circio

Disruptive circRNA technology for genetic medicine

Company presentation
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.

Circio executive summary

The challenge

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

Circio´s Solution

- Unique, proprietary approach to **circRNA, a next generation RNA format**
- **circVec** technology can **enhance** current gold-standard **gene therapy**
- Differentiated ´**remove & replace´ dual functionality** gene therapy format

Financing

- **NOK 50-60 million for twelve months runway to deliver:**
- **In vivo technical PoC for circVec-AAV** protein expression → Q3´24
- **AATD gene therapy disease model data for circVec-AAV** → 9-12 months
- **Enter first strategic partnership,** AAV, disease, or target deal → 1H 2025

AAV: Adeno-Associated Virus **TA**: Therapeutic Area **AATD**: Alpha-1-AntiTrypsin Deficiency **PoC**: Proof of Concept

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The challenge

2. The circVec approach
3. Therapeutic application of circVec
4. Additional cancer vaccine opportunity
5. Summary & finance

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

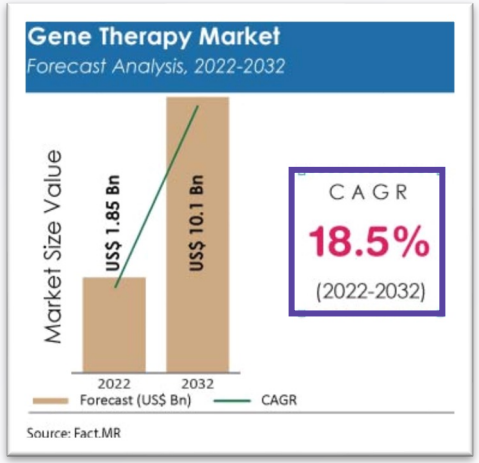
BIOTECH

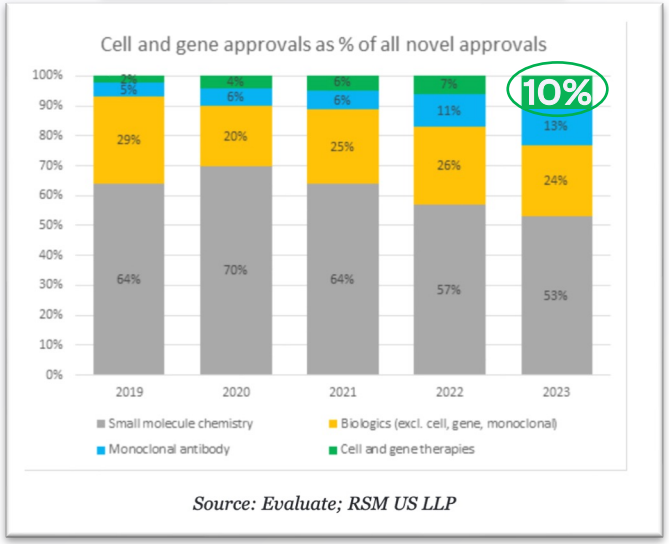
STAT+

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

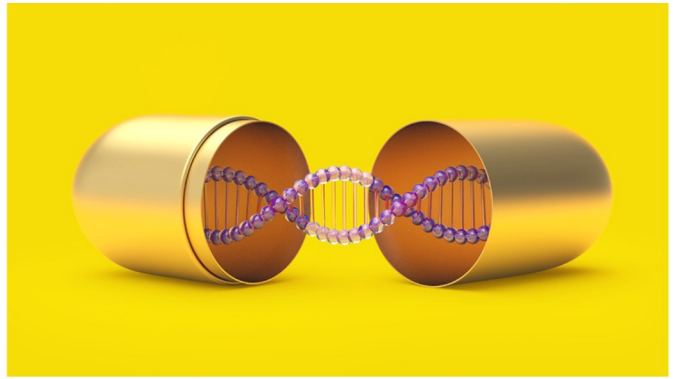
BIOCENTURY

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

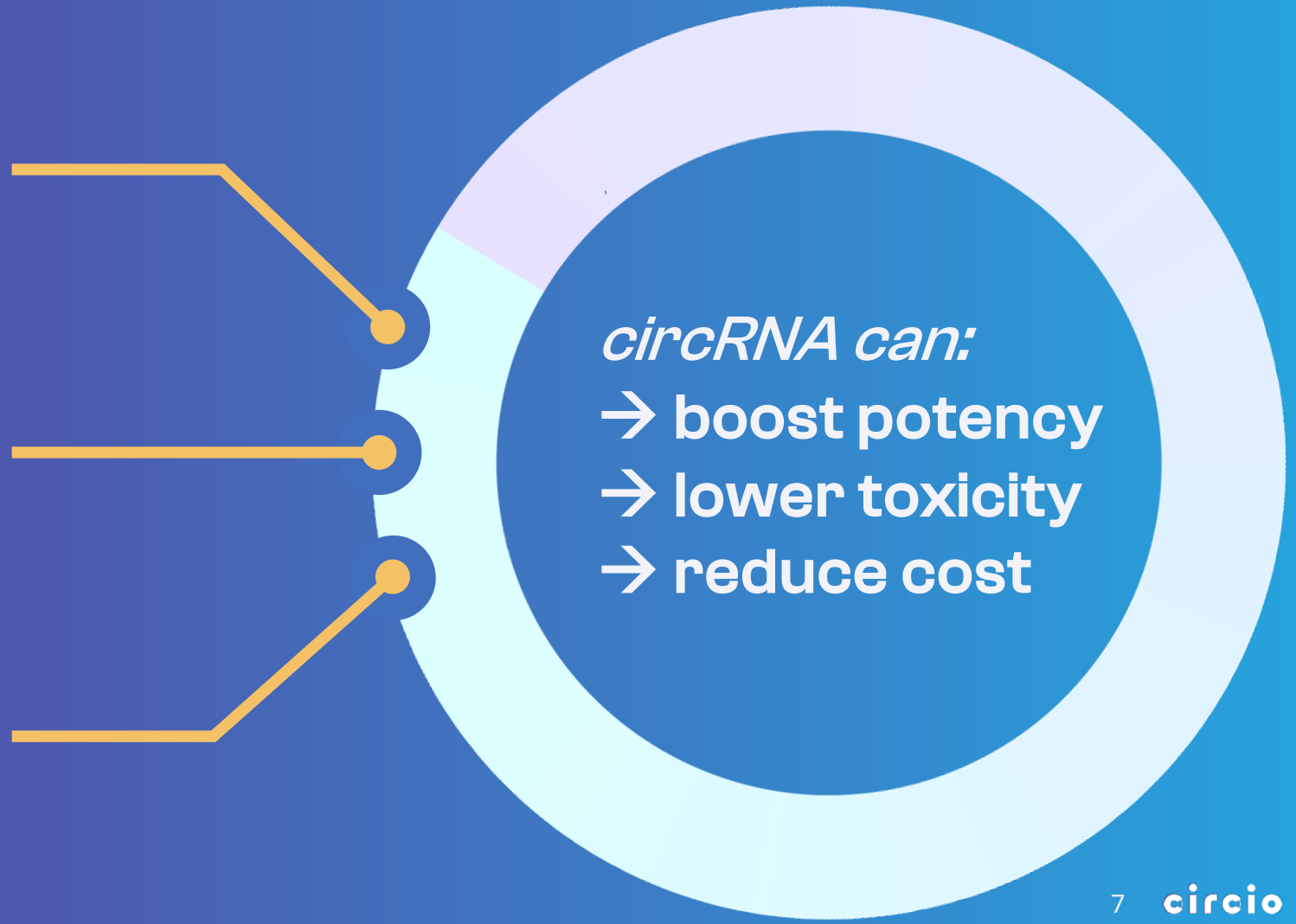
AAV: Adeno-Associated Virus, currently best known vector for long-term protein expression in humans

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

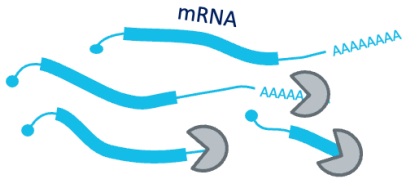
High dosing → High cost
High dose requirement drives high manufacturing cost



circRNA offers increased durability and expression rate, thus enhancing the potency of gene therapy

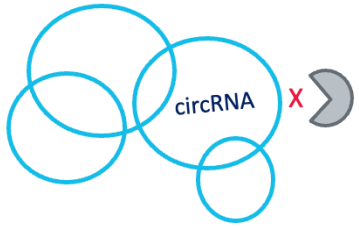
Extended RNA durability

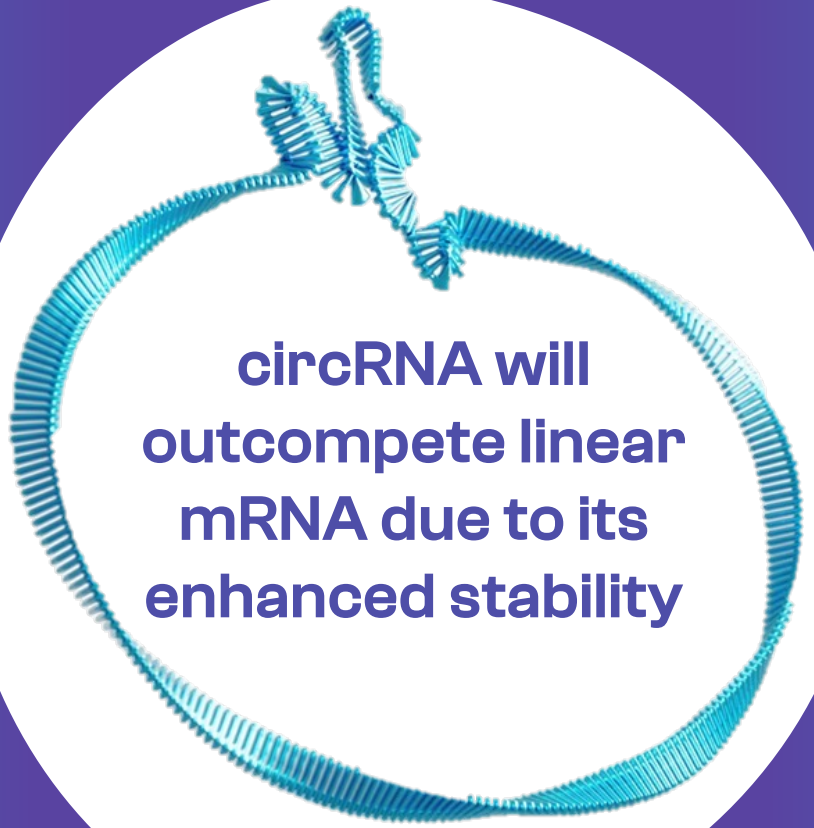
15x half-life vs. mRNA



Higher protein expression

5x translation rate vs. mRNA





circRNA will outcompete linear mRNA due to its enhanced stability

microRNA sponging

mRNA is destabilized by microRNAs

Modular & multi-functional

Enables ´remove & replace´ strategy

Based on these advantages, circRNA is gaining strong industry momentum as a superior RNA platform

Feb 2021
ORNA
$80M
Series A

May/Aug 2021
Series A+B
laronde
$490M

Jul 2022
theroma 圆因生物
$42M
Series A

Aug 2022
Licensing
ORNA MERCK
$150M Upfront
$3,5B Total deal value

Aug 2022
ORNA
$221M
Series B

Oct 2022
Series A
ORBITAL THERAPEUTICS
$270M
April 2023

GINKGO BIOWORKS
Circularis
Undisclosed
M&A

May 2023
Series A
ReNAgade THERAPEUTICS
$300M

Aug 2023
Pfizer
CirCode
$30M
Series A

2

The circVec approach

3. Therapeutic application of circVec
4. Additional cancer vaccine opportunity
5. Summary & finance

The circRNA field was established by Circio scientists

Dr Thomas B Hansen

Dr Erik D Wiklund

nature — 6,373 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 — 922 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

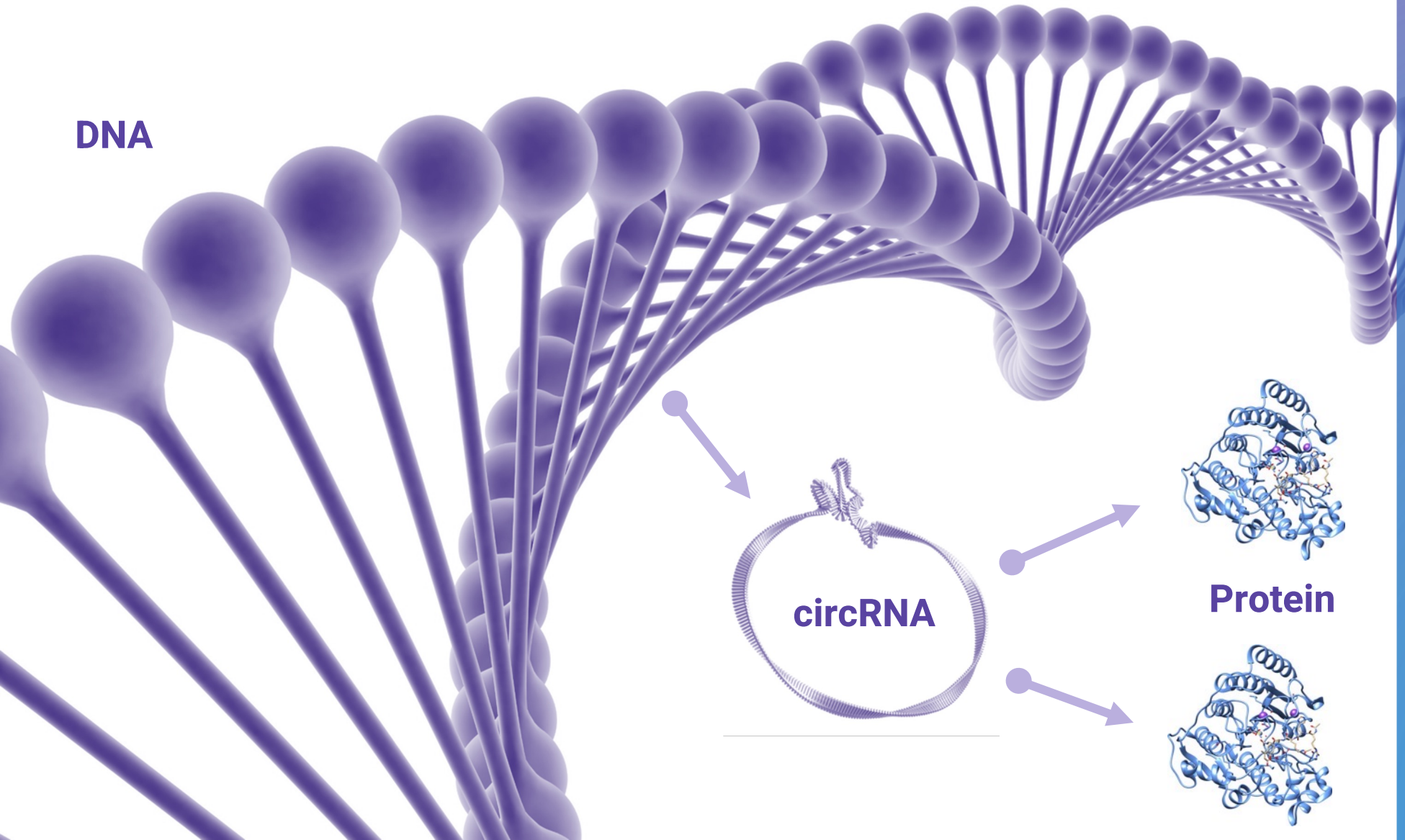
nature reviews genetics — 2,291 citations

Review Article | Published: 08 August 2019

The biogenesis, biology and characterization of circular RNAs

Lasse S. Kristensen, Maria S. Andersen, Lotte V. W. Stagsted, Karoline K. Ebbesen, Thomas B. Hansen & Jørgen Kjems

The circVec expression system:
making circRNA from a DNA starting point



circVec
DNA or viral vector

Inject

circRNA biogenesis

Enhanced and durable protein expression

The circVec platform is technologically differentiated and creates novel possibilities for circRNA

		Expression durability	*Main opportunity in vaccines*	*Suitable for gene therapy*	*Delivery system*	*Existing CDMO manu-facturing*
circio	**circVec vector approach**	**months to years**	✗	✓	Viral or DNA-LNP	✓
ORNA / SAIL BIOMEDICINES	**Synthetic circRNA**	7-10 days	✓	✗	circRNA-LNP	✗
moderna / BIONTECH	**Synthetic mRNA**	2-3 days	✓	✗	mRNA-LNP	✓

Source: Circio analysis

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

Increased expression level

Prolonged durability

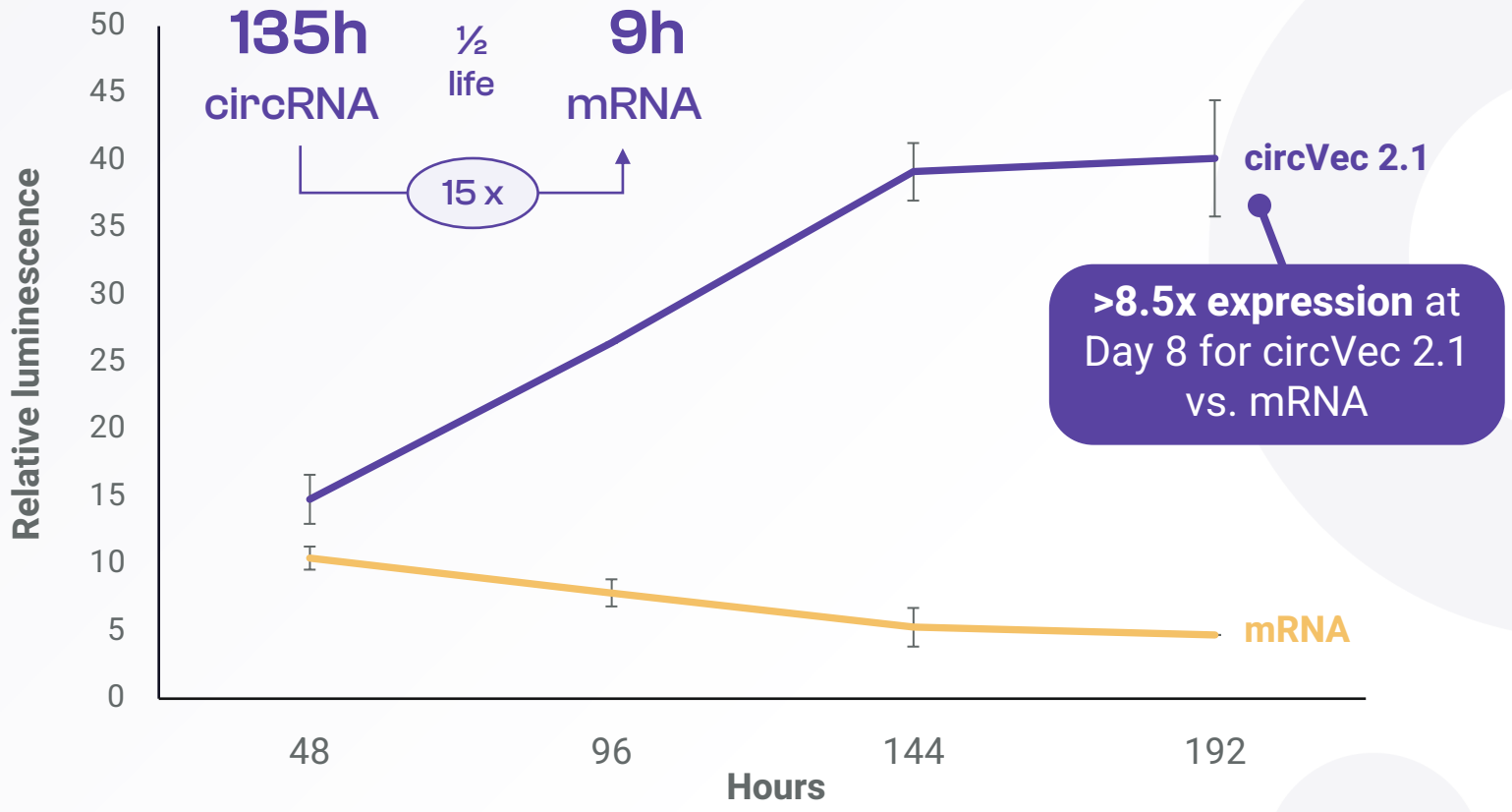
Enhanced therapeutic potency

"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"

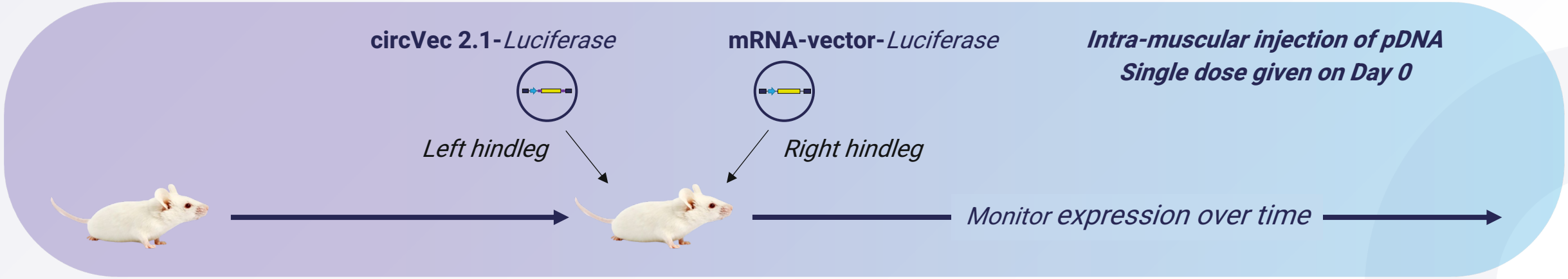
Dr. Alex Wesselhoeft

Scientific founder
oRNA Therapeutics

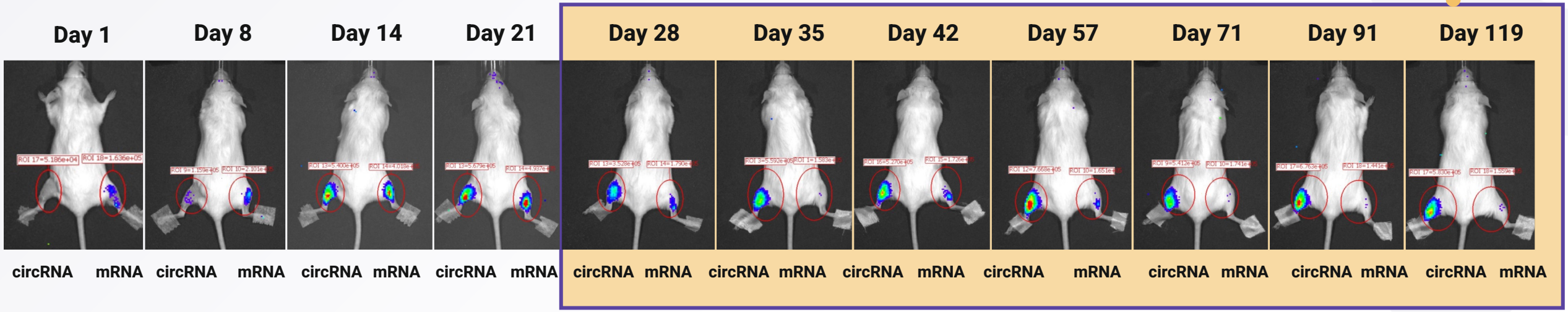
circVec vs. mRNA luciferase reporter expression; time course



circVec 2.1 outperforms mRNA-based expression in vivo with >4 month durability

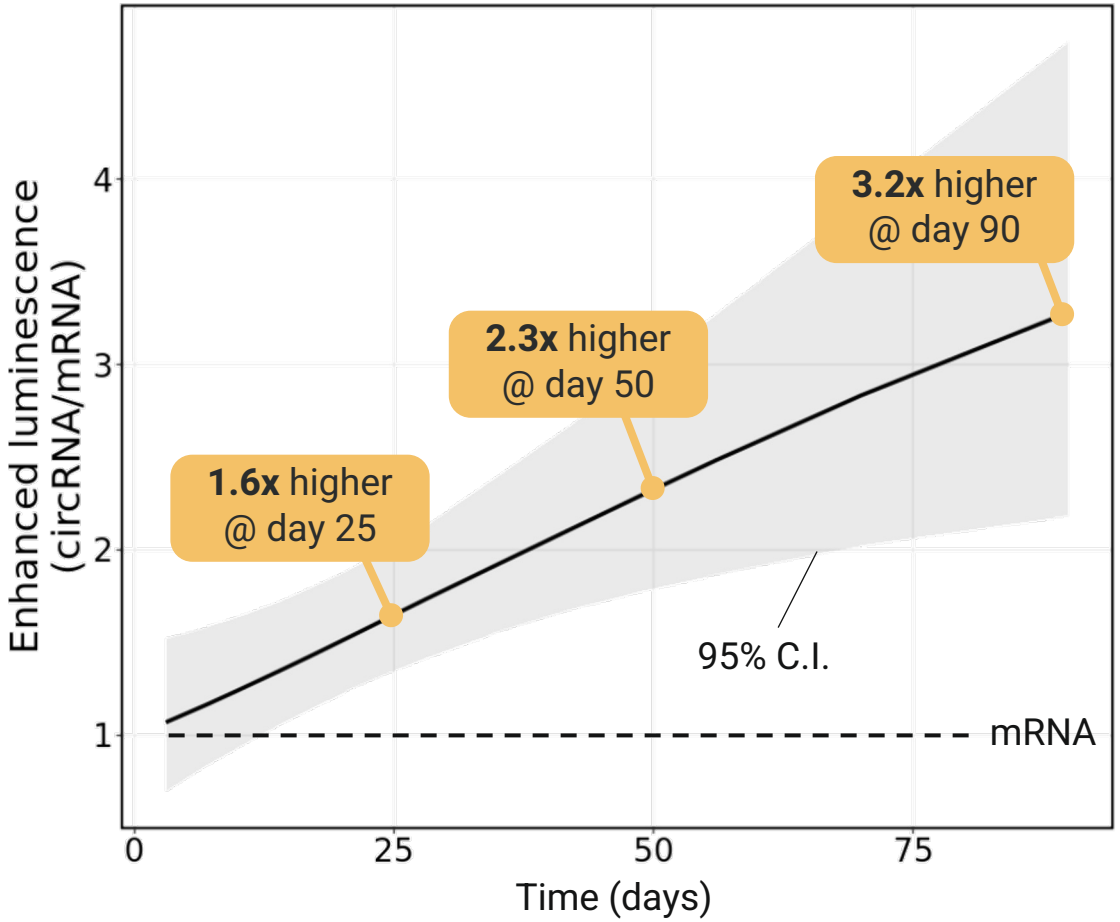


circVec expression ongoing after 4 months; mRNA very low >1 month

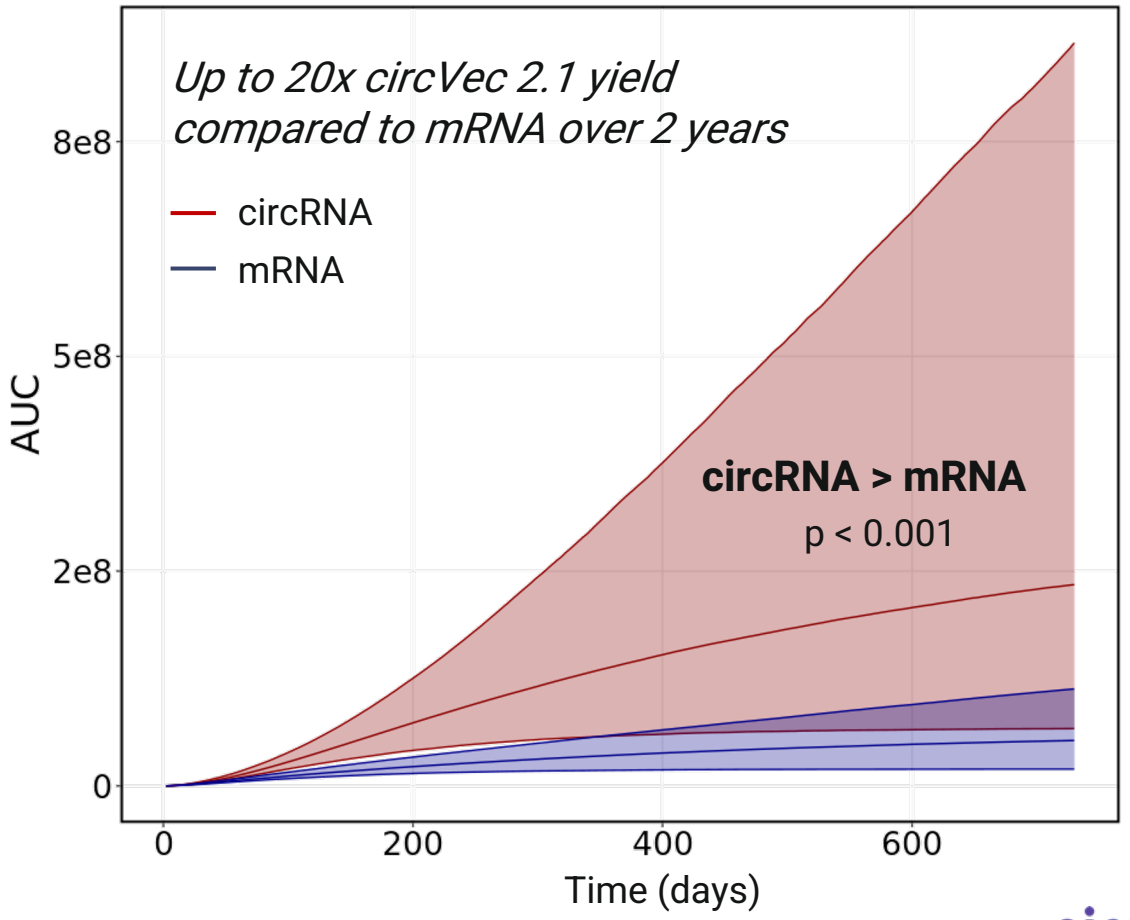


Statistical analysis of in vivo data demonstrates significant advantage vs. mRNA increasing over time

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



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

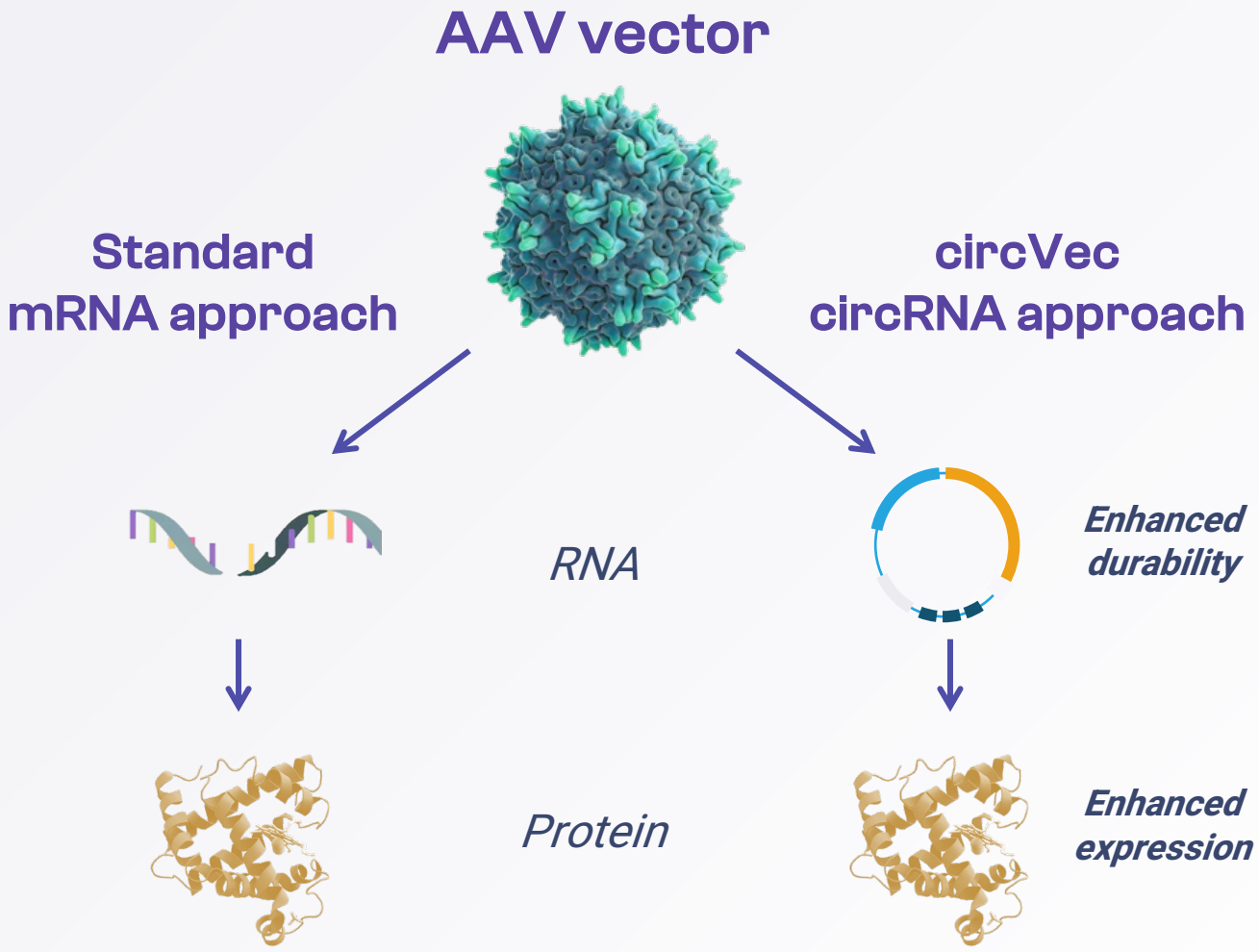
- **6 different cell lines**
- **Skin, lung, liver and muscle cell types**
- **Mouse tissue: liver and muscle**

3

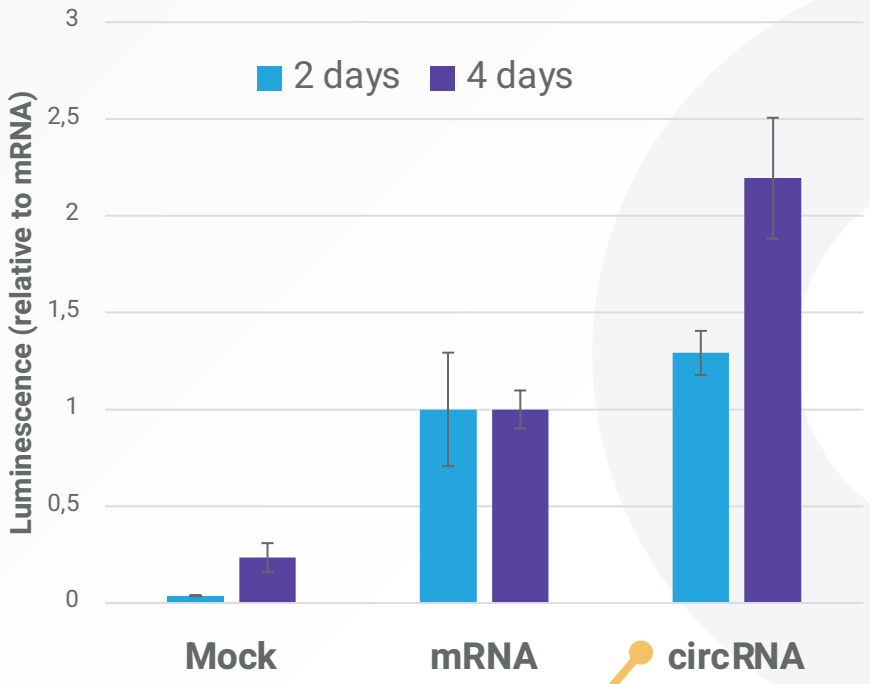
Therapeutic application of circVec

4. Additional cancer vaccine opportunity
5. Summary & finance

circVec can be deployed to enhance AAV gene therapy



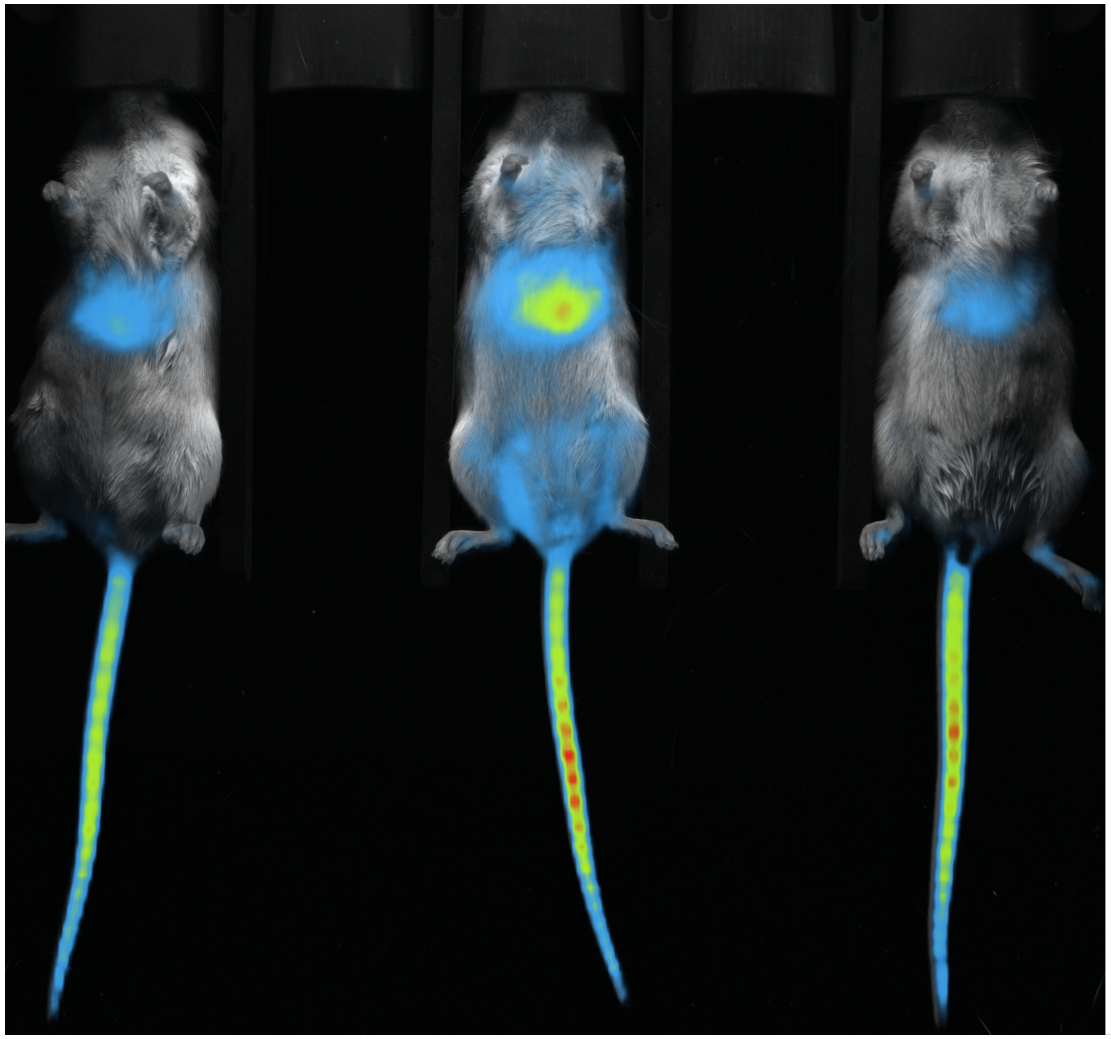
AAV protein expression, luminescence



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

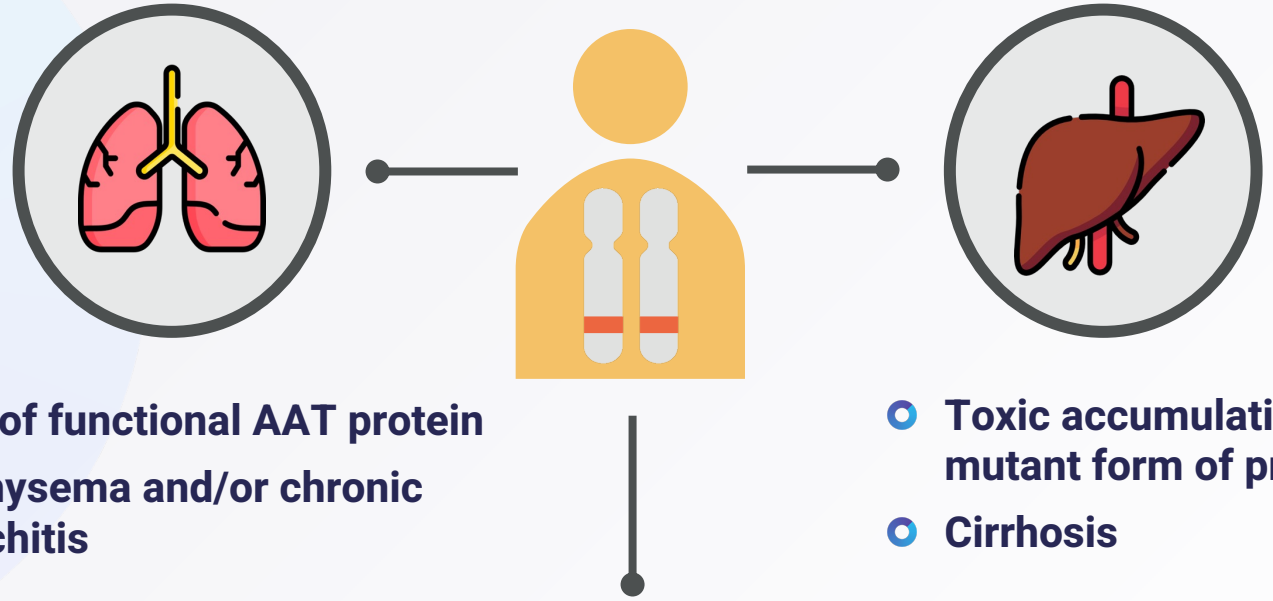


Experimental set-up

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

Lead indication: Alpha-1 antitrypsin deficiency (AATD)

AATD is a genetic disease manifested in liver and lung



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

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

Number of patients:

120K in EU **75K in US**

No satisfactory treatment options → Major unmet medical need
Significant commercial opportunity

Current treatment options

Lung-associated AATD

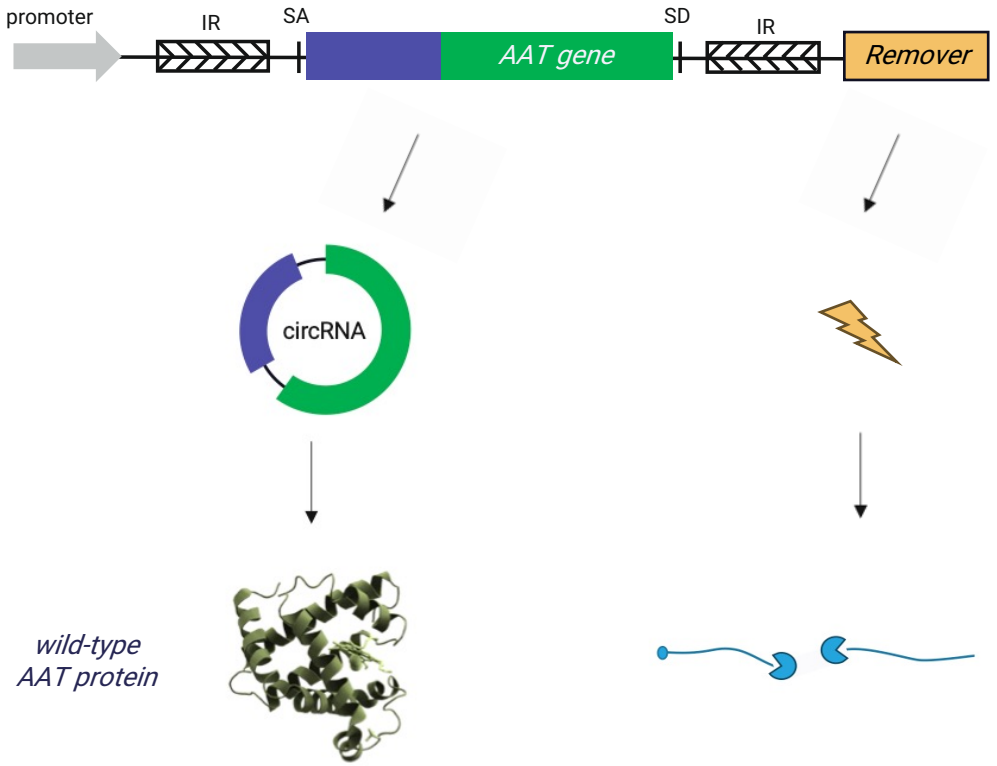
- **Replacement therapy** with an alpha-1 proteinase inhibitors
- **Weekly IV infusions**
- **Bronchodilators** and **inhaled steroids** used for mild symptoms

Liver-associated AATD

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

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

AAV-circVec2.0 AATD R&R design

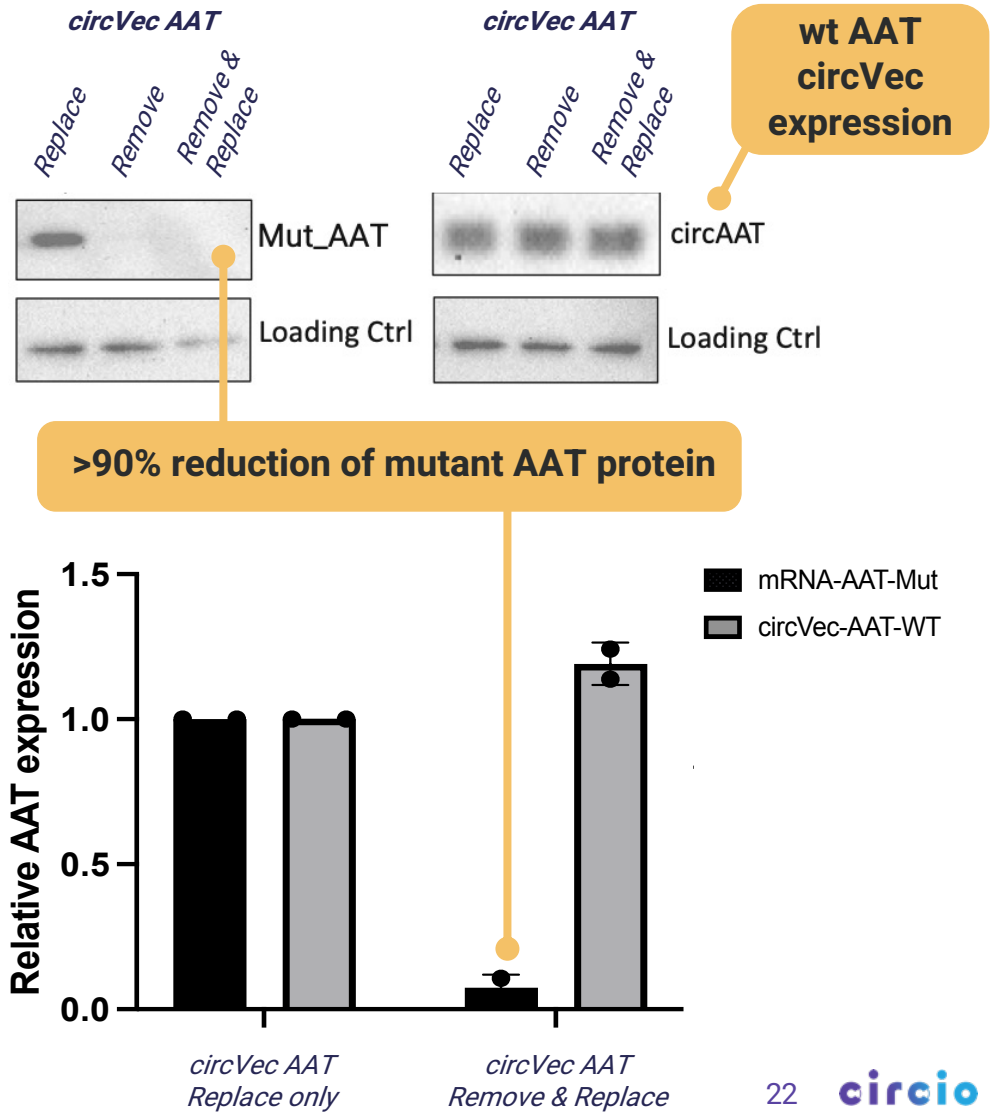


Replace

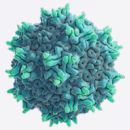
Expression of functional AAT protein

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*	

circVec R&D summary and next steps

In vitro validation

- circVec 2.1 generation outperforms mRNA by 10x
- Validated in various cells, tissues and 20 payloads
- Platform potential, three patent applications filed

In vivo validation

- Statistically significant improvement over mRNA-based expression
- Multiple delivery and dosing strategies confirmed
- circVec-AAV functionality confirmed in pilot study

Next steps

- circVec-AAV in vivo validation and comparison to mRNA-AAV
- circVec disease model data in AATD
- Testing of multiple vector and delivery strategies

4

Additional cancer vaccine opportunity

5. Summary & finance

Ongoing low-cost phase 2 program with legacy KRAS cancer vaccine

Pancreatic Cancer
TG01 + chemotherapy

Phase 1
post-surgery
n = 32 patients

- *>90% immune response*
- *6 mo. OS improvement*

Multiple Myeloma
TG01 monotherapy

Phase 1
post 1L treatment
n = 20 patients

Pancreatic Cancer
TG01 + anti-PD1

Phase 1/2
post-surgery
n = 24 patients

Lung & Pancreatic Cancer
TG01 + aCD38 + aPD-1

Phase 2
Immunotherapy resistant tumors
n = 54 patients

Completed trials Ongoing Trials

Academic study sponsor and industry partners:

Oslo University Hospital

The University of Kansas Cancer Center

agenus

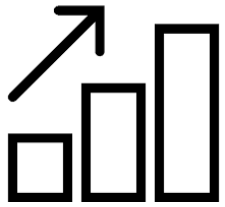
Georgetown University

Bristol Myers Squibb

Johnson & Johnson

circio

TG01 KRAS cancer vaccine legacy program



Past

- **More than 100 patients** treated in total
- **Promising phase 1 data** in post-surgery pancreas cancer
- **10 year survival benefit** shown in legacy study

Present

- **Phase 2 program with three active studies** in different indications and combinations → **multiple shots on goal**
- **Low cost to Circio,** financed through partnerships and grants

Future

- **Clinical data read-outs** expected during Q4 2024 → 2025
- **Aim to out-license TG01** based on positive data from ongoing clinical program

5

Summary & finance

Active strategy to develop shareholder value through revenue-generating partnerships

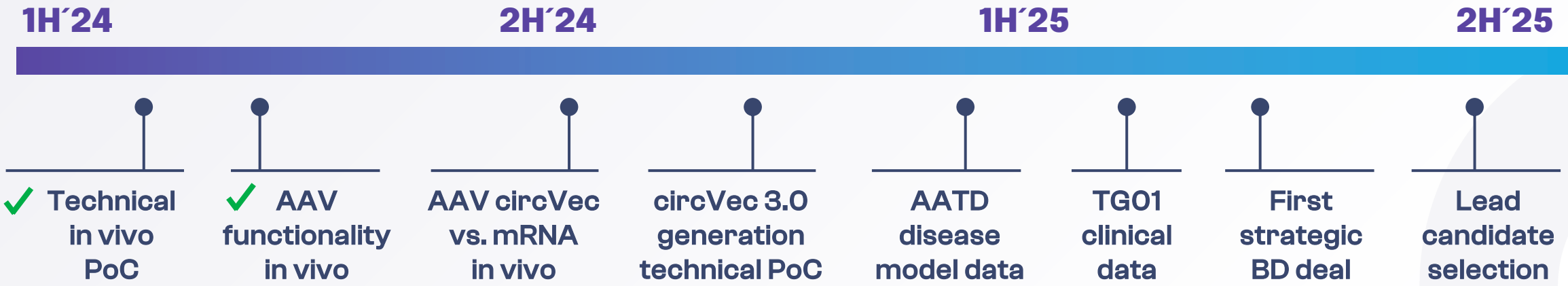
2023	1H 2024	2H 2024	2025
Initiate partner dialogues	**Tailor R&D strategy**	**Generate requested data**	**Enter revenue-generating deals**
• **Indication of interest** in technology • **Feedback on targets** and applications • **Feedback on data** and R&D plan	• **R&D strategy adapted** to BD feedback • Sharpened focus on **gene therapy** • Experimental plan to **address specific partner requests**	• **Revisit partners when requested data** has been generated • Address any follow-up requests • **Short-list** top priority targets	• **Partner negotiations and closing** • Further supportive data generation • Initiate R&D work on secondary priorities

100+ prospective partners contacted – 30+ requested follow-ups – 10 CDAs entered to date

Approximate numbers

Timing and value of BD deals dependent on strength and timing of experimental data

R&D & BD value inflection points: Targeting first partnering deal during 1H´25



Financing strategy

NOK 50-60m financing runway – Q2´24 → Q2´25

BD strategy

Generating AAV data → **Targeted follow-up** → **Negotiation & closing**

Financing to clinic

Data & Timeline: experiments have uncertain outcomes and may need to be repeated

BD deal: highly dependent on experimental data strength and timing

Circio planned short- and long-term deliverables

Pre-clinical PoC and first deal → Q2 2025

- **Further enhance platform and expand IP portfolio**
  - Establish circVec 3.0 generation
  - 3 patents filed to date + 3 patents planned
- **Demonstrate circVec-AAV gene therapy expression advantage *in vivo*** (AAV technical proof-of-concept)
  - Critical technology validation, BD enabling
- **Establish circVec gene therapy *in vivo* proof-of-concept in AATD as first target disease**
  - Lead candidate ready for IND-enabling studies
- **Support TG01 clinical program towards first read-outs**
- **Enter first circVec revenue-generating BD deal**

Clinical readiness → 2026 and beyond

- **Clinical entry of AAV-circVec AATD gene therapy**
  - Phase 1 safety and biomarker data (AAT expression level)
- **Bring 1-2 additional gene therapy programs to IND-readiness**
  - Muscular or kidney/renal genetic diseases
- **Broaden circVec technology into other applications**
  - Novel non-viral repeat-dosable gene therapy
  - Explore potential in cell therapy and vaccines
- **Partner to advance circVec into new TAs**
  - Expand platform and indications
  - Upfront and milestone payments

Full team in place with strong blend of expertise to build and capitalize on Circio´s platform

Dr Erik D Wiklund

CEO

Overall strategy and execution

CV:

- *PhD Molecular Biology*
- *circRNA co-discoverer*
- *Biotech CFO & CBO*
- *McKinsey & Company*

Dr Lubor Gaal

CFO & CBO

Securing financing and partnering deals

CV:

- *PhD Neuroscience*
- *Big pharma BD*
- *Biotech executive*
- *Investment banking*

Dr Thomas B Hansen

CTO

Building technology platform and IP

CV:

- *PhD Molecular Biology*
- *circRNA co-discoverer and scientific pioneer*
- *Big data analysis*

Dr Victor Levitsky

CSO

Leading immunology and virology expert

CV:

- *PhD Virology*
- *Big pharma R&D*
- *Biotech executive*
- *Top academic centers*

Ola Melin

COO

Operational execution

CV:

- *BSc Chem. Eng*
- *Big pharma and biotech manufacturing, clinical and commercial*