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

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Helios

Conficts of Interest

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None

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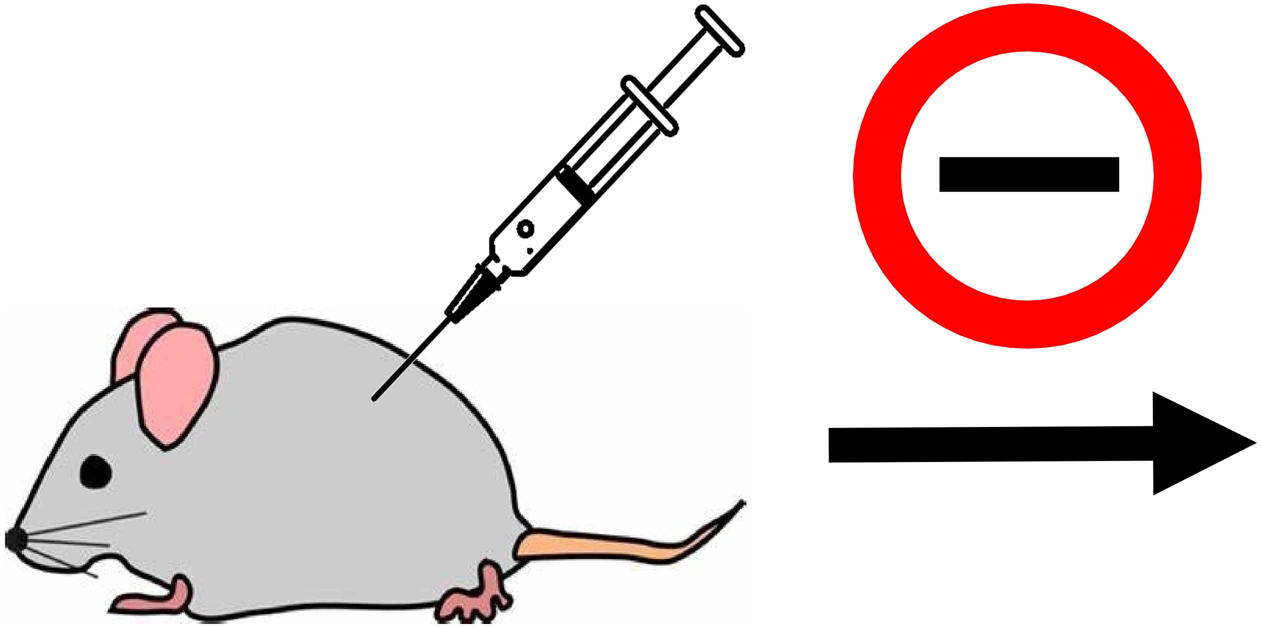
From Mice and Men



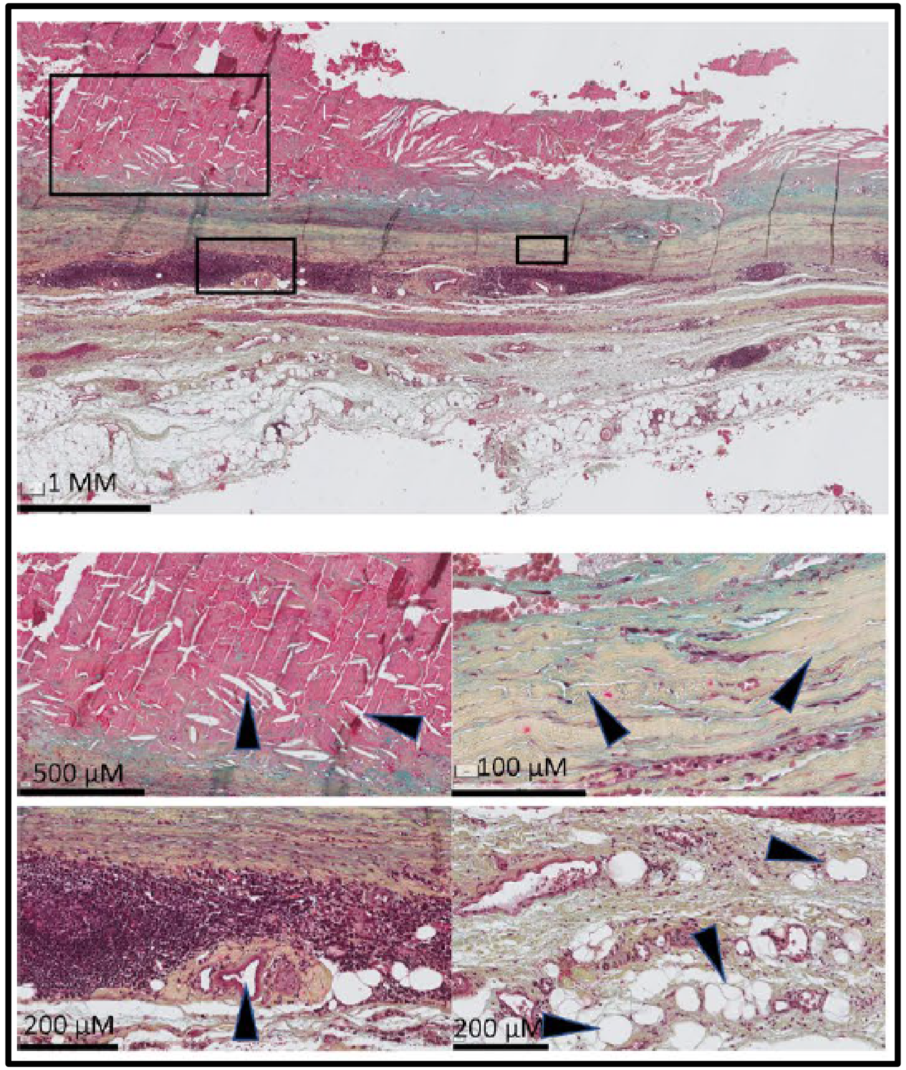
Targeted Cluster	Strategy
Anti-inflammatory	NFκB,[46] AP-1,[47] Rho kinase[48] inhibition
	IL1,[49] TNFα,[50] CCL-1[51]
	B cell,[52] γδT-cell[53] depletion
	Neutrophil inhibition[54]
	Mast cell inhibition[55]
	Complement inhibition[56,57]
	Oxilipin inhibition[58,59]
	Immune suppression[60,61]
Protease inhibition	MMP inhibition[62,63]
	Cysteine protease inhibition[64,65]
	Serine protease inhibition[66,67]
Oxidative stress	Antioxidant enzymes[68,69]
	Secondary antioxidants[70,71]
Blood pressure lowering	β-Blockers[72]
	Ca antagonists[73]
	ACE inhibitors[74,75]
	ATR1 antagonists[76]
	iNOS inhibition[77]
Lipid metabolism	Statins[78,79]
	HDL[80]
	RXR and PPARα/γ activation[81,82]
Cell therapy	Mesenchymal stem cells[83,84]
	Fibroblasts[85]
Matrix/morphogens	Interference with TGFβ signaling[86]
	Interference with NOTCH[87]/Wnt[88] signaling
	Thrombospontin inhibition[89]
	EGFR inhibition[90]
Metabolism	Inhibition of HIF1α[91]
	Activation of AMPK[92]
Nutriceuticals	Polyphenols[93]
	Phytoestrogens[94]
Sex hormones	Castration[95]
	Estrogens[96]

Lindeman & Matsumura *Circ Res* 2019

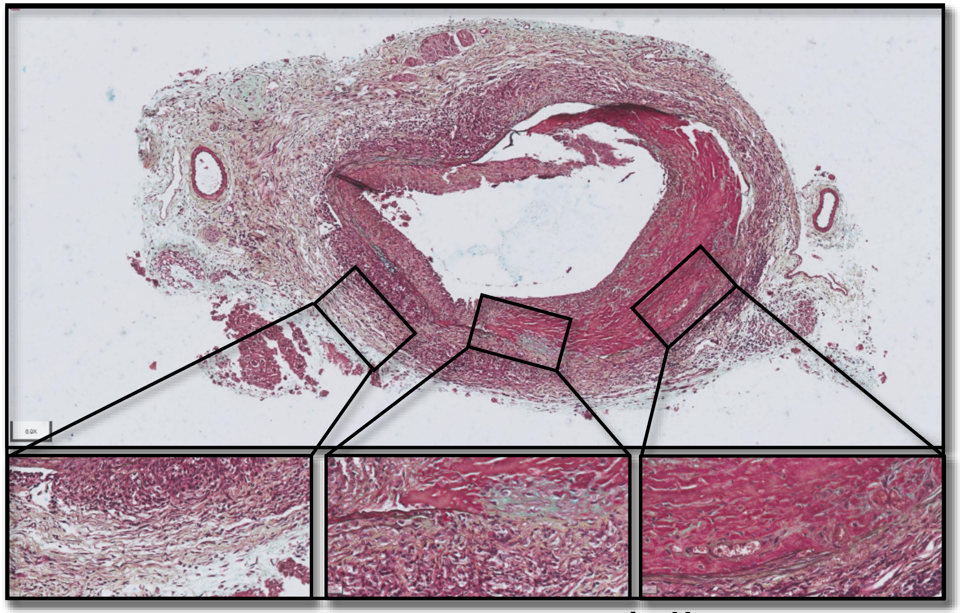
Why is there a translational gap?

Where are differences and parallels between mice and men?

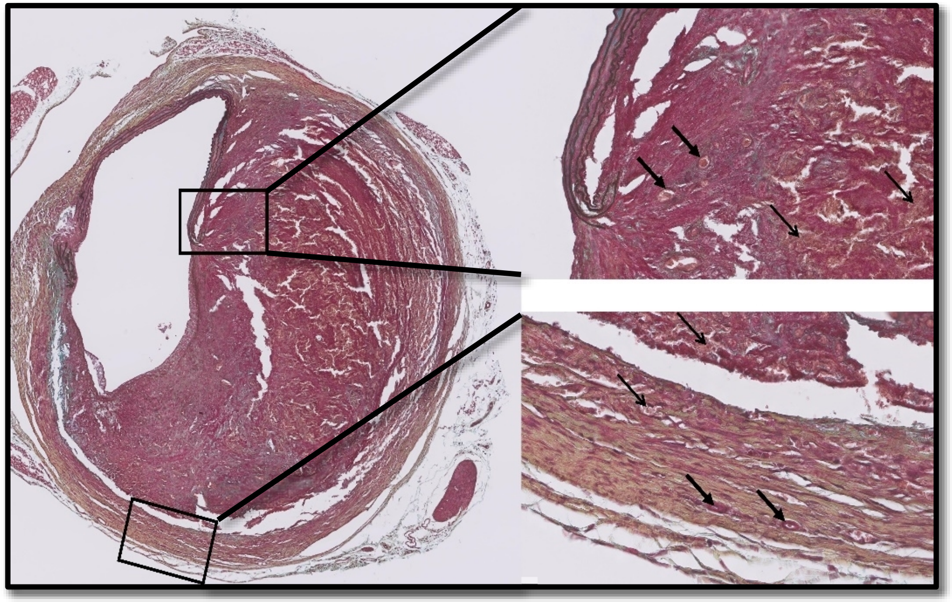
Histologic Changes



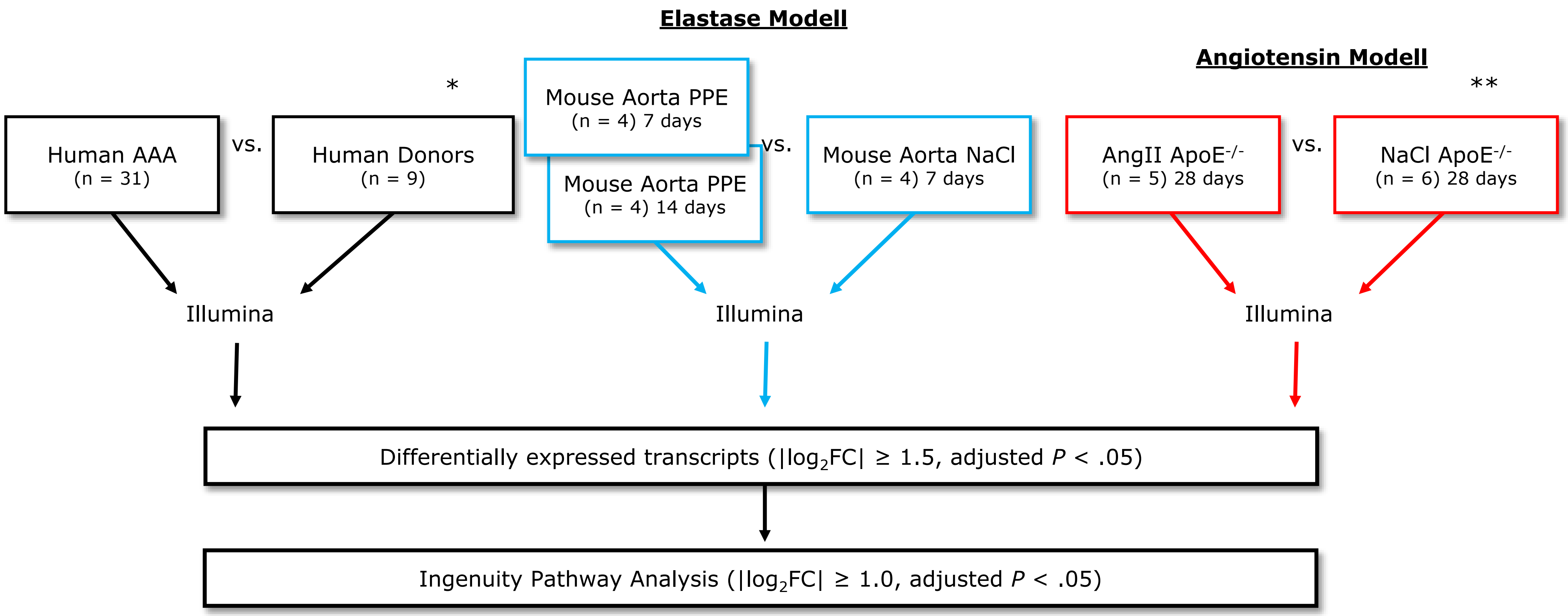
Elastase Modell



Angiotensin Modell



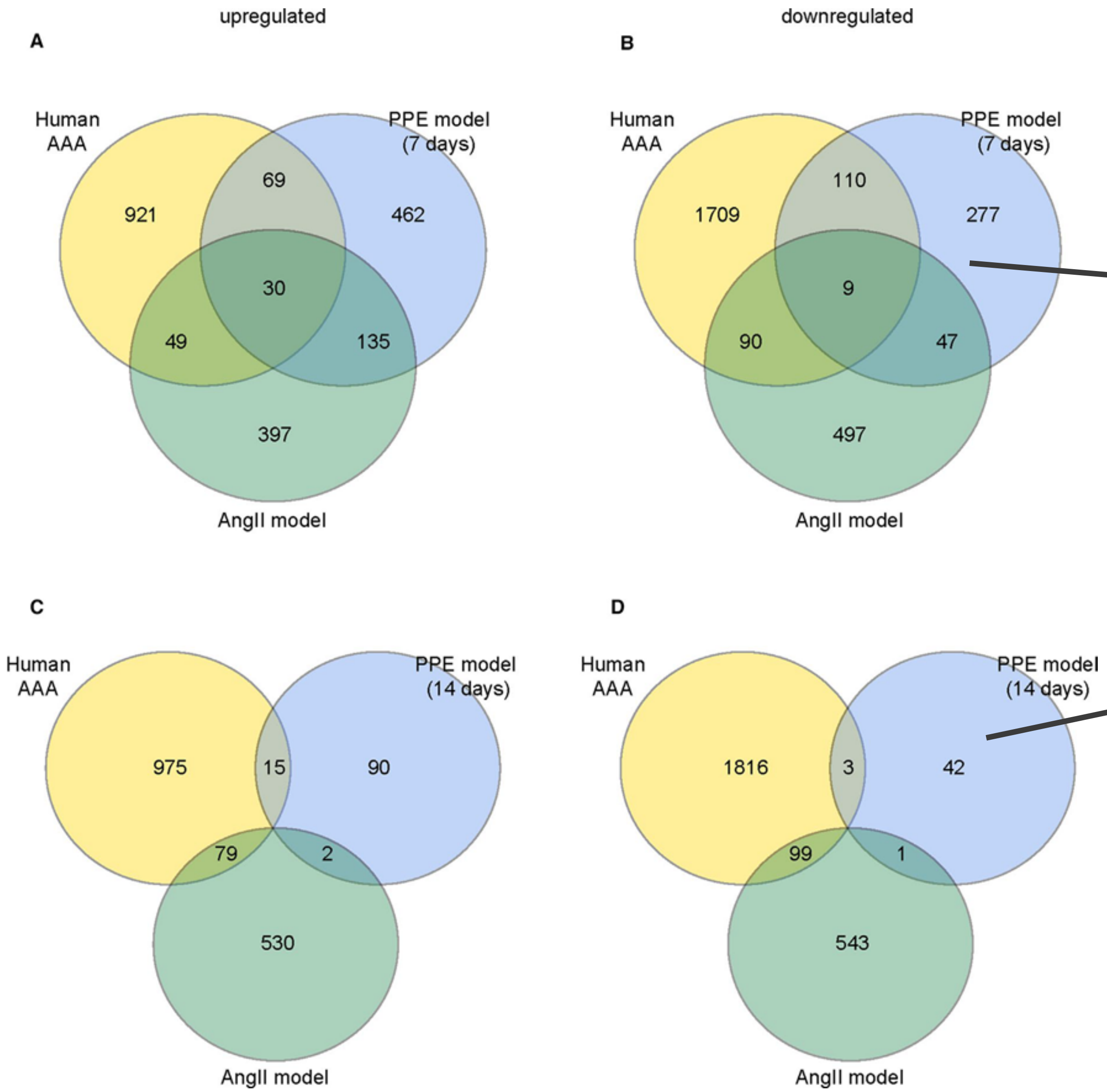
Experimental setup

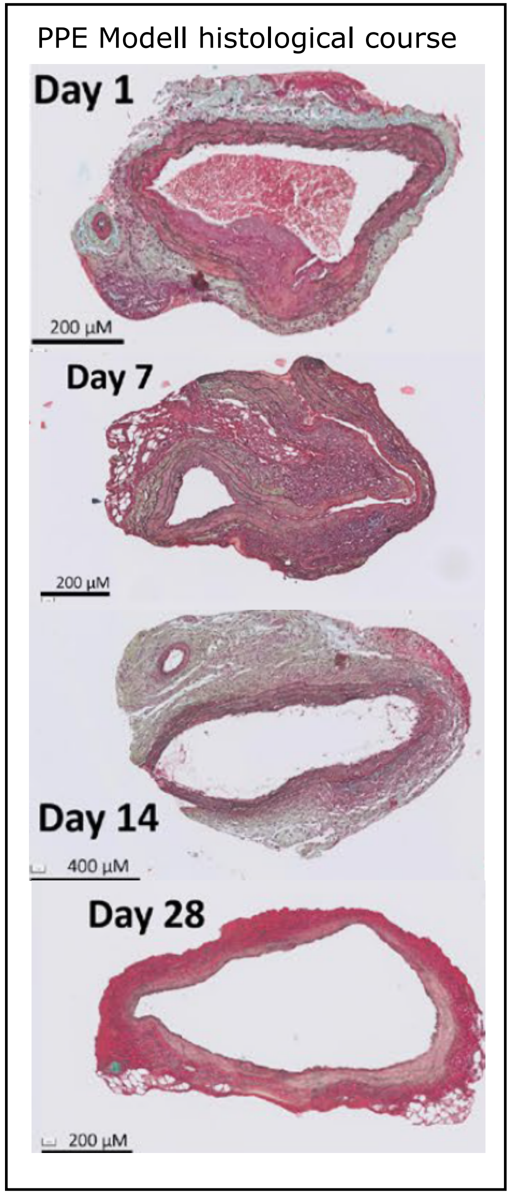


*GEO accession GSE98278

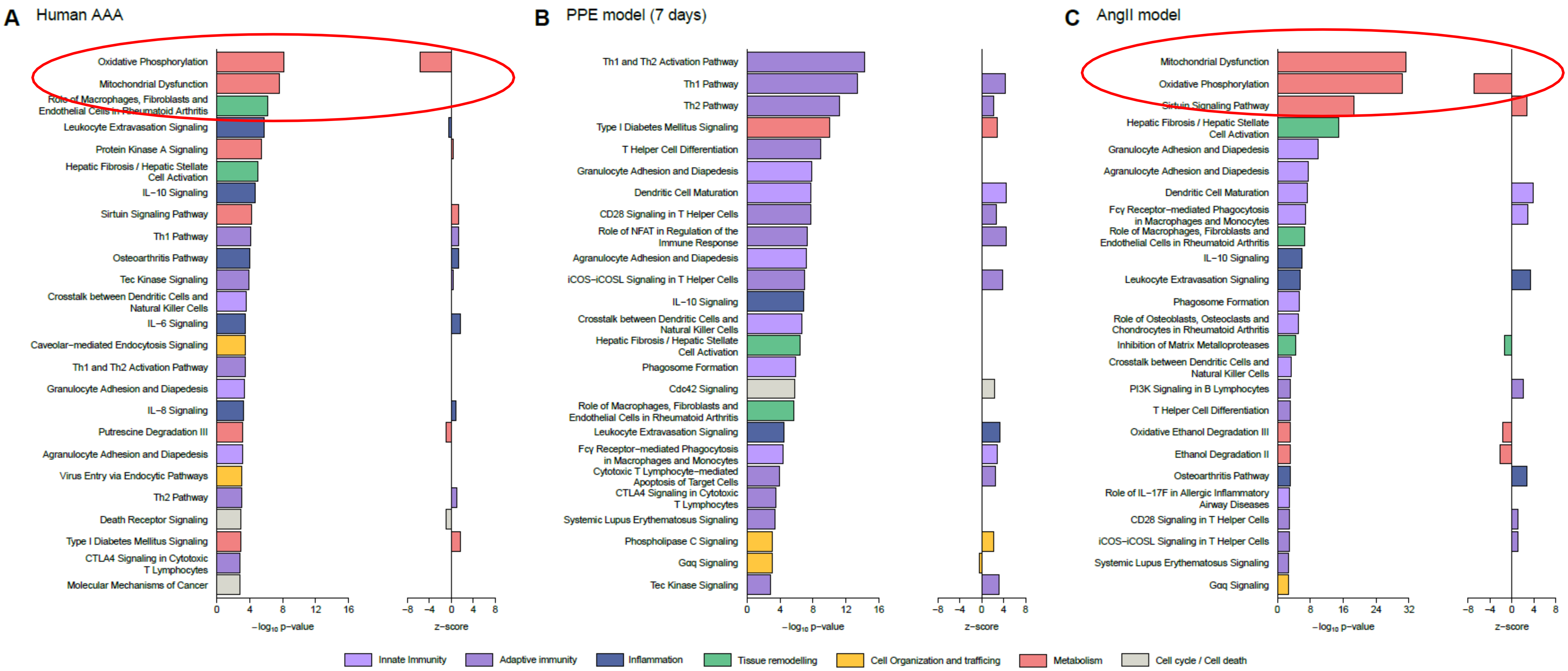
**GEO accession GSE12591

Differential Gene Expression





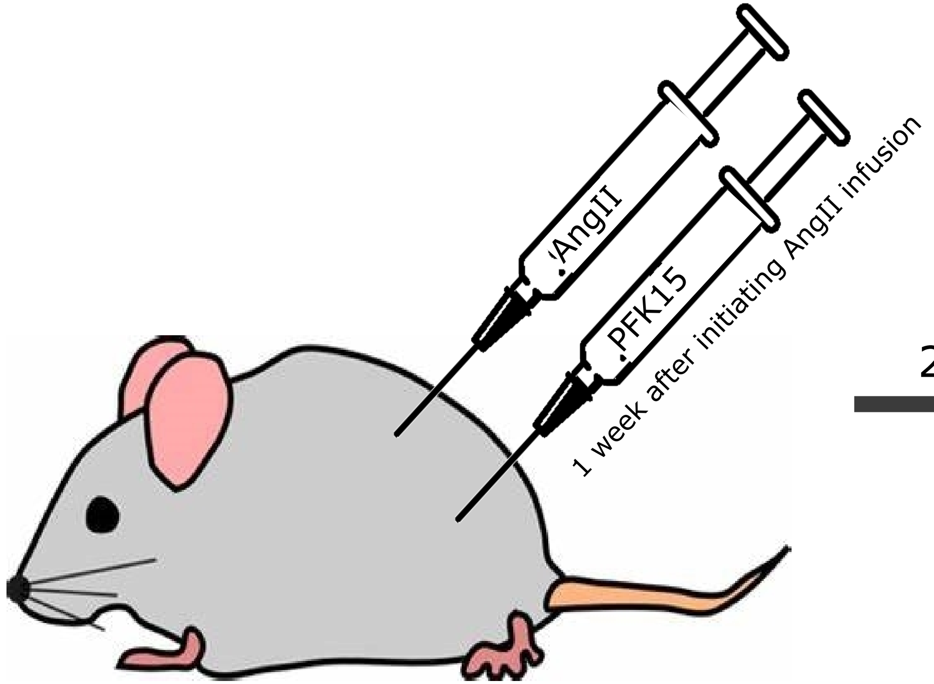
Ingenuity Pathway Analysis



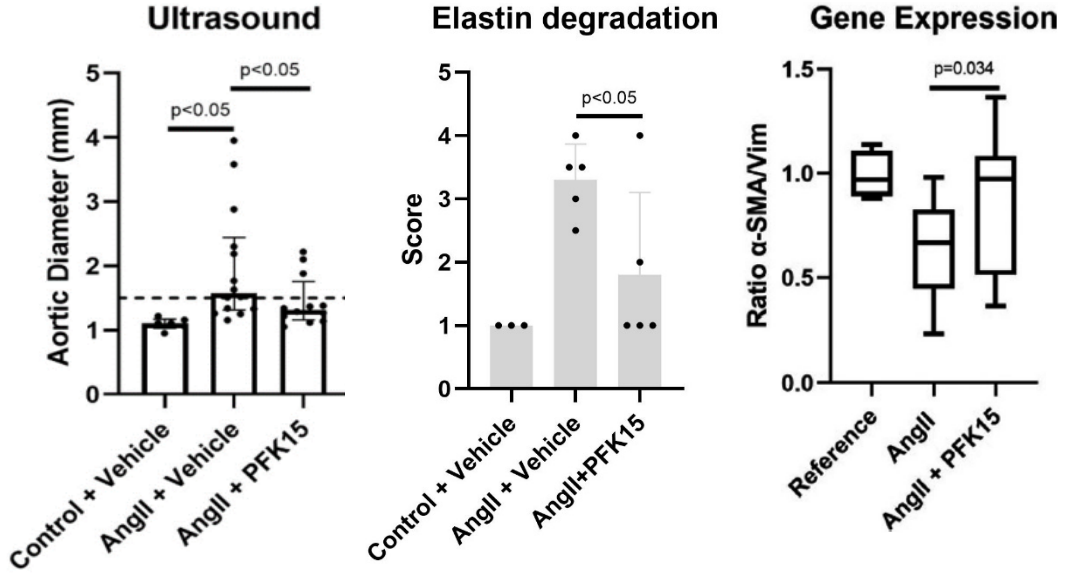
Metabolic Reprogramming

Does it have any influence?

Mouse Modell – Rescue Treatment with Glycolysis Inhibitor



28 days



	Vehicle (Reference) n=6	AngII n=14	AngII + PFK15 n=12	*P* Value (AngII vs. AngII + PFK15)
Aneurysm formed (%)	0%	71%	25%	0.009
Elastin degradation score*	0	2	1	0.046
α-Smooth muscle cell actin expression†	1.00 [0.76–1.24]	0.31 [0.21–0.49]	0.73 [0.20-0.85]	ns
Fructose-1,6-bisphosphatase 1 expression†	0.76 [0.42–1.83]	0.20 [0.12–0.42]	0.78 [0.23–3.06]	0.016
Change in body weight vs. day 0 (g)	+1.0 [0.00–2.00]	+1.5 [1.00–2.00]	+0.1 [−0.50 to 1.00]	0.008
Blood glucose (mmol/L)	8.0 [6.40–9.10]	6.8 [5.65–7.90]	5.4 [4.80–5.90]	0.021

Conclusion

- Histomorphologic experimental AAA models are distinct from clinical AAA disease
  - AngII – intramural hematoma (dissection model)
  - PPE – aneurysm formation limited to first 2 weeks

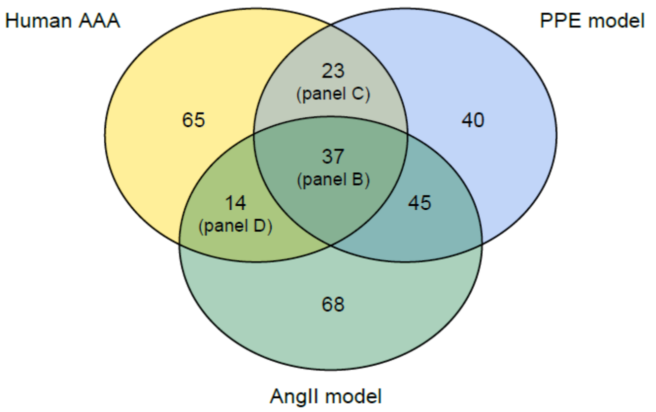
- Genomic response with clear overlaps
  - AngII – metabolic reprogramming (glycolytic shift)
  - PPE – adaptive immunity (at day 7)
  - PPE model mimics initiating stages of disease and AngII model late-stage AAA

- 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

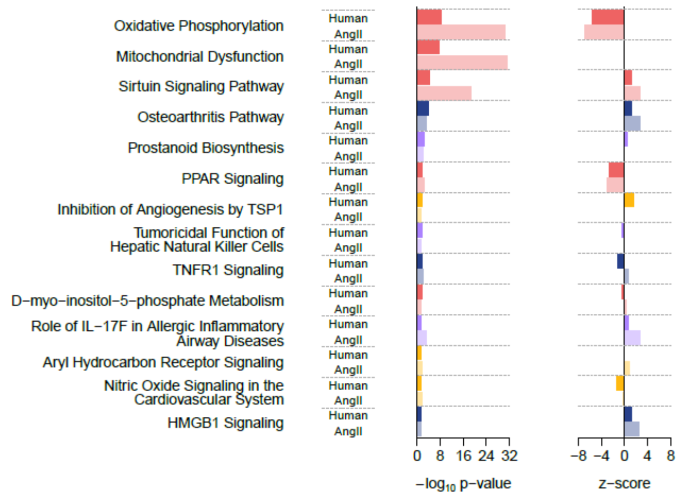
Thank You

Ingenuity Pathway Analysis

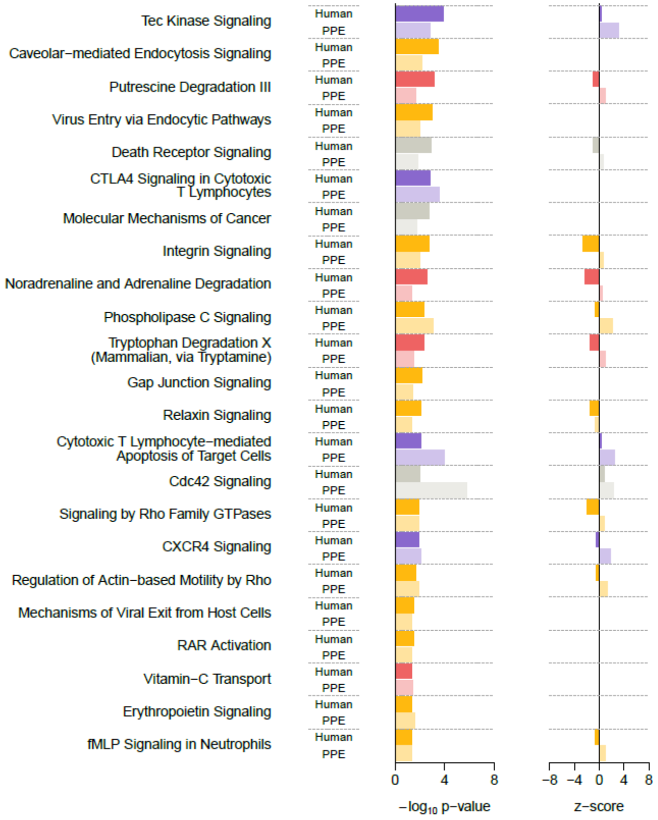
Overlapping cannonical pathways

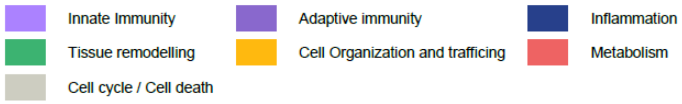


Pathways pertubated in human AAA and AngII model



Pathways pertubated in human AAA and PPE model





Pathways pertubated in human AAA, PPE and AngII model