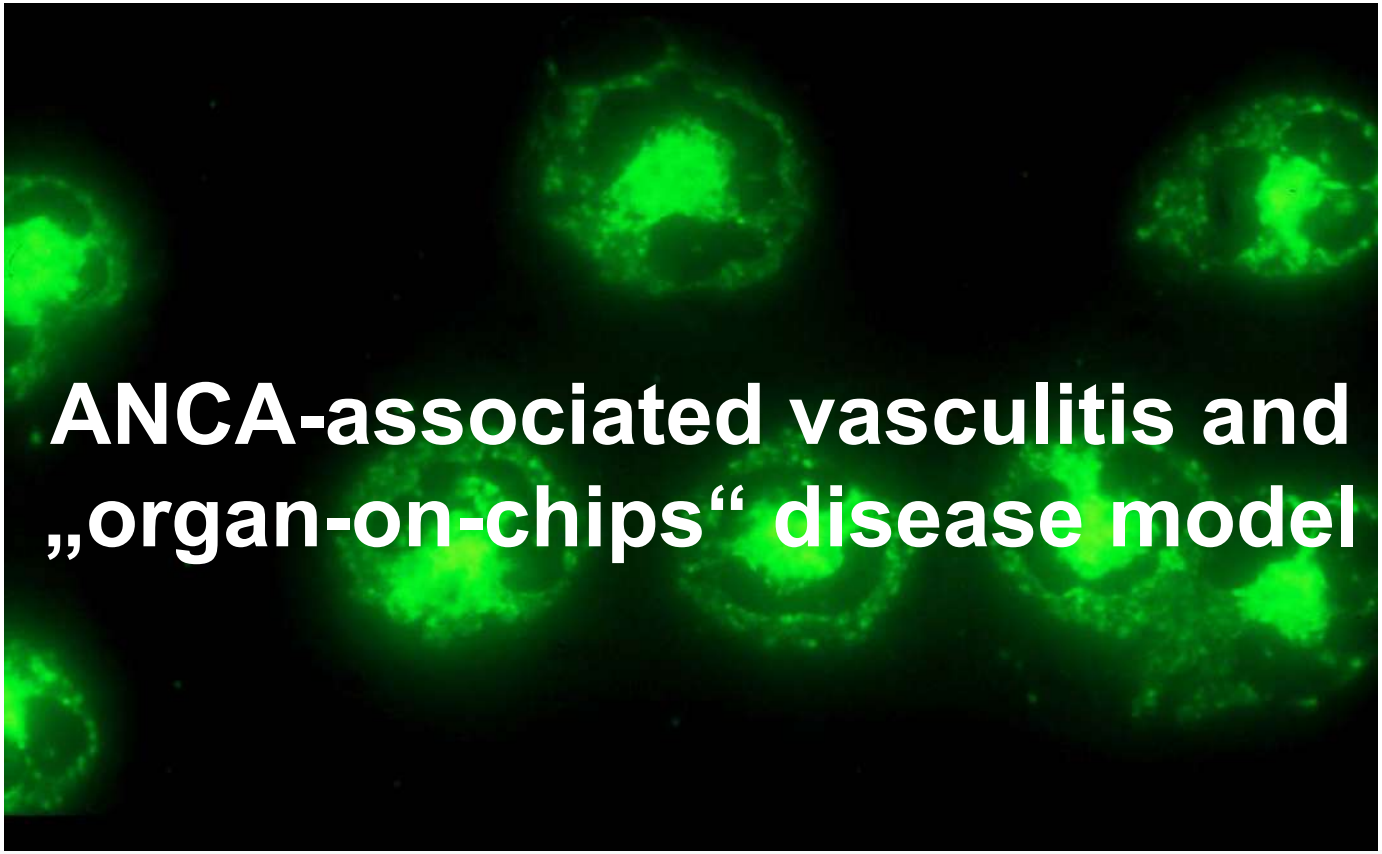
VASKULITIS-ZENTRUM SÜD
TÜBINGEN-KIRCHHEIM



ANCA-associated vasculitis and „organ-on-chips“ disease model

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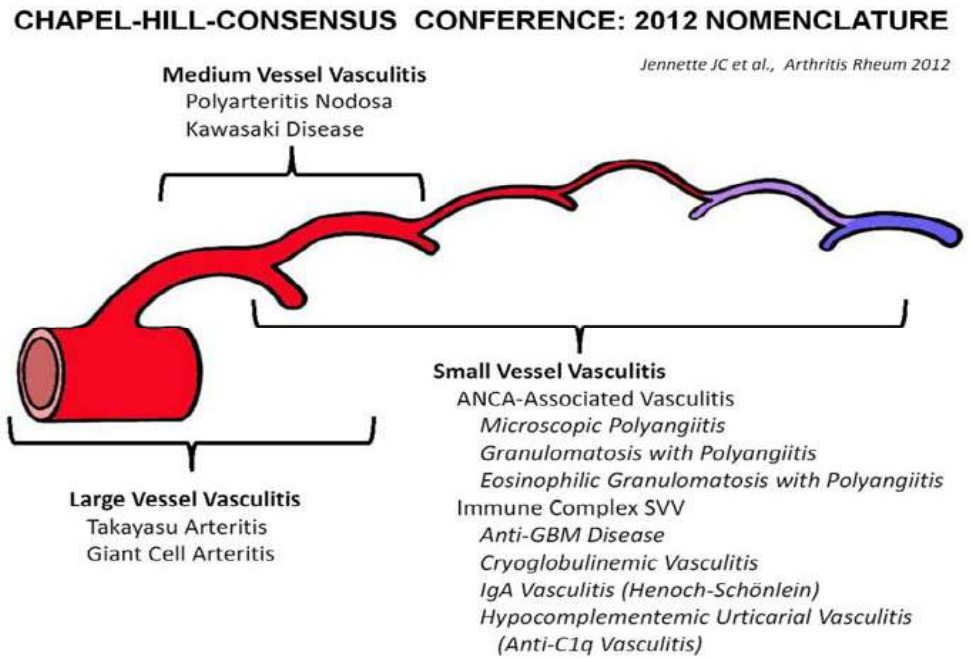
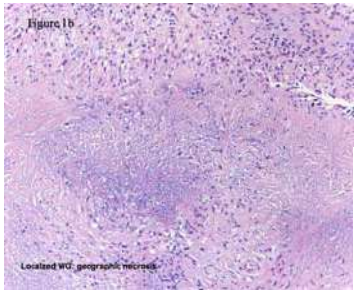
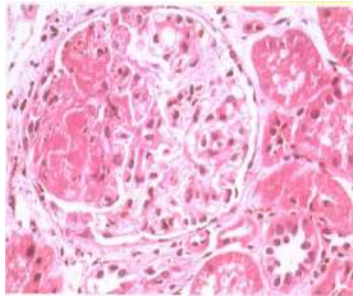
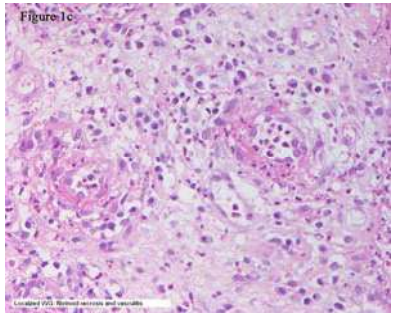
ANCA-associated-vasculitides

- necrotizing inflammation of the small vessels: **vasculitis and granulomata**



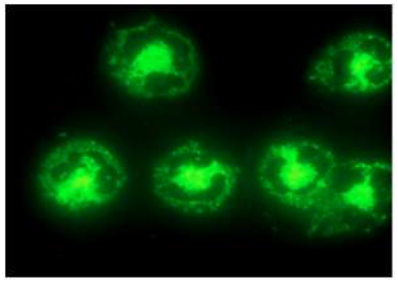




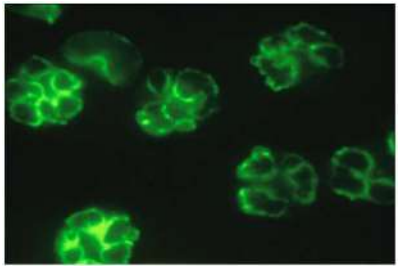


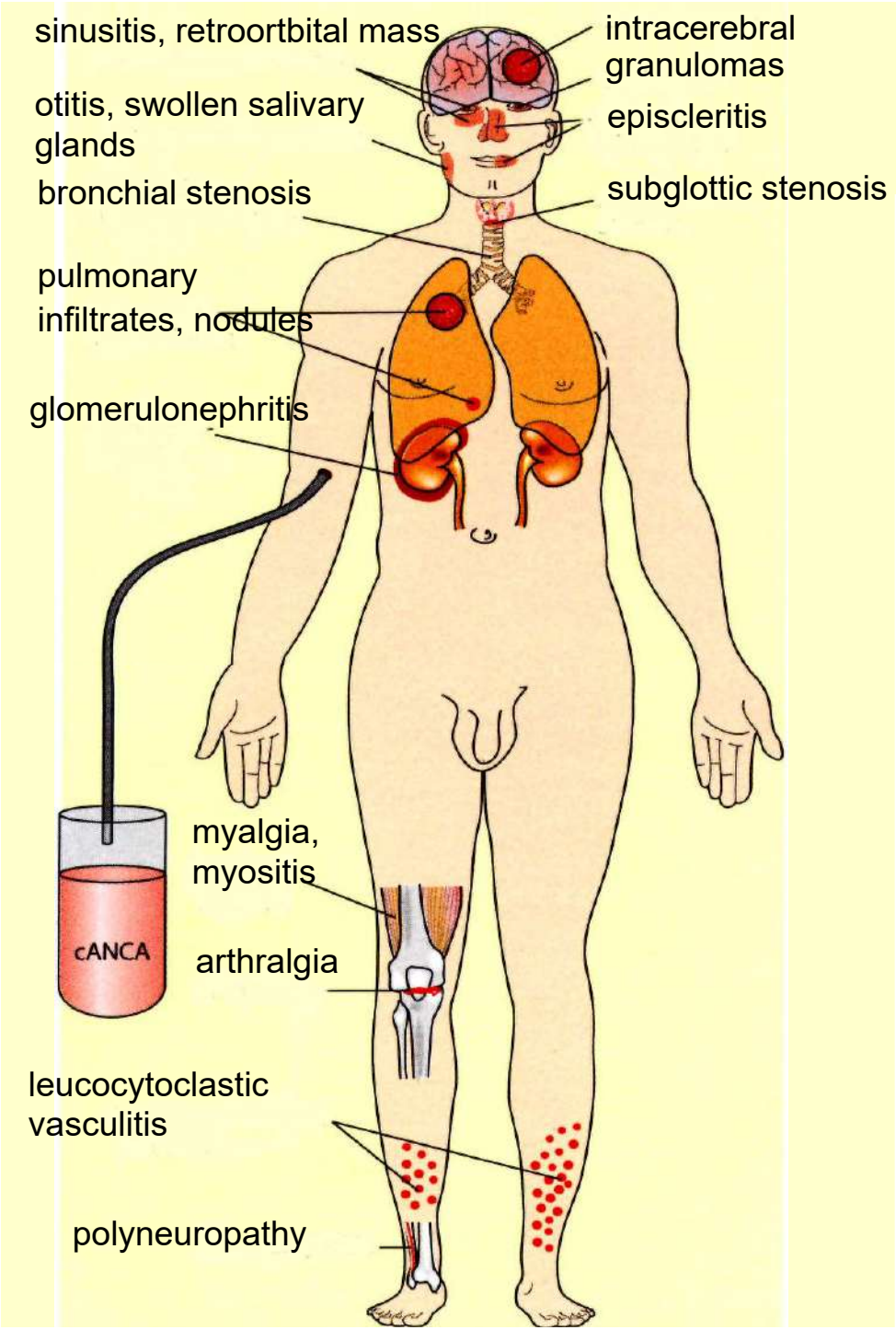
- **Antineutrophil Cytoplasmic Antibodies**

PR3-ANCA



MPO-ANCA





Granulomatosis with polyangiitis

Incidence
8-12 /million/year (Germany)

Prevalence
58/million (Germany)

CHC -1992, 2012 -Definition

granulomatous inflammation involving the respiratory tract

necrotizing vasculitis affecting small to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries)

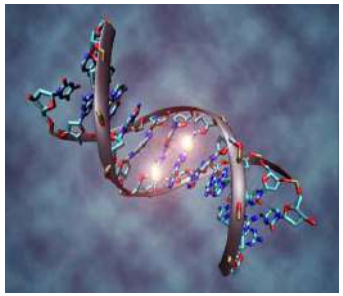
necrotizing glomerulonephritis.

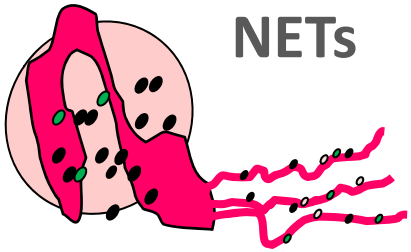
C-/PR3-ANCA are closely associated with vasculitis

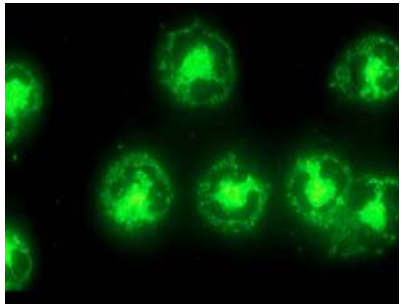
Pathogenesis of ANCA-associated vasculitis

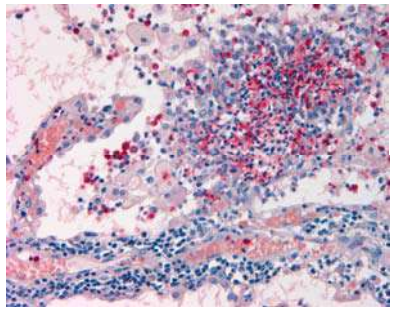
- **complex interactions:**

Risk genes, enviromental factors, epigenetics , innate/adaptive immunity









Whatever the initiating event, a final common pathway of injury entails:

- **leukocyte activation with degranulation, generation of toxic oxygen metabolites**
- **vascular necrosis with fibrinous insudation**

Animal models of ANCA-associated vasculitis

- ***MPO-ANCA-associated vasculitis can be induced in various forms in susceptible rodents***

1. **these models have focused predominantly on kidney involvement**
2. **all models exhibit much milder disease than that seen in pts**
3. **the findings of experiments using MPO-ANCA can not be generalized to all AAV**

- ***PR3-ANCA-associated disease in animals is much less advanced than MPO-ANCA-associated vasculitis:***

1. **differences between human and rodent PR3 (structure and expression)**
2. **pathogenesis of necrotizing granulomatous inflammation is not known**

What is the value of human vs. animal models?

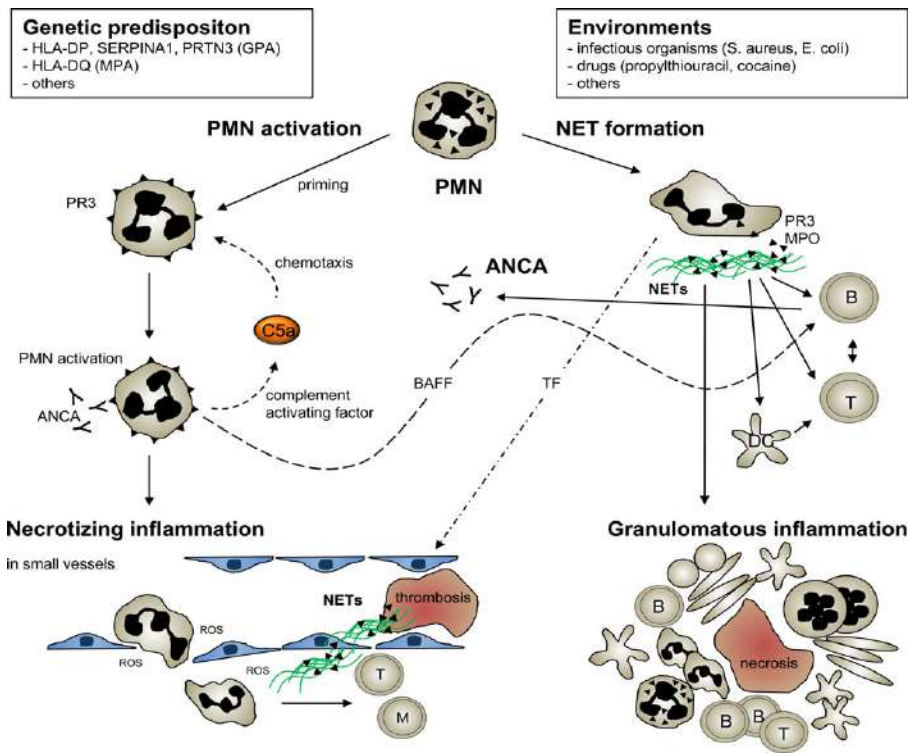
- ***The advantages of using the human „organ-on-chip“ model include*:**

1. **the ability to study different stages of the disease (vasculitis and granulomata) and the specific target organs (i.e., microvascular blood vessel endothelium- renal, lung)**

2. **to focus on the role of specific pathogenic factors (i.e., immune cells, ANCA, NETs)**

3. **to investigate the effect of disease specific drug targets by using molecular blocking agents**

Pathogenesis of AAV: from NETs to disease networks

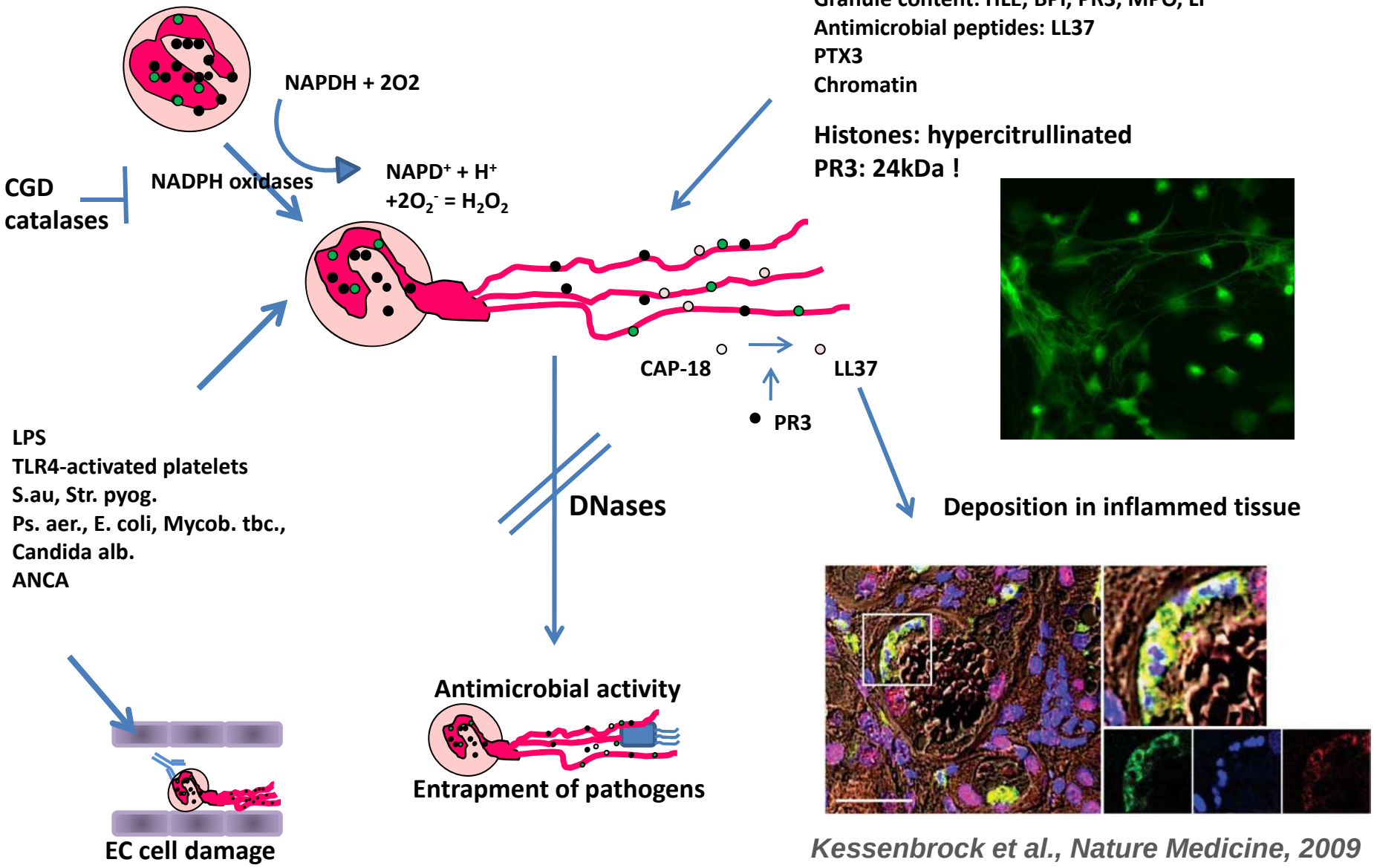


Schönemarck, Csernok, 2013, Nephrol Dial Transplant

Human model systems

- the mechanistic role of the disease-associated genes: HLA-gene variants, PR3, α1-antitrypsin, and the contributions of environments factors (*Staph.aureus*, drugs)
- **deciphering the role of autoantigens (PR3), ANCA and NETs**
- **autoimmune mechanisms that lead to generation of ANCA**
- **to develop novel therapeutic target: anti-NETs therapy**

Update on NETs (Neutrophil extracellular traps)



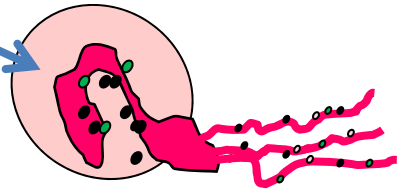
Kessenbrock et al., Nature Medicine, 2009

Deciphering the role of NETS in AAV

microbe (S. aureus)

Drugs (cocaine)

ANCA



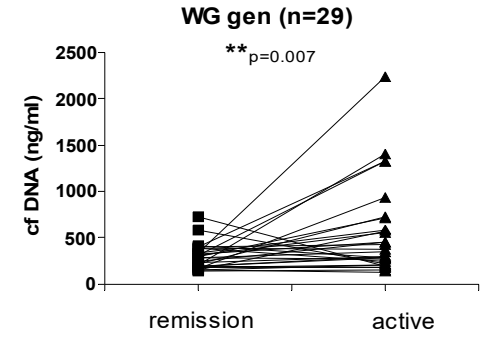
NETs-modified PR3 (citrullination?)

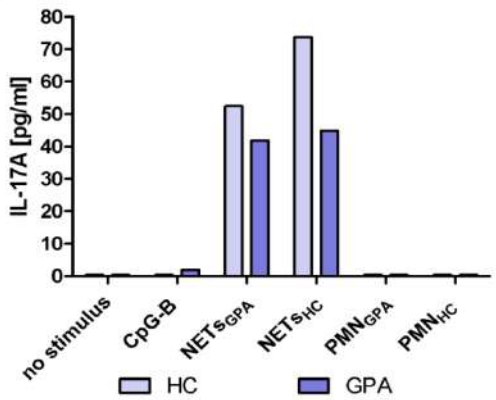
T-cell polarisation

B-cell activation

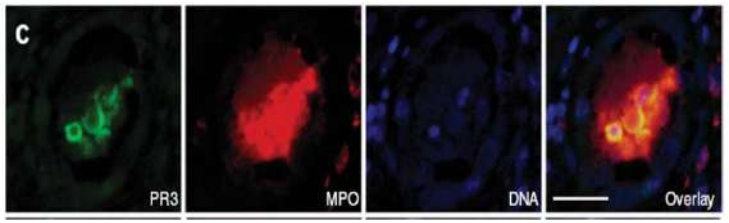
Th1, Th2, Th17?, Treg

PR3-ANCA?



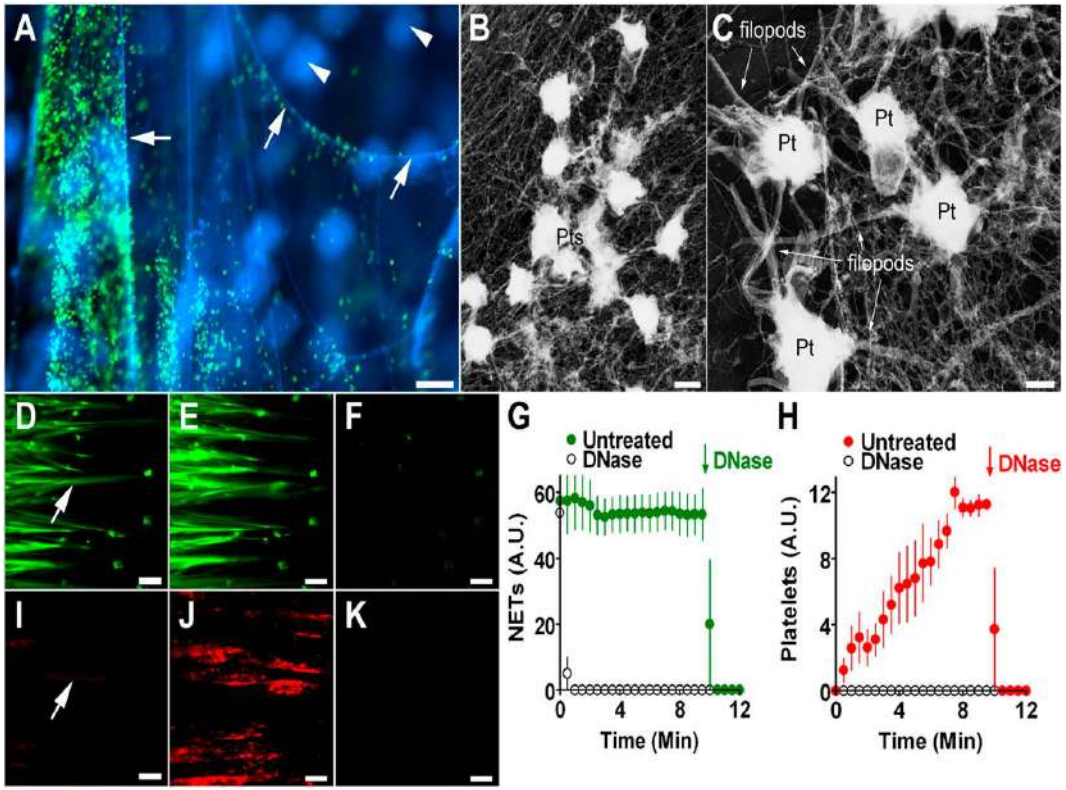


Lange, Csernok et al., 2015, submitted



Kessenbrock et al., Nature Medicine, 2009

NETS as therapeutic target?



Potential targets:

- **extracellular DNA: degradation by nucleases**
- **PAD4: blocking by inhibitors**
- **NADPH-oxidase: inhibition**

NETs promote trombosis: DNAse treatment

Fuchs et al., 2010, PNAS

„Organ-on-chips“ disease model in AAV: promise and challenges

✓**Helps to dissect out the role of genetic/enviromental factors, the pathological basis of disease, and to understand the contribution of neutrophils (i.e., NETs), ANCA and their target antigens in mediating disease**

✓**Offers the possibility to test the efficacy and efficiency of new drugs on „pre-clinical trials–on-chip“**

- **Generation of human „organ-on-chip“ that incorporates both PR3-ANCA-associated vasculitis and granuloma formation is the major challenge facing researchers over the next decade**