



GLOBAL
DOWN SYNDROME FOUNDATION®

Congressional Briefing

Understanding the Increased Risk of Leukemia and the Decreased
Risk of Solid Tumor Cancers for Individuals with Down Syndrome

A Quick Overview & Welcome!

Michelle Sie Whitten

President & CEO Global Down Syndrome Foundation

Friday, September 14, 2018

12:00-1:00 PM

2044 Rayburn House Office Building

A Quick Overview

- ❖ A Personal Journey...
- ❖ A Life-threatening Disparity of Research Funding
- ❖ The Importance of Research
- ❖ The Global Down Syndrome Foundation
 - Research, Medical Care, Education & Advocacy
- ❖ A NEW ERA for Down Syndrome Research (“INCLUDE”)



Down Syndrome Cancer Congressional Briefing

The Inspiration



Anna and John J. Sie



Patrick & Sophia

“Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it's the only thing that ever has.”

Margaret Mead

Research Funding for Down Syndrome

A Life-threatening Disparity

| Year | NIH Budget (Millions) | CF Research Funding | Fragile X Research Funding | Autism Research Funding | Ds Research Funding | Ds Research Funding to NIH Budget |
|----------|-----------------------|---------------------|----------------------------|-------------------------|---------------------|-----------------------------------|
| 2000 | 17,840 | | | | 27 | 0.0015 |
| 2001 | 20,459 | | | | 29 | 0.0014 |
| 2002 | 23,321 | | | | 28 | 0.0012 |
| 2003 | 27,166 | | | | 23 | 0.0008 |
| 2004 | 28,037 | | | | 19 | 0.0007 |
| 2005 | 28,594 | | | | 15 | 0.0005 |
| 2006 | 28,560 | | | | 14 | 0.0005 |
| 2007 | 29,178 | | | | 16 | 0.0006 |
| 2008 | 29,607 | | | | 17 | 0.0006 |
| 2009 | 30,545 | | | | 18 | 0.0006 |
| 2010 | 31,238 | | | | 22 | 0.0007 |
| 2011 | 30,916 | | | | 20 | 0.0006 |
| 2012 | 30,860 | 86 | 27 | 192 | 20 | 0.0006 |
| 2013 | 29,129 | 78 | 30 | 186 | 18 | 0.0006 |
| 2014 | 30,019 | 77 | 36 | 186 | 18 | 0.0006 |
| 2015 | 30,293 | 80 | 38 | 208 | 24 | 0.0008 |
| 2016 | 30,293 | 83 | 40 | 216 | 25 | 0.0008 |
| 2017 Est | 30,293 | 83 | 40 | 216 | 25 | 0.0008 |

Down Syndrome Research Overview

- ❖ **Low Government Funding** - Despite being the leading cause of developmental delay in the U.S. and the world, Down syndrome is one of the least funded genetic conditions by the National Institutes of Health (NIH) and has been since 2001.
- ❖ **Precipitous decline in funding** - From 2001 to 2006, NIH funding for Down syndrome research plummeted from \$29 million to \$14 million despite significant growth of the NIH budget.
- ❖ **Parity** - From 2001 to 2017, Down syndrome funding would have been \$744 million - more than double the actual \$356 million - had this research been funded in parity with the NIH budget.
- ❖ **Comparables** - Annual NIH research funding for Down syndrome is 2x to 45x less per capita compared to diseases with similar prevalence (e.g. Multiple Sclerosis) or chromosomal conditions and developmental disabilities (e.g. Fragile X or Autism).

Why is research so important?

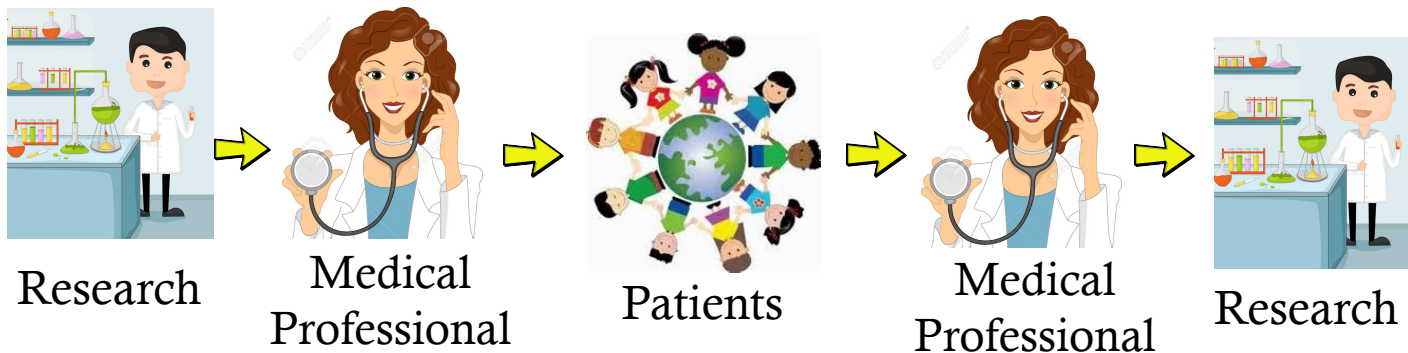
❖ Extends the lifespan

- In the 1980s lifespan was 28 years...today it is approximately 60
- Reasons - De-institutionalization + advances in pediatric heart surgeries

❖ Improves the quality of life throughout life

- ❖ 2001 “Health Supervision for Children with Down Syndrome”; current ones are a “must” and provide a great check-list (Drs. Marilyn J. Bull, William I. Cohen, Nancy Rozien)
- ❖ No current guidelines for adults with Down syndrome (Drs. William I. Cohen and David S. Smith)

❖ People with Down Syndrome have a Different Disease Spectrum!



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 Critical Need

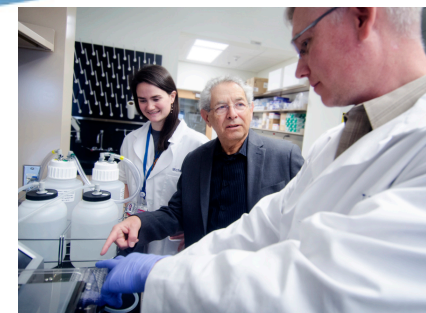
A Population Explosion & A Eugenics Framework

- ❖ There is a population explosion of people with Down syndrome in the U.S. that requires dramatically *more* funding not less
 - **Population** - is somewhere between 250,000 to 430,000
 - **Live Births** - have increased to 1 in 691 today from 1 in 1,000 in 2002
 - **Lifespan** - has more than doubled to 60 years from 28 years in the 1980s
 - **A Mini Population Explosion** - will happen over the next several decades due to increased live births and lifespan
 - **Societal Trends** - include a small but growing number of people with Down syndrome participating in college programs, choosing to get married, and living independently or semi-independently
- ❖ There is a “eugenics framework” in countries like Iceland and Denmark...

Global - Proud of Our Accomplishments

❖ RESEARCH

- Established the Crnic Institute for Down Syndrome, the first and only academic home in the US dedicated to research and medical care benefitting people with Down syndrome
- Funding 30+ labs and over 130 scientists



❖ MEDICAL CARE

- Fourteen full-time equivalents, providing excellent medical care and eight clinics to 1,500+ unique patients from 28 states and 10 countries
- NEW medical care center for adults
- NEW Medical Care Guidelines for Adults with Down Syndrome

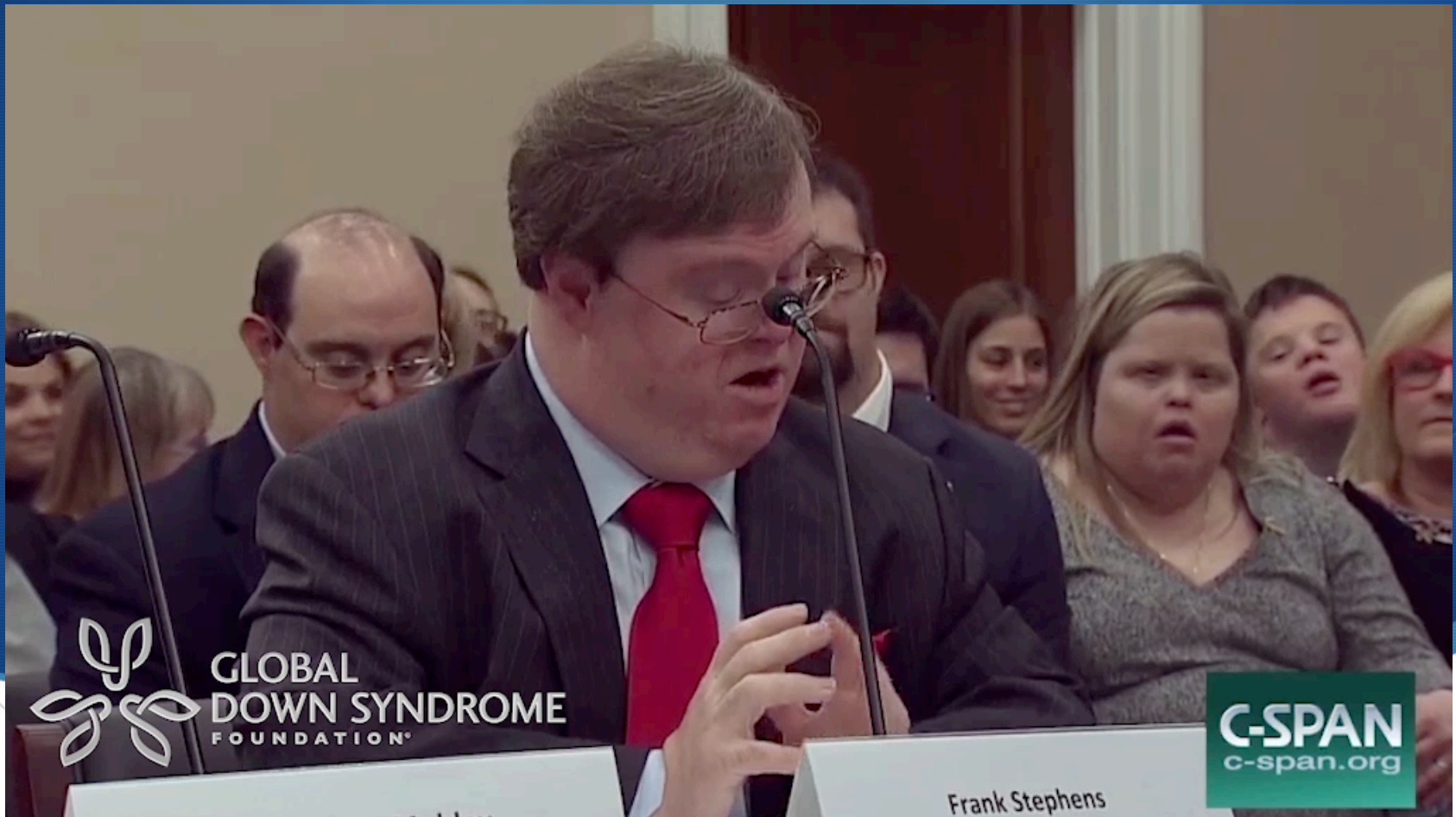


❖ EDUCATION & OUTREACH

- Award-winning quarterly magazine, *Down Syndrome World*TM, and the largest Down syndrome fundraiser in the world, *Be Beautiful Be Yourself Fashion Show*
- Membership grant program, Research & Medical Care Roundtables, and Health & Wellness programs reaching 12K+ people with Down syndrome



Frank Stephens testifies Before Congress ... resulting in a historic 66% increase of NIH's Down syndrome research budget from \$38mil in FY2017 • to \$58 mil in FY2018 • to \$98mil in FY2019



Global - Proud of Our Accomplishments

Lobbying & Advocacy in DC

❖ REPORT LANGUAGE & BRIEFINGS

- Since 2005 powerful report language inquiring into the disparity of NIH funding for Down syndrome research

❖ FIRST DOWN SYNDROME CONFERENCE AT NIH

- (Dec 2010) NIH and Global co-hosted the first Down Syndrome Conference in NIH history that led to the creation of the DS-Connect patient registry

❖ FIRST DOWN SYNDROME RESEARCH HEARING

- The first real increase for Down syndrome research in nearly two decades
- FY18 \$58M (up from \$35M), FY19 \$98M
- The establishment of INCLUDE (Investigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) Project Research Plan
- EIGHTEEN Institutes under the Office of the Director (Trans-NIH)



September 14, 2018

THANK YOU!



The impact of Down syndrome research on our understanding of cancer and leukemia

Joaquín M. Espinosa, PhD

Linda Crnic Institute for Down Syndrome
University of Colorado School of Medicine

LINDA CRNIC INSTITUTE
***for* DOWN SYNDROME**



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People with Down syndrome have a different 'disease spectrum'



The ~6 million human beings alive today with trisomy 21 may hold solutions to many major medical conditions

People with Down syndrome have a different '*malignancy* spectrum'

Breast Cancer down
~5-10 fold

Prostate Cancer down
~5-10 fold

Colon Cancer down ~3
fold

Skin Cancer down 4
fold

The striking exception:
Testicular cancer!



Overall leukemia risk
up ~20 fold

Acute Megakaryocytic
Leukemia (AMKL) up
>400 fold

Acute Lymphocytic
Leukemia (ALL) up
>10 fold

Acute Myeloid
Leukemia (AML) up
>20 fold

Hasle et al , Genetics in Medicine 2016.

**The ~6 million human beings alive today with trisomy 21
may hold the key to treat cancer and leukemia**

Hypotheses:

Chromosome 21 contains one or more genes that slow down tumor development, known as 'tumor suppressor genes'

Chromosome 21 also contains genes that promote leukemias, known as 'leukemogenic genes'

Research goal:

To identify these genes and understand how they work

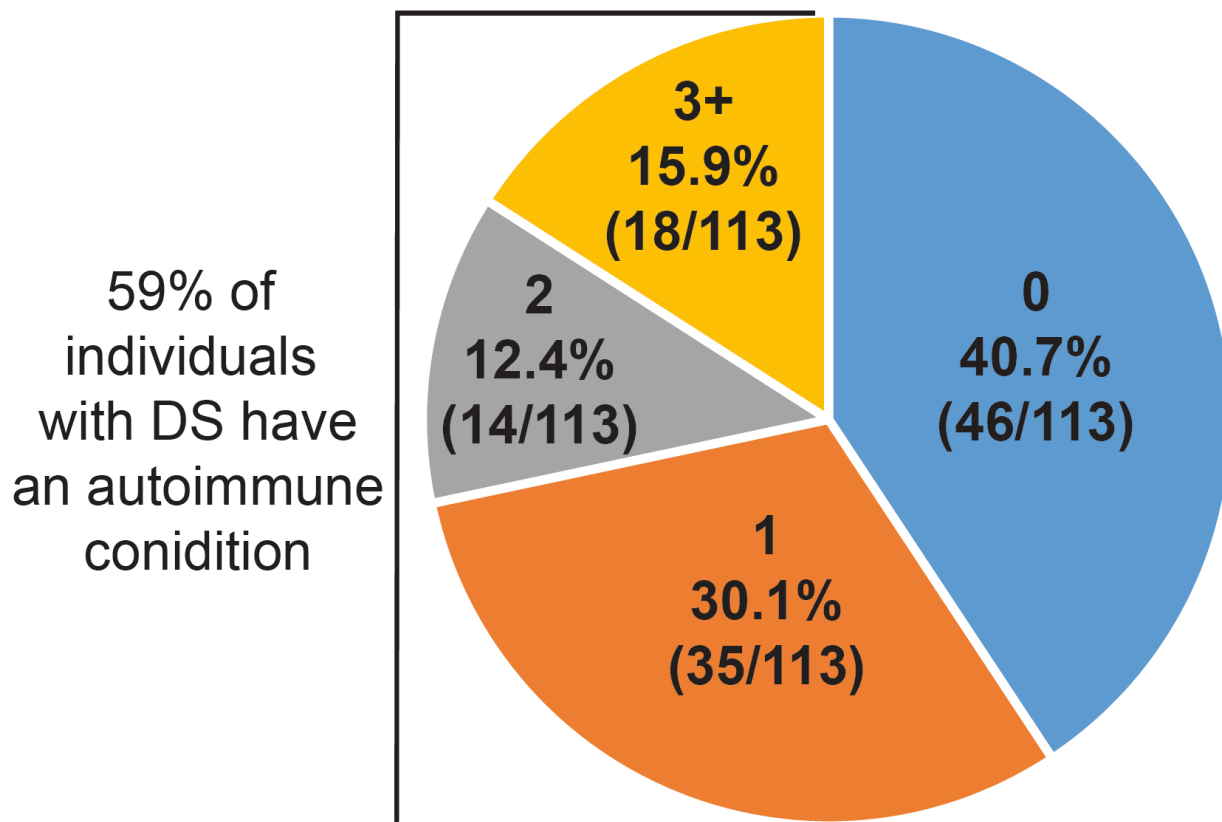
Our favorite hypothesis:

Chromosome 21 contains one or more genes that hyperactivate the immune system.

A hyperactive immune system could explain both, the lower rates of tumors, and the higher rates of leukemias.

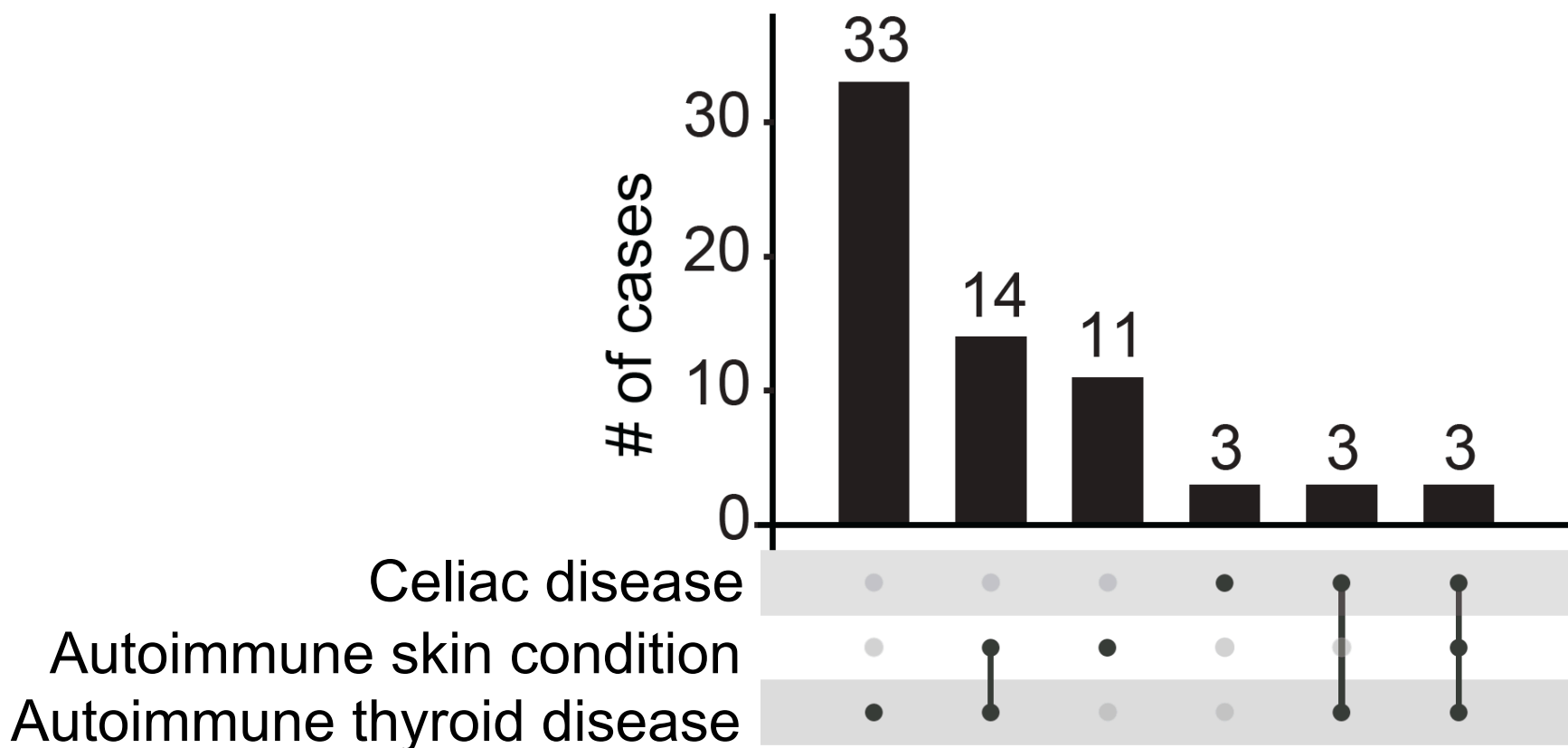
People with Down syndrome show clear dysregulation of the immune system

~60% of adults with Down syndrome are affected by one or more 'autoimmune conditions'



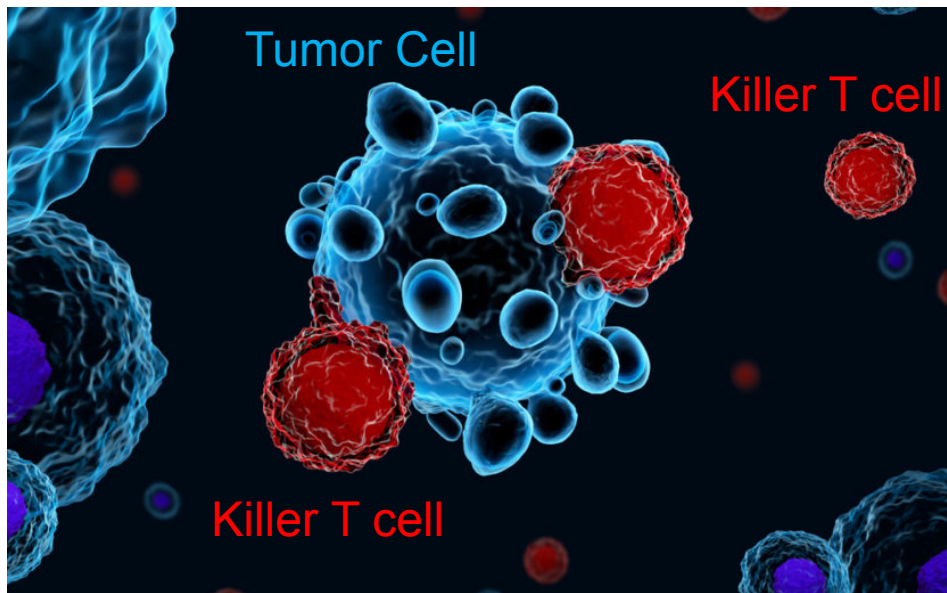
Analysis of 113 medical records from adults in the Denver area

People with Down syndrome show clear dysregulation of the immune system



~60% of adults with Down syndrome are affected by one or more 'autoimmune conditions'

All these autoimmune conditions are driven by immune cells known as 'killer T cells'

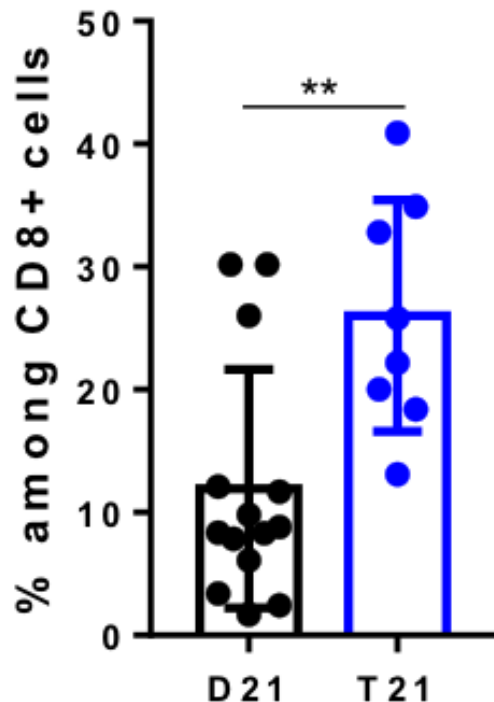


Killer T cells are normally responsible for attacking virus-infected cells and tumor cells

However, killer T cells can mistakenly attack healthy tissues, causing autoimmune disorders

People with Down syndrome have significantly more 'activated killer T cells'

Activated Killer T cells



D21: typical people

T21: people with Down syndrome or trisomy 21

On average, people with Down syndrome have more than twice the amount of activated killer T cells!

When too much of a good thing is not good!

Why do people with Down syndrome
have significantly more
'activated killer T cells'?

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 Smith¹, 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

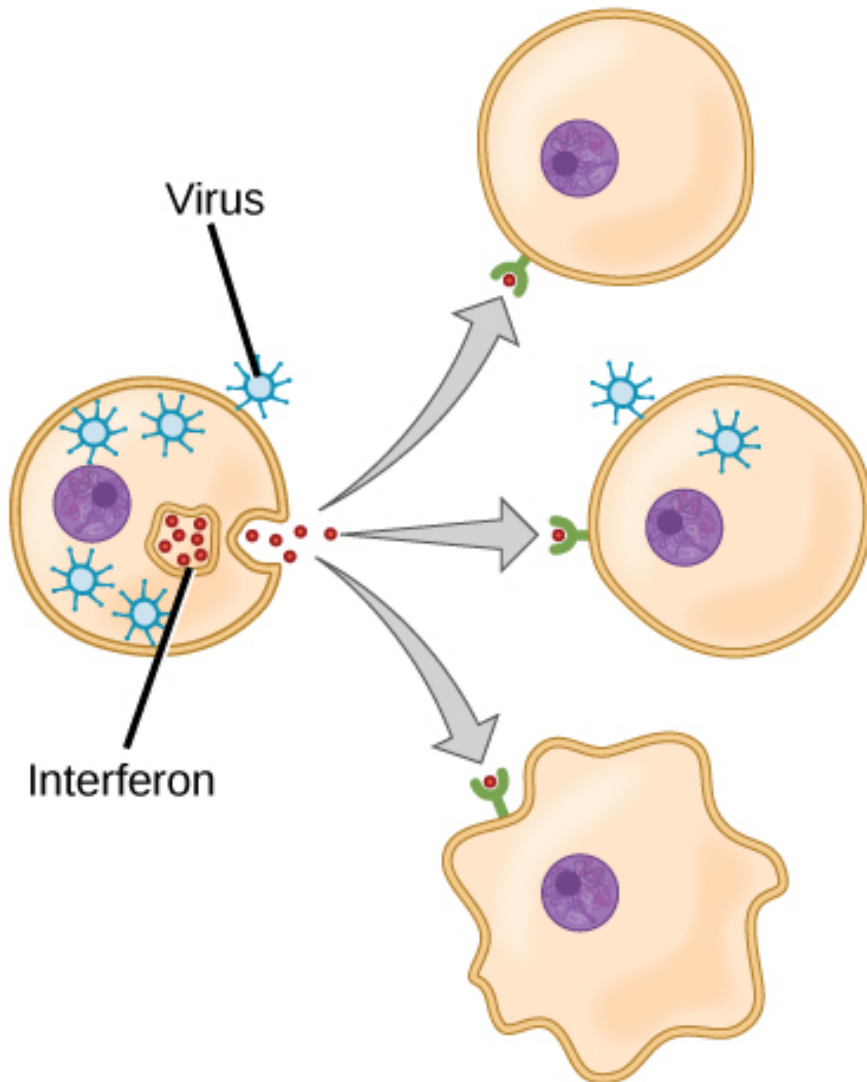
elifesciences.org

Kelly
Sullivan



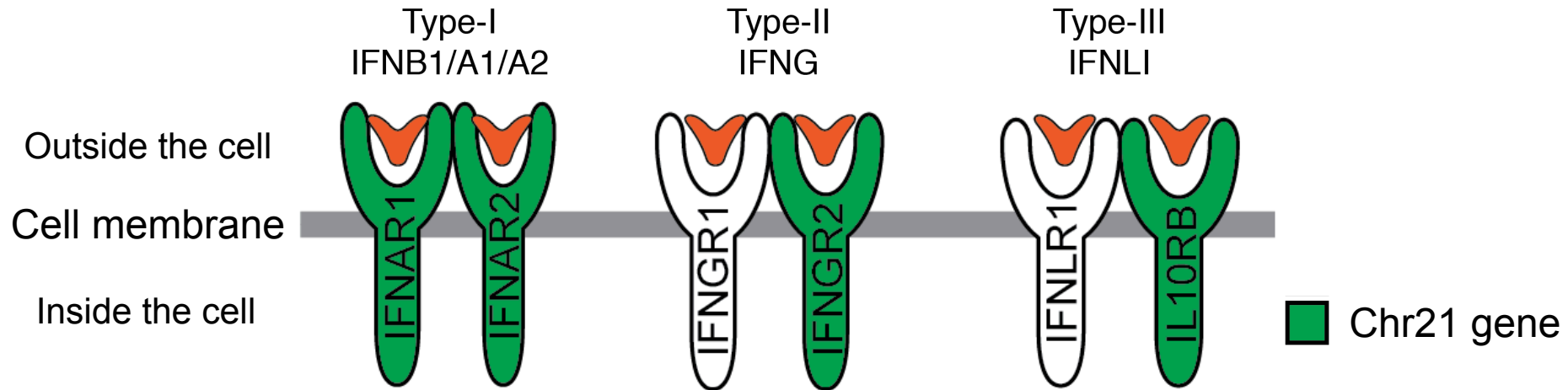
Everywhere we look, it is clear that trisomy 21 causes increased Interferon signaling

What is the Interferon response?

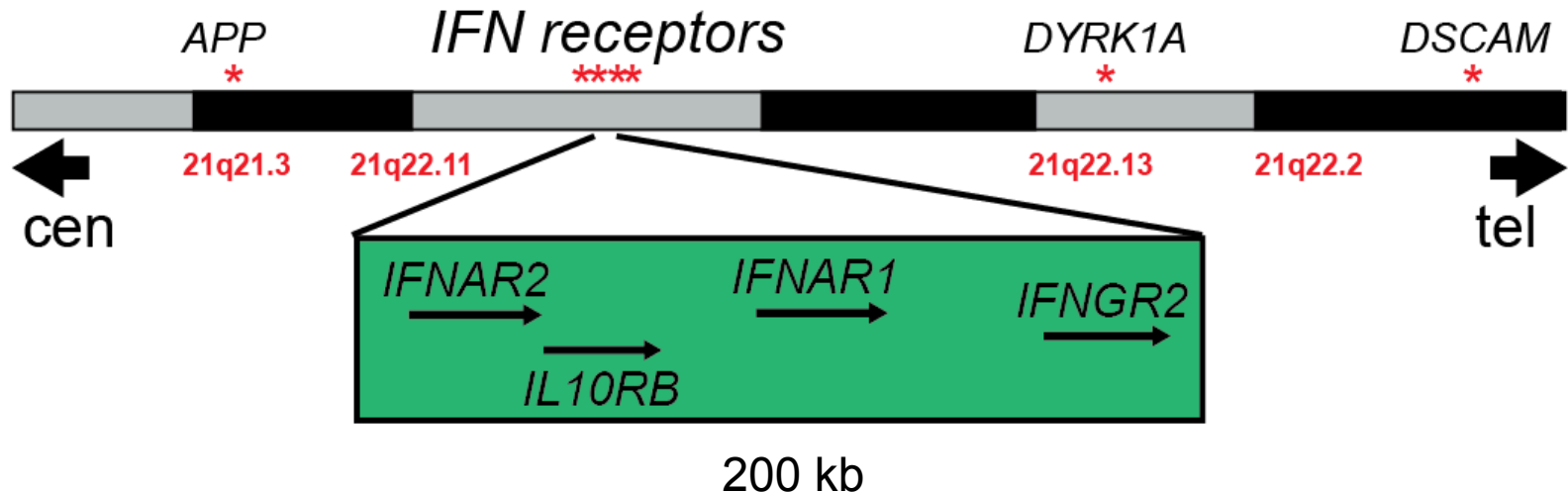


- Interferon signaling is an important part of the immune system involved in the anti-viral defense
- Interferon activates many different types of immune cells, **including killer T cells!**

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



Human chromosome 21



Implications:

Cells from people with Down syndrome, including their killer T cells, are 'hypersensitive' to Interferons.

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

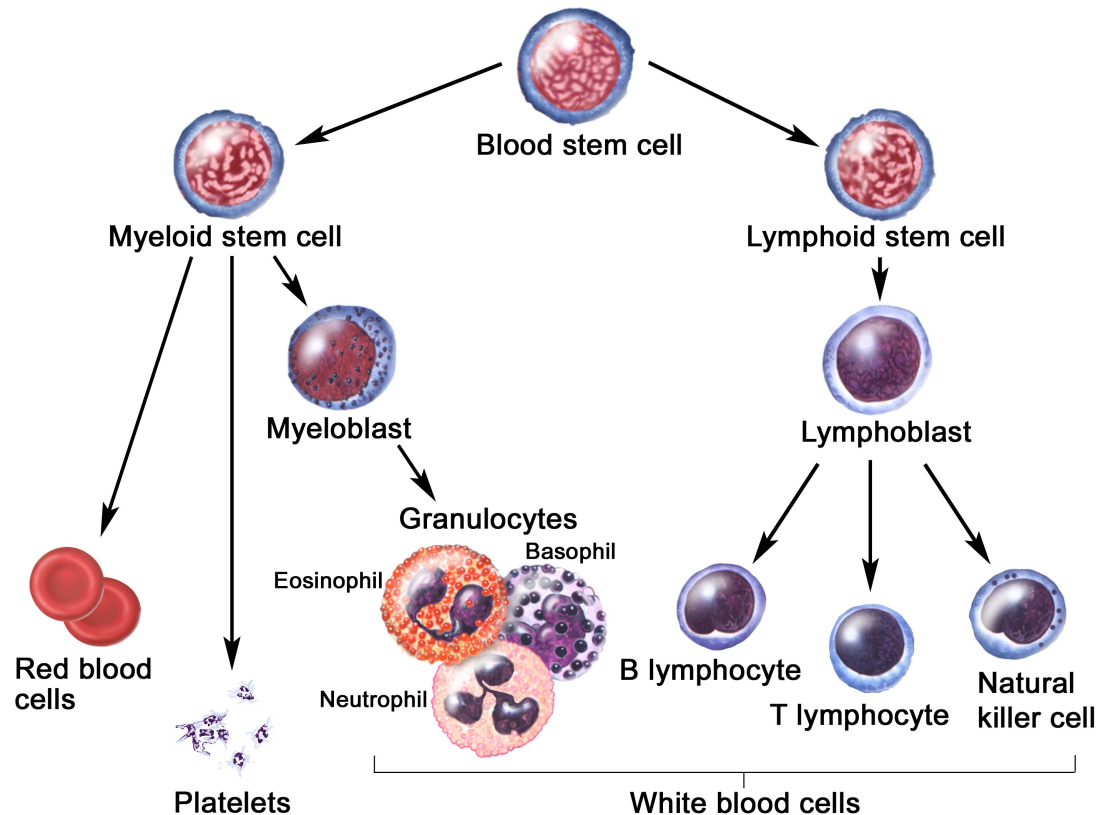
This 'super-charged' state may have both beneficial and harmful effects.

Some aspects of the immune system may be stronger (e.g. anti-viral and anti-tumoral defenses), other aspects would be exhausted (antibacterial defenses).



How about leukemias?

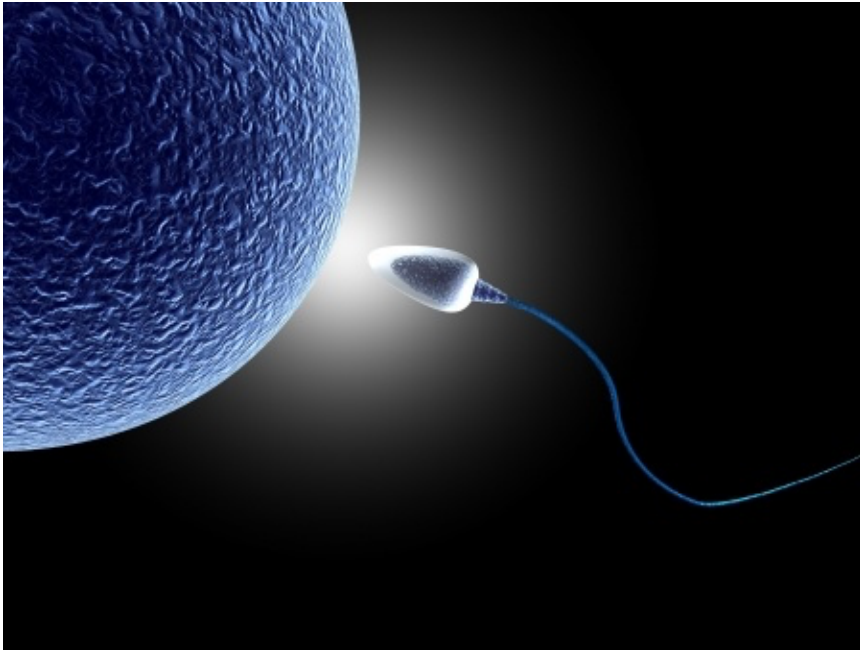
Leukemias are 'cancers' of the immune system, whereby immune cells proliferate out of control and stop doing their normal jobs.



Interferon is a potent regulator of immune cell proliferation and specialization

How about testicular cancer?

The testes are 'immune privileged' tissues,
killer T cells are not allowed in there!



Sperm cells carry 'novel' genetic material, and killer T cells would wipe them out if they could get inside the testes

Can drugs that block the Interferon response cure some of the autoimmune conditions 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

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.

The Increased Risk of Leukemia in Children with Down syndrome

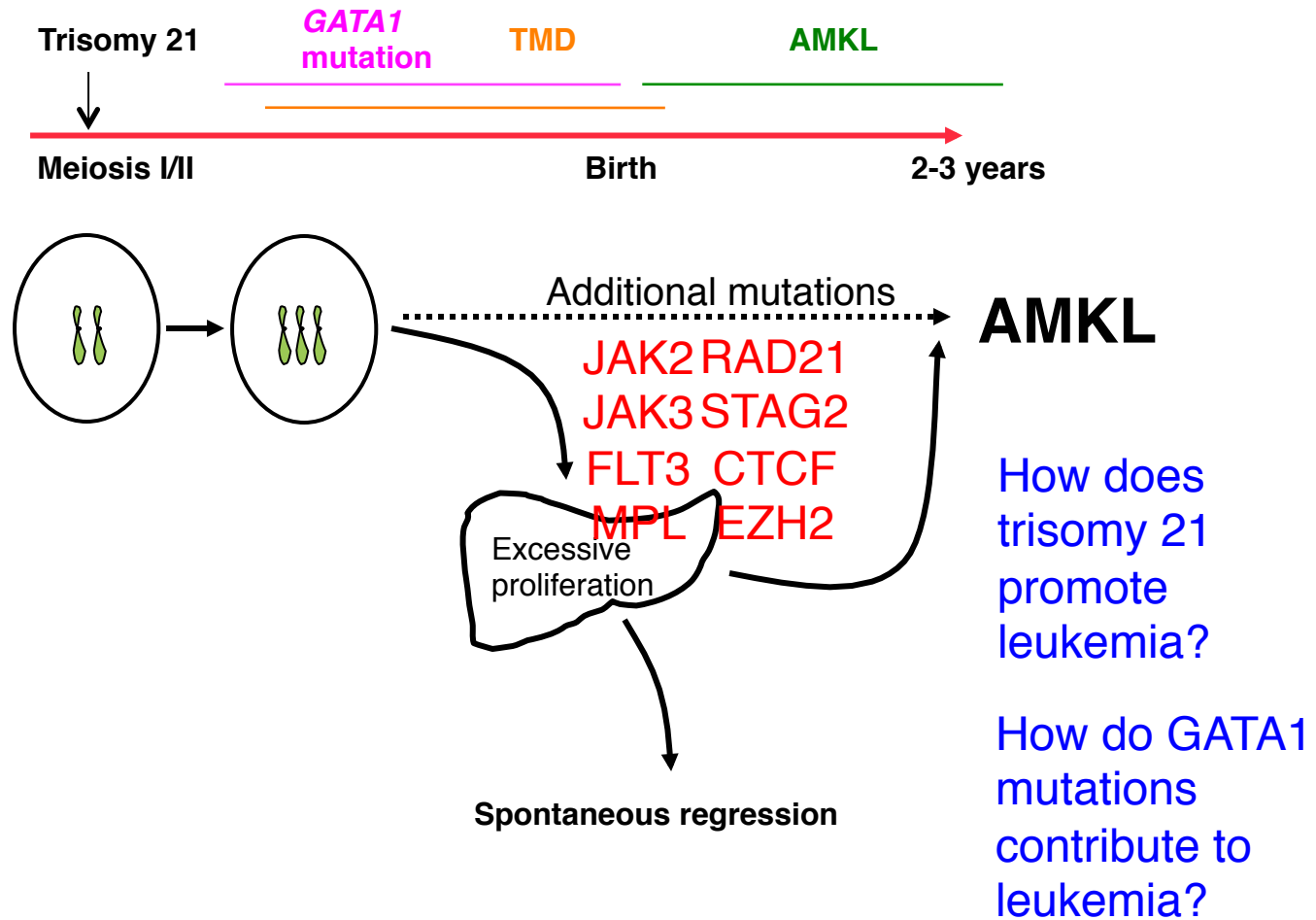
John Crispino, PhD
Northwestern University

Blood disorders in children with Down syndrome

- Uniquely susceptible to **Transient Myeloproliferative Disorder** (at birth; incidence is as high as 30%)
- >150-fold increased risk of **Acute Megakaryoblastic Leukemia** (AMKL), a rare form of myeloid leukemia (ages 1-5)
- 20-fold increased risk of **B-cell Acute Lymphoblastic Leukemia** (ALL), a common childhood leukemia (primarily ages 5 to 20)

Acute Myeloid Leukemia (AML) in DS

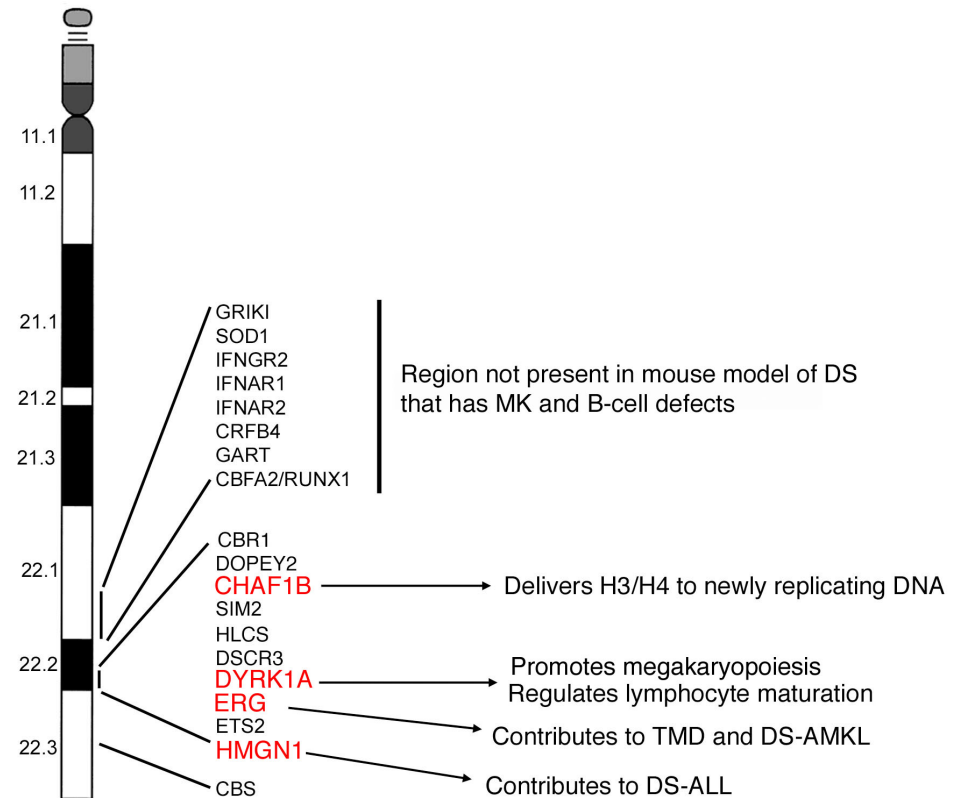
- The most common type is acute megakaryoblastic leukemia
- There is >150-fold increased incidence of AMKL in children with DS
- Many studies report better outcomes for AMKL patients with DS due to the unique genetic features of the leukemia
- Nevertheless, not all children survive the disease: Survival rates for those who relapse are dismal, even after bone marrow transplant



Acute Lymphoblastic Leukemia (ALL) in DS

- B-ALL is the most common form of childhood cancer
- There is a 20 fold increased incidence of B-ALL in children with DS
- Many studies report inferior outcome for DS-ALL patients due to increased relapse rate and higher treatment related mortality
- Children suffer many severe side effects from the three year course of therapy

Candidate leukemia promoting genes on chromosome 21



HMGN1: Lane et al, *Nature Genetics*, 2014

DYRK1A: Malinge et al, *JCI* 2012; Thompson et al, *JEM* 2015

ERG: Stankiewicz et al, *Leukemia* 2009; Rainis et al *Blood* 2005; Ng et al *Blood* 2010; Salek-Ardakani et al, *Cancer Res* 2009

More research is needed!

- We desperately need less toxic and more effective therapies, especially to prevent relapse and treatment related mortality
- Research should focus on the following:
 - Determining the reason why trisomy 21 leads to the increased incidence of leukemia
 - Identifying novel drug targets that will lead to development of safer treatments
 - Leveraging new technologies such as CRISPR to perform comprehensive studies that will identify specific genes that promote the development of leukemia

Impact of research on leukemia in children with DS

- Research into the mechanisms of leukemogenesis in children with DS impacts all Americans:
 - It directly benefits children with DS
 - Many leukemias in typical people are characterized by acquisition of chromosome 21 or increased expression of genes in that location
 - Platforms designed to identify the genes that promote leukemia will also enable studies to find the genes that protect people with DS from solid tumors
 - This, in turn, may lead to the development of novel cancer prevention strategies

Strategies to achieve these research goals

- Support the current group of researchers who are pursuing this area of research
- Entice cancer researchers not in the field to expand their scope to include leukemia in children with DS
- Fund a large scale initiative to perform unbiased high throughput screens to identify genes on chromosome 21 that promote leukemia and suppress formation of solid tumors



**Joan. D. Morris, M.D.,
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