits in Down syndrome?
Blocking the Interferon response with JAK inhibitors

Protein Kinases

JAK1, JAK2, TYK2

JAK inhibitors

Transcription Factors

IRFs and STATs

Interferon Stimulated Genes (ISGs)

APP
TMEM50B
MX1
MX2

IFIT2
CMPK2
IL1A
MYH6
IDO1
IFI27
IFI44L
RSAD2
OAS1
IFITM1
TNFSF10
HERC6
OAS2
BST2
IFI6
ISG15

Genes encoded on chromosome 21
Alopecia areata, treated with JAK inhibitors

Alopecia Areata (autoimmune hair loss) is one of the many autoimmune conditions more prevalent in people with trisomy 21.

Ruxolitinib: An FDA-approved JAK inhibitor

Clynes et al, Nature Medicine 2014
Alopecia areata, treated with JAK inhibitors in people with Down syndrome!

Rachubinski et al, JADCR 2019

Treated for four years!
Alopecia areata, treated with JAK inhibitors in people with Down syndrome!

Rachubinski et al, JADCR 2019
Launching a clinical trial for JAK inhibition in Down syndrome

Partnering with top dermatologists to complete the first clinical trial of a JAK inhibitor in Down syndrome

Drs. Norris and Dunnick have participate in many clinical trials of JAK inhibitors in typical people

Primary endpoint: Safety

Secondary endpoint: to lower inflammation and cure skin disease

Tertiary endpoint: changes in cognition and quality of life
Work ahead

1. To define the impact of immune dysregulation on the various traits of Down syndrome.

2. To test the safety and efficacy of immune therapies for Down syndrome.

Both activities will require a combination of approaches, including animal and human research, and the full spectrum of basic science to clinical trials.
How you can participate

Today you can meet with one of the members of our team and read and sign a Consent Form explaining the study.

You can provide biological samples today, or schedule a convenient time for some time tomorrow, Friday or Saturday.

We have highly trained nurses that can draw blood during the conference, either today or over the next three days.
Frequently asked questions

What happens to my information?
Your information is stored in encrypted, HIPAA-compliant, secure databases. Only ‘de-identified’ information will be provided to researchers. Your identifying information will not be shared or distributed.

Would I be compensated?
Yes. There is a compensation of $100 for a successful blood draw.

Is there a medical benefit for participants?
There is no immediate direct benefit to participants, but if an important finding is made regarding your health, you will be contacted by the study team.
Frequently asked questions

What are the possible discomforts or risks?  
In this study we will need to collect blood from you. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

If I agree to participate and then change my mind, can I be removed from this study?  
Yes, absolutely. Your participation is voluntary at all times, You can withdraw at any time by contacting the study staff.
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Hundreds of research volunteers!!!
‘People with Down syndrome are a gift. By studying their biology we can help them and the rest of humankind.’
- Tom Blumenthal

‘Nothing is impossible. The impossible just takes a little longer.’
- Winston Churchill