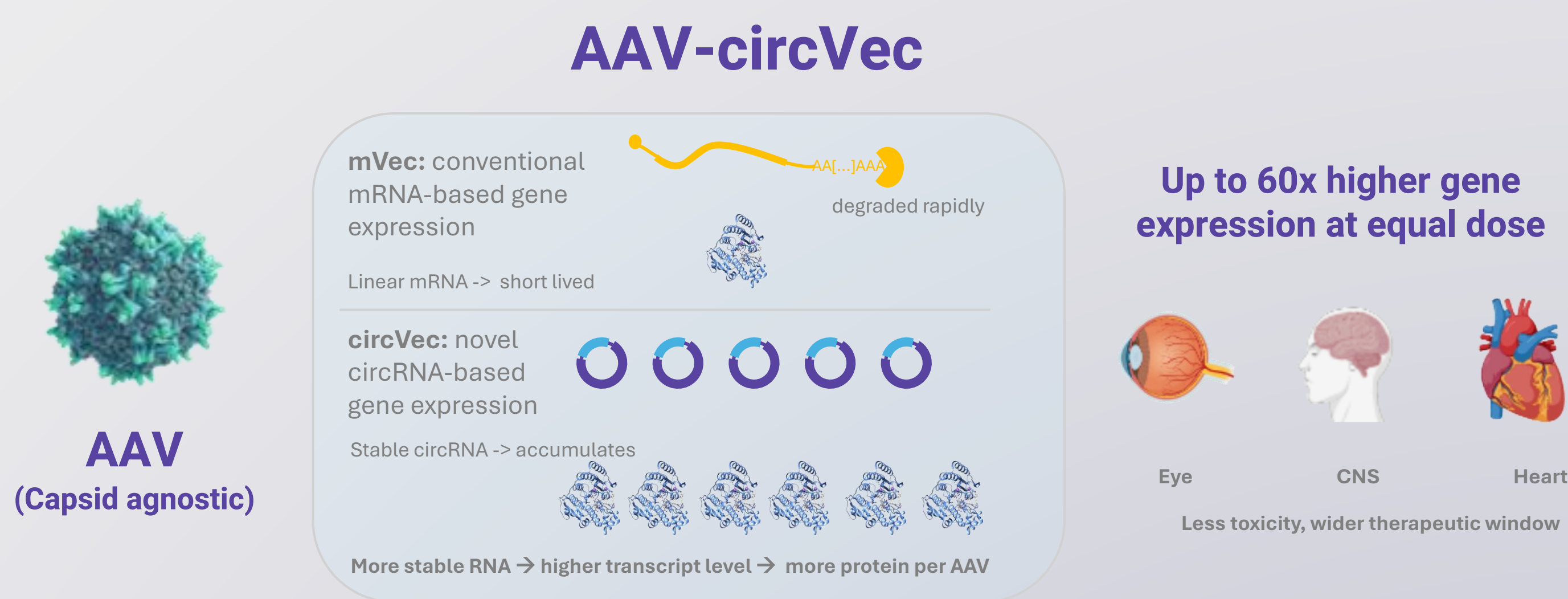
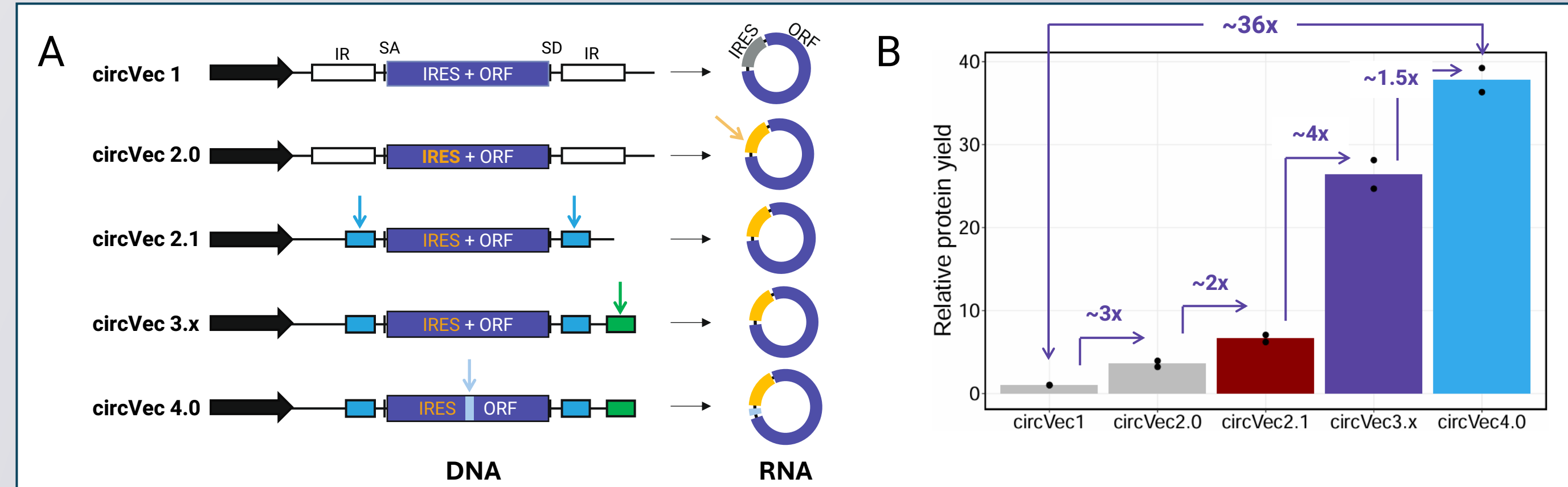


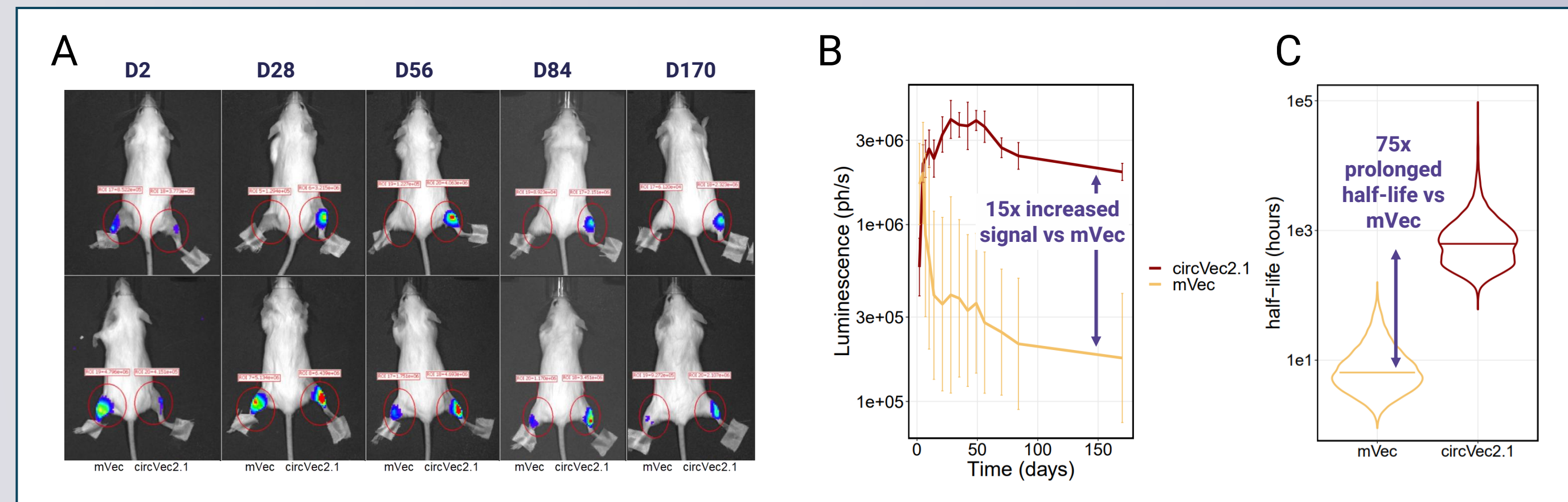
Graphical Abstract



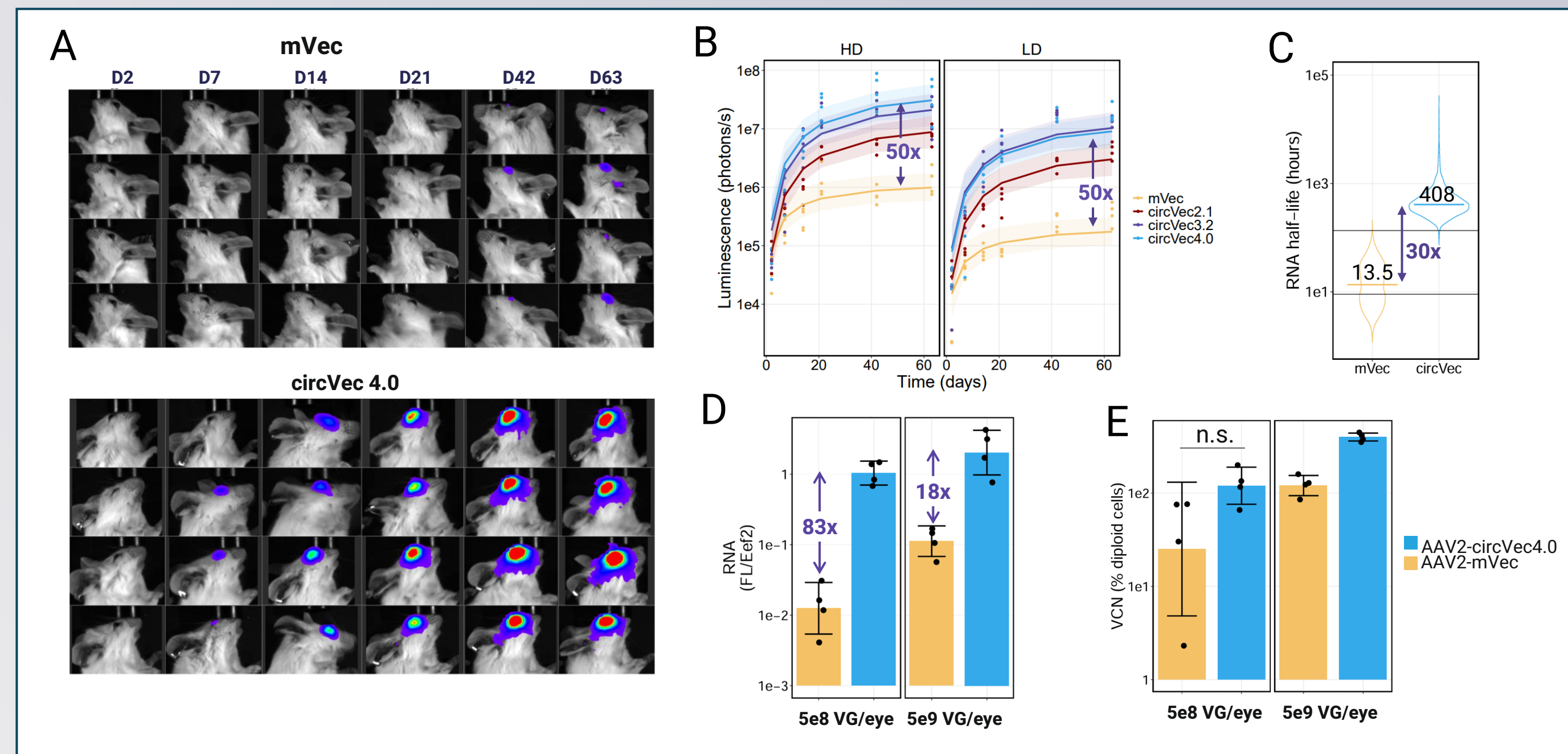
1. Optimized circVec architecture outperforms conventional circRNA expression constructs by ~36x



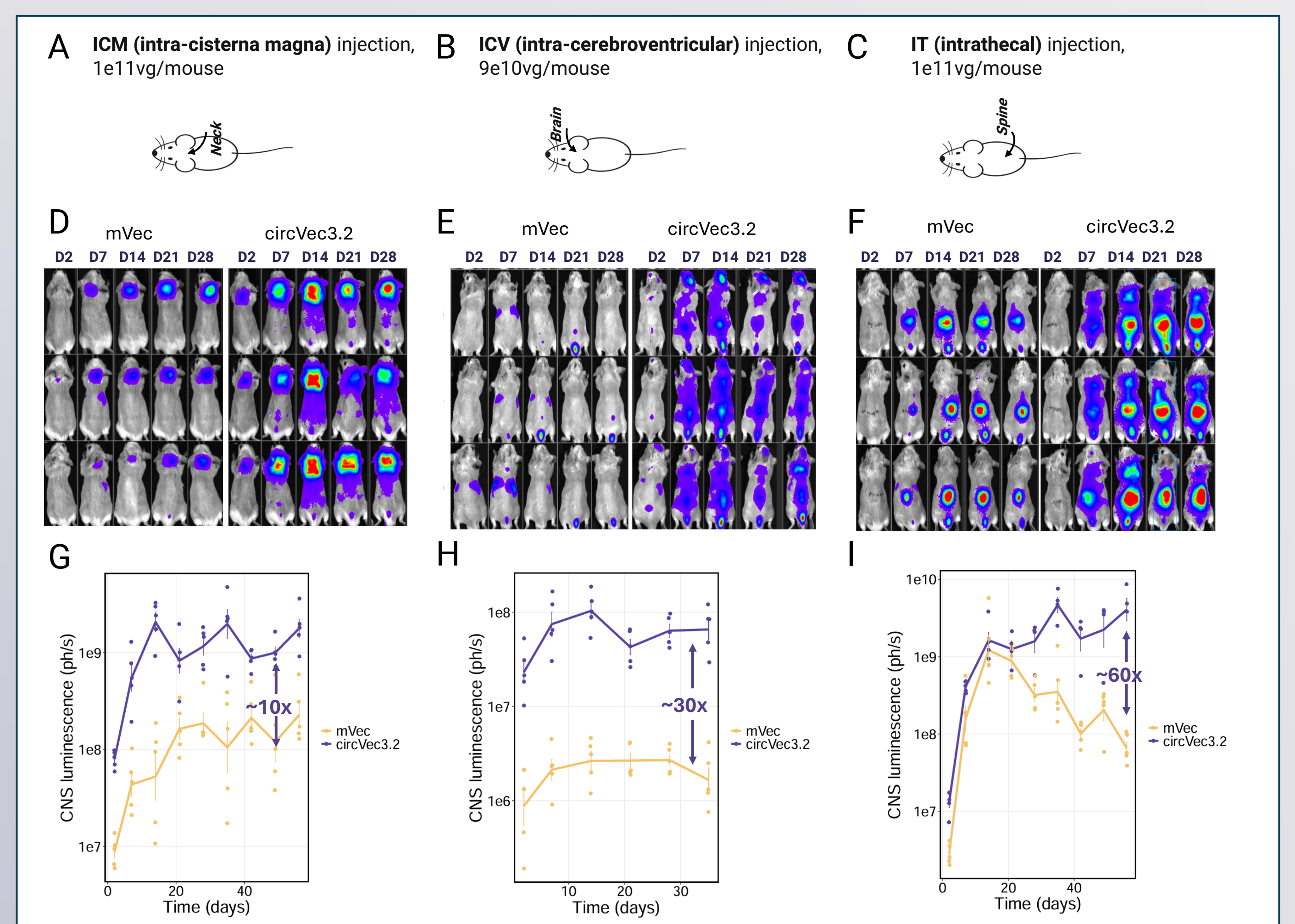
2. circRNA stability confers enhanced protein expression from equal vector dose *in vivo*



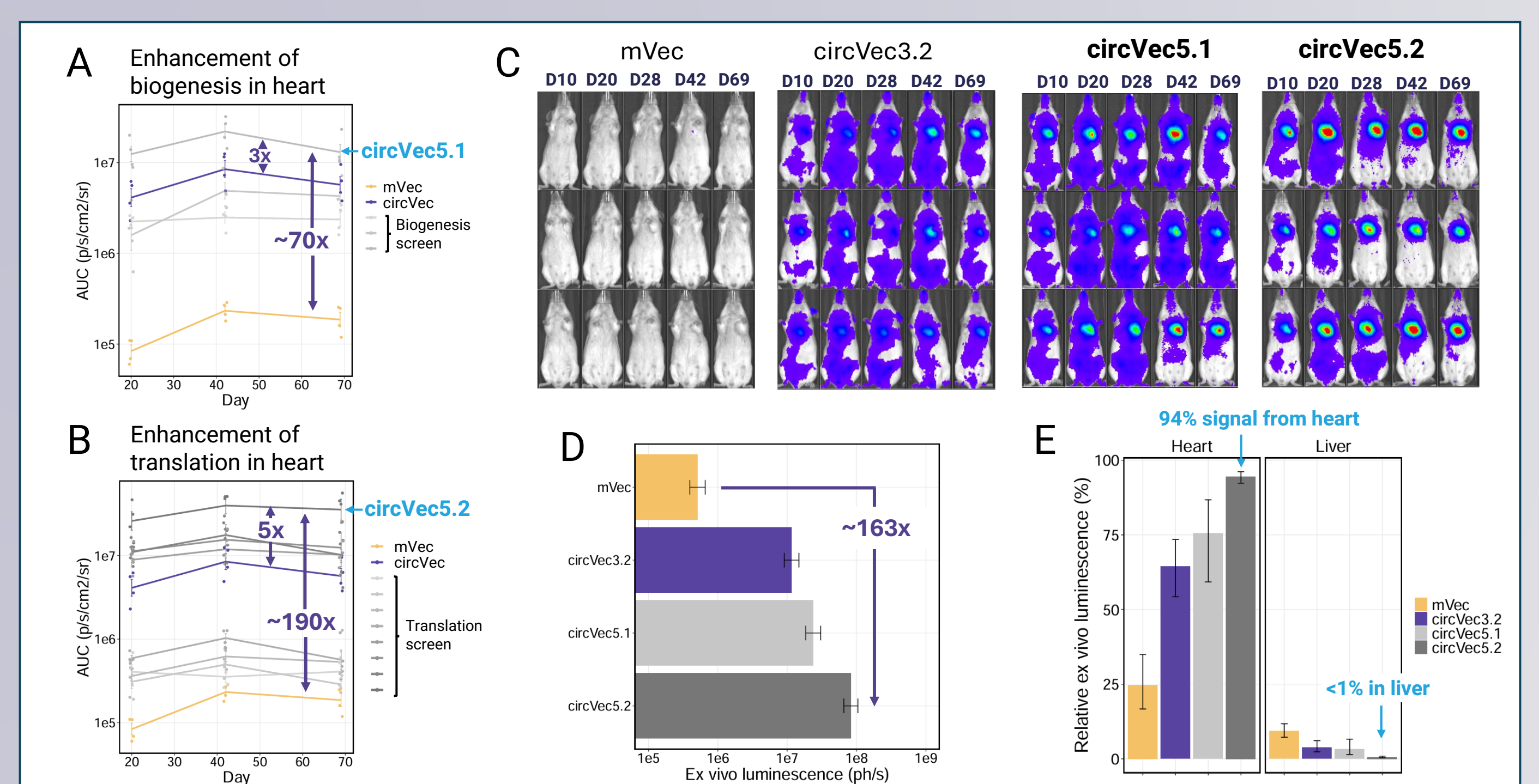
3. Intra-vitreous delivery of AAV2-circVec increases protein expression in eye by up to ~50x



4. Local delivery of AAV9-circVec increases protein expression in CNS by up to 60x



5. Novel circVec5 features unlock up to 5-fold higher cardiac expression



Circio pipeline

Technical concept	In vitro PoC	In vivo technical PoC	In vivo disease model	IND enabling	Expression	Cross-correction	Stress	Off-target expression
Genetic cardiomyopathy – systemic delivery					↑	↑	↓	↓
Ophthalmology - local delivery					↑	tbd	tbd	tbd
CNS - local & systemic					↑	↑	tbd	tbd
B-cell malignancies & autoimmunity					↑	tbd	tbd	↓

Covered in Circio oral presentation
SESSION 3d: Non-viral vectors/nanotechnology and RNA therapeutics I

Conclusions



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- **circVec is a platform technology to generate stable circRNA from viral and non-viral vectors:** circRNA accumulates intra-cellularly, leading to higher and more durable protein expression vs. standard linear-mRNA-based vectors
- **AAV-circVec outperforms conventional mRNA-based AAV by up to 60x across eye, heart and CNS in vivo:** the advantage is driven by increased RNA stability and transcript accumulation, with no change in AAV transduction
- **New heart-optimized circVec 5.2 design achieves significantly higher on target gene expression** than conventional mRNA-based AAV9, with 94% heart-specific expression and less than 1% off-target liver expression.
- **Next steps:** testing circVec in genetic heart disease models, single-cell analysis for eye & CNS, validation in NHPs

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