



**circio**

# Disruptive circRNA technology for genetic medicine

First half-year report  
29 August 2024

# Important notice and disclaimer

This report contains certain forward-looking statements based on uncertainty, since they relate to events and depend on circumstances that will occur in the future and which, by their nature, will have an impact on the results of operations and the financial condition of Circio Holding ASA and the Circio Group. Such forward-looking statements reflect the current views of Circio and are based on the information currently available to the company. Circio cannot give any assurance as to the correctness of such statements.

There are a number of factors that could cause actual results and developments to differ materially from those expressed or implied in these forward-looking statements. These factors include, among other things, risks or uncertainties associated with the success of future clinical trials; risks relating to personal injury or death in connection with clinical trials or following commercialization of the company's products, and liability in connection therewith; risks relating to the company's freedom to operate (competitors patents) in respect of the products it develops; risks of non-approval of patents not yet granted and the company's ability to adequately protect its intellectual property and know-how; risks relating to obtaining regulatory approval and other regulatory risks relating to the development and future commercialization of the company's products; risks that research and development will not yield new products that achieve commercial success; risks relating to the company's ability to successfully commercialize and gain market acceptance for Circio's products; risks relating to the future development of the pricing environment and/or regulations for pharmaceutical products; risks relating to the company's ability to secure additional financing in the future, which may not be available on favorable terms or at all; risks relating to currency fluctuations; risks associated with technological development, growth management, general economic and business conditions; risks relating to the company's ability to retain key personnel; and risks relating to the impact of competition.

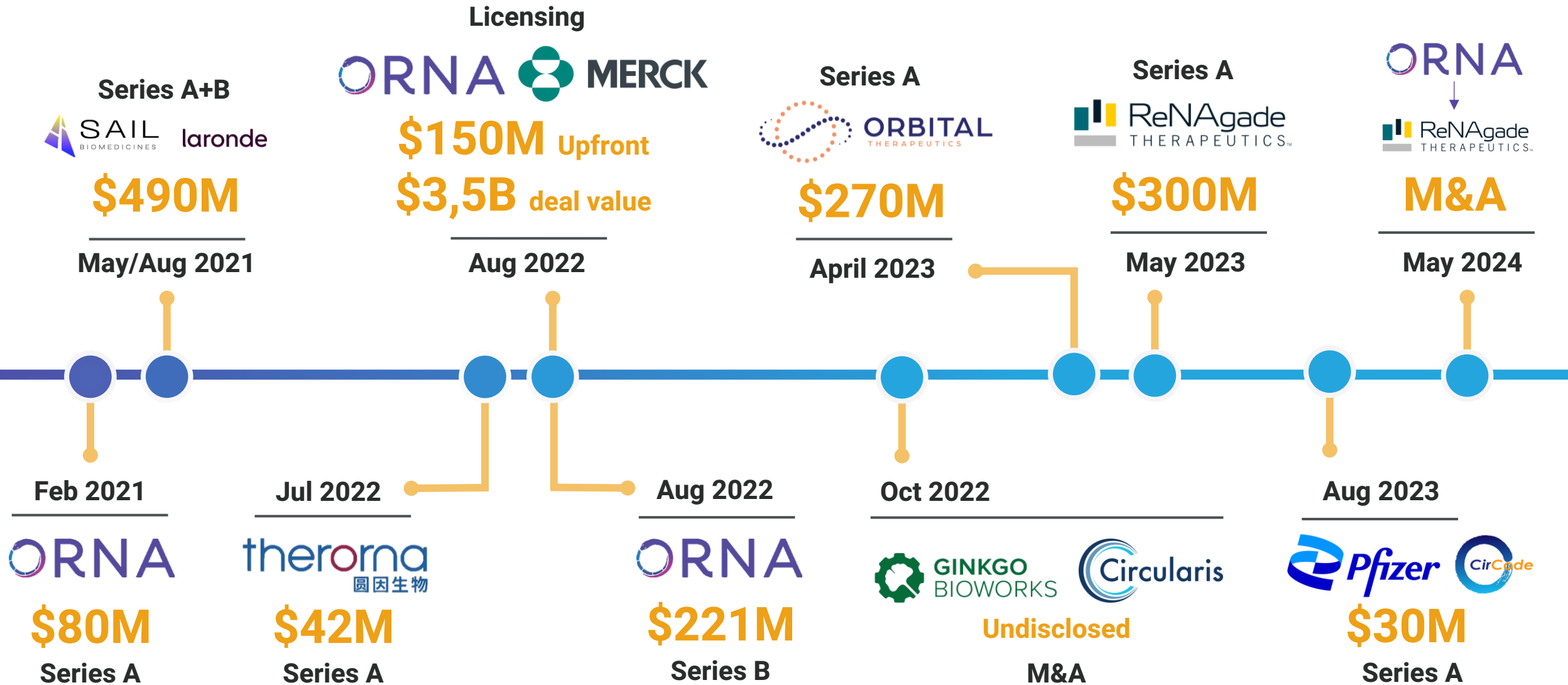
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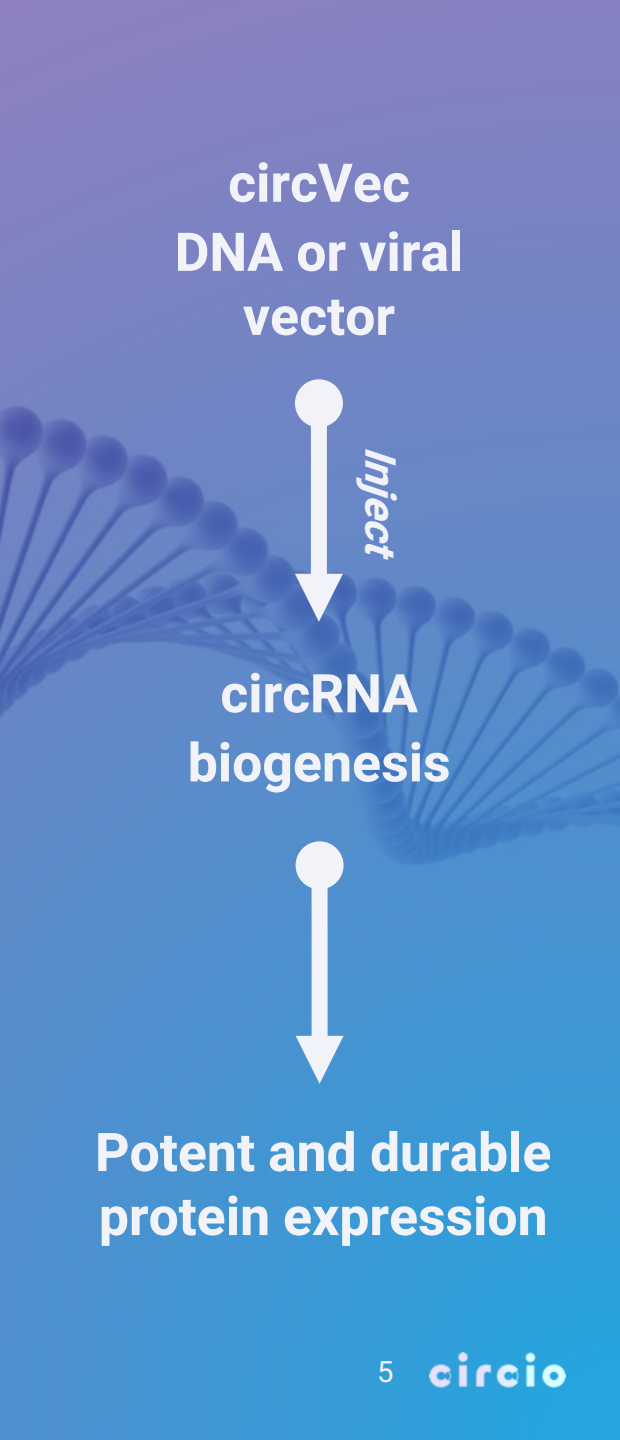
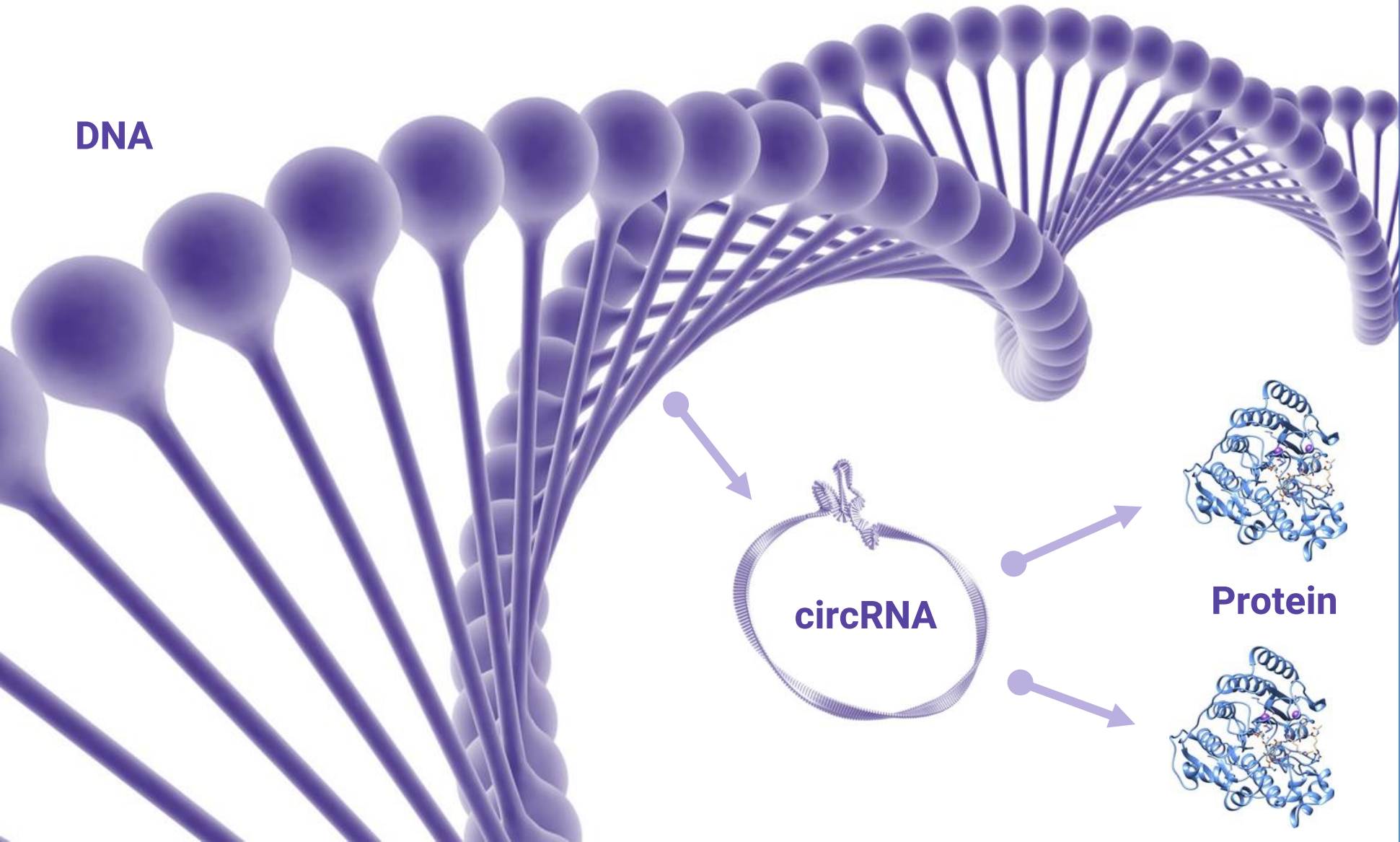
## circVec development

2. circVec gene therapy
3. 1H 2024 financials

# Substantial deal activity in the circular RNA space



# The unique circVec expression system: Turning the patient's cells into circRNA factories



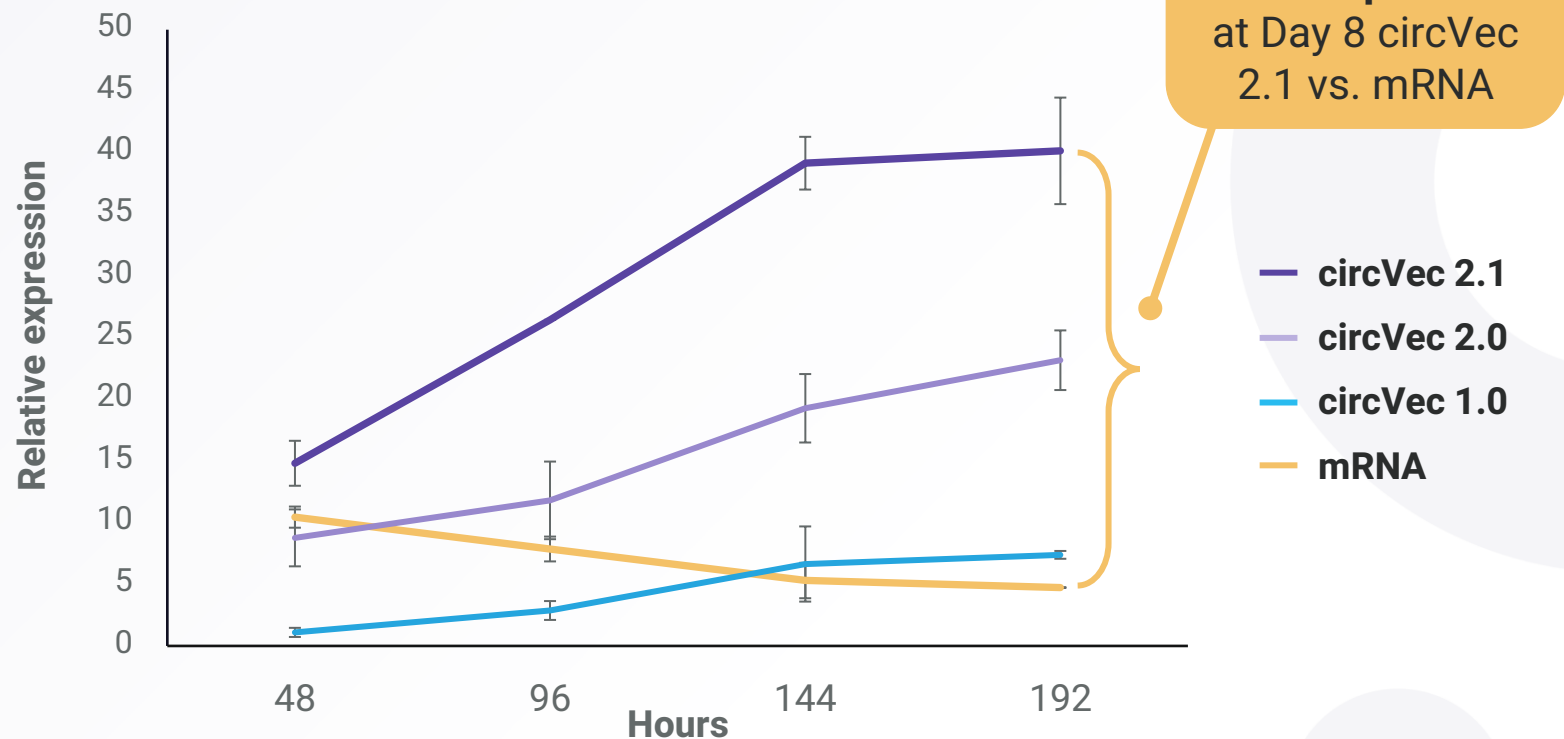
# circVec platform technology continues to strengthen

## circVec RNA stability

**135h** vs. **9h**  
circRNA vs. mRNA

15x

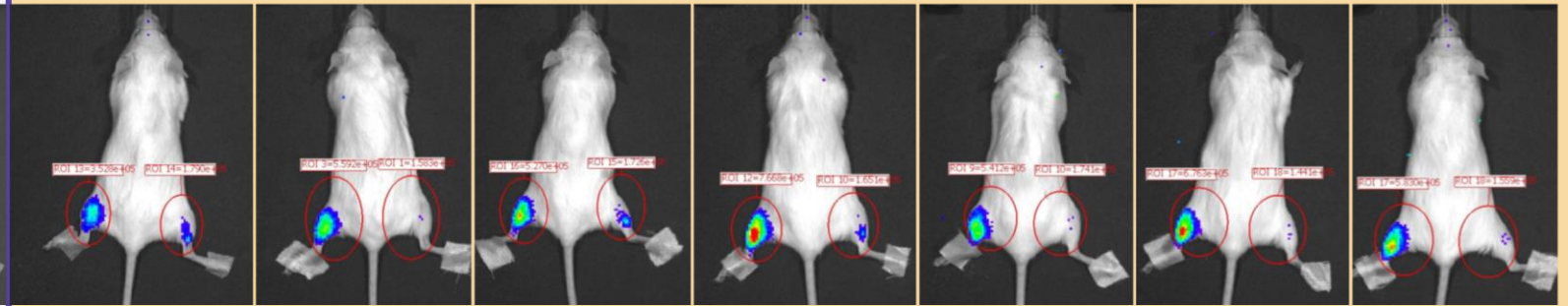
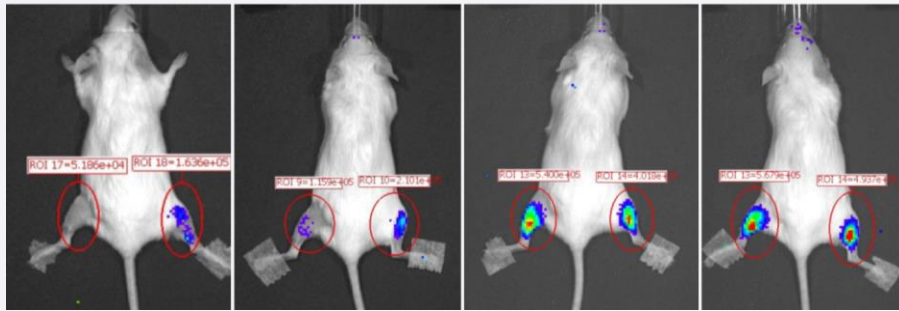
## circVec vs. mRNA protein expression assay; time course



# circVec 2.1 robustly outperforms conventional mRNA-based expression in mouse models

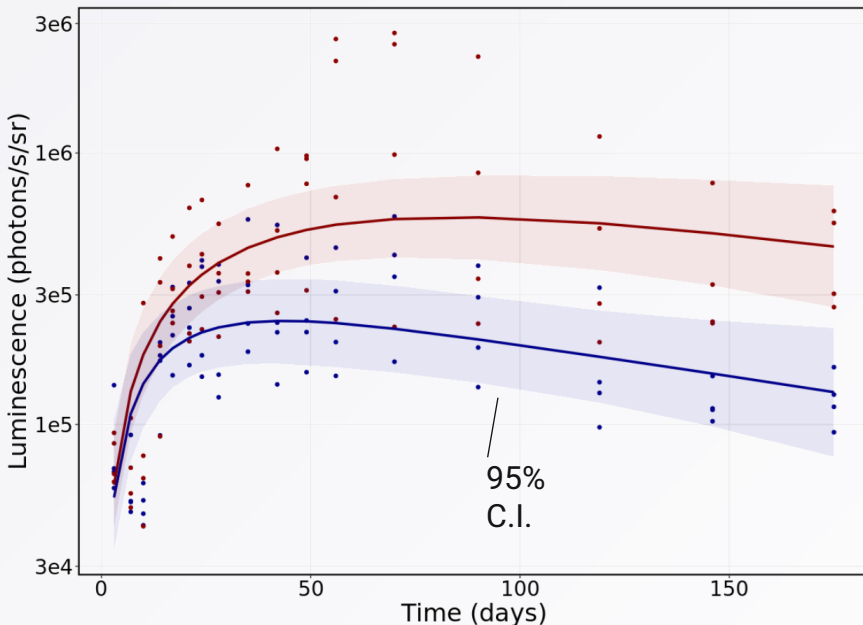
Day 1      Day 8      Day 14      Day 21

Day 28      Day 35      Day 42      Day 57      Day 71      Day 91      Day 119



circRNA mRNA    circRNA mRNA    circRNA mRNA    circRNA mRNA

circRNA mRNA    circRNA mRNA    circRNA mRNA    circRNA mRNA    circRNA mRNA    circRNA mRNA    circRNA mRNA



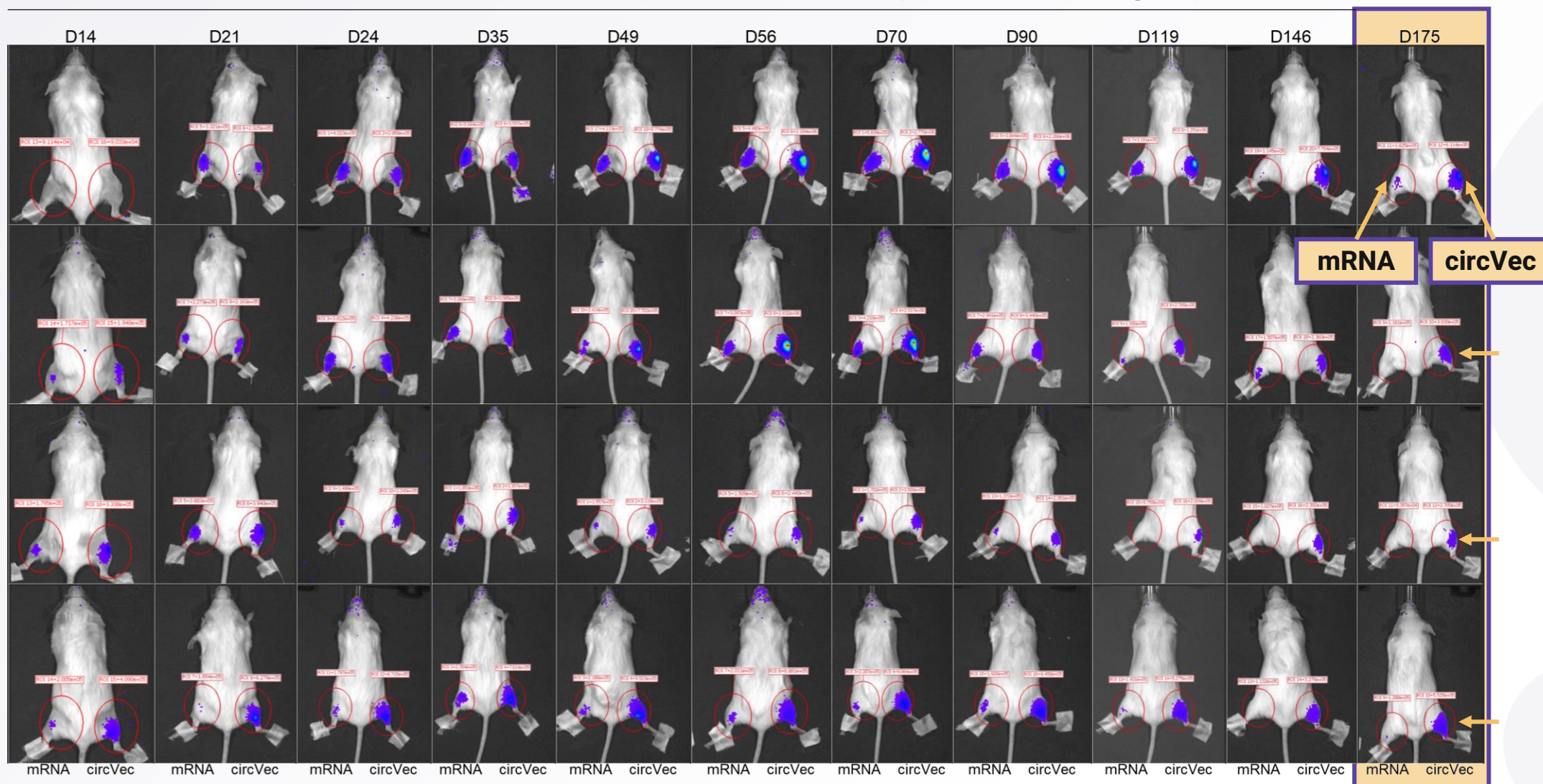
— circRNA  
— mRNA

- circVec 2.1 pDNA constructs show statistically significant enhanced durability vs. mRNA-based expression in vivo
- Major advantage and opportunity in gene therapy

# circVec 2.1 advantage vs. mRNA expression has been validated for up to six months

circVec vs. mRNA Luciferase expression, single intra-muscular injection of pDNA @ day 0

Day 175

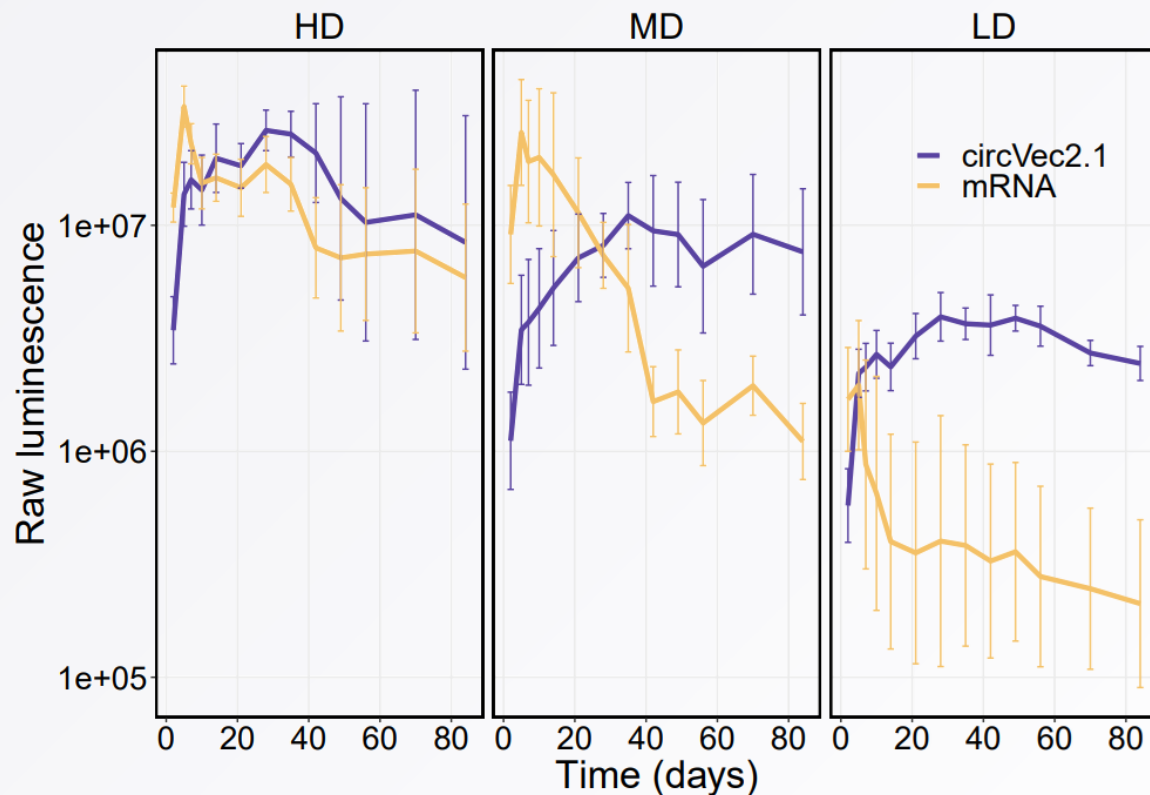




# circVec in vivo advantage enhanced at lower dose levels

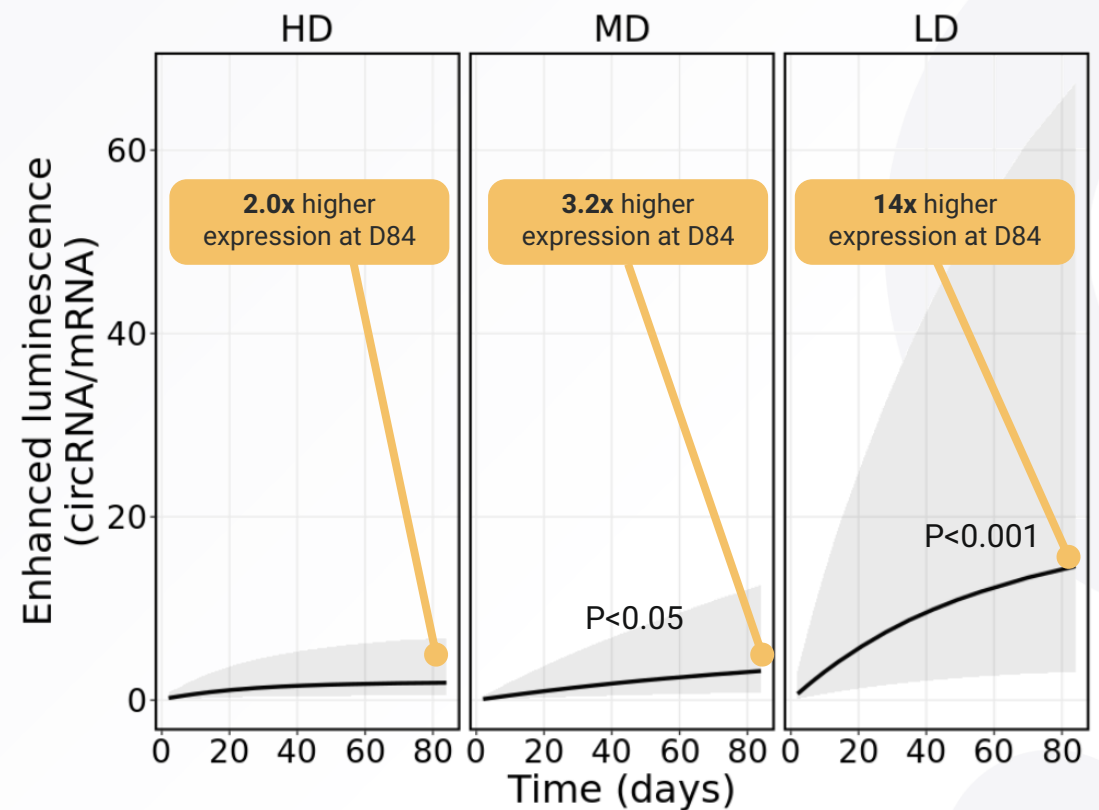
## Absolute expression (luminescence)

circVec 2.1 vs. mRNA pDNA vector expression



## Relative expression (luminescence)

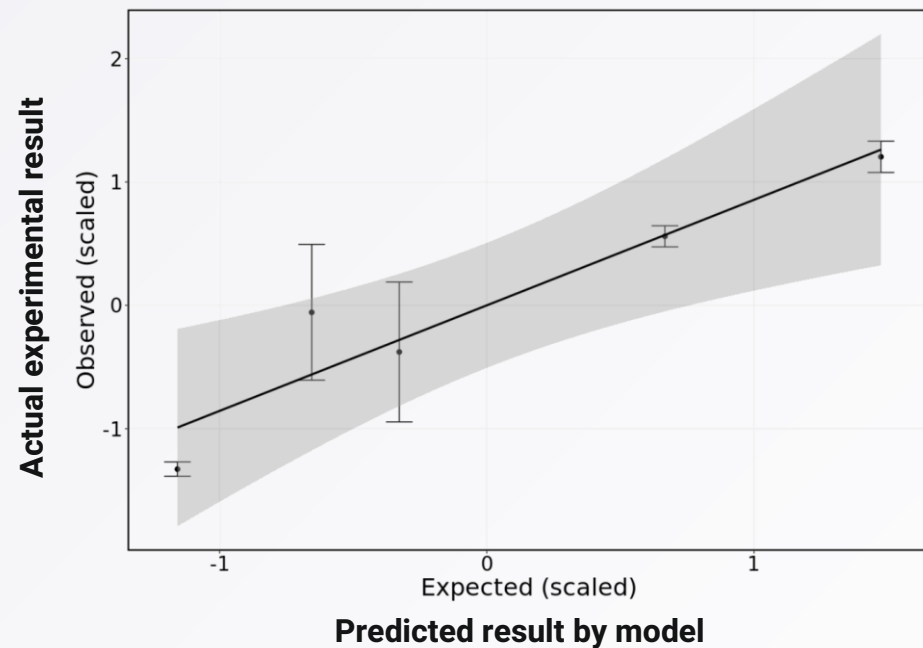
-fold change circVec 2.1 vs. mRNA expression



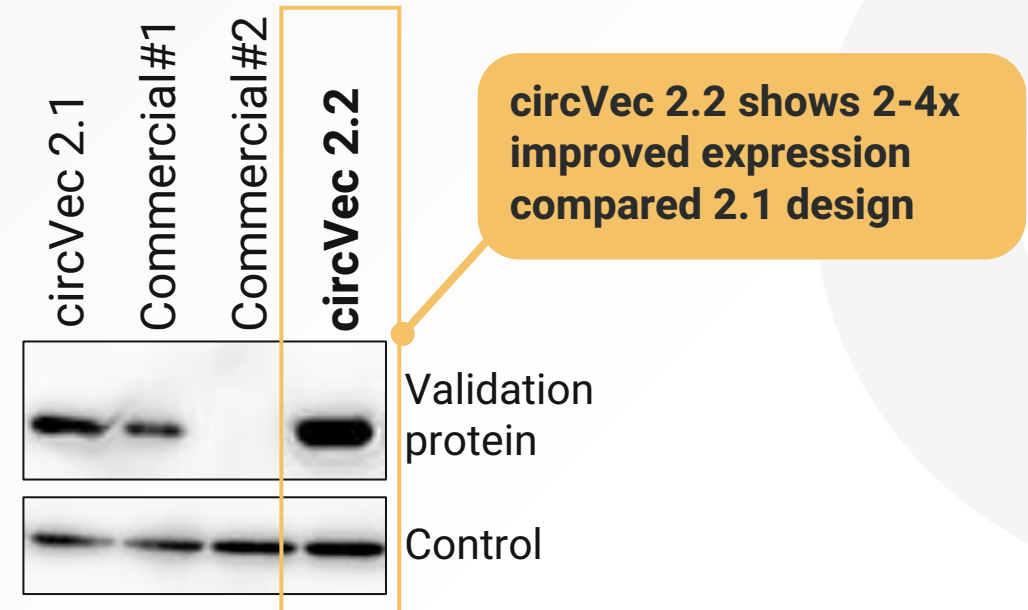
HD: High dose MD: Mid dose LD: Low dose

# Machine learning has been deployed to further optimize circVec design – generation 2.2 and beyond

## Machine learning model validation



## circVec 2.x performance



# Circio is being recognized by industry media as an emerging leader in the circRNA space

## BIOCENTURY

ARTICLE | PRODUCT DEVELOPMENT

### Emerging circular RNA field split on what to deliver and how to deliver it

The rising therapeutic modality is more durable than linear mRNA, promising efficacy and manufacturing advantages

BY DANIELLE GOLOVIN, BIOPHARMA ANALYST

August 17, 2023 11:34 PM UTC

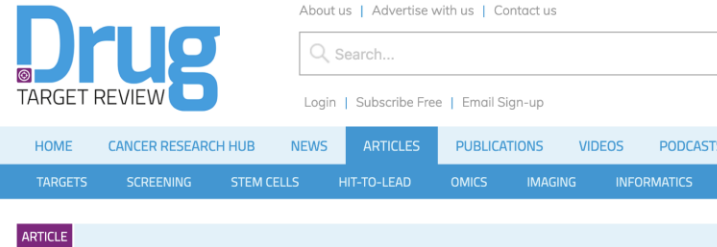


NEWS ▾ JOBS CAREER ADVICE COMPANIES

News > Drug Development

### Opinion: Circular RNA Will Soon Replace mRNA in Biopharma

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



### Enhancing gene therapy with Circio

In this Q&A, Erik Wiklund, CEO of Circio, explains the key findings of their circVec circular RNA platform technology, why they chose AAV-based gene therapy for AATD as the lead programme, and their plans for the future to enhance the potency and reduce the cost of current gold-standard gene therapy.

Features

### Circular RNA: Vaccines, therapeutics and biomarkers could be revolutionised

CircRNA is still in very early days of development, but it is expected to be trialled in vaccines, therapeutics and biomarkers trials in the next few years.

Abigail Beaney | May 15, 2024

Share ↩

Clinical Trials Arena

### How does circVec technology compare to conventional mRNA?



DRUG DISCOVERY WORLD  
**DDW**<sup>TM</sup>  
turning science into business

3 July 2024



Posted in News | Tagged Circio Holding, circular RNAs, Gene therapy, Genetic diseases, In vivo, mRNA

Circio has announced updated *in vivo* data that demonstrates a substantial durability advantage of Circio's circVec technology over conventional mRNA expression. In addition, Circio has undertaken sequence optimisation resulting in a new circVec 2.2 design.

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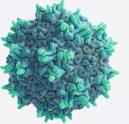
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## circVec gene therapy

3. 1H 2024 financials

# circVec is being explored in both viral and synthetic DNA DNA vector formats for therapeutic applications

## Viral



AAV



Adenovirus

Application

- Gene therapy

- Vaccines
- Oncology

Aim

- Improved expression and reduced dosing vs. mRNA AAV

- Single-dose vaccine
- Therapeutic protein delivery to tumors

**Advantage:** Efficient delivery of genetic material  
**Challenge:** Repeat dosing and immune response

## Synthetic DNA

DNA format 1



DNA format 2

- Gene therapy
- Vaccines

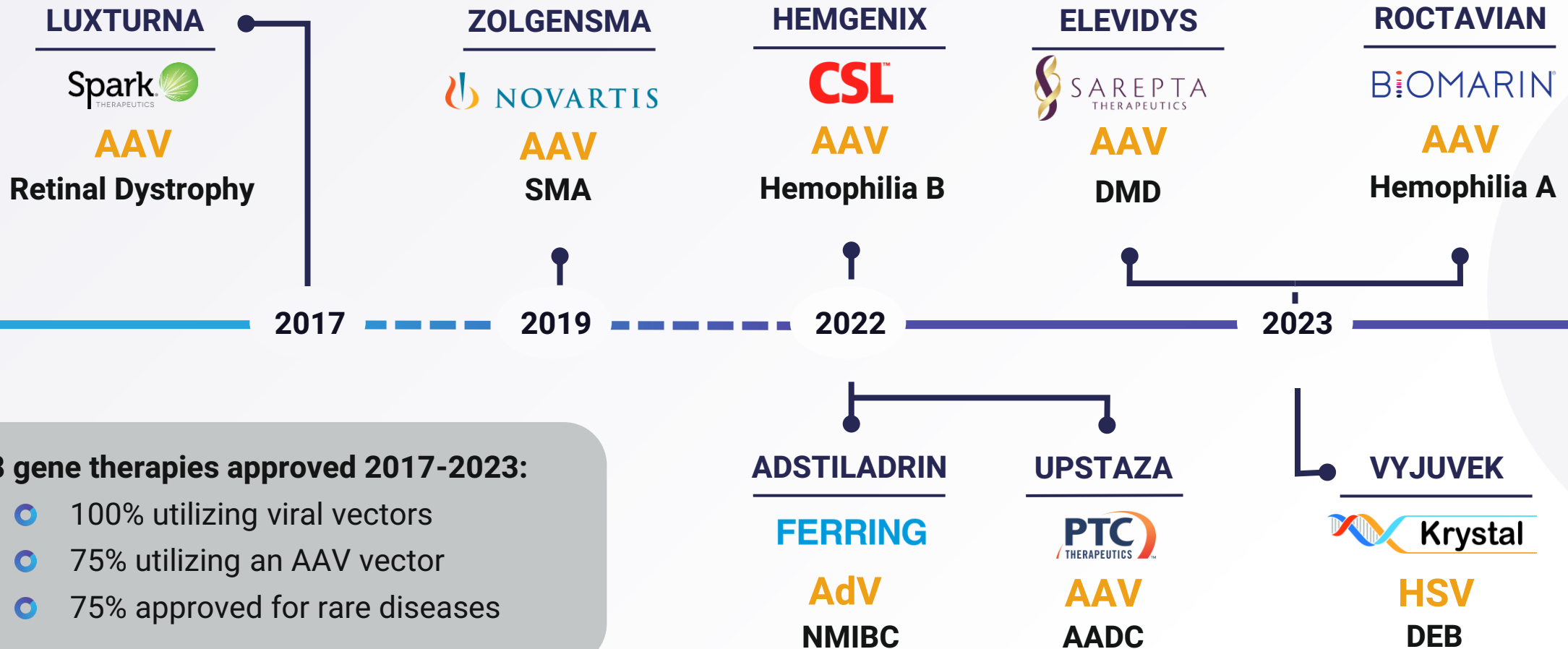
- Gene therapy
- Cell therapy

- Enable repeat-dosing for gene therapy
- Enhanced nuclear uptake

- Improved uptake
- Reduced immunogenicity

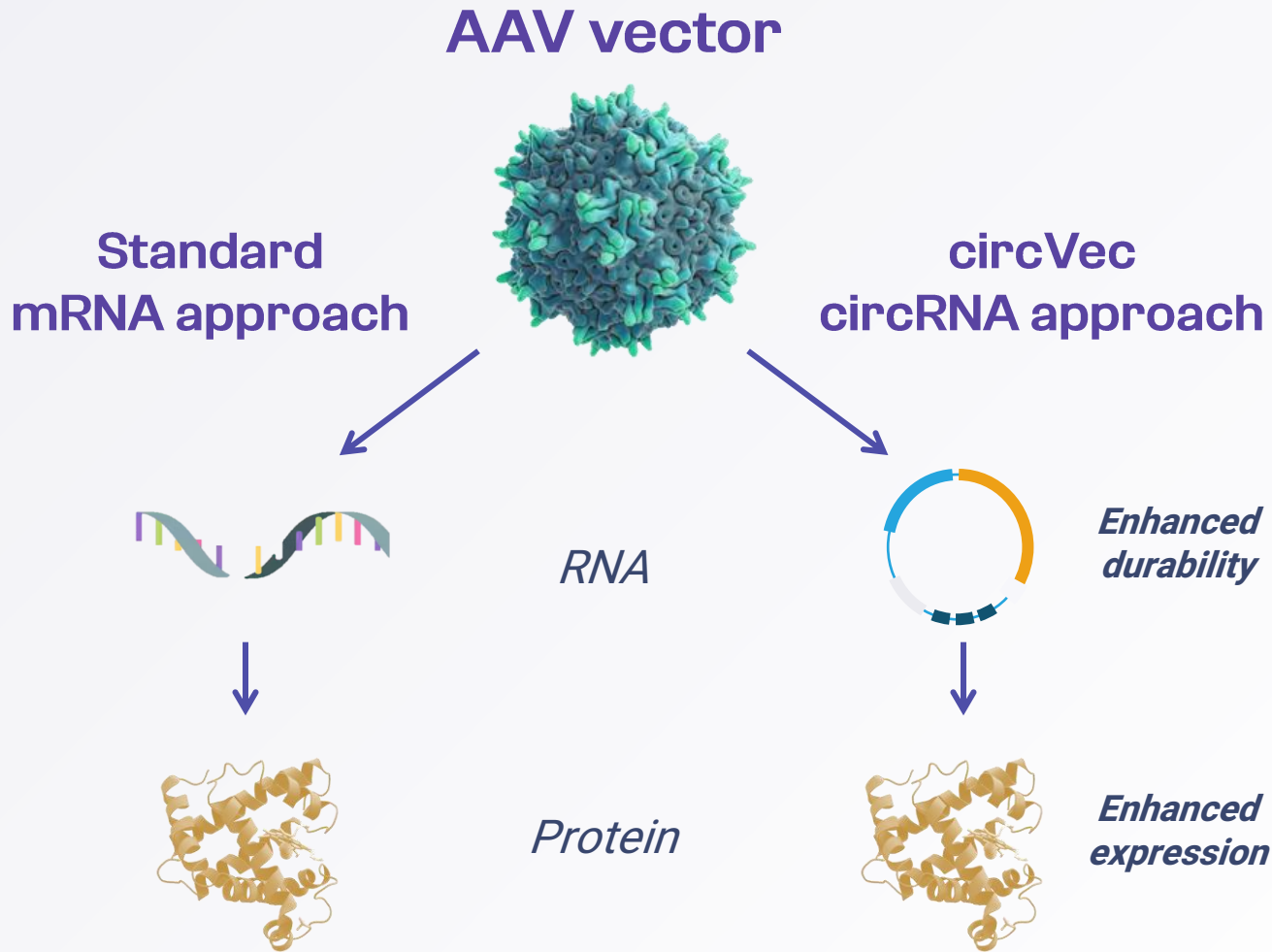
**Advantage:** Repeat dosing and manufacturing  
**Challenge:** Nuclear delivery and innate immunity

# AAV virus is the main gene therapy format today

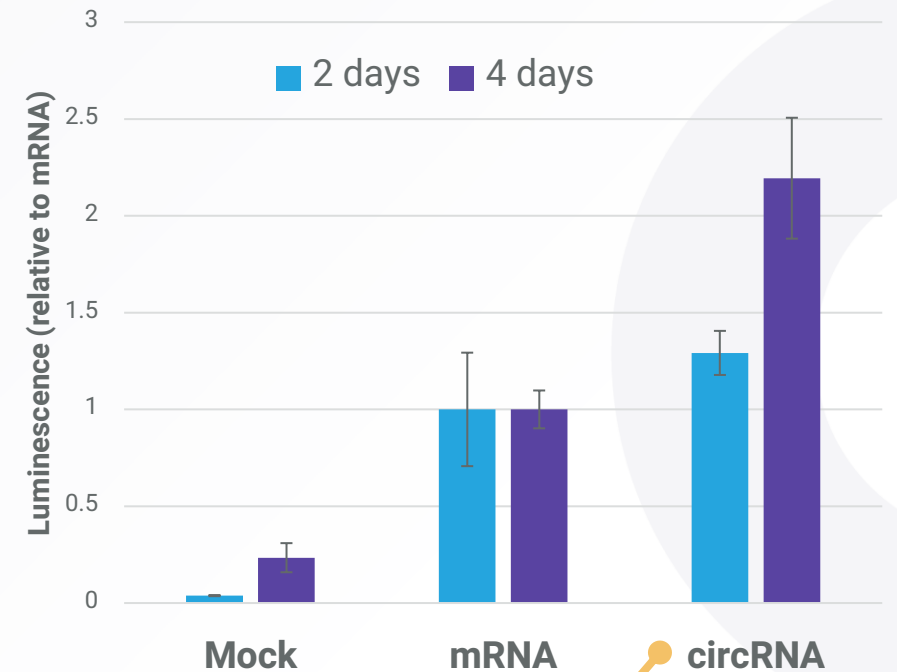


AAV: Adeno-Associated Virus, currently best known vector for long-term protein expression in humans

# Can circVec be deployed to enhance AAV gene therapy?



**AAV protein expression, luminescence**

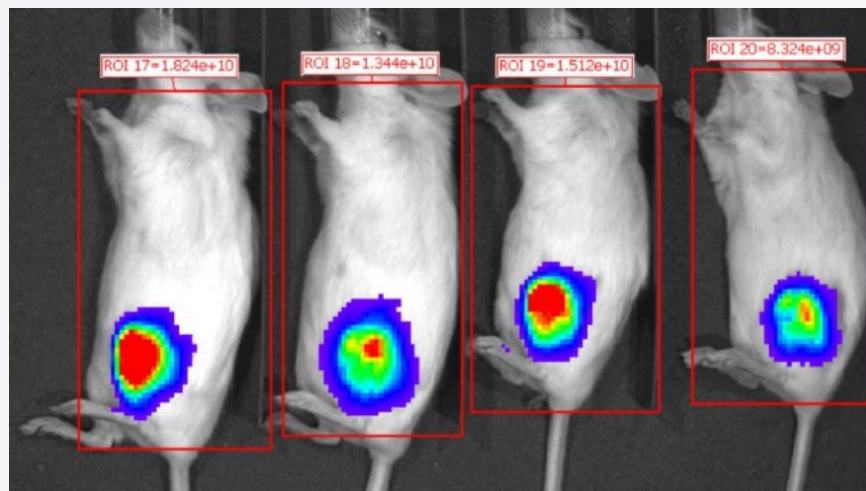


**Enhanced circVec-AAV expression vs. mRNA-AAV, validated by multiple experimental methods *in vitro***

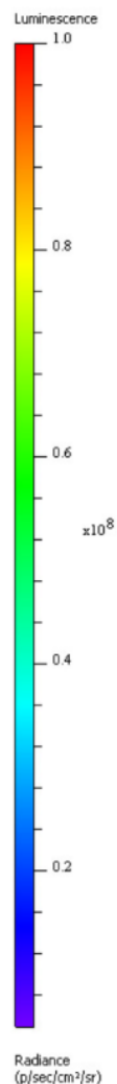
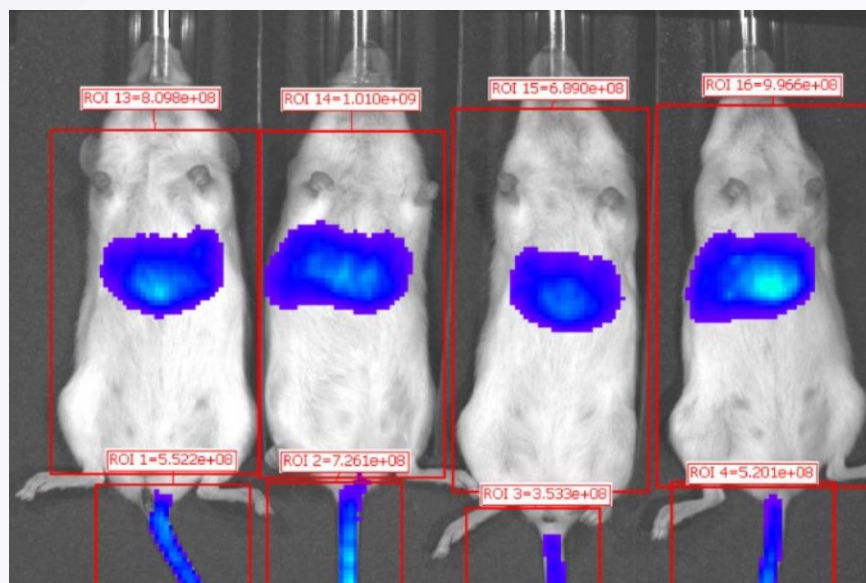
# circVec 2.0 AAV vector expression validated in vivo

circVec-AAV luminescence, F-luc at Day 20

Intra-muscular (I.M.)



Tail vein (I.V.)



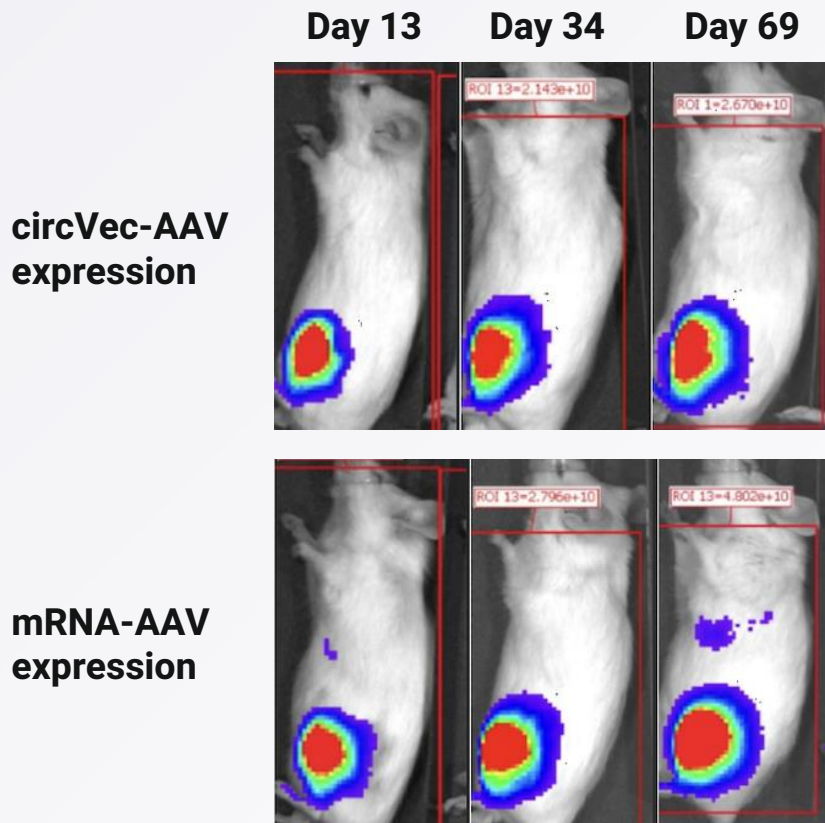
## Experimental set-up

<b>Vector:</b>	AAV8
<b>circVec version:</b>	circVec 2.0
<b>Payload:</b>	Firefly luciferase (F-luc)
<b>Mouse strain:</b>	NOD/SCID/IL-2R $\gamma$ null immunodeficient mice
<b>Delivery route:</b>	Tail vein or intra-muscular injection
<b>Single injection, dose:</b>	$1 \times 10^{10}$ or $1 \times 10^{11}$ viral genomes



# Ongoing experiment testing circVec-AAV vs. mRNA-AAV in vivo

**AAV expression (luminescence), I.M. single inj.**



*Case example animals,  
illustrative expression data*

- **Robust expression in muscle (bioluminescence) achieved with AAV8 virus (liver optimized strain)**
- **Not yet evident advantage vs. mRNA-AAV (ongoing experiment, week 10 data)**
- **Continuous tracking, testing of lower dose level and muscle-specific AAV planned**

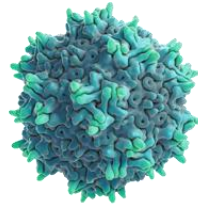
# circVec R&D top priorities and next steps

## circVec platform



- circVec 2.2 generation testing in vivo
- Establish and test circVec 3.0 generation in vitro
- Two new patent filings at drafting / planning stage

## Gene therapy applications



- Explore muscle-specific AAV and lower dose level
- Test delivery and expression in additional tissues
- Implement circVec 2.2 (→ 3.0) features

## Business Development



- Entered / entering five gene therapy delivery collaborations, data generation during next six months
- Seeking research collaborations with AAV companies
- Aiming for a strategic deal during 1H 2025

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## 1H 2024 financials

# Financial highlights



## Rights Issue

- **Gross proceeds: NOK 19.6m, completed in July 2024**
  - **NOK 9.4m pre-subscriptions** (incl. NOK 1.75m from Board and Management)
  - **NOK 8.7m in additional subscriptions**
- **Financing commitment by Atlas until 30 June 2025**



## Business Finland Loan

- **Waiver of total loan value of NOK 71.3m (EUR 6.2m)**
- **Saves NOK 9-11m in annual down-payments and interest**
- **Positive effect on negative equity**
- **Patent estate reduction (Oncos-102)**
- **Targovax Oy under liquidation – no further oper. expense**

# 2024 financials<sup>1</sup> – Continued cost reduction 1H´24

NOK m	1H23	2H23	1H24
<b>Total revenue</b>	0	0	0
R&D expenses <sup>2</sup>	-42	-7	-7
Payroll and related expenses	-22	-12	-10
Other operating expenses <sup>3</sup>	-8	-9	-5
<b>Total operating expenses</b>	<b>-73</b>	<b>-28</b>	<b>-23</b>
Operating loss	-73	-28	-23
Net financial items	-3	-7	67
Profit/loss before income tax	-76	-35	44
Net change in cash	-35	-9	-19
<b>Net cash EOP</b>	<b>31</b>	<b>22</b>	<b>3</b>
<b>Net cash flow from operating activities</b>	<b>-59</b>	<b>-30</b>	<b>-19</b>

**Payroll cost: - 50%**

**Other operating: - 30%**

**Waiver of ONCOS-102 R&D loans**

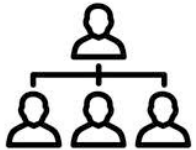
**Cash burn-rate further reduced, -68% vs 1H´23, -37% vs. 2H´23**

1 Unaudited numbers

2 Including patent cost

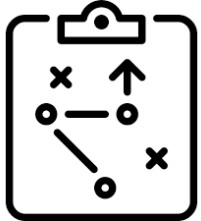
3 Including depreciation and impairment

# Resources focused to maximize R&D output



## Organization

- Lean and efficient organisation – 10 FTEs
- R&D staff prioritized, majority of employees
- Minimal administration as public company



## R&D focus

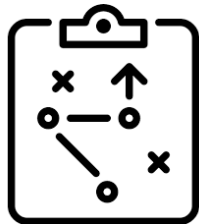
- Generate data package for deal or investment
- Focus on low hanging fruits /short term gains
- Using collaborations to generate new data



## Cost base

- Cash burn rate reduced to NOK ~4m / month
- Tight cost management, further reductions planned (15-25%)

# Financial outlook



## Current situation

- **Financing secured until 30 June 2025**
- **Financing commitment from Atlas available from October 2024**



## Outlook

- **Warrant exercise period December 2024**
- **Aiming to enter first strategic partnership in 2025**
- **Continuous specialist investor dialogues**



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# Q & A Session

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