circio

The leader in circular RNA expression systems

R&D and corporate update
24 November 2025

Human circRNA was first described by Circio scientists

Dr Thomas B Hansen

Dr Erik D Wiklund

nature — 8,000 citations

Published: 27 February 2013

Natural RNA circles function as efficient microRNA sponges

Thomas B. Hansen, Trine I. Jensen, Bettina H. Clausen, Jesper B. Bramsen, Bente Finsen, Christian K. Damgaard & Jørgen Kjems

THE EMBO JOURNAL — EMBOpress — 30 September 2011 — 1,100 citations

CURRENT ISSUE ABOUT INFORMATION ARCHIVE ALERTS SUBMIT

miRNA-dependent gene silencing involving Ago2-mediated cleavage of a circular antisense RNA

Thomas B Hansen, Erik D Wiklund, Jesper B Bramsen, Sune B Villadsen, Aaron L Statham, Susan J Clark, Jørgen Kjems

nature reviews genetics — January 2025

Review Article | Published: 09 January 2025

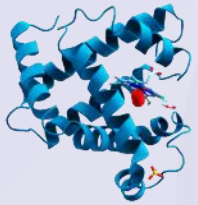
The therapeutic potential of circular RNAs

Eoghan O'Leary, Yanyi Jiang, Lasse S. Kristensen, Thomas B. Hansen & Jørgen Kjems

Nature Reviews Genetics (2025) | Cite this article

Circio has developed a powerful alternative to the main dogma of molecular biology

The circVec dogma:

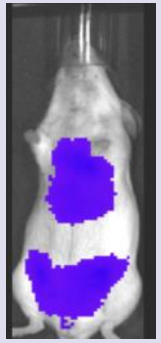


DNA → circular RNA → Protein

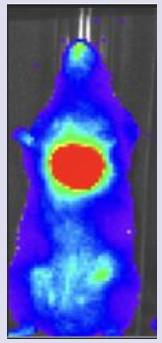
- **circVec** is a platform technology for vector-based gene delivery
- **circVec** enables enhanced and prolonged gene expression
- **Circio** has unique expertise, IP & know-how covering circVec

Circio is deploying the circVec technology to enhance conventional gene and cell therapy

Enhanced expression



AAV benchmark

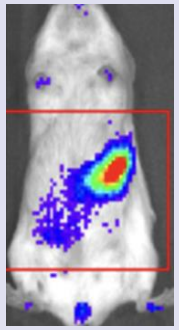


AAV circVec

- **>40x increased protein expression** for circRNA- vs. mRNA-based AAVs
- **Enhanced, safer and lower cost AAV gene therapy**

Improved durability

LNP:DNA benchmark



LNP:DNA circVec

- **>6 month durability for circRNA-** vs. <3 weeks for mRNA-based vectors
- **Durable and re-dosable in vivo CAR-T therapy**

circVec value proposition for AAV gene therapy: unlocking dose reduction to lower toxicity and cost

GEN Genetic Engineering & Biotechnology News

Danon Disease Patient Dies in Rocket Gene Therapy Trial

May 27, 2025

By **Alex Philippidis**

Rocket Pharmaceuticals acknowledged the death of a patient in a pivotal trial assessing its Danon disease gene therapy candidate RP-A501, a study that the FDA has placed on clinical hold.

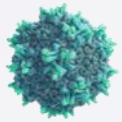
AAV gene therapy for Danon disease:

- Clinical benefit demonstrated, but severe toxicity
- Very high AAV dose level required (= high tox & cost)
- ➢ **Severe adverse events, incl. risk of death**

Circio´s circVec technology can unlock:

- Significant AAV dose reduction with same clinical benefit
- Reduced toxicity and cost, better commercial viability
- ➢ **Better, safer and lower cost AAV gene therapy**

Development plan with near-term R&D milestones

	Technical concept	In vitro PoC	In vivo technical PoC	In vivo disease model	IND enabling	Target milestones next 6-9 months
 circVec-AAV	Heart – Cardiomyopathy					Q4´25 – circVec 3.2/4.0 heart Q4´25 – circVec 3.2 eye + CNS in vivo data Q1´26 – Danon disease construct first data Q1´26 – wAMD disease construct first data
	CNS & eye					
 In vivo CAR-T	Spleen					Q4´25 – circVec CAR vectors in vitro testing Q1´26 – T-cell targeted LNP delivery in vivo Q1´26 – In vivo T-cell reporter expression Q2´26 – In vivo T-cell CAR transduction

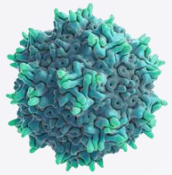
Enhanced, safer and lower cost gene therapy

Durable and re-dosable in vivo CAR-T therapy

PoC: proof of concept IND: investigational new drug LNP: lipid nanoparticle CAR: chimeric antigen receptor AAV: adeno-associated virus

Main updates to be presented today

- circVec generation 4 established, 50% boost vs. generation 3



- Strengthened in vivo validation of circVec-AAV gene therapy in heart, emerging positive data in brain / CNS

- LNP:circVec in vivo cell therapy demonstrated 6 months durability

- Entered first fully funded collaboration with major pharma company

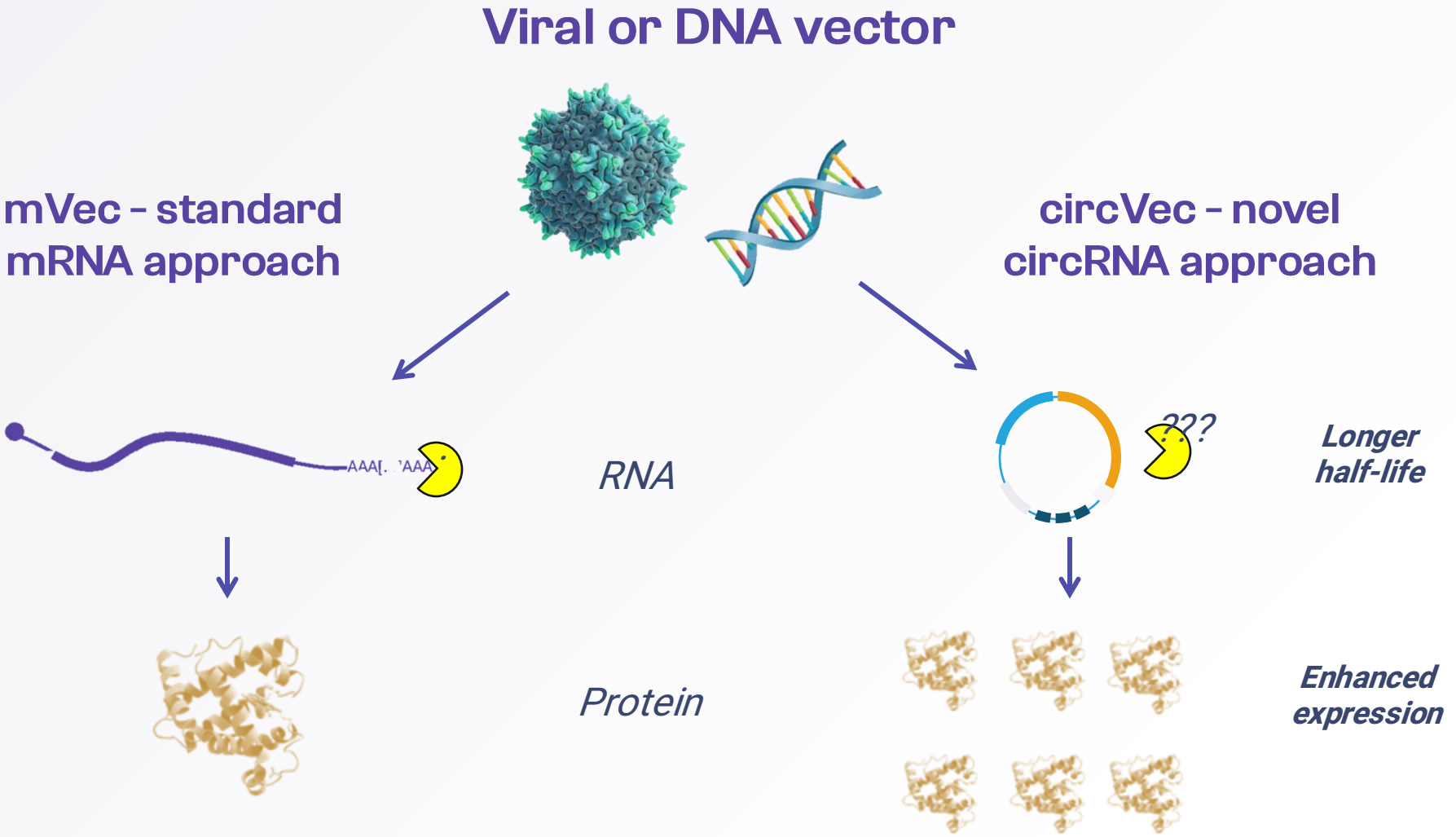
1

Platform development circVec 4.0

2. circVec-AAV gene therapy
3. In vivo cell therapy
4. Summary & outlook

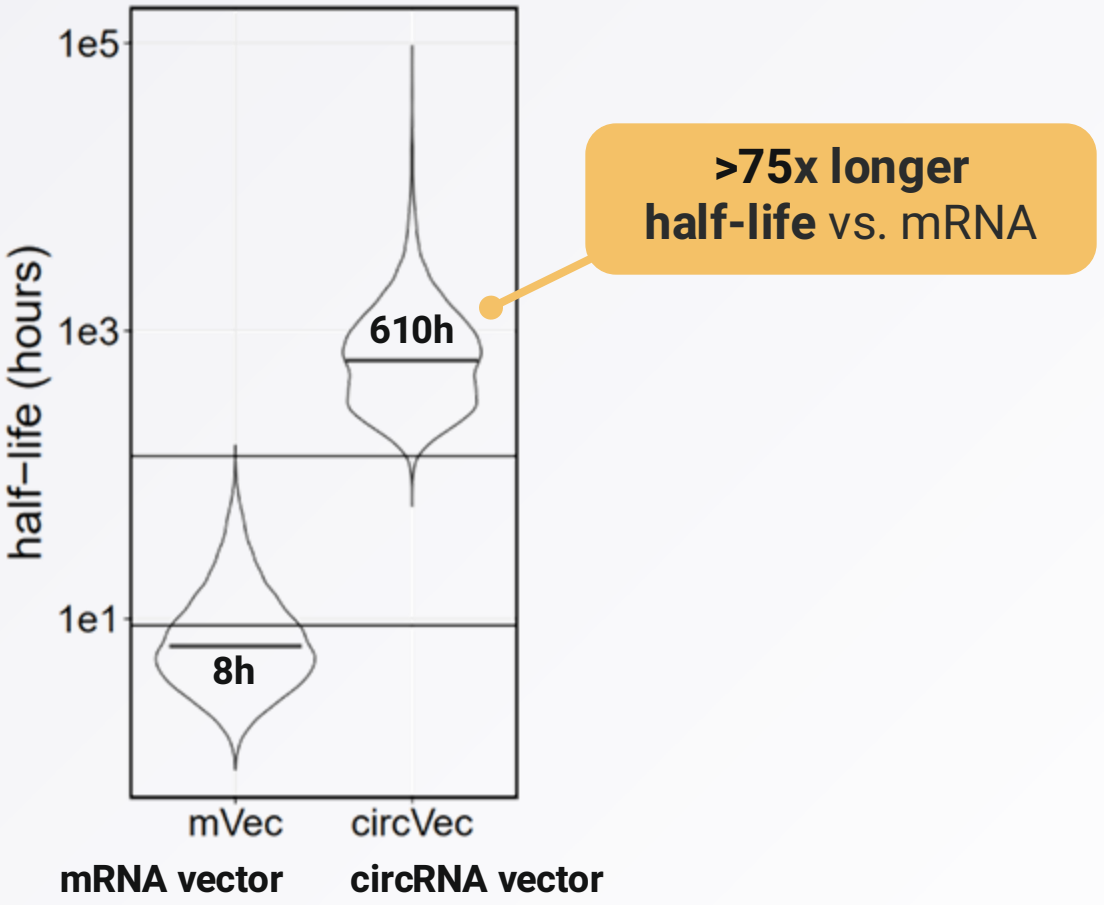
circVec

Circio´s unique and proprietary circRNA-based gene expression platform technology



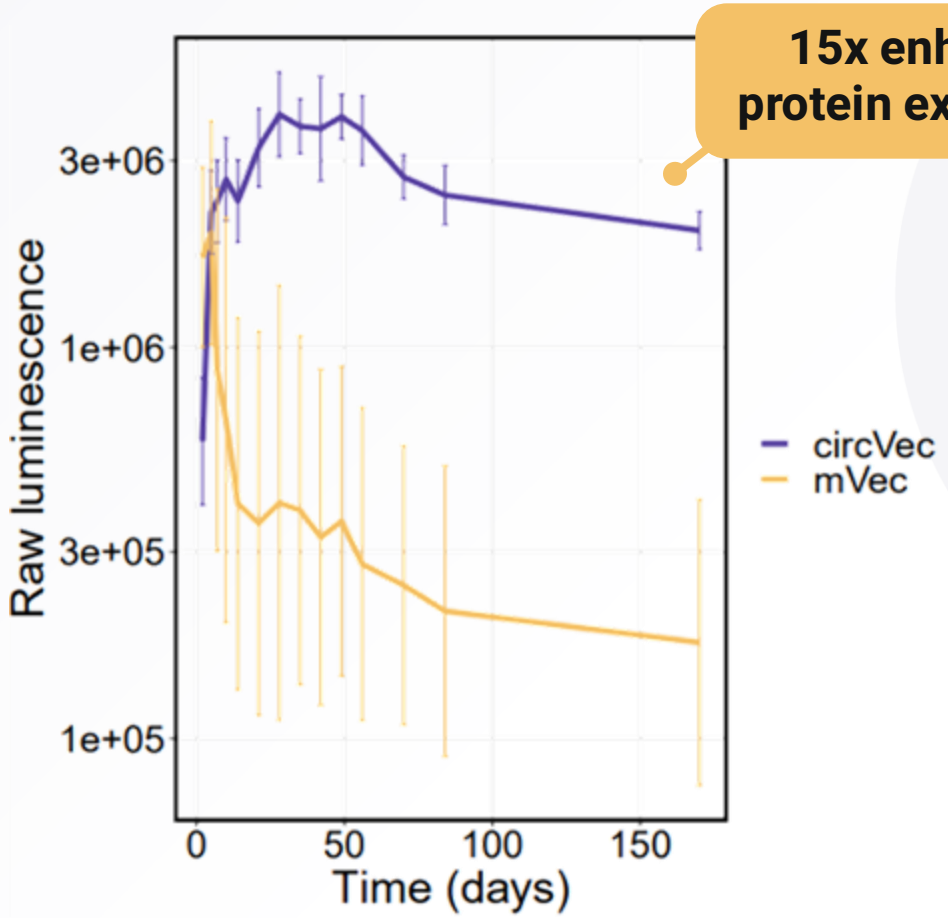
circVec substantially extends RNA half-life and increases protein expression in vivo

In vivo RNA half-life, pDNA vector-expressed RNA



>75x longer half-life vs. mRNA

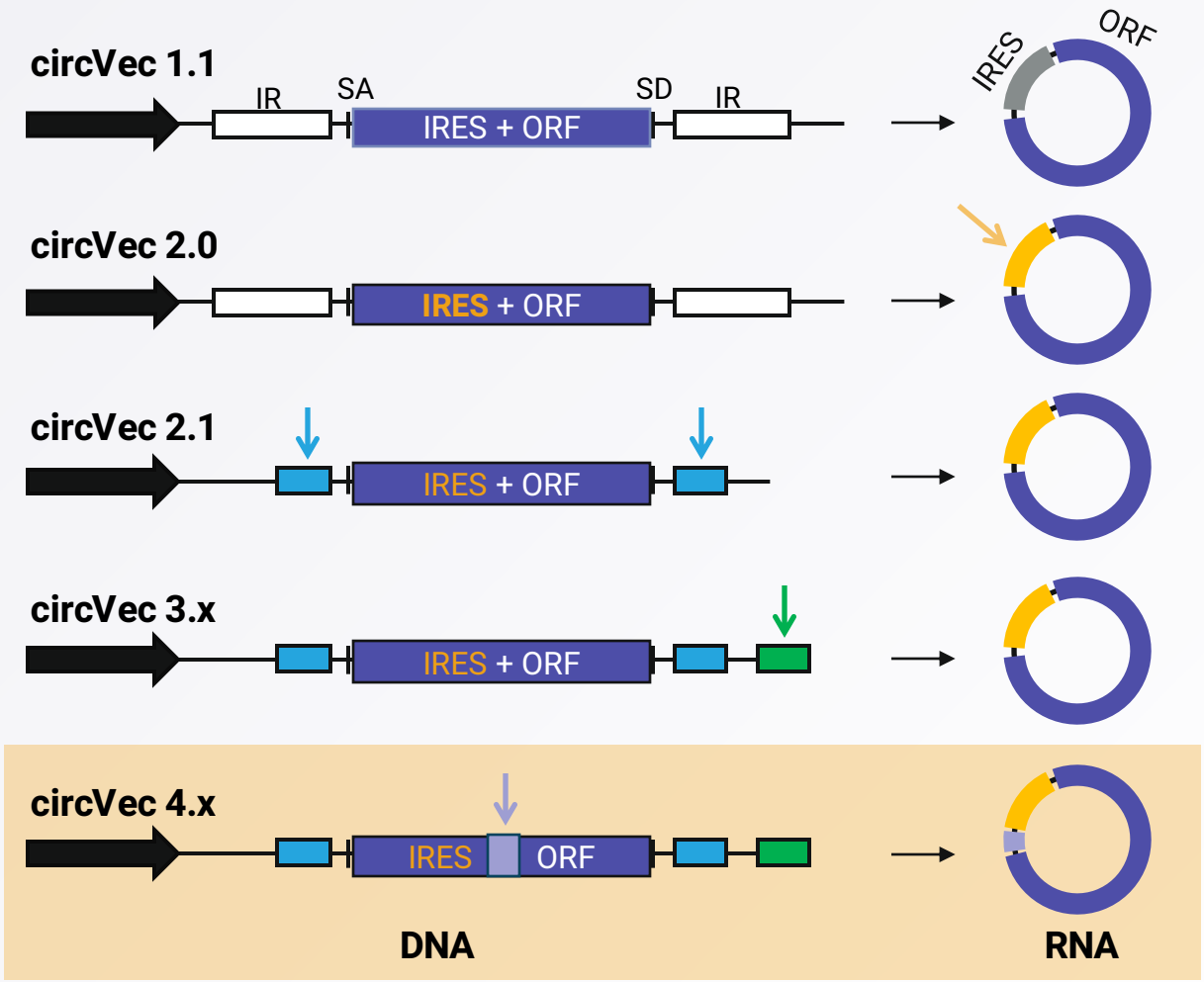
In vivo luminescence; intramuscular injection of pDNA



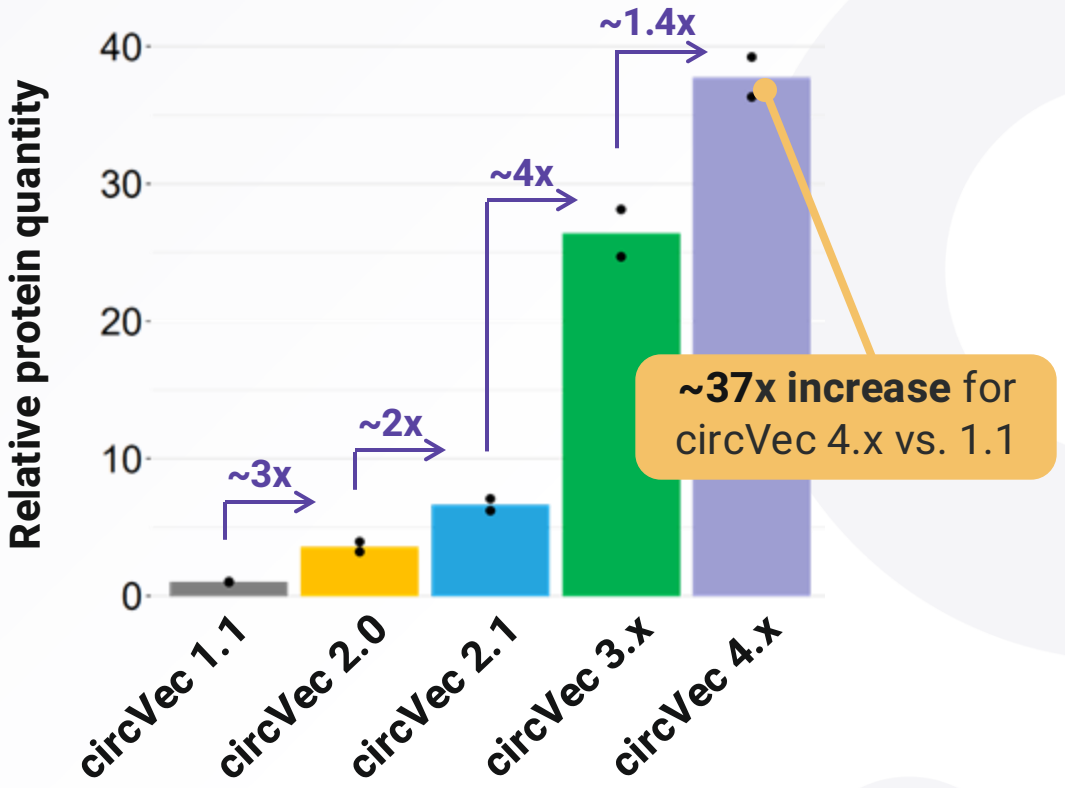
15x enhanced protein expression

New circVec generation 4 established: 40-50% improvement over generation 3

circVec generation 1.X – 4.X, design schematics



circVec protein quantification, Western blot



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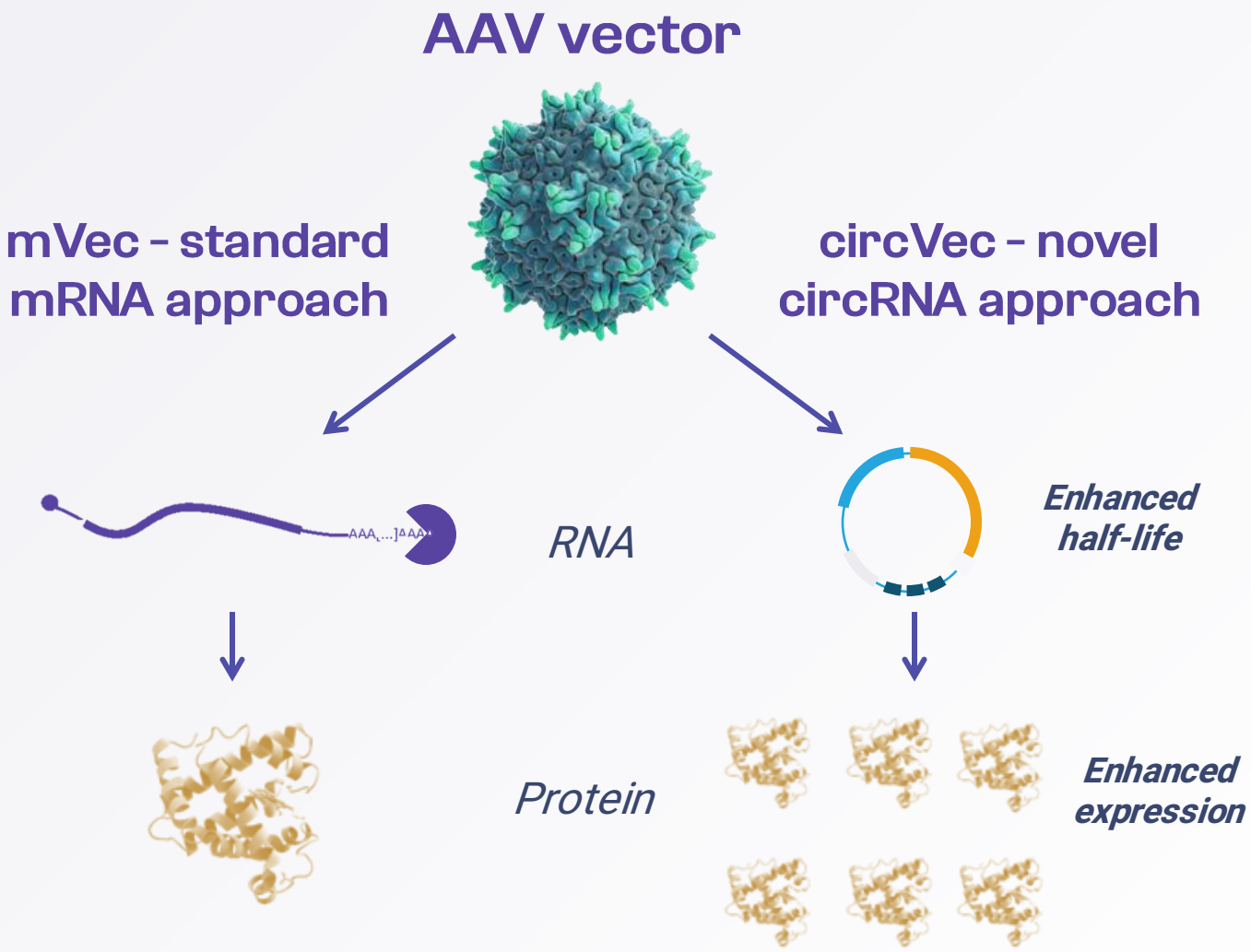
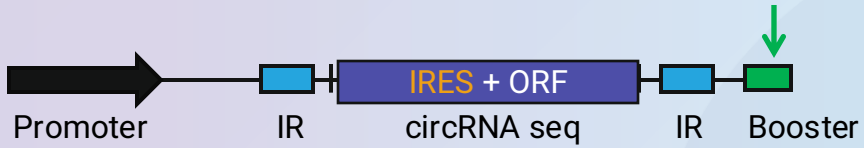
circVec-AAV gene therapy

3. In vivo cell therapy
4. Summary & outlook

AAV-specific circVec 3.2 expression construct



circVec 3rd generation DNA construct design:



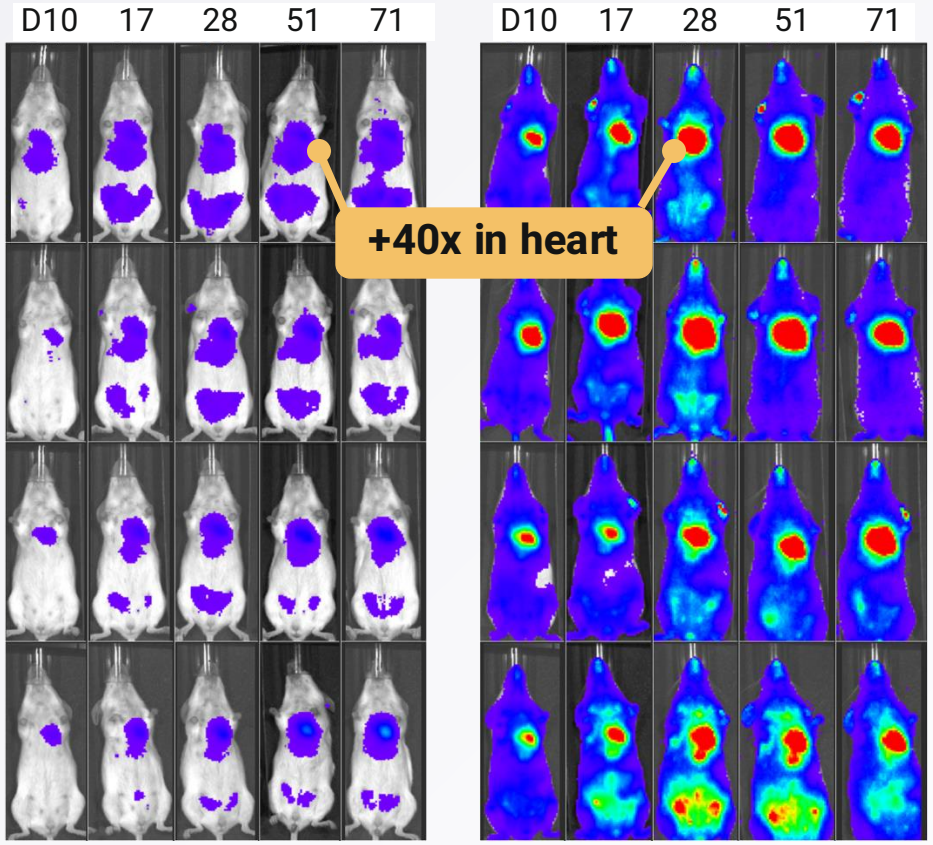
circVec 3.2 – AAV-optimized design

AAV genome DNA

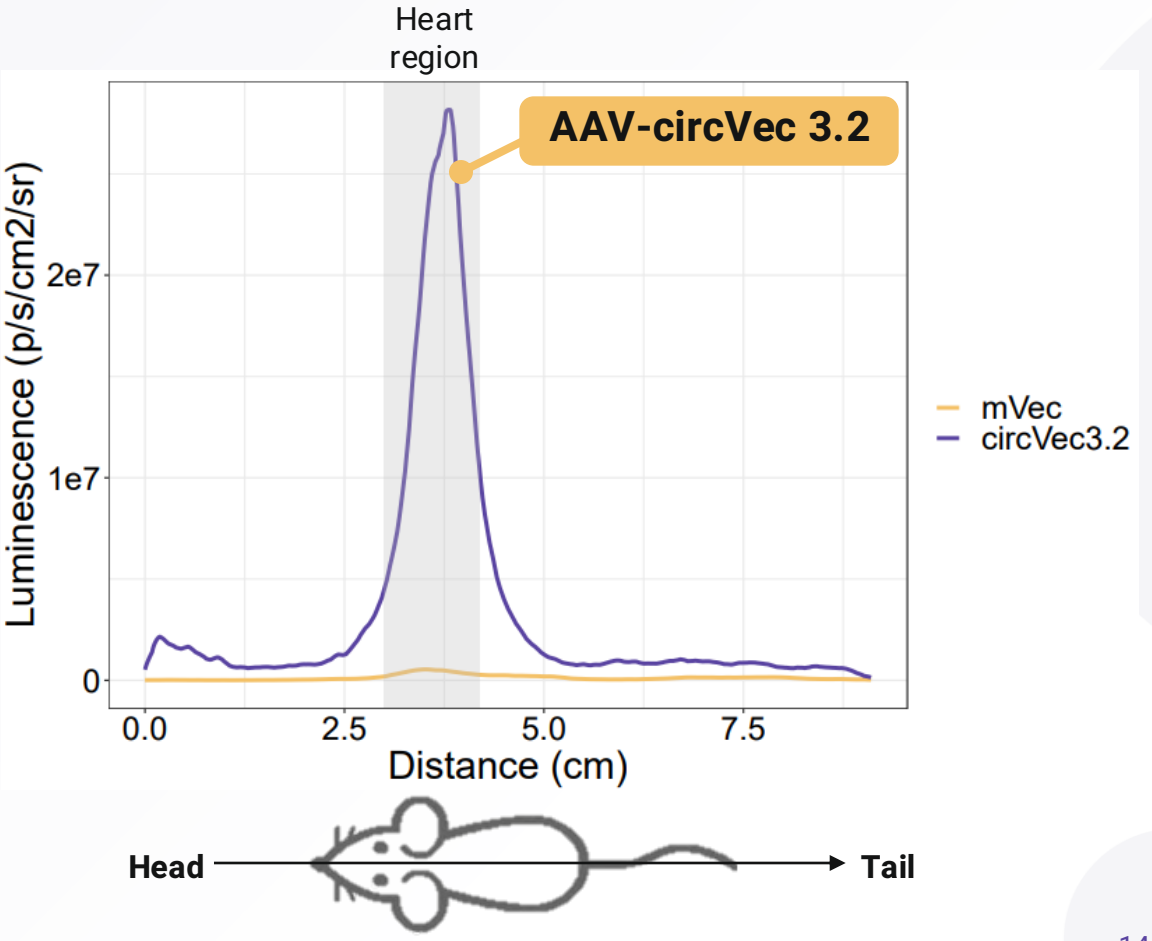
Heart-specific AAV-circVec significantly outperforms a conventional mRNA-based AAV

AAV-mVec

AAV-circVec 3.2

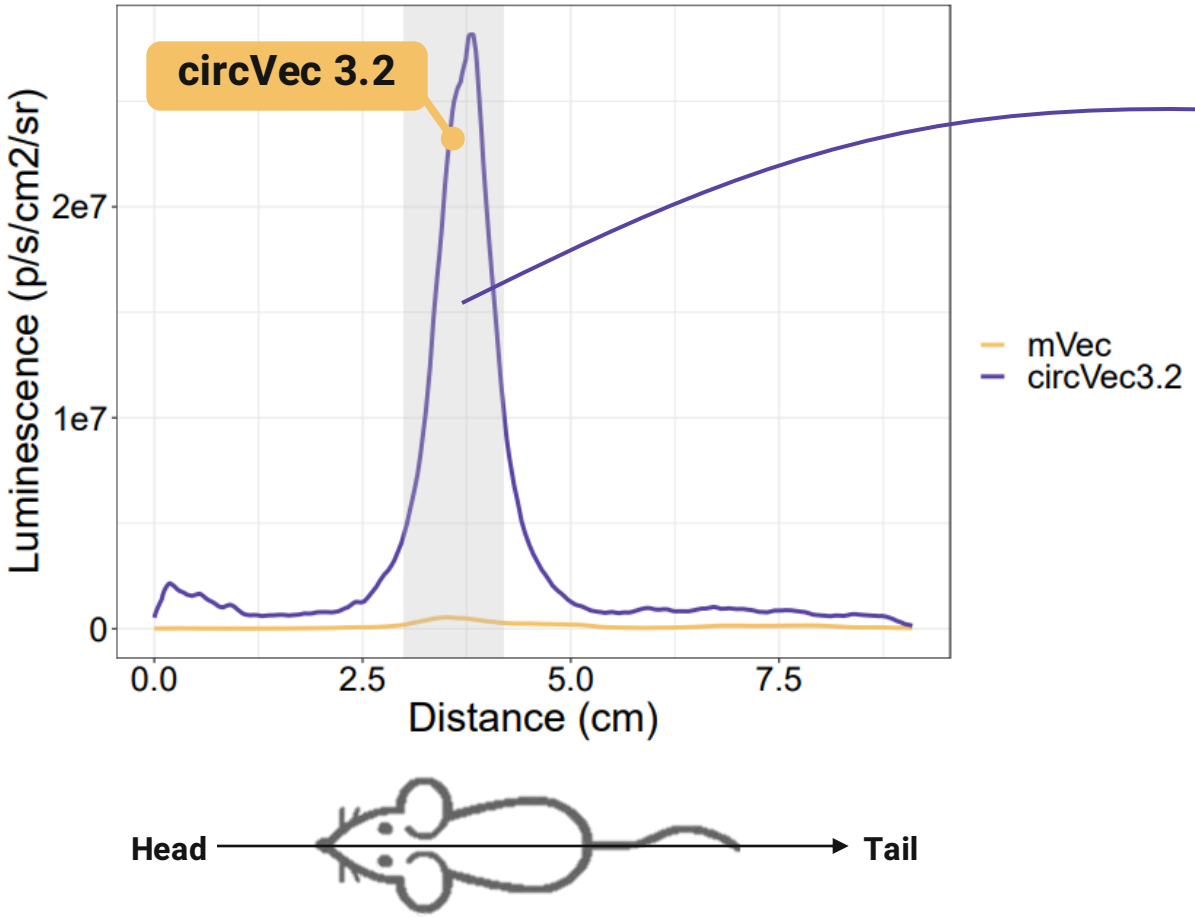


AAV f-luc signal profile from head to tail

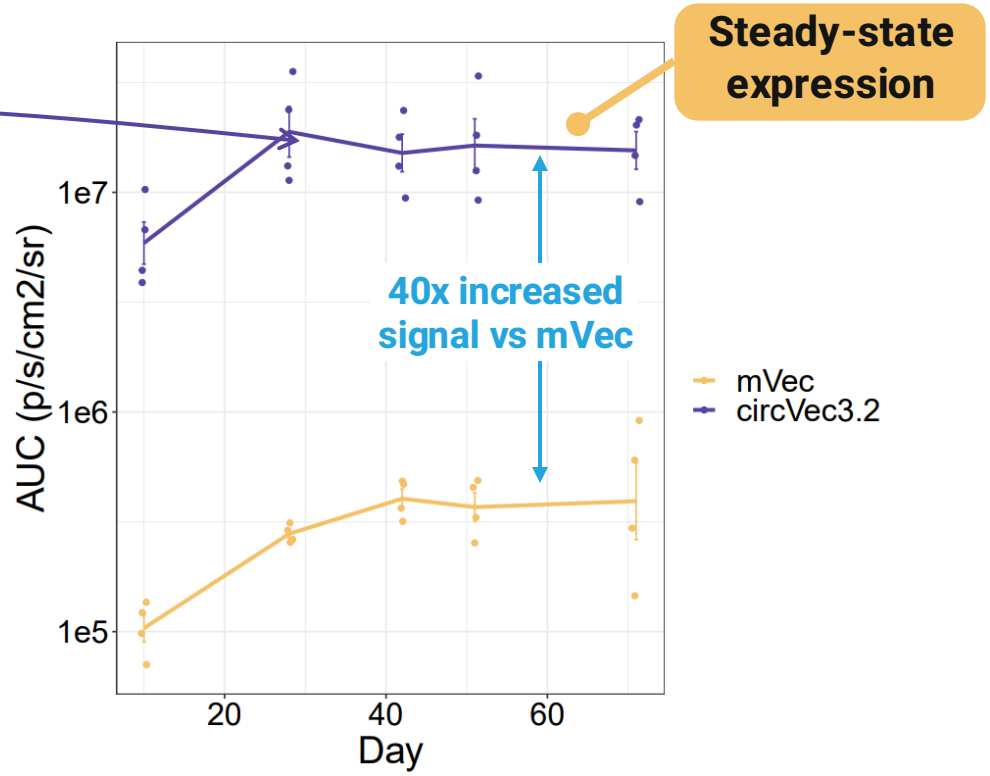


40x enhanced steady-state expression level in heart

AAV f-luc signal profile from head to tail

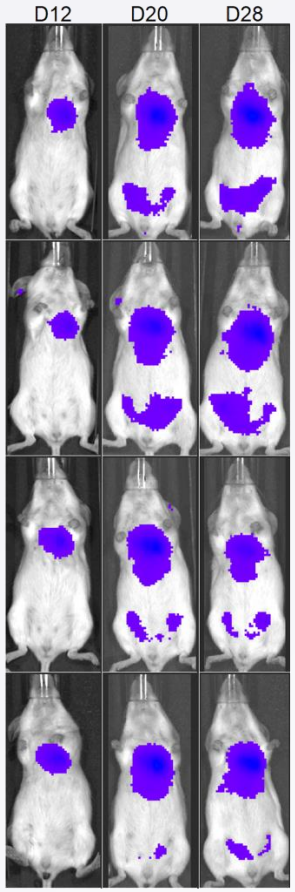


F-luc signal quantification, heart region only

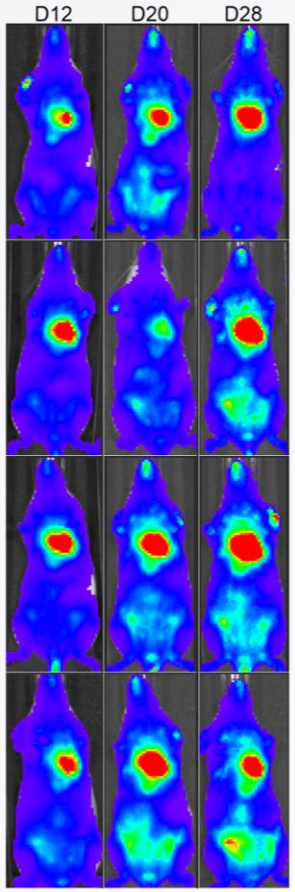


Early circVec 4.0 data shows 50% benefit in vivo vs. optimized circVec 3.2 design

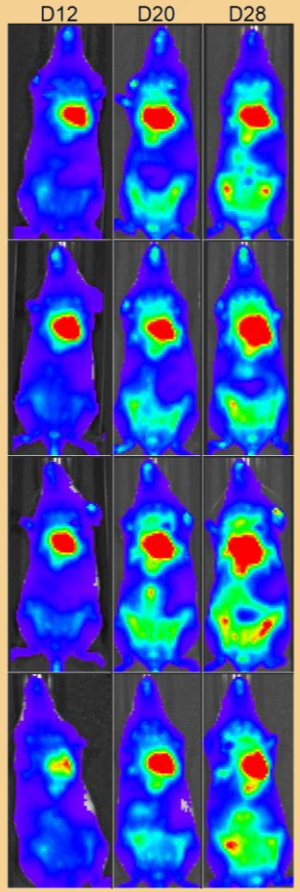
AAV-mVec



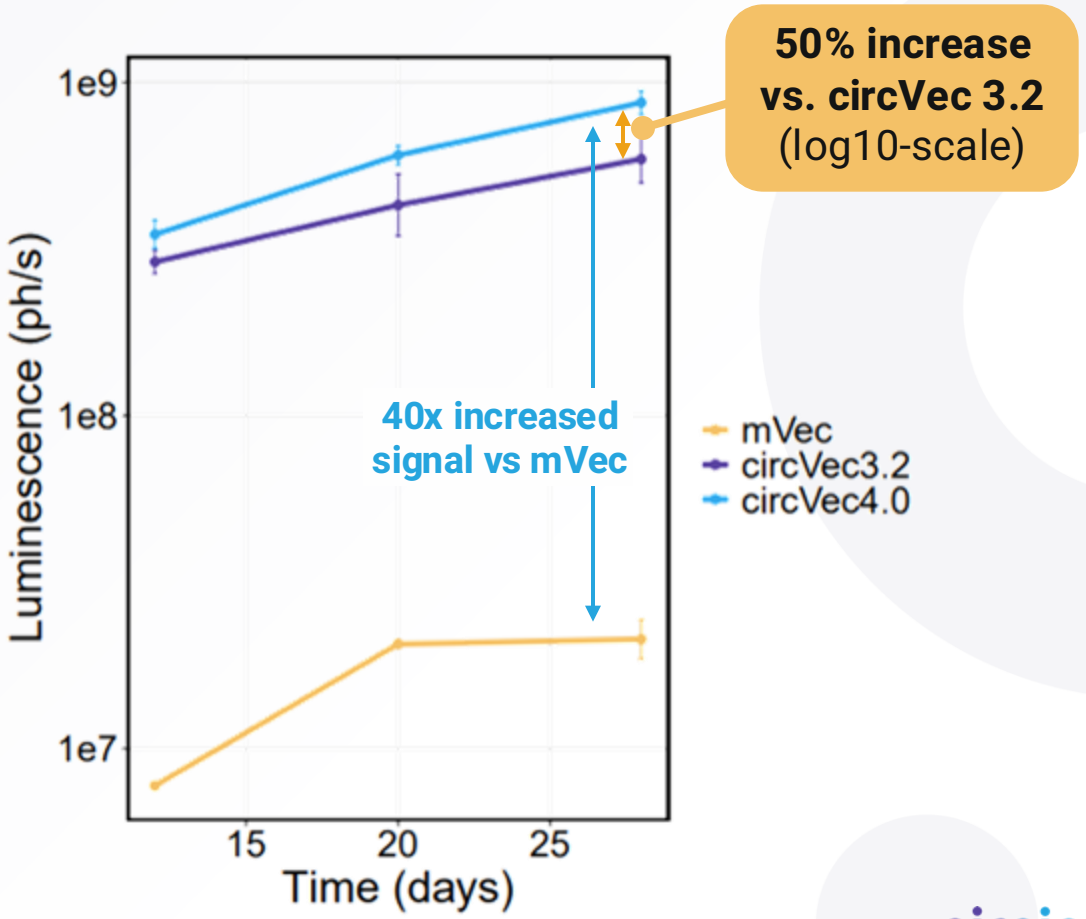
AAV-circVec 3.2



AAV-circVec 4.0



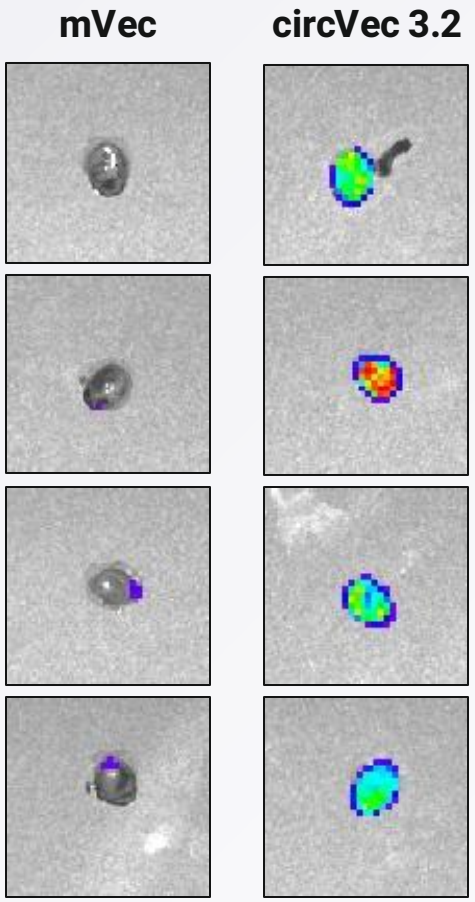
Quantification of f-luc signal, whole body

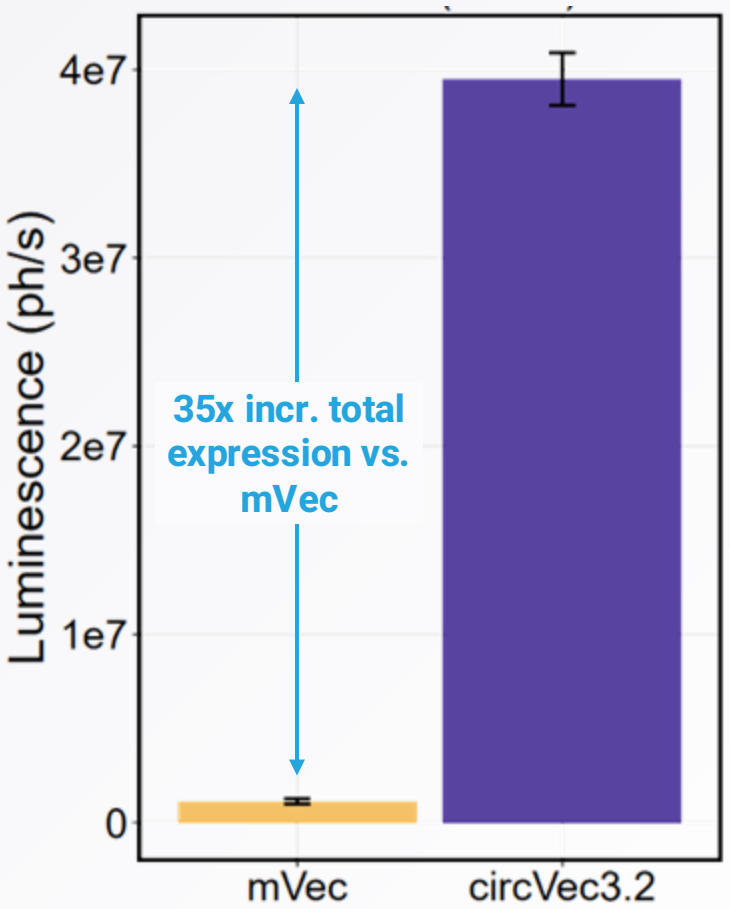


Ongoing study, preliminary data

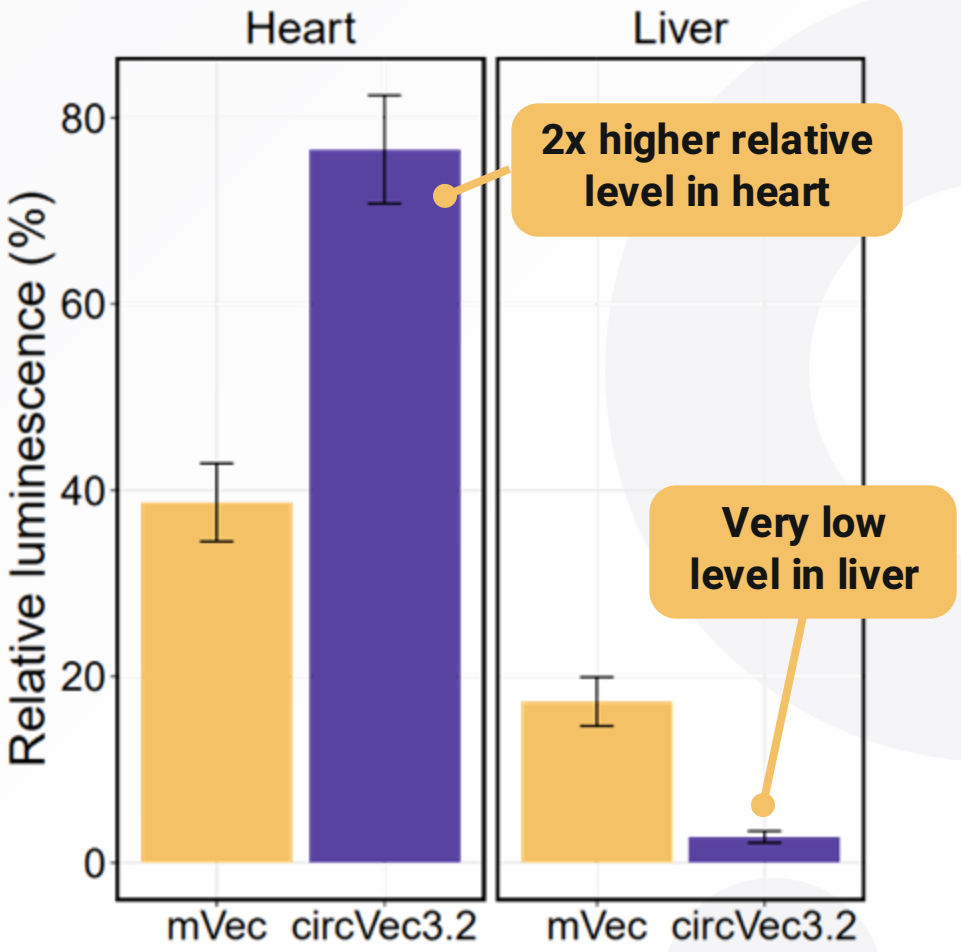
AAV-circVec advantage confirmed by ex vivo analysis, higher and more specific heart expression

Increased gene expression in heart, ex vivo tissue analysis



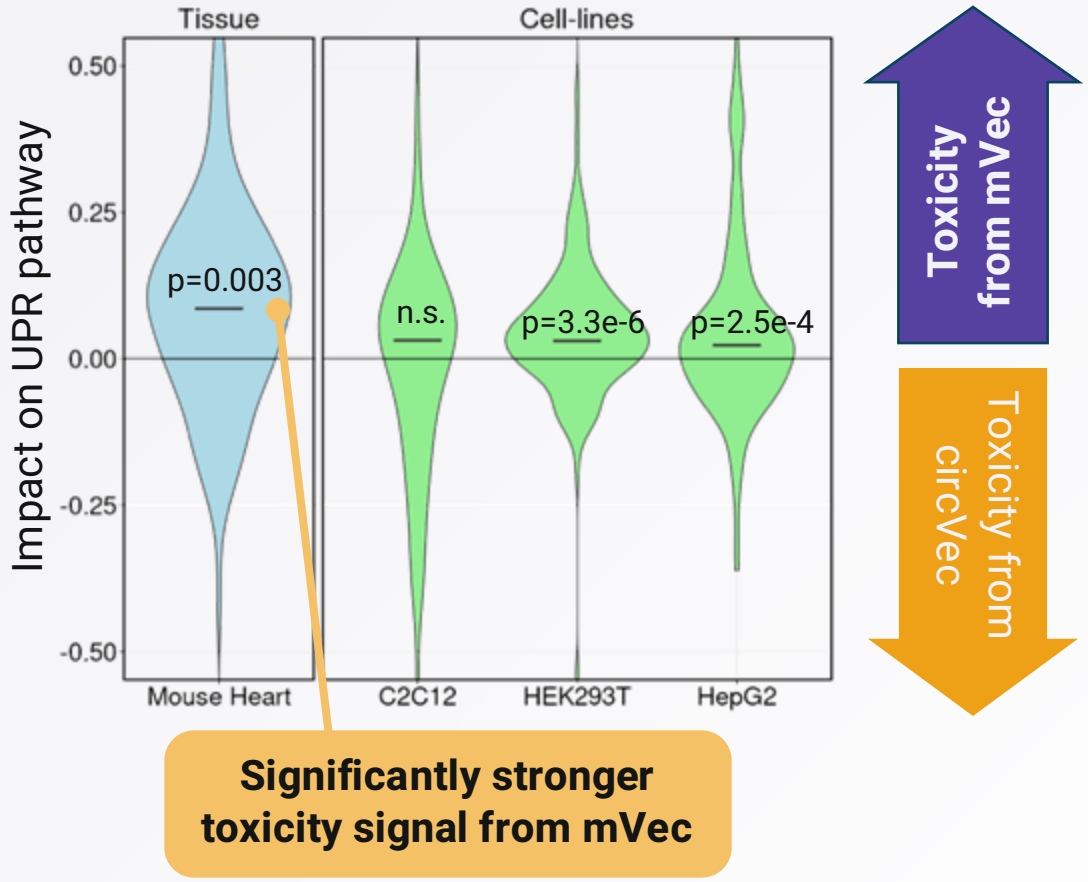


...and reduced off-taget liver expression



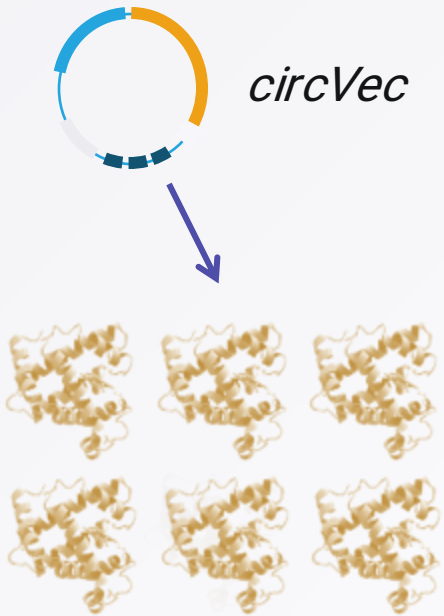
In vivo data supports reduced toxicity of AAV-circVec

Cellular stress response, UPR pathway activation



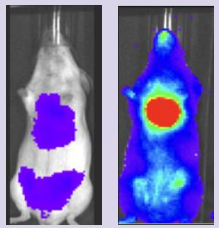
- **Unfolded Protein Response** (UPR) activation is a **major contributor to AAV toxicity** in patients
- AAV-circVec shows **less activation of UPR pathway in heart** than AAV-mVec at **same dose**
  - Despite 40x increased gene expression
  - Confirmed in various cell lines

Summary : AAV-circVec confers three major advantages for the treatment of genetic heart disorders

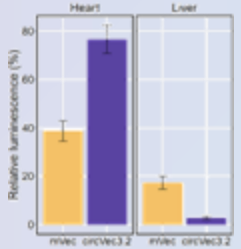


circVec-AAV compared to benchmark mVec-AAV:

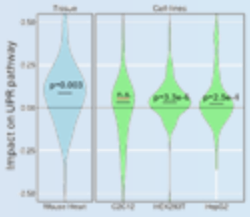
Expression



Specificity

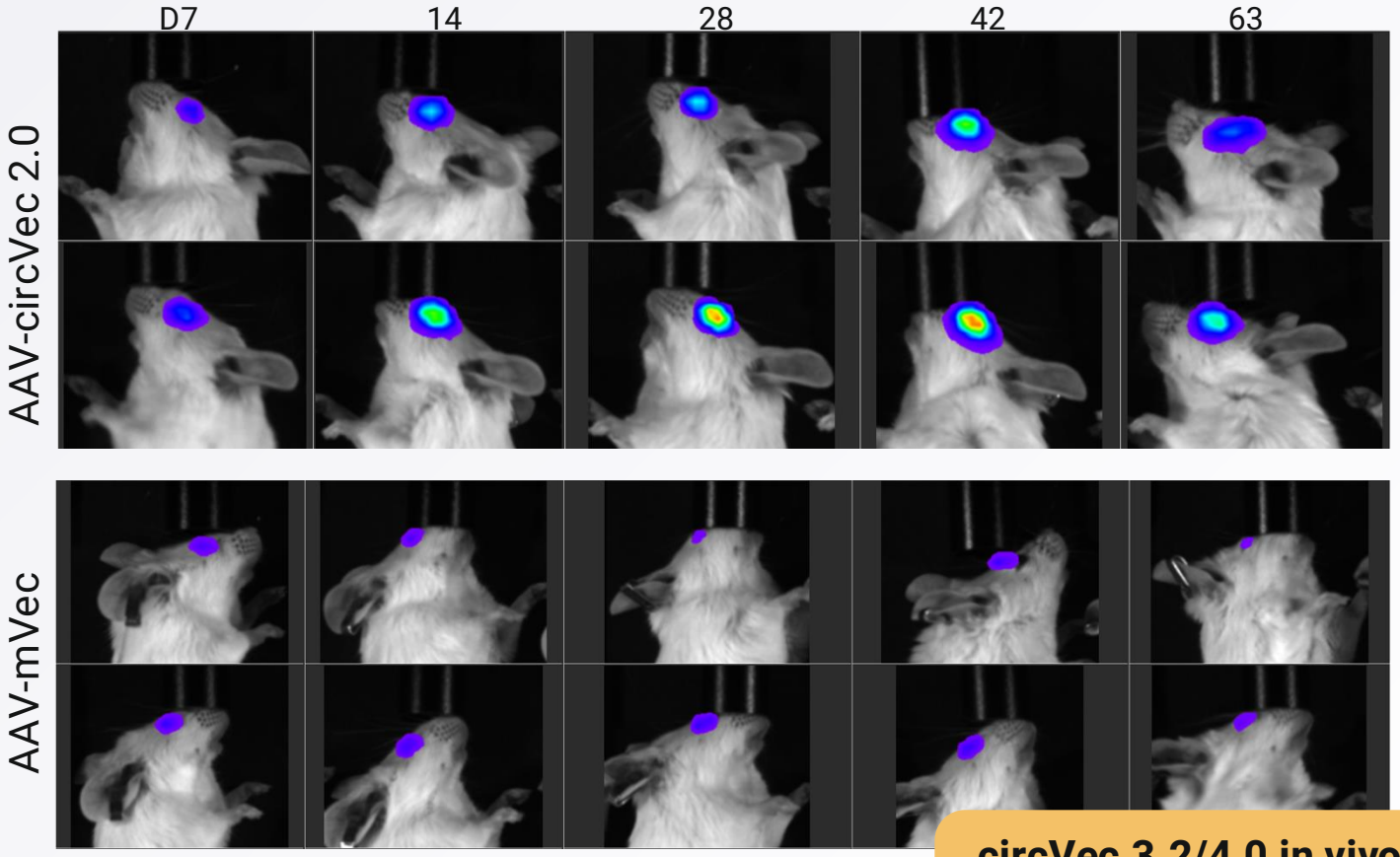


Toxicity



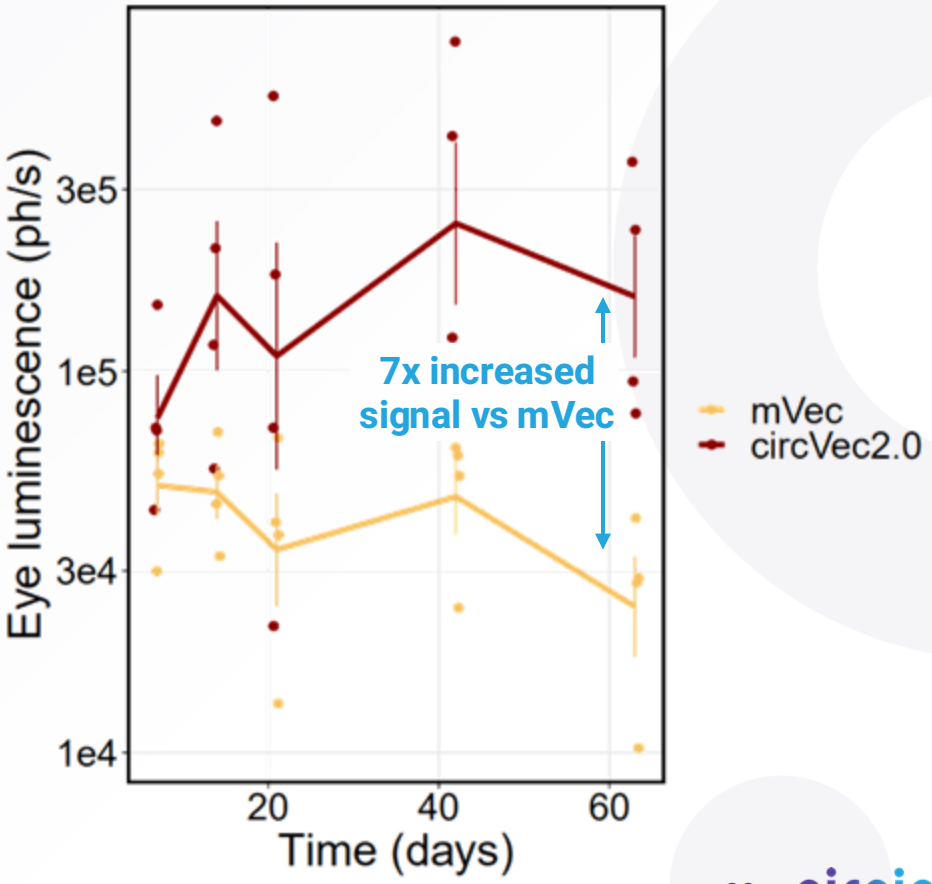
Additional opportunity: circVec-AAV local delivery to eye

Luminescence, local intra-vitreal inj. of AAV-circVec 2.0 vs. AAV-mVec



circVec 3.2/4.0 in vivo testing being initiated

F-luc signal quantification in eye, Day 7-63



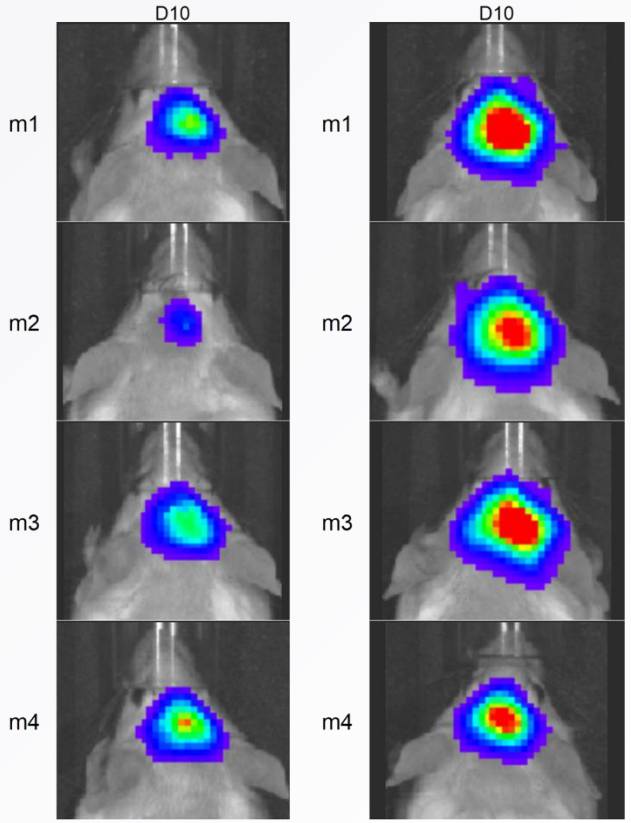
Additional opportunity: circVec-AAV local delivery to brain

Local ICV injection to brain
(intra-cerebro-ventricular)

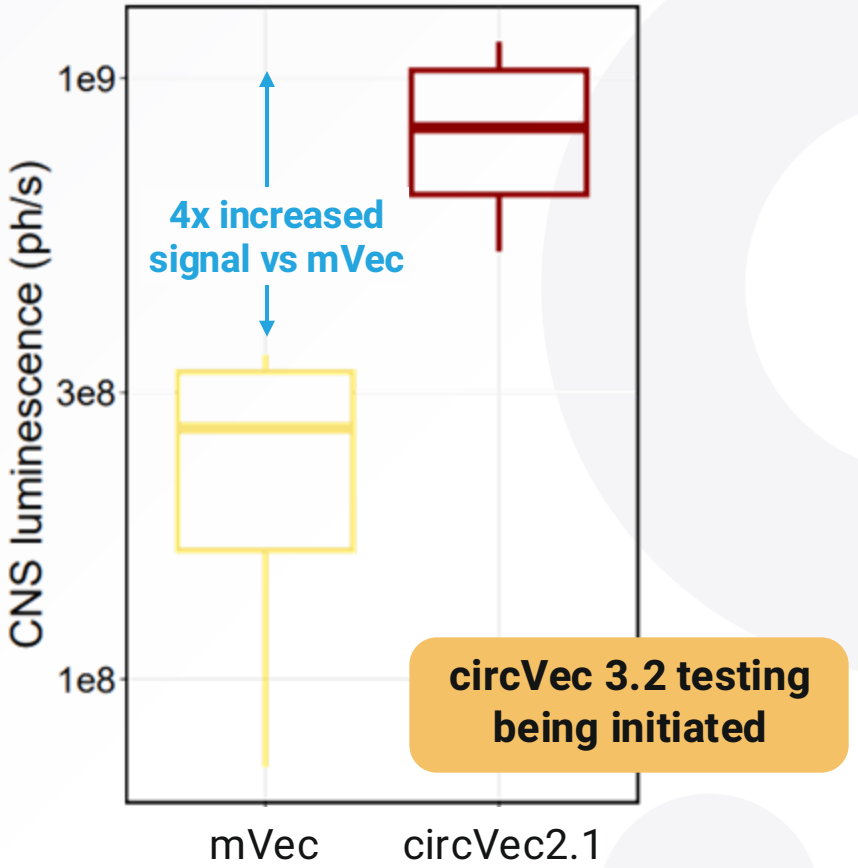
Local injection of AAVs in the brain ventricles, bypassing the blood-brain-barrier

10+ completed/ongoing clinical trials* using ICV injection of AAV for treatment of neurological disorders

mVec **circVec2.1**



Quantification of luminescence, IVIS



Ongoing study, preliminary data

* clinicaltrials.gov

Heart, eye and CNS selected as top three target tissues for continued AAV-circVec development

	Heart 	Eye 	CNS 
In vivo results	• **40x increased activity** for circVec 3.2 • 4.0 testing ongoing	• **7x increased activity** for circVec 2.0 • 3.2/4.0 testing 4Q´25	• **4x increased activity** for circVec 2.1 (ongoing) • 3.2/4.0 testing 1Q´26
Rationale	• **Increase on-target expression** • **Reduce systemic dose, → lower tox and cost**	• **Maximize local payload secretion** • **Reduced local dose → less inflammation, cost**	• **Enhanced local CNS payload expression** • **Open new AAV opportunities in challenging CNS diseases**
Market opportunities	1. **Danon disease** n = 1,500-2,000 2. **Fabry disease** n= 30-40,000	1. **Wet AMD** n = 6-7 mill. 2. **Diabetic Mac´lr Edema (DME)** n= 20-25 mill.	• **Tay-Sachs, Krabbe Gaucher disease ++** • Partner with CNS-AAV companies

Opportunity 1: Danon disease
No approvals, validated target, low technology risk

Opportunity 2: wet AMD
Very large market, delivery issues for approved options

Opportunity 3:
Several diseases with major unmet need, broad pharma activity

AAV-circVec Danon disease (heart) lead program: animal PoC data expected first half 2026

2H´25

- **circVec 3.2 in vivo heart reporter data**
- **circVec 4.0 in vivo heart reporter data**

1H´26

- **Technical PoC Danon disease circVec construct**
- **circVec Danon constructs in vivo PoC data and selection**

2H´26

- **AAV-circVec Danon disease model efficacy data**

2H´27

- **Danon circVec construct GLP-tox & NHP validation**
- **IND filing**
- **Phase 1 start**

Value inflection points: Animal PoC potential partnering trigger

Value inflection point: Out-licensing / M&A opportunity window

Danon disease – facts

apx. 2,000 patients USA + EU + Asia

No approved therapeutic options

AAV studies to date have shown clinical benefit, but too high toxicity

Data & Timeline: current best estimates - experiments have uncertain outcomes and may need to be repeated, impacting plans and timelines

Take-home messages: transforming AAV gene therapy

- **AAV-circVec outperforms on expression, specificity and toxicity**

- **Advantage shown** in three tissues in vivo: **heart, eye and CNS**

- **Several commercial & partnering opportunities, near-term news flow**

In-house

Establish PoC for Danon disease (heart) and **wet AMD** (eye)

- ***Next step:*** *Test specific disease-targeted circVec-AAVs*

Partnering

Entered partnership with major global pharma company

- ***Next step:*** *Establish collaboration for engineered AAV capsids*

3

In vivo cell therapy

4. Summary & outlook

circVec has a unique window of opportunity for in vivo cell therapy applications

In vivo CAR modalities – duration

Days	Months	Permanent
mRNA & circRNA	⟵ **circVec-DNA opportunity** ⟶	Lentiviral

circVec-DNA benefits

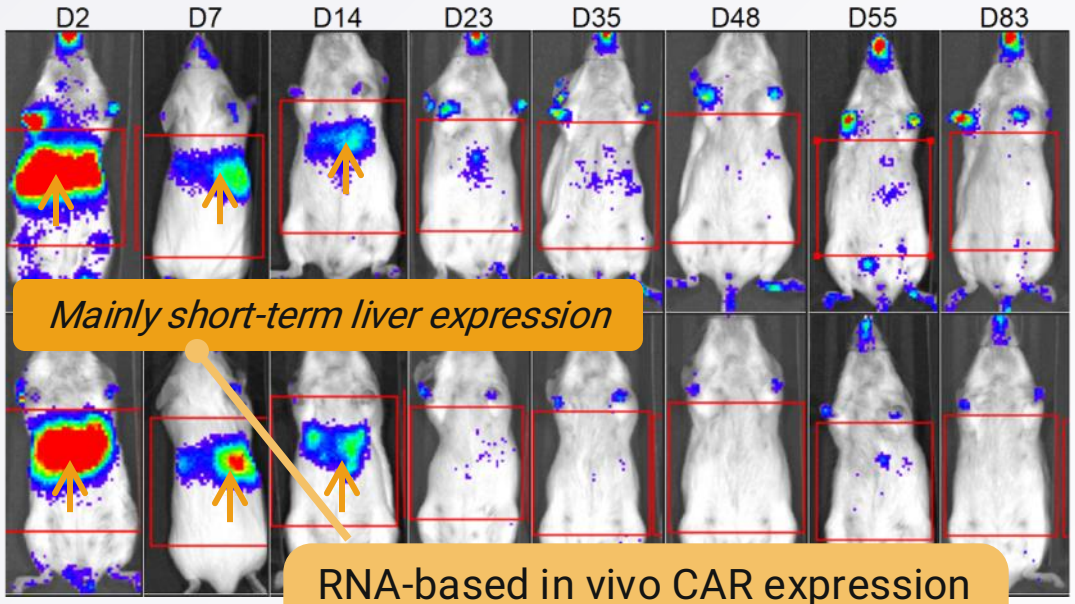
- **Non-genome integrating**
- **> 6 months duration of expression on single dose**
- **Redosable**
- **Avoids liver-expression**

Therapeutic applications

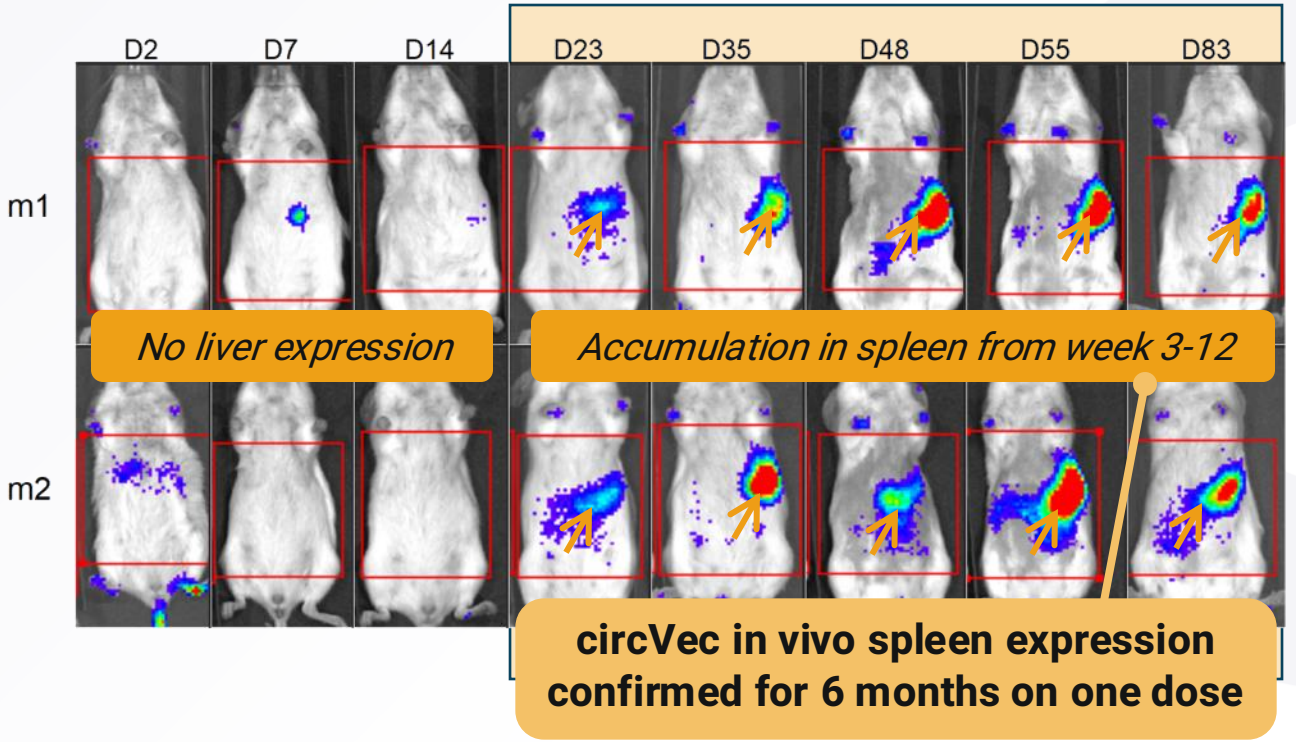
- **Cancer**, e.g. lymphoma
  - Ex vivo CAR-T effective, but expensive
  - Lentiviral risk of secondary malignancies
  - RNA in vivo CAR not sufficient duration
- **Autoimmune disease**, e.g. Lupus
  - secondary opportunity

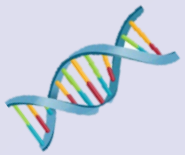
In vivo cell therapy: circVec expression duration now confirmed to over 6 months on single dose

LNP-mVec (mRNA), luminescence
Systemic I.V. delivery, single dose on Day 0

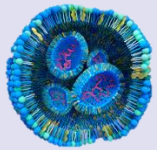


LNP-circVec (circRNA), luminescence
Systemic I.V. delivery, single dose on Day 0





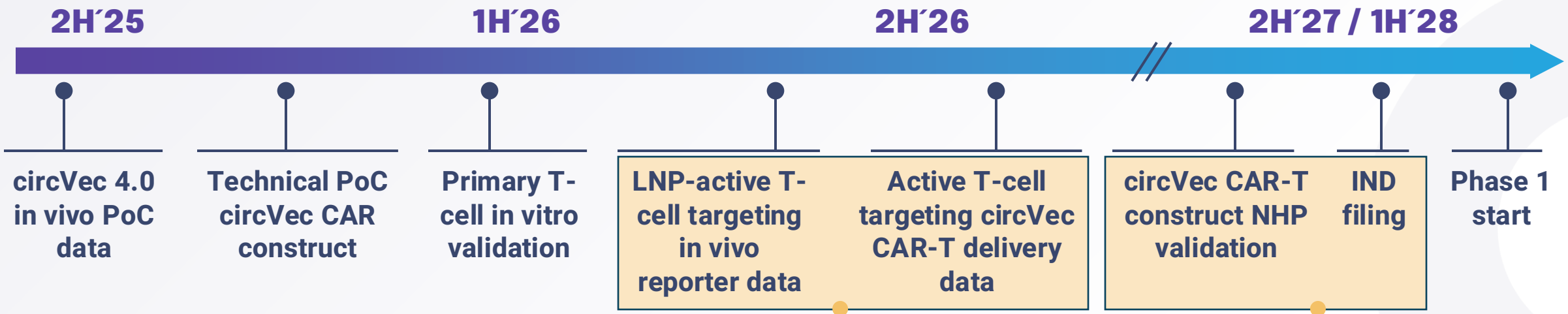
Non-viral synthetic DNA vector format



LNP-delivery formulation

circVec 2.1

DNA-circVec in vivo cell therapy development timeline: animal PoC data expected first half 2026



Value inflection points: Animal PoC potential partnering trigger

Value inflection point: Out-licensing / M&A opportunity window

In vivo CAR-T

Unique position of circVec approach

Mega-trend in biopharma deal activity

2025 deals by Abbvie, Gilead, BMS, AZ

Data & Timeline: current best estimates - experiments have uncertain outcomes and may need to be repeated, impacting plans and timelines

Take-home messages: circVec cell therapy

- **> 6 months duration of expression vs. < 2 days for mRNA in vivo CAR**

- **circVec expression shown in both T- and B-cells in spleen**

- **circVec CD19 CAR-expression technically validated**

In-house

Evaluate T-cell-specific transduction *in vitro* and *in vivo*

- ***Next step:*** *Active T-cell targeting delivery in vivo testing*

Partnering

Establish R&D collaborations with RNA in vivo CAR companies

- ***Next step:*** *Test circVec in validated partner delivery system*

4

Summary & outlook

Recent deal activity highlights substantial commercial opportunities in Circio areas

Lilly → MEIRAGTx

Licensing, November 2025

$75m up-front

+ $400m milestones

AAV gene therapy for genetic eye disease

- AAV engineering platform
- Phase 1, novel therapeutic candidate for vision loss

Bristol Myers Squibb → ORBITAL THERAPEUTICS

M&A, October 2025

$1.5b

in cash buy out

circRNA in vivo CAR-T therapy for autoimmune disease

- LNP-delivered synthetic circular RNA platform
- Pre-clinical, CD19 CAR-T

abbvie → capstan therapeutics

M&A, June 2025

$2.1b

in cash buy out

mRNA in vivo CAR-T therapy for autoimmune disease

- LNP-delivered synthetic mRNA platform
- Phase 1-ready, CD19 CAR-T

Business development update

Big pharma feasibility study

- Initiated a **fully funded feasibility study with a major global pharmaceutical corporation**
- Testing **circVec-AAV** gene therapy in **specific disease area**
- May lead to **subsequent circVec-licensing** if successful

Active R&D collabo - rations

- **Several ongoing and new** 50:50 R&D collaborations
- Mainly for **circVec-DNA delivery and vector technology**
- Expected market **updates during 1H 2026** from progressing collaboration projects

Seeking new partner - ships

- **Big pharma R&D collaborations** in available disease areas
- In vivo cell therapy **T-cell targeted circVec-DNA delivery**
- **Engineered/targeted AAV capsids** for tissues of interest

Efficient cost base and access to required capital

Low cost base

- **Continuing to operate on < NOK 4 million per month**
- **Stream-lined activities and non-core costs**
- **Strict R&D prioritization**

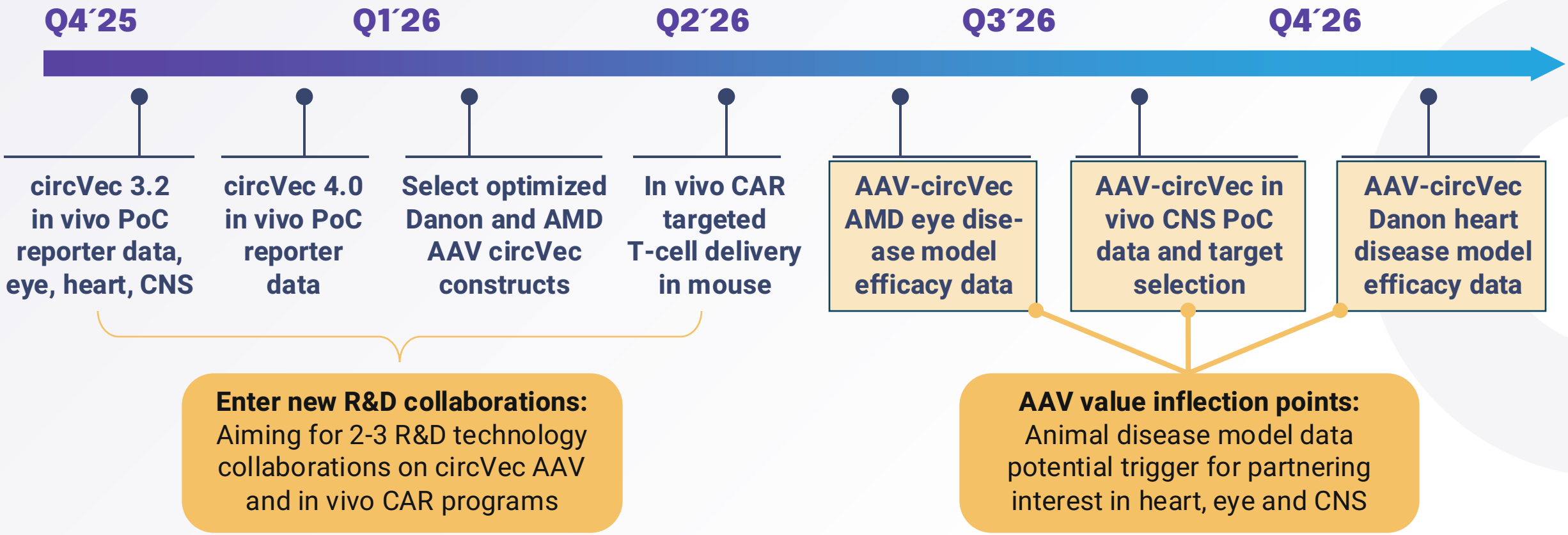
Atlas facility

- **Financing commitment extended** by 3 + 3 tranches in Q3´25
- 2 tranches drawn, **4 tranches @ NOK 4 million remain available**
- Good relationship, potential to **extend beyond Q1´26 if required**

Other financing options

- **Continuously exploring multiple financing options beyond Atlas,** building on recent strong AAV-circVec data and BD traction
- Enabling **expanded operations** and **accelerating R&D**
- **Market conditions remain challenging**, but improving slowly

Rich pipeline of R&D and BD milestones next 12 months



Data & Timeline: current best estimates - experiments have uncertain outcomes and may need to be repeated, impacting plans and timelines

Further reading – Circio in industry and scientific press

nature reviews genetics January 2025

Review Article | Published: 09 January 2025

The therapeutic potential of circular RNAs

Eoghan O'Leary, Yanyi Jiang, Lasse S. Kristensen, Thomas B. Hansen & Jørgen Kjems

Nature Reviews Genetics (2025) | Cite this article

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In Vivo >> Market Intelligence

Circio's Vision For Long-Lasting Nucleic Acid Therapeutics

16 Dec 2024 • By David Wild

Drug TARGET REVIEW

Circular RNA technology: the future of gene therapy

Posted: 13 November 2025 | Drug Target Review | No comments yet

Pioneering circular RNA could redefine what the future of gene therapy looks like. Erik Digman Wiklund, CEO of Circio, shares how his company's platform is enhancing gene expression and tackling toxicity challenges through smarter design and scientific collaboration.

Ag Analyst Group

Intervju med Circios VD Erik Digman Wiklund

"Den som investerar i dag får möjlighet att ta position i en teknik som kan förändra framtidens genterapi innan den blir allmänt etablerad."

the Medicine Maker

Cell & Gene | Bioprocessing | Technology & Manufacturing

Bringing New Ideas to AAV Gene Therapy

As safety concerns and commercial doubts threaten the AAV gene therapy field, new technologies may offer a "well-rounded" solution.

By Erik Wiklund | 11/20/2025 | 3 min read | Discussion

BioSpace

News > Drug Development

Opinion: Circular RNA Will Soon Replace mRNA in Biopharma

July 31, 2024 | 5 min read | Erik Digman Wiklund