GLOBAL DOWN SYNDROME FOUNDATION®

An Unprecedented and Exciting Down Syndrome Research Discovery Engine – The Crnic Institute Human Trisome Project

Global Down Syndrome Foundation's Webinar Series

Presenters: Michelle Sie Whitten, President & CEO & Dr. Joaquin Espinosa, PhD

Wednesday, February 7th, 2018

Global Down Syndrome Foundation
A Unique Affiliate Model!

The Global Down Syndrome Foundation is part of a network of affiliate organizations that work closely together on a daily basis to deliver on our mission, vision, values, and goals:

Global & Affiliates

- **Global:** was established as a 501(c)3 in 2009 and is "Dedicated to significantly improving the lives of people with Down syndrome through Research, Medical Care, Education, and Advocacy"

- **Affiliates are:**
  - Established with a lead gift from Anna & John J. Sie Foundation
  - Must work closely together to benefit people with Down syndrome
  - Must be self-sustaining financially

The Human Trisome Project

Joaquín M. Espinosa, PhD
Linda Crnic Institute for Down Syndrome
University of Colorado School of Medicine

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** different









Our motto:

Nothing in the study of Down syndrome makes sense except in the light of Personalized Medicine

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

The Crnic Institute's Human Trisome Project™ (HTP)

HumanTrisomeProject

SCHOOL OF MEDICINE
Linda Crnic Institute for Down Syndrome
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

HOME LEARN MORE RESEARCH TEAM OUR PARTNERS MEDIA GET INVOLVED

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

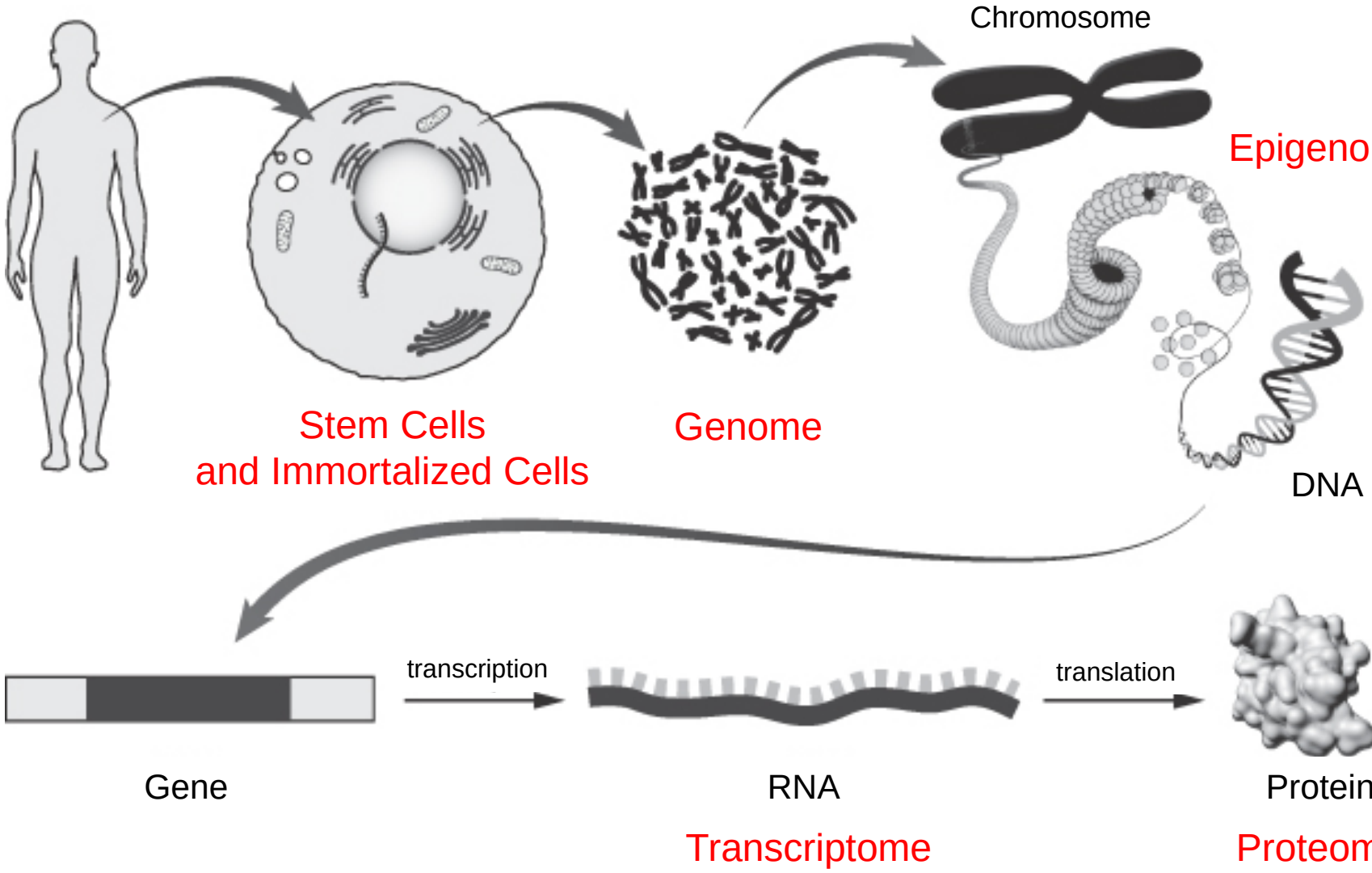
1. To enable a Precision Medicine approach to Down syndrome.
2. To define how trisomy 21 causes a novel disease spectrum.
3. To develop novel diagnostic and therapeutic tools that will benefit those with trisomy 21, and also millions of typical individuals.

Project goals – short term

1. To massively accelerate the pace of Down syndrome research.
2. To complete the most comprehensive cohort study of a population of individuals with trisomy 21 to date.
3. To create the largest public database for Down syndrome research to date.
4. To create the most comprehensive biobank of biological samples for Down syndrome research.

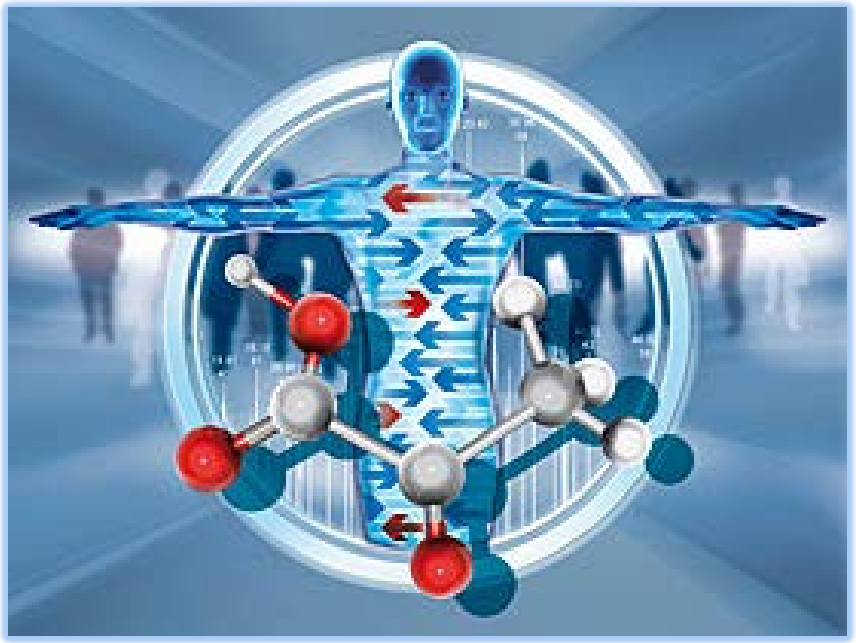
Opening the Black Box: The Ten Layers

Digital Phenotypes



Opening the Black Box: The Ten Layers

Metabolome



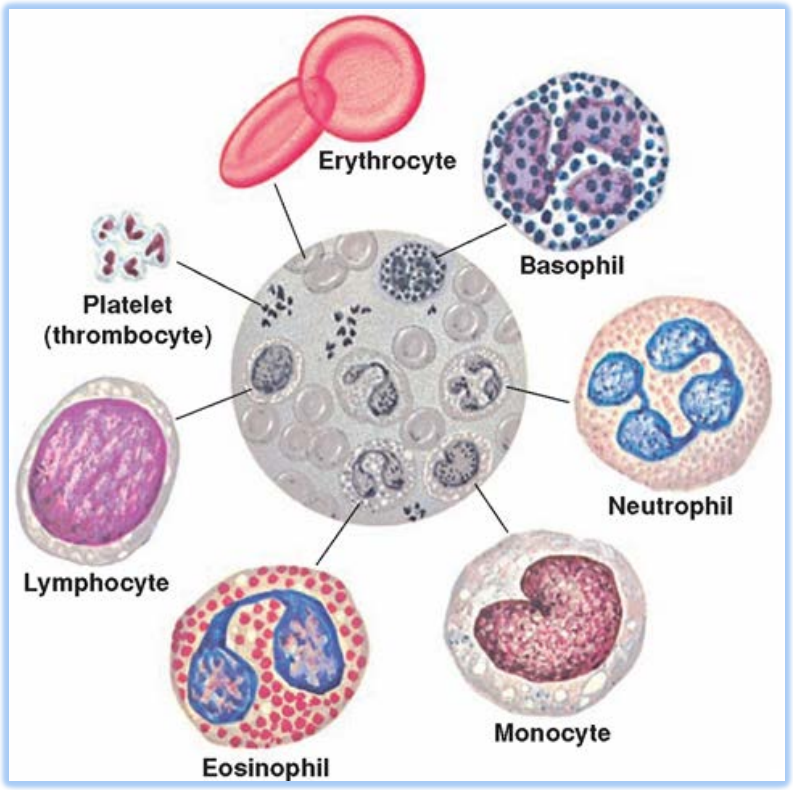
Metabolites (e.g. sugars, lipids, aminoacids, neurotransmitters)

Microbiome

Our ‘other genome’

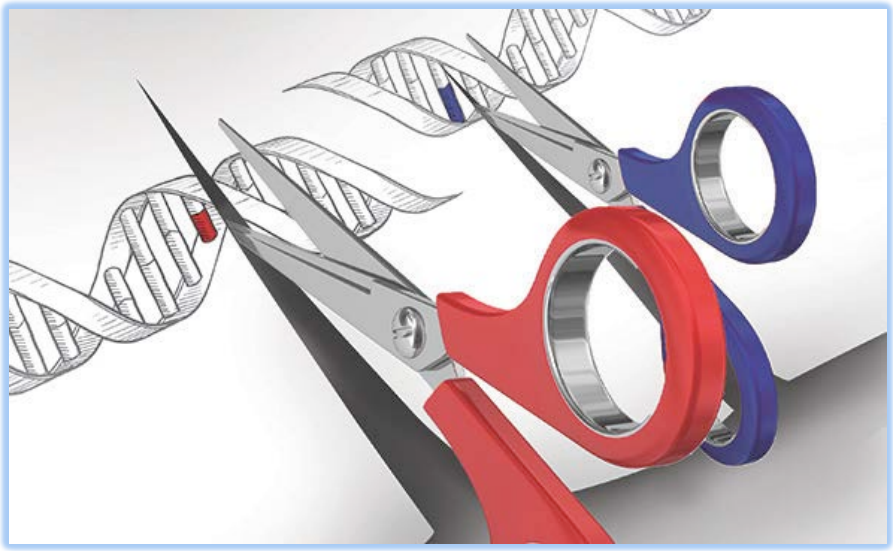
Opening the Black Box: The Ten Layers

Bloodworks and Immune Phenotype



Characterizing the blood and the immune system with exquisite detail

Functional Genomes



Using molecular scissors (CRISPR-Cas9) to find the genes that matter

A large cohort study with multi-omics datasets, deep clinical data and a matching multi-dimensional biobank

Datasets

Biobank samples

Intermediates

Blood Extraction

Plasma

RBCs

Monocytes

White blood cells

B cells

LCLs

Digital Phenotypes

Proteomes, Exosomes, Metabolomes, Antibody Profiling

Genomes, Transcriptomes, Epigenomes

Genomes, Transcriptomes, Epigenomes, Functional Assays, CyTOF Immunophenotyping

Functional Genomes

Metabolomes

Bloodwork

Urine Sample

Kidney Epithelial Progenitor Cells

iPSCs

Differentiated Cell Types

Saliva and stool

Microbiomes

LCLs: lymphoblast cell lines, iPSCs: induced pluripotent stem cells, RBCs: red blood cells

One of the largest datasets ever produced for any medical condition

SCHOOL OF MEDICINE
Biomedical Informatics & Personalized Medicine
UNIVERSITY OF COLORADO **ANSCHUTZ MEDICAL CAMPUS**

- Digital Phenotypes
- Genomes
- Transcriptomes
- Proteomes
- Epigenomes
- Functional Genomes
- Metabolomes
- Microbiomes
- Bloodwork
- Immune Phenotypes

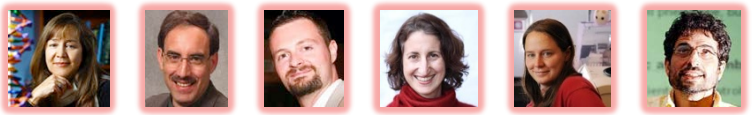
Rosalind

Central Data Repository

5 petabytes
700+ CPUs

- Researcher Gateway
- Deep Blue Team
- DREAM CHALLENGES *powered by Sage Bionetworks*

Barnes Kahn Costello Kechris Dowell Stolovitzky



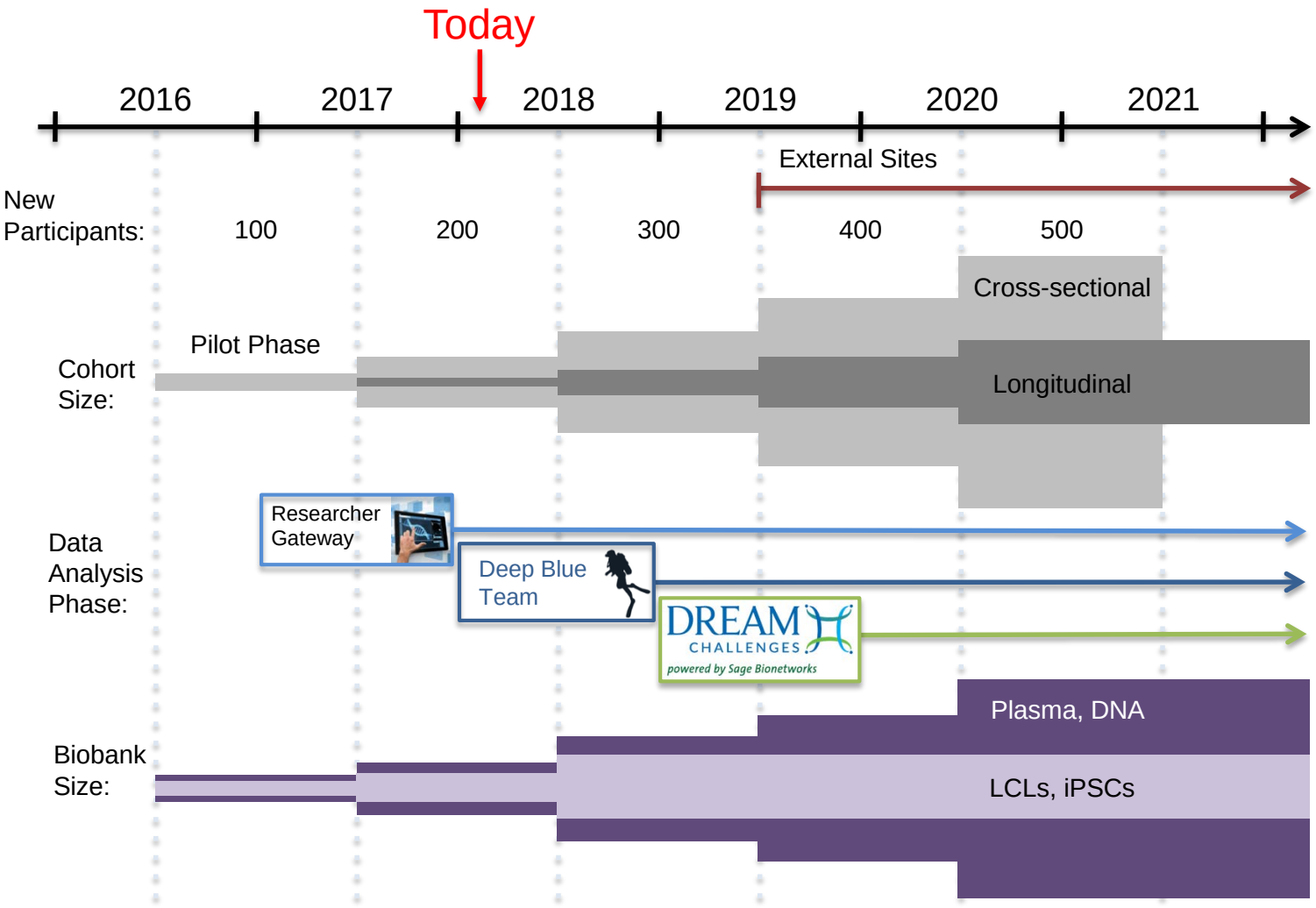
Turning data into discoveries

Discoveries!

The Power of Multidimensional Datasets

Going beyond the blueprint

The project involves cross-sectional and longitudinal aspects, a large multi-dimensional biobank and eventual participation of external sites



Original timeline proposed in December 2015

LCLs: lymphoblast cell lines, iPSCs: induced pluripotent stem cells

336 participants consented to date!

HTP00001

October 10, 2016

HTP00300

September 7, 2017

Any cool results yet?

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]*

July 2016

Kelly Sullivan

TRISOMY 21

Signaling a link between interferon and the traits of Down syndrome

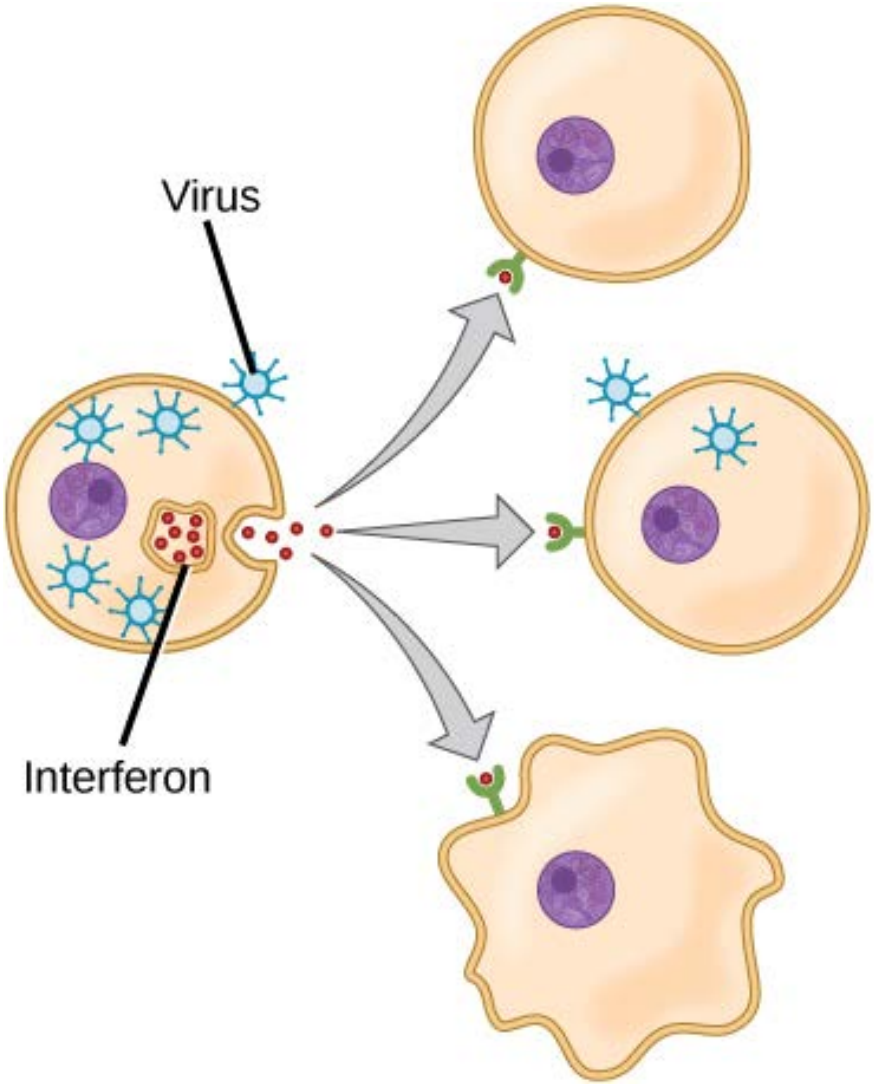
Elevated interferon signaling is a hallmark of Down syndrome.

GINA KIRSAMMER AND JOHN D CRISPINO

eLIFE elifesciences.org

Everywhere we look, it is clear that trisomy 21 causes increased Interferon signaling

What is interferon signaling?

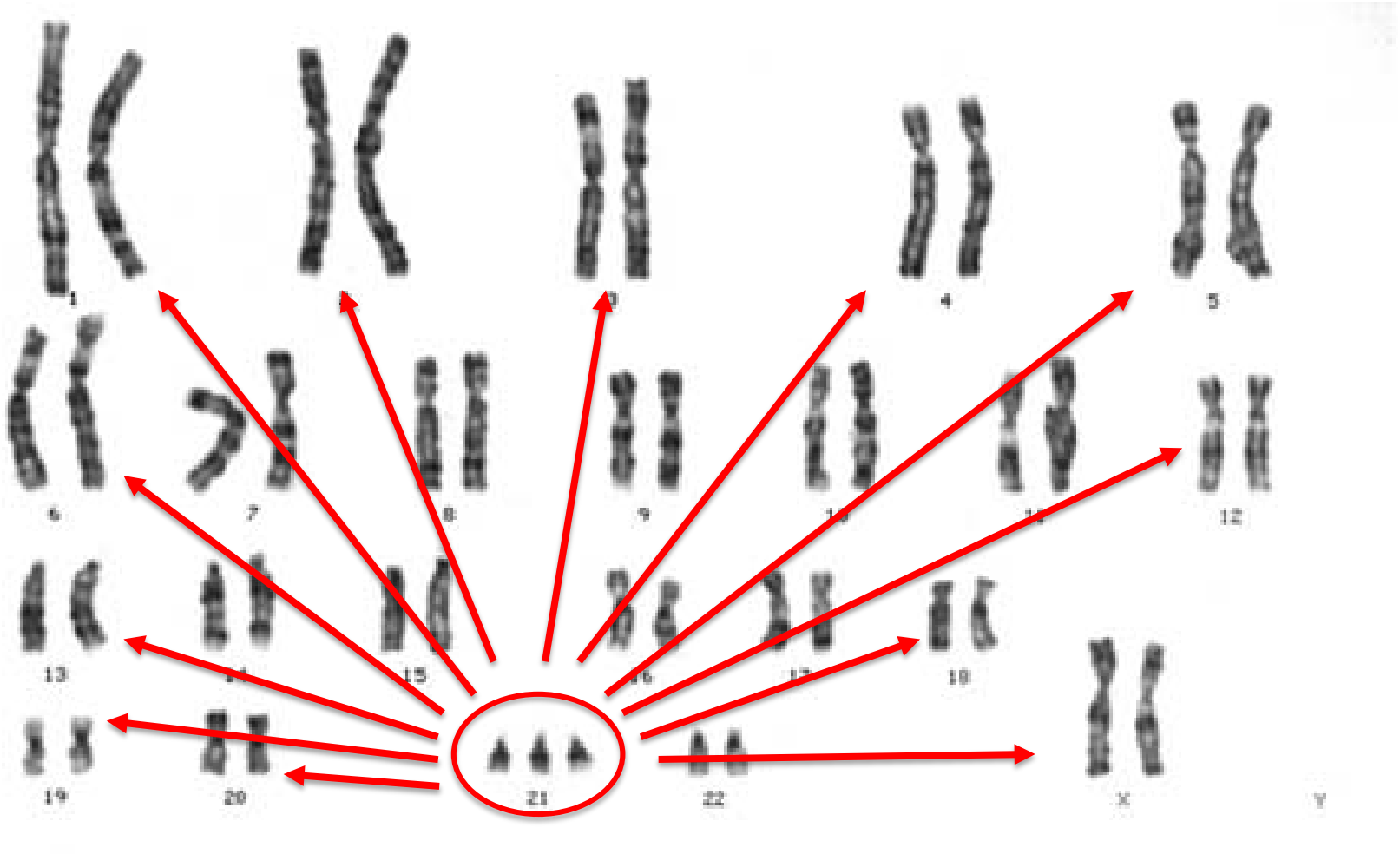


- Interferon signaling is an important part of the innate immune system
- Interferon activates many different types of immune cells
- Interferon signaling shuts down RNA and protein synthesis

What is interferon signaling?

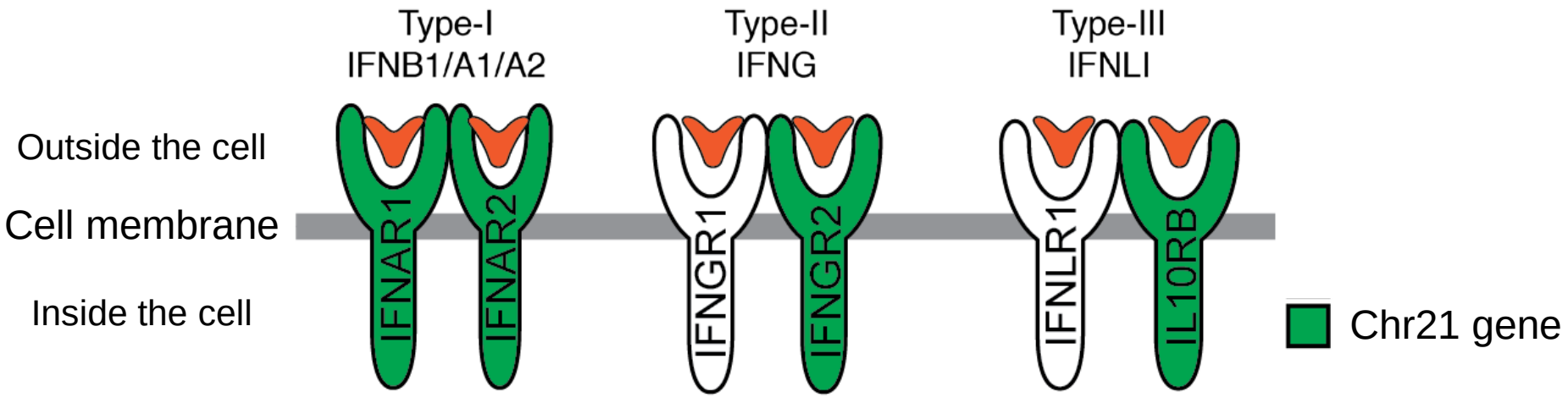
- The bodies of individuals with Trisomy 21 are constantly fighting and infection that isn’t there
- Long term activation of interferon signaling can contribute to autoimmune disorders
- Individuals with Trisomy 21 may mount stronger immune responses to infection than typicals, with potentially adverse effects

Trisomy 21 activates signaling pathways that affect gene expression throughout the genome

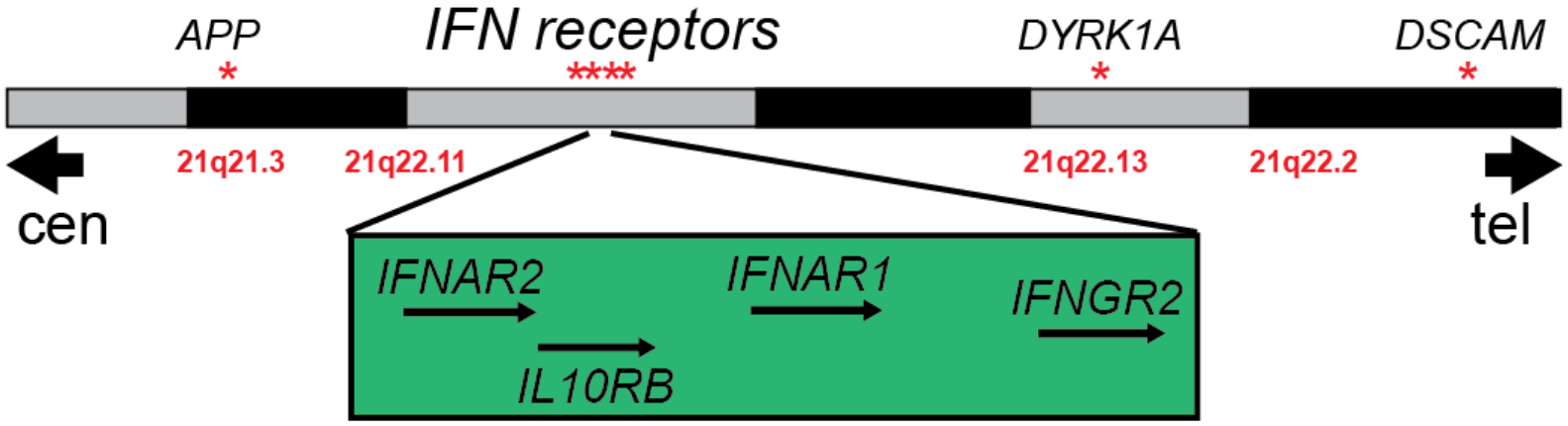


These signaling pathways are dominated by the ‘Interferon response’

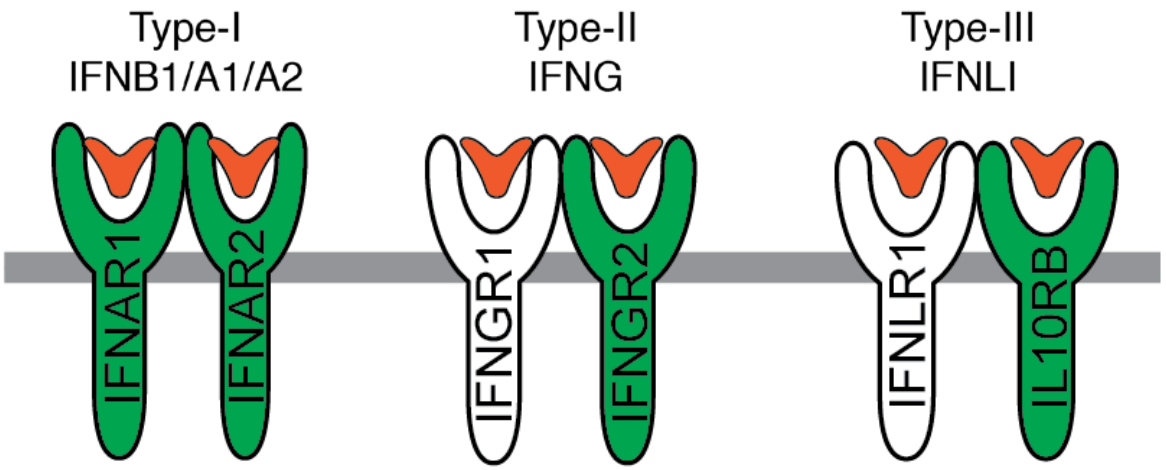
4 of the 6 IFN receptors are encoded on chr21!!



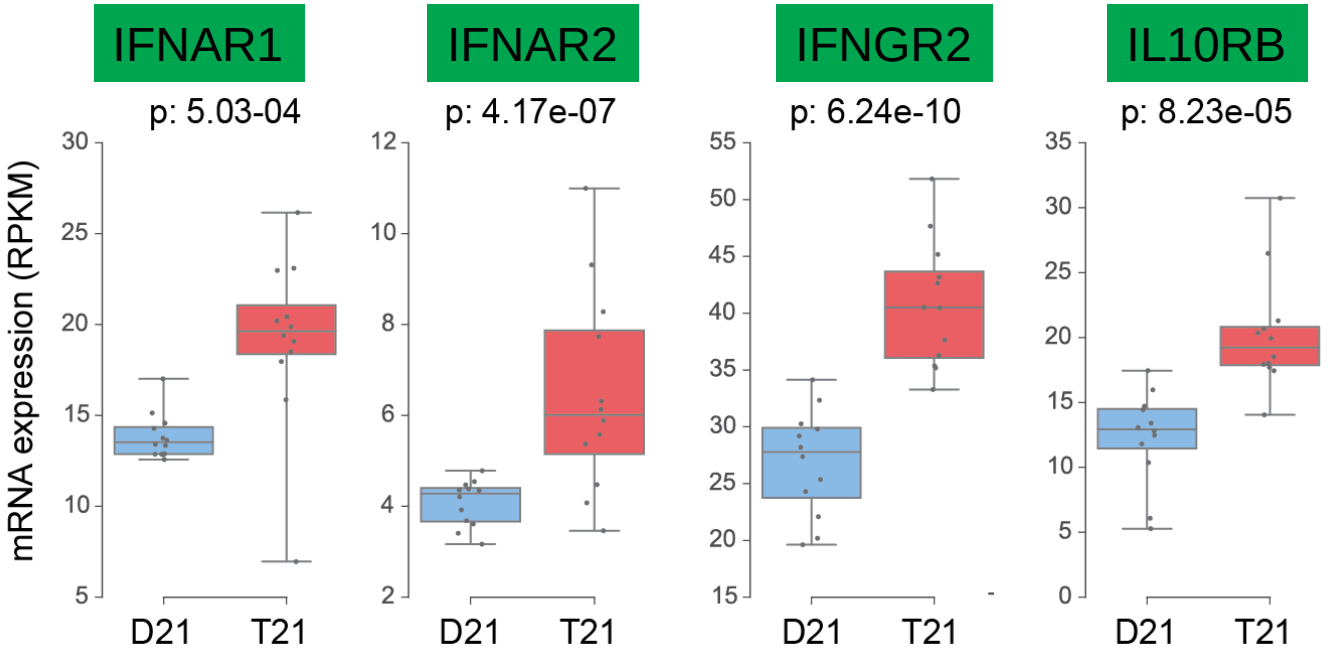
Human chromosome 21



IFNRs are overexpressed in every cell type we tested



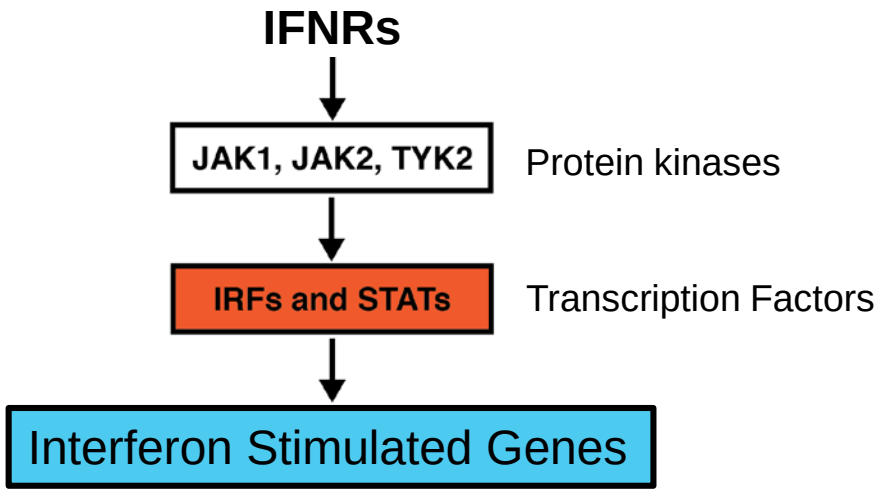
Chr21 gene



D21: euploid T21: trisomy 21

RNA-seq
Skin fibroblasts (n=12)

Trisomy 21 cells show massive induction of Interferon Stimulated Genes (ISGs)



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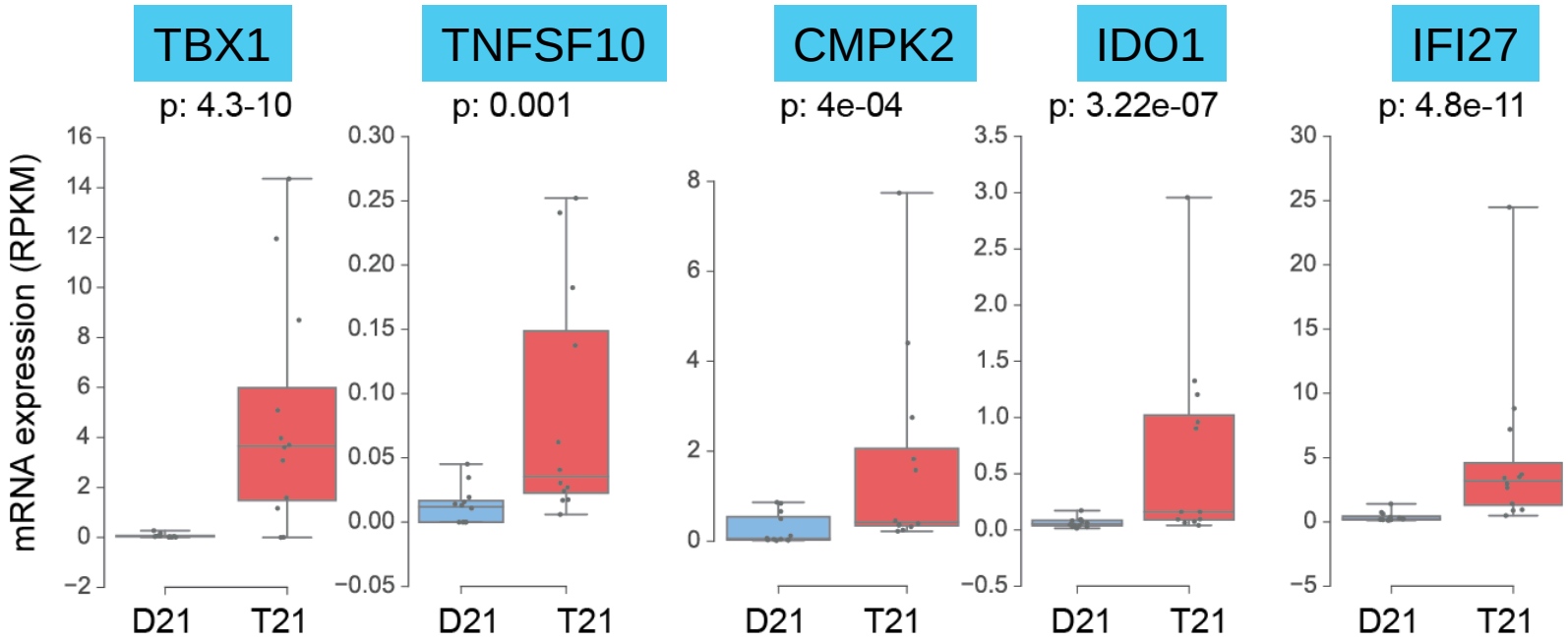


What would be the consequence of a chronic Interferon response?

Understanding Down syndrome as an immune disorder

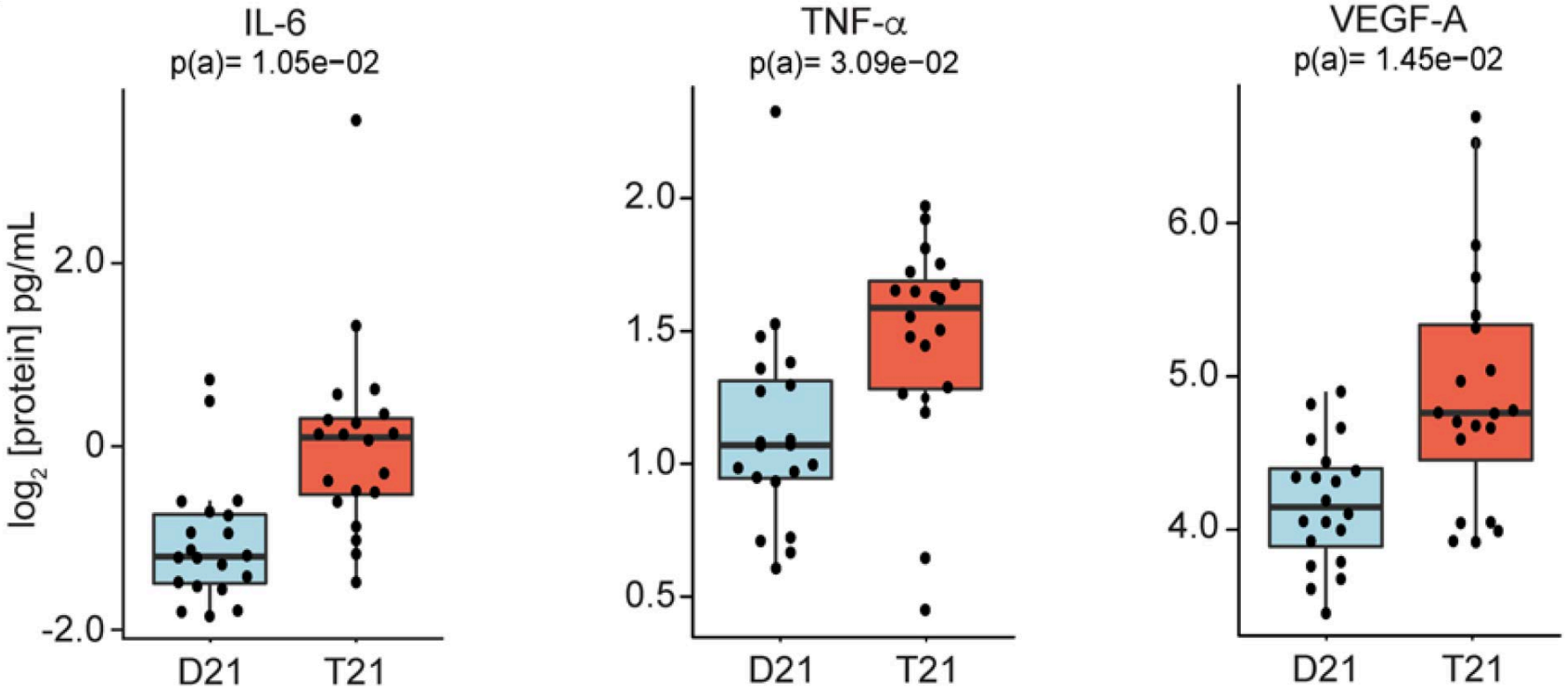
Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation

Kelly D. Sullivan[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

Published November 1st , 2017

Understanding Down syndrome as an immune disorder



On average, people with Down syndrome have significantly elevated levels of **inflammatory proteins**

Conclusion:

Down syndrome could be understood,
in good measure,
as an Interferonopathy.

What is an Interferonopathy?

Interferonopathies are a group of genetic disorders characterized by activation of the Interferon response

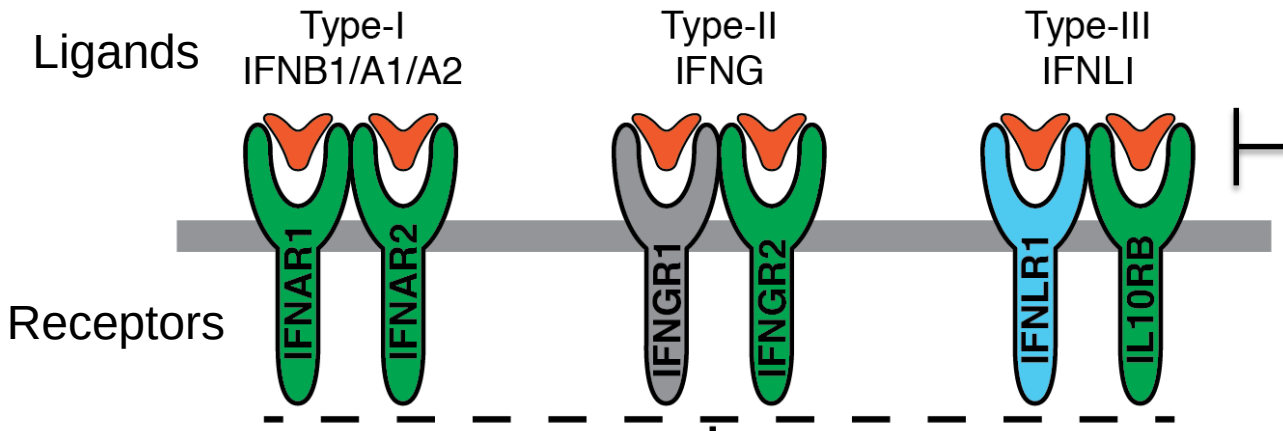
Aicardi-Goutieres Syndrome, SAVI, CANDLE, Singleton–Merten syndrome, spondyloenchondrodysplasia, dyschromatosis symmetrica hereditaria, familial chilblain lupus, Nakajo-Nishimura syndrome, spondylochondromatosis, etc.

Many features shared with Down syndrome:

- Neurological dysfunction
- Developmental delay
- Less white matter in the brain
- Seizures
- Cerebellar atrophy
- Spastic diplegia, a form of cerebral palsy (CP), a chronic neuromuscular condition of hypertonia and spasticity
- Dystonic posturing
- Hyper- or hypotonia
- Psychomotor difficulties
- Thrombocytopenia (deficiency of platelets)
- CSF lymphocytosis (too many white blood cells in the spinal fluid)
- Systemic immune abnormalities, strong predisposition to autoimmunity
- Hypocomplementia
- Common skin lesions (e.g. acrosyanosis)

Can drugs that block the Interferon response cure some of the co-morbidities associated with Down syndrome?

Blocking the Interferon response



Monoclonal Antibodies
(e.g. Sifalimumab)
Decoy Receptors
Viral IFN-binding
Proteins (e.g. B18R)

MedImmune

AstraZeneca

Protein Kinases — **JAK1, JAK2, TYK2**

JAK inhibitors
(e.g. ruxolitinib,
baricitinib)

Meiogen

Transcription Factors — **IRFs and STATs**

NOVARTIS

Pfizer

Lilly

Interferon Stimulated Genes (ISGs)

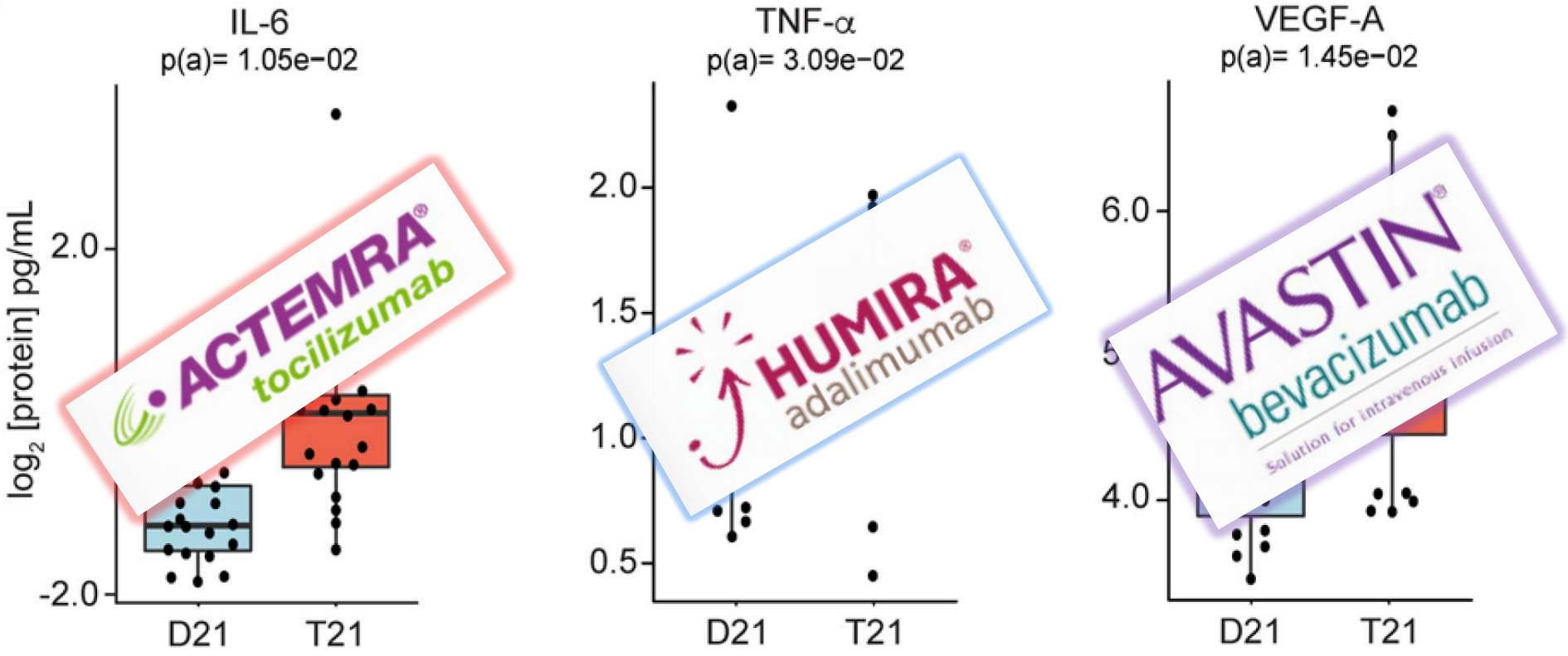
APP	IFIT2	CMPK2	IL1A	MYH6
TMEM50B	IDO1	IFI27	IFI44L	RSAD2
MX1	OAS1	IFITM1	TNFSF10	HERC6
MX2	OAS2	BST2	IFI6	ISG15

IDO1 inhibitors
and more…

Incyte

Genes encoded on chromosome 21

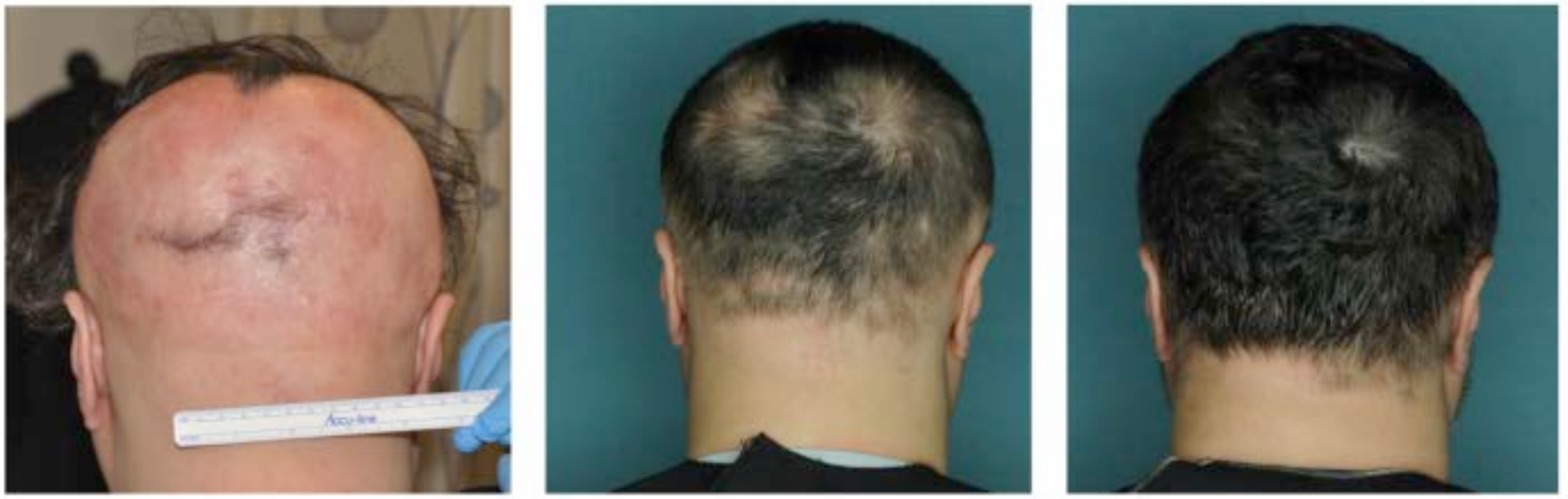
Inflammatory proteins elevated in Down syndrome can also be inhibited with existing drugs



These inflammatory proteins can be inhibited with <u>FDA-approved drugs!</u>

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



baseline 3 months 4 months

Ruxolitinib: An FDA-approved JAK inhibitor

Clynes et al, Nature Medicine 2014

Conclusions

Down syndrome could be classified as an Interferonopathy, along with other genetic conditions leading to gain-of-function alterations in the IFN pathway.

Many of the ill effects of trisomy 21 could be ameliorated, even perhaps eliminated, with inhibitors of the IFN pathway.

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.

Credits

At Crnic:
Tom Blumenthal
Donnie Evans
Neil Markham
Alex Erckenbeck
Keith Smith
Juana Marmolejo
Angela Rachubinski
Keith Smith
Kate Waugh
Ross Granrath
Eric Butcher
Angela Kirkpatrick
Diane Lim

At the Sie Center:
Fran Hickey and the phenomenal staff at the Sie Center, specially Kristy Wolter-Warmerdam

Proteomics: Team at SomaLogic, specially Tom Hraha

Metabolomics: Rani Powers, Jim Costello, Angelo D'Alessandro, Kirk Hansen

CyTOF: Elena Hsieh and the Flow Cytometry Core

Team at Biogen, specially Marc Muskavitch

Espinosalab.org:
Special thanks to **Kelly Sullivan**!
Amanda Hill, Hannah Lewis, Awhan Pandey
Matthew Galbraith, Zdenek Andrysik, Anna Guarnieri
Joseph Cabral and many many more!

Other collaborators: James DeGregori, Roy Parker, Ken Krauter, Michalis Lionakis, Stephanie James.

Hunt Potter and the Rocky Mountain Alzheimer's Disease Center.

Funding support

Anna and John J. Sie

Michelle Sie Whitten
President and CEO

Dean John Reilly

ANNA & JOHN J. SIE FOUNDATION

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School of Medicine
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

‘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