Physiopathologie des vascularites nécrosantes

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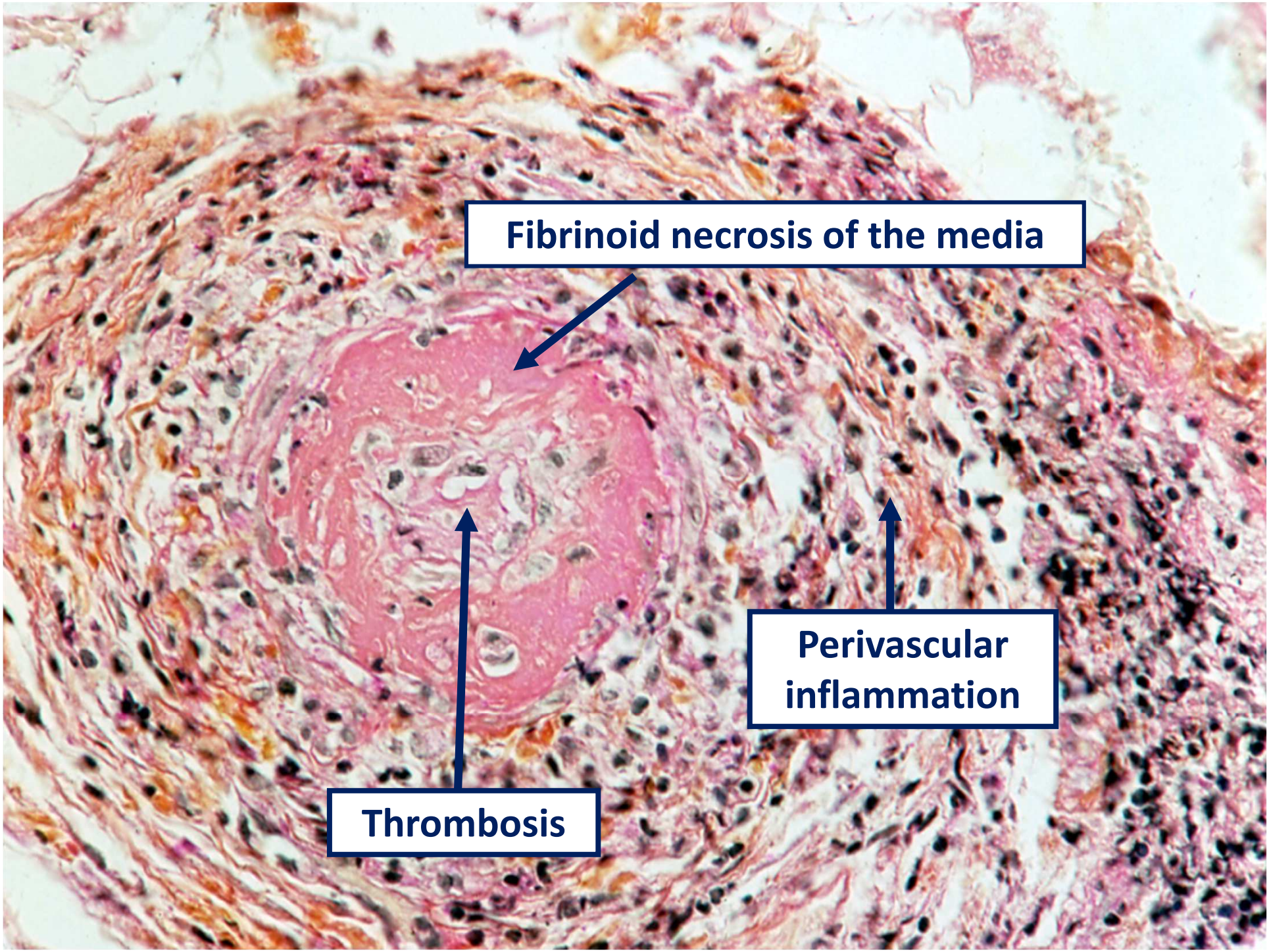
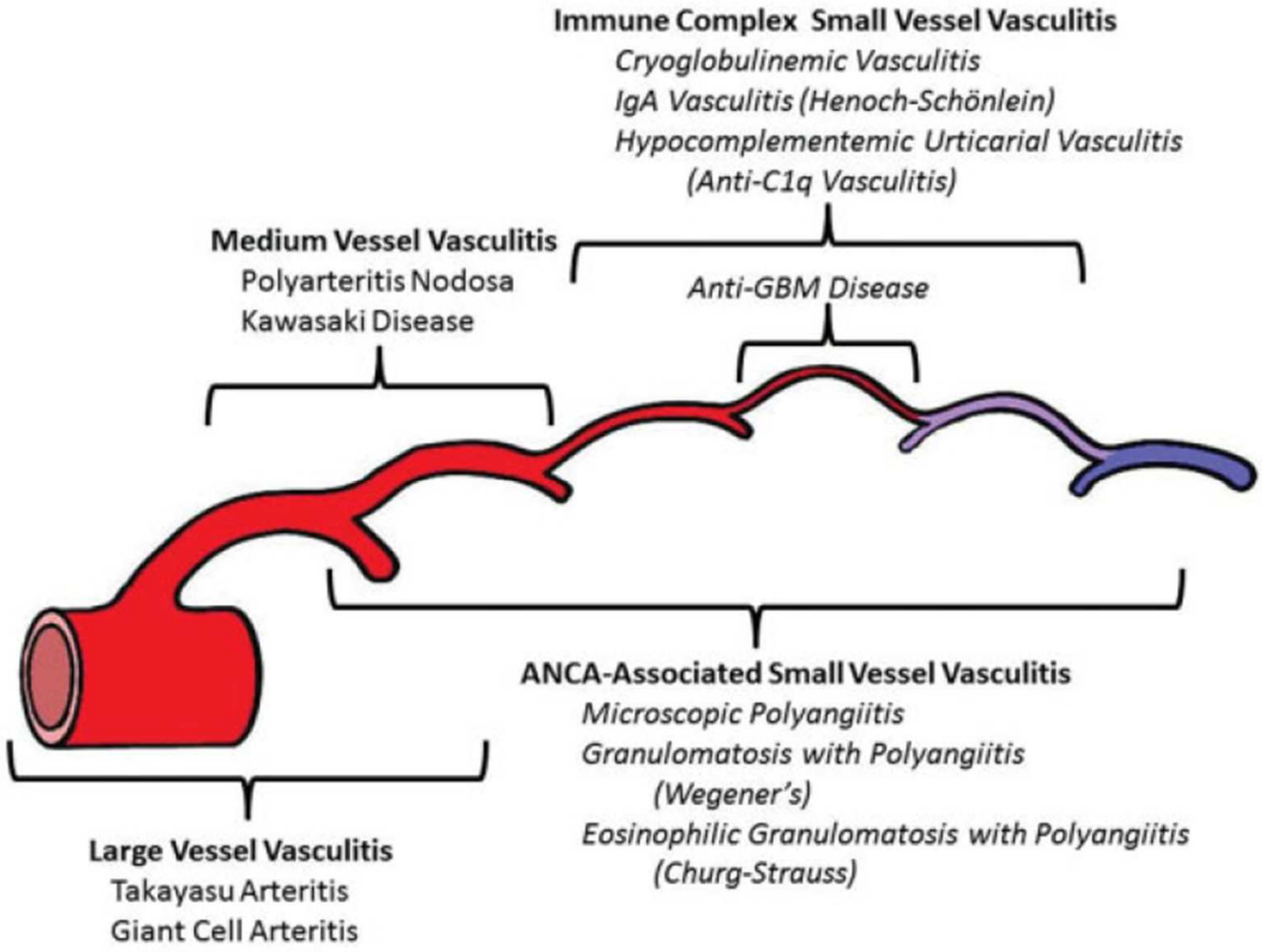
Paris, France

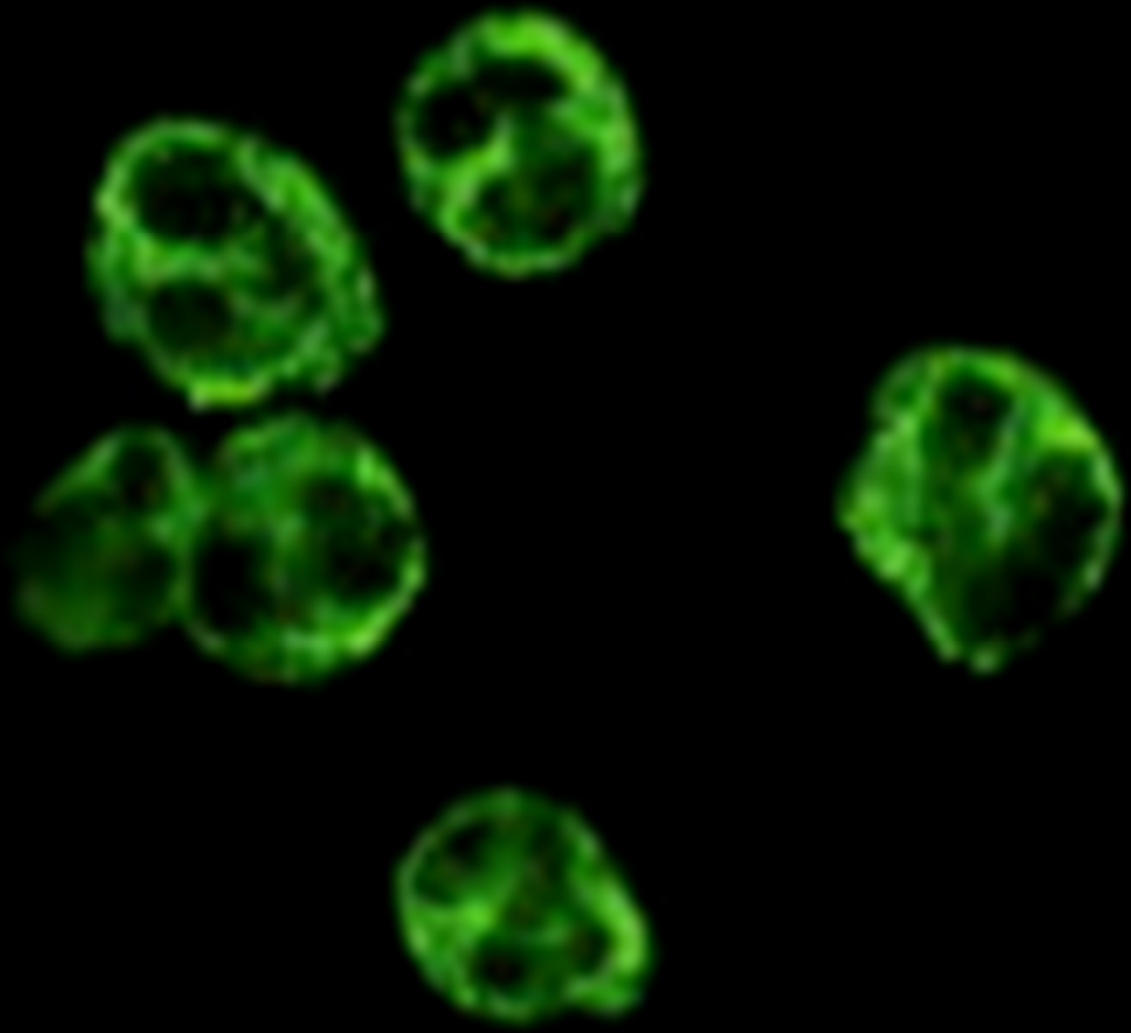

Fibrinoid necrosis of the media
Perivascular inflammation
Thrombosis

Systemic vasculitides



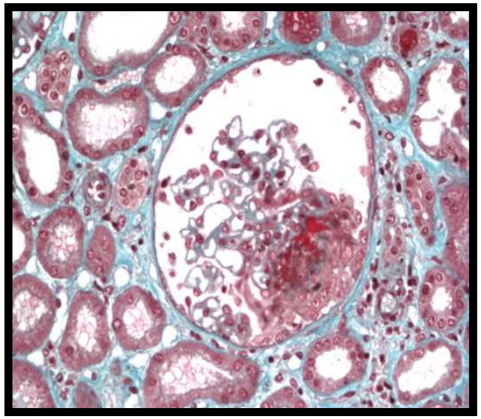
Jennette, Arthritis Rheum, 2012

Anti-neutrophil cytoplasmic antibodies (ANCA)



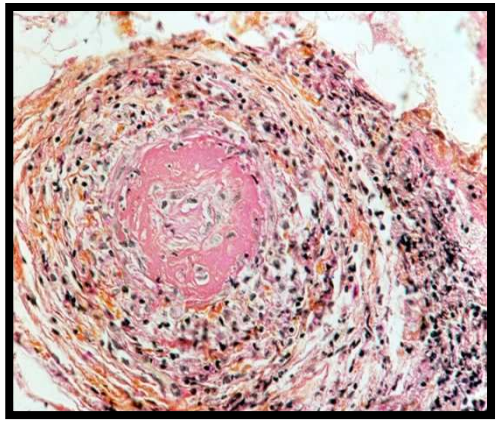
Davies, Br Med J, 1982
Van der Woode, Lancet, 1985

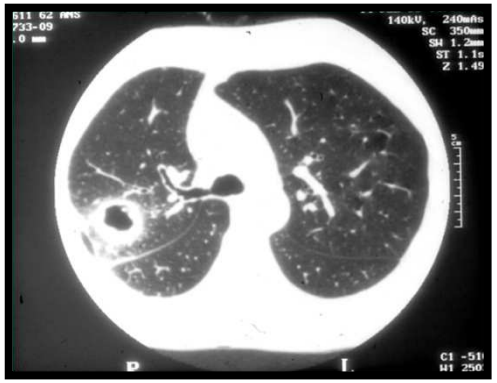
ANCA-associated vasculitides (AAV)

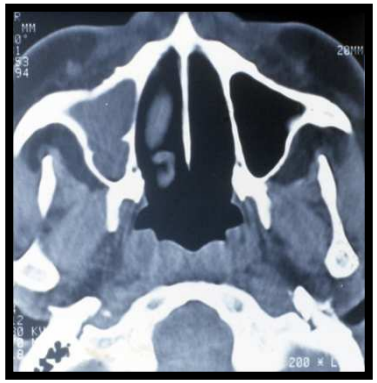


Necrotizing vasculitis

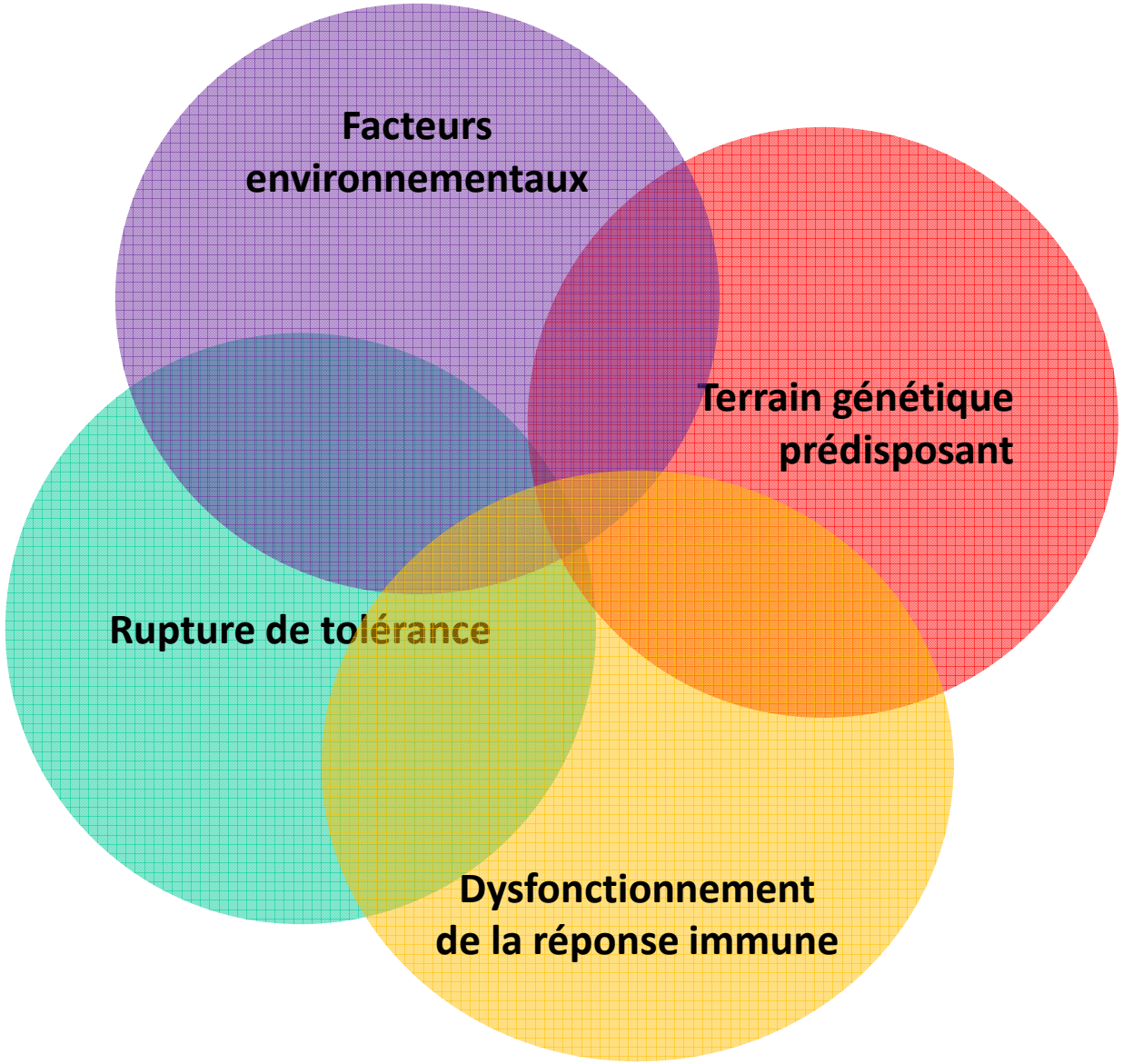
Systemic disease with ENT, pulmonary and renal involvements







Physiopathologie des vascularites



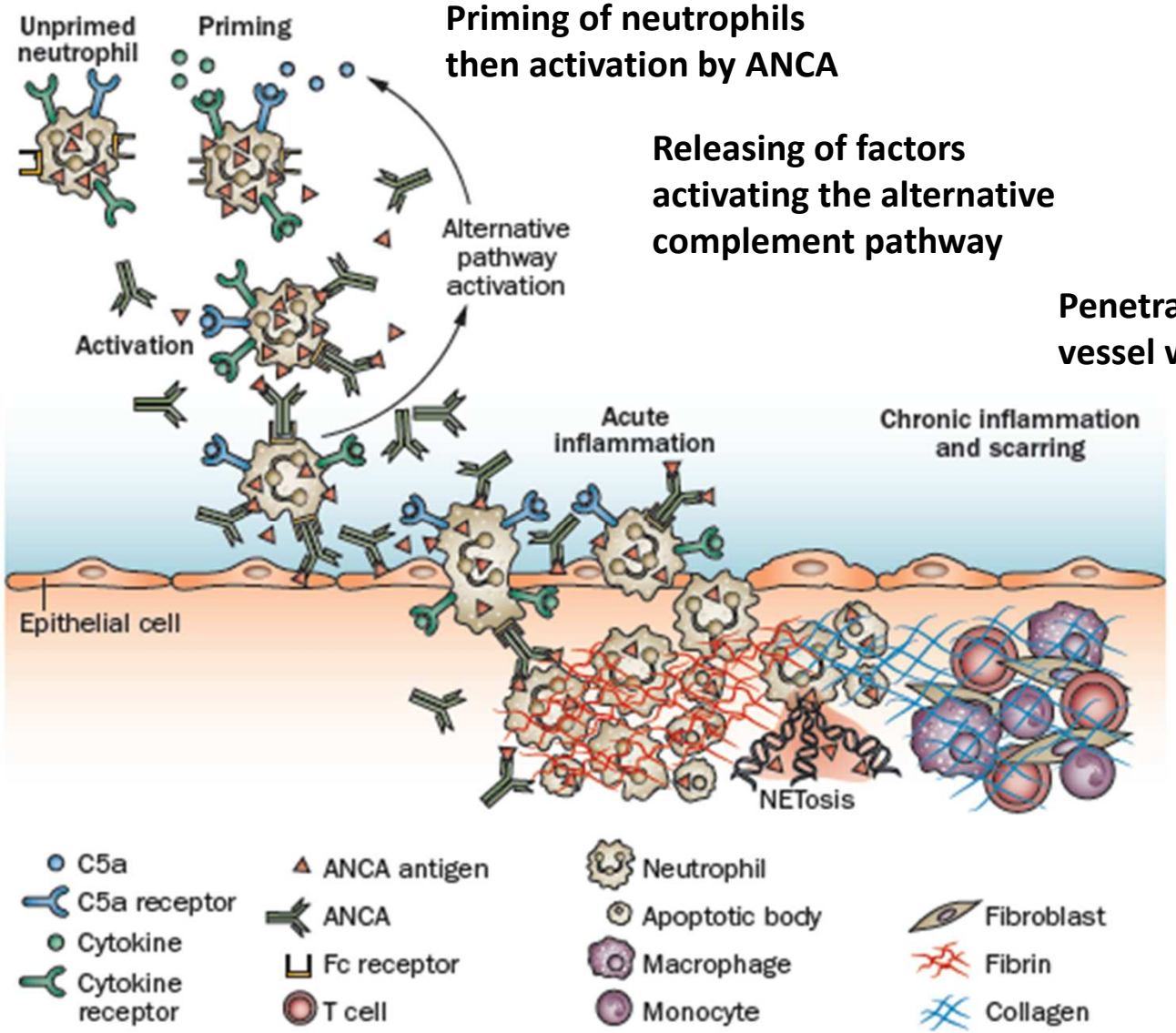
The leading theory

- **Circulating neutrophils and monocytes primed by inflammatory stimuli display ANCA antigens (PR3 or MPO) at or near the cell surface**

- **Interaction of these antigens with ANCA results in neutrophils activation and initiation of vascular inflammation**

- ***(Primed extravascular neutrophils could interact with interstitial ANCA, causing necrotizing inflammation and reactive granulomatous inflammation)***

The leading theory



Priming of neutrophils then activation by ANCA

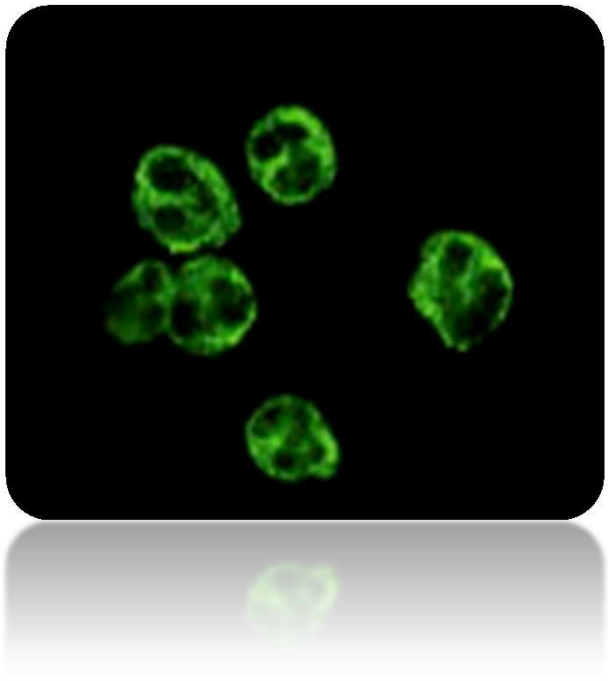
Releasing of factors activating the alternative complement pathway

Penetration of neutrophils into vessel walls and inflammation

Disruption of endothelium and activation of coagulation cascade

Jennette, Nat Rev Rheumatol,2014

Role of genetic background



The NEW ENGLAND JOURNAL of MEDICINE

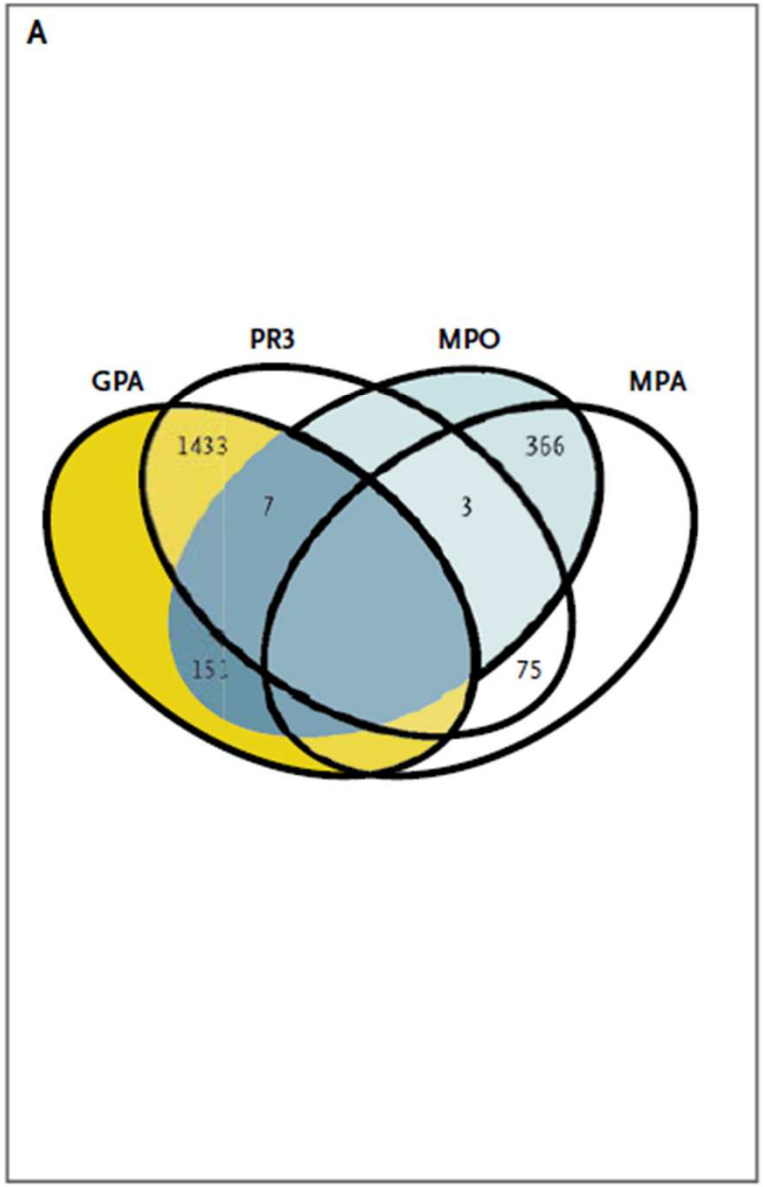
ORIGINAL ARTICLE

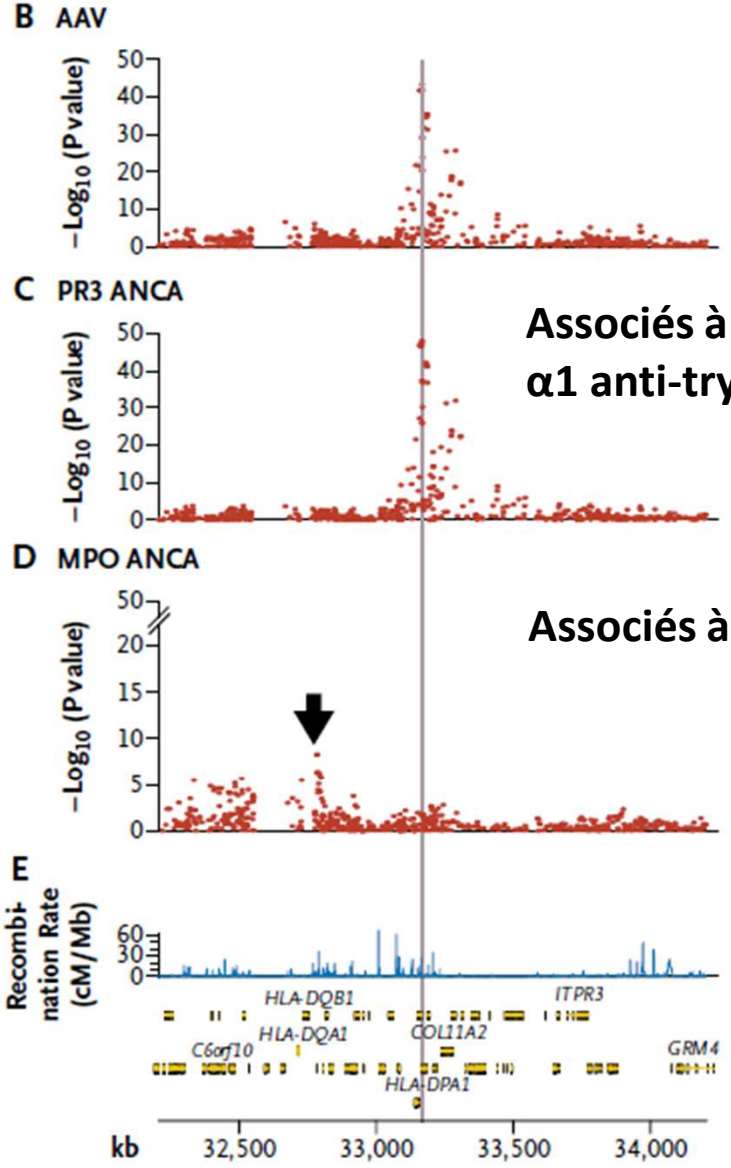
Genetically Distinct Subsets within ANCA-Associated Vasculitis

Paul A. Lyons, Ph.D., Tim F. Rayner, Ph.D., Sapna Trivedi, M.R.C.P., M.Phil., Julia U. Holle, M.D., Ph.D., Richard A. Watts, D.M., F.R.C.P., David R.W. Jayne, M.D., F.R.C.P., Bo Baslund, M.D., Ph.D., Paul Brenchley, Ph.D., Annette Bruchfeld, M.D., Ph.D., Afzal N. Chaudhry, Ph.D., F.R.C.P., Jan Willem Cohen Tervaert, M.D., Ph.D., Panos Deloukas, Ph.D., Conleth Feighery, M.D., Wolfgang L. Gross, M.D., Ph.D., Loic Guillevin, M.D., Iva Gunnarsson, M.D., Ph.D., Lorraine Harper M.R.C.P., Ph.D., Zdenka Hrušková, M.D., Mark A. Little, M.R.C.P.I., Ph.D., Davide Martorana, Ph.D., Thomas Neumann, M.D., Sophie Ohlsson, M.D., Ph.D., Sandosh Padmanabhan, M.D., Ph.D., Charles D. Pusey, D.Sc., F.Med.Sci., Alan D. Salama, F.R.C.P., Ph.D., Jan-Stephan F. Sanders, M.D., Ph.D., Caroline O. Savage, F.Med.Sci., Ph.D., Mårten Segelmark, M.D., Ph.D., Coen A. Stegeman, M.D., Ph.D., Vladimir Tesař, M.D., Ph.D., Augusto Vaglio, M.D., Ph.D., Stefan Wieczorek, M.D., Benjamin Wilde, M.D., Jochen Zwerina, M.D., Andrew J. Rees, M.B., F.Med.Sci., David G. Clayton, M.A., and Kenneth G.C. Smith, F.Med.Sci., Ph.D.

N Engl J Med 2012;367:214-23.
DOI: 10.1056/NEJMoa1108735

Relationships between Clinical Subtype and ANCA Specificity in ANCA-Associated Vasculitis and Associations of the MHC Locus with Proteinase 3 ANCA and Myeloperoxidase ANCA



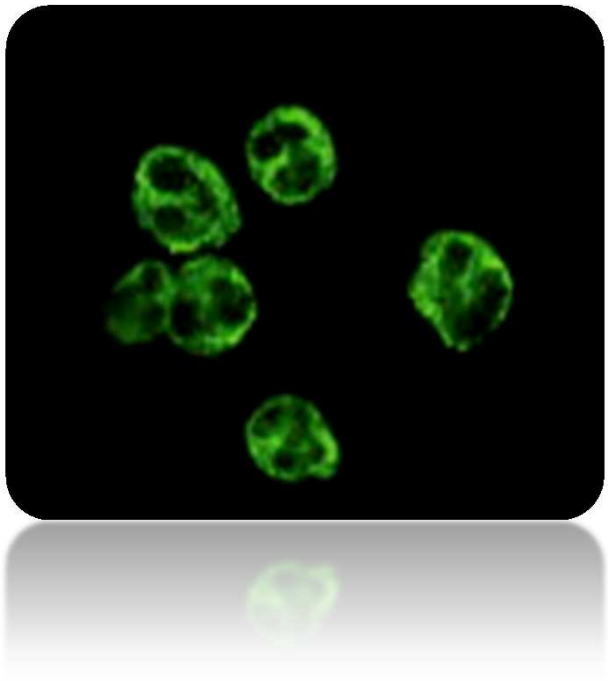


Associés à gènes HLA-DP, α1 anti-trypsine, protéinase 3

Associés à gènes HLA-DQ

Lyons PA et al, NEJM 2012

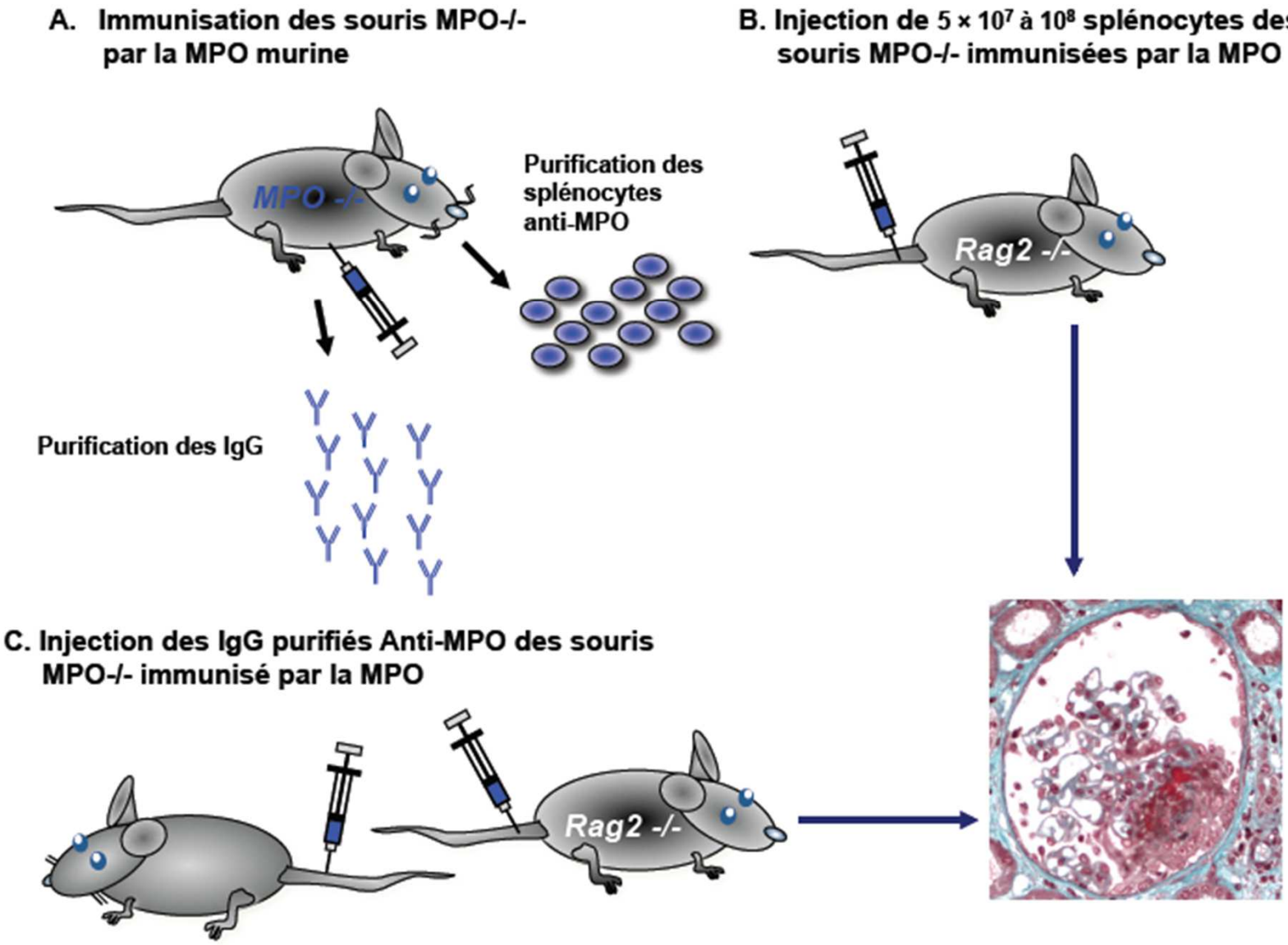
Role of ANCA



From natural to pathogenic ANCA

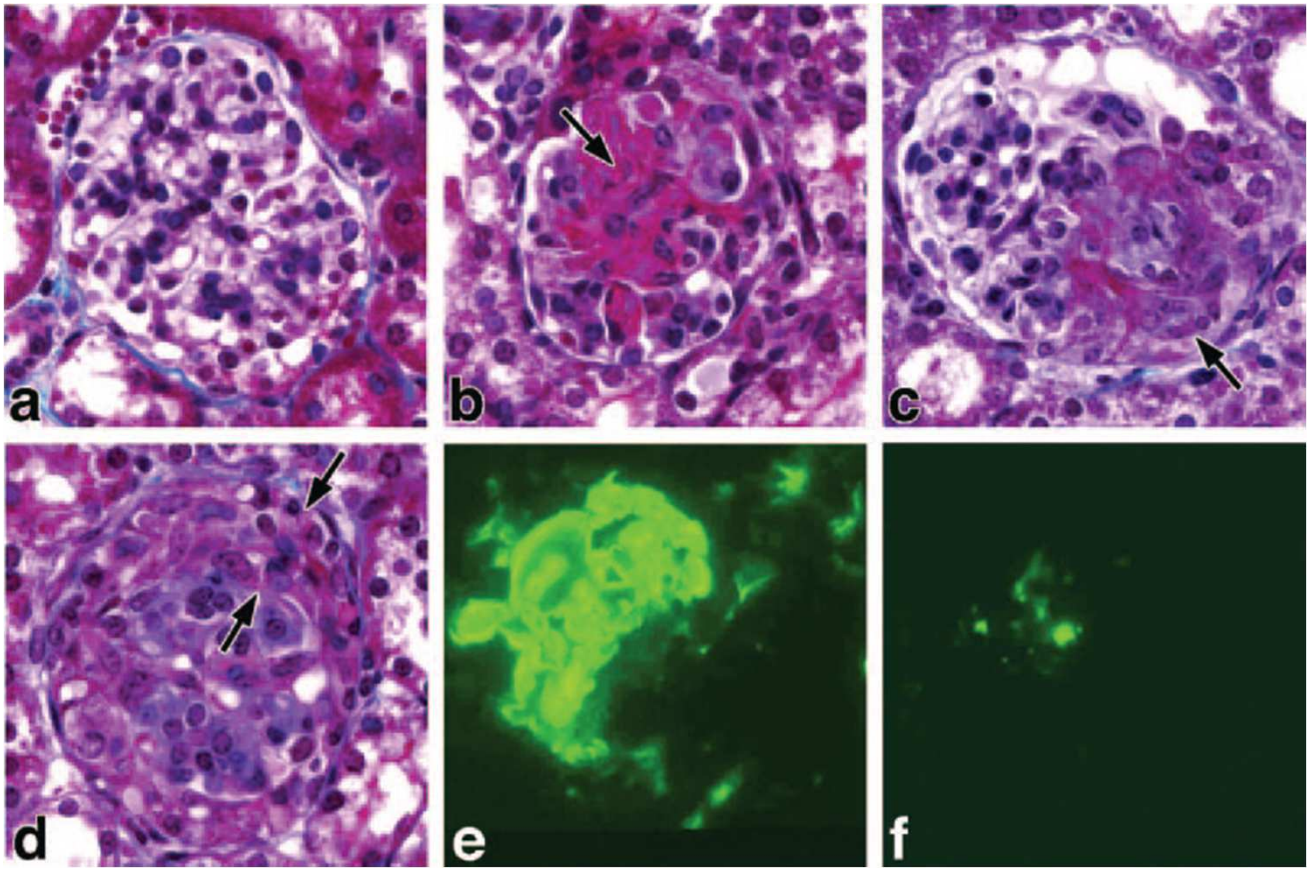
- **Exposure to exogenous antigens that influence ANCA epitope specificity (drugs or microbes, ex: PTU)**
- **Newly expressed or modified ANCA autoantigens (alternative splice transcripts or antisense transcripts)**
- **Immunogenic display of ANCA autoantigens (apoptotic cells or NETs)**
- **Loss of effective suppression of the ANCA autoimmune response (role of lymphocytes +++)**

Pathogenic role of MPO-ANCA



Xiao, J Clin Invest, 2002

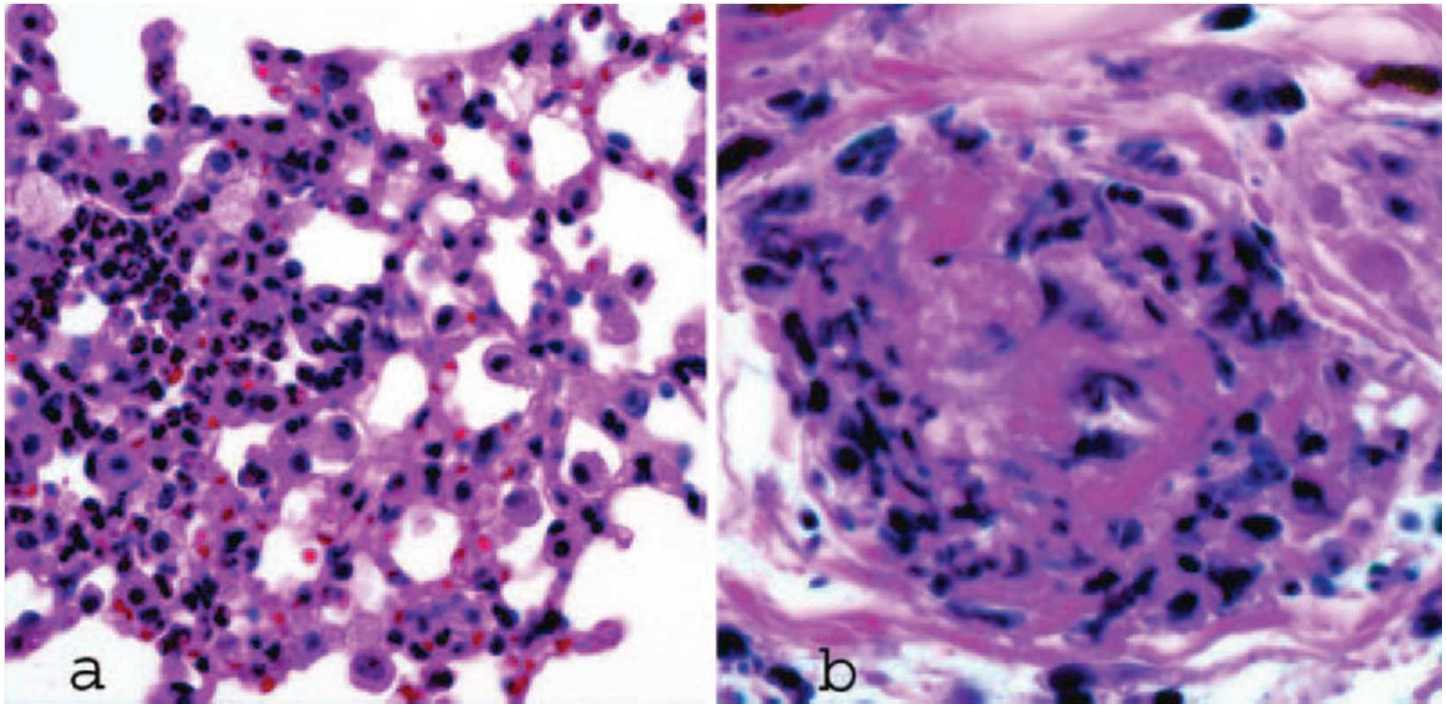
Glomeruli from a Rag2-/- mouse 6 d after intravenous injection of anti-myeloperoxidase (anti-MPO) IgG



No histologic lesion (a), segmental fibrinoid necrosis (b), segmental fibrinoid necrosis with a small cellular crescents (c), large circumferential crescent (d), fibrin in a crescent (e), and a paucity of segmental IgG (f)

Xiao, J Clin Invest, 2002

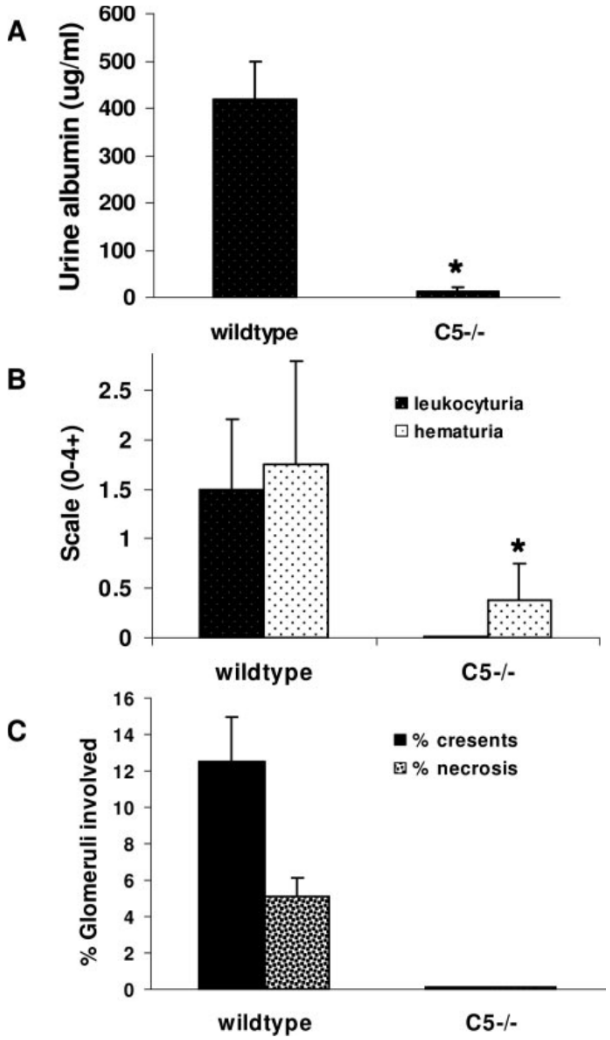
Vasculitis lesions from a wild-type mouse 6 d after intravenous injection of anti-MPO IgG

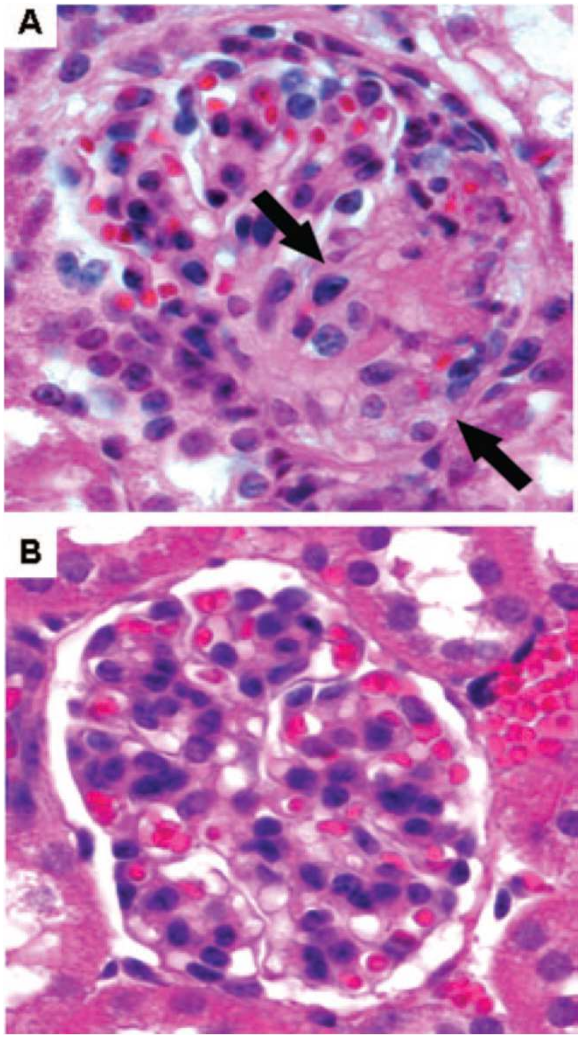


Pulmonary alveolar capillaritis with septal infiltration of neutrophils (a) and necrotizing arteritis with leukocytoclasia in the dermis of the ear (b)

Xiao, J Clin Invest, 2002

Role of alternative complement pathway



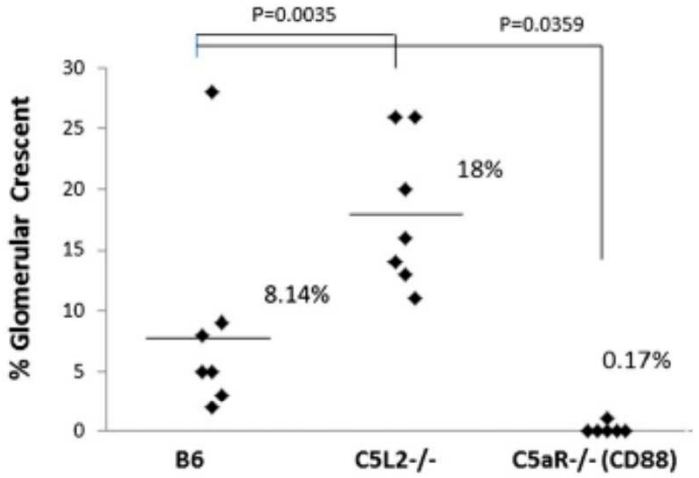


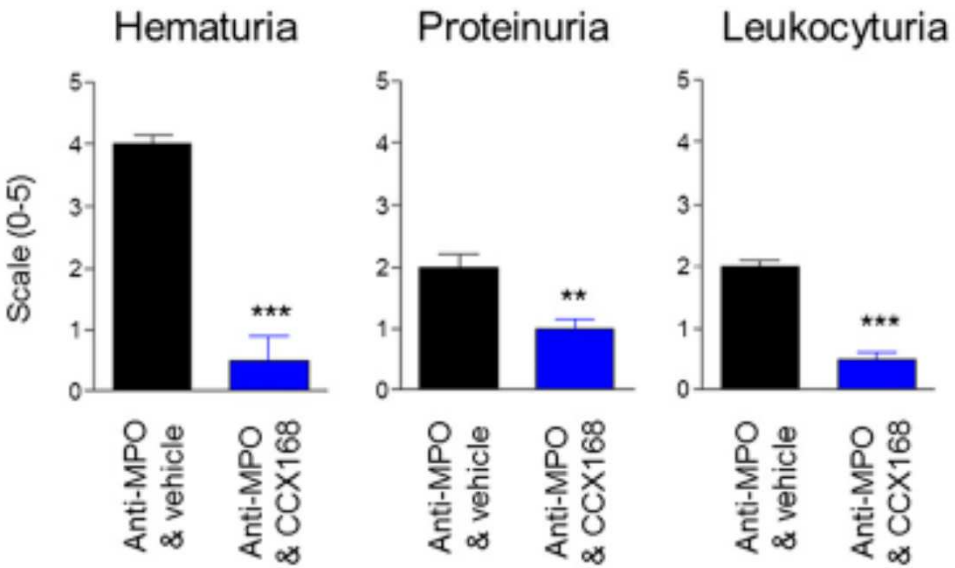
WT

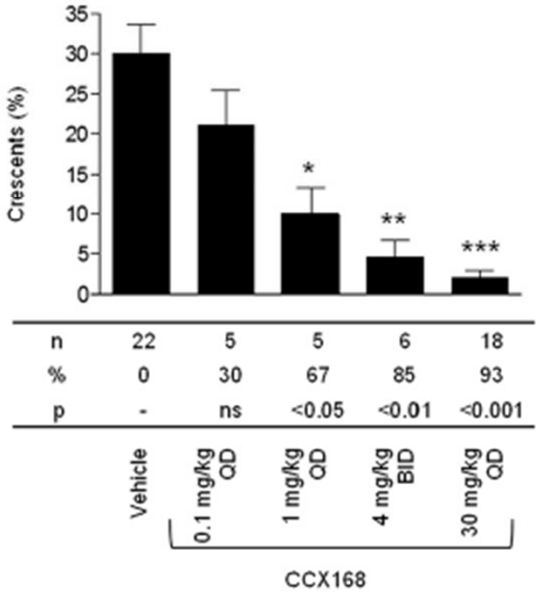
C5-/- mice

Xiao, Am J Pathol, 2005

Role of C5a blocking







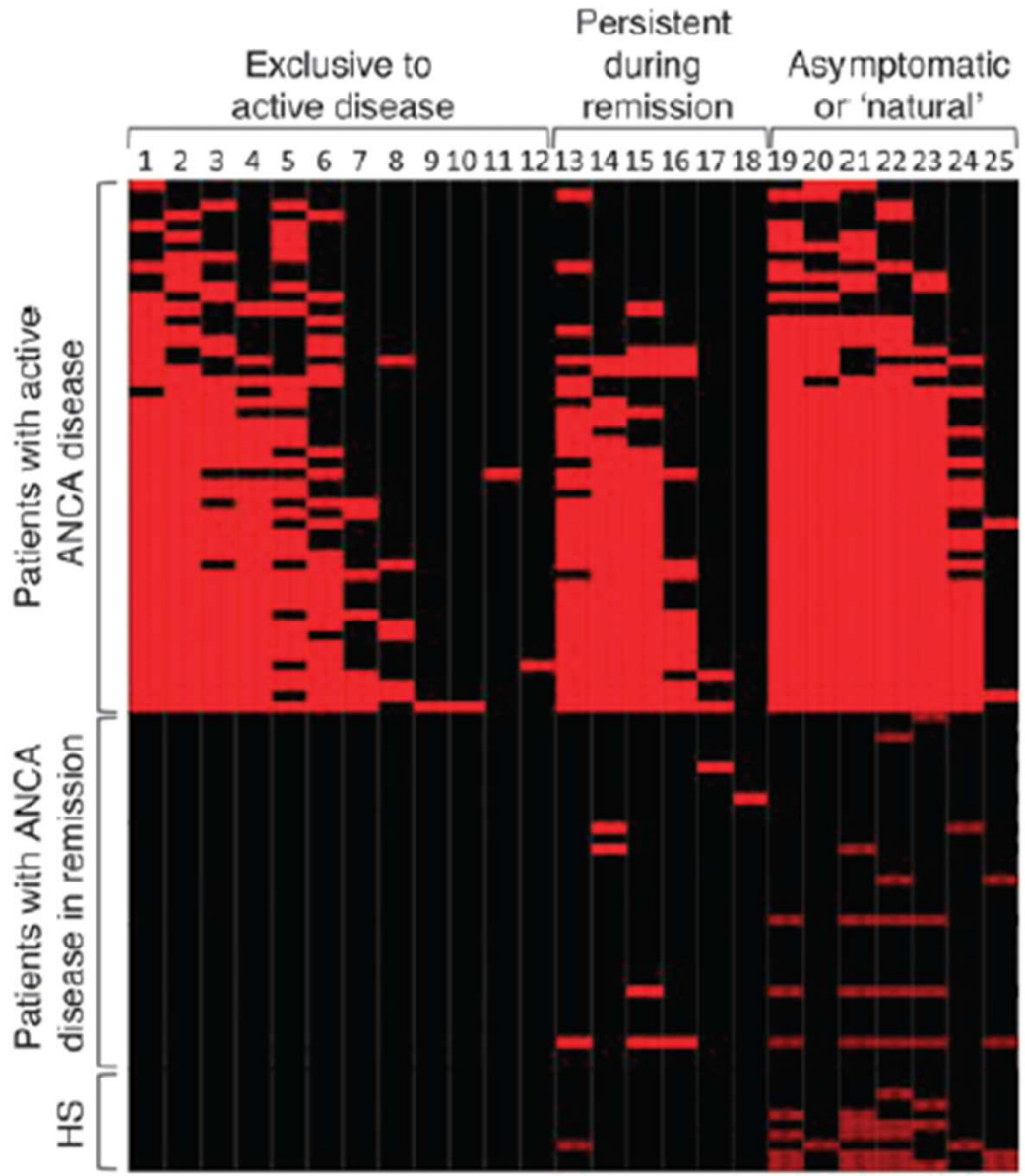
Xiao, JASN, 2013

Research article

Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis

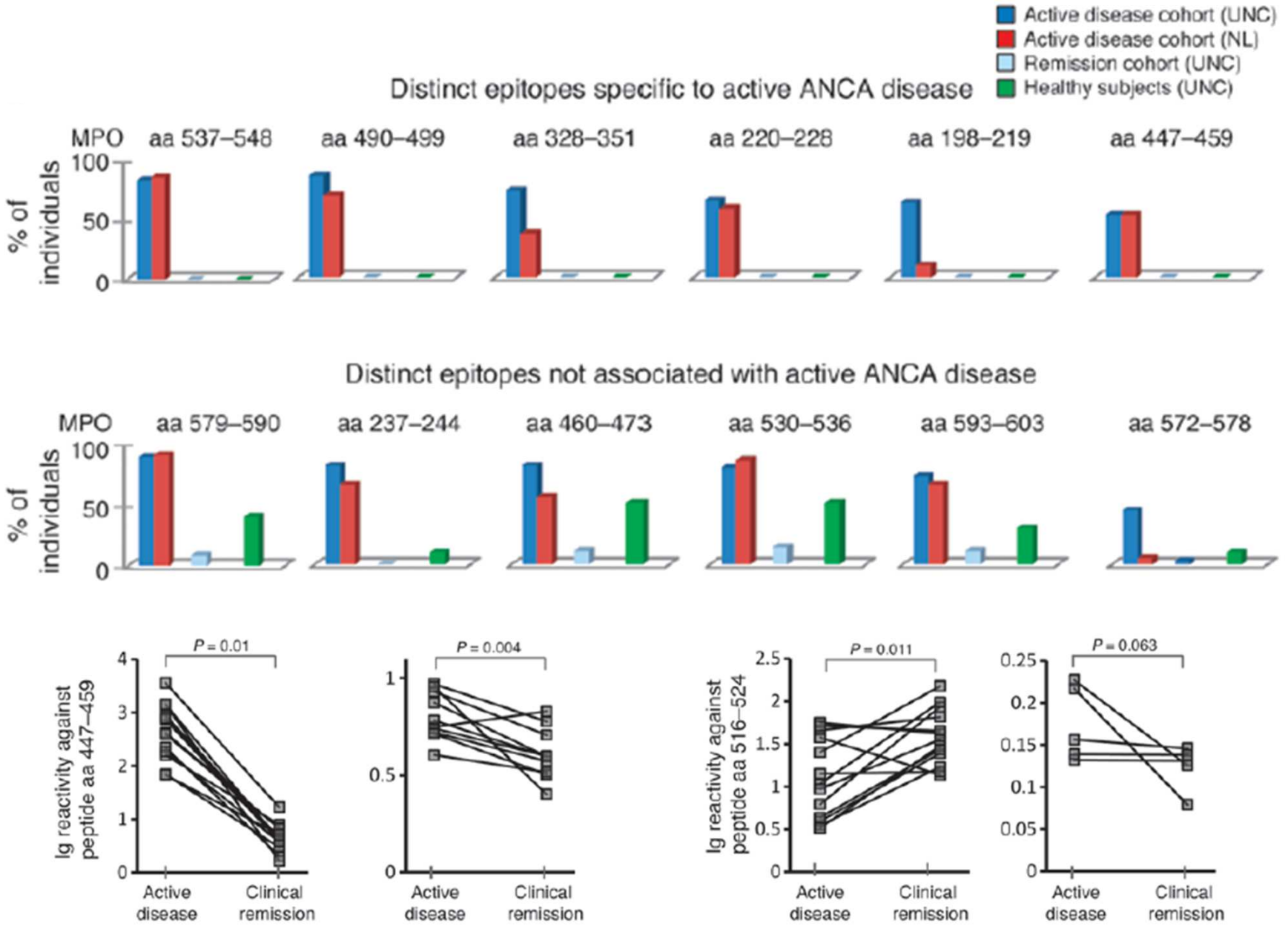
Aleeza J. Roth,[1] Joshua D. Ooi,[2] Jacob J. Hess,[1] Mirjan M. van Timmeren,[3] Elisabeth A. Berg,[1] Caroline E. Poulton,[1] JulieAnne McGregor,[1] Madelyn Burkart,[1] Susan L. Hogan,[1] Yichun Hu,[1] Witold Winnik,[4] Patrick H. Nachman,[1] Coen A. Stegeman,[3] John Niles,[5] Peter Heeringa,[3] A. Richard Kitching,[2] Stephen Holdsworth,[2] J. Charles Jennette,[1] Gloria A. Preston,[1] and Ronald J. Falk[1]

MPO-ANCA epitope specificity



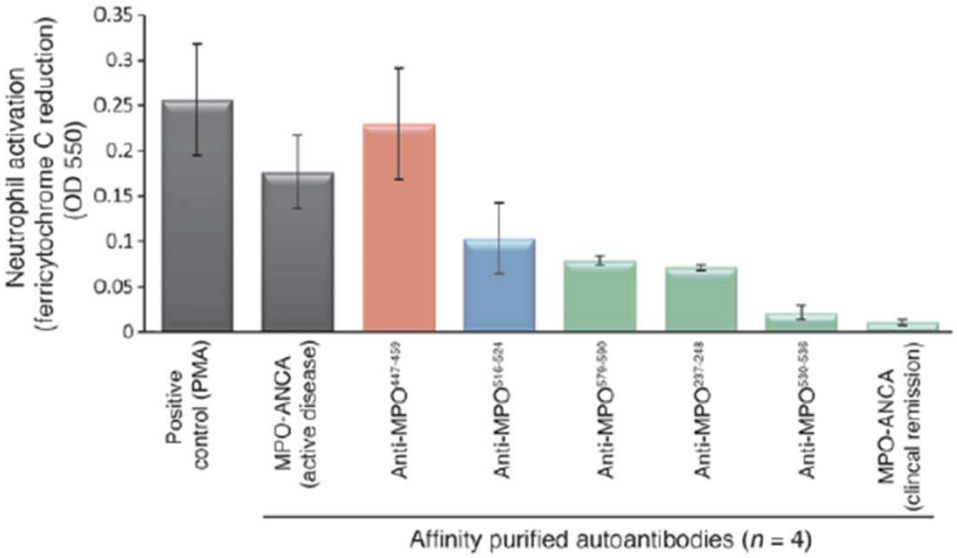
Roth, J Clin Invest, 2013

MPO-ANCA epitope specificity

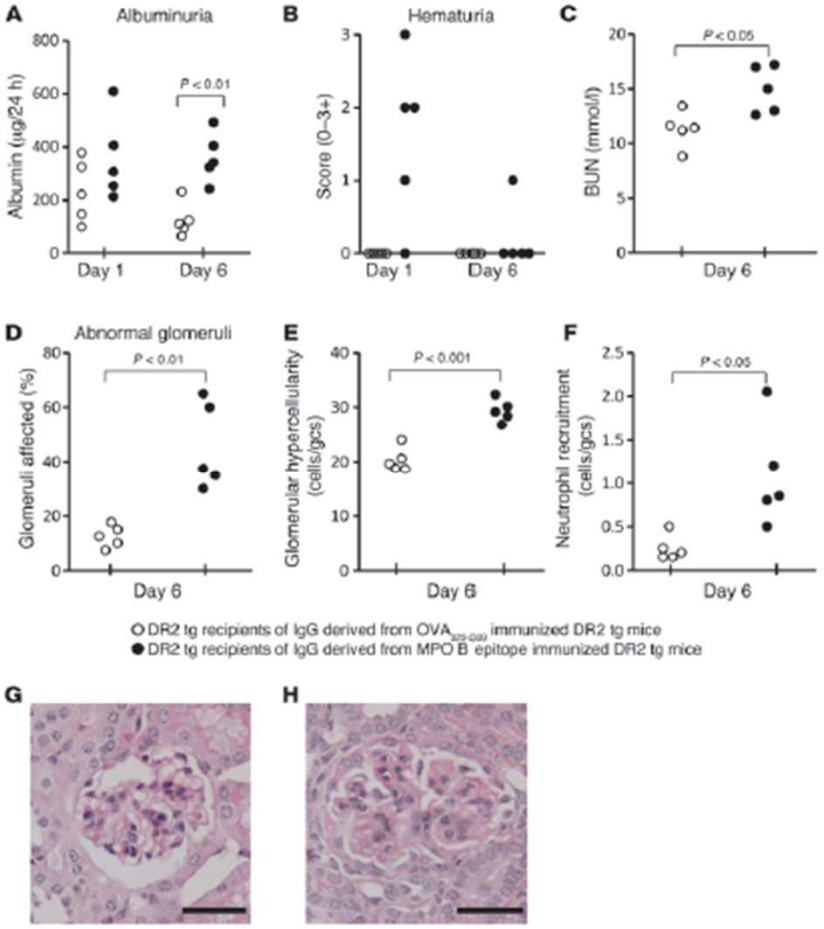


In vitro and *in vivo* pathogenic effect of MPO-ANCA directed against 447-459 epitope

In vitro



In vivo



Roth, J Clin Invest, 2013

Evidences for ANCA pathogenicity

Clinical

- **Disease strongly associated with ANCA**
- **Partial correlation of ANCA titers with disease activity**
- **Correlation of ANCA epitope with disease activity**
- **Disease induction by transplacental transfer of MPO-ANCA**
- **Response to immunosuppressive therapy targeting B cells**

In vitro

- **Activation of cytokine-primed neutrophils by ANCA**
- **Endothelial injury by ANCA-acitvated neutrophils**

In vivo

- **Induction of vasculitis in mice and rats by anti-MPO**
- **Prevention of murine anti-MPO-induced disease by deficiency of neutrophils or blocking complement pathway activation**

Pathogenicity of PR3-ANCA ?

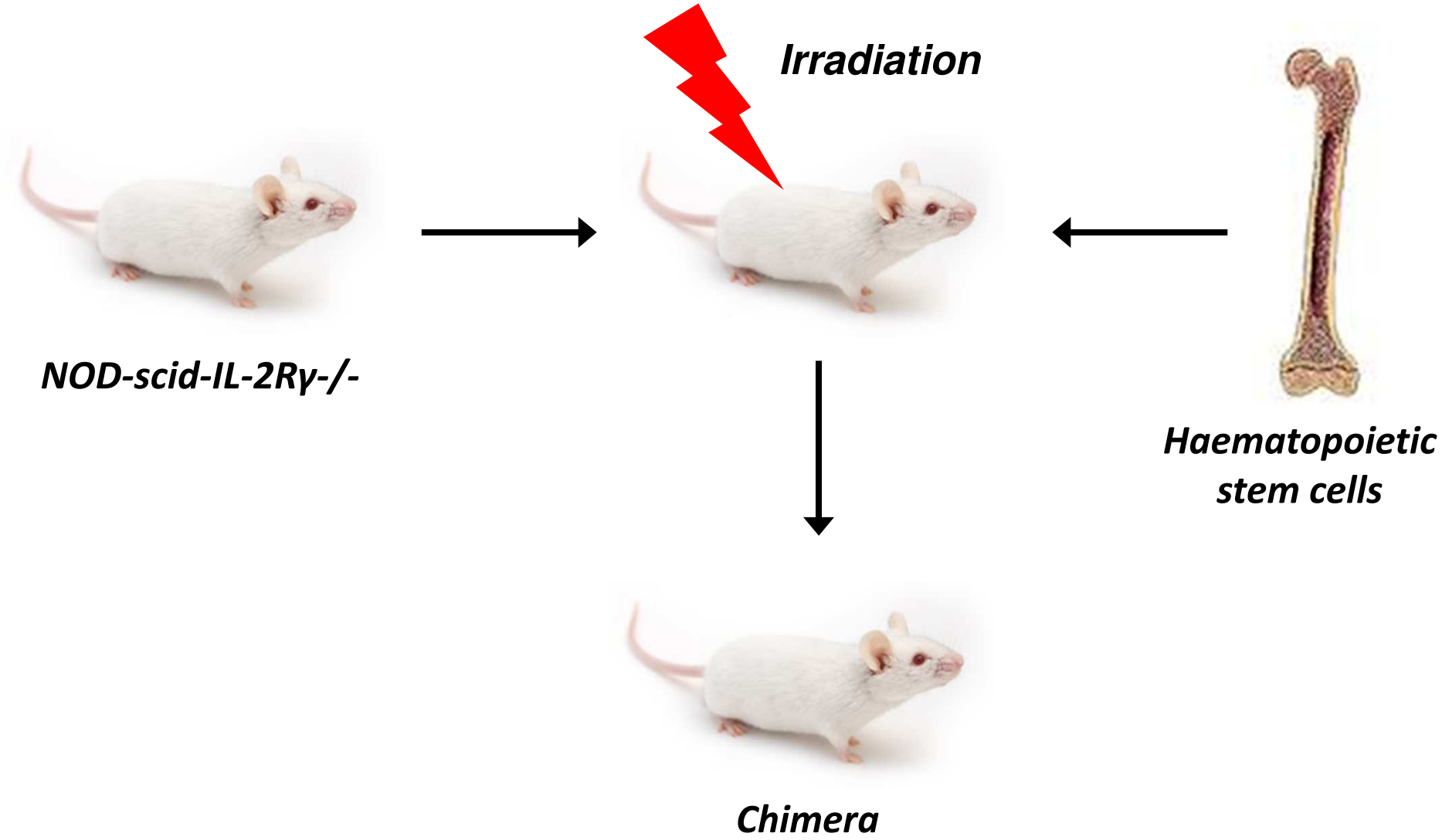
- **No spontaneous models of glomerulonephritis or of vasculitis associated with anti-PR3 antibodies, or indeed of PR3-ANCA in association with other autoantibodies, have been reported in rodents**

- **More recently, Little et al. have reported the use of humanised immunodeficient NOD SCID IL2R knock-out mice, which received human haemopoetic stem cells and developed a human-mouse chimeric immune system**

- **These mice developed mild glomerulonephritis and lung haemorrhage (but no evidence of granuloma) following passive transfer of PR3-ANCA containing IgG derived from patients with severe systemic vasculitis**

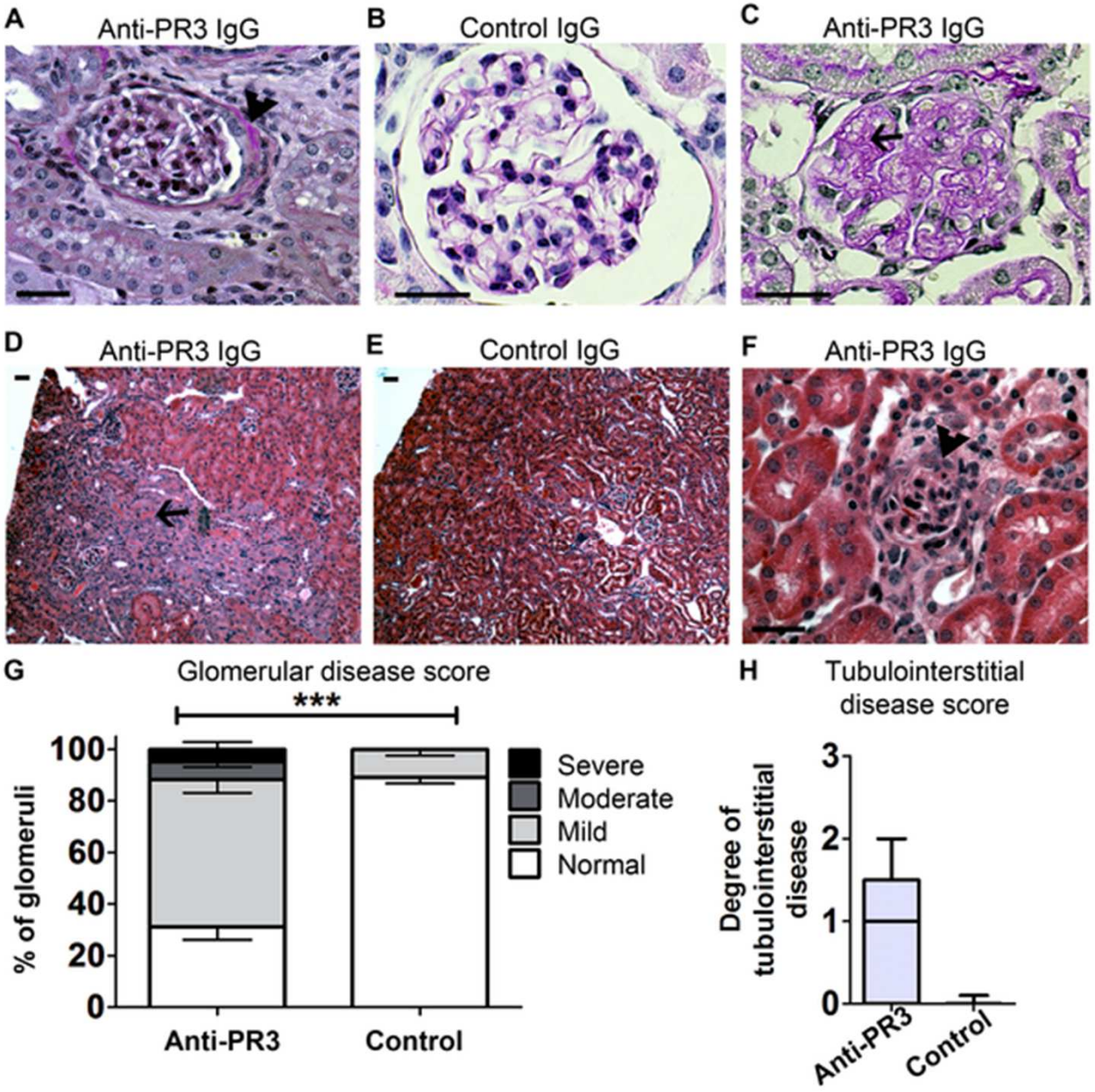
Salama, Curr Opin Rheumatol, 2012

Pathogenicity of PR3-ANCA ?



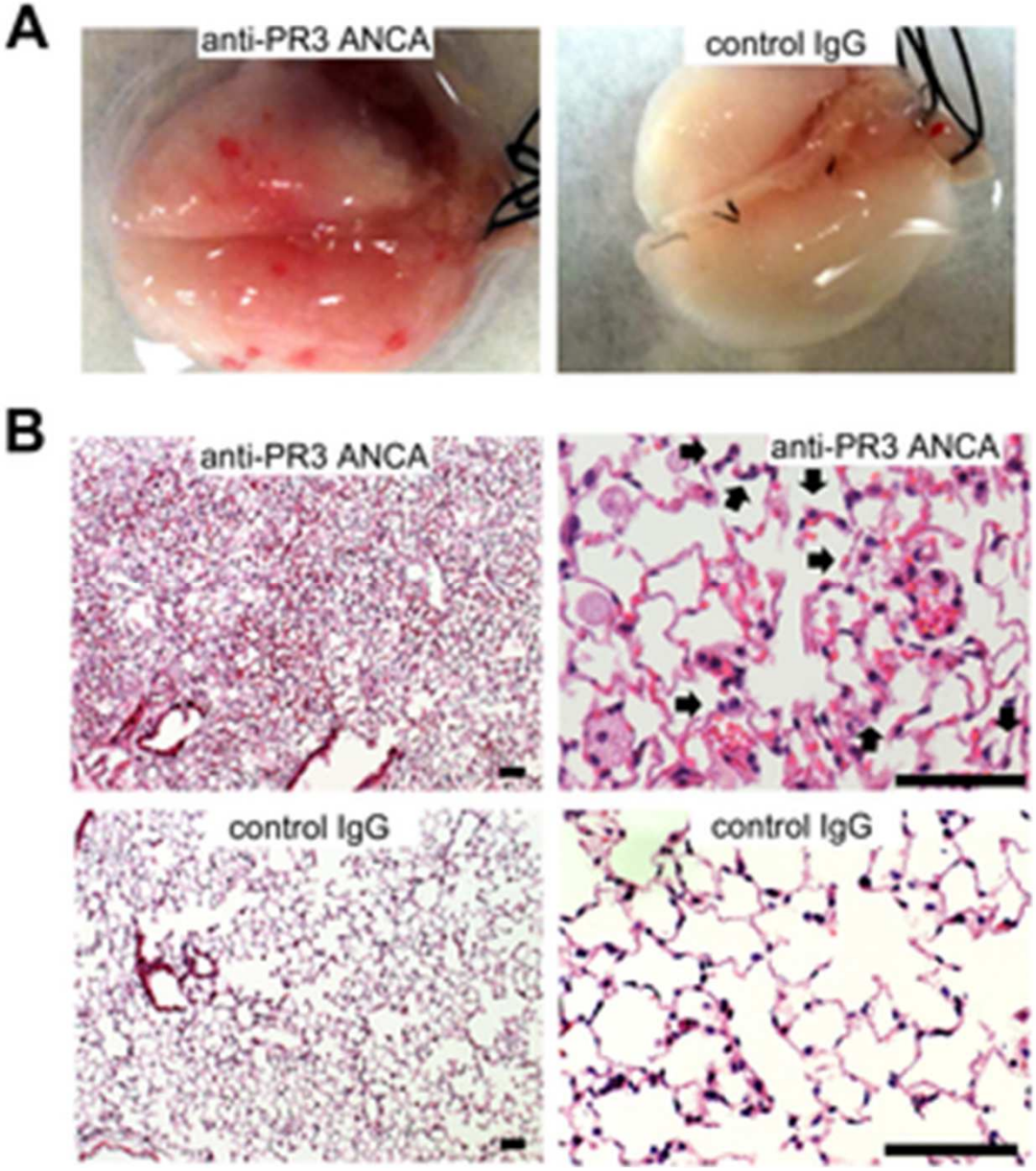
Little, PLoS One, 2012

Pathogenicity of PR3-ANCA ?



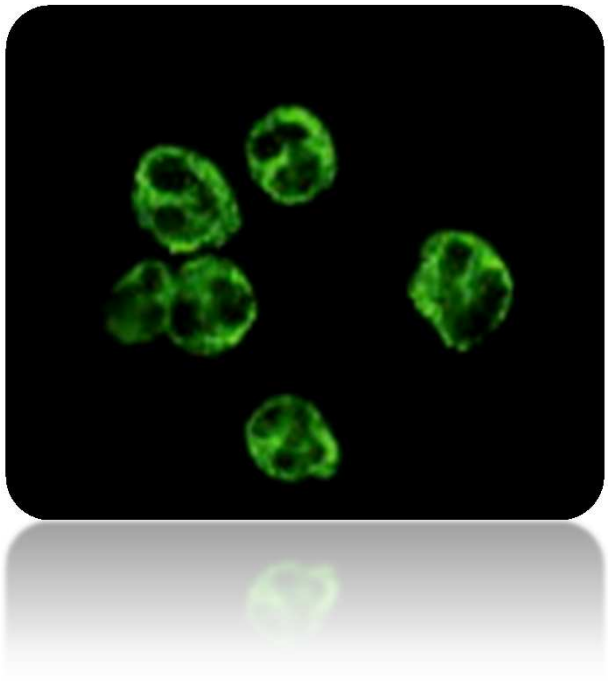
Little, PLoS One, 2012

Pathogenicity of PR3-ANCA ?



Little, PLoS One, 2012

Role of neutrophils



Expression membranaire de la PR3 et GPA

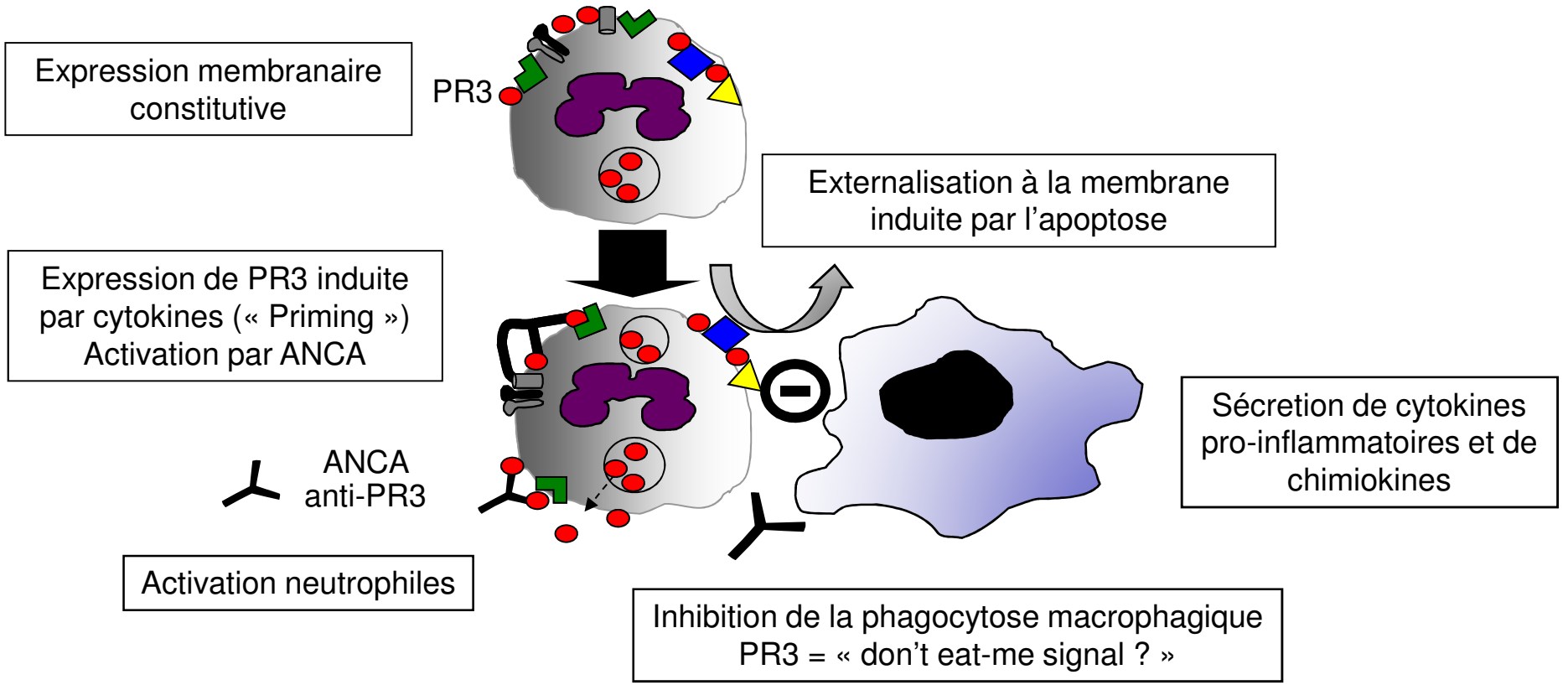
- **Chez un individu donné, coexisteraient dans des proportions constantes, des PNN exprimant à leur surface une grande quantité de PR3 membranaire et des PNN l'exprimant peu**

- **Expression de PR3 membranaire par une proportion importante de PNN : risque accru de développer une maladie inflammatoire, en particulier la GPA (Witko-Sarsat, J Am Soc Nephrol 1999)**

- **Forte expression membranaire de la PR3 pourrait être corrélée avec l'activité de la GPA (Muller Kobold AC, J Rheumatol 1998) et associée à un risque plus élevé de rechutes (Rarok AA, J Am Soc Nephrol 2002)**

- **L'allèle rare A-564 G du promoteur du gène de la PR3 : observée plus fréquemment chez des malades atteints de GPA (Gencik et al, Kideny int 2000)**

Physiopathologie de la PR3 dans la GPA



Witko-Sarsat et al, *Curr Opin Rheumatol* 2010

How proteinase 3 contribute to the inflammatory process and the immune dysregulation ?

The Journal of Clinical Investigation

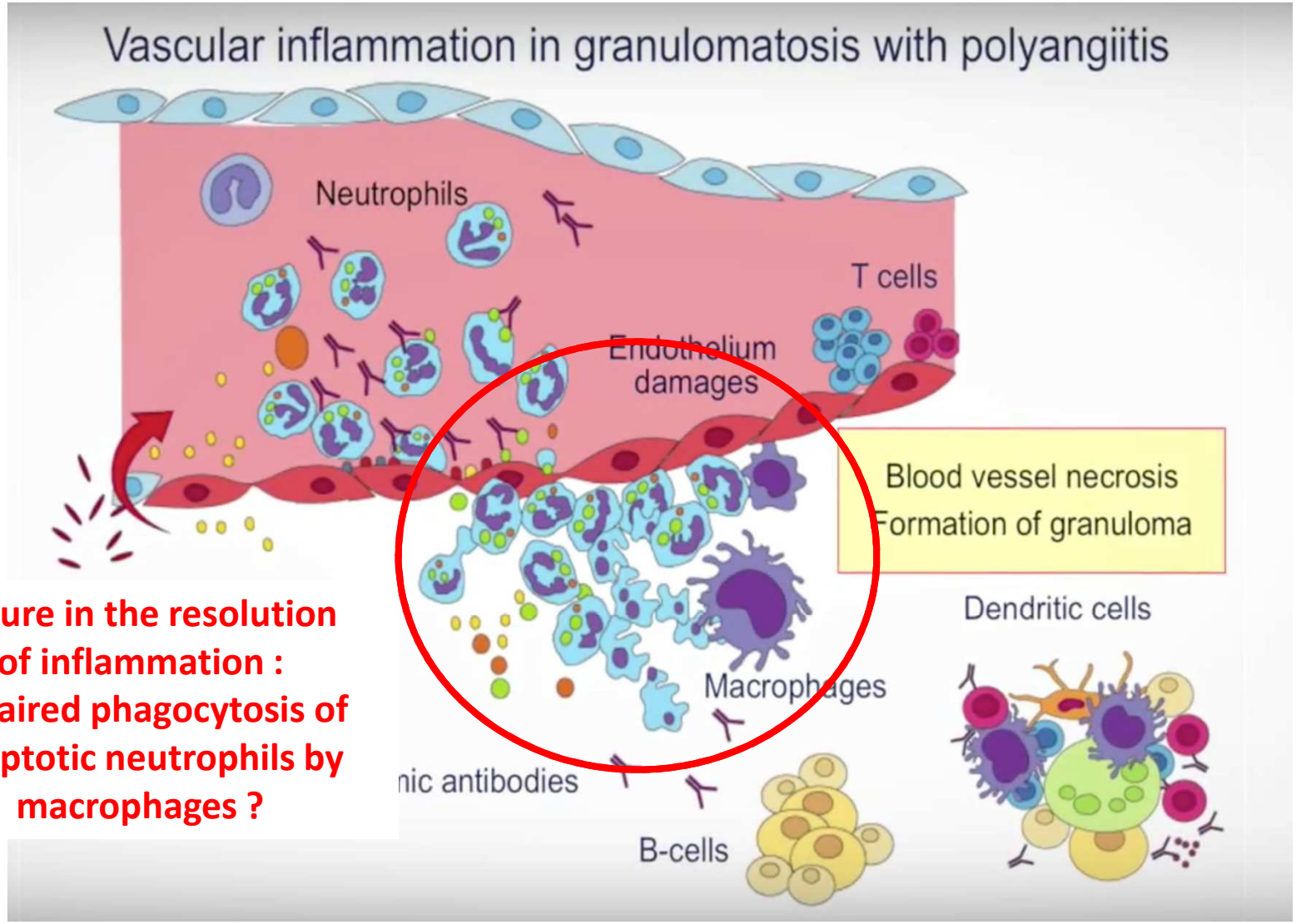
RESEARCH ARTICLE

Proteinase 3 on apoptotic cells disrupts immune silencing in autoimmune vasculitis

Arnaud Millet,[1,2,3,4] Katherine R. Martin,[1,2,3,4] Francis Bonnefoy,[5] Philippe Saas,[5] Julie Mocek,[1,2,3,4] Manal Alkan,[1,2,3,4] Benjamin Terrier,[1,2,3,4,6] Anja Kerstein,[7] Nicola Tamassia,[8] Senthil Kumaran Satyanarayanan,[9] Amiram Ariel,[9] Jean-Antoine Ribeil,[3,10] Loïc Guillevin,[6] Marco A. Cassatella,[8] Antje Mueller,[7] Nathalie Thieblemont,[1,2,3,4] Peter Lamprecht,[7] Luc Mouthon,[1,2,3,4,6] Sylvain Perruche,[5] and Véronique Witko-Sarsat[1,2,3,4]

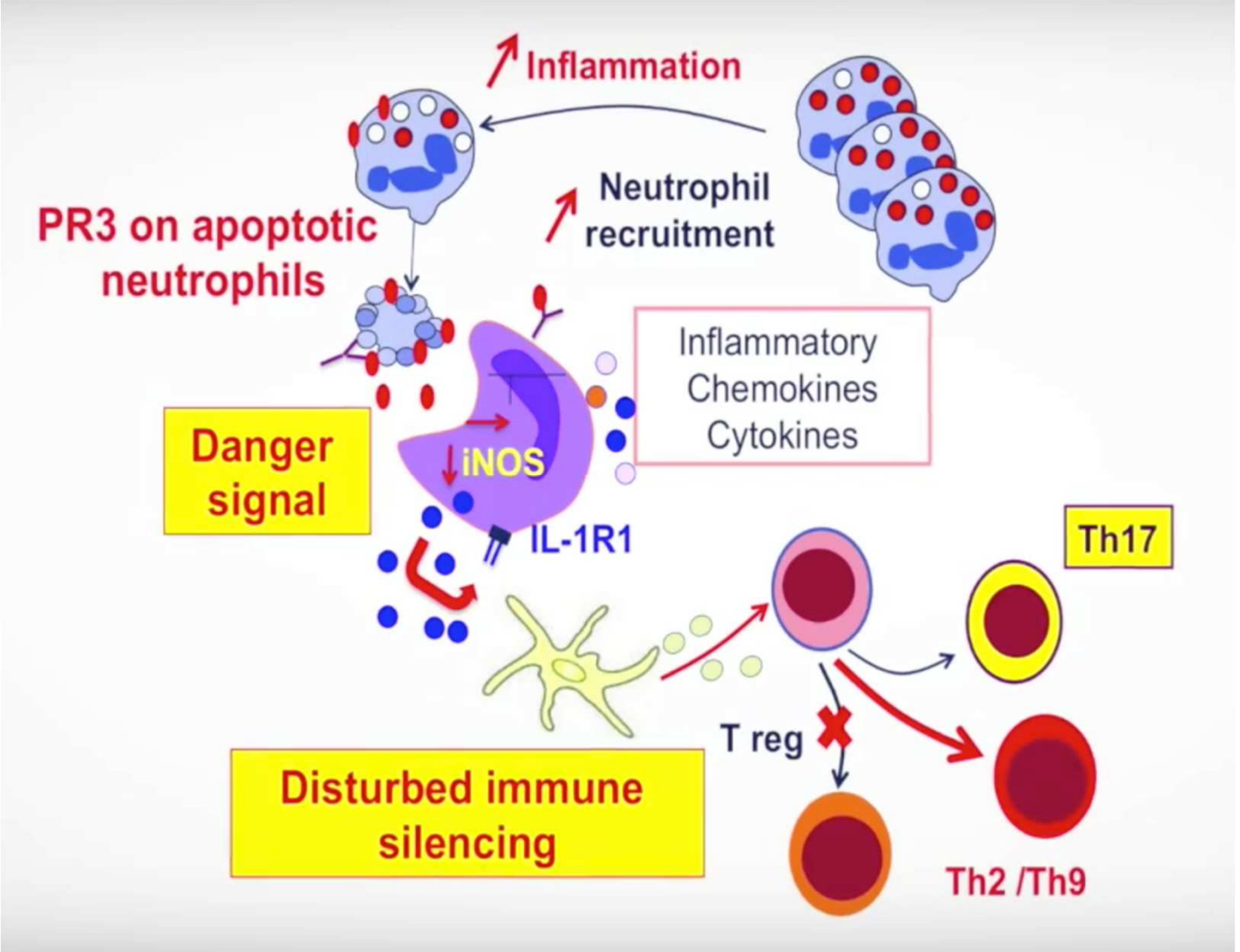
Millet, J Clin Invest, 2015

Failure in the resolution of inflammation in GPA

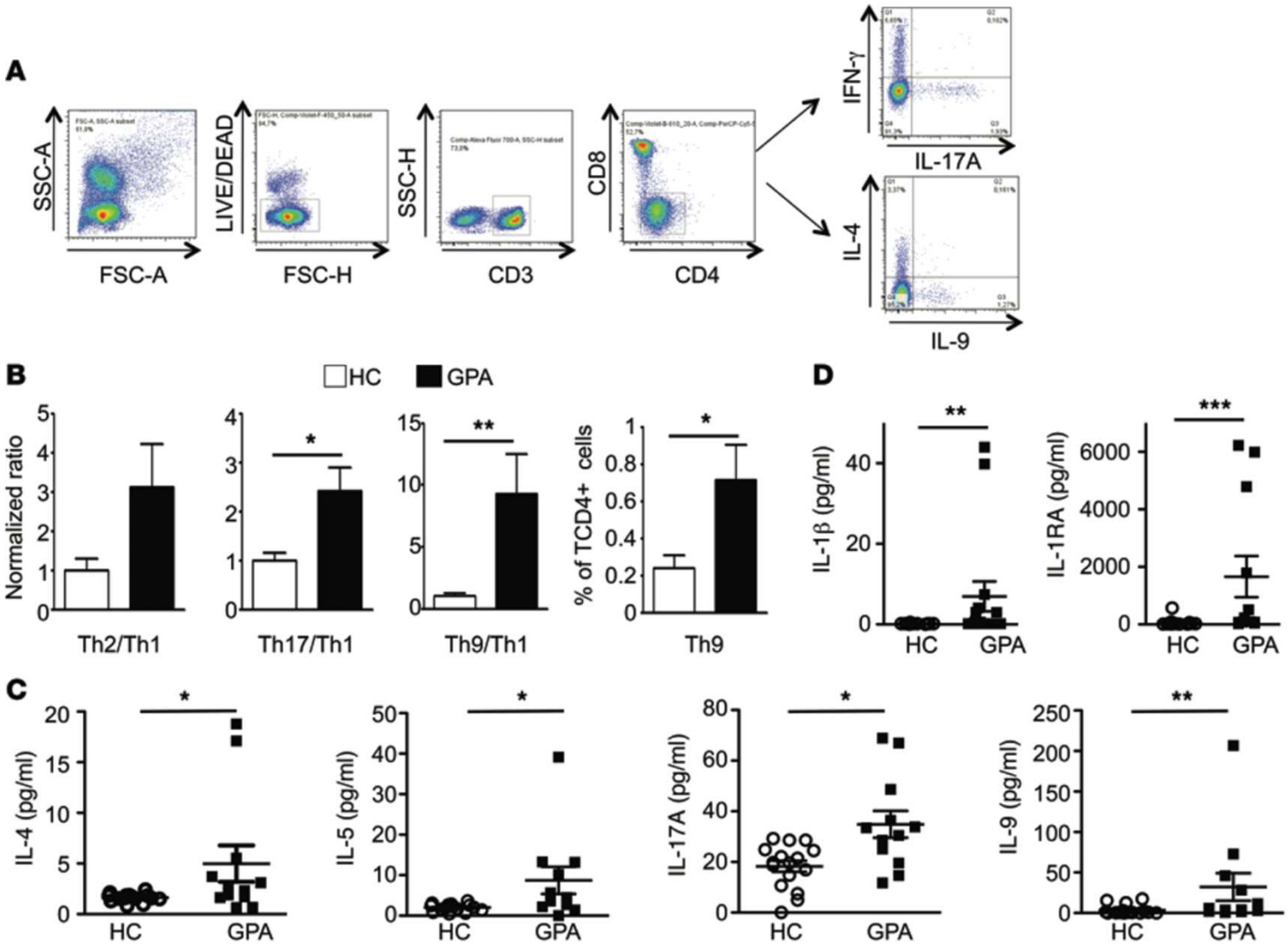


Failure in the resolution of inflammation : Impaired phagocytosis of apoptotic neutrophils by macrophages ?

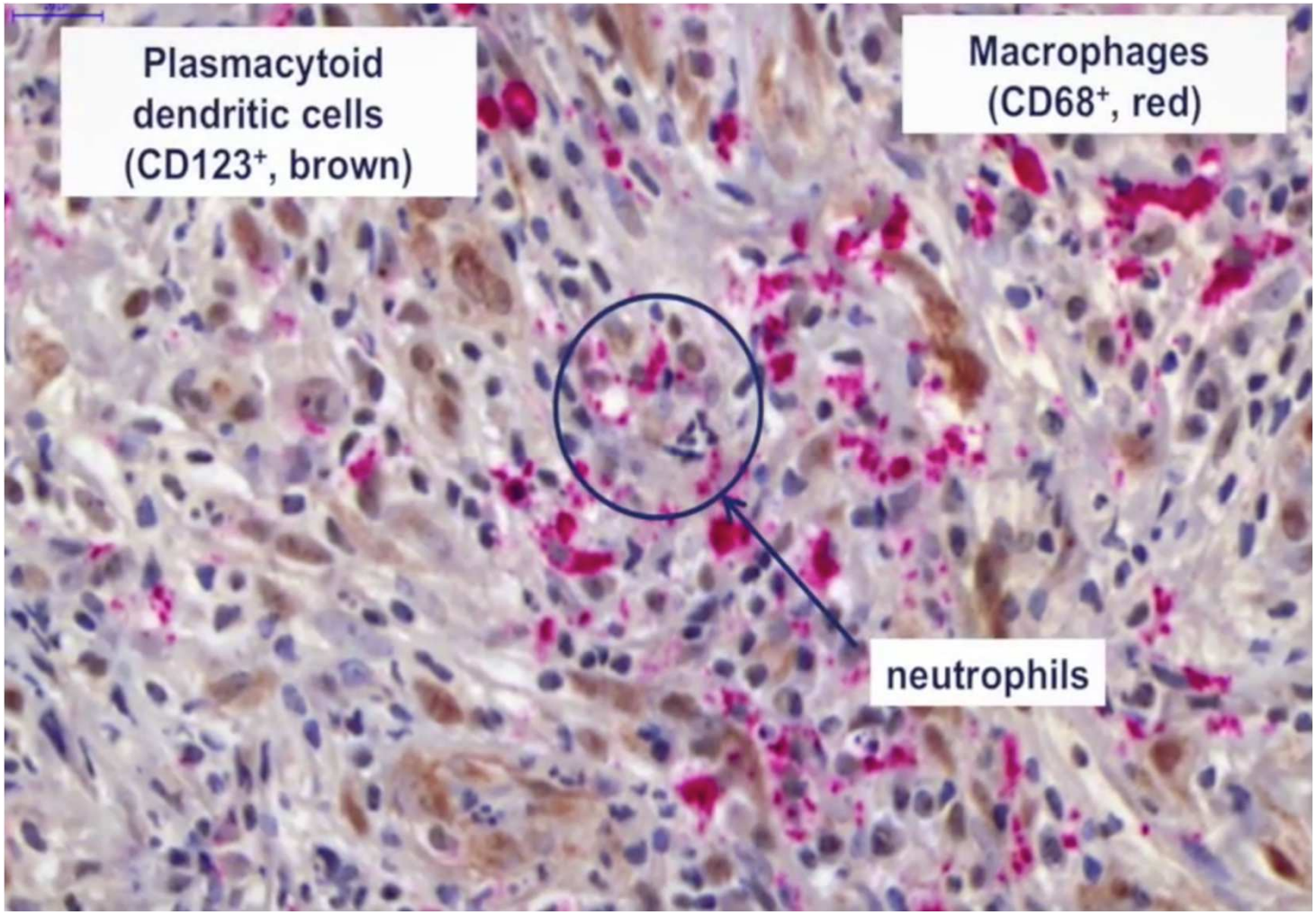
PR3 as a danger signal for macrophages



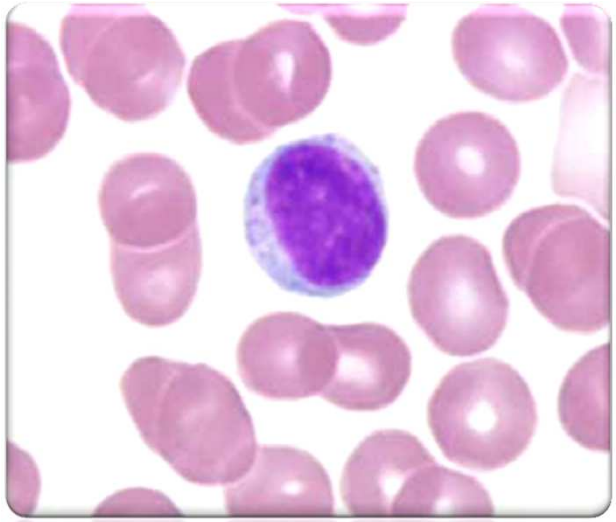
CD4 T cells from GPA patients have a skewed distribution of Th2/Th9/Th17



pDC, macrophages and neutrophils are found within the granulomatous lesions in GPA patients



Regulation of the ANCA immune response: Role of lymphocytes

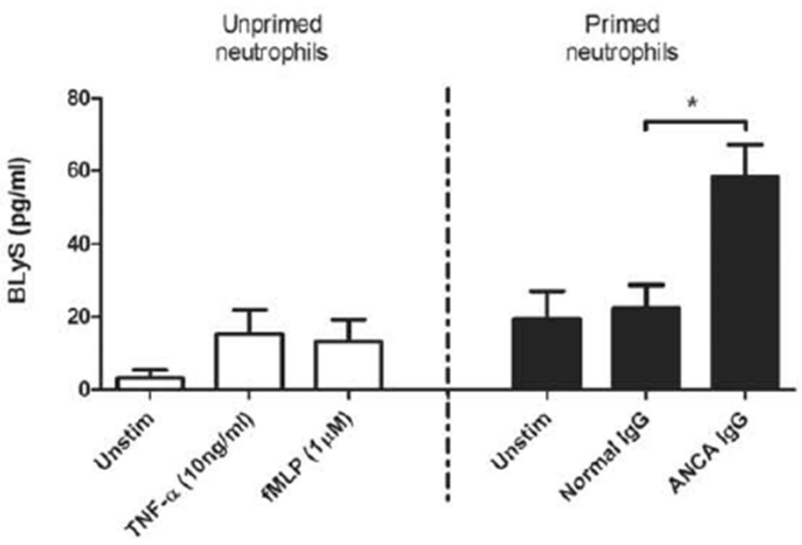


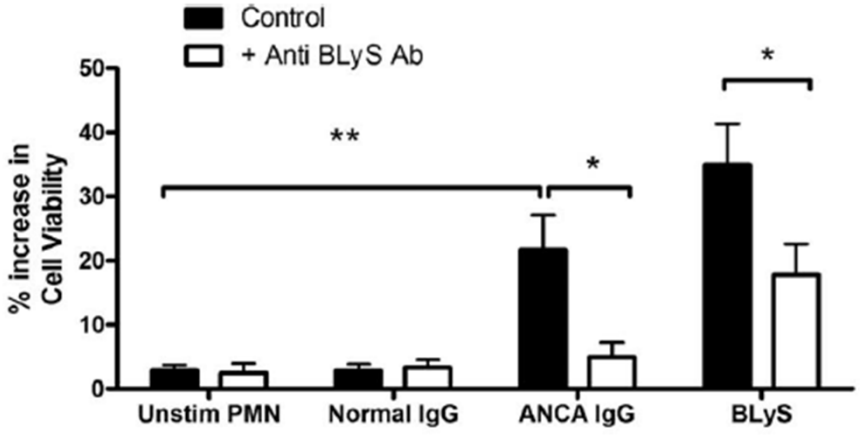
Regulation of the ANCA immune response

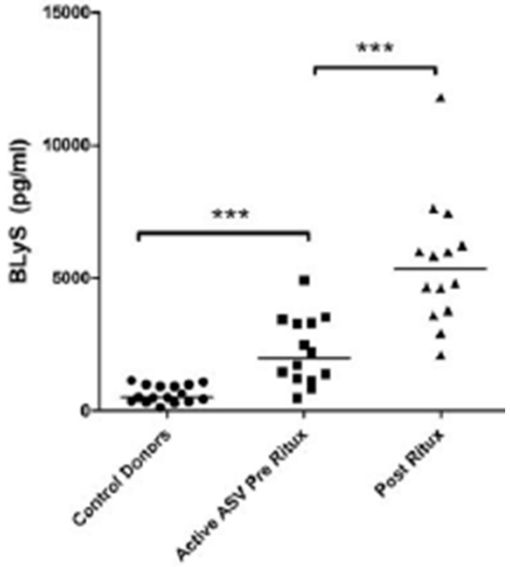
- **Impaired T-cell and B-cell suppression**
  - **Dysfunction of regulatory T cells: loss of tolerance and emergence of pathogenic ANCA response**
  - **Decreased PD-1 expression on effector T cells**
  - **Increased IL-17A production**
  - **Reduced regulatory $CD5^+$ B cells**

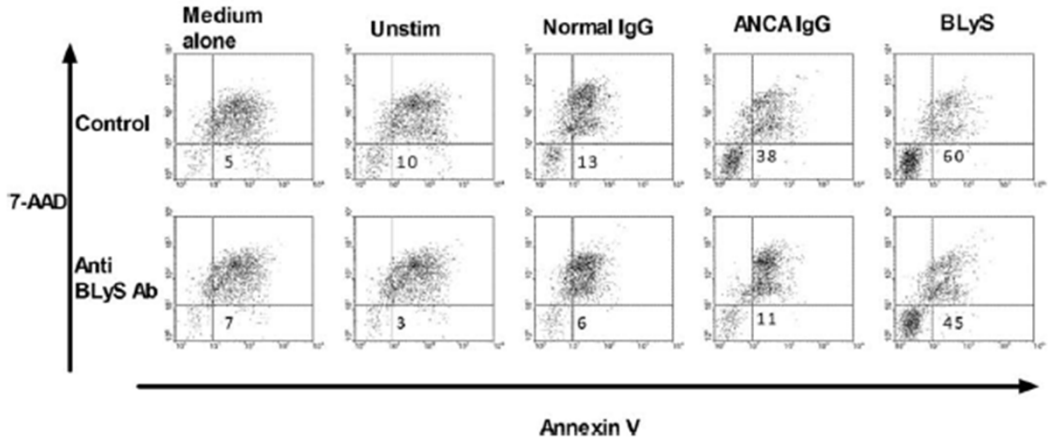
- **Increased B-cell activation and proliferation**
  - **Released of B-cell activating factors by ANCA-activated neutrophils**
  - **Enhanced B-cell proliferation and production of ANCA by ANCA-activated neutrophils**

Enhanced B-cell stimulation by ANCA-activated neutrophils









Holden, Ann Rheum Dis, 2011

Conclusion

- **Appearance of pathogenic ANCAs in response to various triggers**
- **Activation of primed neutrophils by ANCAs**
- **Pathogenic role demonstrated for MPO-ANCA and modulation of the immune response for PR3-ANCA**
- **Dysregulation of T cells and B cells leading to the ANCA immune response**