



# 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

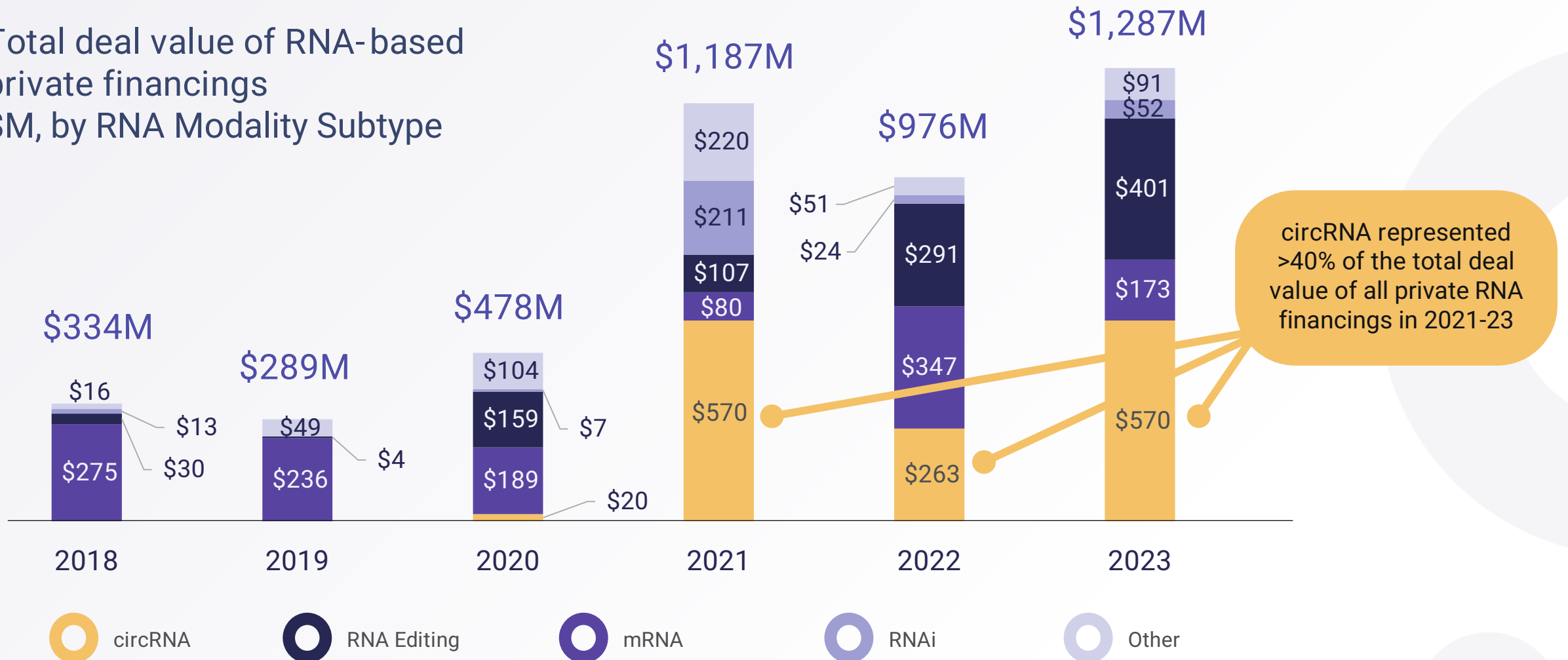


## Value drivers

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

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

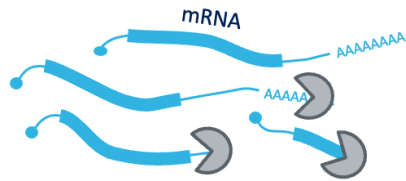
Total deal value of RNA-based private financings  
\$M, by RNA Modality Subtype



# Circular RNA (circRNA) is a novel disruptive RNA format

## Extended RNA durability

*15x half-life vs. mRNA*



## microRNA sponging

*mRNA is destabilized by microRNAs*

## Higher protein expression

*5x translation rate vs. mRNA*



**circRNA will  
outcompete linear  
mRNA due to its  
enhanced stability**

## 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



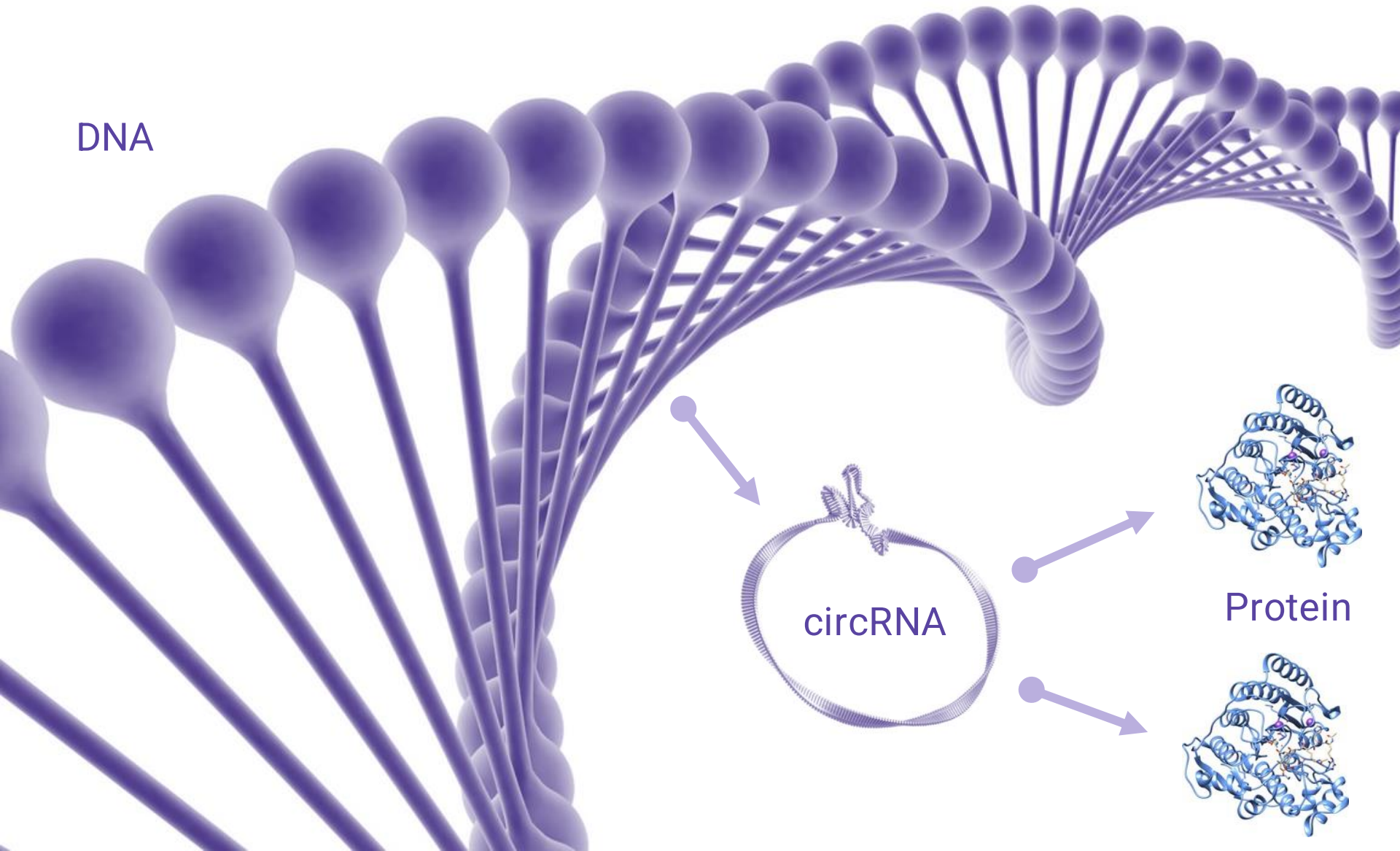
**Ola Melin**  
**COO**

Operational  
execution

*CV:*

- BS Biochemical eng.
- Big pharma and biotech manufacturing, clinical and commercial

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



circVec  
DNA or viral  
vector

*Inject*

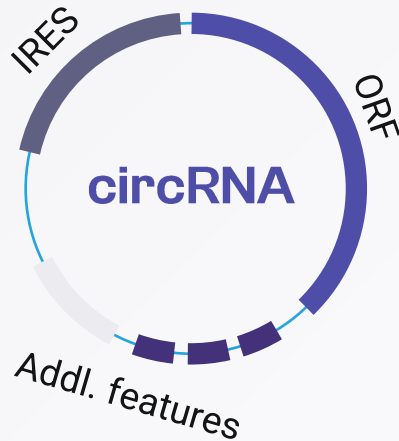
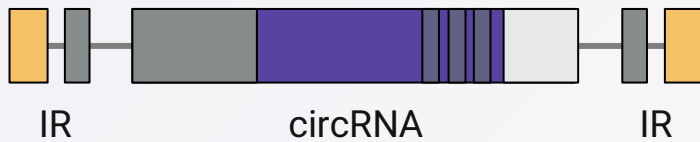
circRNA  
biogenesis

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

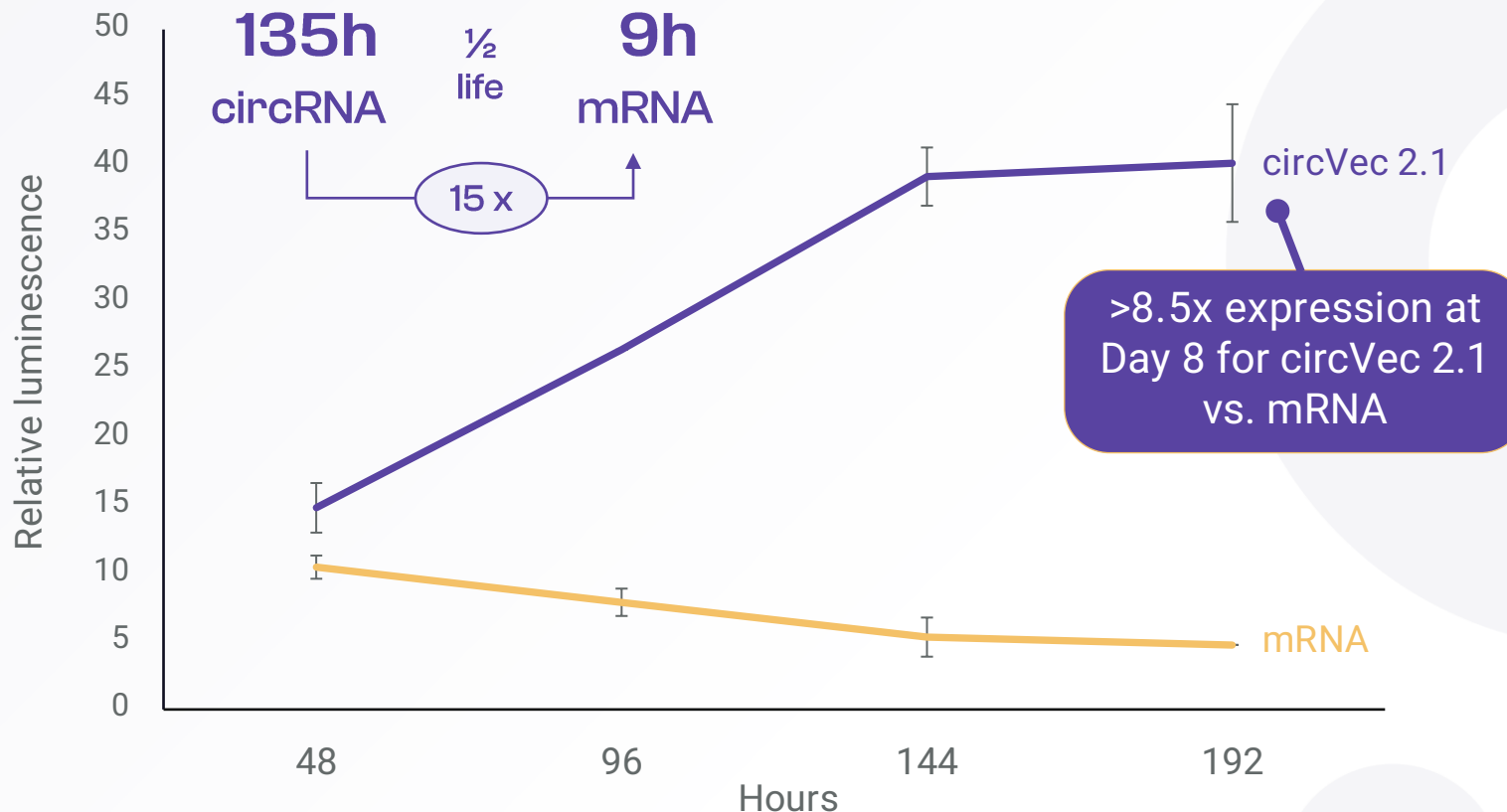
Prolonged durability

Enhanced therapeutic potency

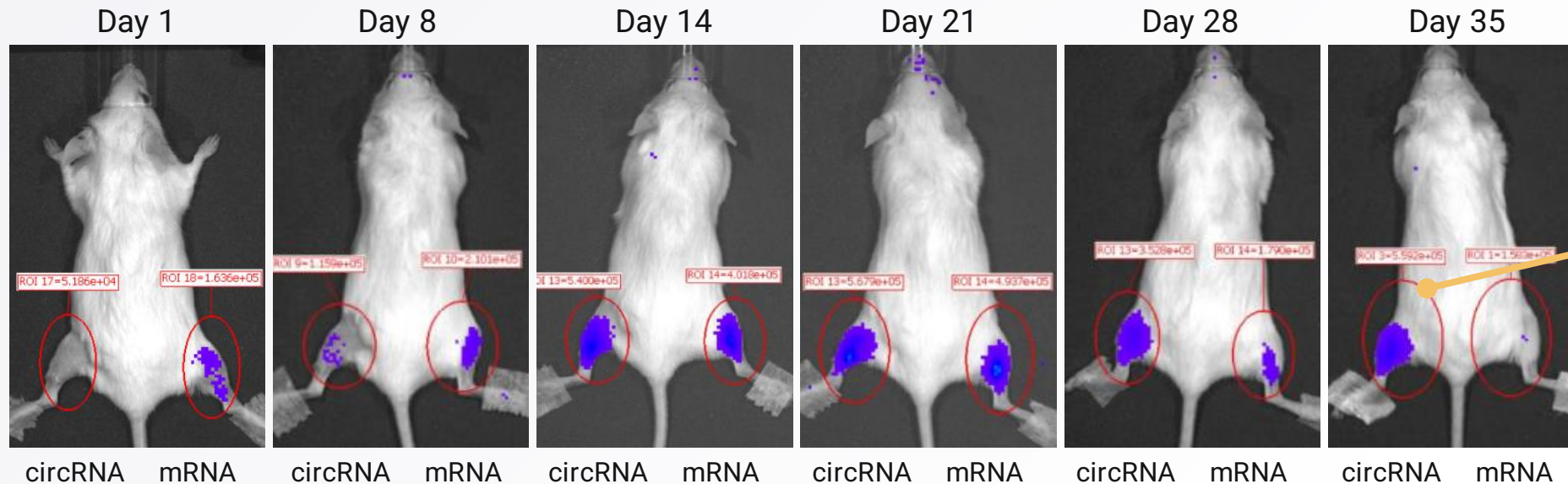
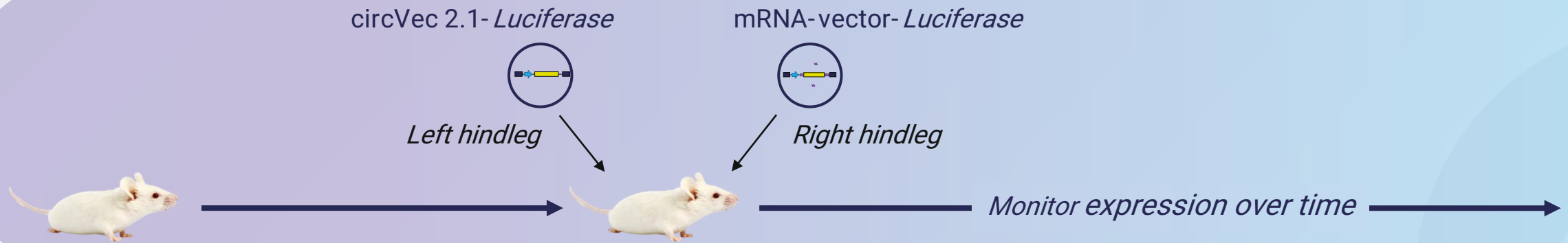
*“Due to its significant advantages, circRNA systems can be expected to replace mRNA-based expression for DNA format therapeutics in the future – just as synthetic circRNA can be expected to replace current mRNA formats”*

Dr. Alex Wesselhoeft  
Scientific founder  
oRNA Therapeutics

circVec vs. mRNA Luciferase reporter expression; time course



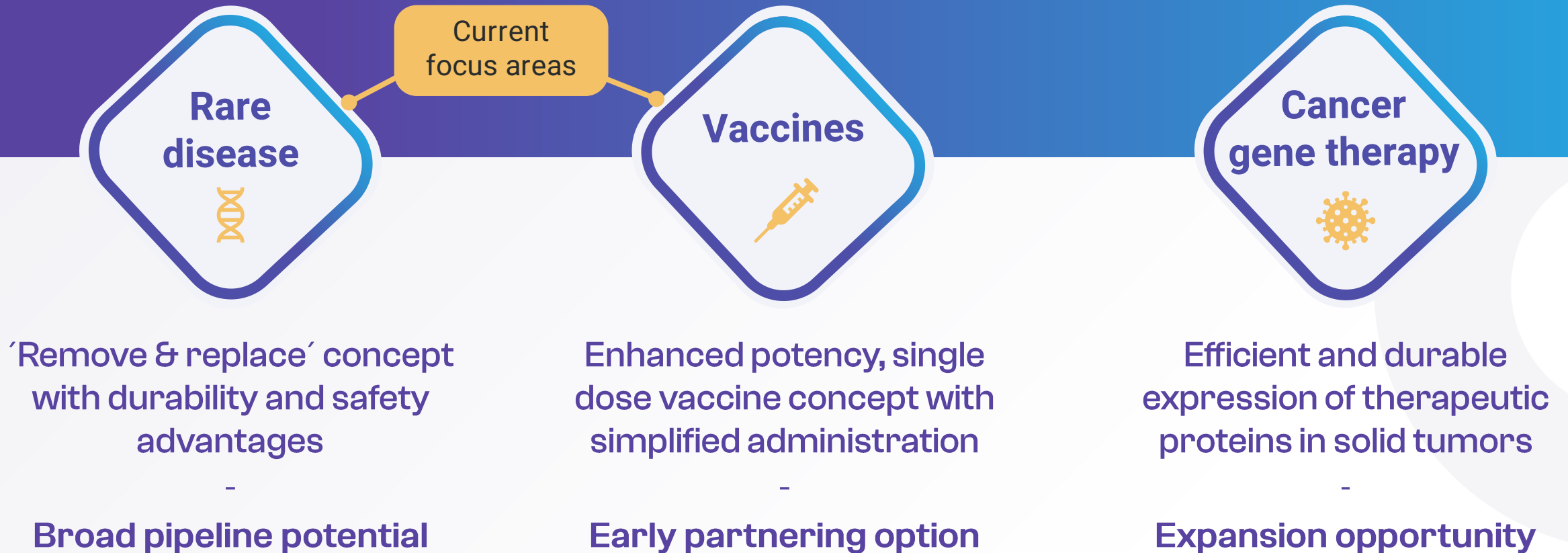
# *In vivo* reporter pilot study: circVec 2.1 outperforms mRNA over time



*Real-time monitoring ongoing*

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

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

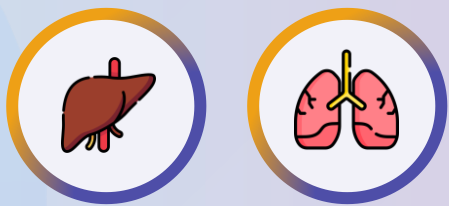


Designed for intra-cellular circRNA supply driving strong and durable protein expression



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

Lead  
Indication



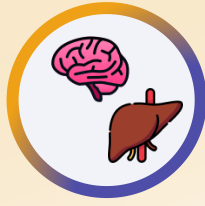
Alpha-1 Antitrypsin  
Deficiency

**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**

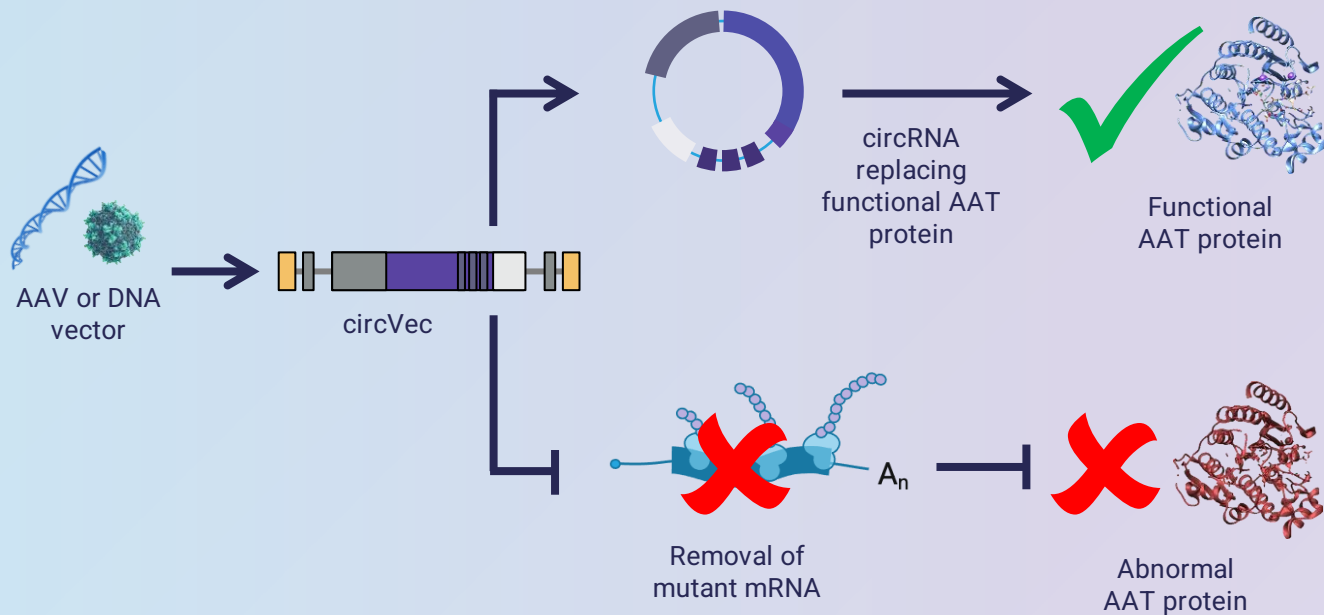
*Treatment options:* **Enzyme replacement**  
**No approved gene therapy**

**Gene therapy, approved for  
one variant only**

# Unique 'remove & replace' concept for AATD

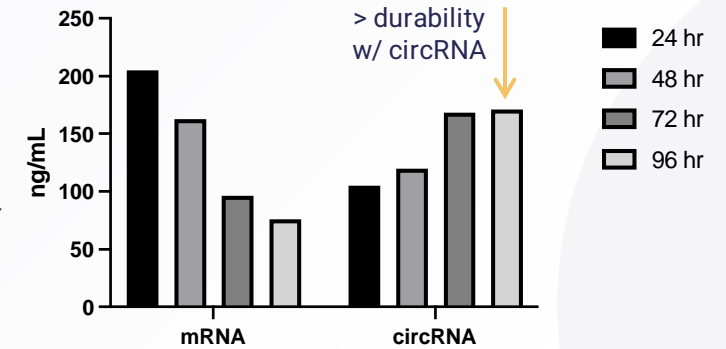
Depleting mutant form and replenishing functional protein by circVec

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

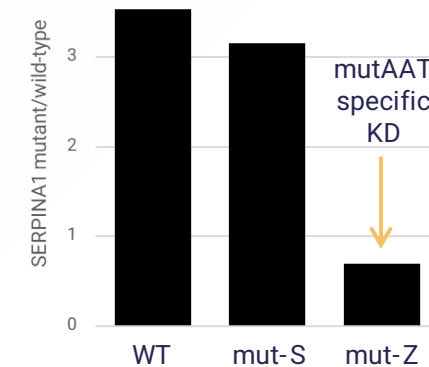


circVec v1.0 AAT expression in liver cells

HepG2 AAT1 Protein Expression



circVec mutAAT knock-down



# 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*



## 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