circio

The leader in circular RNA expression systems

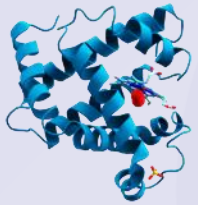
Company presentation
Q4 2025

Circio has developed a powerful alternative to the central 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

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

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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

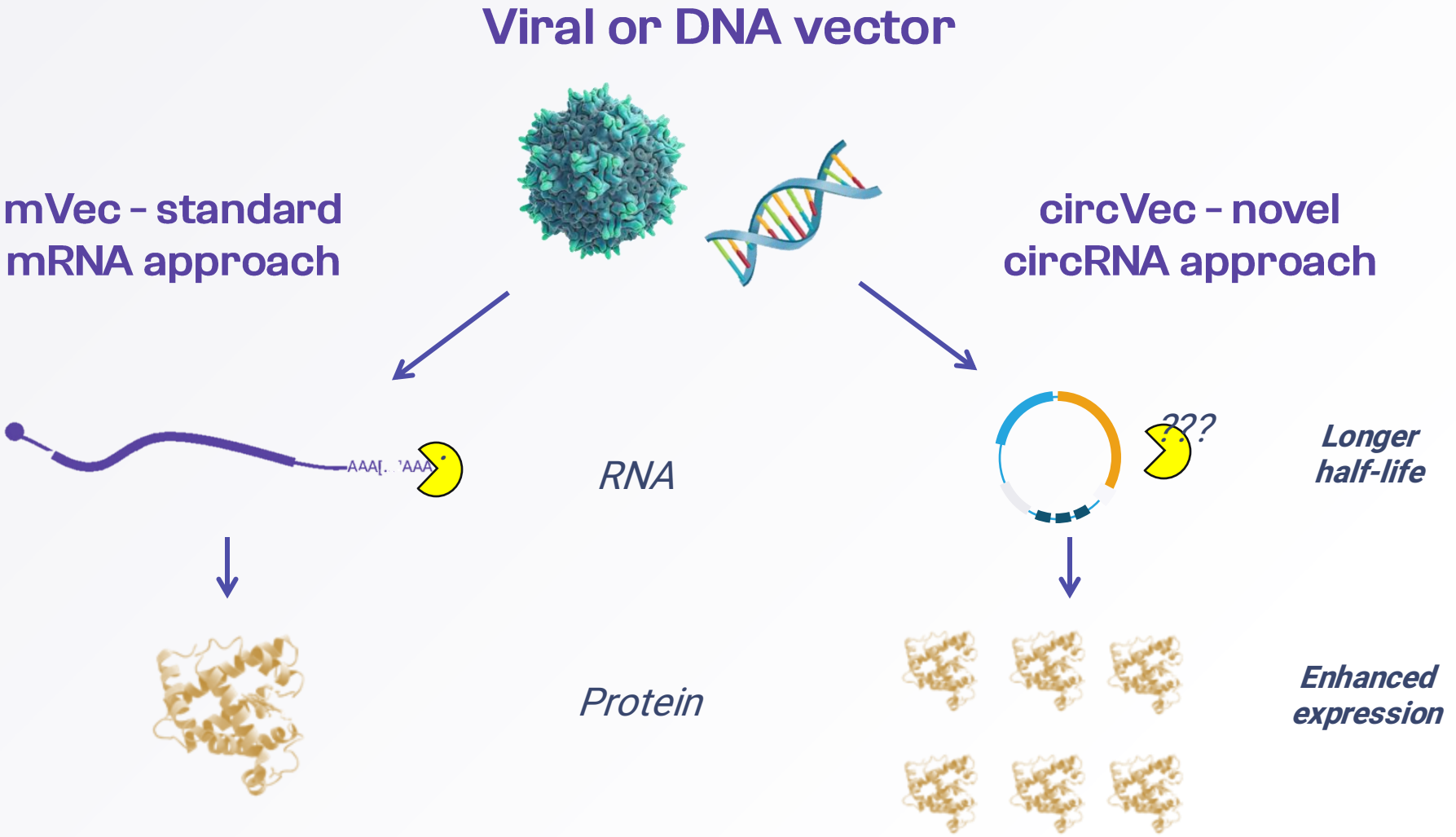
The therapeutic potential of circular RNAs

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

Nature Reviews Genetics (2025) | Cite this article

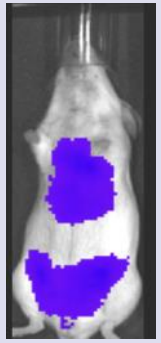
circVec

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

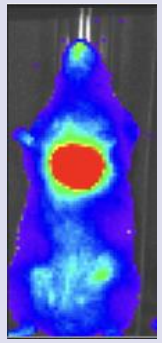


Circio is deploying the circVec technology to enhance conventional gene and cell therapy

Enhanced expression



AAV benchmark

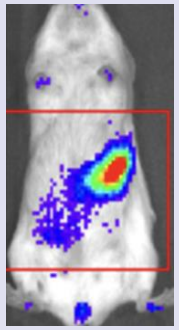


AAV circVec

- **>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: a first-in-class, industry-leading circRNA expression system with platform potential in several disease areas

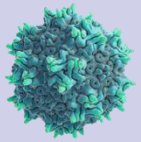
Gene therapy

Heart, eye and CNS genetic disease

1 mill. patients in target diseases

Enhanced, safer and lower cost AAVs

Research collaboration with global pharma



Next Gen AAV

Cell therapy

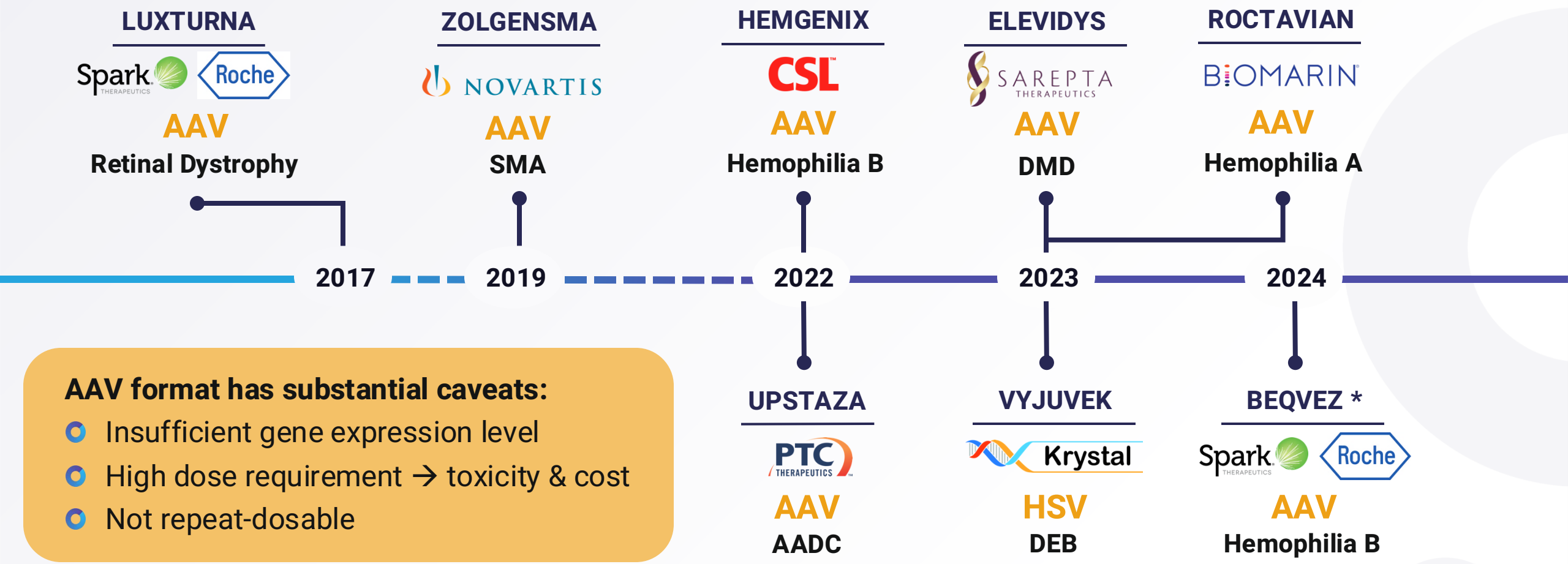
Cancer, autoimmune disease

LNP: DNA format, redosable

Very large patient population, only autologous options available today

In vivo CAR

The AAV vector is the main gene therapy format today, 7 approved products to date



AAV format has substantial caveats:

- Insufficient gene expression level
- High dose requirement → toxicity & cost
- Not repeat-dosable

AAV: Adeno-Associated Virus, currently best known vector for long-term protein expression in humans

* Not commercially available

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:

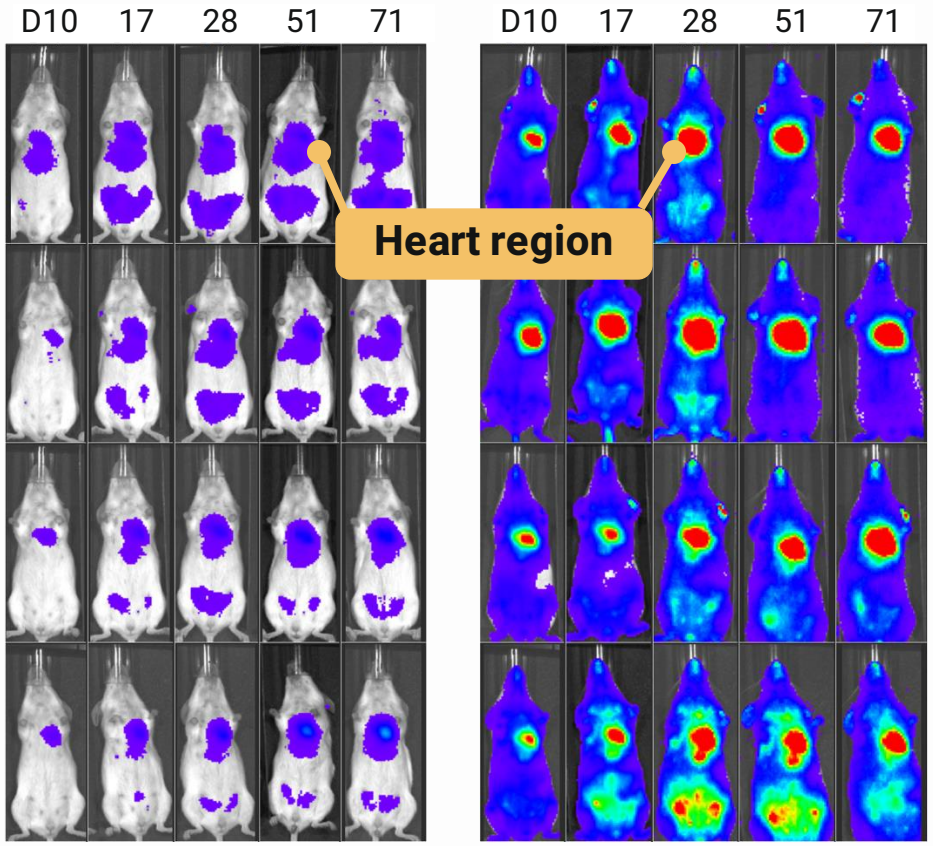
- Clinical benefit demonstrated, but severe toxicity
- Very high AAV dose level required (= high tox & cost)
- ➢ **Severe adverse events, incl. risk of death**

Circio´s circVec technology can unlock:

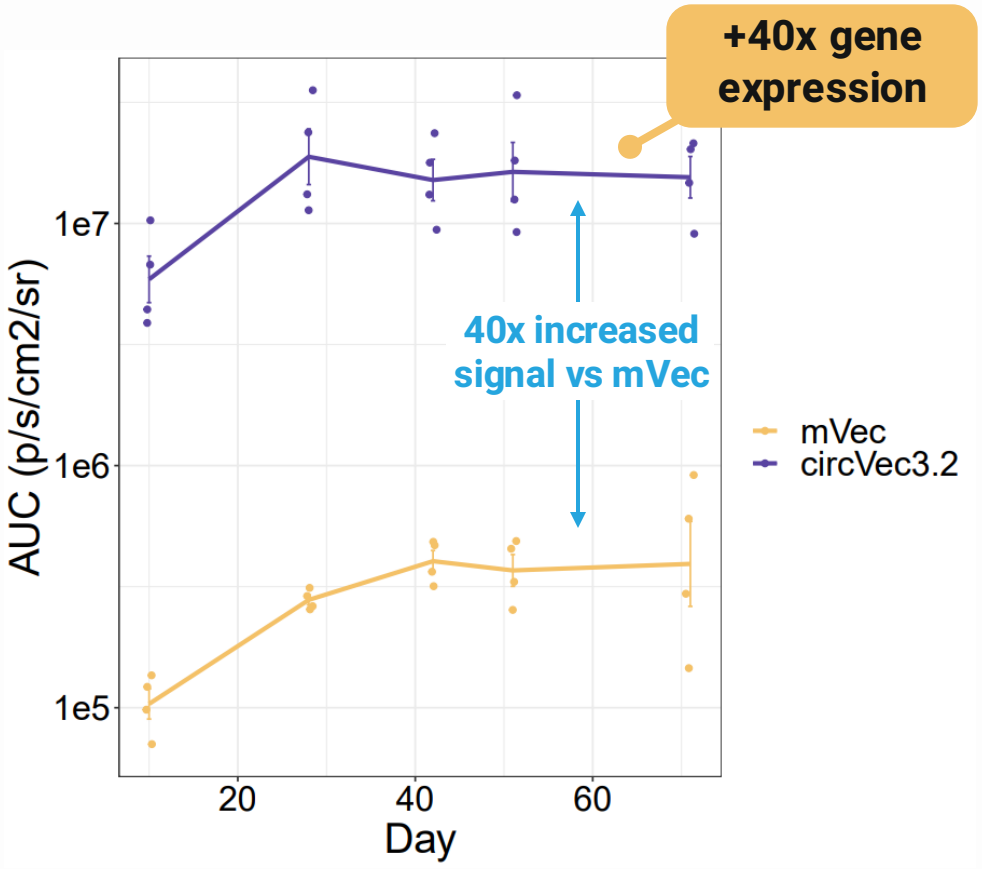
- Significant AAV dose reduction with same clinical benefit
- Reduced toxicity and cost, better commercial viability
- ➢ **Better, safer and lower cost AAV gene therapy**

40-fold enhanced expression in heart for circVec-AAV vs. conventional mRNA-based AAV

AAV-mVec **AAV-circVec 3.2**

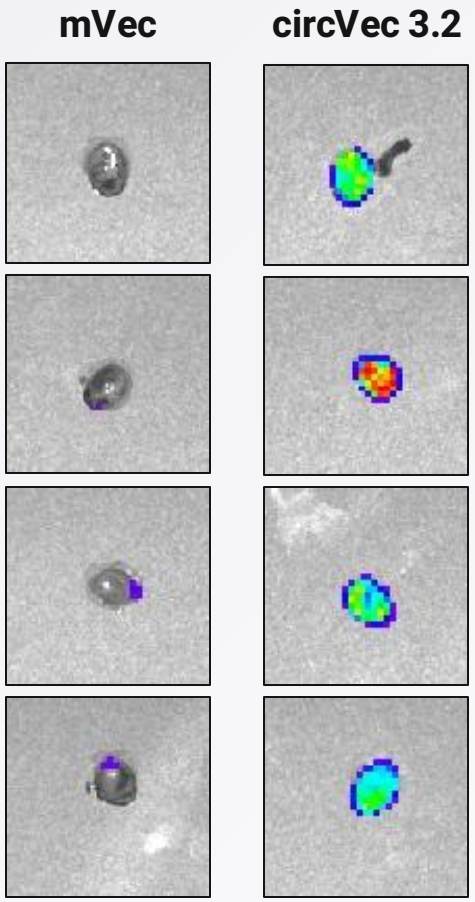


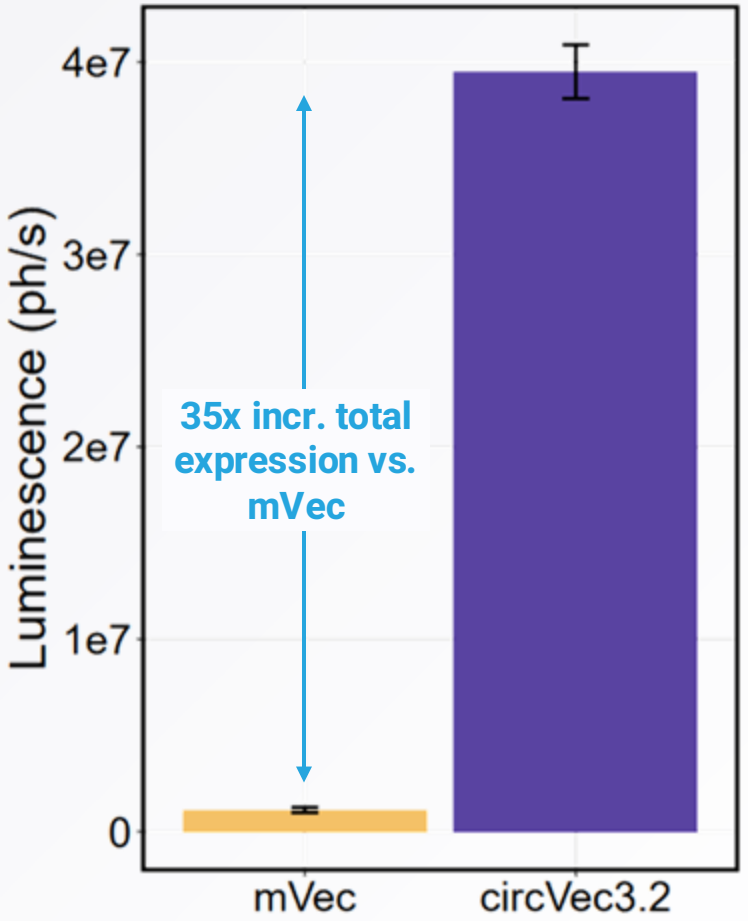
Gene expression quantification, f-luc IVIS signal



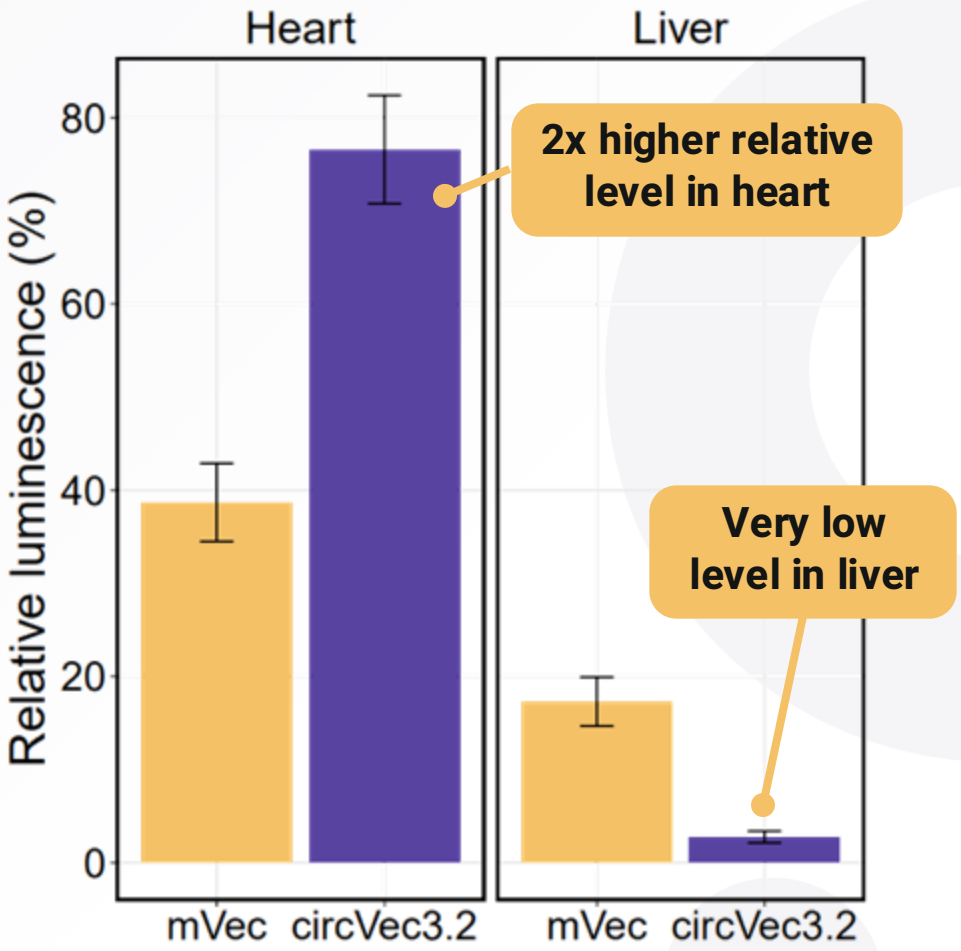
Increased target specificity of circVec-AAV: more expression in heart, less in liver

Increased expression in heart, ex vivo tissue analysis week 10



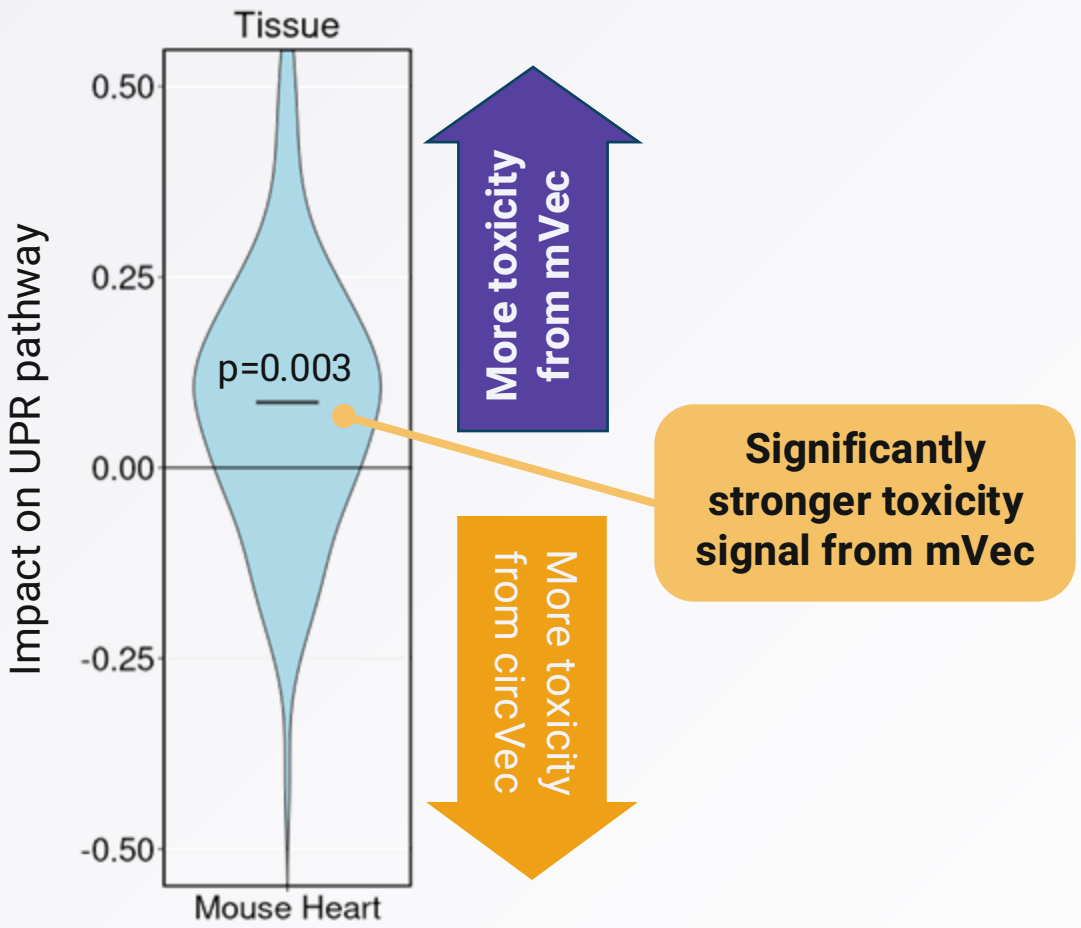


...and reduced off-target liver expression



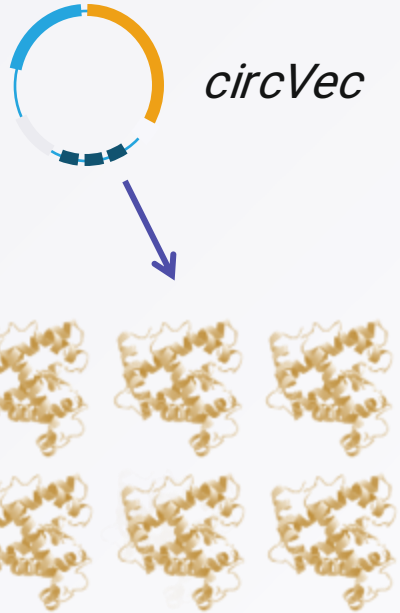
Reduced toxicity of circVec-AAV in heart, despite 40-fold higher gene expression

Cellular stress response, UPR pathway activation



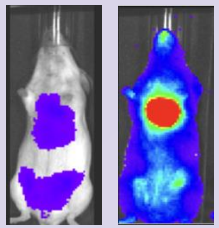
- **Unfolded Protein Response** (UPR) activation is a **major contributor to AAV toxicity** in patients
- AAV-circVec shows **less activation of UPR pathway in heart** than AAV-mVec at **same dose**
  - Despite 40x increased gene expression
  - Confirmed in various cell lines

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

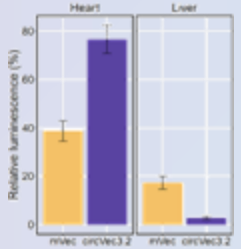


circVec-AAV compared to benchmark mVec-AAV:

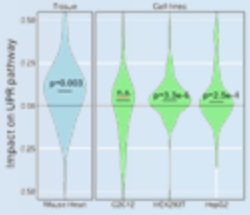
Expression



Specificity



Toxicity



Heart, eye and CNS selected as top three target tissues for 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

circVec: a first-in-class, industry-leading circRNA expression system with platform potential in several disease areas

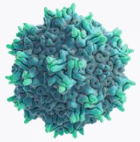
Gene therapy

Heart, eye and CNS genetic disease

1 mill. patients in target diseases

Enhanced, safer and lower cost AAVs

Research collaboration with global pharma



Next Gen AAV

Cell therapy

Cancer, autoimmune disease

LNP: DNA format, redosable

Very large patient population, only autologous options available today

In vivo CAR

circio

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

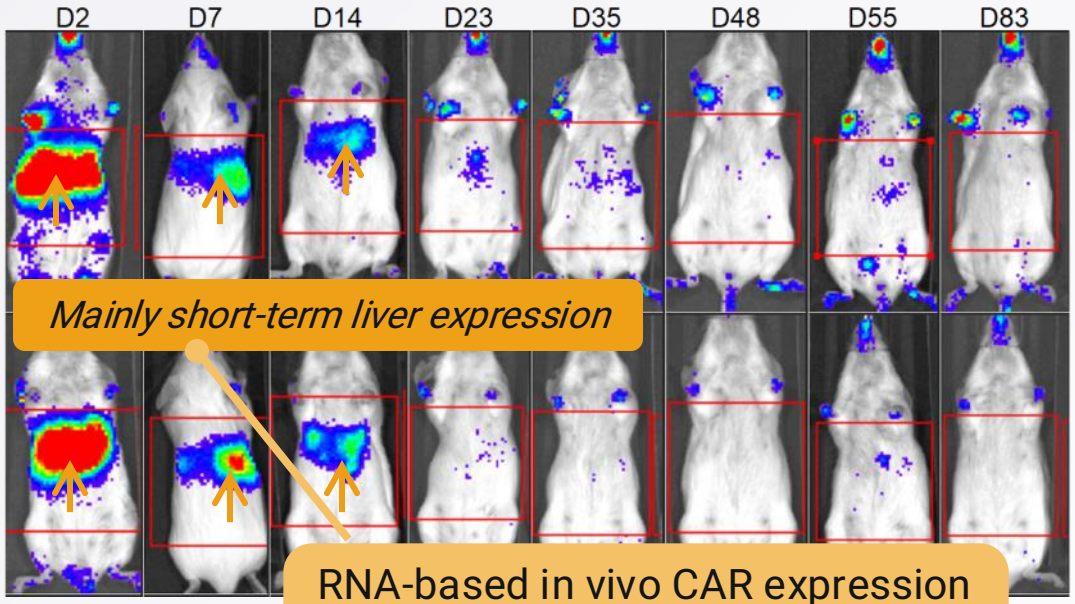
- **Non-genome integrating**
- **> 6 months duration of expression on single dose**
- **Redosable**
- **Avoids liver-expression**

Therapeutic applications

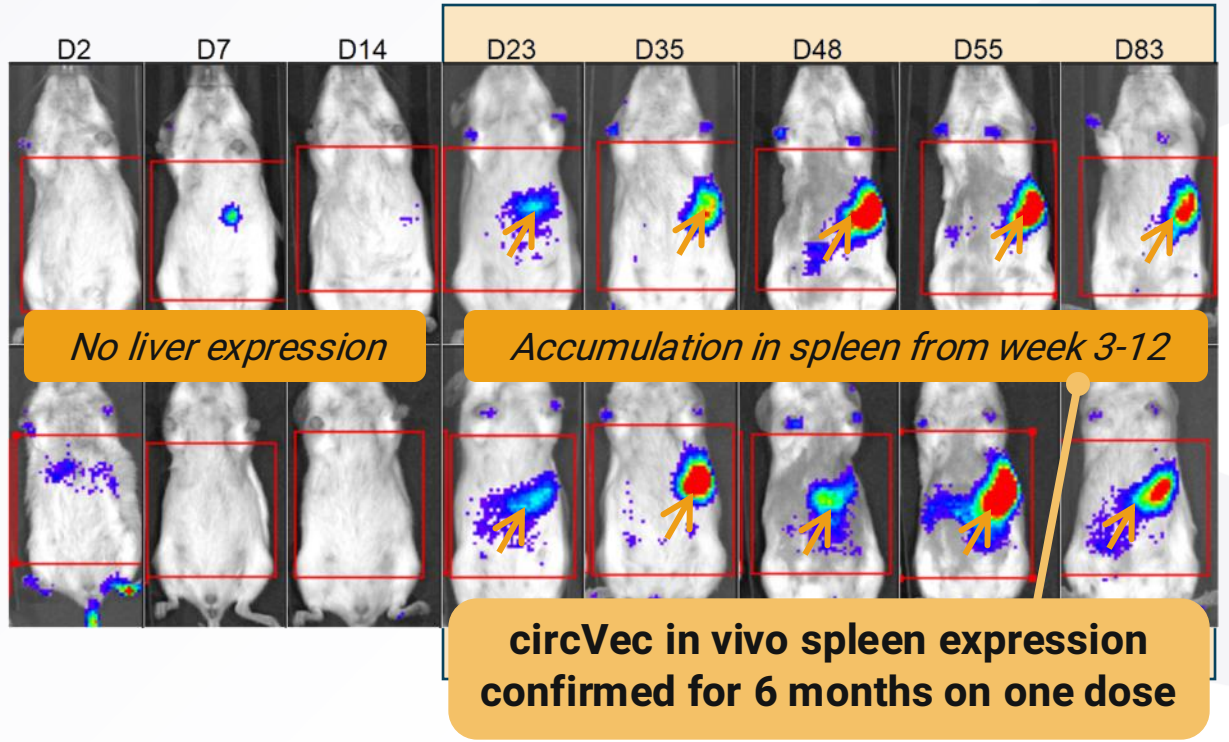
- **Cancer**, e.g. lymphoma
  - Ex vivo CAR-T effective, but expensive
  - Lentiviral risk of secondary malignancies
  - RNA in vivo CAR not sufficient duration
- **Autoimmune disease**, e.g. Lupus
  - secondary opportunity

In vivo cell therapy: circVec expression duration > 6 months vs. 2 weeks for mVec

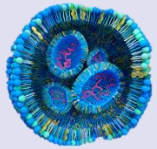
LNP-mVec (mRNA), luminescence
Systemic I.V. delivery, single dose on Day 0



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

Recent deal activity highlights substantial commercial opportunities in Circio areas

AAV gene therapy

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

In vivo cell therapy

Bristol Myers Squibb™ → ORBITAL THERAPEUTICS

M&A, October 2025

$1.5b

in cash buy out

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

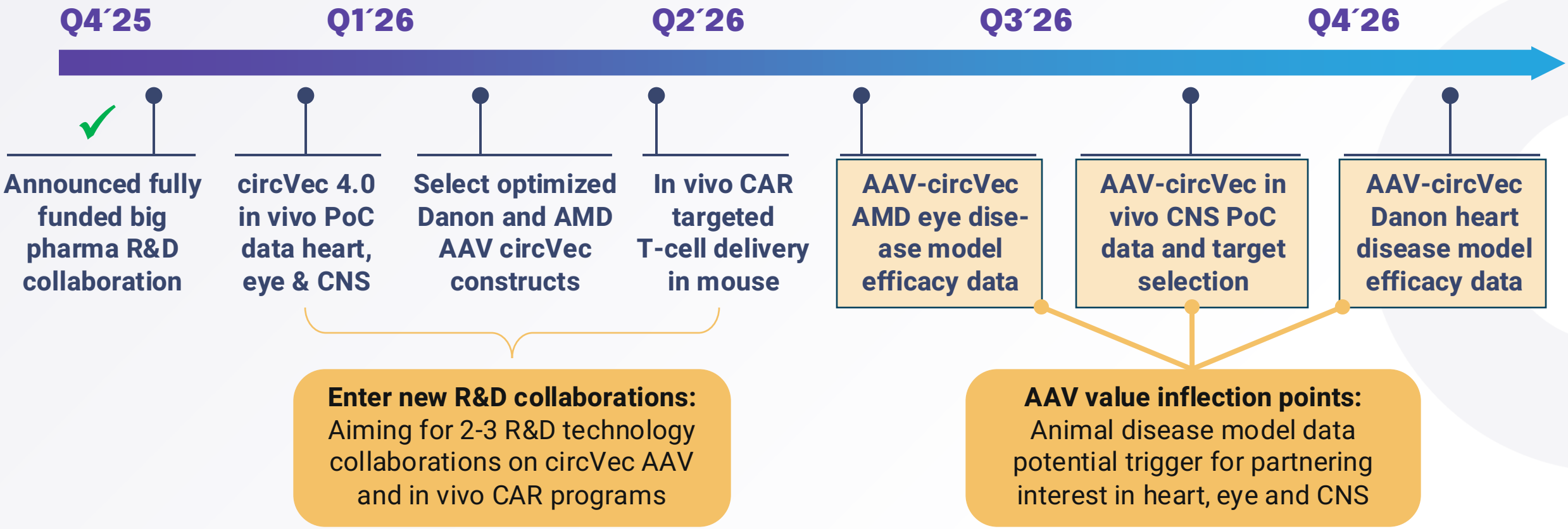
$2.1b

in cash buy out

In vivo CAR-T therapy for autoimmune disease

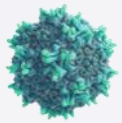
- LNP-delivered synthetic mRNA platform
- Phase 1-ready, CD19 CAR-T

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



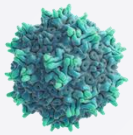
Data & Timeline: current best estimates - experiments have uncertain outcomes and may need to be repeated, impacting plans and timelines

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			*Enhanced, safer and lower cost gene therapy*		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			*Durable and re-dosable in vivo CAR-T therapy*		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

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

circVec is a first-in-class, industry-leading circRNA expression system: Take-home messages



- **AAV-circVec outperforms** conventional heart gene therapy on **expression, specificity and toxicity**

- **In vivo cell therapy** approach with **new and differentiated window-of-opportunity** in area of very high deal activity

- **Rich pipeline** of R&D milestones and news flow in 2026: **multiple shots on goal**

In-house

circVec in vivo validation in relevant tissues and disease models

- ***Next step:*** *Testing circVec-AAVs for Danon disease and AMD*

Partnering

Entered first partnership with global pharma company in Q4´25

- ***Next step:*** *Additional partnerships in open disease areas*

Circio features broadly in international industry media

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."

BioSpace

News > Drug Development

Opinion: Circular RNA Will Soon Replace mRNA in Biopharma

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

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