circio

Disruptive circRNA technology for genetic medicine

Company update
17 April 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.

1

The challenge

2. The circVec approach
3. Therapeutic application of circVec
4. 2023 financials
5. Intended financing

Gene therapy for rare disease is rapidly gaining momentum with investors, pharma and regulators

POLICY

FDA adopts Operation Warp Speed lessons for rare disease pilot program

The FDA announced the launch of a pilot program, dubbed START, to address challenges associated with rare disease development and speed up the regulatory process.

Lecia Bushak | November 22, 2023 | 10:51 AM

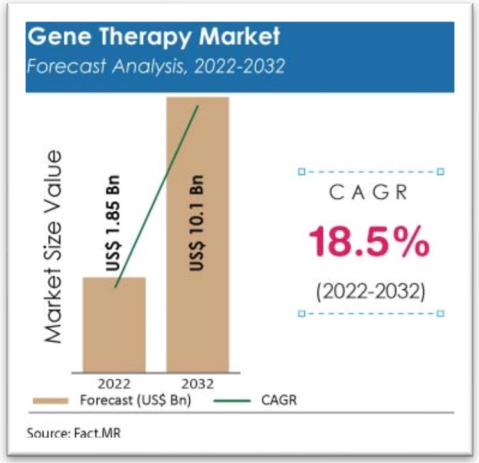
BIOTECH

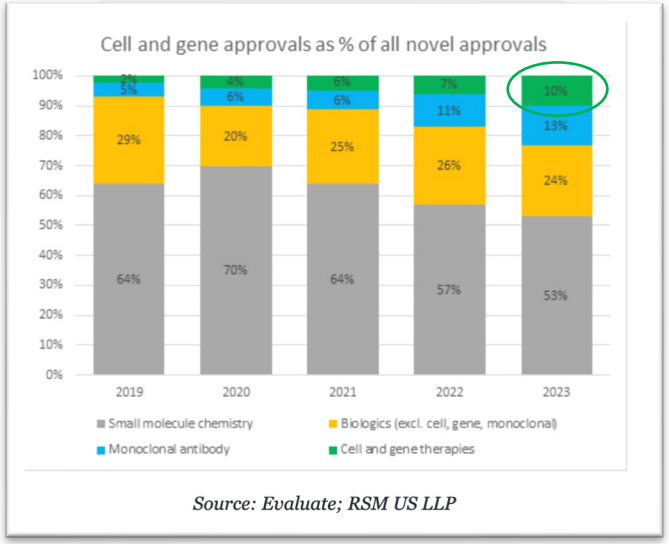
STAT+

Peter Marks on creating Operation Warp Speed, but for rare diseases

By Jason Mast Oct. 12, 2023 Reprints

Peter Marks, Director of the Center for Biologics Evaluation and Research at the Food and Drug Administration.
SUSAN WALSH-POOL/GETTY IMAGES





Source: Evaluate; RSM US LLP

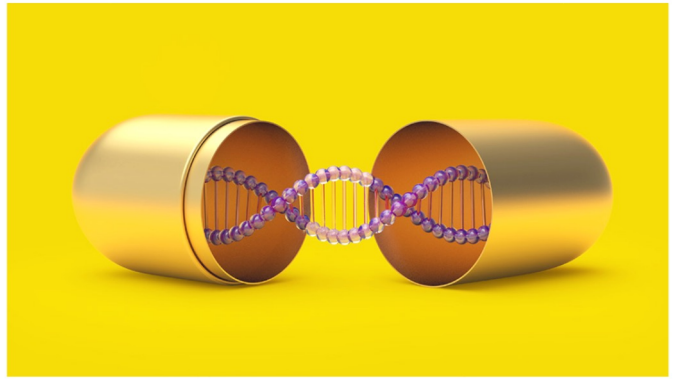
BIOCENTURY

DATA GRAPHICS | DATA BYTE

Novartis' Zolgensma first gene therapy to top $1B

TECHNOLOGY

Have Million-Dollar Gene Therapies Finally Reached An Inflection Point?



The era of effective, but pricey, gene therapies is at hand for patients with serious diseases. (© ravital/stock.adobe.com)

Licensing

ALLISON GATLIN | 12:50 PM ET 09/15/2023

Get ready for a world of million-dollar drugs. Pricey gene therapies that could cure devastating genetic disorders in one fell swoop are gaining momentum, brightening the horizon for biotech stocks like **Sarepta Therapeutics** (SRPT) and **BioMarin Pharmaceutical** (BMRN).

Focus area for regulators → Fastest growing class of new approvals → Commercial success

Circio aims to improve current gold-standard gene therapy: 6 out of 8 approved gene therapies are AAV-based

2017

LUXTURNA

Spark Therapeutics

AAV

Retinal Dystrophy

2019

ZOLGENSMA

NOVARTIS

AAV

SMA

2022

HEMGENIX

CSL

AAV

Hemophilia B

ADSTILADRIN

FERRING

AdV

NMIBC

UPSTAZA

PTC Therapeutics

AAV

AADC

2023

ELEVIDYS

SAREPTA THERAPEUTICS

AAV

DMD

ROCTAVIAN

BIOMARIN

AAV

Hemophilia A

VYJUVEK

Krystal

HSV

DEB

8 gene therapies approved 2017-2023:

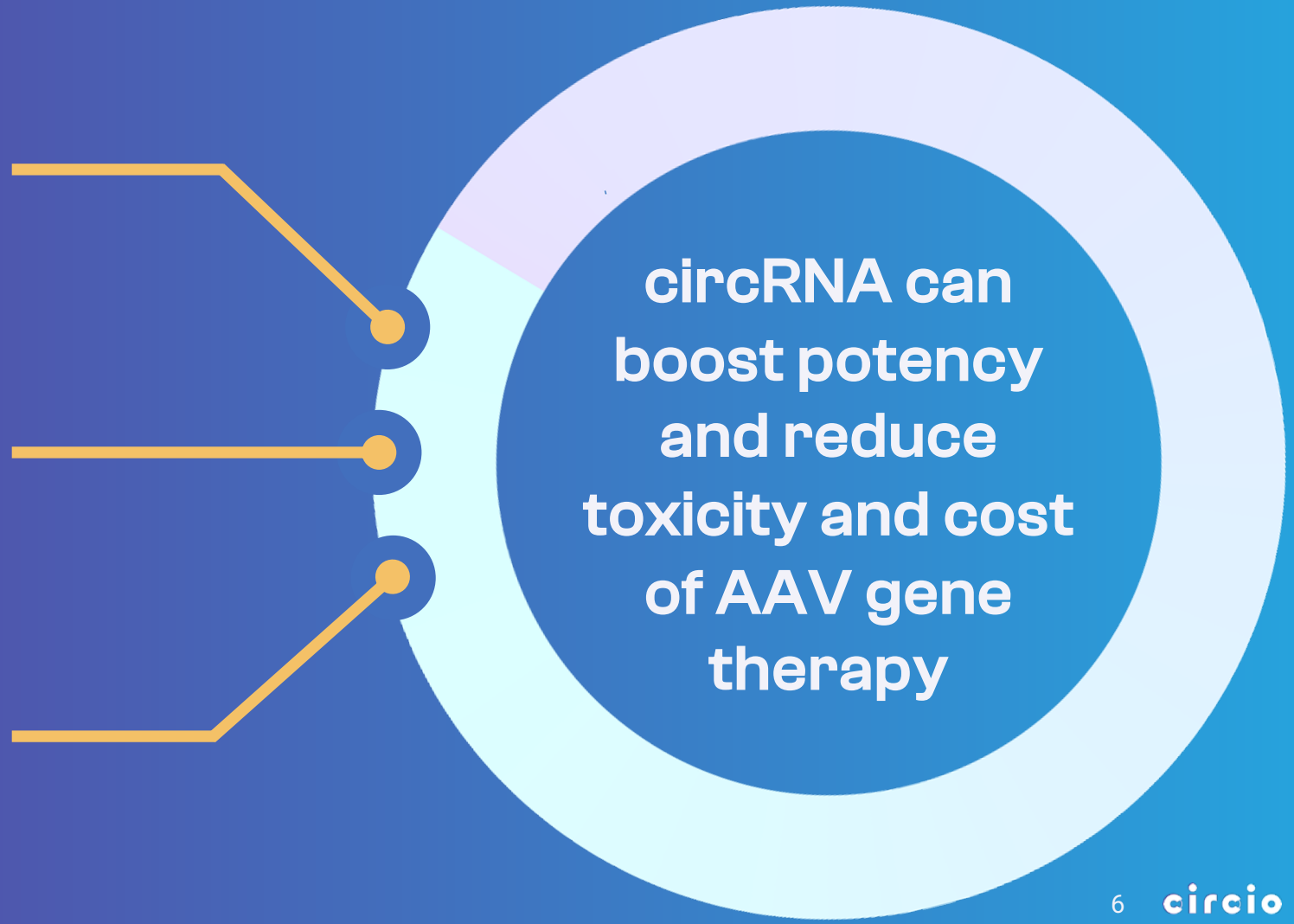
- 100% utilizing viral vectors
- 75% utilizing an AAV vector
- 75% approved for rare diseases

The need for high dosing is a major limitation for current gold-standard AAV gene therapy

Limited applicability
Low expression level not sufficient for many genetic diseases

Low expression → High dosing
Safety issues, liver and immunological toxicity

High dosing → High cost
High dose requirement drives high manufacturing cost



2

The circVec approach

3. Therapeutic application of circVec
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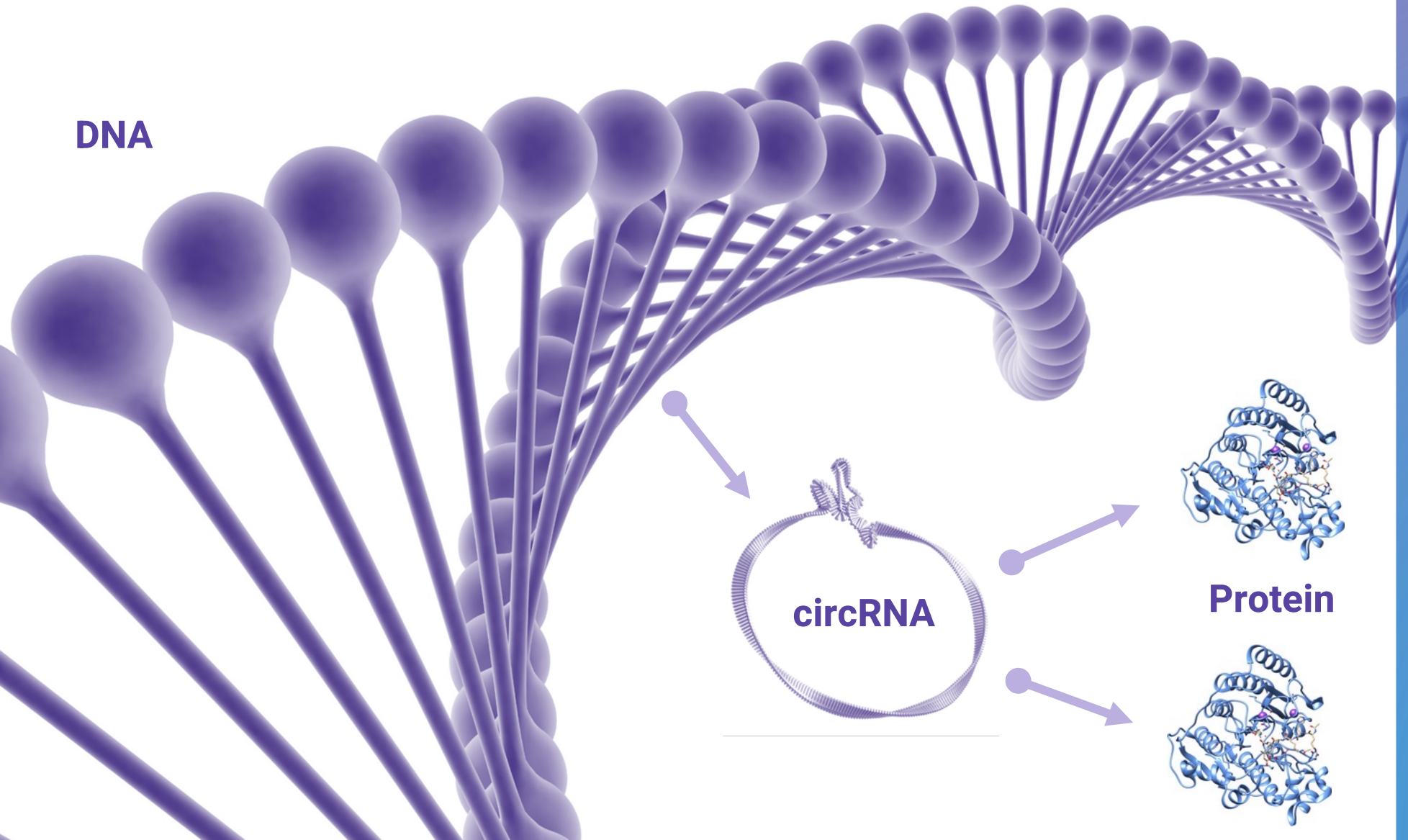
The circVec expression system:
making circRNA from a DNA starting point



circVec
DNA or viral
vector

Inject

circRNA
biogenesis

Potent and durable protein expression

circVec expression has been validated for a broad set of different protein and cell types

20 payloads validated

- **Intra-cellular, membrane-bound and secreted proteins**
- **Various reporter genes**
- **Immunological proteins**
- **Infectious disease vaccine antigens**

Broad size-range

- **20 - 170 kDa** (150 - 1,270 amino acid residues)
- **460 - 3,800 nt open reading frame** (ORF)
- **Maximum size limit not yet reached**

Confirmed in multiple cell and tissue types

- **6 different cell lines**
- **Skin, lung, liver and muscle cell types**
- **Mouse tissue: liver and muscle**

circVec substantially outperforms the expression level and durability of mRNA-based systems

Increased expression level

Prolonged durability

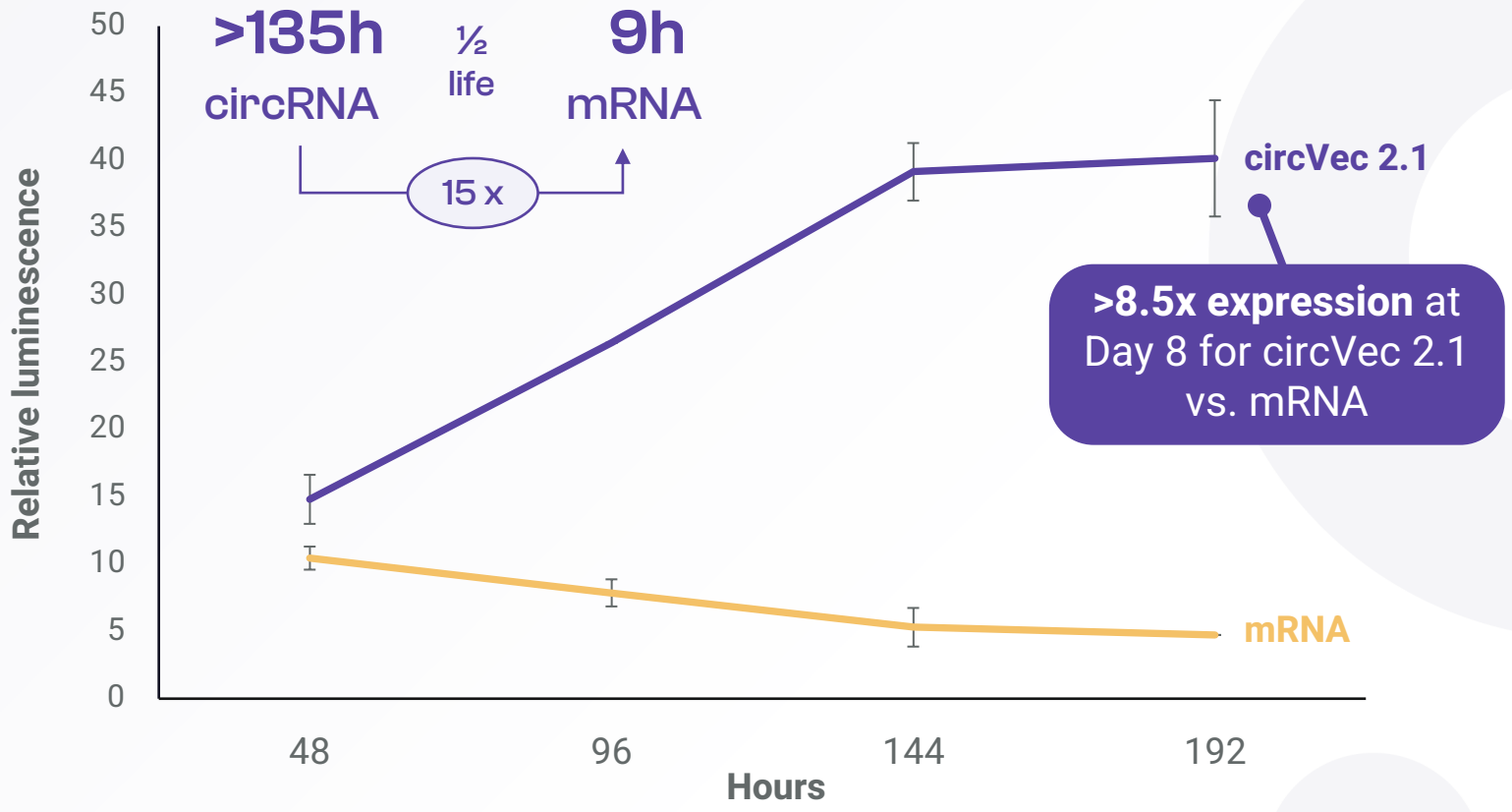
Enhanced therapeutic potency

"Due to its significant advantages, circRNA systems can be expected to replace mRNA-based expression for DNA format therapeutics in the future – just as synthetic circRNA can be expected to replace current mRNA formats"

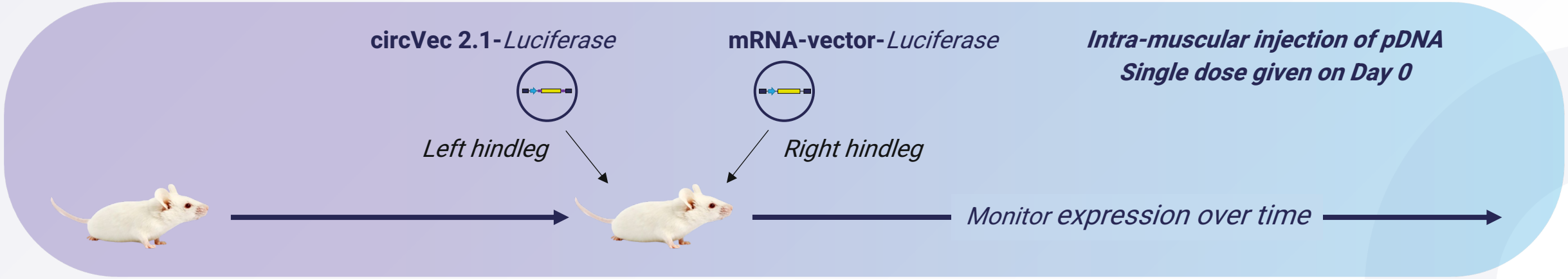
Dr. Alex Wesselhoeft

Scientific founder
oRNA Therapeutics

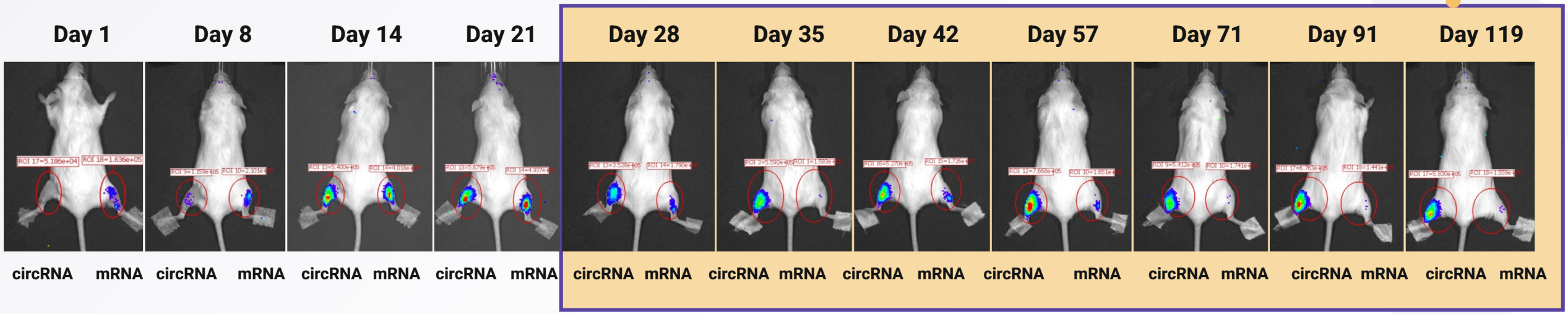
circVec vs. mRNA luciferase reporter expression; time course



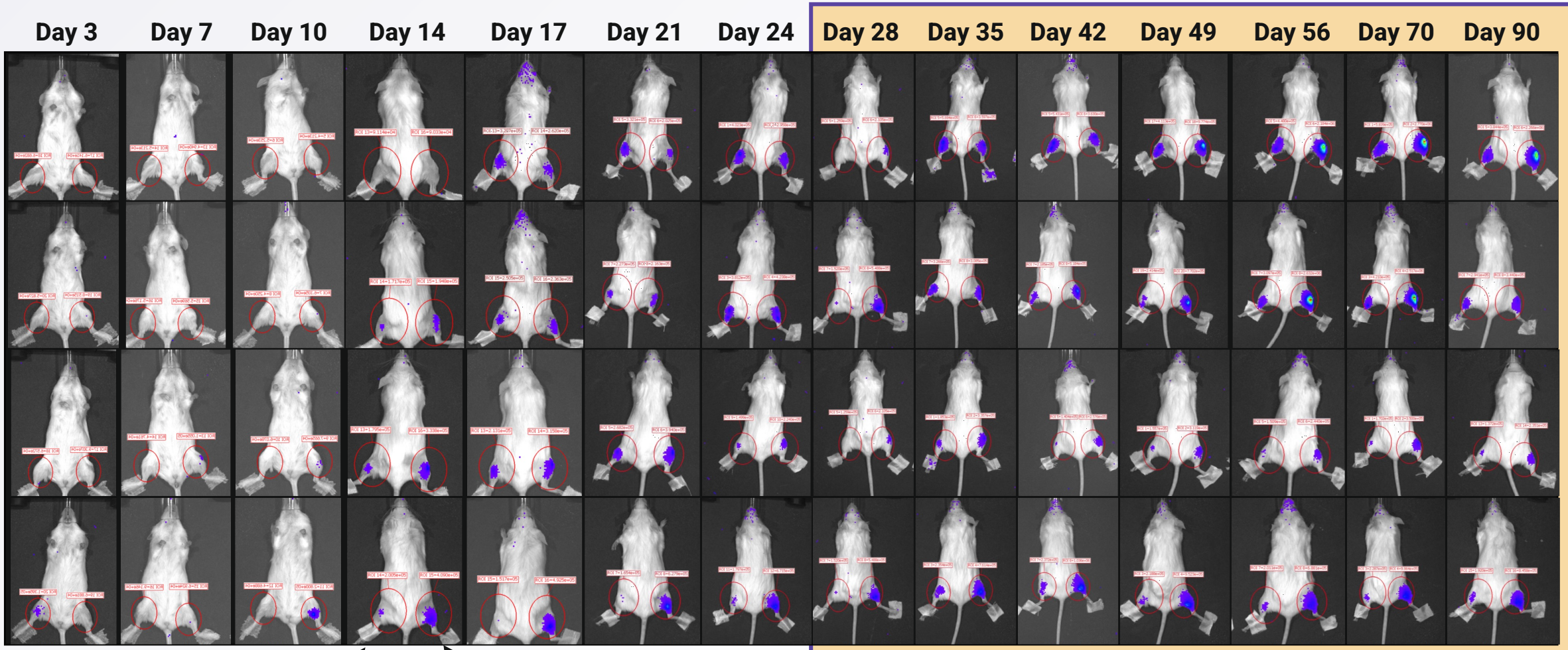
In vivo reporter pilot study: circVec 2.1 outperforms mRNA over time and shows >4 month durability



circVec expression ongoing after 4 months; mRNA very low >1 month



Confirmatory in vivo study validates circVec expression advantage vs. mRNA up to 3 months

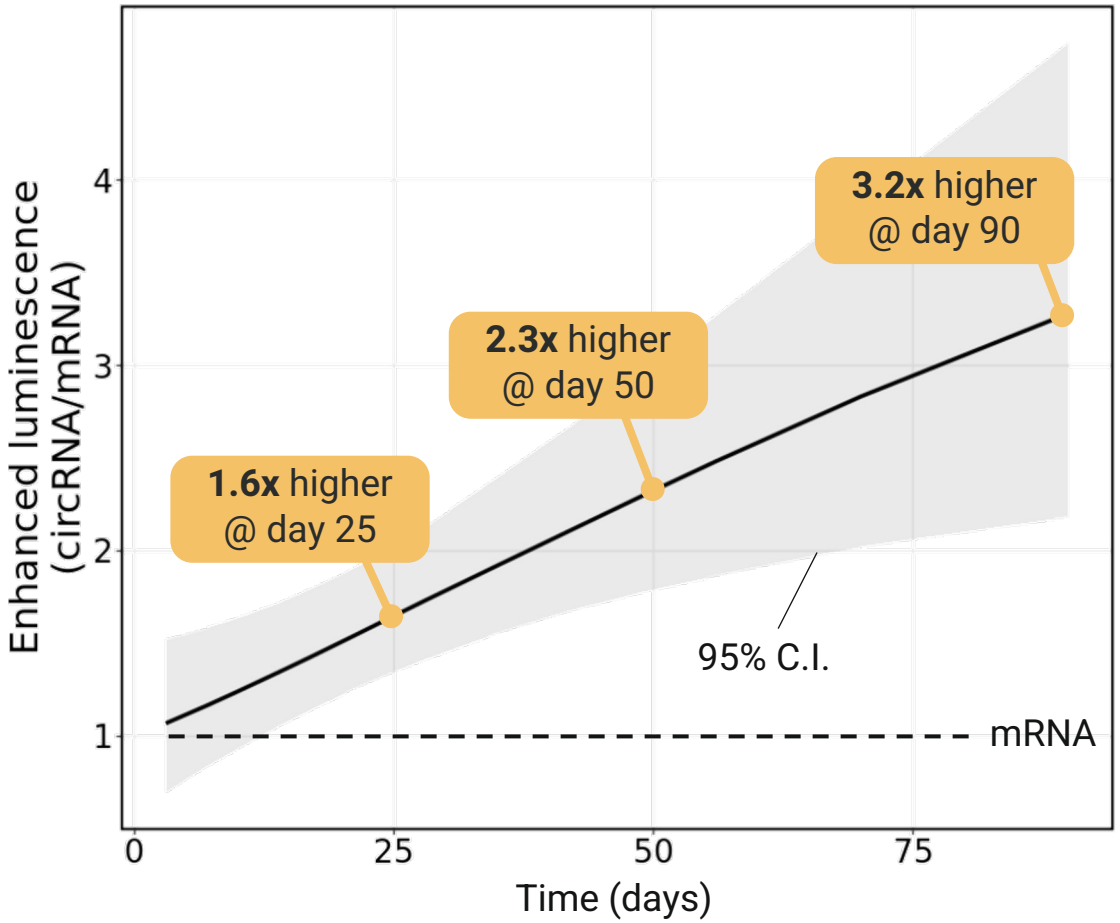


Consistently superior circVec expression from week 4

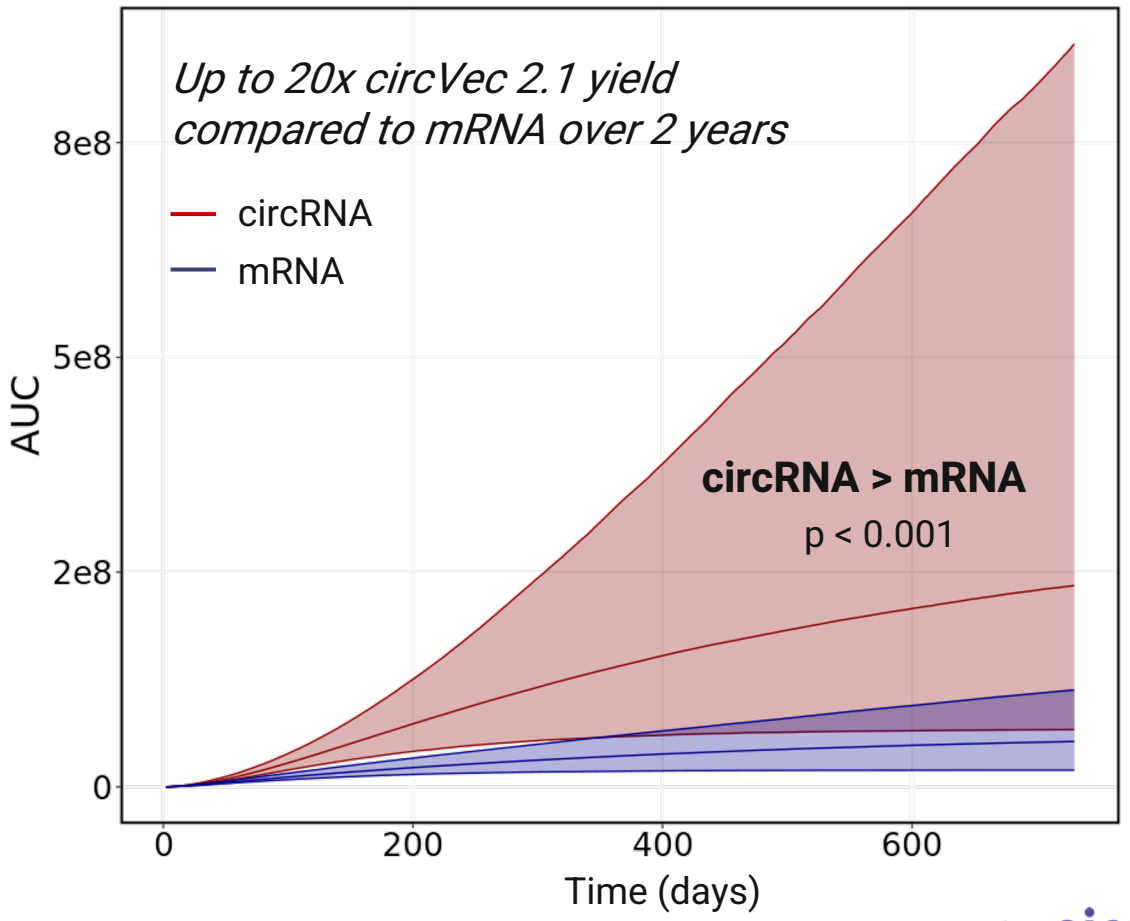
circio

circVec 2.1 in vivo data analysis demonstrates statistically significant improvement over mRNA vector expression

Luciferase signal in vivo, -fold change
circVec 2.1 vs. mRNA pDNA vector expression

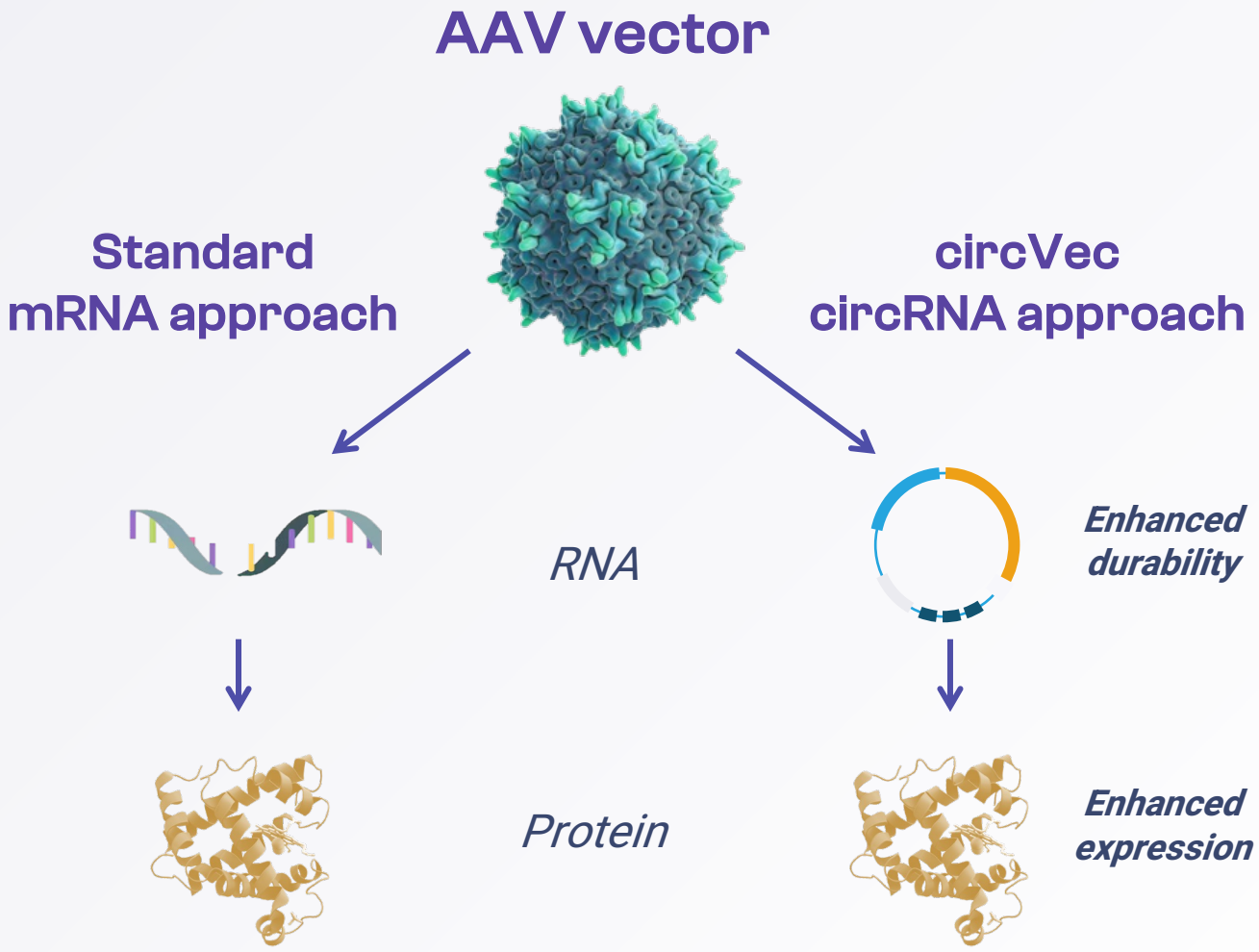


Statistical modelling of long-term expression
circVec 2.1 vs. mRNA expression dynamics, 2 years

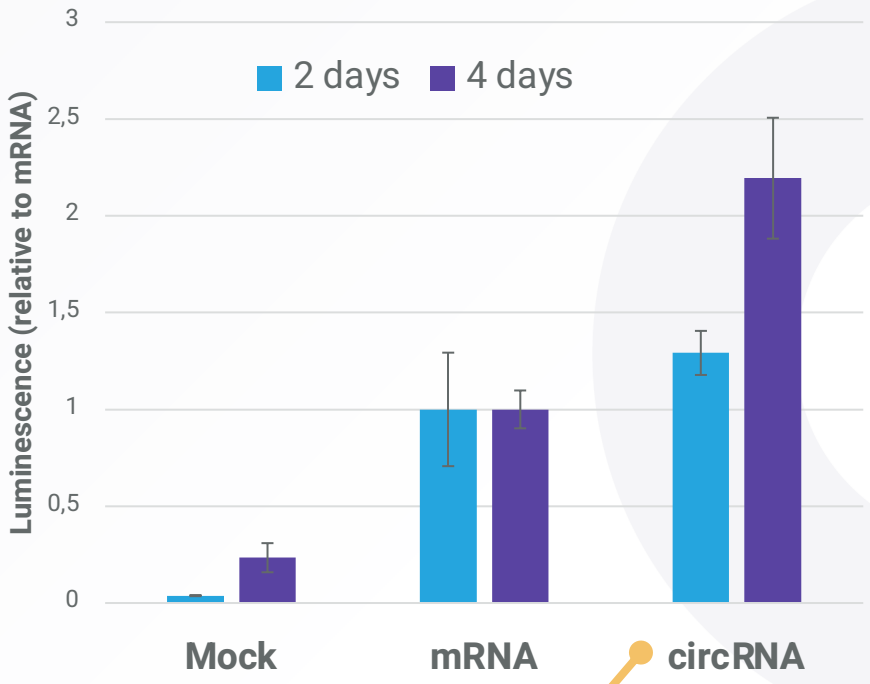


circio

circVec can be deployed to enhance AAV gene therapy



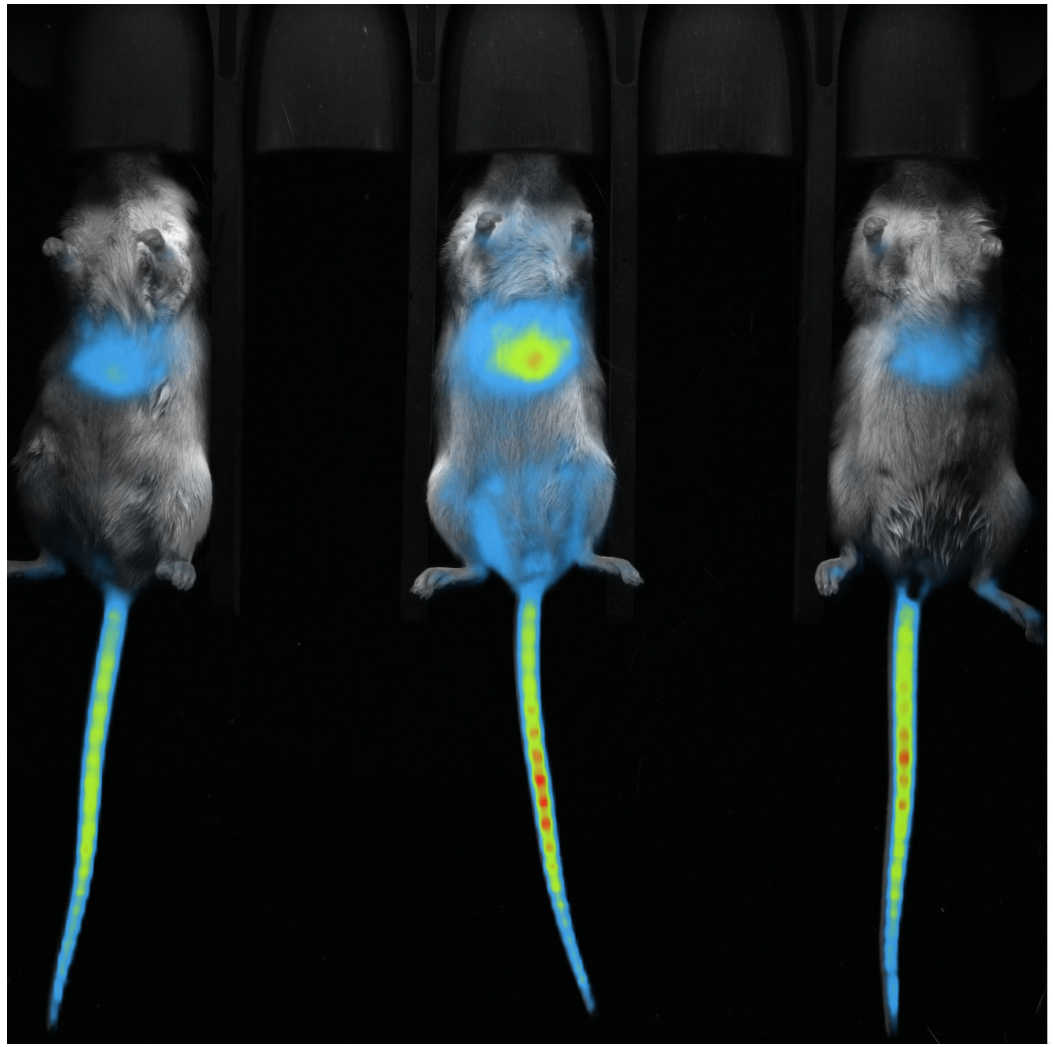
AAV protein expression, luminescence



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

circVec 2.0 AAV vector functionality validated in vivo

circVec-AAV luminescence; F-luc at Day 14 post injection



Experimental set-up

Vector:	AAV8
circVec version:	circVec 2.0
Payload:	Firefly luciferase (F-luc)
Mouse strain:	NOD/SCID/IL-2Rγnull immuno-deficient mice
Delivery route:	Intravenous tail vein injection
Single injection, dose:	$1x10^{11}$ viral genomes

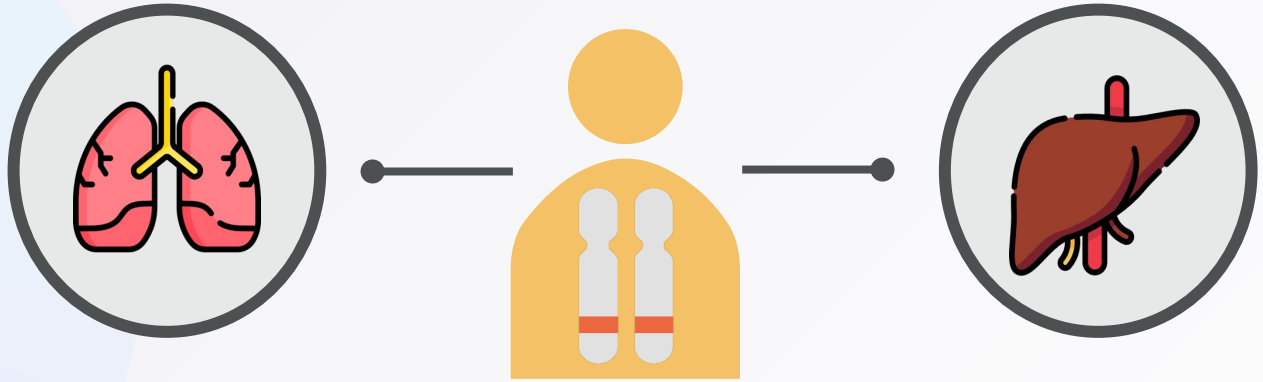
3

Therapeutic application of circVec

4. 2023 financials
5. Intended financing

Lead indication: Alpha-1 antitrypsin deficiency (AATD)

AATD is a major unmet medical need manifested in liver and lung



- **Lack of functional AAT protein**
- **Emphysema and/or chronic bronchitis**

- **Toxic accumulation of mutant form of protein**
- **Cirrhosis**

Moderate to severe AATD Diagnosed Patients

120K in EU

75K in US

Lung-associated AATD

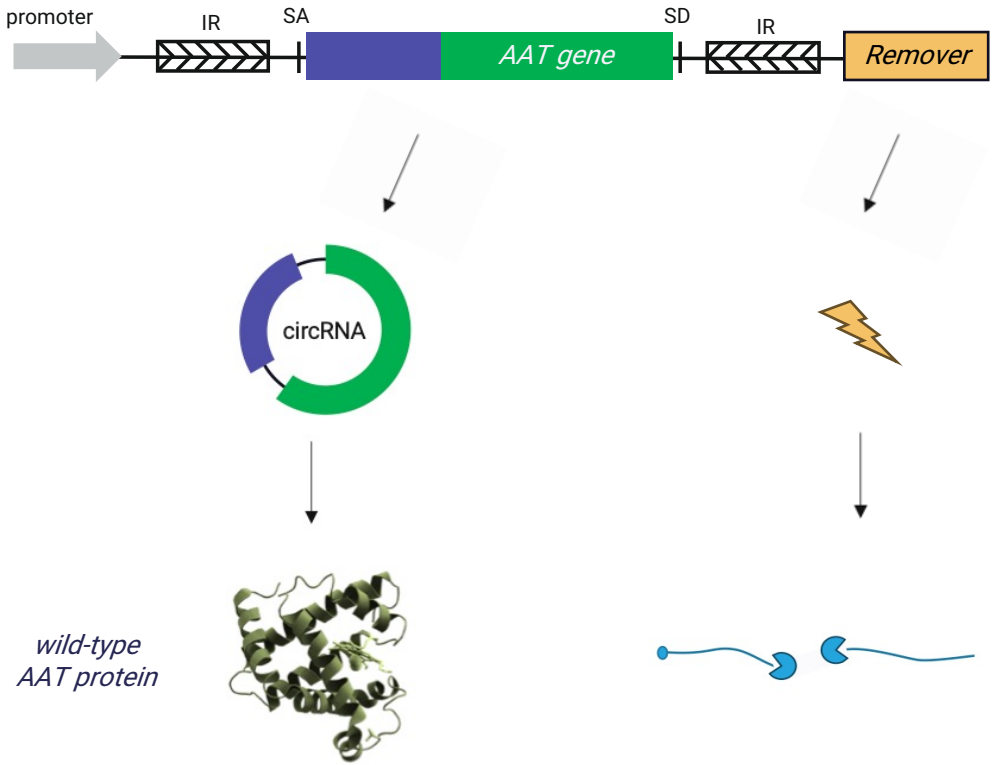
- **Replacement therapy** with an alpha-1 proteinase inhibitors
- **Weekly IV infusions**
- **Bronchodilators** and **inhaled steroids** used for mild symptoms

Liver-associated AATD

- **No approved therapeutics**
- **Liver transplantation** is the only treatment alternative in severe cases

Lead gene therapy program for proof-of-concept: circVec ´Remove-&-Replace´ for AATD

AAV8 circVec 2.1 AAT R&R design

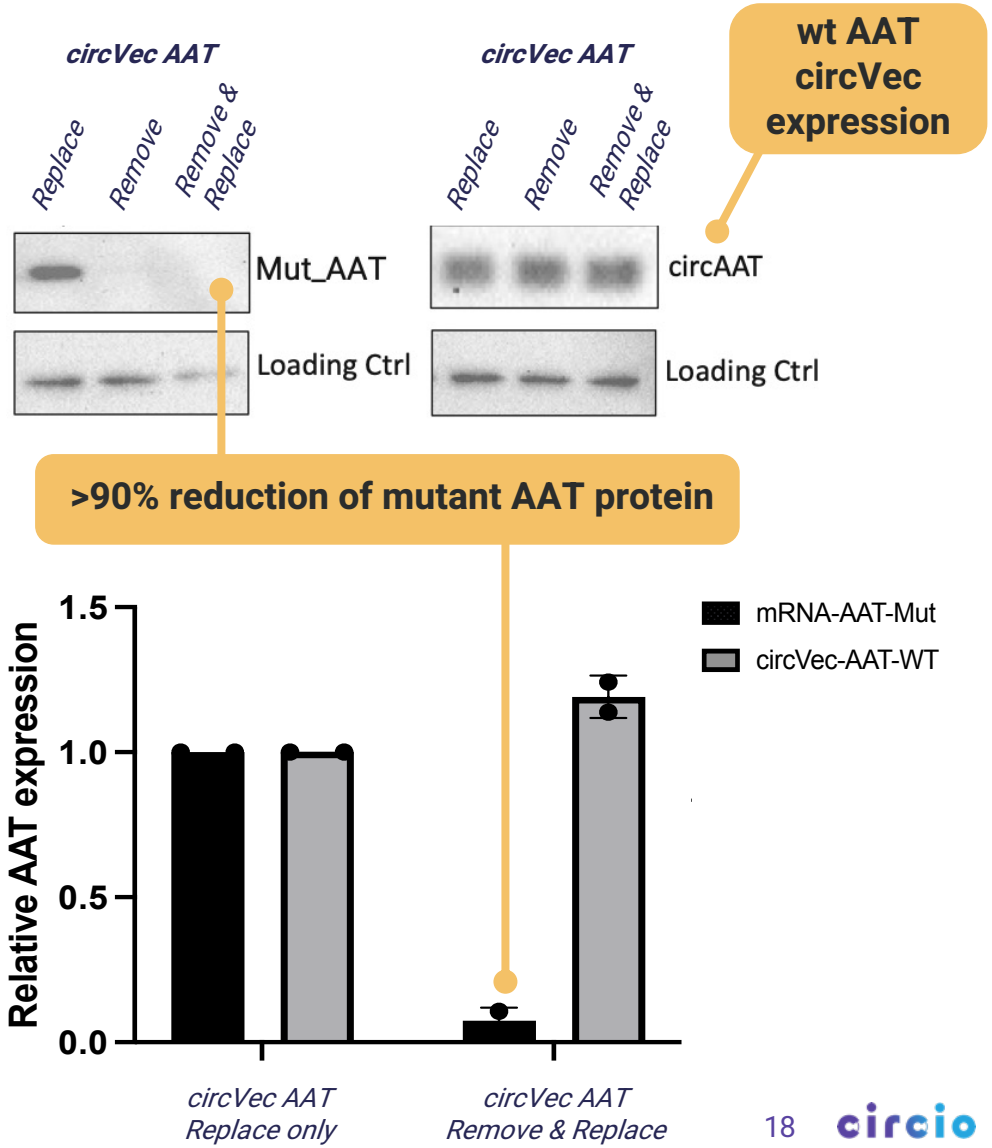


Replace

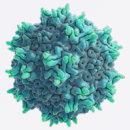
Expression of functional AAT protein

Remove

Degradation of mutant AAT mRNA



circVec has been validated in both viral and synthetic DNA vector formats for therapeutic applications

	Viral		Synthetic DNA	
	 AAV	 Adenovirus	DNA format 1 	DNA format 2
Application	• **Gene therapy, incl. AATD**	• **Vaccines** • **Oncology**	• **Gene therapy, incl. AATD** • **Vaccines**	• **Gene therapy** • **Cell therapy**
Aim	• **Improved expression and reduced dosing** vs. mRNA AAV	• **Single-dose** vaccine • **Therapeutic protein delivery** to tumors	• **Enable repeat-dosing** for gene therapy • Enhanced **nuclear uptake**	• **Improved uptake** • Reduced **immunogenicity**
	Advantage: *Efficient delivery of genetic material* ***Challenge***: *Repeat dosing and immune response*		***Advantage***: *Repeat dosing and manufacturing* ***Challenge***: *Nuclear delivery and innate immunity*	

R&D summary – boosting gene therapy

The challenge

- **Gene therapy market** is expected to **grow sharply** during the next decade
- However, **high cost and safety issues** are holding back progress
- **Urgent need** for strategies that can increase potency, improve safety and reduce cost → **effective and affordable gene therapy for all**

Circio´s Solution

- **circVec technology has the potential to improve the potency** of current gold-standard gene therapy
- Higher and more durable protein expression → **reduced dosing and cost**
- **Unique ´remove & replace´ functionality** → killing two birds with one stone

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Value drivers

- **In vivo technical PoC for circVec,** reporter expression in mice → Q1´24
- **In vivo PoC for AAV vector** driven circVec reporter expression → Q3´24
- **In vivo AATD disease model data** for circVec-AAV → 9-12 months
- **First partnering deals** → AAV or target partnership within 12 months

4

2023 financial report

5. Intended financing

2023 financials[1] – substantially reduced spend in 2H´23

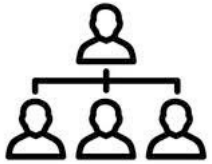
NOK m	1H22	2H22	1H23	2H23
Total revenue	**0**	**10**	**0**	**0**
R&D expenses[2]	-23	-24	-42	-7
Payroll and related expenses	-30	-22	-22	-12
Other operating expenses[3]	-7	-398	-8	-9
Total operating expenses	**-60**	**-444**[4]	**-73**	**-28**
Operating loss	-60	-434	-73	-28
Net financial items	0	-2	-3	-7
Loss before income tax	-60	-436	-76	-35
Net change in cash	-56	-60	-35	-9
Net cash EOP	**126**	**66**	**31**	**22**
Net cash flow from operating activities	**-58**	**-51**	**-59**	**-30**

Payroll cost reduced by 45%

Cash burn-rate cut in half

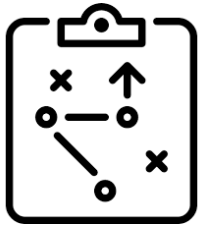
1 Unaudited numbers 2 Including patent cost 3 Including depreciation and impairment 4 Includes write-down of ONCOS-102 asset (391 mNOK)

Resources focused to maximize R&D output



Organization

- Staff level reduced from 23 to 10 FTEs
- Board and management streamlined
- R&D staff prioritized, minimal back-office



R&D strategy

- Building a strong technology platform
- Focusing on gene therapy, AATD lead program
- Using collaborations to complement circVec

Cost base

- Continue to control costs vs. 2023 level
- 2024 burn rate reduced to <5 mNOK / month
- Priority is R&D, minimizing everything else

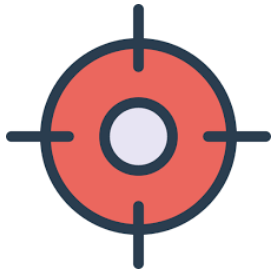
5

Intended financing

Intended rights issue of NOK 50-60 million planned to be completed during 2Q 2024

Transaction structure

- **Partially guaranteed rights issue**
- Completion by **June 2024**
- Target size **NOK 50-60m** gross proceeds
- **Circio board and mgmt have pre-committed NOK 1.5m**
- **Atlas is supportive and will contribute** to the transaction



Aim

- Extend runway to achieve **multiple circVec value inflection points** during the next **12 months**
- Generate pre-clinical **proof-of-concept in AATD**
- Enter one or more **strategic partnering deals**

Financial advisor

- Sole bookrunner

REDEYE

circio

Q & A Session

Company update
17 April 2024