Inflammatory Responses in Abdominal Aortic Aneurysm: Emerging Targets for Therapy?

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Disclosures

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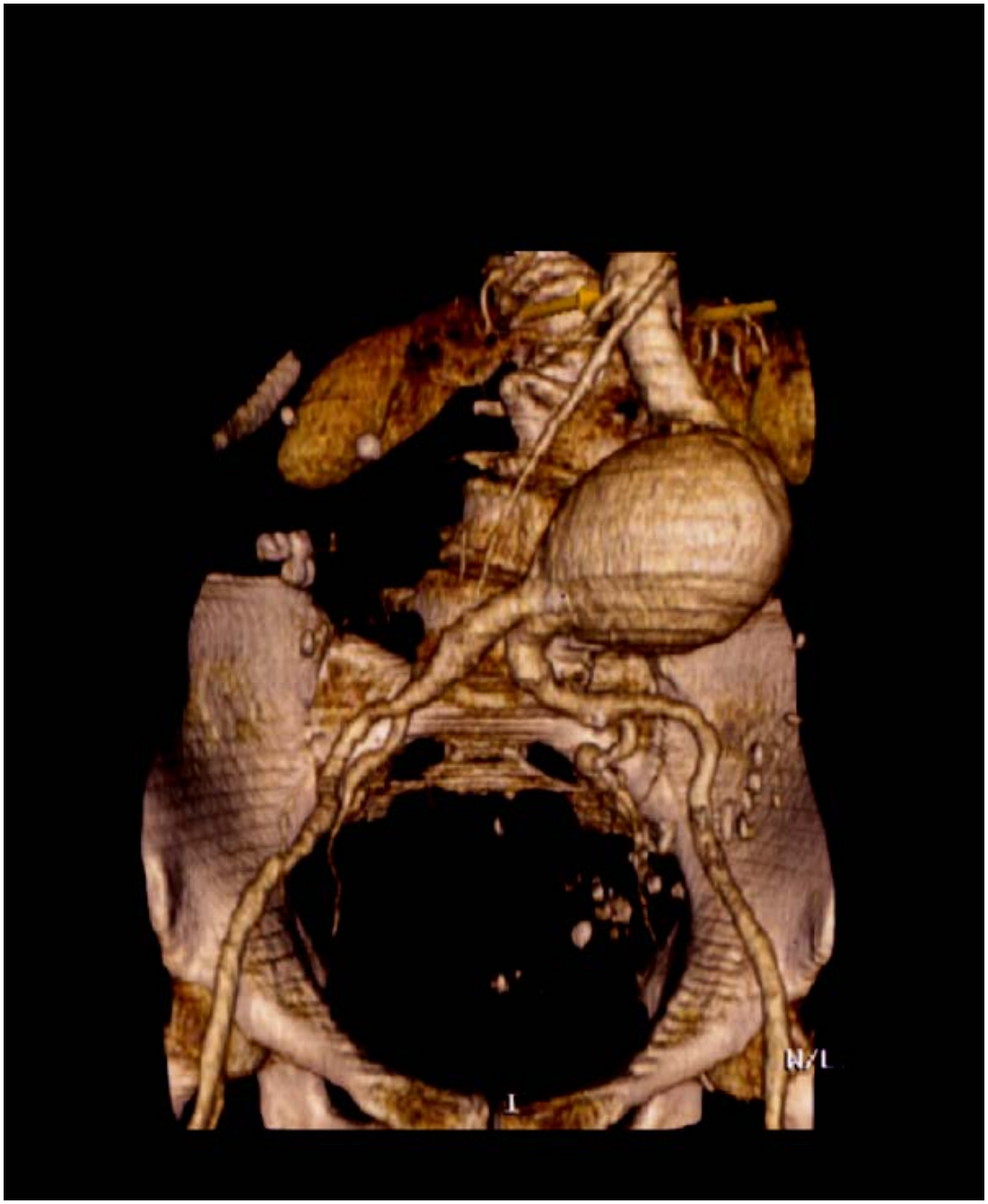
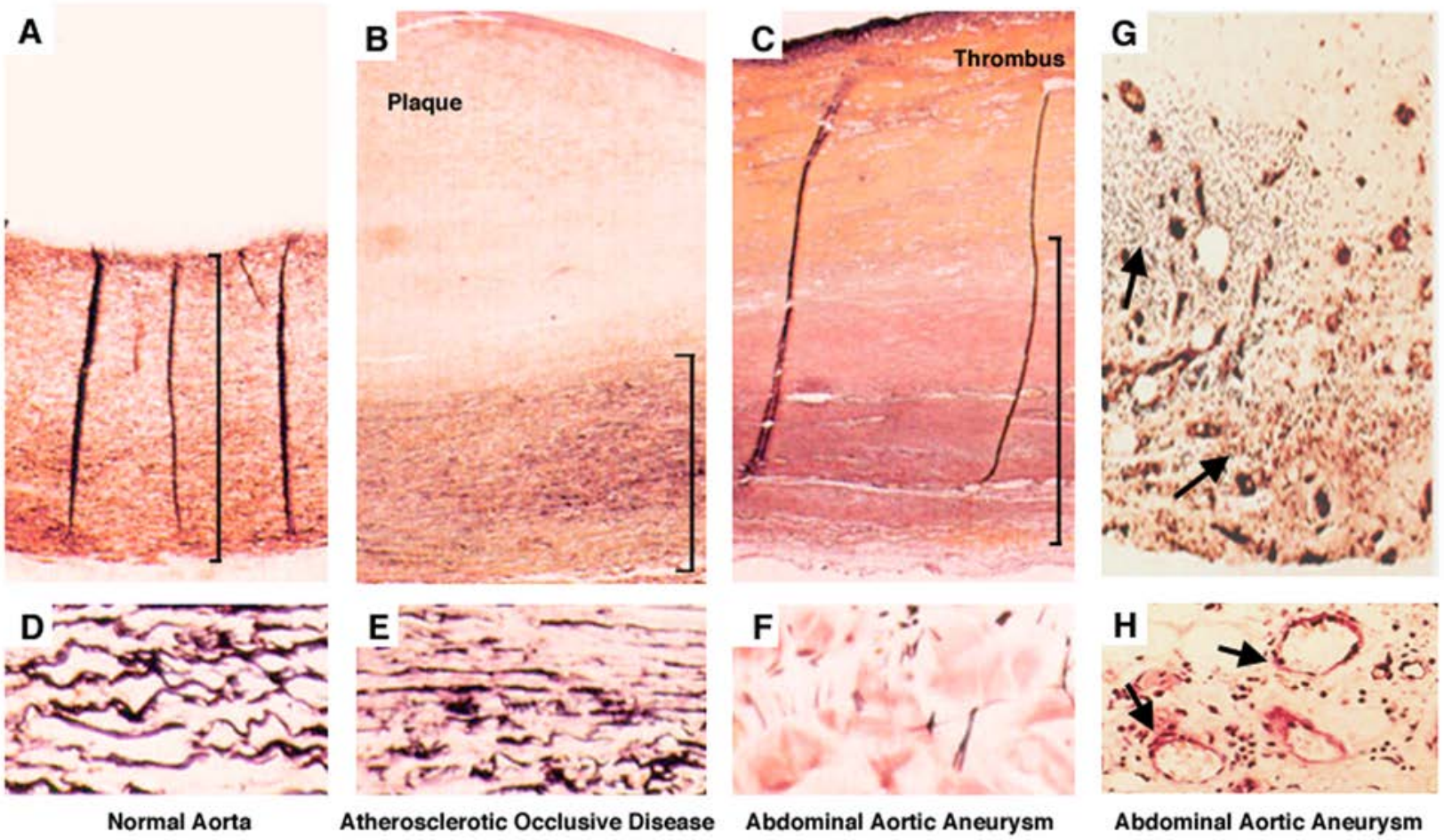
AAA

- Common disease in individuals age 60 and over
- Among top 20 leading causes of death in the US



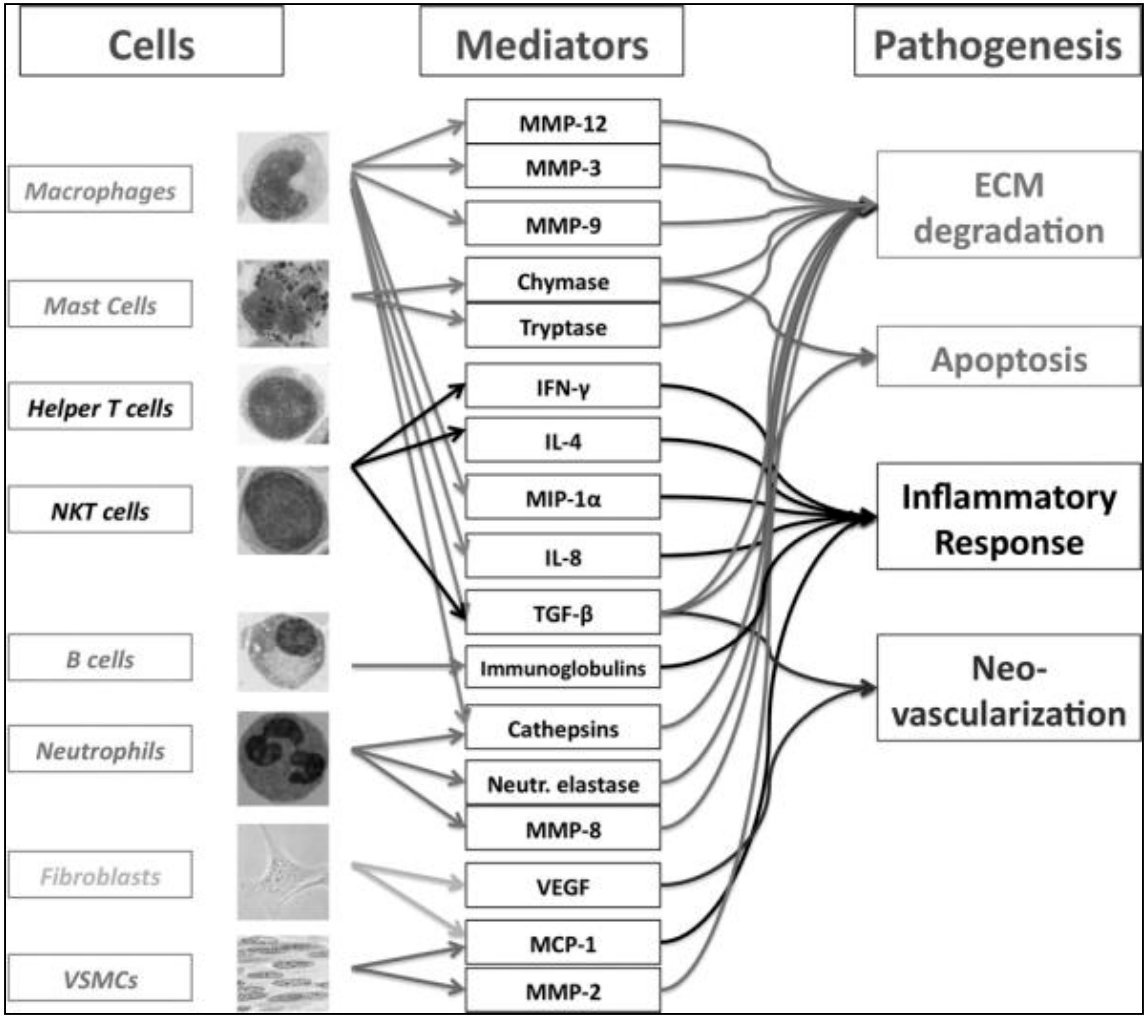
Courtesy of RW Thompson

AAA is an inflammatory disease



Courtesy of RW Thompson

Immune cells and inflammatory mediators in AAA



Immune Cells and Molecular Mediators in the Pathogenesis of the Abdominal Aortic Aneurysm.
Rizas, Konstantinos; Ippagunta, Nikalesh; MD, MS; Tilson, Martin

Cardiology in Review. 17(5):201-210, September/October 2009.
DOI: 10.1097/CRD.0b013e3181b04698

Does anti-inflammatory intervention halt the progression of AAA?

Anti-inflammatory intervention in AAA

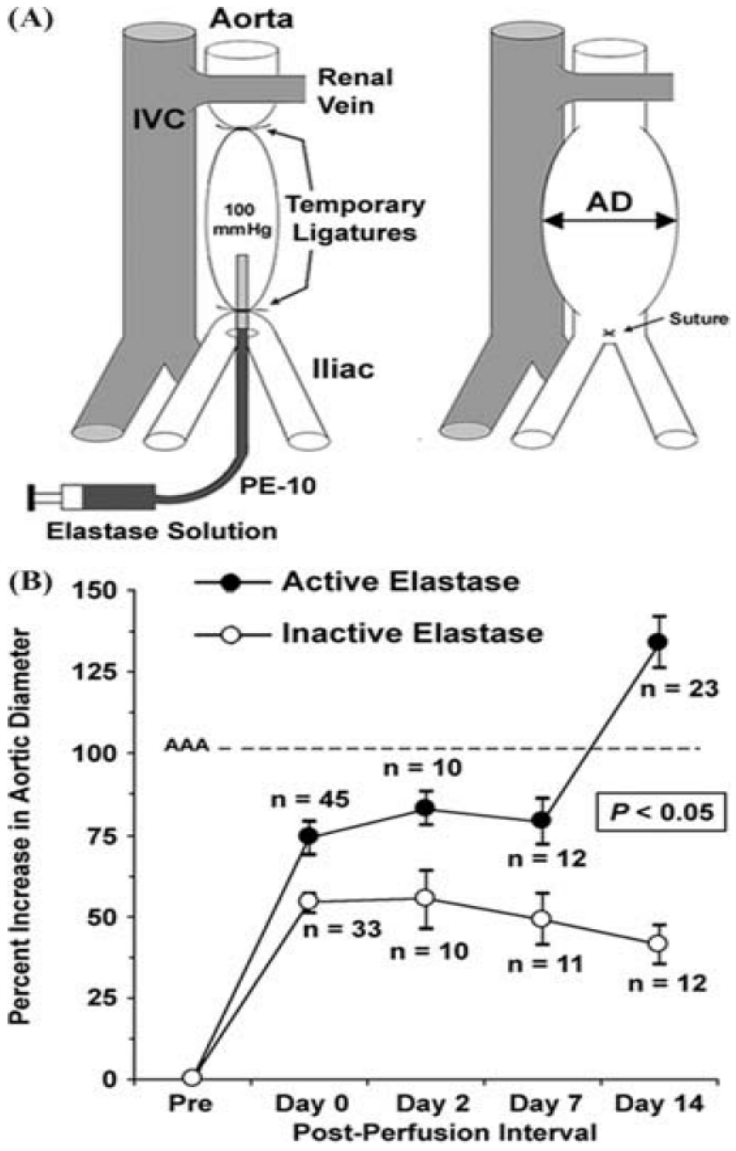
- A large body of preclinical evidence suggests that interference with the inflammatory process blocks or slows the progression of experimental AAA (reviewed in Dale *et al.* Arterioscler Thromb Vasc Biol 2015)
- Clinical trials, however, are far and few between and the results so far have been inconsistent (reviewed in Kokje *et al*. Eur J Vasc Endovasc Surg 2015)

Why the discordance?

- Mice (rats) are not human
  - preclinical data do not always translate to clinical successes
- The dosing/timing not optimal
  - Dosing/timing in preclinical studies is easily controlled; disease process in animals is uniform
  - Humans have different genetic makeup; they respond differently and progress at different rate
- It’s the wrong target(s)
  - C5aR vs TNF in RA

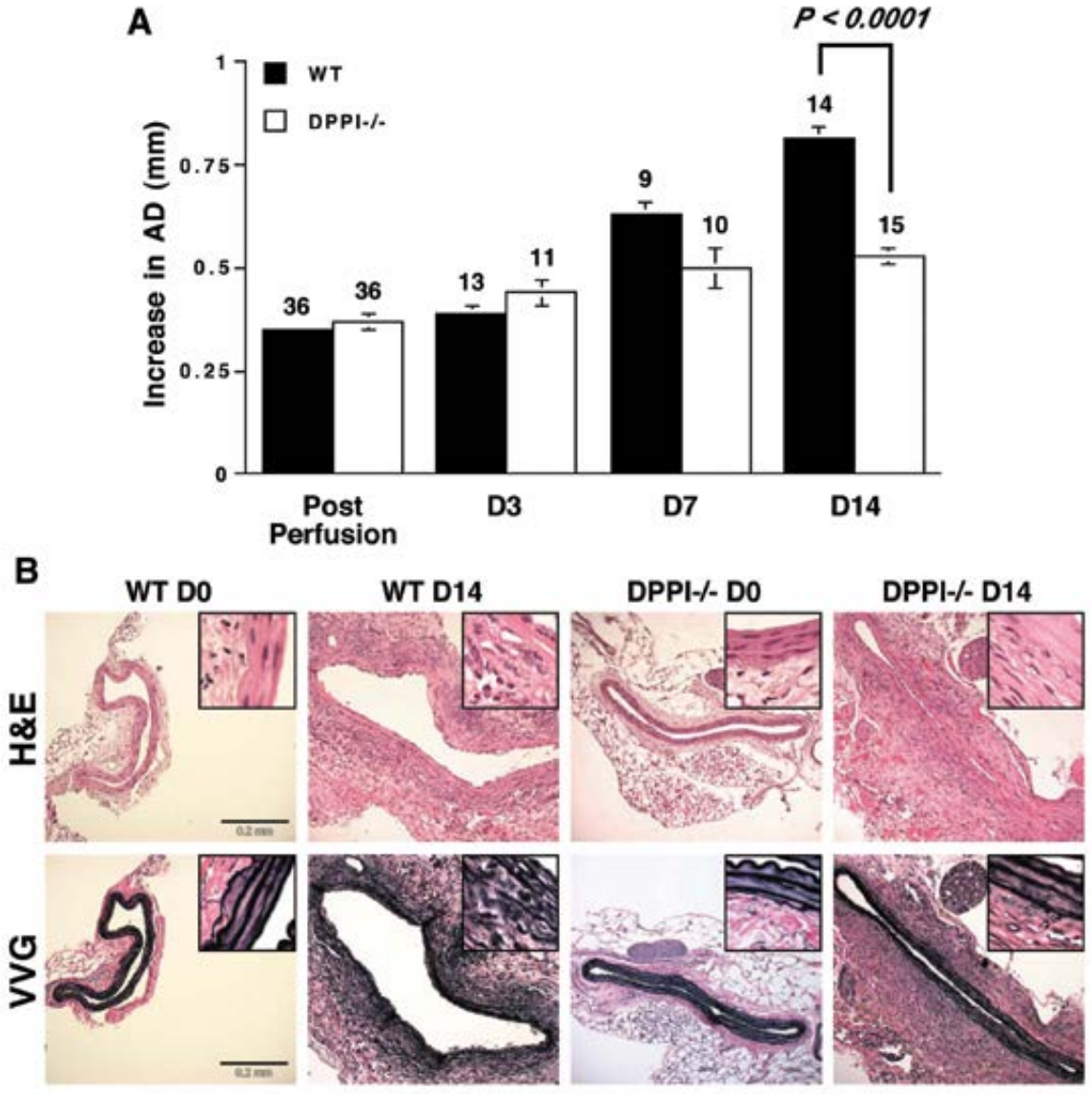
The search for inflammatory/immune targets continues…

Elastase-induced AAA



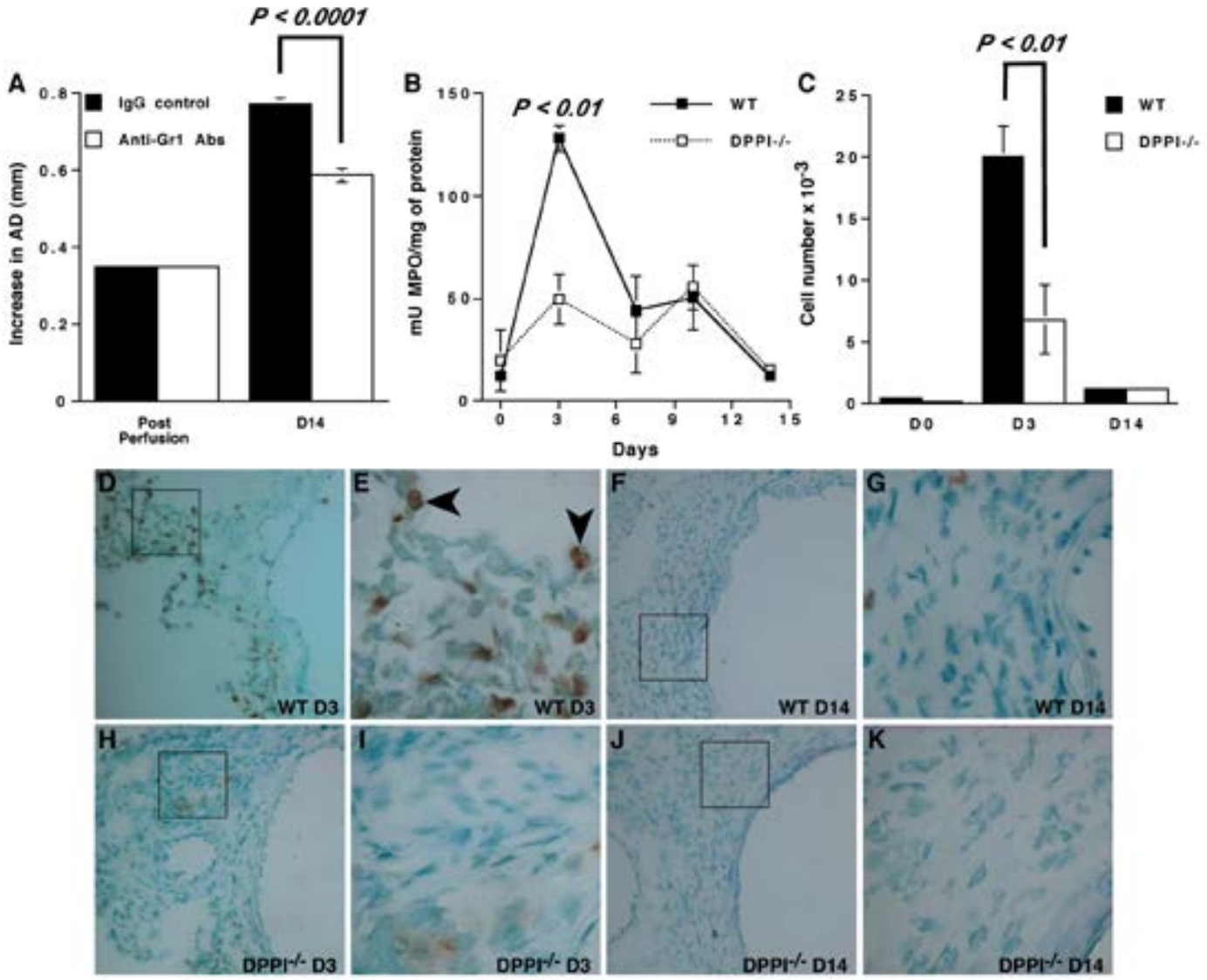
Thompson *et al*. Ann NY Acad Sci 2006

Cathepsin C (DPPI) deficiency protects against elastase-induced AAA



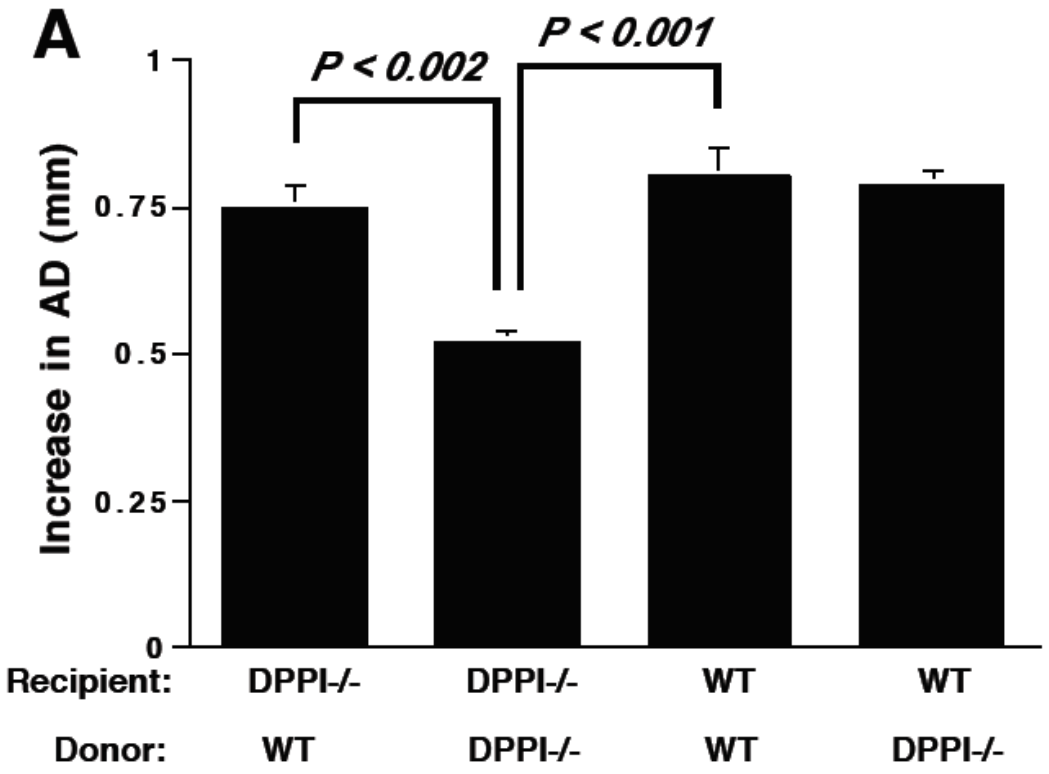
Pagano *et al*. PNAS 2007

DPPI promotes early PMN recruitment in AAA



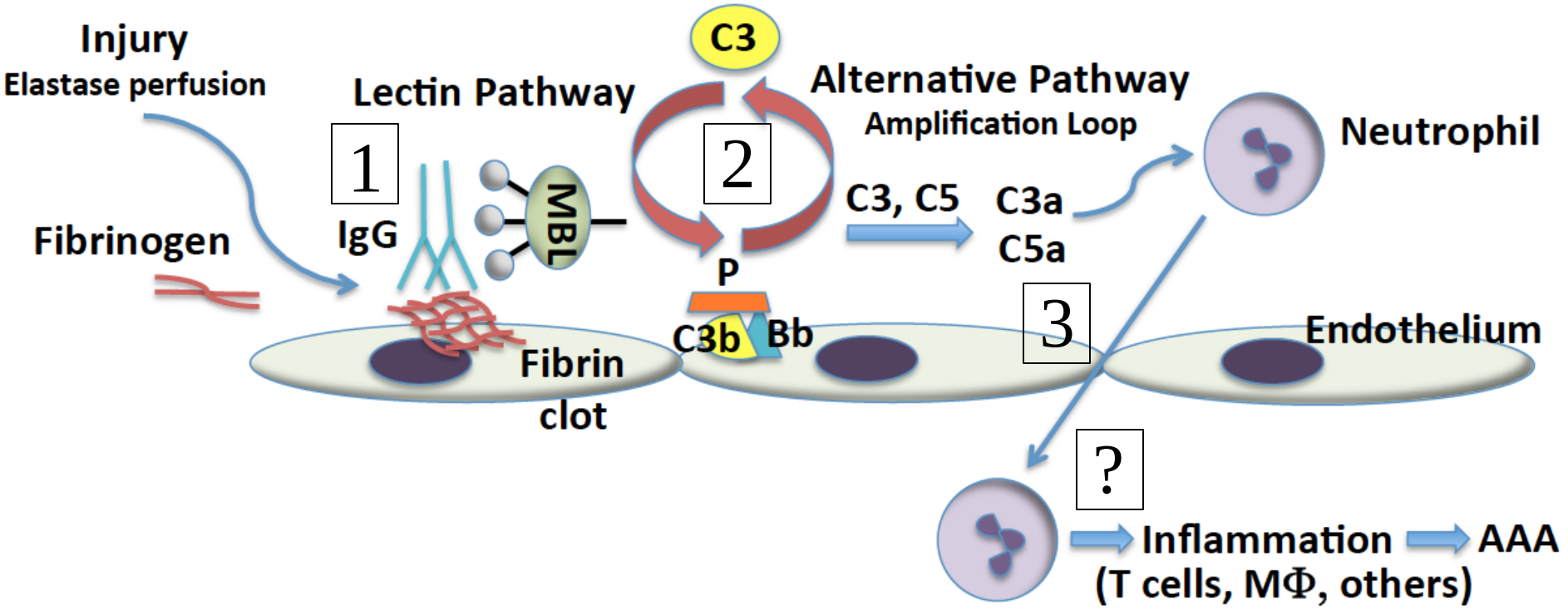
Pagano *et al*. PNAS 2007

Reconstitution with WT PMN restores susceptibility to AAA in DPPI-deficient mice



Pagano *et al.* PNAS 2007

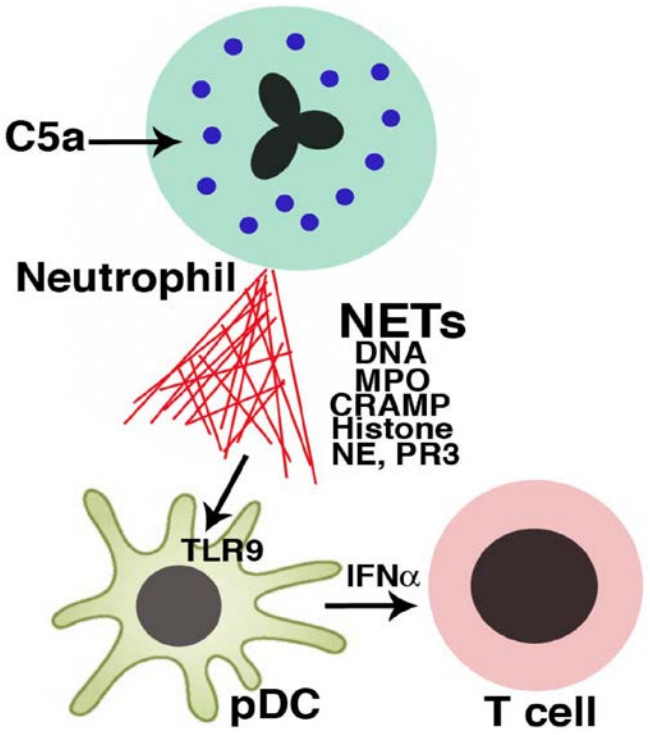
Inflammatory responses in elastase-induced AAA



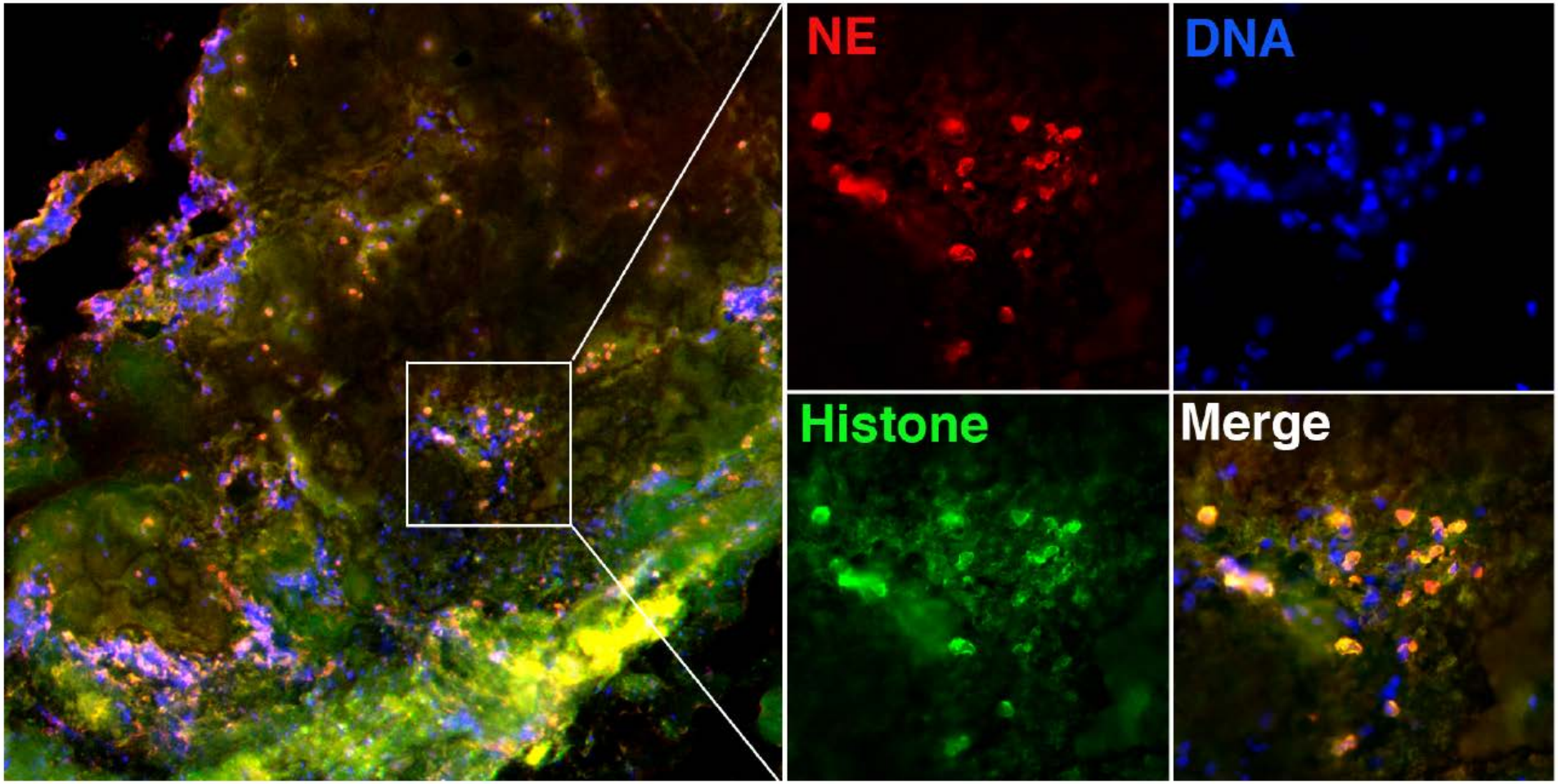
Pagano *et al*. PNAS 2007
Pagano & Zhou *et al*. Circulation 2009
Zhou *et al*. PNAS 2012
Zhou & Yan *et al*. PNAS 2013
Zhou & Yan *et al*. J. Immunol 2013

Neutrophil extracellular traps (NETs)

- Innate immune response to bacterial infection (Brinkman *et al.* Science 2004)
- NETs have since been implicated in:
  - Atherosclerosis (Doring *et al.* Circulation 2012; Warnatsch *et al.* Sci Transl Med 2013); Systemic lupus erythematosus (Carmona-Rivera *et al.* Ann Rheum Dis 2015); Small vessel vasculitis (Kessenbrock *et al*. Nat Med 2009); COPD (Grabcanovic-Musija *et al*. Resp Res 2015); Diabetes (Wong *et al.* Nat Med 2015)

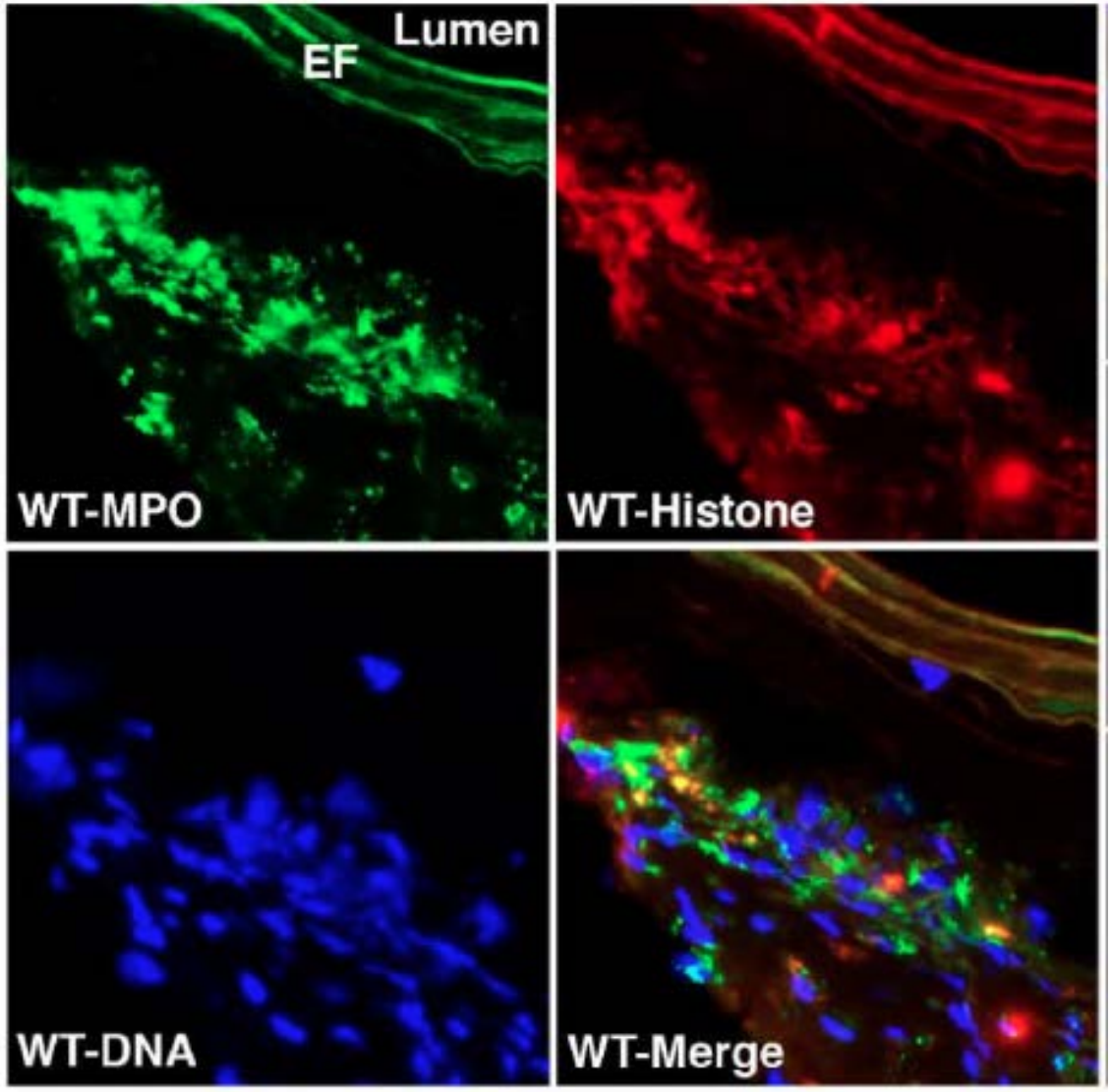


NETs are found in human AAA



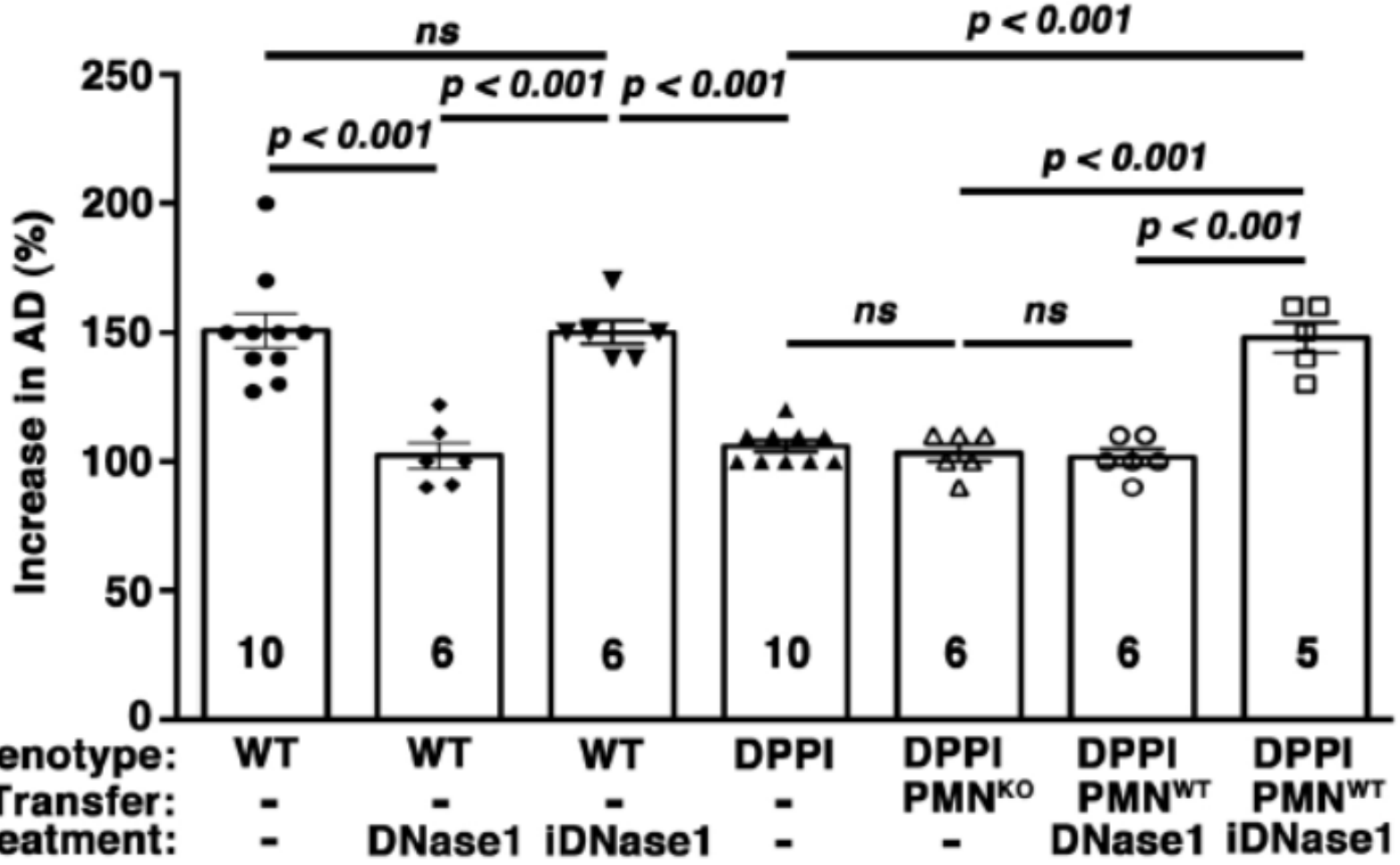
- Unpublished data (Pham lab)
- Delbosc *et al.* Plos One 2011

NETs are formed in elastase-perfused aortas



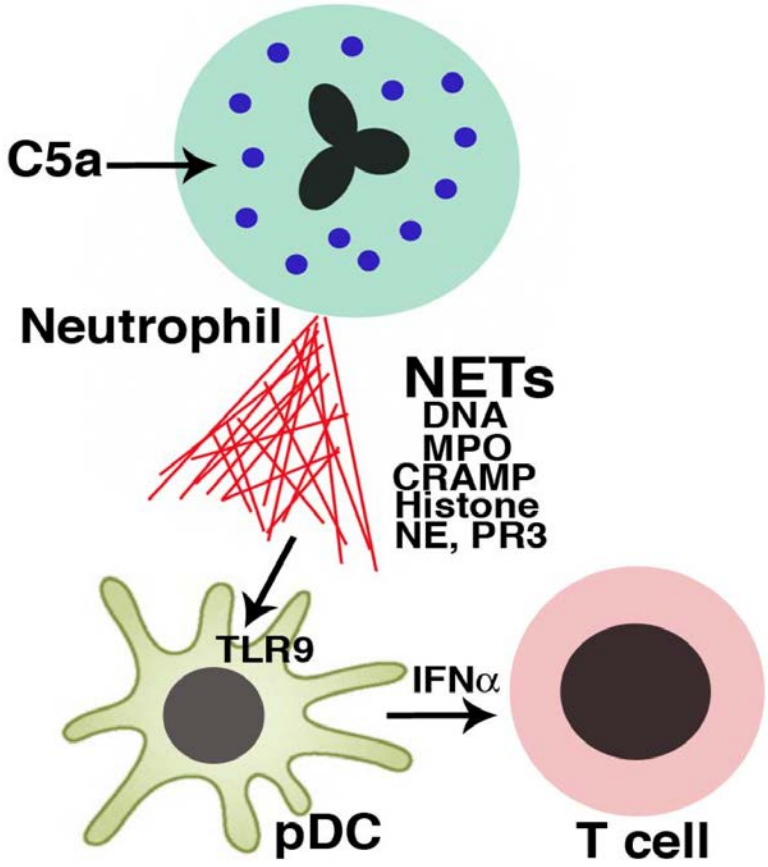
Yan & Zhou *et al.* under submission

DNase 1 dismantles NETs and protects against AAA

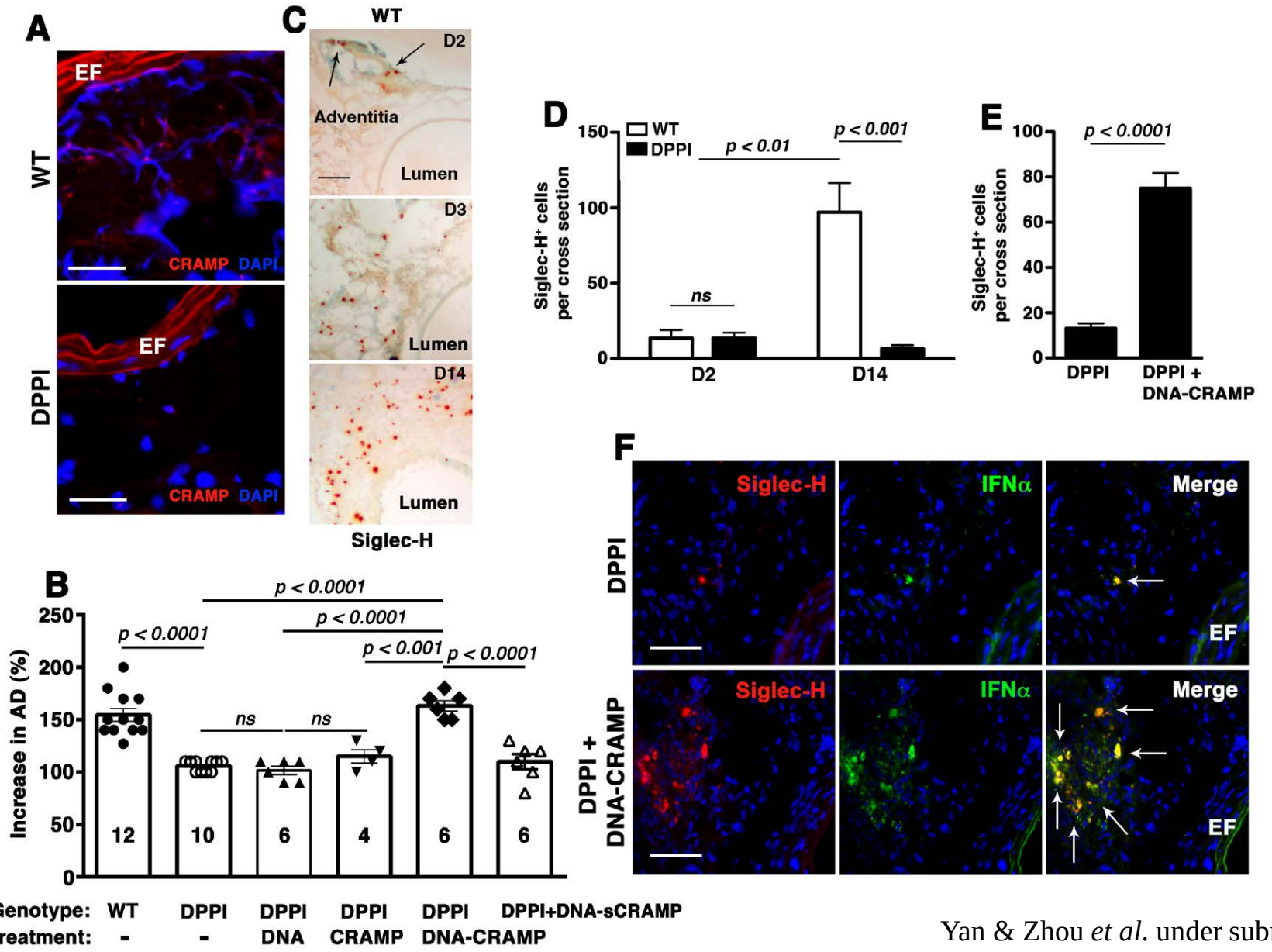


Yan & Zhou *et al*. under submission

Neutrophil extracellular traps (NETs)

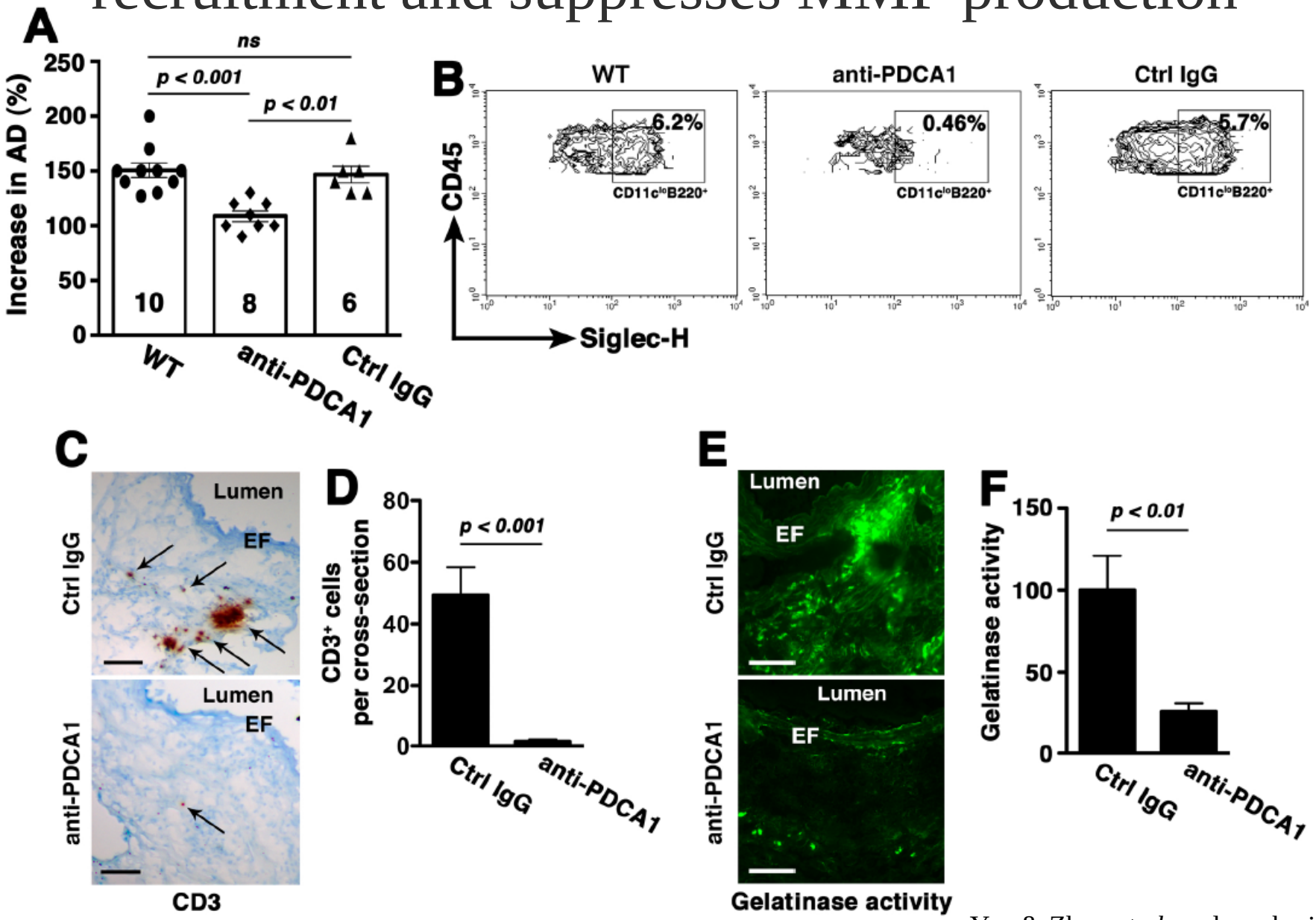


DNA-CRAMP complexes induce AAA



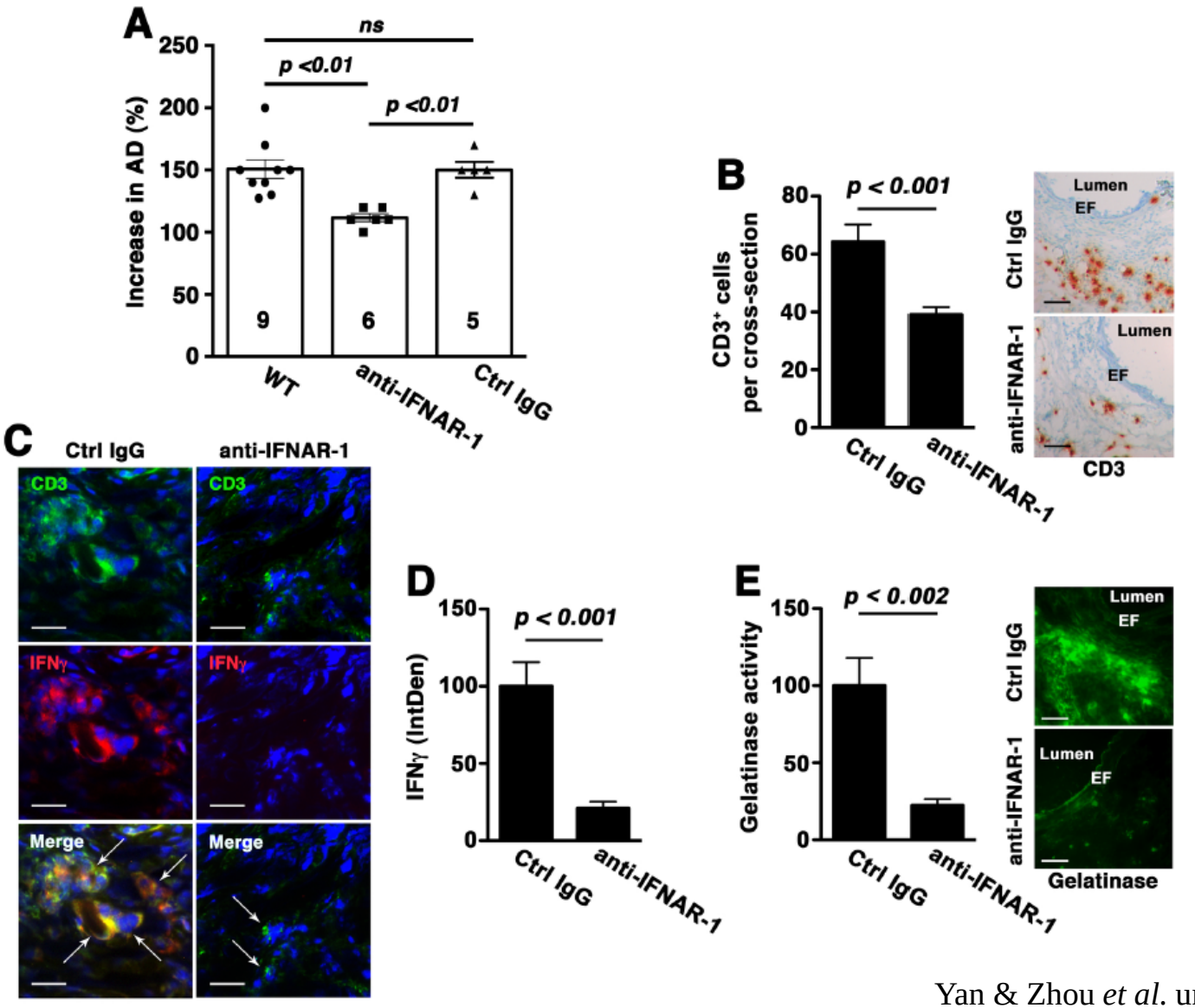
Yan & Zhou *et al.* under submission

pDC depletion attenuates AAA, blocks T cell recruitment and suppresses MMP production



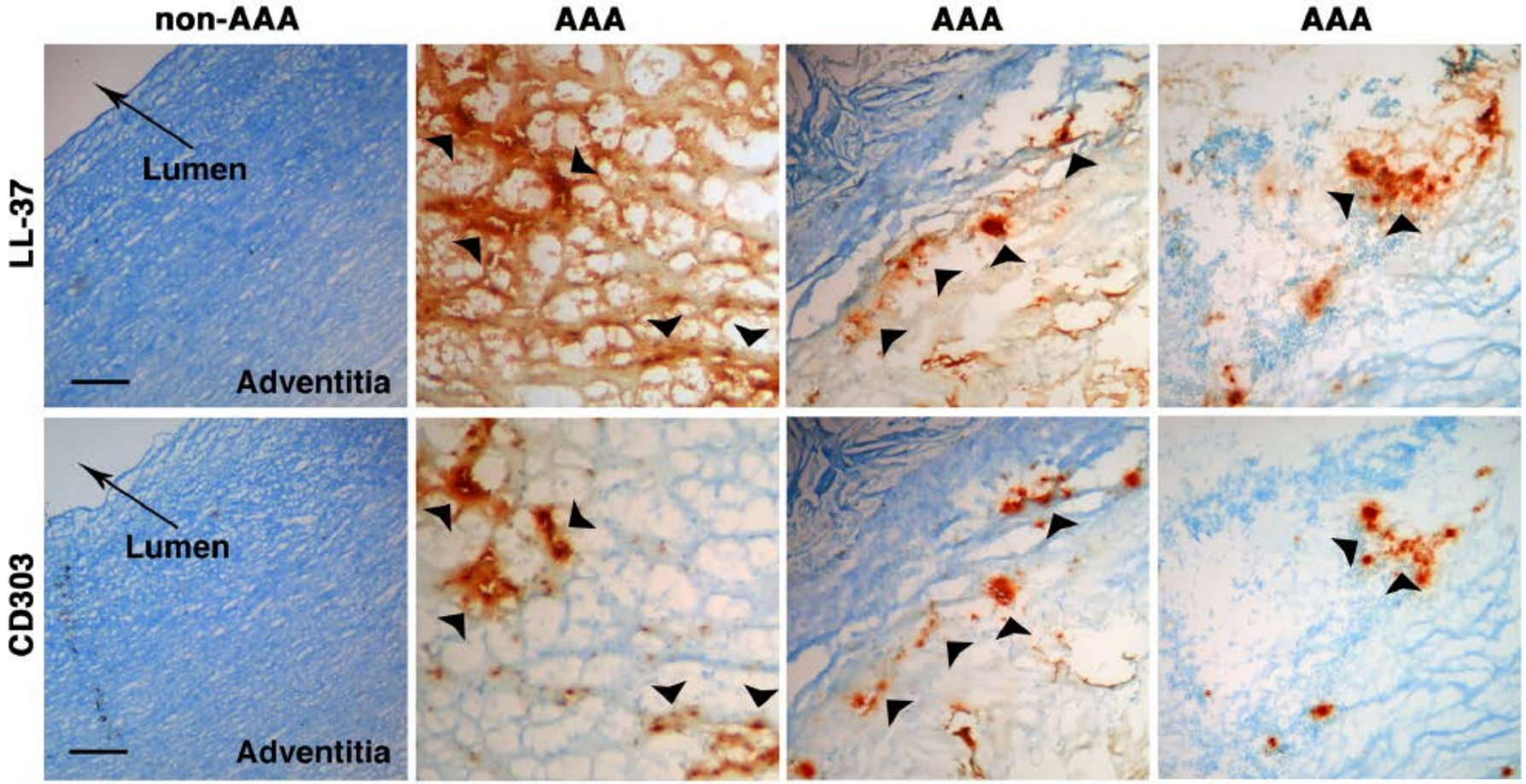
Yan & Zhou *et al.* under submission

Type I IFN blockade attenuates AAA, T cell recruitment and MMP production



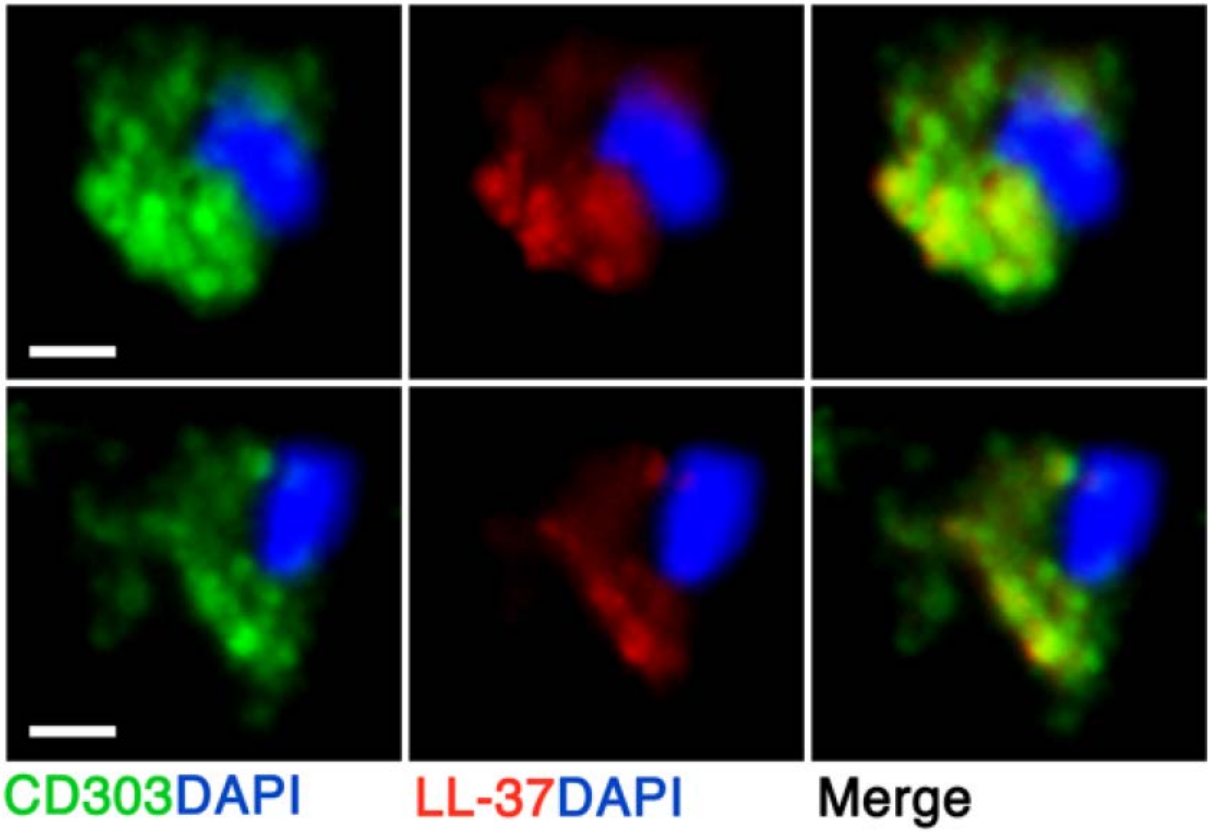
Yan & Zhou *et al.* under submission

NET component LL-37 is abundantly expressed in human AAA tissues



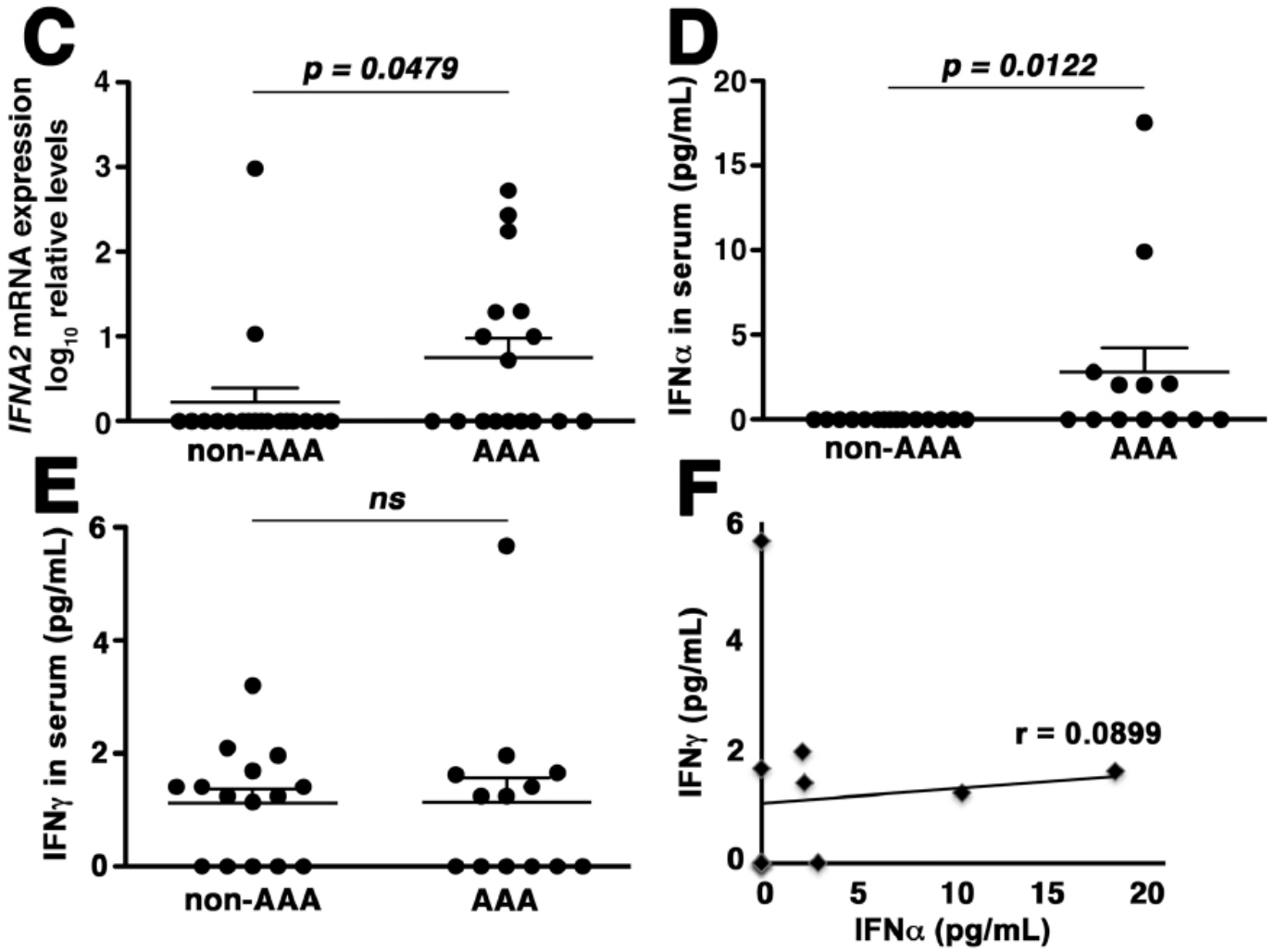
Yan & Zhou *et al.* under submission

LL-37 co-localizes with pDCs in human AAA tissues



Yan & Zhou *et al.* under submission

IFNα expression is elevated in AAA tissues and in the circulation



Yan & Zhou *et al.* under submission

Summary and remaining unanswered questions

- In the elastase-induced AAA model:
  - Neutrophils recruited to abdominal aortic wall elaborate NETs
  - NETs stimulate pDCs to release type I interferons
  - Type I interferons recruit and activate T cells (others) to perpetuate the chronic inflammatory responses
- Are NETs, pDCs, and type I interferons good therapeutic targets?
- What about other targets?
- Which targets do we pick and when is the best time for intervention?
- Should intervention be personalized given the wide range of manifestation/progression?

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