Immune System Dysregulation in Down Syndrome

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LINDA CRNIC INSTITUTE
for DOWN SYNDROME

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DOWN SYNDROME FOUNDATION®

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

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Alzheimer's and Cognition Center
UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**

People with Down syndrome have a unique disease spectrum

INCREASED incidence compared to typicals

100% — **Alzheimer's** brain pathology by age 40.
Cognitive deficits.

~10x — **Autism.**
Epilepsy.

Up to 400x — Pediatric **hematological proliferative disorders:** TMD, AMKL, AML, ALL.

2-25x — **Autoimmune disorders:** Alopecia, arthritis, celiac, Hashimoto's, T1D, vitiligo.

50% — **Obstructive sleep apnea.**
37x — **Pulmonary hypertension.**

DECREASED incidence compared to typicals

~5x — **Coronary artery disease.**
High blood pressure.

Over 10x — **Solid Malignancies** (except testicular cancer).

We know very little about how trisomy 21 causes Down syndrome

Trisomy 21

Down syndrome

100%

~10x

Up to 400x

2-25x

50%

37x

~5x

Over 10x

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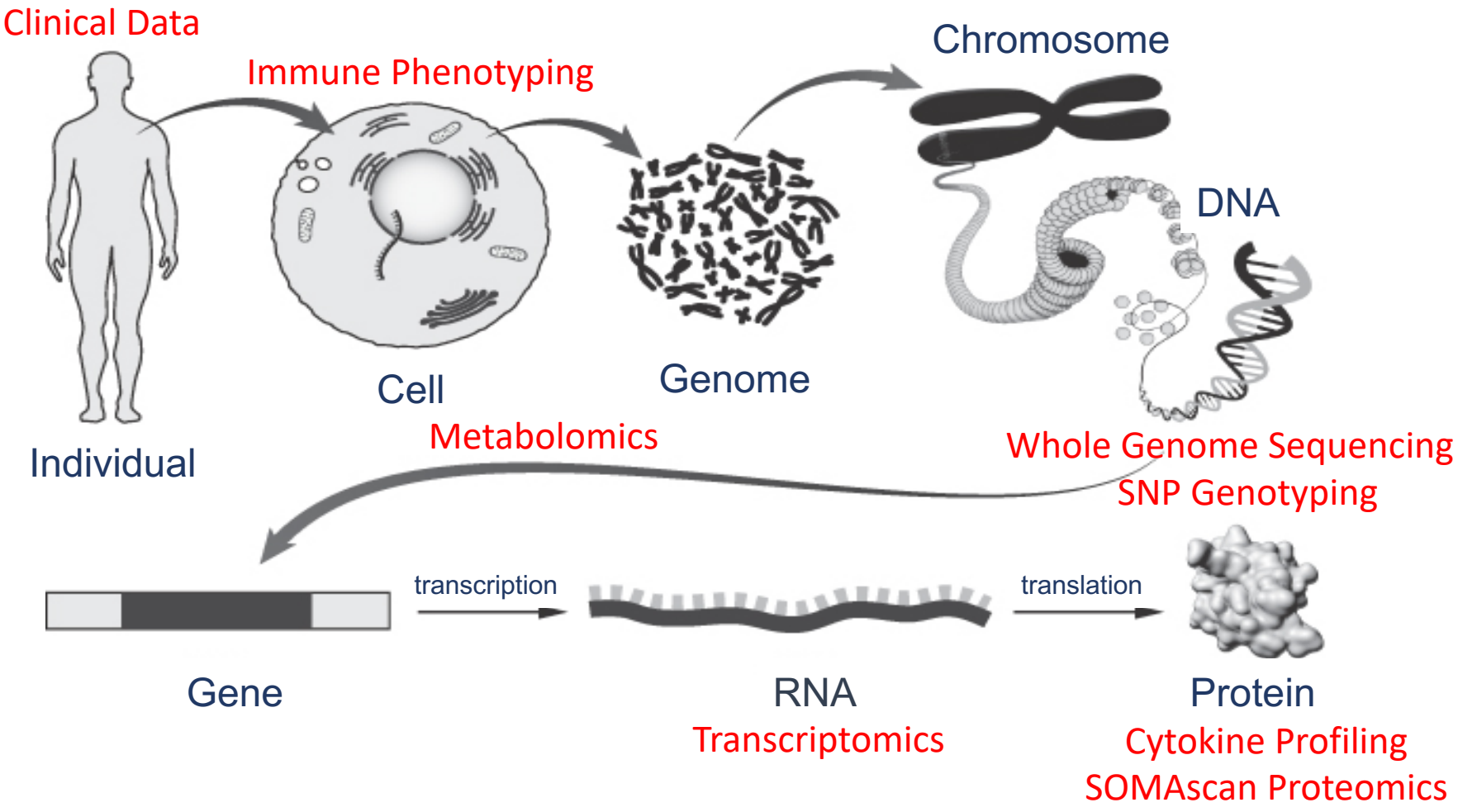
HUMAN TRISOME PROJECT™
GLOBAL DOWN SYNDROME FOUNDATION

A pan-omics cohort study with deep clinical metadata
and a multidimensional biobank
www.trisome.org



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
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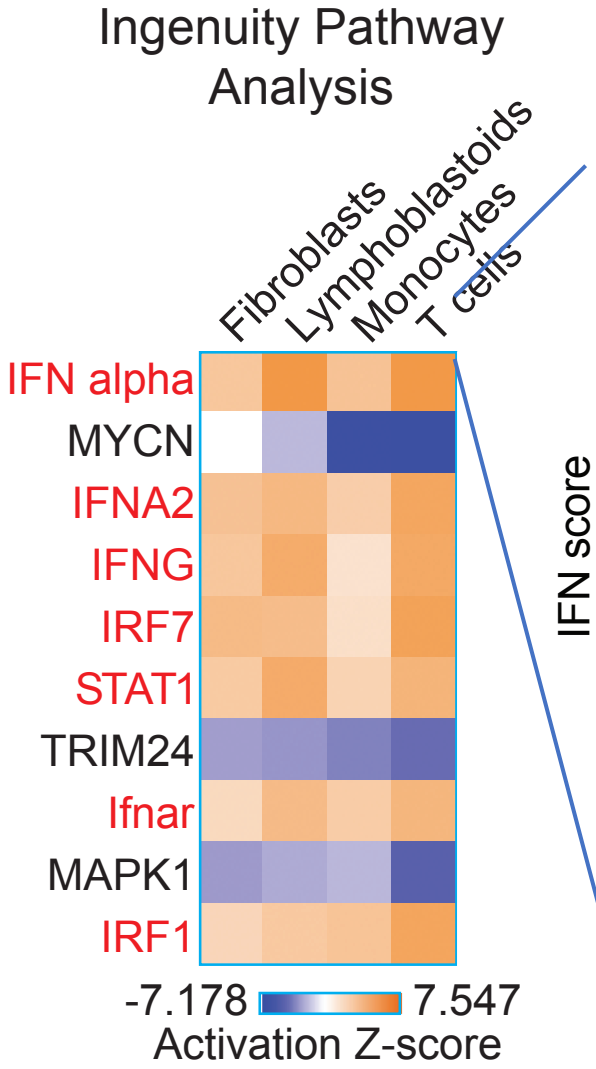
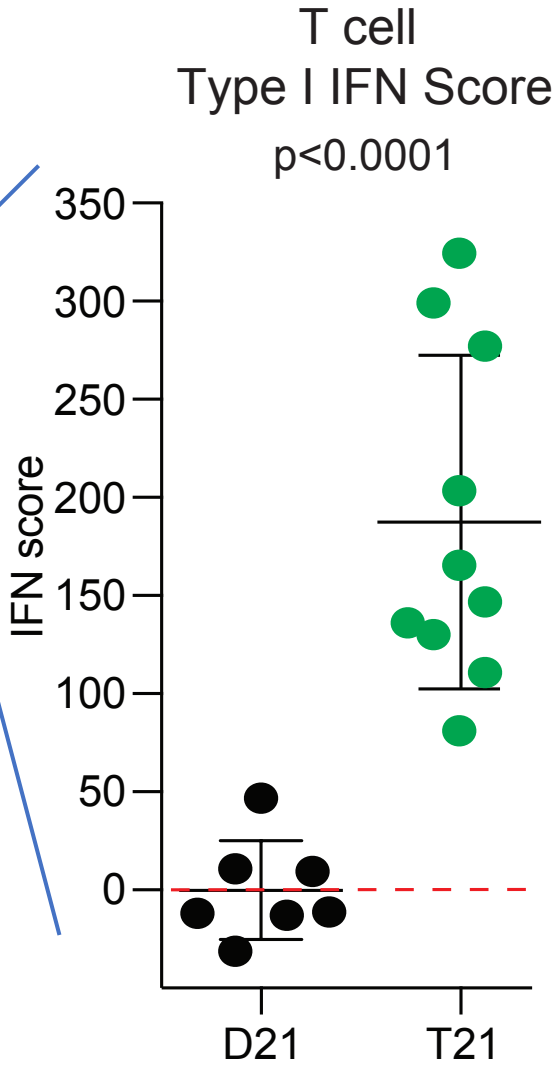
A transcriptional signature indicative of hyperactive Interferon signaling is observed in multiple cell types



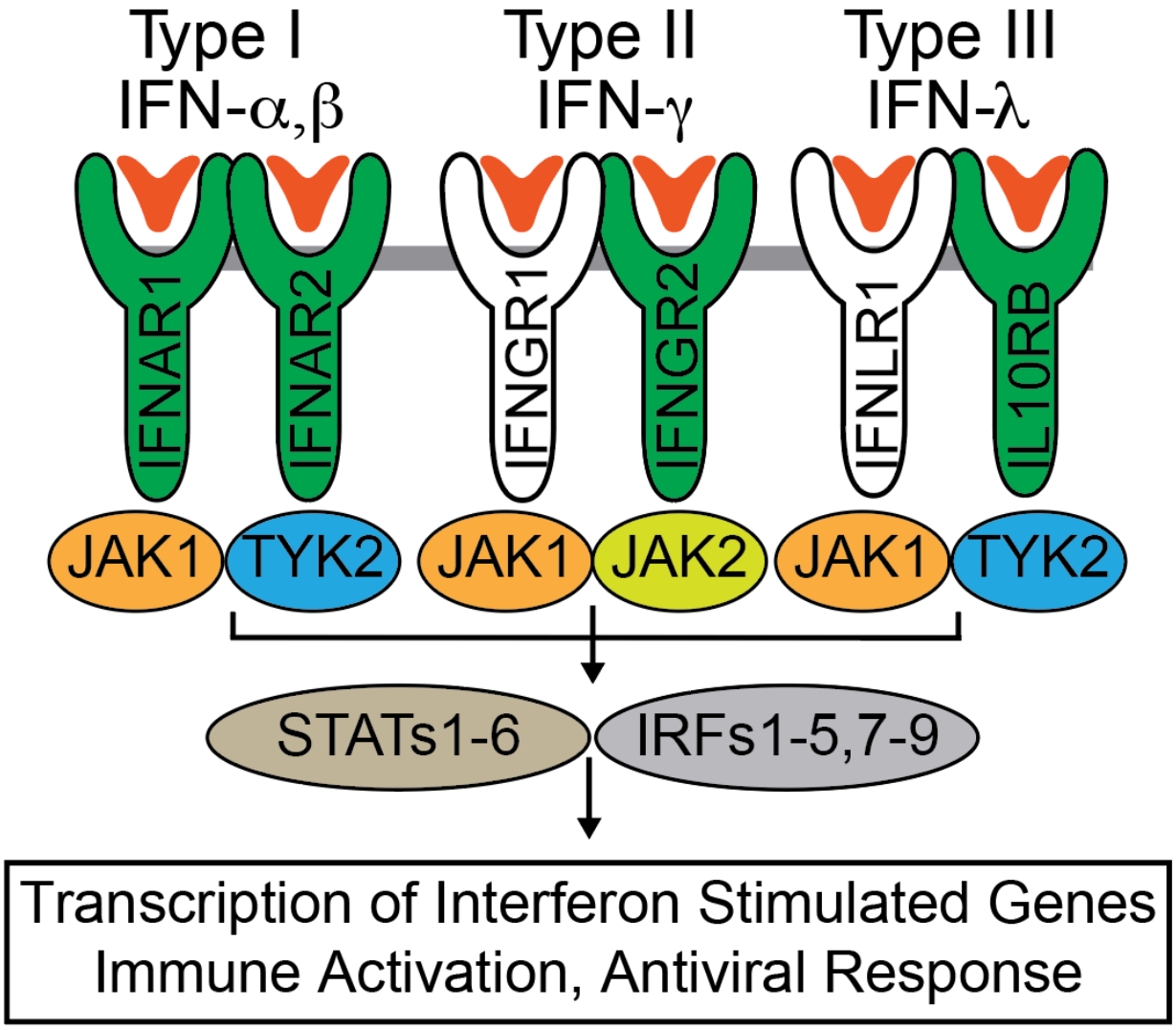


Hyperactive T cells have been implicated in the etiology of:

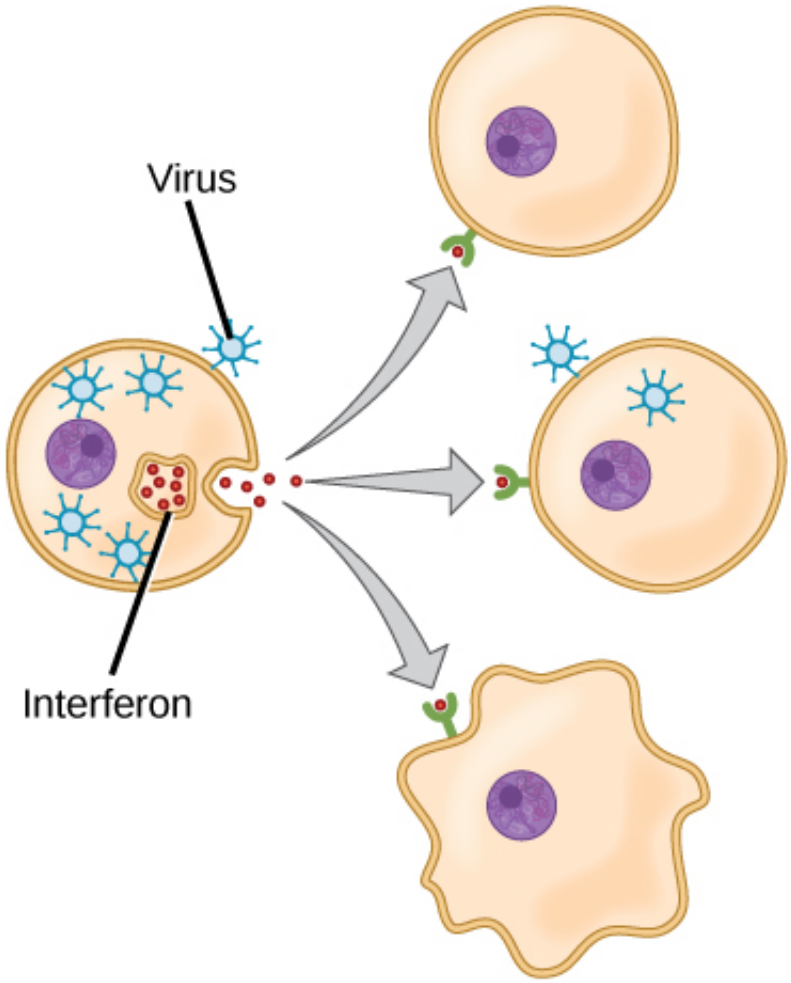
- Hypothyroidism
- Atopic dermatitis
- Alopecia Areata
- Psoriasis
- Hidradenitis suppurativa
- Vitiligo
- Celiac disease
- Type I diabetes
- Down syndrome arthropathy

D21: typical controls
T21: trisomy 21

Interferon, Interferon, Interferon



Trisomy 21 activates the Interferon response



People with Down syndrome show a hyperactive ‘Interferon response’

The Interferon response is a key aspect of the innate immune system acting throughout the human body

Exacerbated Interferon signaling is known to cause autoimmunity (e.g. during treatment of chronic HCV infections with IFN-α)

Polymorphisms in components of the IFN pathway are commonly associated with autoimmunity

People with Down syndrome are undergoing ‘systemic sterile inflammation’

SCIENTIFIC REPORTS

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

Kelly D. Sullivan[1,2], Donald Evans[1], Ahwan Pandey[1,2], Thomas H. Hraha[3], Keith P. Smith[1], Neil Markham[1], Angela L. Rachubinski[4], Kristine Wolter-Warmerdam[5], Francis Hickey[5], Joaquin M. Espinosa[1,2,6] & Thomas Blumenthal[1,6,7]

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

Rani K. Powers[1,2,3], Rachel Culp-Hill[4], Michael P. Ludwig[1,3], Keith P. Smith[1], Katherine A. Waugh[1], Ross Minter[1], Kathryn D. Tuttle[1], Hannah C. Lewis[1], Angela L. Rachubinski[1,5], Ross E. Granrath[1], María Carmona-Iragui[6,7], Rebecca B. Wilkerson[4], Darcy E. Kahn[1], Molishree Joshi[8], Alberto Lleó[6], Rafael Blesa[6], Juan Fortea[6,7], Angelo D'Alessandro[1,4], James C. Costello[2,3], Kelly D. Sullivan[1,3,5,8*] & Joaquin M. Espinosa[1,3,8,9*]

nature COMMUNICATIONS

Cell Reports

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

Katherine A. Waugh,[1] Paula Araya,[1] Ahwan Pandey,[1,2,3] Kimberly R. Jordan,[4] Keith P. Smith,[1] Ross E. Granrath,[1] Santosh Khanal,[2] Eric T. Butcher,[1] Belinda Enriquez Estrada,[1] Angela L. Rachubinski,[1,5] Jennifer A. McWilliams,[4] Ross Minter,[1] Tiana Dimasi,[1] Kelley L. Colvin,[1,5,6] Dmitry Baturin,[7] Andrew T. Pham,[1] Matthew D. Galbraith,[2] Kyle W. Bartsch,[1] Michael E. Yeager,[1,5,6] Christopher C. Porter,[8] Kelly D. Sullivan,[1,2,5] Elena W. Hsieh,[1,4,5] and Joaquin M. Espinosa[1,2,3,9,*]

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

Paula Araya[a,b], Katherine A. Waugh[a], Kelly D. Sullivan[a,c,d], Nicolás G. Núñez[b,1], Emiliano Roselli[b], Keith P. Smith[a], Ross E. Granrath[a], Angela L. Rachubinski[a,d], Belinda Enriquez Estrada[a], Eric T. Butcher[a], Ross Minter[a], Kathryn D. Tuttle[a], Tullia C. Bruno[e,f], Mariana Maccioni[b,2], and Joaquín M. Espinosa[a,c,g,2]

PNAS Proceedings of the National Academy of Sciences of the United States of America

What is the impact of trisomy 21 on the circulating proteome?

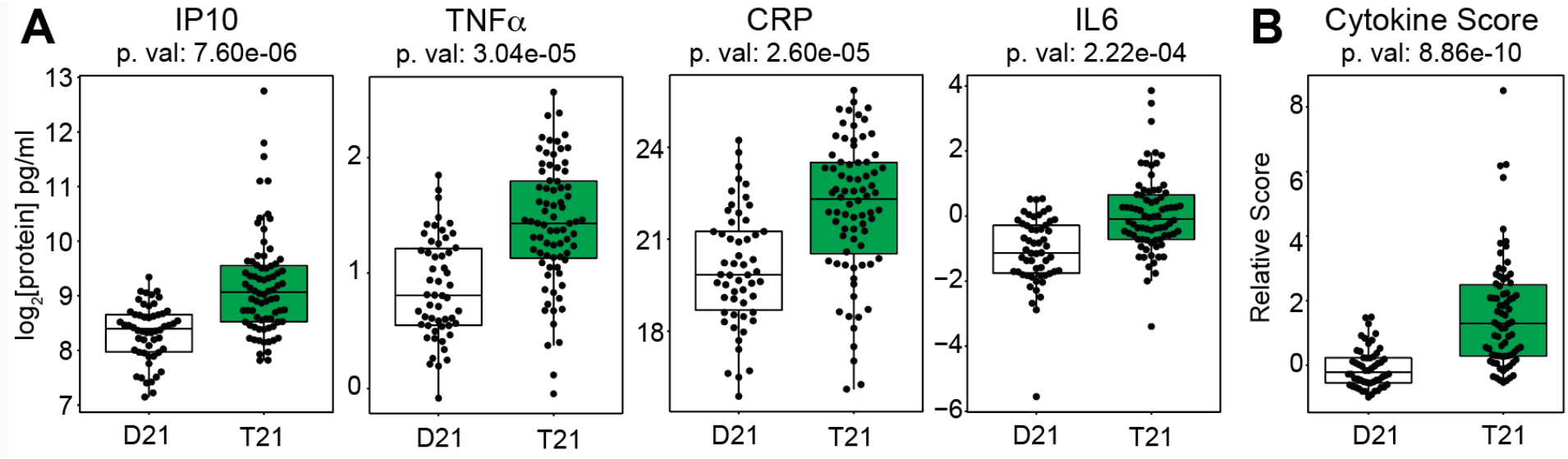
Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation

Kelly D. Sullivan[1,2], Donald Evans[1], Ahwan Pandey[1,2], Thomas H. Hraha[3], Keith P. Smith[1], Neil Markham[1], Angela L. Rachubinski[4], Kristine Wolter-Warmerdam[5], Francis Hickey[5], Joaquin M. Espinosa[1,2,6] & Thomas Blumenthal[1,6,7]

SCIENTIFIC REPORTS

People with Down syndrome show much elevated levels of IFN-inducible cytokines

MesoScale Discovery assay, 129 subjects, 75 with trisomy 21



IP10:
Interferon-inducible protein 10

Each of these cytokines is induced in circulation by Interferon

Each of these cytokines has been implicated in the progression of autoimmune disorders (and Alzheimer's disease)

What is the impact of trisomy 21 on the immune cell repertoire?

High resolution mapping of the immune system in Down syndrome

Employing CyTOF technology to map the immune system of people with Down syndrome

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

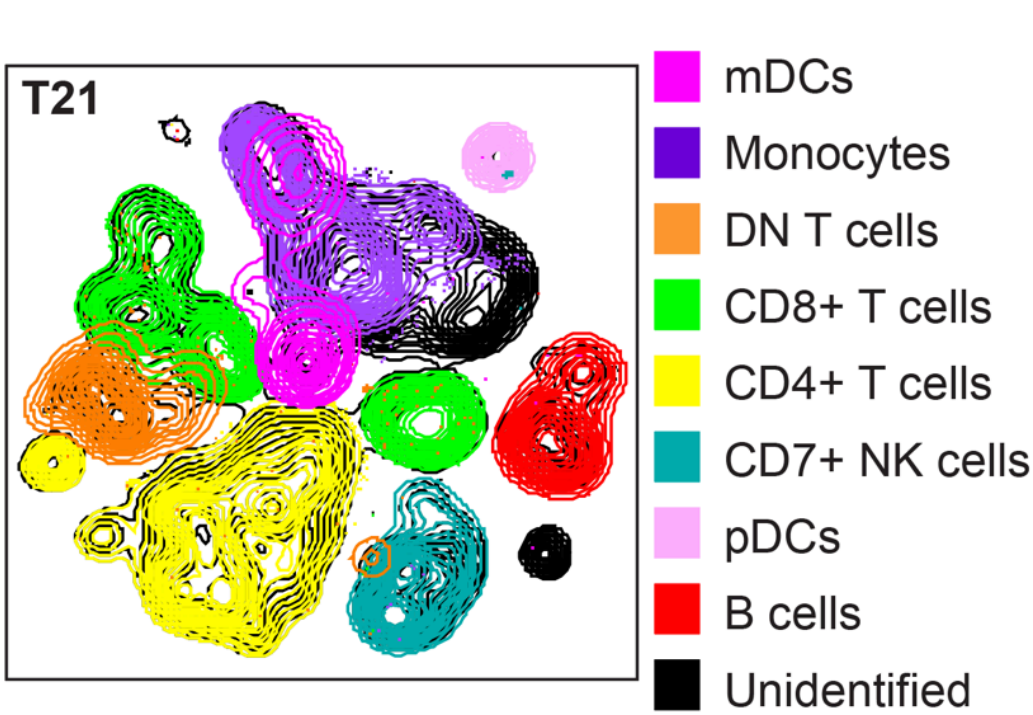
Katherine A. Waugh,[1] Paula Araya,[1] Ahwan Pandey,[1,2,3] Kimberly R. Jordan,[4] Keith P. Smith,[1] Ross E. Granrath,[1] Santosh Khanal,[2] Eric T. Butcher,[1] Belinda Enriquez Estrada,[1] Angela L. Rachubinski,[1,5] Jennifer A. McWilliams,[4] Ross Minter,[1] Tiana Dimasi,[1] Kelley L. Colvin,[1,5,6] Dmitry Baturin,[7] Andrew T. Pham,[1] Matthew D. Galbraith,[2] Kyle W. Bartsch,[1] Michael E. Yeager,[1,5,6] Christopher C. Porter,[8] Kelly D. Sullivan,[1,2,5] Elena W. Hsieh,[1,4,5] and Joaquin M. Espinosa[1,2,3,9,*]

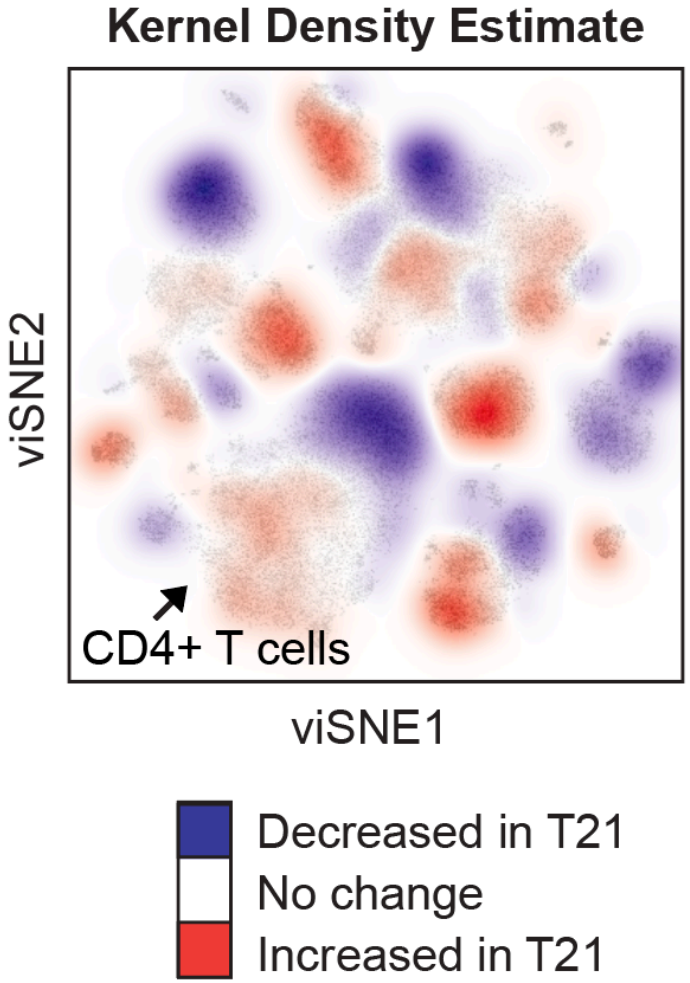
November 2019

Cell Reports

Topographic analysis highlights global immune dysregulation among individuals with Trisomy 21

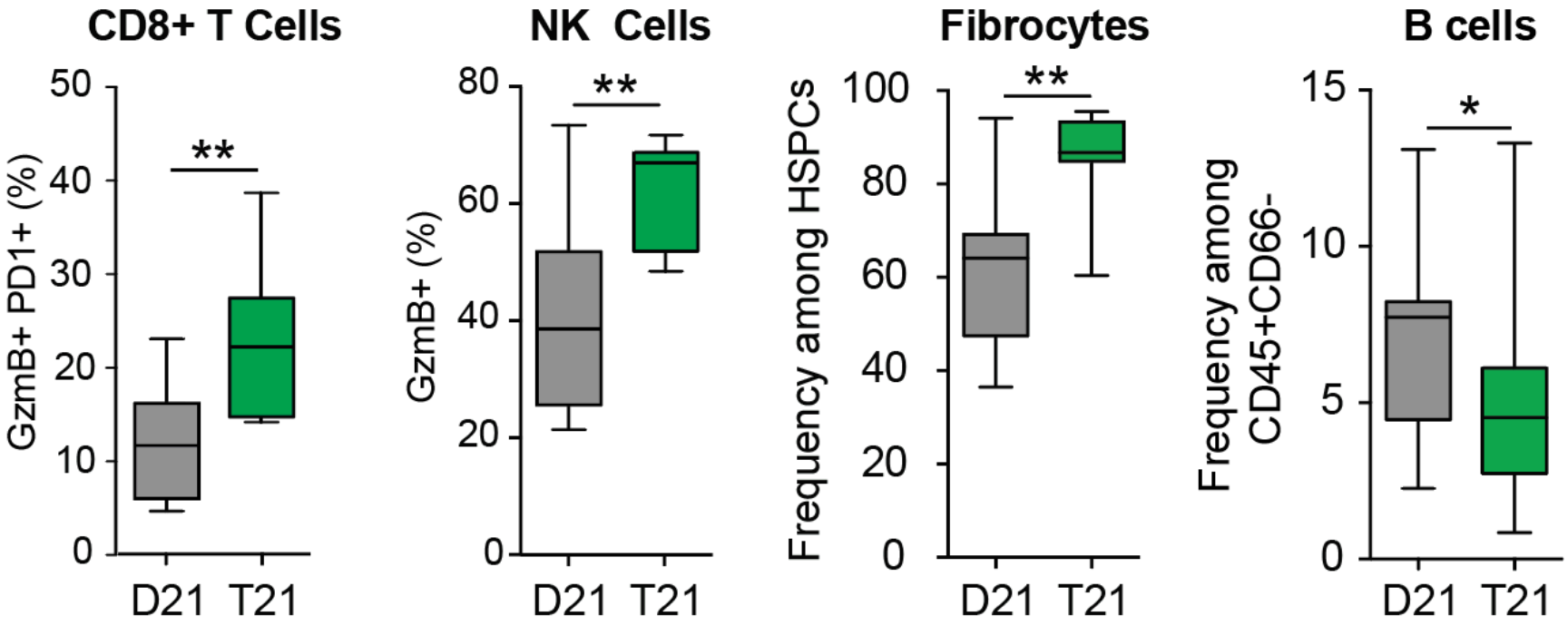
Kernal Density Estimate (KDE) of viSNE plots to quantitatively compare densities:





Adults with Down syndrome display many alterations in immune cell types consistent with a hyperinflammatory state

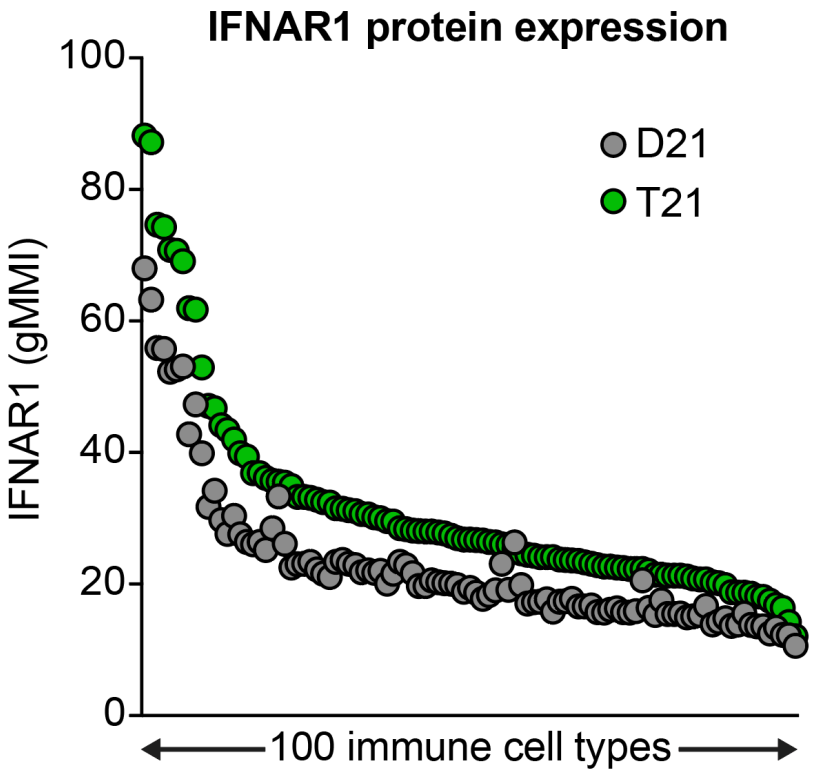
These changes have been observed in typical people affected by chronic autoinflammatory conditions



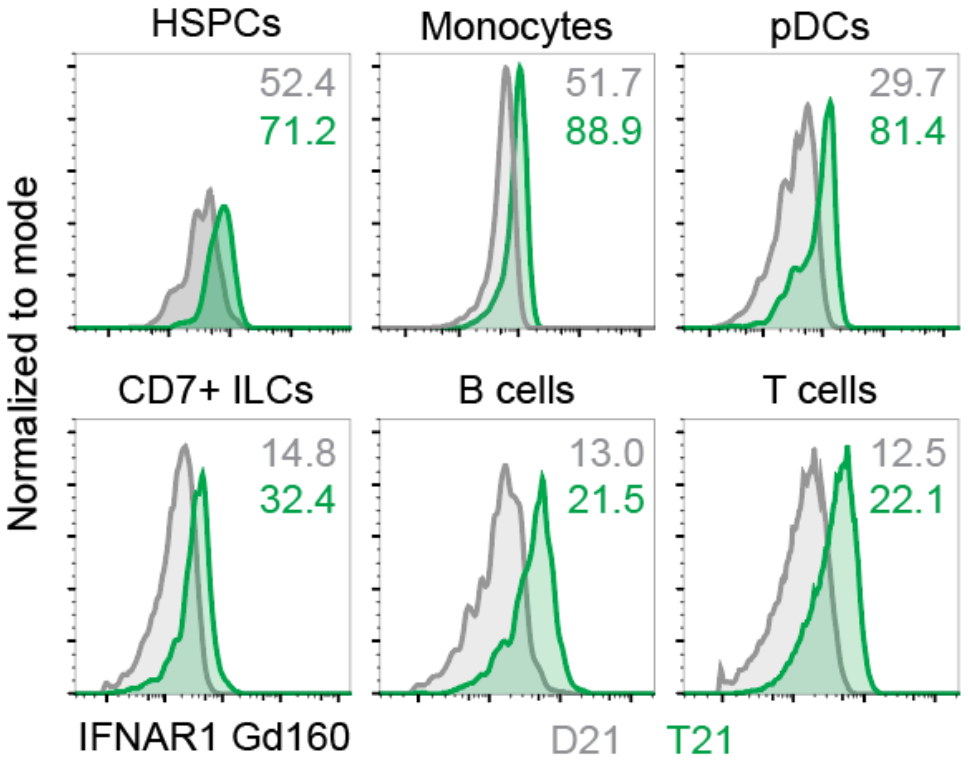
Time and time again, these alterations could be linked conceptually to IFN hyperactivity

Widespread overexpression of IFNRs across the immune system of people with Down syndrome

IFNAR1 surface protein expression (CyTOF)



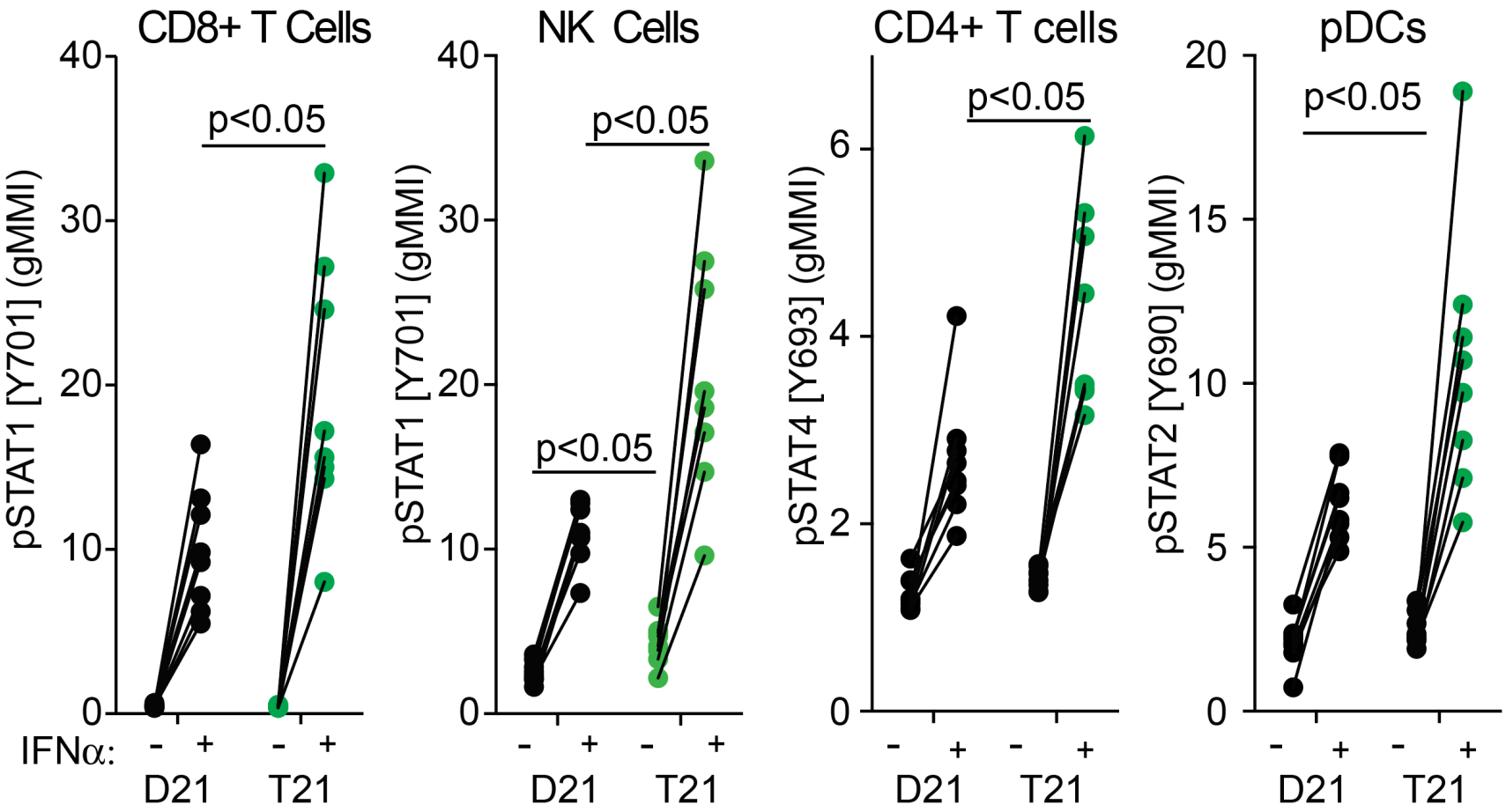
N=36, 18 with trisomy 21



IFNAR2, IFNGR2 and IL10RB are also overexpressed in cells with trisomy 21

People with Down syndrome are hypersensitive to Interferon stimulation

Ex vivo IFNα stimulation of fresh blood samples
STAT phosphorylation measured by CyTOF



Immune cells with trisomy 21 are ‘super-responders’ to Interferon

What are the impacts of trisomy 21 on the metabolome?

Employing mass-spectrometry approaches to map the metabolic impacts of trisomy 21

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

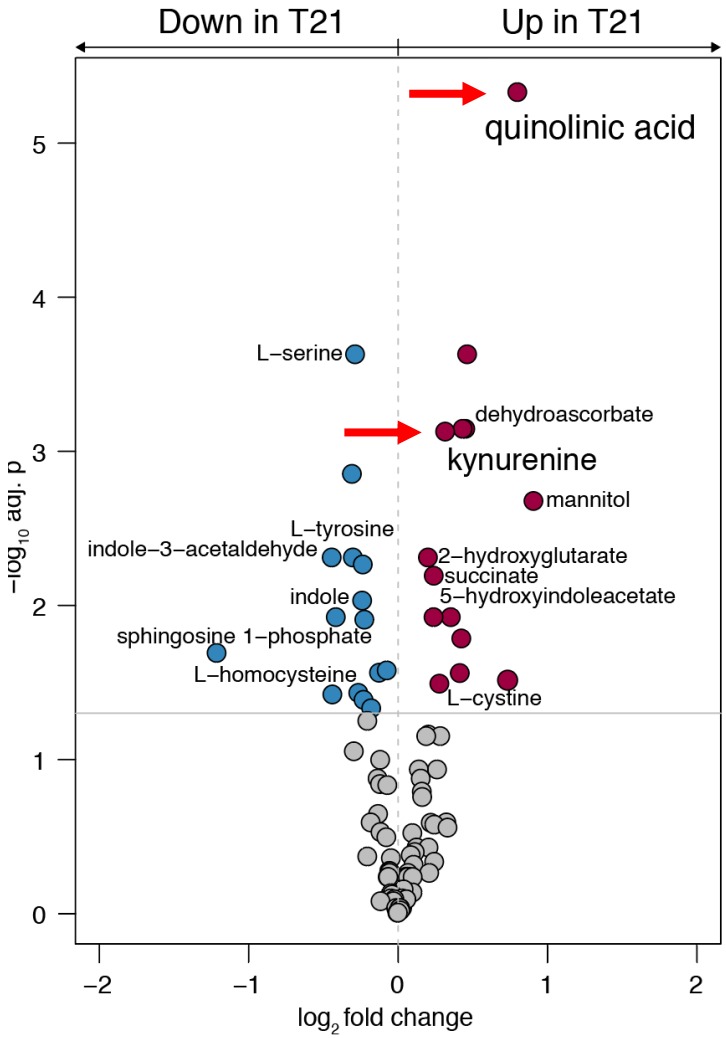
Rani K. Powers[1,2,3], Rachel Culp-Hill[4], Michael P. Ludwig[1,3], Keith P. Smith[1], Katherine A. Waugh[1], Ross Minter[1], Kathryn D. Tuttle[1], Hannah C. Lewis[1], Angela L. Rachubinski[1,5], Ross E. Granrath[1], María Carmona-Iragui[6,7], Rebecca B. Wilkerson[4], Darcy E. Kahn[1], Molishree Joshi[8], Alberto Lleó[6], Rafael Blesa[6], Juan Fortea[6,7], Angelo D'Alessandro[1,4], James C. Costello[2,3], Kelly D. Sullivan[1,3,5,8*] & Joaquin M. Espinosa[1,3,8,9*]

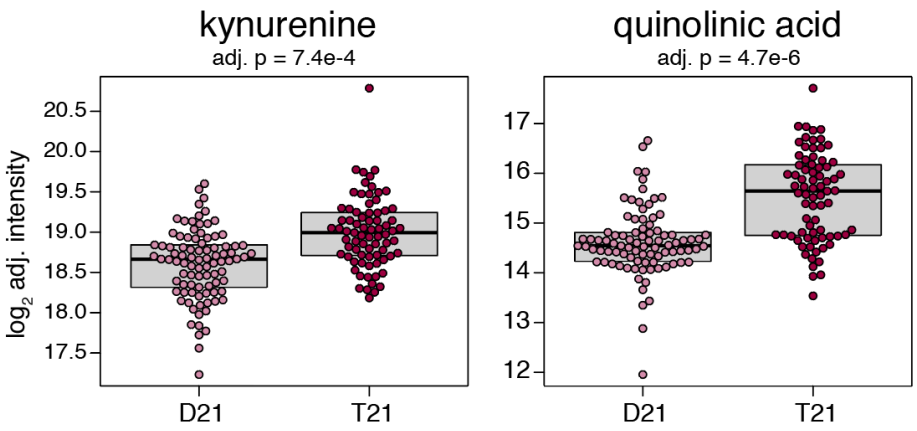
November 2019

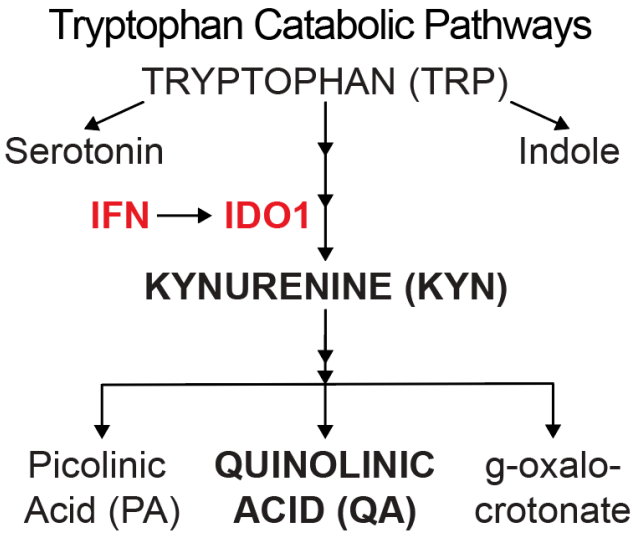
nature COMMUNICATIONS

People with Down syndrome display activation of the kynurenine pathway

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

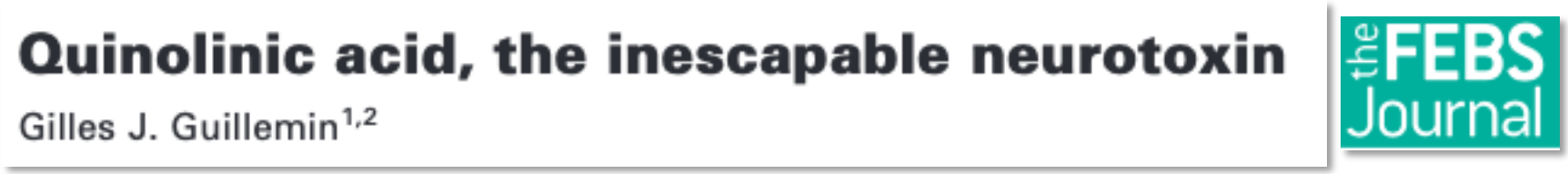






Quinolinic acid, the inescapable neurotoxin

- Quinolinic acid (QA) is super-agonist of NMDA receptors
- QA induces excitatory toxicity
- Memantine (an NMDR *antagonist*) protects from QA-mediated neurotoxicity in mice
- Circulating levels of QA were **associated with lower cognition in older adults with AD** in the typical population
- QA is a potent **convulsant** involved in the etiology of **epilepsy** and **seizures**



Is there a way to ‘normalize’ the Interferon response in people with Down syndrome?

FDA-approved therapies that decrease the Interferon response: JAK inhibitors

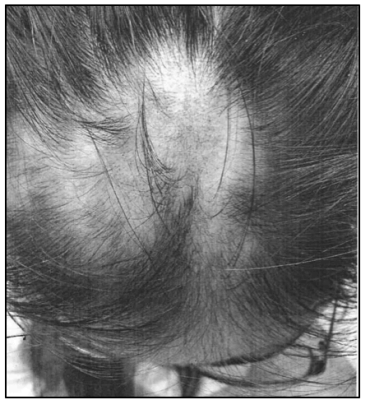
Company	Marketed Name	Target	Indication
Incyte	Jakafi® ruxolitinib (tablets)	JAK1&2	Myelofibrosis (2011), polycythemia vera (2011), GVHD (2019)
Pfizer	XELJANZ® [tofacitinib]	JAK1&3	Rheumatoid arthritis (2012), psoriatic arthritis (2017), ulcerative colitis (2018)
Lilly	olumiant® (baricitinib) tablets	JAK1&2	Rheumatoid arthritis (2018)
abbvie	RINVOQ™ upadacitinib 15mg tablets	JAK1	Rheumatoid arthritis (2019)

Also tested in clinical trials for conditions more common in people with Down syndrome, including:

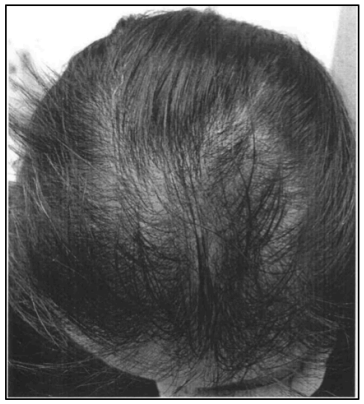
- Alopecia areata
- Atopic dermatitis
- Depression
- Hidradenitis suppurativa
- Juvenile idiopathic arthritis
- Leukemia
- Psoriasis
- Vitiligo

Off-label use of the JAKi Tofacitinib for alopecia areata in Down syndrome

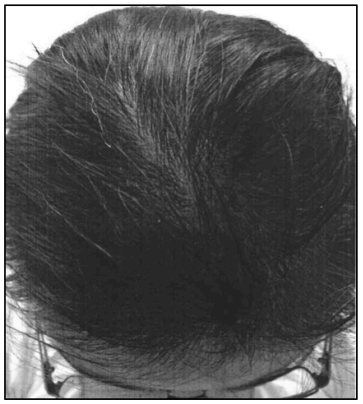
1 month



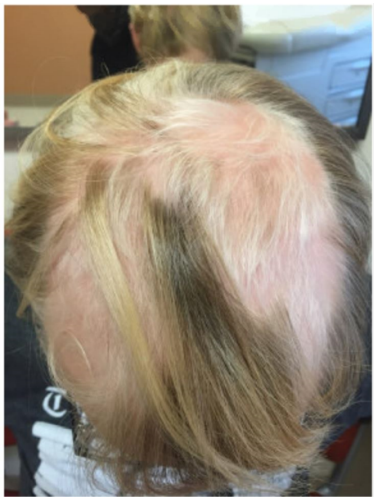
2 months



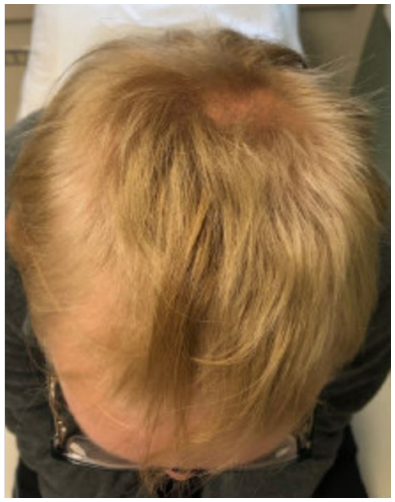
3 months



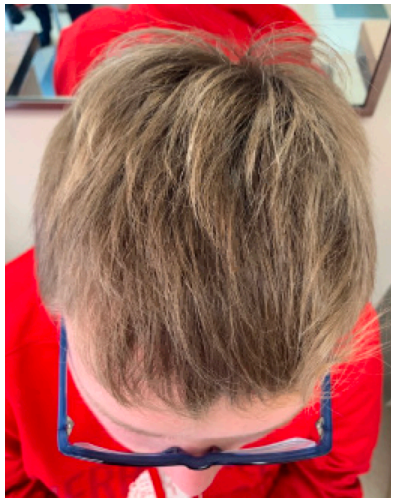
Before



2 months



7 months



Rachubinski et al, JADCR 2019

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

JAK inhibition in Down syndrome

Joaquín M. Espinosa, PhD
Executive Director
Linda Crnic Institute for Down Syndrome

Cory A. Dunnick, MD
Clinical Trials Director
Department of Dermatology

David Norris, MD
Chair
Department of Dermatology

THE INCLUDE PROJECT

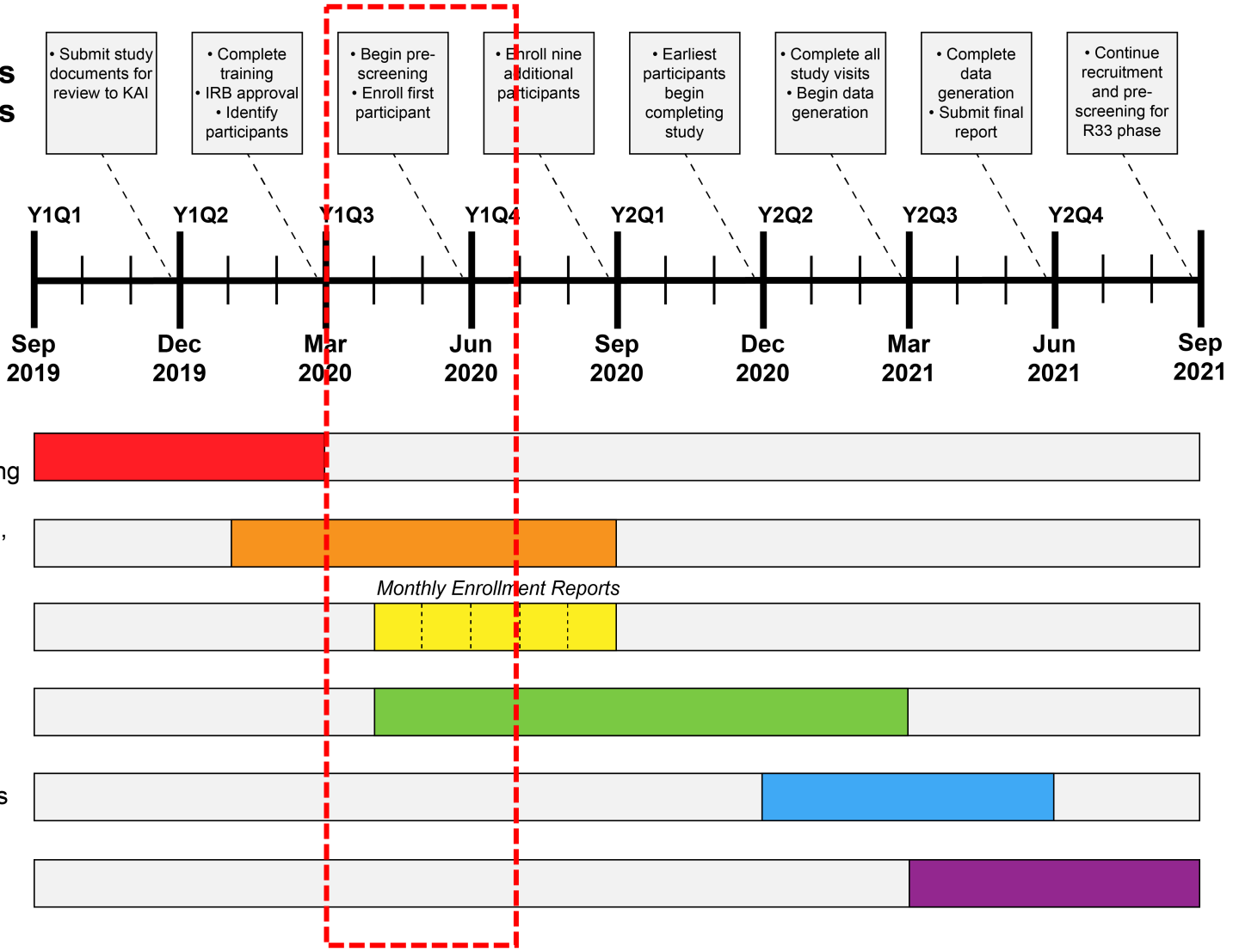
JAK inhibition in Down syndrome

- Phase II, single arm, open-label
- 16-week treatment with Tofacitinib and 2-week follow-up
- IND exempted
- Adults with Down syndrome ages 18-60
- 10 participants during R61, additional 30 during R33
- Active autoimmune skin conditions:
  - Alopecia areata
  - Psoriasis
  - Vitiligo
  - Hidradenitis suppurativa
  - Atopic dermatitis

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.

Timeline

Quarterly milestones and status updates



Credits

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Funding:

THE INCLUDE PROJECT

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

GLOBAL DOWN SYNDROME FOUNDATION

NIH National Institute of Allergy and Infectious Diseases

ANNA & JOHN J. SIE FOUNDATION

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

NIH National Cancer Institute

NIH National Center for Advancing Translational Sciences

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