

Targeting Pathways of Neutrophil Extracellular Trap Formation to Inhibit Progression of Abdominal Aortic Aneurysms in Preclinical Models

Sonja Bleichert¹, Nahla Ibrahim¹, Viktoria Knöbl¹, Annika Brandau¹, Hubert Hayden¹, Albert Busch², Marc Bailey³, Wolf Hans Eilenberg¹, Christoph Neumayer¹, Christine Brostjan¹

¹ Department of Surgery, Medical University of Vienna, Vienna General Hospital, Austria

² Department of Vascular and Endovascular Surgery, Klinikum Rechts der Isar, Technical University Munich, Germany

³ Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Faculty of Medicine and Health, Leeds, UK

Introduction

- Neutrophil extracellular traps (NETs) are formed by the expulsion of nuclear or mitochondrial DNA to destroy pathogens
- NETs are also known to promote the formation of abdominal aortic aneurysms (AAAs) by propagating inflammatory responses
- NETs may represent a target to inhibit AAA development

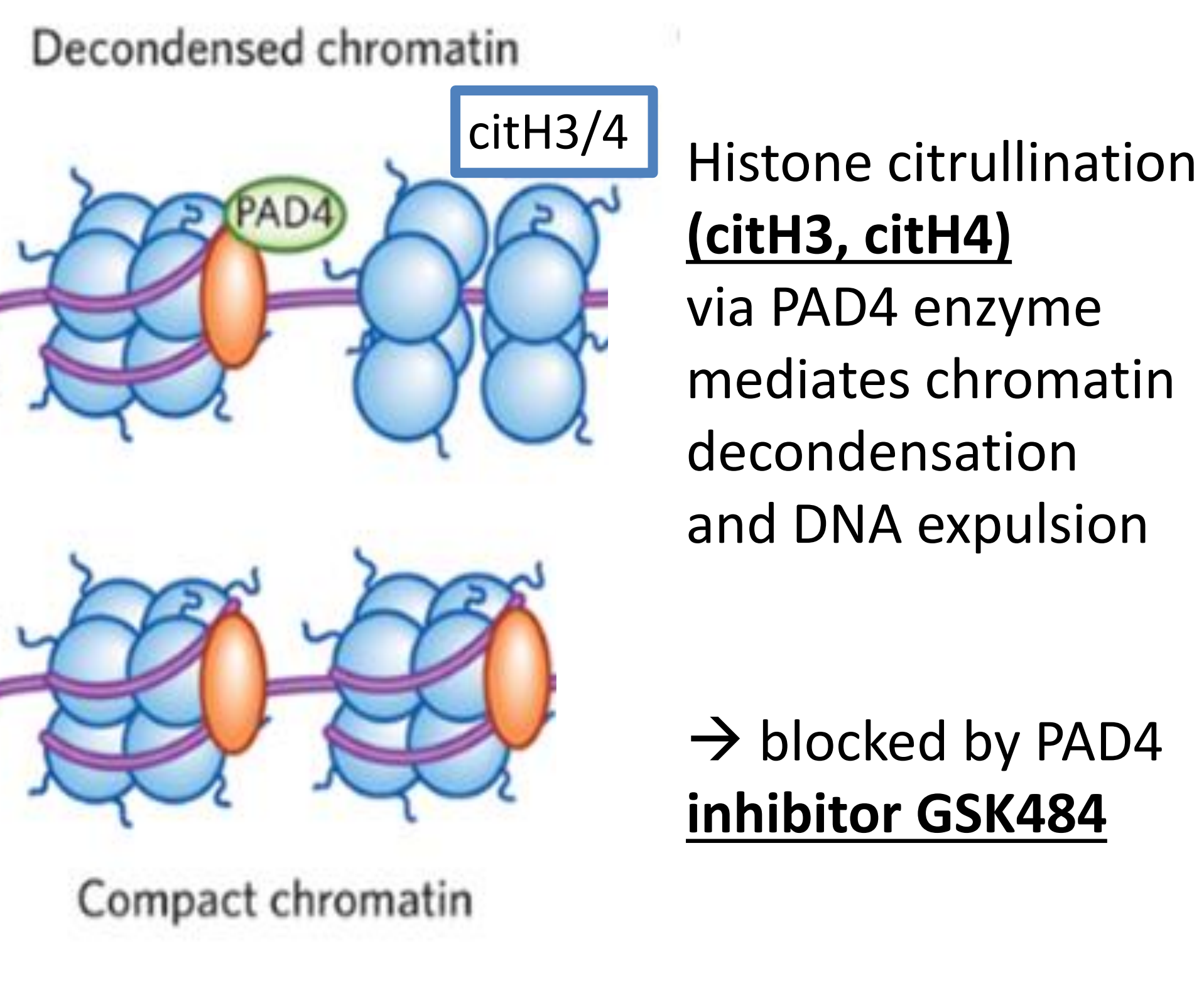
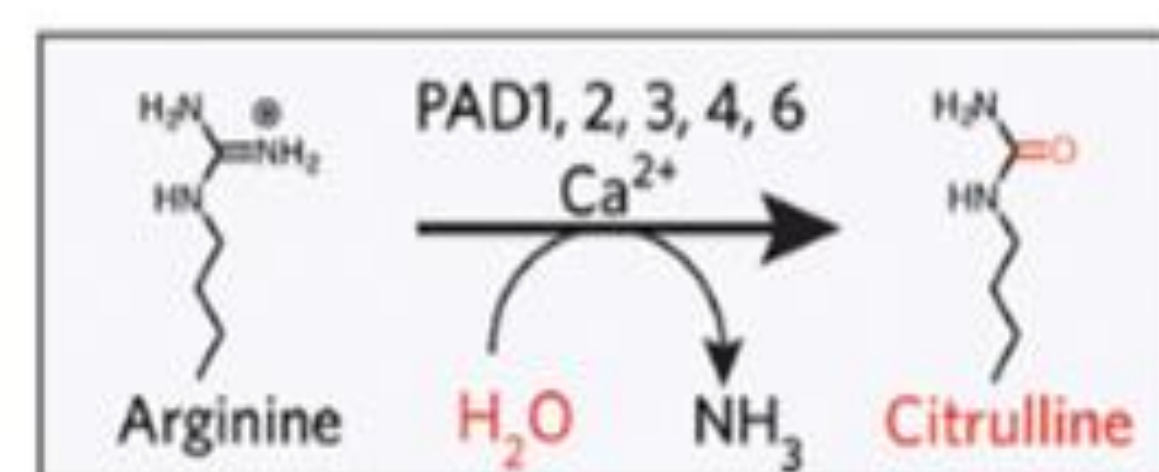
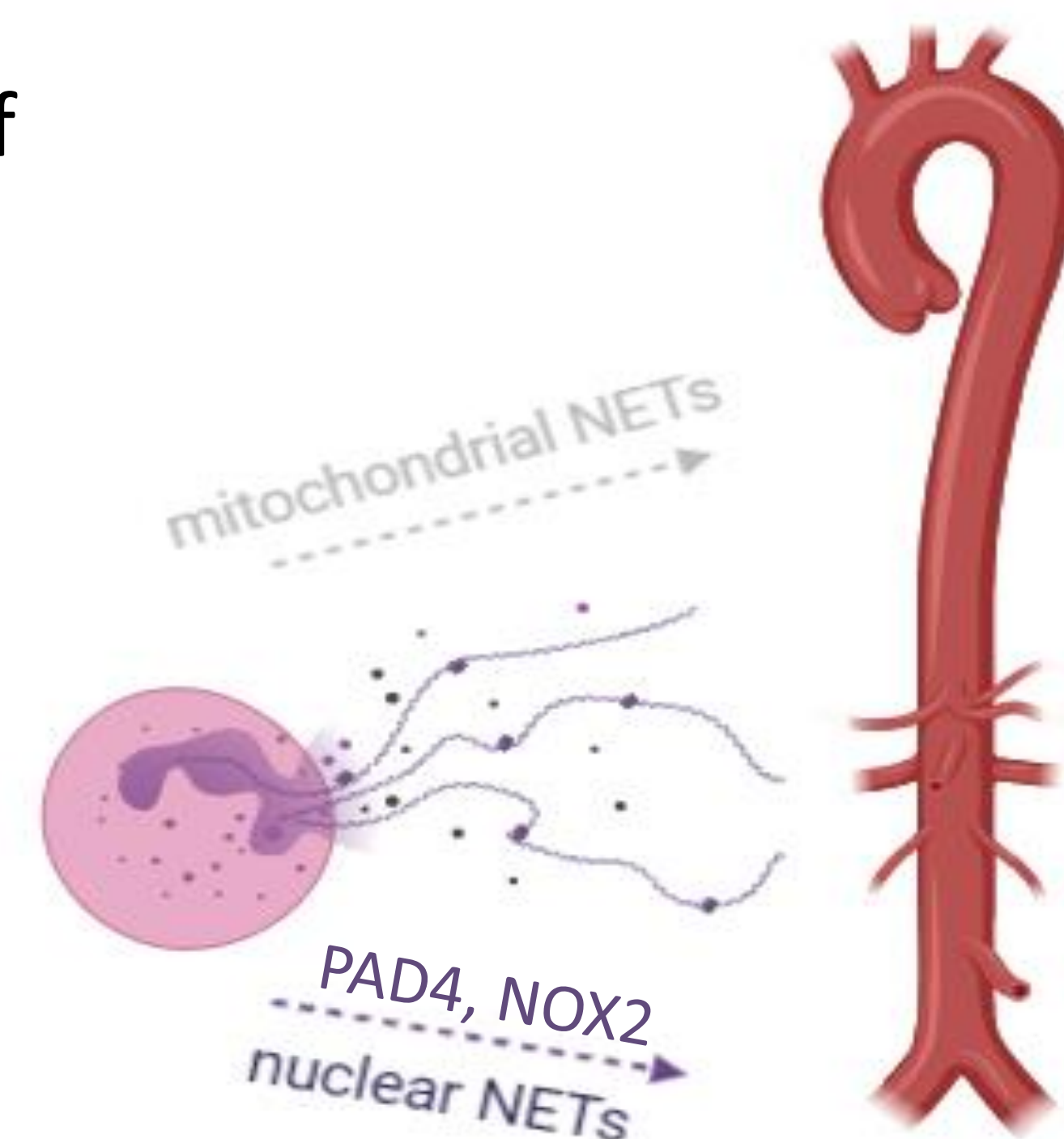
Brinkmann et al. (2004) | Delbosc et al. (2011)

Yan et al. (2016) | Meher et al. (2018)

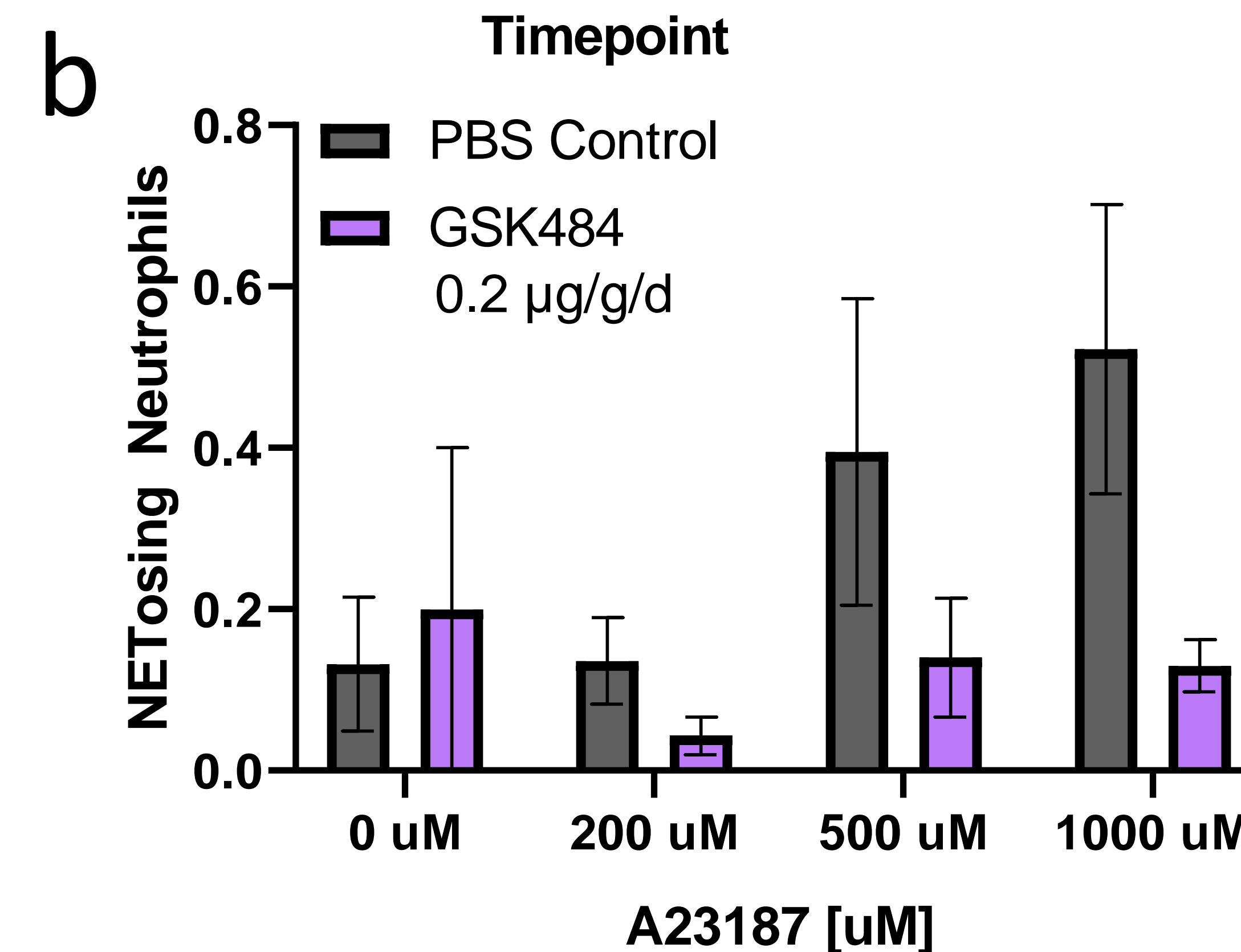
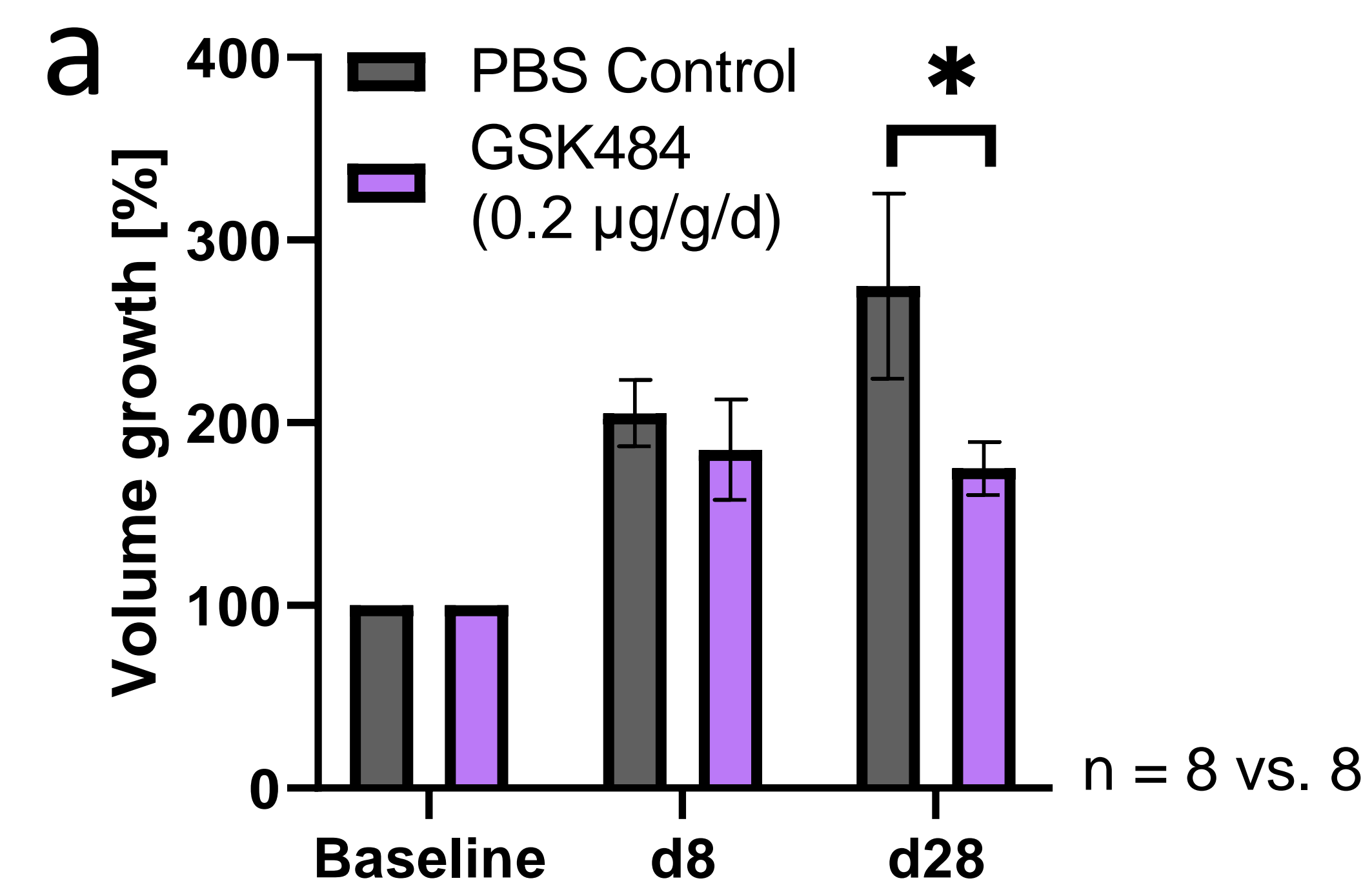
Aim

- Elucidate the therapeutic potential of NET inhibitors on established AAA in mice by targeting pathways of NET formation:

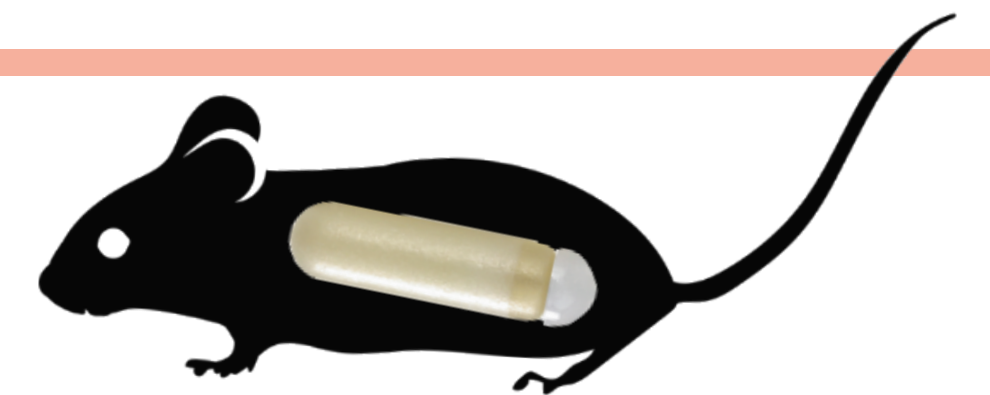
- PAD4 pathway
- NOX2 pathway
- mitochondrial ROS pathway



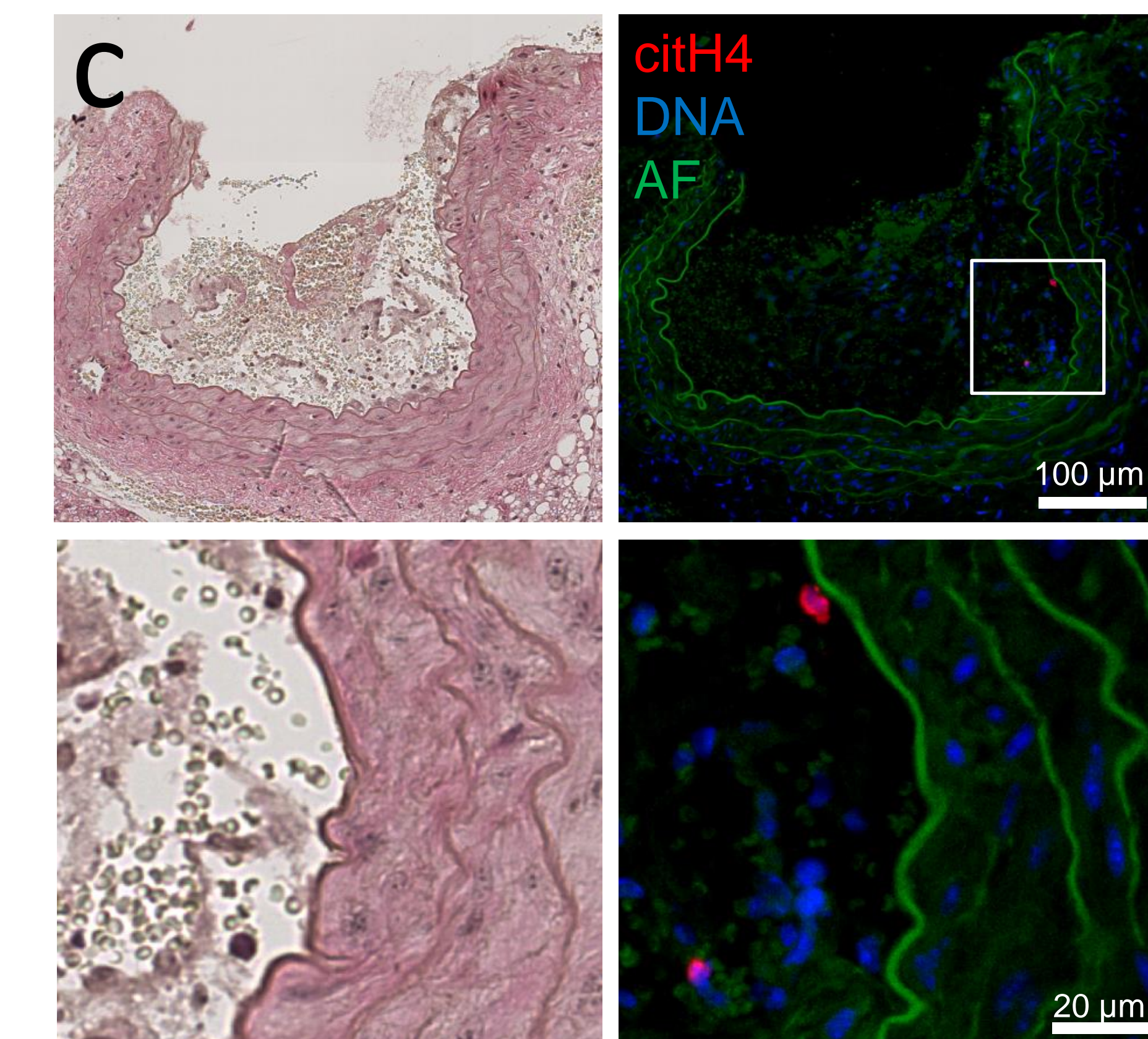
Results



Methods



- Induction of aneurysms in ApoE KO mice: subcutaneous osmotic pump with angiotensin-II
- Randomization at established disease (d8)
- Catheterization of the external jugular vein: daily intravenous injection of GSK484 (d10-28)
- a. AAA monitoring by 3D ultrasound
Tissue and blood collection on day 29:
- b. NET induction in *ex vivo* stimulated whole blood
- c. Immunostaining of citrullinated histones (citH4) in AAA tissue



Conclusions

- Lower AAA progression in GSK484-treated group: 175% vs. 275% growth of aortic volume by d28; $p=0.040$
- Lower NETosis capacity of *ex vivo* stimulated blood in GSK484-treated group
- Inhibition of the PAD4 pathway in NET formation is a promising target in AAA management
- Currently, other NET inhibitors are evaluated