circio

Disruptive circRNA technology for genetic medicine

Dr Erik Digman Wiklund – CEO

Redeye Regenerative Medicine/Cell Therapy Event
14 February 2024

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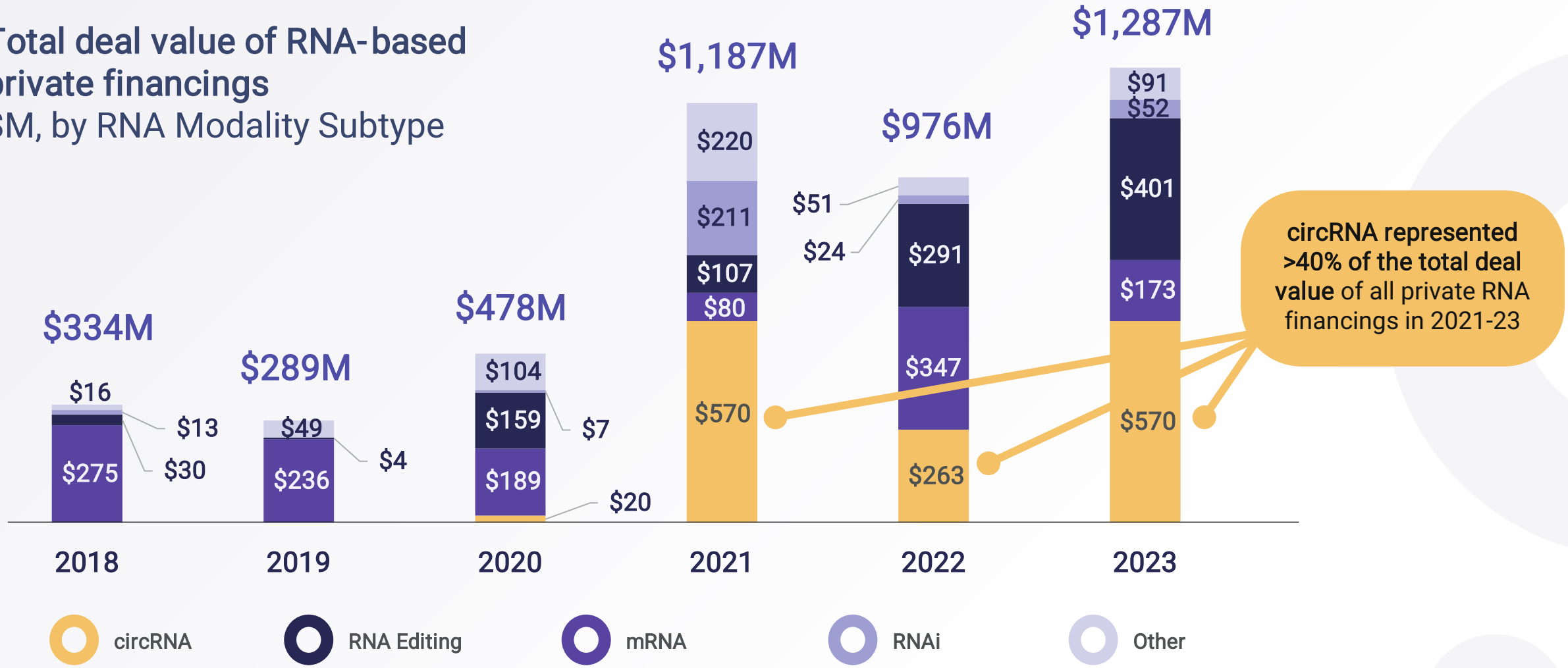
Circio overview

2. circVec gene therapy

RNA financing has flowed from mRNA towards circular RNA during 2021-23

Total deal value of RNA-based private financings
$M, by RNA Modality Subtype



circRNA represented >40% of the total deal value of all private RNA financings in 2021-23

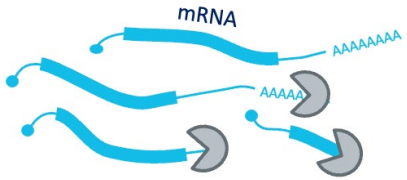
Source: BioEquity

Note: Other includes ASOs, saRNAs and tRNA private financing deals

Circular RNA (circRNA) is a novel disruptive RNA format

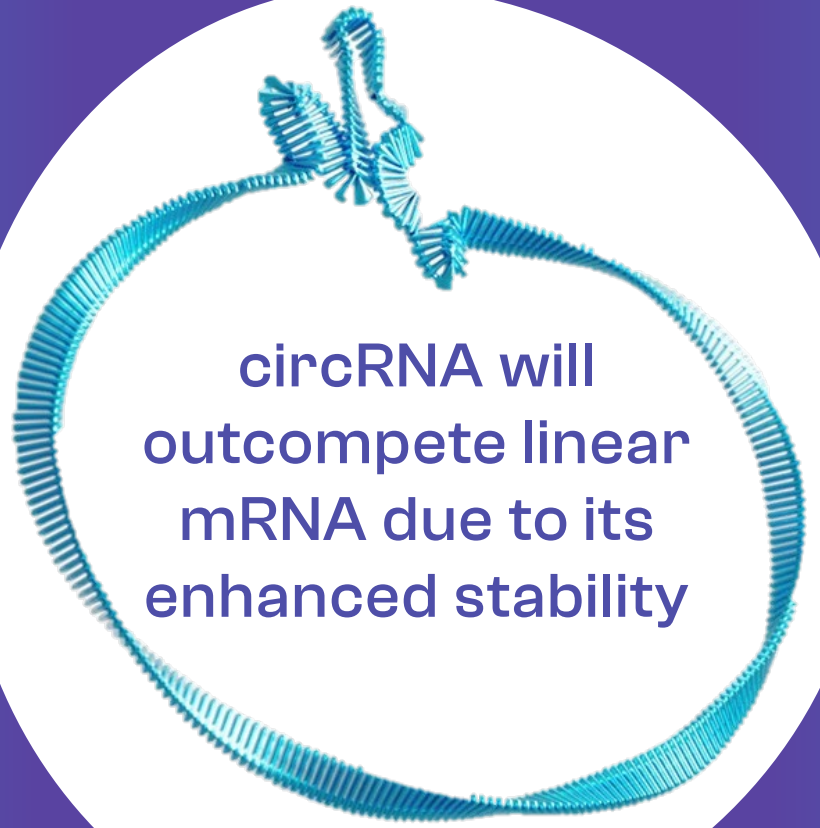
Extended RNA durability

15x half-life vs. mRNA



microRNA sponging

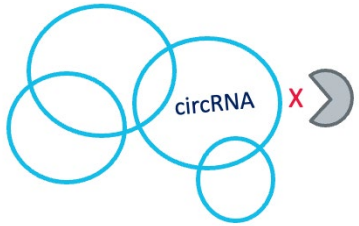
mRNA is destabilized by microRNAs



circRNA will outcompete linear mRNA due to its enhanced stability

Higher protein expression

5x translation rate vs. mRNA



Modular & multi-functional

Enables ´remove & replace´ strategy

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

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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

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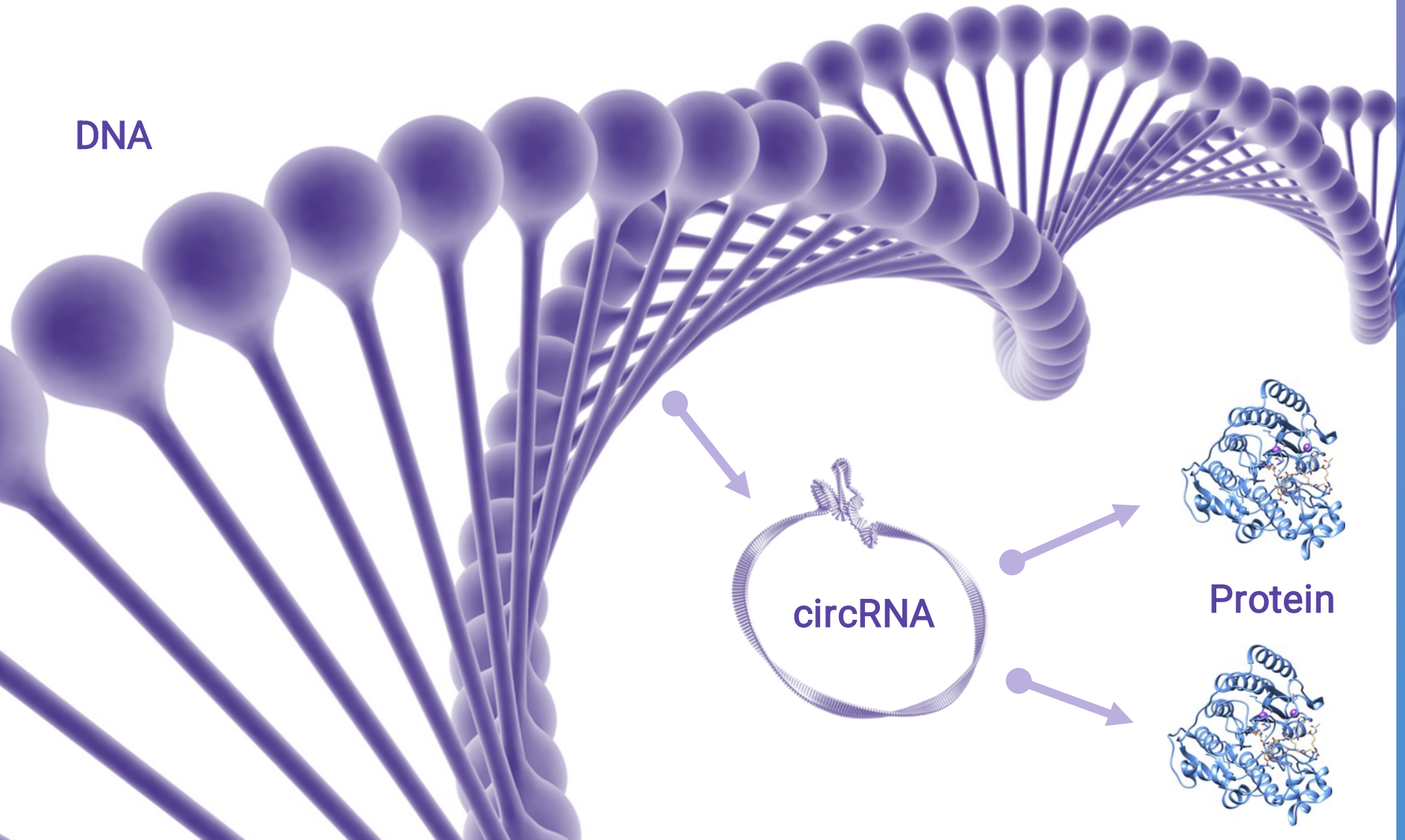
The circVec expression system: making circRNA from a DNA starting point



Protein

circVec
DNA or viral vector

Inject

circRNA biogenesis

Intra-cellular protein expression

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

Increased expression level

Prolonged durability

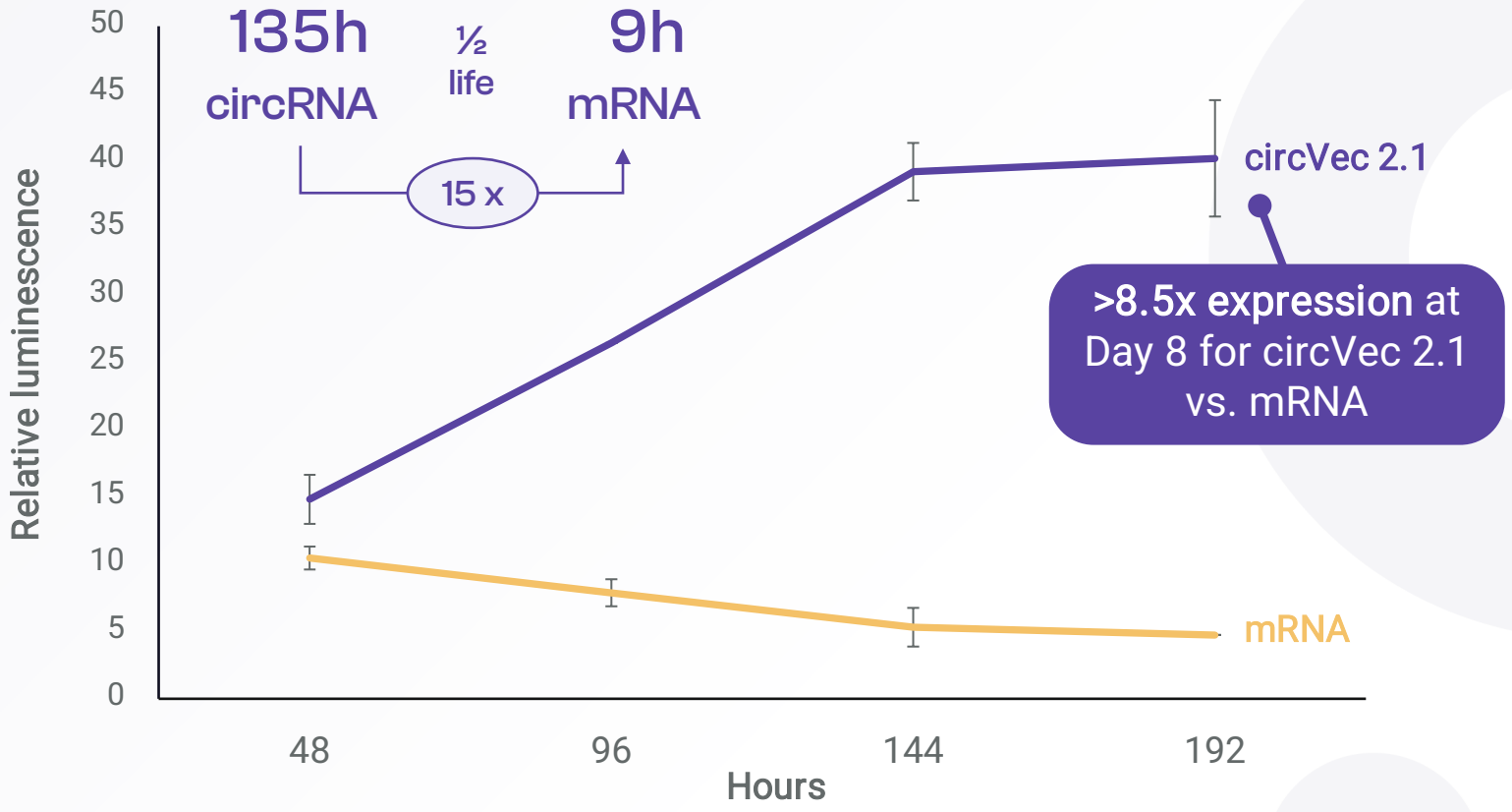
Enhanced therapeutic potency

"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"

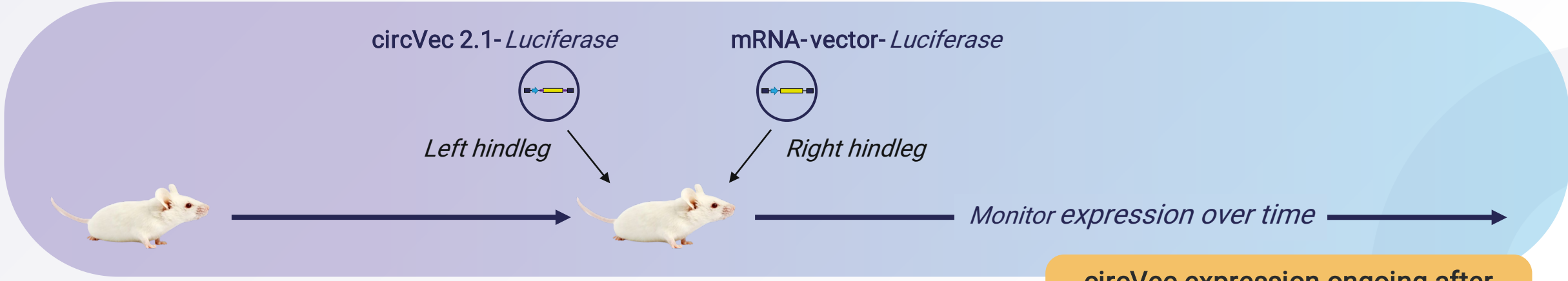
Dr. Alex Wesselhoeft

Scientific founder
oRNA Therapeutics

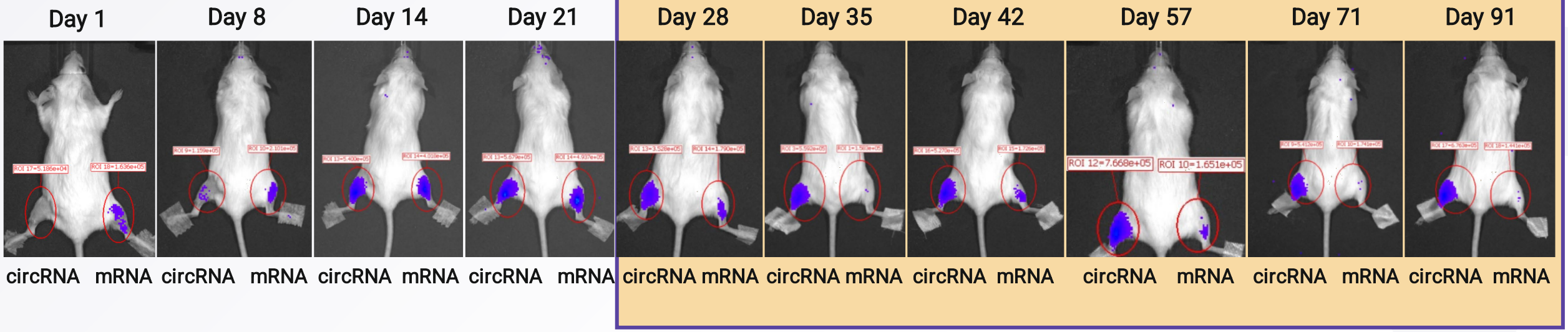
circVec vs. mRNA luciferase reporter expression; time course



In vivo reporter pilot study: circVec 2.1 outperforms mRNA over time



circVec expression ongoing after 3 months; mRNA very low >1 month



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

15 payloads validated

- Intra-cellular, membrane-bound and secreted proteins
- Immunological proteins, vaccine antigens, reporters

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

- Melanoma, lung, liver and muscle cell types
- Mouse tissue: liver and muscle

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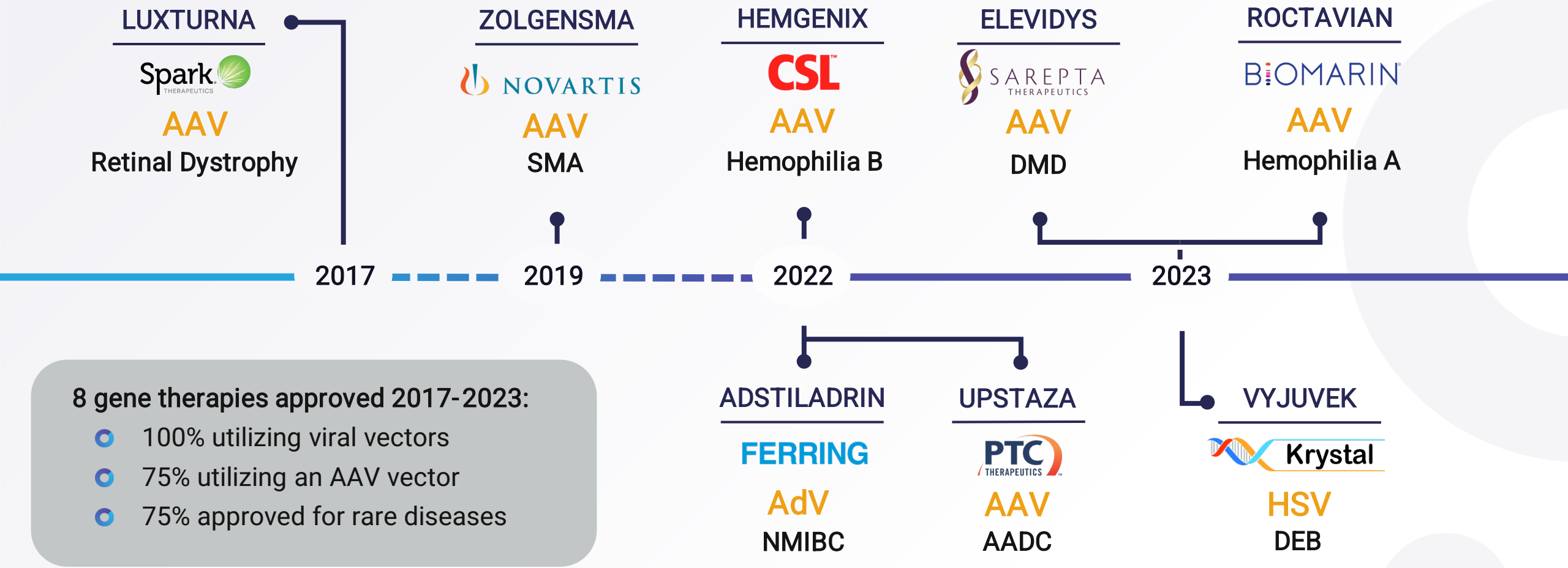
circVec gene therapy

circVec can improve the potency of current gold-standard gene therapy:

6 out of 8 approved gene therapies are AAV-based



8 gene therapies approved 2017-2023:

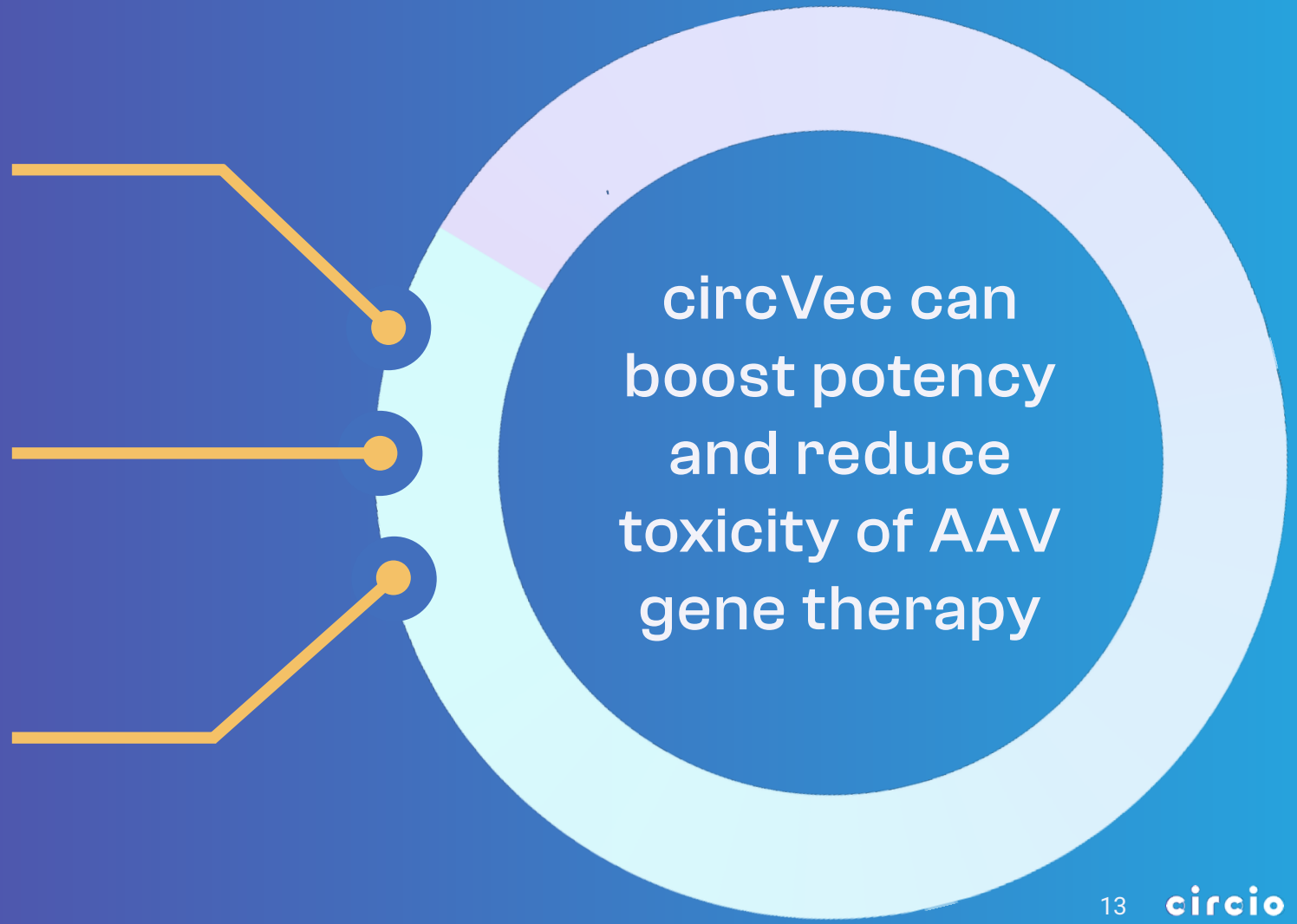
- 100% utilizing viral vectors
- 75% utilizing an AAV vector
- 75% approved for rare diseases

High dosing requirement is a substantial shortcoming for current AAV-based gene therapy

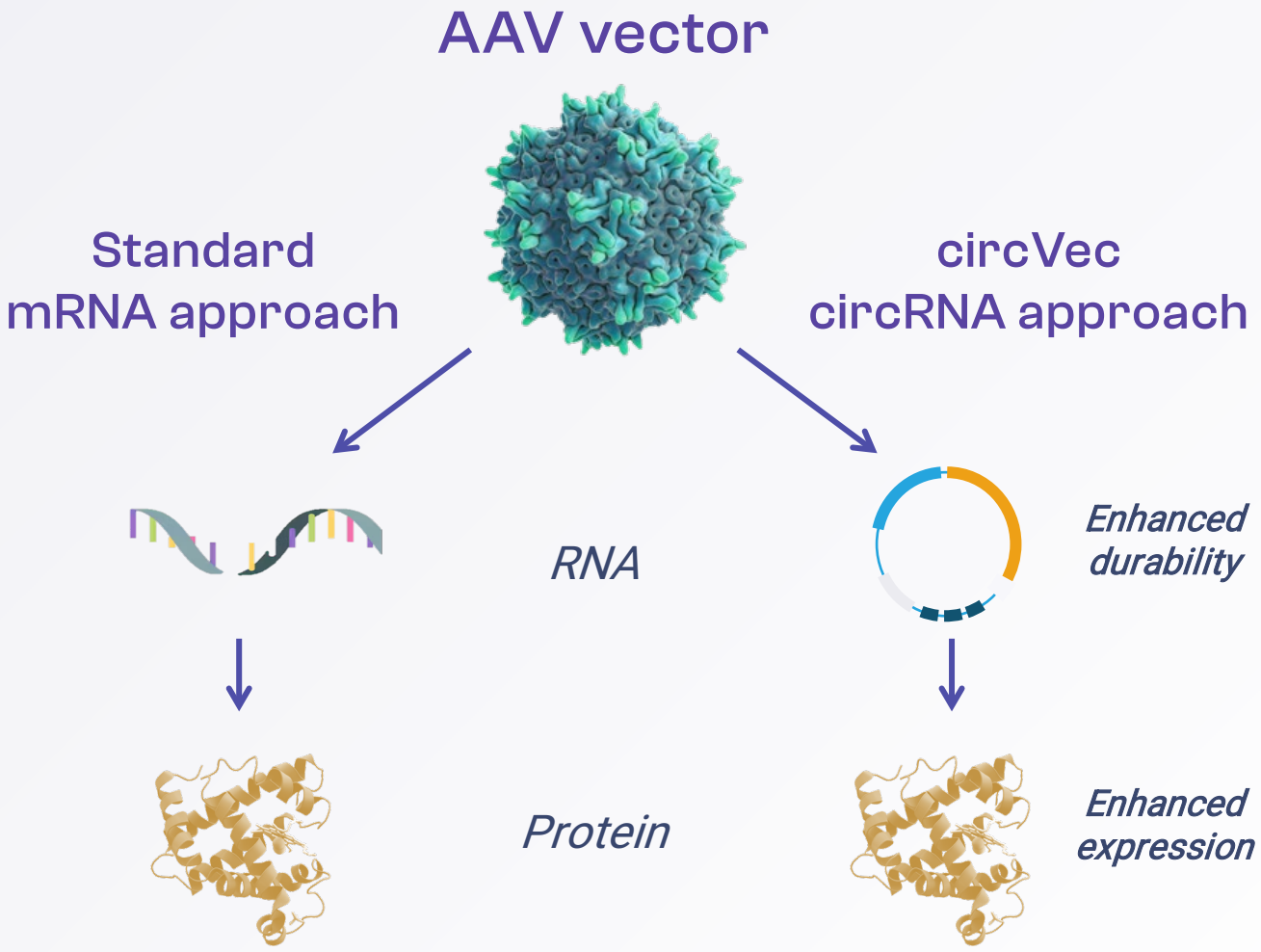
Safety issues
Liver toxicity, innate immunity

High dose = high immunogenicity
No repeat dosing

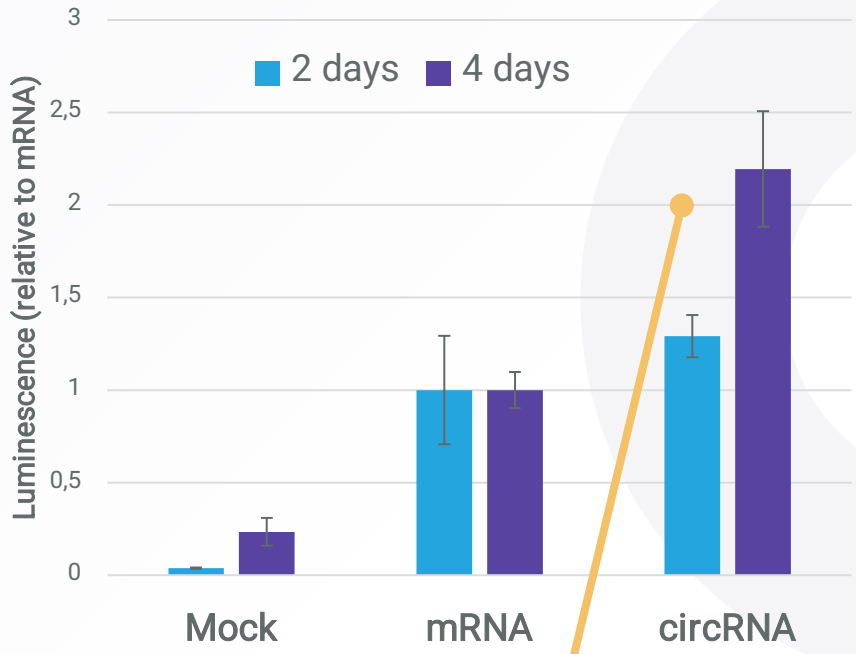
Manufacturing cost
10^{14} – 10^{15} VPs per dose



circVec can be deployed to enhance AAV gene therapy



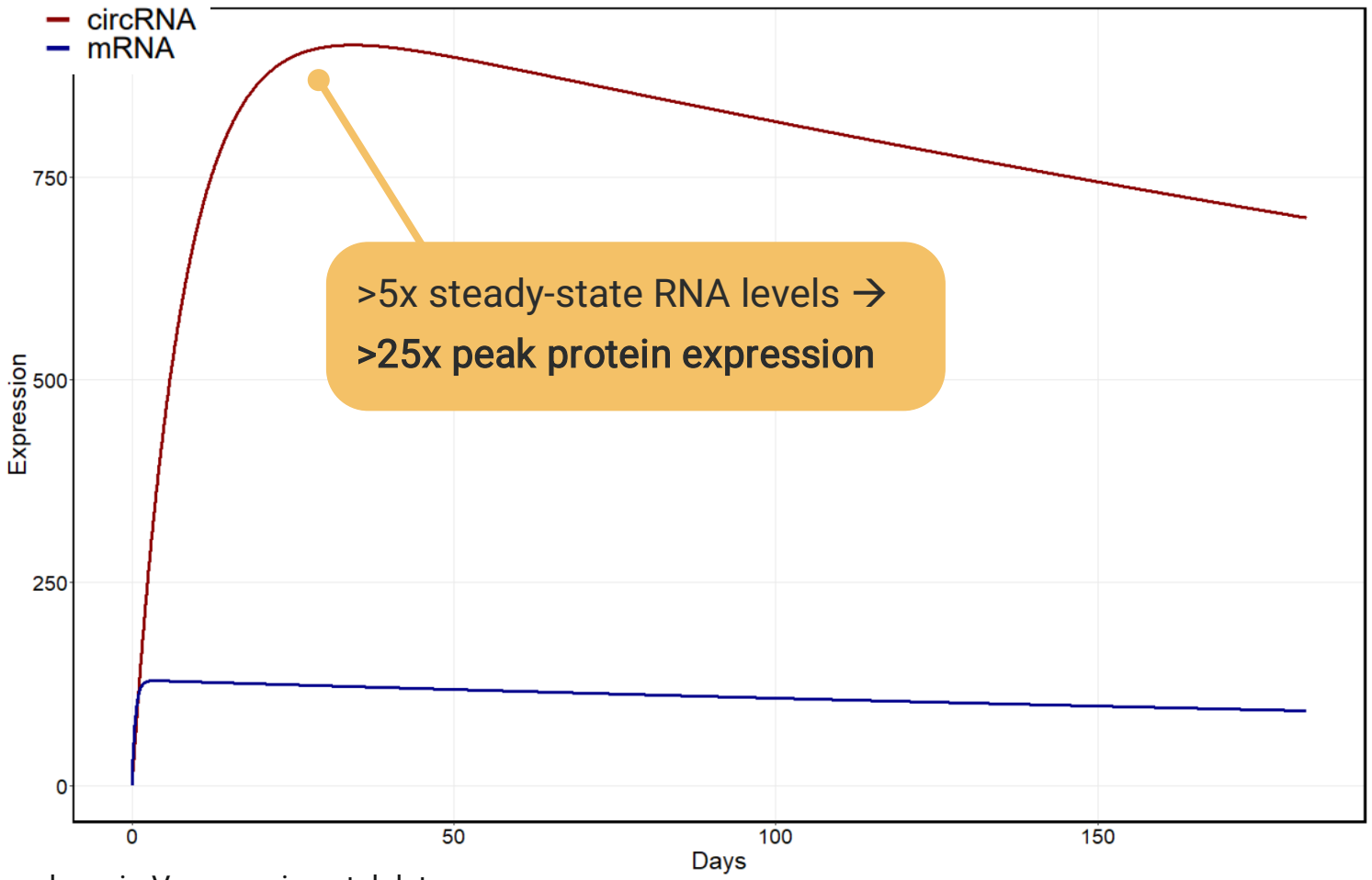
AAV protein expression, luminescence



Enhanced circVec AAV expression vs. mRNA-AAV after 4 days *in vitro*

circVec-based AAV therapy can improve potency and solve the high dosing issue for AATD

Temporal AAV-based RNA expression dynamics; circRNA vs. mRNA



* Based on circVec experimental data

Input assumptions for simulation:

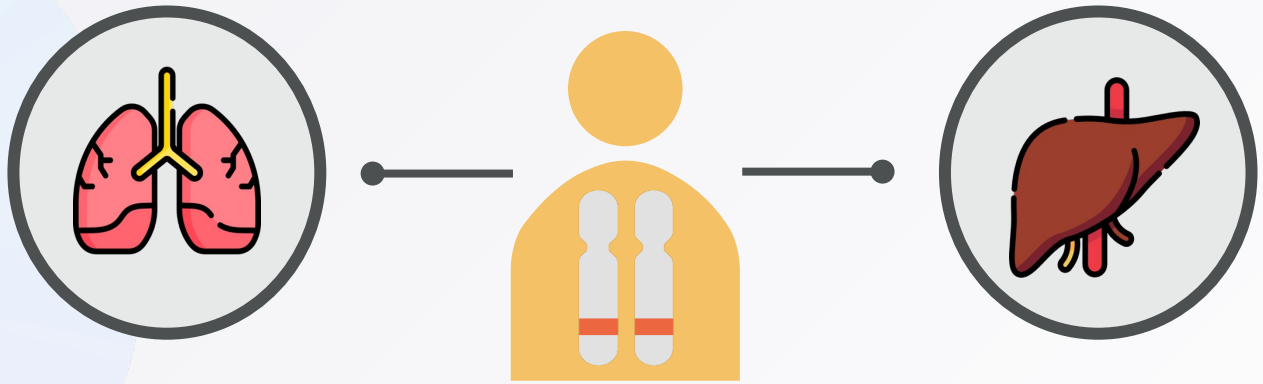
Non-dividing target cells

AAV half-life:	365 days
mRNA production:	10 molecules / hr
mRNA half-life:	9 hrs *
circRNA production:	5 molecules / hr
circRNA half-life:	135 hrs * *15x mRNA ½-life*

*→ circRNA translation **5x mRNA rate*** gives >**25x peak protein** expression*

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

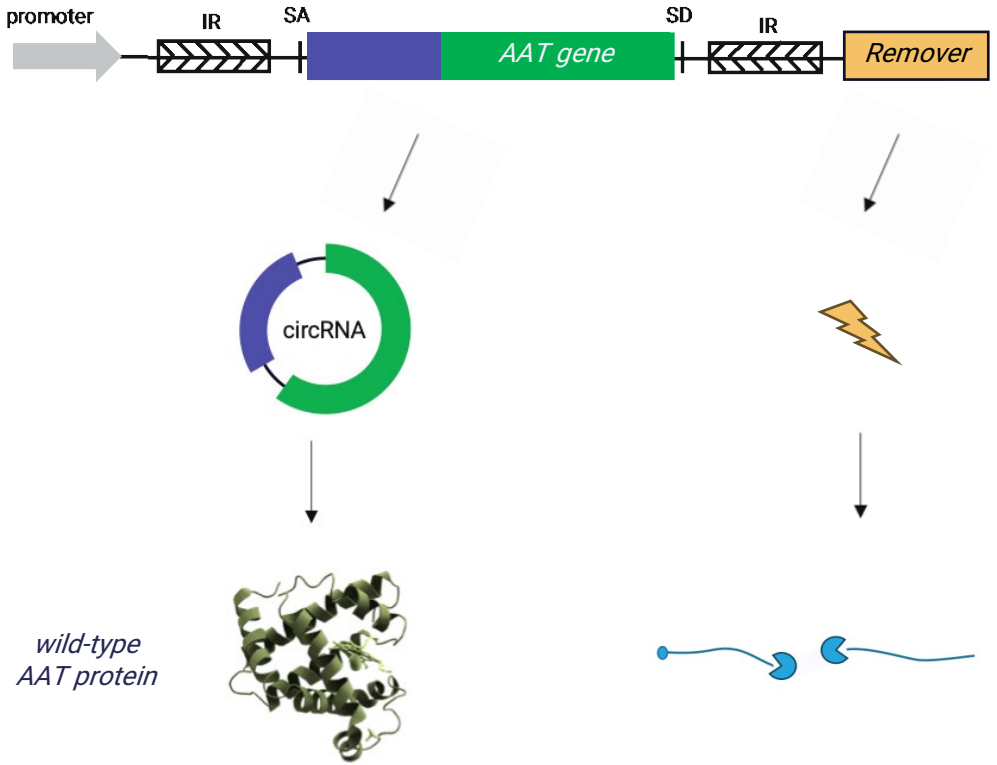
- **Replacement therapy** with an alpha-1 proteinase inhibitors
- **Weekly IV infusions**
- **Bronchodilators** and **inhaled steroids** used for mild symptoms

Liver-associated AATD

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

circVec ´Remove-&-Replace´ gene therapy for AATD

circVec 2.1 AAT R&R design

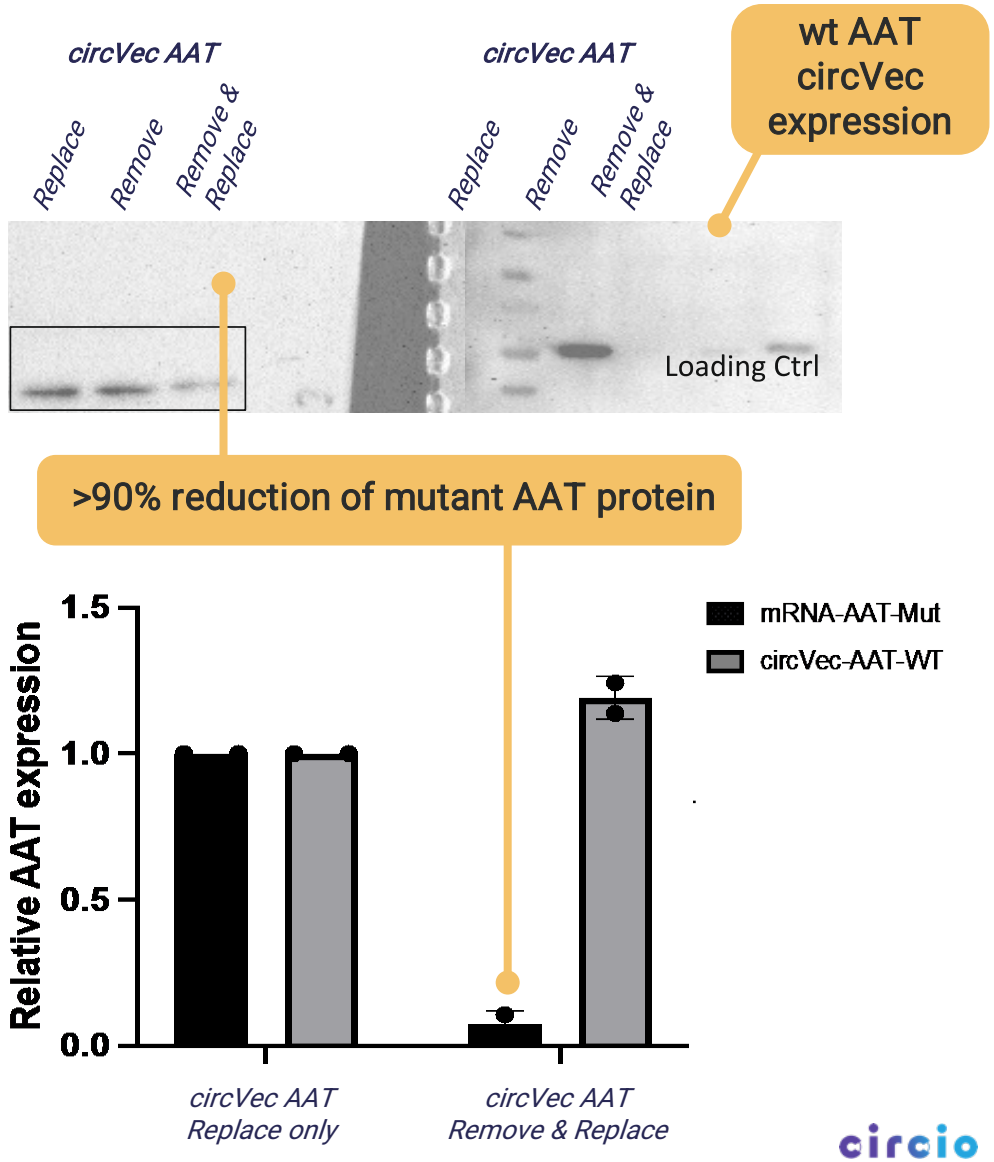


Replace

Expression of functional AAT protein

Remove

Degradation of mutant AAT mRNA



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Circio executive summary

Disruptive technology

- Circular RNA (circRNA) is a **next generation mRNA format**
- Proprietary circVec expression system has **potential to disrupt the genetic medicine and vaccine fields**

Circio´s unique position

- Deep expertise: the **discoverers of circRNA** work for Circio
- Vector-approach with **substantially improved durability**
- **Unique ´remove & replace´ concept for AATD gene therapy**

Value drivers

- Aiming to enter several **partnering deals during 2024-2025**
- Targeting to **enter the clinic** with **AAT gene therapy in 2026**