The Crnic Institute Human Trisome Project: improving the lives of people with Down syndrome through biomedical research

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

Rocky Mountain Alzheimer's Disease Center
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DOWN SYNDROME FOUNDATION®

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

DENVER HEALTH
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Adult Down Syndrome Clinic

Our research mission:

To help people with Down syndrome live their happiest healthiest life

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 through advanced biomedical research

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.

Individuals with Down syndrome have alterations in disease incidence

Heart Disease

Solid Tumors

Alzheimer's disease

Severe respiratory infections

Leukemias

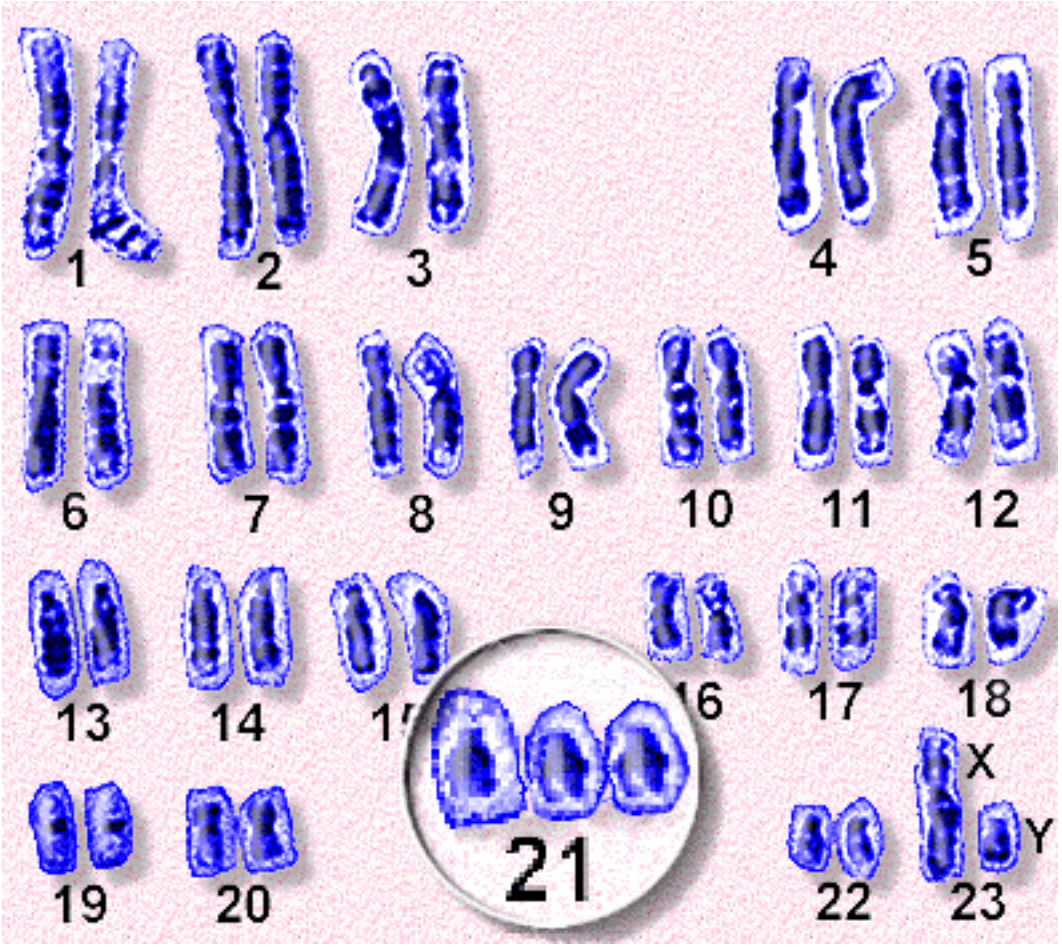
Autoimmunity

Autism

Obstructive sleep apnea

The ~6 million people with Trisomy 21 alive in the world today may hold solutions to major medical conditions

Trisomy 21,the molecular cause of Down syndrome, is defined by 3 copies of chromosome 21 rather than 2

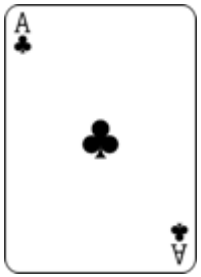
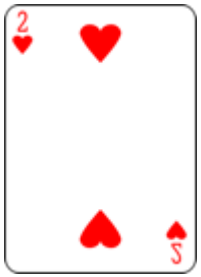
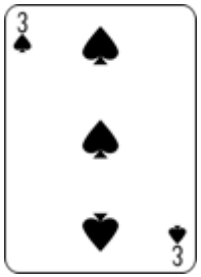
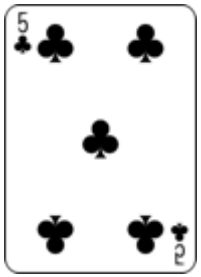
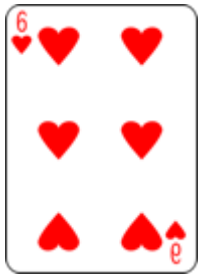


http://www.sbs.utexas.edu/sanders/bio309/Lectures/2006/Lecture%208%202006.htm

We know very little about how trisomy 21 causes Down syndrome

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%

Each person is dealing with Down syndrome in his/her own unique, personal way

They are more awesome than different!

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

HumanTrisomeProject

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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

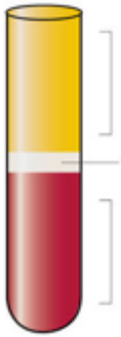
1. To enable a Precision Medicine approach to Down syndrome.
2. To define how trisomy 21 causes a novel disease spectrum.
3. To develop novel diagnostic and therapeutic tools that will benefit those with trisomy 21, and also millions of typical individuals.

Project goals – short term

1. To massively accelerate the pace of Down syndrome research.
2. To complete 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.

Crnic Institute Human Trisome Project™ (www.trisome.org)

Blood draw



Blood fractions

Datasets

Medical Records & Participant Survey

Saliva and Stool

Digital Phenotypes

Proteomes, Exosomes
Metabolomes, Antibody Profiling

Genomes
Epigenomes
Transcriptomes
Proteomes
Functional Genomics
Functional Assays
Cell Line Generation
Immunophenotyping

Metabolomes

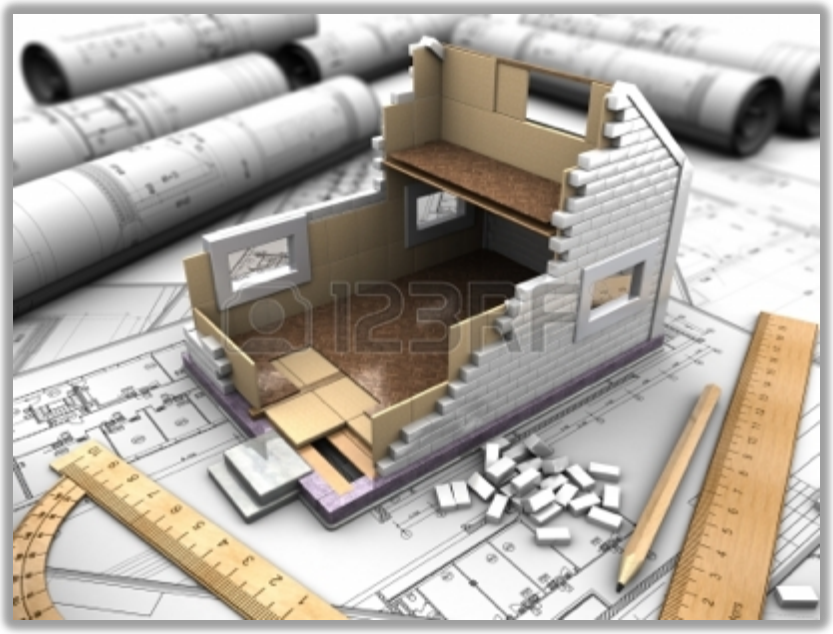
CBCs, blood smears

Differentiated Cell Types

Microbiomes

Crnic Institute Human Trisome Project™ (www.trisome.org)

The Power of Multidimensional Datasets



Going beyond the blueprint

Digital Phenotypes

Proteomes, Exosomes

Metabolomes, Antibody Profiling

Genomes

Epigenomes

Transcriptomes

Proteomes

Functional Genomics

Functional Assays

Cell Line Generation

Immunophenotyping

Metabolomes

CBCs, blood smears

Differentiated Cell Types

Microbiomes

All this information from a single blood draw and a mouth swab!

691 participants to date!

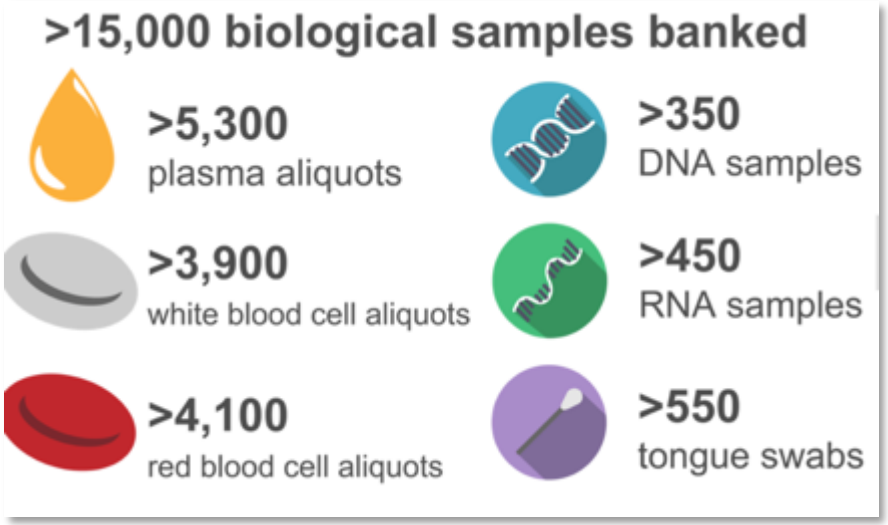
HTP00001

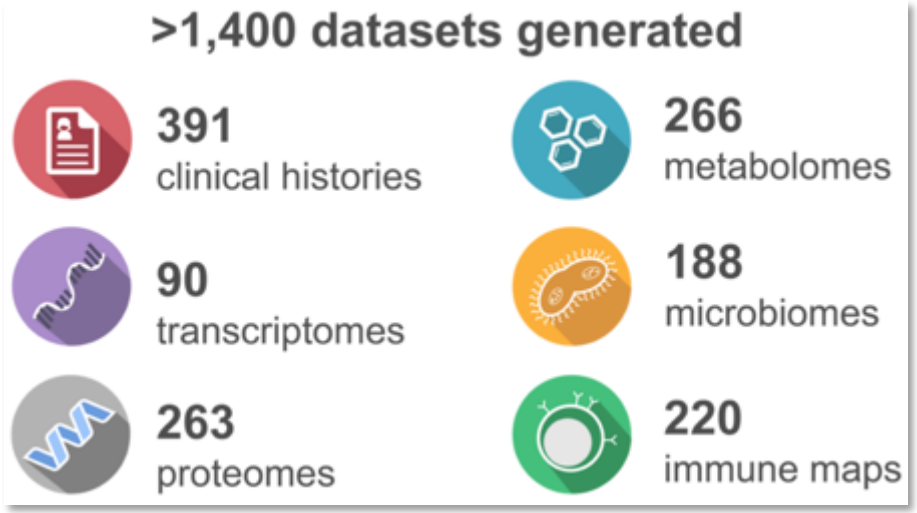
October 2016

HTP00500

January 2019

A massive ‘research accelerator’





20
Research projects currently supported

8
Publications already enabled

4
Additional manuscripts in review or 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 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]*

2016 eLIFE elifesciences.org

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]

2017 SCIENTIFIC REPORTS

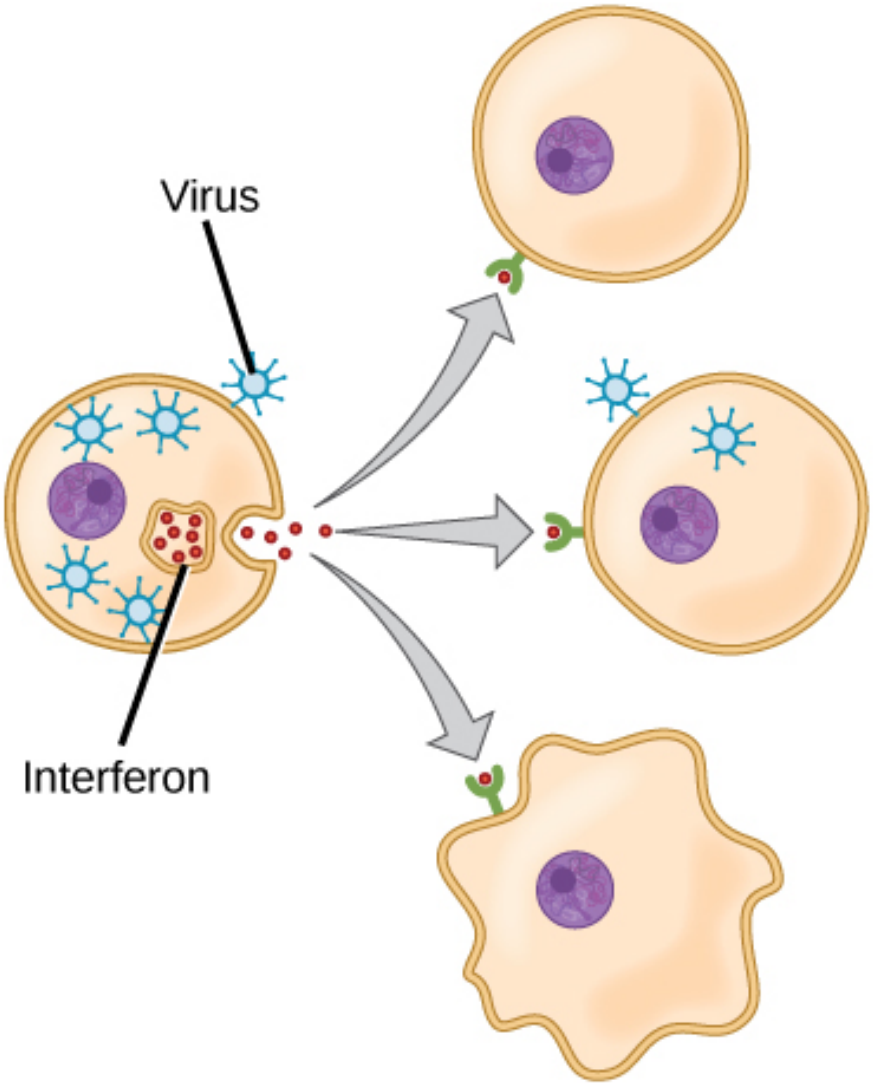
Trisomy 21 induces the kynurenine pathway via increased dosage of interferon receptor genes

Rani K Powers, Kelly D Sullivan, Rachel Culp-Hill, Michael P. Ludwig, Keith P Smith, Katherine A Waugh, Ross Minter, Kathryn D. Tuttle, Angela L Rachubinski, Ross E Granrath, Rebecca B Wilkerson, Angelo D'Alessandro, James C Costello, Joaquín M Espinosa

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

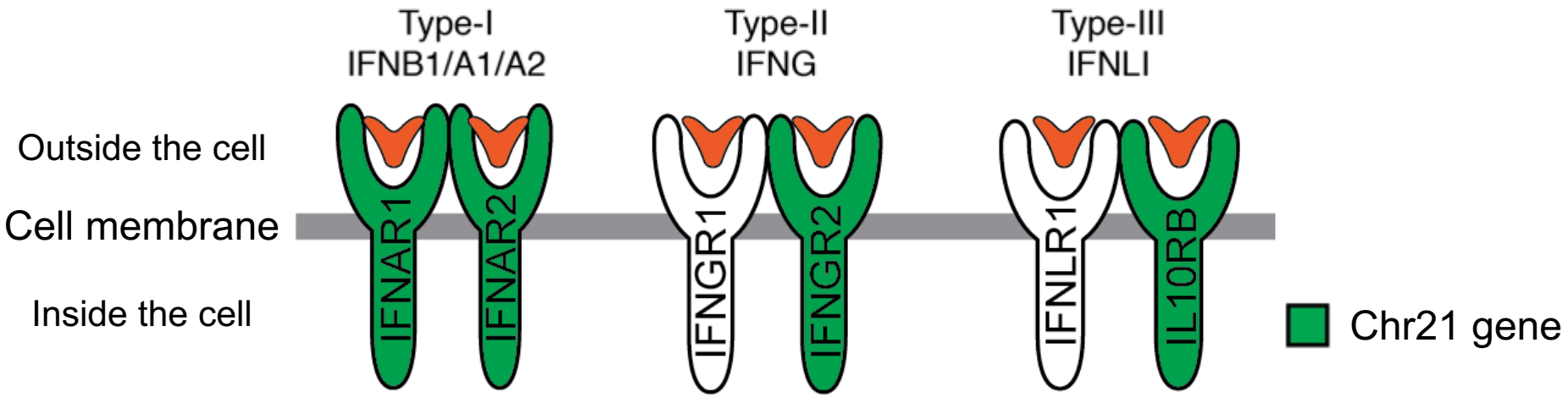
2019 nature COMMUNICATIONS

What is interferon signaling?

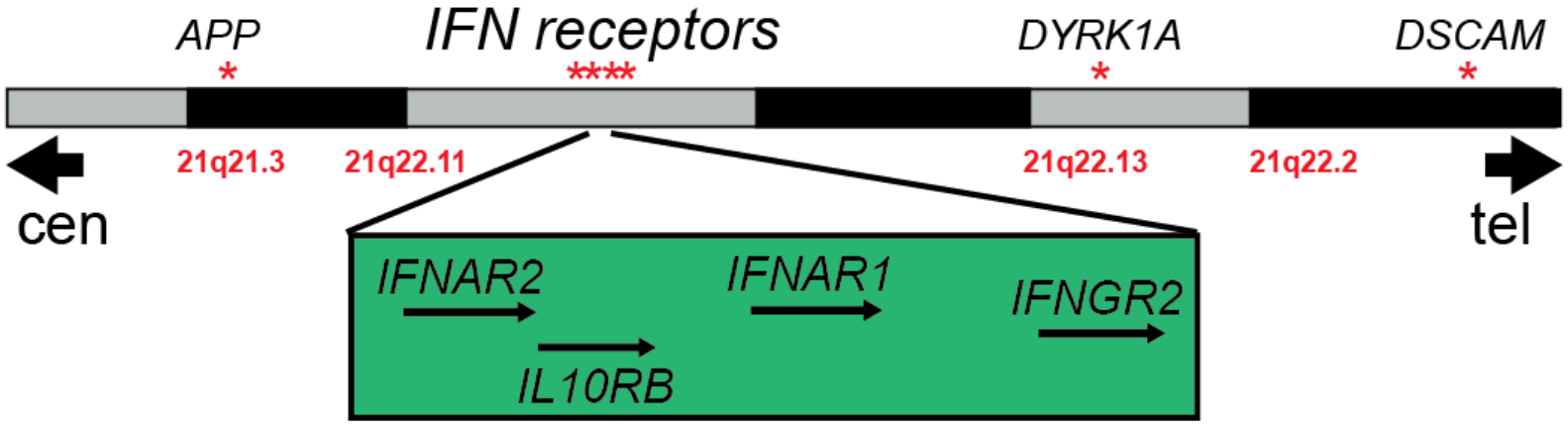


- Interferon signaling is an important part of the immune system
- Interferons activate many different types of immune cells
- Interferon signaling is important to fight off viruses and tumors

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



Human chromosome 21



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 ‘super-charged’, 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 could be the impact of hyperactive Interferon on the immune system?

Understanding Down syndrome as an immune disorder

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

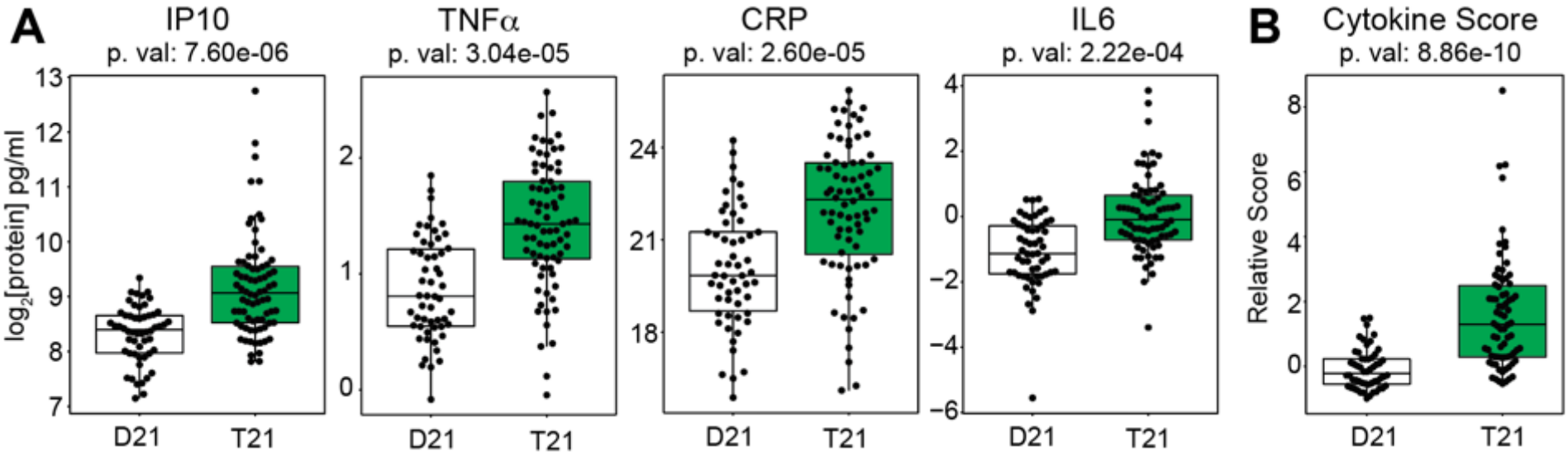
Kelly D. Sullivan[1,2], Donald Evans[1], Ahwan Pandey[1,2], Thomas H. Hraha[3], Keith P. Smith[1], Neil Markham[1], Angela L. Rachubinski[4], Kristine Wolter-Warmerdam[5], Francis Hickey[5], Joaquin M. Espinosa[1,2,6] & Thomas Blumenthal[1,6,7]

SCIENTIFIC REPORTS

Published November 1st , 2017

People with Down syndrome show much elevated levels of ‘inflammatory markers’

129 subjects, 75 with trisomy 21

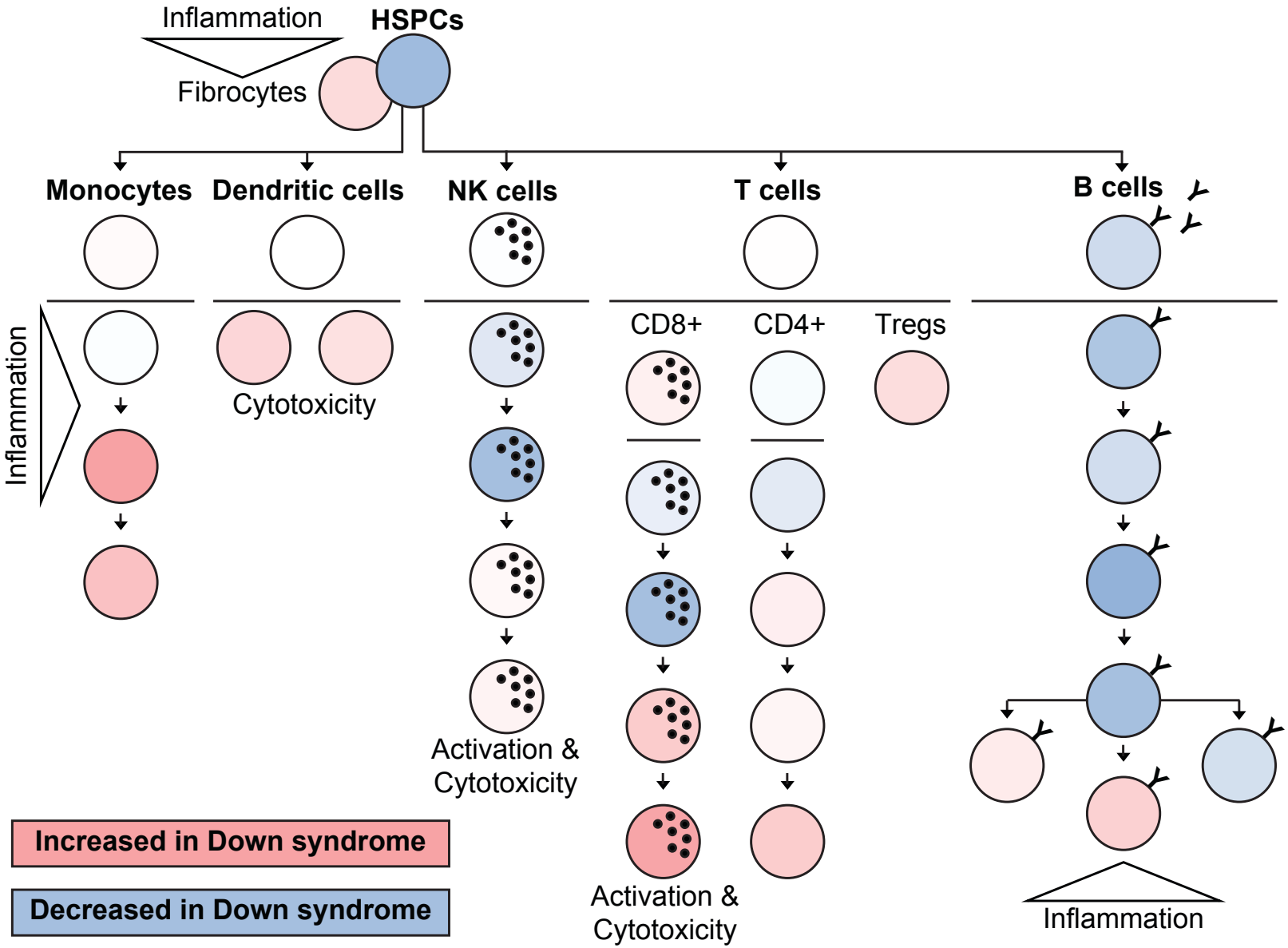


IP10:
Interferon-inducible protein 10

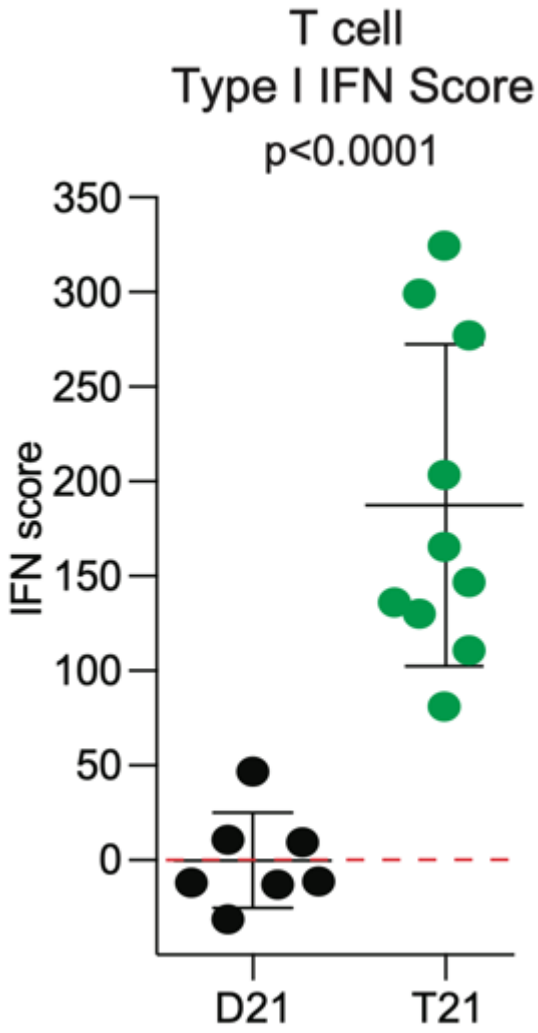
Each of these inflammatory markers is induced by Interferon signaling

Each of these has been positively correlated with risk and/or progression of autoimmune disorders and Alzheimer’s disease in the typical population.

Adults with Down syndrome have global immune dysregulation



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

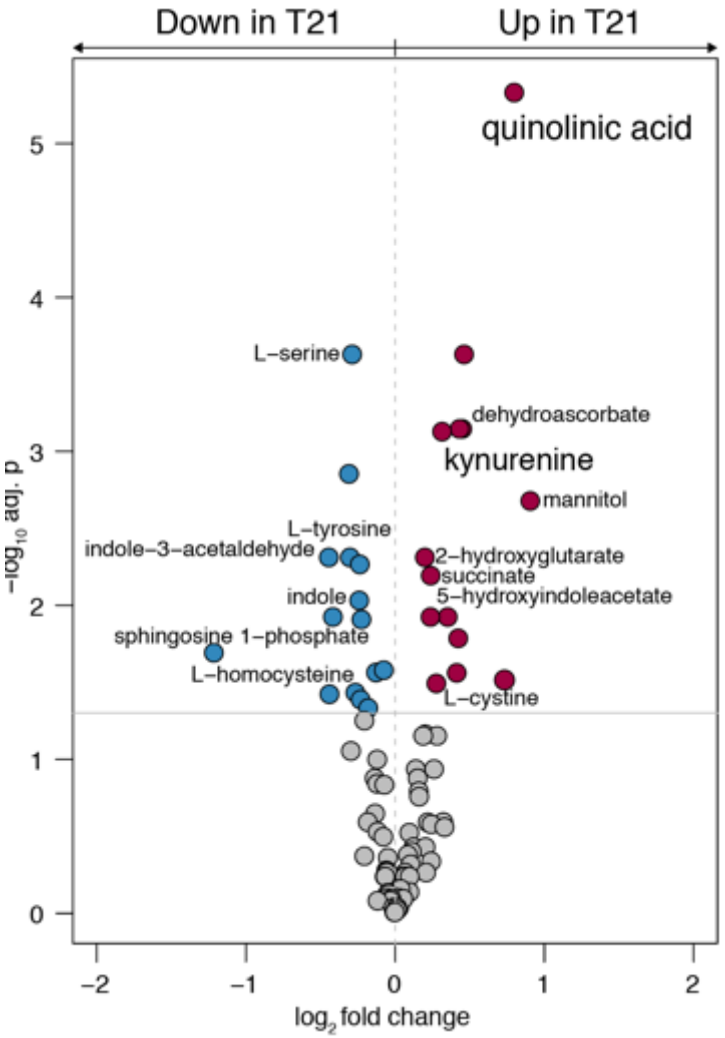
This hyperactive state could drive autoimmune disorders

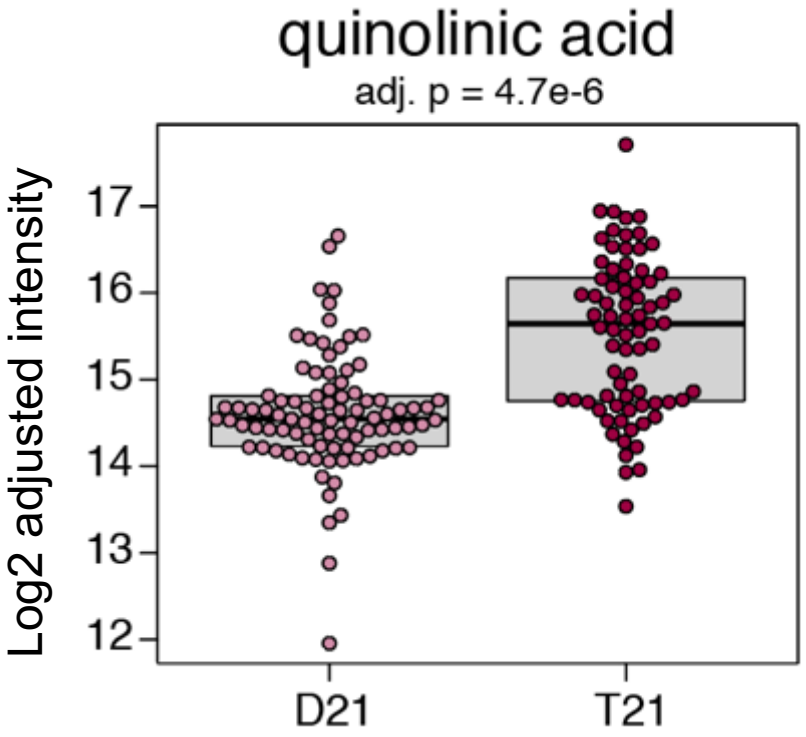
D21: typical control
T21: participant with trisomy 21

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





D21: typical people
T21: people with trisomy 21

Quinolinic acid is a 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.

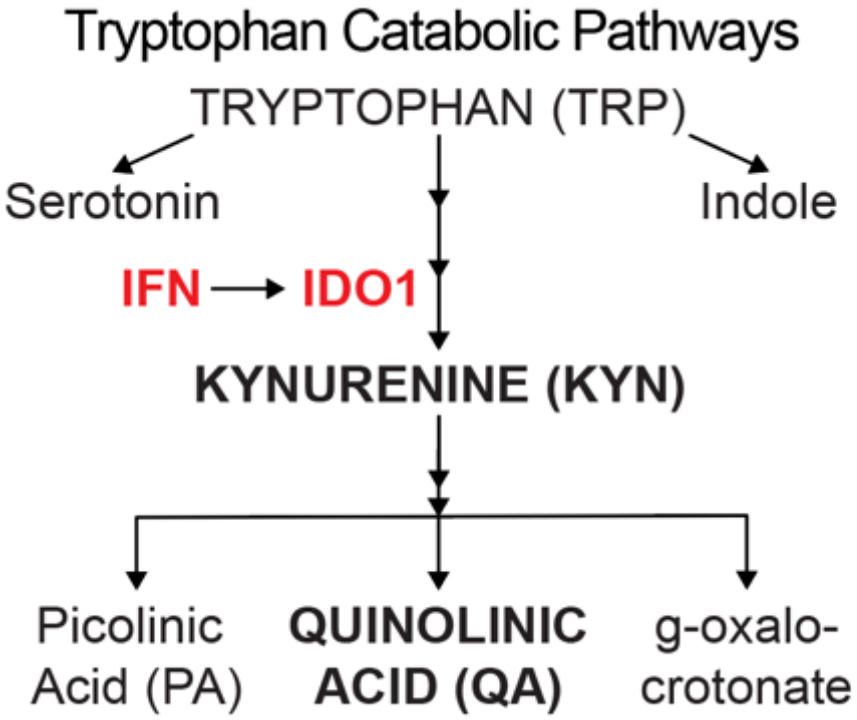
Quinolinic acid, the inescapable neurotoxin

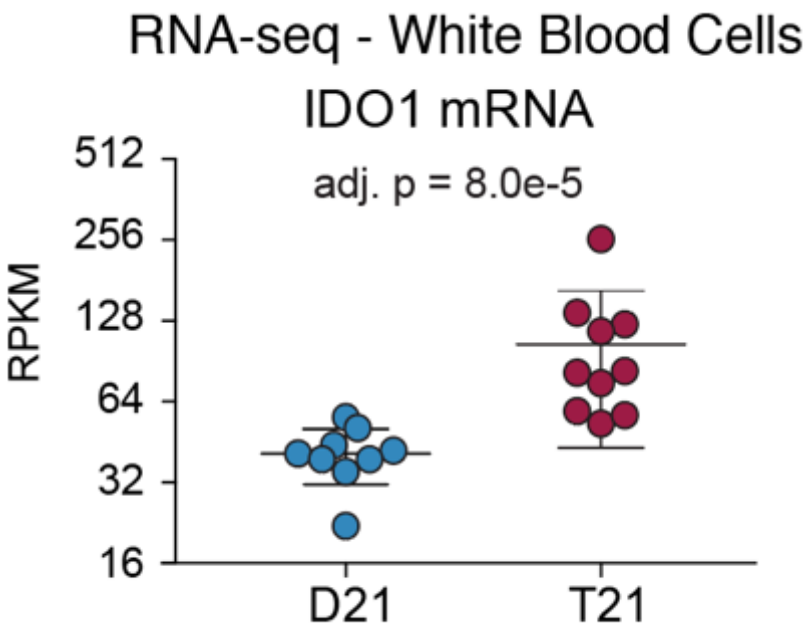
Gilles J. Guillemin[1,2]

the FEBS Journal

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

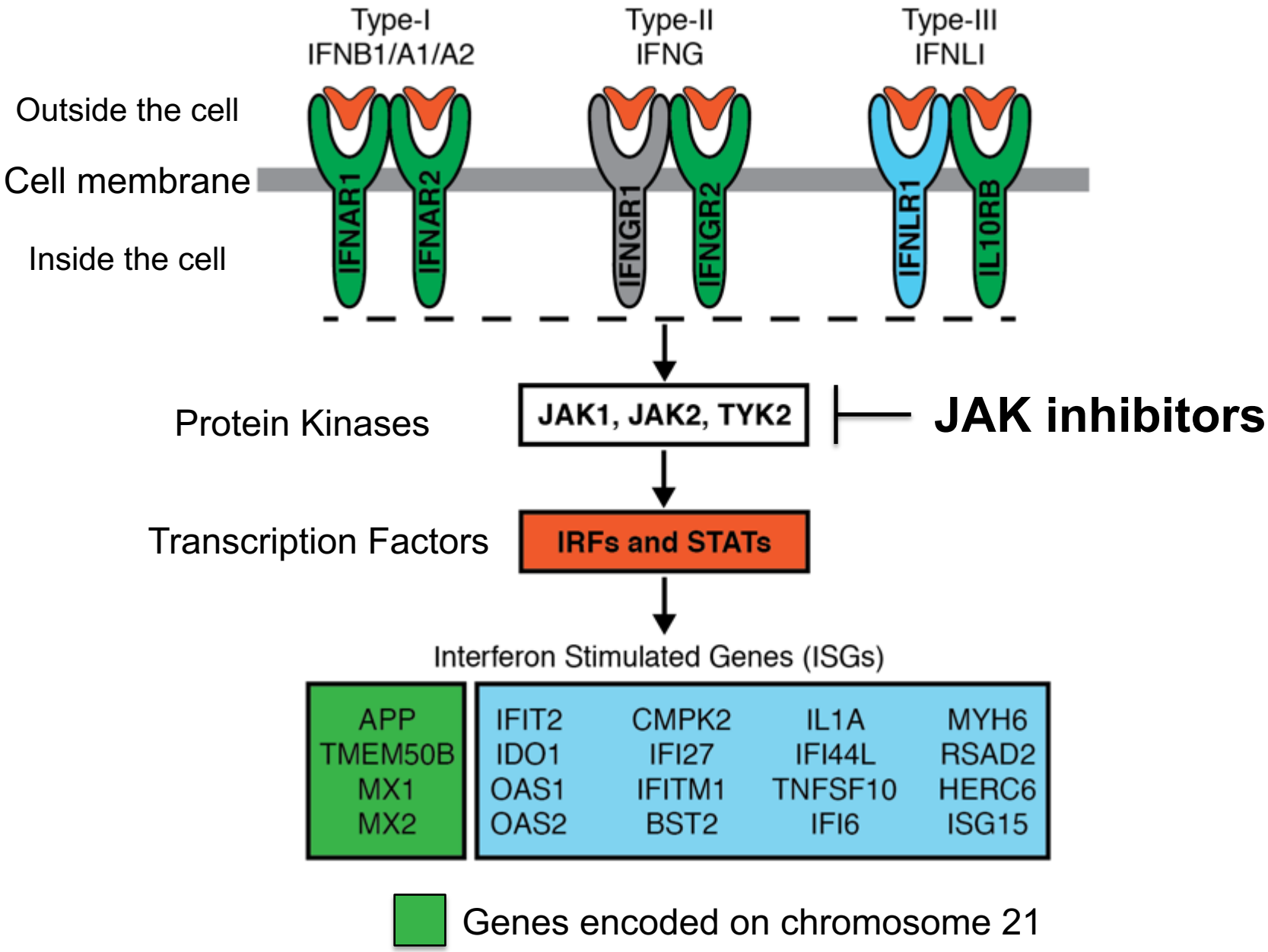




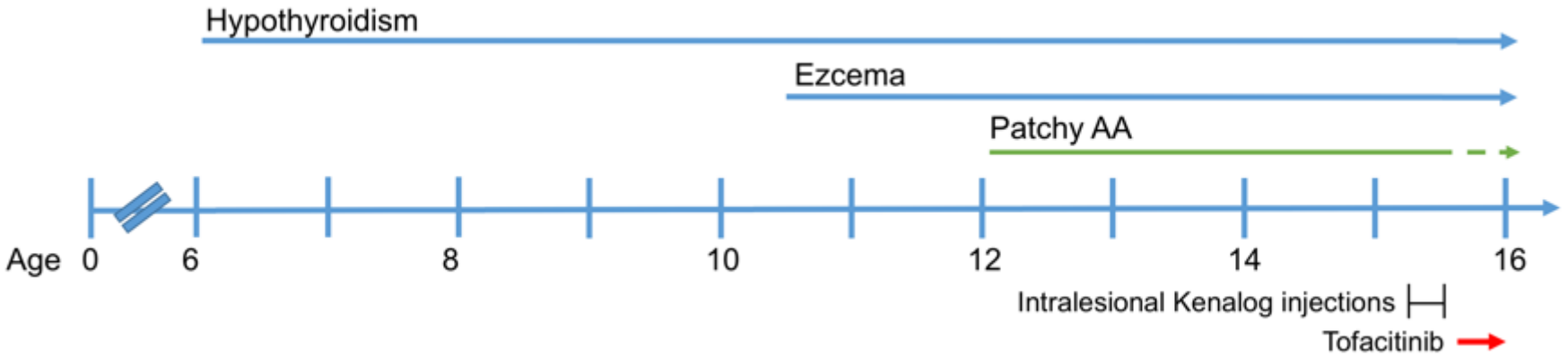
The IDO1 enzyme is much elevated in the blood of people with Down syndrome

Can drugs that block the Interferon response have therapeutic benefits in Down syndrome?

Blocking the Interferon response with JAK inhibitors

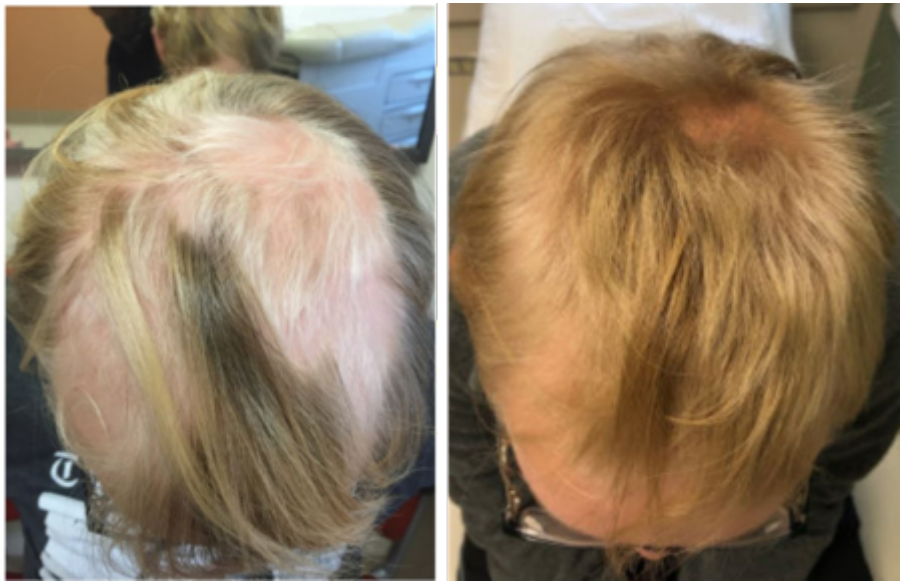


Alopecia areata, treated with JAK inhibitors in people with Down syndrome!



Before treatment

2 months



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

David Norris, MD
Chairman and Professor
Dermatology

Cory Dunnick, MD
Associate Professor
Dermatology

Drs. Norris and Dunnick have participated 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.

‘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









Acknowledgments

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Juana Marmolejo

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

Sie Center for Down Syndrome. Dr. Fran Hickey and staff.

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

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Hundreds of research volunteers!!!