The Crnic Institute's Human Trisome Project

Advanced biomedical research to improve the lives of people with Down syndrome

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LINDA CRNIC INSTITUTE
for DOWN SYNDROME

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

GLOBAL
DOWN SYNDROME FOUNDATION®

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

Mission

Significantly improve the lives of all people with Down syndrome

Vision

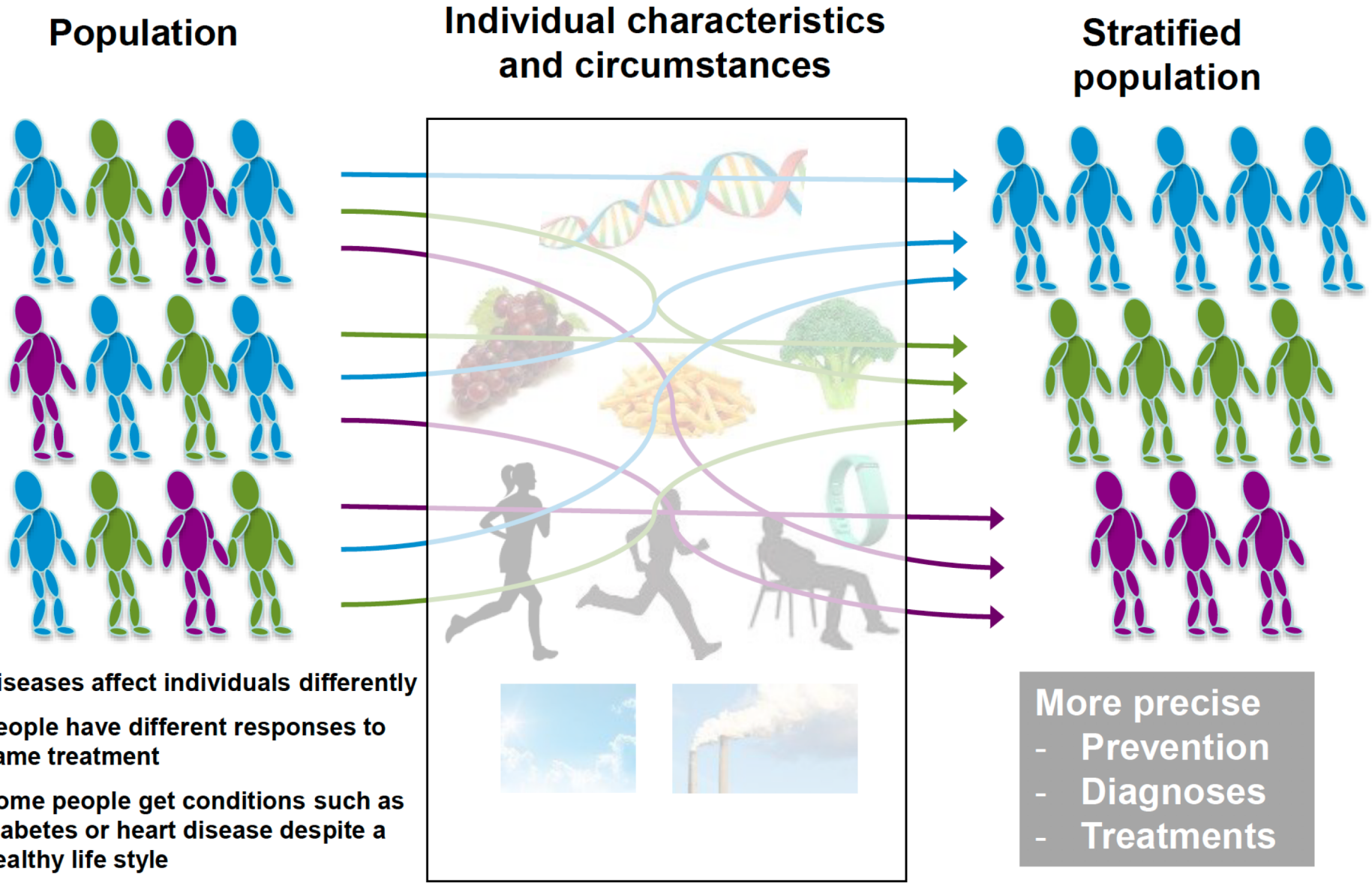
Provide the world's first fully integrated institute for Down syndrome with the highest quality basic, translational and clinical research, clinical trials, therapeutic development, medical care, education and advocacy in the pursuit of the mission.

Our motto:

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

One size **does not** fit all

The benefits of precision personalized 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









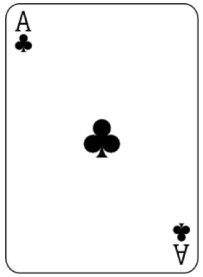
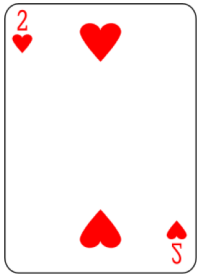
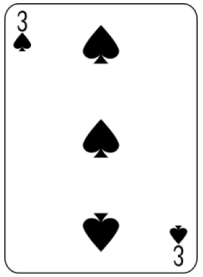
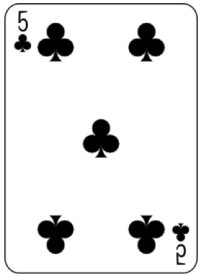
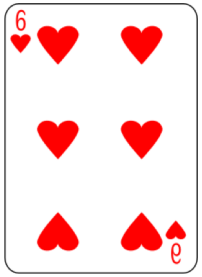
Our motto:

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

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
						
up to 12%	~12%	up to 50%	up to 13%	~1%	40-50%	up to 10%

Strategy:

Clearly, the study of Down syndrome does not belong to any **individual** scientific discipline.

Therefore, we must create a **collaborative, multidisciplinary**, and **integrative** research enterprise.

Tearing down academic boundaries
to serve people with Down syndrome

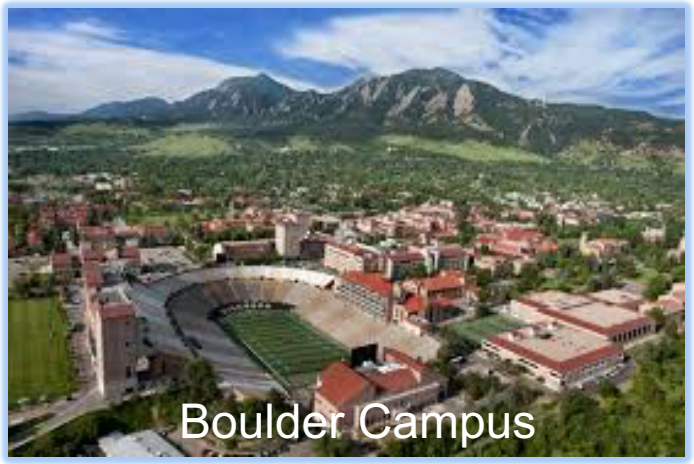
The Linda Crnic Institute for Down Syndrome

The largest geographical cluster of scientists investigating Down syndrome in the world

38 research teams, >150 scientists, 11 academic departments

University of Colorado

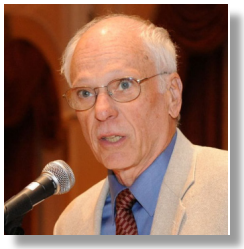
34 miles



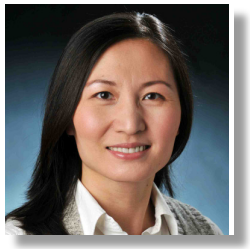
Keywords:

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 to improve cognitive function, treat seizures, infantile spasms, and autism.

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

These research projects are already leading to new clinical trials for the treatment of Alzheimer's disease in people with Down syndrome

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.

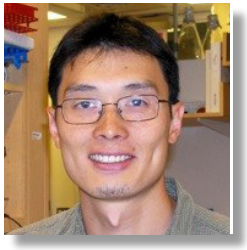
Richard Spritz, PhD
Investigates novels genes driving autoimmunity
in Down syndrome – thyroid disease, Type I diabetes, rheumatoid arthritis and vitiligo.

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

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.

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 of past research achievements by the field:

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. Hashimoto’s, type I diabetes, alopecia areata, vitiligo, rheumatoid arthritis)
- etc, etc

How to prevent or treat these conditions?

The Human Trisome Project

The 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.

A multidimensional cohort study

What makes us unique?

Our family history, environment, and lifestyle.

Our genes.

Our metabolism.

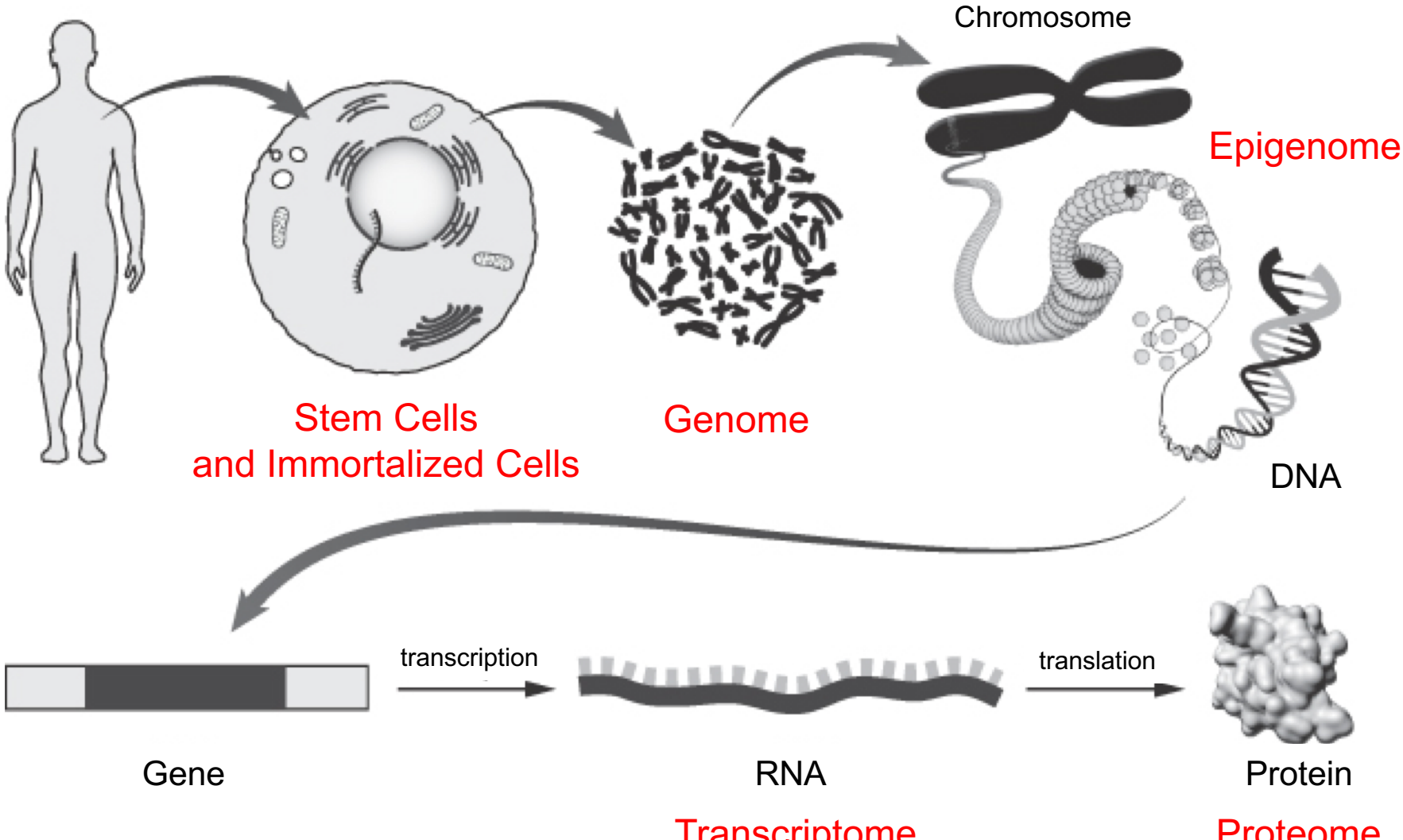
Our cellular ‘memories’.

Our microbes.

And much more….

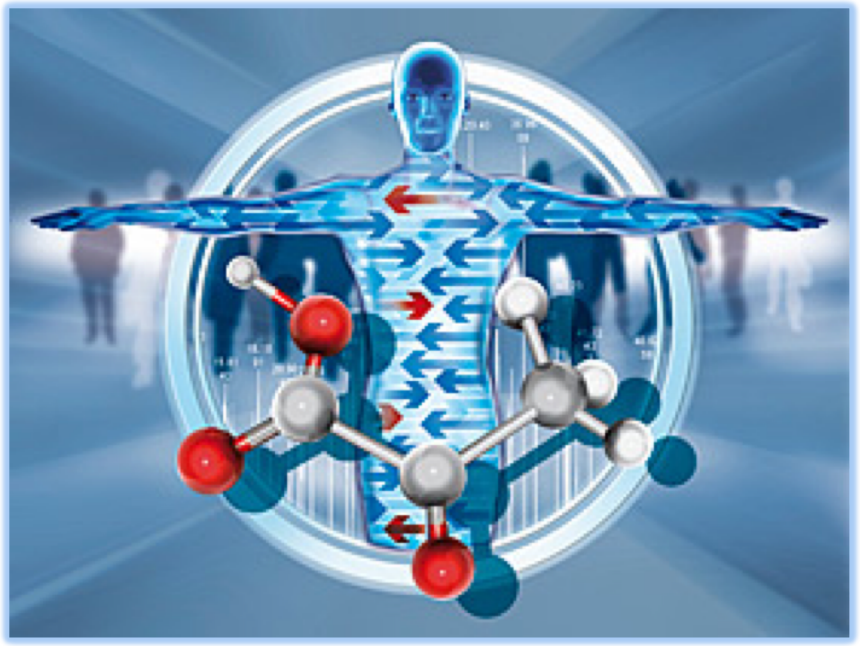
Opening the Black Box: The Ten Layers

Digital Phenotypes



Opening the Black Box: The Ten Layers

Metabolome



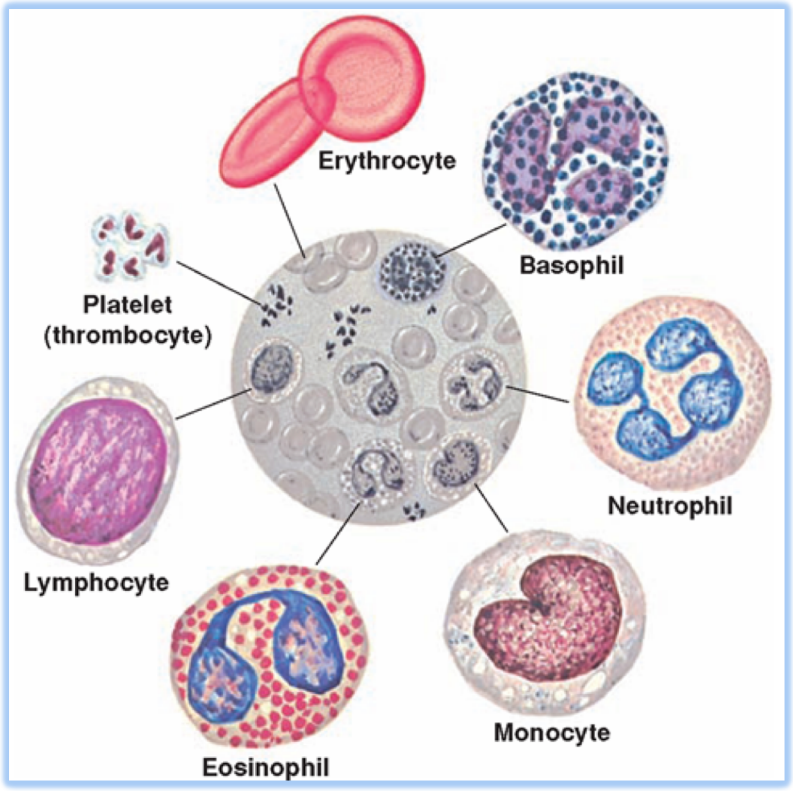
Metabolites (e.g. sugars, lipids, aminoacids, neurotransmitters)

Microbiome

Our ‘other genome’

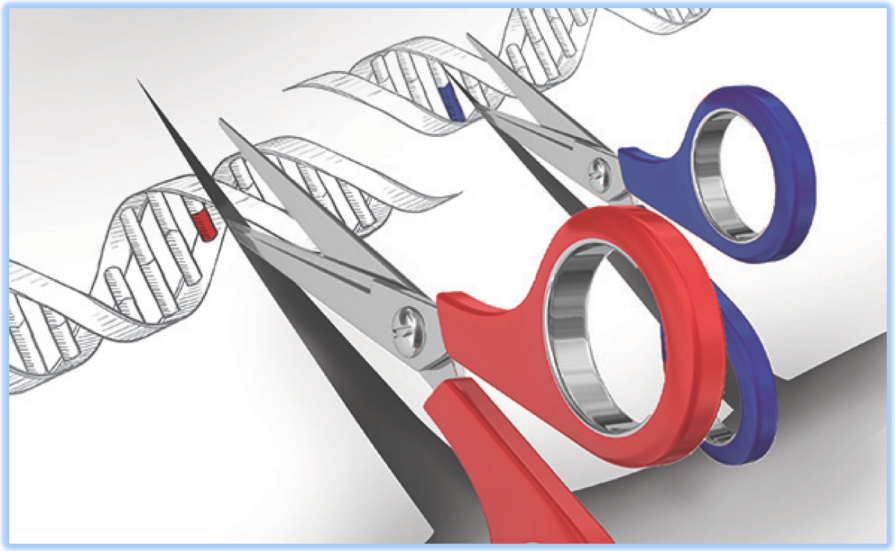
Opening the Black Box: The Ten Layers

Immune Mapping



Characterizing the blood and the immune system with exquisite detail

Functional Genomes



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

Remarkably, all these data can be obtained from a single visit to the clinic!

A single blood sample suffices to produce these datasets!
with the exception of the ‘microbiome’ which is obtained from saliva and/or stool samples.

This weekend, at NDSC,
you can become part of this study!

The Human Trisome Project team is here today to provide information and enroll new participants.

~400 participants consented to date!

HTP00001

October 10, 2016

HTP00300

September 7, 2017

Any cool results yet?

Down syndrome could be understood, in good measure, as an immune system disorder.

Down syndrome is undoubtedly a chromosomal disorder, caused by an extra copy of chromosome 21 (trisomy 21).

However, Down syndrome is often classified as a form of ‘intellectual disability’ or a ‘developmental disorder’.

Our research results **recast Down syndrome as an immune disorder caused by the extra chromosome**, and which in turn can cause many of the neurological, developmental, and clinical impacts of the extra chromosome.

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

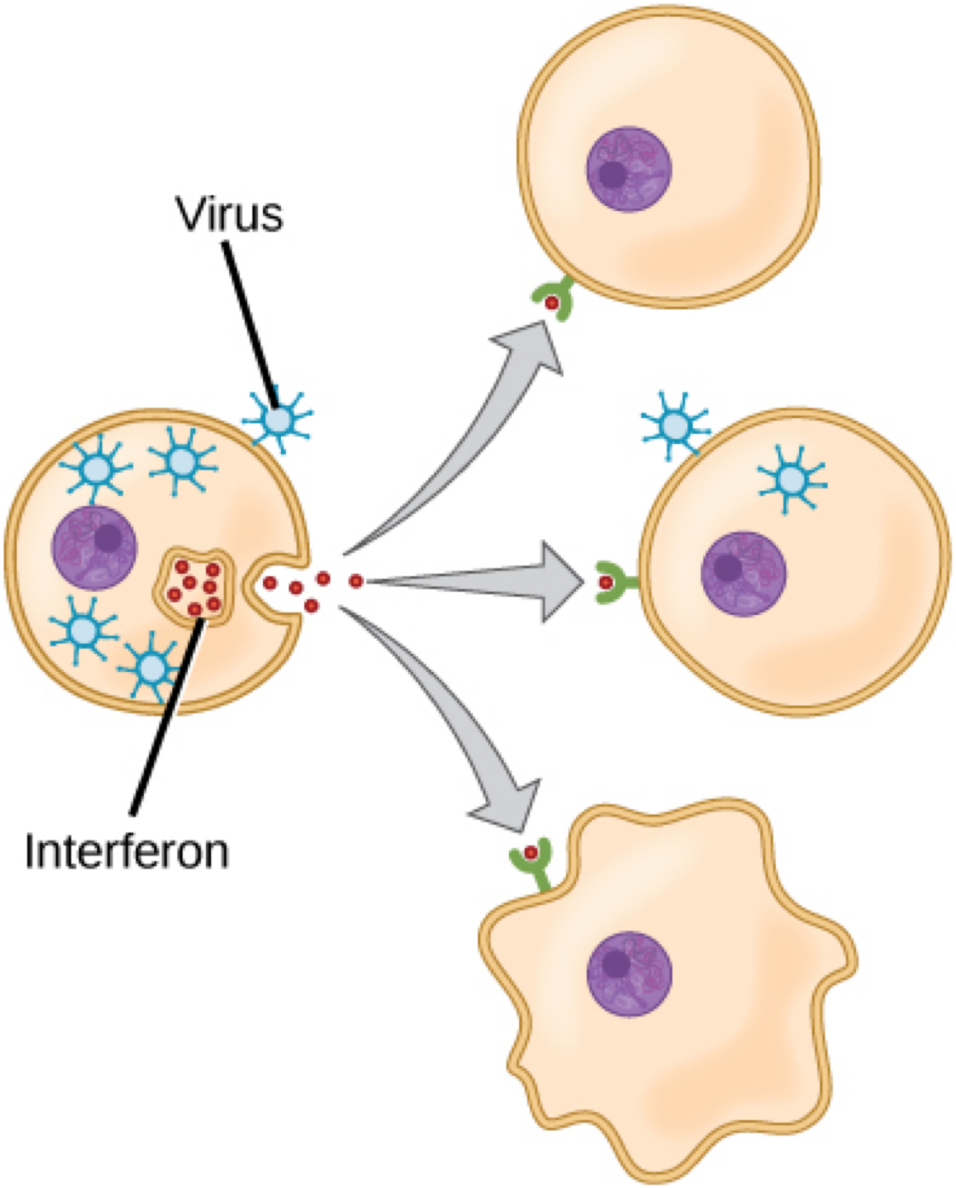
Elevated interferon signaling is a hallmark of Down syndrome.

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?

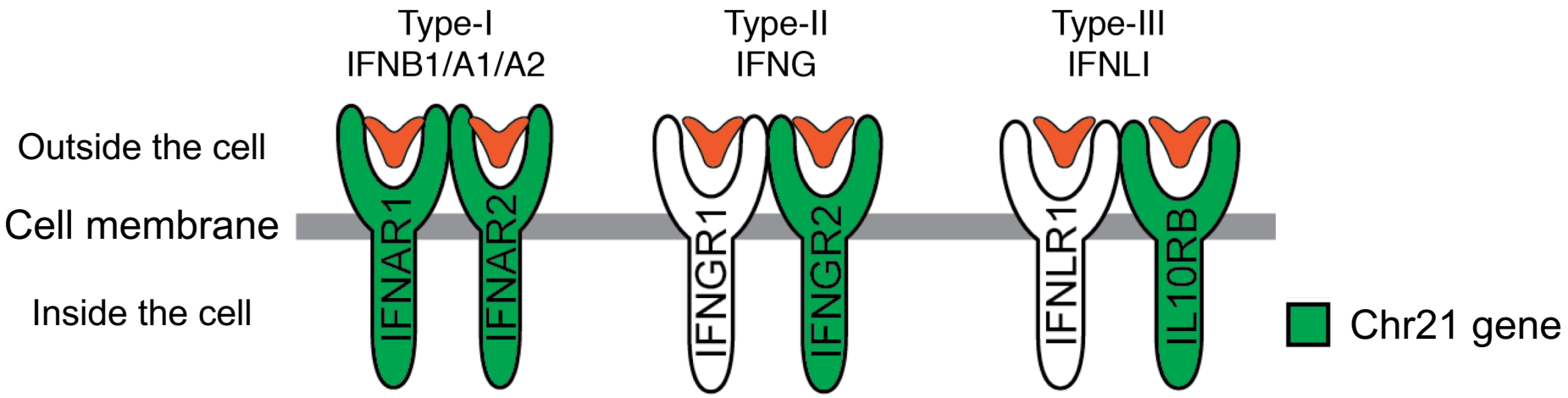


- Interferon signaling is an important part of the innate immune system
- Interferon activates many different types of immune cells
- Interferon signaling shuts down RNA and protein synthesis

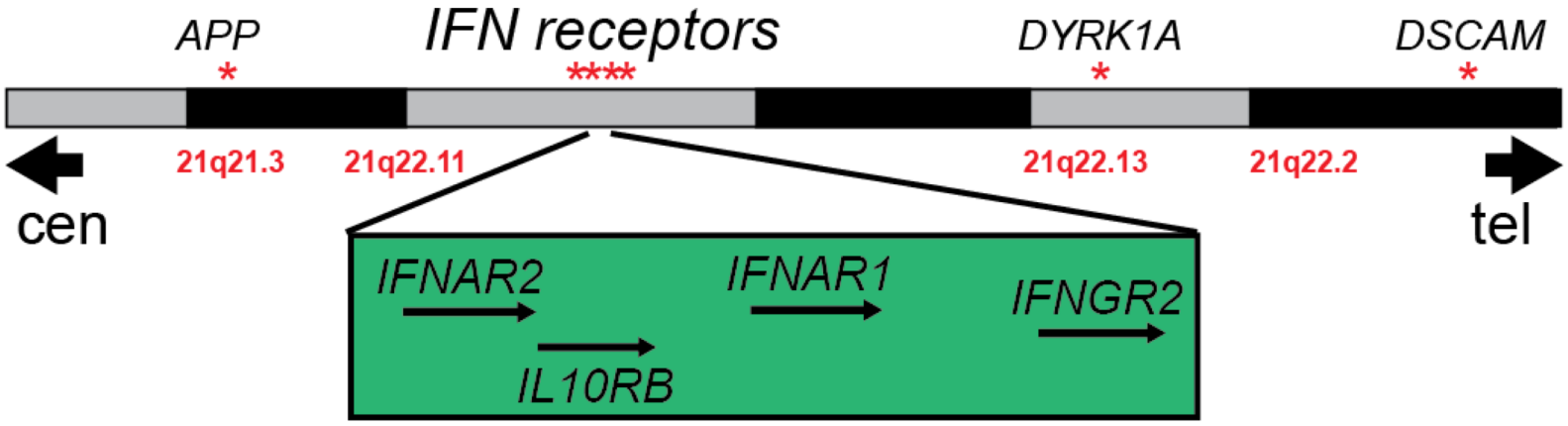
What is interferon signaling?

- The bodies of individuals with trisomy 21 are constantly fighting and infection that isn’t there
- Long term activation of interferon signaling can drive many of the symptoms of Down syndrome
- 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 (anti-bacterial defenses).

Understanding Down syndrome as an immune disorder

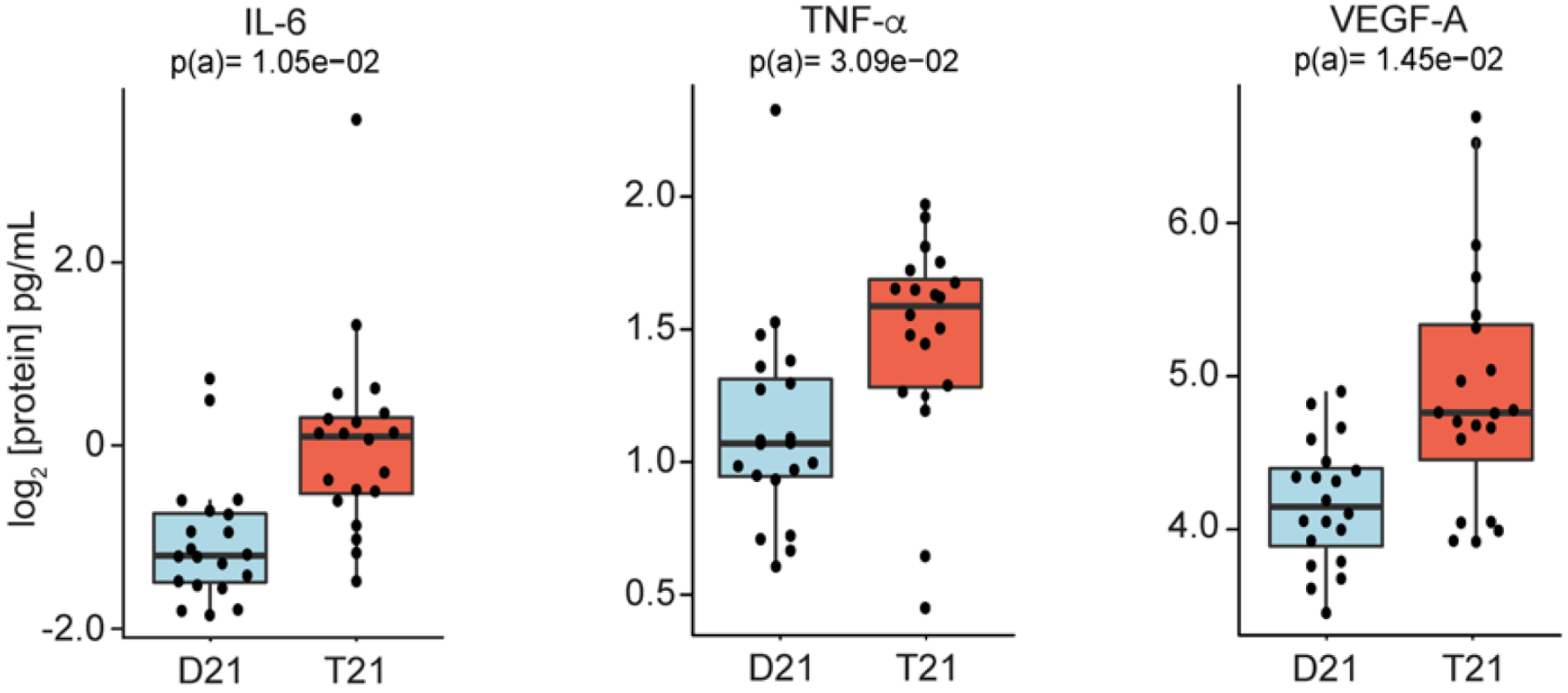
Trisomy 21 causes changes in the circulating proteome indicative of chronic autoinflammation

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



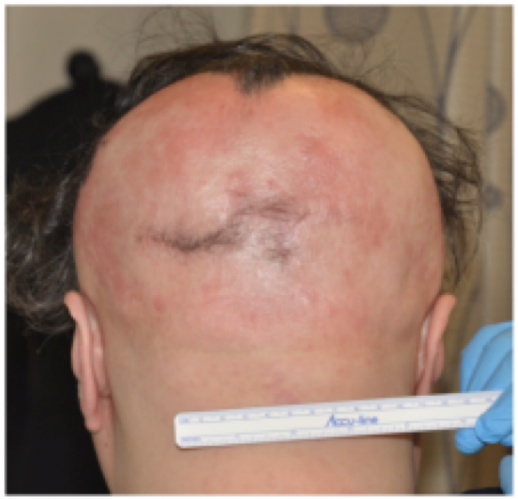
D21: typical person T21: Down syndrome

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

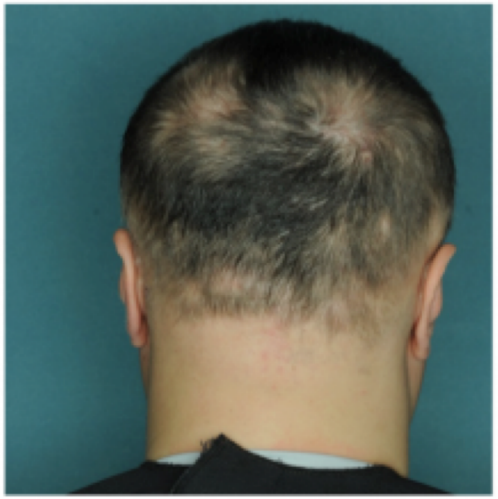
Can drugs that block the Interferon response cure some of the co-morbidities associated with Down syndrome?

Alopecia areata, treated with Interferon antagonists

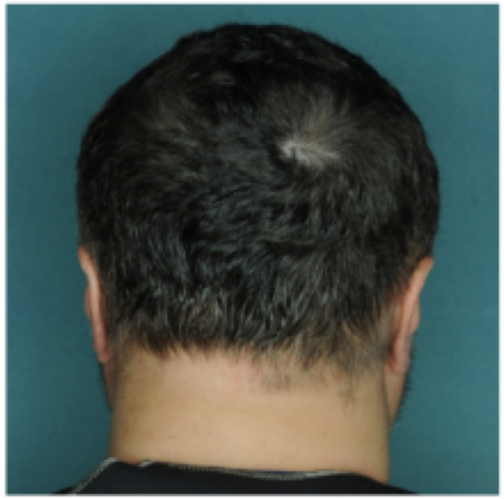
Alopecia Areata (autoimmune hair loss) is one of the many autoimmune conditions more prevalent in people with trisomy 21



baseline



3 months

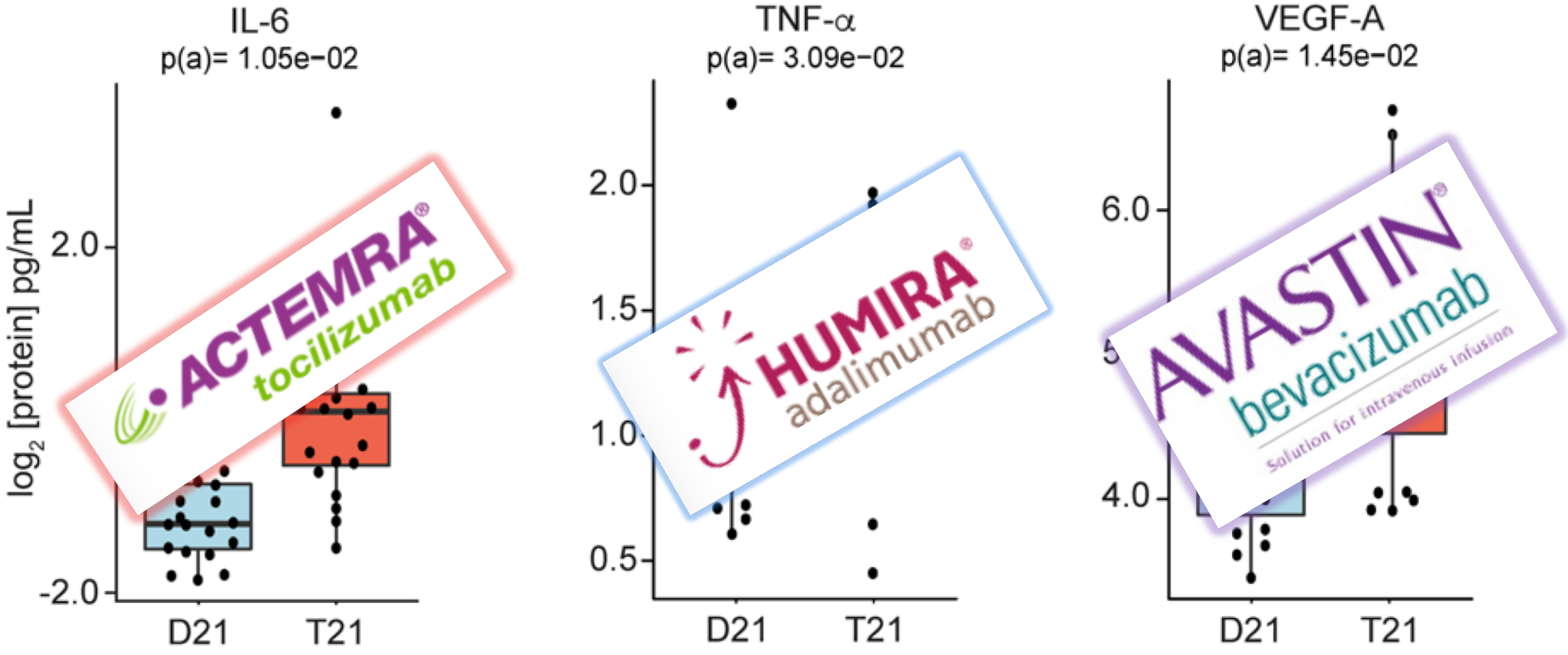


4 months

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 the Human Trisome Project
  - Blood sample for analyses of immune dysregulation
  - Mouth swab for microbiome research
- Host a Human Trisome Project Educational Event
- Highlight our work on your website, blogs and newsletter
- Host a fundraiser for the Crnic Institute research

Frequently asked questions

What happens to my information?
Your information is stored in encrytped, 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 the research performed will benefit others in the future.

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.

‘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