circio

Disruptive circRNA technology for genetic medicine

Company presentation
January 2024

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Circio investment case – executive summary

Disruptive technology

- Circular RNA (circRNA) is a next generation mRNA format
- Potential to disrupt the genetic medicine and vaccine fields

Circio´s unique position

- Deep expertise: the discoverers of circRNA work for Circio
- Differentiated approach to circRNA, with substantially improved durability and unique ´remove & replace´ functionality
- Proprietary circVec expression system with platform potential

Value drivers

- Aiming to enter several partnering deals during 2024-2025
- Targeting to enter the clinic with first in-house candidate in 2026

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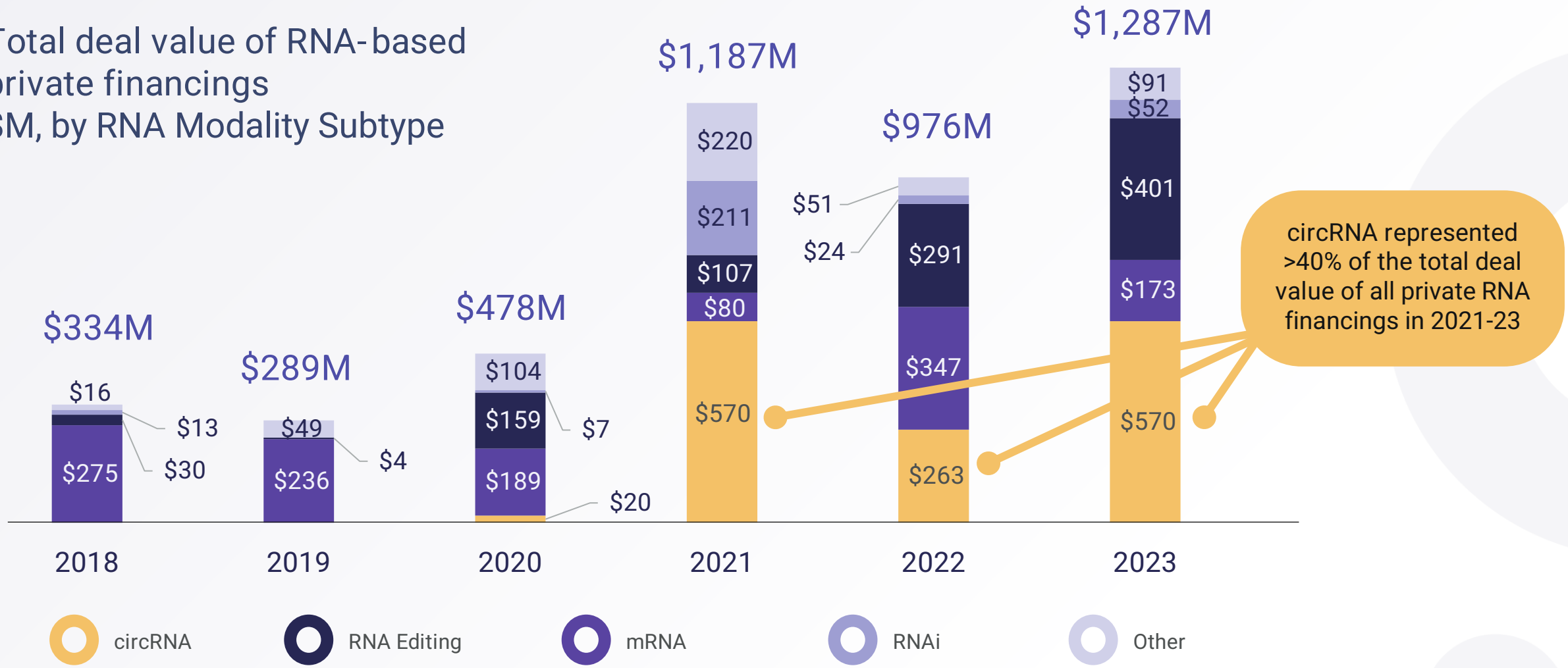
Circio overview

2. circVec R&D strategy

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



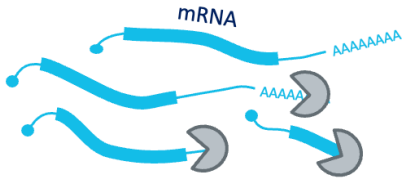
Source: BioEquity

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

Circular RNA (circRNA) is a novel disruptive RNA format

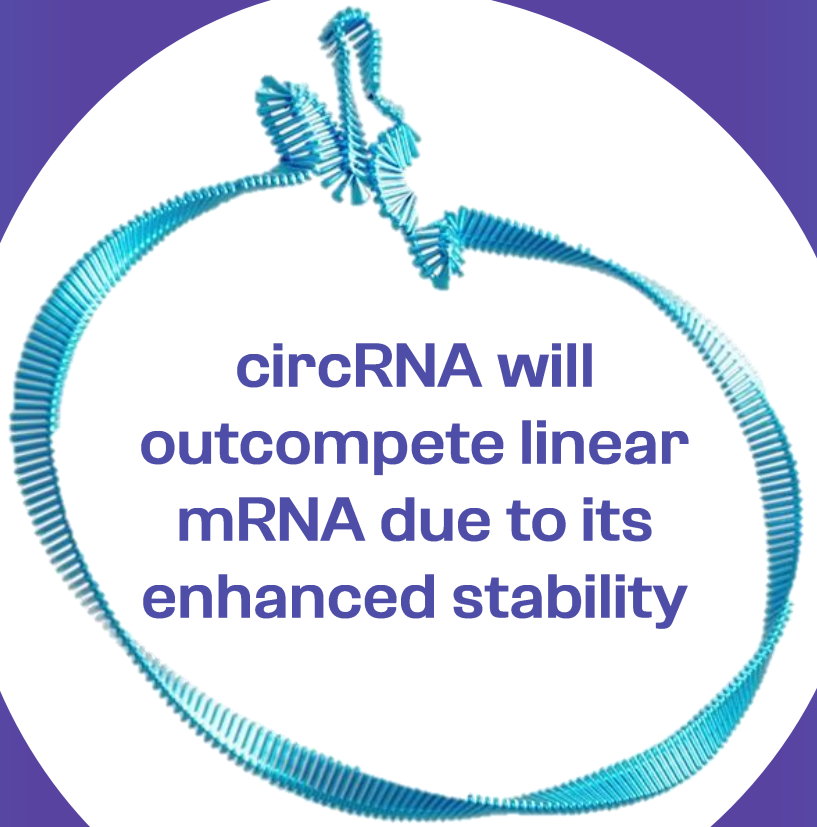
Extended RNA durability

15x half-life vs. mRNA



microRNA sponging

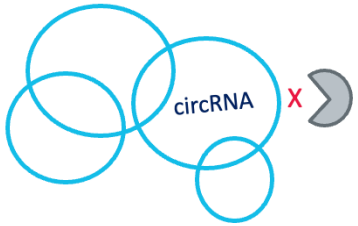
mRNA is destabilized by microRNAs



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 discoverers of circRNA are in the Circio leadership team

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

Full team in place with optimal 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

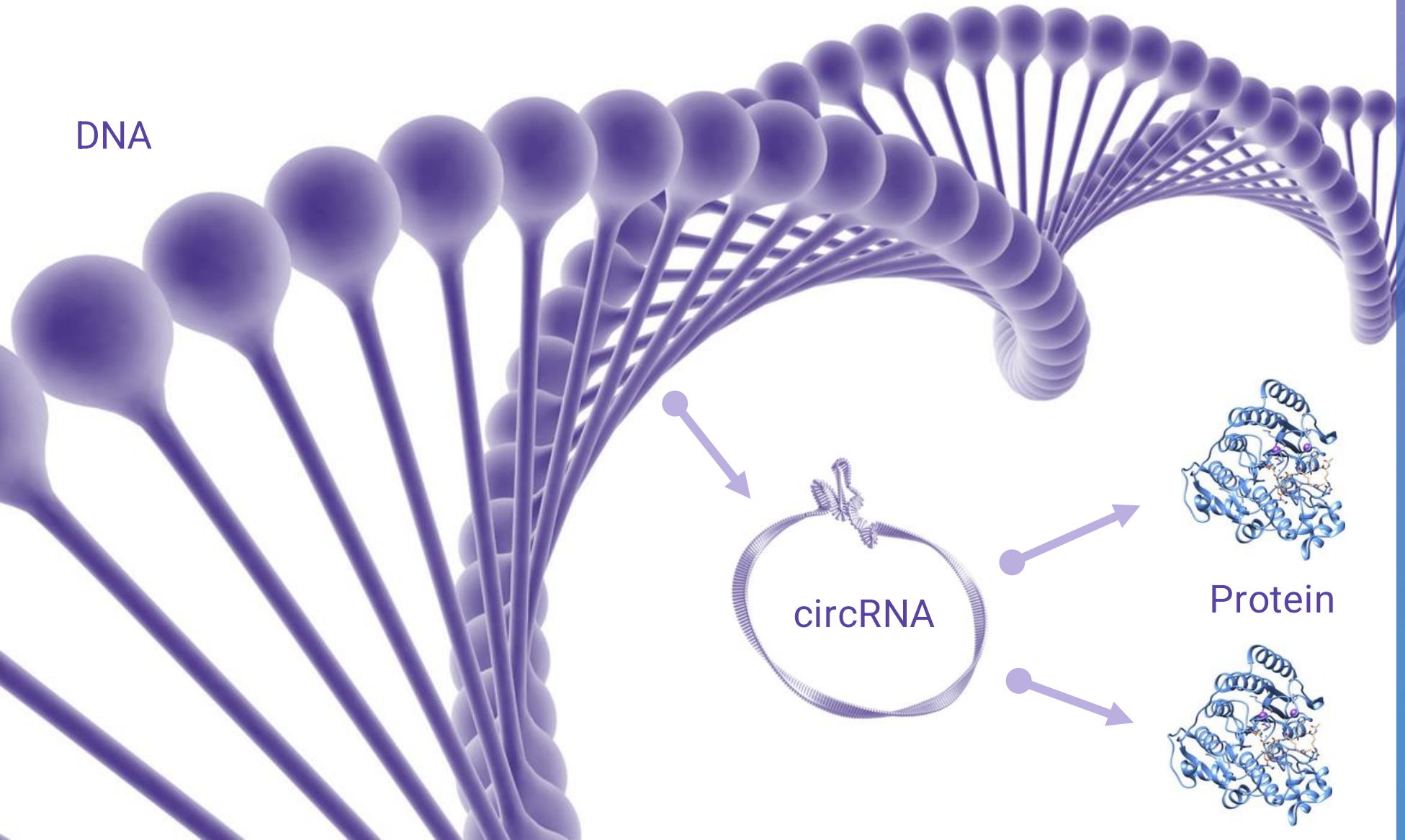
COO

Operational execution

CV:

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

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



circRNA

Protein

circVec
DNA or viral
vector

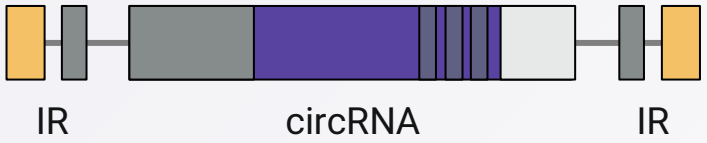
Inject

circRNA
biogenesis

Intra-cellular
protein expression

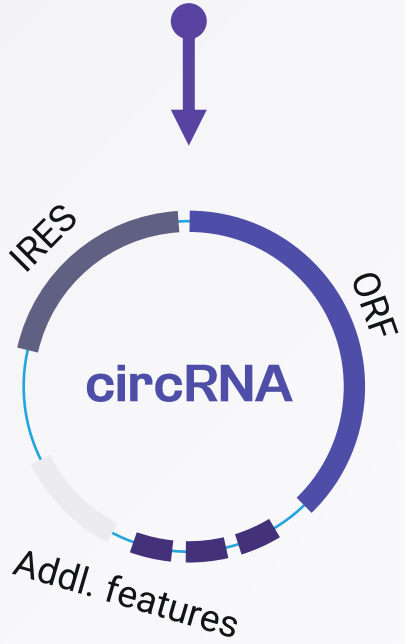
circVec is a modular genetic cassette for circRNA-driven protein expression

circVec - DNA



Genetic cassette

+



Multi-functional circRNA

- Best known circRNA biogenesis rate
- ´Remove & replace´ functionality
- Vector agnostic – viral or DNA
- IP protected

- Flexible, modular design
- 15x extended half-life vs. mRNA
- 5x enhanced translation rate vs. mRNA
- Anti-miRNA functionality

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

Increased expression level

Prolonged durability

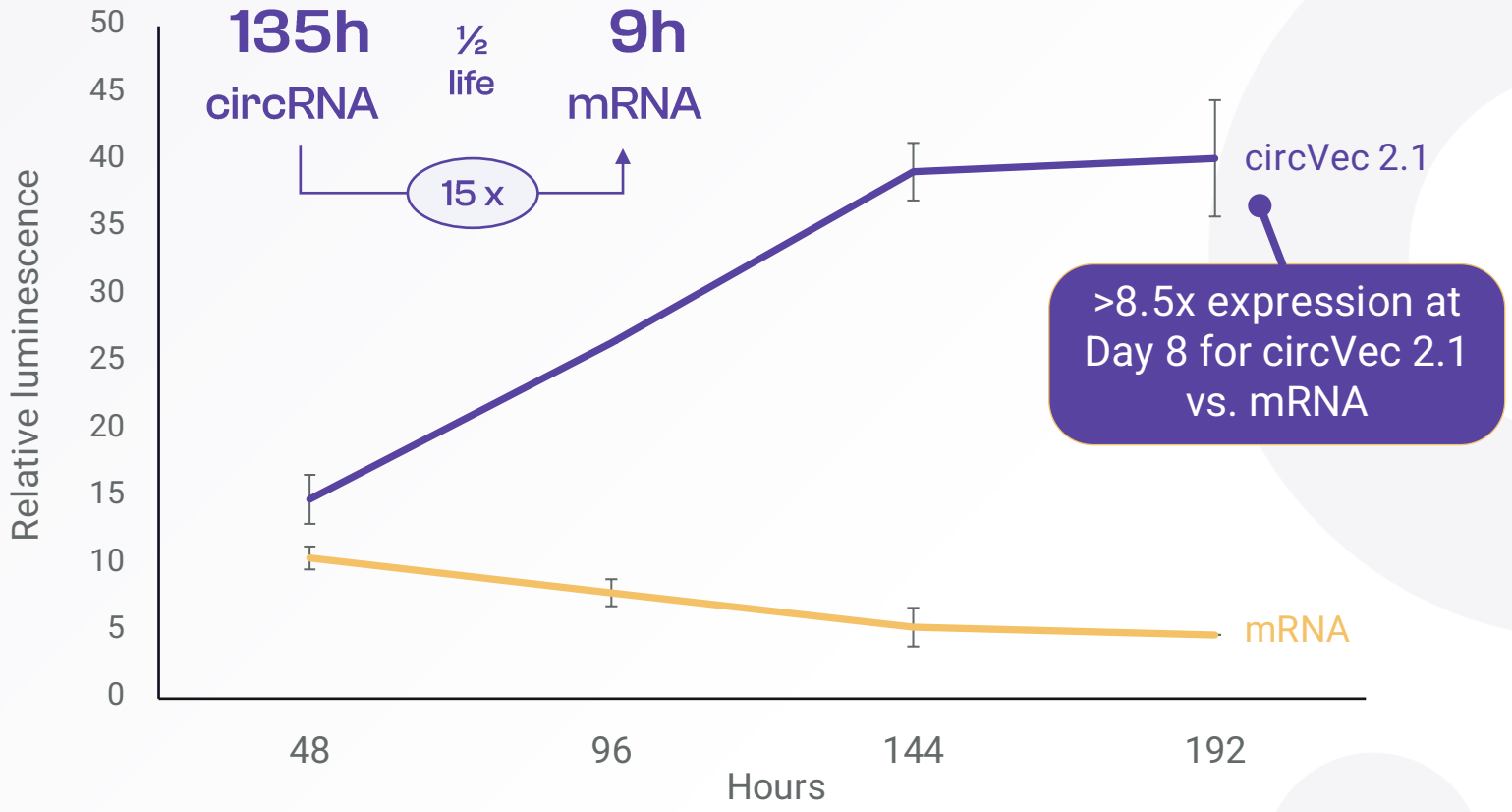
Enhanced therapeutic potency

"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"

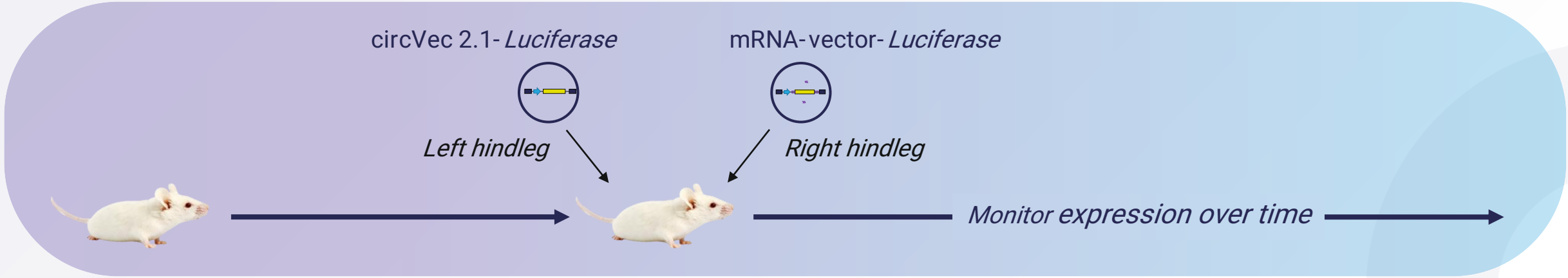
Dr. Alex Wesselhoeft

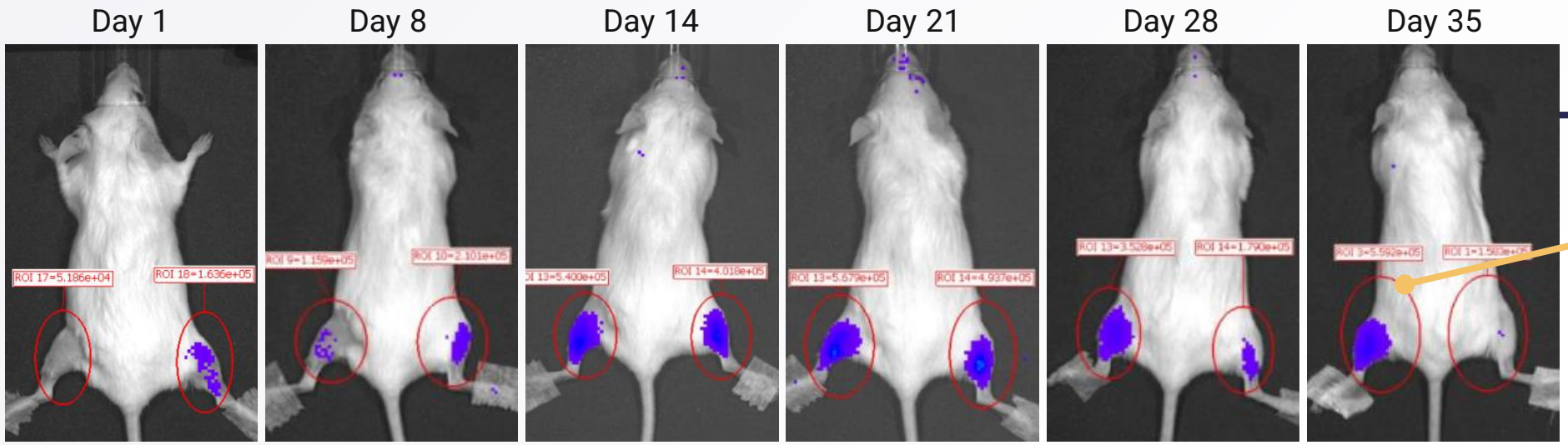
Scientific founder
oRNA Therapeutics

circVec vs. mRNA luciferase reporter expression; time course



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





Real-time monitoring ongoing

Increasing circVec expression: highest at Day 35, mRNA lowest at Day 35

Strategy to develop a new class of circRNA medicines and create value from unique circVec system

Build platform

- Test and validate applicability of circVec system
- Identify and select lead applications and targets
- Build robust IP portfolio

Demonstrate efficacy

- Demonstrate superiority of circVec system vs. gold standard for selected lead applications
- Design and test targeted circVec candidates *in vivo*
- Go / No Go for continued development or partnering

Strategic partnerships

- Capitalize on platform potential to partner early for specific applications (e.g. vaccines)
- Access complementary technology to address major unmet medical needs in genetic disease

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circVec R&D Strategy

Major opportunities identified for the circVec platform in gene therapy and vaccines

Current focus areas

Rare disease

´Remove & replace´ concept with durability and safety advantages

-

Broad pipeline potential

Vaccines

Enhanced potency, single dose vaccine concept with simplified administration

-

Early partnering option

Cancer gene therapy

Efficient and durable expression of therapeutic proteins in solid tumors

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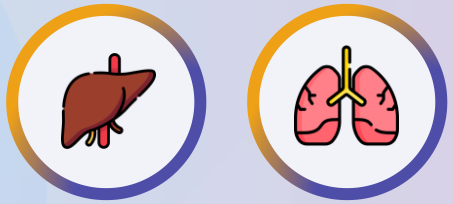
Expansion opportunity

Designed for intra-cellular circRNA supply driving strong and durable protein expression

AATD and Urea Cycle Disorders identified as lead circVec rare disease targets

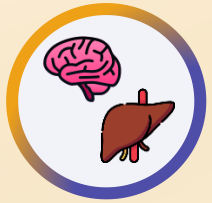
Lead Indication



Alpha-1 Antitrypsin Deficiency

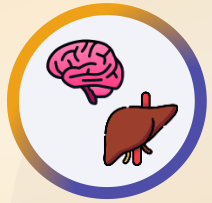
AATD

Second priority



Ornithine Transcarbamylase Deficiency (OTCD)

Citrullinemia Type I (CTLN1)



Argininosuccinate Synthetase Lyase Deficiency (ASLD)

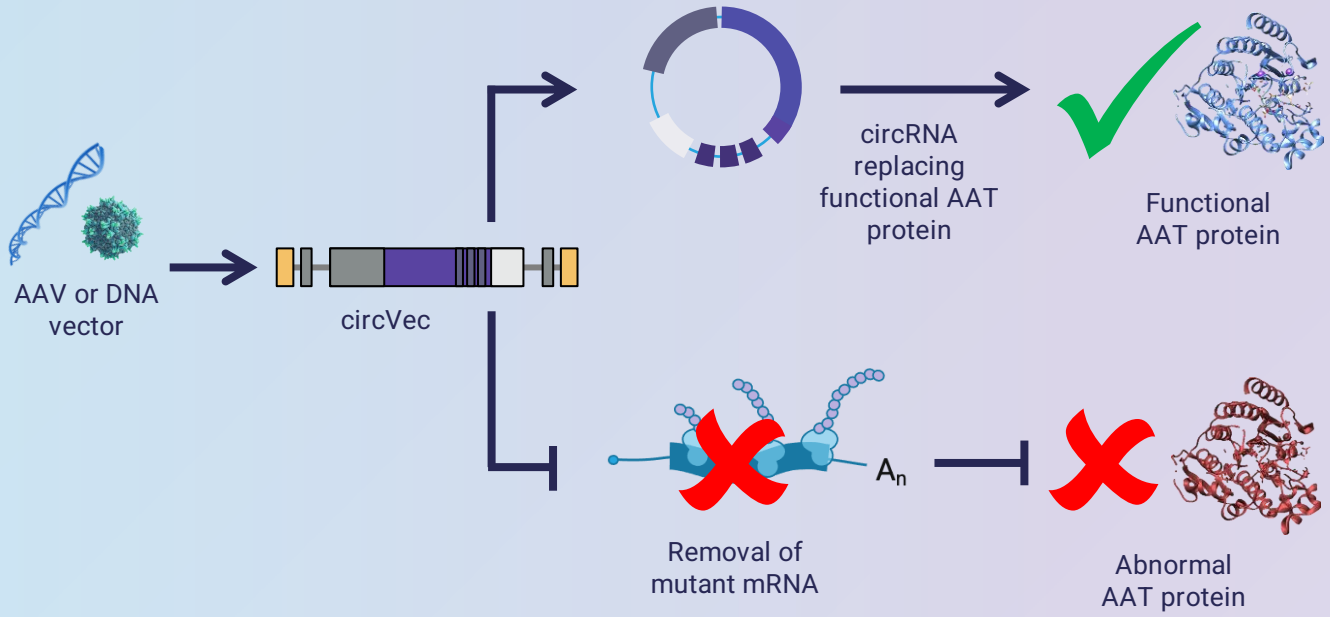
Urea Cycle Disorders (UCDs)

Incidence:	**EU 120k US 75k**	**EU 12k US 8k**
Treatment options:	**Enzyme replacement** **No approved gene therapy**	**Gene therapy, approved for one variant only**

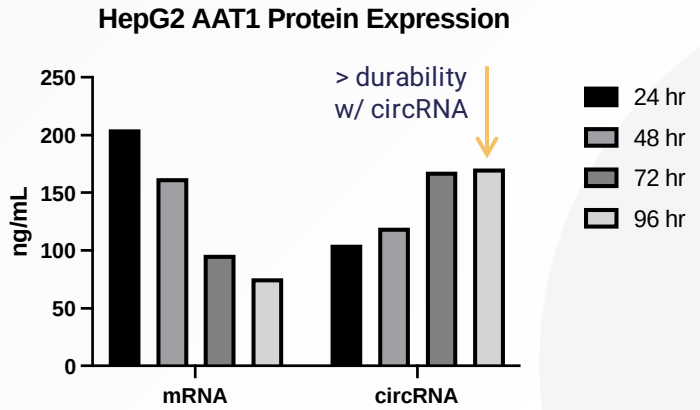
Unique ´remove & replace´ concept for AATD

Depleting mutant form and replenishing functional protein by circVec

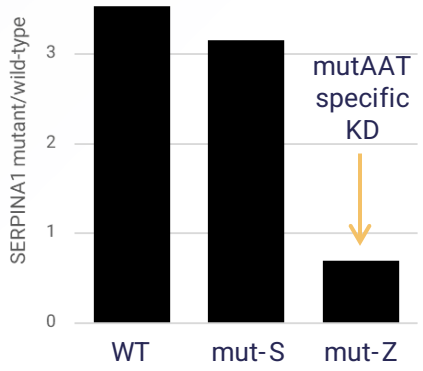
- *reverses toxic protein accumulation in liver and restores normal function in lung*



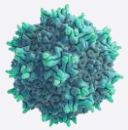
circVec v1.0 AAT expression in liver cells



circVec mutAAT knock-down



circVec will be deployed in both viral and synthetic DNA vector formats for therapeutic applications

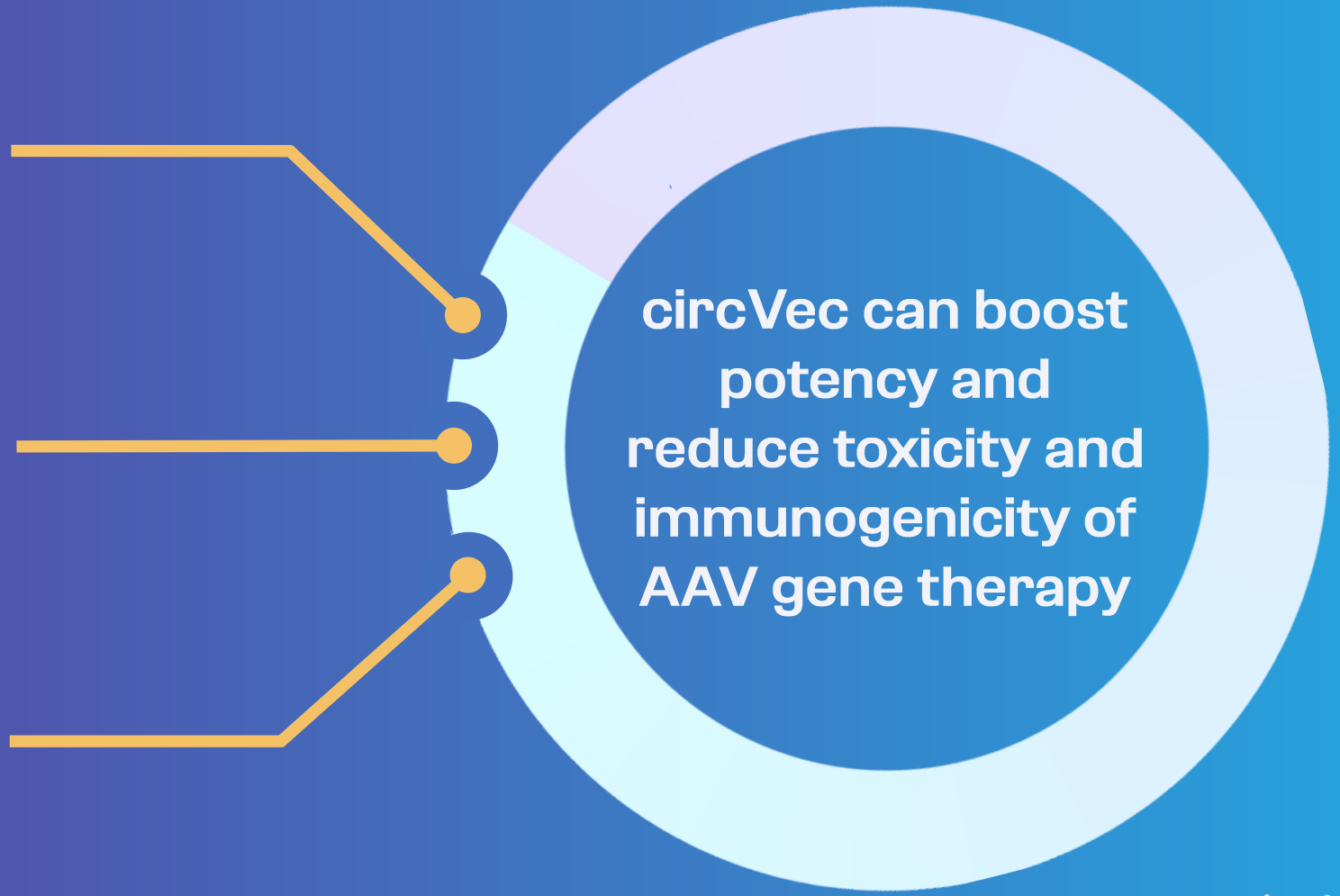
	Viral		Synthetic DNA	
	 AAV	 Adenovirus	DNA format 1 	DNA format 2
Application	• Gene therapy, incl. AATD	• Vaccines • Oncology	• Gene therapy, incl. AATD • Vaccines	• Gene therapy • Cell therapy
Aim	• Improved expression and reduced dosing vs. mRNA AAV	• Single-dose vaccine • Therapeutic protein delivery 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*	

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

Safety issues
Liver toxicity, innate immunity

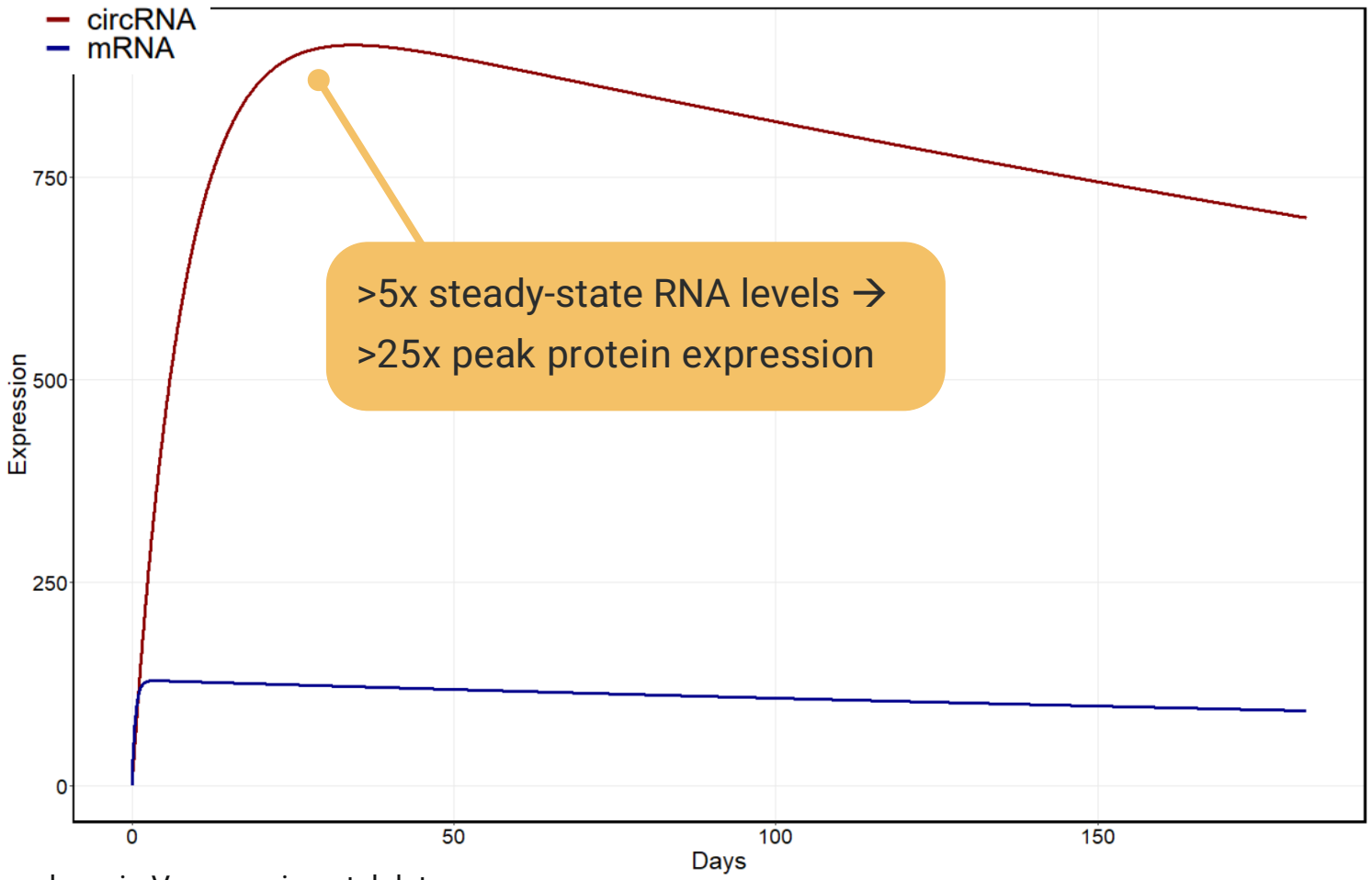
High dose = high immunogenicity
No repeat dosing

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



circVec-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

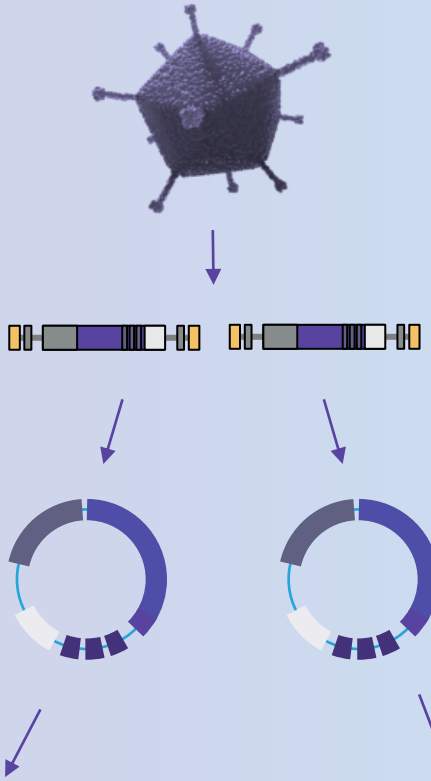
→ circRNA translation 5x mRNA rate gives >25x peak protein expression*

circVac: high potency viral vaccine format

circVac
replication-deficient
AdV vector

circVec inserts
>7kb cargo capacity

1-2 circRNAs
2-6kb in size



Durable antigen
expression

Immune response
booster

Development plan & target indication

- Major infectious diseases, incl. influenza, shingles, malaria
- Establish single dose vaccine concept
- Out-license technical concept for clinical development following pre-clinical PoC

Upcoming milestones

4Q´23:	COVID Spike circVac 1.0 *in vivo* data
1Q´24:	circVac 2.0 *in vivo* Spike data
1H´24	circVac-2.0 *in vivo* Flu data

Circio has a unique position in the circRNA field

- Circio is the only significant player in the DNA-format circRNA space

- Enhanced durability and protein expression from circRNA is expected to translate into lower dosing of DNA-format applications, which may solve both potency, toxicity and cost challenges facing current gold-standard gene therapy

- Vector-expressed circRNA has the potential to become the preferred format for any DNA-based therapeutic in the future
  - *Just as synthetic circRNA is expected to become the preferred format for long RNA-based therapeutics in the future*