The impact of RF and ACPA on bone erosion in RA

Ennio G. Favalli

Department and Chair of Rheumatology
Gaetano Pini Institute
Milan

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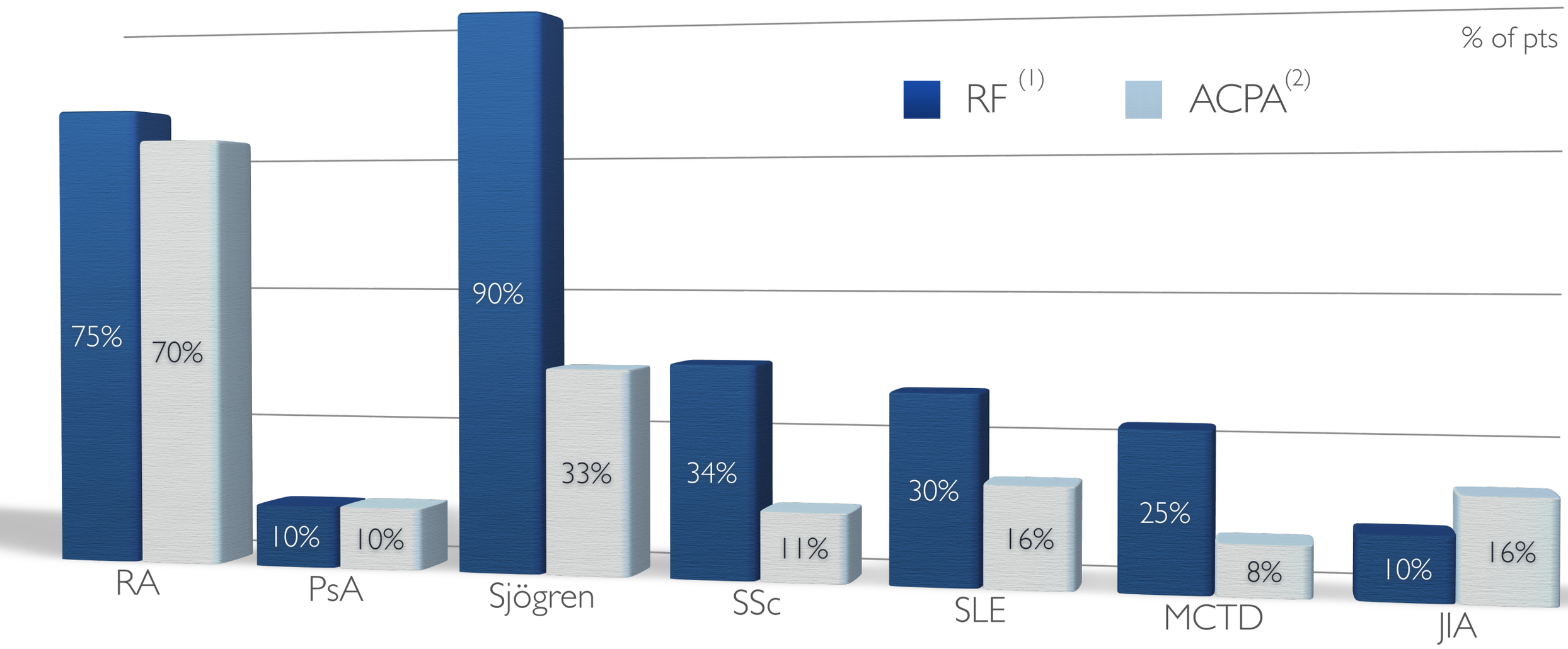
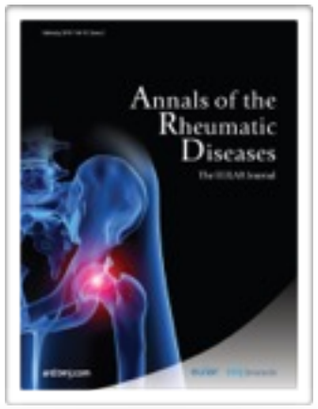
Prevalence of RF and ACPA in rheumatic diseases



(1) Dörner T, et al. Curr Opin Rheumatol 2004

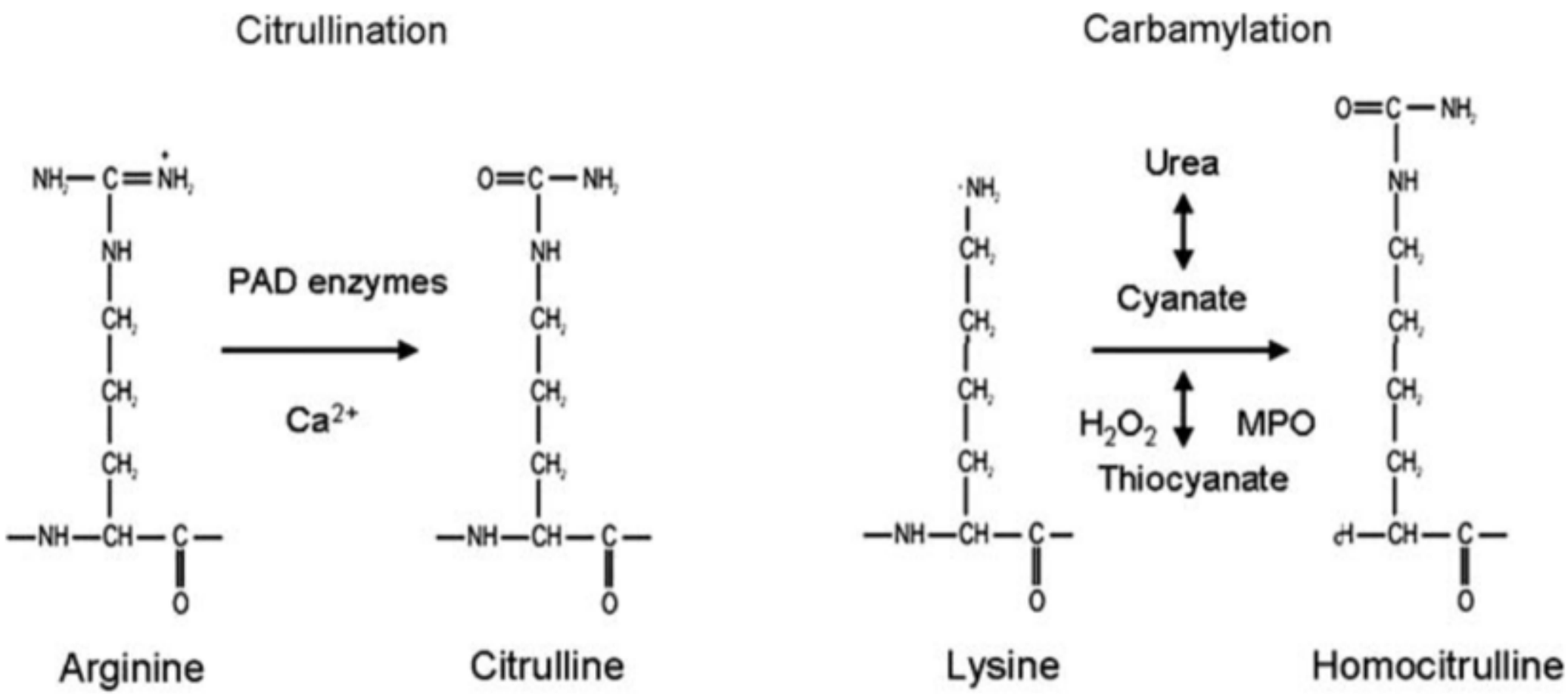
(2) Payet J et al. J Rheumatol 2014

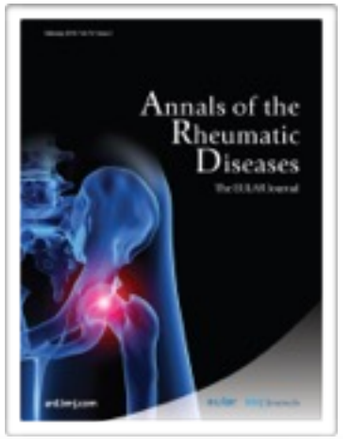


Autoimmunity in rheumatoid arthritis: different antigens—common principles

L A Trouw, Tom W J Huizinga, René E M Toes

Ann Rheum Dis 2013

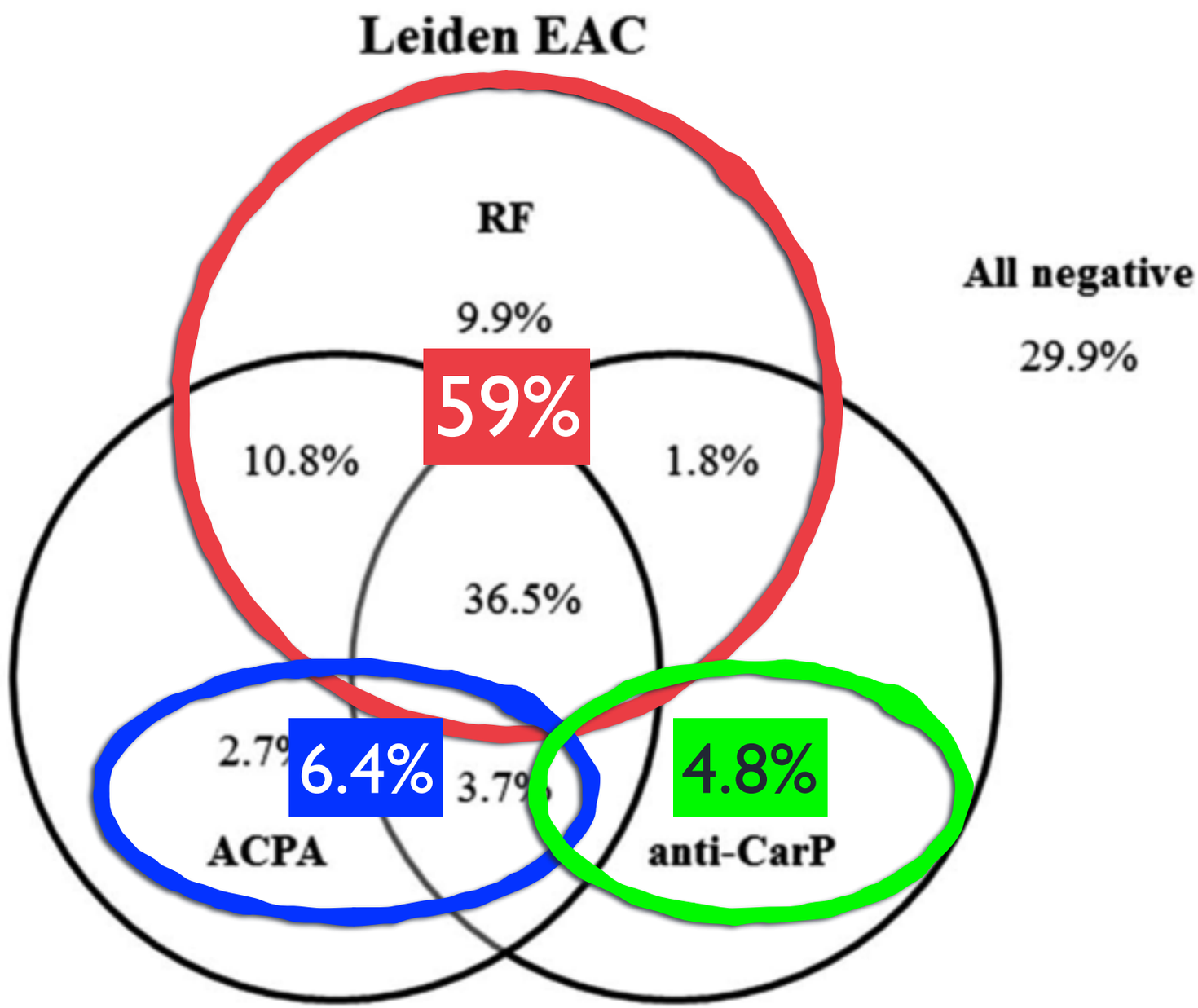


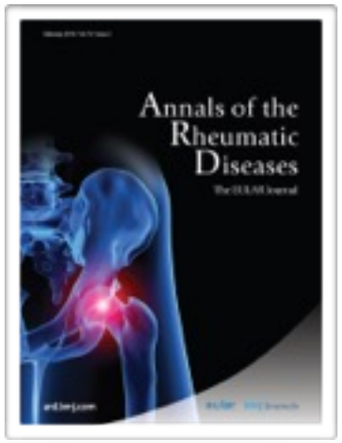


The association between anti-carbamylated protein (anti-CarP) antibodies and radiographic progression in early rheumatoid arthritis: a study exploring replication and the added value to ACPA and rheumatoid factor

S Ajeganova,[1,2] H W van Steenbergen,[1] M K Verheul,[1] K Forslind,[3,4] I Hafström,[2] R E M Toes,[1] T W J Huizinga,[1] B Svensson,[5] L A Trouw,[1] A H M van der Helm-van Mil[1]

Ann Rheum Dis 2016

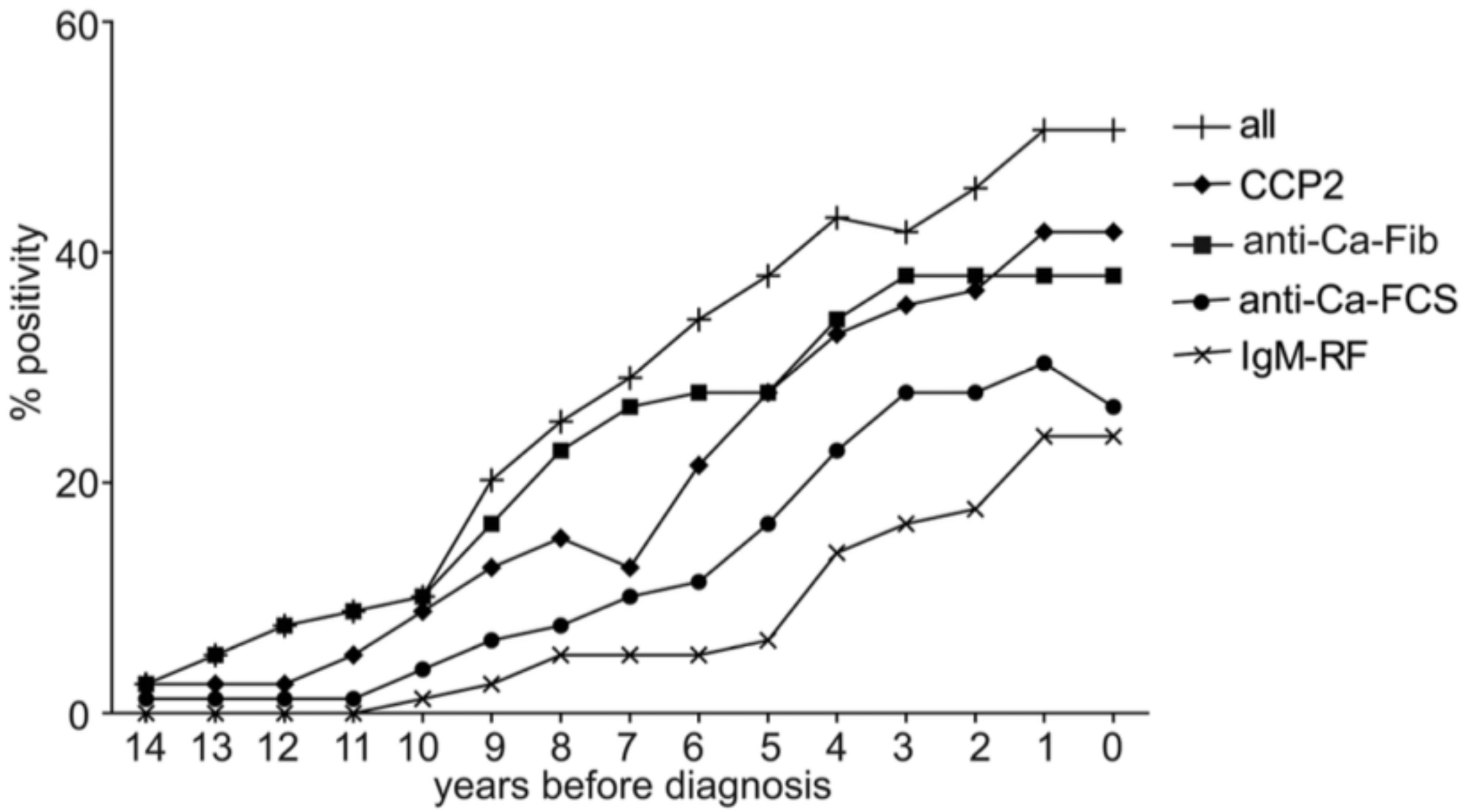




Anti-carbamylated protein (anti-CarP) antibodies precede the onset of rheumatoid arthritis

Jing Shi,[1] Lotte A van de Stadt,[2,3] E W Nivine Levarht,[1] Tom W J Huizinga,[1]
Dörte Hamann,[4] Dirkjan van Schaardenburg,[2,5] René E M Toes,[1] Leendert A Trouw[1]

Ann Rheum Dis 2014



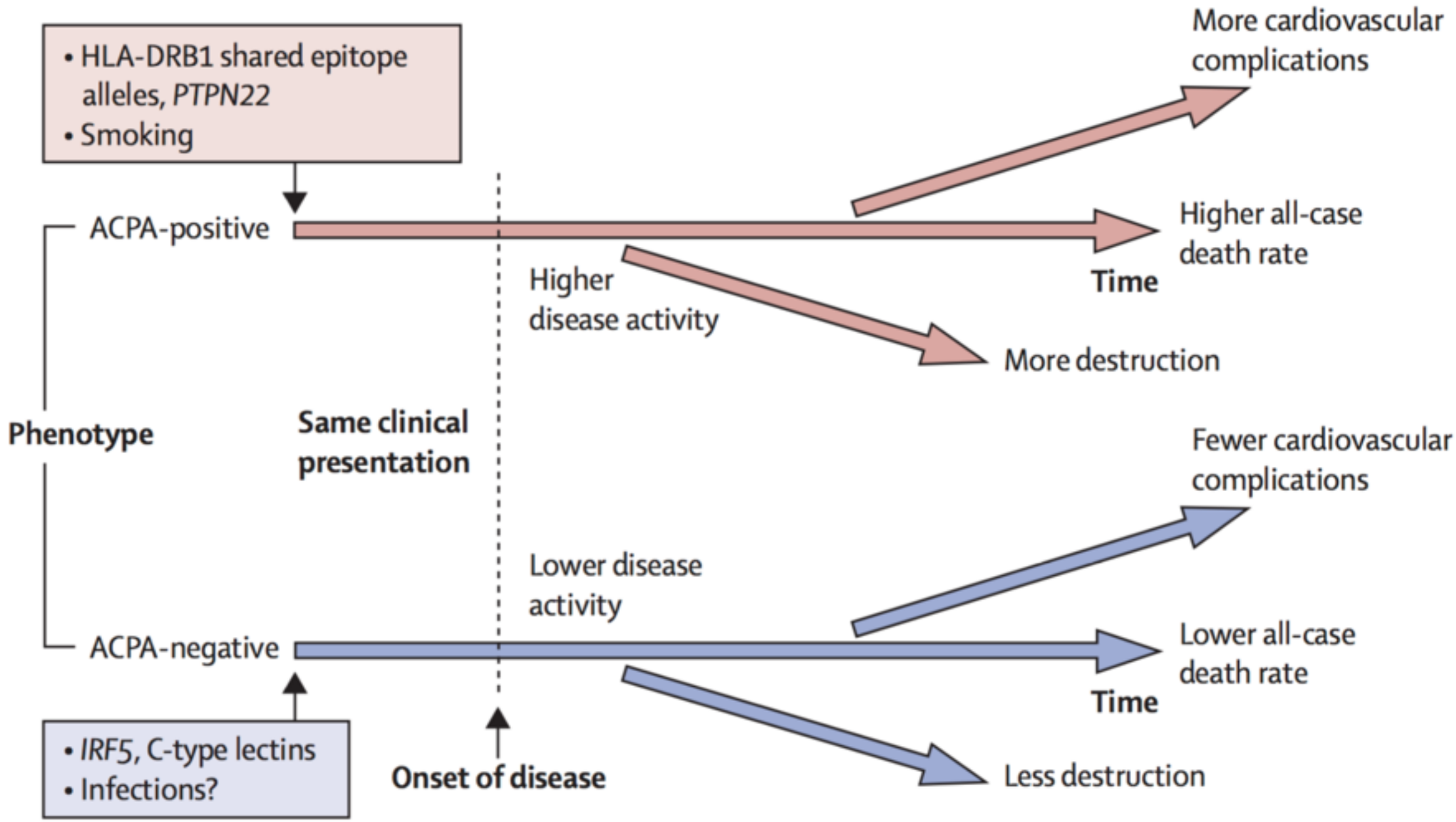
The predictive role of autoantibodies in RA

- Development of full-blown RA in arthralgia/UA patients
- Higher incidence of extra-articular manifestations
- Increased risk for CV diseases and mortality rate
- Higher radiographic progression

Rheumatoid arthritis

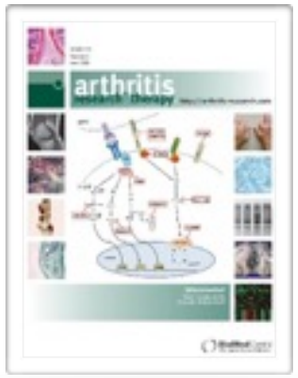
Lars Klareskog, Anca Irinel Catrina, Stephen Paget

Lancet 2009



Talk composition

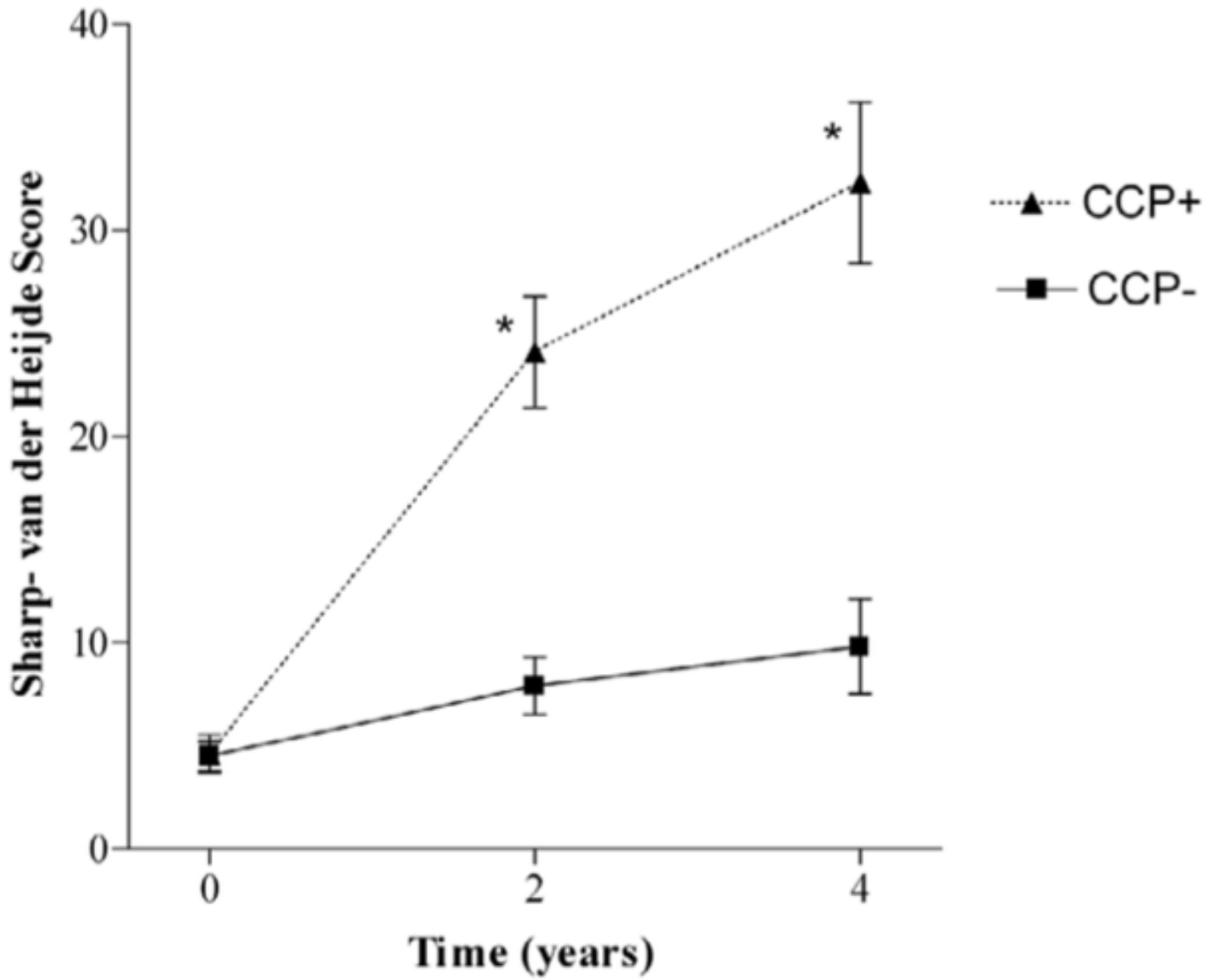
- The impact of autoantibodies on damage progression



Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis

Annette HM van der Helm-van Mil, Kirsten N Verpoort, Ferdinand C Breedveld, René EM Toes and Tom WJ Huizinga

Arthritis Res Ther 2005

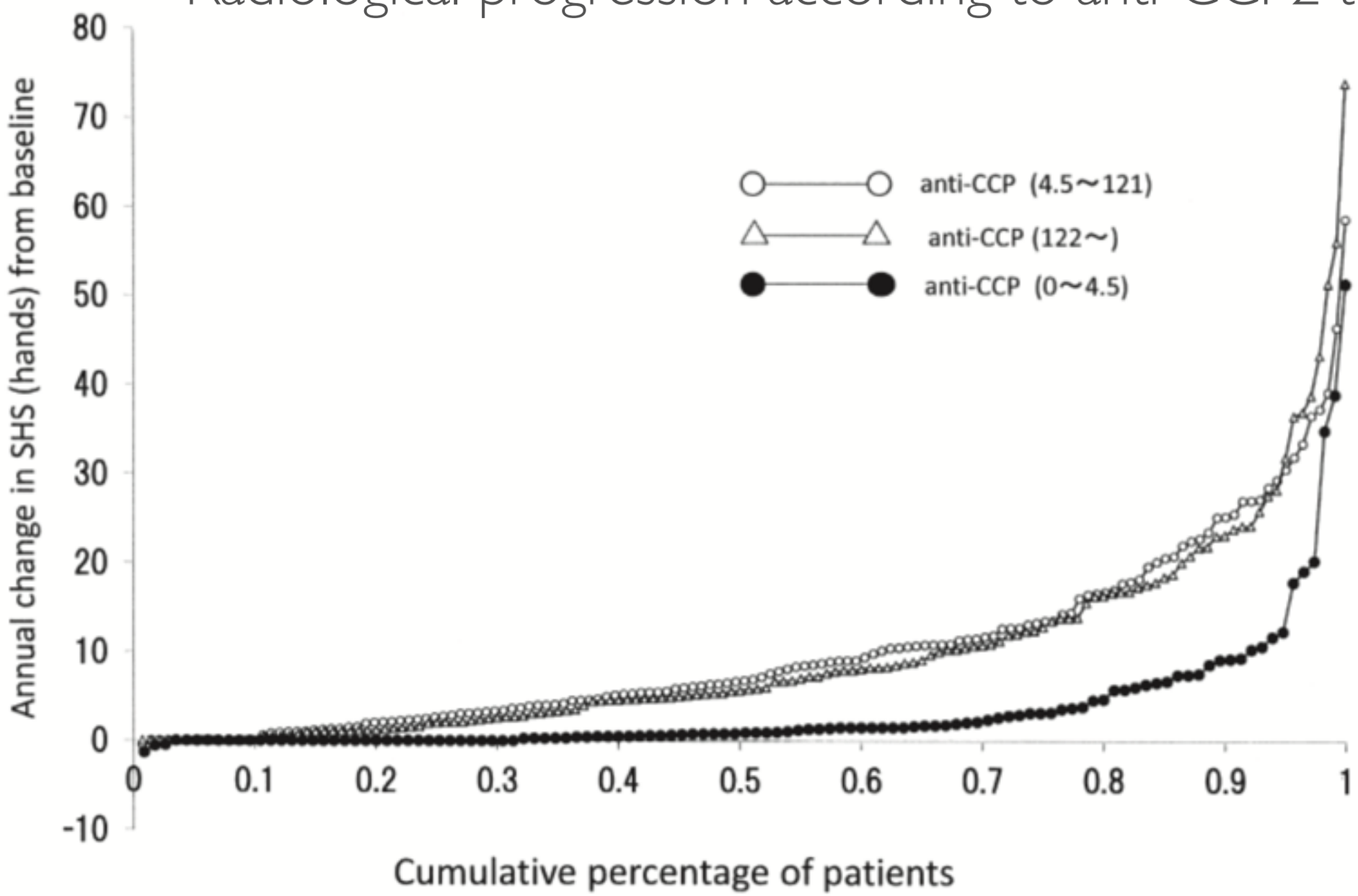


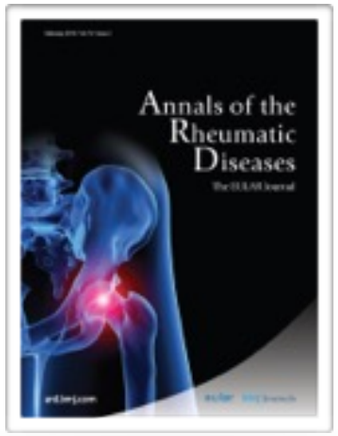
Anticitrullinated Protein Antibody, But Not Its Titer, Is a Predictor of Radiographic Progression and Disease Activity in Rheumatoid Arthritis

KAZUKO SHIOZAWA, YOSHIKO KAWASAKI, TAKASHI YAMANE, RYOSUKE YOSHIHARA, YASUSHI TANAKA, KENICHI UTO, and SHUNICHI SHIOZAWA

J Rheumatol 2012

Radiological progression according to anti-CCP2 titer

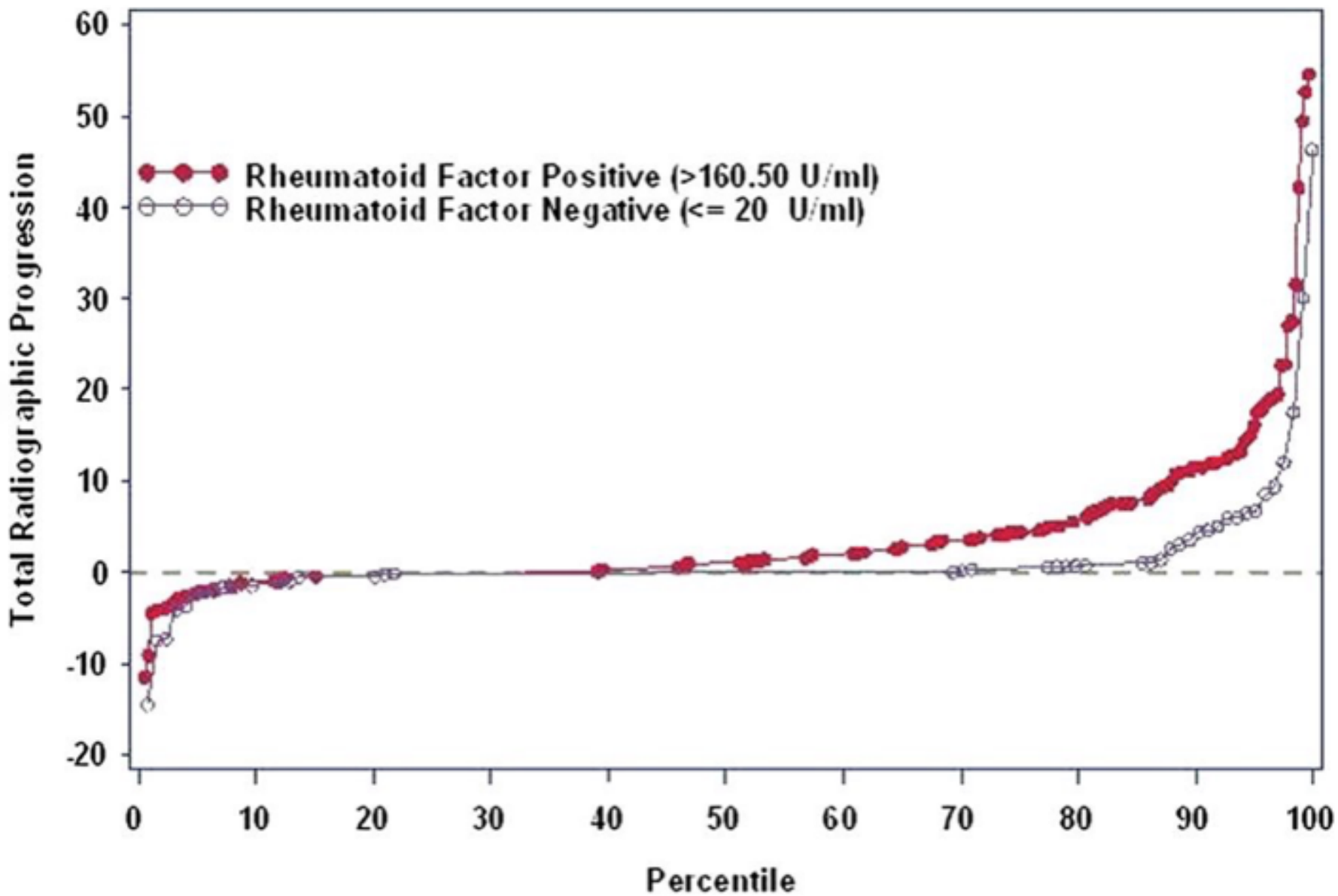


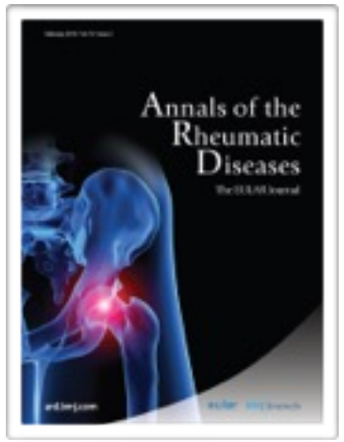


Rheumatoid factor determines structural progression of rheumatoid arthritis dependent and independent of disease activity

Daniel Aletaha,[1] Farideh Alasti,[1] Josef S Smolen[1,2]

Ann Rheum Dis 2013

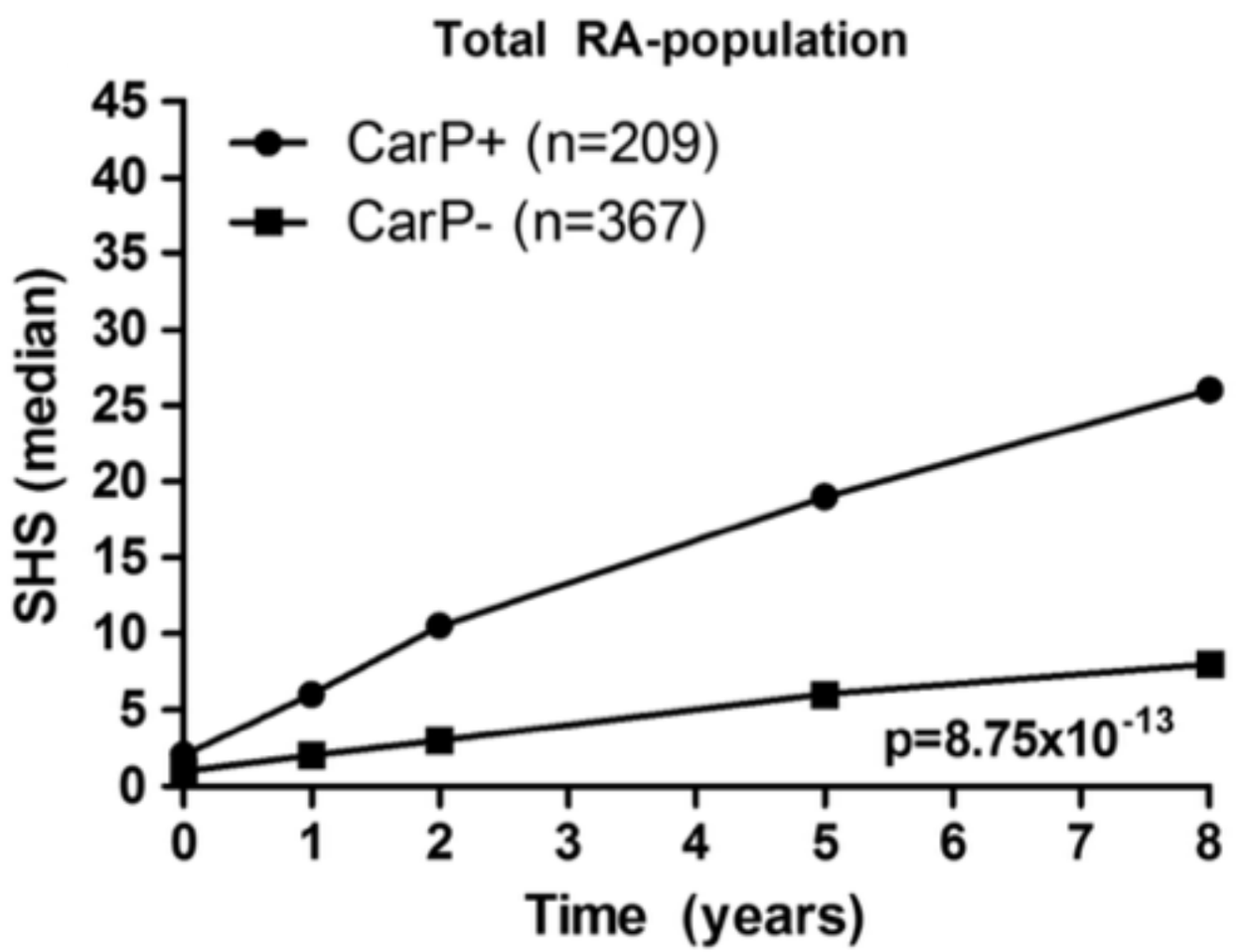


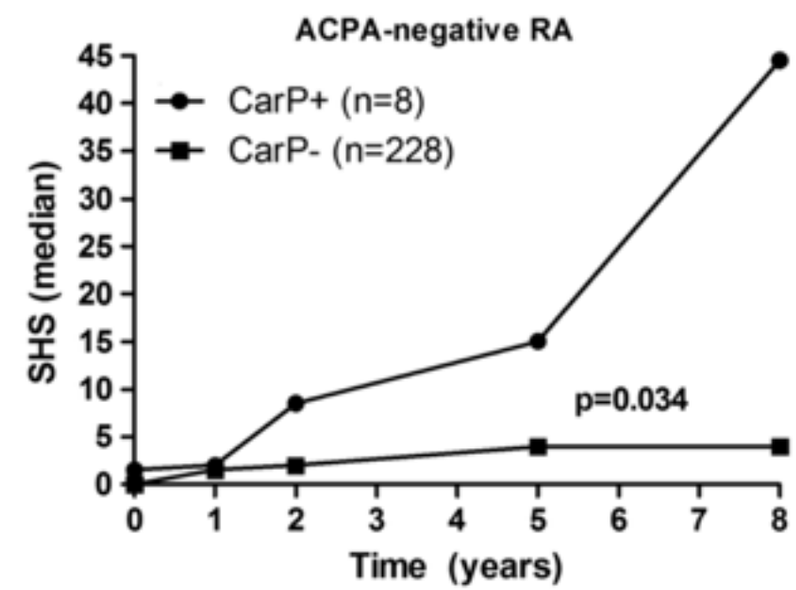


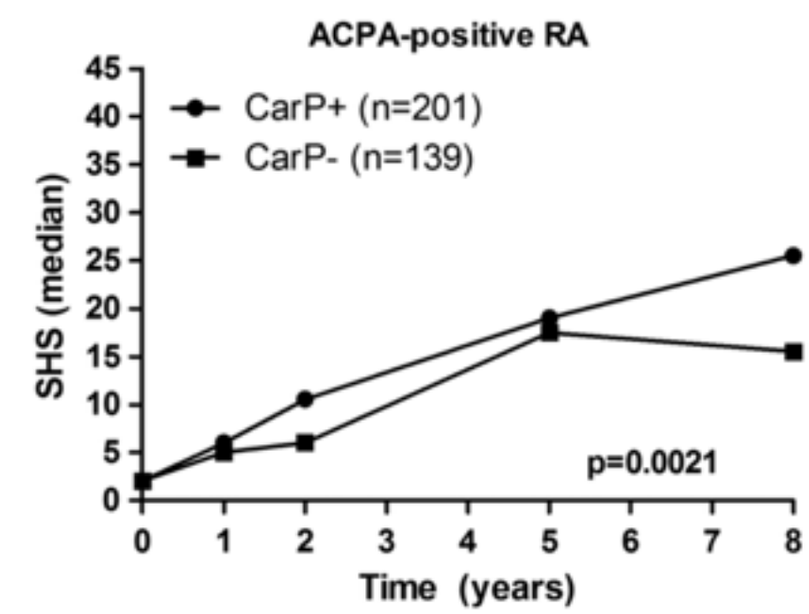
The association between anti-carbamylated protein (anti-CarP) antibodies and radiographic progression in early rheumatoid arthritis: a study exploring replication and the added value to ACPA and rheumatoid factor

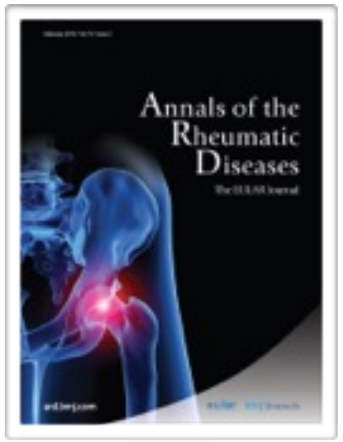
S Ajeganova,[1,2] H W van Steenbergen,[1] M K Verheul,[1] K Forslind,[3,4] I Hafström,[2] R E M Toes,[1] T W J Huizinga,[1] B Svensson,[5] L A Trouw,[1] A H M van der Helm-van Mil[1]

Ann Rheum Dis 2016







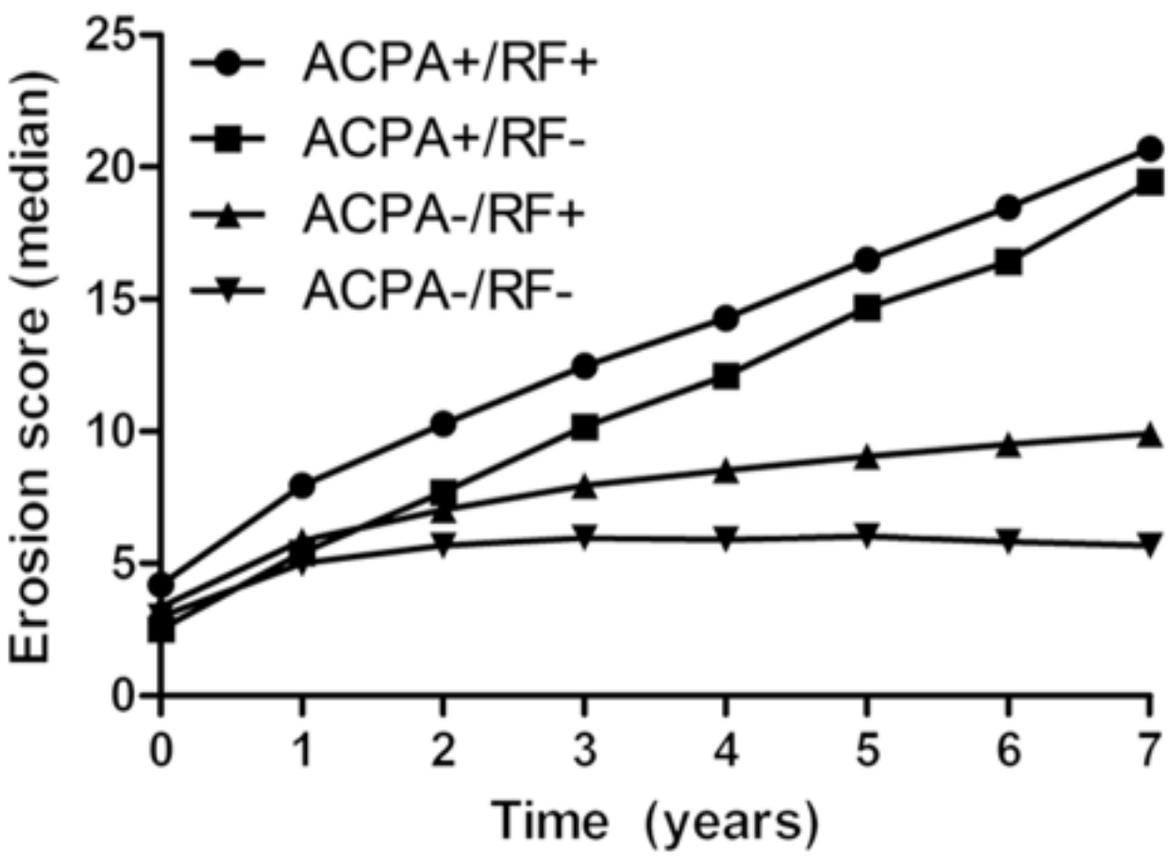


The effects of rheumatoid factor and anticitrullinated peptide antibodies on bone erosions in rheumatoid arthritis

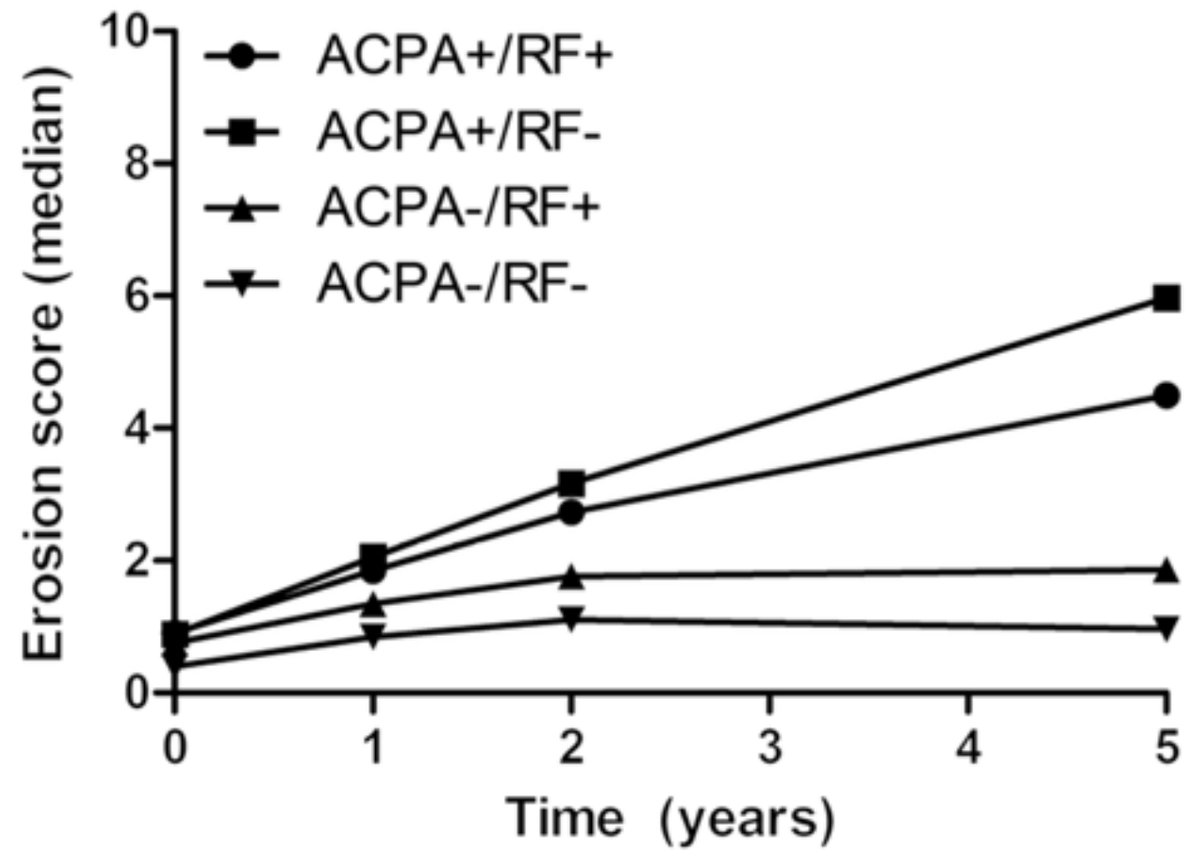
H W van Steenbergen,[1] S Ajeganova,[2] K Forslind,[3,4] B Svensson,[3]
A H M van der Helm-van Mil[1]

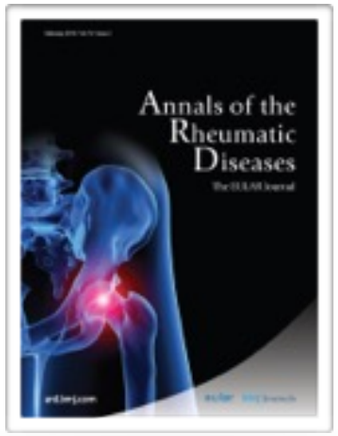
Ann Rheum Dis 2015

Leiden cohort



BARFOT cohort



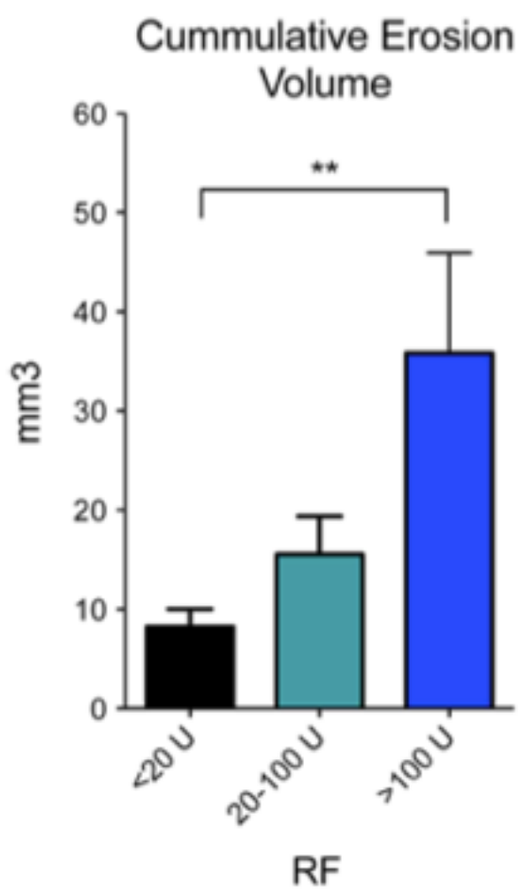


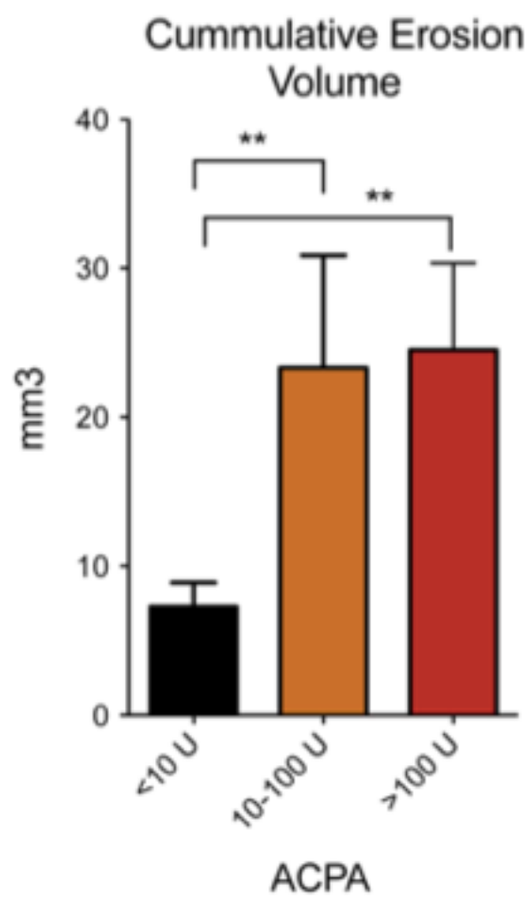
EXTENDED REPORT

Additive effect of anti-citrullinated protein antibodies and rheumatoid factor on bone erosions in patients with RA

Carolin Hecht,[1] Matthias Englbrecht,[1] Jürgen Rech,[1] Sarah Schmidt,[1] Elizabeth Araujo,[1] Klaus Engelke,[2] Stephanie Finzel,[1] Georg Schett[1]

Ann Rheum Dis 2014





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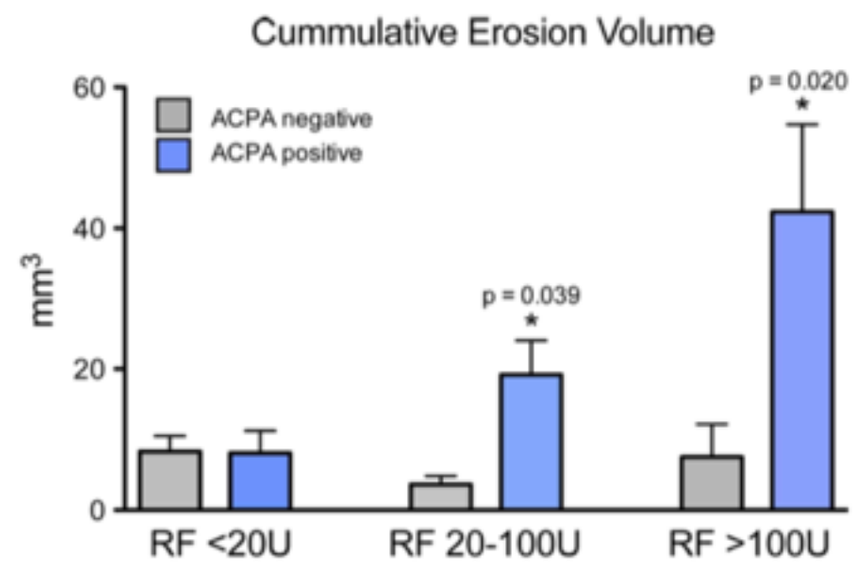
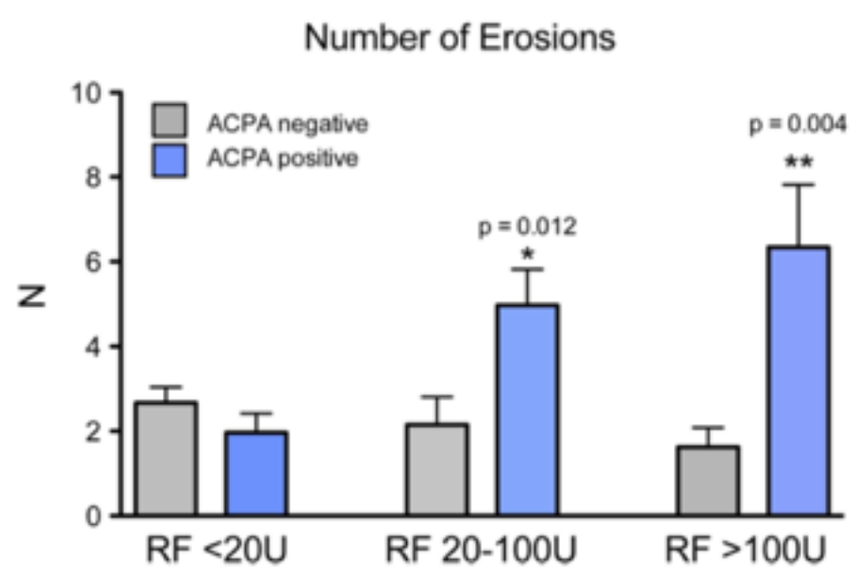


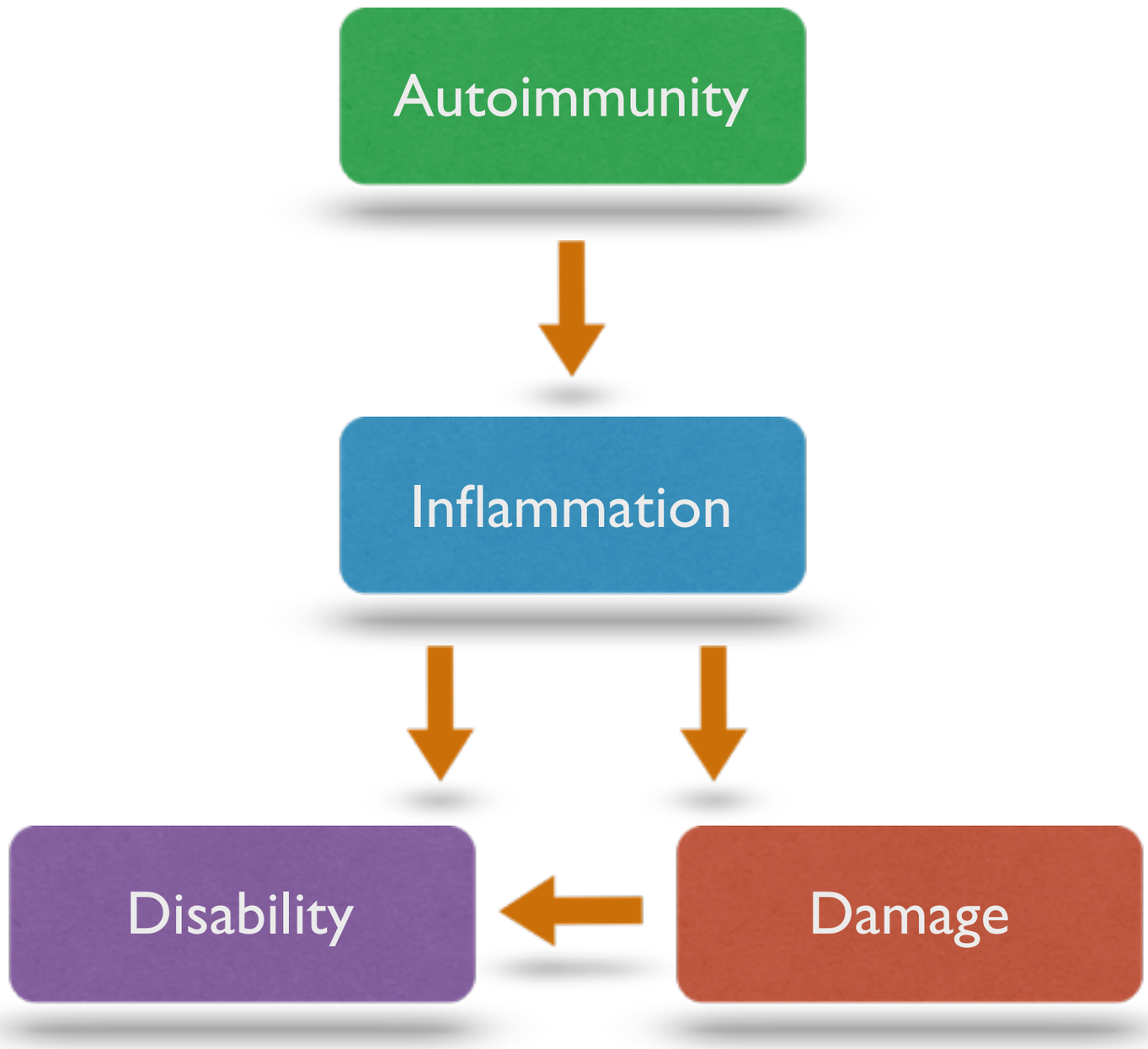


Talk composition

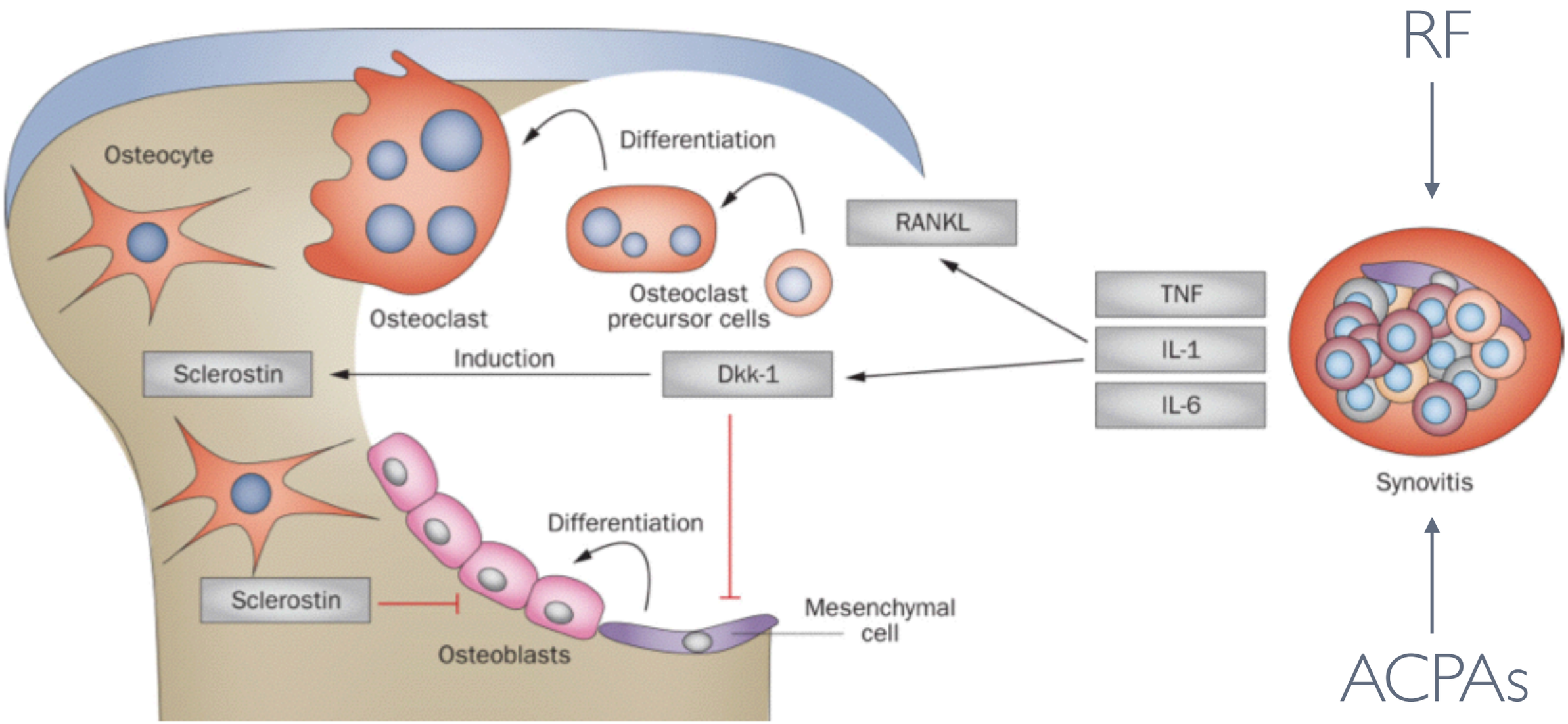
- The impact of autoantibodies on damage progression

- Mechanisms of bone erosion in RA

The RA paradigm



Pathogenesis of erosions: disruption of bone homeostasis by synovitis

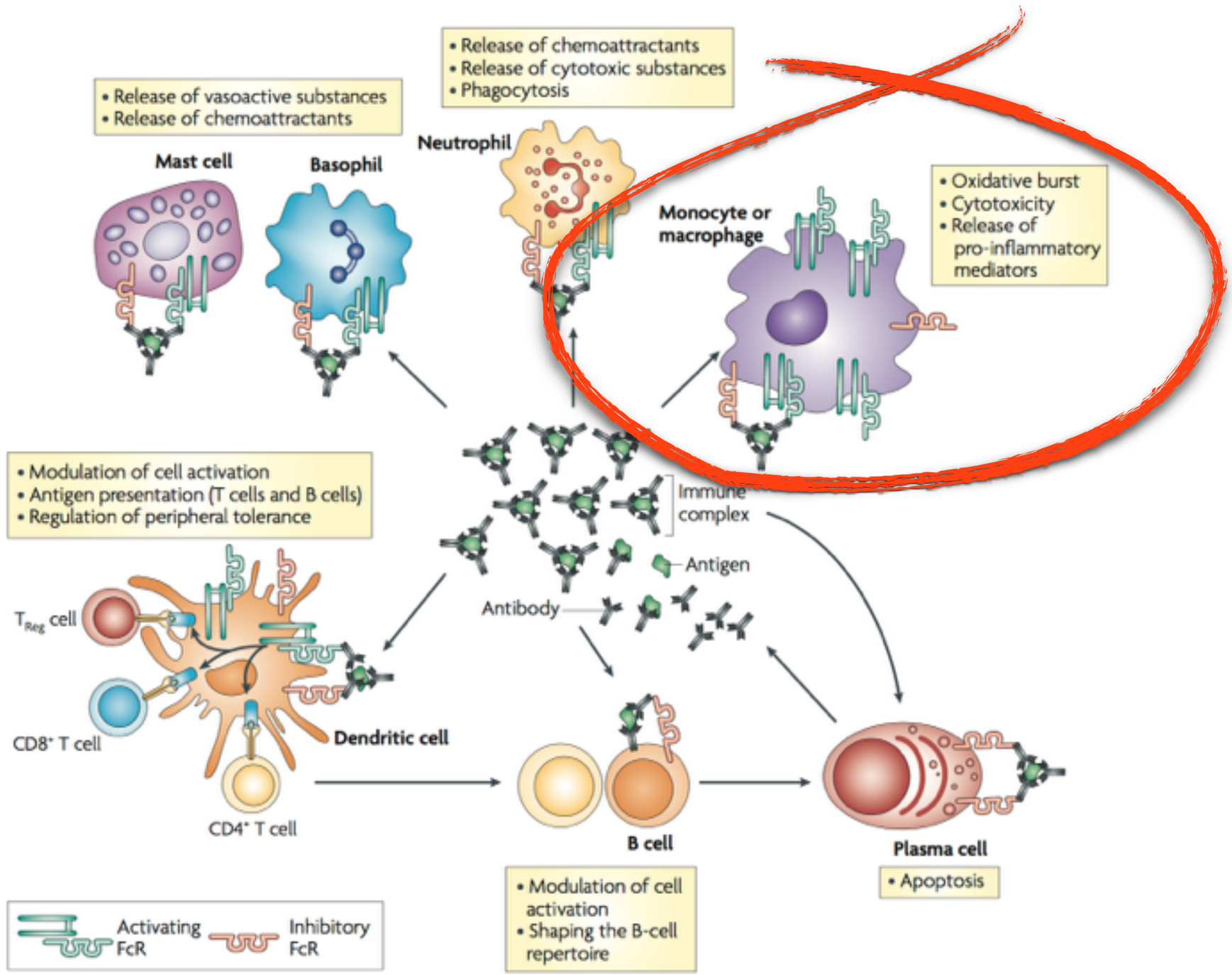


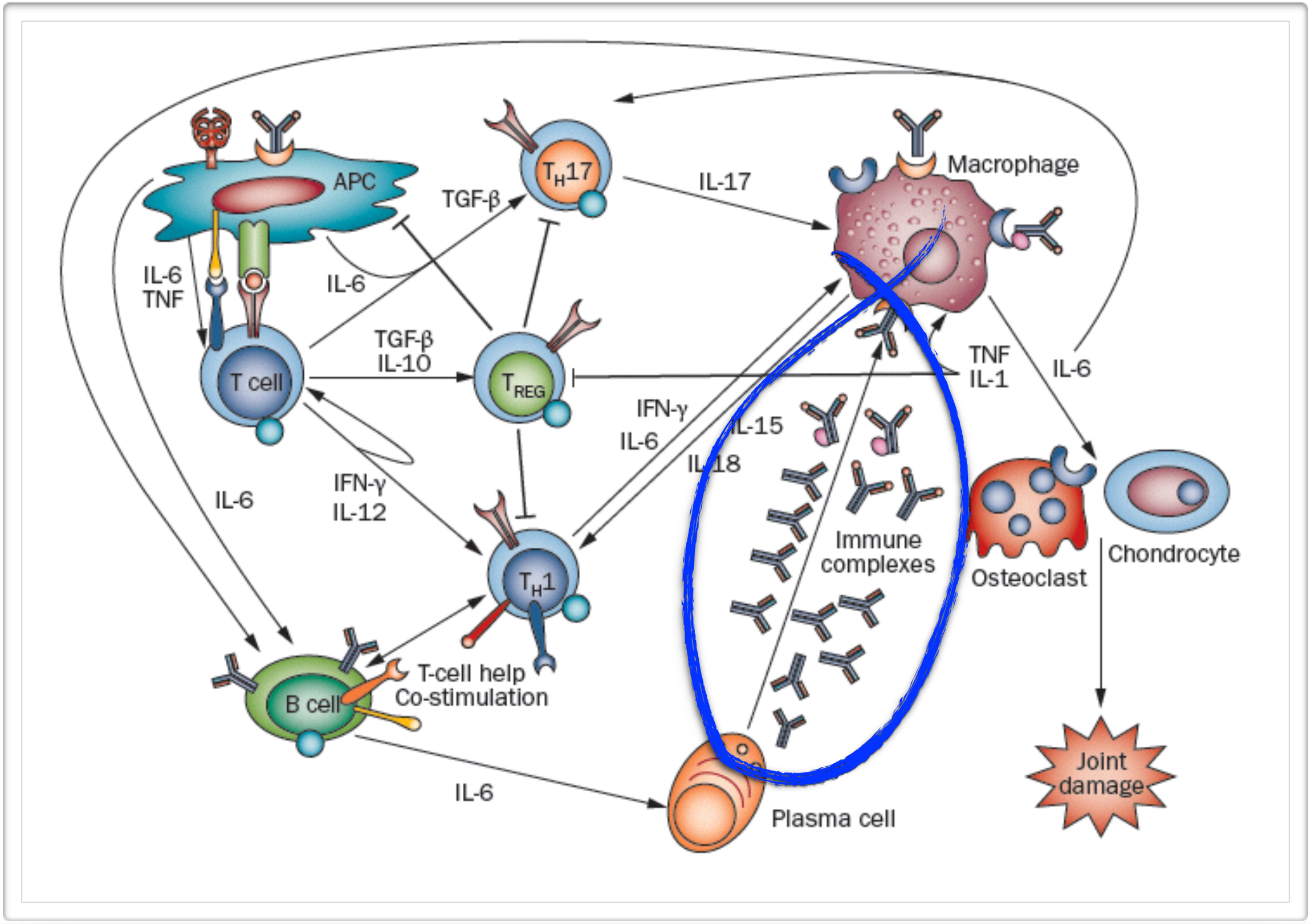
Schett G, et al. Nat Rev Rheumatol 2012

Fcγ receptors as regulators of immune responses

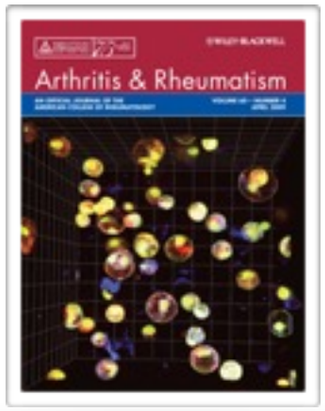
Falk Nimmerjahn and Jeffrey V. Ravetch‡*

Nat Rev Immunol 2008





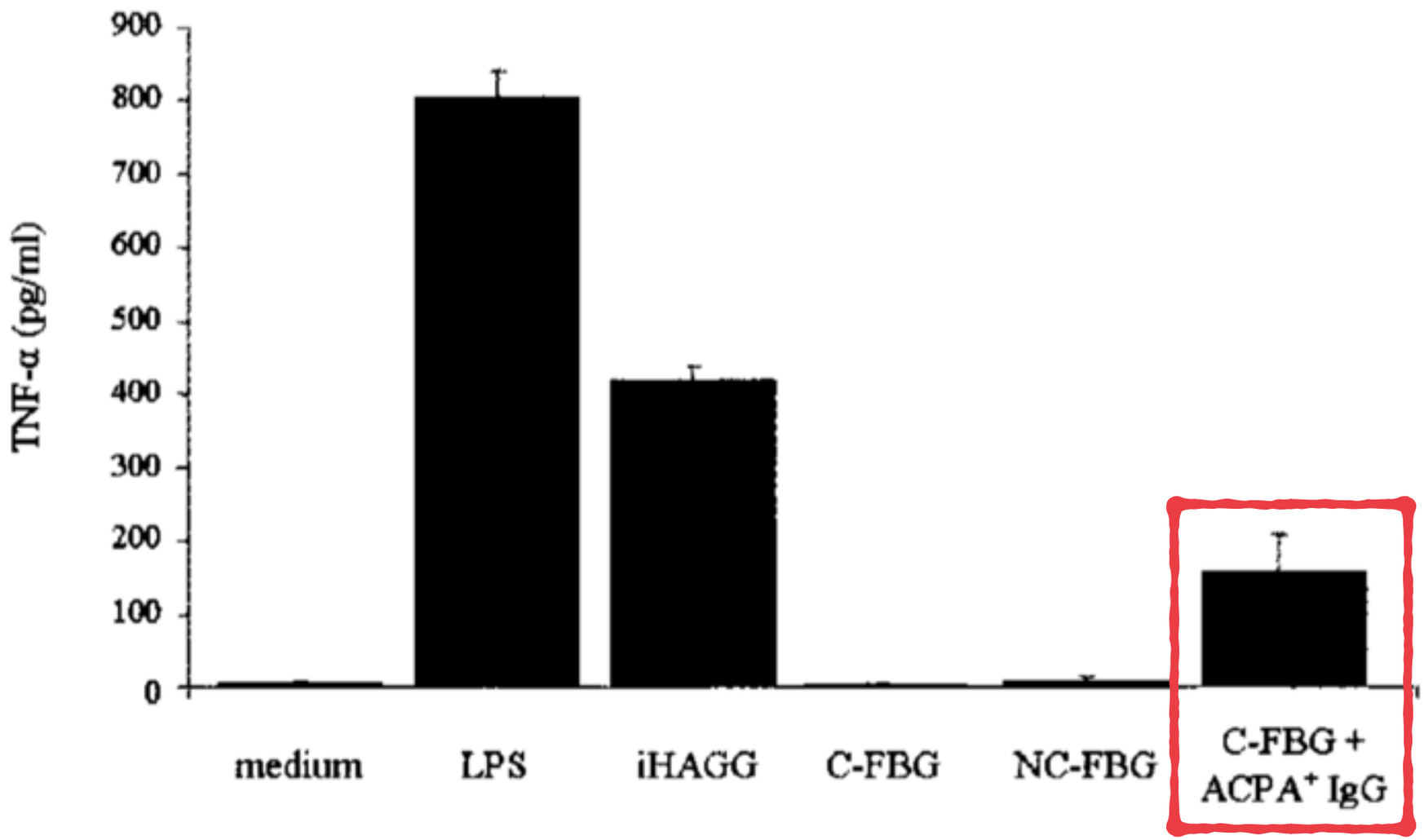
Smolen J, et al. Nat Rev Rheumatol 2012

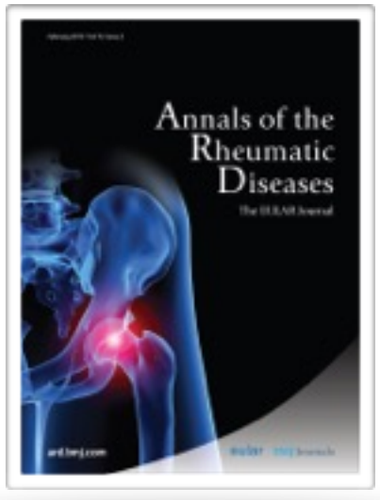


Induction of Macrophage Secretion of Tumor Necrosis Factor α Through Fcγ Receptor IIa Engagement by Rheumatoid Arthritis–Specific Autoantibodies to Citrullinated Proteins Complexed With Fibrinogen

Cyril Clavel,[1] Leonor Nogueira,[1] Laetitia Laurent,[2] Cristina Iobagiu,[1] Christian Vincent,[3] Mireille Sebbag,[2] and Guy Serre[1]

Arthritis Rheum 2008

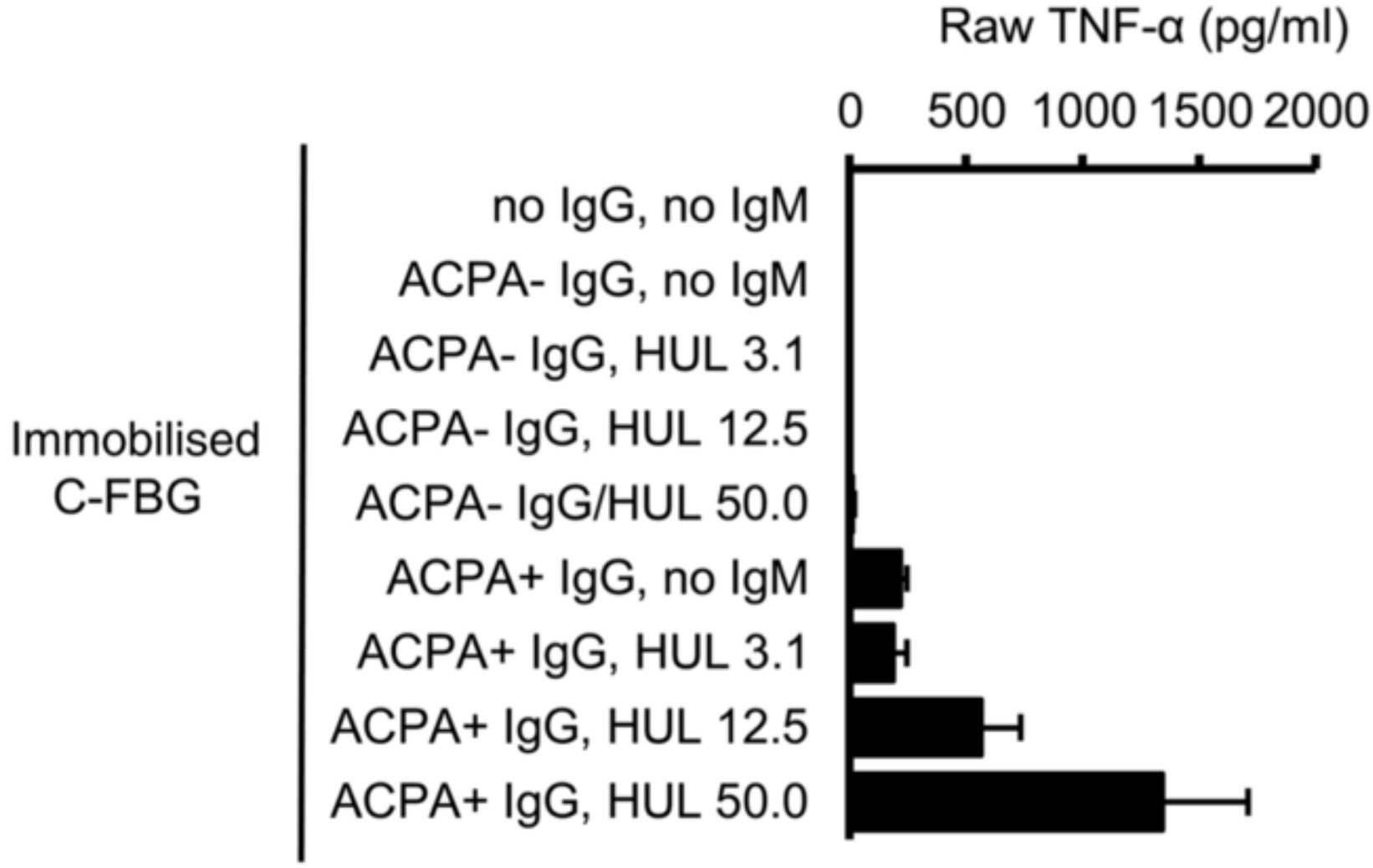




IgM rheumatoid factor amplifies the inflammatory response of macrophages induced by the rheumatoid arthritis-specific immune complexes containing anticitrullinated protein antibodies

Lætitia Laurent,[1,2,3] Florence Anquetil,[1,2,3,4] Cyril Clavel,[1,2,3,4] Ndiémé Ndongo-Thiam,[5] Géraldine Offer,[1,2,3] Pierre Miossec,[5] Jean-Louis Pasquali,[6] Mireille Sebbag,[1,2,3] Guy Serre[1,2,3,4]

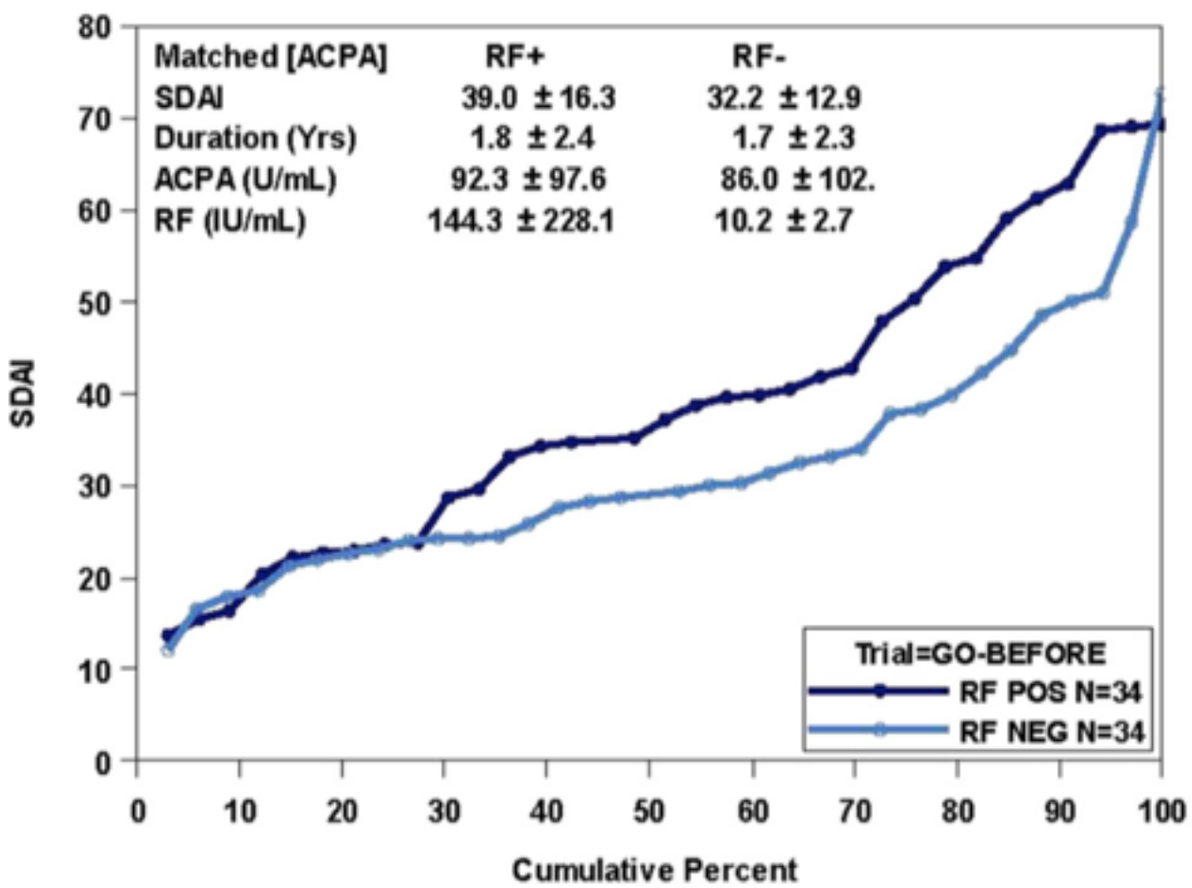
Ann Rheum Dis 2015

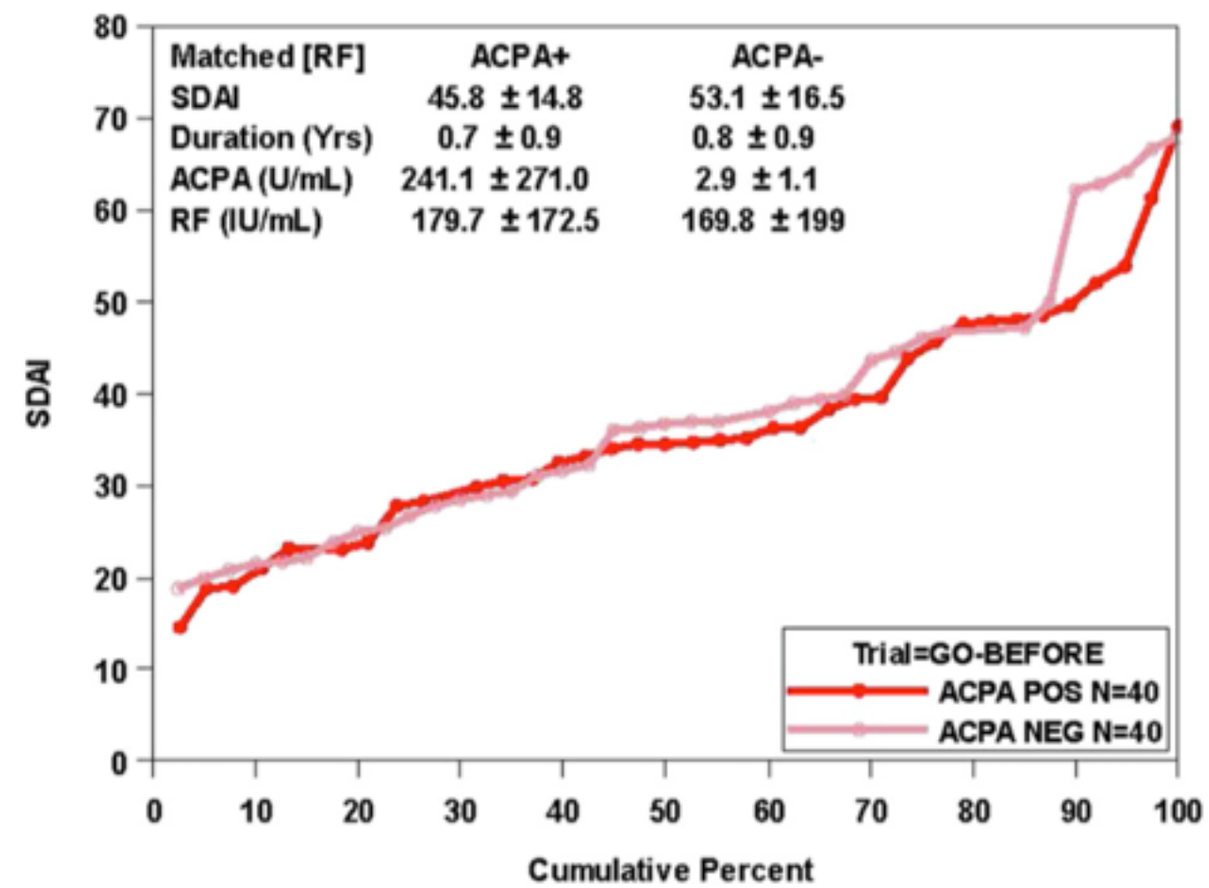


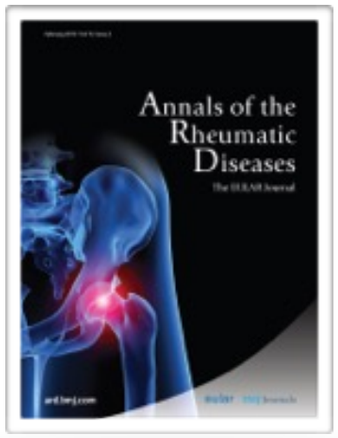
Rheumatoid factor, not antibodies against citrullinated proteins, is associated with baseline disease activity in rheumatoid arthritis clinical trials

Daniel Aletaha[1*], Farideh Alasti[1] and Josef S. Smolen[1,2]

Arthritis Res Ther 2015



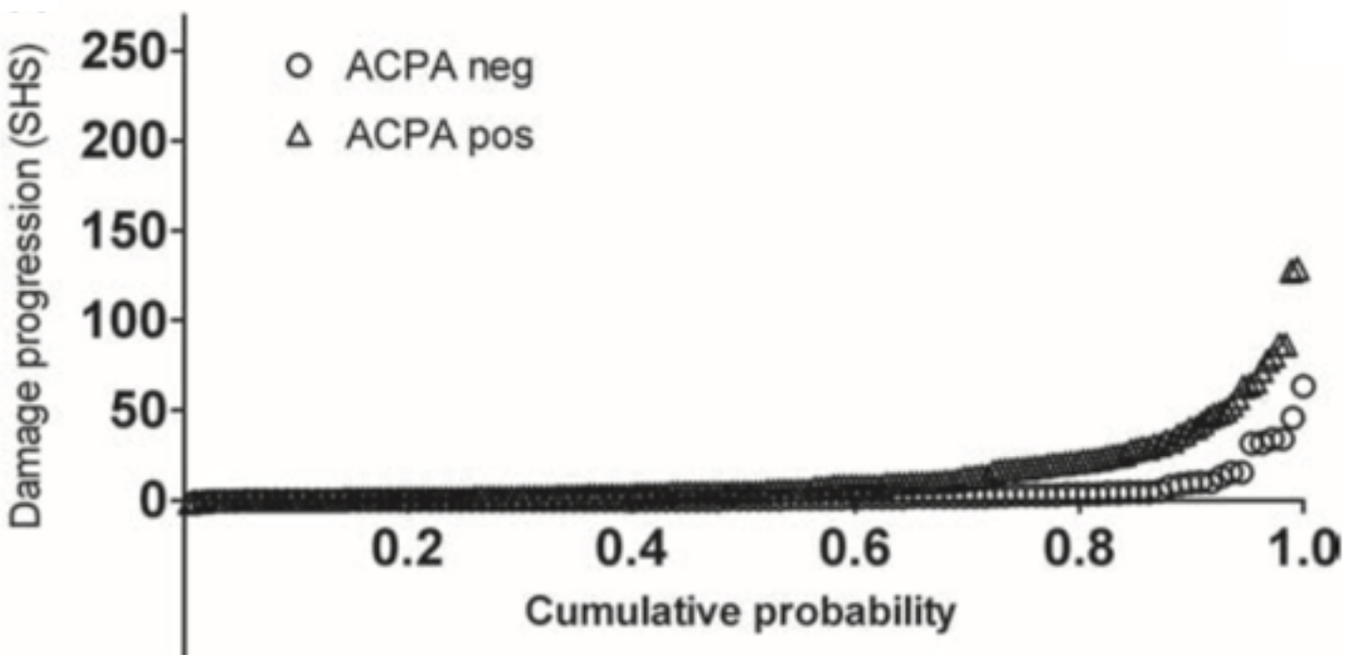


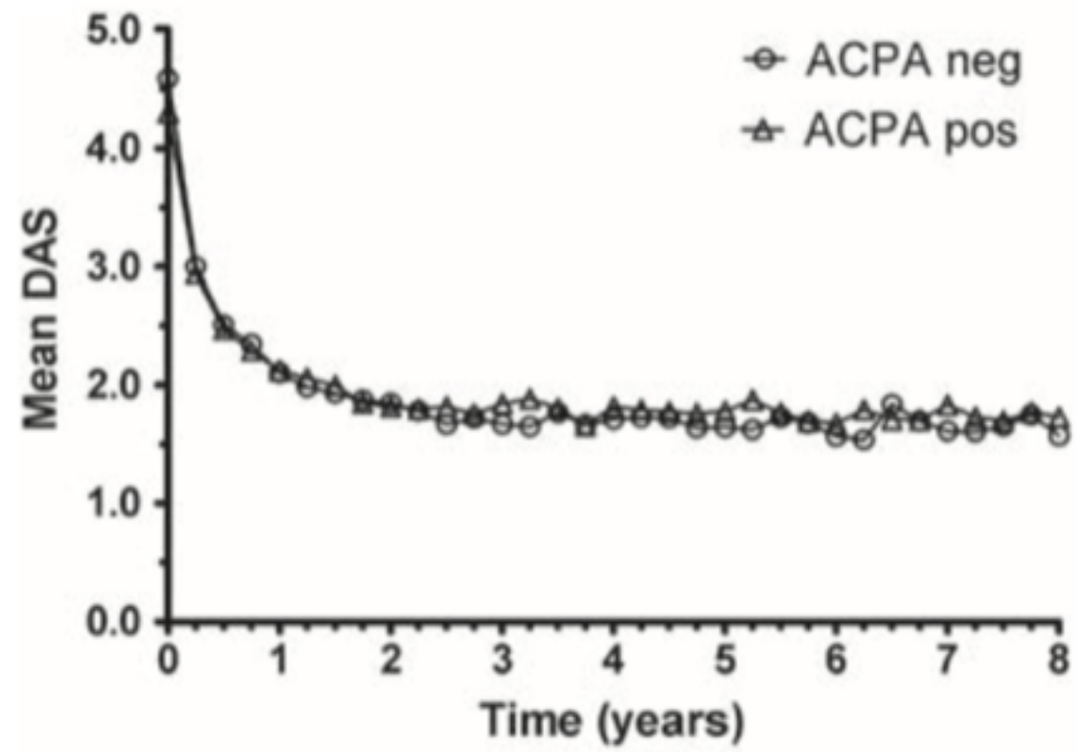


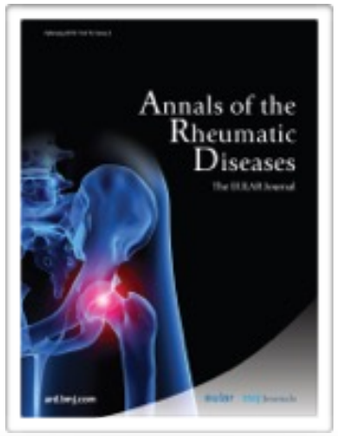
The association of treatment response and joint damage with ACPA-status in recent-onset RA: a subanalysis of the 8-year follow-up of the BeSt study

M van den Broek,[1] L Dirven,[1] NB Klarenbeek,[1] THE Molenaar,[2] KH Han,[3] PJSM Kerstens,[4] TWJ Huizinga,[1] BAC Dijkmans,[4,5] CF Allaart[1]

Ann Rheum Dis 2011





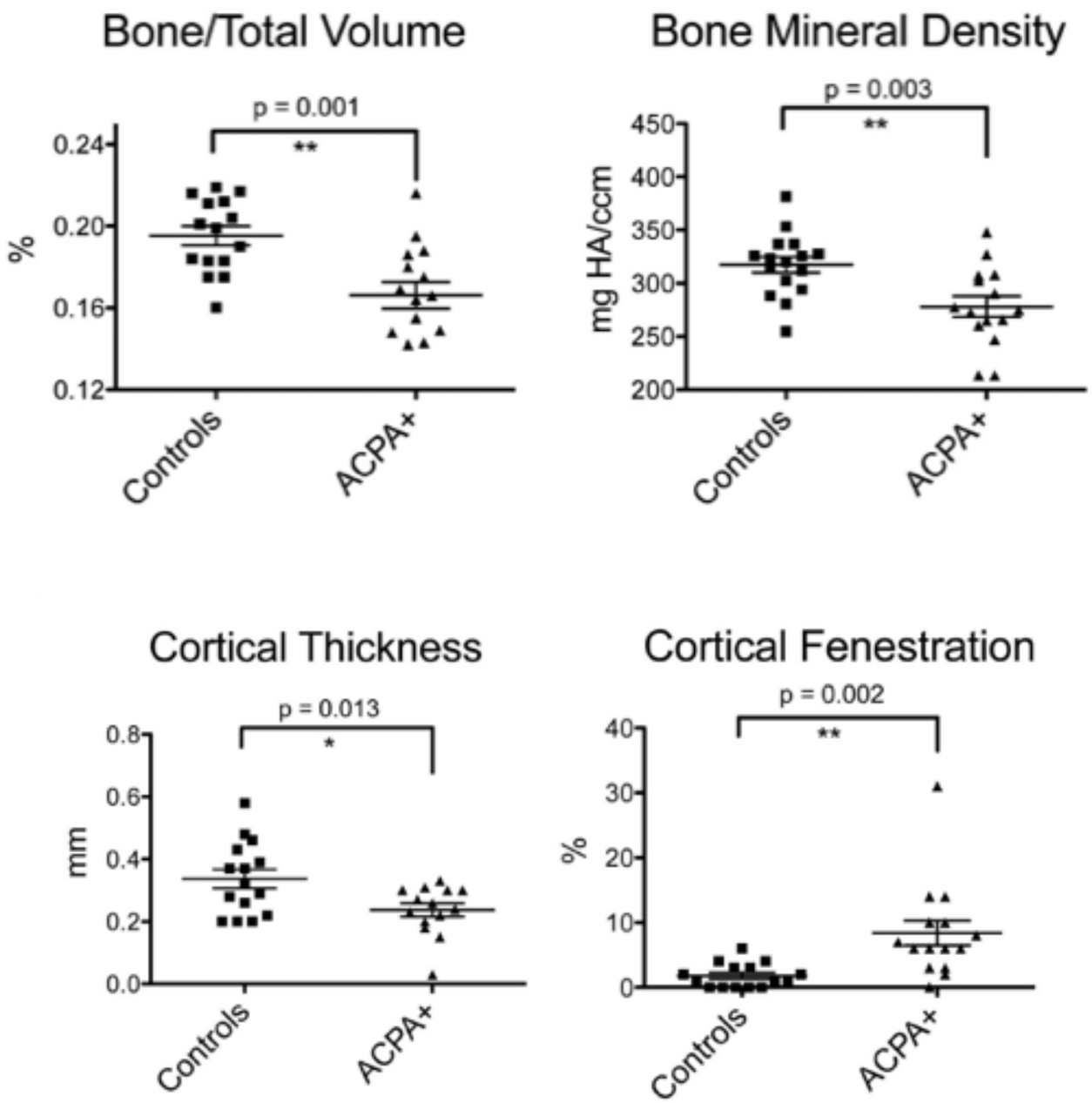


EXTENDED REPORT

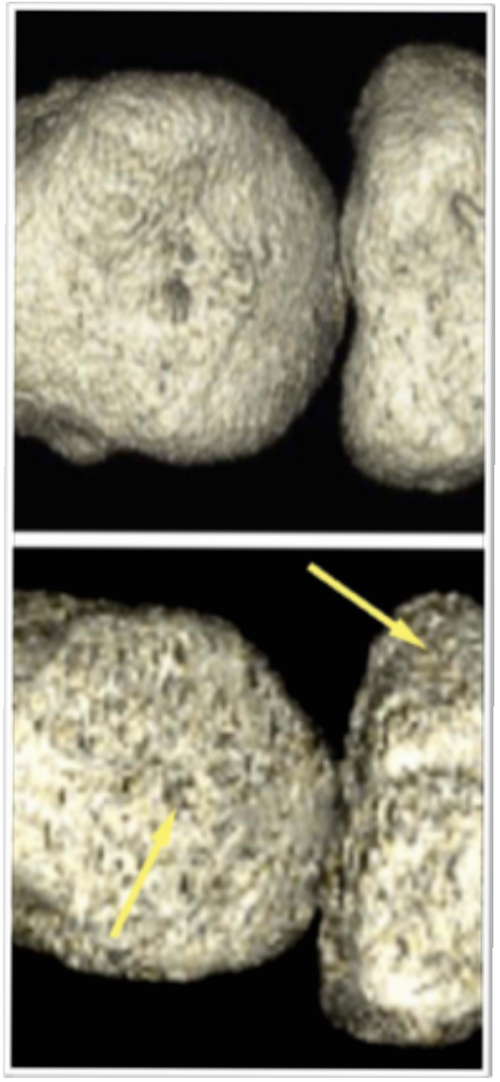
Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies

Arnd Kleyer,[1] Stephanie Finzel,[1] Jürgen Rech,[1] Bernhard Manger,[1] Manuel Krieter,[1] Francesca Faustini,[1] Elisabeth Araujo,[1] Axel J Hueber,[1] Ulrike Harre,[1] Klaus Engelke,[2] Georg Schett[1]

Ann Rheum Dis 2014



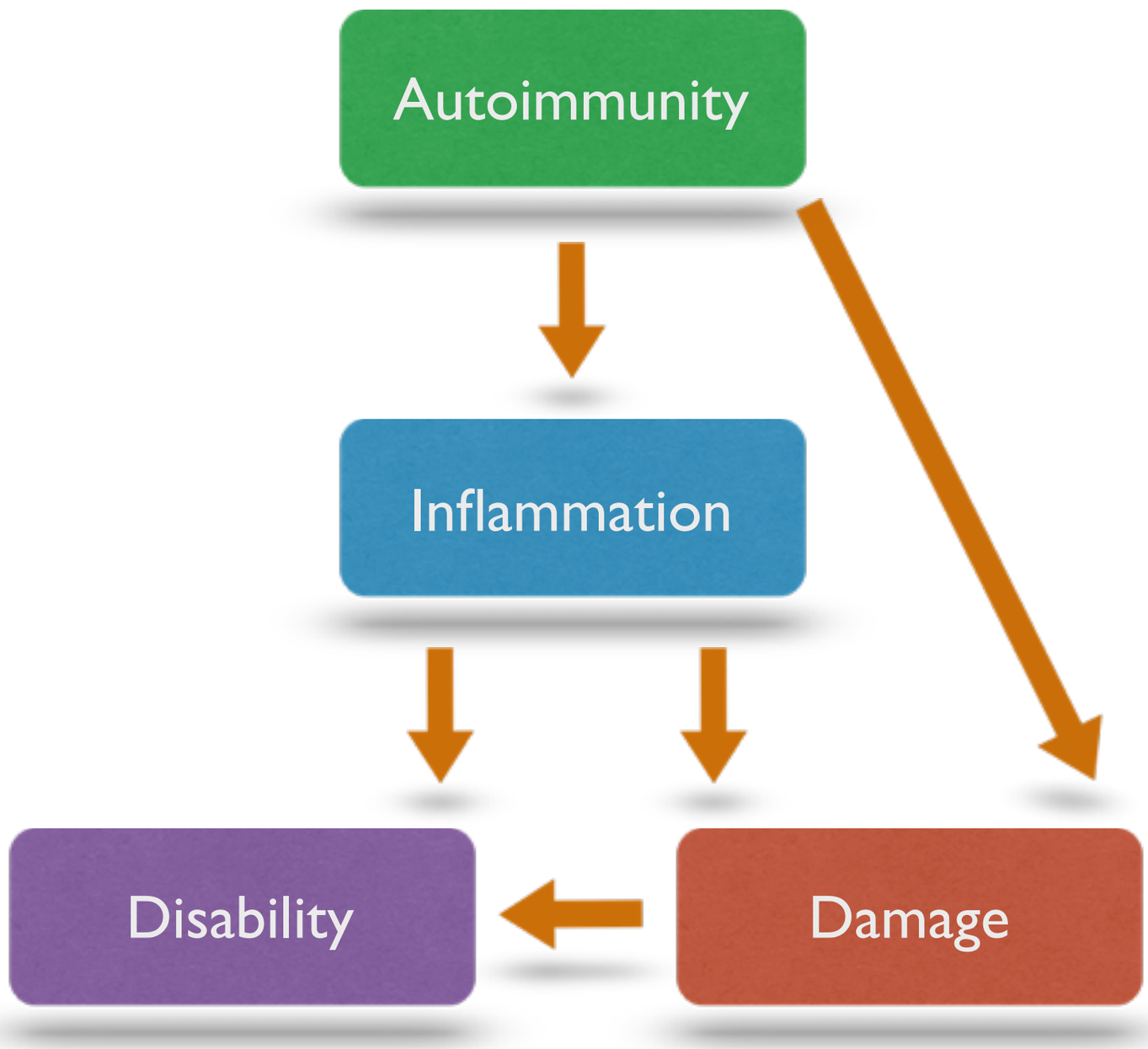
Micro CT



ACPA neg.

ACPA pos.

The RA paradigm



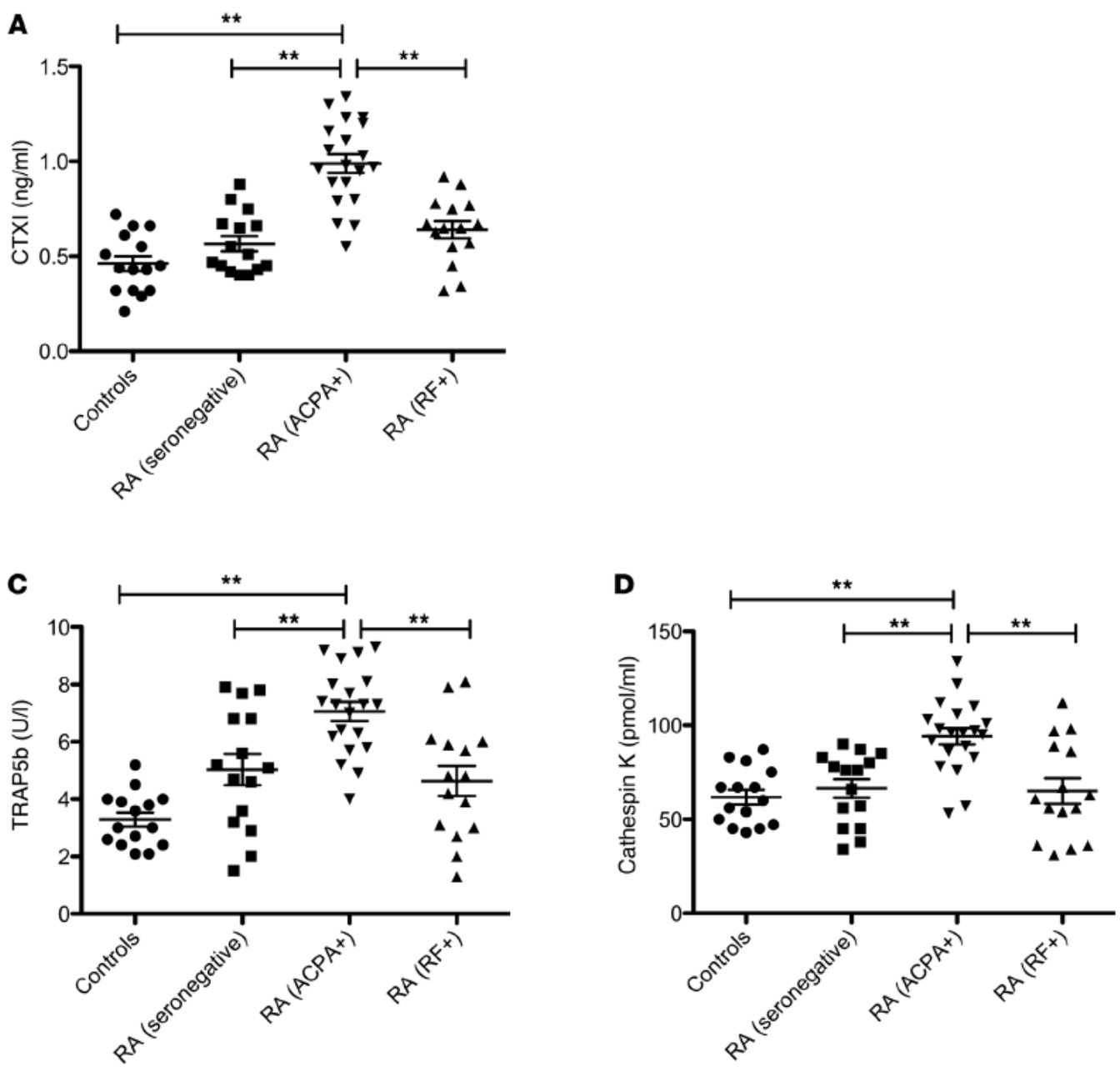
Talk composition

- The impact of autoantibodies on damage progression
- Mechanisms of bone erosion in RA
- Which link between autoimmunity and bone damage?

Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin

Ulrike Harre,[1] Dan Georgess,[2] Holger Bang,[3] Aline Bozec,[1] Roland Axmann,[1] Elena Ossipova,[4] Per-Johan Jakobsson,[4] Wolfgang Baum,[1] Falk Nimmerjahn,[5] Eszter Szarka,[6] Gabriella Sarmay,[6] Grit Krumbholz,[7] Elena Neumann,[7] Rene Toes,[8] Hans-Ulrich Scherer,[8] Anca Irinel Catrina,[3] Lars Klareskog,[3] Pierre Jurdic,[2] and Georg Schett[1]

J Clin Investig 2012

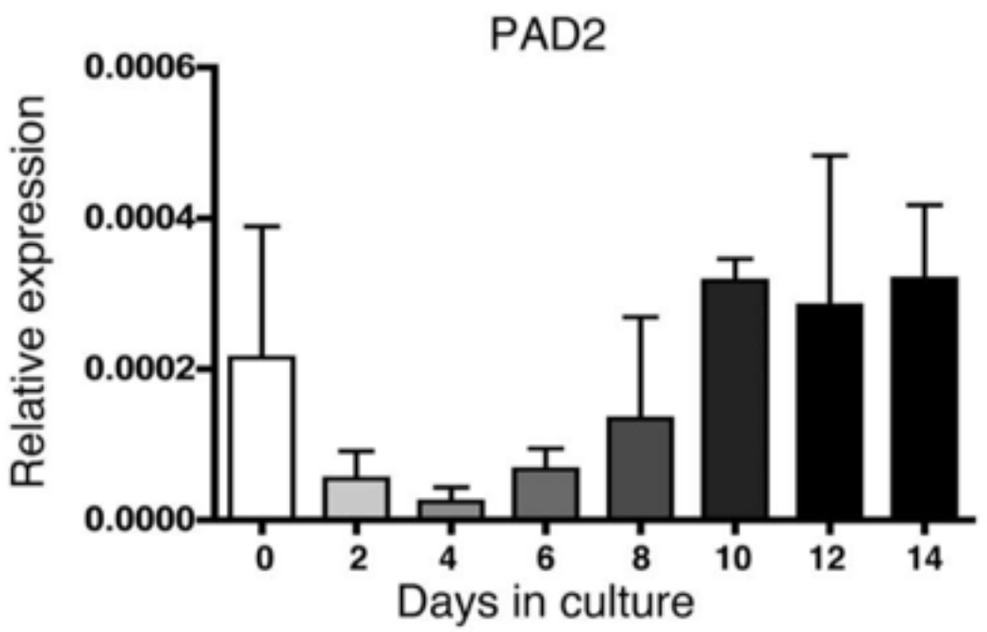


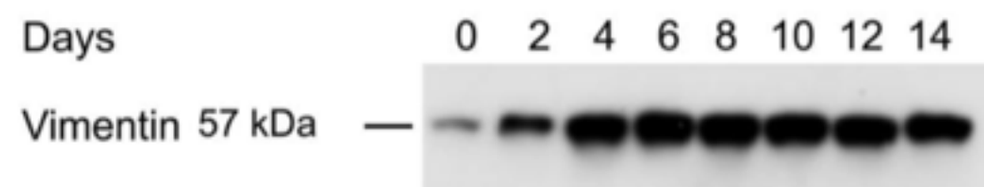
ACPAs are associated with increased **bone resorption** in patients with RA.

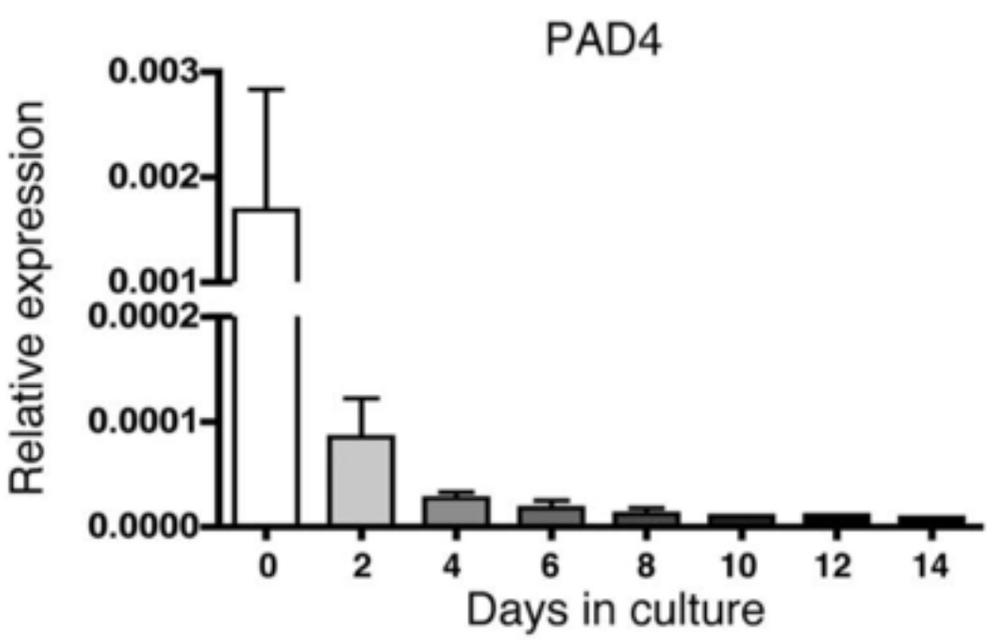
Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin

Ulrike Harre,[1] Dan Georgess,[2] Holger Bang,[3] Aline Bozec,[1] Roland Axmann,[1] Elena Ossipova,[4] Per-Johan Jakobsson,[4] Wolfgang Baum,[1] Falk Nimmerjahn,[5] Eszter Szarka,[6] Gabriella Sarmay,[6] Grit Krumbholz,[7] Elena Neumann,[7] Rene Toes,[8] Hans-Ulrich Scherer,[8] Anca Irinel Catrina,[3] Lars Klareskog,[3] Pierre Jurdic,[2] and Georg Schett[1]

J Clin Investig 2012





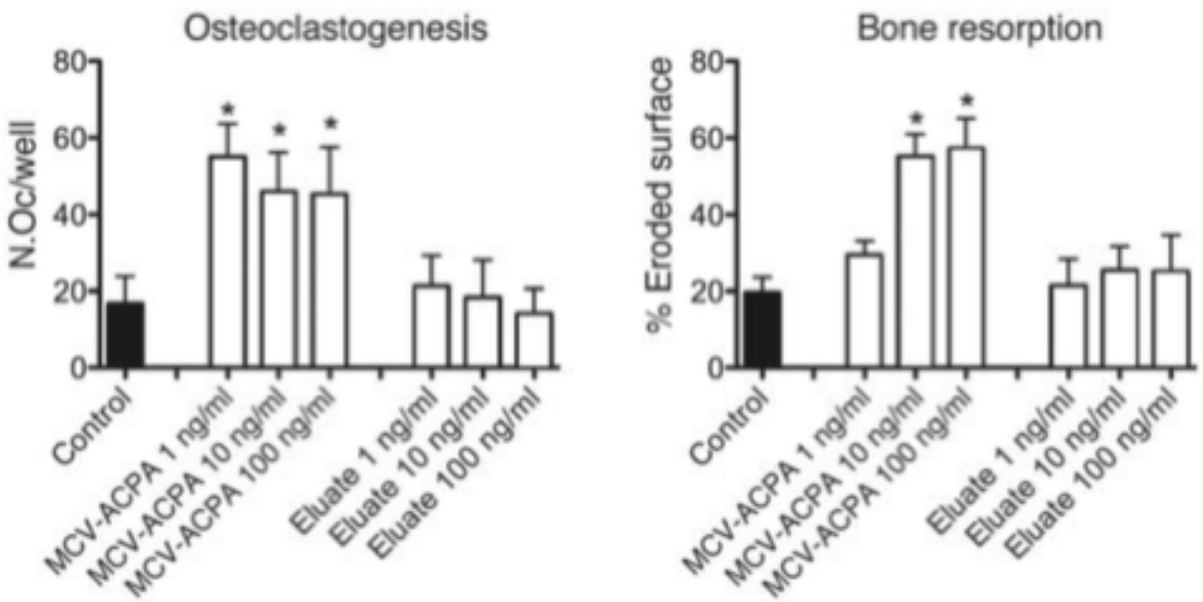


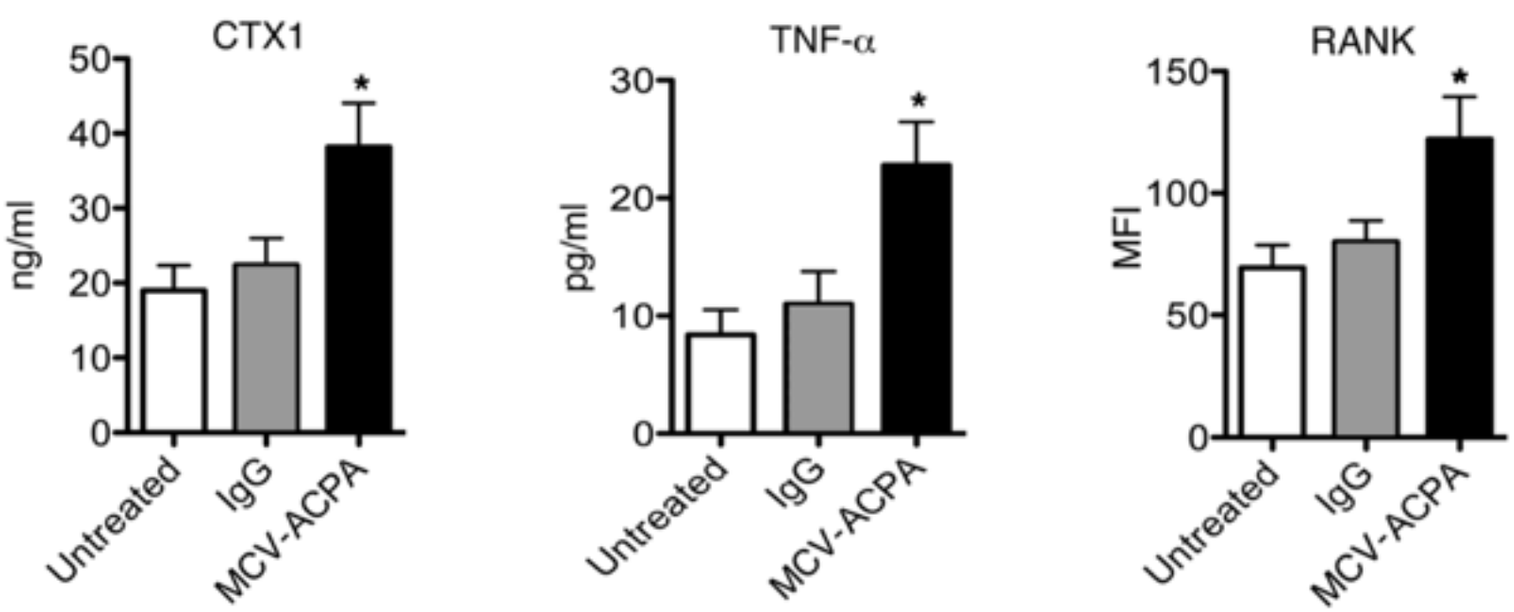
Osteoclasts express enzymes involved in citrullination (**PAD**) and show citrullination of **vimentin**

Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin

Ulrike Harre,[1] Dan Georgess,[2] Holger Bang,[3] Aline Bozec,[1] Roland Axmann,[1] Elena Ossipova,[4] Per-Johan Jakobsson,[4] Wolfgang Baum,[1] Falk Nimmerjahn,[5] Eszter Szarka,[6] Gabriella Sarmay,[6] Grit Krumbholz,[7] Elena Neumann,[7] Rene Toes,[8] Hans-Ulrich Scherer,[8] Anca Irinel Catrina,[3] Lars Klareskog,[3] Pierre Jurdic,[2] and Georg Schett[1]

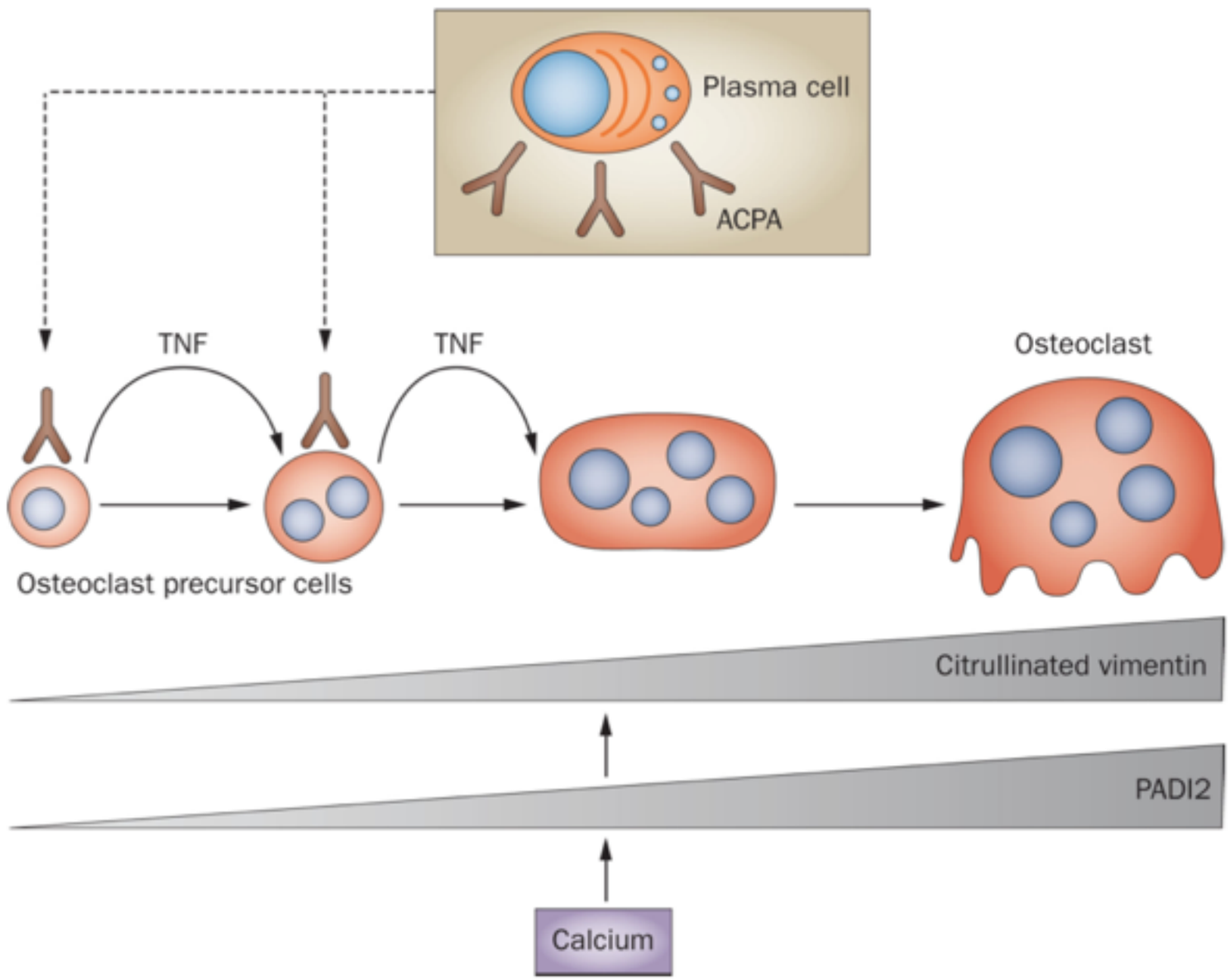
J Clin Investig 2012

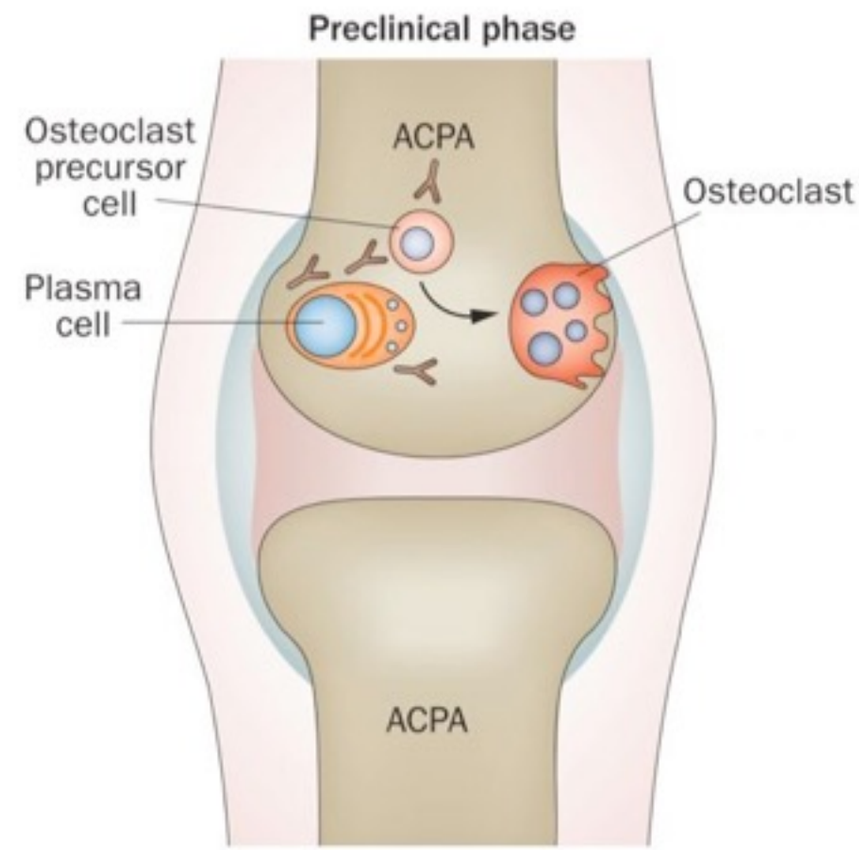




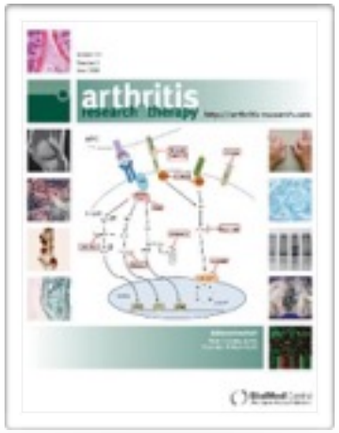
MCV-ACPAs induce osteoclastogenesis and **bone resorption**

The direct link between autoimmunity and damage: the role of ACPA





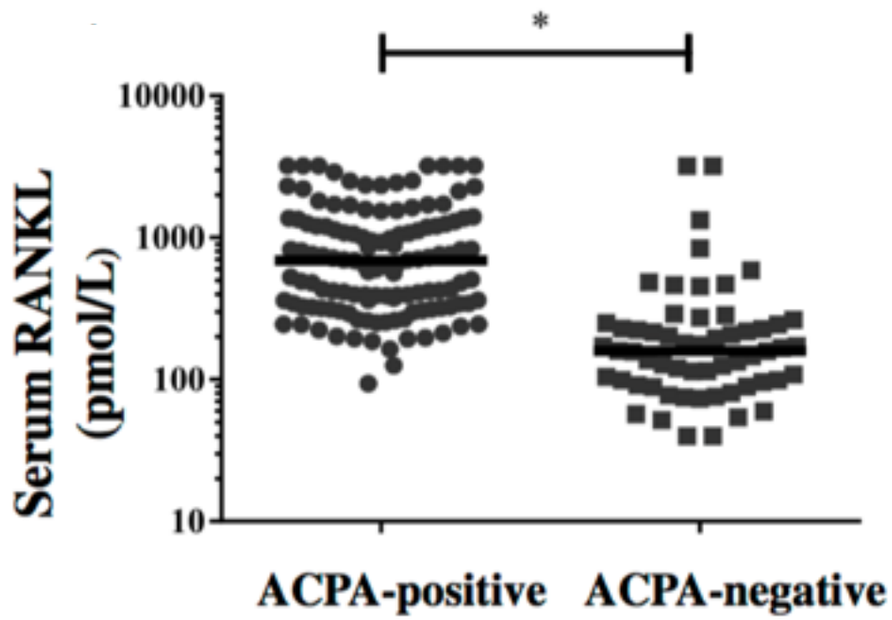
Schett G, et al. Nat Rev Rheumatol 2012

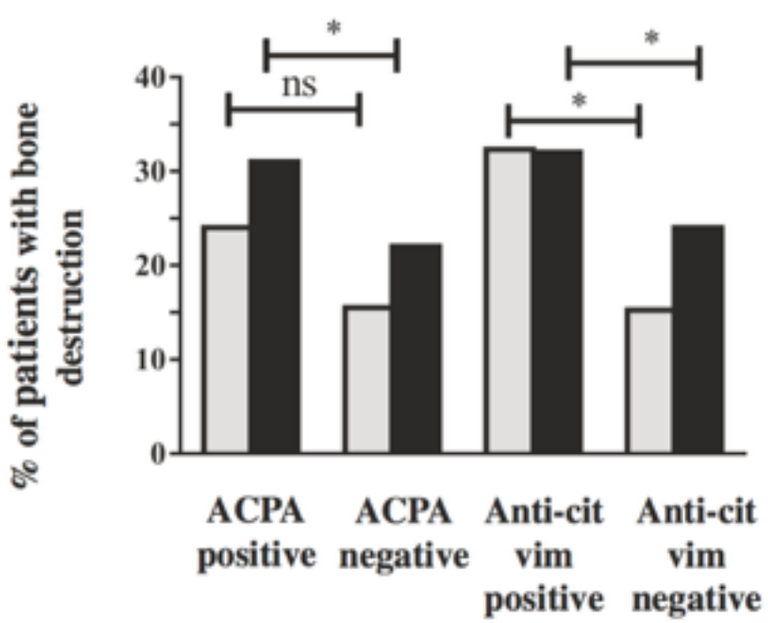


Serum RANKL levels associate with anti- citrullinated protein antibodies in early untreated rheumatoid arthritis and are modulated following methotrexate

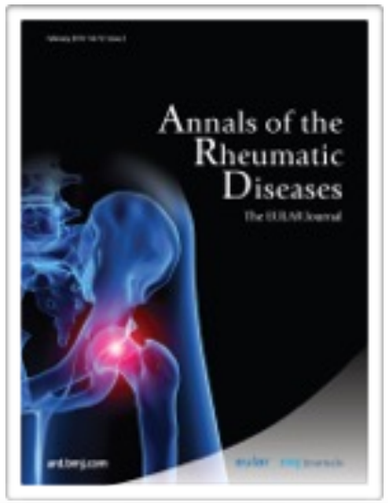
Aase Haj Hensvold[1*], Vijay Joshua[1], Wanying Li[2], Michaela Larkin[1], Ferhan Qureshi[2], Lena Israelsson[1], Leonid Padyukov[1], Karin Lundberg[1], Nadine Defranoux[2], Saedis Saevarsdottir[1,3] and Anca Irinel Catrina[1]

Arthritis Res Ther 2015





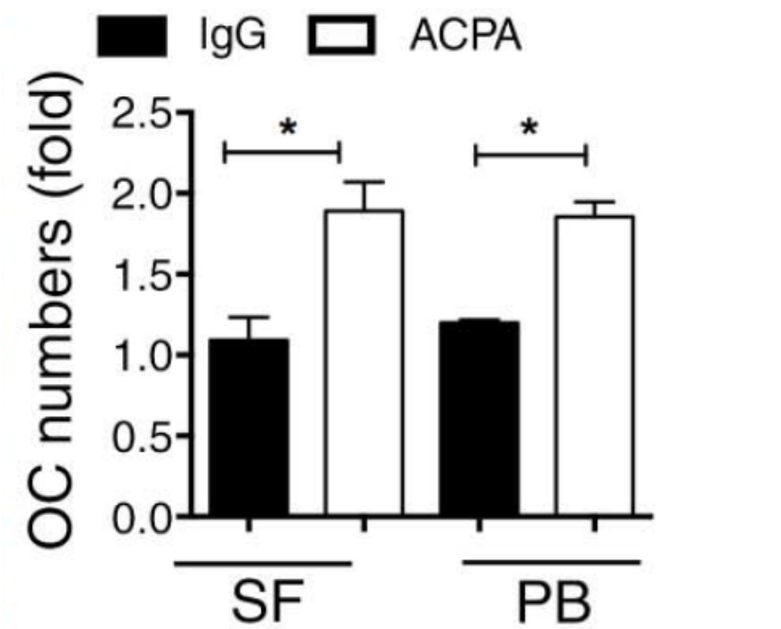
RANKL was elevated in **ACPA-positive** and in **anti-cit-vimentin-positive** RA patients and was associated with **bone erosions**

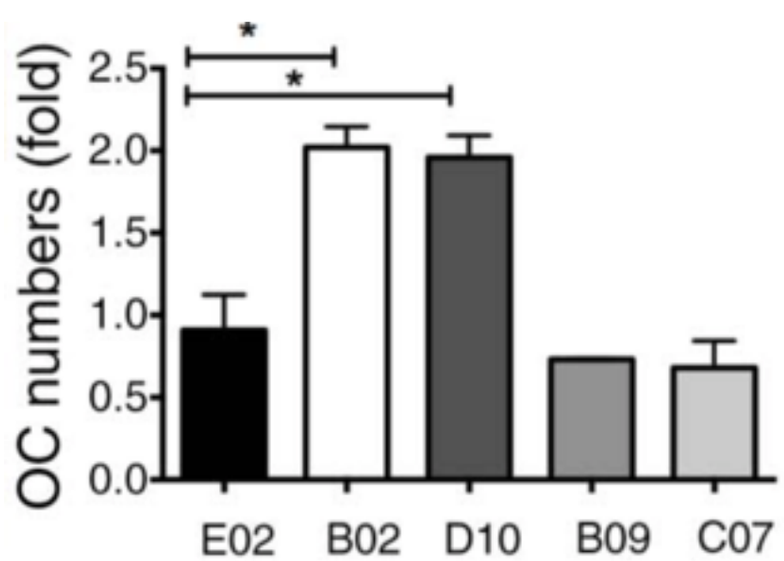


Identification of a novel chemokine-dependent molecular mechanism underlying rheumatoid arthritis-associated autoantibody-mediated bone loss

Akilan Krishnamurthy,[1] Vijay Joshua,[1] Aase Haj Hensvold,[1] Tao Jin,[2] Meng Sun,[1] Nancy Vivar,[1] A Jimmy Ytterberg,[1,3] Marianne Engström,[1] Cátia Fernandes-Cerqueira,[1] Khaled Amara,[1] Malin Magnusson,[2] Gustaf Wigerblad,[4] Jungo Kato,[4] Juan Miguel Jiménez-Andrade,[5] Kerry Tyson,[6] Stephen Rapecki,[6] Karin Lundberg,[1] Sergiu-Bogdan Catrina,[7] Per-Johan Jakobsson,[1] Camilla Svensson,[4] Vivianne Malmström,[1] Lars Klareskog,[1] Heidi Wähämaa,[1] Anca I Catrina[1]

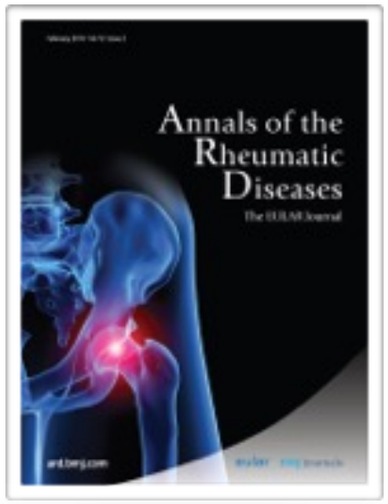
Ann Rheum Dis 2016





Polyclonal ACPAs from both synovial fluid and peripheral blood promote **osteoclastogenesis**

Epitope specificity of monoclonal ACPAs (**vimentin** and enolase) derived from single SF B-cells is essential for their capacity to **activate OCs**



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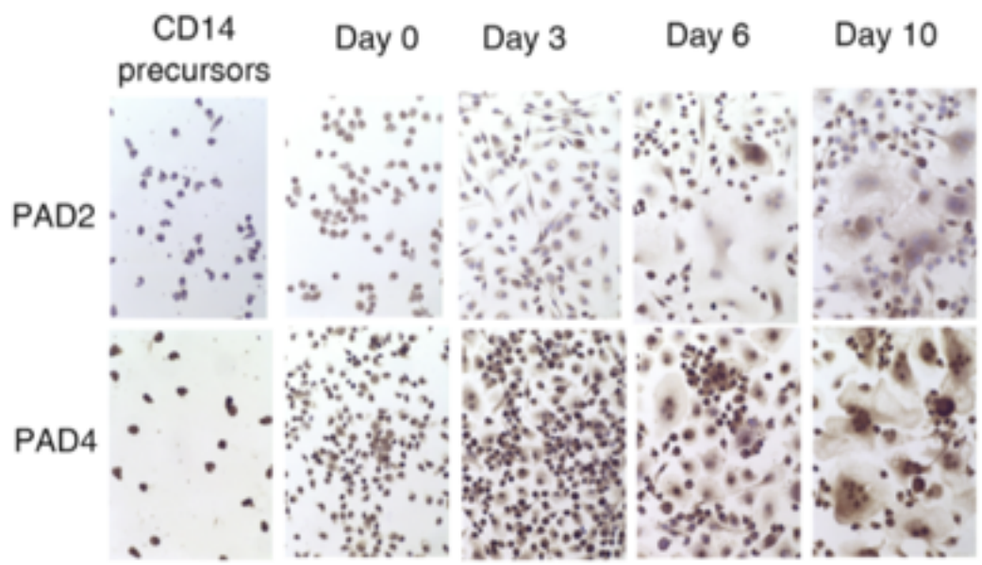
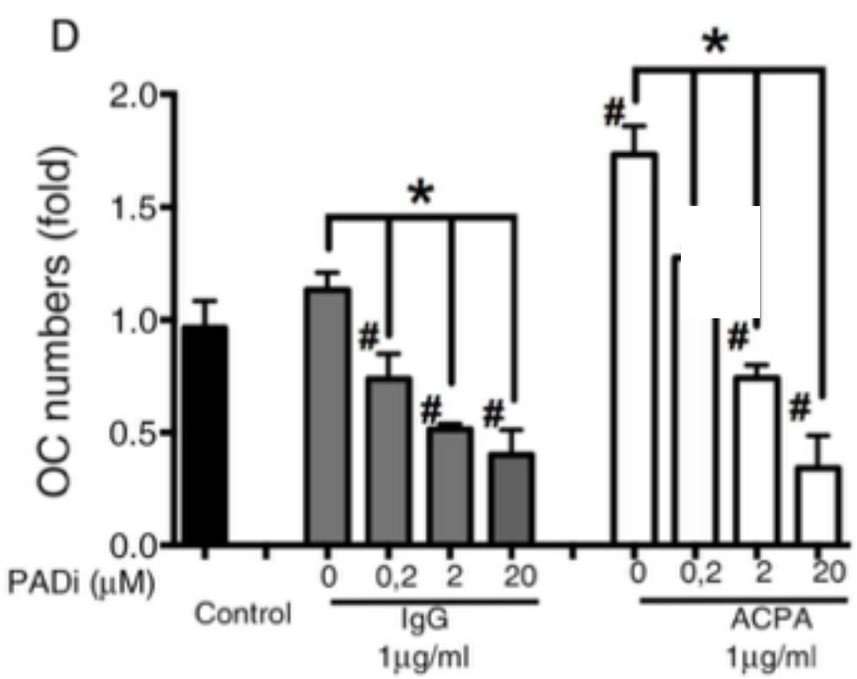
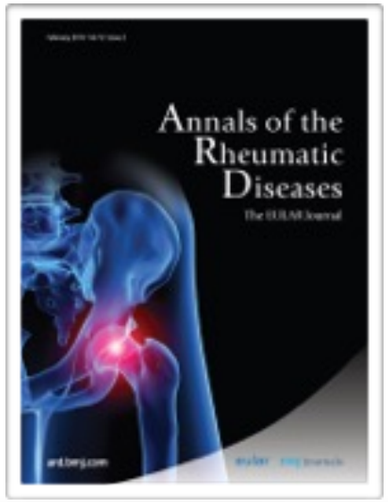


PAD **enzymes** and citrullination are essential for OC differentiation and **ACPA-induced activation**



Addition of a **PAD inhibitor** decreases ACPA-mediated osteoclastogenesis

EG Favalli, Istitut



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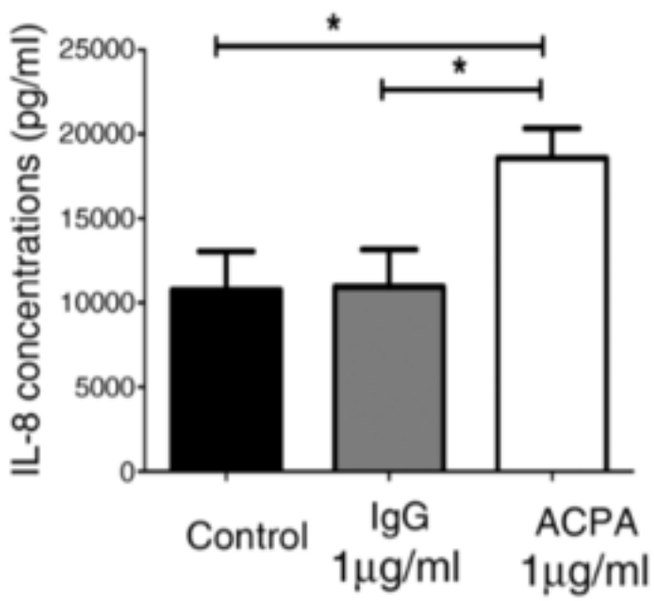
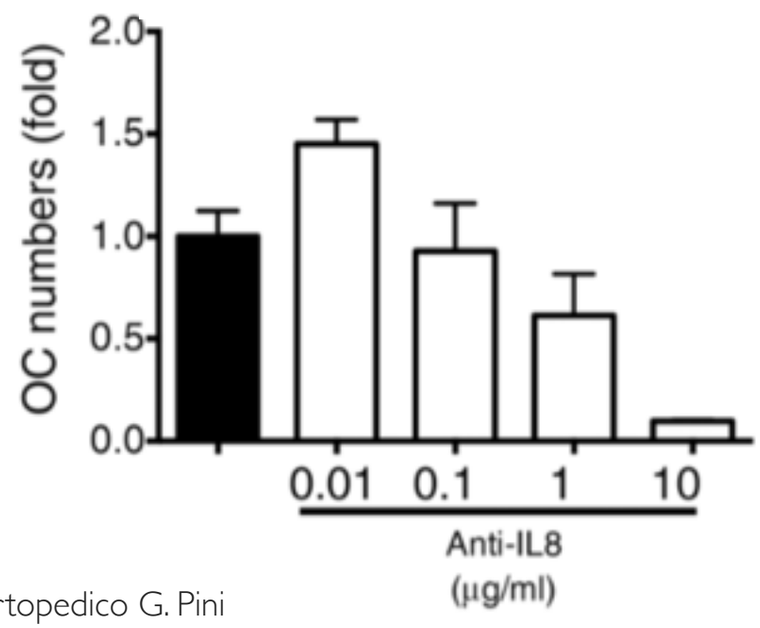
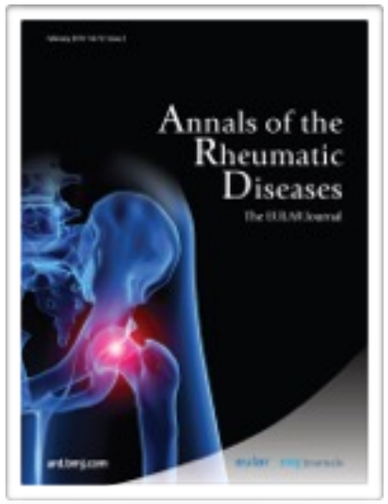




IL-8 is an essential mediator of **ACPA-driven** OC activation



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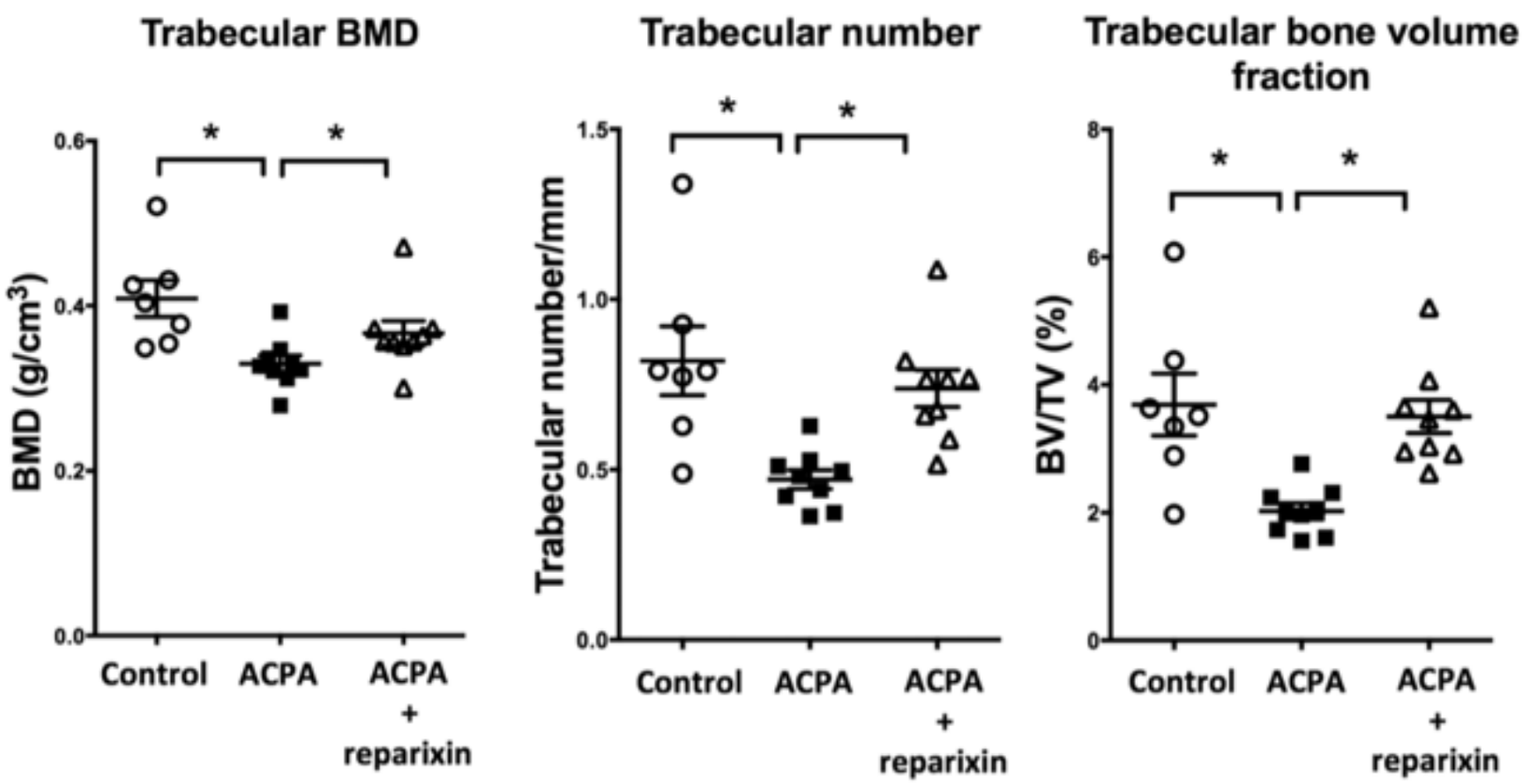
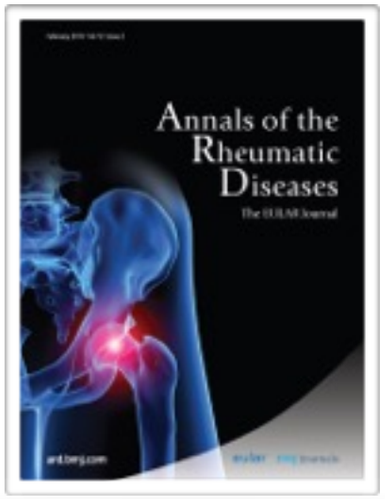


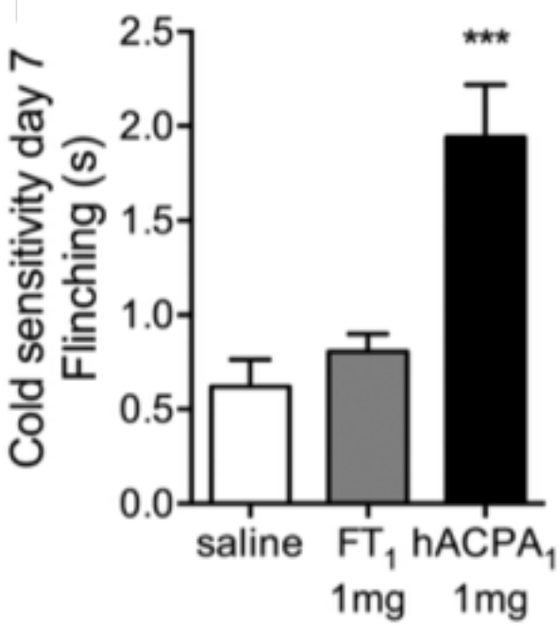
In vivo ACPA-induced systemic bone loss is **reversed by an IL-8 antagonist**

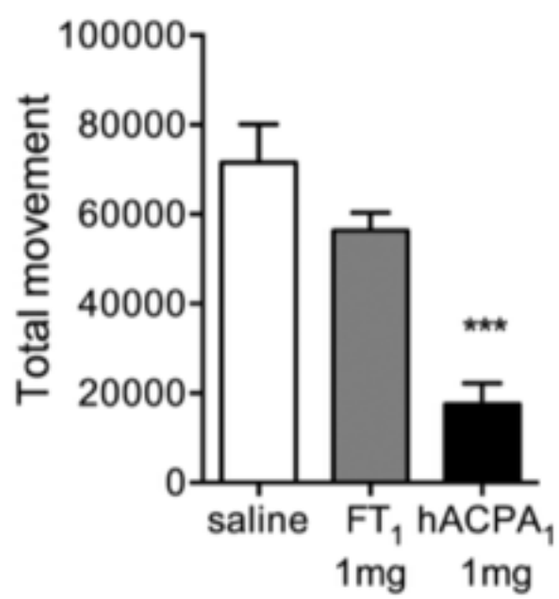


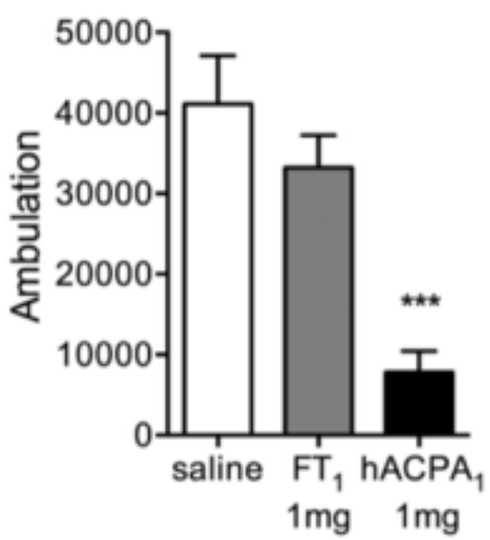
Autoantibodies to citrullinated proteins induce joint pain independent of inflammation via a chemokine-dependent mechanism

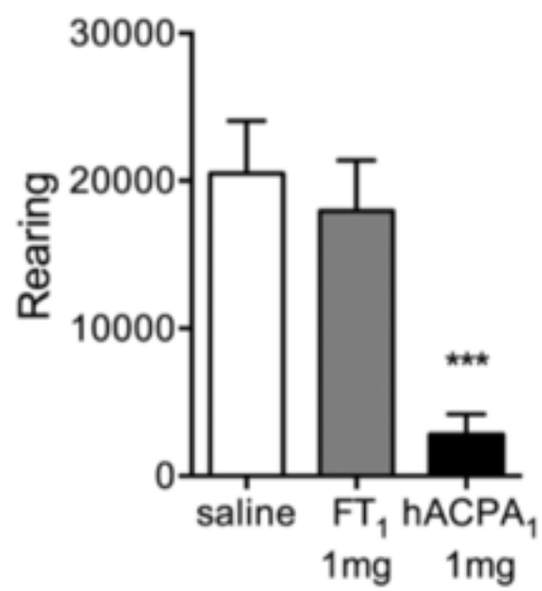
Gustaf Wigerblad,[1] Duygu B Bas,[1] Cátia Fernades-Cerqueira,[2] Akilan Krishnamurthy,[2] Kutty Selva Nandakumar,[3] Katarzyna Rogoz,[1] Jungo Kato,[1] Katalin Sandor,[1] Jie Su,[1] Juan Miguel Jimenez–Andrade,[4] Anja Finn,[1] Alex Bersellini Farinotti,[1] Khaled Amara,[2] Karin Lundberg,[2] Rikard Holmdahl,[3] Per-Johan Jakobsson,[2] Vivianne Malmström,[2] Anca I Catrina,[2] Lars Klareskog,[2] Camilla I Svensson[1]

Ann Rheum Dis 2015

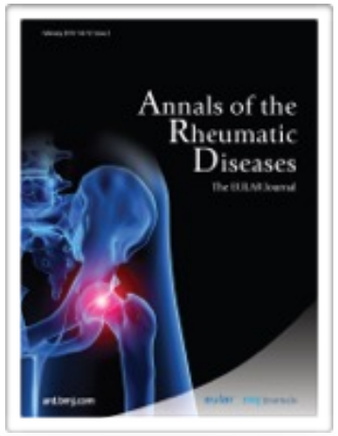








IL-8, released from **osteoclasts** in an autoantibody-dependent manner, produces **pain** by activating **sensory neurons**.



Bone loss, pain and inflammation: three faces of ACPA in RA pathogenesis

Jeremy Sokolove,[1] David Pisetsky[2]

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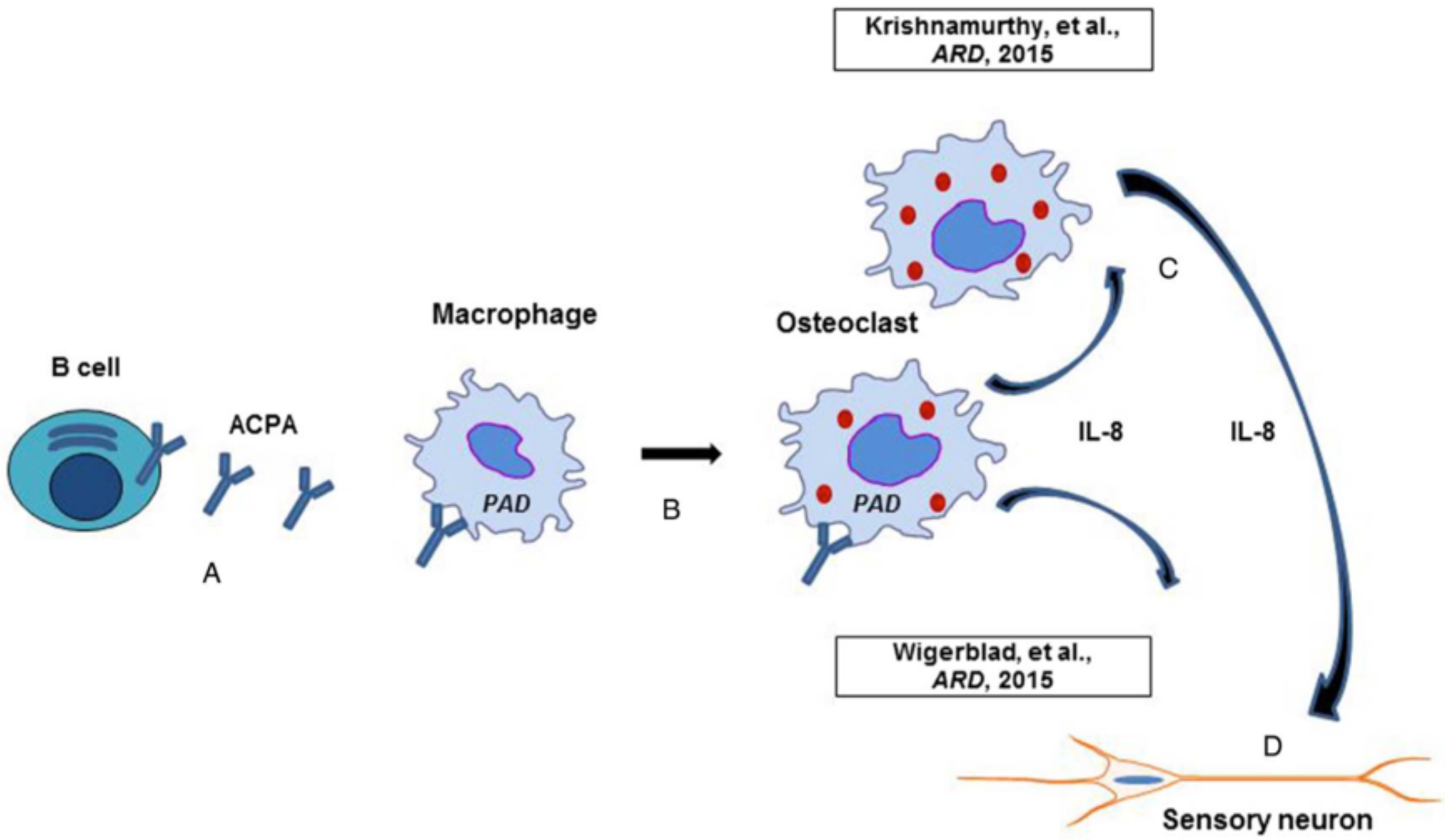


Talk composition

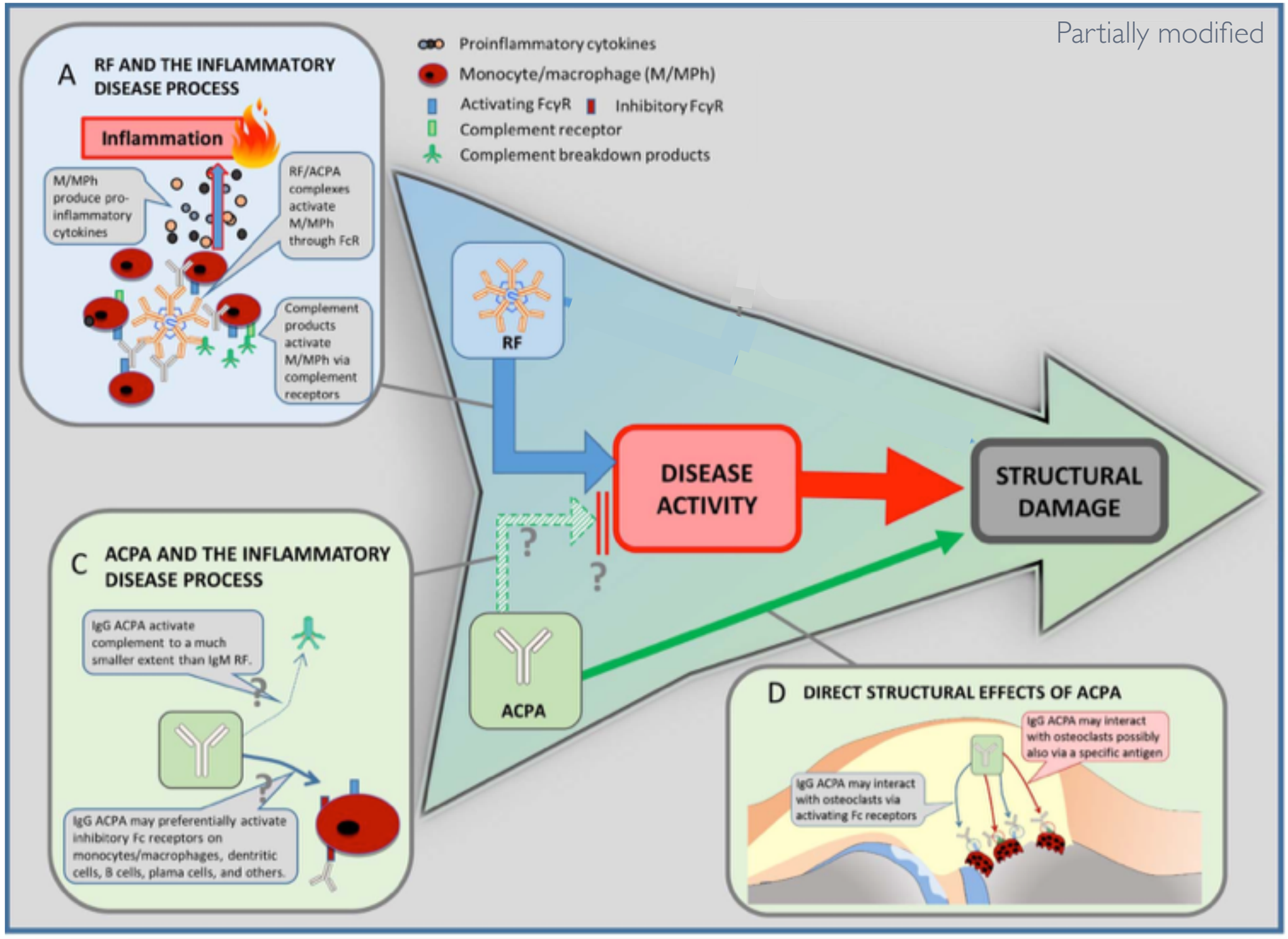
- The impact of autoantibodies on damage progression
- Mechanisms of bone erosion in RA
- The direct link between autoimmunity and bone damage
- Conclusions

RMD Open
Rheumatic & Musculoskeletal Diseases

Therapeutic implications of autoantibodies in rheumatoid arthritis

Daniel Aletaha, Stephan Blüml

RMD Open 2016



Thank you

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