circio

Disruptive circRNA technology for nucleic acid medicine

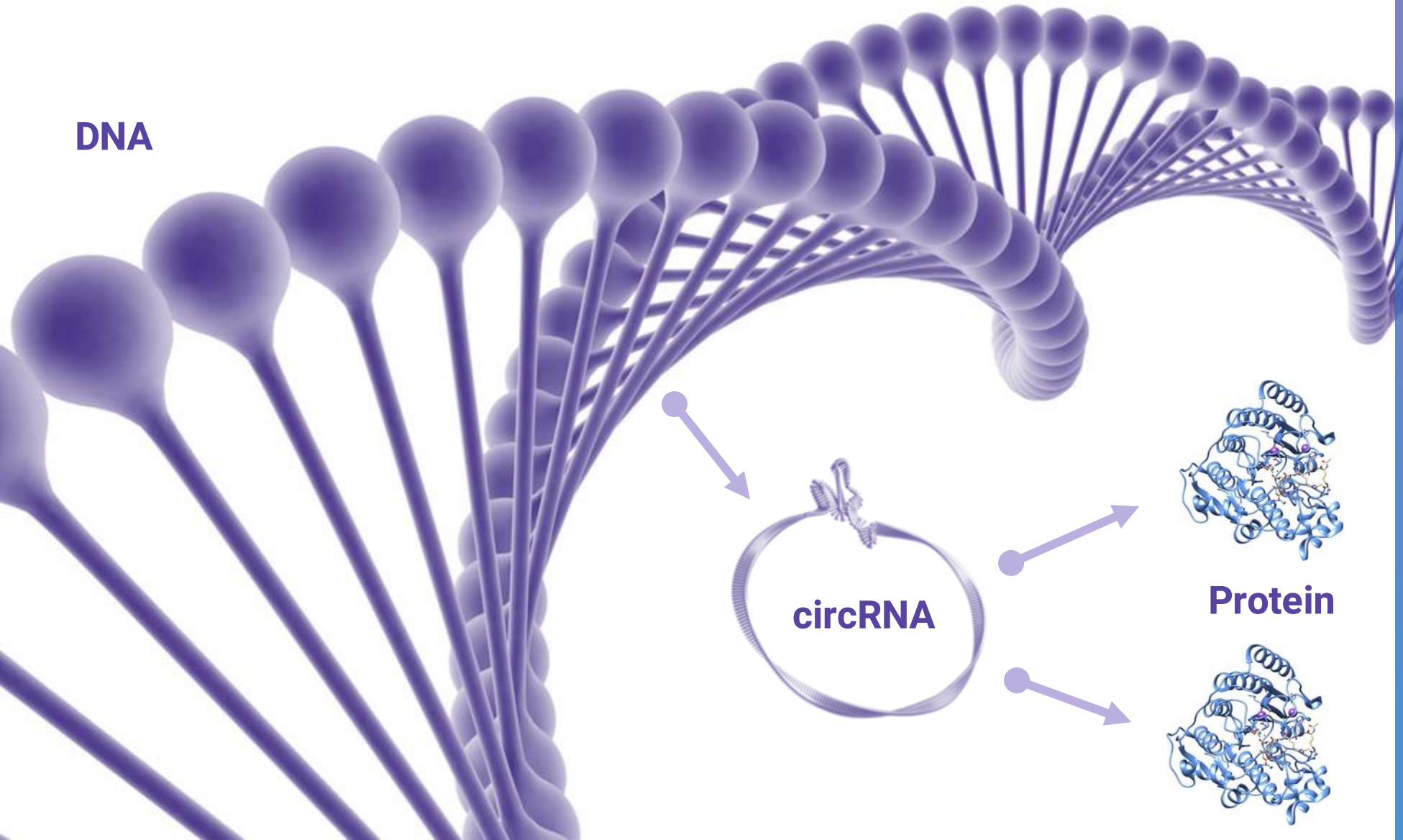
Company update webcast
4 December 2024

1

circVec introduction

2. circVec generation 3.0
3. circVec in vivo data
4. circVec therapeutic application
5. Warrant exercise information

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



circVec
DNA or viral vector

Inject

circRNA biogenesis

Potent and durable protein expression

The circVec platform is technologically differentiated and creates novel opportunities 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

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

Drug TARGET REVIEW

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ARTICLE

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.

How does circVec technology compare to conventional mRNA?

3 July 2024

DRUG DISCOVERY WORLD

DDW™

turning science into business

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.

BioSpace

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

Features

Circular RNA: Vaccines, therapeutics and biomarkers could be revolutionised

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

Abigail Beaney | May 15, 2024

Share

Clinical Trials Arena

2

circVec generation 3.0

3. circVec in vivo data
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5. Warrant exercise information

circVec 2.1 has shown 15x prolonged circRNA half-life and up to 10x protein expression vs. mRNA in vitro

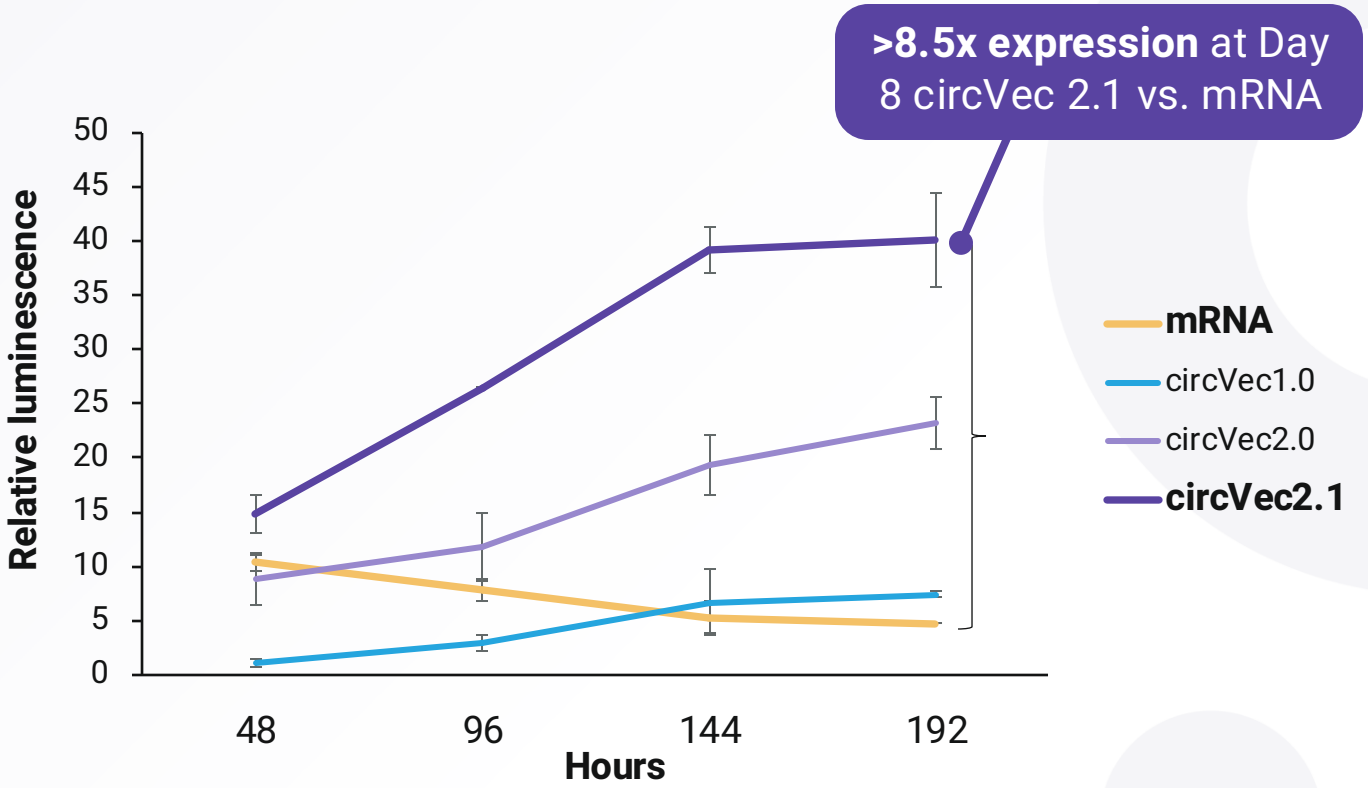
circVec *in vitro* RNA half-life
RT-qPCR, nascent vs. total RNA

135h vs. **9h**

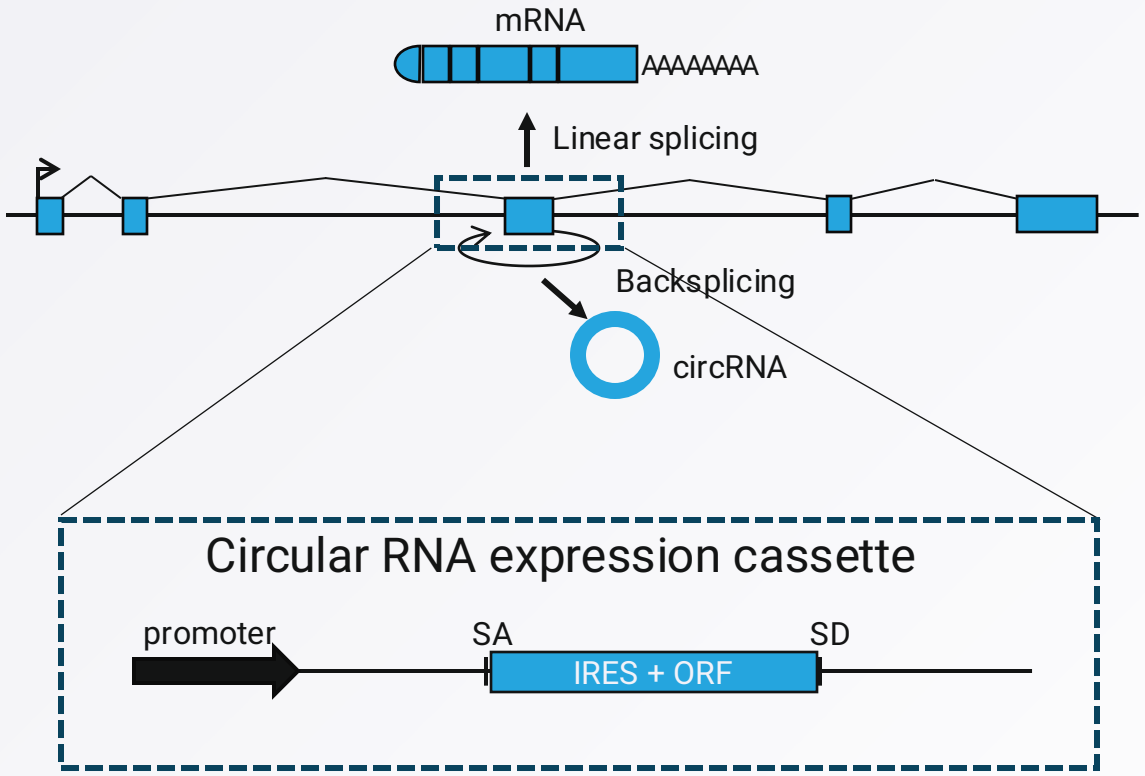
circRNA mRNA

15 x

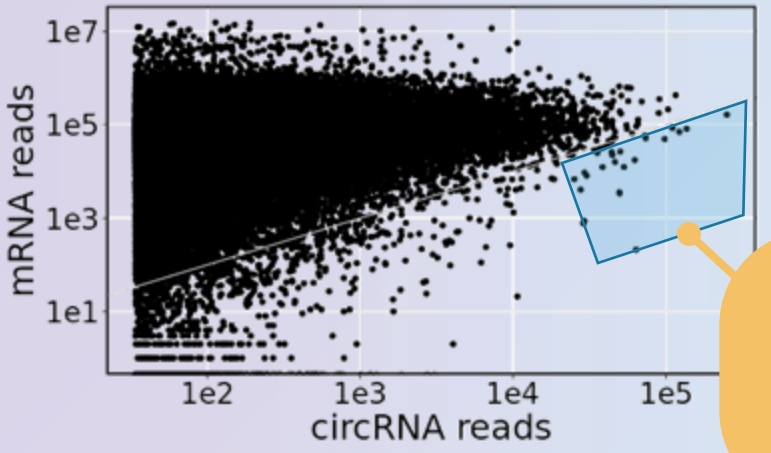
circVec vs. mRNA luciferase reporter expression;
in vitro time course



The starting point for the circVec construct is based on nature´s best design



Expression of human endogenous circRNA
NGS analysis of 300+ RNAseq datasets

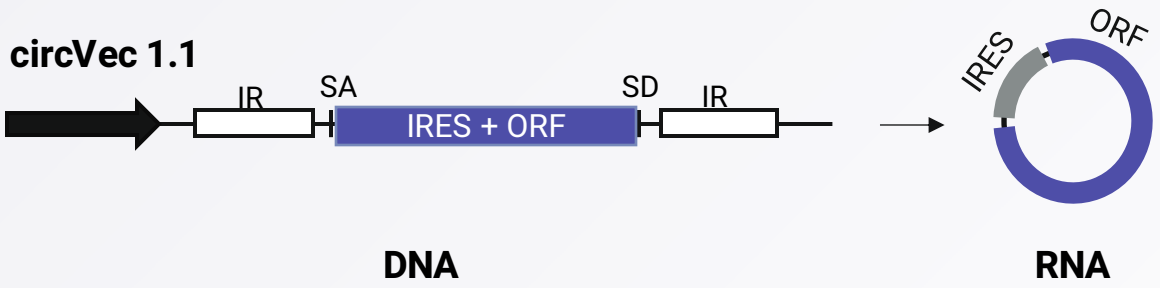


Maximum biogenesis-rate of endogenous circRNA

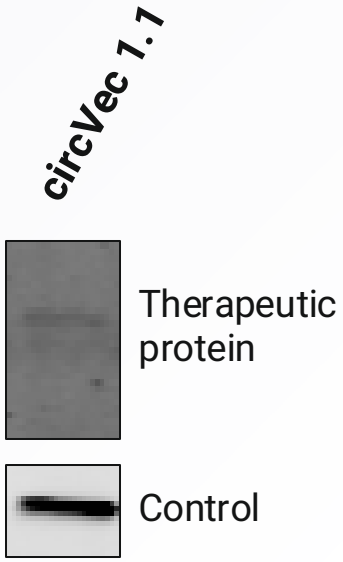
Screen and optimize the most effective loci in the human genome

Optimizing nature´s best design to build circVec 3.0

circVec generation 1.X – 3.X, design schematics

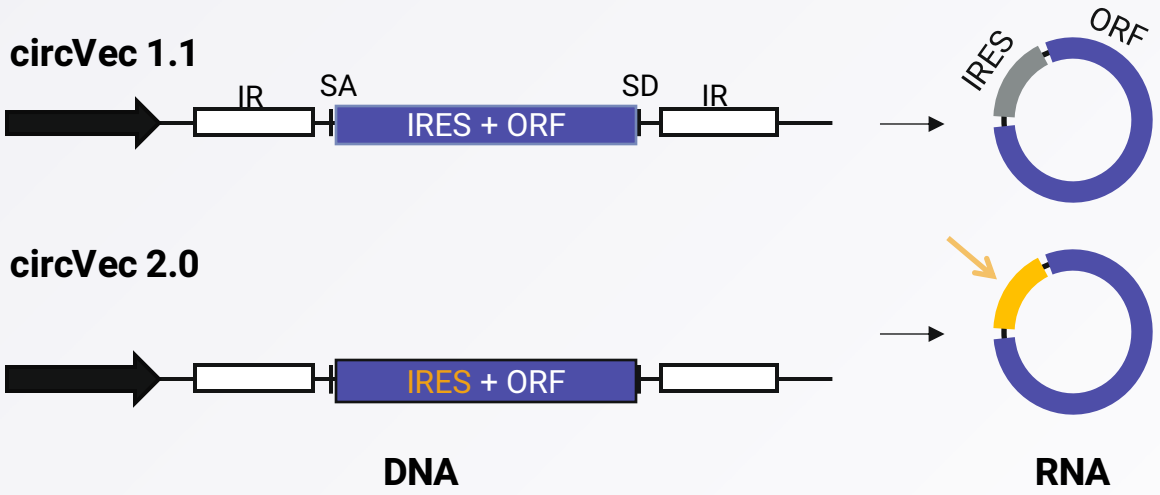


circVec protein expression, Western blot

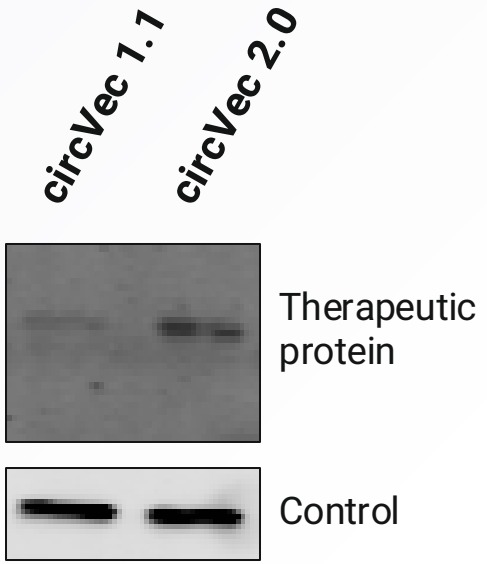


Optimizing nature´s best design to build circVec 3.0

circVec generation 1.X – 3.X, design schematics

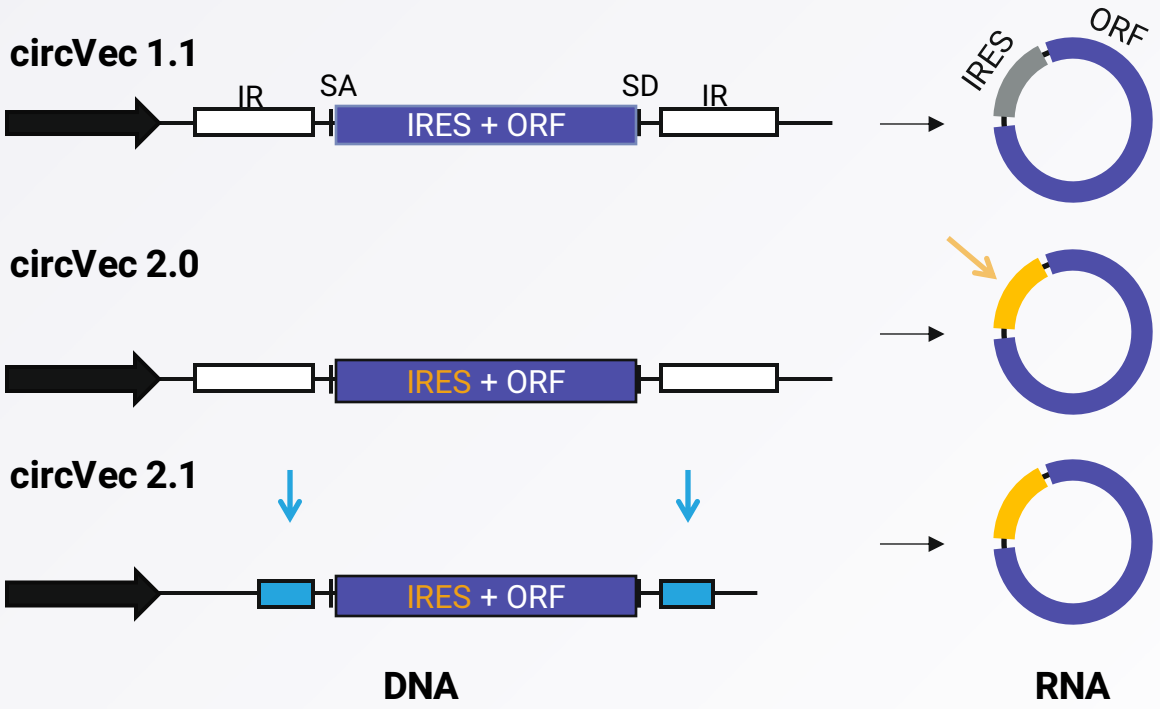


circVec protein expression, Western blot

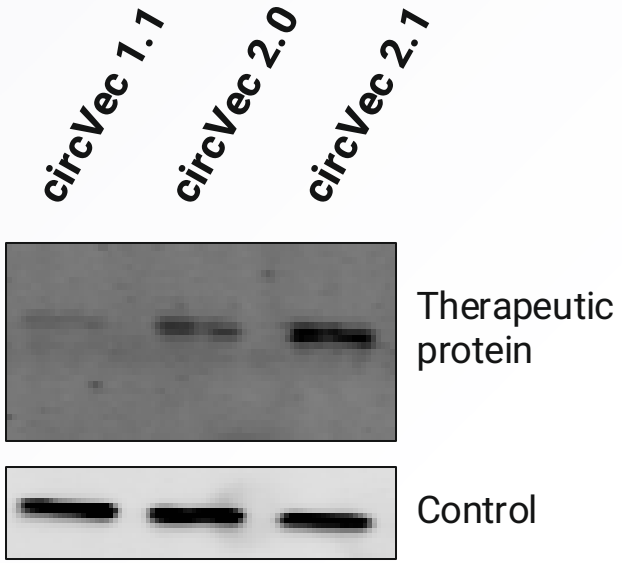


Optimizing nature´s best design to build circVec 3.0

circVec generation 1.X – 3.X, design schematics

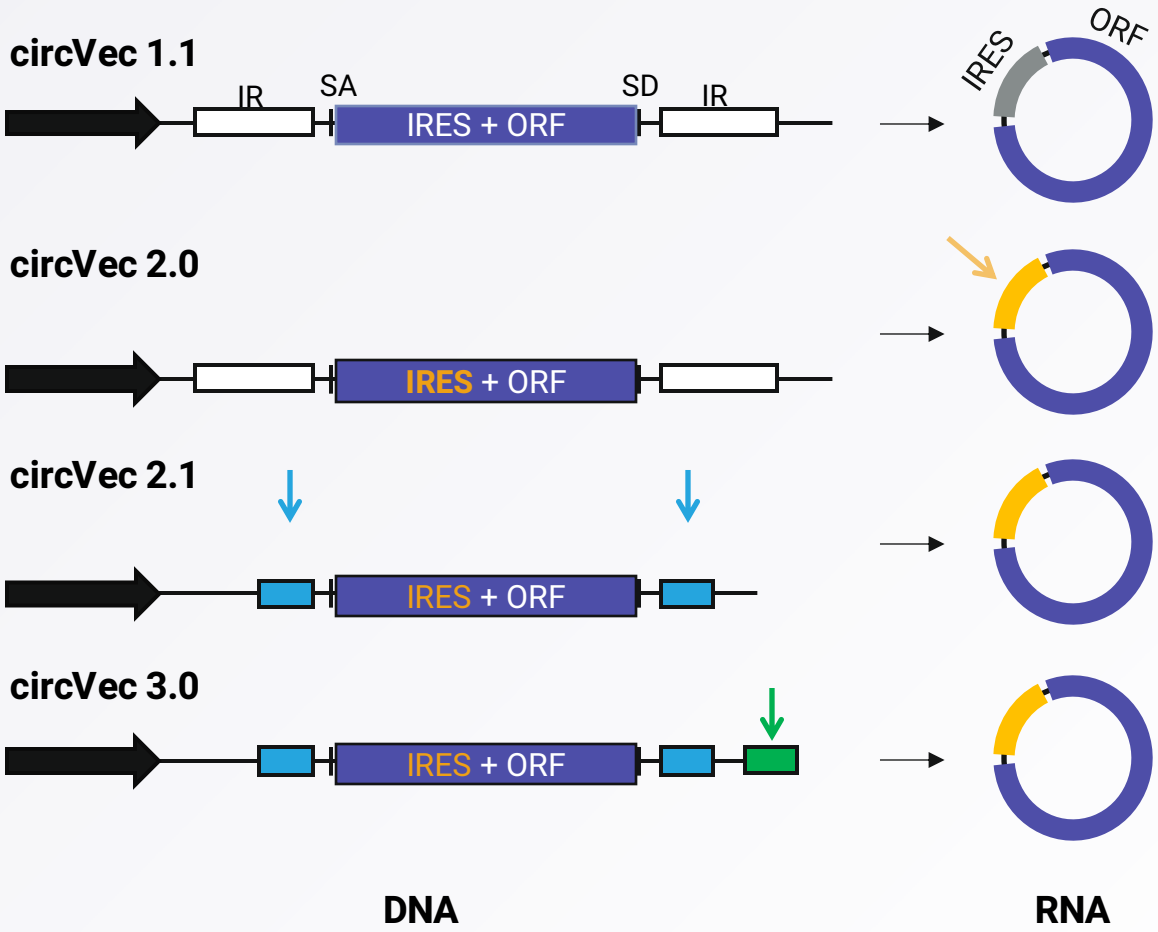


circVec protein expression, Western blot

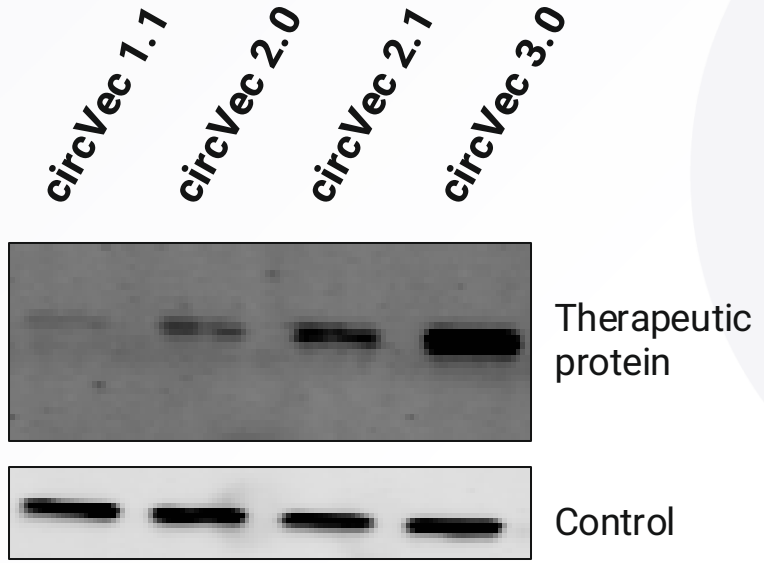


Optimizing nature´s best design to build circVec 3.0

circVec generation 1.X – 3.X, design schematics

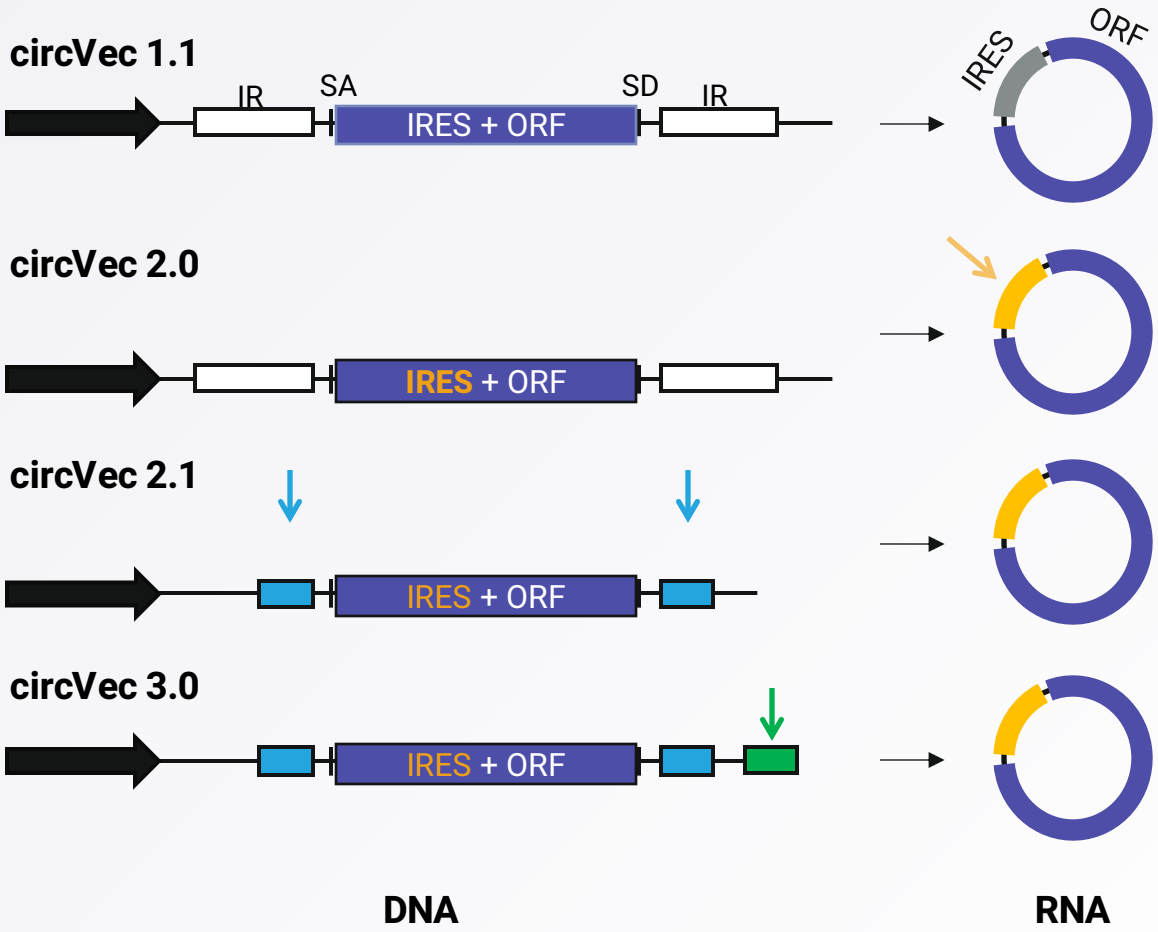


circVec protein expression, Western blot

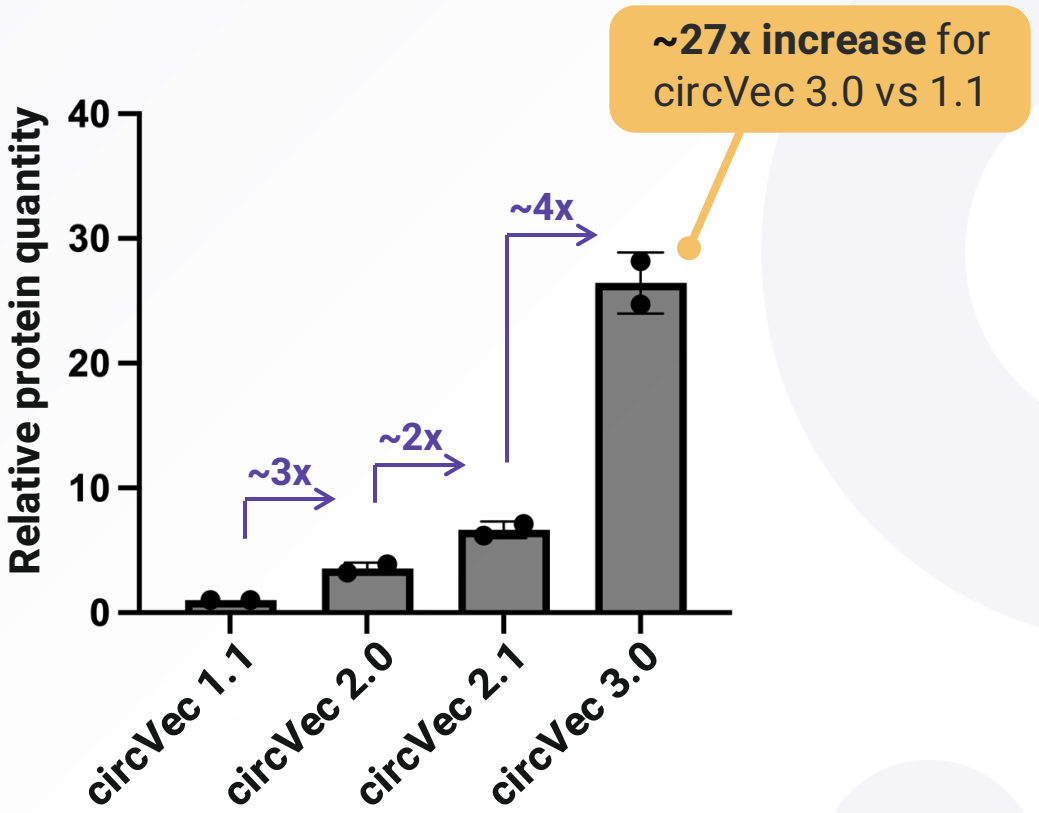


Optimizing nature´s best design to build circVec 3.0

circVec generation 1.X – 3.X, design schematics



circVec protein quantification, Western blot



3

circVec in vivo data

4. circVec therapeutic application
5. Warrant exercise information

circVec 2.1 achieves > 6 month expression durability on one single injection in immuno-competent mouse muscle

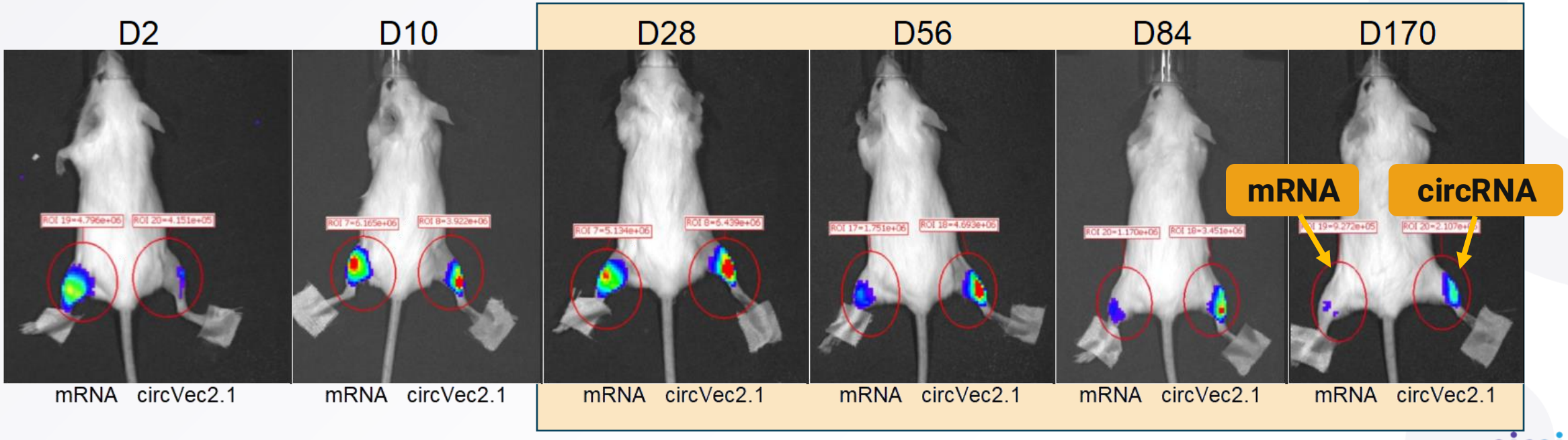
BALB/c
Immuno-competent mice

mRNA-vector-*Luciferase*
Left hindleg

circVec 2.1-*Luciferase*
Right hindleg

Intra-muscular injection
3 dose levels

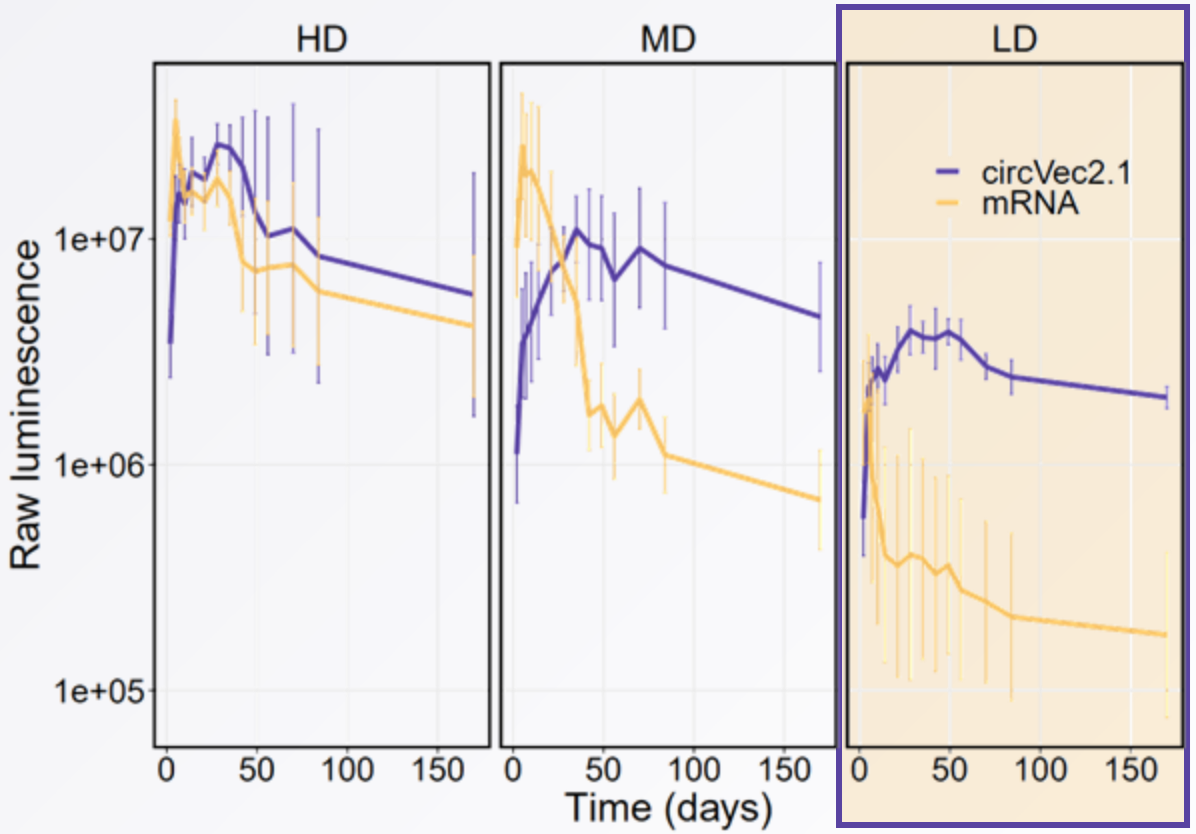
Monitor expression over time



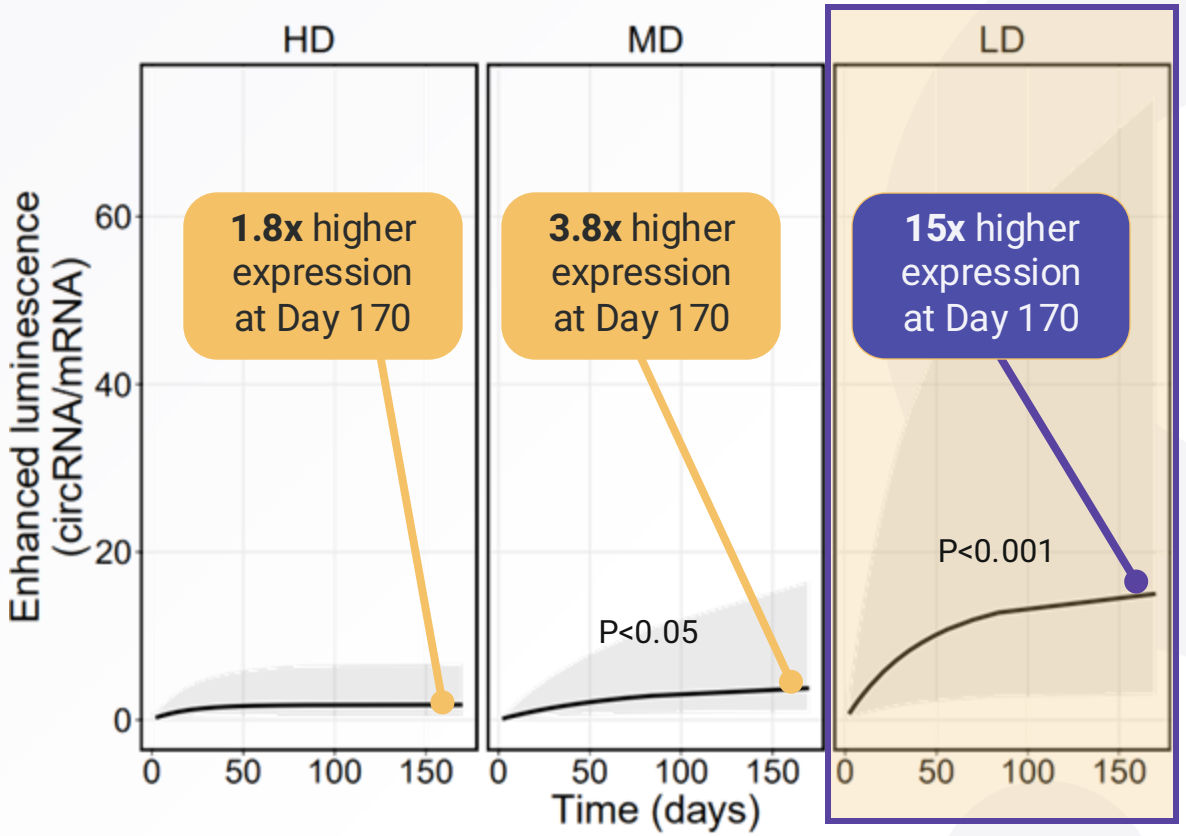
Low dose example animal

circVec 2.1 dose response in vivo - strongest advantage vs. mRNA observed at low dose, high therapeutic relevance

Absolute expression (luminescence)
circVec 2.1 vs. mRNA pDNA vector expression



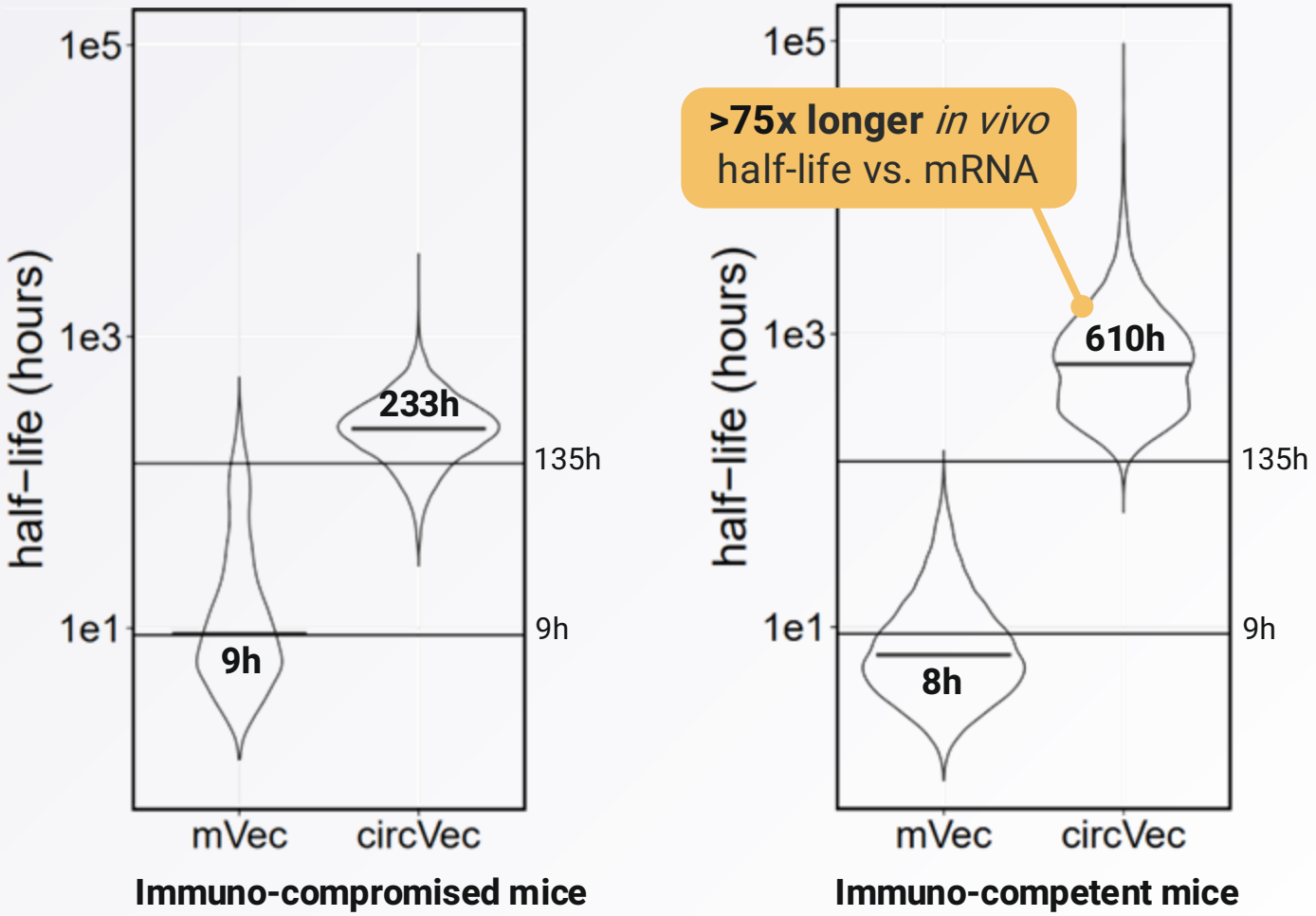
Relative expression (luminescence)
-fold change circVec 2.1 vs. mRNA expression



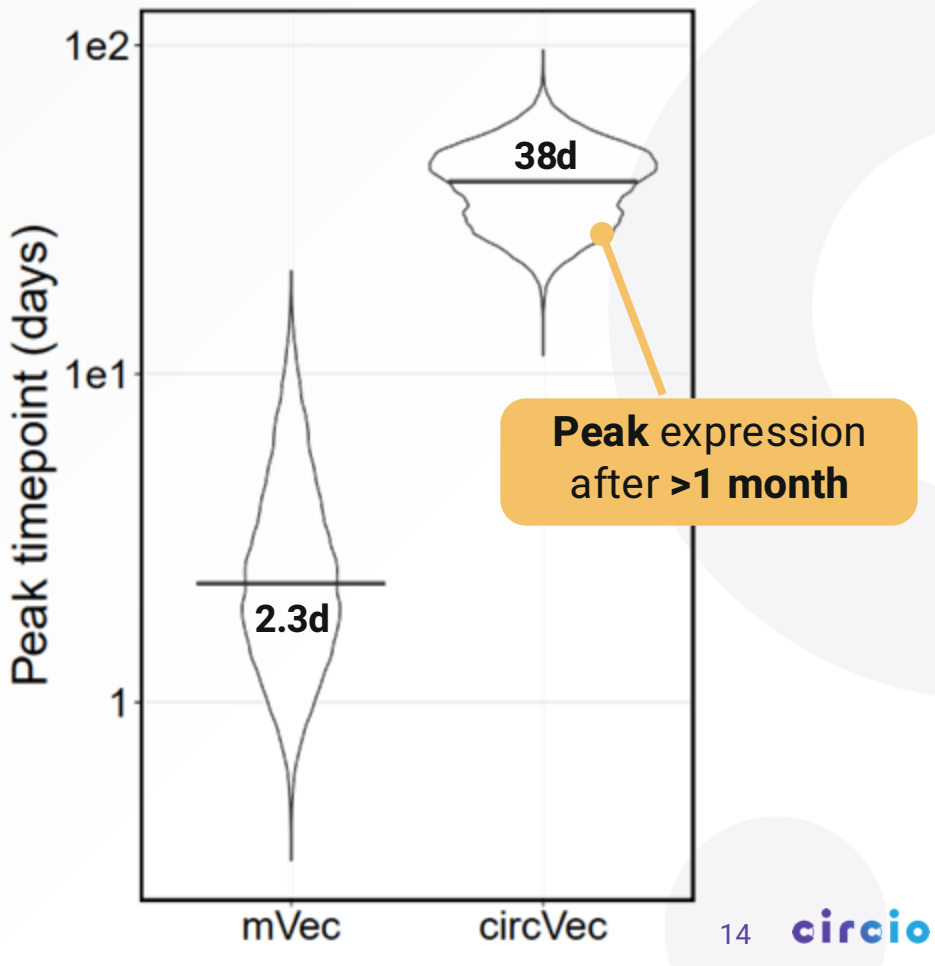
HD: High dose MD: Mid dose LD: Low dose

Bioinformatic analysis of circVec 2.1 in vivo data indicates up to 75 times increased half-life of circRNA vs. mRNA

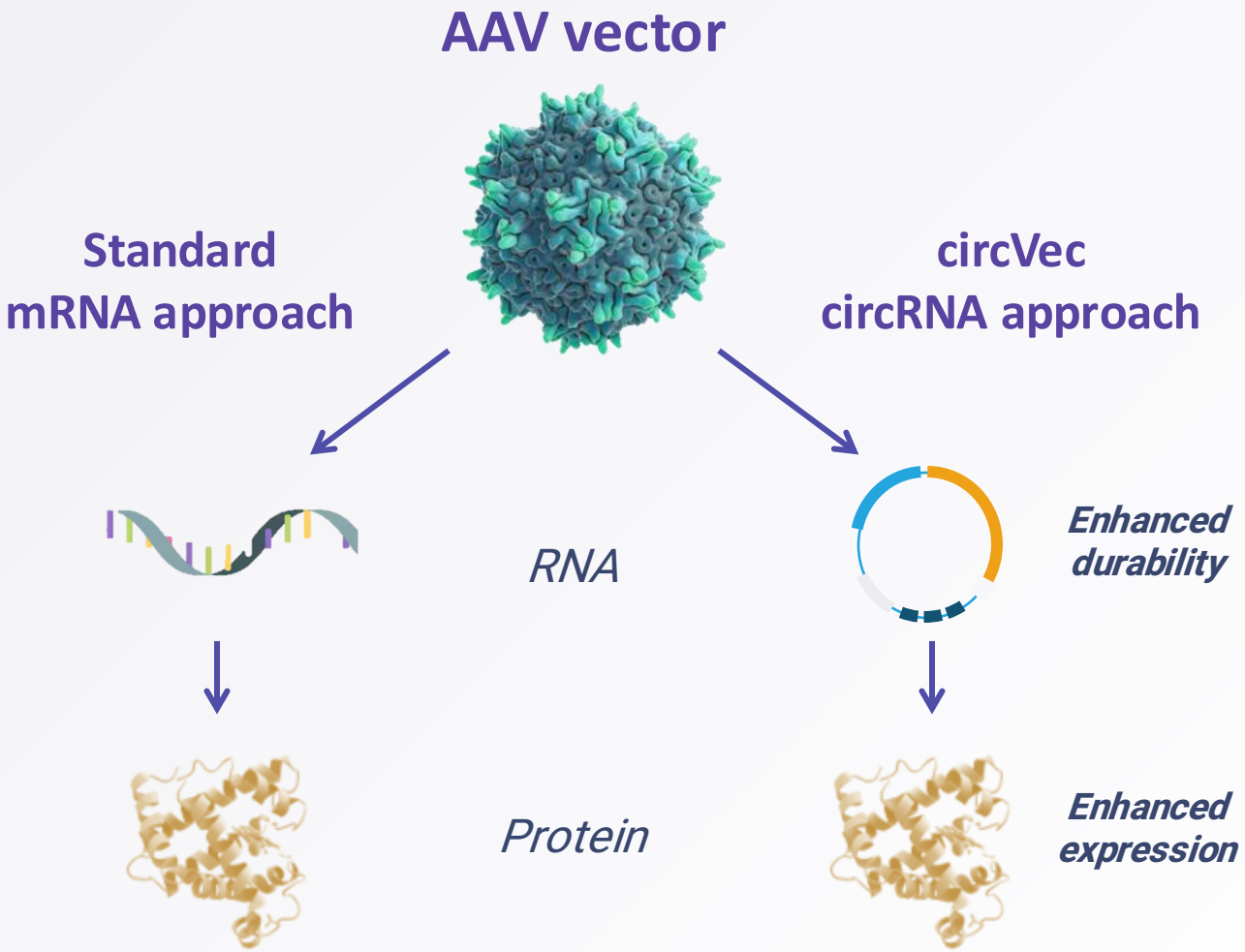
Inferred RNA half-life (hours), bioinformatic modelling



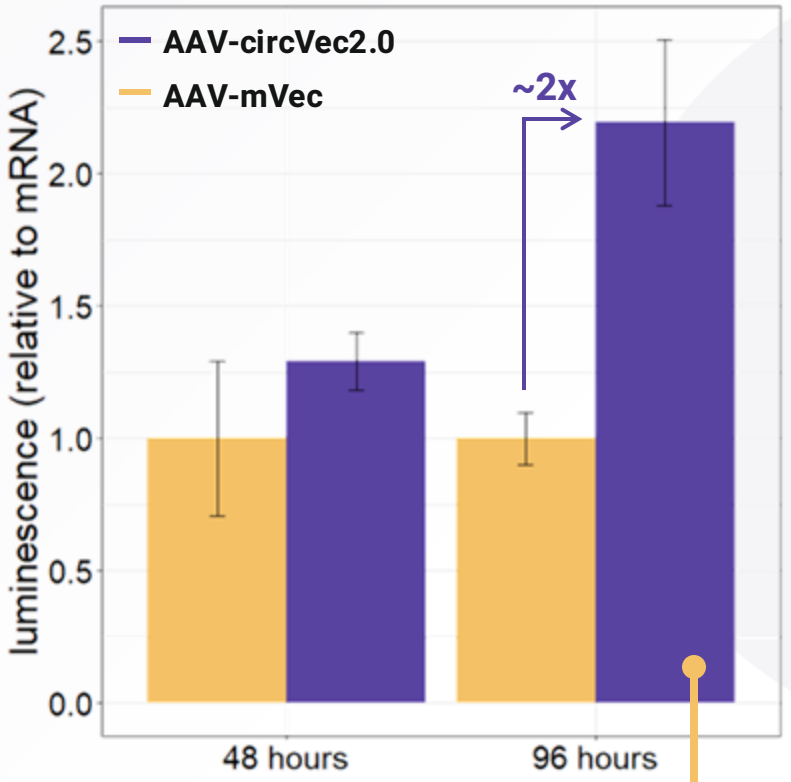
Inferred peak expression (days)



Deploying circVec to enhance AAV gene therapy



AAV protein expression, luminescence



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

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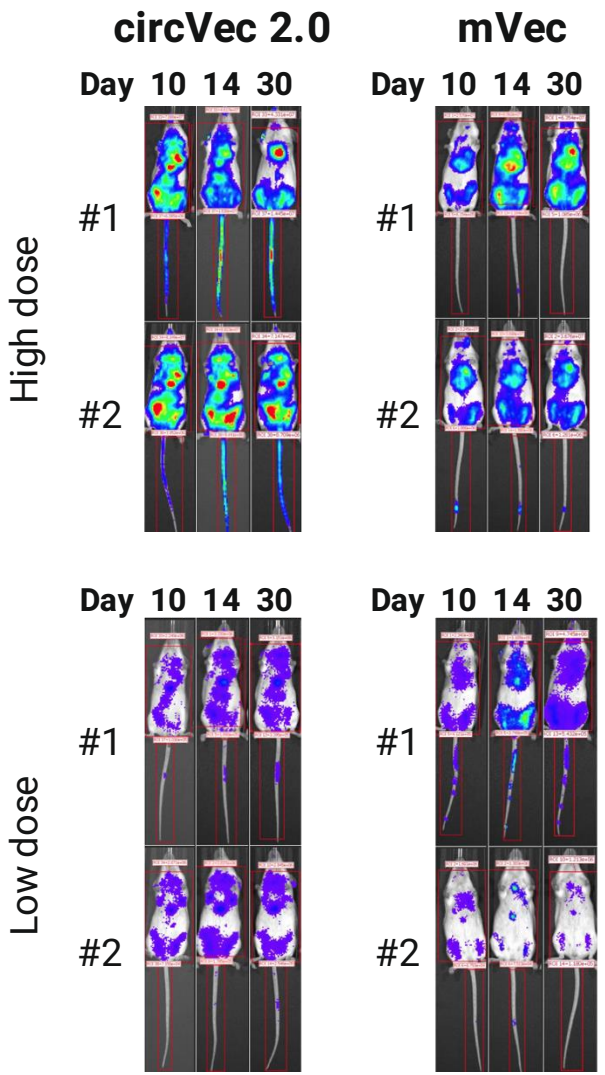
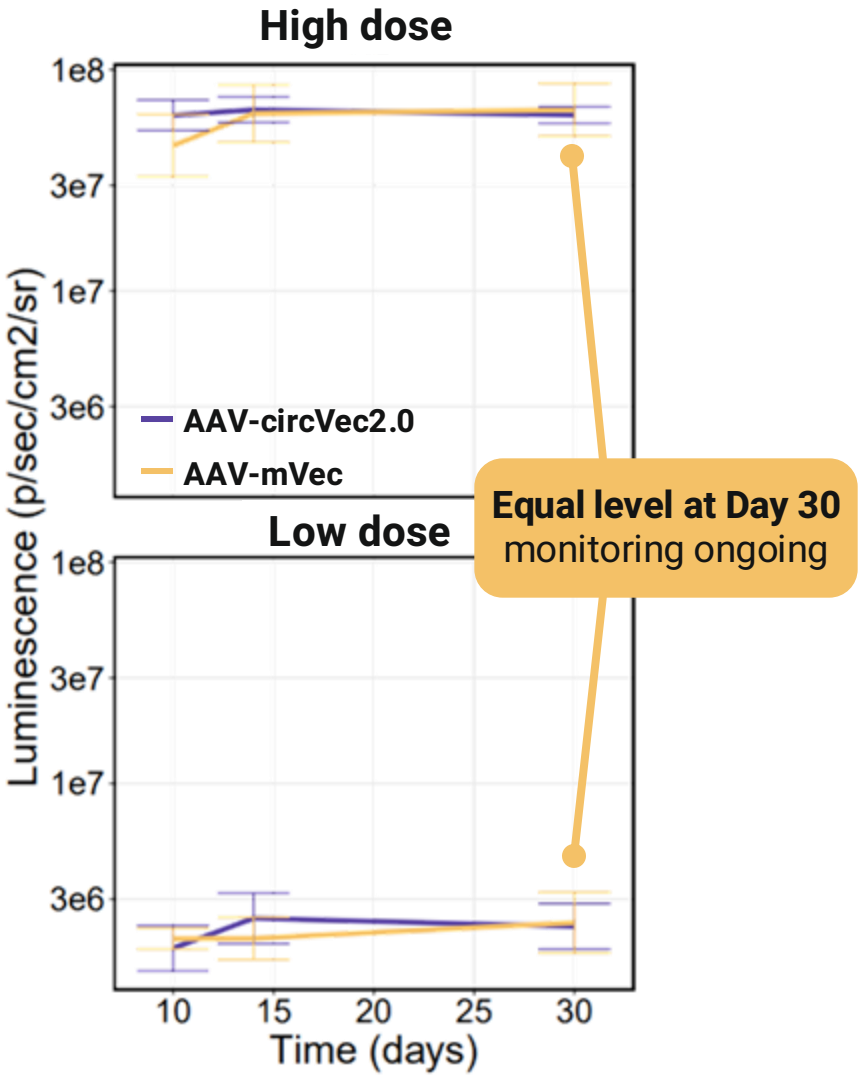
AAV9 circVec 2.0 vs. mRNA in vivo experiment ongoing: circVec functionality validated systemically





Experimental set-up

Vector:	AAV9, muscle-specific promoter
circVec version:	circVec 2.0
Payload:	Firefly luciferase (F-luc)
Mouse strain:	BALB/c
Delivery route:	Tail vein injection
Single injection, dose:	$1x10^{10}$ or $1x10^{11}$ viral genomes

Ongoing R&D activities aim to further evolve circVec platform and validate activity in new tissues in vivo

circVec platform

- Implement circVec 2.2 feature in 3.0 → **circVec 3.1**
- Set up **circVec 3rd generation in vivo testing**
- Implement **circVec 3.0** feature into **AAV vectors**
- **File patent(s)** to cover **circVec 3.0 design** feature

In vivo screening program

- Ongoing **circVec 2.1 in vivo** testing in **multiple tissues**
- **Testing of delivery** systems for **non-viral DNA-circVec** format, Certest and others
- Ongoing **AAV8-circVec 2.0 in vivo** testing in **brain**

Business Development

- **Entered / entering five gene therapy delivery collaborations**, data generation during next six months
- Select **1-2 internal lead programs,** and seek R&D **partnerships in adjacent areas** (during 2025)

4

circVec therapeutic application

5. Warrant exercise information

circVec is a platform that can be deployed in multiple disease areas and therapeutic settings

Initial focus

Gene therapy

High durability ´Remove & Replace´ concept for rare genetic disease

-

AAV and DNA format

Mid-term

Cell therapy

Non-integrating approach for safer, repeat dosable immune cell transduction

-

VLP-circRNA format

Long-term

Chronic disease

Durable expression of biologics for auto-immune and metabolic disease

-

AAV and DNA format

Lead target and disease to be prioritized based on data from ongoing in vivo program

circVec offers multiple modes-of-action (MoA) customizable to each specific target and disease

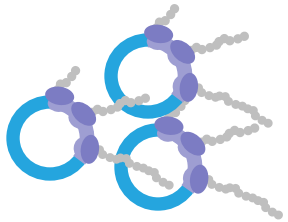
customized circVec cassette

2

Removal of mutant or pathogenic mRNA

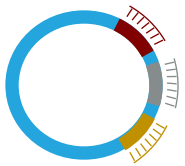
1

Best-in-class protein expression and durability



3

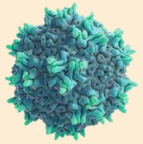
Neutralization of pathogenic miRNAs



circVec is a unique platform to build mono-, bi- or tri-modal therapeutic candidates tailored to maximize impact for each specific disease pathology

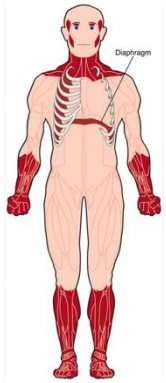
Gene therapy development plan

Modality and disease to be selected based on experimental data

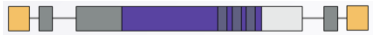
Therapeutic modality	Ongoing in vivo screening	Pipeline opportunities
 AAV-circVec	 Muscle	Myotonic and Limb-girdle dystrophy, Sarcopenia
 LNP-DNA circVec	 Heart	Fabry, Danon disease
Payload: Wild-type gene	 Lung	Cystic fibrosis, AATD
	 Brain	Canavan, Krabbe, Tay Sachs disease
	Payload: reporter gene	

Data expected during December-January

circVec lead muscular genetic disease targets

	Limb-Girdle muscular dystrophy (type 2)	Myotonic dystrophy (type 1)
Pathology	 **Progressive muscle-wasting in hip and shoulder** **Breathing and heart issues**	 **Adult onset muscle-wasting** **Prolonged muscle-contraction** **Issues in other organs**
No. of patients	**Estimated apx. 50,000 USA + EU**	**>100,000 USA + EU (symptomatic cases)**
circVec USP	**Best-in-class protein expression level and durability in muscle**	**First-in-class tri-modal activity**
Competition	**No approved therapies,** Sarepta, AskBio AAV gene therapy in clin.dev.	**No approved therapies**, mainly sub-optimal ASO/siRNA approaches in clin.dev

circVec R&D update summary



circVec 3.0

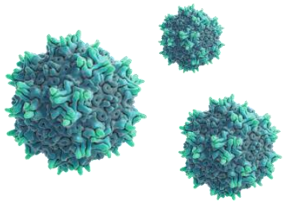
New circVec 3.0 generation has been established

- 27x / 4x improvement vs. circVec 1.1 / 2.1, respectively
- circVec 1.1 was 1.5-2x better than mRNA *in vitro*, depending on time and context

circRNA half-life

>600 hours circRNA half-life in vivo vs. <10 hours for mRNA

- >75x prolonged RNA durability
- Peak expression after 38 days vs. 2 days for mRNA



AAV

circVec-AAV vector functionality validated in vivo

- circVec 2.0-AAV on par with mRNA-AAV already after 30 days
- Expression level advantage expected to manifest over time

Muscular dystrophies

Two muscular dystrophies identified as circVec opportunities

- Data suggest robust circVec advantage in muscle tissue

5

Warrant exercise

Exercise of warrants issued in connection with the rights issue completed in July 2024

Exercise period	**4 – 18 December**
Exercise price	**NOK 0.60**
Total number of warrants	**13,864,852**
Maximum gross proceeds	**NOK 8.32m**
Publication of outcome	**19 December**
Share settlement	**Subscribed shares will be transferred as soon as practically possible given holiday period**

See Circio webpage for full details regarding warrants and exercise process

How to exercise warrants

1

- **Complete and send signed warrant exercise form in PDF format to email: contact@circio.com**
- **The exercise form is available on the Circio webpage**

2

- **Request the holding bank to transfer the warrants to: Nordea VPS account number 06001.2222.000**

3

- **Transfer the subscription amount to Circio by 18 December:**

Account holder: Circio Holding ASA

SWIFT: NDEANOKK

Account no.: 6005.06.60667

IBAN#: NO5160050660667

Subscription amount equals:

Number of warrants x NOK 0.60

Payment must be received by:

16:30 CEST on 18 December 2024

See Circio webpage for full details regarding warrants and exercise process