Lessons learnt from the guinea pig to rat transplantation model of AAA

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- AAA animal models are far from human disease
- Plate-form of 4 AAA models: each designed to answer a set of questions
- Microsurgical replacement of rat subrenal aorta

![Diagram showing AAA animal models and their outcomes](image)
A chimeric injured, dilated aorta

SDS-decellularized aortic guinea pig aorta: ECM

AAA: gp ECM + recipient rat cells and proteins

Pg elastin  V-alpha actin + cells (VSMCs?)  Macrophages, Lymphocytes PMNs MMPs, plasmin pathway  Adventitial microvessels
MMPs activated by fibrinolytic system

Inflammatory cells
Wall cells

serum → plasminogen

PAI-1

PA

Inflammatory cells
Wall cells

inactive MMP-3
inactive MMP-9

plasmin

active MMP-3
active MMP-9

TIMP-1

Arterial ECM

E Allaire, JCI, Circulation 1998
Luminal fresh thrombus: blood/fibrin interface
Light and shadows

humans
Genetic / environment → trigger → xenograft
Rejection of xenogeneic ECM

injury
Response to injury

AAA
“AAA”

formed AAA stabilization by healing
Light and shadows

humans
Genetic / environment

trigger

xenograft
Rejection of xenogeneic ECM

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Genetic / environment
Preclinical model to test therapeutic hypotheses

Pathophysiology?

Therapeutic

\[
\% \text{ diameter increase} = \left( \frac{d_{2 \text{ months}} - d_0}{d_0} \right) \times 100
\]
Local endovascular biotherapies

PCR / construction AdnlsLacZ à j3

thrombus

aneurysmal wall
1. VSMC enrichment stabilizes expanding AAAs with protease-injured ECM

1. 1. No hemodynamic substraction

1. 2. VSMC/ Inflammation containment

Allaire et al., Ann Surg 2004
Losy JVS 2005
2. AAA wall reprogrammation

Recovered aortic stability and structure

unstable

stable

: VSMC
: endothelial cells
2. AAA wall reprogrammation

Recovered aortic stability and structure

Concept of endovascular healing induction through reprogrammation

- cells (VSMCs, MSCs, endothelial cells)
- genes (TGF-beta1)
- drug (Cyclosporine A)
2. AAA wall reprogramming

Recovered aortic stability and structure

Concept of endovascular healing induction through reprogramming

- cells (VSMCs, MSCs, endothelial cells)
- genes (TGF-beta1)
- drug (Cyclosporine A)
Exogenous TGF-b1 induces endogenous rat TGF-b1

mRNA

Protein
2. AAA wall reprogrammation

Diameter

Exogenous TGF-beta1

1 shot interventional delivery
2. AAA wall reprogramming

1 shot interventional delivery
2. AAA wall reprogrammation

1 shot interventional delivery

- Exogenous TGF-beta1
- Endogenous TGF-beta1
- VSMCs

Graph showing destruction and reconstruction processes.
2. AAA wall reprogramming

- Adenovirus
- RECONSTRUCTION
- Exogenous TGF-beta1
- Diameter
- Endogenous TGF-beta1
- VSMCs
- DESTRUCTION
- 1 shot interventional delivery
3. AAA wall reprogramming by inductive pharmacology

Ciclosporin A induces TGF-beta1 in human AAA explants
3. AAA wall reprogrammation by inductive pharmacology

CsA induces a TGF-beta1-dependant healing process in AAAs
3. AAA wall reprogrammation by inductive pharmacology

Study in AAA patients
1. VSMC enrichment stabilizes expanding aorta with protease-injured ECM, without hemodynamic substraction
2. AAA wall reprogramming to gain stability beyond treatment stimulation to avoid systemic side effects
3. Pre-clinical means in formed, expanding experimental AAAs
Science describes facts with words that need to be as precise as words in poetry