Leiden University
Medical Center

De klinische waarde van de C1q bepaling; aandacht voor zowel lage als hoge levels.

Leendert Trouw

Dept Immunohematology and
Bloodtransfusion

Overview of the presentation

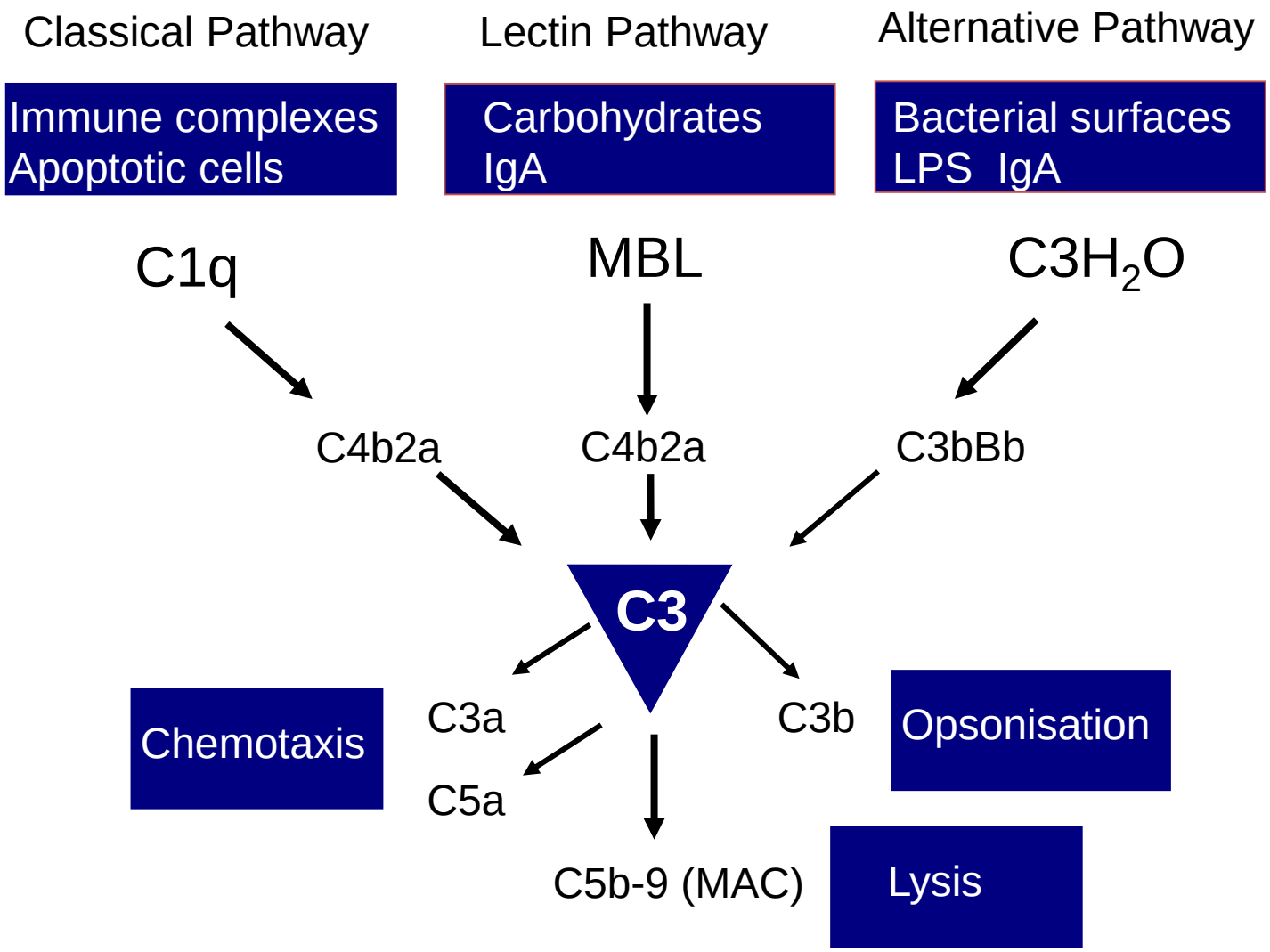
Introduction on complement and C1q

Low levels of C1q (C1q deficiency)

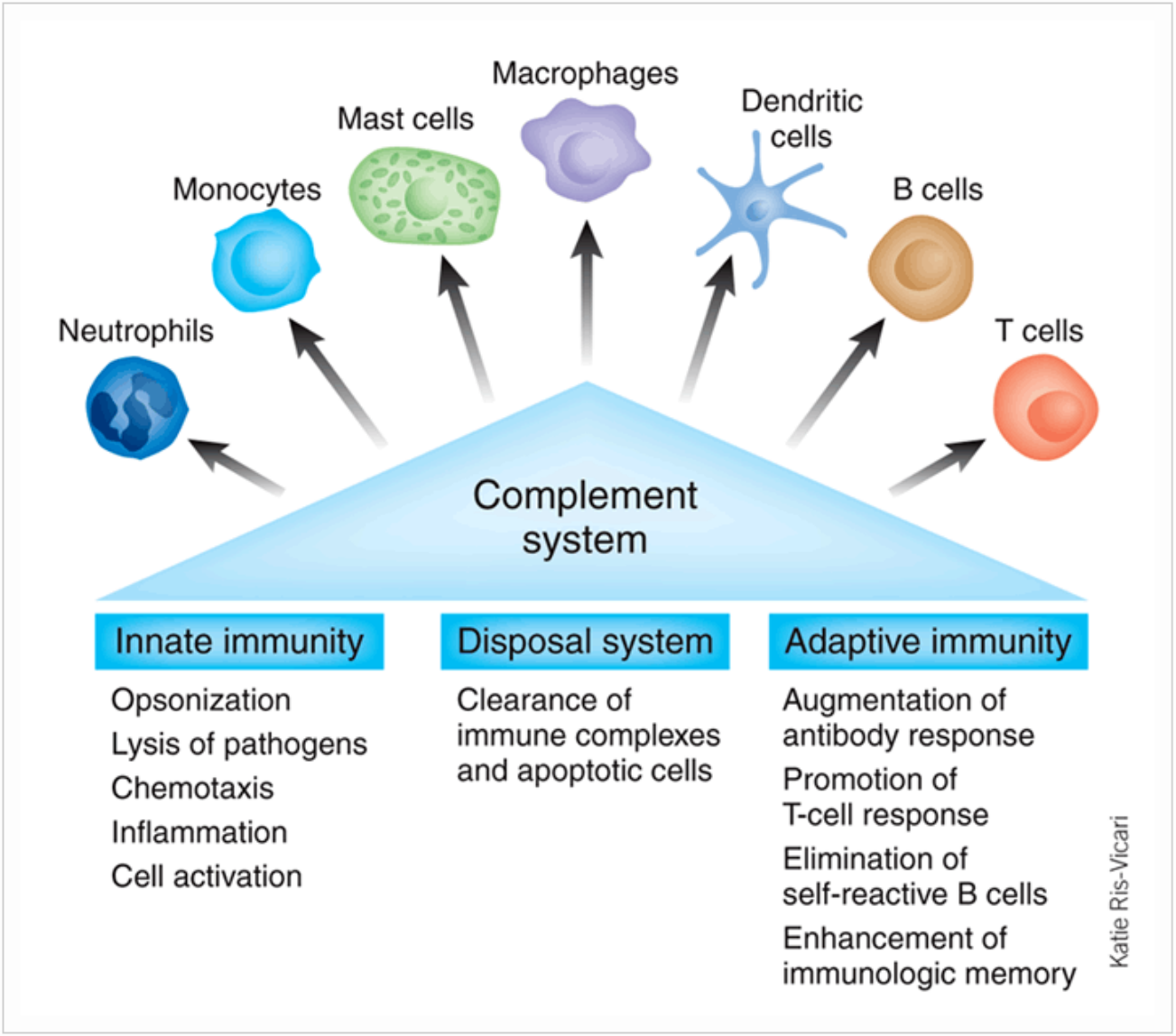
High levels of C1q (Tuberculosis)

Implications and future directions

The complement system

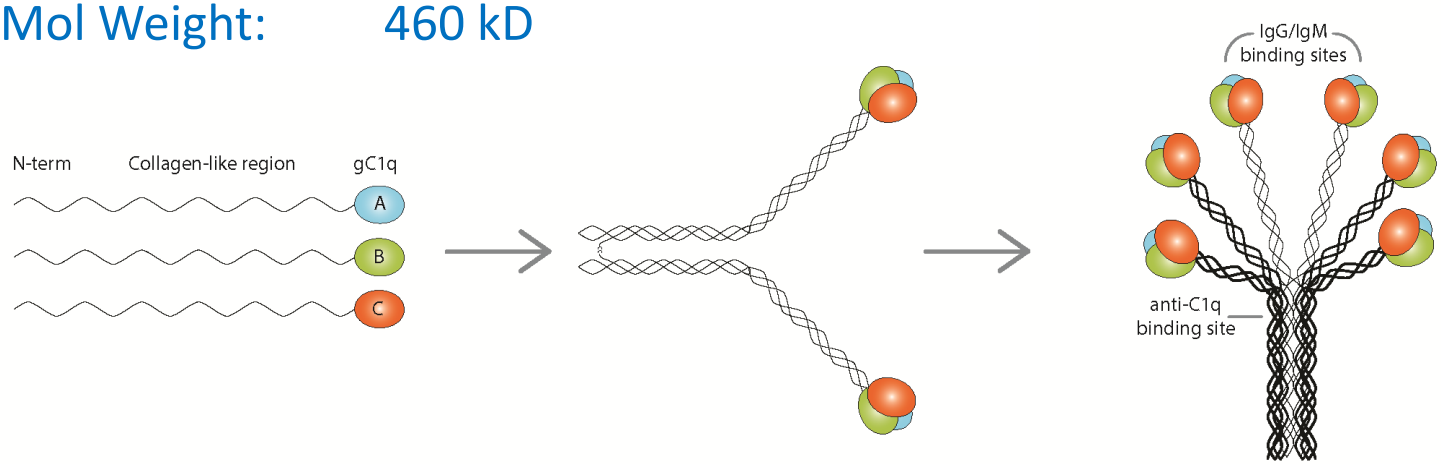


Roles of the complement system

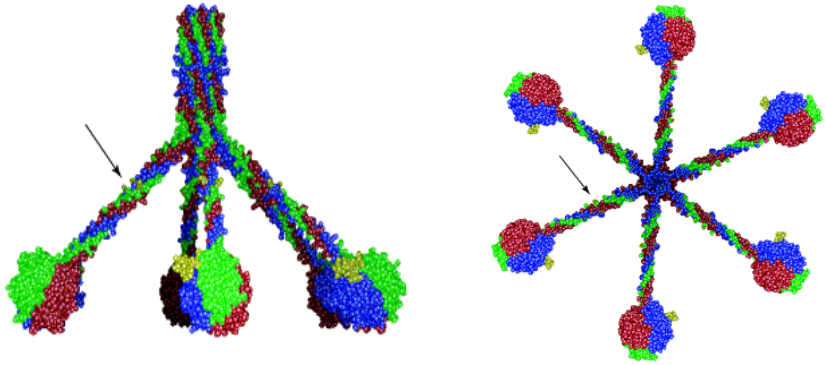


Assembly and functions of C1q

Produced by: Macrophages, Dendritic cells
Serum conc.: 200 µg/ml
Mol Weight: 460 kD



Beurskens Mol Immunol 2015



Gaboriaud Trends Imm 2004

C1q binding to IgG.

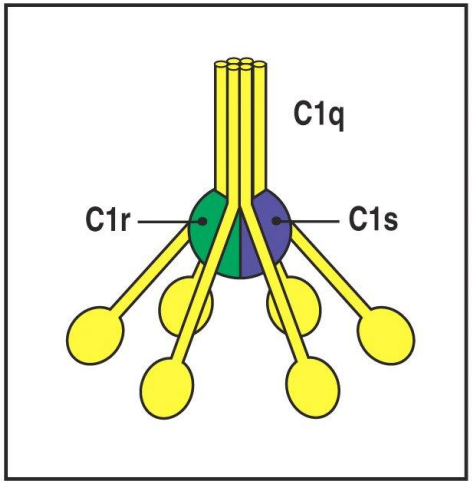


Figure 7-31 The Immune System, 2/e (© Garland Science 2005)

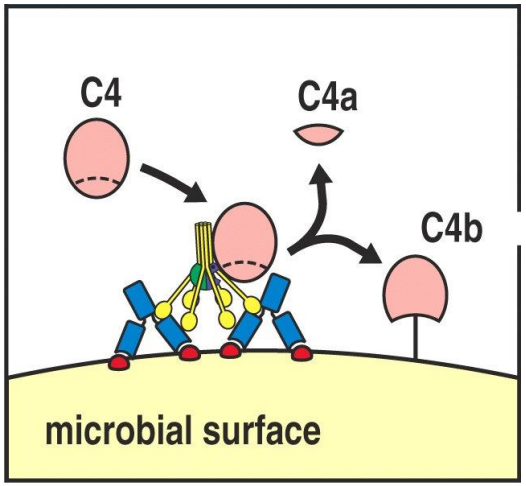
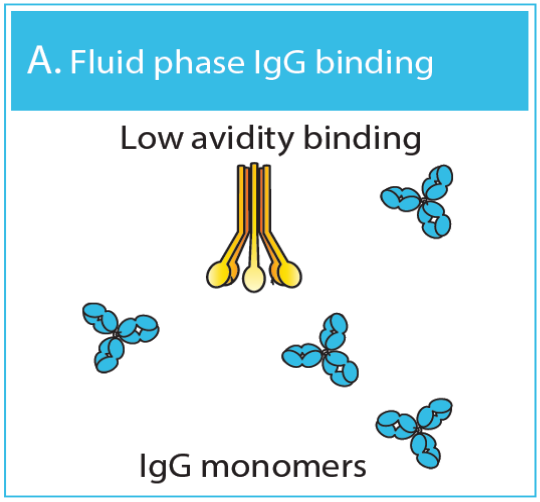
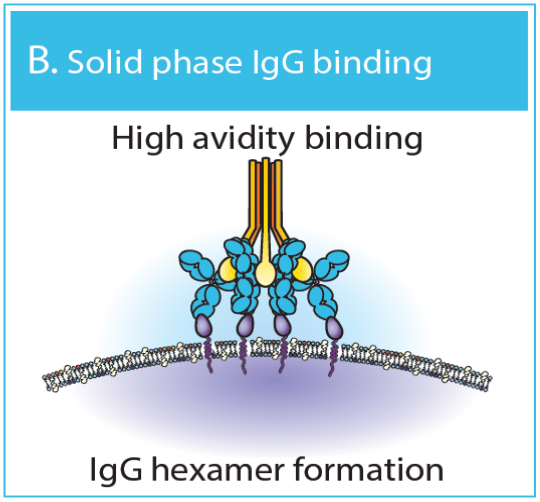
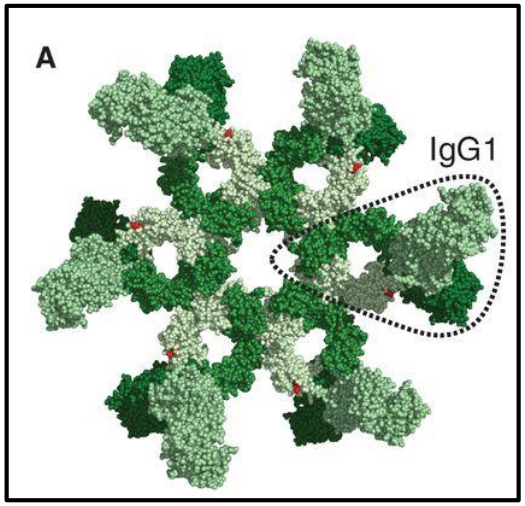


Figure 7-34 part 1 of 2 The Immune System, 2/e (© Garland Science 20



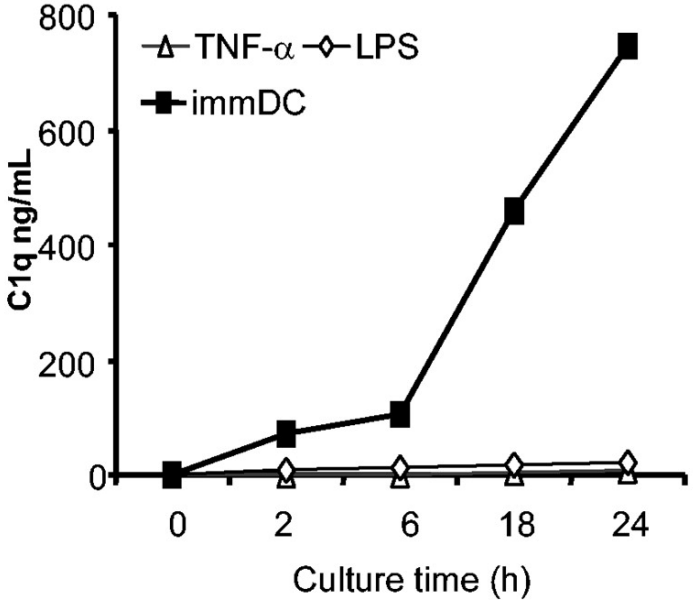


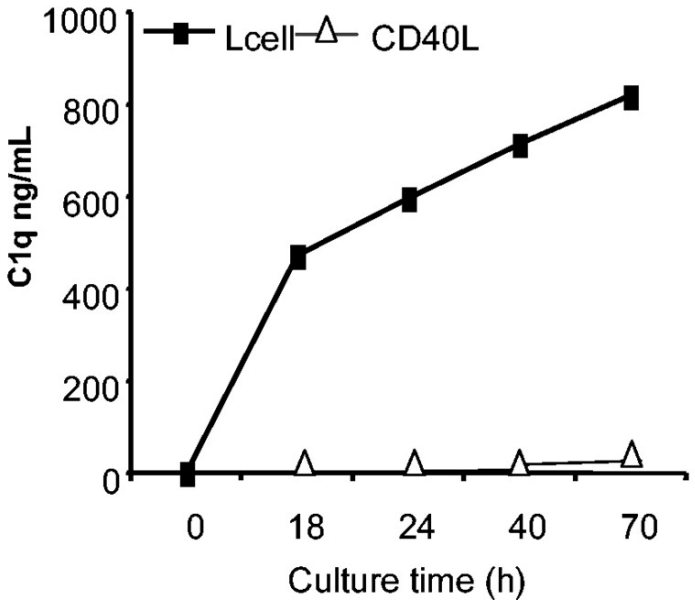


Beurskens et al. Mol Immunol. 2015

C. Diebolder et al. Science 2014

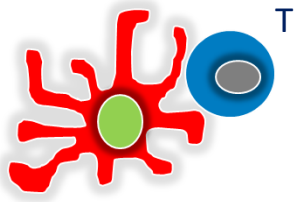
Maturation of Dendritic cells abrogates C1q production





C1q ⇑

Immature DC



C1q X

Mature DC

Complement deficiencies and clinical presentation

Complement protein	Effects of deficiency
C1, C2, C4	Immune-complex disease
C3	Susceptibility to capsulated bacteria
C5–C9	Only effect is susceptibility to *Neisseria*
Factor D, properdin (factor P)	Susceptibility to capsulated bacteria and *Neisseria* but no immune-complex disease
Factor I	Similar effects to deficiency of C3
DAF, CD59	Autoimmune-like conditions including paroxysmal nocturnal hemoglobinuria

Figure 9-9 The Immune System, 2/e (© Garland Science 2005)

Parham 2005

Complement and onset of SLE

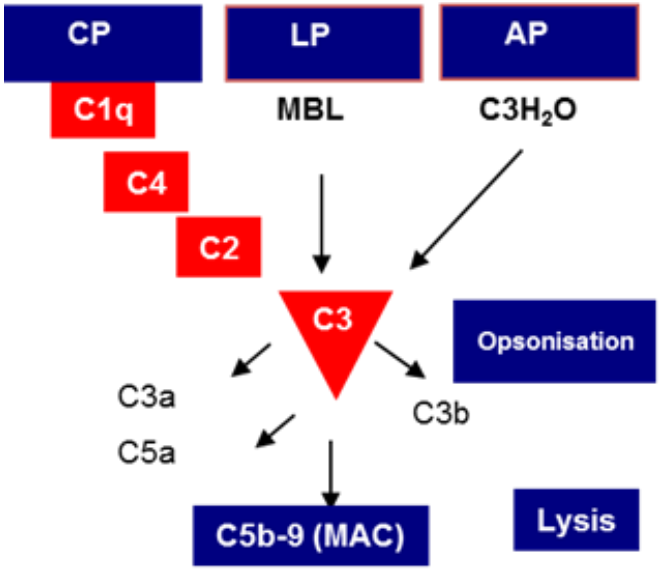
Human genetic deficiencies

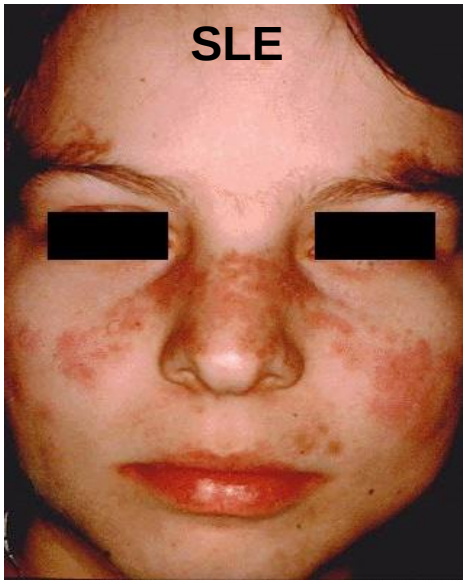
C1q - 80% SLE

C4 - 70% SLE

C2 - 10% SLE

C3 - 5% SLE





The complement system is involved in the prevention of SLE

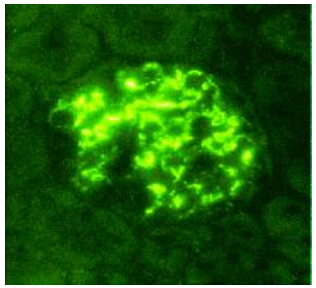
Complement and onset of SLE

news & views

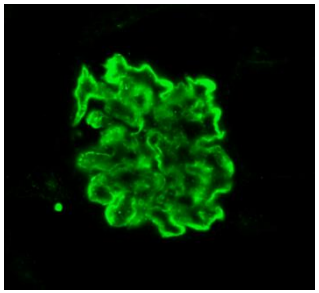
The lupus paradox

Michael C. Carroll

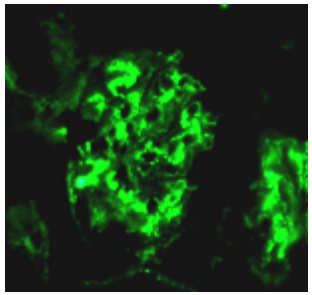
Department of Pathology, Harvard Medical School, Boston, Massachusetts 02115, USA. e-mail: mcarroll@warren.med.harvard.edu



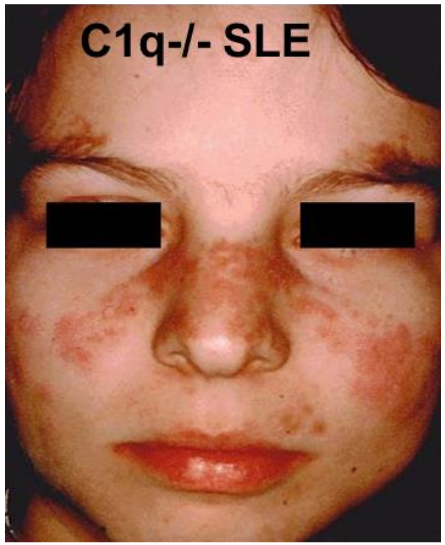
IgG

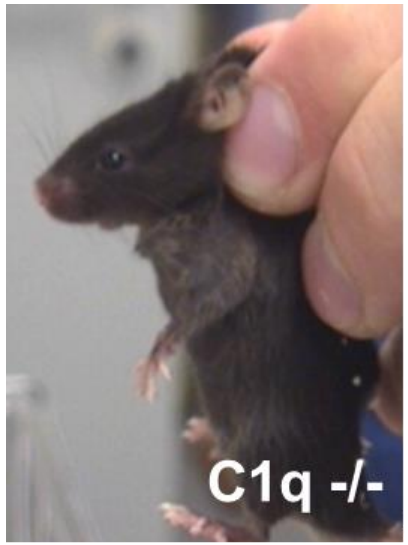


C1q



C3





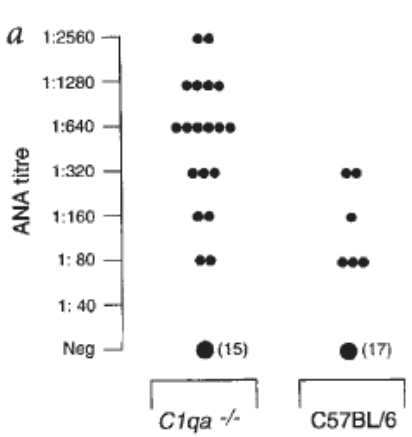
Caroll Nat genet 1998

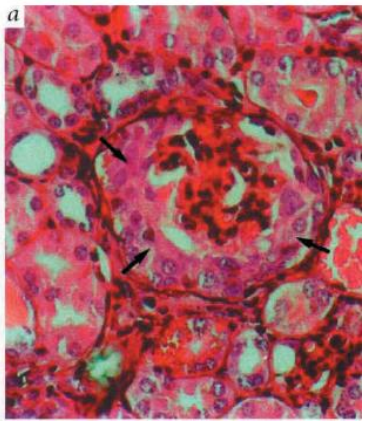
C1q deficient mice develop lupus like disease

letter

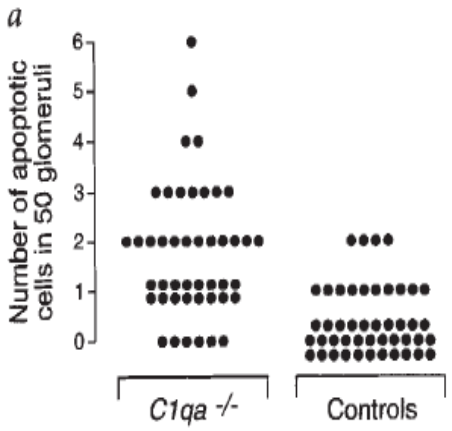
Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies

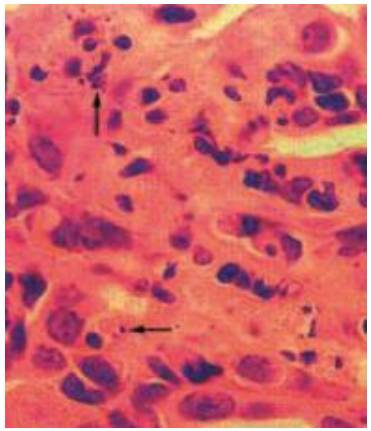
Marina Botto[1], Chiara Dell'Agnola[1], Anne E. Bygrave[1], E. Mary Thompson[2], H. Terence Cook[3], Franz Petry[4], Michael Loos[4], Pier Paolo Pandolfi[5] & Mark J. Walport[1]





Onset of autoimmune disease

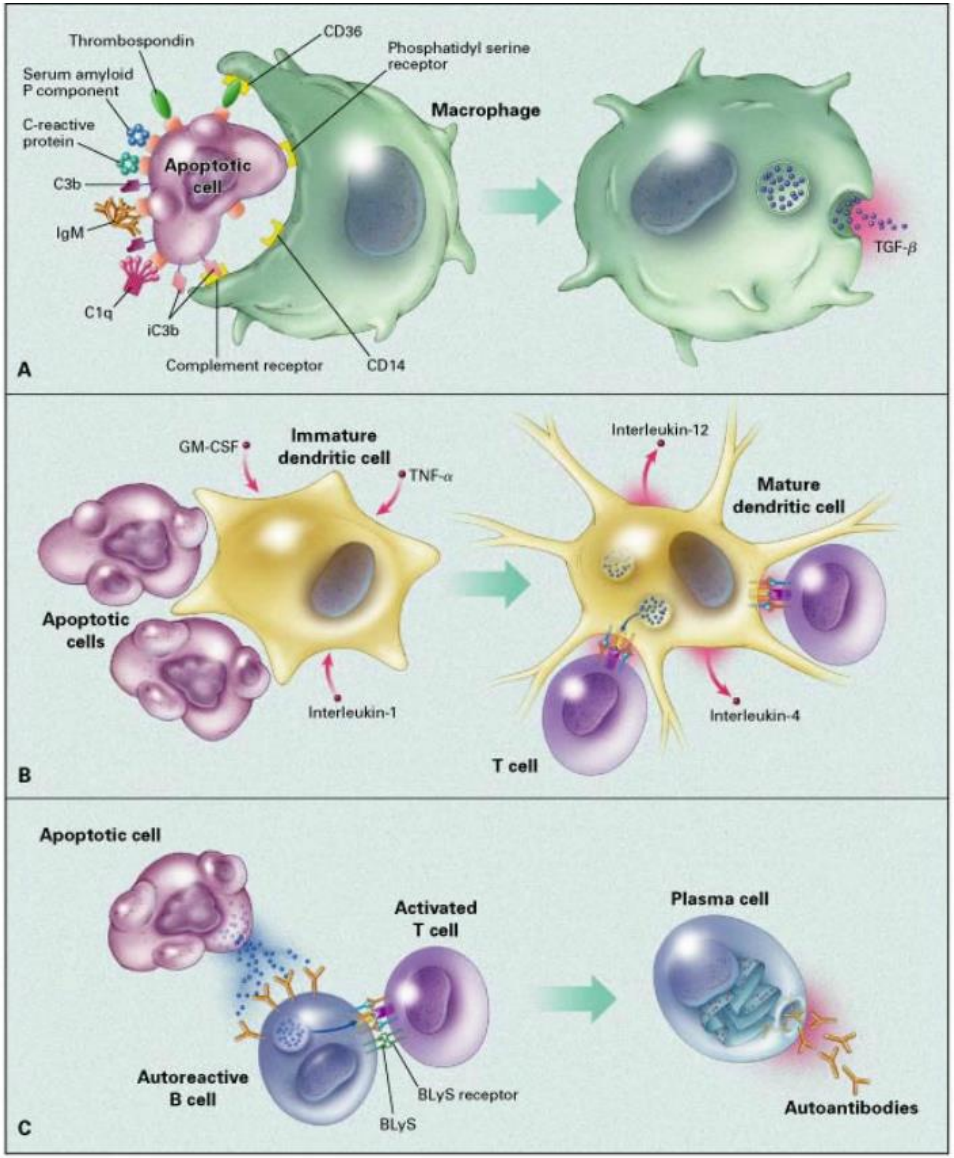




Defective clearance of apoptotic cells

Botto et al. Nat genet 1998

Waste disposal hypothesis

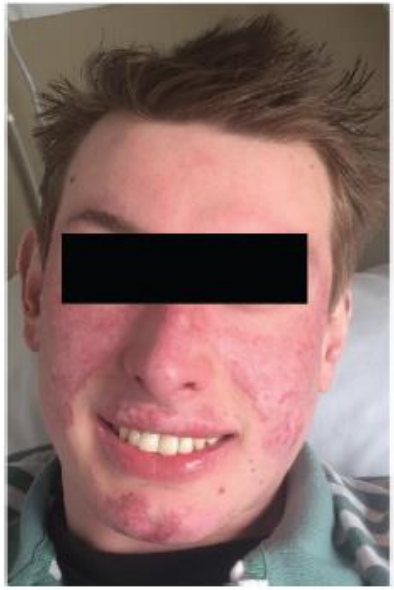


Walport et al. NEJM 2001

C1q deficient patient **with SLE**

Male, 24 years old

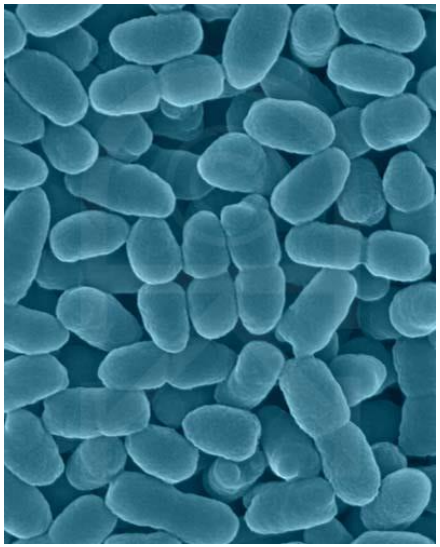
Age 1 Systemic lupus erythematosus
Butterfly rash, sunlight hypersensitivity, ANA, ENA



C1q deficient patient **with SLE**

Male, 24 years old

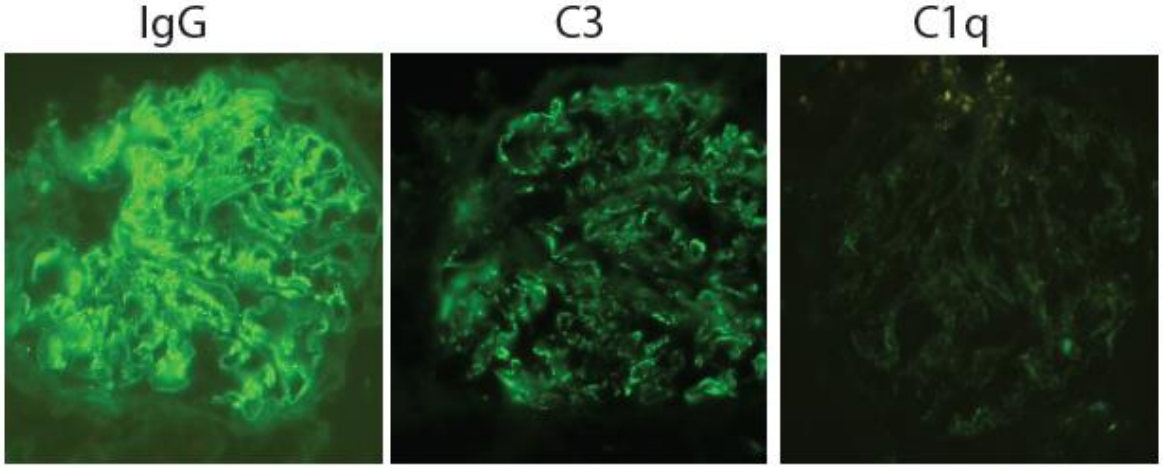
Age 1	Systemic lupus erythematosus
	Butterfly rash, sunlight hypersensitivity, ANA, ENA
Age 3	Poly-arthritis, oral ulcers, fever/malaise.
Age 7	Frequent upper airway infections, skin infections
Age 19	*Staph aureus* septicemia - bloedvergiftiging
Age 20	*Varicella zoster* - gordelroos



C1q deficient patient **with SLE**

Male, 24 years old

Age 1	Systemic lupus erythematosus
	Butterfly rash, sunlight hypersensitivity, ANA, ENA
Age 3	Poly-arthritis, oral ulcers, fever/malaise.
Age 7	Frequent upper airway infections, skin infections
Age 19	*Staph aureus* septicemia
Age 20	*Varicella zoster*
Age 24	Nephritis



Class V LN,
'nearly' full-house IF

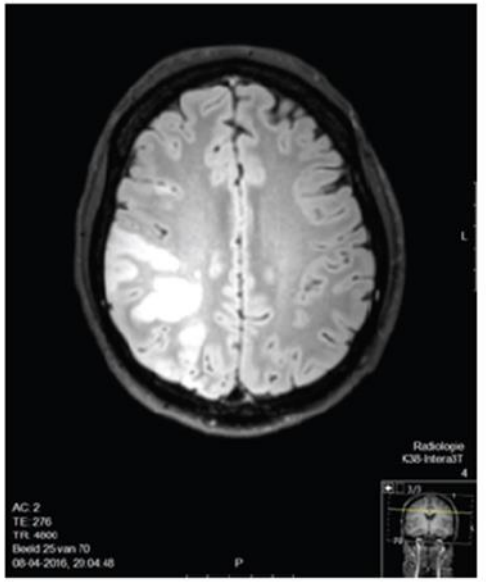
C1q deficient patient **with SLE**

Male, 24 years old

Age 1	Systemic lupus erythematosus Butterfly rash, sunlight hypersensitivity, ANA, ENA
Age 3	Poly-arthritis, oral ulcers, fever/malaise.
Age 7	Frequent upper airway infections, skin infections
Age 19	*Staph aureus* septicemia
Age 20	*Varicella zoster*
Age 24	Nephritis
Age 24	Neuro-psychiatrical SLE

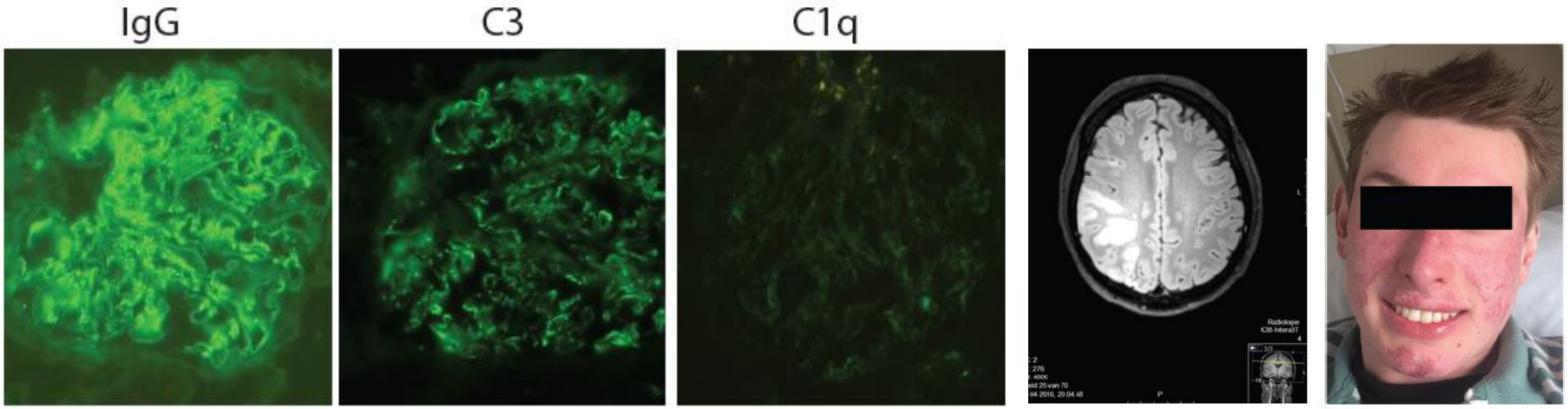
NP-SLE with an inflammatory and ischemic phenotype

Patient presented with low minimal state examination for age and education level. Decreased vision and decreased function of left arm.



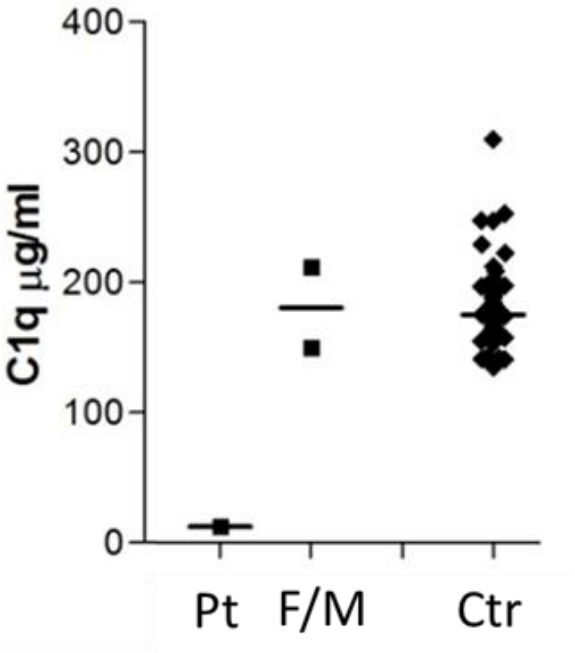
Van Schaarenburg et al. Front Imm 2016

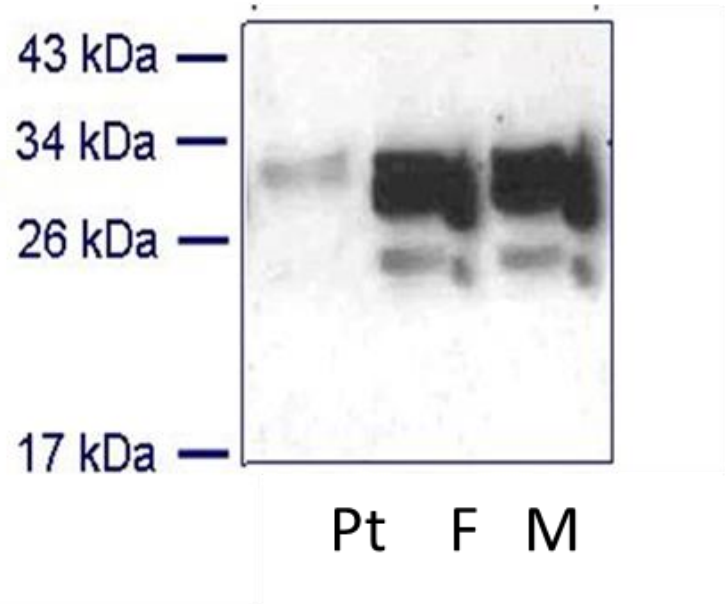
C1q deficient patient **with SLE**



Repeatedly low/undetectable CH50 (classical pathway activity) !!

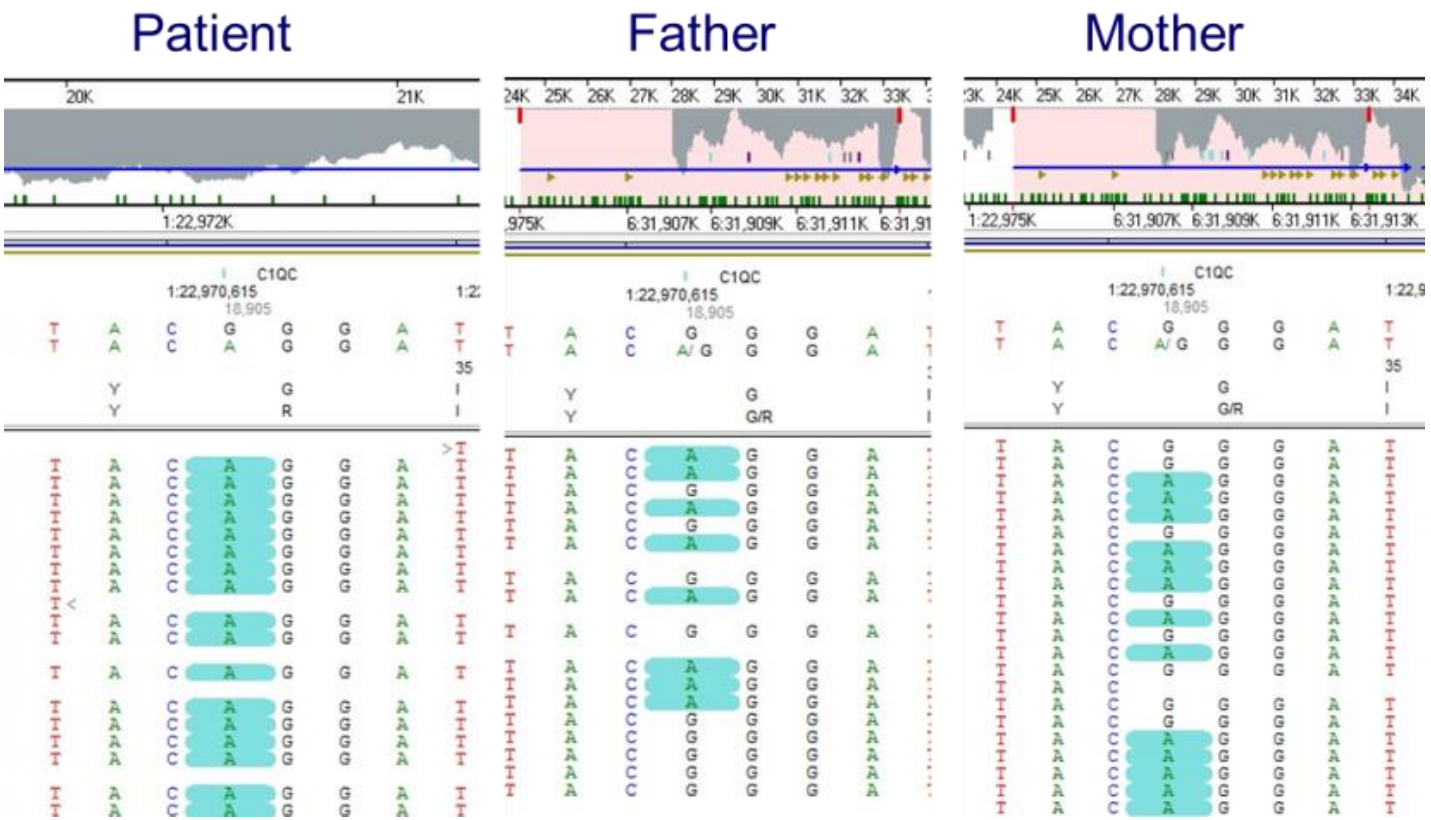
C1q deficient patient **with SLE**



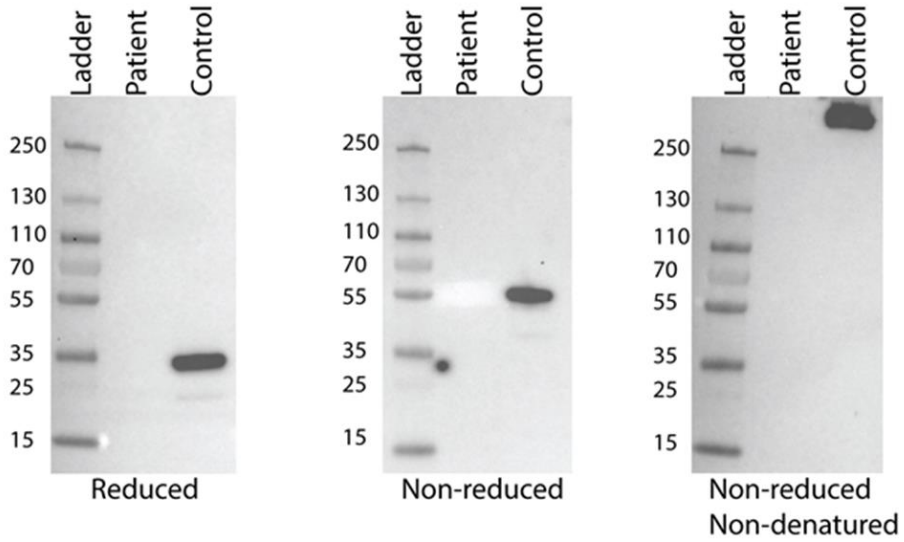


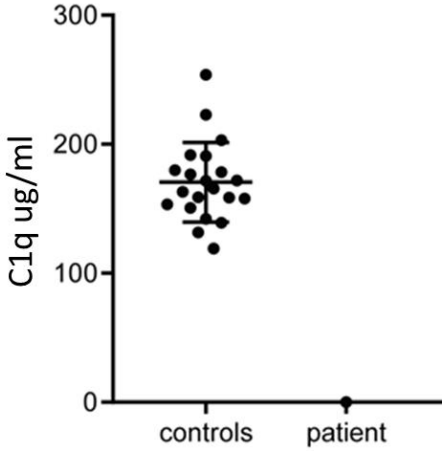
C1q deficient patient **with SLE**

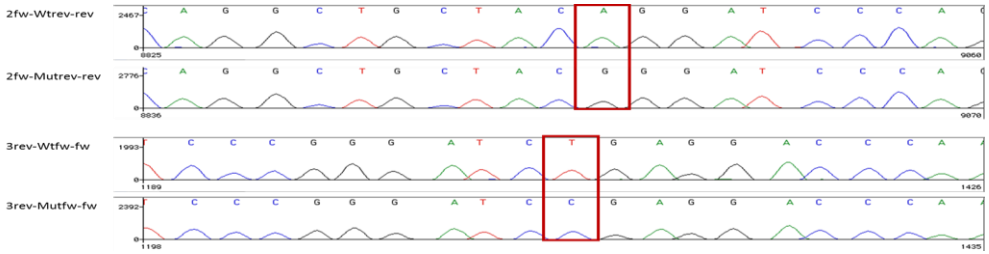
Mutation : Gly>Arg on pos 34 C1qC



Female C1q deficient patient **with SLE**







Compound heterozygous mutations of C1QC : c.100G>A p.(Gly34Arg);
c.205C>T p.(Arg69X).

Female C1q deficient patient **with SLE**

Infections

Age 0 - recurring infections
Age 6 - sepsis caused by *Strep pneumoniae*
Age 12 - herpes zoster infection
Age 18 - hospitalized for infections; *Escheria coli* and candidiasis.

SLE (-like disease)

Age 4 - SLE, many symptoms but no anti-dsDNA.
SLE treated with immunosuppressives with serious side effects.
SLE with C1q deficiency; treatment with Fresh Frozen Plasma, also side effects.

Cerebral involvement

Age 14 - she was hospitalized with cerebral problems, EEG confirmed lesions.
Age 18 - repeated episodes of anxiety and difficulty in speech.

C1q def. and Neuro-Psychiatrical problems

C1q def. and Neuro-Psychiatrical problems

NP-SLE in C1q def >20% and in wt SLE <5%

Supplementary Table 1. Cases reported with C1q deficiency and neuropsychiatric systemic lupus erythematosus

Age at onset/Sex /Flare	Country	Clinical features	NPSLE manifestation	Notes	Immunological tests	Complement functional tests	Neuroimaging	Medication	Mutation	Consequence/ Type C1q deficiency	Ref.
1/M/ND	Yougoslavia	Malar rash, oral ulcers, photosensitivity, arthritis, LN (MPGN), NPSLE (Seizure)	Seizure								
13/F/2	Saoudi Arabia	Malar rash, discoid rash, oral ulcers, arthritis, leukopenia, thrombopeina, alopecia	Seizures, mononeuritis multiplex								
7/F/7 and 20	Dutch	Malar rash, oral ulcers, LN, fever, alopecia, lymphadenopathy, myositis	Seizure, hemiplegia and lethargy. Probably cerebral vasculitis								
9/F/9	Japan	Malar rash, discoid rash, photosensitivity, oral ulcers, proteinuria (no biopsy), arthralgia	Seizure								
6/F/18,24 and 29	Germany	Malar rash, oral ulcers, photosensitivity, leukopenia, pleuritis, arthritis, glomerulonephritis (Type V) and Libman-Sacks endocarditis, peritonitis	Seizure and psychosis								
9/F/25	England	Malar rash, photosensivity, leukopenia, alopecia	Seizure and cognitive dysfunction								
5/F/ND	Saudi Arabian	Discoid lupus, photosensitivity, lupus nephritis (non-specified), alopecia	CNS involvement with cerebral atrophy, non-specified								

Cell

The Classical Complement Cascade Mediates CNS Synapse Elimination

Beth Stevens,[1,*] Nicola J. Allen,[1] Luis E. Vazquez,[1] Gareth R. Howell,[3,4] Karen S. Christopherson,[1] Navid Nouri,[1] Kristina D. Micheva,[2] Adrienne K. Mehalow,[3,4] Andrew D. Huberman,[1] Benjamin Stafford,[5] Alexander Sher,[5] Alan M. Litke,[5] John D. Lambris,[6] Stephen J. Smith,[2] Simon W.M. John,[3,4] and Ben A. Barres[1]
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[2]Department of Molecular and Cellular Physiology
[3]Stanford University School of Medicine, Stanford, CA 94305, USA
Howard Hughes Medical Institute
[4]The Jackson Laboratory, Bar Harbor, ME 04609, USA
[5]Santa Cruz Institute for Particle Physics, University of California, Santa Cruz, Santa Cruz, CA 95064, USA
[6]Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical School, Pennsylvania, PA 19104, USA
*Correspondence: beths@stanfordmedalumni.org
DOI 10.1016/j.cell.2007.10.036

Stevens et al. Cell 2017

Complement and onset of SLE

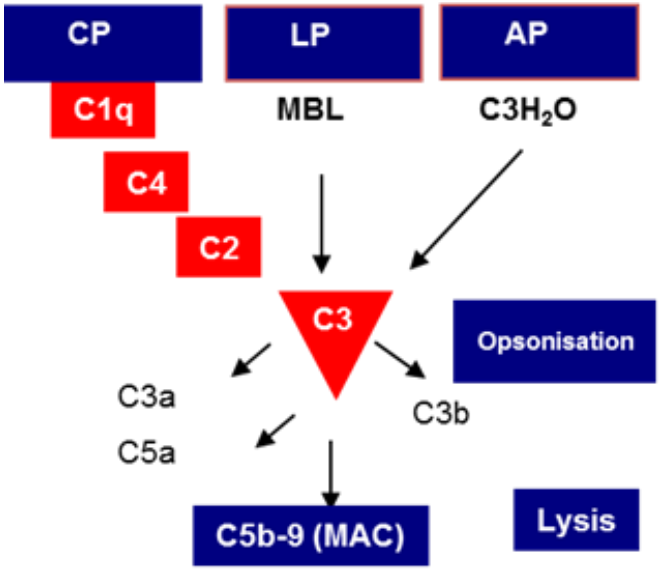
Human genetic deficiencies

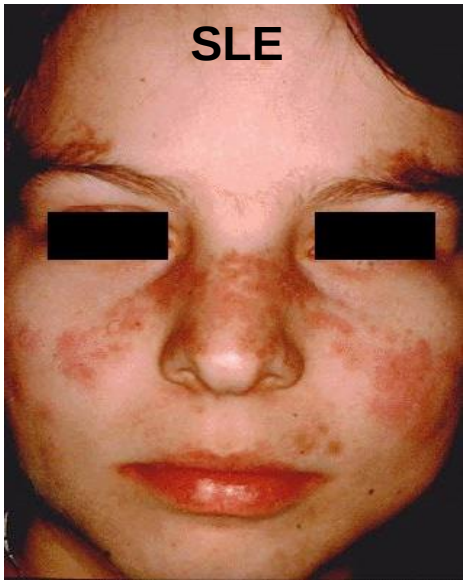
C1q - 80% SLE

C4 - 70% SLE

C2 - 10% SLE

C3 - 5% SLE





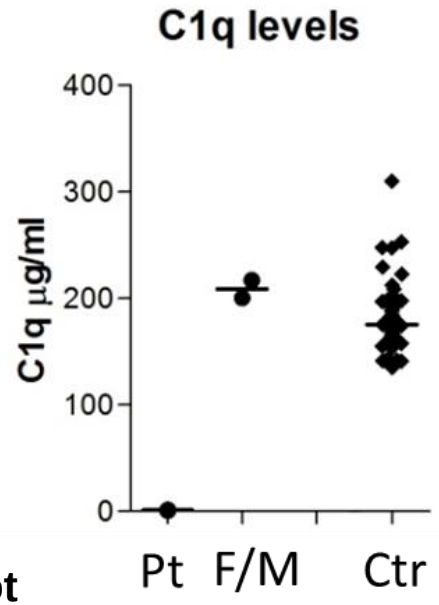
The complement system is involved in the prevention of SLE

C1q deficient patient **with no SLE**

Male
7 years old

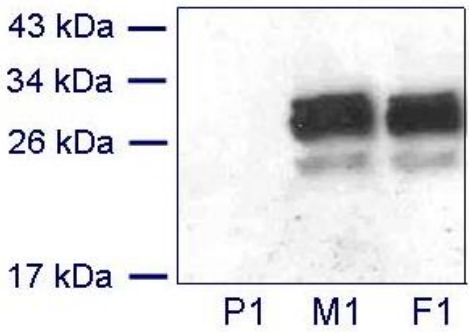
Recurrent infections of the airways
Osteomyelitis of the tibia
Pneumococcal meningitis
No signs of autoimmunity

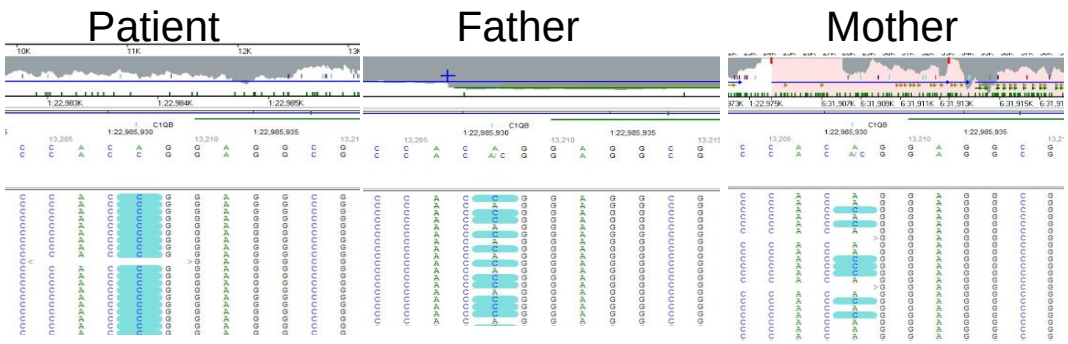
ELISA



Splice site mutation within *C1qB*

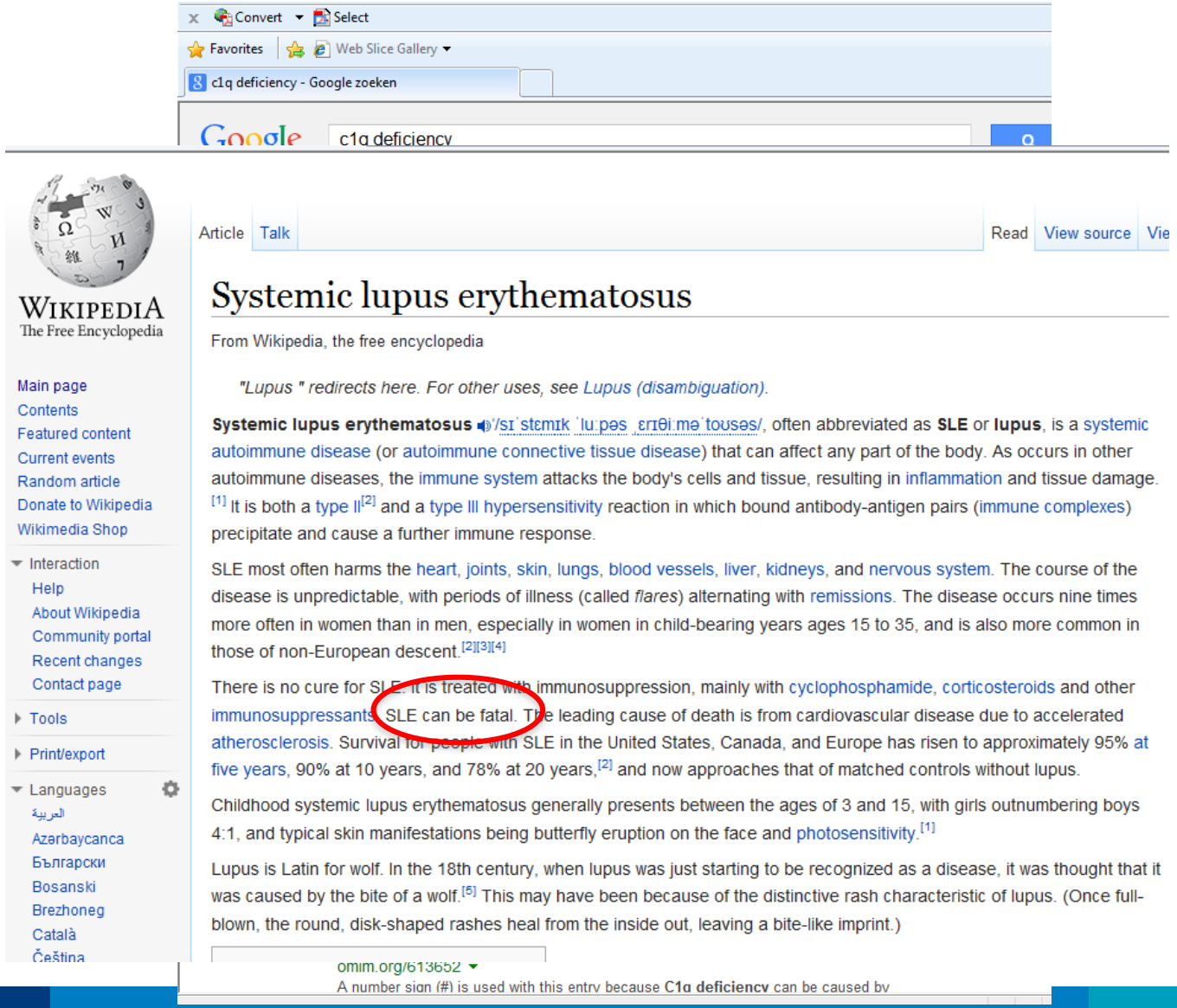
Western blot





Van Schaarenburg et al. Immunobiol 2014

C1q deficiency



C1q deficiency

Problem:

Most papers only report on the moment of identification of C1q deficiency and the mutation involved, but no follow up.

C1q deficiency

Questionnaire on life expectancy and complications

Gender
Age of diagnosis
Parents related?
SLE (Diagnosis)
Still alive? (No, cause of death)
Received Plasma
Stem cell transplantation consideration
Quality of life
Age of diagnosis vs current age

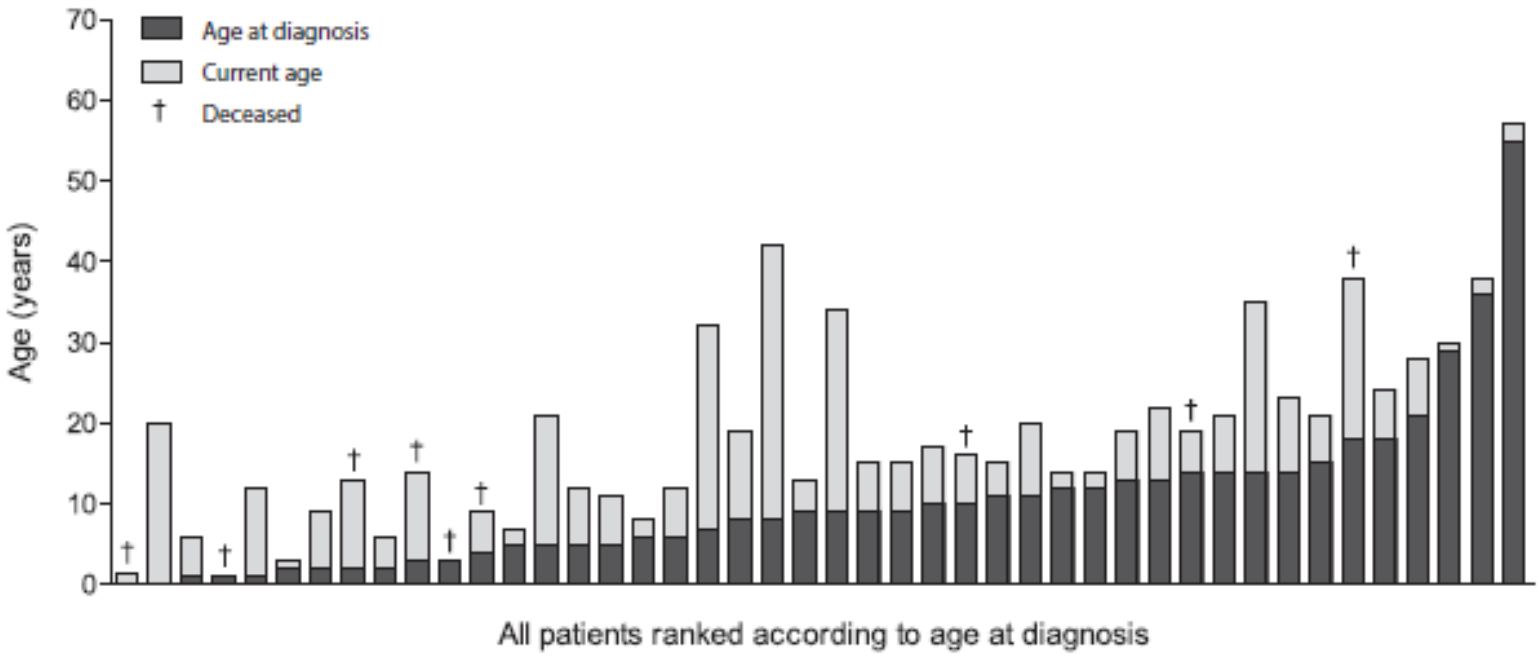
C1q deficient patients

Country of origin	Number of patients
Australia	1
Greenland	3
Iraq	1
Kosovo	1
Netherlands	7
Pakistan	7
Saudi Arabia	9
Spain	1
Sweden	4
Sudan	2
Tunisia	2
Turkey	4
United Kingdom	2
USA	1

C1q deficient individuals	Number of cases	Percentage of cases
Sex M/F	22/23	49/51
Deceased Y/N	9/36	20/80
Deceased Males	3	14
Deceased Females	6	26
Clinical presentation		
SLE Y/N	36/9	80/20
Only SLE	20	44
Only Infections	6	13
Both SLE + Infections	16	36
No symptoms	3	7
Therapy		
FFP given	14	31
HSCT performed	3	7
HSCT considered	10	22

Van Schaarenburg et al. J Autoimmun. 2015

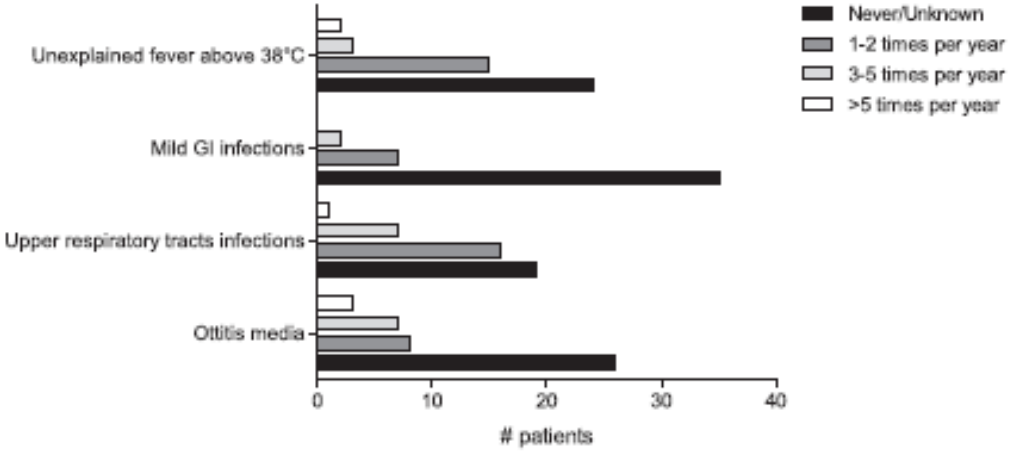
C1q deficient patients



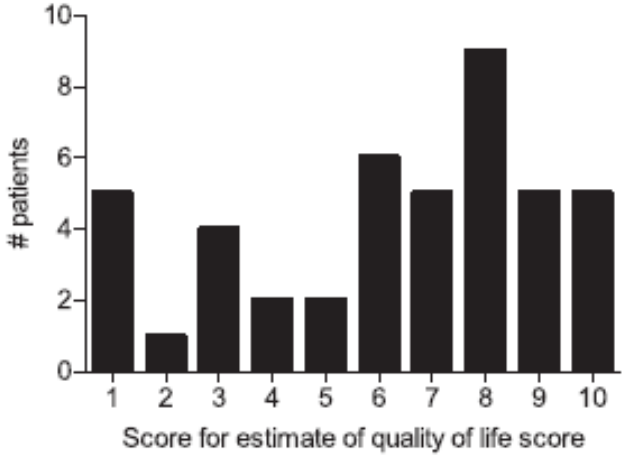
Age of diagnosis vs. current age

Outcome of disease

Infections



Quality of life



The median quality of life is 7

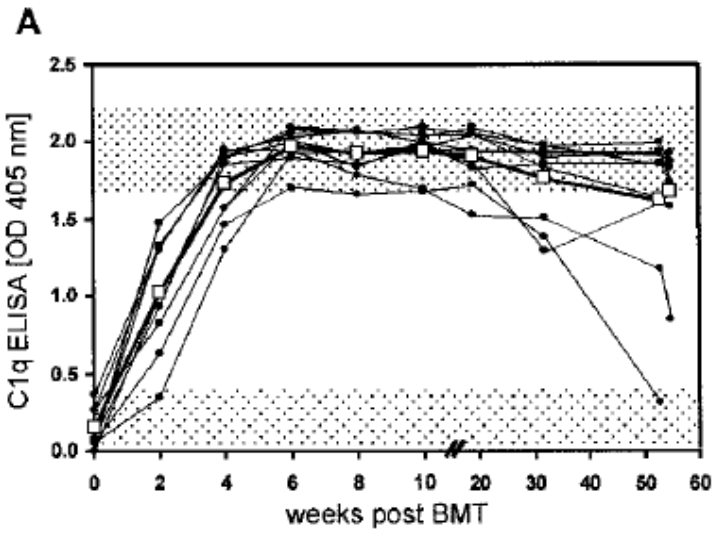
Therapy options

C1q deficient individuals	Number of cases	Percentage of cases
Sex M/F	22/23	49/51
Deceased Y/N	9/36	20/80
Deceased Males	3	14
Deceased Females	6	26
Clinical presentation		
SLE Y/N	36/9	80/20
Only SLE	20	44
Only Infections	6	13
Both SLE + Infections	16	36
No symptoms	3	7
Therapy		
FFP given	14	31
HSCT performed	3	7
HSCT considered	10	22

Bone marrow transplantation in mice restores C1q levels and reduces autoimmunity

Reconstitution of the Complement Function in C1q-Deficient ($C1qa^{-/-}$) Mice with Wild-Type Bone Marrow Cells[1]

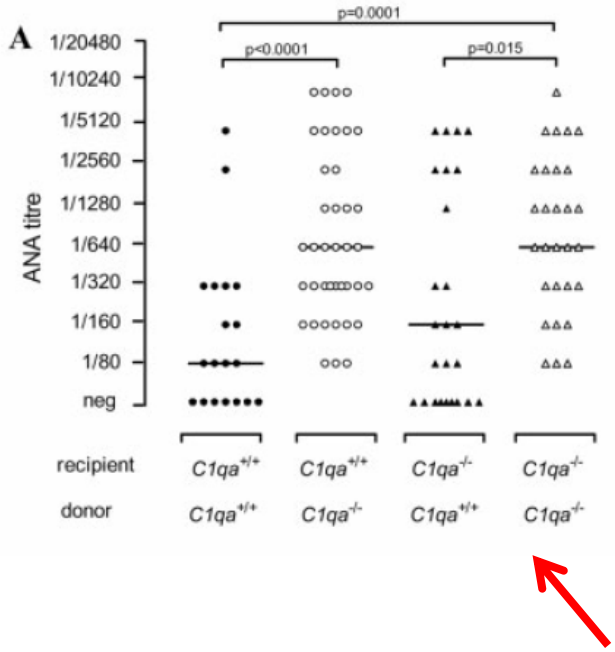
Franz Petry,[2]* Marina Botto,† Rafaela Holtappels,‡ Mark J. Walport,† and Michael Loos*



Petry et al. J.Immunol 2001

Restoration of C1q levels by bone marrow transplantation attenuates autoimmune disease associated with C1q deficiency in mice

Josefina Cortes-Hernandez[1], Liliane Fossati-Jimack[1], Franz Petry[2], Michael Loos[2], Shozo Izui[3], Mark J. Walport[1], H. Terence Cook[4] and Marina Botto[1]



Cortes-Hernandez et al. Eur.J.Immunol 2004

HSCT in humans can restore C1q production

Journal of Allergy and Clinical Immunology

Volume 133, Issue 1, January 2014, Pages 265–267

Letter to the editor

Successful cure of C1q deficiency in human subjects treated with hematopoietic stem cell transplantation

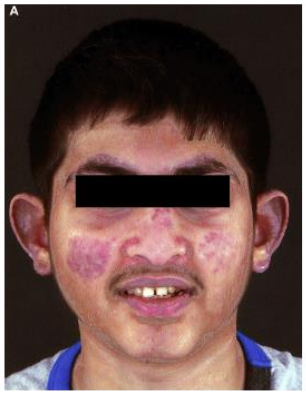
Peter D. Arkwright, MD, PhD[a, b], Philip Riley, MD[b], Stephen M. Hughes, MD, PhD[b], Hana Alachkar, MD[c], Robert F. Wynn, MD[b]

TABLE I. Changes in complement and autoantibody titers after matched sibling bone marrow transplantation for C1q deficiency

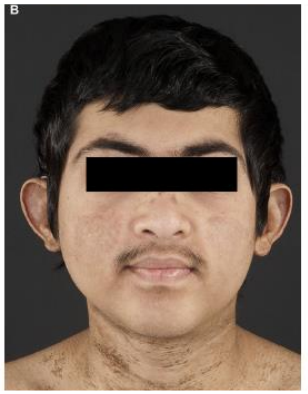
Parameter	Normal range	Before BMT	Weeks after BMT						
			1	2	4	6	12	16	24
Leukocyte engraftment									
Neutrophils (× 10^9/L)	1.50-6.00	1.50	0.05	1.18	3.58	5.15	3.09	1.01	3.20
Lymphocytes (× 10^9/L)	1.50-4.50	1.62	0.07	0.25	0.40	0.12	0.29	0.46	0.30
Monocytes (× 10^9/L)	0.10-1.50	0.20	0.54	0.65	0.36	0.36	0.21	0.23	0.22
CD3 (× 10^6/L)	622-2402	761				32	36	233	96
Complement									
CH50 (U/mL)	392-1019	<275	<275	588	838	967		978	659
C1q (mg/L)	70-140	<10	<10	<0	75	70		69	76
Autoantibodies									
SS-A60 (Ro) AI	0-0.9	>8.0	>8.0	>8.0	>8.0	>8.0	5.2	4.0	3.3
SS-B (La) AI	0-0.9	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3	<0.3
dsDNA (IU/mL)	0-0.9	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0	<1.0
Anti-cardiolipin IgG (GPLU)	0-5.7	18.0	18.0	18.0	18.0	18.0	12.0	6.9	5.3

BMT, Bone marrow transplantation; *dsDNA*, double-stranded DNA; *GPLU*, IgG phospholipid units; *SS-A60*, Sjögren syndrome A 60-kDa protein autoantibody (equivalent to anti-Ro).

Before



After



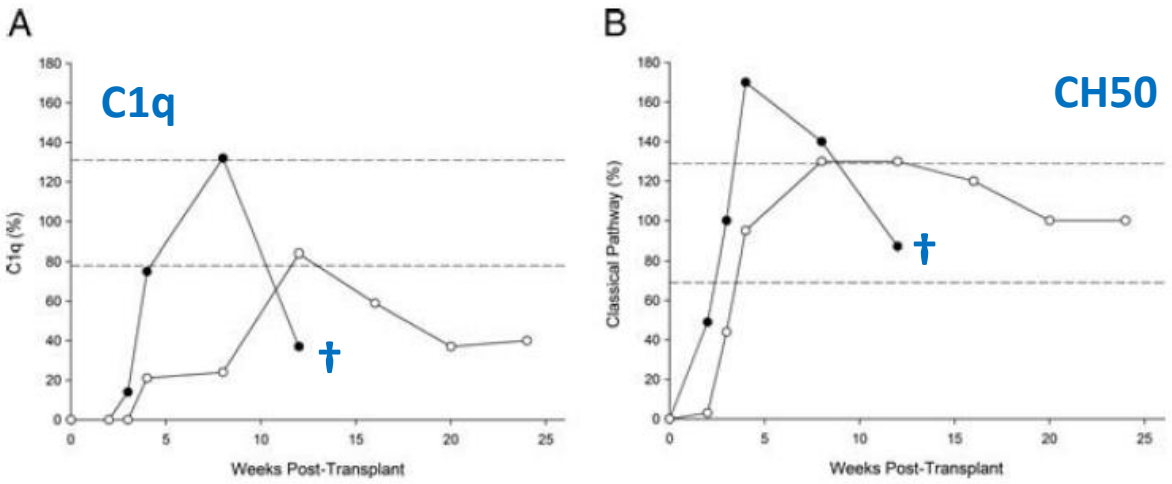
Arkwright et al. J. Allergy Clin Immunol 2014

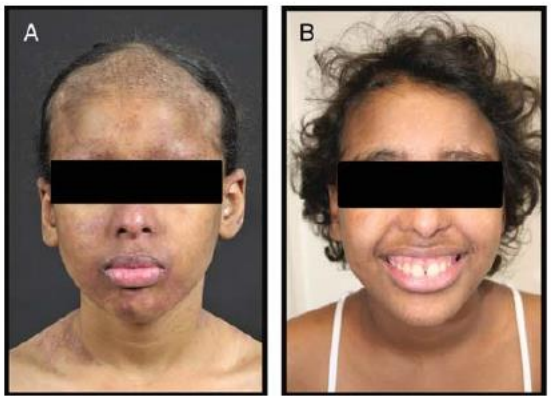
HSCT in humans can restore C1q production

Original Clinical Science

Allogeneic Hematopoietic Stem Cell Transplantation in the Treatment of Human C1q Deficiency: The Karolinska Experience

Richard F. Olsson, MD, PhD,[1,2,3] Stefan Hagelberg, MD, PhD,[4] Bodil Schiller, MD,[5] Olle Ringdén, MD, PhD,[1,2] Lennart Truedsson, MD, PhD,[6] and Anders Åhlin, MD, PhD[5]





Unfortunately, the boy developed severe acute GVHD and died 4 months after transplantation due to intracerebral haemorrhage and multiorgan failure.

Olsson et al. Transplantation 2016

Conclusions C1q deficiency

Absence of early classical components is associated with SLE

Remarkable differences between deficient individuals

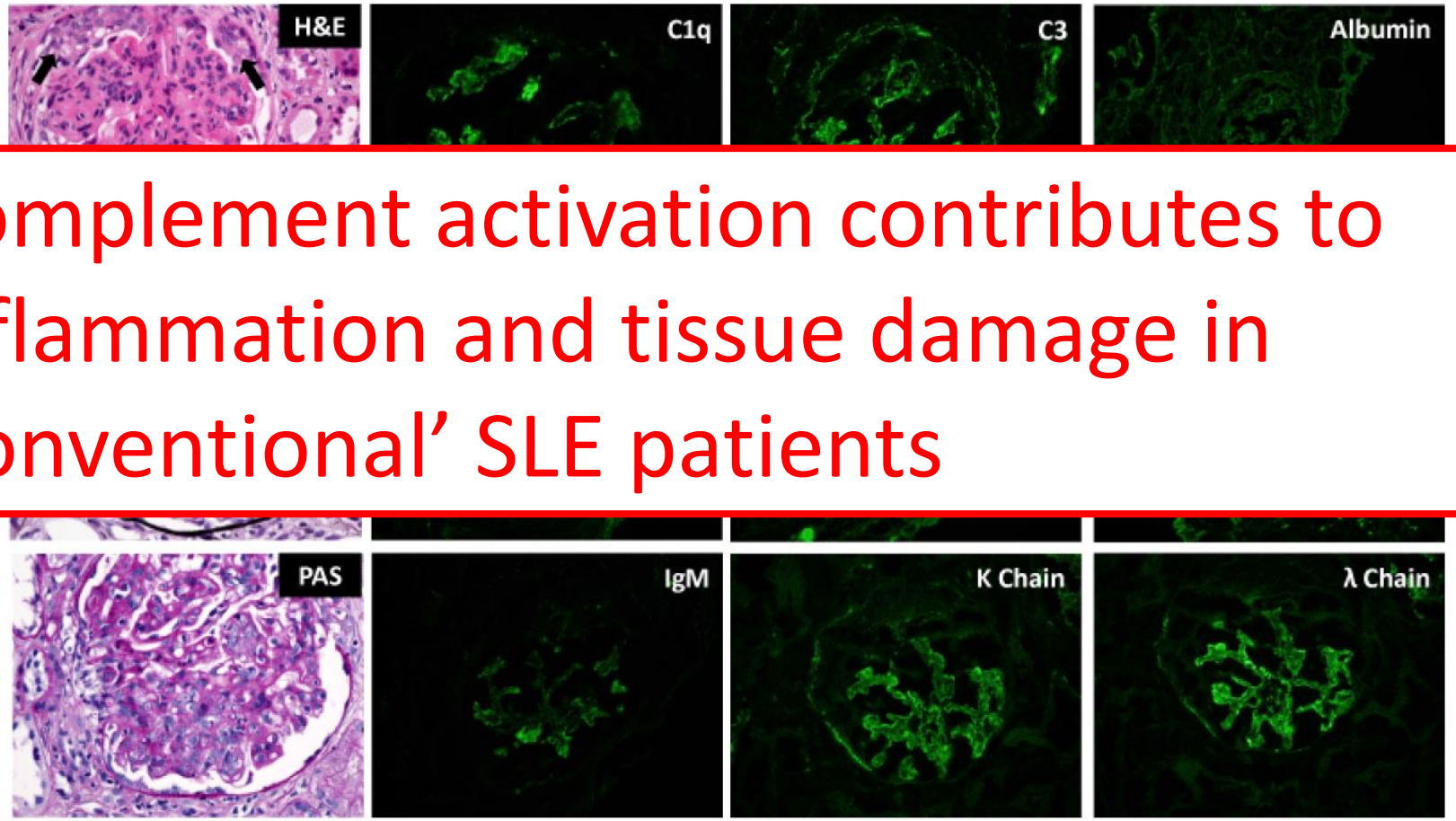
Not only SLE but also infections very prominent risk in CP deficiency

Neurological problems are prominent

HSCT now tested as a therapeutical option in C1q deficiency

Most SLE patients are NOT genetically deficient

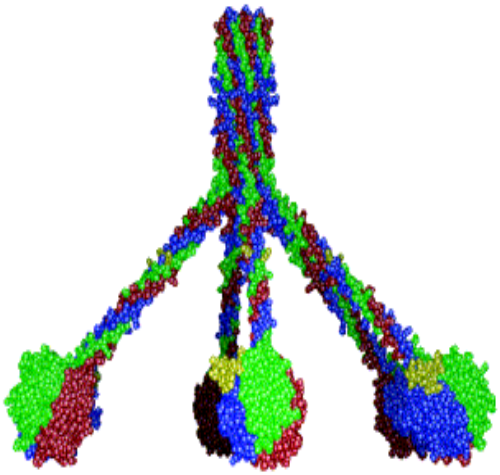
Full-House Immunofluorescence



Complement activation contributes to inflammation and tissue damage in 'conventional' SLE patients

C1q low in SLE but what about C1q high ?

SLE



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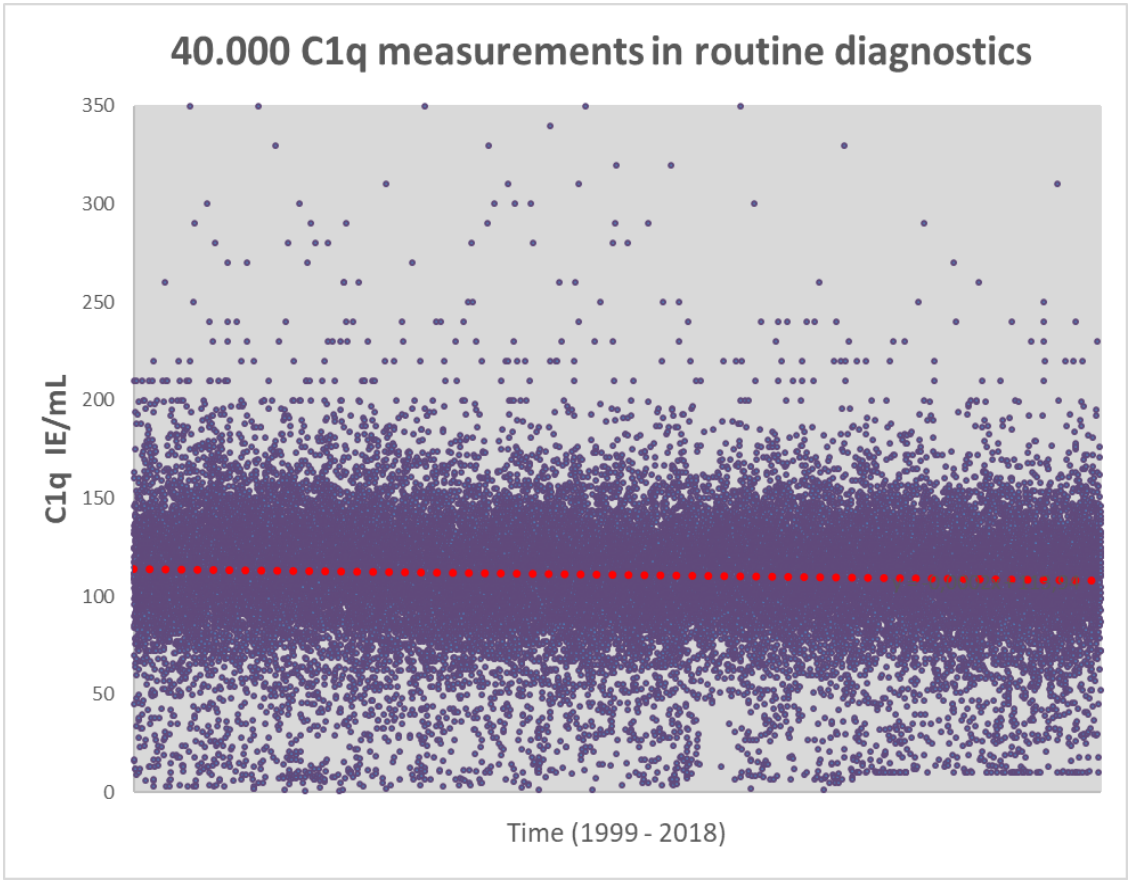
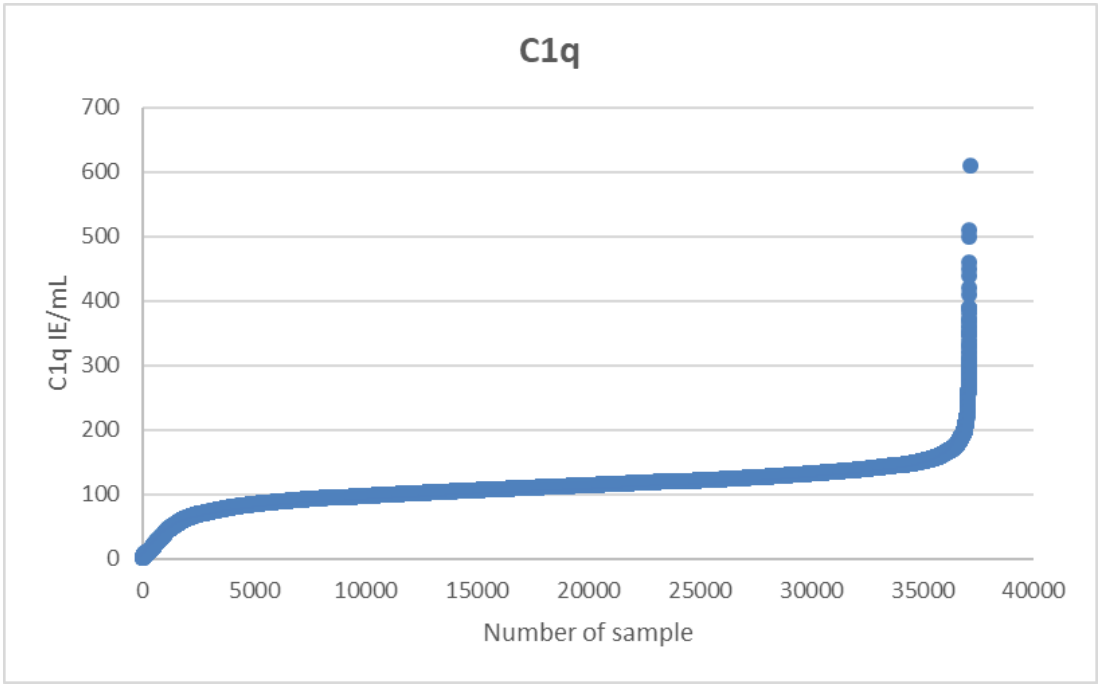
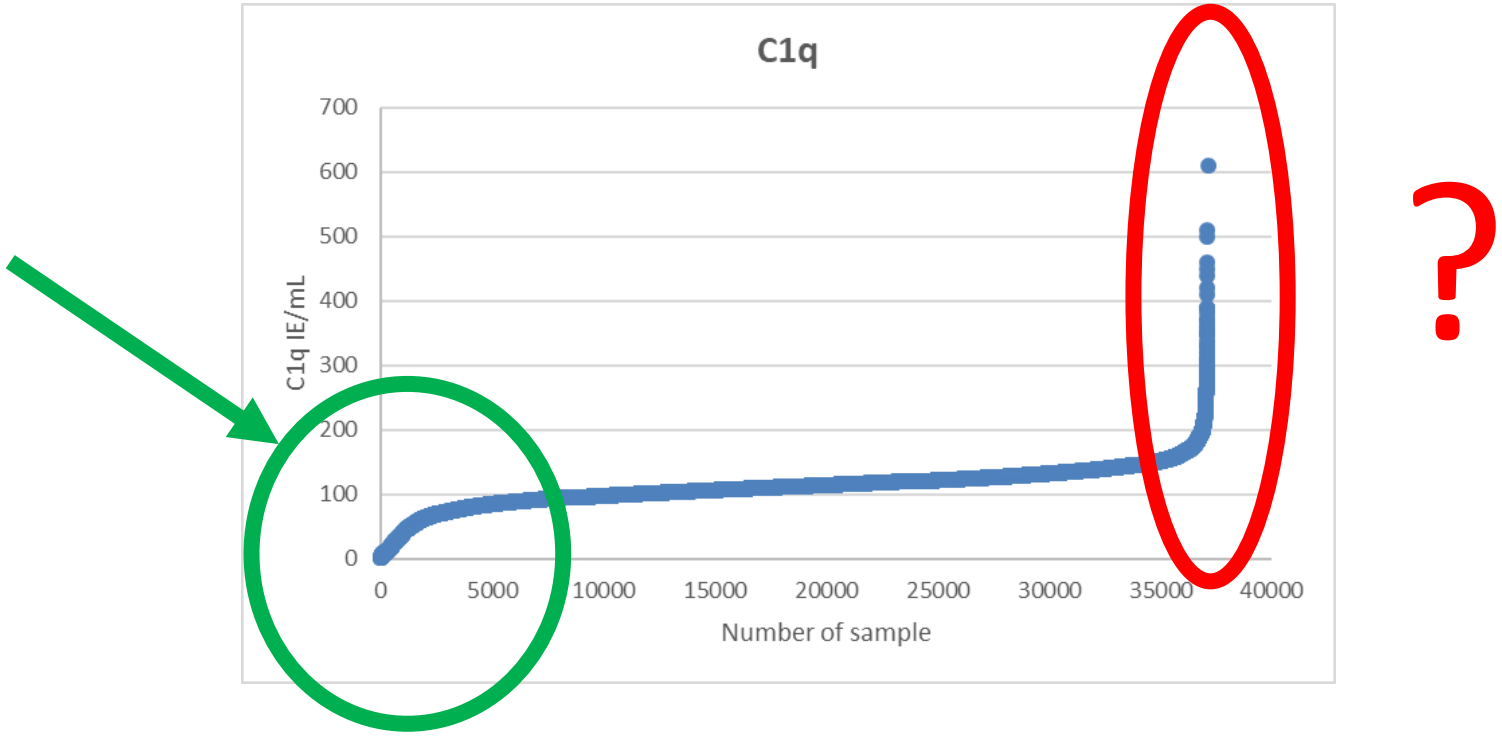
C1q low in SLE but what about C1q high ?



C1q low in SLE but what about C1q high ?



C1q low in SLE but what about C1q high ?



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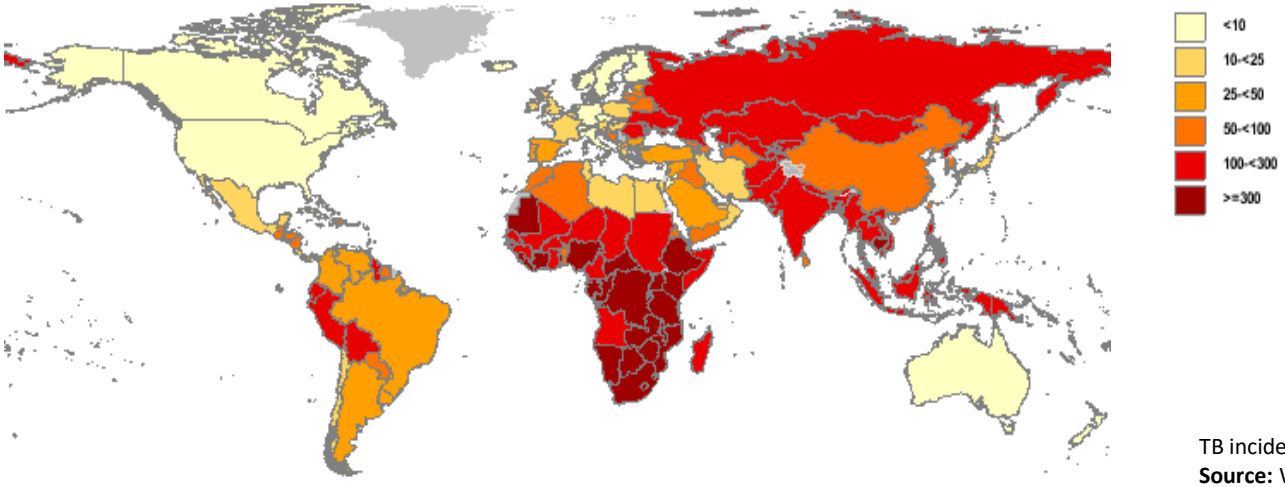
Tuberculosis

Tuberculosis Today



TB incidence, all forms (per 100 000 per year)
Source: WHO Stop TB Department, www.who.int/tb

Mycobacterium tuberculosis (Mtb) infection:

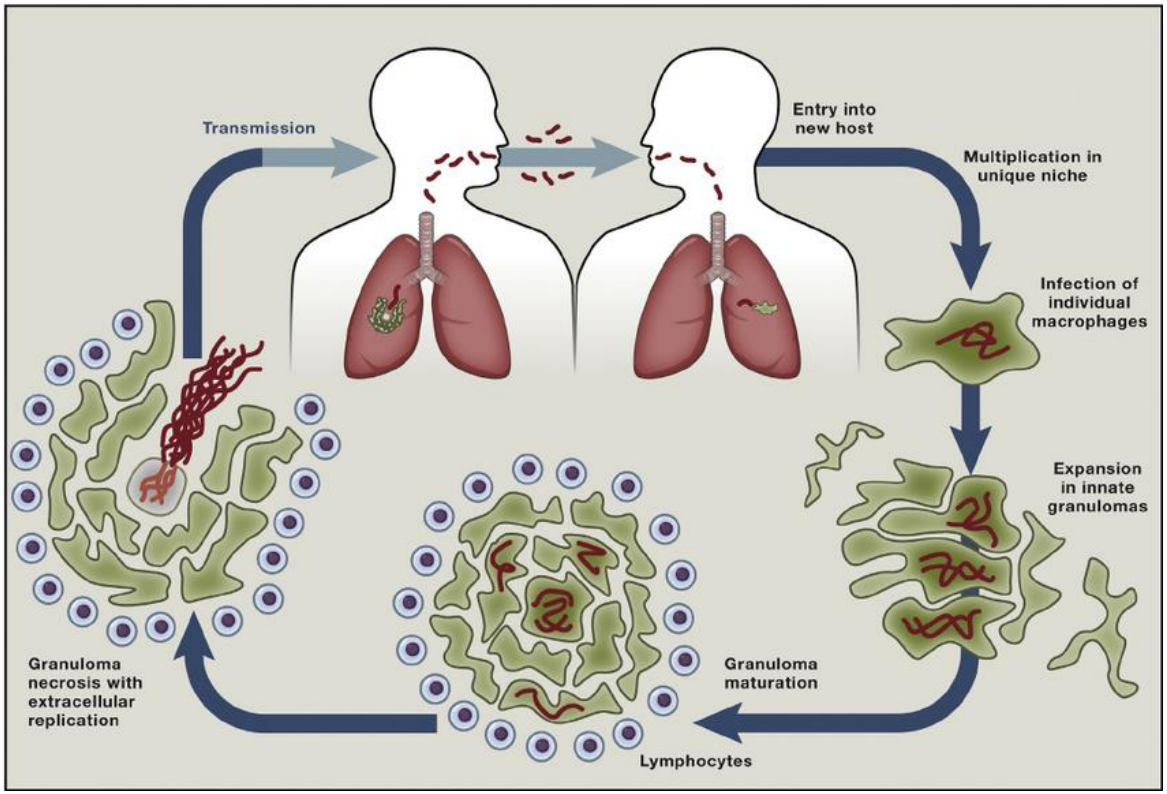
1/4 - 1/3 of the world population is infected

> 10,4 million people develop TB disease

~ 1,7 million die every year of TB (incl. 370.000 HIV coinfected)

WHO report, 2017

Background



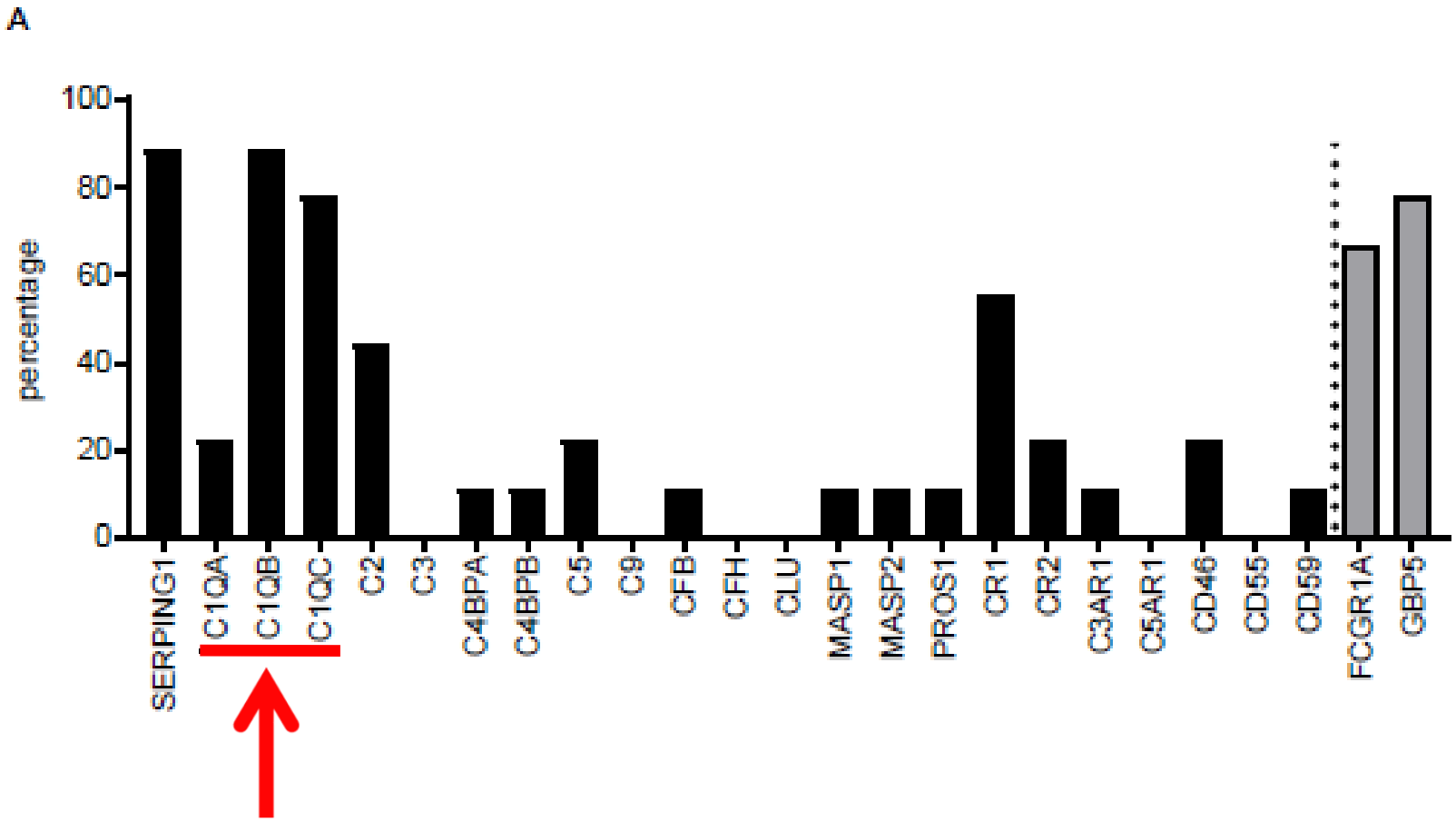
Mycobacterium tuberculosis

Phases: **Active disease**

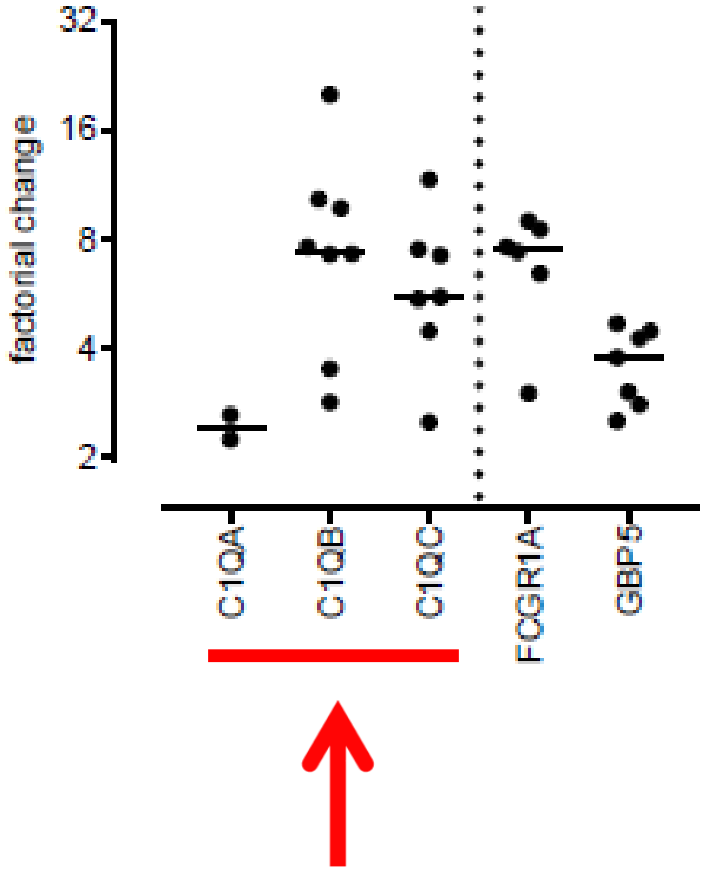
Latent infected TB

Biomarkers do not discriminate !!

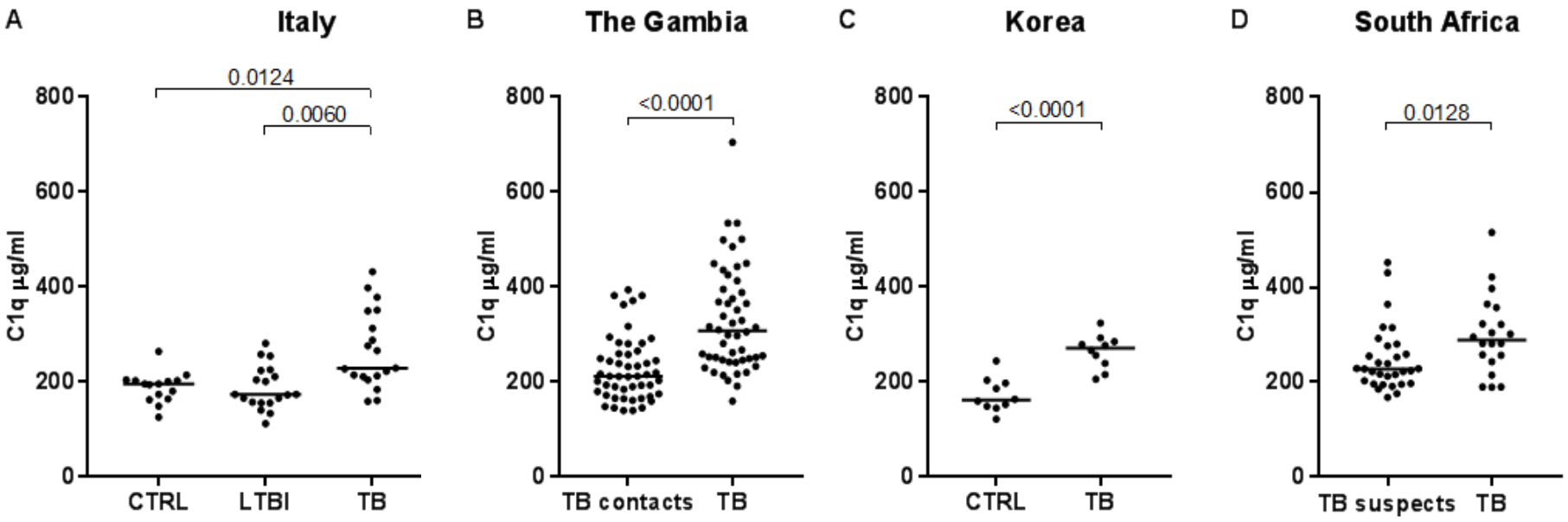
C1q expression in PBMCs in several large studies



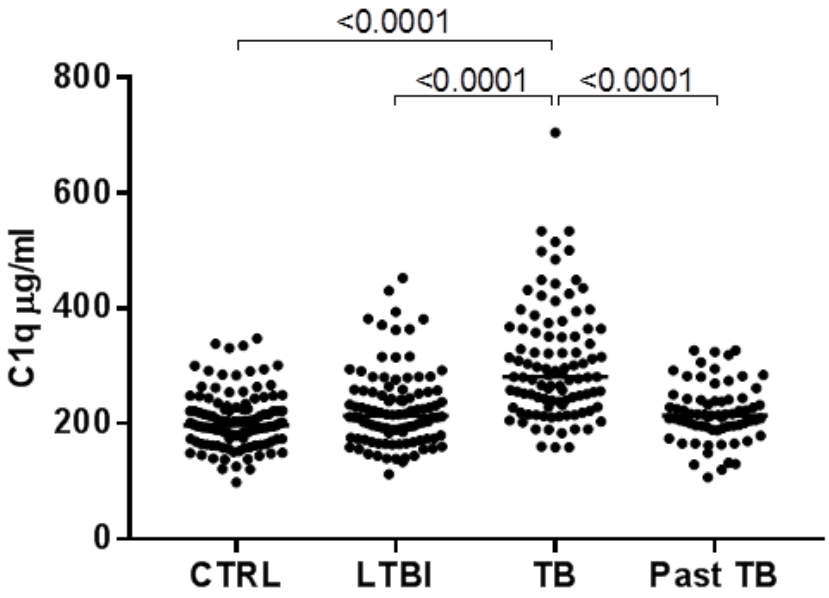
C1q expression in PBMCs in several large studies



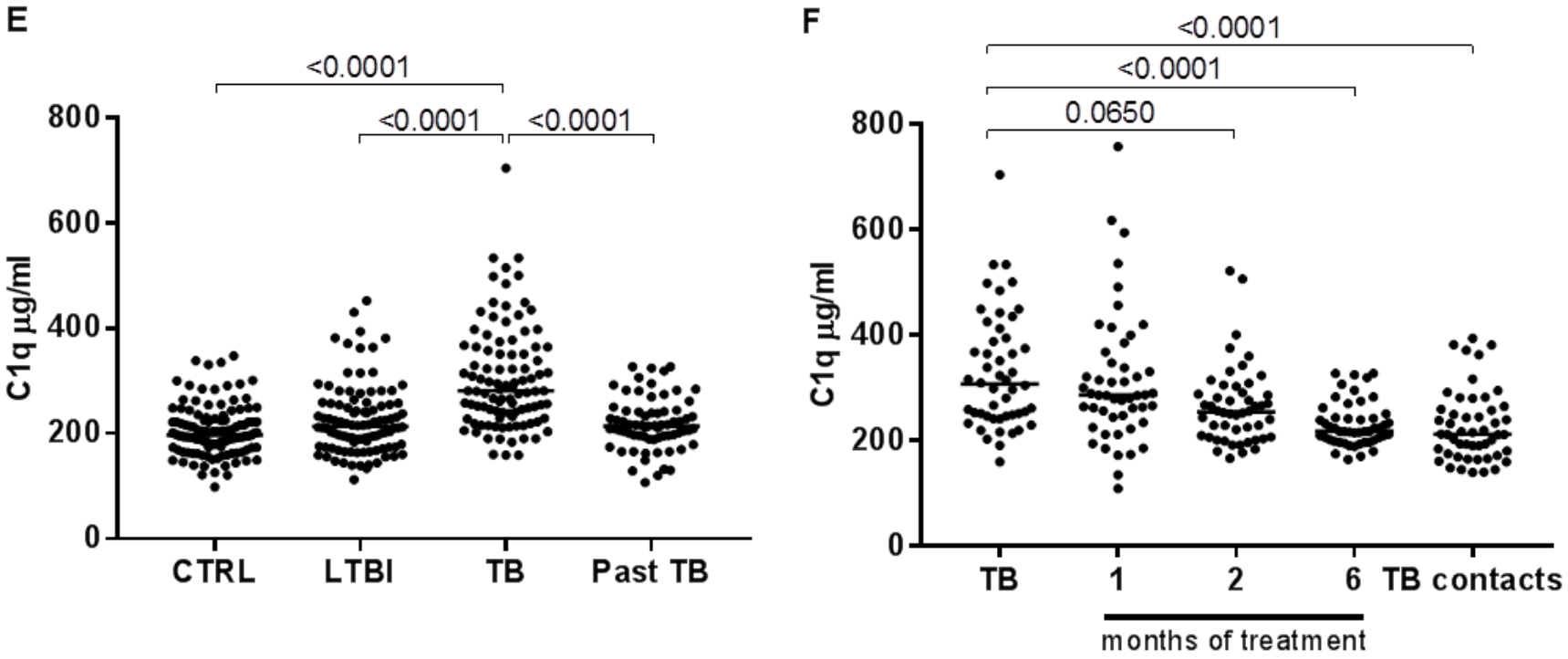
C1q protein levels are increased in active TB



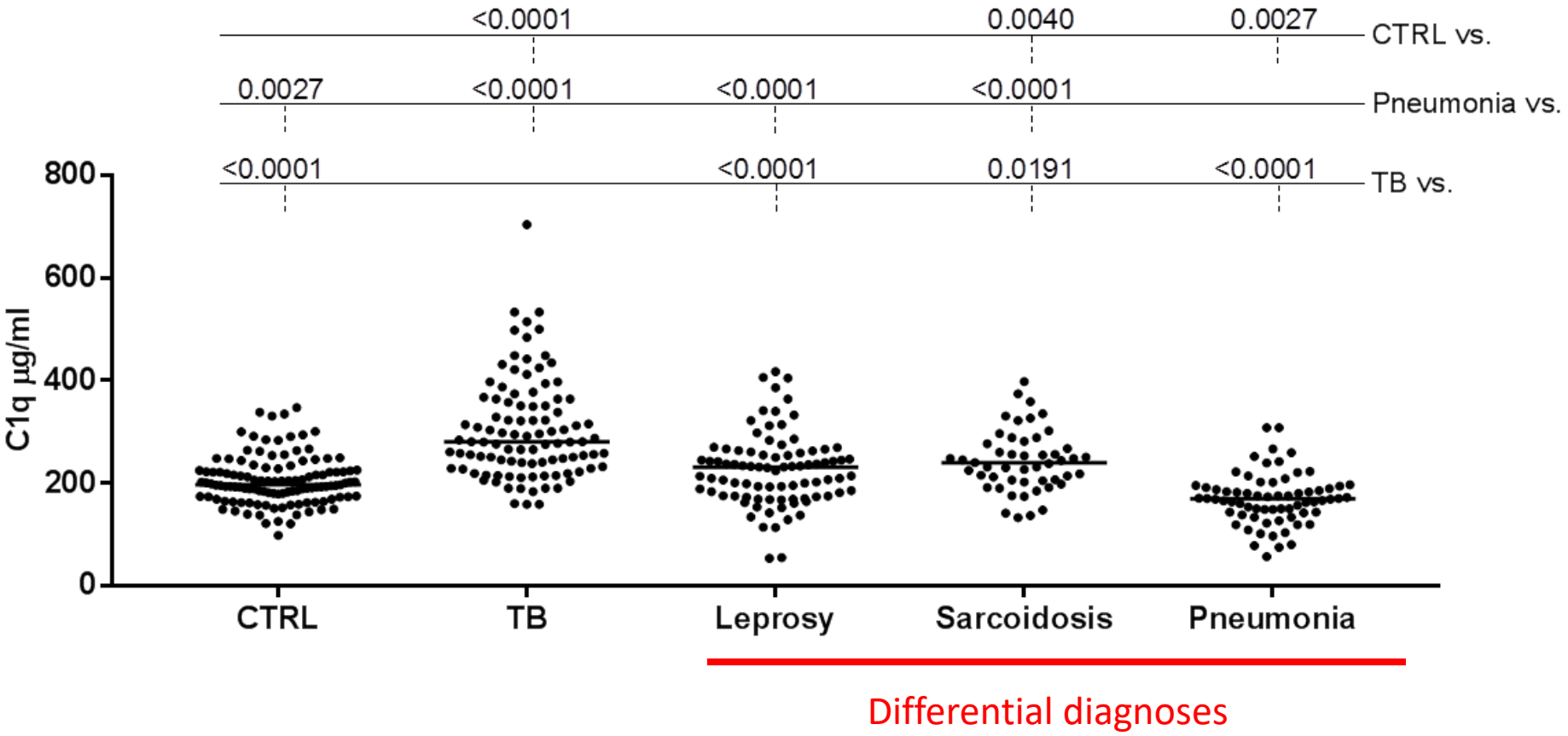
Increased C1q levels normalize following treatment



C1q levels normalize following successful treatment

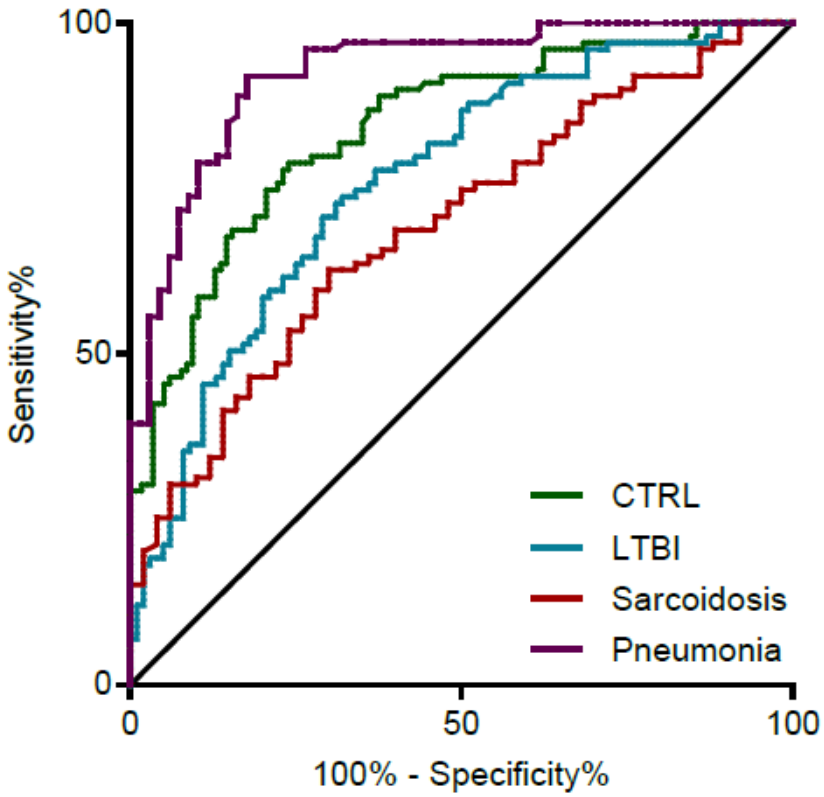


Increased C1q levels are rather specific for active TB



Discrimination of active TB vs rest using C1q serum levels

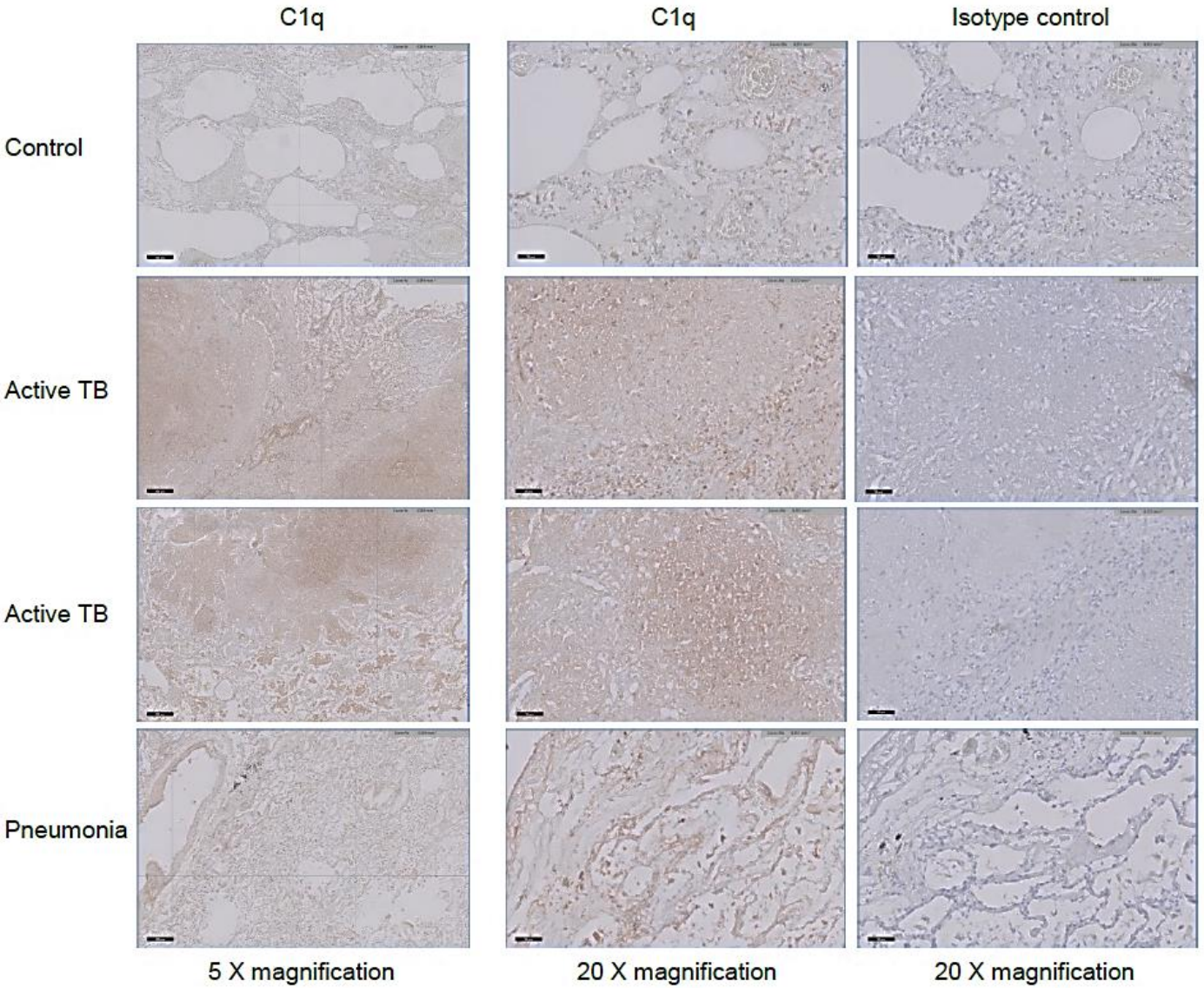
B



C

TB vs	AUC	Std Error	95% CI
CTRL	0,841	0,027	[0,789 ; 0,893]
LTBI	0,765	0,033	[0,699 ; 0,830]
PastTB	0,789	0,034	[0,722 ; 0,856]
Leprosy	0,749	0,036	[0,680 ; 0,819]
Sarcoidosis	0,693	0,044	[0,607 ; 0,779]
Pneumonia	0,925	0,020	[0,889 ; 0,965]
All	0,799	0,024	[0,752 ; 0,845]

C1q also present in the lungs of active TB



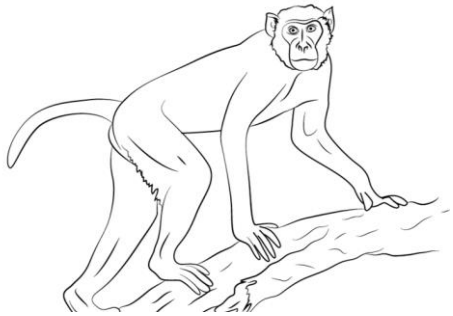
Lubbers et al Front Immunol. 2018

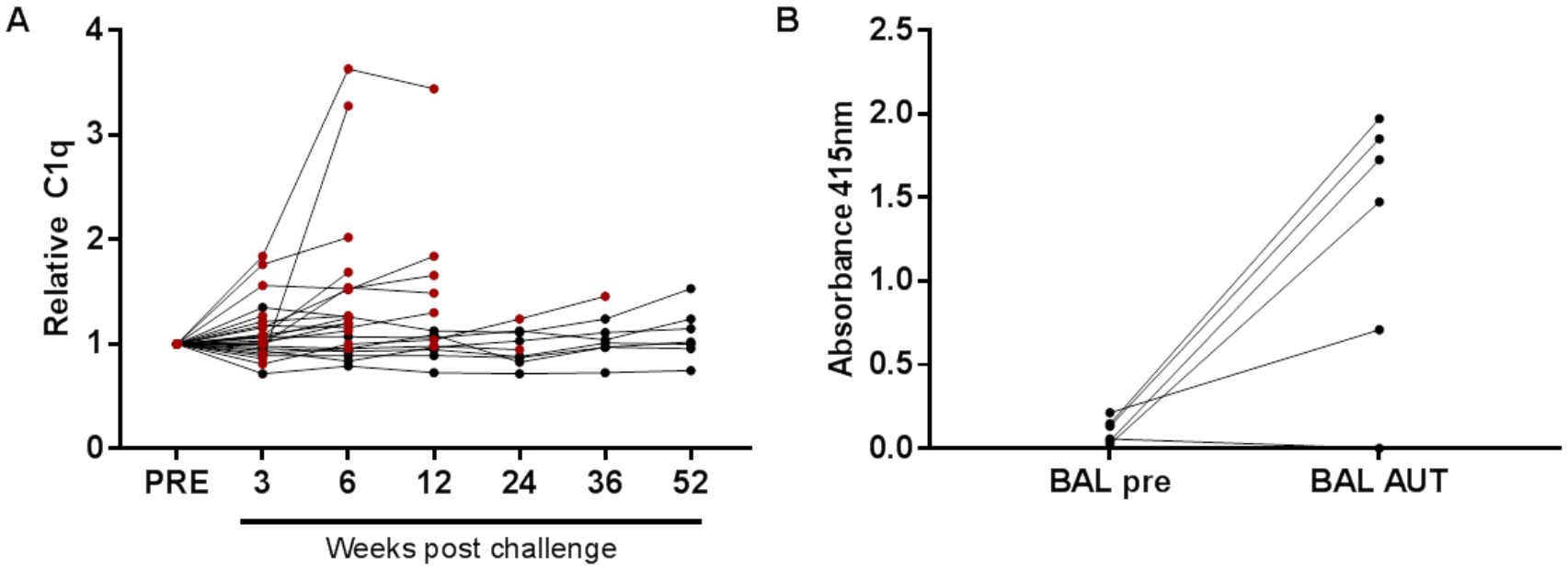
Non-human primates – TB – C1q

Collaboration with Karin Dijkman at the BPRC in Rijswijk

Non-human primate TB model in Macaques.

BCG vaccination trial with post-hoc analysis of sera and BAL.



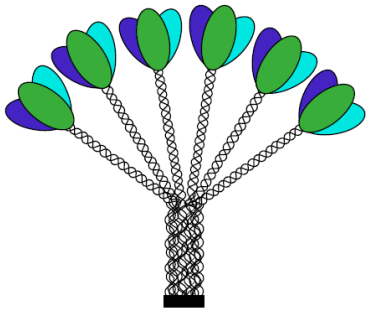


Summary

C1q mRNA's are upregulated in PBMCs, indicating indirect stimulation

C1q protein levels are increased in patients with active TB compared to controls

Non human primates show similar increase in C1q after experimental TB challenge



Lubbers et al. *Frontiers in Immunology* 2018

Summary

C1q mRNA's are upregulated in PBMCs, indicating indirect stimulation

C1q protein levels are increased in patients with active TB compared to controls

Non human primates show similar increase in C1q after experimental TB challenge

But why would a pathogen want more C1q?

Summary

RESEARCH

IMMUNOLOGY

C1q restrains autoimmunity and viral infection by regulating CD8$^+$ T cell metabolism

Guang Sheng Ling,[1] Greg Crawford,[1] Norzawani Buang,[1] Istvan Bartok,[1] Kunyuan Tian,[1] Nicole M. Thielens,[2] Isabelle Bally,[2] James A. Harker,[1] Philip G. Ashton-Rickardt,[1] Sophie Rutschmann,[1] Jessica Strid,[1] Marina Botto[1]*

Deficiency of C1q, the initiator of the complement classical pathway, is associated with the development of systemic lupus erythematosus (SLE). Explaining this association in terms of abnormalities in the classical pathway alone remains problematic because C3 deficiency does not predispose to SLE. Here, using a mouse model of SLE, we demonstrate that C1q, but not C3, restrains the response to self-antigens by modulating the mitochondrial metabolism of CD8$^+$ T cells, which can themselves propagate autoimmunity. C1q deficiency also triggers an exuberant effector CD8$^+$ T cell response to chronic viral infection leading to lethal immunopathology. These data establish a link between C1q and CD8$^+$ T cell metabolism and may explain how C1q protects against lupus, with implications for the role of viral infections in the perpetuation of autoimmunity.

ect stimulation

with active TB compared

experimental challenge

nt more C1q?

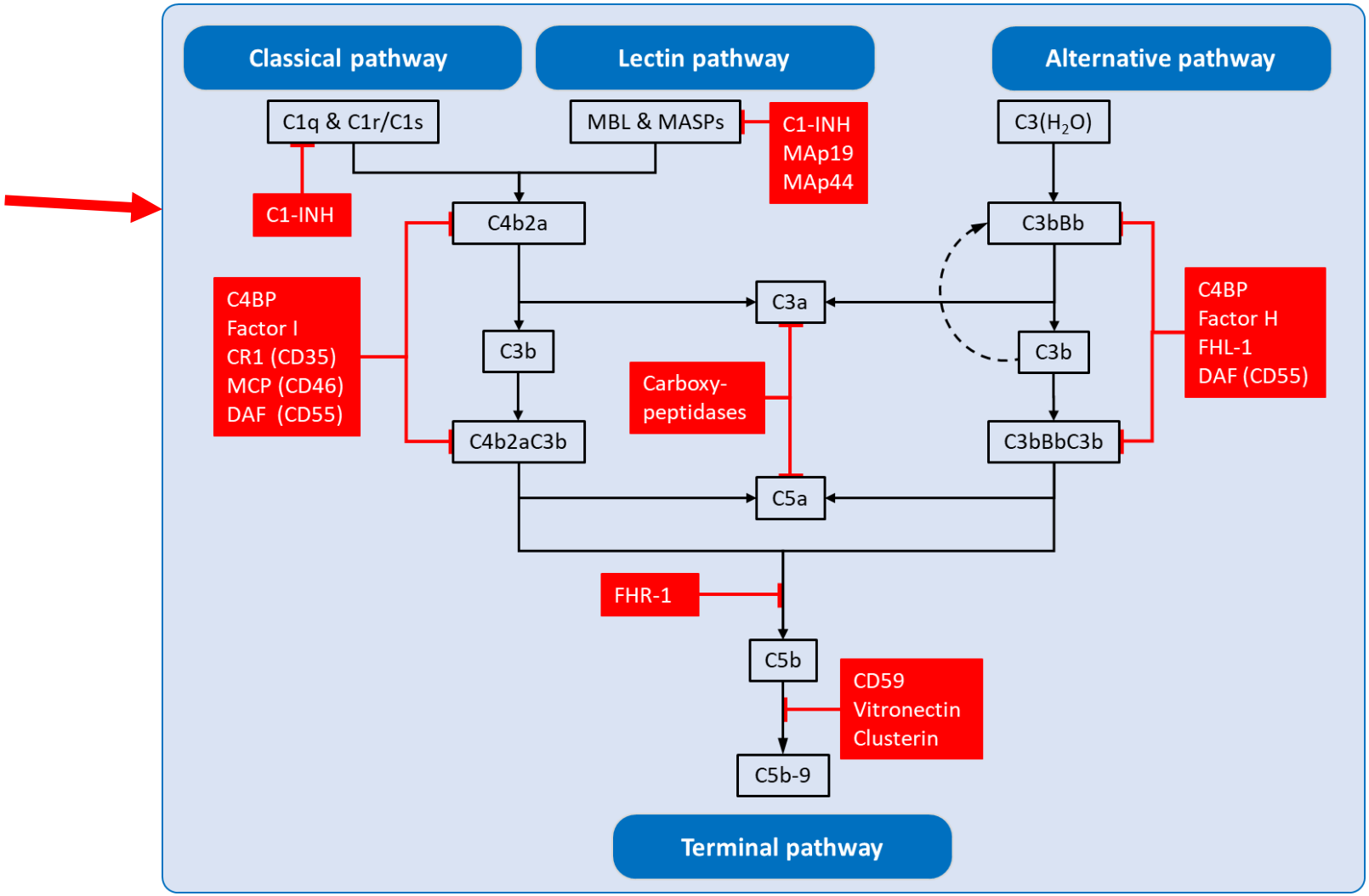
Ling et al Science 2018

TB is using C1q as an immune evasion strategy

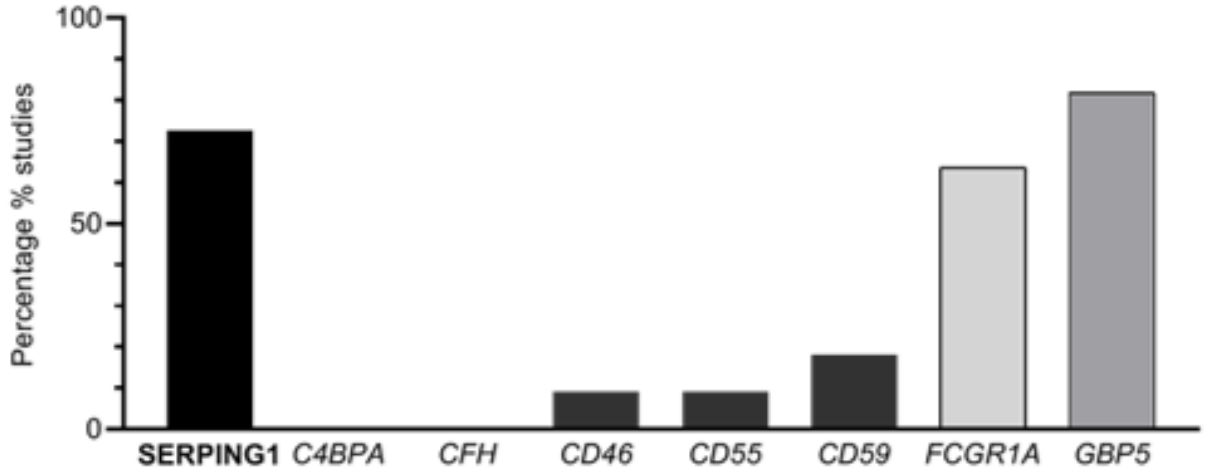
But increased C1q would mean more classical pathway

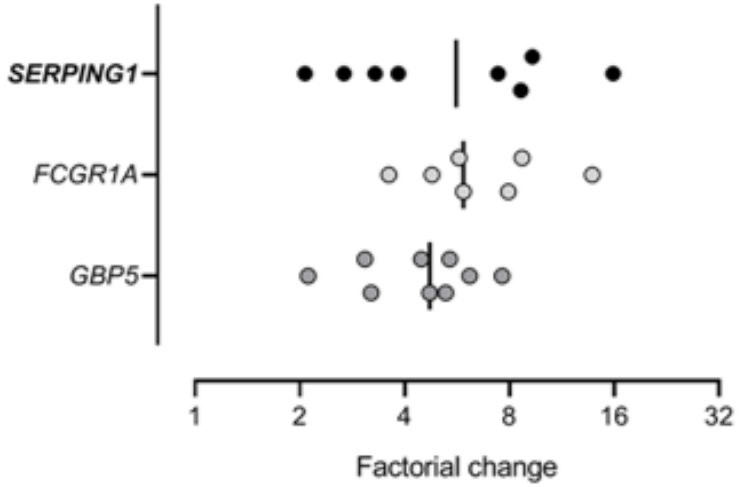
Unless there is also enhanced complement inhibition

Endogenous complement inhibitors

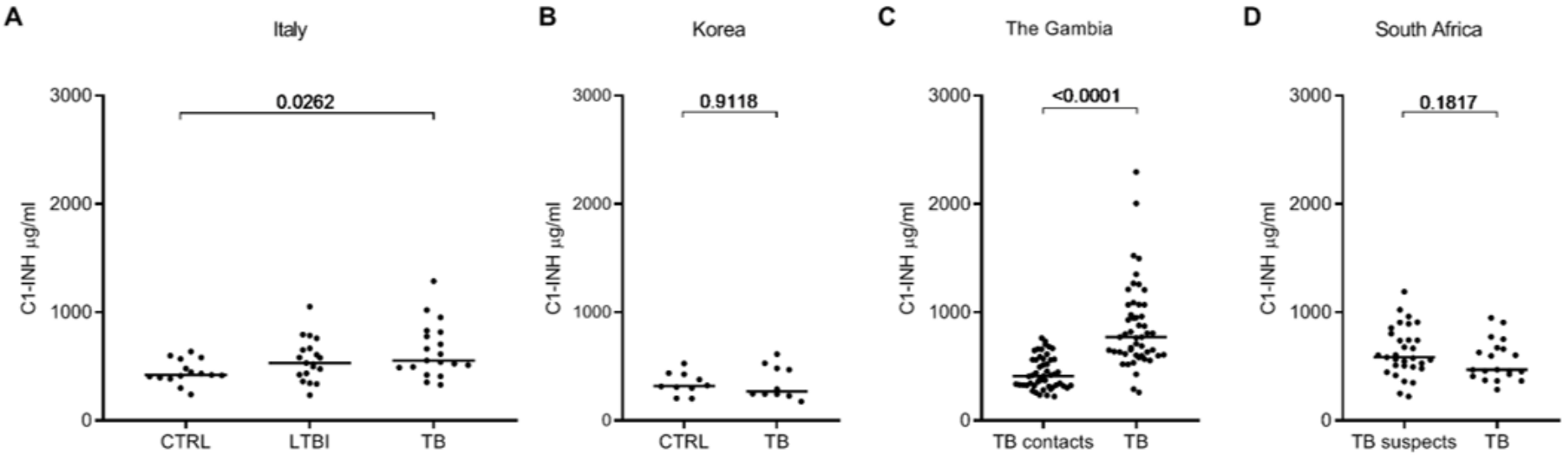


Expression of complement inhibitors in active TB



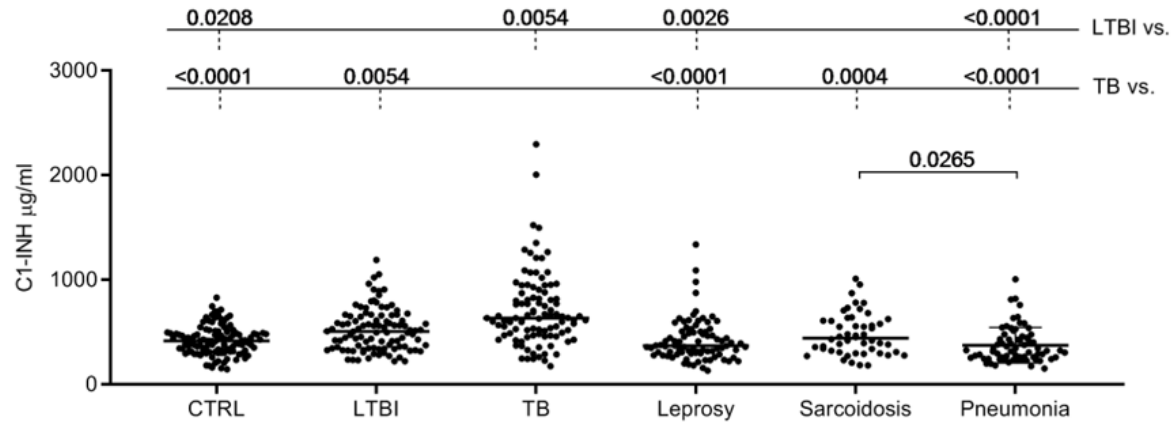


C1-INH protein levels



C1-INH in active TB versus differential diagnoses

A



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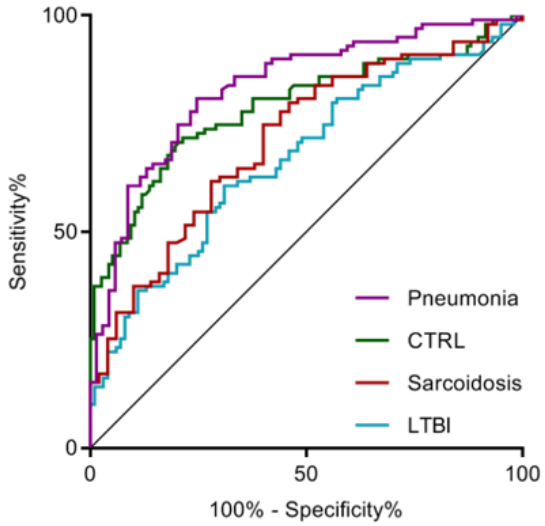
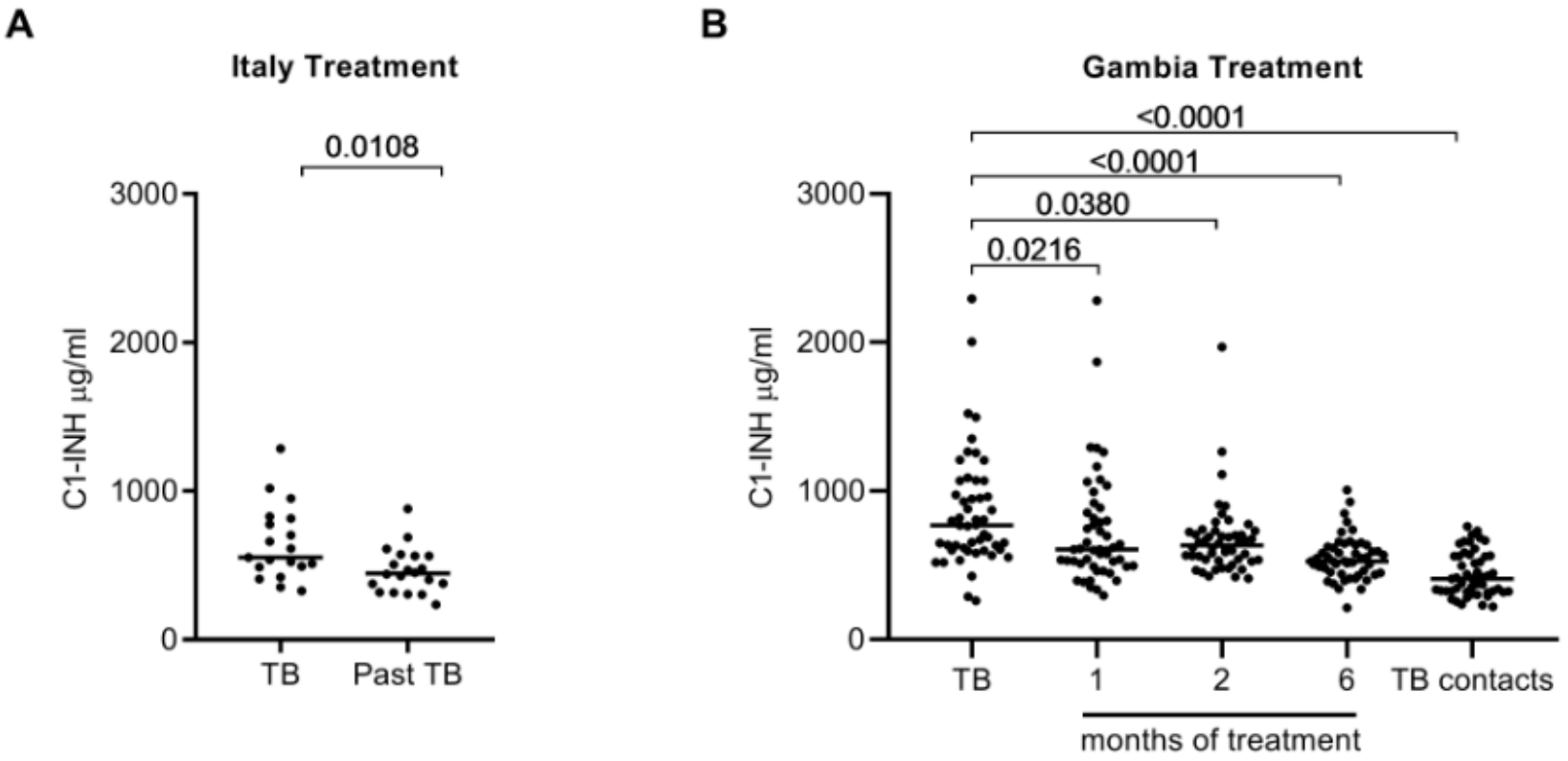


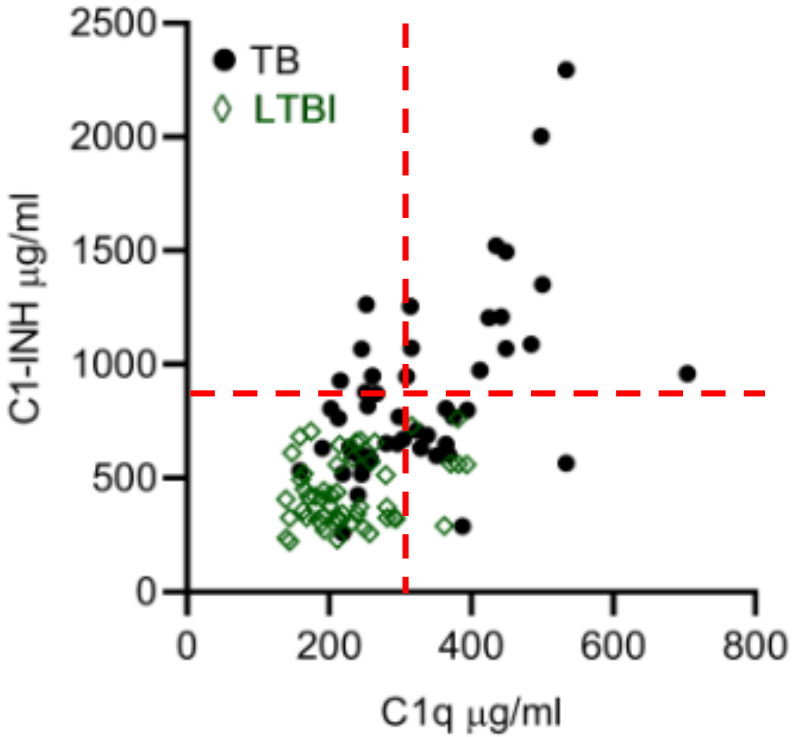
C

TB vs	AUC	Std Error	95% CI
CTRL	0.789	0.032	[0.726 ; 0.852]
LTBI	0.669	0.038	[0.594 ; 0.744]
Leprosy	0.791	0.034	[0.725 ; 0.857]
Sarcoidosis	0.713	0.044	[0.628 ; 0.798]
Pneumonia	0.834	0.032	[0.772 ; 0.900]
ALL	0.747	0.029	[0.690 ; 0.804]

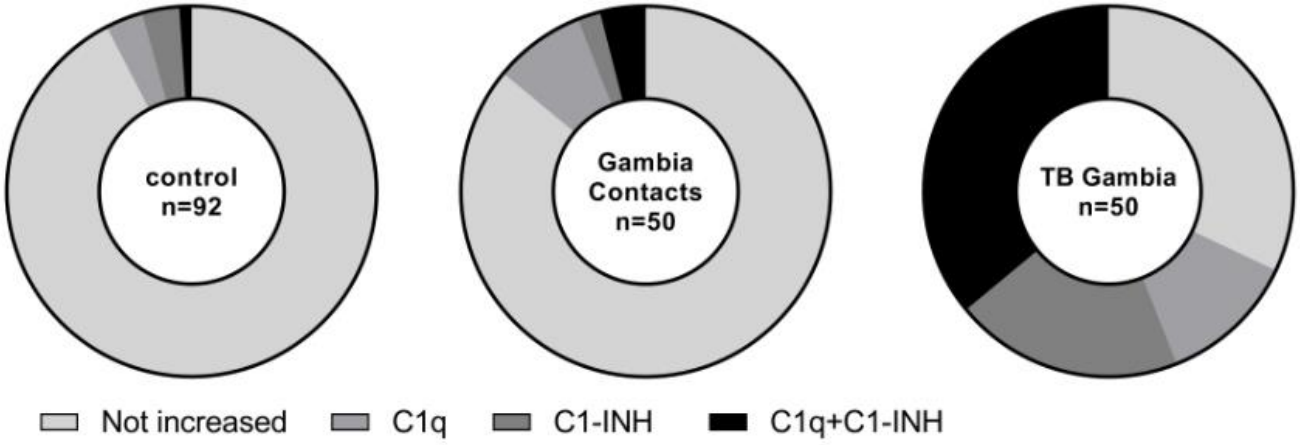
C1-INH levels normalize after successful treatment

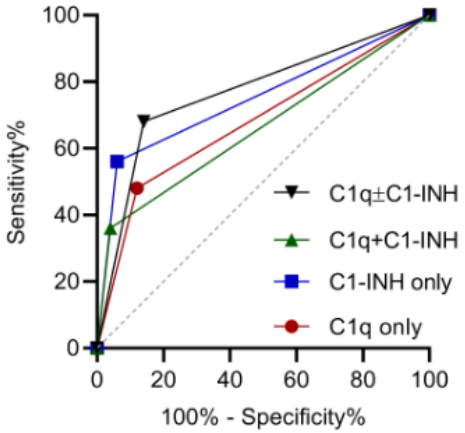


C1q and C1-INH



C1q and C1-INH as biomarkers for active TB





Score	AUC	95% CI	Sensitivity	Specificity
C1q	0.68	[0.57 ; 0.79]	48%	88%
C1-INH	0.75	[0.65 ; 0.85]	56%	94%
C1q+C1-INH	0.66	[0.55 ; 0.77]	36%	96%
C1q±C1-INH	0.77	[0.67 ; 0.87]	68%	86%

Conclusions

C1q expression and protein levels are increased in active TB vs latent disease

C1-INH, the inhibitor of C1q, is also increased in active TB

Together C1q levels and C1-INH levels are a reasonable biomarker for active TB

Upregulation of both proteins is suggesting immune escape mechanisms


Research Article

Cancer Immunology Research

Tumor Cells Hijack Macrophage-Produced Complement C1q to Promote Tumor Growth

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Main message:
C1q suppresses T cell activity

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JCI insight

RESEARCH ARTICLE

Cigarette smoke–induced reduction of C1q promotes emphysema

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Main message:
C1q suppresses Th-17 activity
and stimulates T-reg function

JCI Insight. 2019 May 21;5.

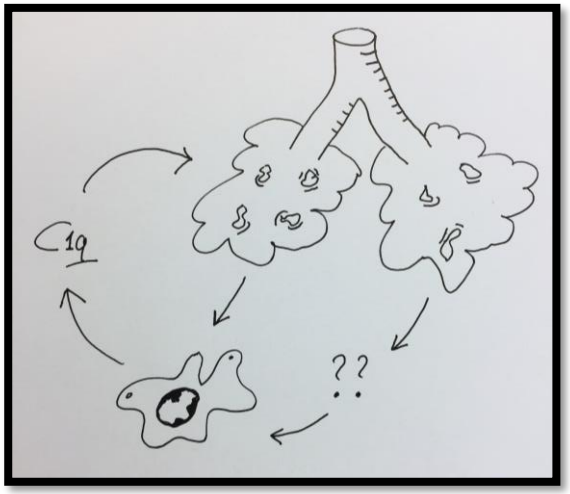
Future directions

How is the local TB infection driving systemic C1q / C1-INH levels?

Do other intracellular pathogens use the same mechanism?

What is the relative contribution of C1q on the immune response to TB?

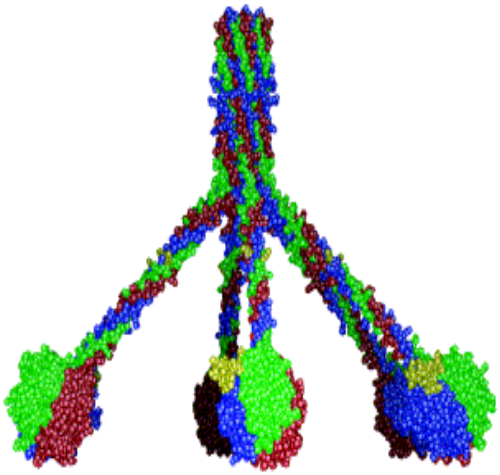
How does C1q impact on the (adaptive) immune system?



Both ends of the spectrum are informative !!

Bacterial immune escape

SLE



TB

Neuro-psychiatrical problems

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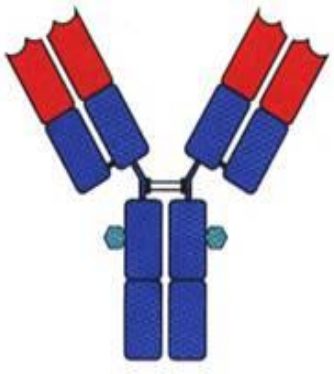
LUMC

Inova Diagnostics
A Werfen Company

Genmab

NWO
Netherlands Organisation for Scientific Research

COMPLEMENT



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