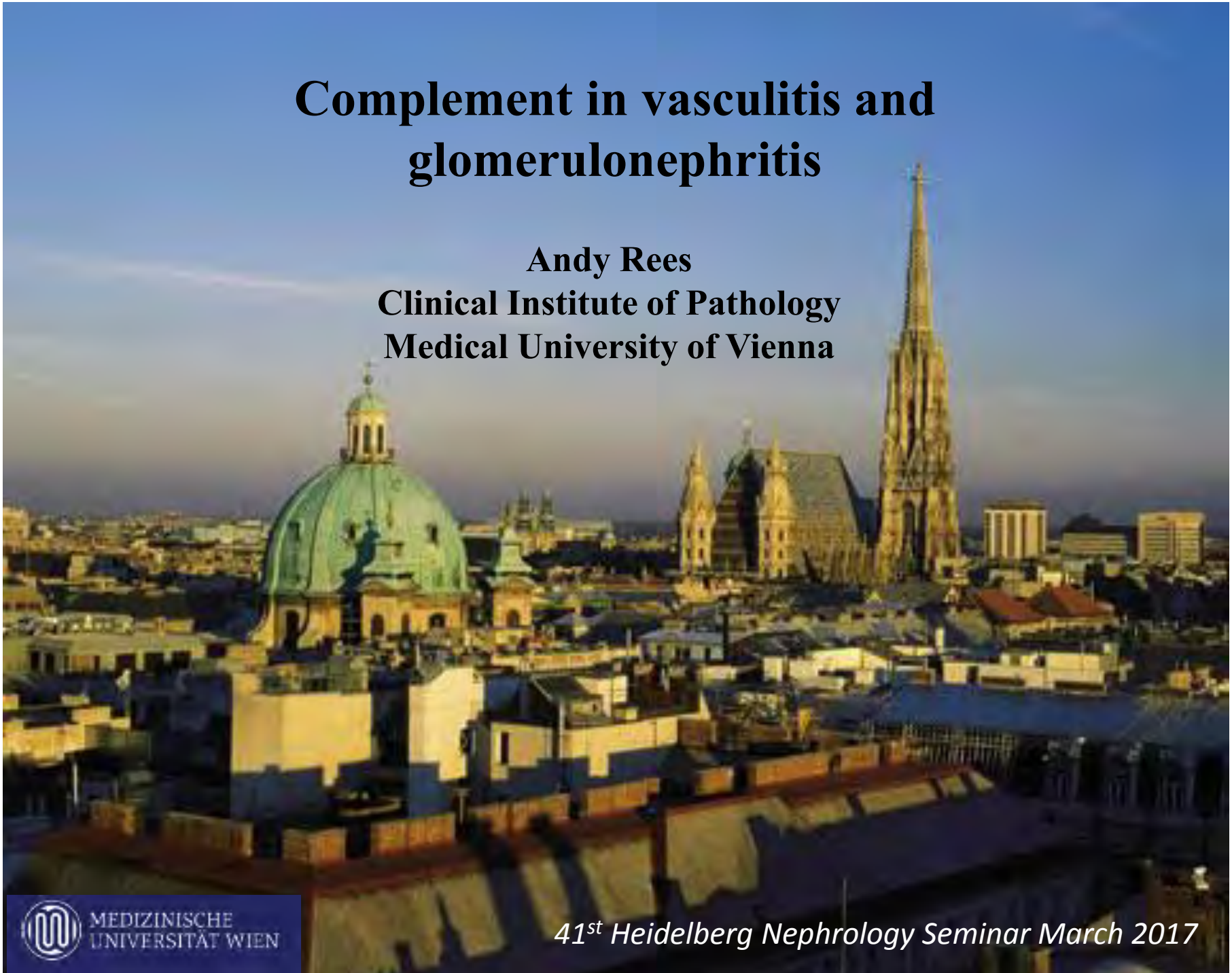
Complement in vasculitis and glomerulonephritis

Andy Rees
Clinical Institute of Pathology
Medical University of Vienna



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41st Heidelberg Nephrology Seminar March 2017

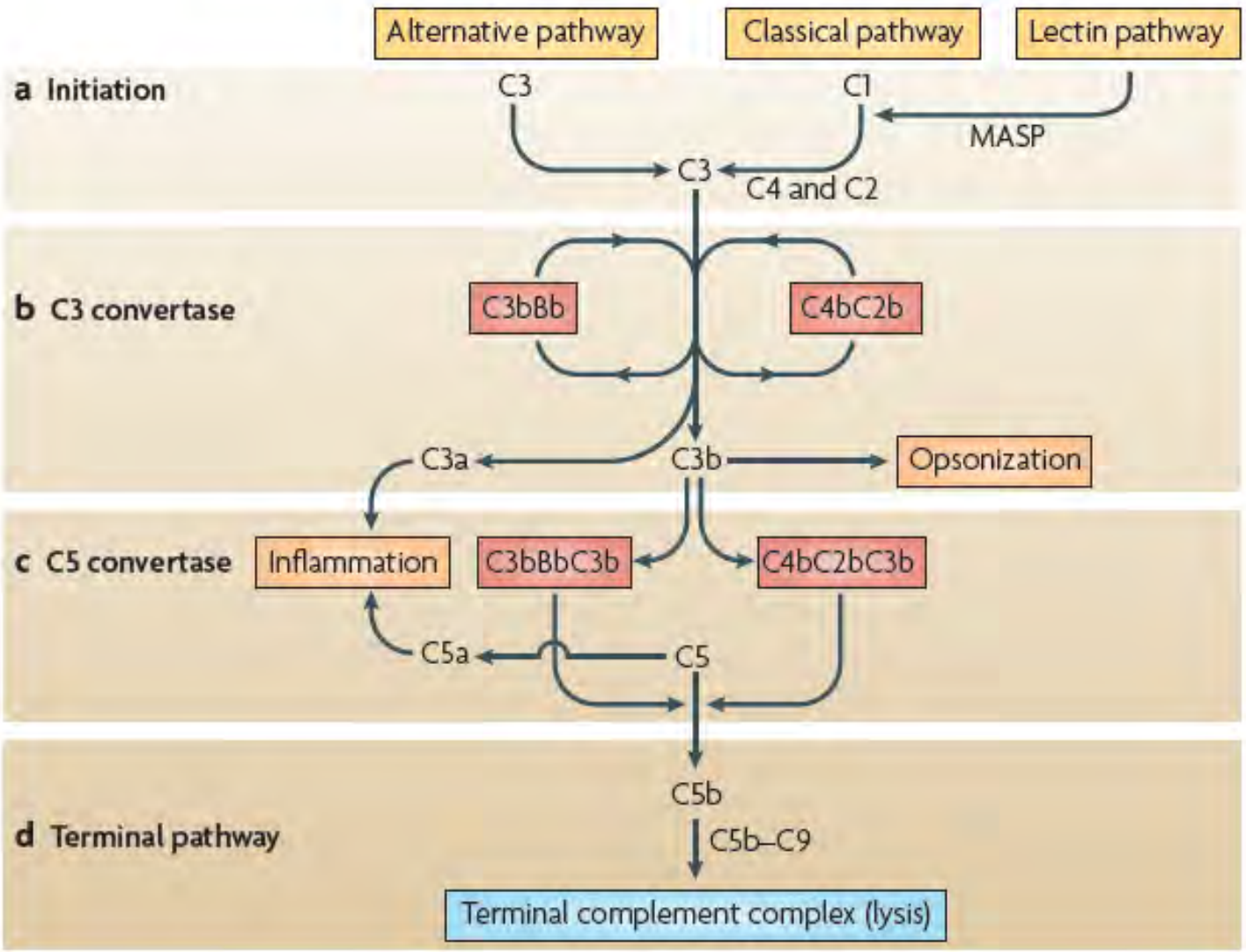
The complement system

An evolutionary conserved pathway central to maintenance of host defense

Destruction of pathogens
Elimination of virally infected cells
Removal of immune complexes and cell debris
Facilitating efficient B and T cell responses
Sensing danger signals

Prevention of autoimmune disease

The complement system



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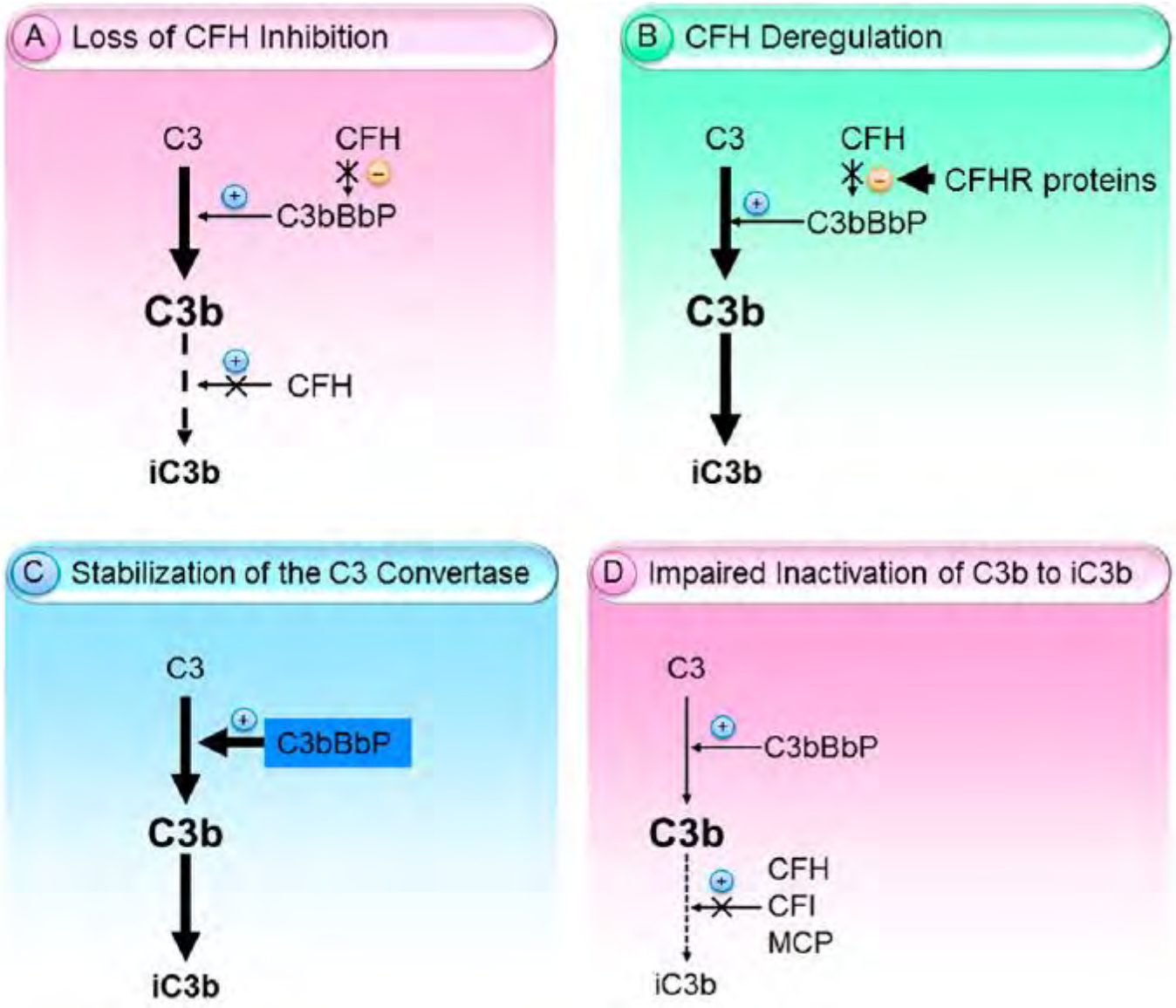
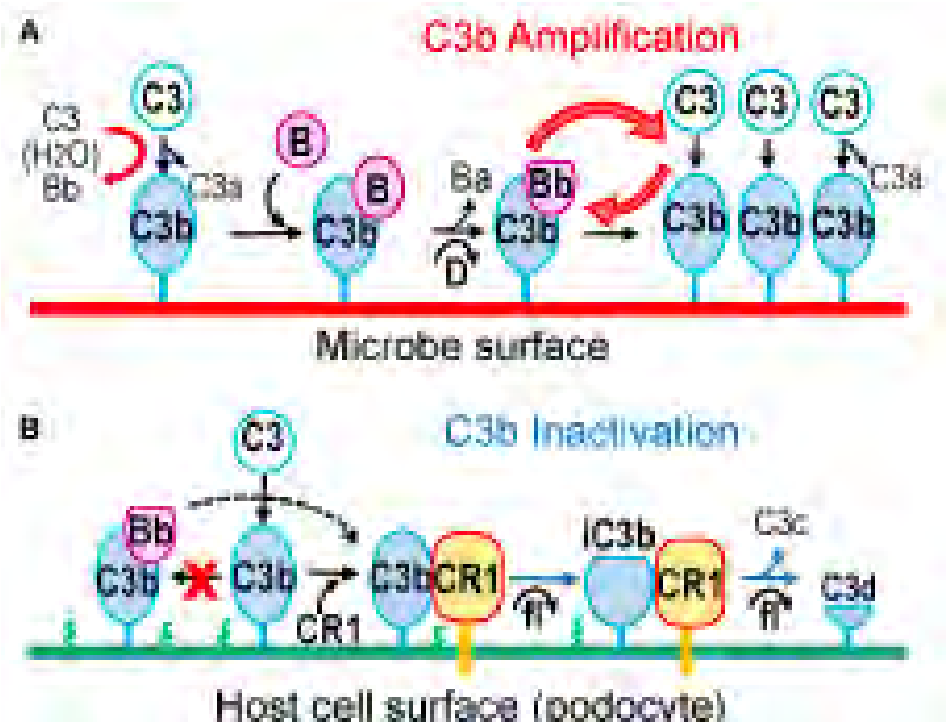
Zipfel and Skerka Nat Immunol 2009

Control of C3 activation



De Vriese et al JASN 2015

The complement system selectively targets microbial surfaces



Borza Frontiers of Immunology 2017

Autoimmunity in complement deficiency

Complement deficiency	Frequency	SLE (%)	Recurrent bacterial Infections
C1q	75 cases	90%	88%
C1r	12 cases	65%	85%
Cis	8 cases	65%	65%
C4	Rare	75%	Common
C2	1 in 20,000	10%	Rare
C3	Very rare	Rare	Very common

Data from Vignesh Clin Chim Acta 2017

Complement and glomerulonephritis
an overview

Complement and predisposition to glomerulonephritis

- C1q, C4 and C2 deficiency and SLE

Complement abnormalities as a cause of glomerulonephritis

- C3 glomerulopathy
  - Dense deposit disease
  - C3 glomerulonephritis
- C4 glomerulonephritis

Complement proteins as effectors of injury

- Membranous nephropathy
- Focal necrotizing glomerulonephritis

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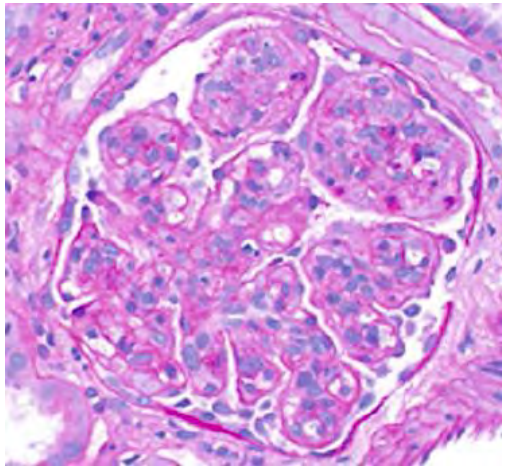
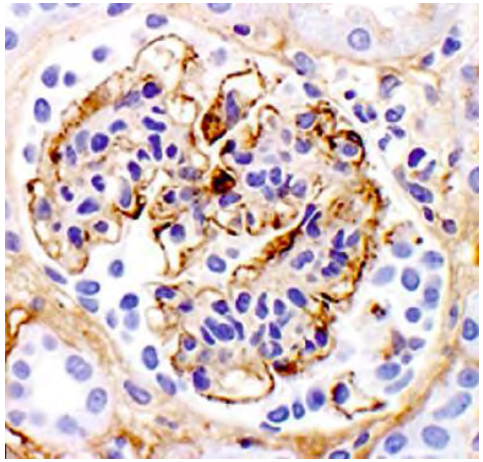
Dense Deposit Disease
The Prototypic C3 nephropathy

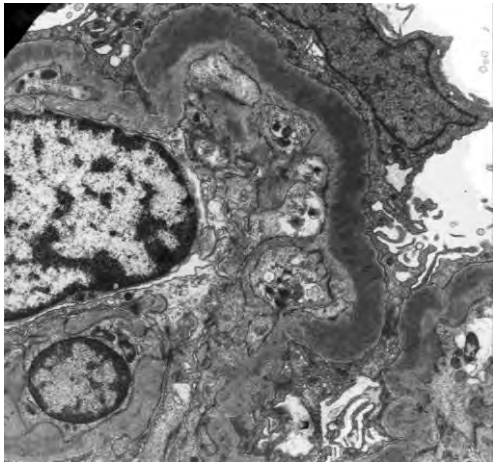
Identified as a unique entity in 1962 by Berger and Galle

- Progressive glomerulonephritis presenting in the young
- Membrano-proliferative appearance on light microscopy
- Glomerular C3 deposition in absence of IgG
- Band-line dense deposit within the GBM

Dense Deposit Disease







- Low C3 with alternative pathway activation
- Unrestrained intravascular complement activation
- Associated with autoantibodies to C3Bb convertase (C3NeF)
- Frequent recurrence in renal allografts

Subsumed into membranoproliferative glomerulonephritis more generally

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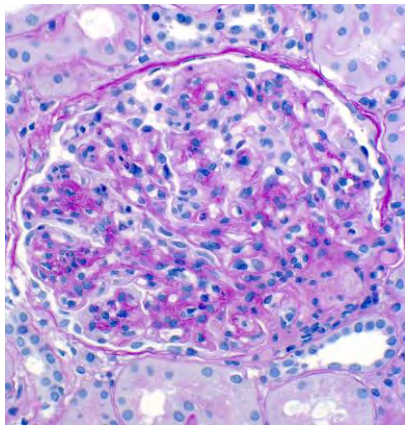
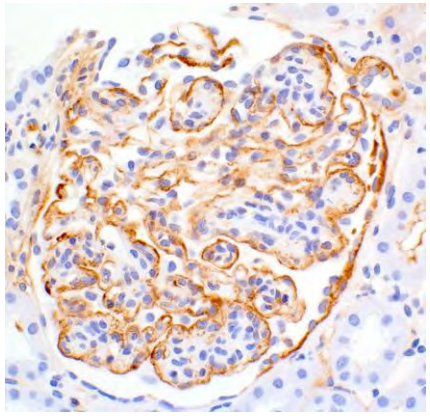
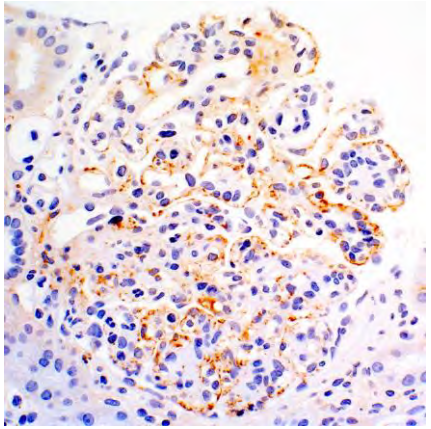
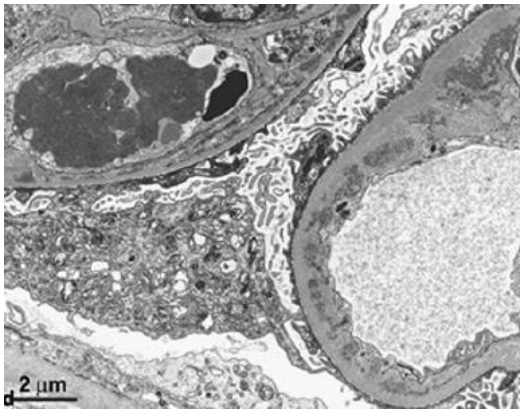
Membranoproliferative glomerulonephritis

MPGN Type 1 – Subendothelial and subepithelial deposits
Deposition IgG and complement (C**3)**

MPGN Type 2 - Intramembranous dense deposits
Deposition of complement without IgG

(**MPGN Type 3 -** As Type 1 but prominent subepithelial deposits)

Membranoproliferative glomerulonephritis

MPGN Type 1 – Subendothelial and subepithelial deposits
Deposition IgG and complement (C**3)**

Some MPGN type 1 have - no IgG deposits
- low C3 concentrations
- C3Nef

MPGN Type 2 - Intramembranous dense deposits
Deposition of complement without IgG

Some dense deposit disease - don't have MPGN
Gn with isolated C3 deposition not invariable MPGN

Membranoproliferative glomerulonephritis

MPGN Type 1 – Subendothelial and subepithelial deposits
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New pathogenetically informed terminology
C3 Nephropathy

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PERSPECTIVES

OPINION

C3 glomerulopathy: a new classification

Fadi Fakhouri, Véronique Frémeaux-Bacchi, Laure-Hélène Noël, H. Terence Cook and Matthew C. Pickering

http://www.kidney-international.org

meeting report

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OPEN

C3 glomerulopathy: consensus report

Matthew C. Pickering[1], Vivette D. D'Agati[2], Carla M. Nester[3,4], Richard J. Smith[3,4], Mark Haas[5], Gerald B. Appel[6], Charles E. Alpers[7], Ingeborg M. Bajema[8], Camille Bedrosian[9], Michael Braun[10], Mittie Doyle[9], Fadi Fakhouri[11], Fernando C. Fervenza[12], Agnes B. Fogo[13], Véronique Frémeaux-Bacchi[14], Daniel P. Gale[15], Elena Goicoechea de Jorge[1], Gene Griffin[9], Claire L. Harris[16], V. Michael Holers[17], Sally Johnson[18], Peter J. Lavin[19], Nicholas Medjeral-Thomas[1], B. Paul Morgan[16], Cynthia C. Nast[5], Laure-Hélène Noel[20], D. Keith Peters[21], Santiago Rodríguez de Córdoba[22], Aude Servais[23], Sanjeev Sethi[24], Wen-Chao Song[25], Paul Tamburini[9], Joshua M. Thurman[17], Michael Zavros[26] and H. Terence Cook[1]

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C3 glomerulopathy: a process not a disease

A disease process due to **abnormal control** of complement activation, deposition, or degradation

Characterized by **predominant** glomerular C3 fragment deposition with electron-dense deposits on EM

Caused by unrestrained **alternative pathway activation within** the circulation either due to mutations of or autoantibodies to complement regulatory proteins

Results in a spectrum of glomerular appearances separated into **Dense Deposit Disease** and **C3 glomerulonephritis**

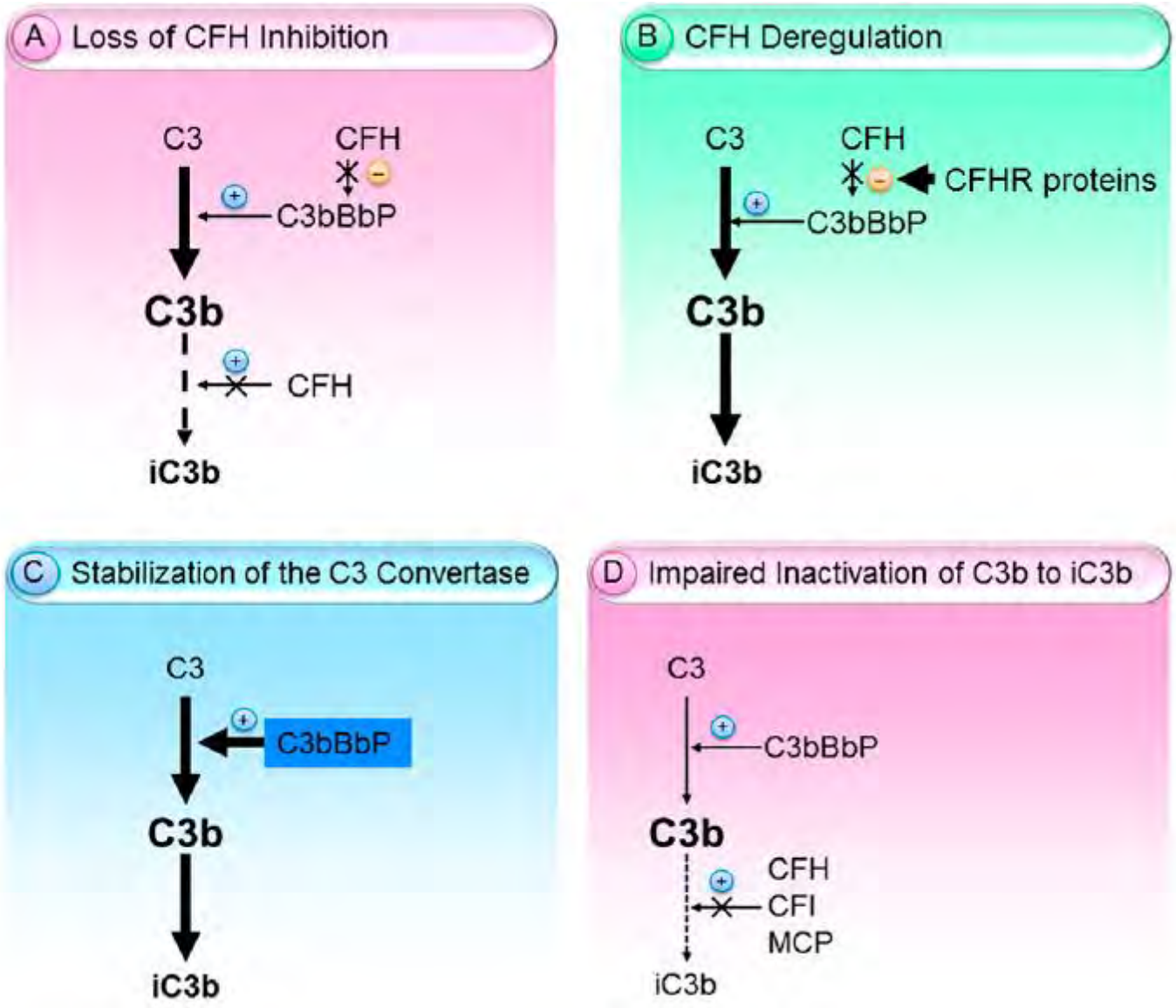
C3 glomerulopathy - features

Morphology
variable and includes mesangial proliferative Gn, MPGN and endocapillary Gn ± crescents

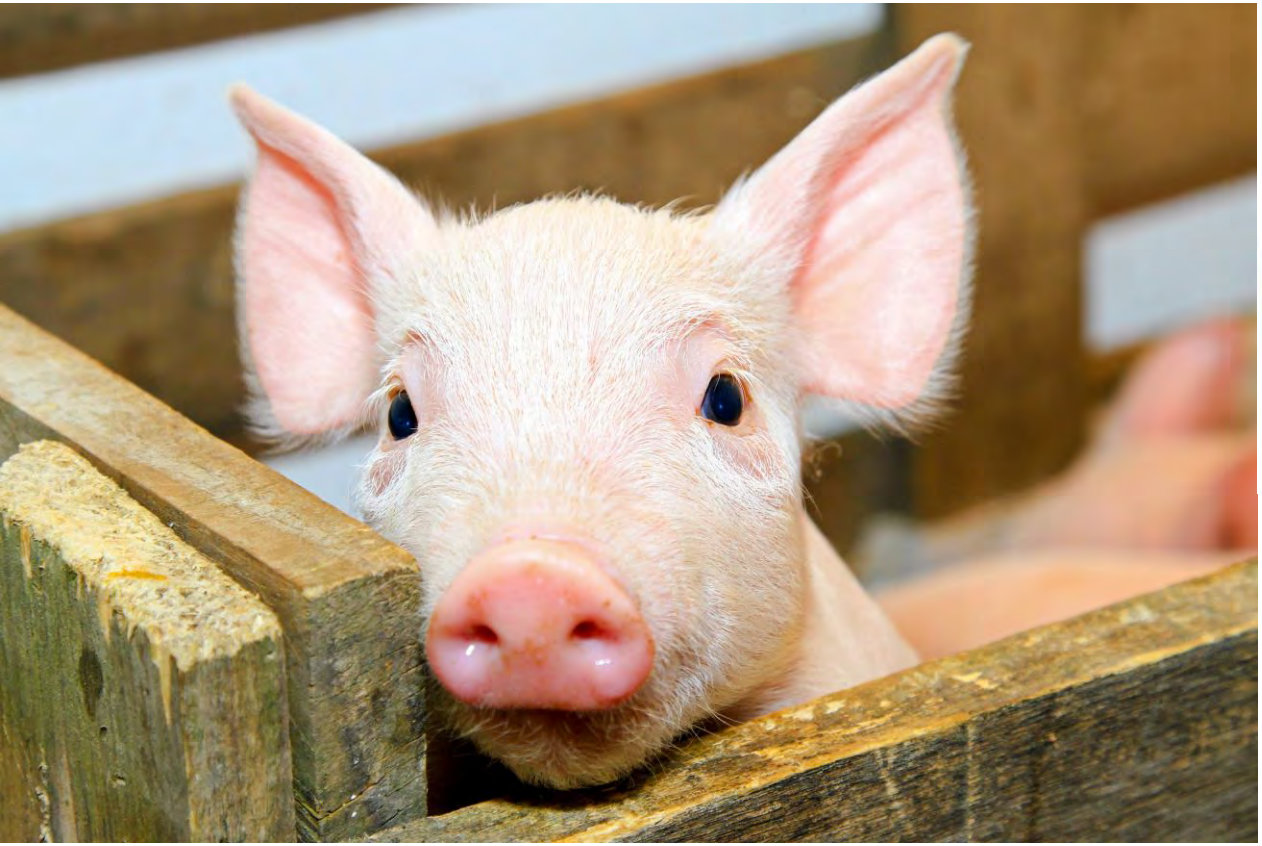
Electron microscopy
Dense intra membranous deposits ± subendothelial deposits (DDD) or varied subendothelial and mesangial deposits

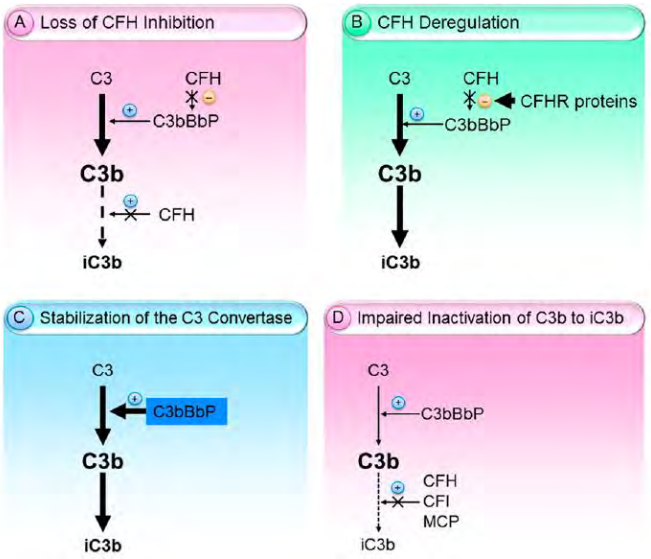
Immunohistology/fluorescence
Predominant C3 with or without lesser amounts of IgG – many with MPGN type I have C3Nef

Control of C3 activation



De Vriese et al JASN 2015





Factor H deficient Yorkshire strain pigs
Spontaneous early onset DDD

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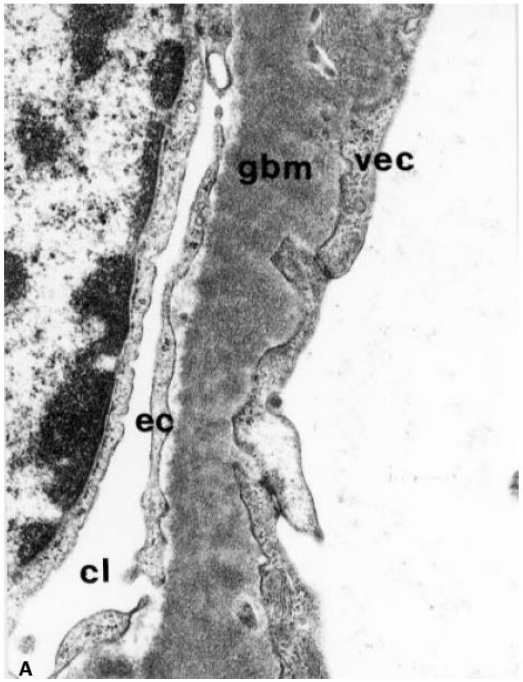
Høgâsen K et al JCI 1995,

Kidney International, Vol. 53 (1998), pp. 331–340

In situ complement activation in porcine membranoproliferative glomerulonephritis type II

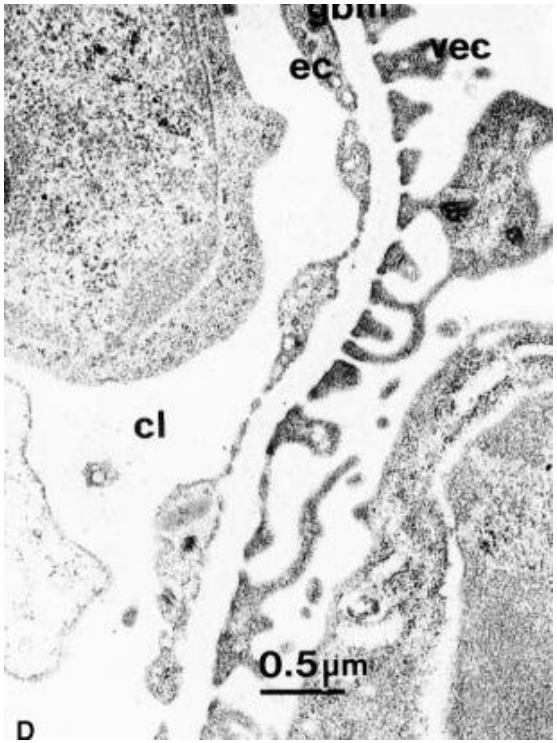
Johan H. Jansen, Kolbjorn Høgåsen, Morten Harboe, and Torstein Hovig

CFH deficient



CFH deficient – C3

CFH sufficient control



Immuno-EM very early C3 and C5-9 deposition followed by dense intramembranous deposits

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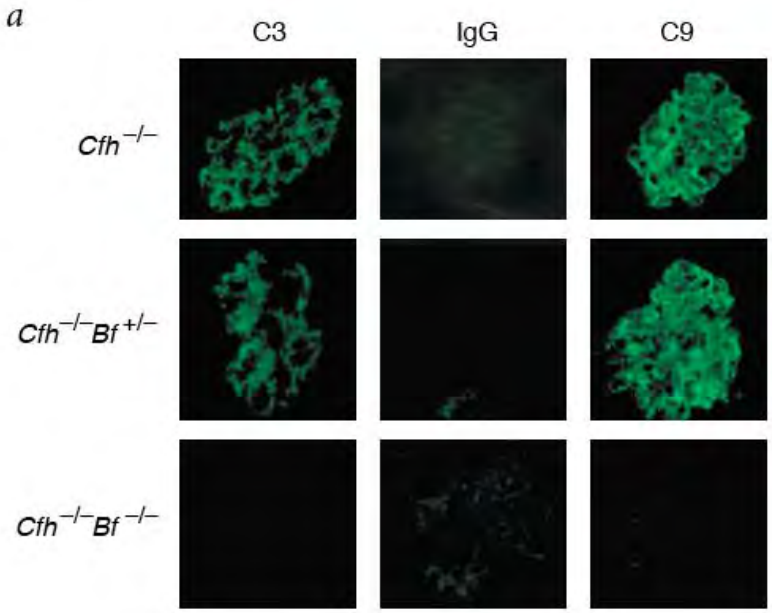
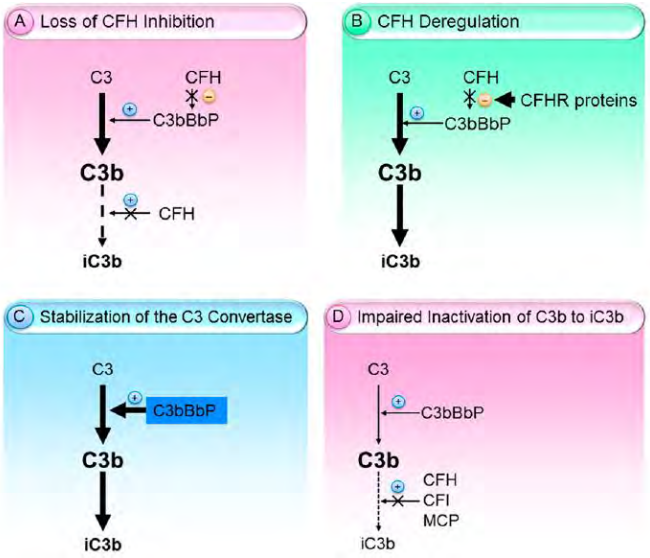
Uncontrolled C3 activation causes membranoproliferative glomerulonephritis in mice deficient in complement factor H

Matthew C. Pickering[1], H. Terence Cook[2], Joanna Warren[1], Anne E. Bygrave[1], Jill Moss[3], Mark J. Walport[1] & Marina Botto[1]





Rescued by infusions of human CFH
CFI essential for GBM localisation but not mesangial
C5 deficiency is protective but C6 deficiency is not
Aggravated by coincident CR3 deficiency
Trials of potential therapies CR2-FH and truncated CFH

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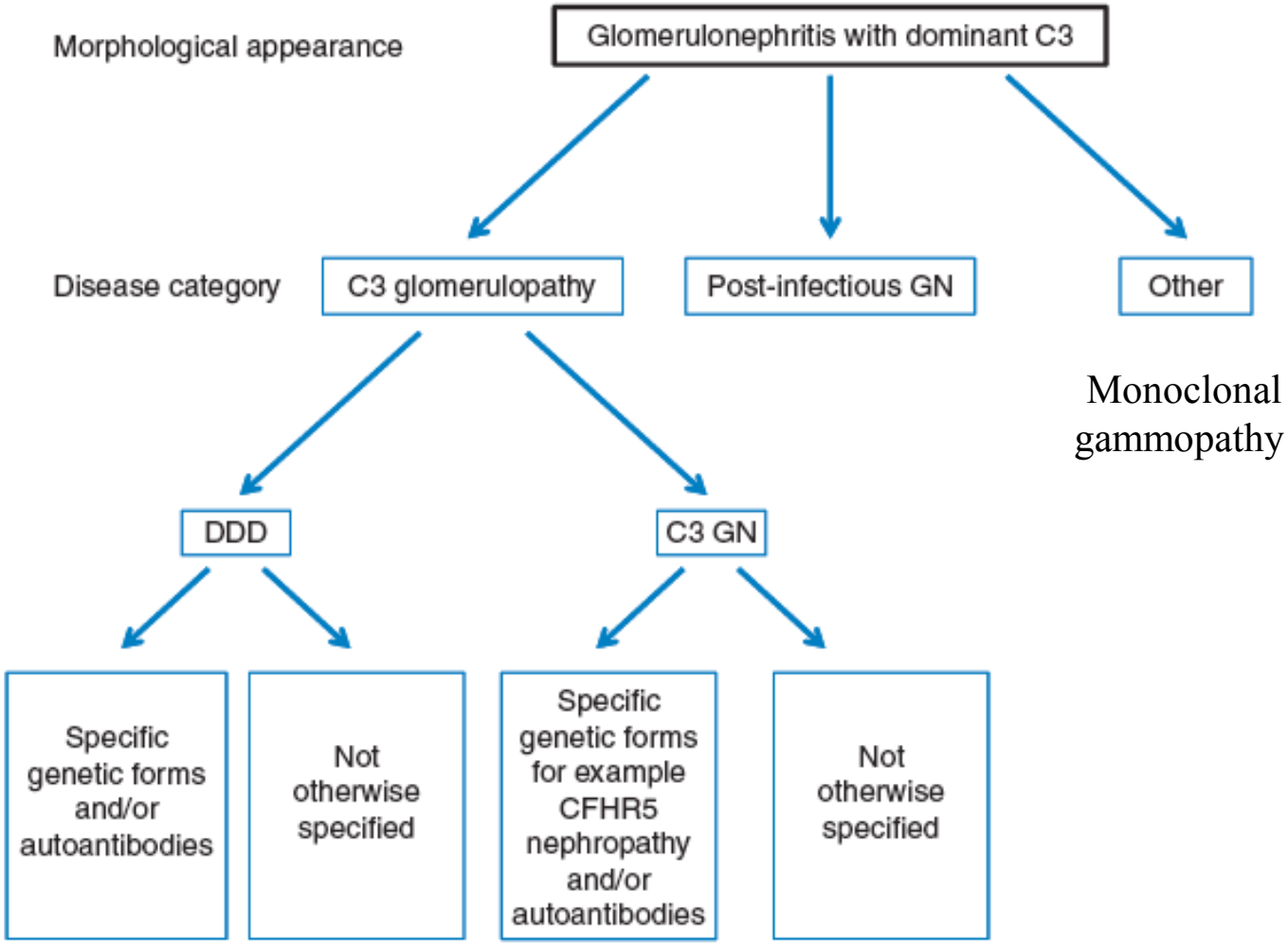
Nature Genetics 2002

C3 glomerulopathy – consensus report



Atypical postinfectious glomerulonephritis is associated with abnormalities in the alternative pathway of complement

Sanjeev Sethi[1], Fernando C. Fervenza[2], Yuzhou Zhang[3], Ladan Zand[2], Nicole C. Meyer[3], Nicolò Borsa[3], Samih H. Nasr[1] and Richard J.H. Smith[3,4,5]

Table 3 | Complement abnormalities

Patient	*CFH*	*CFHR5*	FH antibodies[a]
1	c.2171delC, p.Thr724fsX, 725	No mutations	Negative
2	No mutations	c.646-647, AA>TT, p.Asn216Phe	Negative
3	No mutations	No mutations	Negative
4	No mutations	No mutations	Negative
5	No mutations	No mutations	Negative
6	No mutations	No mutations	Negative
7	c.3350A>G, p.Asn1117Ser	No mutations	Negative
8	No mutations	No mutations	Negative
9	No mutations	No mutations	Negative
10	c.1699A>G, p.Arg567Gly	No mutations	Negative
11	No mutations	No mutations	Negative

In addition 7 had C3NeF (including 6 without mutations)

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Kidney International 2012

ORIGINAL ARTICLE

C3 Glomerulopathy and post-infectious glomerulonephritis define a disease spectrum

Badria Al-Ghaithi[1] · Rahul Chanchlani[1,2,3] · Magdalena Riedl[4] · Paul Thorner[5,6] · Christoph Licht[1,4,7]

Complete recovery %

Group A
N=14

67 %

Post infectious GN

Group B
N=9

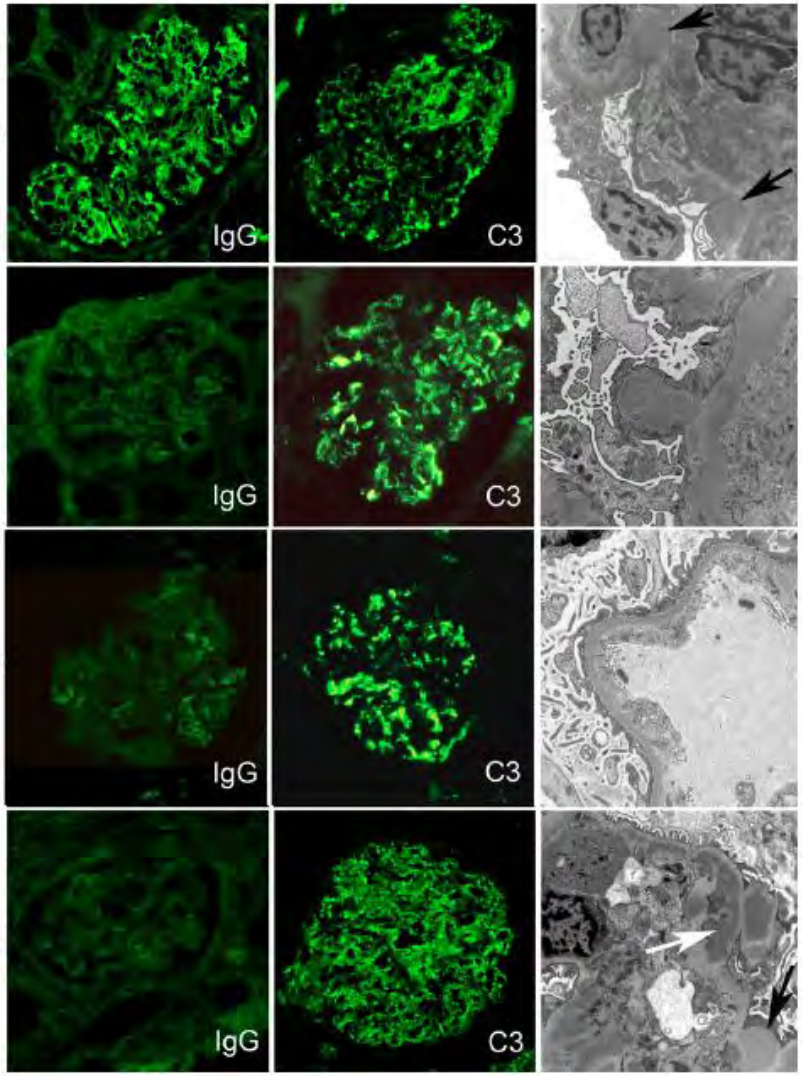
86 %

Group C
N=6

C3 nephropathy

25 %

Group D
N=2



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Pediatric Nephrology 2016

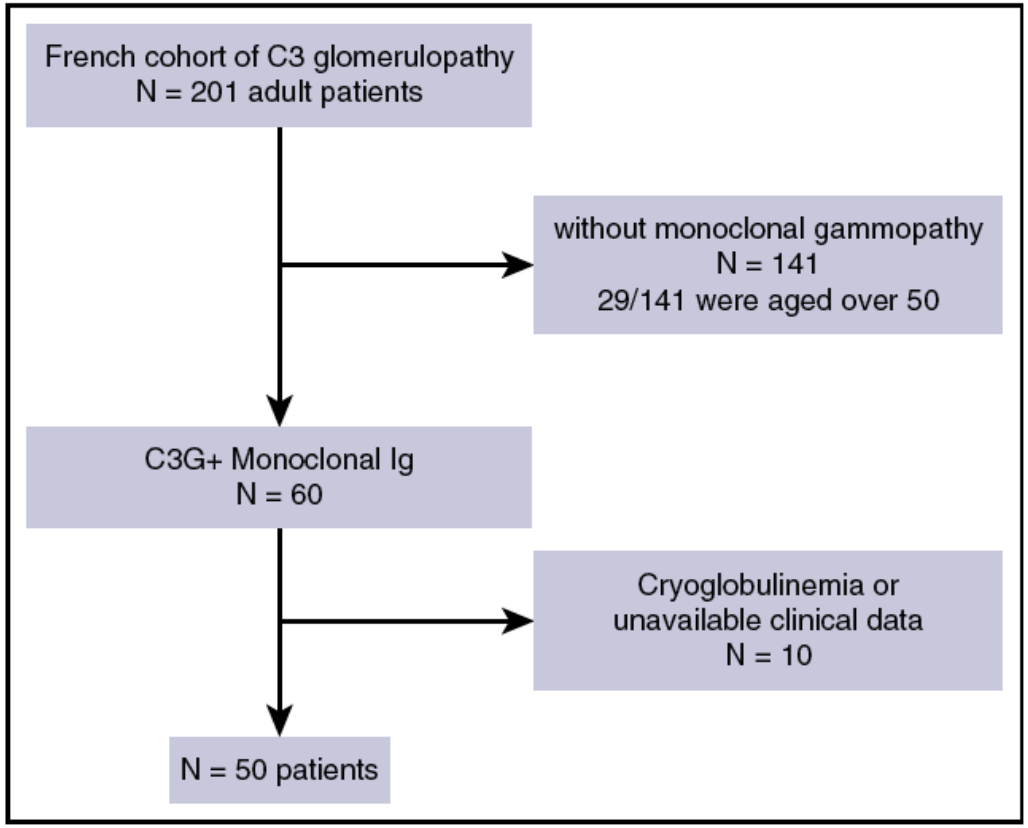
Regular Article

blood

CLINICAL TRIALS AND OBSERVATIONS

Treatment of B-cell disorder improves renal outcome of patients with monoclonal gammopathy–associated C3 glomerulopathy

Sophie Chauvet,[1-3] Véronique Frémeaux-Bacchi,[2,4] Florent Petitprez,[5] Alexandre Karras,[1] Laurent Daniel,[6] Stéphane Burtey,[7] Gabriel Choukroun,[8] Yahsou Delmas,[9] Dominique Guerrot,[10] Arnaud François,[11] Moglie Le Quintrec,[12] Vincent Javaugue,[13,14] David Ribes,[15] Laurence Vrigneaud,[16] Bertrand Arnulf,[17] Jean Michel Goujon,[14,18] Pierre Ronco,[19] Guy Touchard,[13,14] and Frank Bridoux[13,14]



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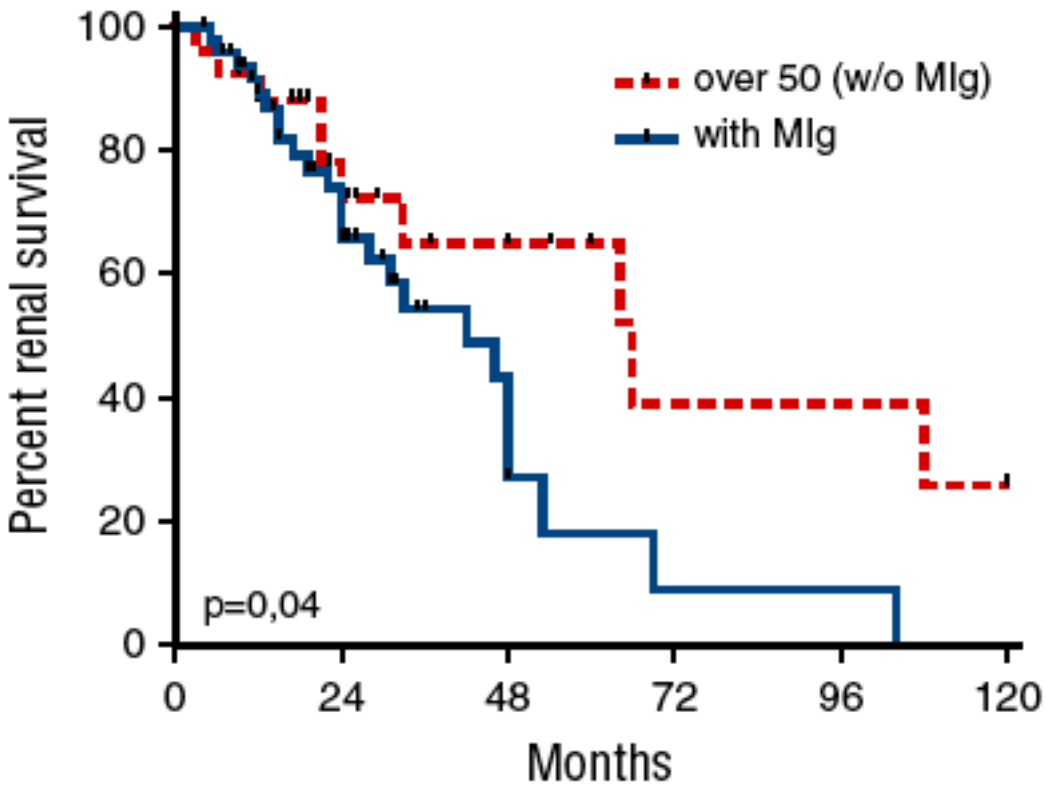
Chauvet et al Blood 2017

Renal prognosis of C3 nephropathy worse with coincident monoclonal glomerulopathy



Without MIg	26	14	8	4	4	2
With MIg	50	27	8	2	2	0

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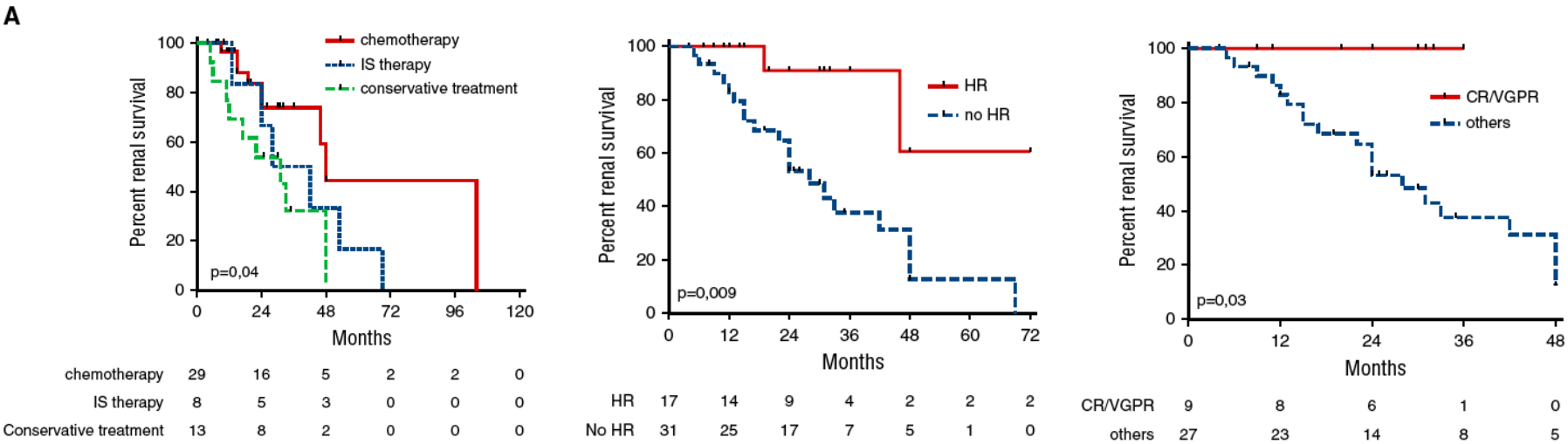
Chauvet et al Blood 2017

Treatment of monoclonal glomerulopathy improves renal prognosis in C3 nephropathy



C3 concentrations returned to normal with complete remission

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Chauvet et al Blood 2017

C3 glomerulopathy – consensus report Investigations

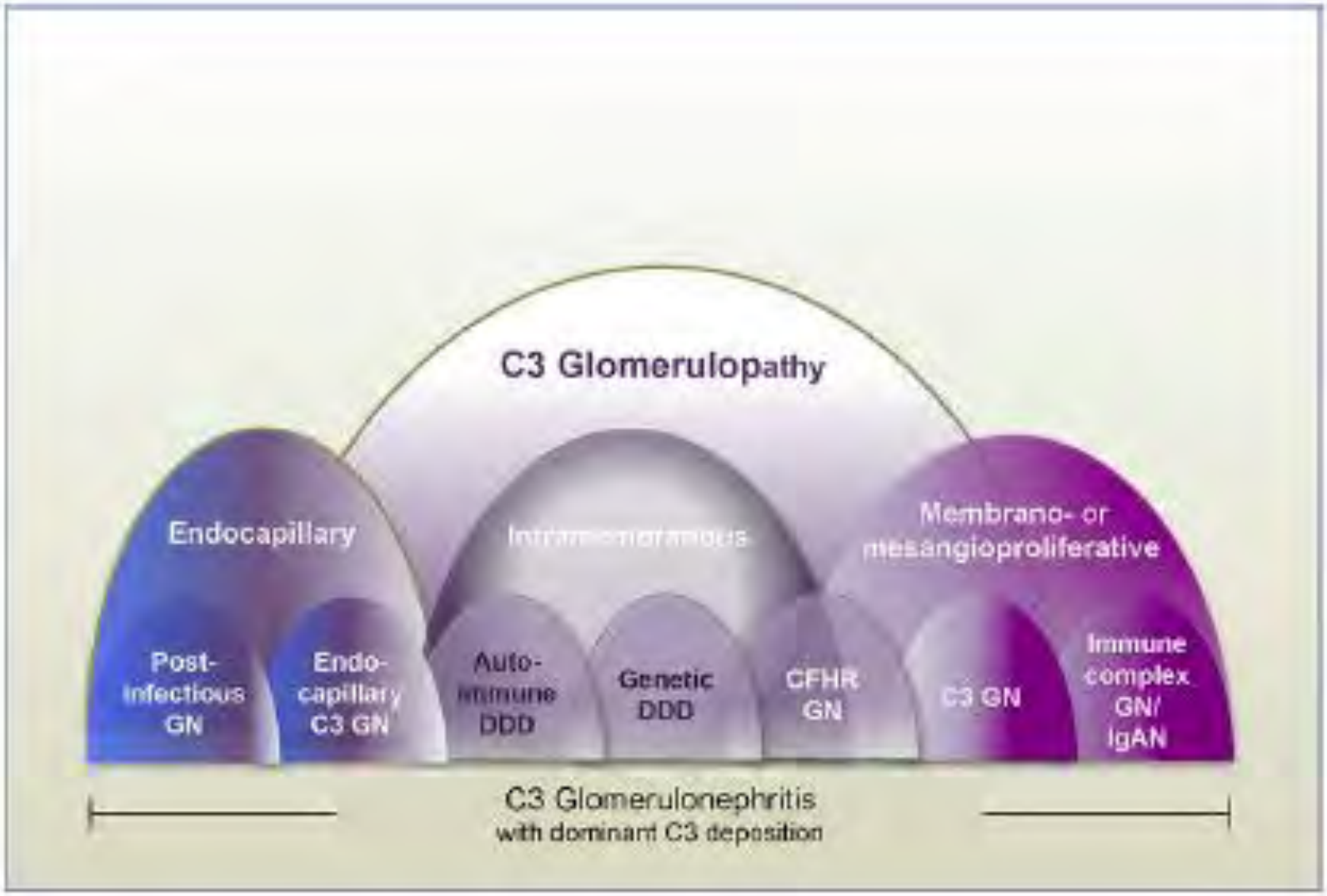
Serology

All patients:	C3, C4, CFH, (CFP)
	Paraprotein screen
	C3NeF
Selected:	CFB,C3 activation, C5 cativation
	Autoantibodies to CFB and CFH

Genetic screening

All patients:	CFHR5
Selected:	C activating and regulatory factors
	CNV CFH-CTHR locus

Spectrum of C3 nephropathy



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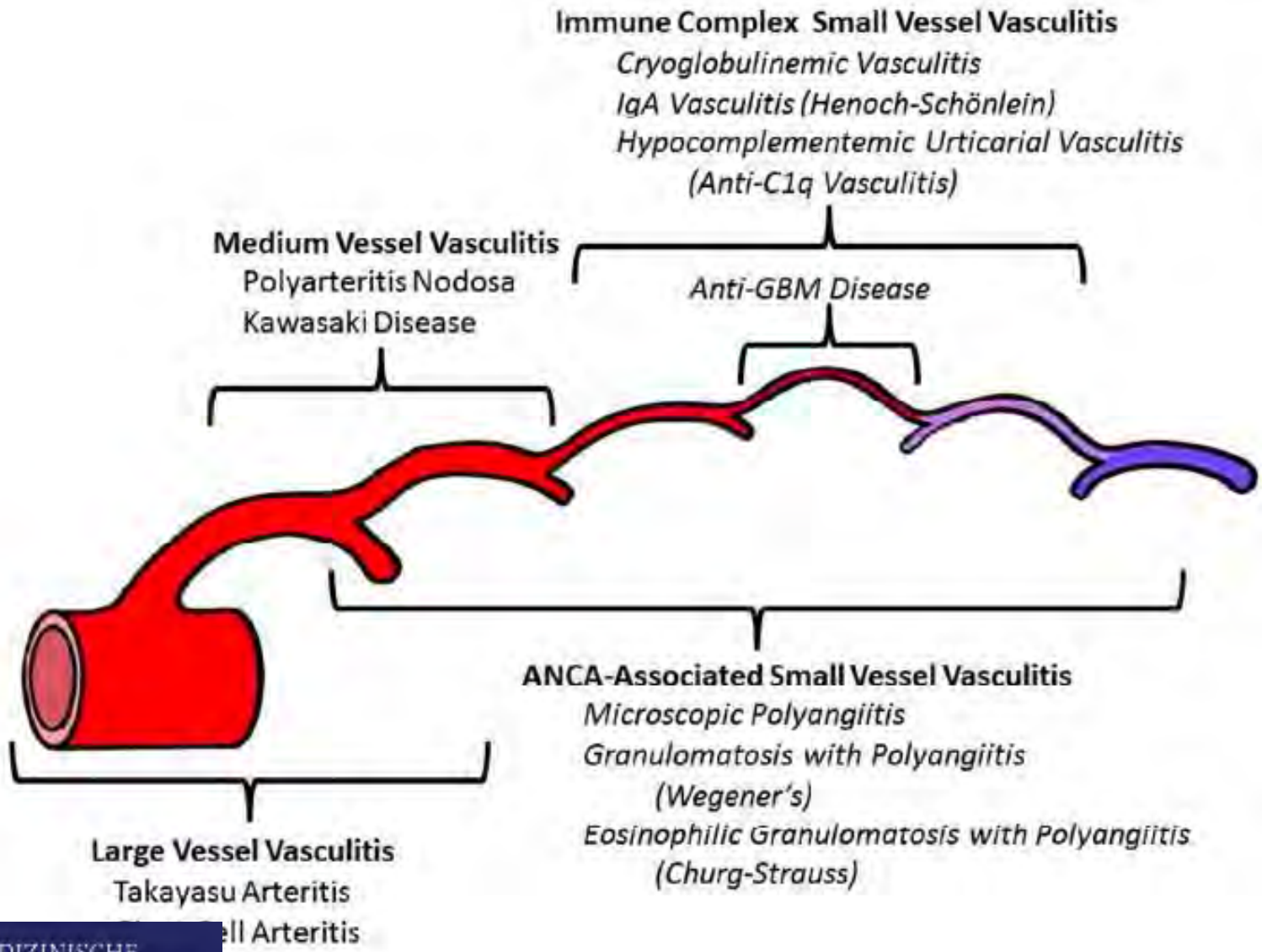
From Zipfel et al. Molec Immunol 2015

Revised Chapel Hill Consensus Conference nomenclature for vasculitis – 2012



Jennette et al Arthritis and Rheumatism 2013

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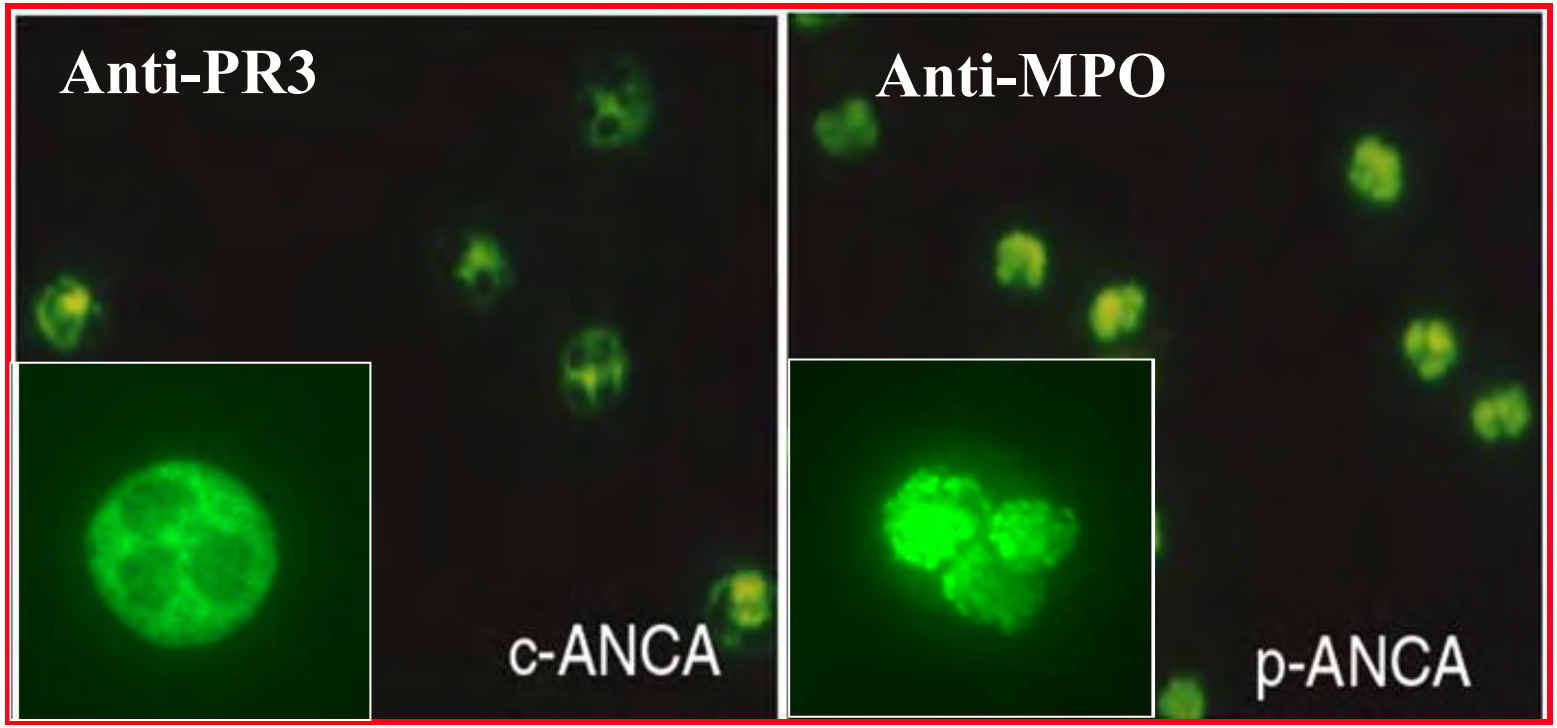
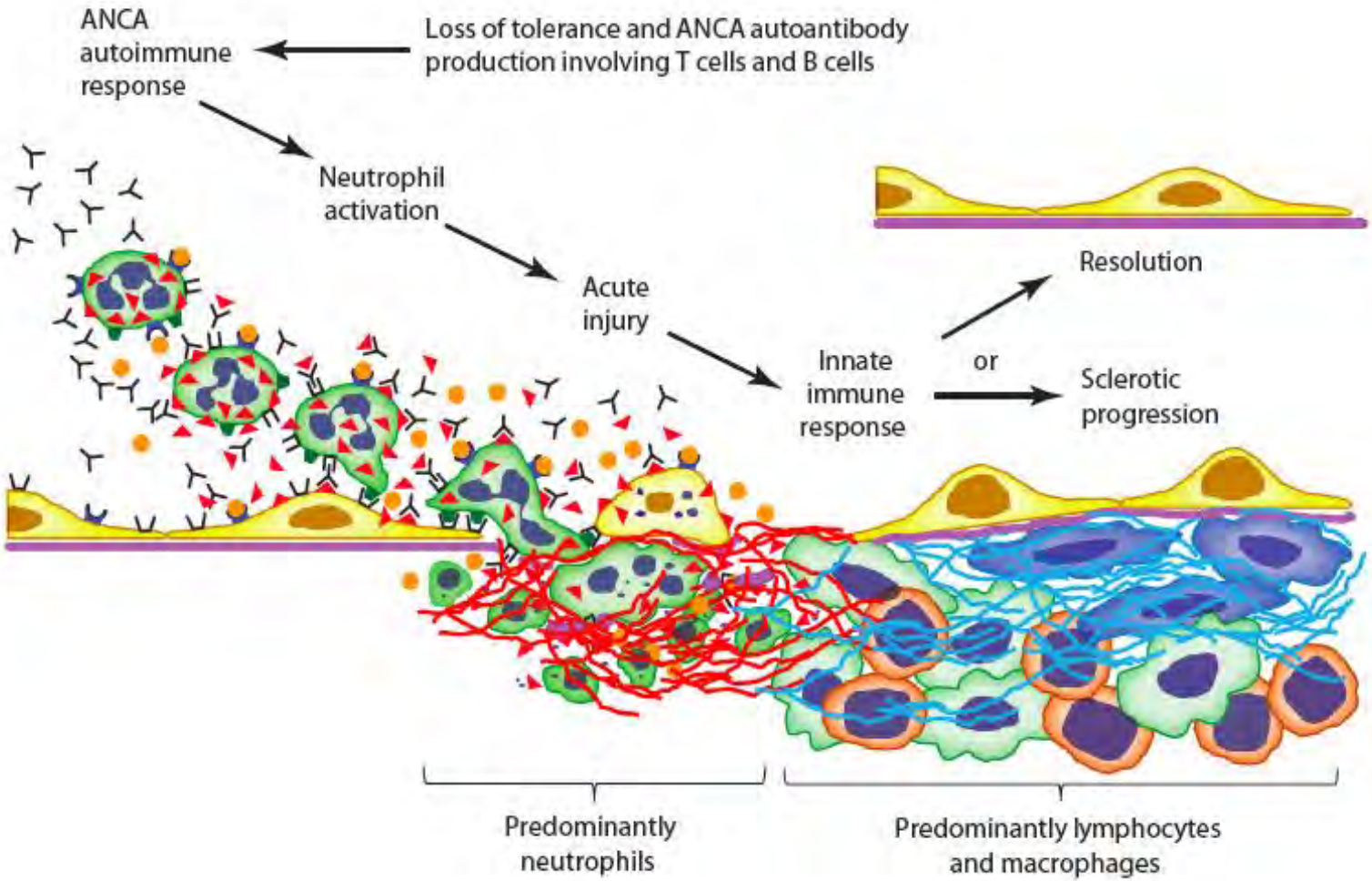
Anti-Neutrophil Cytoplasmic Antibodies



	Sensitivity	Specificity
Fluorescence alone	80 -85 %	75%
Fluorescence plus ELISA	90%	90%

ANCA-associated vasculitis: the standard model



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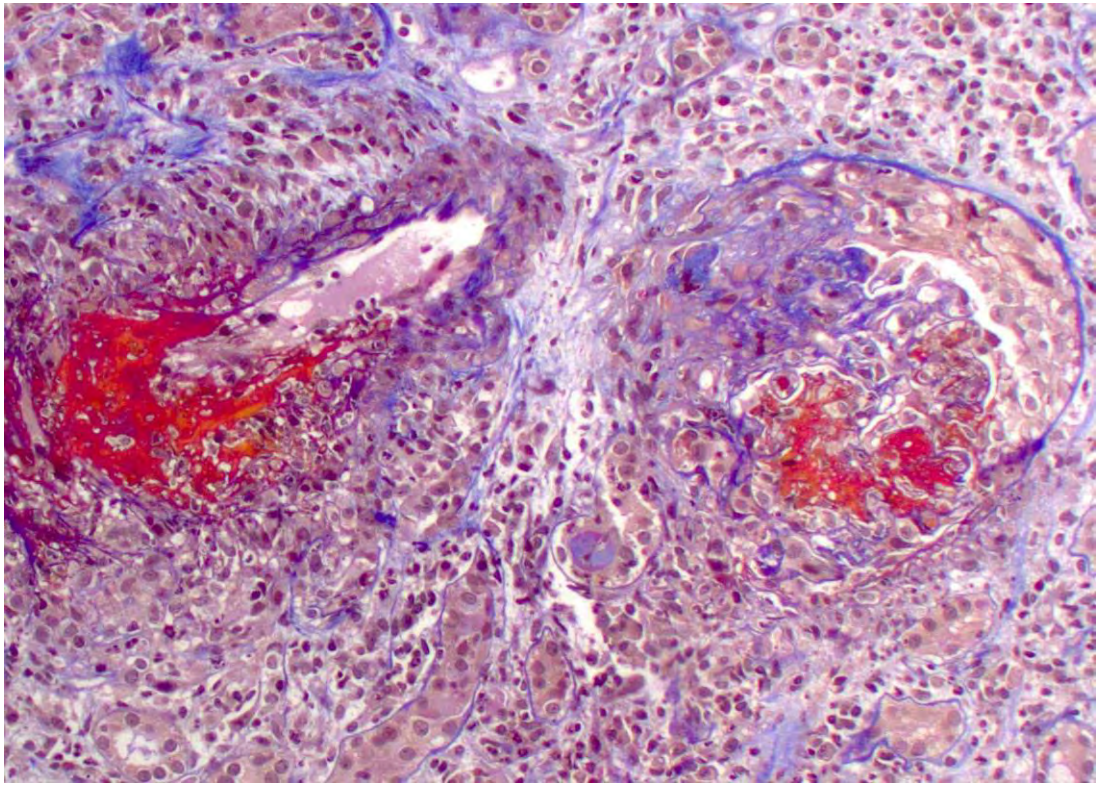
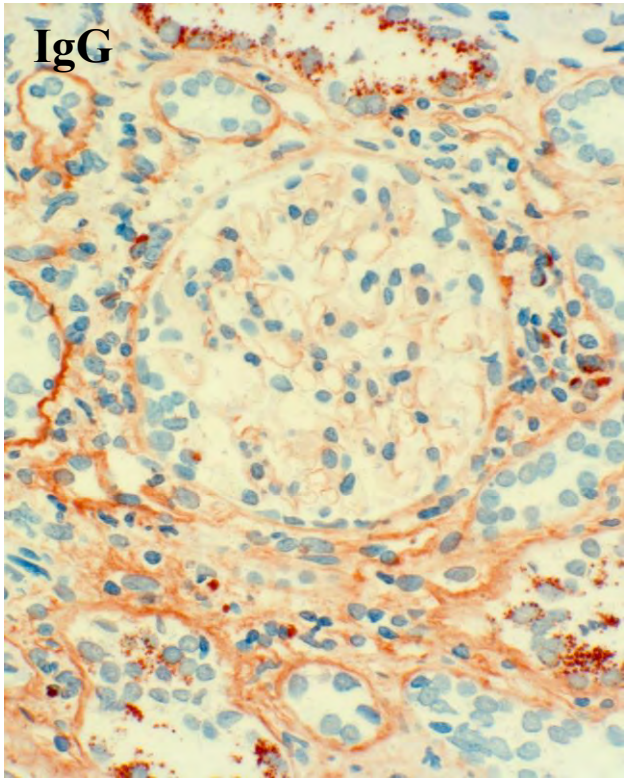
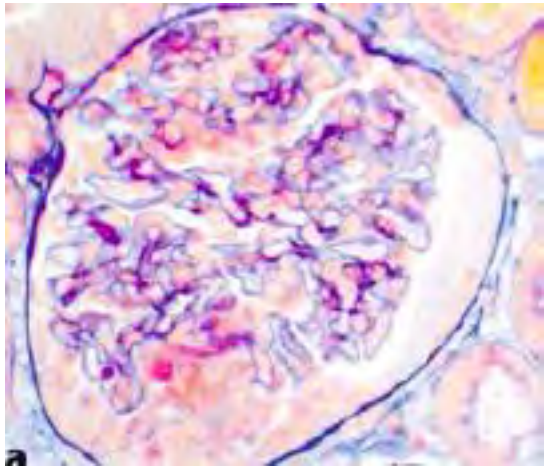
Jennette Ann Rev Pathol 2013

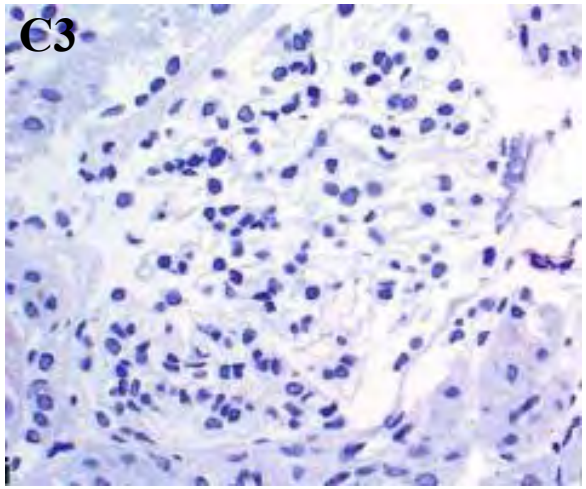
Pauci-immune FNGN and ANCA-associated vasculitis

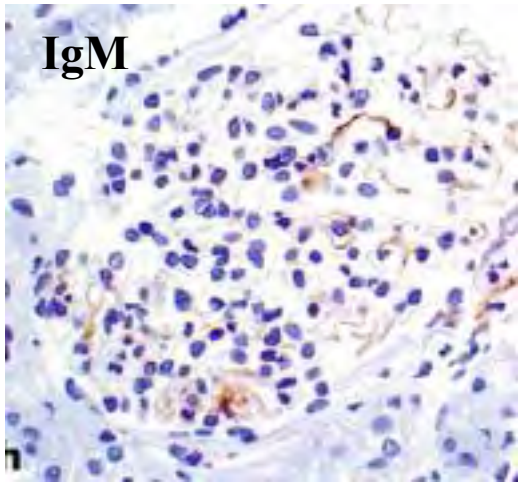




Pauci-immune FNGN and ANCA-associated vasculitis





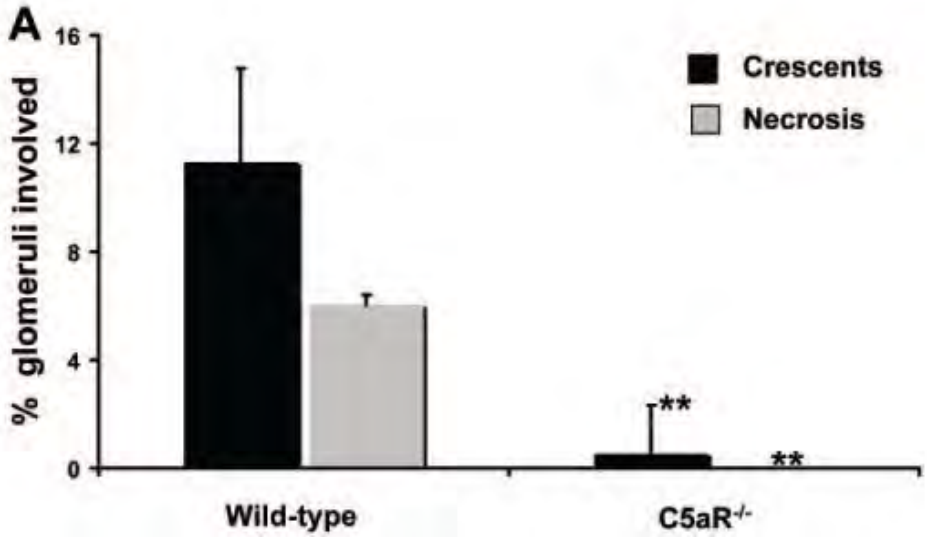


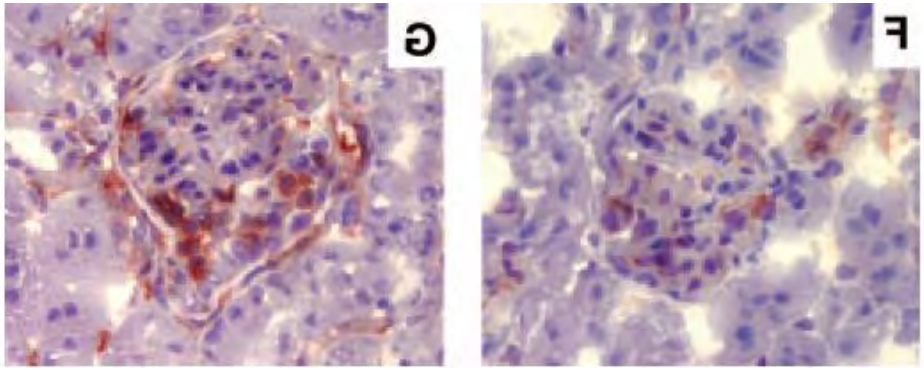
C dependent injury caused by passive anti-MPO nephritis
Antibodies to MPO and PR3 activate neutrophils to release C5a

BASIC RESEARCH www.jasn.org

C5a Receptor Mediates Neutrophil Activation and ANCA-Induced Glomerulonephritis

Adrian Schreiber,* Hong Xiao,† J. Charles Jennette,† Wolfgang Schneider,*
Friedrich C. Luft,* and Ralph Kettritz*





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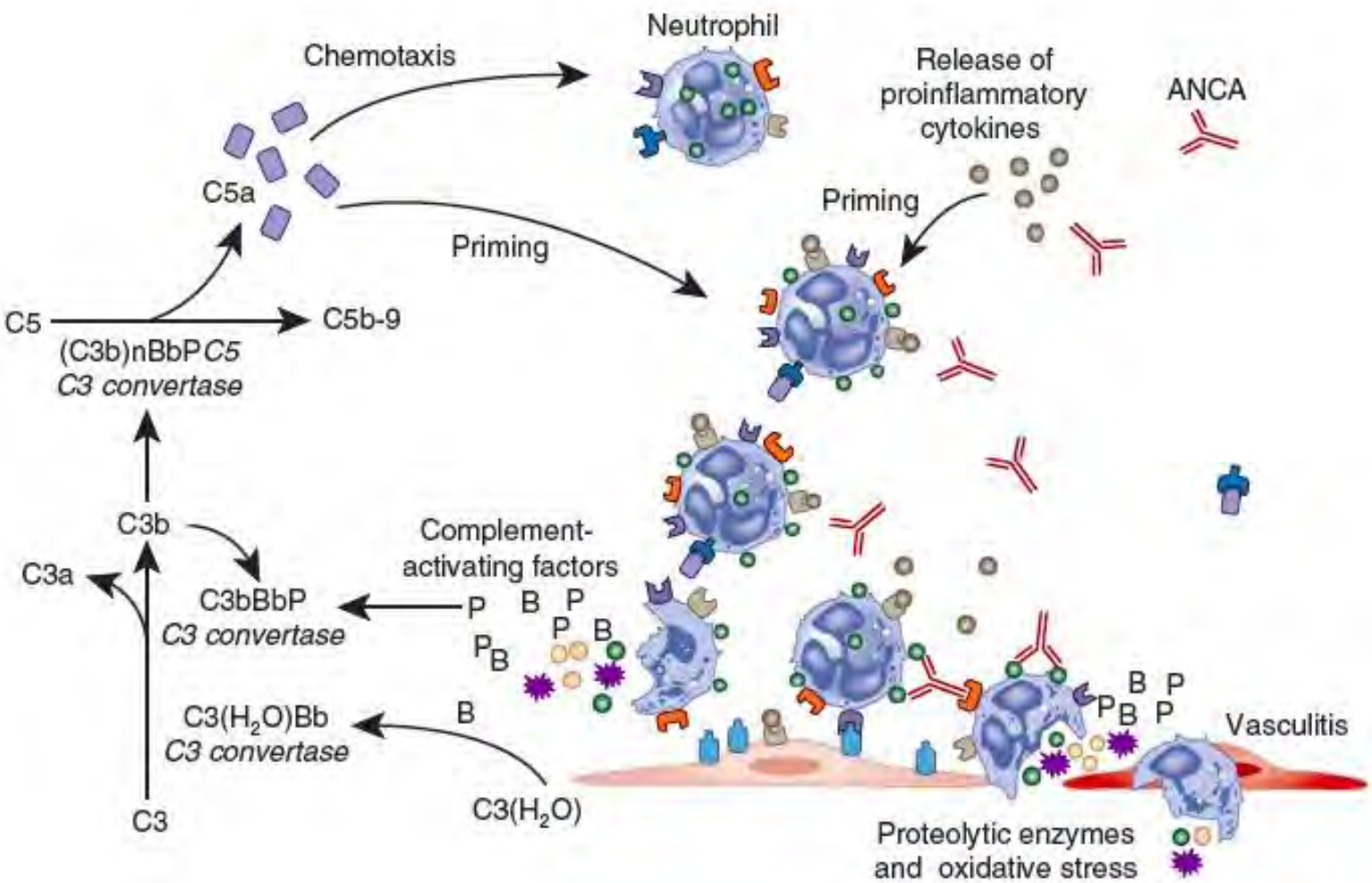
JASN 2010

Complement and AAV



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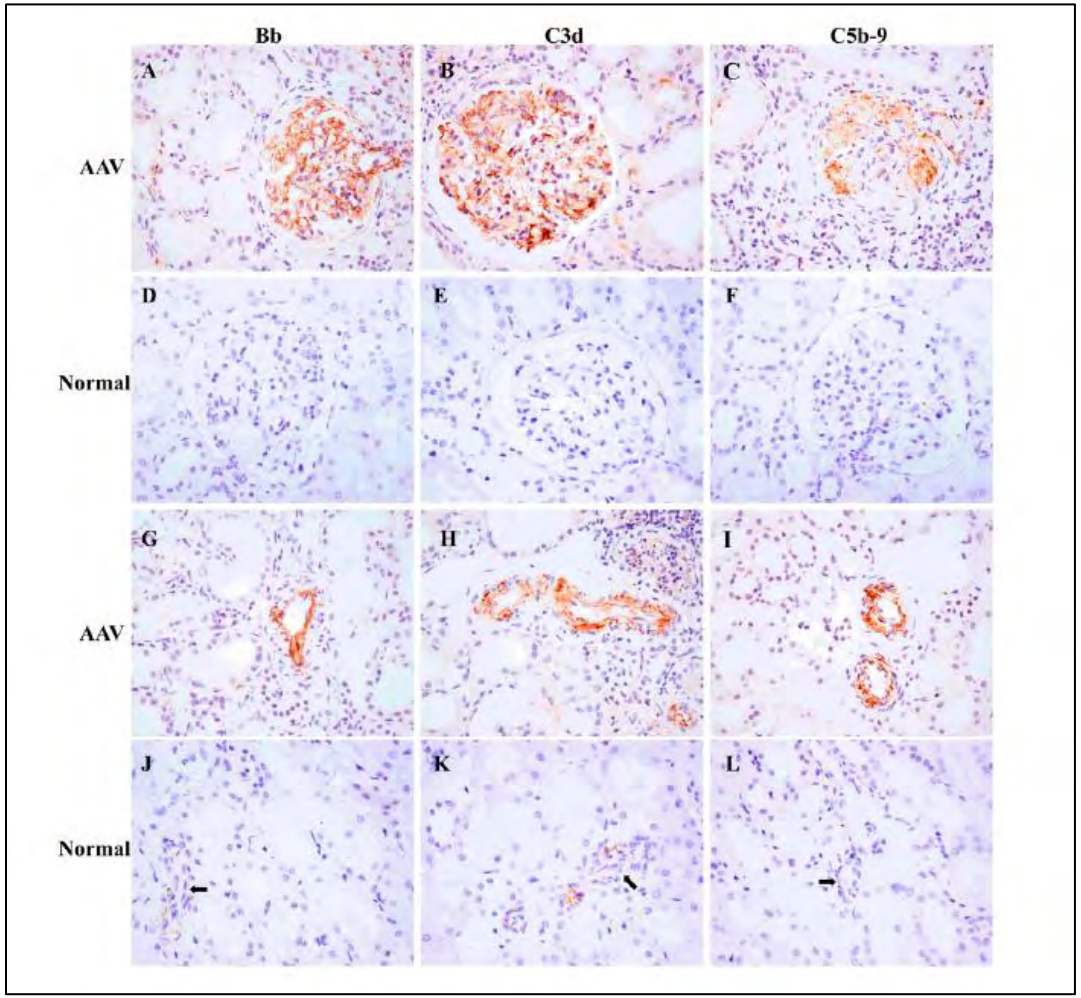
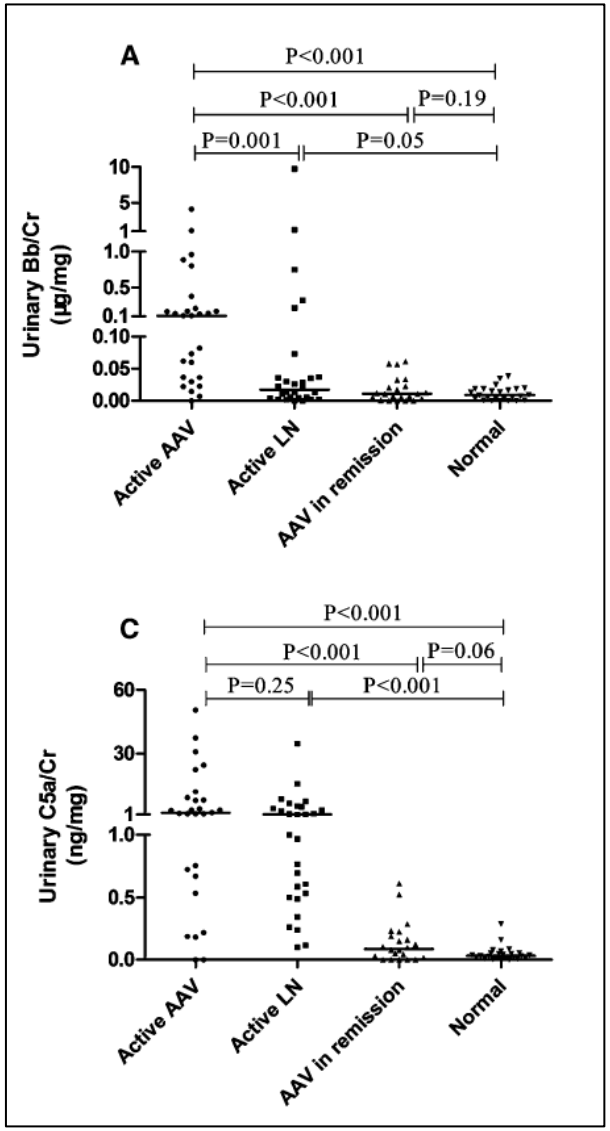
Adapted from Kallenberg & Heeringa Kidney Int 2012

Alternative Complement Pathway Activation Products in Urine and Kidneys of Patients with ANCA-Associated GN

Shen-Ju Gou, Jun Yuan, Chen Wang, Ming-Hui Zhao, and Min Chen





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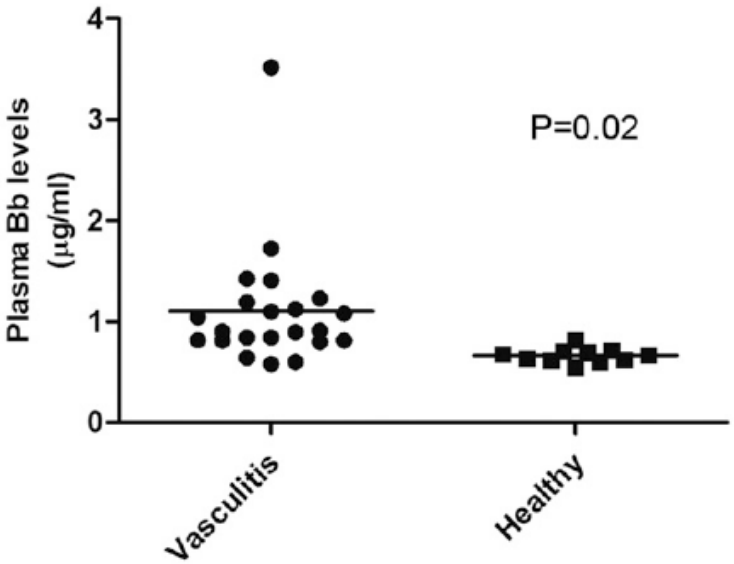
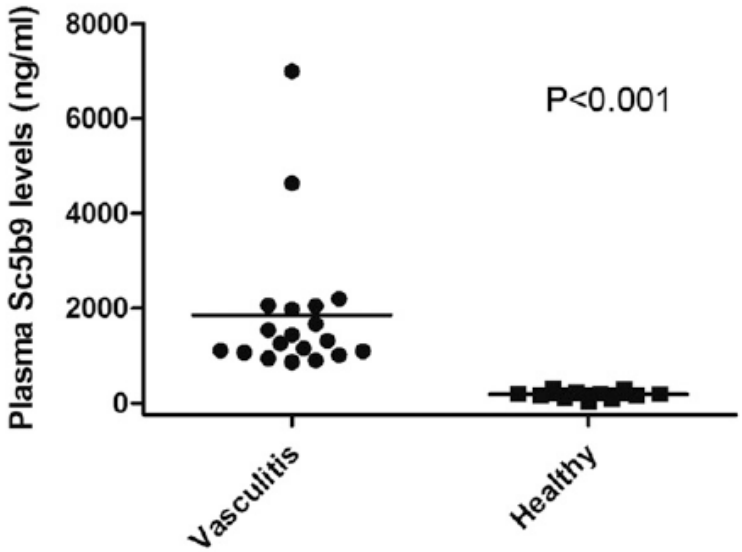
CJASN 2013

Association of Serum C3 Concentration and Histologic Signs of Thrombotic Microangiopathy with Outcomes among Patients with ANCA-Associated Renal Vasculitis

Lucio Manenti, Augusto Vaglio,* Elisa Gnappi,* Umberto Maggiore,* Landino Allegri,* Marco Allinovi,* Maria L. Urban,* Marco Delsante,* Maricla Galetti,* Maria Nicastro,* Francesco P. Pilato,† and Carlo Buzio**





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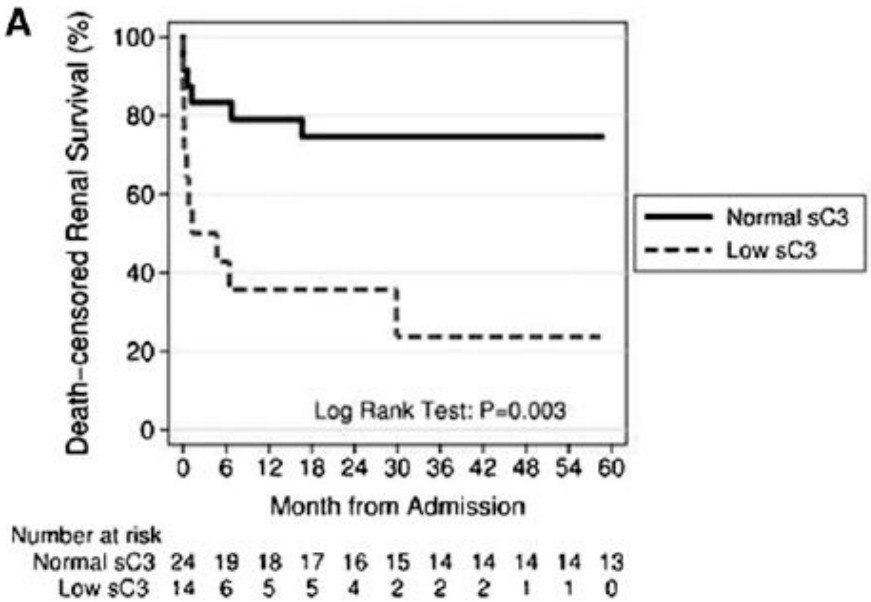
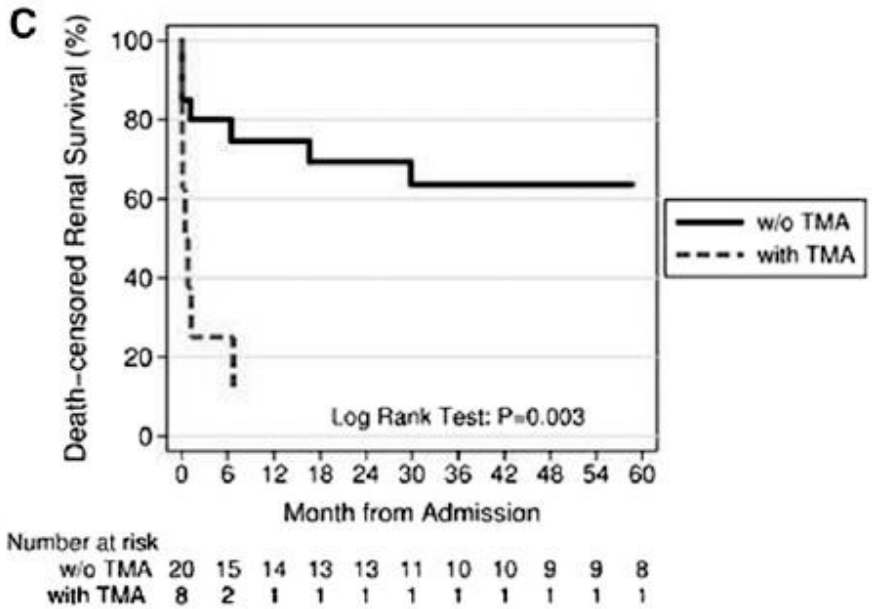
CJASN 2015

Association of Serum C3 Concentration and Histologic Signs of Thrombotic Microangiopathy with Outcomes among Patients with ANCA-Associated Renal Vasculitis

Lucio Manenti, Augusto Vaglio,* Elisa Gnappi,* Umberto Maggiore,* Landino Allegri,* Marco Allinovi,* Maria L. Urban,* Marco Delsante,* Maricla Galetti,* Maria Nicastro,* Francesco P. Pilato,† and Carlo Buzio**





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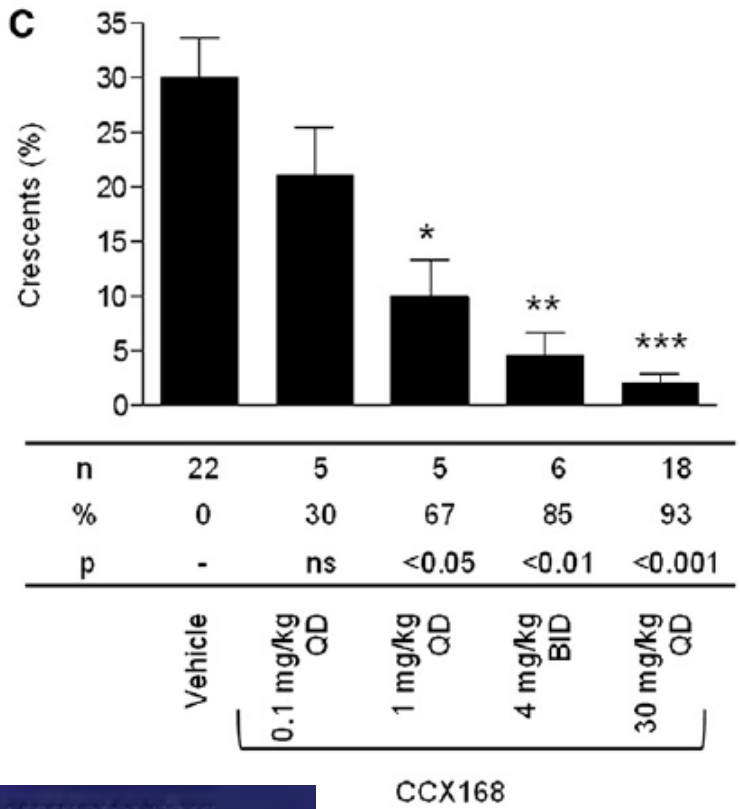
CJASN 2015

C5a Receptor (CD88) Blockade Protects against MPO-ANCA GN

Hong Xiao,*† Daniel J. Dairaghi,‡ Jay P. Powers,‡ Linda S. Ertl, ‡ Trageen Baumgart,‡
Yu Wang,‡ Lisa C. Seitz,‡ Mark E.T. Penfold,‡ Lin Gan,§ Peiqi Hu,*† Bao Lu,§ Norma P. Gerard,‖
Craig Gerard,‖ Thomas J. Schall,‡ Juan C. Jaen,‡ Ronald J. Falk,*† and J. Charles Jennette*†



CCX168 is an orally active C5aR inhibitor from Chemocentrix

Phase II double blind RCT of CCX168 in AAV recently completed – shows benefit

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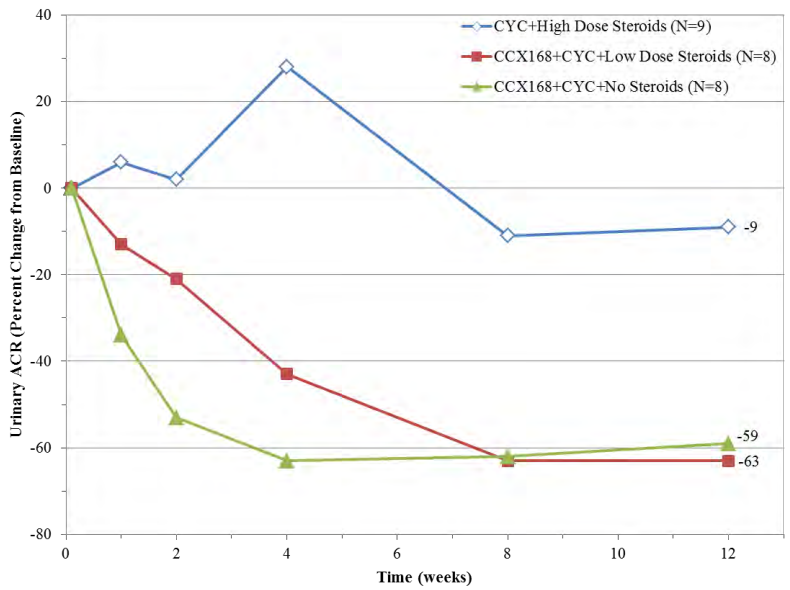
JASN 2014

Phase II clinical trial of the oral C5a receptor inhibitor CCX168 in AAV

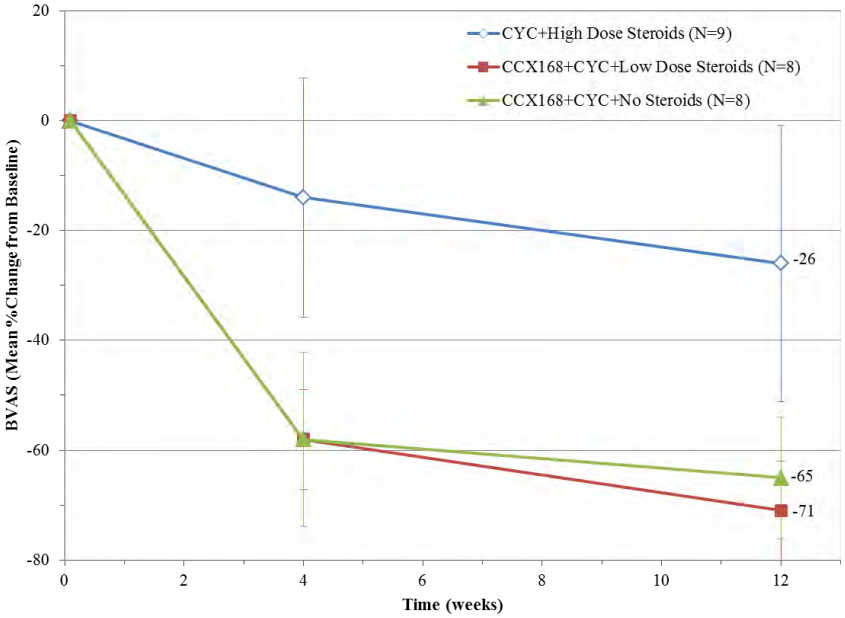
First Morning Urine Albumin:Creatinine Ratio

Mean % change from baseline



BVAS Total Score

%Change from Baseline



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David Jayne – ACR 2014

Complement in active AAV

Raised circulating concentrations of Bb and sC5-9 are proof of active alternative pathway and terminal component activity

Glomerular deposition Bb and C5-9 together with raised urinary concentrations are proof of local activation

Initial results of C5aR blockade suggest complement makes an important contribution to injury