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Circular RNA expression systems for enhanced gene and cell therapies

R&D and corporate update webcast
28 May 2025

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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.
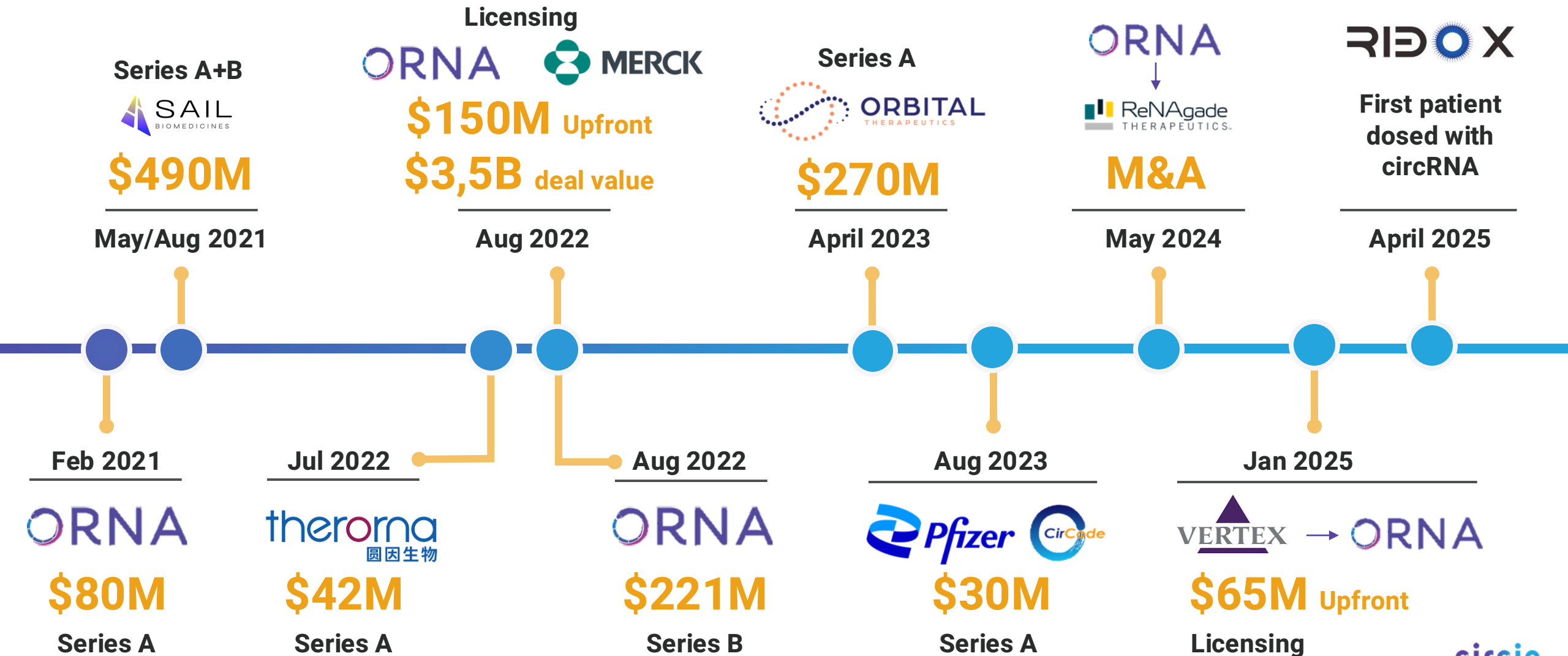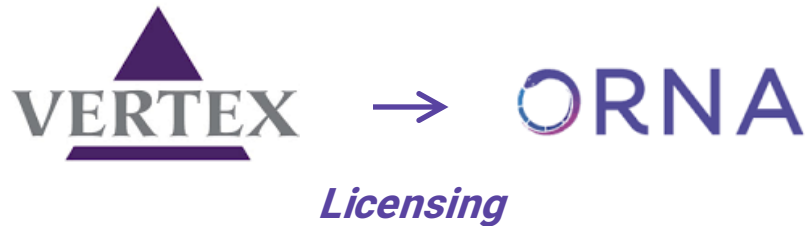
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Market update

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Continued high deal activity in circular RNA space

Series A+B
SAIL BIOMEDICINES
$490M
May/Aug 2021

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

Series A
ORBITAL THERAPEUTICS
$270M
April 2023

ORNA → ReNAgade THERAPEUTICS
M&A
May 2024

RIBOX
First patient dosed with circRNA
April 2025

Feb 2021
ORNA
$80M
Series A

Jul 2022
theroma 圆因生物
$42M
Series A

Aug 2022
ORNA
$221M
Series B

Aug 2023
Pfizer · CirCode
$30M
Series A

Jan 2025
VERTEX → ORNA
$65M Upfront
Licensing

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4

Two recent circRNA and gene therapy deals highlight substantial commercial opportunity in Circio areas

VERTEX → ORNA
Licensing

$65m up-front
+ up to $635m in milestones

LNP-circRNA for *in vivo* gene editing in blood diseases

- circRNA (oRNA) manufacturing and LNP delivery platform
- Develop two novel therapeutic candidates for sickle cell disease and beta thalassemia

NOVARTIS → KATE THERAPEUTICS
M&A

$1.1b
in up-front + milestones

AAV gene therapy for muscular dystrophies

- AAV capsid engineering technology platform
- Three preclinical neuromuscular therapeutic candidates for DM1, DMD and FSHD

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Circio´s circVec platform is technologically differentiated, opportunity in next generation gene and cell therapies

Lead program, in house focus
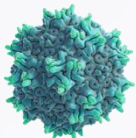
Gene therapy

Next step / partnership

Cell therapy

Muscle and cardiac genetic disease

Tissue-specific AAV format

>150,000 patients in target diseases, with no approved therapies

Next Gen AAV

Auto-immune disease, oncology

LNP: DNA format, redosable

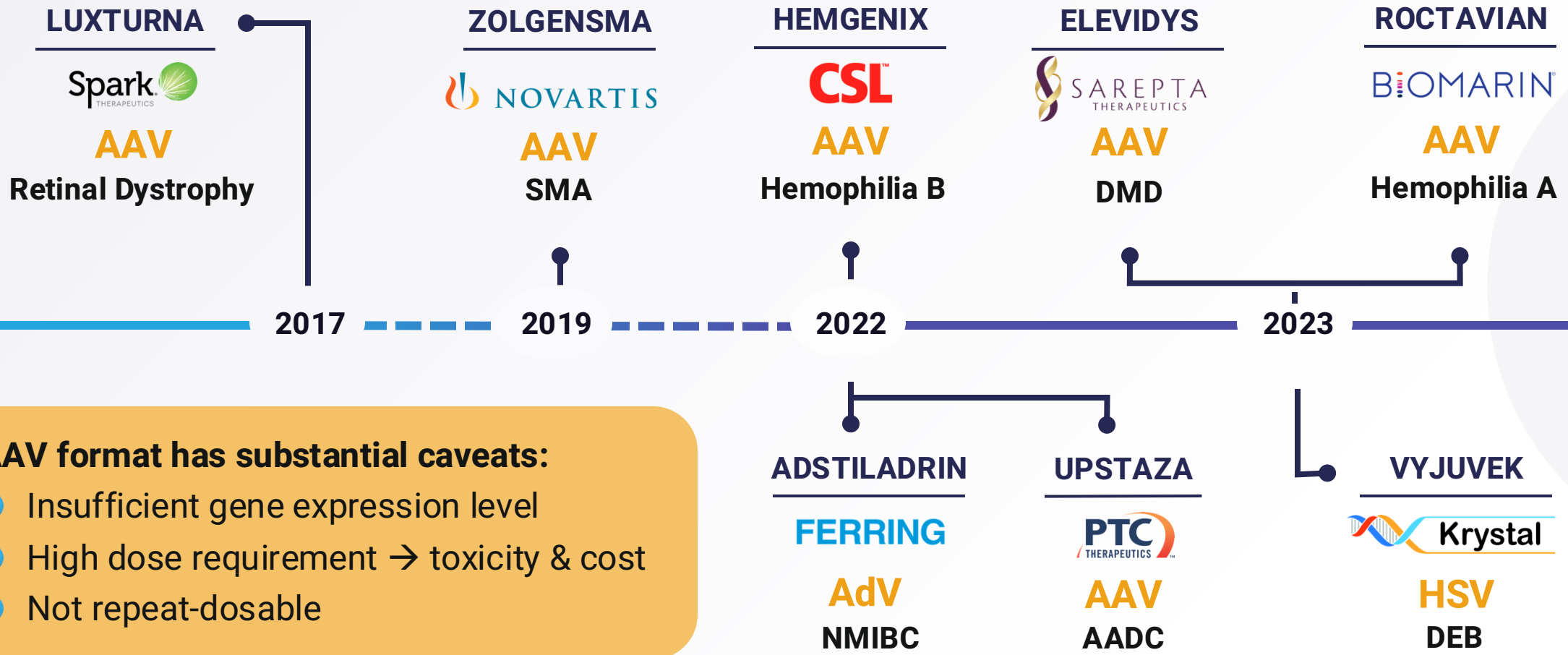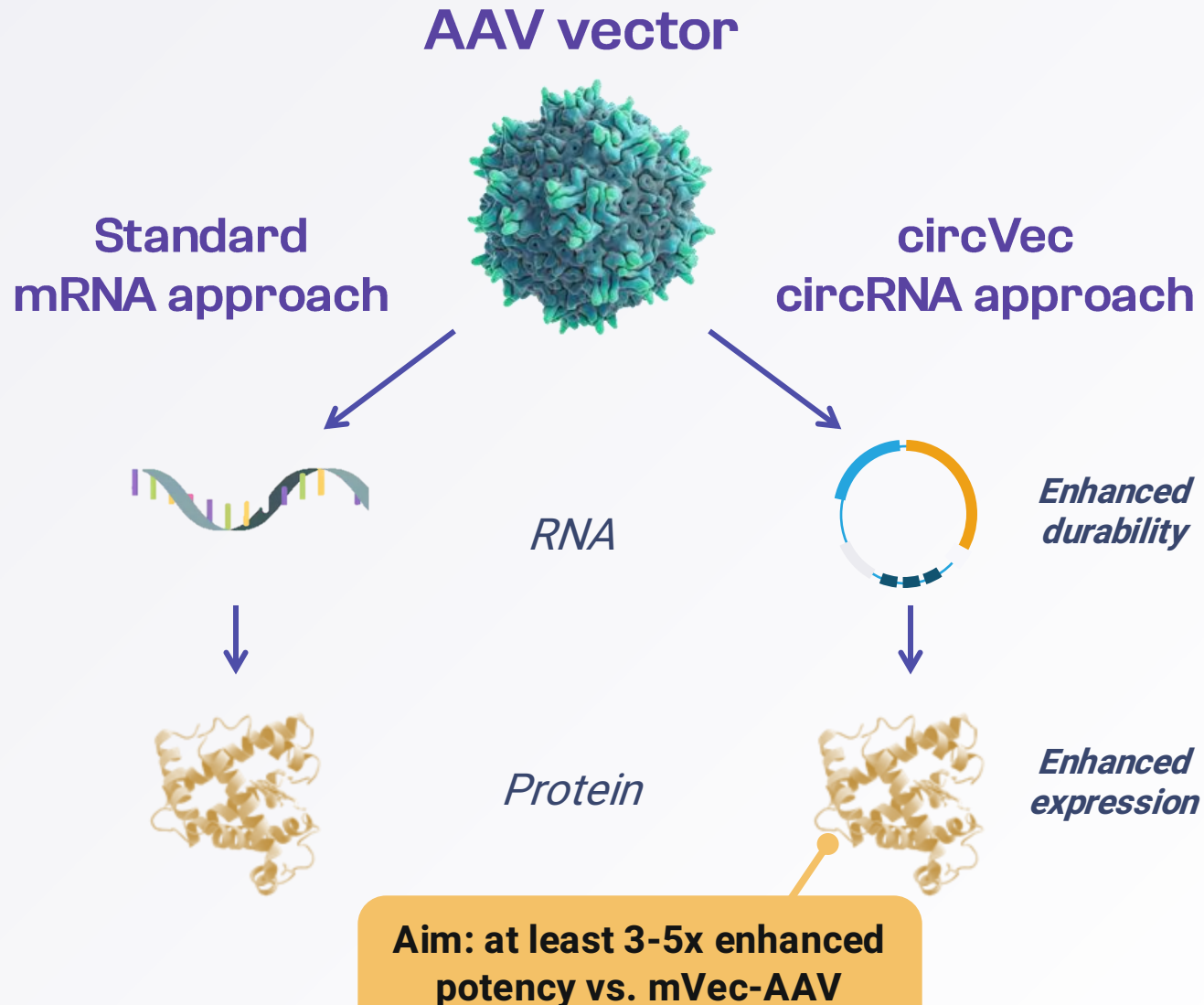Very large patient population, only autologous options available today

In vivo CAR
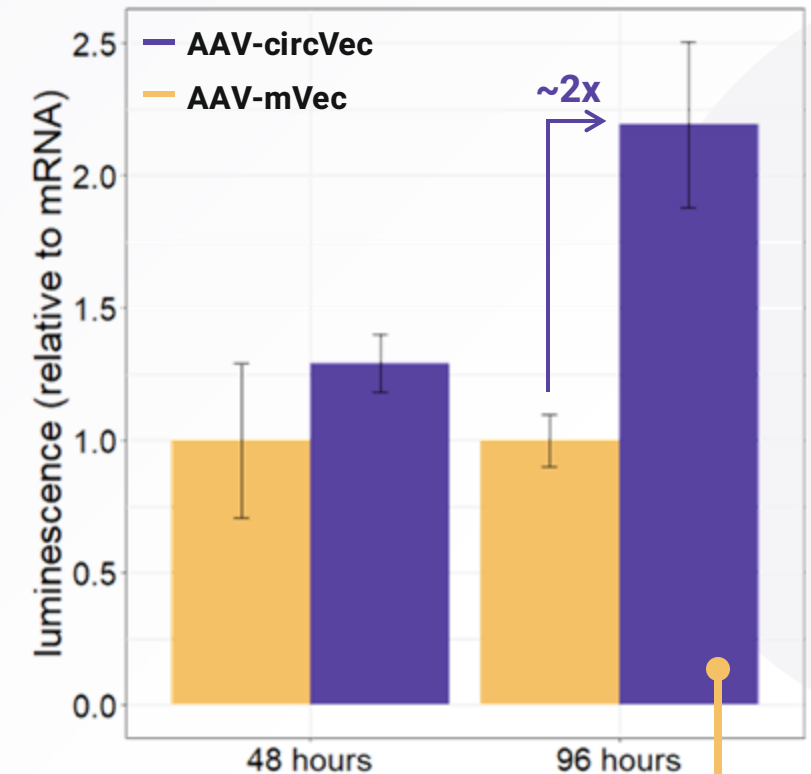
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R&D: circVec AAV

3. Corporate update

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AAV virus is the main gene therapy format today, circVec addresses major caveats

LUXTURNA

Spark THERAPEUTICS

AAV

Retinal Dystrophy

ZOLGENSMA

NOVARTIS

AAV

SMA

HEMGENIX

CSL

AAV

Hemophilia B

ELEVIDYS

SAREPTA THERAPEUTICS

AAV

DMD

ROCTAVIAN

BIOMARIN

AAV

Hemophilia A

2017 — **2019** — **2022** — **2023**

AAV format has substantial caveats:
- Insufficient gene expression level
- High dose requirement → toxicity & cost
- Not repeat-dosable

ADSTILADRIN

FERRING

AdV

NMIBC

UPSTAZA

PTC THERAPEUTICS

AAV

AADC

VYJUVEK

Krystal

HSV

DEB

8

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

circVec for gene therapy – enhancing AAV vectors

AAV vector

Standard mRNA approach

circVec circRNA approach

RNA

Enhanced durability

Protein

Enhanced expression

Aim: at least 3-5x enhanced potency vs. mVec-AAV

AAV protein expression, *in vitro* f-Luc

- AAV-circVec
- AAV-mVec

~2x

luminescence (relative to mRNA)

48 hours   96 hours

circVec-AAV feasibility validated, testing and optimization of constructs ongoing

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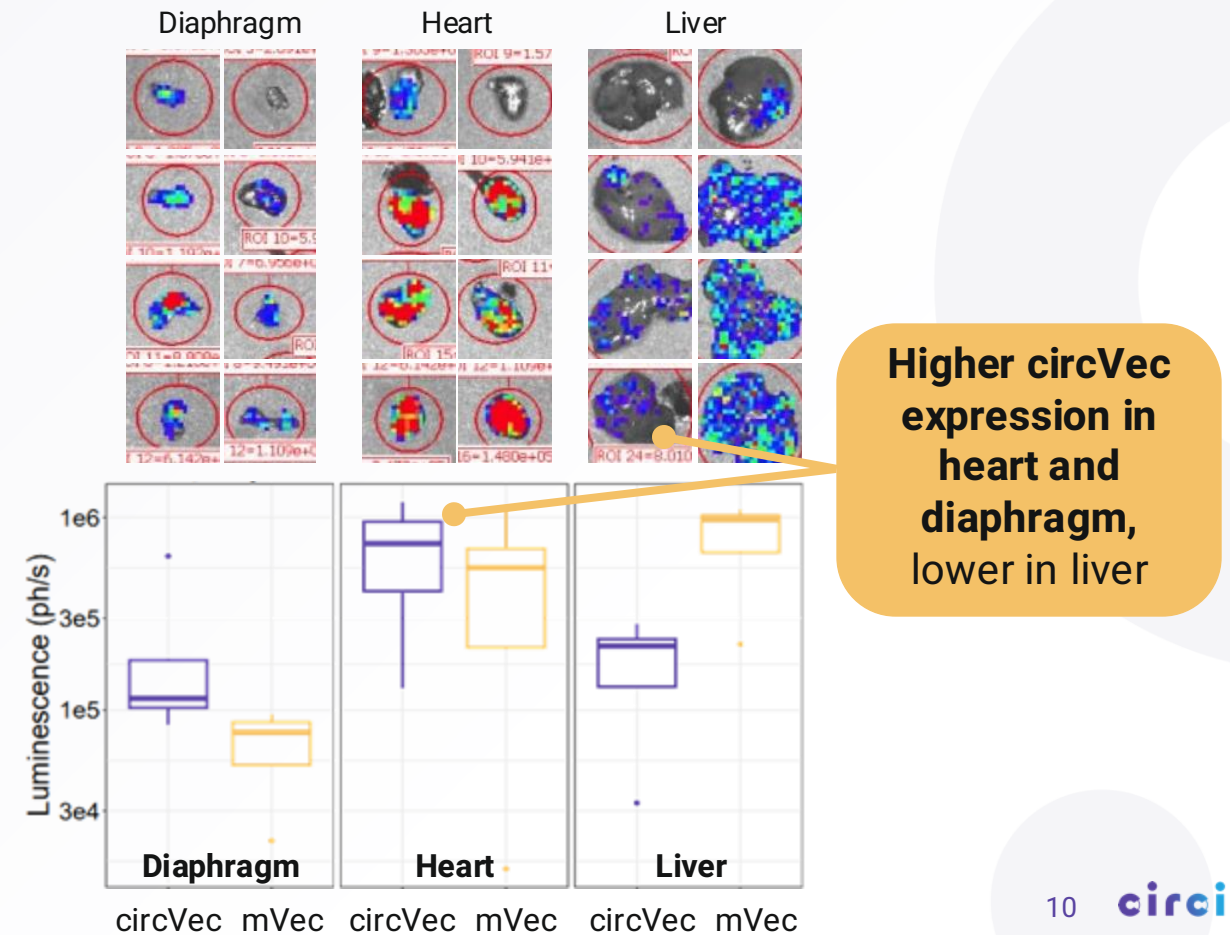# Multiple circVec-AAV designs have been tested in various tissues and delivery routes

AAV-circVec, <u>muscle</u> specific
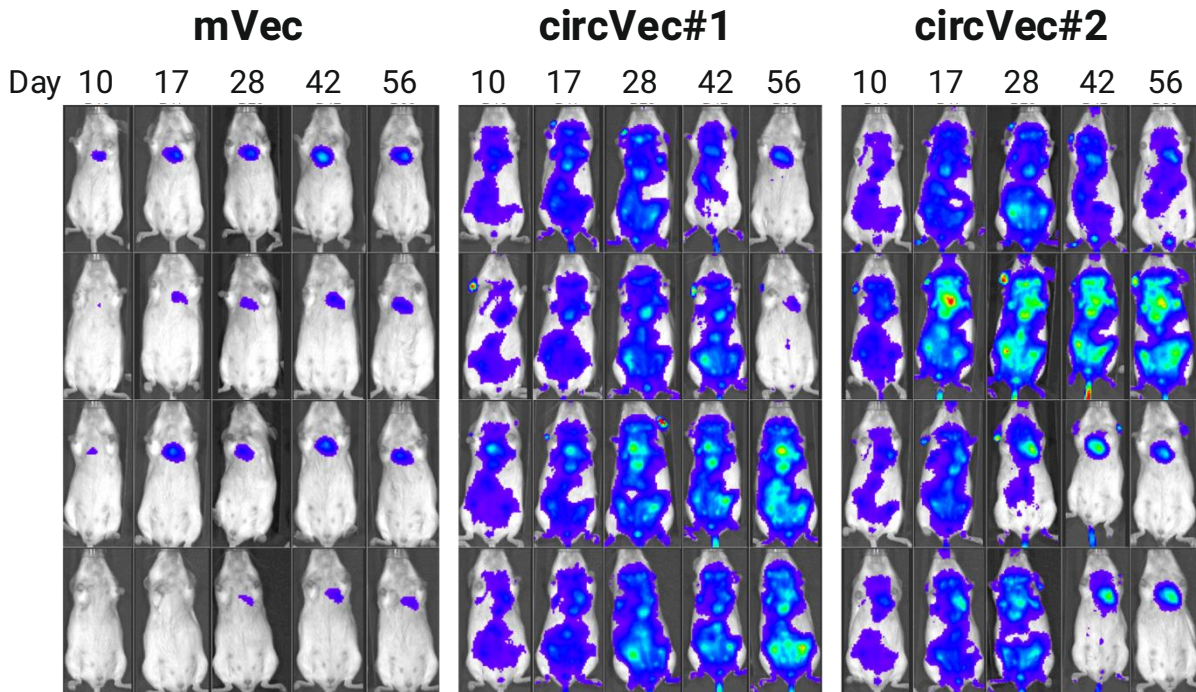Quantification of signal (luminescence)

n = 4 per group

> **circVec advantage** from D60, stabilizing at **+50% expression** up to D170

vector
- circVec
- mVec

Tissue-specific signal from AAV-circVec
Post mortem ex vivo analysis (luminescence)

Diaphragm   Heart   Liver

> **Higher circVec expression in heart and diaphragm,** lower in liver

Diaphragm   Heart   Liver

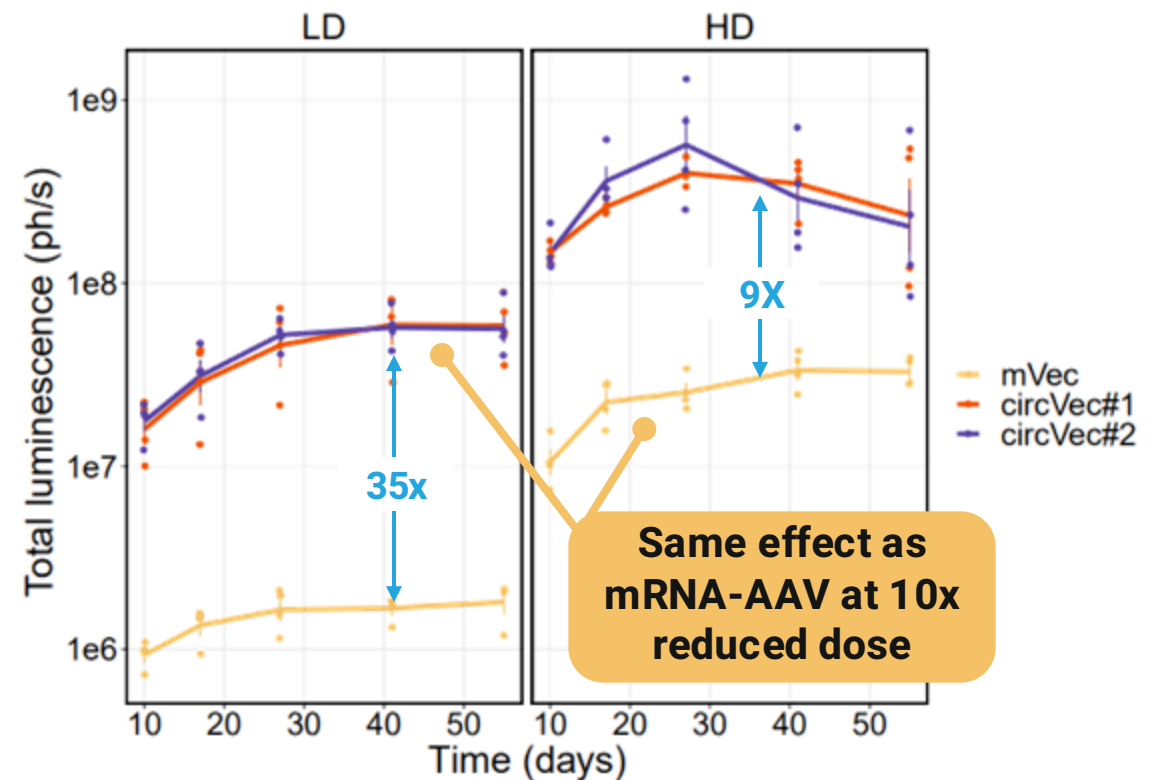circVec mVec   circVec mVec   circVec mVec

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Early data shows 10-fold increased potency for heart-specific circVec-AAV

AAV circVec, <u>heart</u> specific – two AAV designs
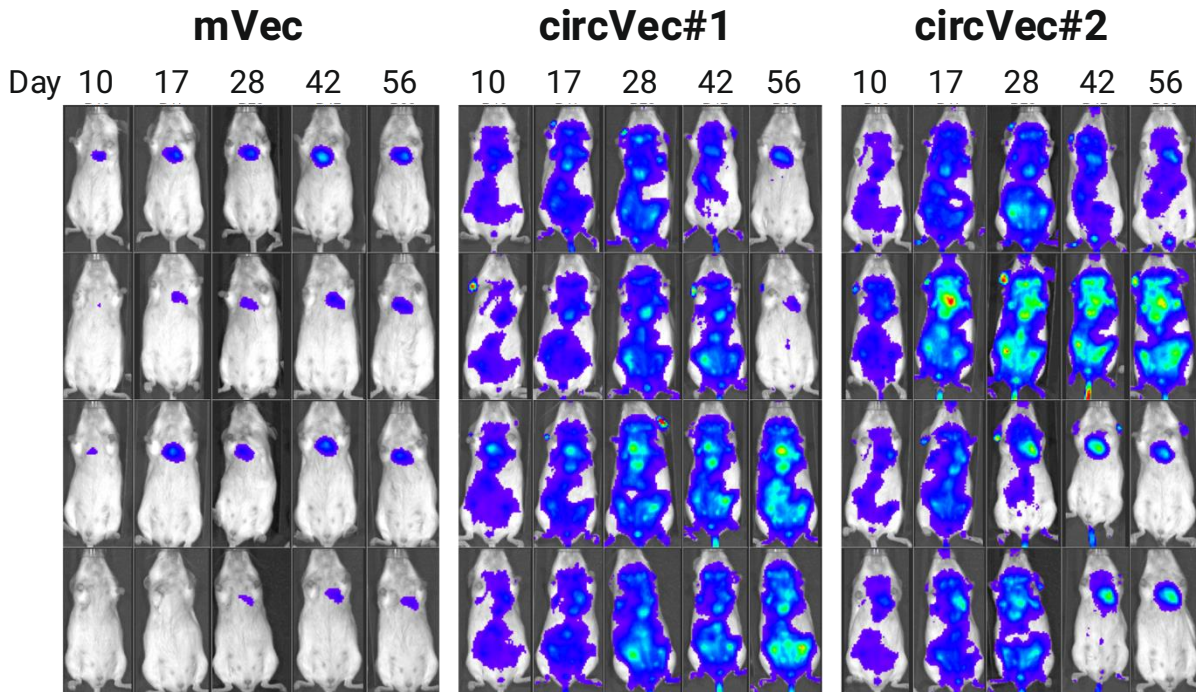Quantification of signal (luminescence), high dose

AAV-circVec, <u>heart</u> specific – two AAV designs
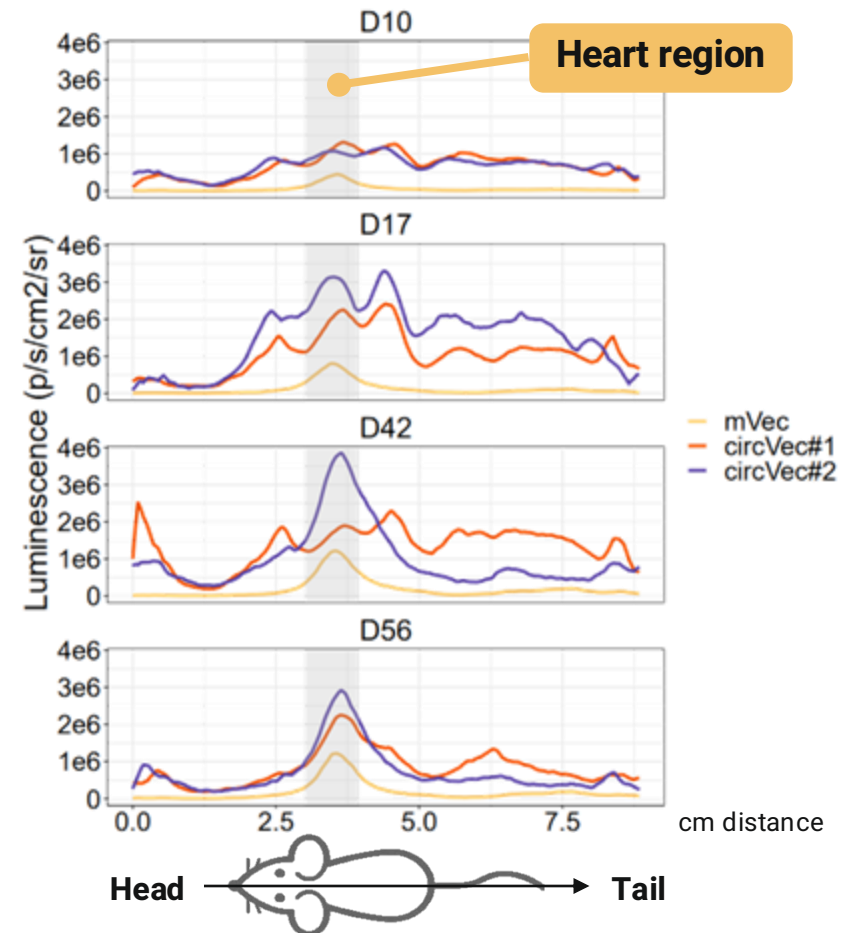Quantification of signal, high/low dose comparison

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Early data shows 10-fold increased potency for circVec-AAV: peak signal from heart region

AAV circVec, <u>heart</u> specific – two AAV designs
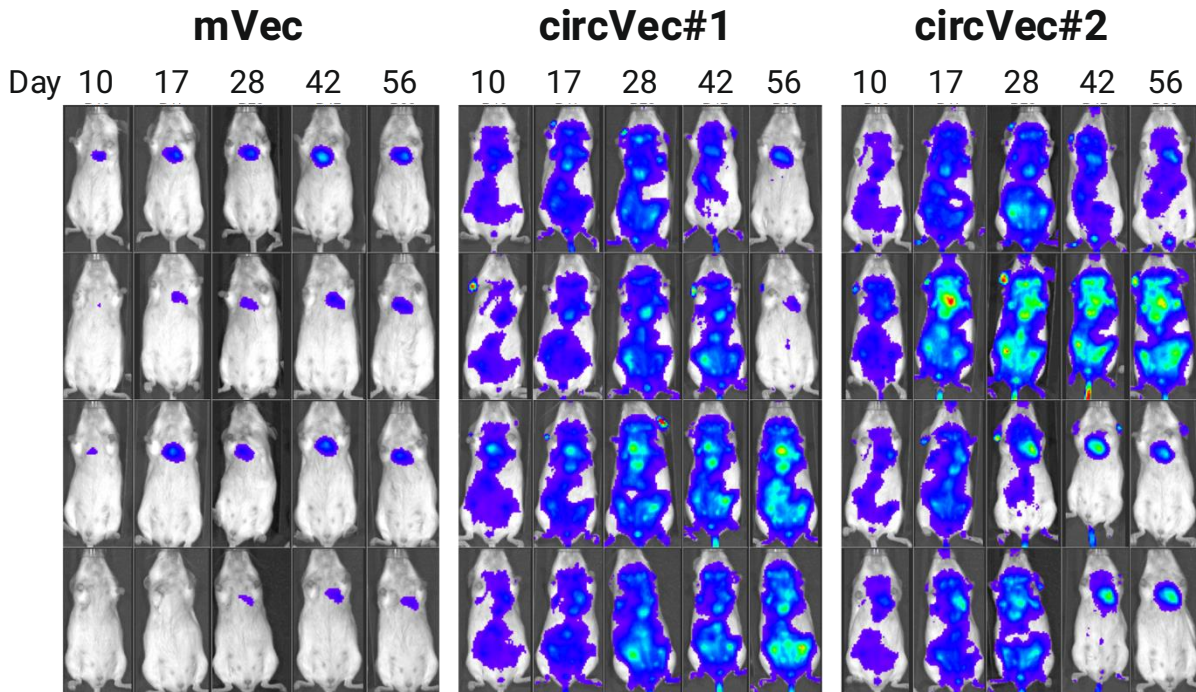Quantification of signal (luminescence), high dose

AAV circVec, <u>heart</u> specific
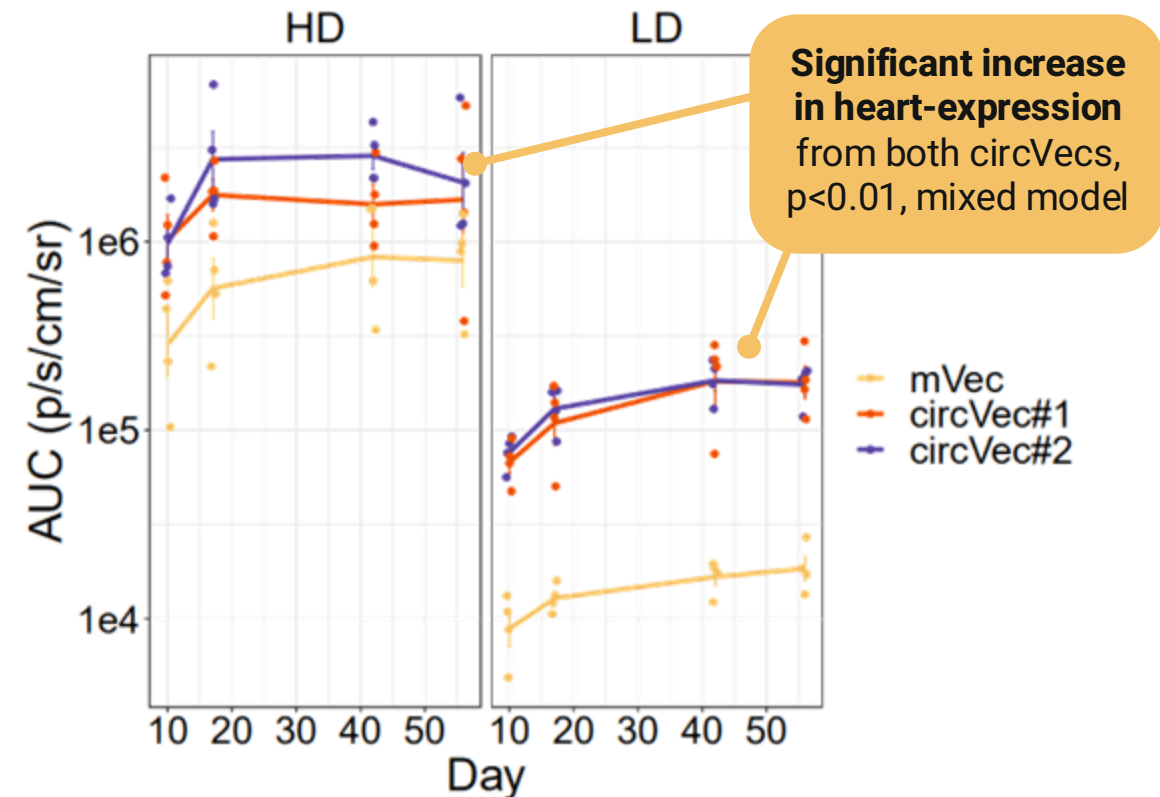Vertical signal profile from head to tail

Early data shows 10-fold increased potency for circVec-AAV: significant signal increase in heart vs. mVec

AAV circVec, <u>heart</u> specific – two AAV designs
Quantification of signal (luminescence), high dose

AAV circVec, <u>heart</u> specific
Total signal (luminescence), heart region

Significant increase in heart-expression from both circVecs, p<0.01, mixed model

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Summary and next steps: circVec AAV

Current status

- circVec validated in AAV format, multiple designs tested
- Identified tissue-specific circVec AAV expression profile
- 10-fold increased potency vs. mRNA for heart-specific AAV

Next steps

- Further exploration and enhancement of tissue-specific circVec performance using AAV vectors
- Development and testing of AAV-circVec for treatment of muscular dystrophies and cardiomyopathies in relevant mouse disease models

Business Development

- Establish research collaborations with AAV specialist companies in tissue / target specific setting
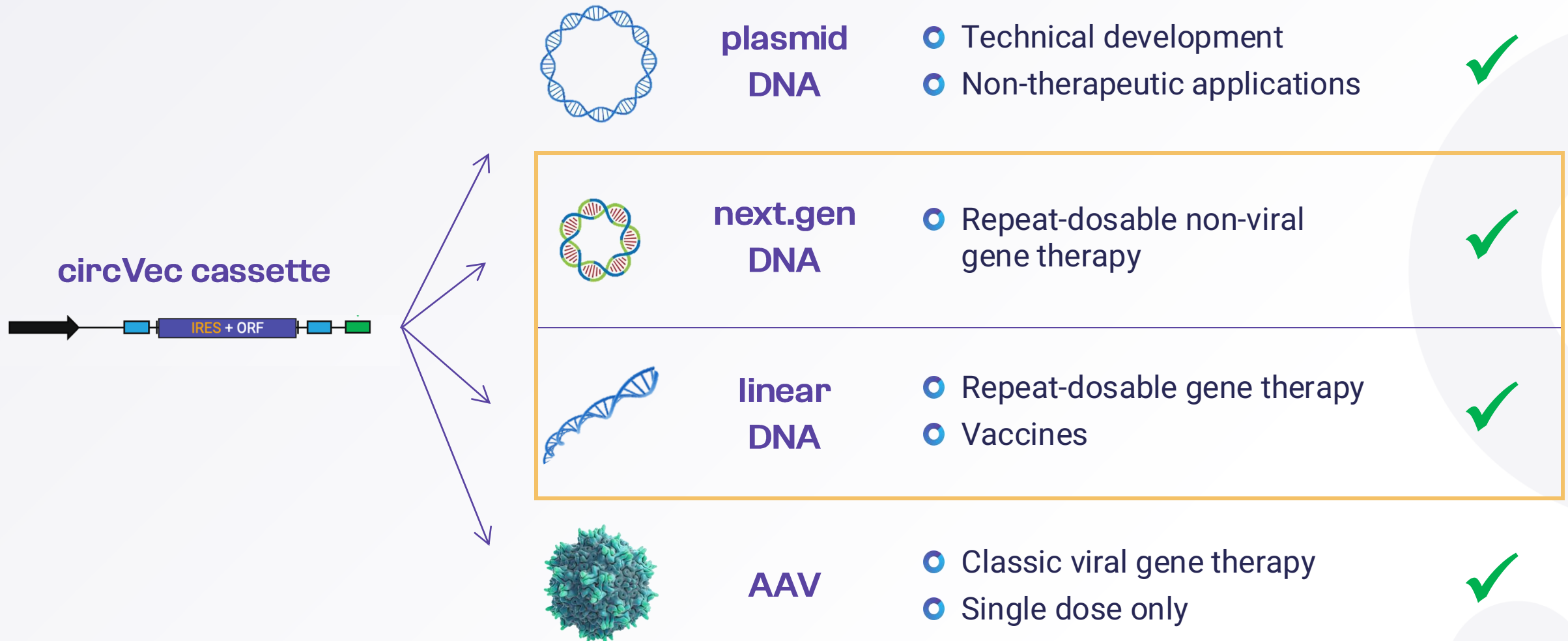- External testing and validation of circVec-AAV advantage
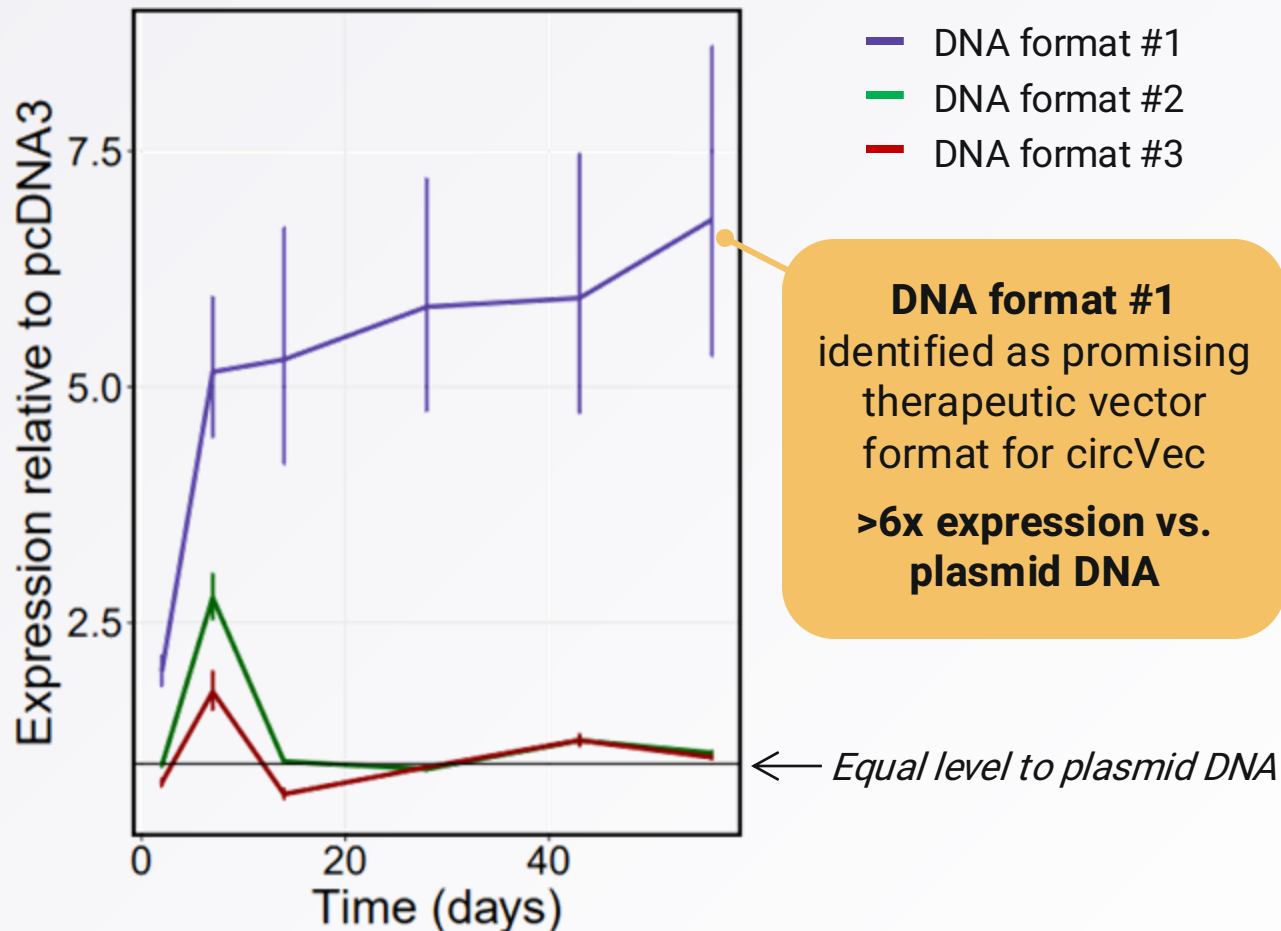
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R&D: circVec DNA

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Testing and validation of circVec in therapeutic vectors

circVec cassette

IRES + ORF

plasmid DNA
- Technical development
- Non-therapeutic applications ✓

next.gen DNA
- Repeat-dosable non-viral gene therapy ✓

linear DNA
- Repeat-dosable gene therapy
- Vaccines ✓

AAV
- Classic viral gene therapy
- Single dose only ✓

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Optimal format for therapeutic DNA vectors identified for continued development

DNA vector expression relative to plasmid DNA
Quantification of in vivo signal, time course

Legend:
- DNA format #1
- DNA format #2
- DNA format #3

DNA format #1 identified as promising therapeutic vector format for circVec

>6x expression vs. plasmid DNA
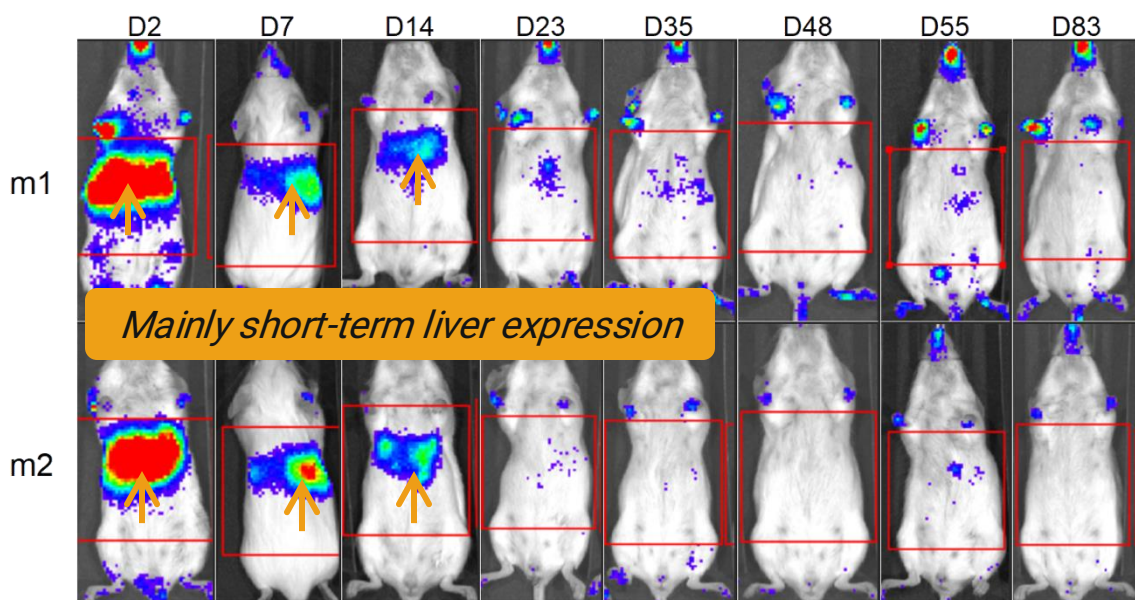
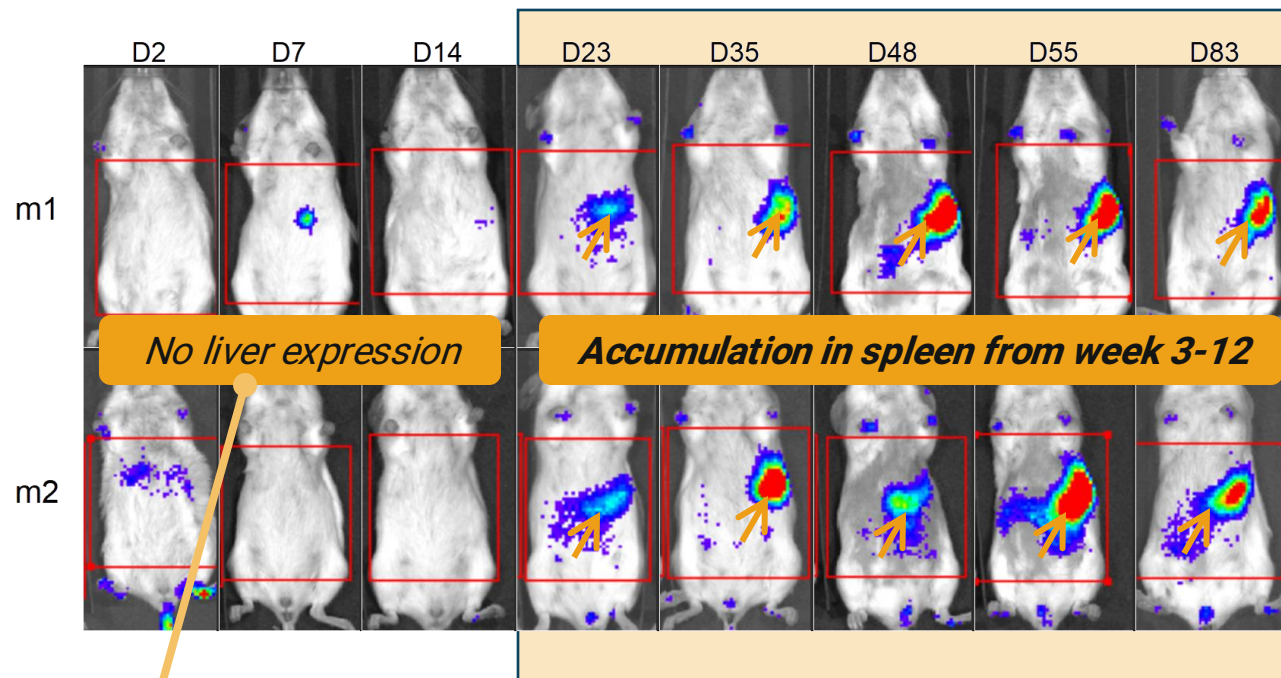*Equal level to plasmid DNA*

DNA format gene & cell therapy

- *Reduced cost vs. current approaches*
- *Repeat-dosable*
- *Larger payload capacity than AAV*
- *Longer expression than RNA*

- **Considered the future format for gene and cell therapy**
- **Substantial efforts ongoing to establish enhanced vectors and delivery systems**
- **Technologies to target and extend expression are highly sought after**

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LNP-circVec expressing selectively in spleen, unique opportunity for in vivo cell therapy

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

Mainly short-term liver expression

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

No liver expression

Accumulation in spleen from week 3-12

circVec de-targets liver expression

LNP collaboration partner

Summary and next steps: circVec DNA

Current status

- Novel therapeutically relevant DNA format identified
- circVec LNP-delivery to spleen confirmed

Next steps

- Analysis of circVec spleen delivery at cellular level
- Testing new DNA format in advanced and targeted LNP formulations and non-LNP delivery systems
- Establish platform for durable circVec in vivo CAR approach using circVec DNA + spleen delivery system

Business Development

- Several ongoing collaborations with innovative DNA delivery companies: Certest, Entos, 4BB and others
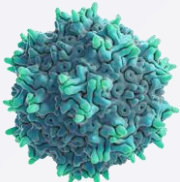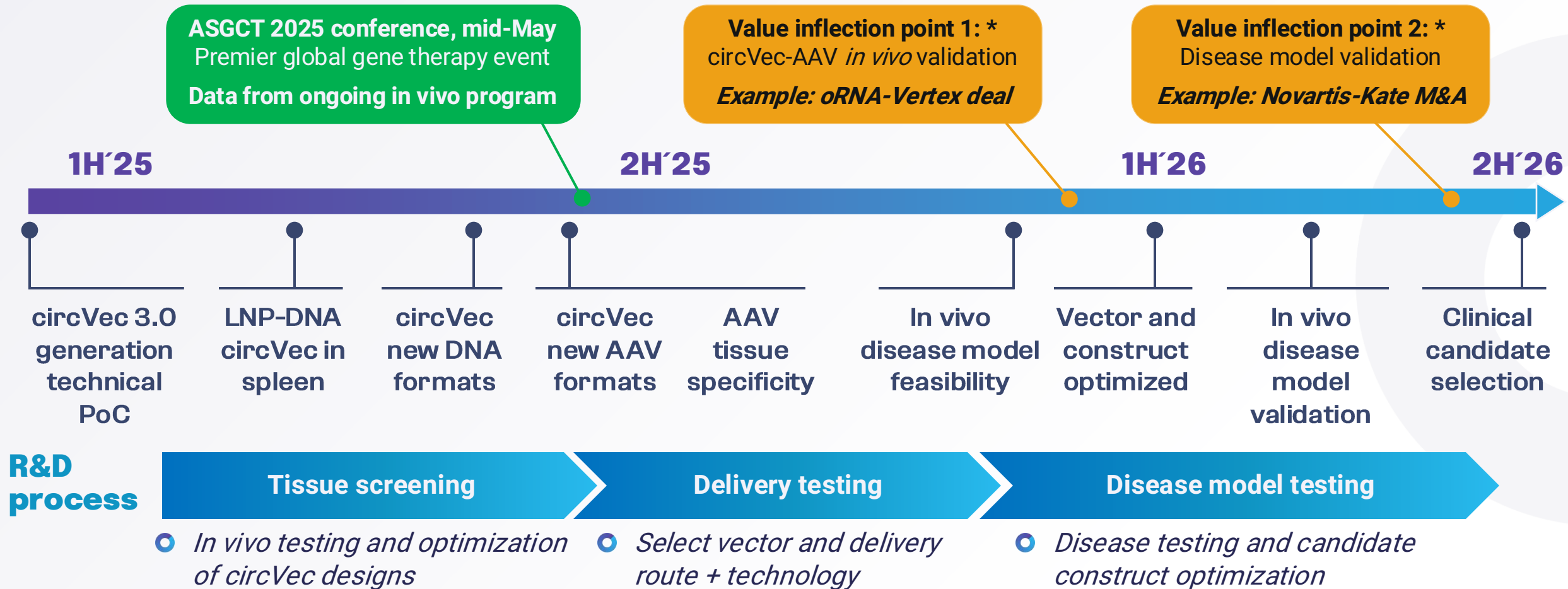- Seeking collaboration partners for in vivo cell therapy

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3

Corporate update

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circVec summary – next milestones and BD activities

	Next milestone	**BD activities**
AAV gene therapy	○ Validate heart data ○ Test additional tissues ○ Testing in disease models	○ Establish collaborations with AAV companies ○ External circVec AAV testing
DNA cell therapy	○ Replicate findings w/new format ○ circVec CAR expression ○ Ex vivo T cell experiments	○ Establish collaborations with in vivo CAR companies ○ External circVec DNA testing
DNA delivery	○ Test additional LNP formulations ○ Test other delivery systems ○ Validate w/new DNA format	○ Several ongoing collaborations ○ Certest, Entos, 4BB + others, data during 2H´2025

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Upcoming milestones and timelines: rich pipeline of R&D milestones with multiple shots on goal

ASGCT 2025 conference, mid-May
Premier global gene therapy event
Data from ongoing in vivo program

Value inflection point 1: *
circVec-AAV *in vivo* validation
Example: oRNA-Vertex deal

Value inflection point 2: *
Disease model validation
Example: Novartis-Kate M&A

1H´25	2H´25	1H´26	2H´26

- circVec 3.0 generation technical PoC
- LNP-DNA circVec in spleen
- circVec new DNA formats
- circVec new AAV formats
- AAV tissue specificity
- In vivo disease model feasibility
- Vector and construct optimized
- In vivo disease model validation
- Clinical candidate selection

R&D process

Tissue screening	Delivery testing	Disease model testing

- *In vivo testing and optimization of circVec designs*
- *Select vector and delivery route + technology*
- *Disease testing and candidate construct optimization*

* Expected data package necessary to drive interest to initiate partnering discussions and negotiations
Data & Timeline: current best estimates - experiments have uncertain outcomes and may need to be repeated, impacting plans and timelines

22

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AGM notice – main items

Reverse split & capital reduction

- The Board selected to withdraw the proposals after careful consideration of the current situation
- Evaluating alternatives to manage OSE share price rule

Share issue mandate

- Proposed 40% level enables more flexibility for fundraising in tough market conditions
- Higher likelihood to attract new and international investors

RSU and option mandate

- RSU/option program important compensation component
- Aligns shareholder and employee long-term goals
- Reduces cash expenditure for the company

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Q & A Session