Chronic Granulomatous Disease: Still Teaching After All These Years

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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

1959

FATAL GRANULOMATOUS DISEASE OF CHILDHOOD

An Inborn Abnormality of Phagocytic Function

BEULAH HOLMES
M.S. Washington
RESEARCH FELLOW, DEPARTMENT OF MICROBIOLOGY,
UNIVERSITY OF MINNESOTA

PAUL G. QUIE
M.D. Yale
JOHN AND MARY R. MARKLE SCHOLAR IN ACADEMIC
CAREER DEVELOPMENT AWARDEE, NATIONAL INSTITUT
AND INFECTIOUS DISEASES

DOROTHY B. WINDHORST
M.D. Chicago
SPECIAL FELLOW,
NATIONAL INSTITUTE OF ARTHRITIS AND METABOL

ROBERT A. GOOD
Ph.D., M.D. Minnesota
AMERICAN LEGION MEMORIAL HEART RESEARCH
OF PEDIATRICS AND MICROBIOLOGY

From the Pediatric Research Laboratories of the
Heart Hospital, the Departments of Pediatrics and
and the Division of Dermatology, University o

The Lancet · Saturday 4 June 1966

Impaired
Staphylococcal killing

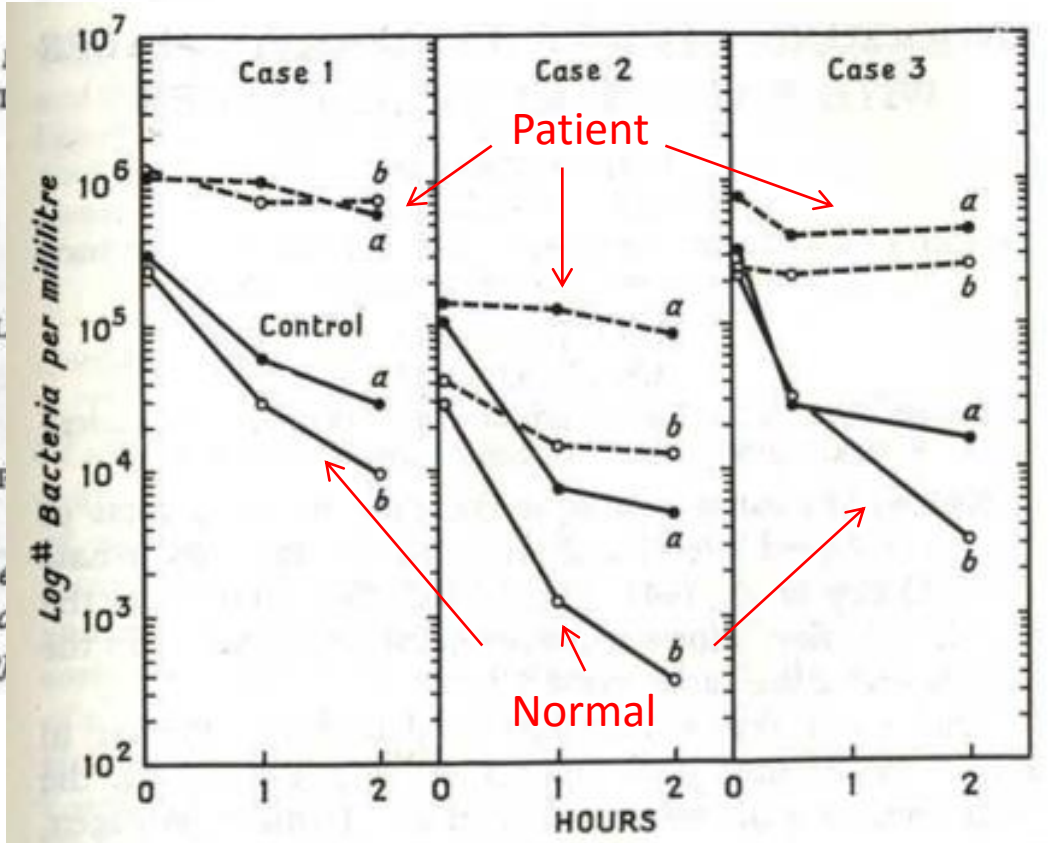
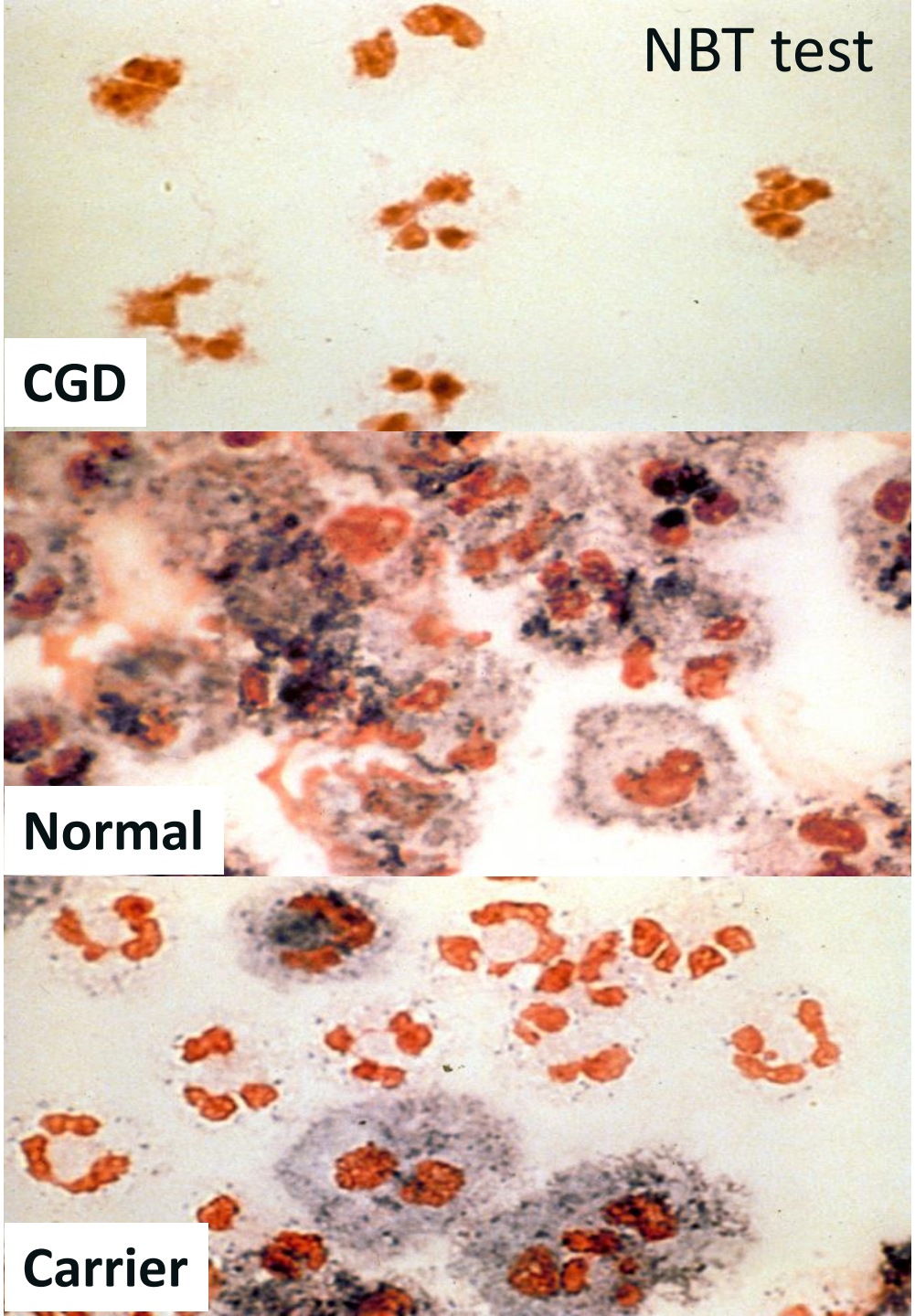


Fig. 5—The rate of survival of *Staph. aureus* in the presence of white blood-cells. Two separate experiments (a and b) are shown.

Leukocyte Oxidase: Defective Activity in Chronic Granulomatous Disease

Abstract. *The intact leukocytes of two children with chronic granulomatous disease fail to reduce nitroblue tetrazolium during phagocytosis. This is due to defective operation of an oxidase of reduced nicotinamide adenine dinucleotide that is insensitive to cyanide and that indirectly stimulates the oxidation of glucose-6-phosphate in leukocytes. Such leukocytes undergo no increase in oxygen consumption or in activity of the hexose monophosphate shunt during phagocytosis, although lactate production is normal. The addition of nitroblue tetrazolium to a leukocyte suspension appears to provide a sensitive diagnostic screening test for this disease.*

ROBERT L. BAEHNER
DAVID G. NATHAN
SCIENCE, VOL. 155 1967

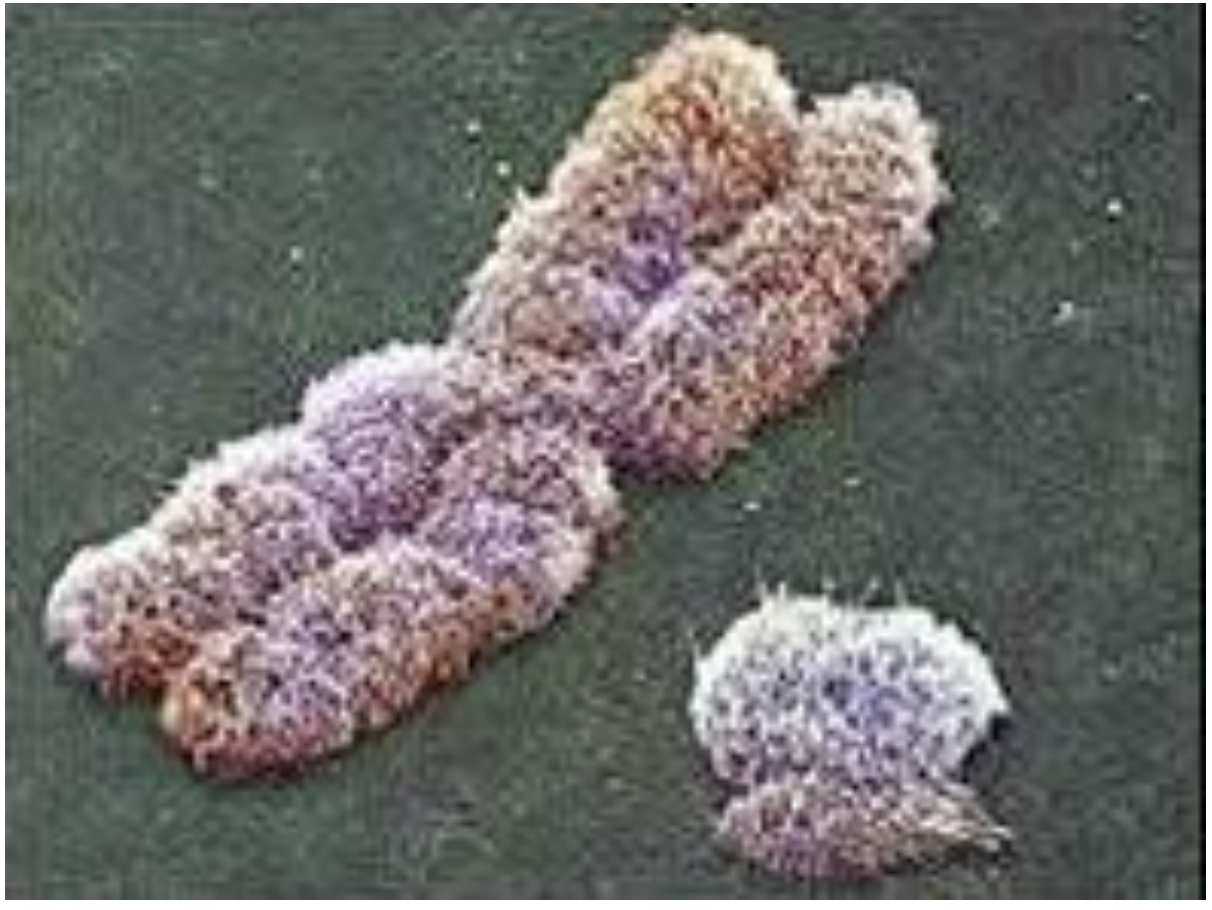


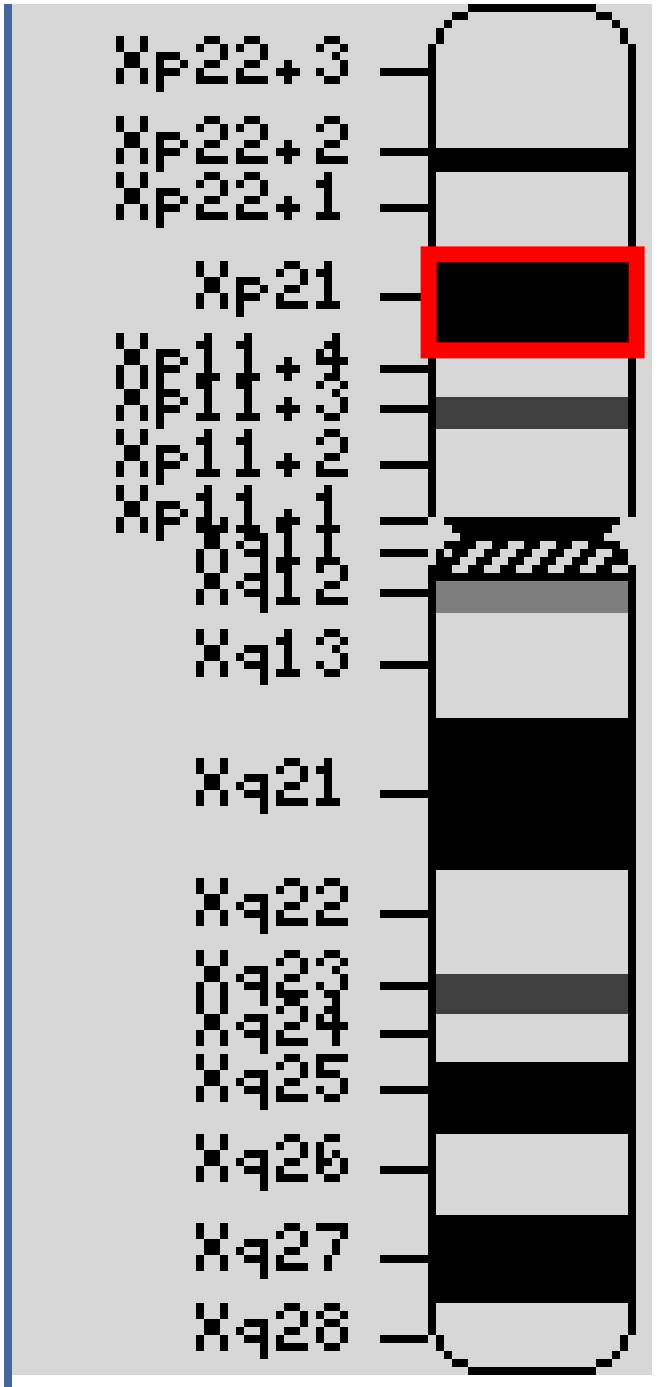
Cloning the gene for an inherited human disorder—chronic granulomatous disease—on the basis of its chromosomal location

Brigitte Royer-Pokora*, Louis M. Kunkel†, Anthony P. Monaco†, Sabra C. Goff*, Peter E. Newburger‡, Robert L. Bachner*, F. Sessions Cole‡, John T. Curnutte‡ & Stuart H. Orkin*†§

Nature 1986;322:32

CGD-RP-DMD





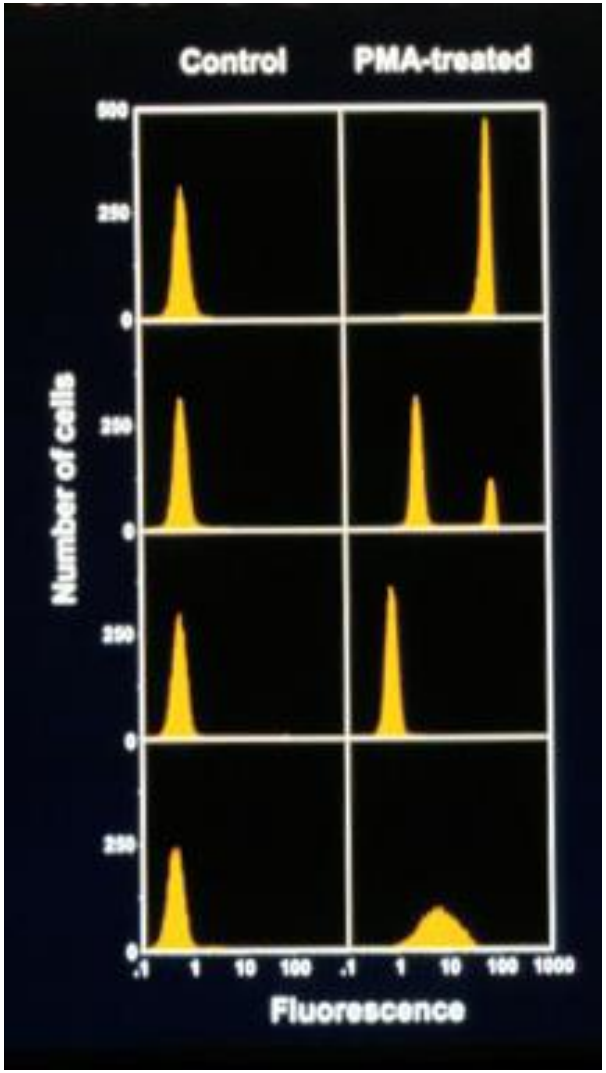
Dihydrorhodamine oxidation (DHR)

Normal

X-carrier

X-CGD

p47phox



Wild type

gp91$^{-/+}$

X gp91^{-}

AR p47$^{-/-}$

Vowells et al, 1995, 1996

We know a lot about CGD

Described over 60 years ago

Thousands of patients worldwide

Diagnosis is understood

Mechanisms and pathophysiology known

Prophylaxis proven for bacteria and fungi

Transplantation is common and successful

What is left to learn about CGD?

Why do the infections happen?

How should we treat them?

Why does the inflammation happen?

How should we treat that?

Why does the autoimmunity happen?

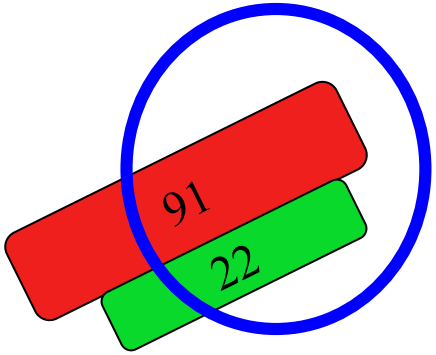
Who should be transplanted?

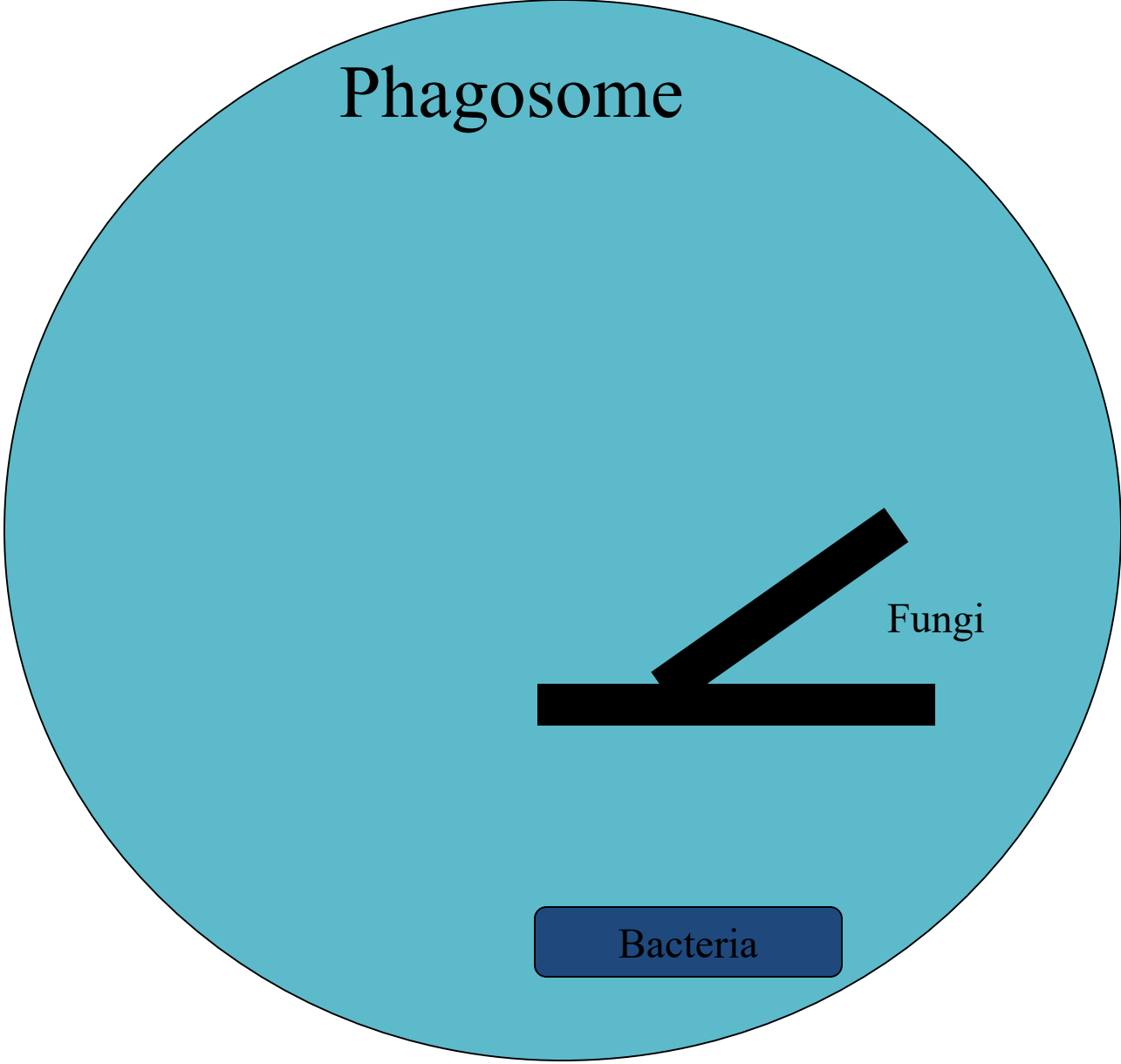
What about X-linked carriers?

1º granule

Cytoplasm

2º granule

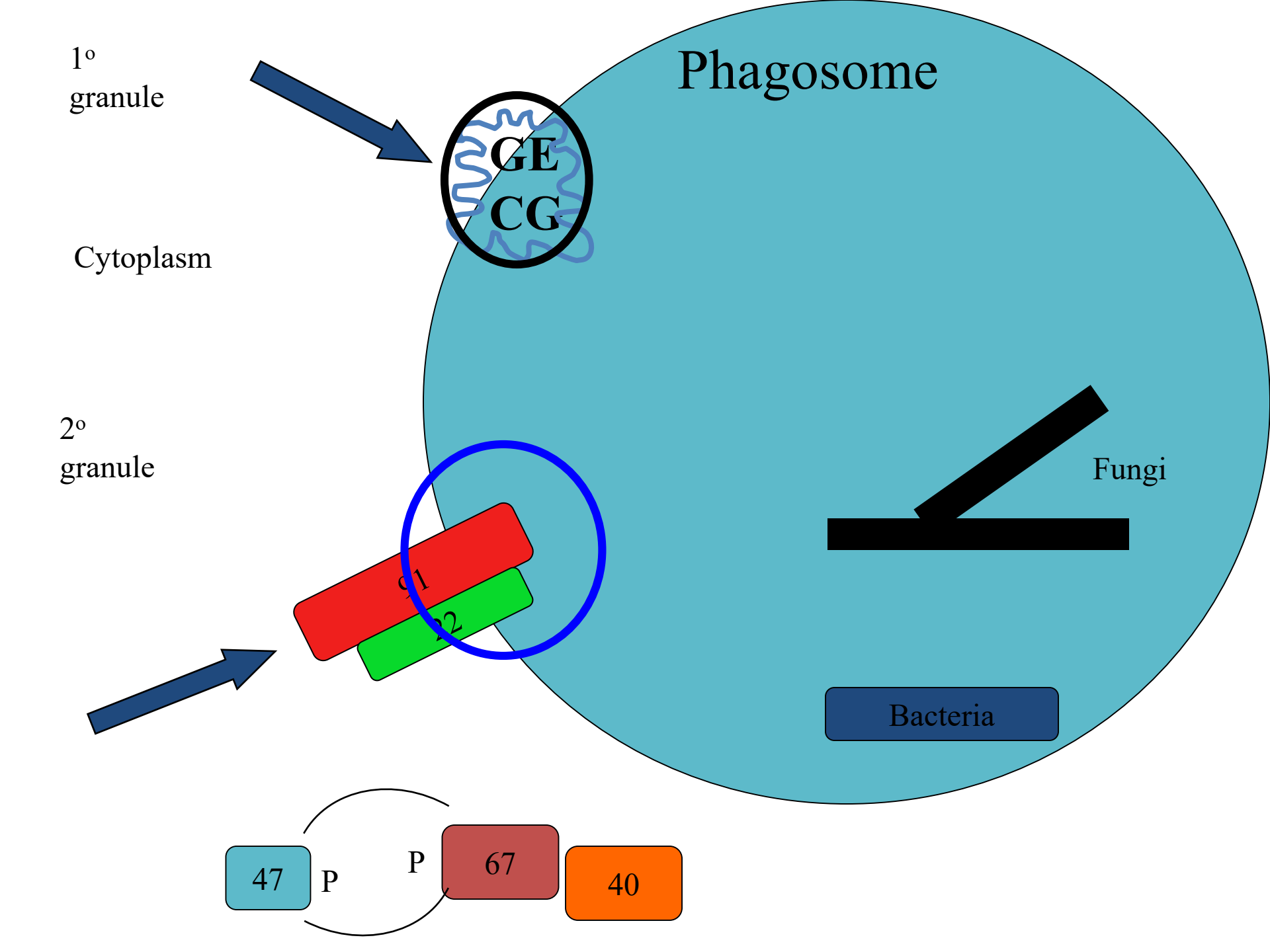


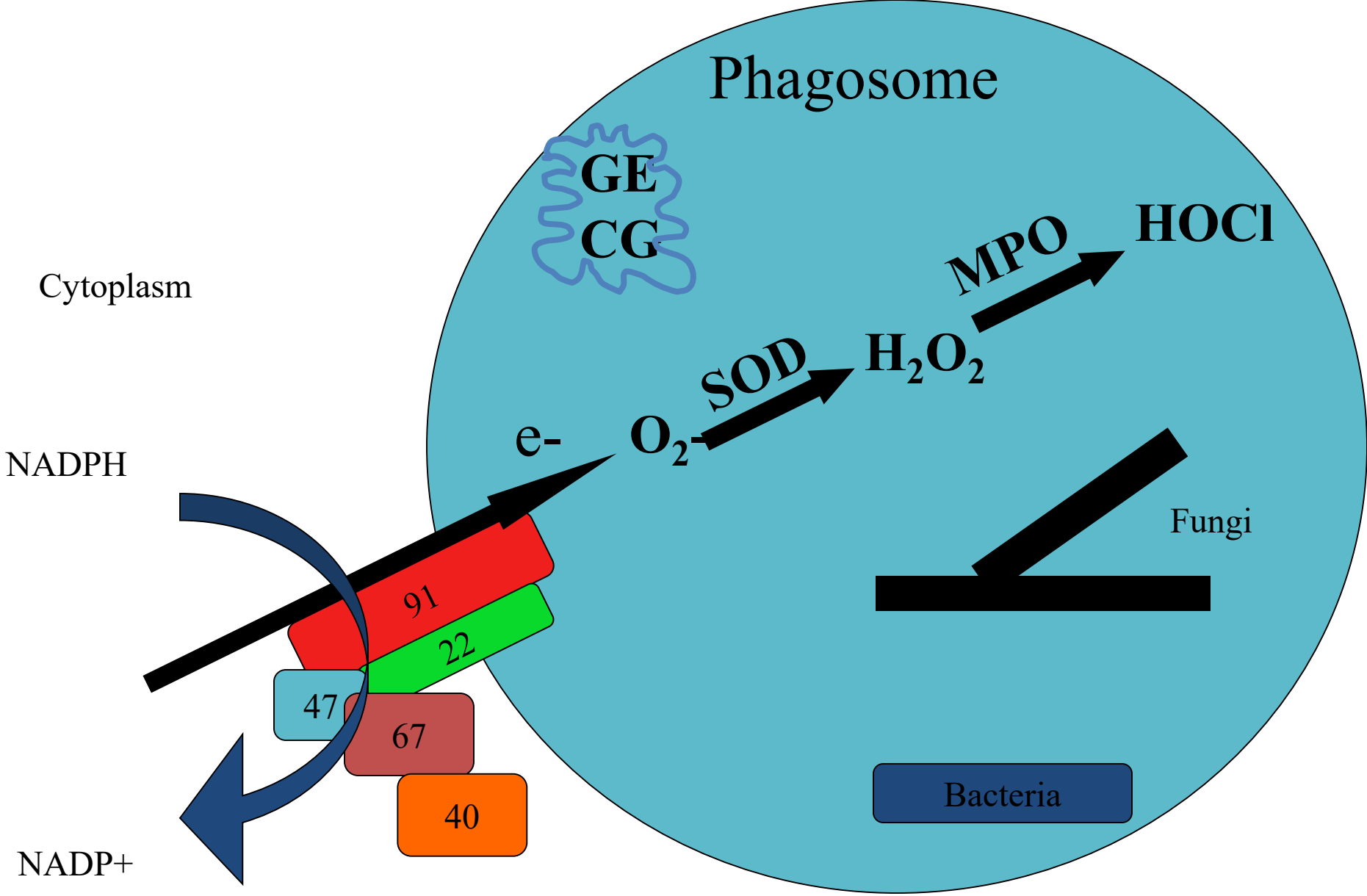


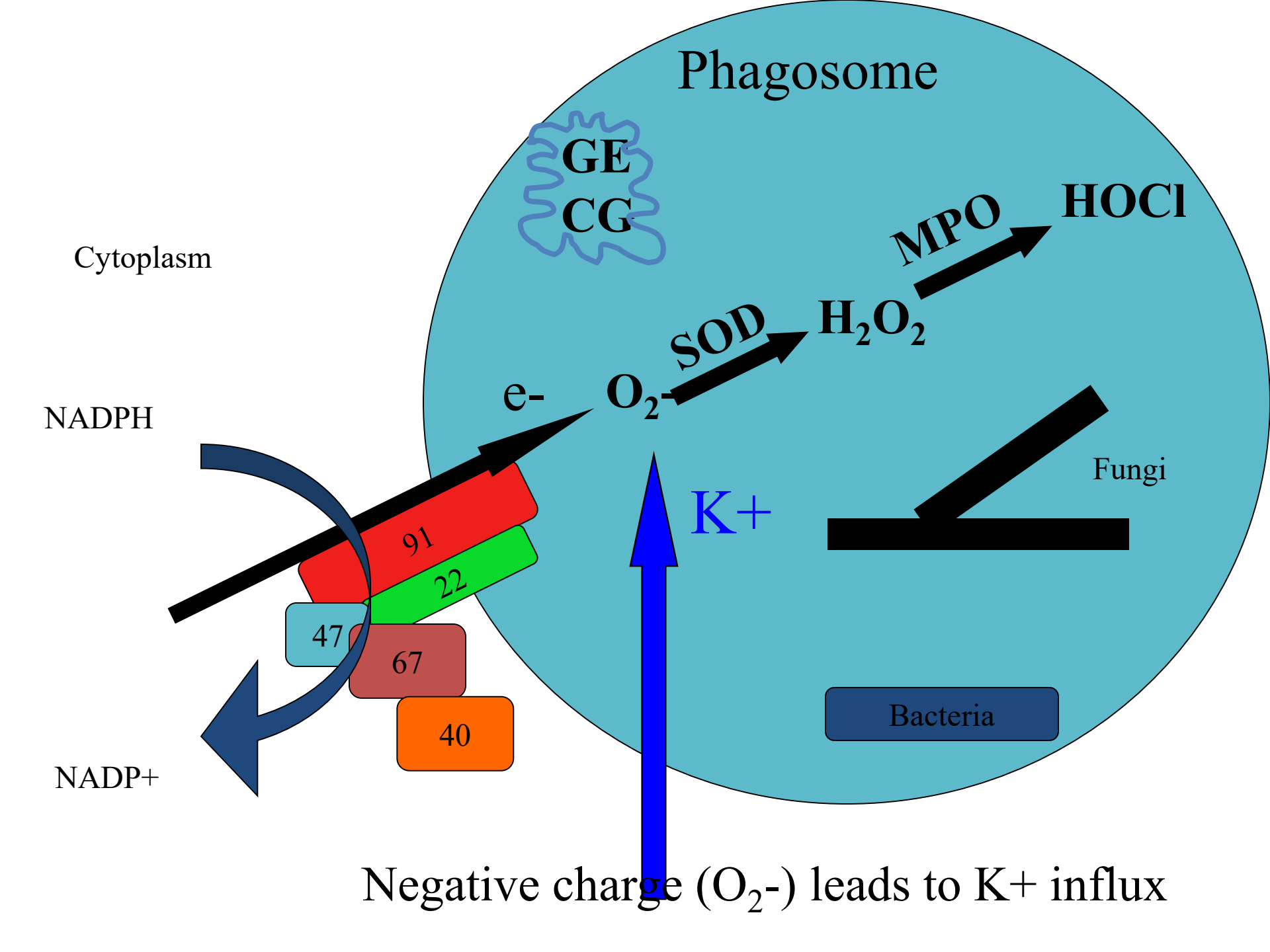
47

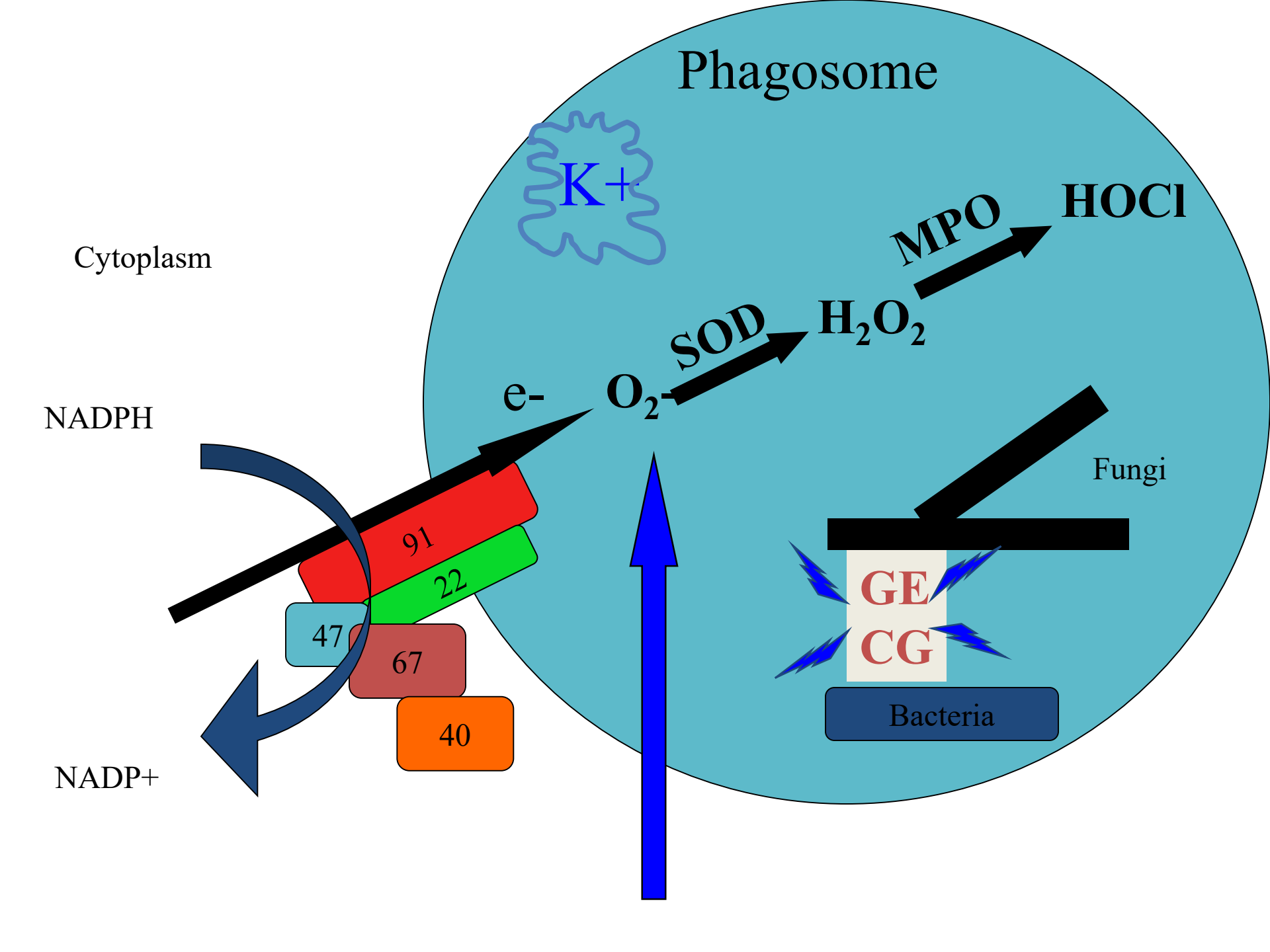
67

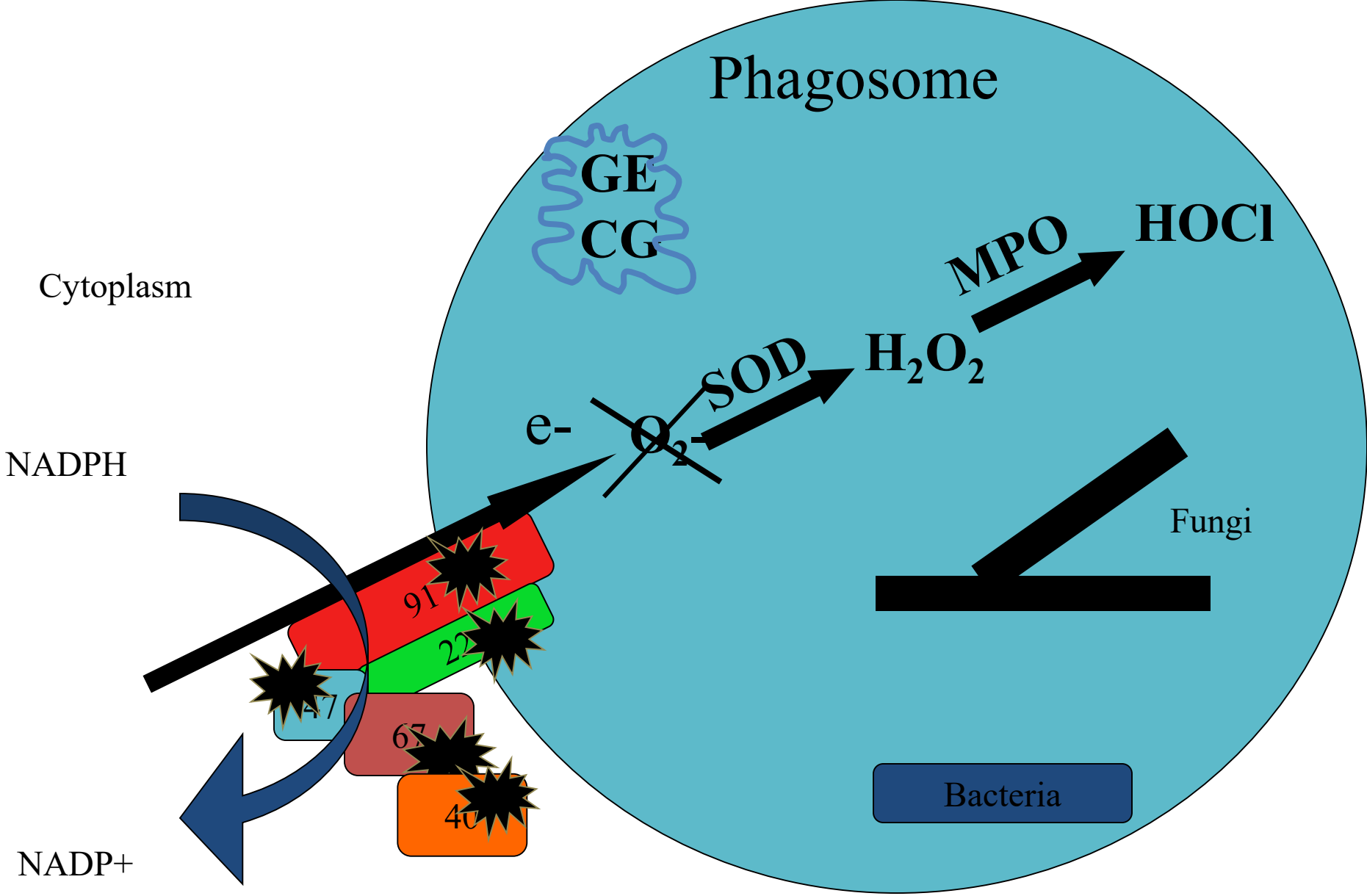
40


1º
granule
GE
CG
Phagosome
Cytoplasm
2º
granule
91
22
Fungi
Bacteria
47
P
P
67
40


Phagosome
GE
CG
Cytoplasm
MPO
HOCl
SOD
H_2O_2
e-
O_2-
NADPH
Fungi
91
22
47
67
40
Bacteria
NADP+


Phagosome
GE
CG
Cytoplasm
MPO
HOCl
SOD
H_2O_2
e-
O_2-
NADPH
Fungi
K+
91
22
47
67
40
Bacteria
NADP+
Negative charge (O_2-) leads to K+ influx


Phagosome
K+
Cytoplasm
MPO
HOCl
SOD
H_2O_2
e-
O_2-
NADPH
Fungi
91
22
47
67
40
GE
CG
Bacteria
NADP+


Phagosome
GE
CG
Cytoplasm
MPO
HOCl
SOD
H_2O_2
e-
O_2-
NADPH
Fungi
91
22
47
67
40
Bacteria
NADP+

CGD: One phenotype, 5 genotypes

Gene	chromosome	%
gp91phox	Xp21	65%
Autosomal		
p22phox	16	<5%
p47phox	7	25%
p67phox	1q42	<5%
p40phox	22	2 cases

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

- diagnosis usually in childhood
- adult cases recognized, especially autosomal

Infections in North American CGD

S. aureus	(liver, lymph nodes,osteo)
S. marsescens	(skin, lung, lymph nodes)
B. cepacia	(pneumonia, bacteremia)
Nocardia spp.	(pneumonia, brain, liver)
Aspergillus spp.	(lung, esp. miliary, spine)
Salmonella spp.	(sepsis, diarrhea, osteo)
BCG	(local and regional dz)

Infections that prove you are an expert:

Chromobacterium violaceum *(brackish water, e.g. Disney World)*

Francisella philomiragia *(brackish water, Chesapeake Bay)*

Granulibacter bethesdensis *(widespread)*

J Clin Immunol (2013) 33:1302–1309

Chronic Granulomatous Disease: A 25-Year Patient Registry Based on a Multistep Diagnostic Procedure, from the Referral Center for Primary Immunodeficiencies in Greece

Maria Raptaki · Ioanna Varela · Kleopatra Spanou · Marianna Tzanoudaki · Sofia Tantou · Manolis Liatsis · Nikki Constantinidou · Chryssa Bakoula · Dirk Roos · Maria Kanariou

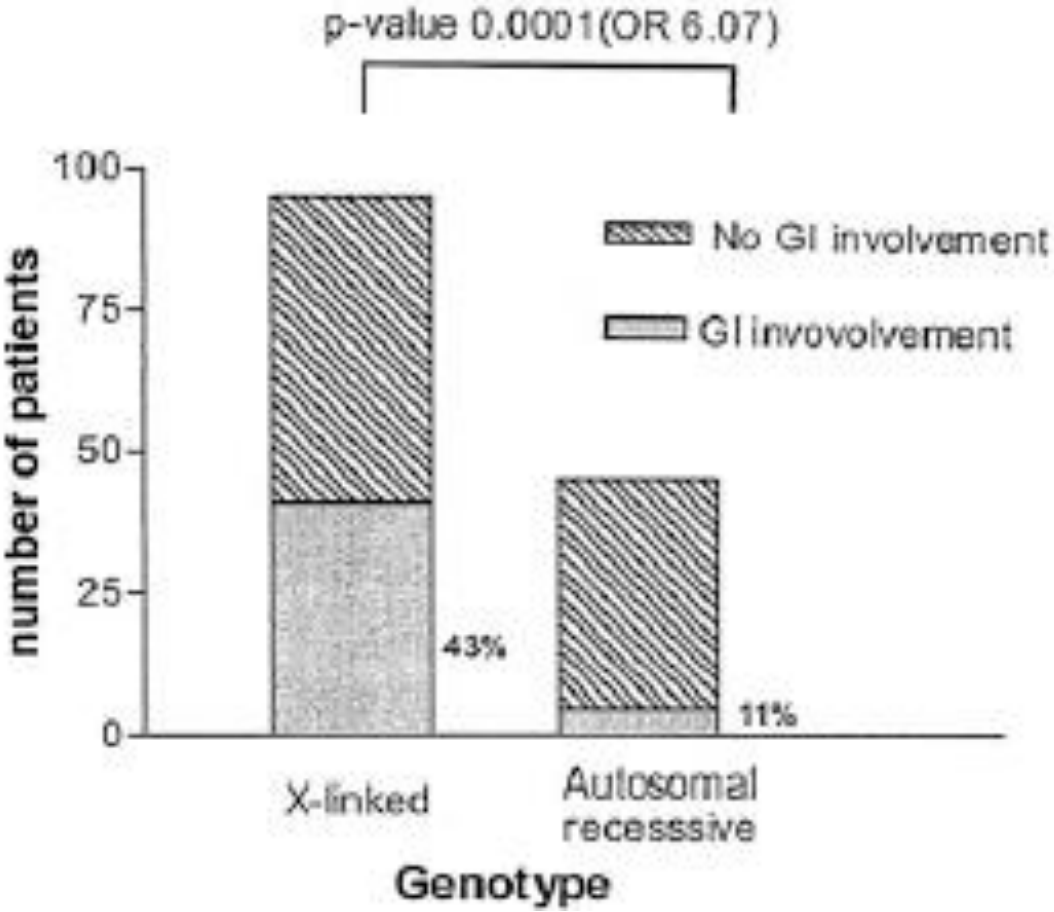
X-CGD= 16

AR-CGD=7

Clinical manifestations before diagnosis	X-CGD	AR-CGD	TOTAL
Gastrointestinal Manifestations	10	4	14
Respiratory Tract Infections	8	4	12
Lymphadenopathy	9	4	14
Skin Infections	7	5	13
Hepatic Abscesses	4	1	5
Urinary Tract Infections	2	2	4
Lung Abscesses	4	0	4
Septicaemia	2	1	3
Cerebral Abscesses	0	1	1

Gastrointestinal Involvement in Chronic Granulomatous Disease

Beatriz E. Marciano, MD*; Sergio D. Rosenzweig, MD*; David E. Kleiner, MD‡; Victoria L. Anderson, MSN, CRNP*; Dirk N. Darnell, RN, MSN*; Sandra Anaya-O'Brien, RN, MSN*; Dianne M. Hilligoss, MSN, CRNP*; Harry L. Malech, MD*; John I. Gallin, MD*; and Steven M. Holland, MD*



Pediatrics 2004;114;462-468

Hepatic Abnormalities in Patients with Chronic Granulomatous Disease

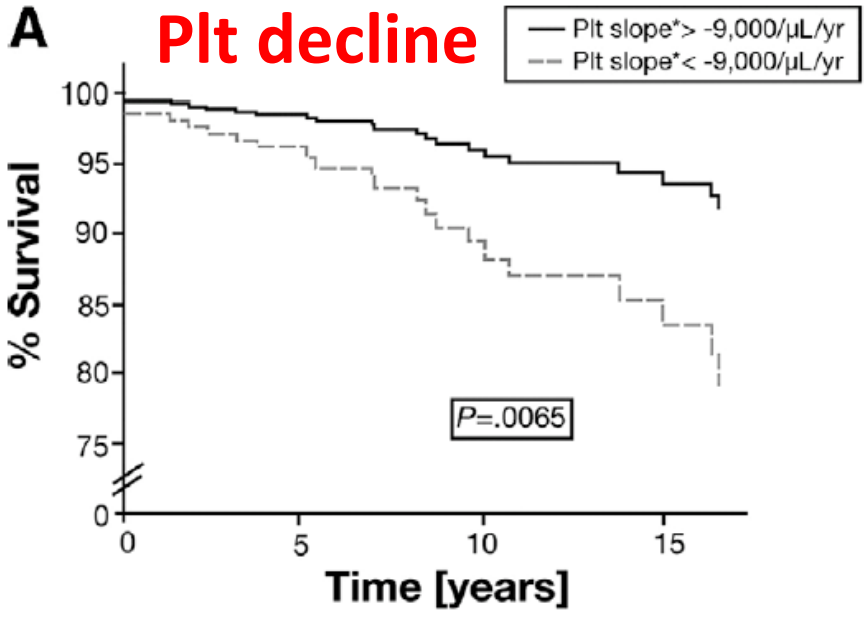
Nadeem Hussain,[1,2,7*] Jordan J. Feld,[1,7*] David E. Kleiner,[5,7] Jay H. Hoofnagle,[1,7] Reyes Garcia-Eulate,[3,7] Sushil Ahlawat,[2,7] Deloris E. Koziel,[4,7] Victoria Anderson,[6,7] Dianne Hilligoss,[6,7] Peter Choyke,[3,7] John I. Gallin,[6,7] T. Jake Liang,[1,7] Harry L. Malech,[6,7] Steven M. Holland,[6,7] and Theo Heller[1,7]

(HEPATOLOGY 2007;45:675-683.)

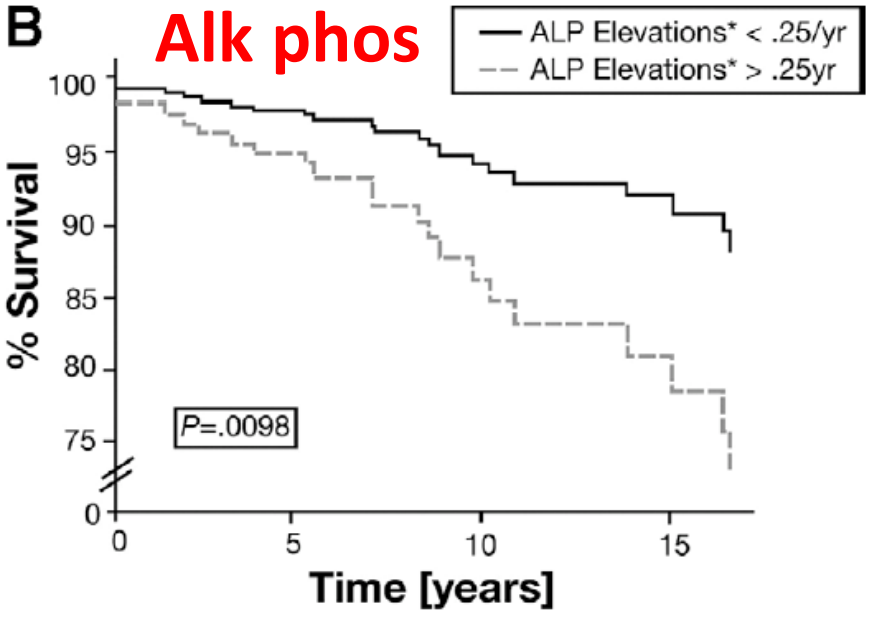
Hepatic Involvement and Portal Hypertension Predict Mortality in Chronic Granulomatous Disease

JORDAN J. FELD,* NADEEM HUSSAIN,‡ ELIZABETH C. WRIGHT,§ DAVID E. KLEINER,‖ JAY H. HOOFNAGLE,* SUSHIL AHLAWAT,‡ VICTORIA ANDERSON,¶ DIANNE HILLIGOSS,¶ JOHN I. GALLIN,¶ T. JAKE LIANG,* HARRY L. MALECH,¶ STEVEN M. HOLLAND,¶ and THEO HELLER*

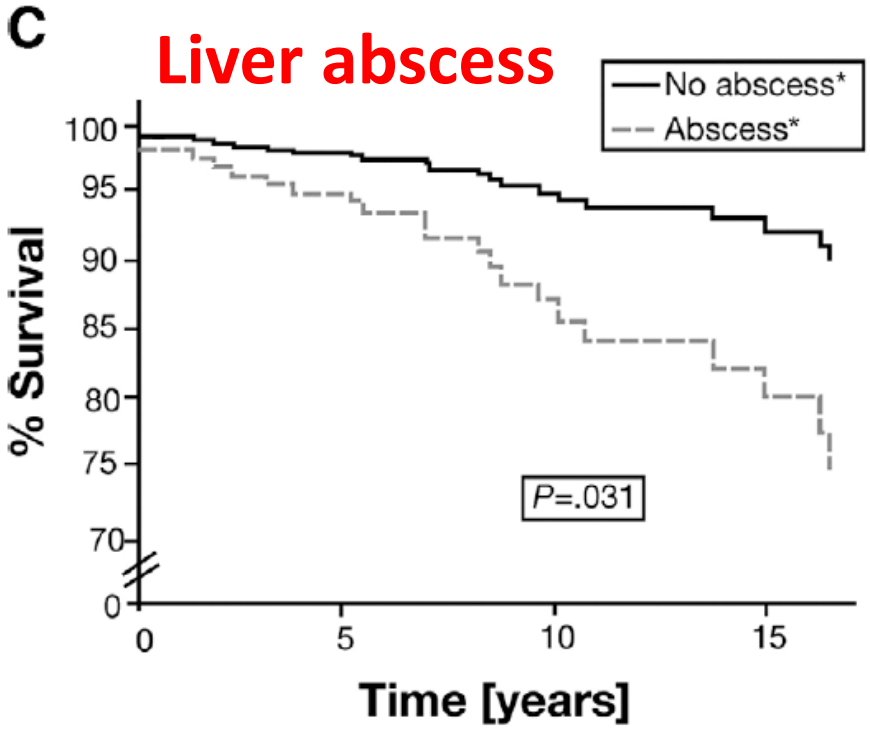
Gastroenterology 2008;134:1917-1926

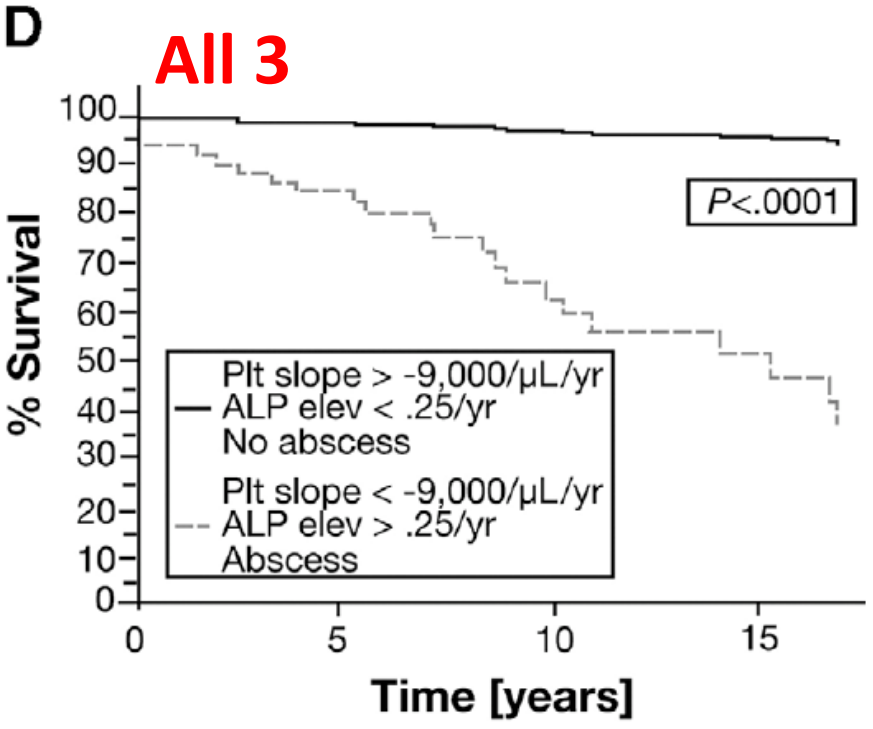


*Adjusted for ALP elevations and history of liver abscess

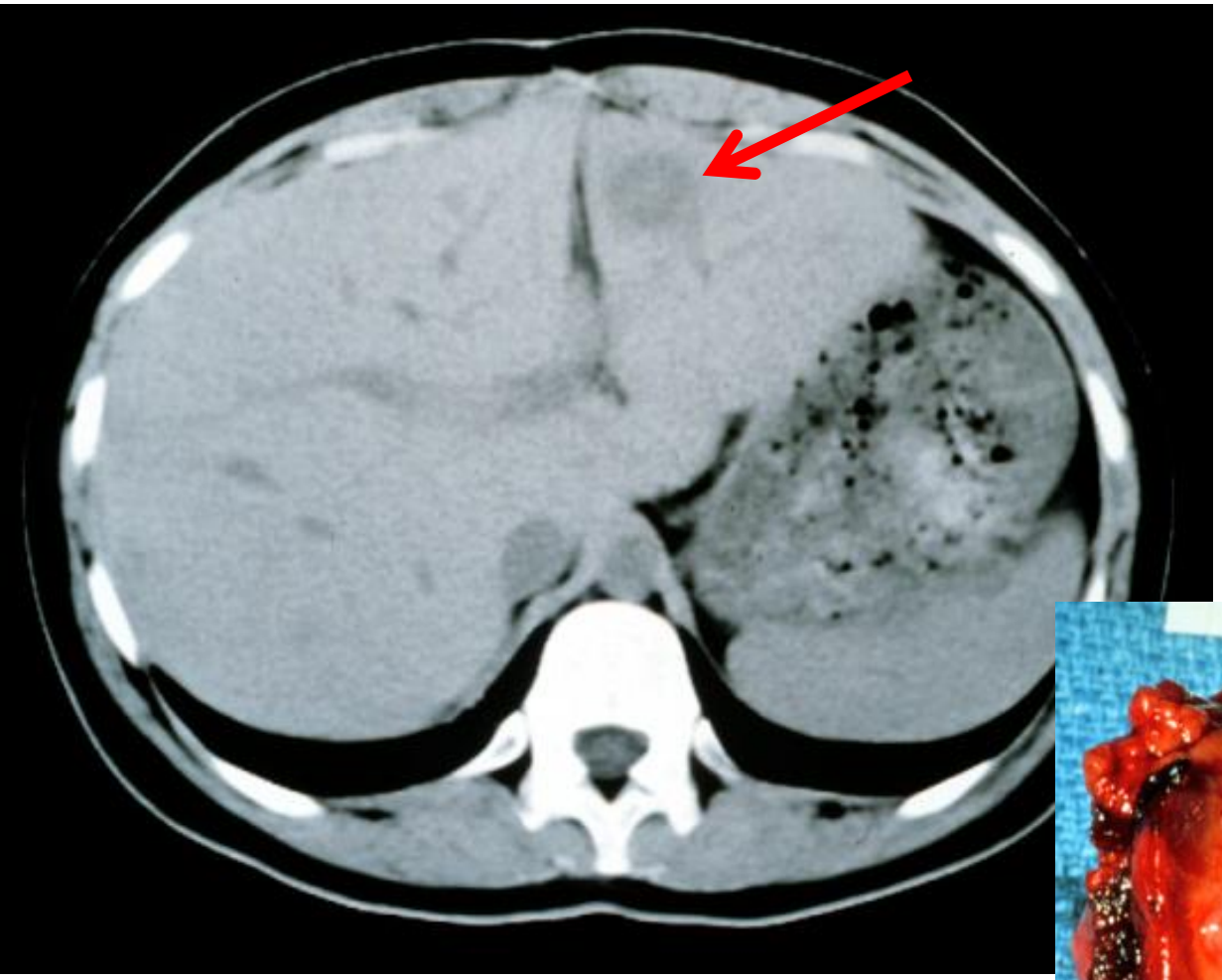


*Adjusted for platelet slope and history of liver abscess

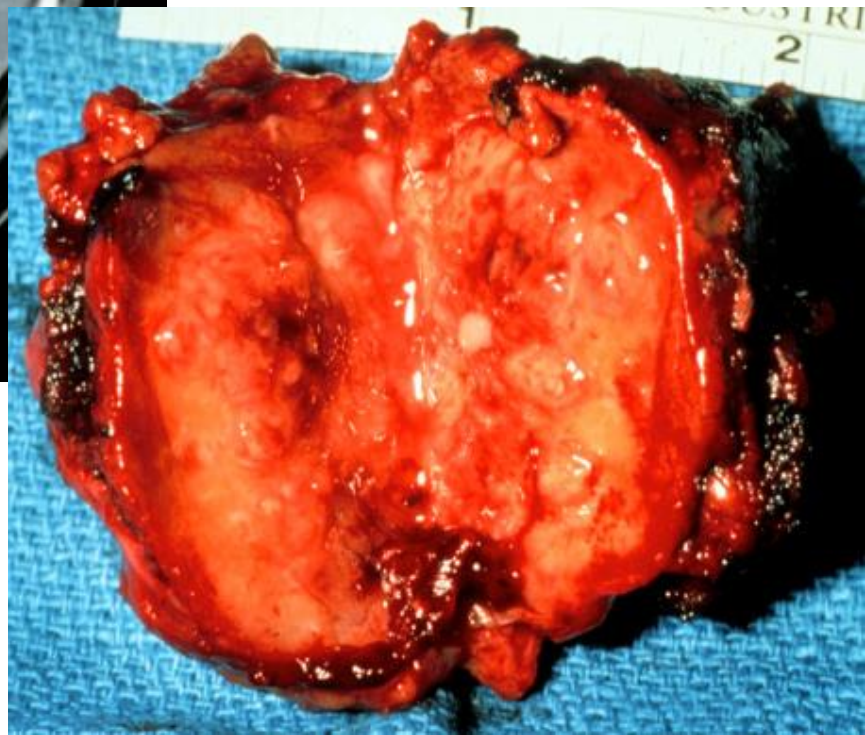


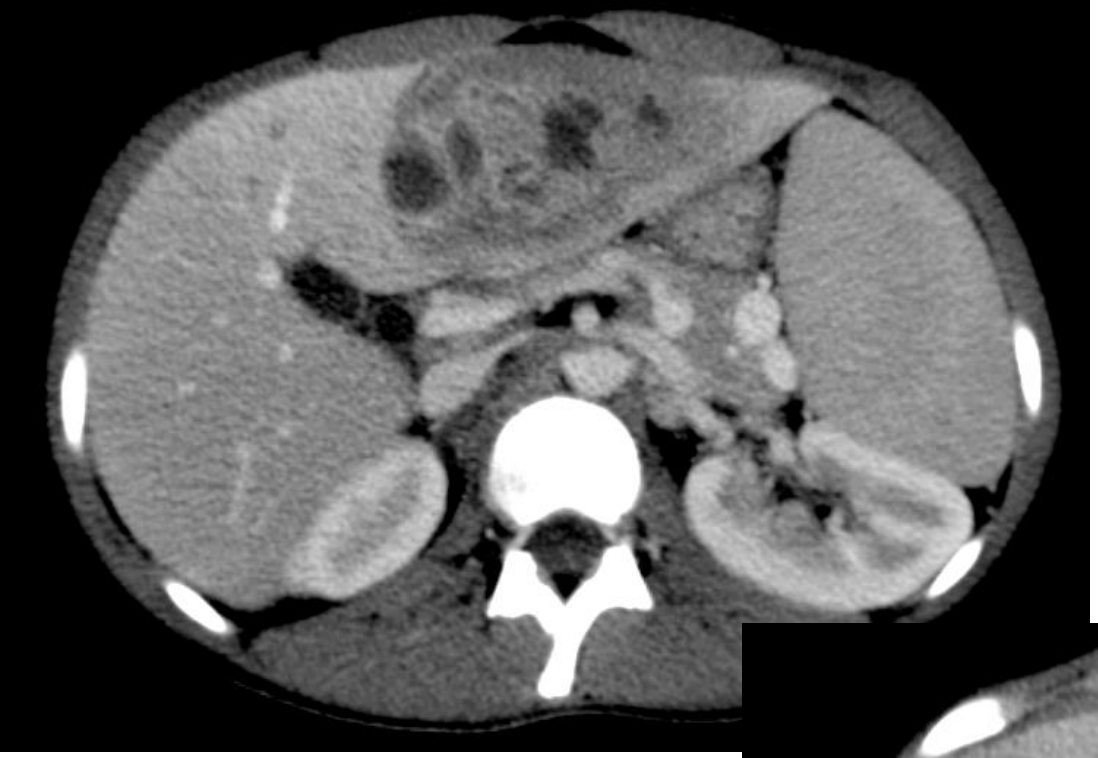


~30% of CGD patients get liver abscess : Usually *S. aureus*.

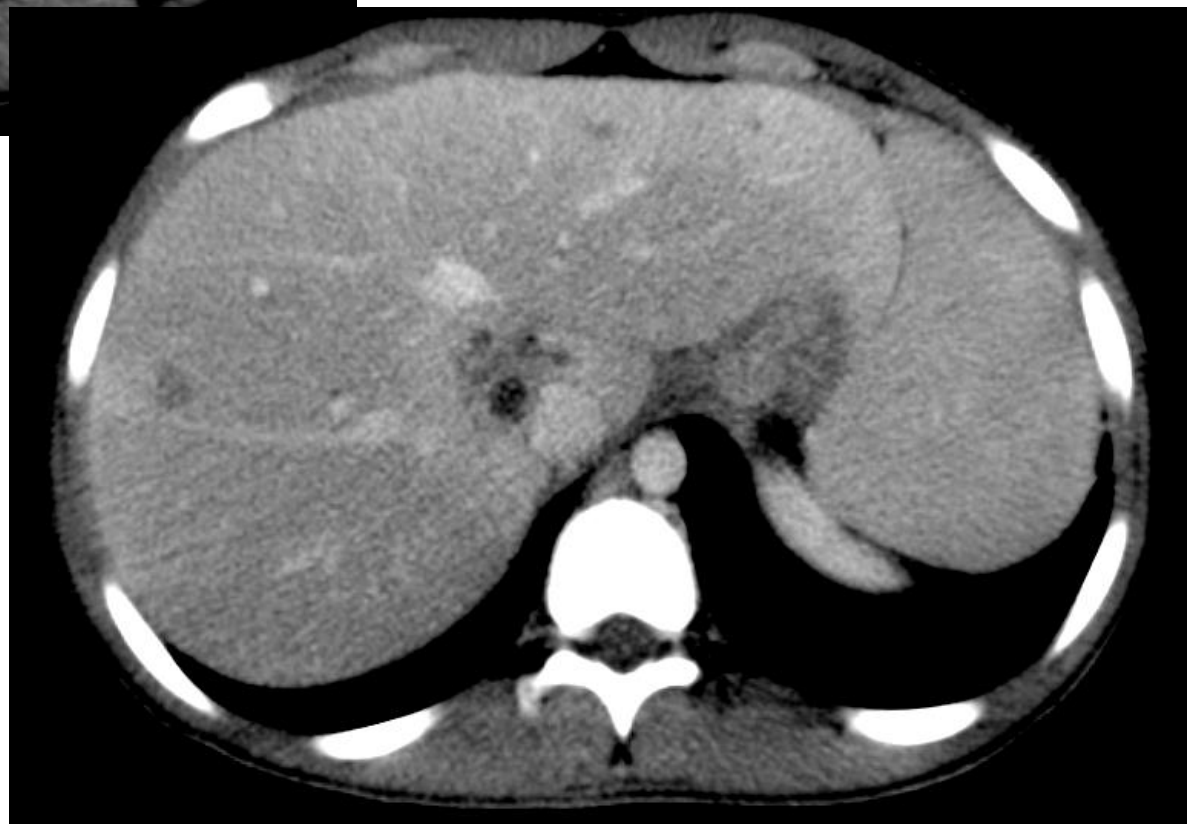


Dense,
Granulomatous
Not much liquid pus

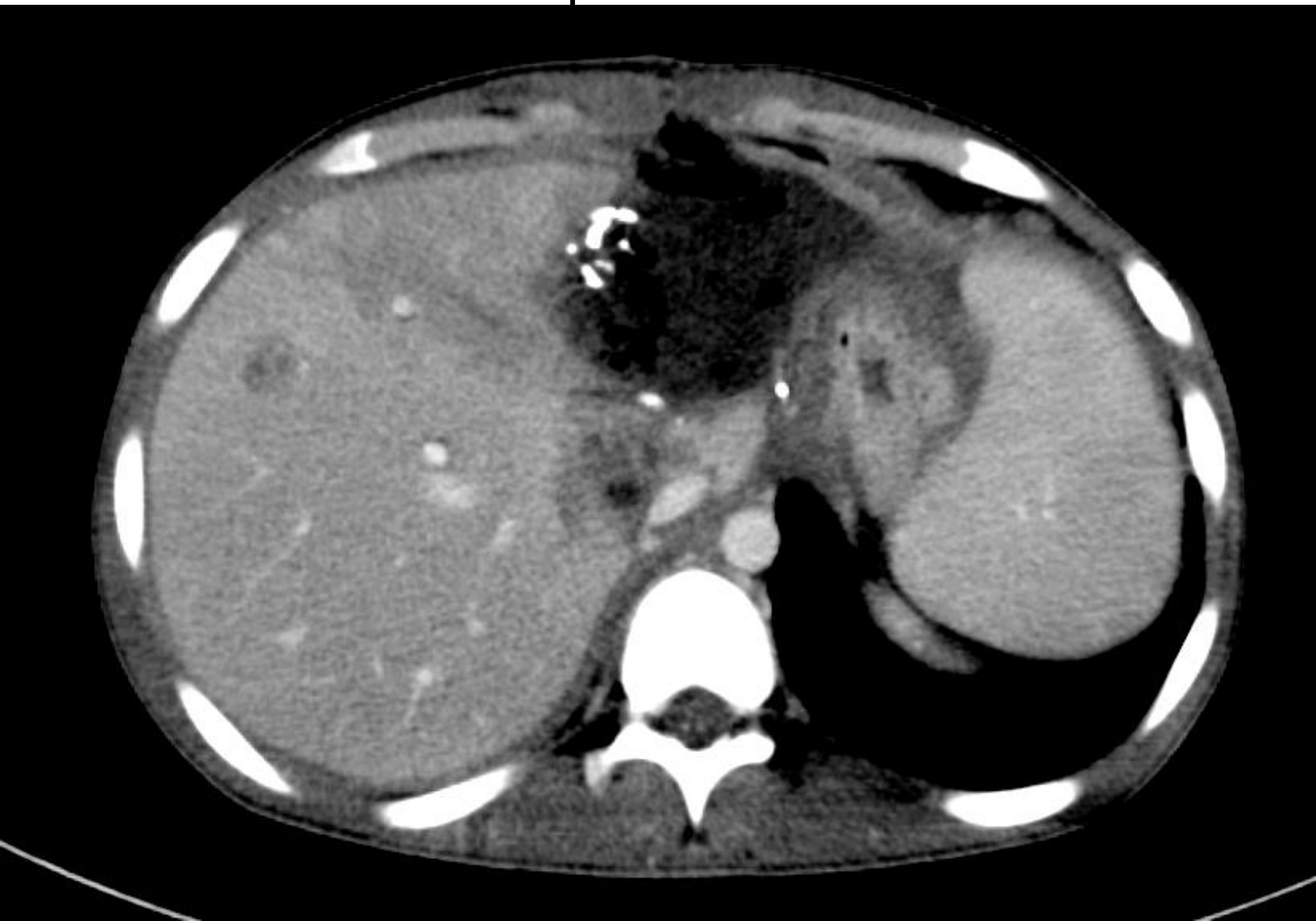




19 year old X-CGD



Incomplete resection



Case report

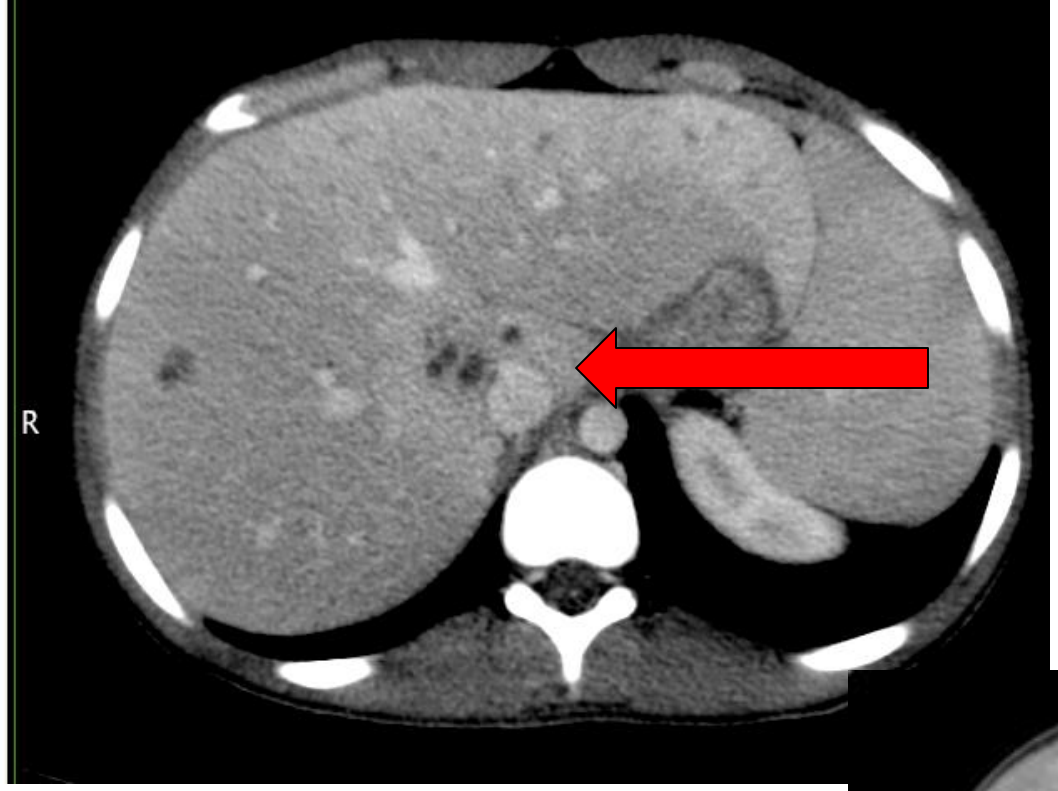
Corticosteroid therapy for refractory infections in chronic granulomatous disease: case reports and review of the literature

Marco A. Yamazaki-Nakashimada, MD*; E. Richard Stiehm, MD†;
Dino Pietropaolo-Cienfuegos, MD*; Victor Hernandez-Bautista, MD*; and
Francisco Espinosa-Rosales, MD*

5 yo girl with CGD

- 2 liver abscesses, one close to the portal vein
- Surgery too dangerous
- Added steroids to antibiotics
- Resolution fever after 6 days
- Resolution of liver abscess weeks later

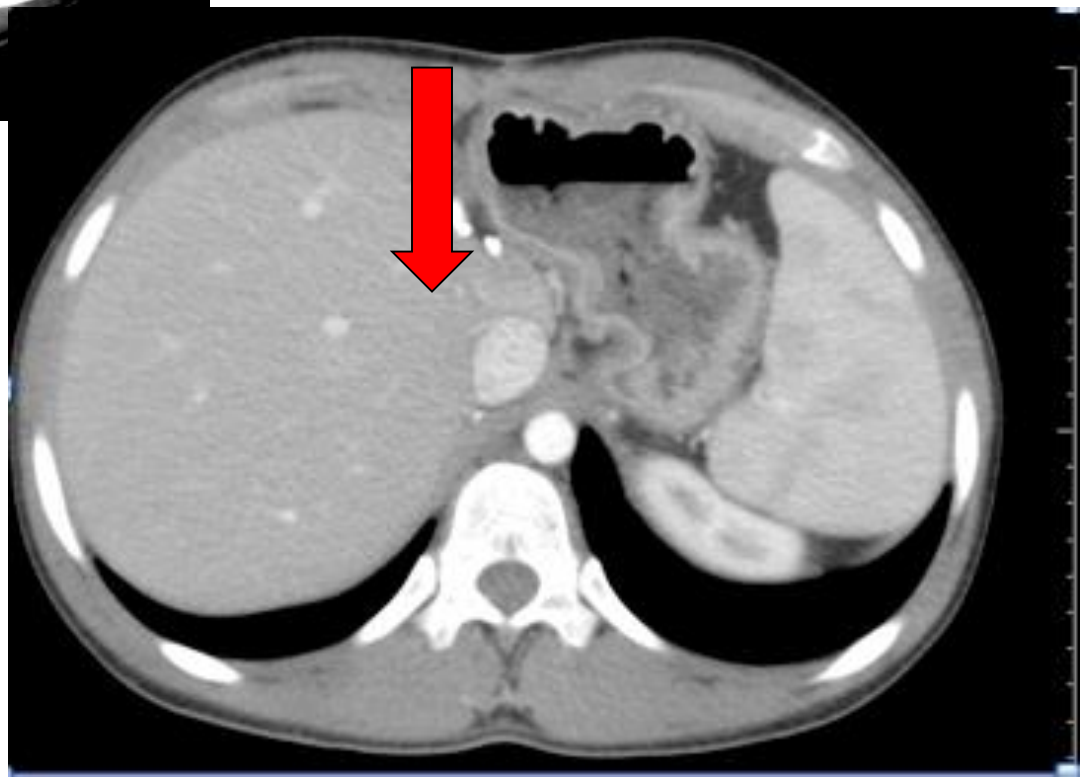
Ann Allergy Asthma Immunol. 2006;97:257–261.



Before

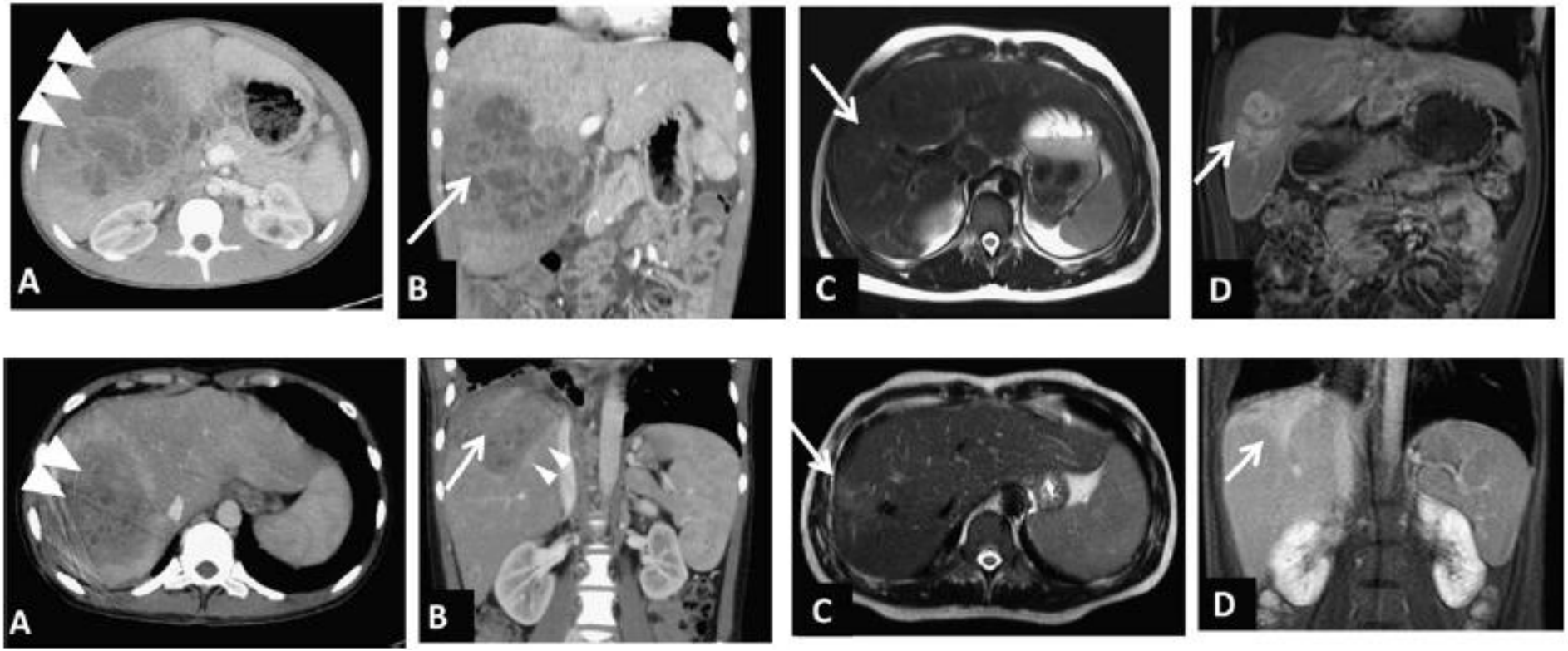
Prednisone 1 mg/kg

After



CGD Staph Liver Abscesses

Biopsy to prove *Staph aureus*
Intravenous anti-staphylococcal antibiotics
Steroids ~1mg/kg for 2-3 weeks then taper

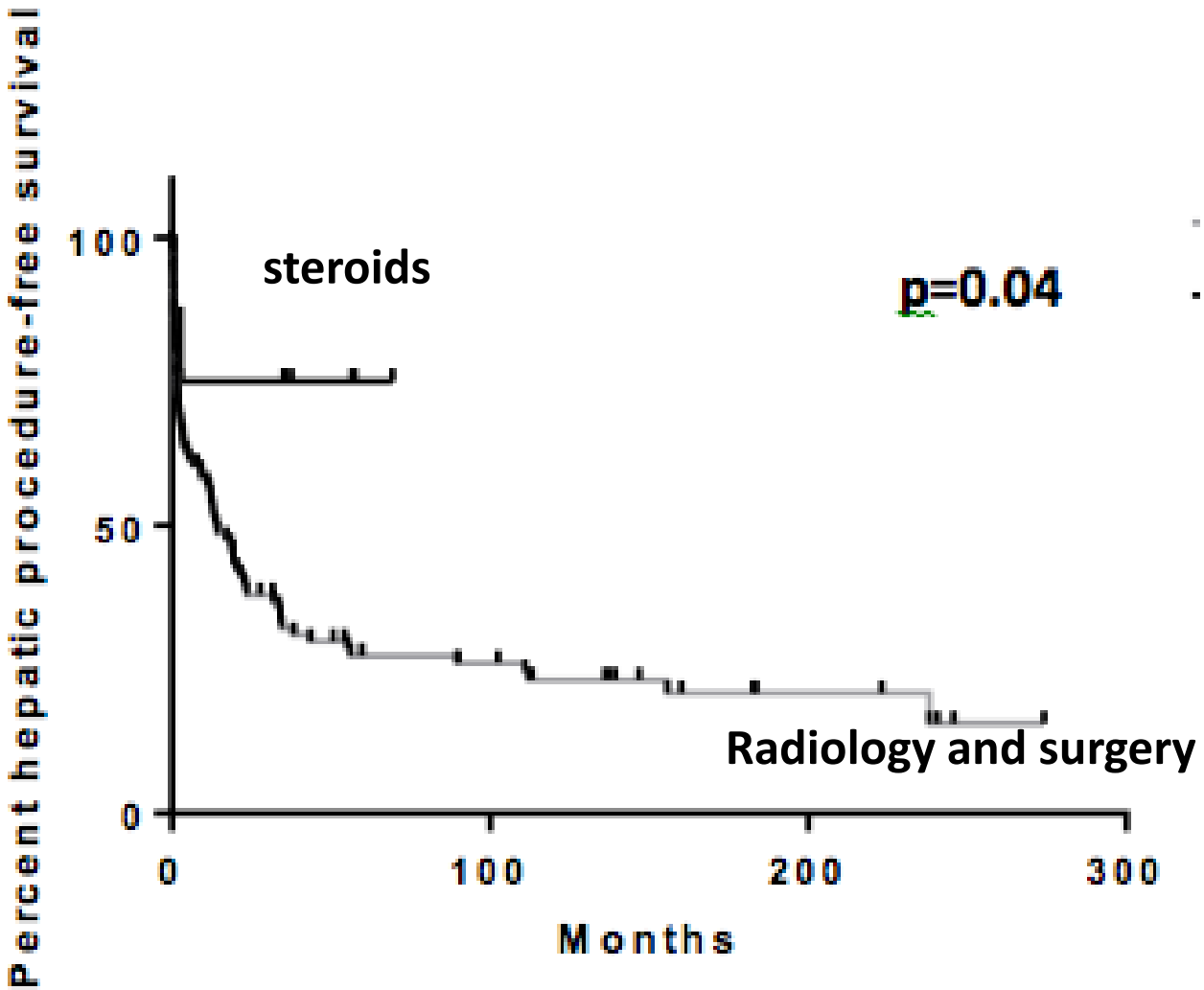


Leiding J et al, Clin Infect Dis 2012; 54:694-700

But how does it compare to

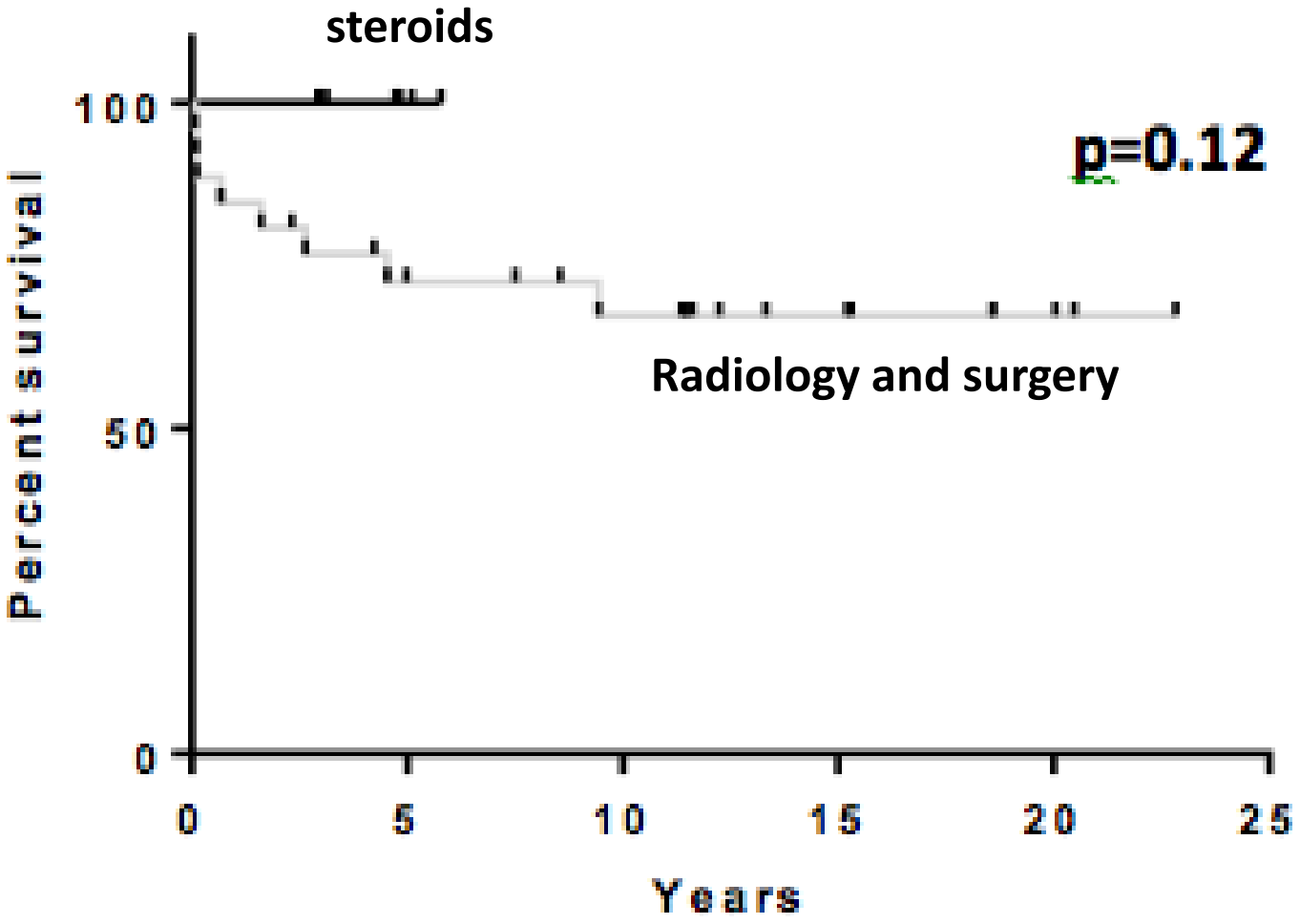
surgery or interventional radiology drainage?

Steroid Treatment Was Associated with Fewer Repeat Liver Procedures



Jennifer Leiding, Udo Rudloff

Survival Difference after Treatment of Liver Abscess



Why are Steroids So Helpful in CGD Liver Abscess?

Less liver inflammation,
a major contributor to mortality

Less nodular regenerative hyperplasia (NRH),
less portal hypertension

Less abscess encapsulation, so better drug entry

Altered cell trafficking into and out of abscess

Macrophage survival and activation

Liver Abscess in CGD

Steroids plus antibiotics work

Allow avoidance of surgery

Steroids plus antibiotics have less relapse

Steroids plus antibiotics may have better survival

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Residual NADPH Oxidase and Survival in Chronic Granulomatous Disease

Douglas B. Kuhns, Ph.D., W. Gregory Alvord, Ph.D., Theo Heller, M.B., Ch.B., Jordan J. Feld, M.D., M.P.H., Kristen M. Pike, M.S., Beatriz E. Marciano, M.D., Gulbu Uzel, M.D., Suk See DeRavin, M.D., Ph.D., Debra A. Long Priel, M.S., Benjamin P. Soule, M.D., Kol A. Zarember, Ph.D., Harry L. Malech, M.D., Steven M. Holland, M.D., and John I. Gallin, M.D.

N Engl J Med 2010;363:2600-10.

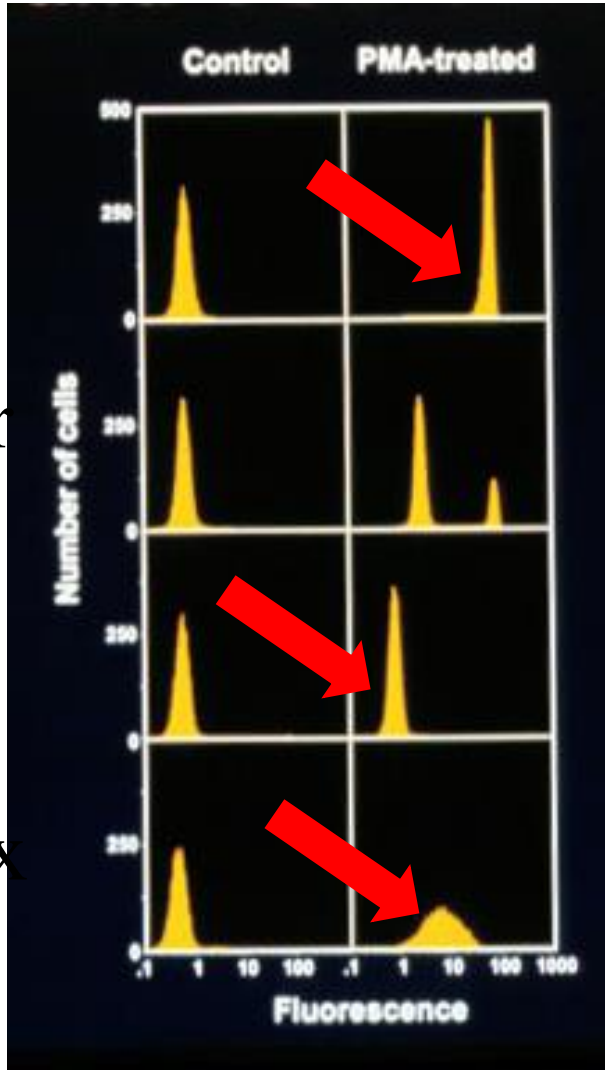
Dihydrorhodamine oxidation (DHR)

Normal

X-carrier

X-CGD

p47phox



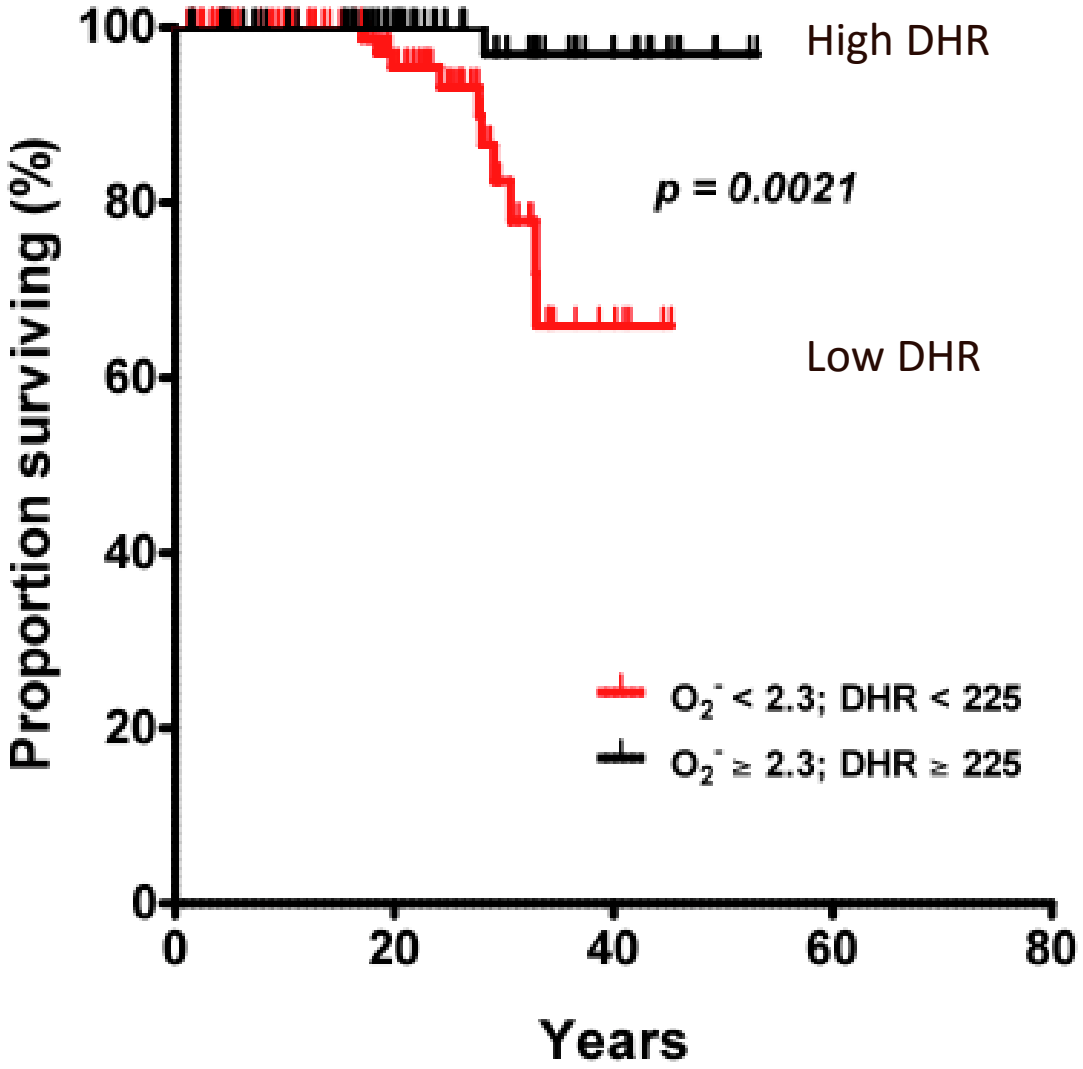
Wild type

gp91-/+

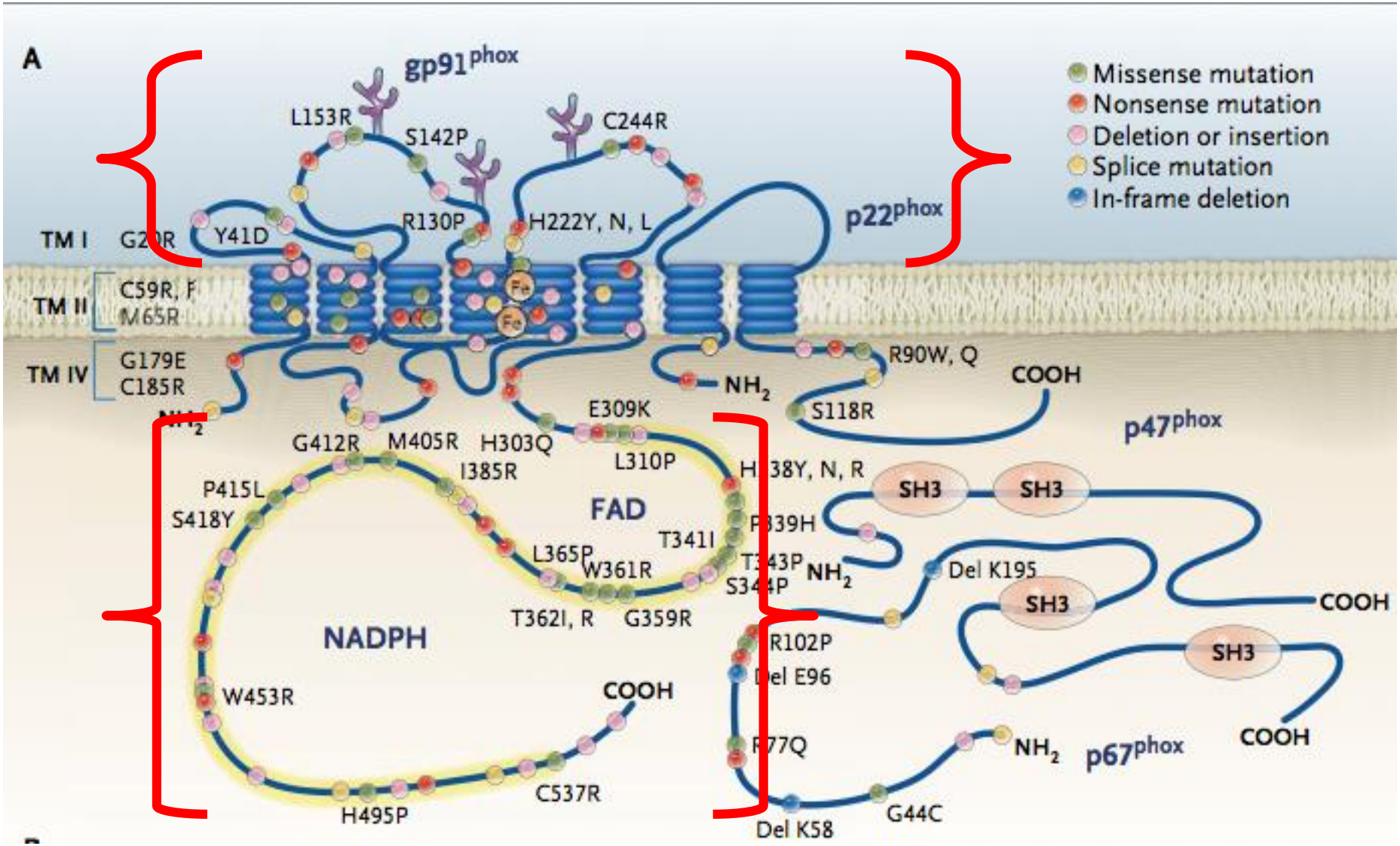
X gp91-

AR p47-/-

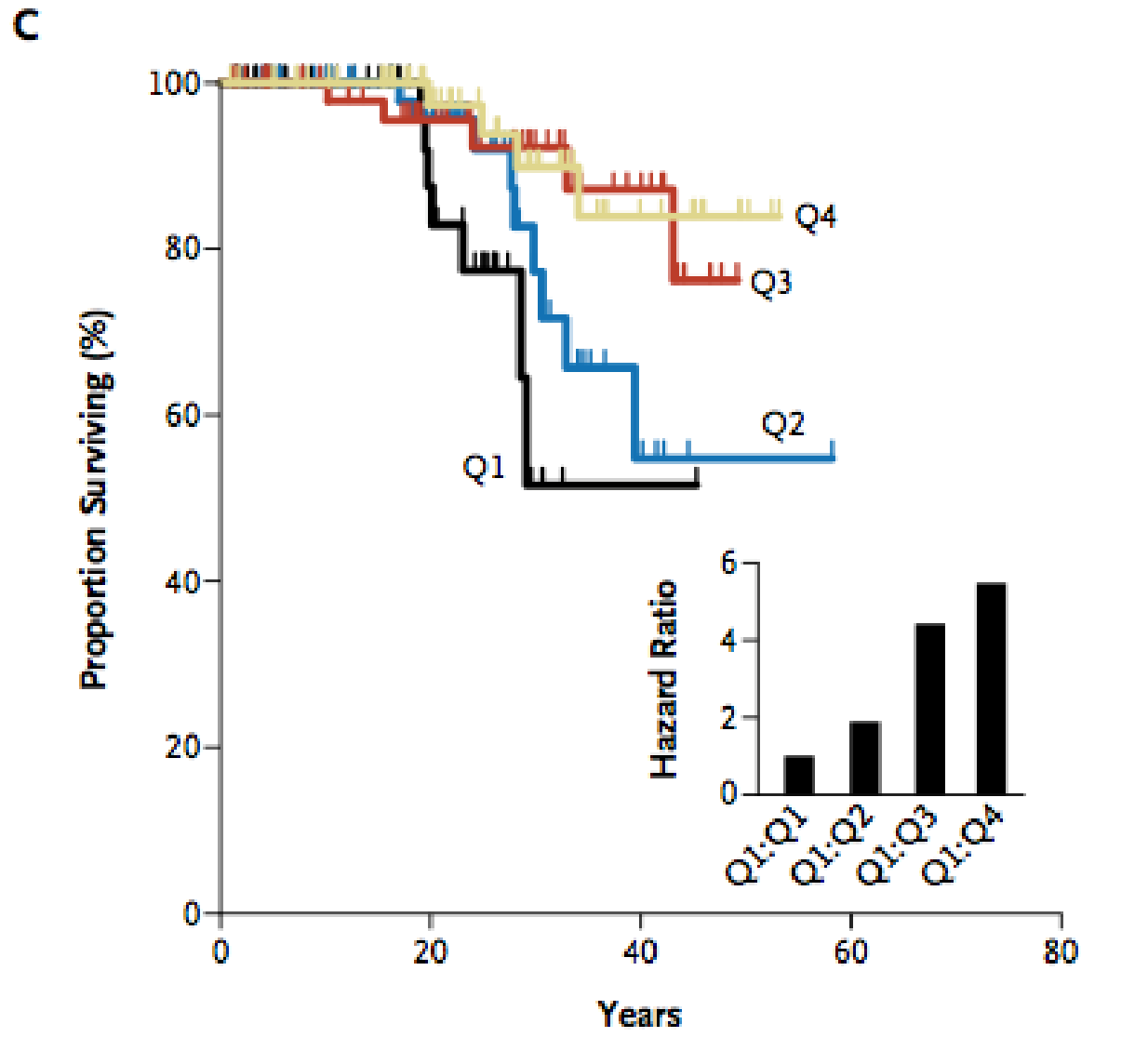
Survival Separates by DHR value



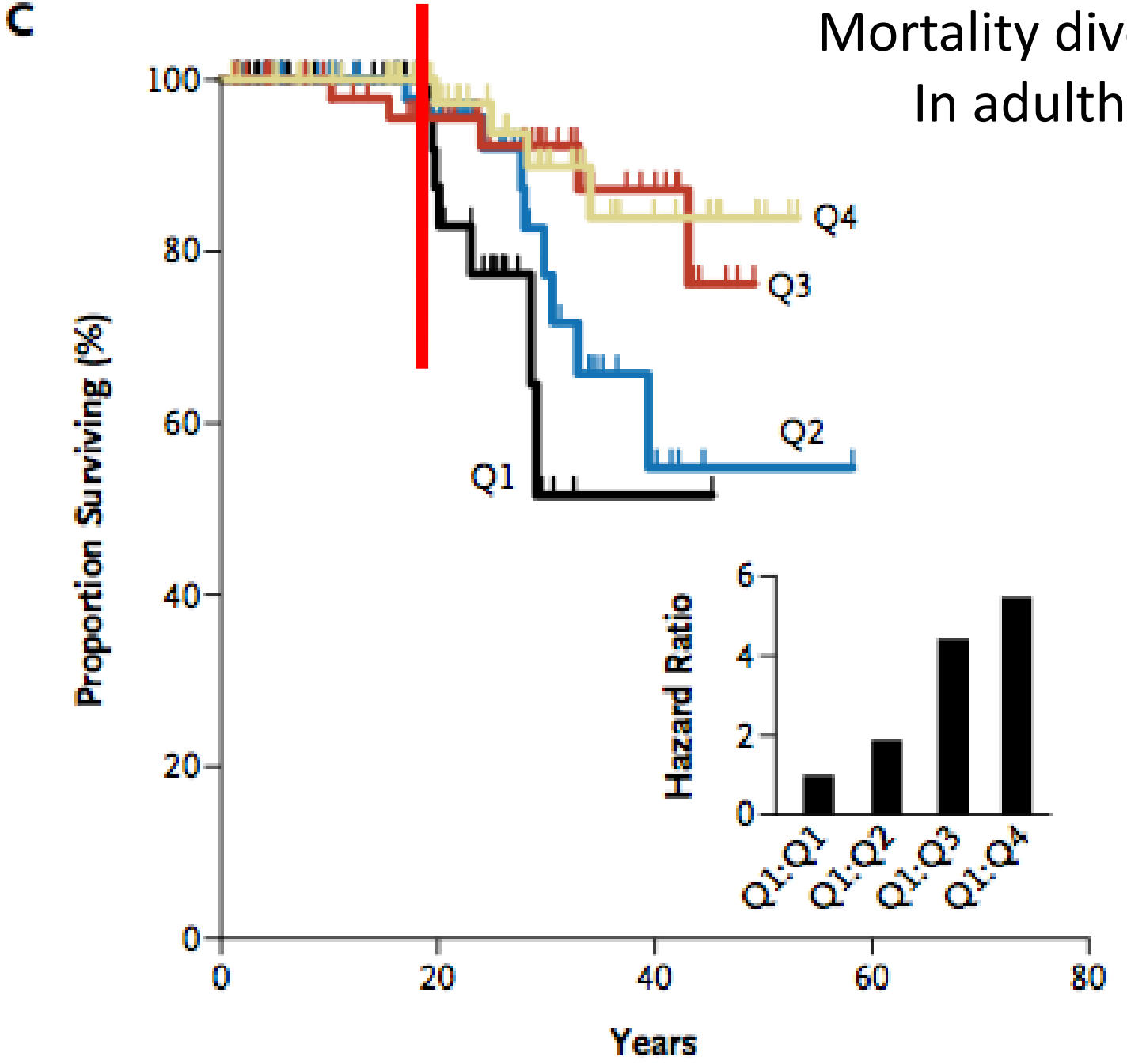
Stringent Intracellular, Loose Extracellular Requirements



O_2^- as a Continuous Variable



Mortality divergence
In adulthood



Residual Superoxide Production

Strong genotype-phenotype association

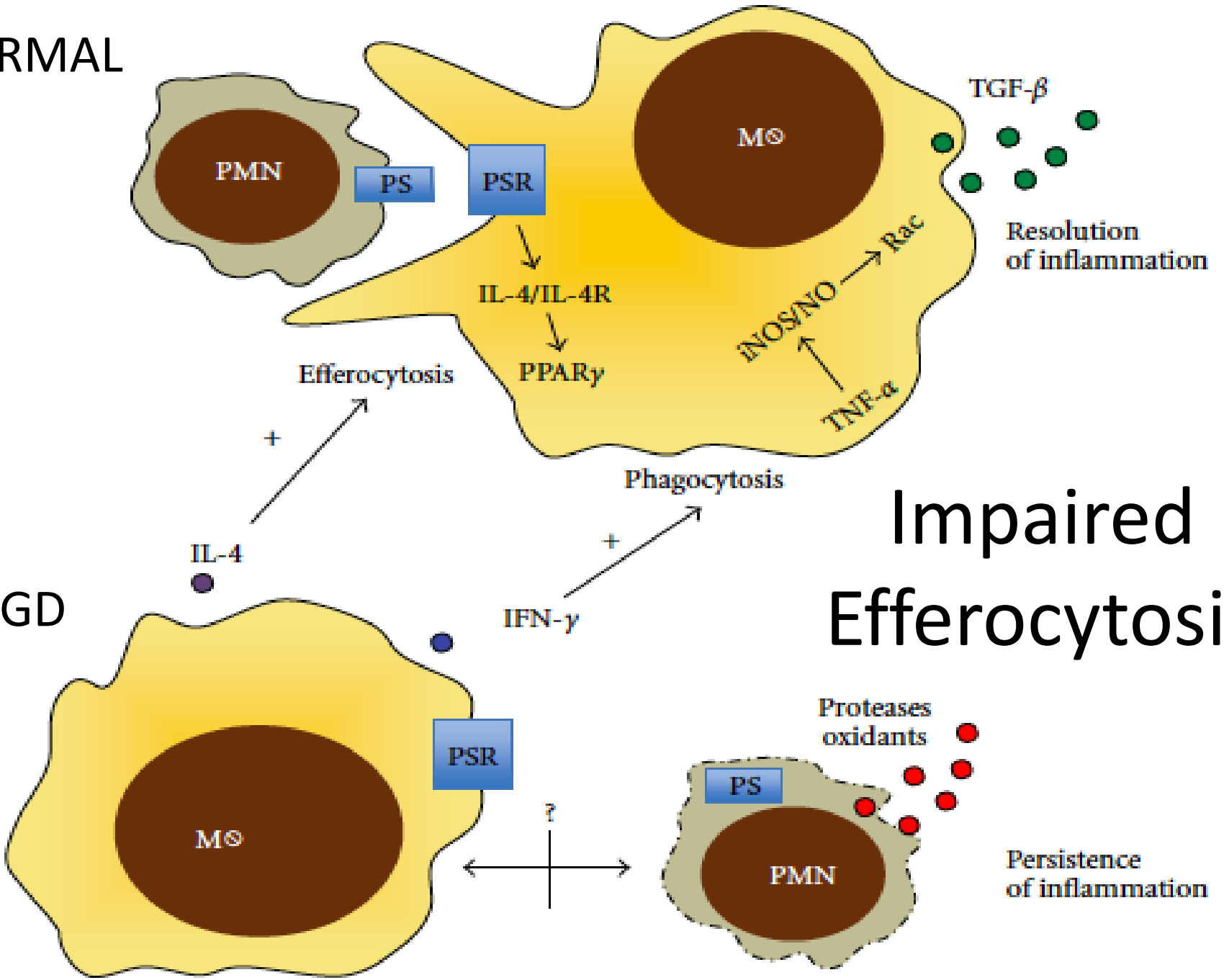
Residual superoxide production is important

You can predict superoxide production from the mutation

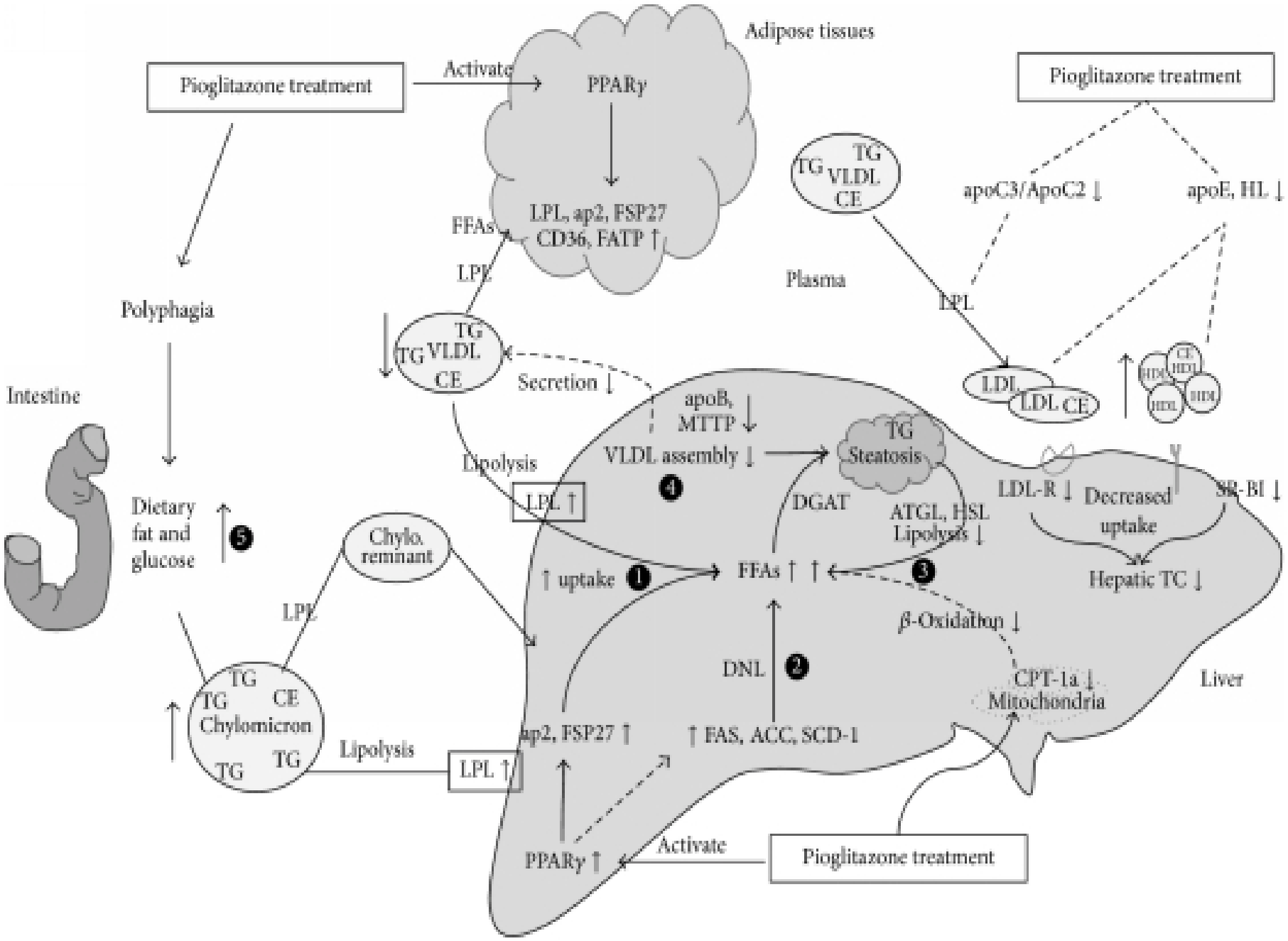
Affects mortality

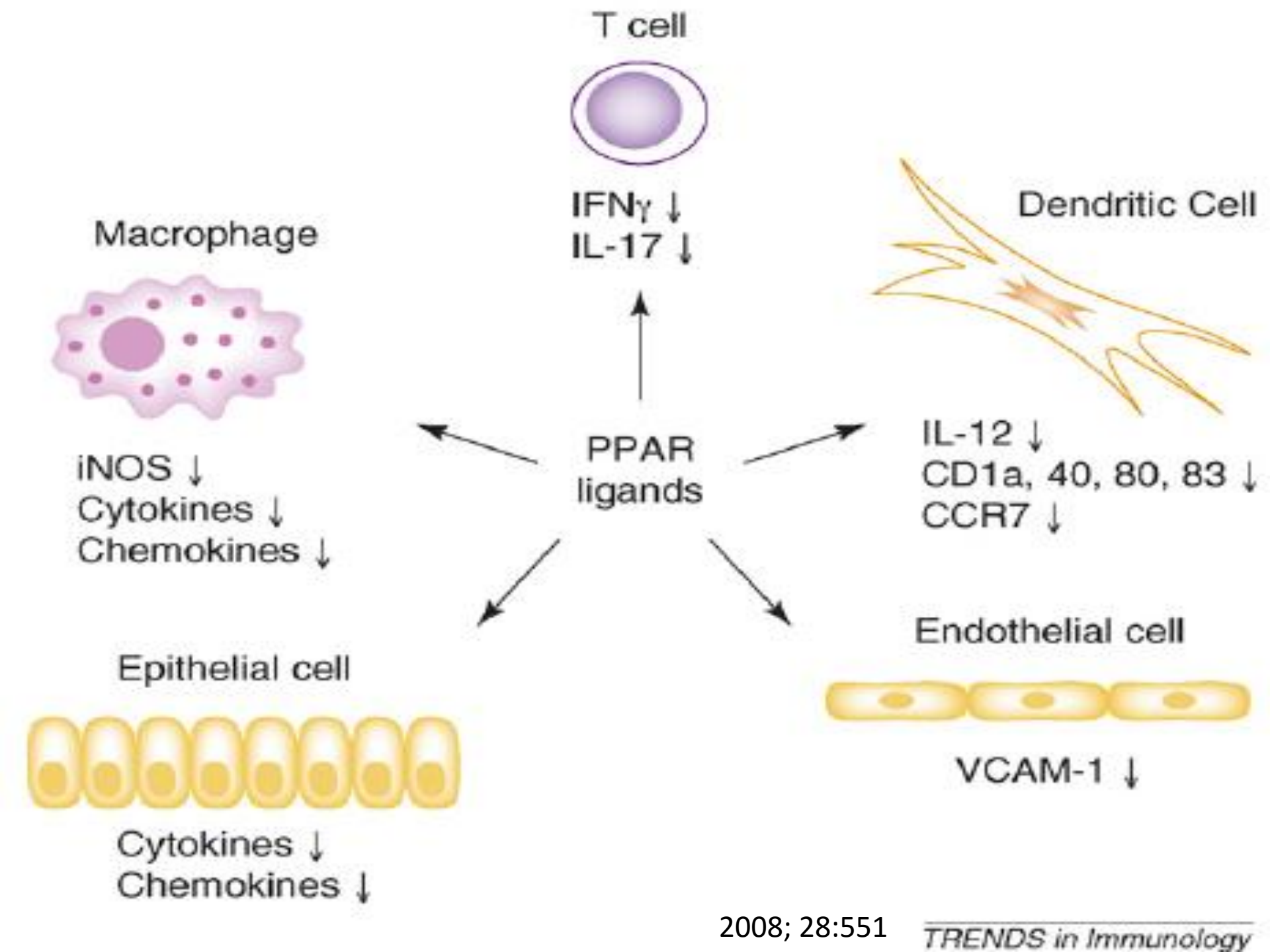
Can it be affected?

NORMAL



Impaired Efferocytosis


Adipose tissues
Pioglitazone treatment
Activate
PPARγ
LPL, ap2, FSP27
CD36, FATP ↑
FFAs
LPL
TG
TG VLDL
CE
Secretion ↓
Plasma
TG
TG VLDL
CE
apoC3/ApoC2 ↓
apoE, HL ↓
LPL
LDL
LDL CE
HDL
Pioglitazone treatment
Polyphagia
Intestine
Dietary
fat and
glucose
5
Chylo.
remnant
LPL
TG
TG CE
Chylomicron
TG TG
Lipolysis
LPL ↑
apoB,
MTTP ↓
VLDL assembly ↓
4
Lipolysis
LPL ↑
TG
Steatosis
DGAT
ATGL, HSL
Lipolysis ↓
LDL-R ↓
Decreased
uptake
SR-BI ↓
↑ uptake
1
FFAs ↑ ↑
3
Hepatic TC ↓
β-Oxidation ↓
DNL
2
CPT-1a ↓
Mitochondria
Liver
ap2, FSP27 ↑
↑ FAS, ACC, SCD-1
PPARγ ↑
Activate
Pioglitazone treatment



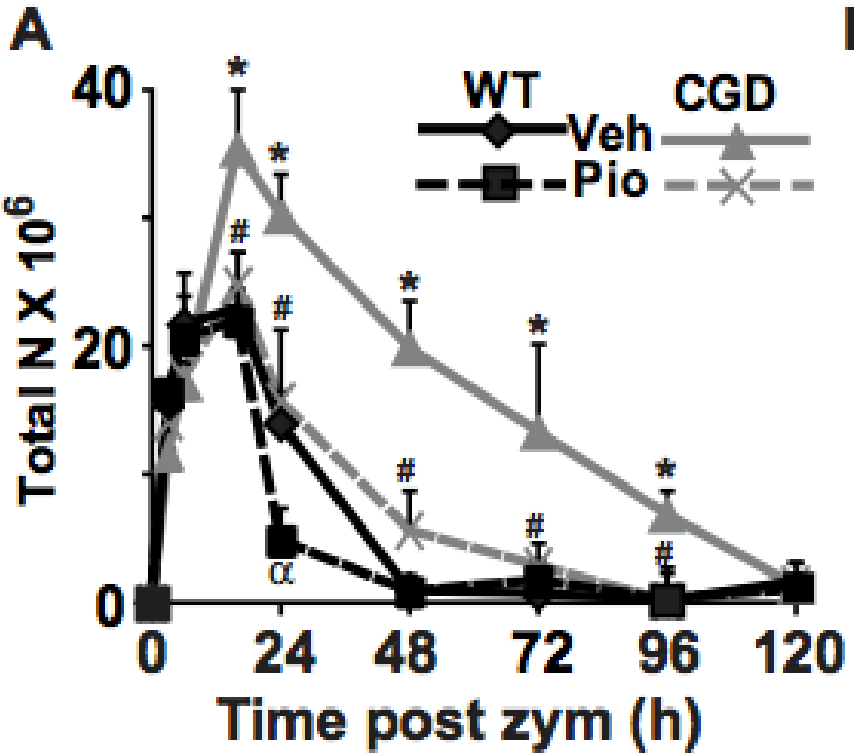
2008; 28:551 TRENDS in Immunology

blood

2010 116: 4512-4522
Prepublished online Aug 6, 2010;
doi:10.1182/blood-2010-02-272005

PPAR{gamma} activation normalizes resolution of acute sterile inflammation in murine chronic granulomatous disease

Ruby Fernandez-Boyanapalli, S. Courtney Frasch, David W. H. Riches, R. William Vandivier, Peter M. Henson and Donna L. Bratton



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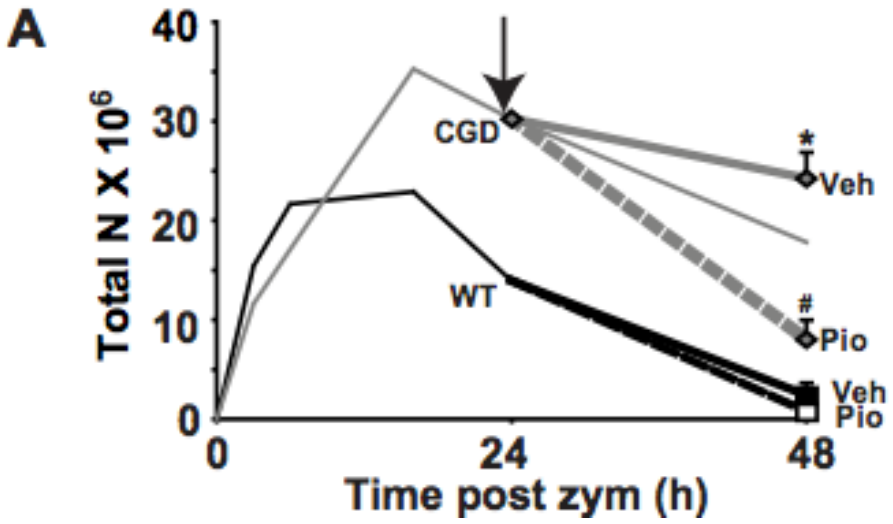
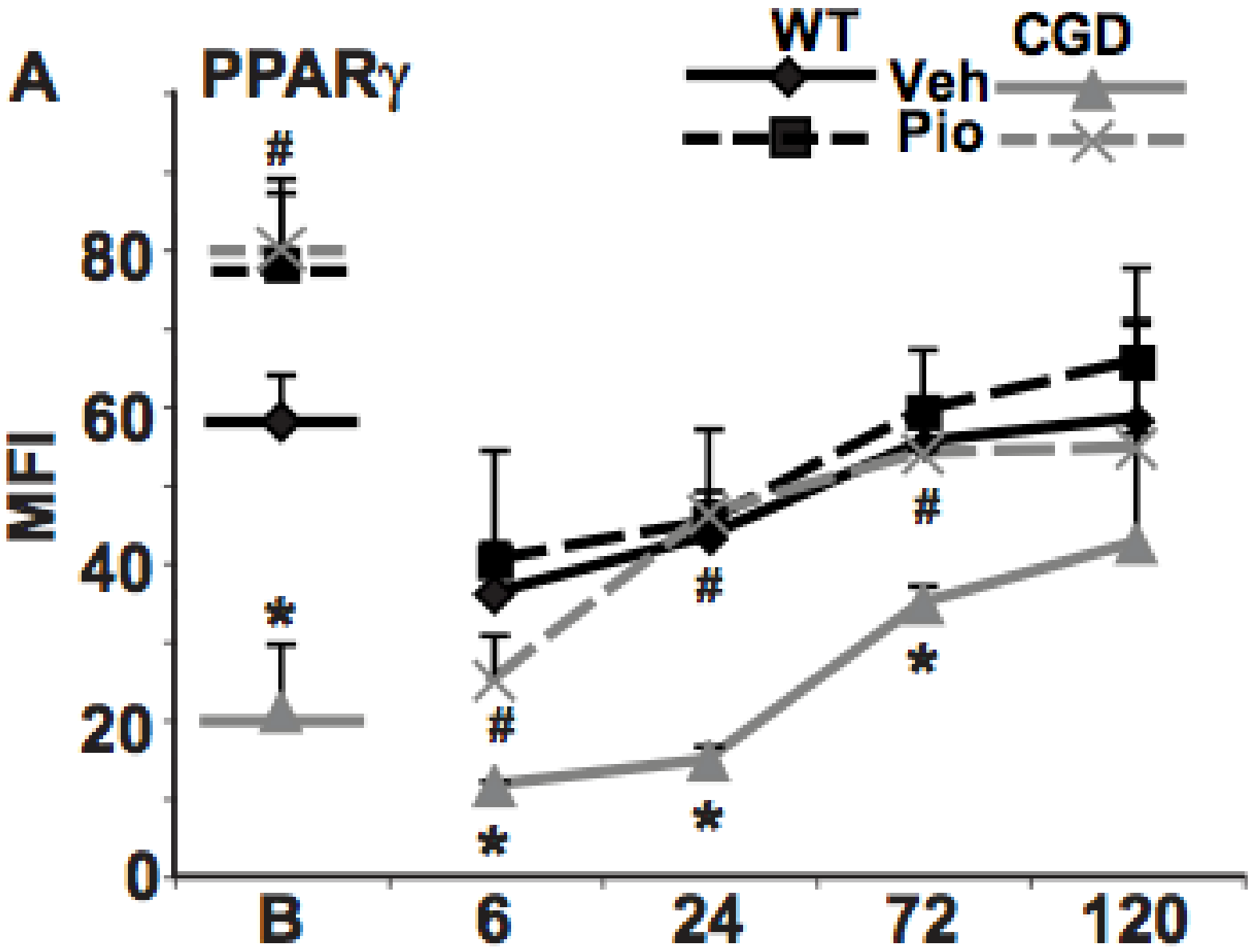
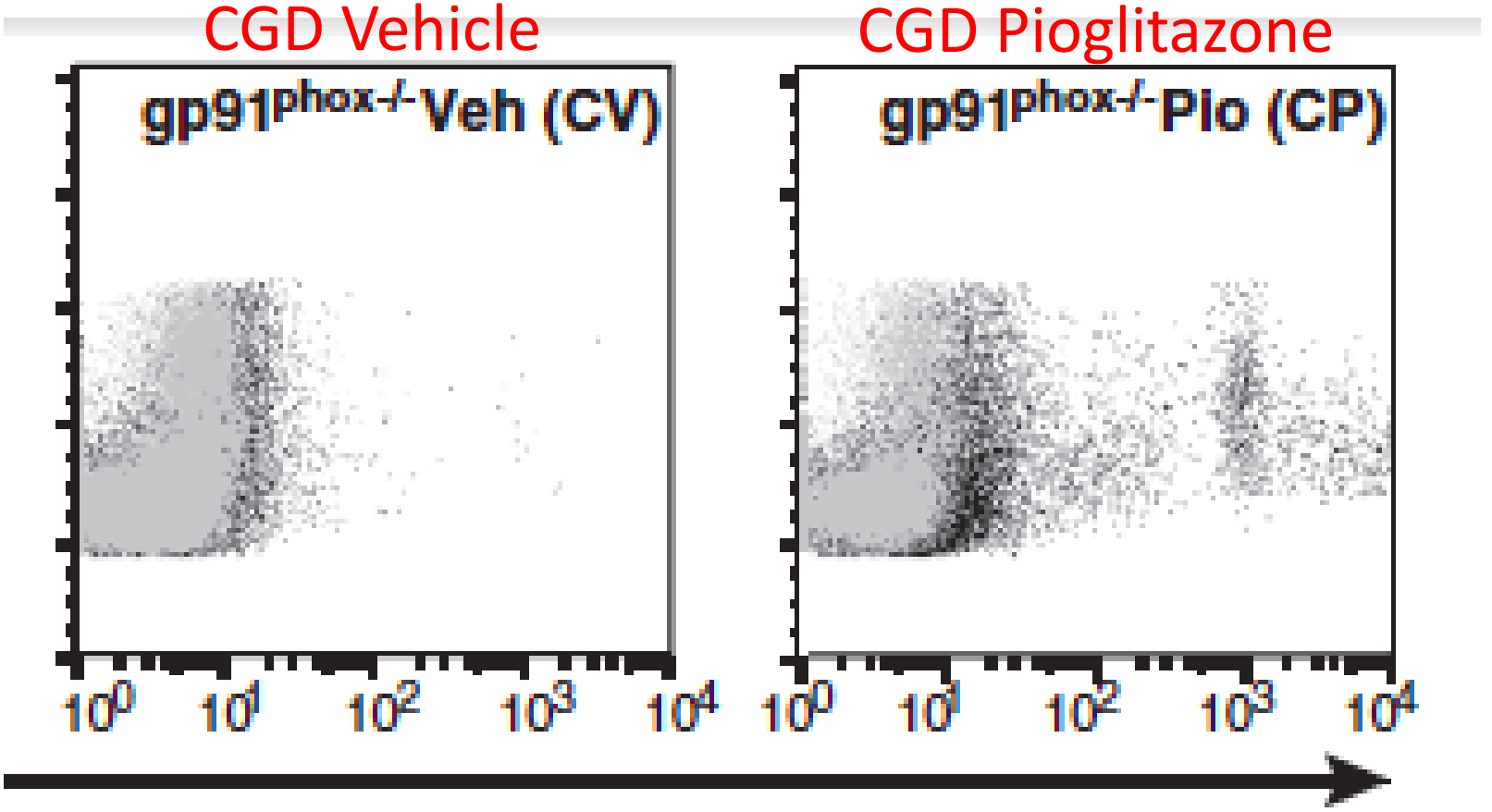


Pioglitazone increases PPARγ



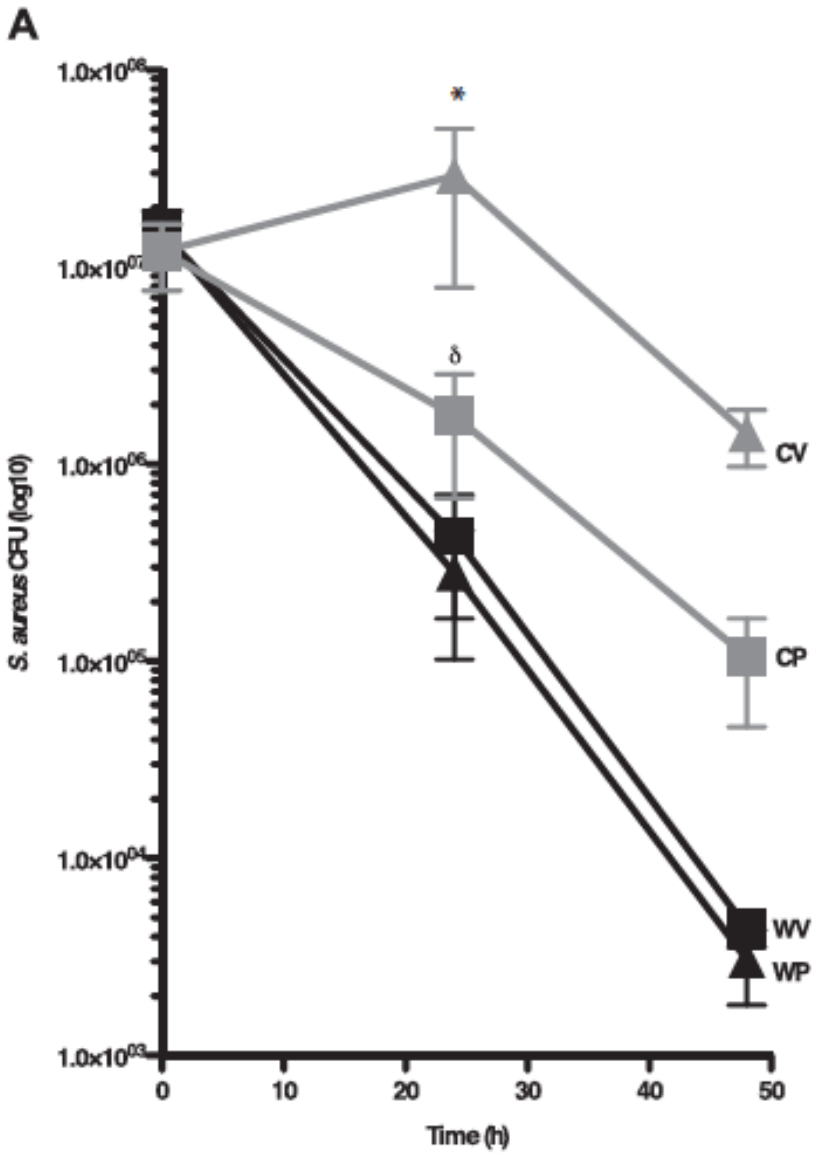
Pioglitazone restores phagocyte mitochondrial oxidants and bactericidal capacity in chronic granulomatous disease

Ruby F. Fernandez-Boyanapalli, PhD,[a] S. Courtney Frasch, PhD,[a] Stacey M. Thomas, MS,[a] Kenneth C. Malcolm, PhD,[b] Michael Nicks, PhD,[a] Ronald J. Harbeck, PhD,[a,b,c] Claudia V. Jakubzick, PhD,[a] Raphael Nemenoff, PhD,[d] Peter M. Henson, MD, PhD,[a,b,c] Steven M. Holland, MD,[e] and Donna L. Bratton, MD[a] *Denver, Colo, and Bethesda, Md*



JACI 2015;135:517-27

Pioglitazone Restores Staphylococcal killing in vivo in mice

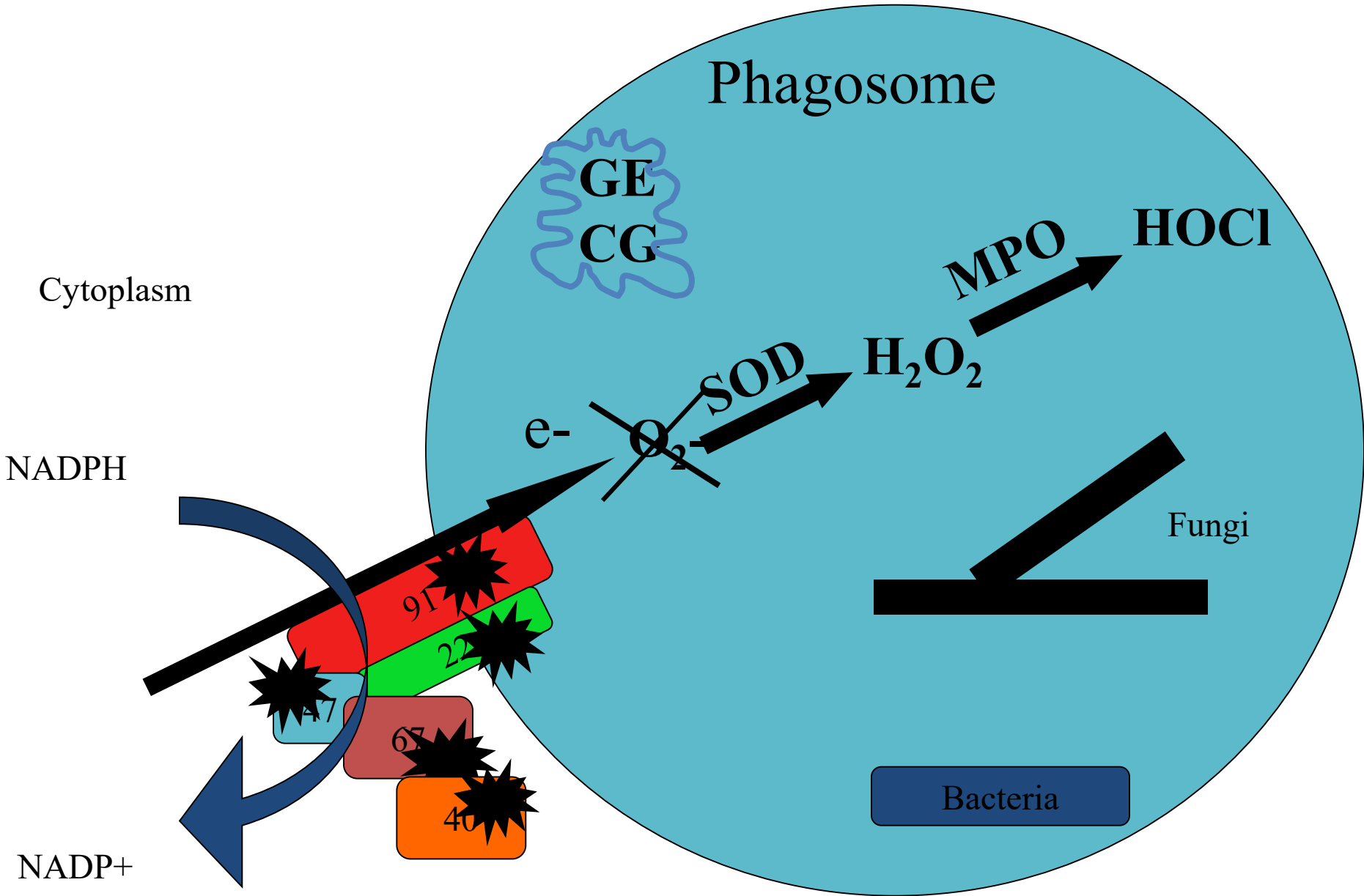


Vehicle

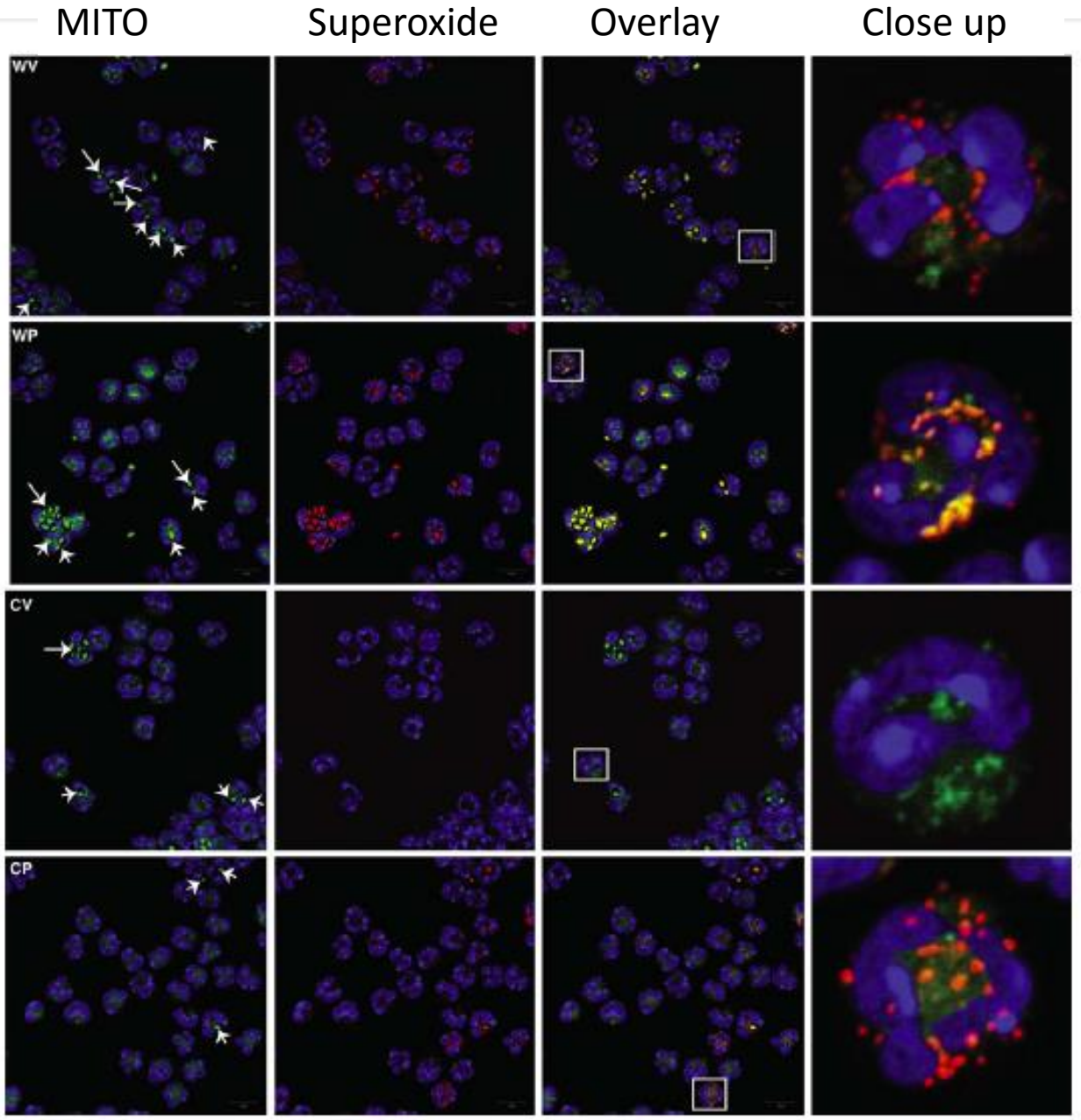
Pioglitazone

Wild type

But the NADPH Oxidase is Still Broken

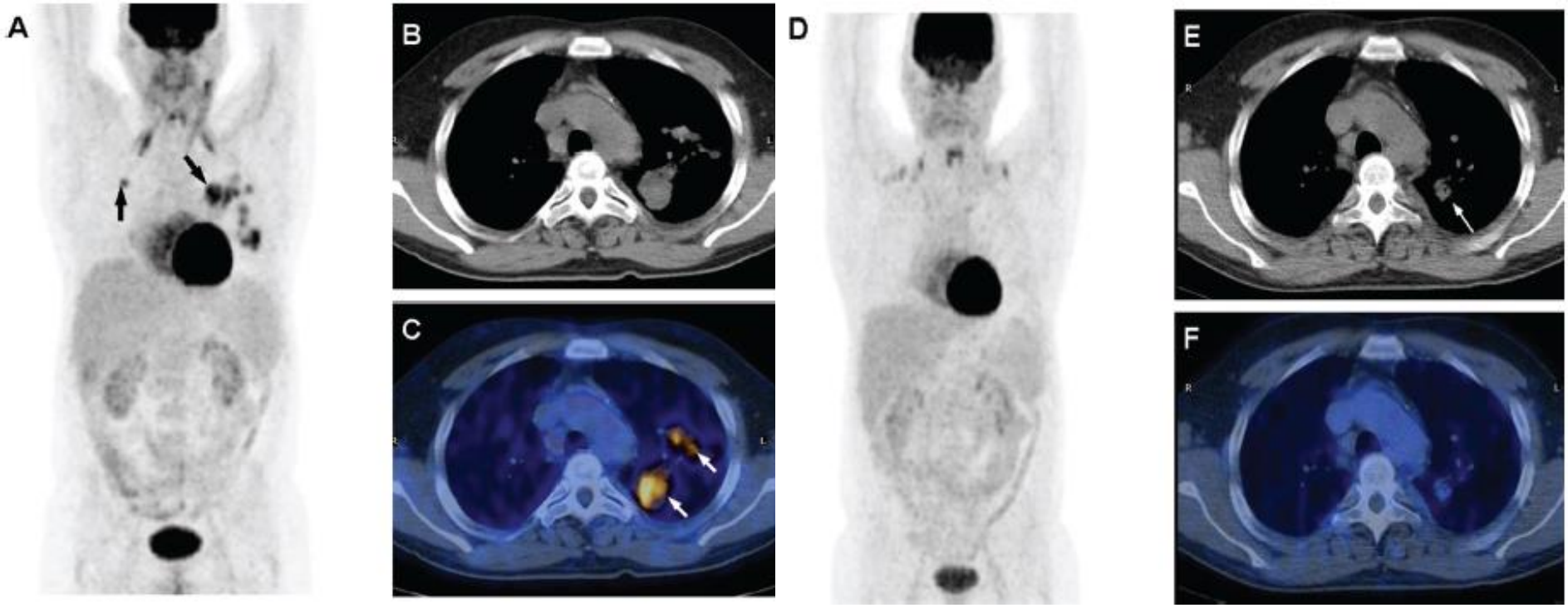


Pioglitazone induces mitochondrial superoxide production



Successful Low Toxicity Hematopoietic Stem Cell Transplantation for High-Risk Adult Chronic Granulomatous Disease Patients

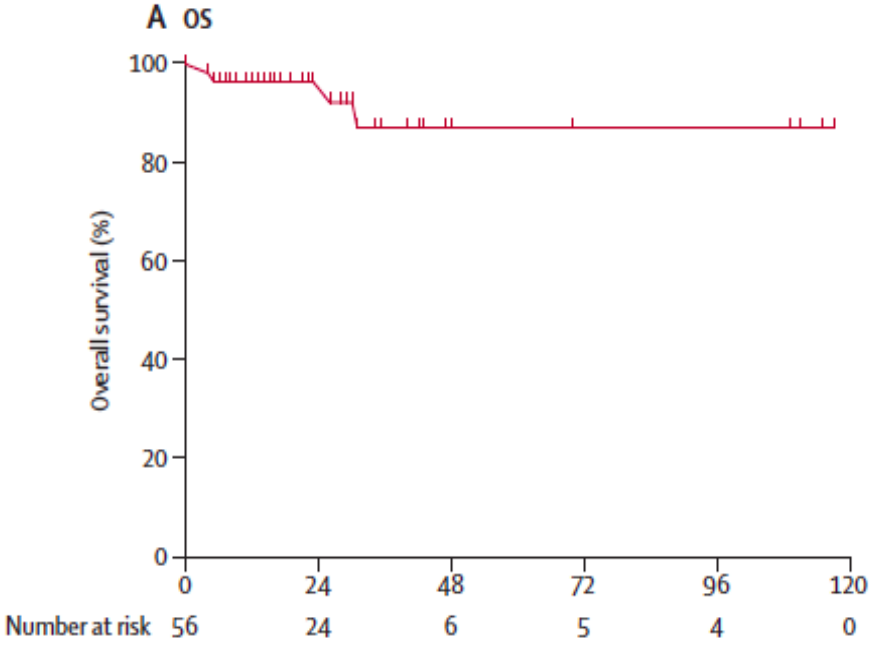
Tayfun Güngör,[1, 4] Jörg Halter,[2] Anne Klink,[2] Sonja Junge,[1] Katrin D. M. Stumpe,[3] Reinhard Seger,[1] and Urs Schanz[2]

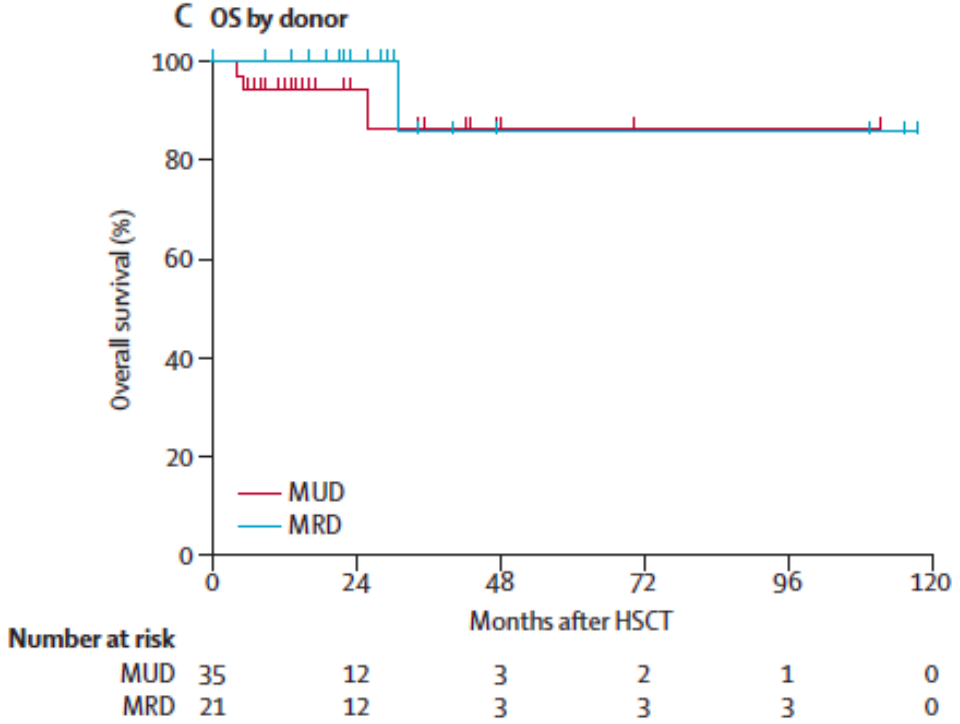


Transplantation 2005;79: 1596–1606)

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

Tayfun Güngör, Pierre Teira, Mary Slatter, Georg Stussi, Polina Stepensky, Despina Moshous, Clementien Vermont, Imran Ahmad, Peter J Shaw, José Marcos Telles da Cunha, Paul G Schlegel, Rachel Hough, Anders Fasth, Karim Kentouche, Bernd Gruhn, Juliana F Fernandes, Silvy Lachance, Robbert Bredius, Igor B Resnick, Bernd H Belohradsky, Andrew Gennery, Alain Fischer, H Bobby Gaspar, Urs Schanz, Reinhard Seger, Katharina Rentsch, Paul Veys, Elie Haddad, Michael H Albert, Moustapha Hassan*, on behalf of the Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation†*



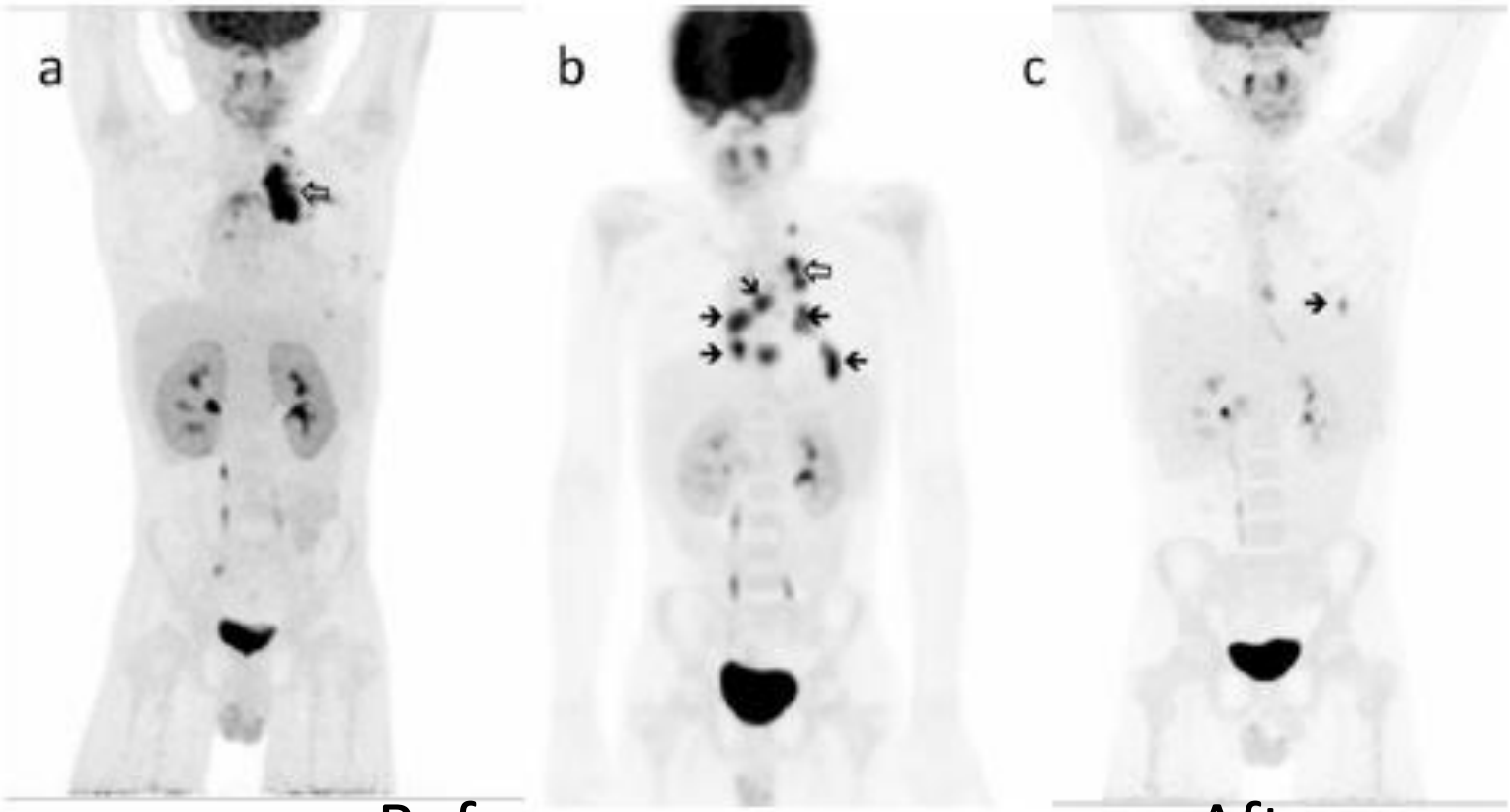


Lancet 2014

Haploidentical Hematopoietic Cell Transplantation with Post-Transplant Cyclophosphamide in a Patient with Chronic Granulomatous Disease and Active Infection: A First Report

Mark Parta[1] · Dianne Hilligoss[2] · Corin Kelly[2] · Nana Kwatemaa[2] · Narda Theobald[2] · Harry Malech[2] · Elizabeth M. Kang[2]

Scedosporium apiospermum



Before

After

Unpublished Results: NIH CGD BMT
Elizabeth Kang, Mark Parta, Harry Malech

15 CGD BMT with active infection/inflammation

OVERALL SURVIVAL: 13 of 15 (87%)

No deaths due to prior infection

EVENT FREE SURVIVAL: 13 of 15

Full myeloid donor engraftment

All infections resolved in survivors

GRAFT versus HOST DISEASE: 1 of 15

Granulocyte infusions: 8 patients (1-5 infusions)

BMT for CGD

BMT can be $\geq$ 90% successful

Even with active infection/inflammation

Resolves refractory infections (mostly fungal)

X-linked Carriers

Retrospective analysis of 162 females

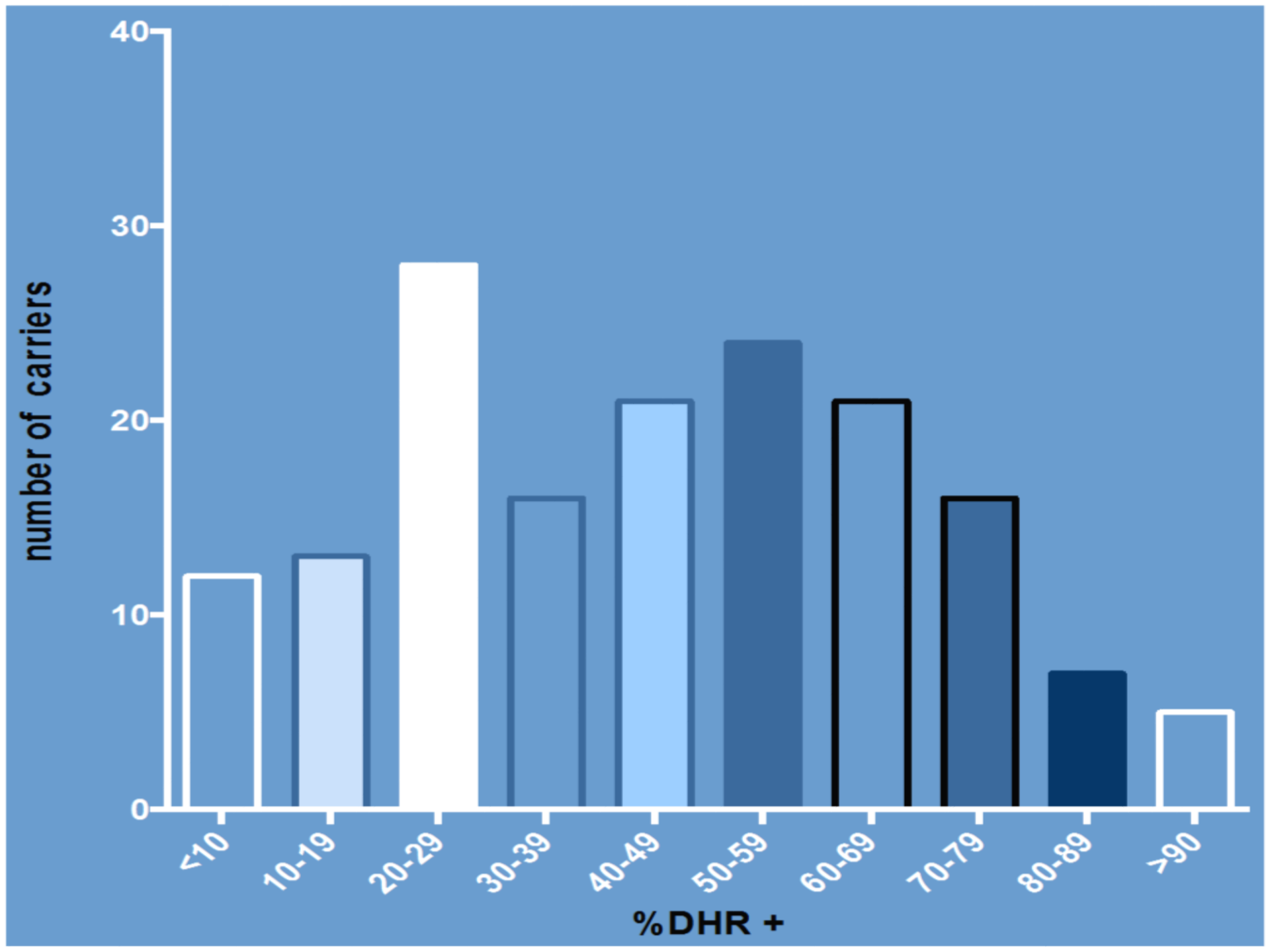
DHR or NBT on all

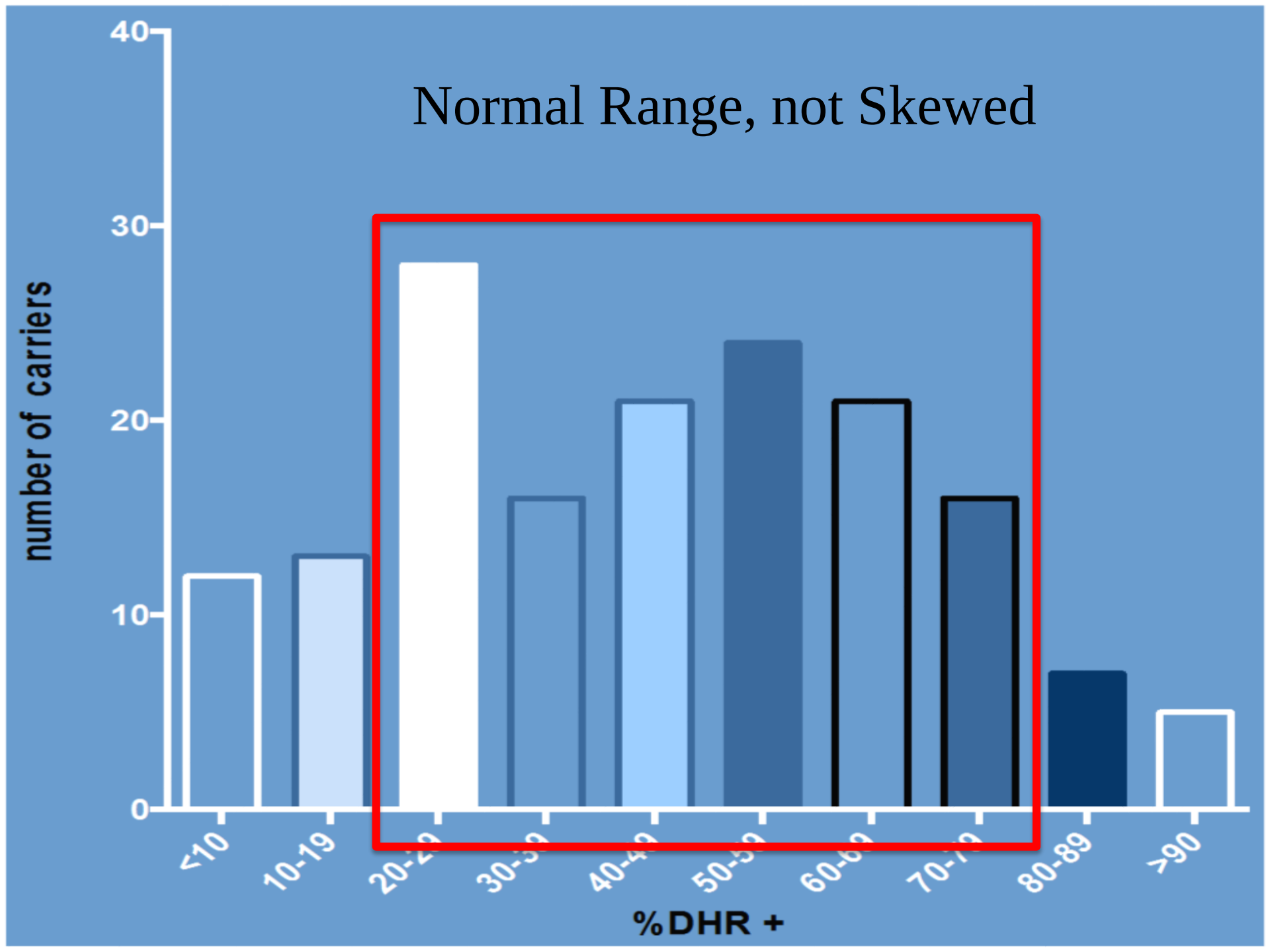
Clinical data on 94 females

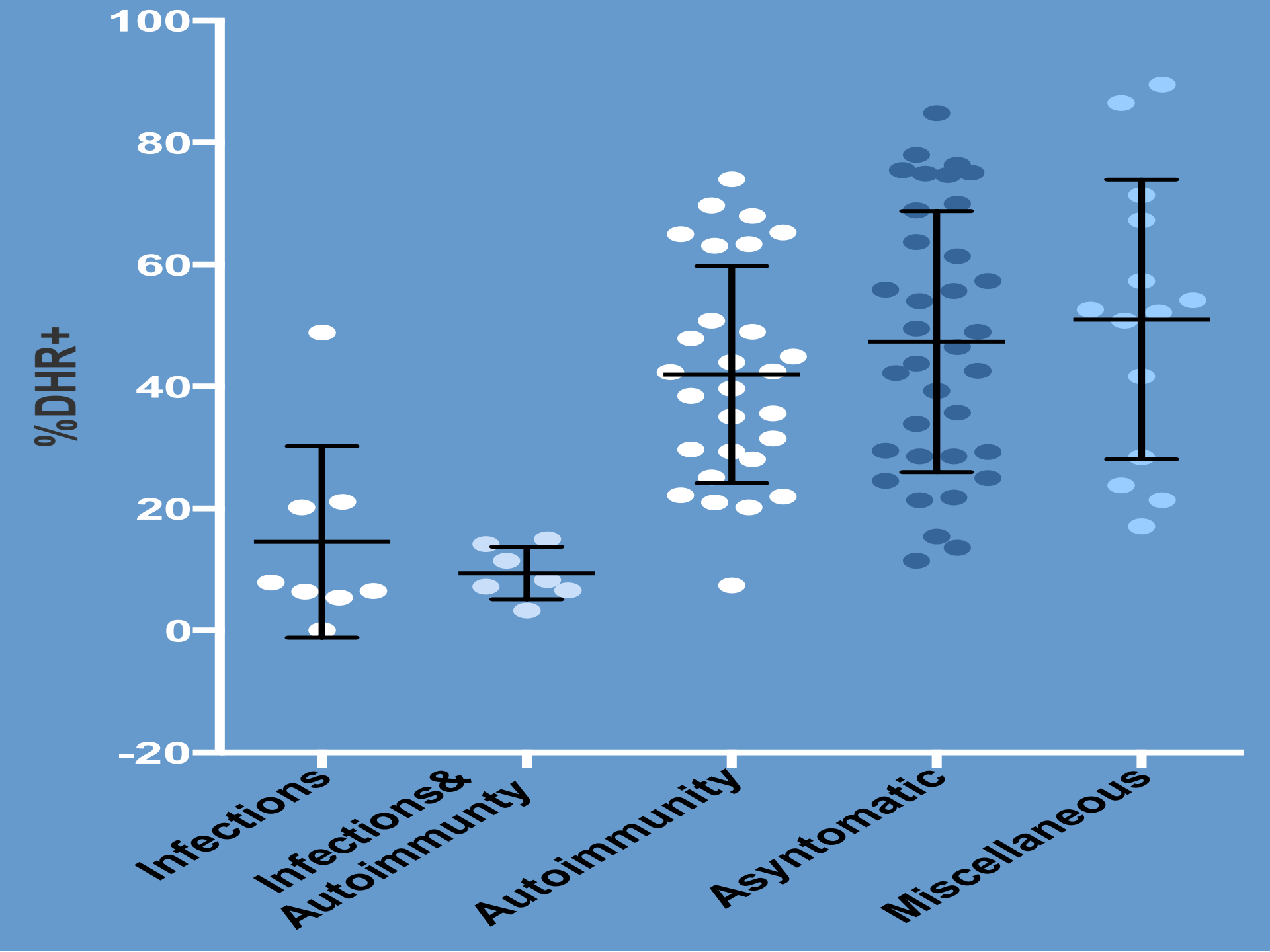
Median age 36 years (range: 3 months-80 y)

DHR mean 46%DHR+

median 47%DHR+


40
30
20
10
0
number of carriers
<10
10-19
20-29
30-39
40-49
50-59
60-69
70-79
80-89
>90
%DHR +

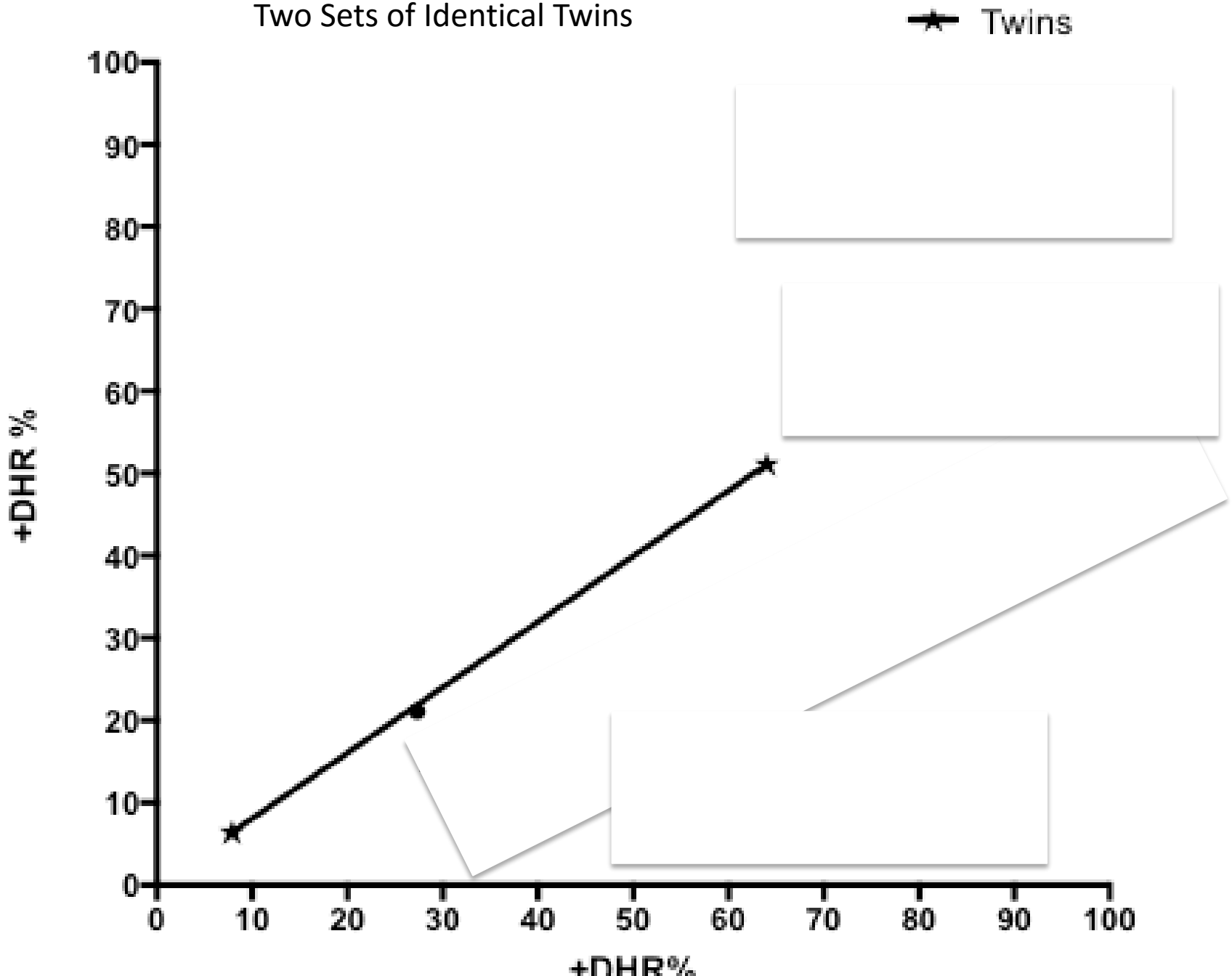

Normal Range, not Skewed
number of carriers
40
30
20
10
0
<10
10-19
80-89
>90
%DHR +

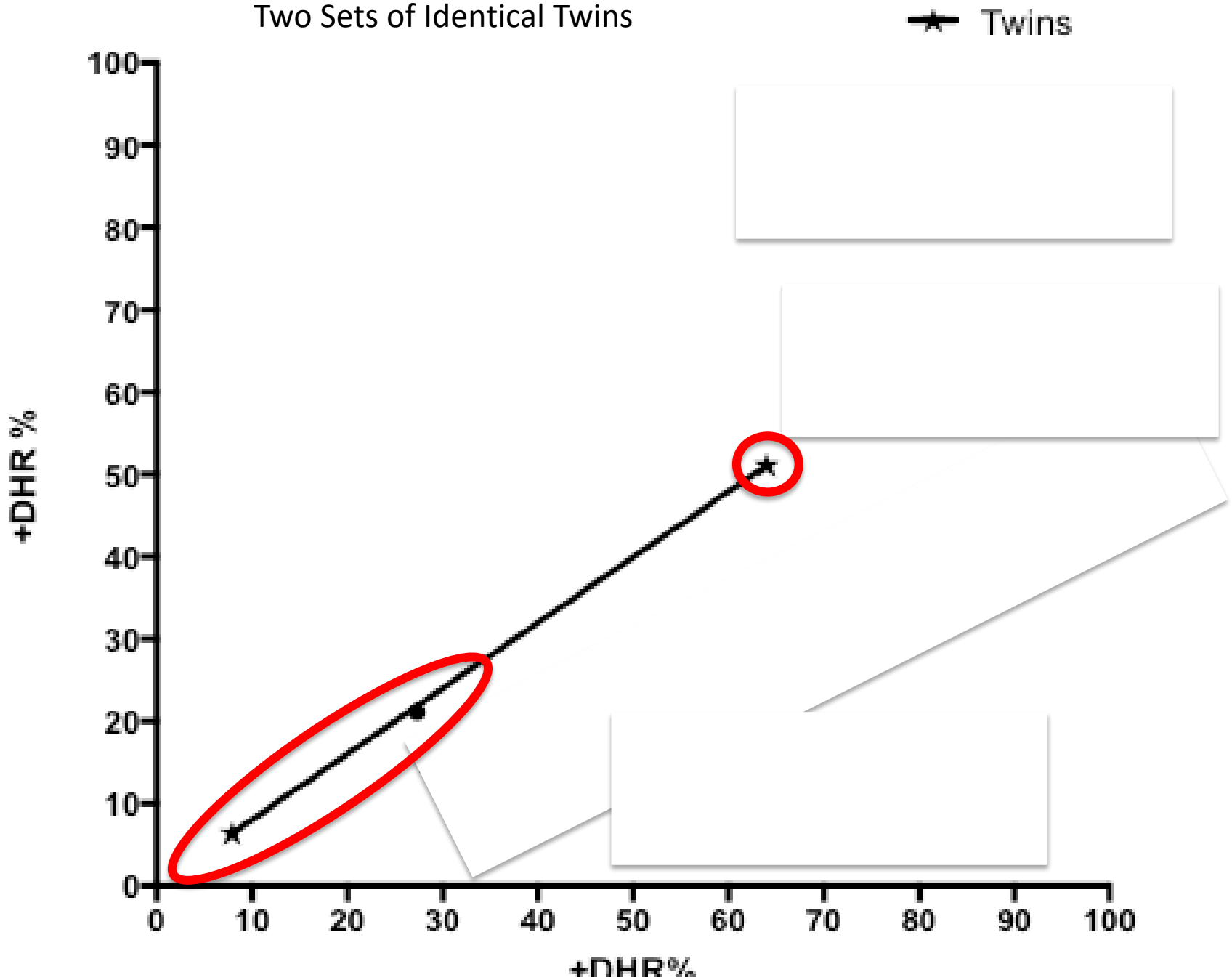

100
80
60
40
20
0
-20
%DHR+
Infections
Infections&
Autoimmunty
Autoimmunity
Asyntomatic
Miscellaneous

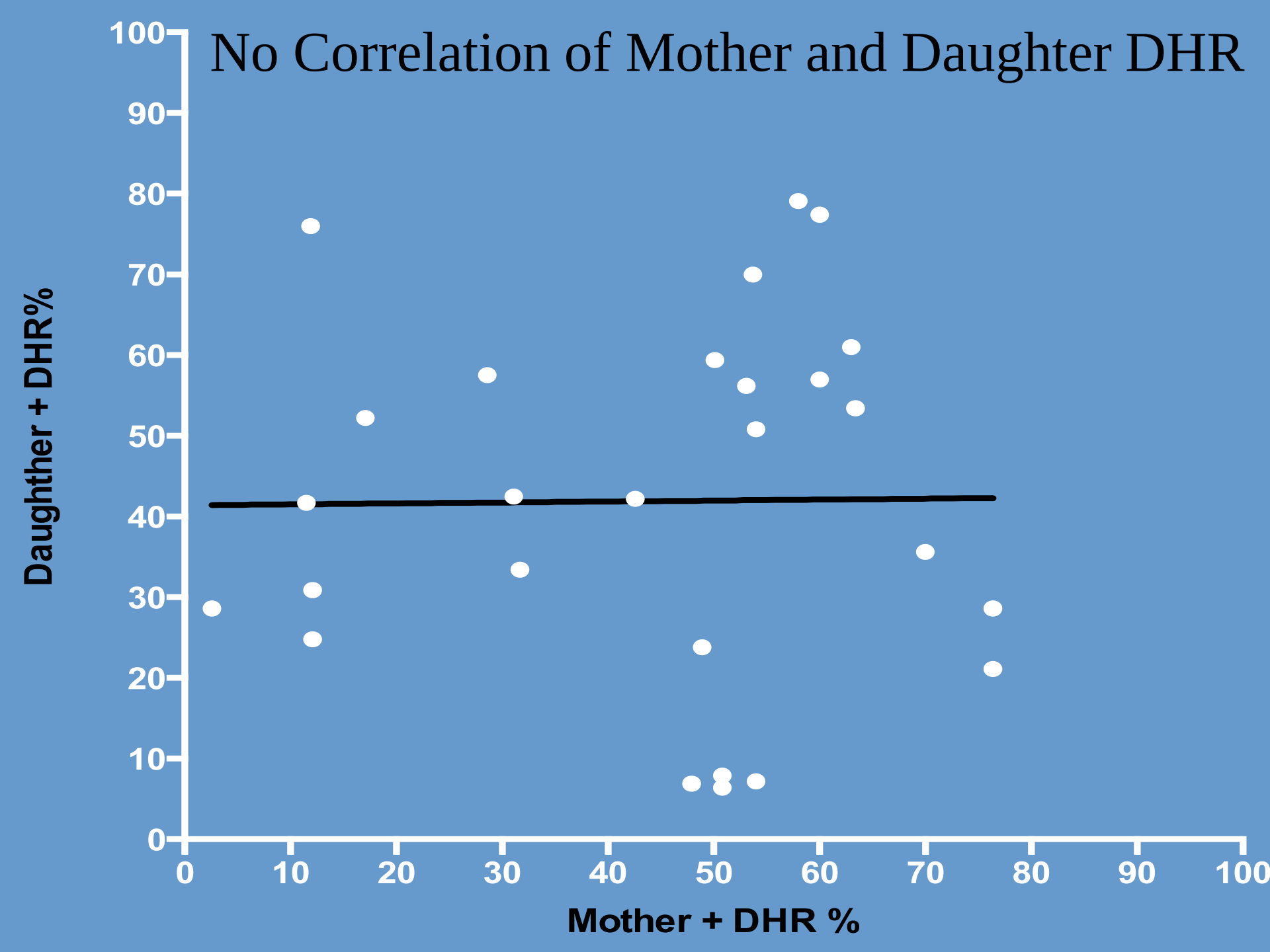
Strength of infection association	%DHR+	Strength of autoimmunity association
15.12* (6.3-36.27)	<10	0.28 (0.04-1.83)
8.55 (2.01-36.28)**	<20	0.4 (.06-2.3)
5 (0.47-52.4)	<30	1.25 (0.61-2)
n/a	>30	1-6 (0.6-41)

Autoimmunity and Inflammatory manifestations	Number of Carriers
Discoid Lupus Erythematous	14
Oral ulcers	7
Photosensitivity	5
Imflammatory bowel disease (Crohn's like disease)	7
Raynaud syndrome	3
Systemic lupus erythematous	3

Two Sets of Identical Twins




Two Sets of Identical Twins
Twins
100
90
80
70
60
50
40
30
20
10
0
+DHR %
0
10
20
30
40
50
60
70
80
90
100
+DHR%


No Correlation of Mother and Daughter DHR
Daughther + DHR%
Mother + DHR %
0
10
20
30
40
50
60
70
80
90
100

X-linked Carriers

CGD infections occur below 20%DHR+, sometimes higher

Autoimmunity and inflammation are more common in carriers but not related to %DHR+

%DHR+ can change over time

%DHR+ Correlates within sibships, but not across generations

What is left to learn about CGD?

1. Treatment of liver abscesses is changing, steroids and antibiotics work
2. Residual superoxide is important, and it can be effected by drugs
3. Bone marrow transplantation is highly effective and increasingly safe
4. X-linked carriage of CGD has clinical effects and can change over time

Acknowledgements

Douglas B. Kuhns
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Debra Long Priel
Benjamin P. Soule
Kol A. Zarember
Joe Church
Harry L. Malech
John I. Gallin