

Chronic Granulomatous Disease: Latest Management Advances



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Hypergammaglobulinemia Associated with Severe Recurrent and Chronic Nonspecific Infection. DR. CHARLES A. JANEWAY, Boston, DR. JOHN CRAIG (by invitation), Boston, DR. MURRAY DAVIDSON (by invitation), New York, DR. WILLIAM DOWNEY (by invitation), New Bedford, Mass., DR. DAVID GITLIN (by invitation), Boston, and Julia C. Sullivan, M.P.H. (by invitation), Boston.

patients who fit the criteria outlined here this morning. The four children we have studied at Minnesota and the three that Dr. Thomas Good has studied at Utah were discovered to have hypergammaglobulinemia and extreme susceptibility to infection while we were searching for patients with agammaglobulinemia.

May 3-5, Buck Hills Pa., 1954

A Fatal Granulomatous Disease of Childhood

The Clinical, Pathological, and Laboratory Features of a New Syndrome

ROBERT A. BRIDGES, M.D.; HEINZ BERENDES, M.D., and ROBERT A. GOOD, M.D., Ph.D., Minneapolis

CGD Timeline

Genetics ~10 years (both X and AR)

General mechanism ~12 years

Diagnostic test (and renaming) ~13 years

Positional cloning 32 years

Current diagnostic test (DHR) 41 years

At 70 years...

We know a lot about CGD

Thousands of patients worldwide

Diagnosis is understood

Mechanisms and pathophysiology known

Prophylaxis proven for bacteria and fungi

Transplantation is common and successful

A lot, but not enough

Why *those* infections?

Why does the inflammation happen?

Why does the inflammation persist?

Why does the autoimmunity happen?

What about X-linked carriers?

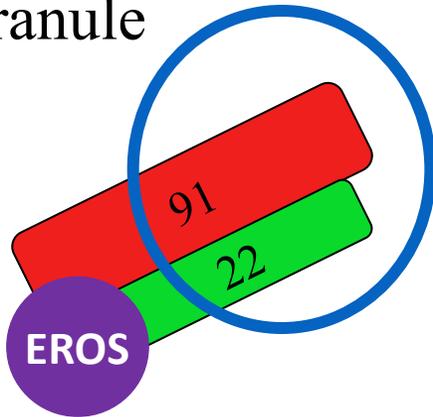
Who should get HSCT or gene therapy?

1°
granule



Cytoplasm

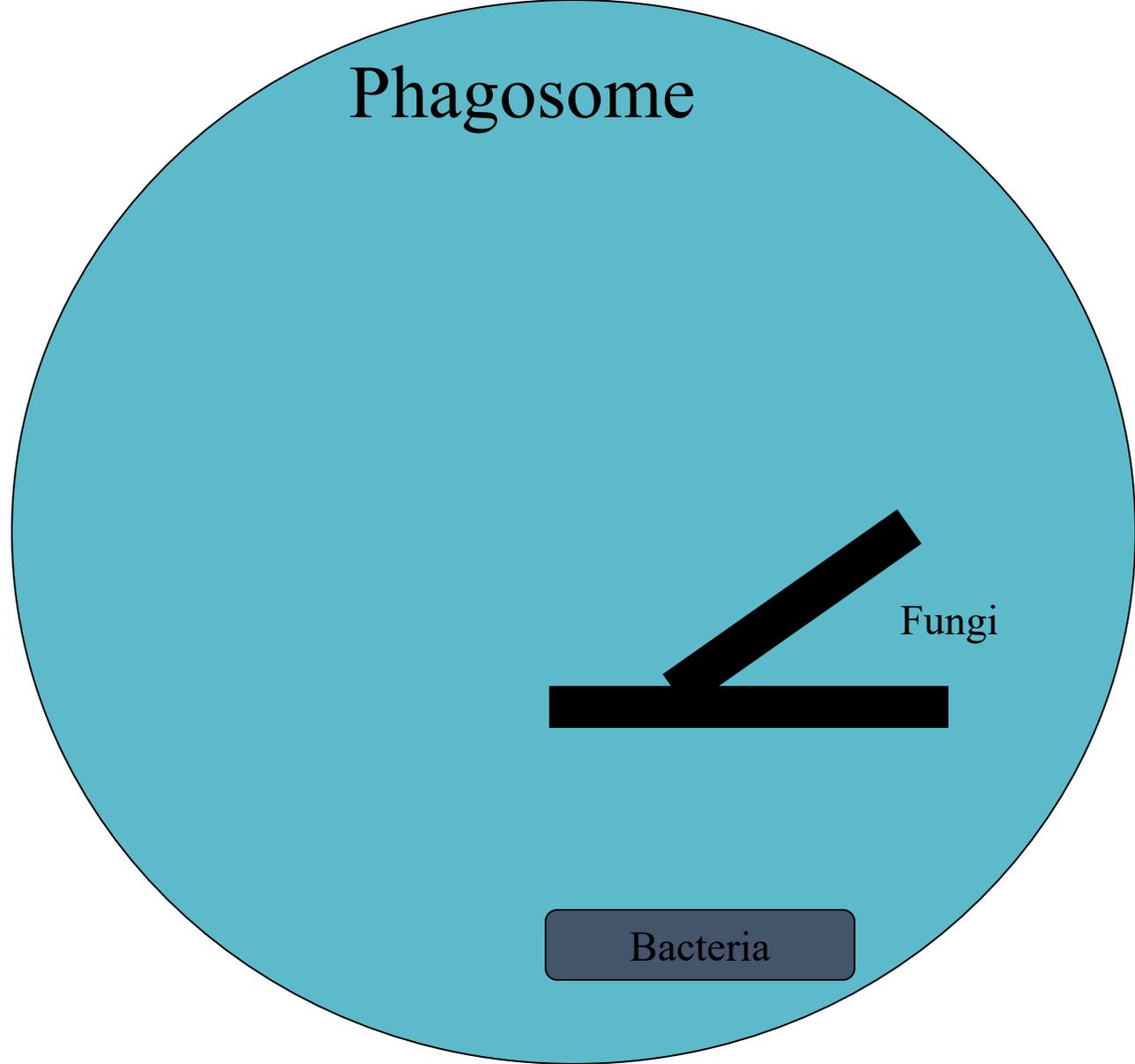
2°
granule



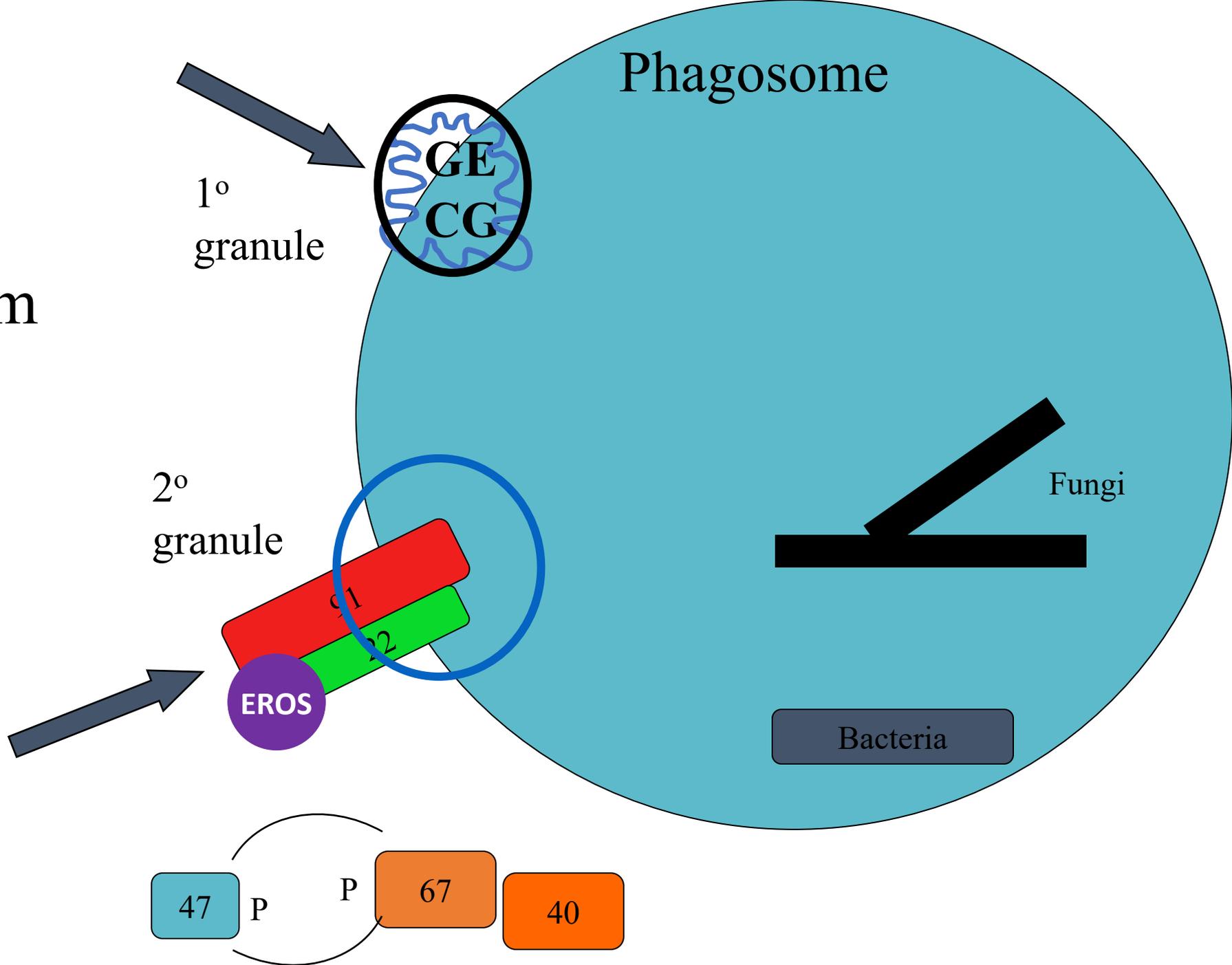
47

67

40



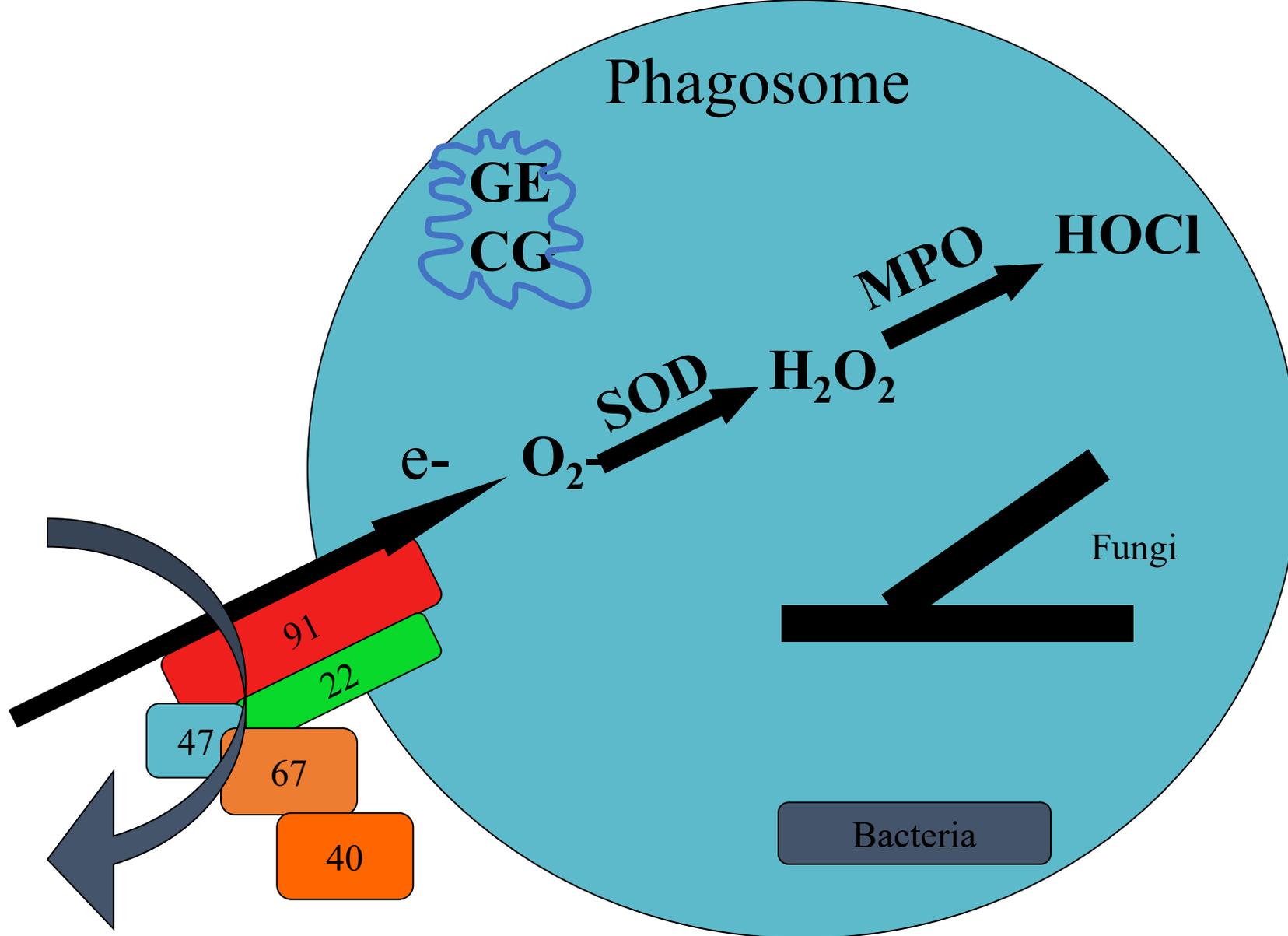
Cytoplasm



Cytoplasm

NADPH

NADP+

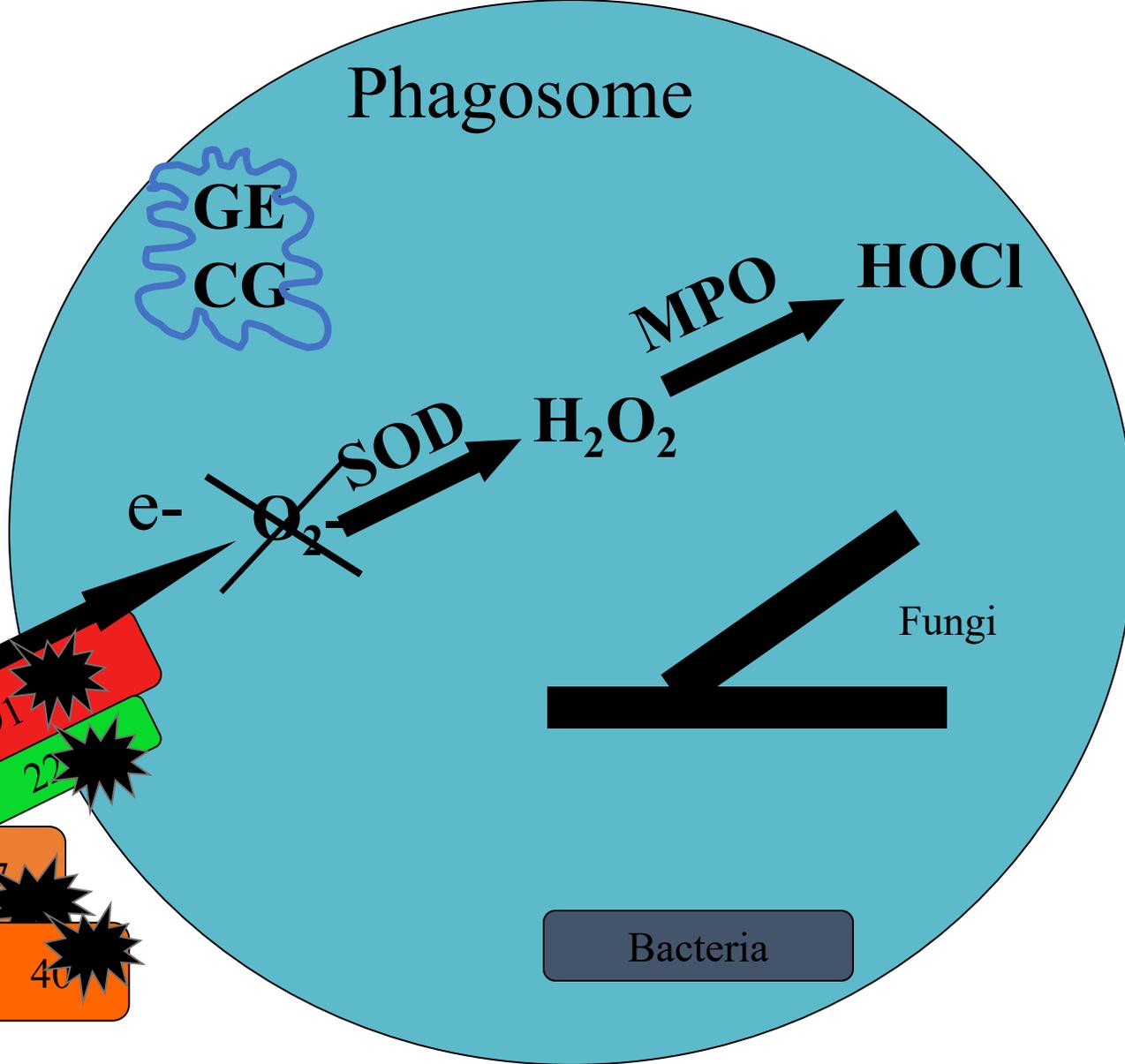
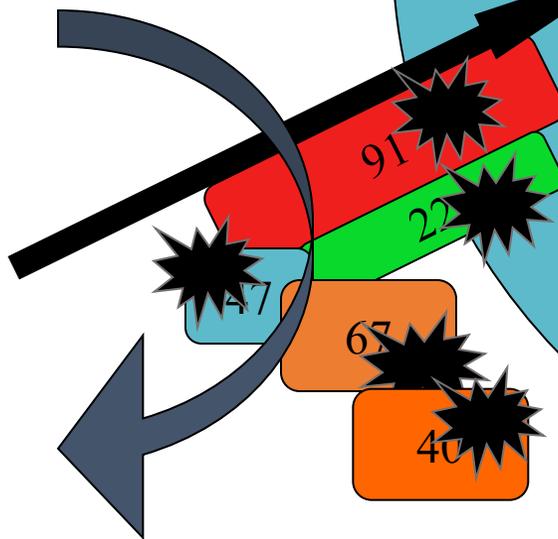


Cytoplasm



NADPH

NADP+



Phagosome

GE
CG

HOCl

MPO

H₂O₂

SOD

e⁻

O₂

Fungi

Bacteria

CGD: One phenotype, 6 genotypes

<u>Gene</u>	<u>chromosome</u>	<u>%</u>
gp91phox	Xp21	65%
<u>Autosomal</u>		
p22phox	16	<5%
p47phox	7	25%
p67phox	1q42	<5%
p40phox	22	29 cases
EROS (<i>CYBC1</i>)	17	4 cases

frequency 1/100,000 - 1/200,000

diagnosis usually in childhood

adult cases recognized, especially autosomal

CGD: ~One phenotype, 6 genotypes

<u>Gene</u>	<u>chromosome</u>	<u>%</u>
gp91phox	Xp21	65%
<u>Autosomal</u>		
	16	<5%
	7	25%
	1q42	<5%
	22	<5% (mostly IBD)
EROS (<i>CYBC1</i>)	17	few cases

frequency 1/100,000 - 1/200,000

diagnosis usually in childhood

adult cases recognized, especially autosomal

Often
missed
WES/WGS

So what are the questions for today?

What should be standard treatment for CGD?

What about the inflammatory bowel disease?

What are the data for HSCT?

What about gene therapy?

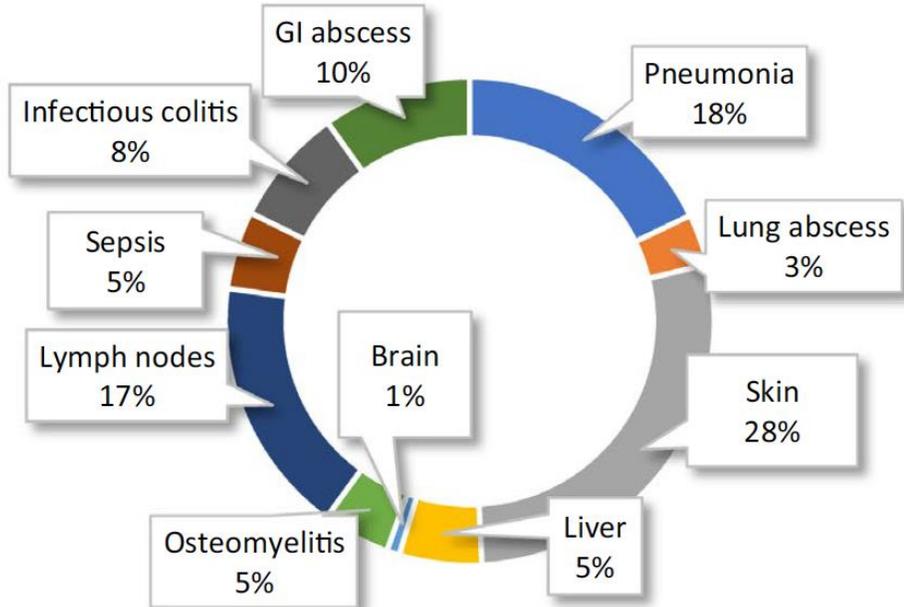
What is coming in the future?

Compiled European Untransplanted CGD Experience

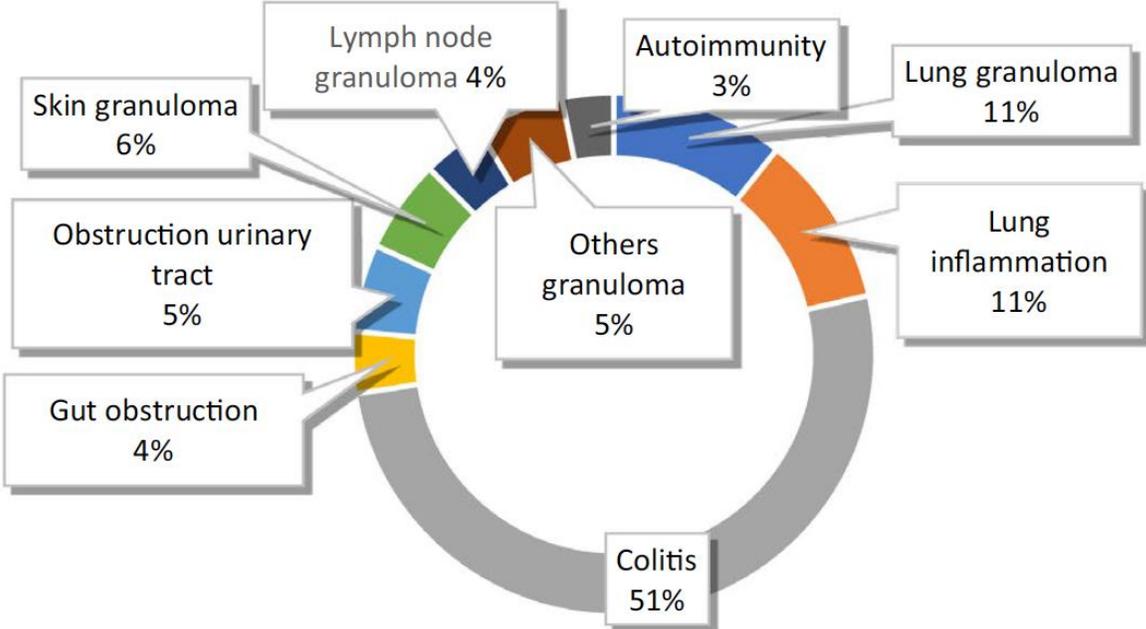
Infections and Inflammation

(n = 104)

(A) Infectious complications on conventional treatment (before/without HSCT) (% of all infections, n = 1045)



(B) Inflammatory complications on conventional treatment (before/without HSCT) (% of all inflammatory complications, n = 627)



Standard Prophylaxis

TMP/SMX

160/800 twice daily

Alternatives:

TMP 100 twice daily; fluoroquinolone; ??

Itraconazole*

200 mg once daily

Alternatives:

posaconazole 300 once daily

voriconazole 250 twice daily (skin issues)

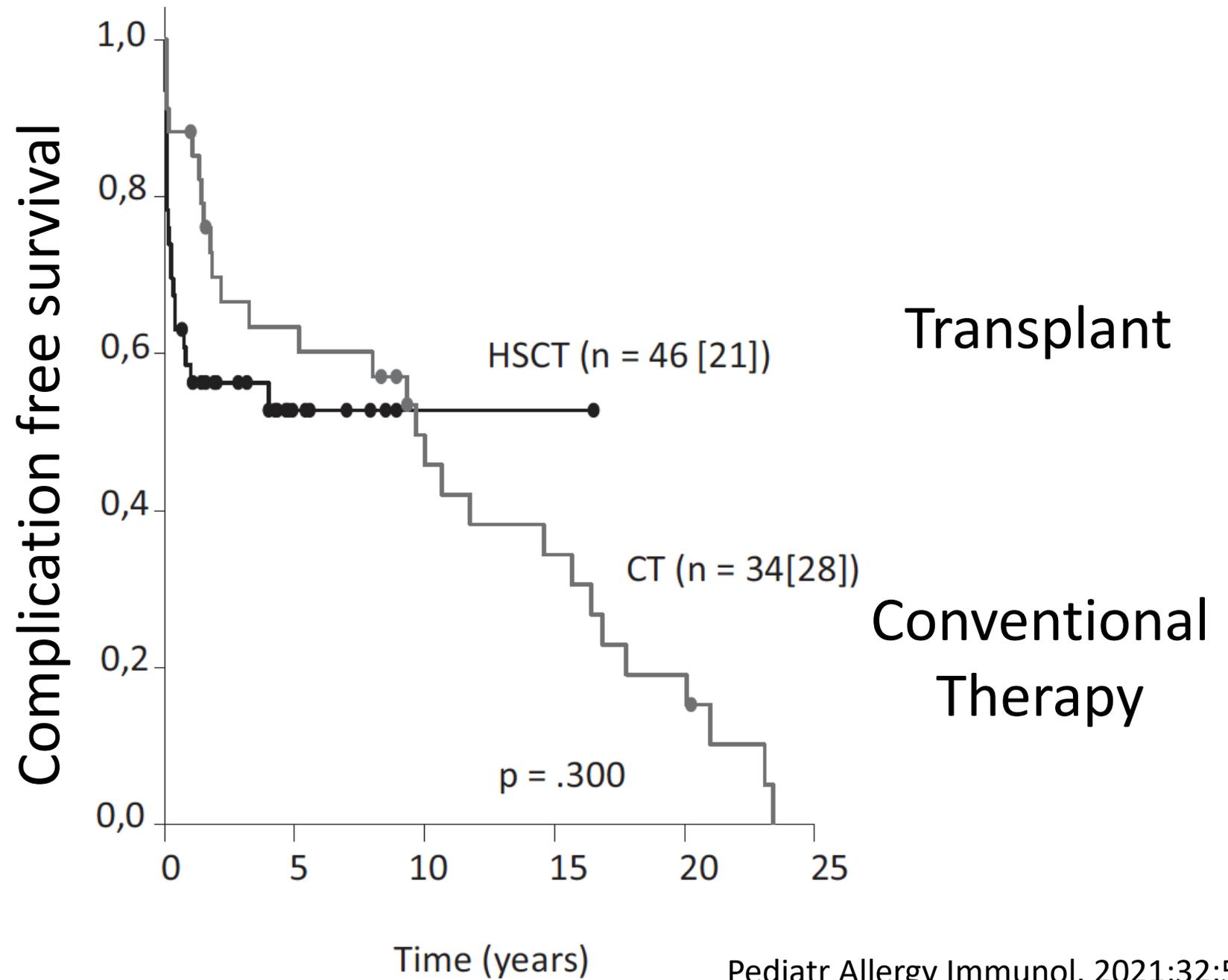
IFN γ *

50 mcg/m² three times weekly

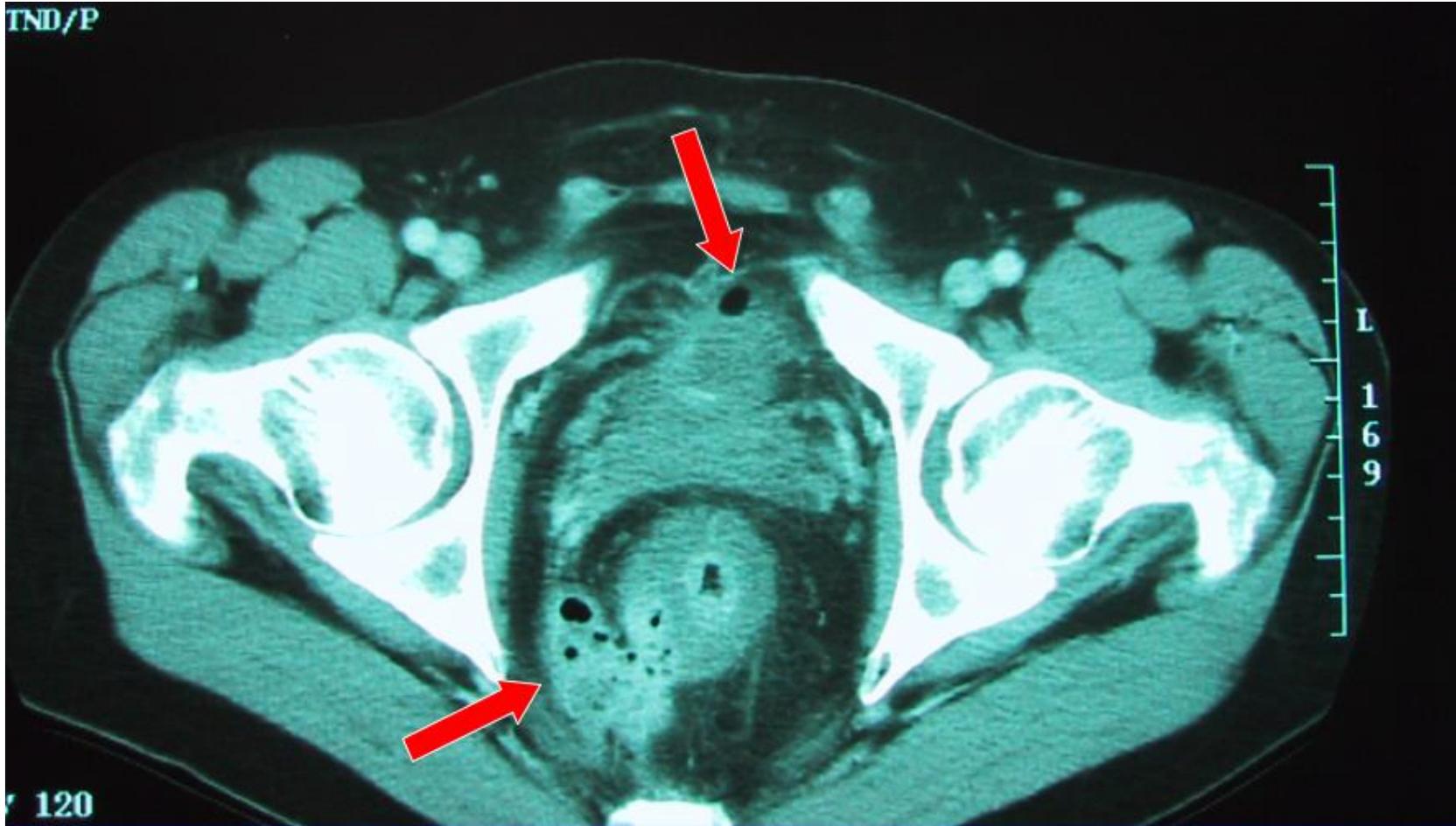
Alternatives:

chocolate?

* Prospective randomized double blind trials



Inflammatory bowel disease



Inflammatory Bowel Disease

~ 50% of patients

No effect on mortality

Usually steroid responsive and often steroid dependent

Often requires immunomodulator: Azathioprine, sulfasalacylic acid

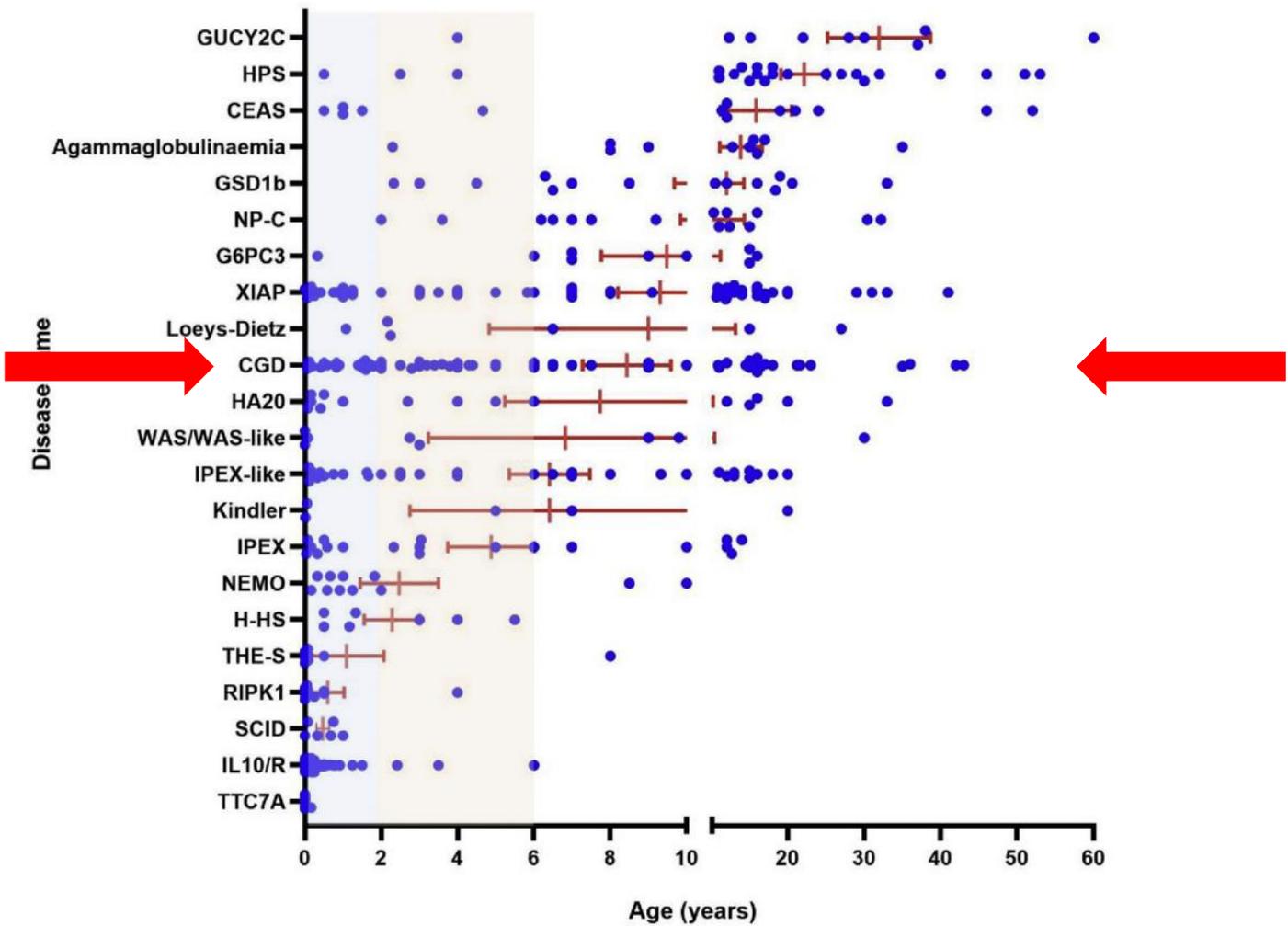
Biologics: TNF blockers, IL12/23 blockers effective but infections

Lymphocyte trafficking: vedolizumab safe but modest effect

Resolves with HSCT

A Systematic Review of Monogenic Inflammatory Bowel Disease

Ryusuke Nambu,^{*,‡,§} Neil Warner,^{*,‡} Daniel J. Mulder,^{*,‡} Daniel Kotlarz,^{||}
 Dermot P. B. McGovern,^{||} Judy Cho,[#] Christoph Klein,^{||} Scott B. Snapper,^{**}
 Anne M. Griffiths,^{*,‡,§} Itaru Iwama,[§] and Aleixo M. Muise^{*,‡,‡‡}



HSCT for CGD

HSCT can be very successful

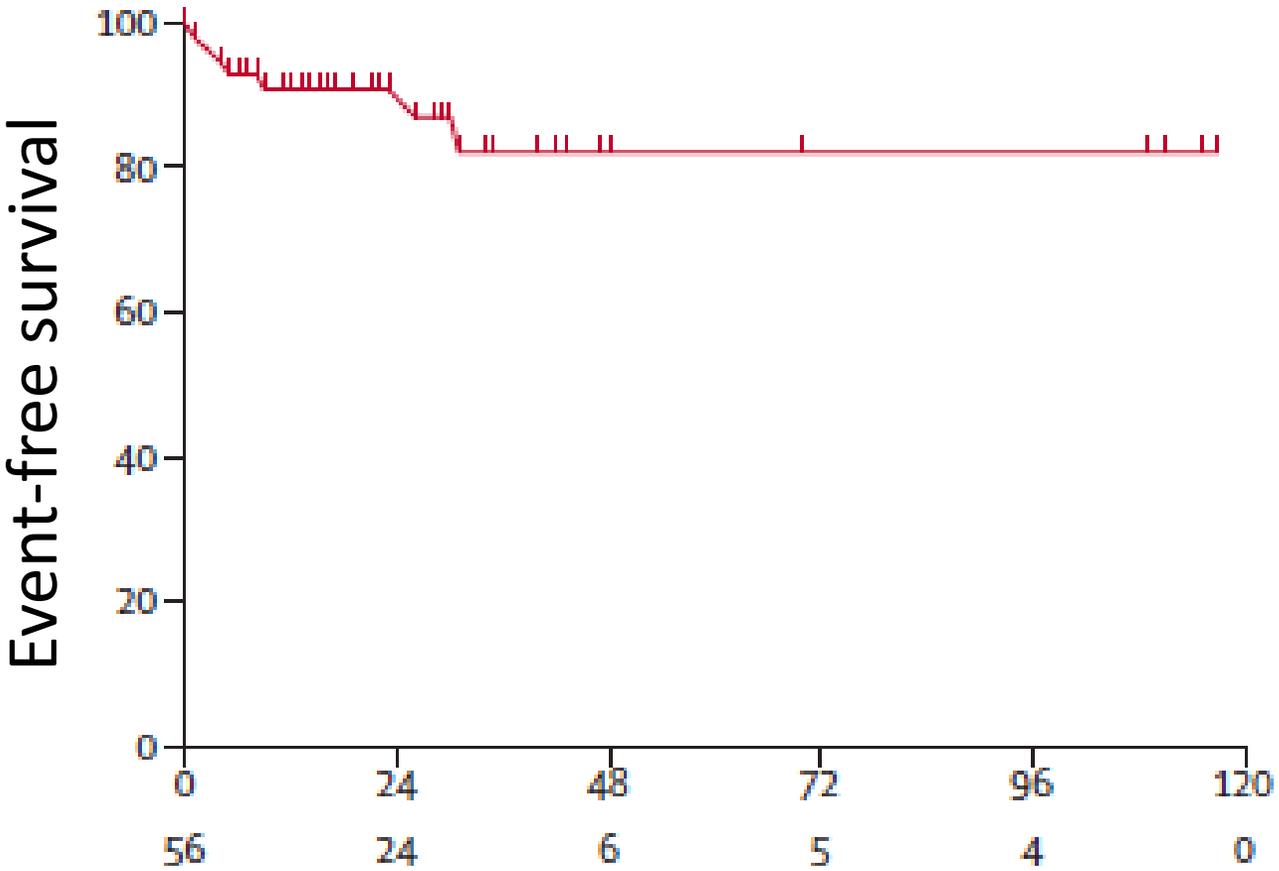
Even with active infection/inflammation

Resolves refractory infections (mostly fungal)

Resolves refractory inflammatory bowel disease

Beware of granulocyte transfusions pre-transplant

Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study



Gungor et al
Flu/bu/sero

Cyclo/tacro
MMF

75% infected/
Inflamed

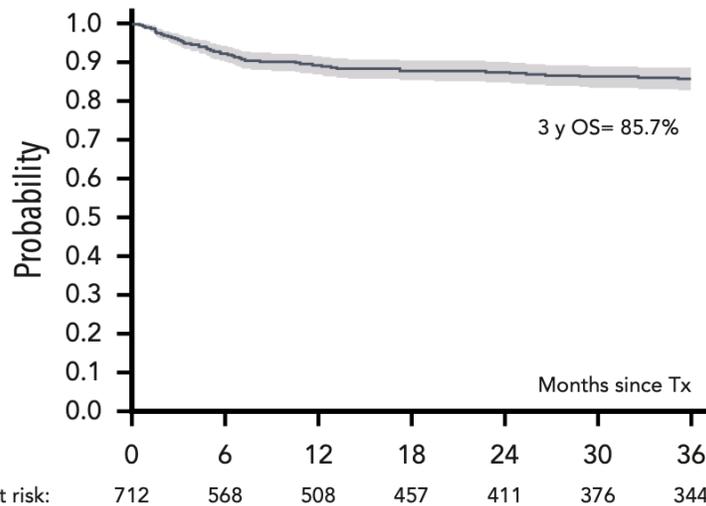
N=56

Hematopoietic cell transplantation in chronic granulomatous disease: a study of 712 children and adults

Robert Chiesa,¹ Junfeng Wang,^{2,3} Henric-Jan Blok,² Sheree Hazelaar,² Benedicte Neven,⁴ Despina Moshous,⁴ Ansgar Schulz,⁵ Manfred Hoenig,⁵ Fabian Hauck,⁶ Amal Al Seraihy,⁷ Jolanta Gozdzik,⁸ Per Ljungman,⁹ Caroline A. Lindemans,^{10,11} Juliana F. Fernandes,^{12,13} Krzysztof Kalwak,¹⁴ Brigitte Strahm,¹⁵ Urs Schanz,¹⁶ Petr Sedlacek,¹⁷ Karl-Walter Sykora,¹⁸ Serap Aksoylar,¹⁹ Franco Locatelli,²⁰ Polina Stepensky,²¹ Robert Wynn,²² Su Han Lum,^{23,24} Marco Zecca,²⁵ Fulvio Porta,²⁶ Mervi Taskinen,²⁷ Brenda Gibson,²⁸ Susanne Matthes,²⁹ Musa Karakukcu,³⁰ Mathias Hauri-Hohl,³¹ Paul Veys,¹ Andrew R. Gennery,^{23,32} Giovanna Lucchini,¹ Matthias Felber,³¹ Michael H. Albert,⁶ Dmitry Balashov,³³ Arjan Lankester,²⁴ Tayfun Güngör,^{31,*} and Mary A. Slatter,^{23,32,*} for the EBMT Inborn Errors Working Party

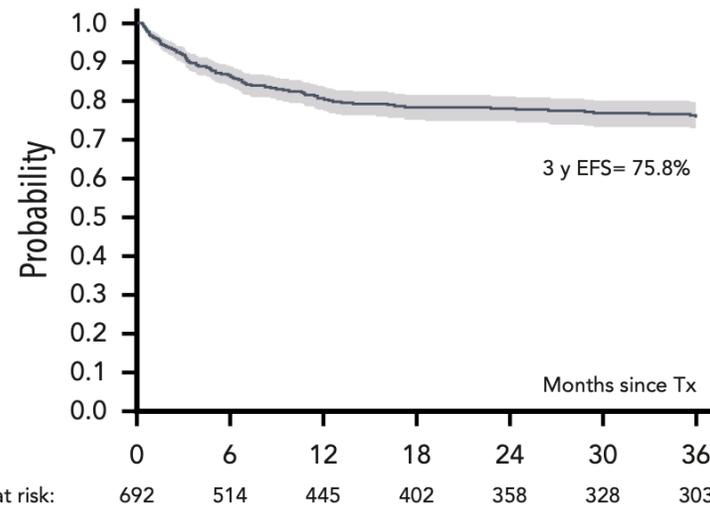
A

Overall Survival



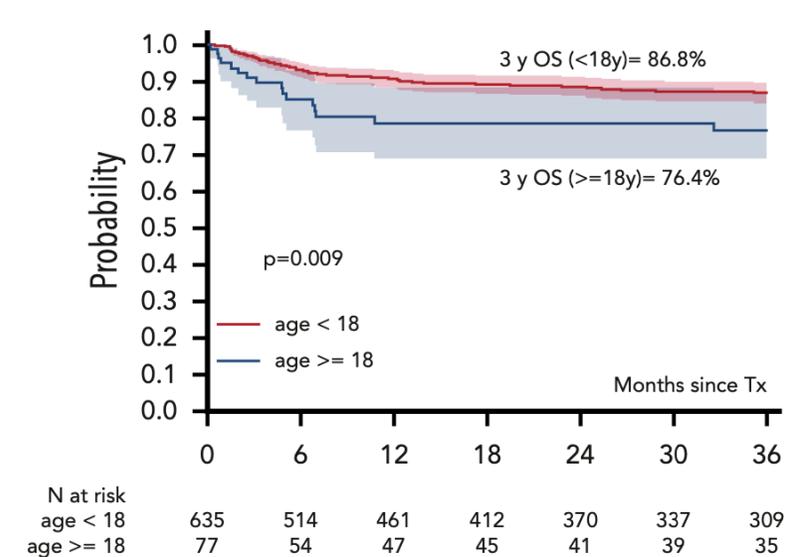
B

Event-free Survival



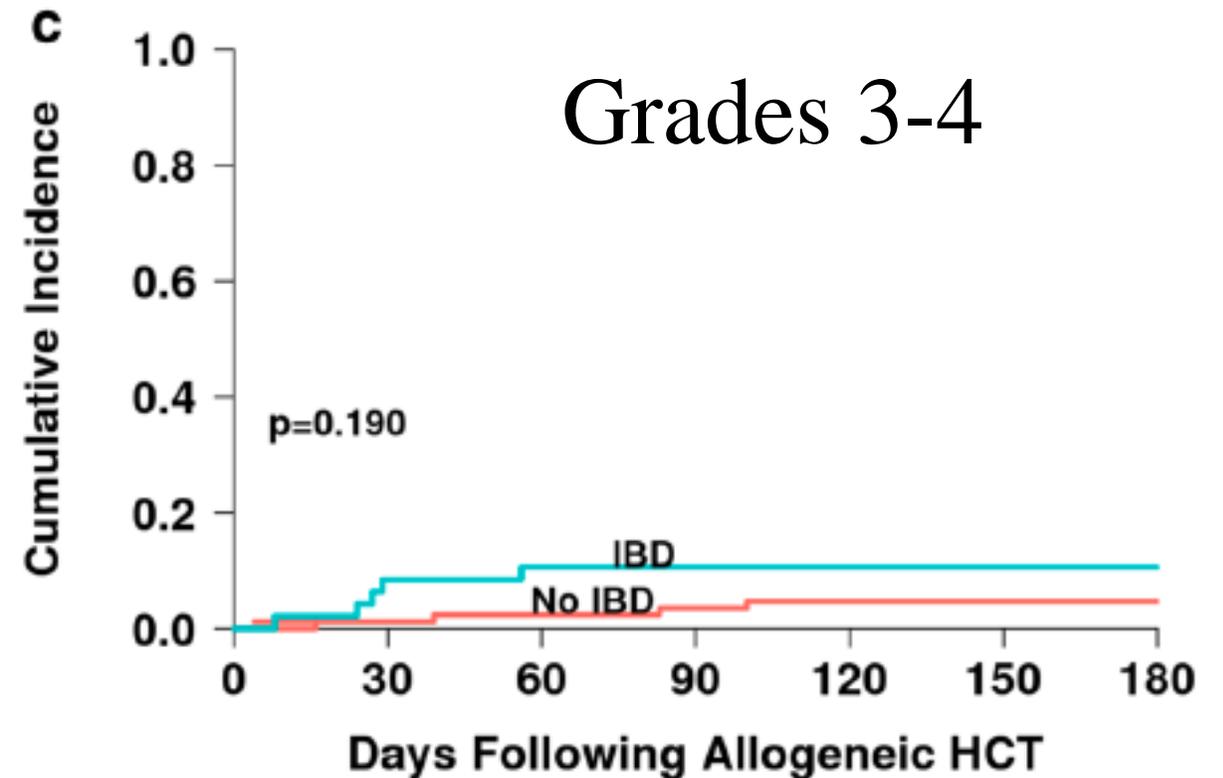
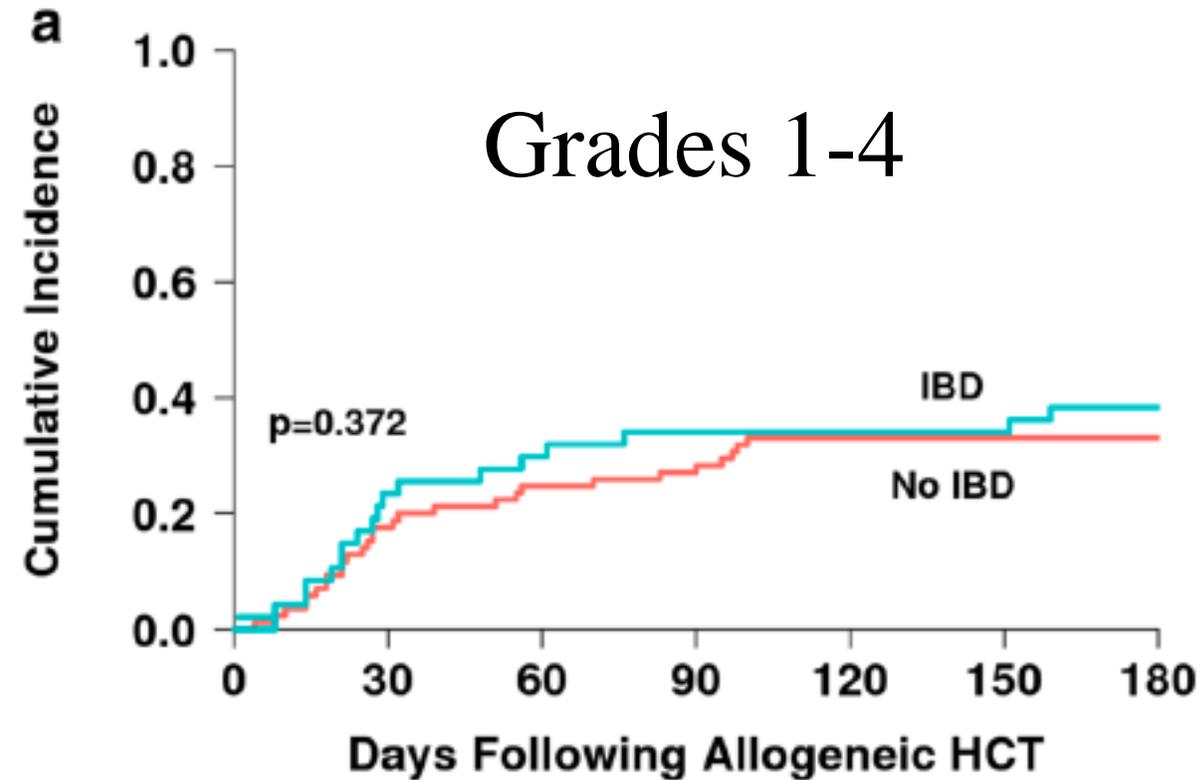
C

Overall Survival by Age

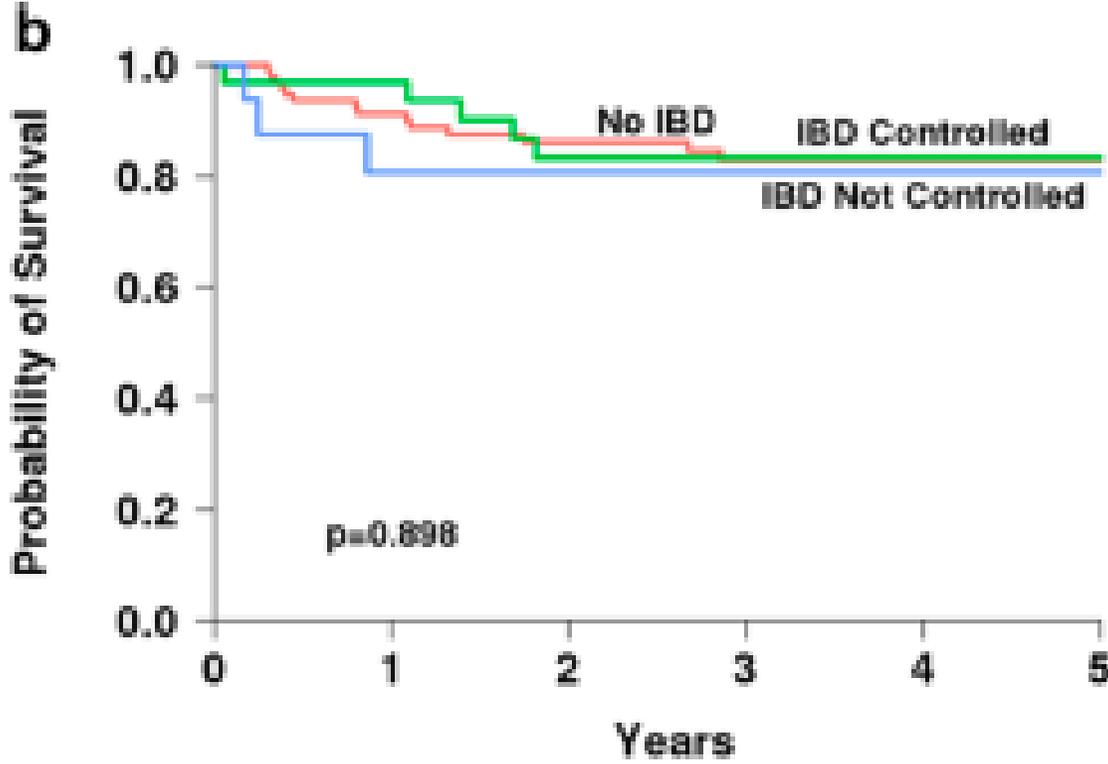
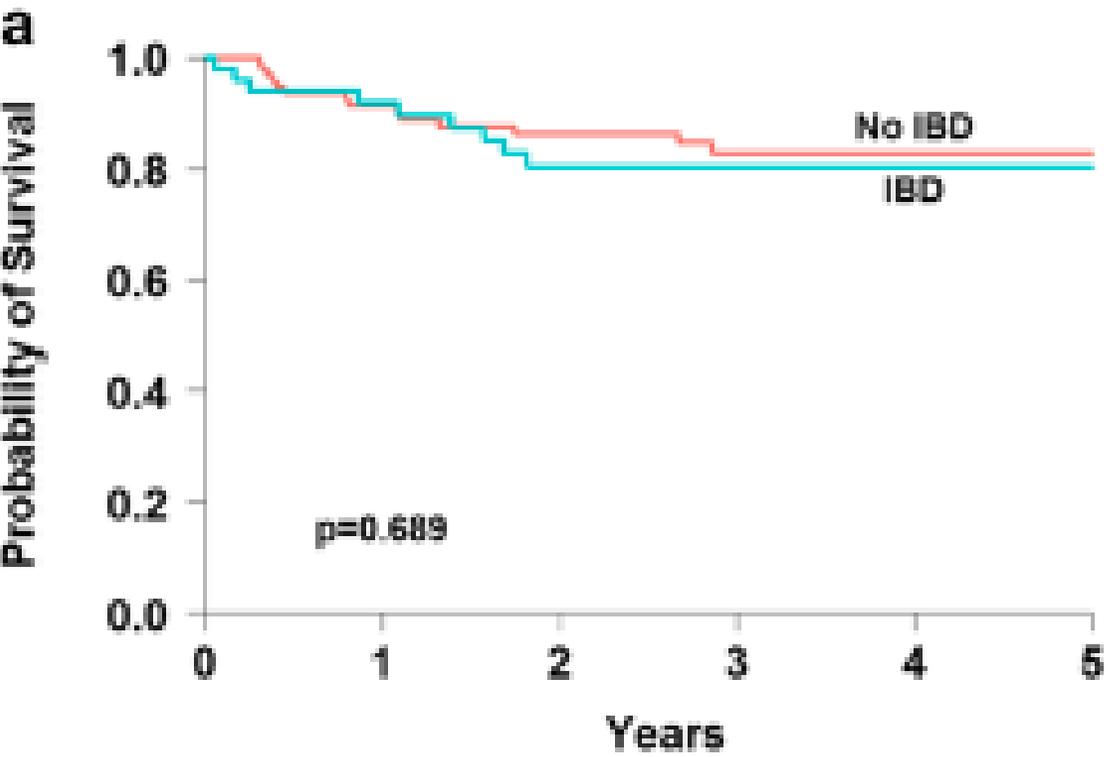


Chronic Granulomatous Disease-Associated IBD Resolves and Does Not Adversely Impact Survival Following Allogeneic HCT

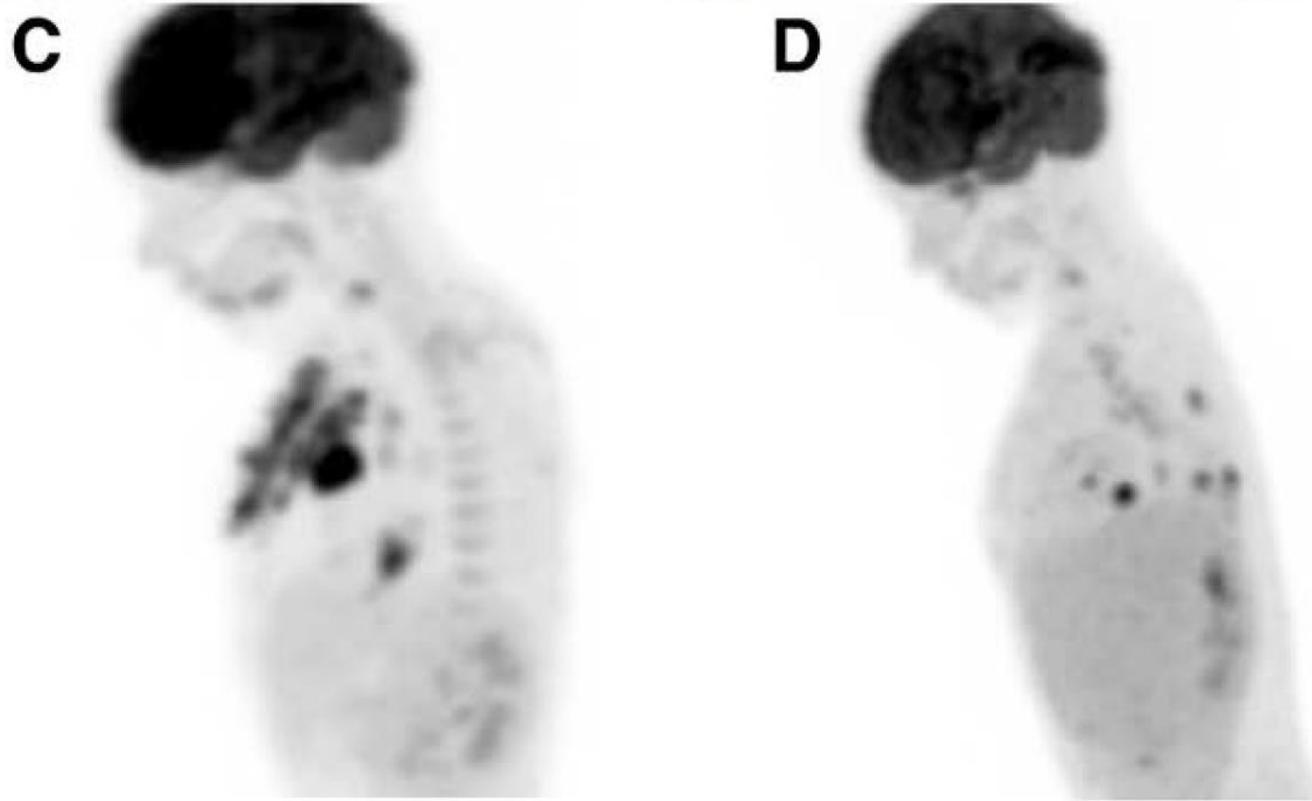
Risk of acute GVHD



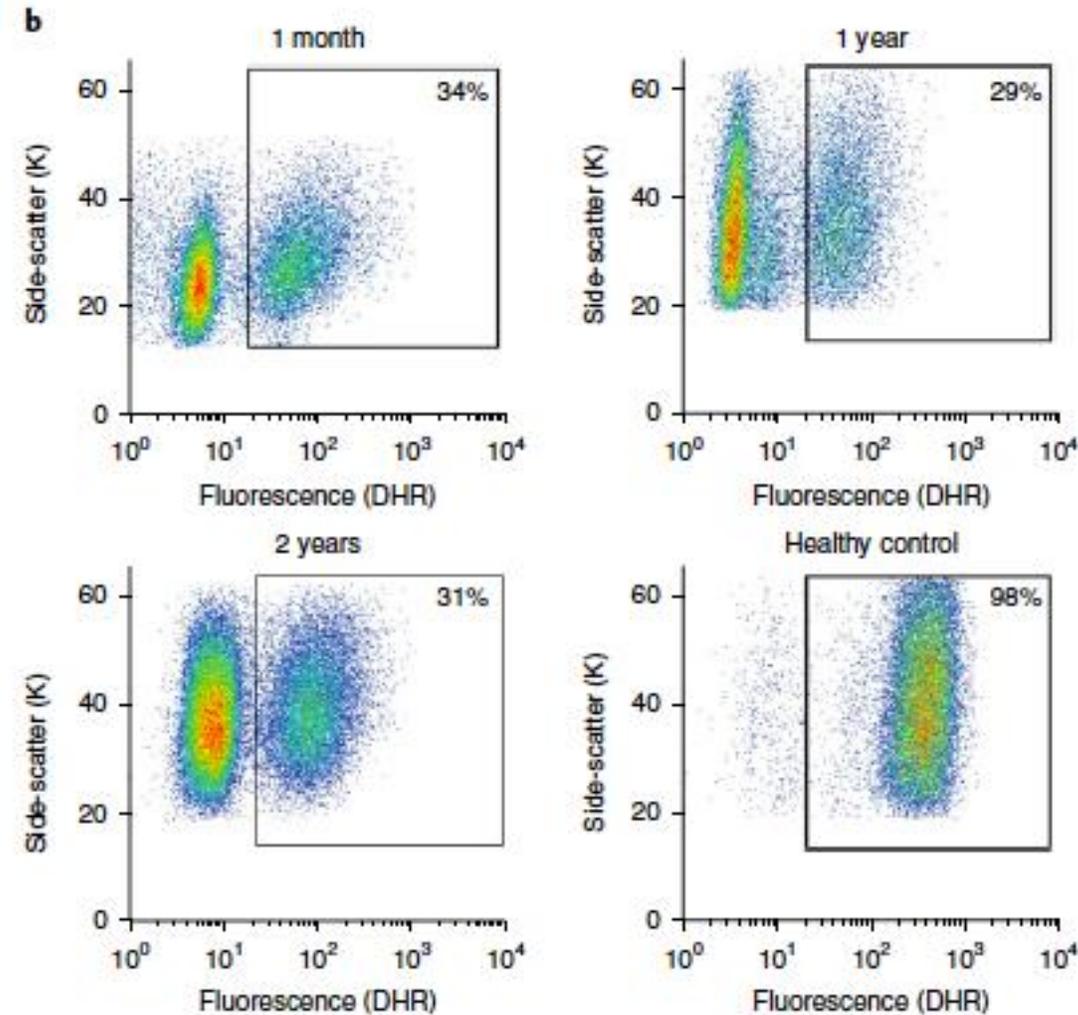
Effect of IBD on Overall HSCT Outcome

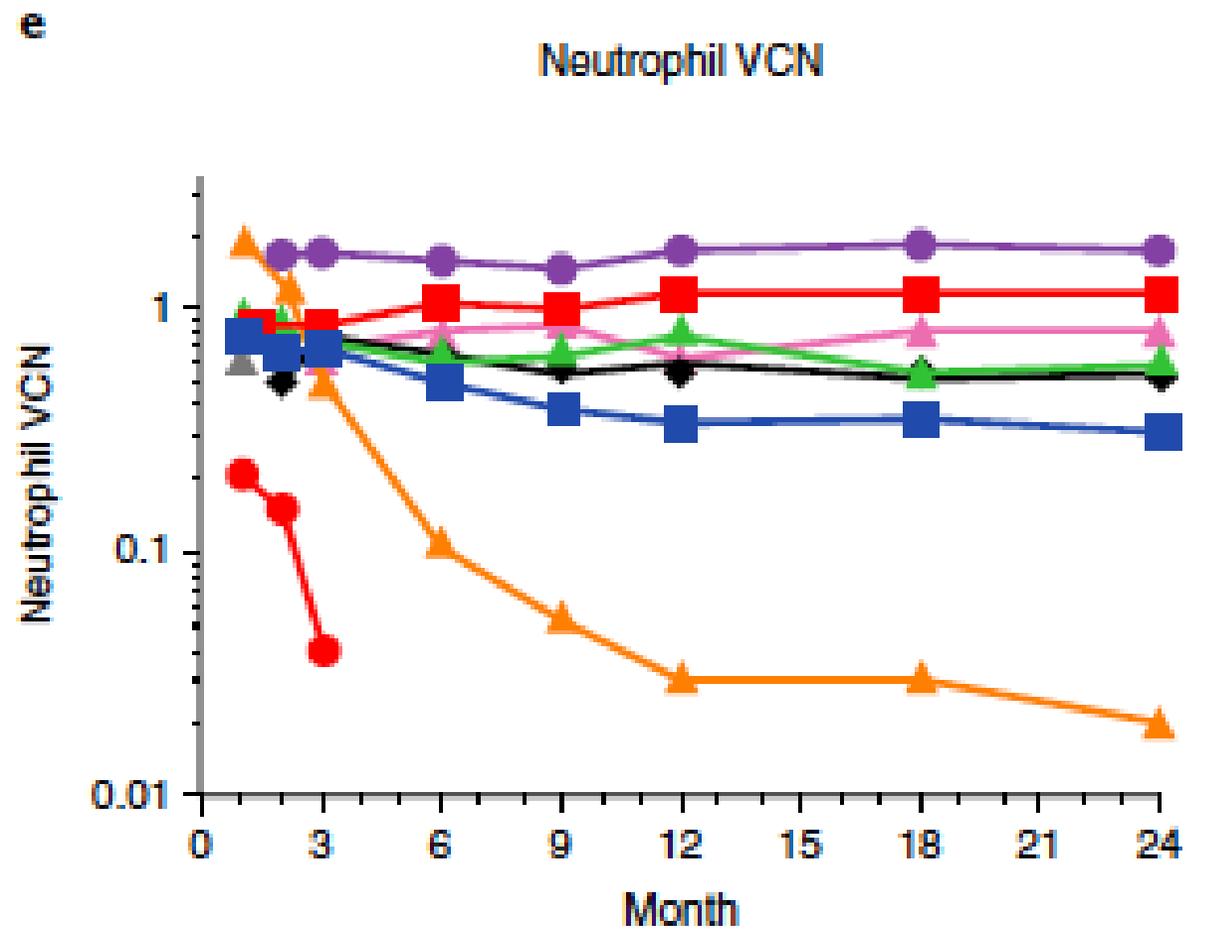
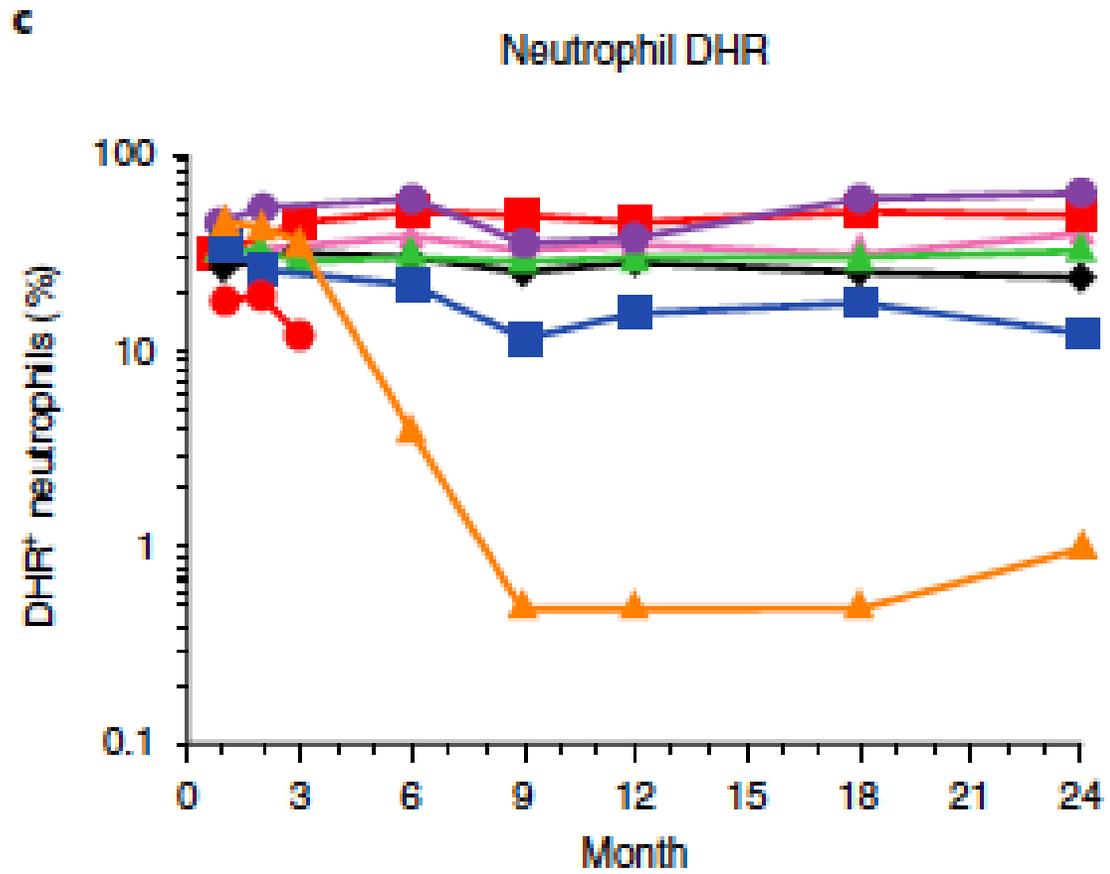


Hematopoietic Stem Cell Transplantation Cures Therapy-refractory Aspergillosis in Chronic Granulomatous Disease



Lentiviral gene therapy for X-linked chronic granulomatous disease





9 Patients
 2 early Deaths
 1 loss of DHR/VCN

XCGD-N104: Chronic *Inocutis* (*Phellinus*) pneumonia



GTX

6 months post



Gene Therapy for CGD

GTX can be successful

Even with active infection/inflammation

Resolves refractory infections (mostly fungal)

May resolve inflammatory bowel disease

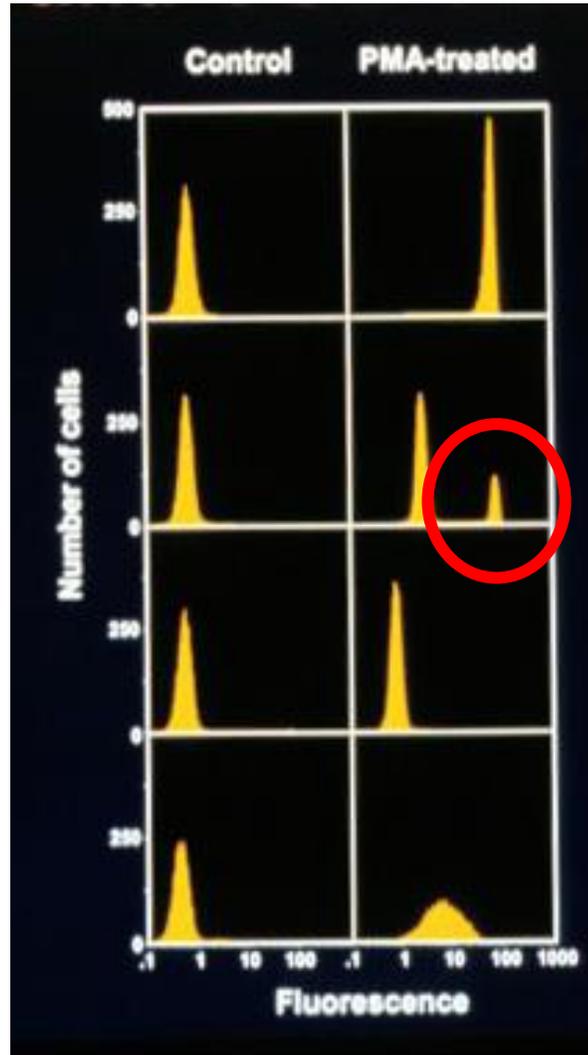
Dihydrorhodamine oxidation (DHR)

Normal

X-carrier

X-CGD

p47^{phox}



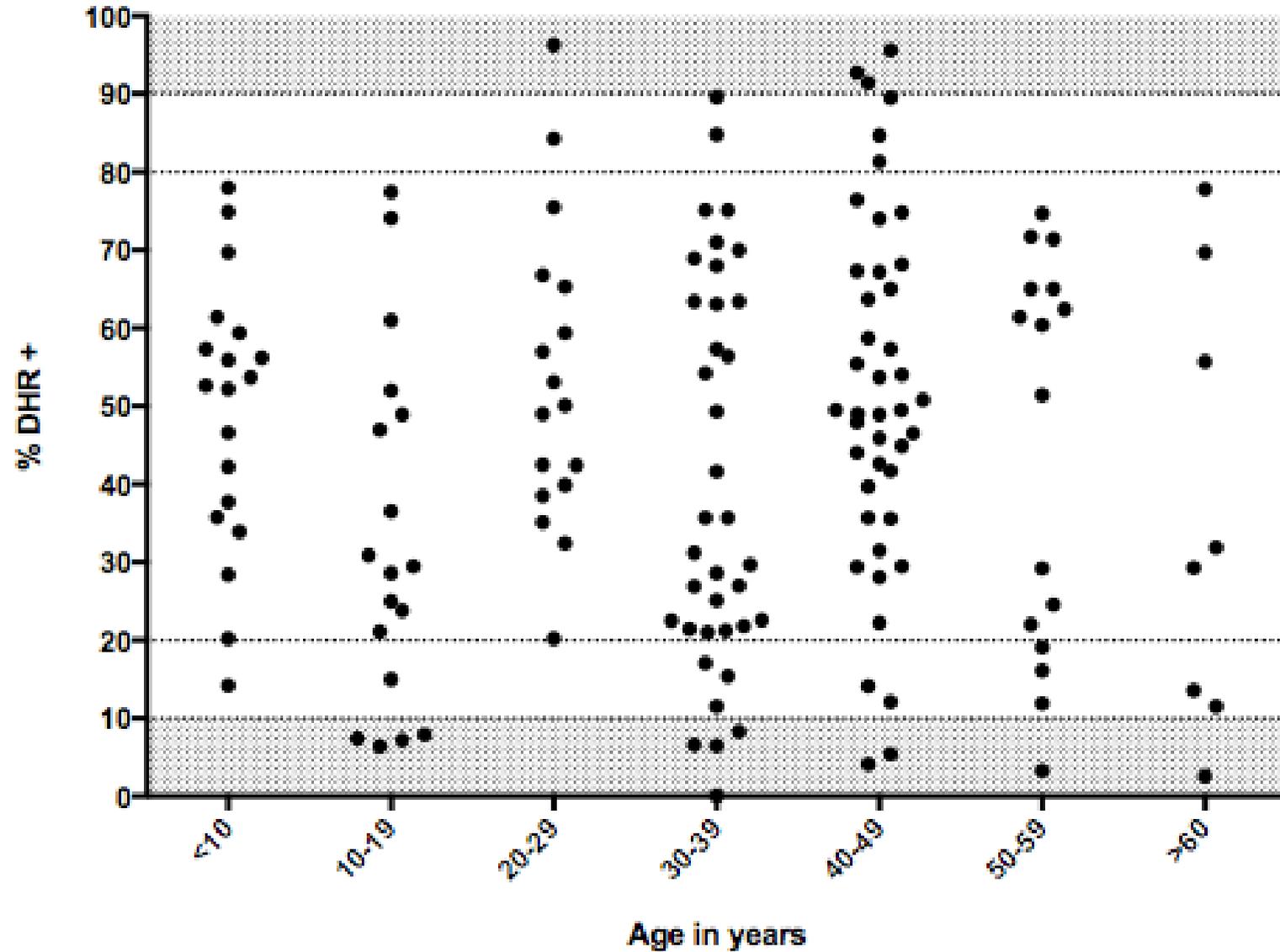
Wild type

10% DHR+

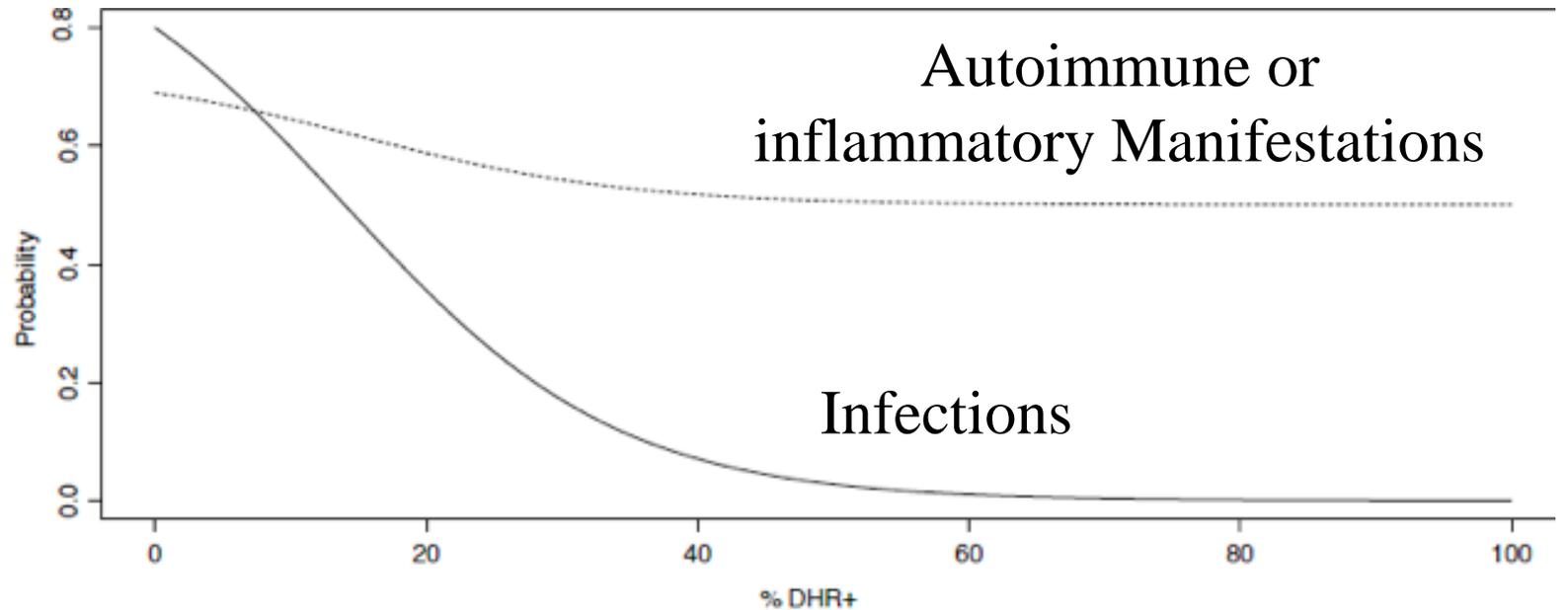
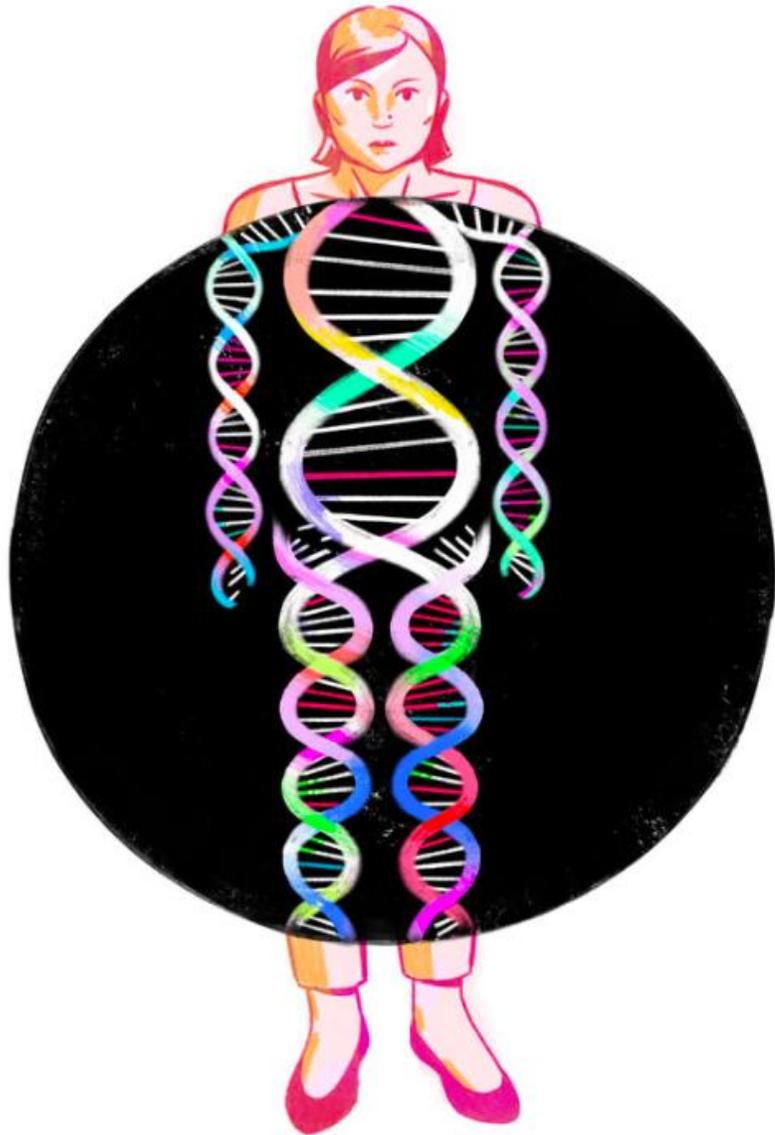
X gp91⁻

AR *p47^{-/-}*

Distribution of %DHR+ by Age



What about X-linked carriers? They have trouble too



CGD-like infections happen as the % +DHR falls below ~30%
Autoimmune or inflammatory complications are unaffected by % +DHR

What is coming for CGD?

Jak inhibitors for inflammatory complications

Microbiome studies for inflammatory bowel disease

New antifungals

Base editing for gene repair (instead of gene replacement)

New forms of HSCT that might spare fertility



Andrea Gressani



John I. Gallin