The Human Trisome Project

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

HumanTrisomeProject

A network of affiliate organizations working together to improve the lives of people with Down syndrome

Mission & Vision

Mission

Significantly improve the lives of all people with Down syndrome

Vision

Provide the world's first fully integrated institute for Down syndrome with the highest quality basic, translational and clinical research, clinical trials, therapeutic development, medical care, education and advocacy in the pursuit of the mission.

Our motto:

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

What are the ill effects of trisomy 21?

Conditions commonly affecting children with trisomy 21:

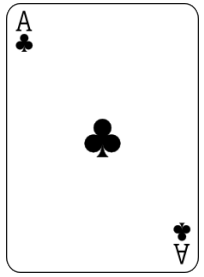
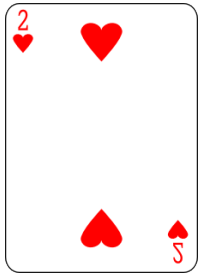
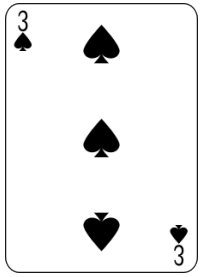
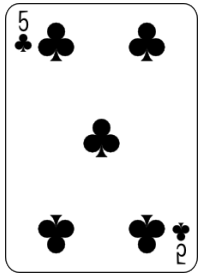
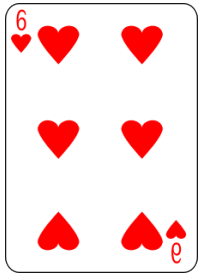
Condition	**%**
Hearing Problems	75
Vision Problems	60
Cataracts	15
Refractive errors	50
Obstructive Sleep Apnea	50-75
Otitis Media	50-70
Congenital Heart Disease	40-50
Hypodontia and delayed dental eruption	23
Gastrointestinal Atresias	12
Thyroid Disease	4-18
Seizures	1-13
Hematologic Problems	
Anemia	3
Iron Deficiency	10
Transient Myeloproliferative Disorder	10
Leukemia	1
Celiac Disease	5
Autism	1-10%

Observation: there is no **100%** in this table

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

Trisomy 21

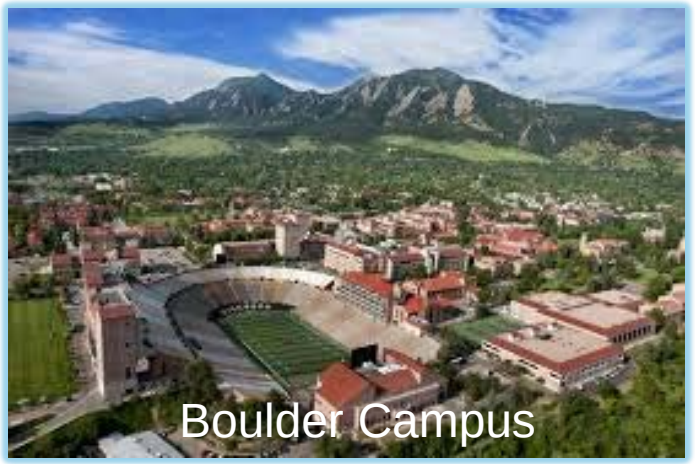
Down syndrome

Celiac Disease	Intestinal Atresias	Thyroid Dysfunction	Seizures	Leukemia	Congenital Heart Defects	Autism
						
~5%	~12%	up to 18%	up to 13%	~1%	40-50%	up to 10%

The largest geographical cluster of scientists investigating Down syndrome

5 Intramural Research Teams
~40 Extramural Research Teams
2 campuses
11 academic departments

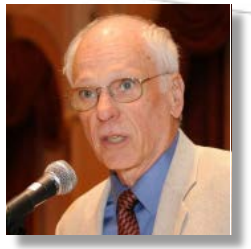
34 miles



Keywords:

Collaborative, Multidisciplinary, Integrative

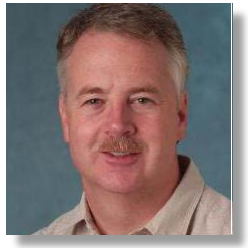
Research on cognition, autism and brain function at the Crnic Institute



Steven Maier, PhD
Understand the contribution of inflammation in the brain to cognitive deficits in Down syndrome

Zhe Chen, PhD
Study how trisomy 21 affects the formation of neuron axons in the brain

Ken Maclean, PhD
Test the impact of the cellular response to unfolded proteins caused by trisomy 21 on cognitive deficits in Down syndrome



Jerry Stitzel, PhD
Study gene expression changes in a key set of neurons strongly affected in people with Down syndrome

Kevin Jones, PhD
Investigate the impact of the protein BDNF in the brain pathology of Down syndrome using mouse models

Tamim Shaikh, PhD
Research on genetic modifiers of autism spectrum disorders in people with Down syndrome

All these research projects have the potential to reveal novel therapeutic approaches

Research on the immune system and autoimmune conditions at the Crnic Institute

Elena Hsieh,MD
Investigates how variations in the immune cell repertoire may affect autoimmunity in people with Down syndrome.

Michael Yeager, PhD
Investigates the role of the immune system
in lung function and bacterial infections in Down syndrome.

Richard Spritz, PhD
Investigates novels genes driving autoimmunity
in Down syndrome – thyroid disease, Type I diabetes, rheumatoid arthritis and vitiligo.

Kelly Sullivan, PhD
Investigates the role of the interferon pathway, a branch of the immune system that is constitutively activated in people with Down syndrome

These research projects could illuminate new ways to diagnose and treat autoimmune disorders in people with Down syndrome

Alzheimer's research at the Crnic Institute

Huntington Potter, PhD
Currently performing clinical trials to test the efficacy of the protein GMCSF in the treatment of Alzheimer's disease

Matthew Kennedy, PhD
Investigates how increased beta-amyloid production causes loss of neuron function to find targets for future therapies

Brianne Bettcher, MD
Investigating the role of inflammation in cognitive decline and progression of Alzheimer's disease.

Mark Dell'Acqua, PhD
Studies the role of of calcium signaling in inhibition of neuronal function by beta-amyloid plaques in Down syndrome

Charles Hoeffer, PhD
Investigates the impact of the RCAN1 gene on chromosome 21 in the development of Alzheimer's disease-related neuropathology

Stem cell research at the Crnic Institute

Bradley Olwin, PhD
Investigates the role of muscle stem cells in dysfunction of the muscular-skeletal system in Down syndrome

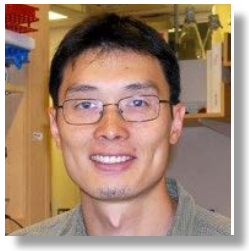
Christopher Link, PhD
Investigates changes in gene expression caused by trisomy 21 in pluripotent stem cells and neurons derived from these cells

William Old, PhD
Employs advanced mass-spectrometry technology to investigate changes in protein expression caused by trisomy 21 in stem cells and neuronal progenitors

Stem cell research is of fundamental importance, because stem cell dysfunction could explain many of the conditions associated with Down syndrome

Leukemia research at the Crnic Institute

James DeGregori, PhD
Studies problems with blood cell production
in individuals with Down syndrome to understand
the increase risk of leukemia and immune dysfunction



Rui Yi, PhD
Investigates the effect of trisomy 21 on gene expression
control in blood cells, with a focus on oncogenes that could
drive leukemia development.

Holly Pacenta, MD
Investigates novel non-toxic therapeutic strategies
for the treatment of the various types leukemia showing
increased incidence in people with Down syndrome

The goal of these projects is not only to reveal why there is an increased risk of leukemia,
but also to identify and test gentler, non-toxic therapies.

Advanced genetic and genomics research at the Crnic Institute

Robin Dowell, PhD
Employs advanced genomics approaches to understand how trisomy 21 leads to changes in gene activity across the genome

Chad Pearson, PhD
Investigates differences in how cells with trisomy 21 sense their environment and undergo proliferation

Tom Blumenthal, PhD
Investigates changes in the levels of thousands of proteins in the blood of people with Down syndrome, which could reveal new diagnostics and therapeutics

Changwei Liu, PhD
Investigates the gene USP16 on chromosome 21, which as known ‘epigenetic regulator’ with a role in stem cell function

The goal of these projects is to gain better mechanistic understanding of how trisomy 21 affects cellular and organismal behavior at the molecular level, with the potential for far reaching impacts in the clinic.

How will this research benefit people with Down syndrome?

The ultimate goal of the research portfolio is to enable the design of:

1. **Novel diagnostics tools for early detection of common co-morbidities.**

2. **Personalized therapeutic interventions.**

Examples:
Prenatal detection of congenital heart defects leading to early heart surgery.

Early diagnosis of hypothyroidism leading to hormone supplementation therapy.

How will this research benefit people with Down syndrome?

Some key outstanding questions:

What are the ‘biomarkers’ that could predict the appearance and severity of:

- Early onset of Alzheimer’s-related dementia
- Infantile spasms/seizures/epilepsy
- Autism
- Pulmonary arterial hypertension (PAH)
- Autoimmune disorders (e.g. type I diabetes, alopecia areata, vitiligo, rheumatoid arthritis)
- etc, etc

The Human Trisome Project

The largest, most detailed study of the human population with trisomy 21

Employing the most advanced technology in precision personalized medicine to understand the multiple effects of trisomy 21

Project goals

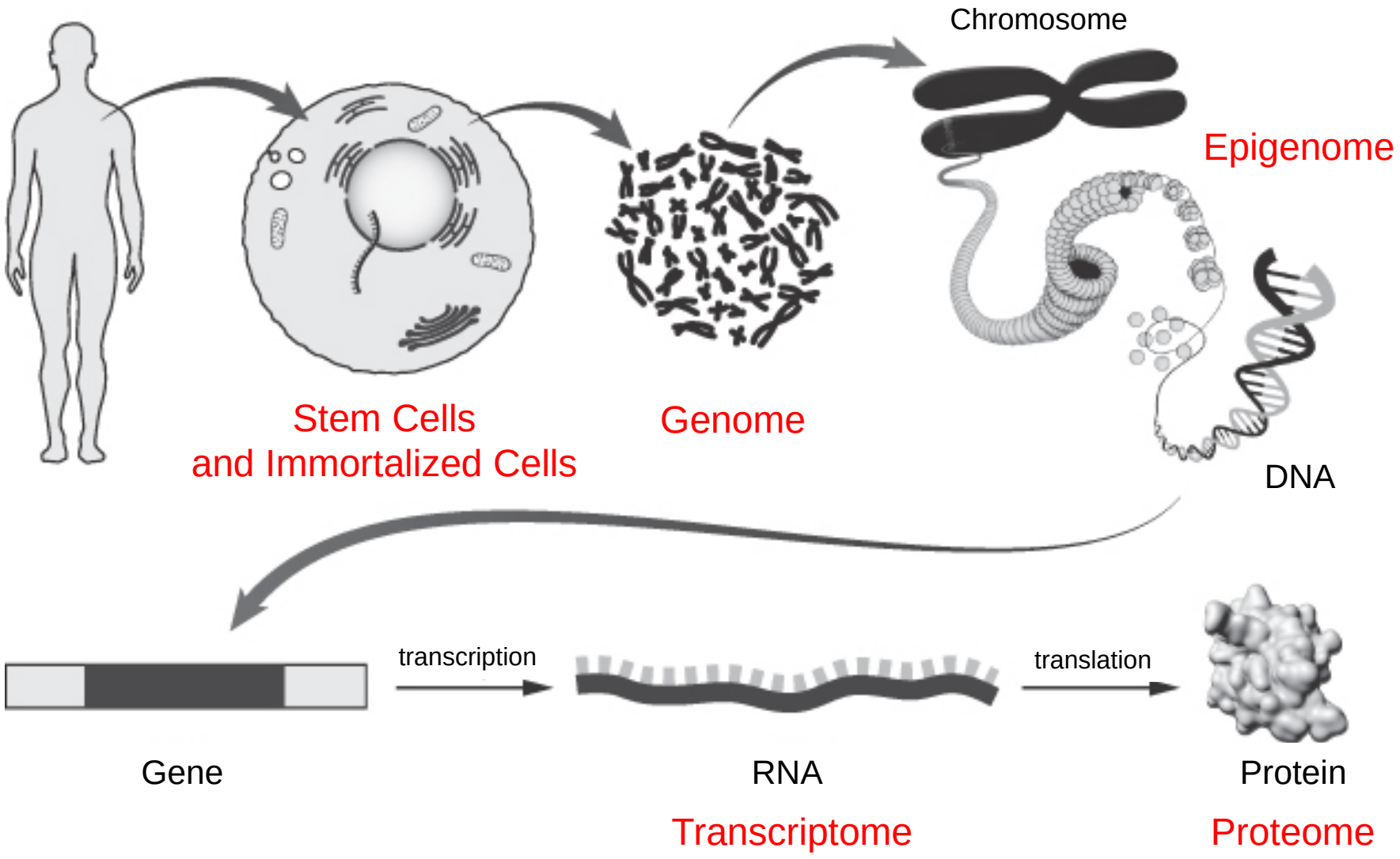
1. To enable a Precision Medicine approach to Down syndrome.
2. To define how trisomy 21 causes a novel disease spectrum.
3. To develop novel diagnostic and therapeutic tools that will benefit those with trisomy 21, and also millions of typical individuals.

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

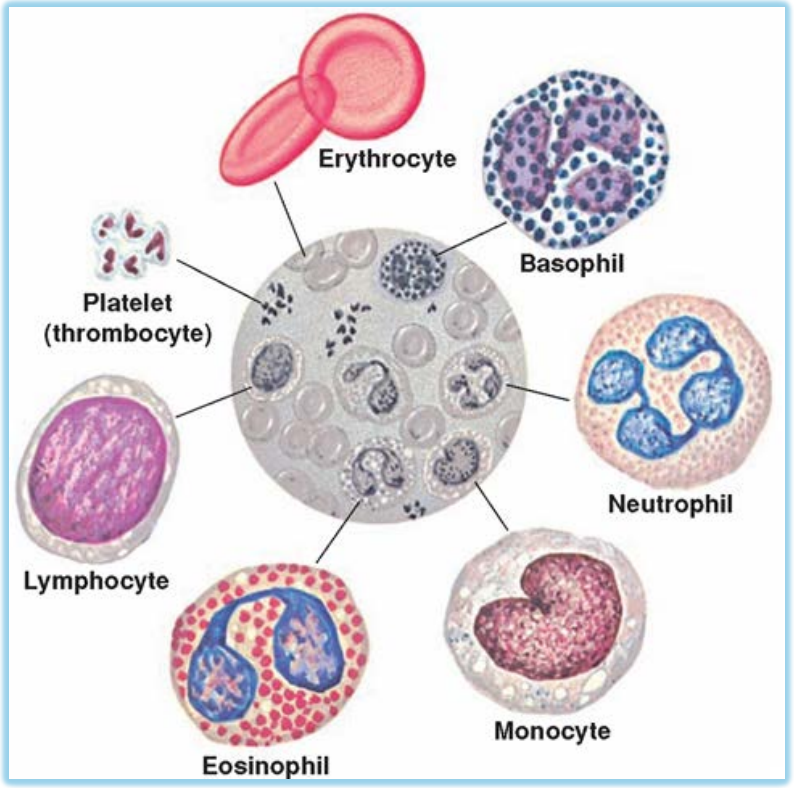
Metabolites (e.g. sugars, lipids, aminoacids, neurotransmitters)

Microbiome

Our ‘other genome’

Opening the Black Box: The Ten Layers

Bloodworks and Immune Phenotype

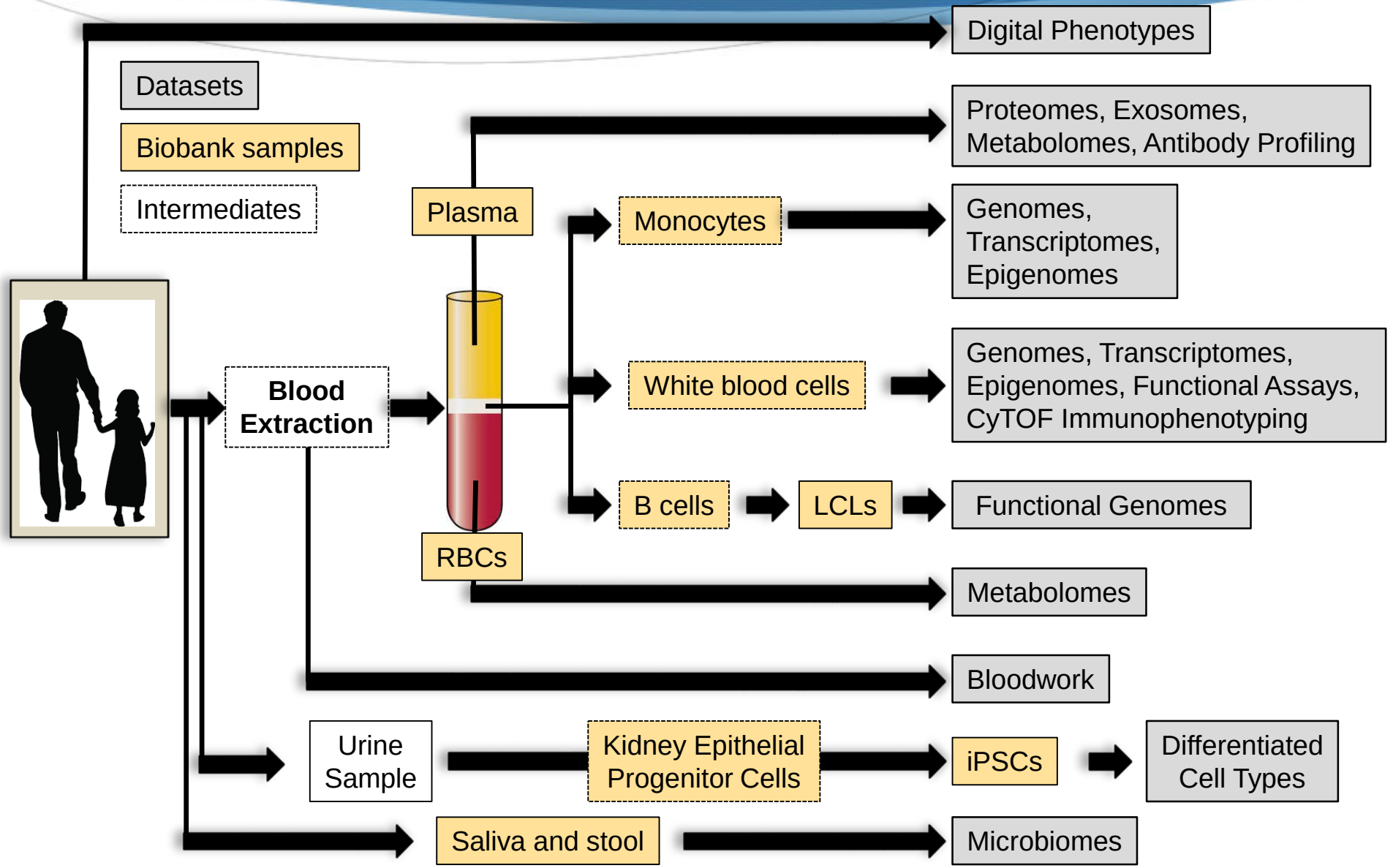


Characterizing the blood and the immune system with exquisite detail

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



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

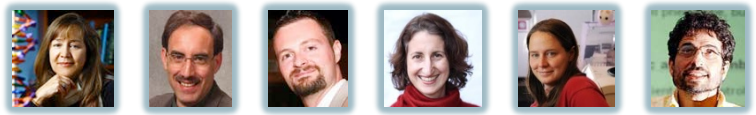
Rosalind

Central Data Repository

5 petabytes
700+ CPUs

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

Barnes Kahn Costello Kechris Dowell Stolovitzky



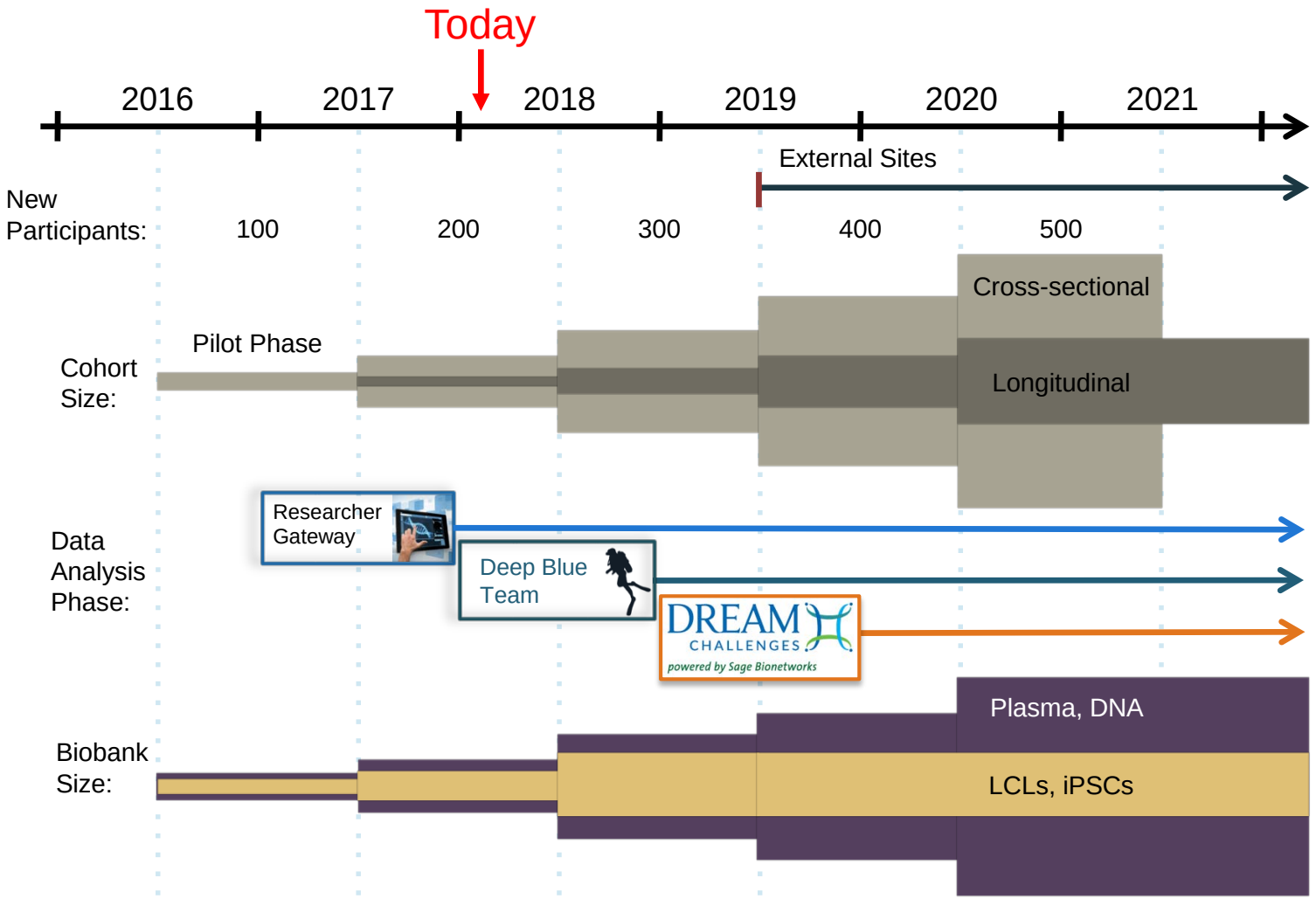
Turning data into discoveries

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

343 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

TRISOMY 21

Signaling a link between interferon and the traits of Down syndrome

Elevated interferon signaling is a hallmark of Down syndrome.

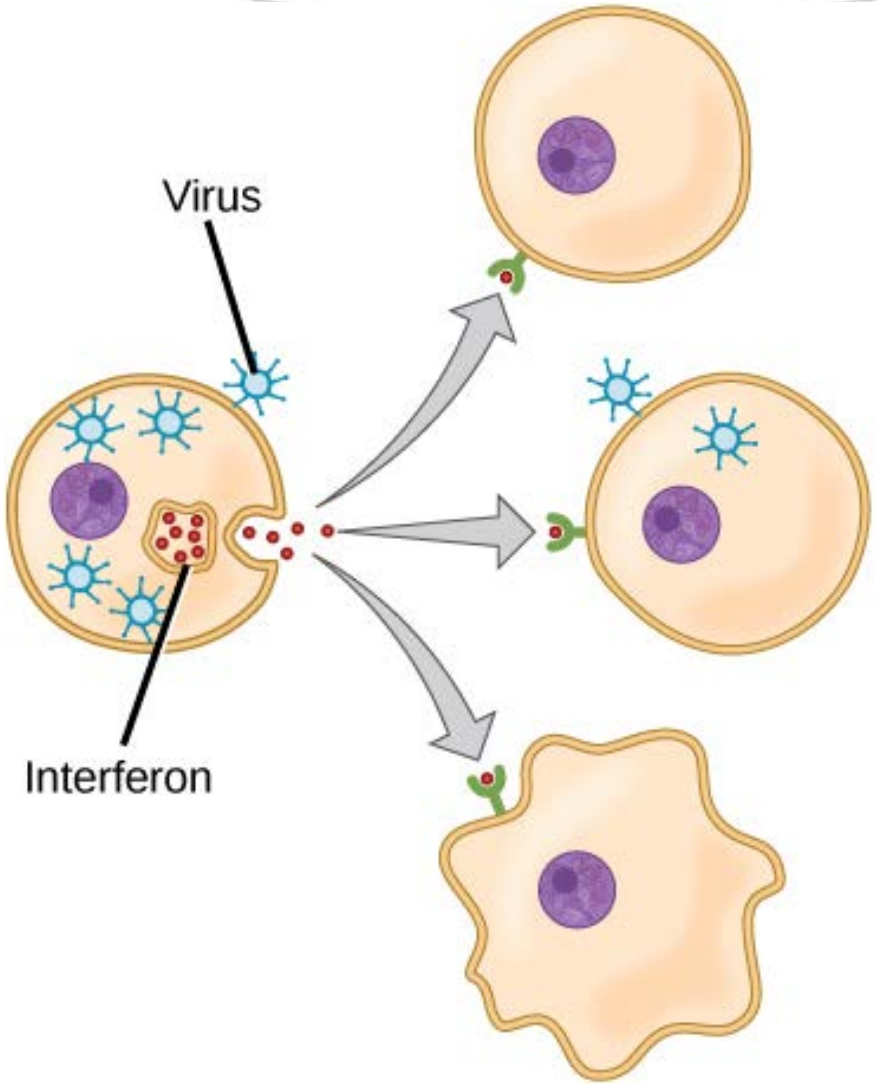
GINA KIRSAMMER AND JOHN D CRISPINO

eLIFE
elifesciences.org

Kelly Sullivan

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

What is interferon signaling?

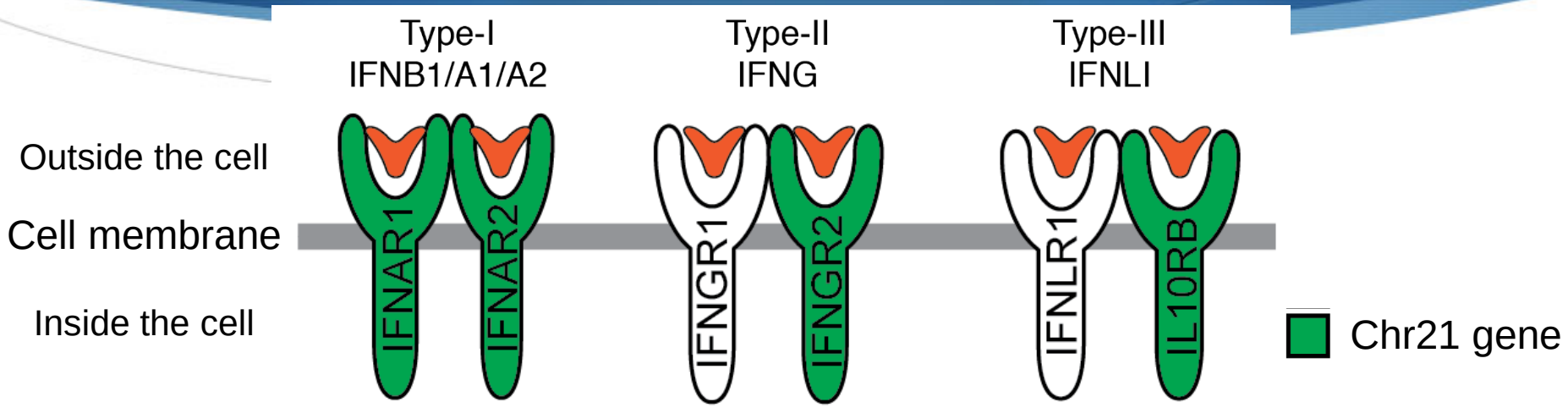


- Interferon signaling is an important part of the innate immune system
- Interferon activates many different types of immune cells
- Interferon signaling shuts down RNA and protein synthesis

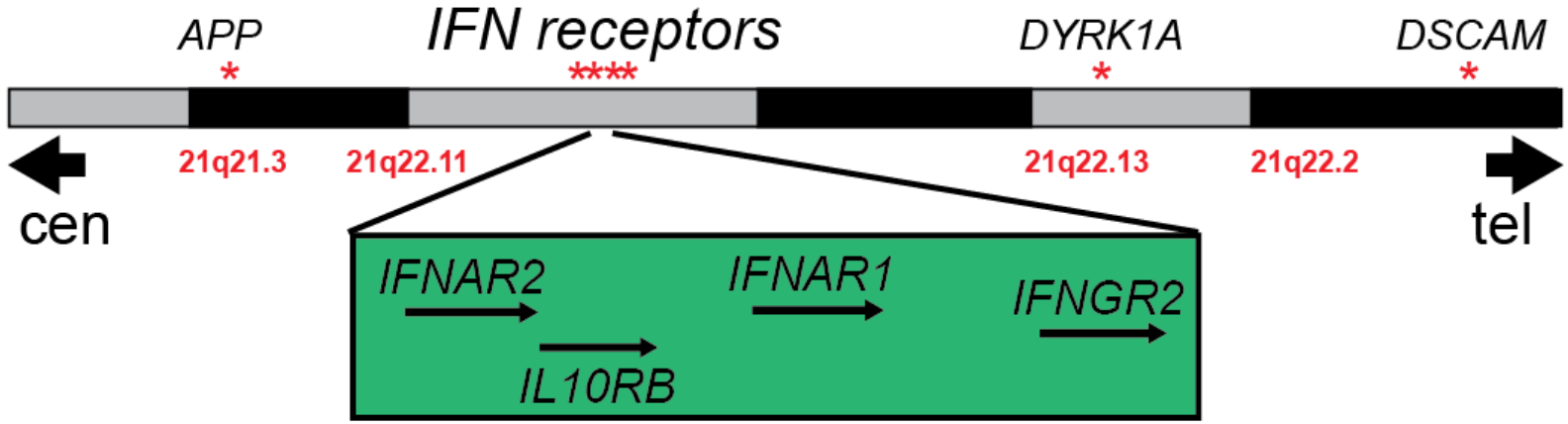
What is interferon signaling?

- 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 viral infection than typicals, with potential adverse effects

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



Human chromosome 21



Implications:

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

The immune system of people with Down syndrome is ‘super-charged’.

This ‘super-charged’ state 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).

Understanding Down syndrome as an immune system disorder

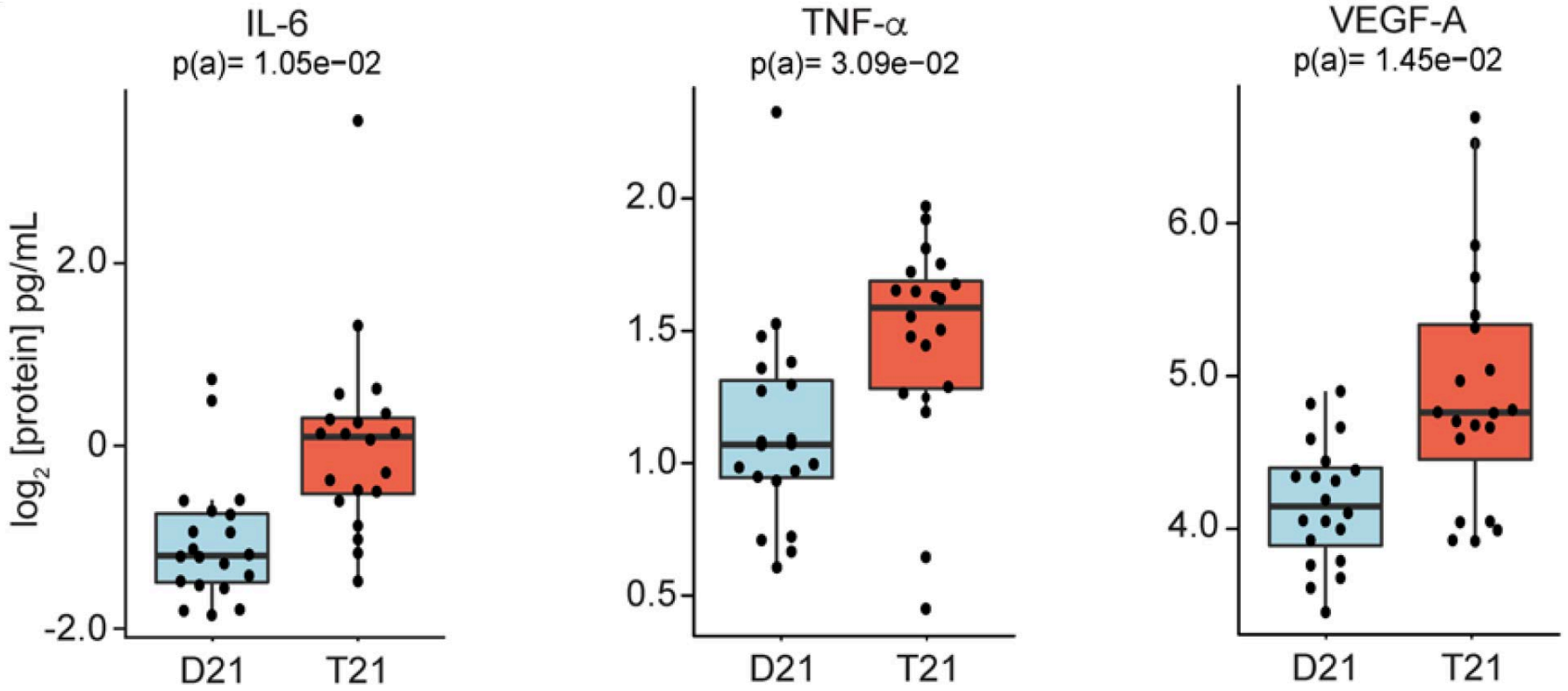
Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation

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 system disorder



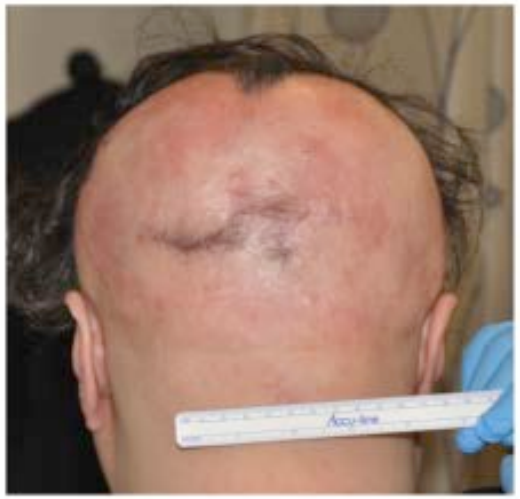
D21: typical person T21: Down syndrome

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

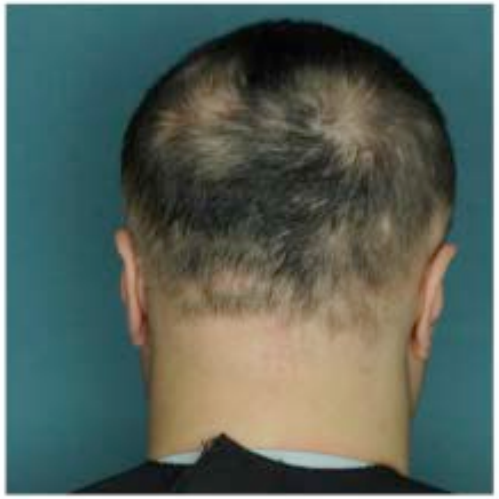
Can drugs that block the Interferon response cure some of the co-morbidities associated with Down syndrome?

Alopecia areata, treated with Interferon antagonists

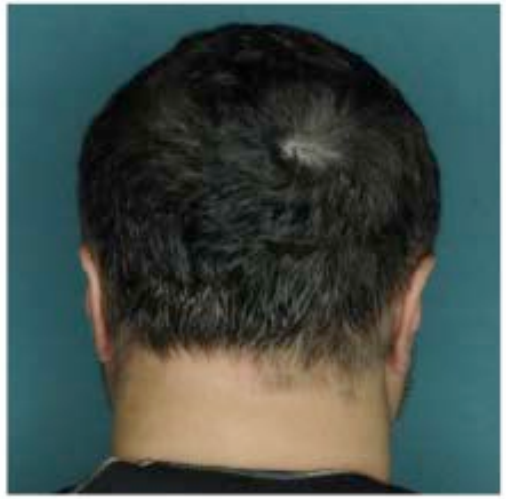
Alopecia Areata (autoimmune hair loss) is one of the many autoimmune conditions more prevalent in people with trisomy 21



baseline



3 months

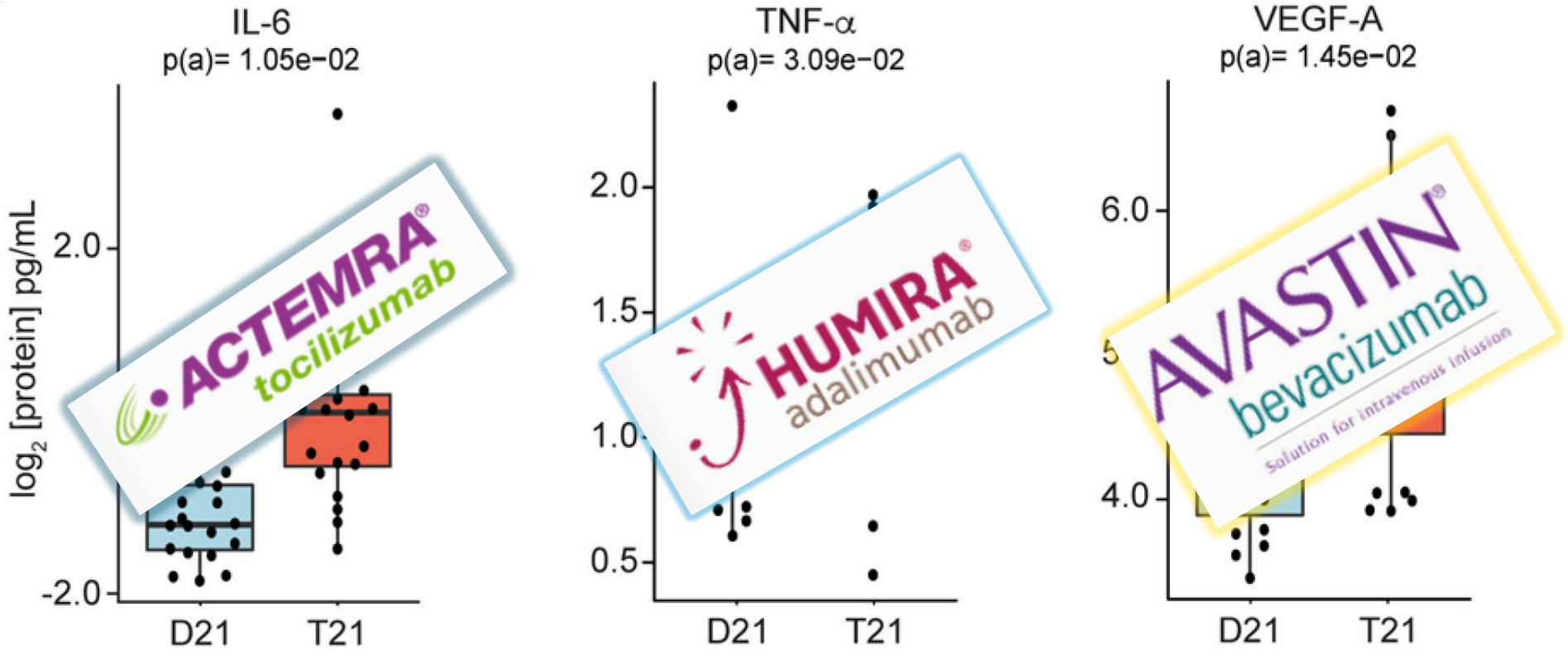


4 months

Ruxolitinib: An FDA-approved JAK inhibitor,
a class of drugs that block the Interferon response

Clynes et al, Nature Medicine 2014

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>

Conclusions

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

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

We need YOUR help

with increased awareness and participation

- **Together we can create a brighter future for our children and adults with Down syndrome** …
- Participate in Crnic Research in YOUR area
  - mouth swab for important autoimmune disease research
  - Stool samples fro analysis of gut microbiome
- Host a Human Trisome Project Educational Event
- Highlight our work on your website, blogs and newsletter
- Host a fundraiser for the Crnic Institute Research