The cell strikes back: disease-responsive gene therapy for aortic aneurysms

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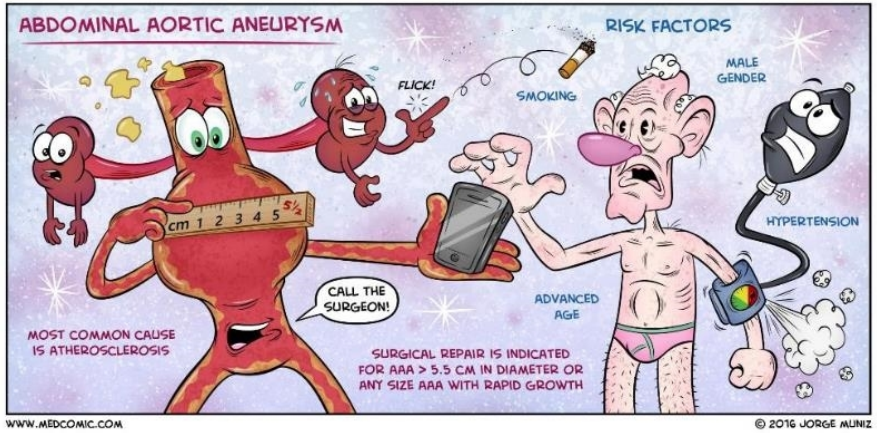
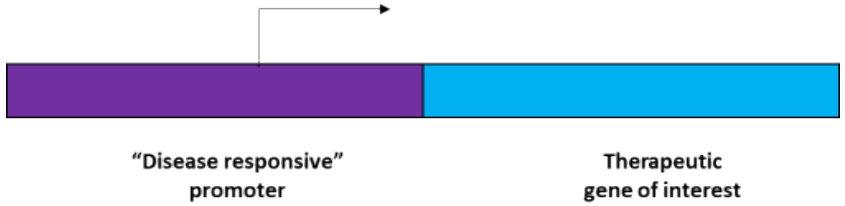
Unclear pathophysiology hinders therapy

- The pathophysiology of aortic aneurysms (AA) is unclear

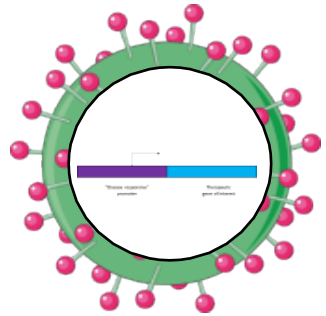


- Some known molecular processes: disturbed smooth muscle cell (SMC) contraction, SMC apoptosis, disturbed TGFβ signalling and inflammation
- SMC function
- Due to the lack of understanding of the molecular mechanisms, pharmacological therapy is limited
- **Aim: proof of concept gene therapy for AA**

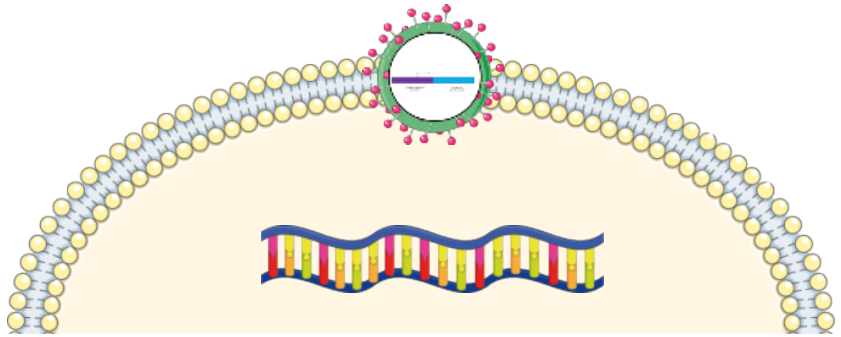
Using viral vectors responsive to disease stimuli to deliver therapeutic gene of interest



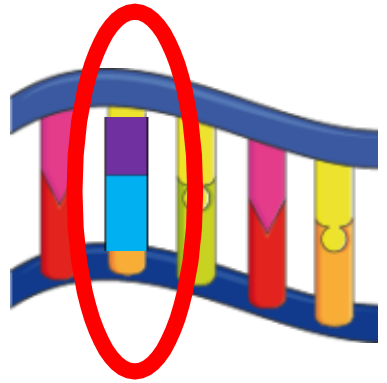
Designed sequence



"Empty" virus that brings in the sequence – viral vector

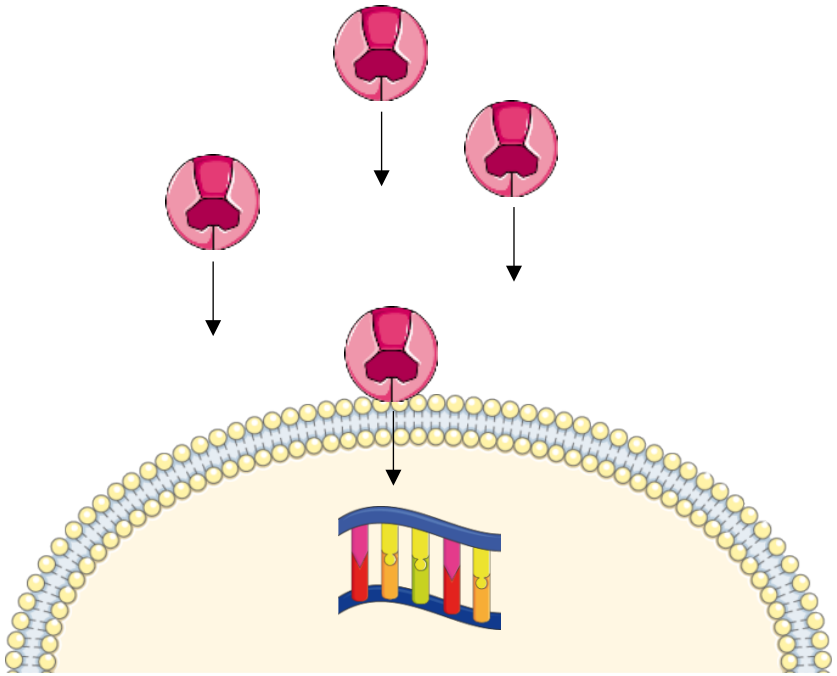


Viral vector brings the sequence into the target cell

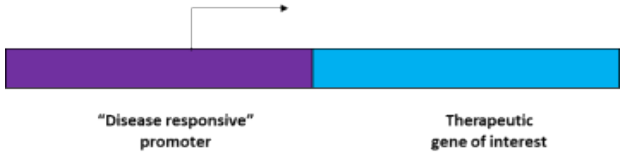


Sequence is integrated in target cell DNA

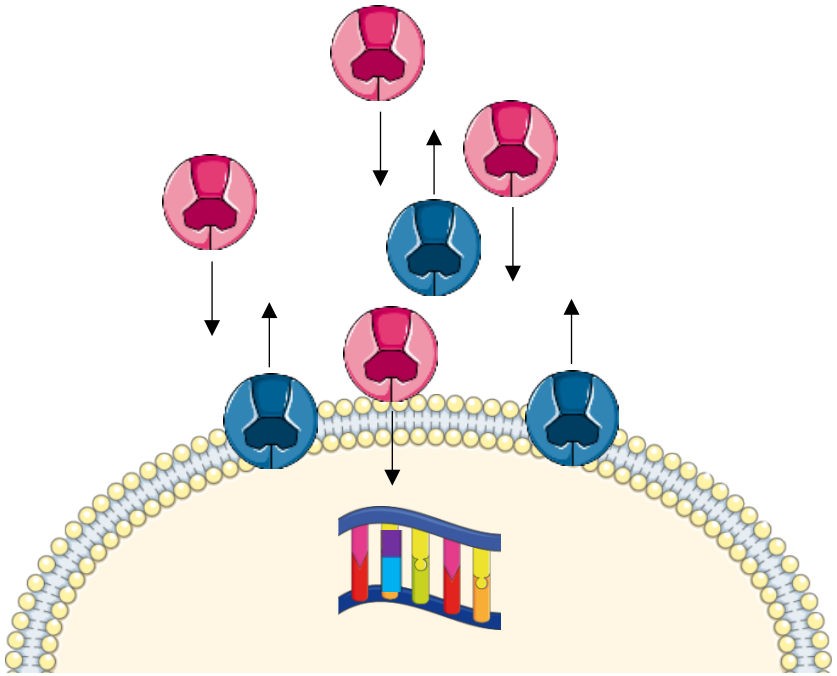
Disease specific signaling: Proinflammatory cytokines or increased TGFβ signaling



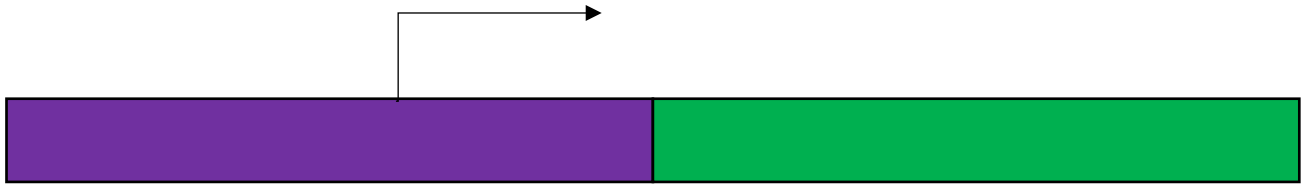
Transcription of therapeutic protective gene is triggered by disease stimuli



Cell produces proteins that counteract disease signaling



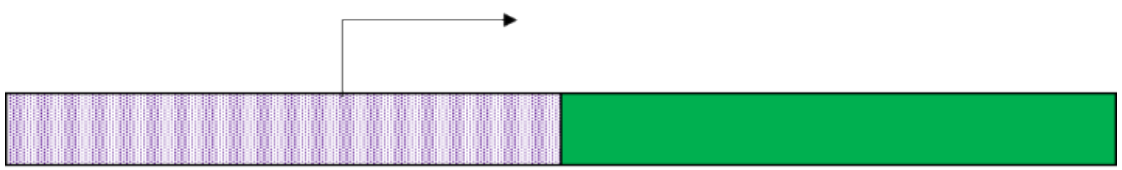
Optimizing in healthy aortic SMC using GFP for easy detection



"Disease responsive" promoter

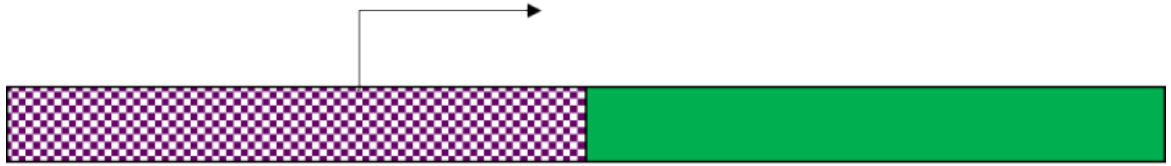
Green fluorescent protein (GFP)

Optimizing viral vector (VV) and stimulus dose and timing



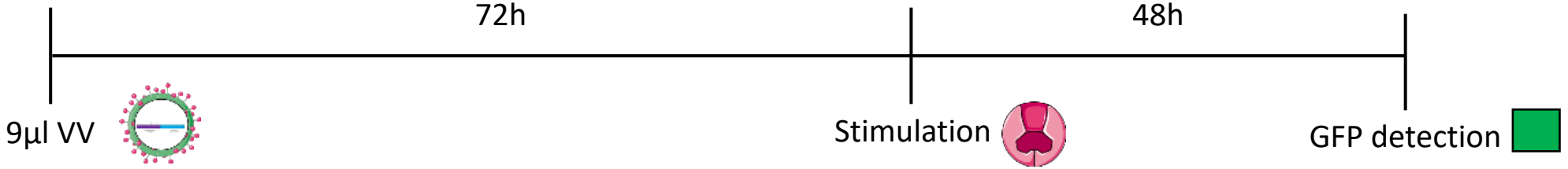
TNFα responsive promoter

GFP

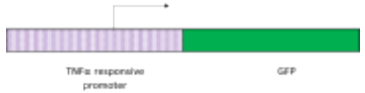


TGFβ responsive promoter

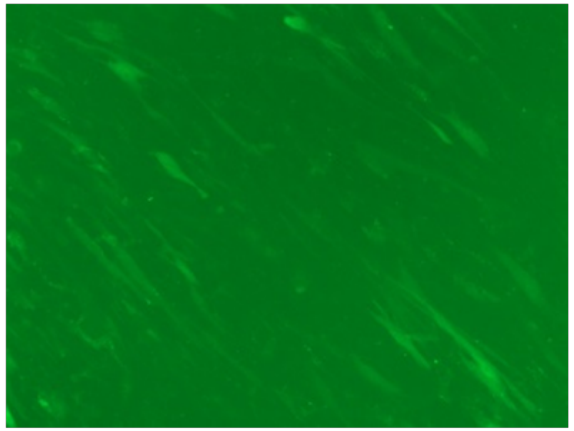
GFP



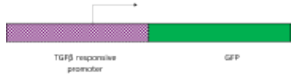
Control SMC with incorporated viral vectors are responsive to disease stimuli



Unstimulated



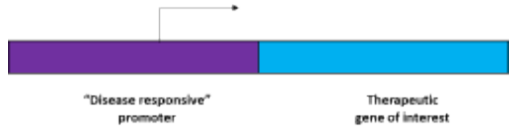
Cells express GFP upon TNFα stimulation, showing responsiveness to inflammation



Unstimulated

Cells express GFP upon TGFβ stimulation, showing responsiveness to increased TGFβ signaling

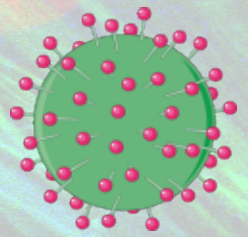
Next steps



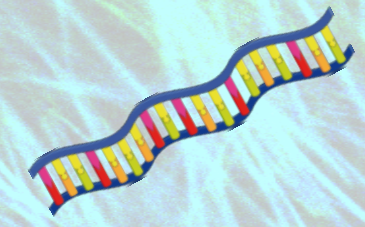
- Testing viral vectors in available AA patient SMC
- Replacing GFP with therapeutic genes and measuring decrease in disease signaling
- Testing viral vectors in animal models of AA

Next next steps

- Developing gene therapy for vascular diseases
- Testing therapeutic genes using clinically validated viral vectors that are SMC specific
- Testing therapeutic genes that can prevent dilation or restore the structure of the aortic wall



Thank you for your attention!



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