**C** Helios



# Parallel Murine and Human Aortic Wall Genomics Reveals Metabolic Reprogramming as Key Driver of Abdominal Aortic Aneurysm Progression

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#### **Conficts of Interest**



#### **Disclosures:**

None

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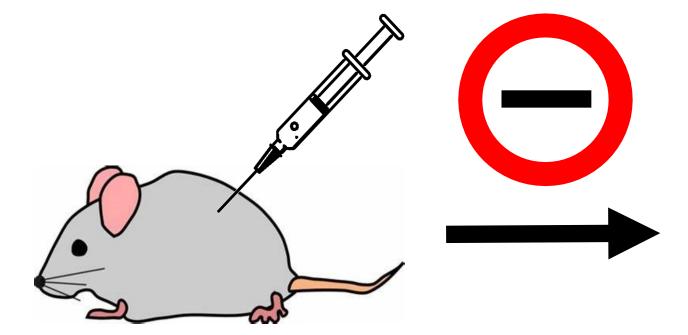
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#### **From Mice and Men**



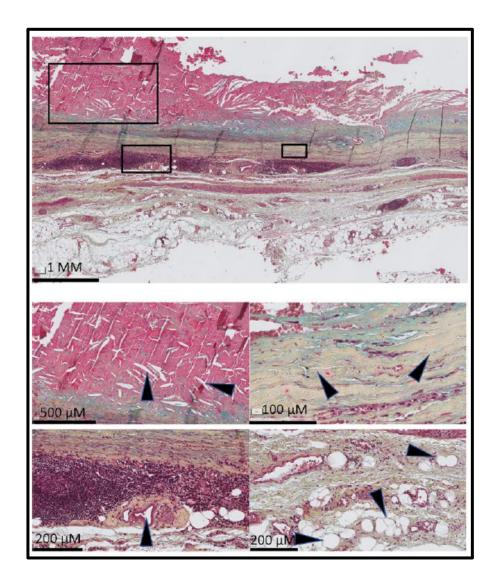
Targeted Cluster	Strategy	
Anti-inflammatory	$NF\kappa B,^{46}$ AP-1, $^{47}$ Rho kinase $^{48}$ inhibition	
	IL1,49 TNFa,50 CCL-151	
	B cell, $^{52}$ $\gamma\delta T\text{-cell}^{53}$ depletion	
	Neutrophil inhibition54	
	Mast cell inhibition <sup>55</sup>	
	Complement inhibition56,57	
	Oxilipin inhibition58,59	
	Immune suppression60,61	
Protease inhibition	MMP inhibition <sup>62,63</sup>	
	Cysteine protease inhibition <sup>64,65</sup>	
	Serine protease inhibition66,67	
Oxidative stress	Antioxidant enzymes68,69	
	Secondary antioxidants <sup>70,71</sup>	
Blood pressure lowering	β-Blockers <sup>72</sup>	
	Ca antagonists <sup>73</sup>	
	ACE inhibitors74,75	
	ATR1 antagonists <sup>76</sup>	
	iNOS inhibition77	
Lipid metabolism	Statins <sup>78,79</sup>	
	HDL <sup>80</sup>	
	RXR and PPARα/γ activation <sup>81,82</sup>	
Cell therapy	Mesenchymal stem cells <sup>83,84</sup>	
	Fibroblasts <sup>85</sup>	
Matrix/morphogens	Interference with TGF $\beta$ signaling <sup>86</sup>	
	Interference with NOTCH87/Wnt88 signaling	
	Thrombospontin inhibition89	
	EGFR inhibition <sup>90</sup>	
Metabolism	Inhibition of HIF1 $\alpha^{_{91}}$	
	Activation of AMPK <sup>92</sup>	
Nutriceuticals	Polyphenols93	
	Phytoestrogens <sup>94</sup>	
Sex hormones	Castration <sup>96</sup>	
	Estrogens <sup>96</sup>	

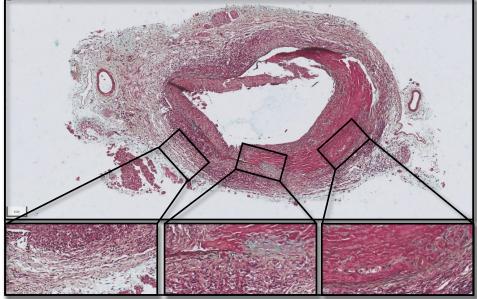
# Why is there a translational gap?

Where are differences and parallels between mice and men?

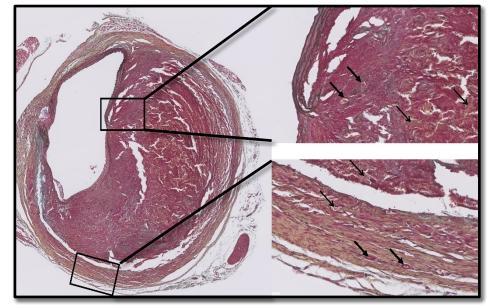
#### Elastase Modell

## **Histologic Changes**

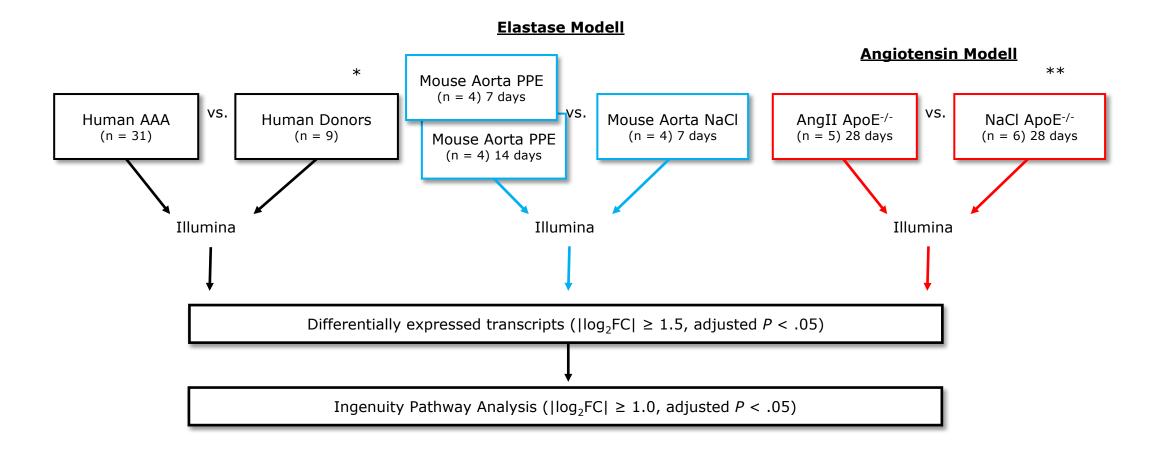




Angiotensin Modell

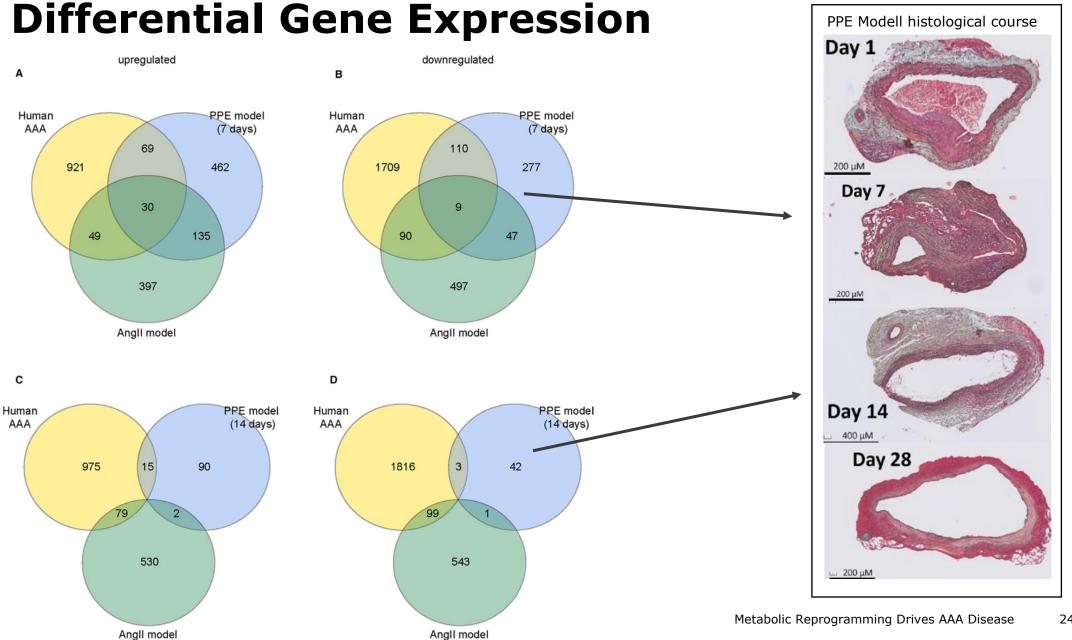


## **Experimental setup**



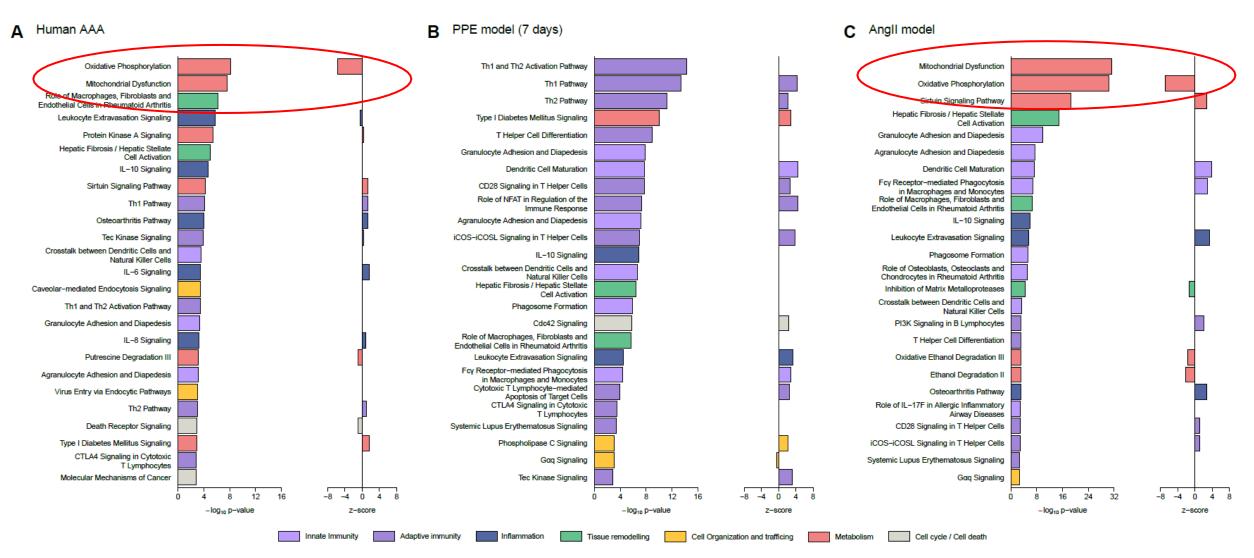
\*GEO accession GSE98278

\*\*GEO accession GSE12591



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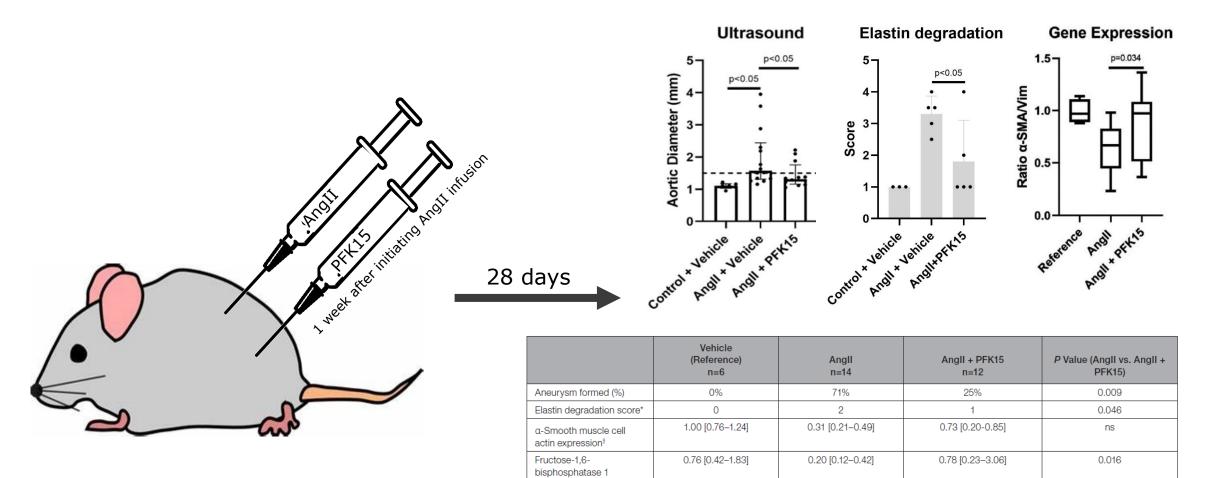
## **Ingenuity Pathway Analysis**



# **Metabolic Reprogramming**

Does it have any influence?

#### **Mouse Modell** – Rescue Treatment with Glycolysis Inhibitor



expression<sup>†</sup>

day 0 (g)

Change in body weight vs.

Blood glucose (mmol/L)

+1.0 [0.00-2.00]

8.0 [6.40-9.10]

+0.1 [-0.50 to 1.00]

5.4 [4.80-5.90]

0.008

0.021

+1.5 [1.00-2.00]

6.8 [5.65-7.90]

## Conclusion

- Histomorphologic experimental AAA models are distinct from clinical AAA disease
  - AngII intramural hematoma (dissection model)
  - PPE aneurysm formation limited to first 2 weeks
- Genomic response with clear overlaps
  - AngII metabolic reprogramming (glycolytic shift)
  - PPE adaptive immunity (at day 7)
  - PPE model mimics initiating stages of disease and AngII model late-stage AAA
- PFKFB3 intervention trial suggests that glycolytic switch drives AAA progression
  - Rationale for beneficial effects of metformin therapy
  - Explaination for negative association between diabetes and AAA progression



# Thank You



Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis Leukocyte Extravasation Signaling

Crosstalk between Dendritic Cells and

Granulocyte Adhesion and Diapedesis

Agranulocyte Adhesion and Diapedesis

Type I Diabetes Mellitus Signaling

PI3K Signaling in B Lymphocytes Fcy Receptor-mediated Phagocytosis in Macrophages and Monocytes Systemic Lupus Ervthematosus Signaling

Role of Osteoblasts, Osteoclasts and Chondrocytes in Rheumatoid Arthritis Role of NFAT in Regulation of the Immune Response

iCOS-iCOSL Signaling in T Helper Cells

Dendritic Cell Maturation Primary Immunodeficiency Signaling

Axonal Guidance Signaling

Macropinocytosis Signaling Ethanol Degradation IV

Ethanol Degradation II

TWEAK Signaling

Oxidative Ethanol Degradation III

3-phosphoinositide Biosynthesis Colorectal Cancer Metastasis Signaling CD28 Signaling in T Helper Cells

STAT3 Pathway Goq Signaling Phagosome Formation Superpathway of Inositol Phosphate Compounds Inhibition of Matrix Metalloproteases T Helper Cell Differentiation

Th1 and Th2 Activation Pathway

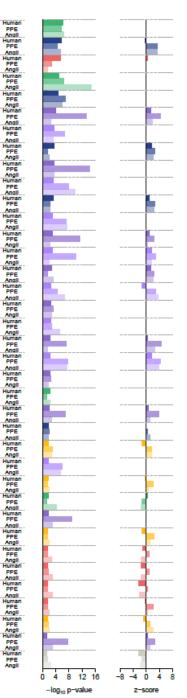
Protein Kinase A Signaling Hepatic Fibrosis / Hepatic Stellate

Cell Activation IL-10 Signaling Th1 Pathway

Natural Killer Cells IL-6 Signaling

IL-8 Signaling

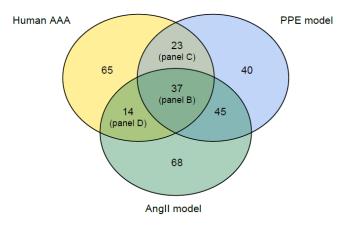
Th2 Pathway



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# **Ingenuity Pathway Analysis**

Overlapping cannonical pathways



#### Pathways pertubated in human AAA and AngII model

Oxidative Phosphorylation	Human		
Oxidative Phosphorylation	Angli		
Mitochondrial Dysfunction	Human		
Millochonanar Dystancion	Angli		
Sirtuin Signaling Pathway	Human		
on tail originaling Faannay	Angli		
Osteoarthritis Pathway	Human		
,	Angli		
Prostanoid Biosynthesis	Human		
,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	Angli		
PPAR Signaling	Human		_
5 5	Angli Human		
Inhibition of Angiogenesis by TSP1	Angli		-
Tumoricidal Function of	Human		
Hepatic Natural Killer Cells	Angli		
	Human		
TNFR1 Signaling	Angli		
	Human	·	
D-myo-inositol-5-phosphate Metabolism	Angli		1
Role of IL-17F in Allergic Inflammatory	Human		
Airway Diseases	Angli		
	Human		
Aryl Hydrocarbon Receptor Signaling	Angli		
Nitric Oxide Signaling in the	Human		
Cardiovascular System	Angli		
HMGB1 Signaling	Human		
Filviob Foighailing	Angli		
		0 8 16 24 32	-8-404
		0 0 10 24 32	-0-404
		-log <sub>10</sub> p-value	z-score

Pathways pertubated in human AAA and PPE model

	Human	
Tec Kinase Signaling	PPE	
Caveolar-mediated Endocytosis Signaling	Human PPE	
Putrescine Degradation III	Human PPE	
Virus Entry via Endocytic Pathways	Human PPE	
Death Receptor Signaling	Human PPE	
CTLA4 Signaling in Cytotoxic T Lymphocytes	Human PPE	
Molecular Mechanisms of Cancer	Human PPE	
Integrin Signaling	Human PPE	
Noradrenaline and Adrenaline Degradation	Human PPE	
Phospholipase C Signaling	Human PPE	
Tryptophan Degradation X (Mammalian, via Tryptamine)	Human PPE	
Gap Junction Signaling	Human PPE	
Relaxin Signaling	Human PPE	
Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells	Human PPE	
Cdc42 Signaling	Human PPE	
Signaling by Rho Family GTPases	Human PPE	
CXCR4 Signaling	Human PPE	
Regulation of Actin-based Motility by Rho	Human PPE Human	
Mechanisms of Viral Exit from Host Cells	PPE Human	
RAR Activation	PPE Human	
Vitamin-C Transport	PPE	
Erythropoietin Signaling	PPE	
fMLP Signaling in Neutrophils	PPE	
	0 4	8 -8 -4 0 4 8
	−log <sub>10</sub> p−va	alue z-score
		_
Innate Immunity	Adaptive immunity	Inflammation
Tissue remodelling	Cell Organization and tra	afficing Metabolism
Cell cycle / Cell death		

Regulation of Actin-bas Mechanisms of Viral Ei Vit Erythr fMLP Signa