



circio

Disruptive circRNA technology for genetic medicine

Company presentation
13 June 2024

Important notice and disclaimer

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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The opportunity

2. The circVec approach
3. Therapeutic application of circVec
4. Summary & finance

Gene therapy is one of the fastest growing therapeutic areas, with increasing priority from industry and regulators

POLICY

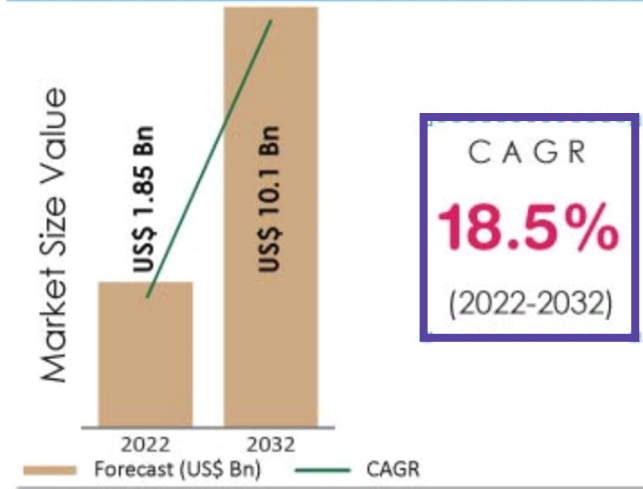
FDA adopts Operation Warp Speed lessons for rare disease pilot program

The FDA announced the launch of a pilot program, dubbed START, to address challenges associated with rare disease development and speed up the regulatory process.

Lecia Bushak | November 22, 2023 | 10:51 AM



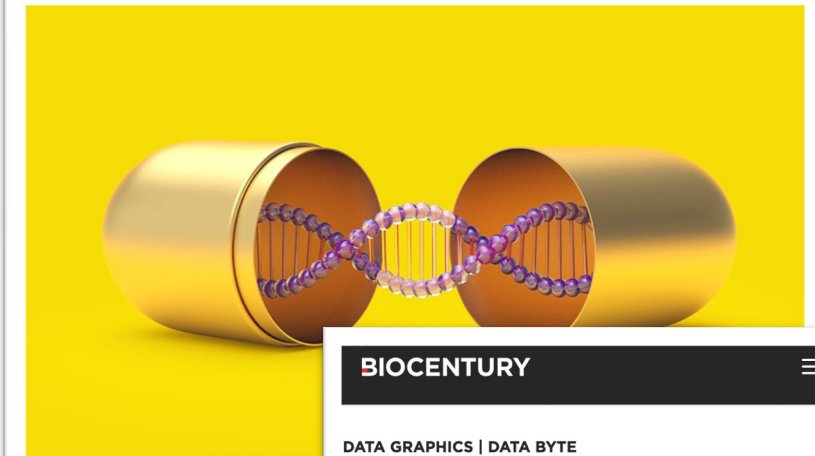
Gene Therapy Market Forecast Analysis, 2022-2032



Source: Fact.MR

TECHNOLOGY

Have Million-Dollar Gene Therapies Finally Reached An Inflection Point?



BIOCENTURY

DATA GRAPHICS | DATA BYTE

Novartis' Zolgensma first gene therapy to top \$1B

The era of effective, but pricey, gene therapies is at hand

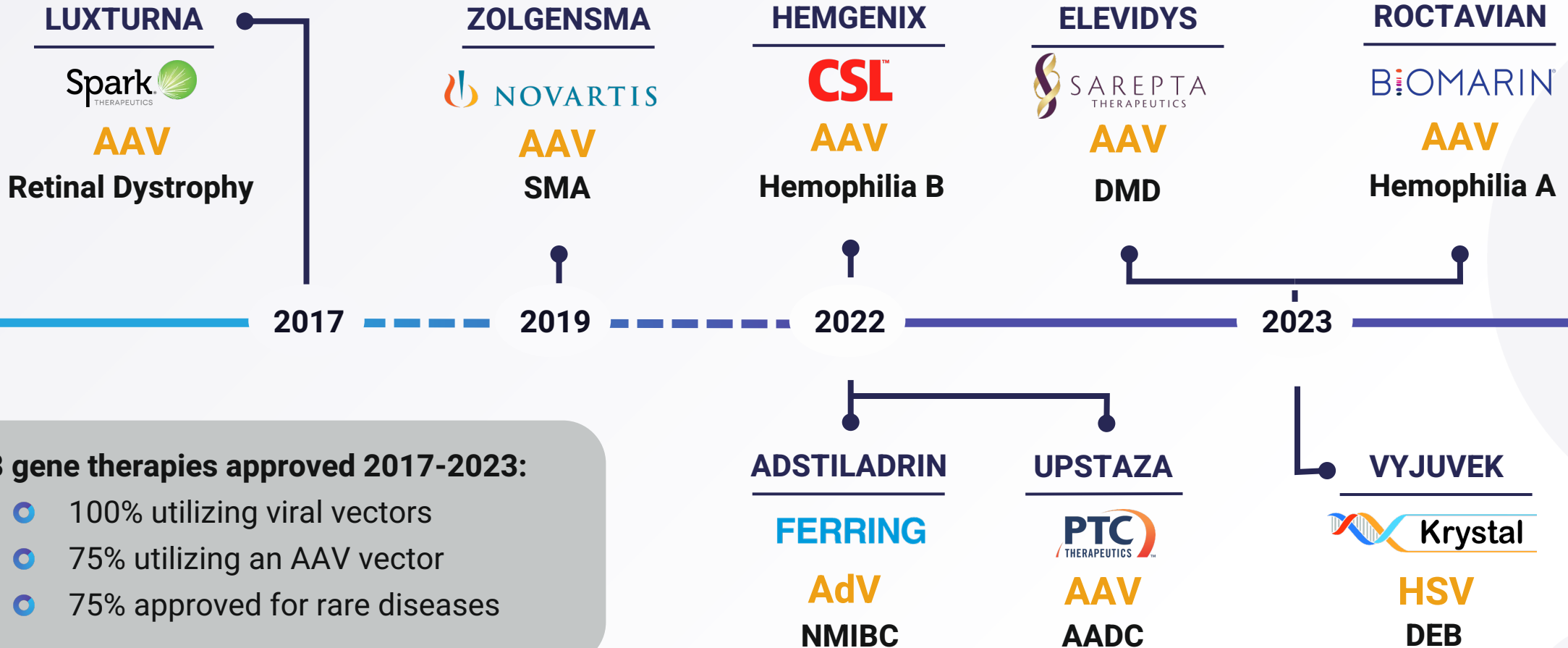
f t in Licensing

ALLISON GATLIN | 12:50 PM ET 09/15/2023

Get ready for a world of million-dollar drugs. Pricey gene therapies that could cure devastating genetic disorders in one fell swoop are gaining momentum, brightening the horizon for biotech stocks like Sarepta Therapeutics (SRPT) and BioMarin Pharmaceutical (BMRN).

Focus area for regulators → Fastest growing class of new approvals → Commercial success

Circio aims to improve 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

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

The need for high dosing is a major limitation for current gold-standard AAV gene therapy

Limited applicability

Low expression level not sufficient for many genetic diseases

Low expression → High dosing

Safety issues, liver and immunological toxicity

High dosing → High cost

High dose requirement drives high manufacturing cost

circRNA can:

→ boost potency

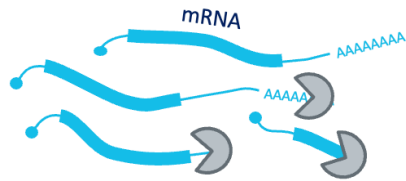
→ lower toxicity

→ reduce cost

circRNA can increase durability and expression level, thus enhancing the potency of gene therapy

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

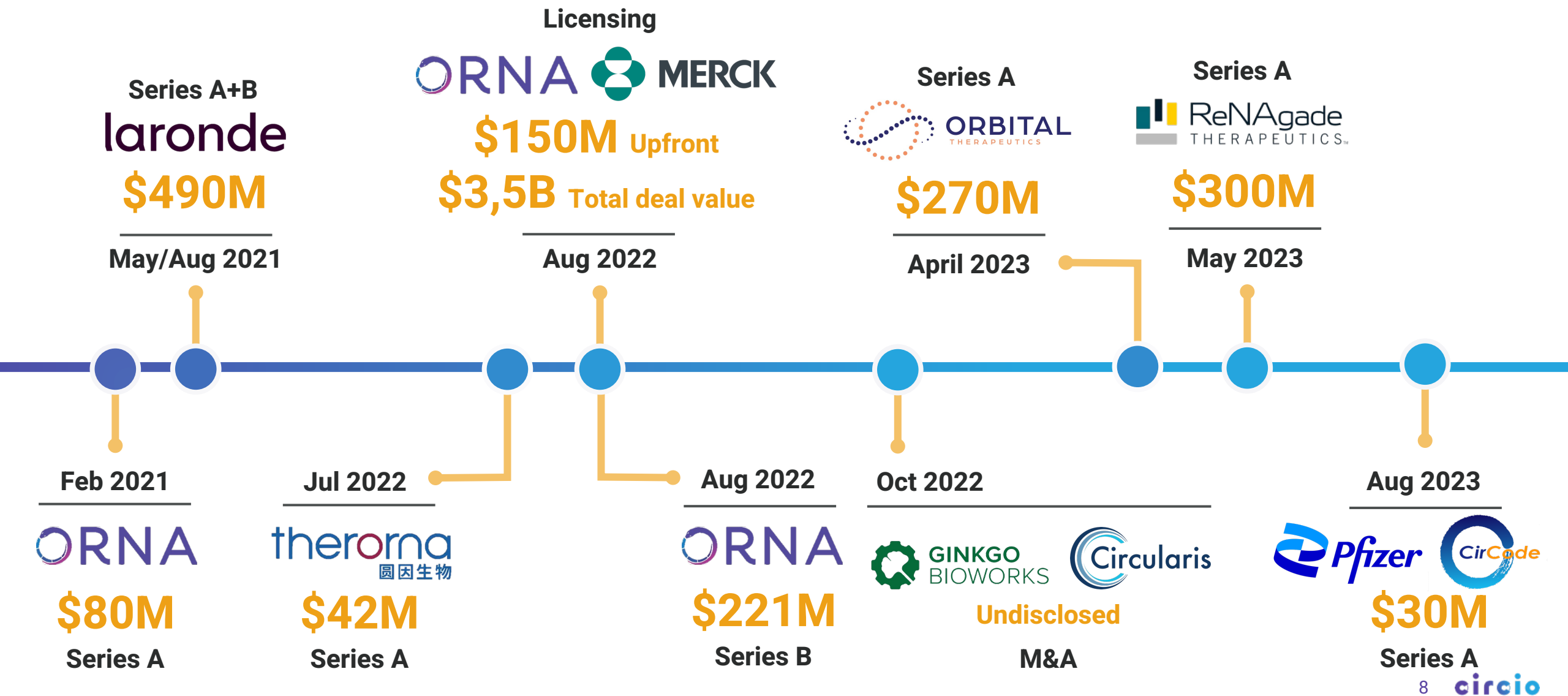
5x translation rate vs. mRNA



Modular & multi-functional

Enables 'remove & replace' strategy

Based on these advantages, circRNA is gaining strong industry momentum as a superior RNA platform



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The circVec approach

3. Therapeutic application of circVec
4. Summary & finance

The circRNA field was established by Circio scientists



Dr Thomas B Hansen

Dr Erik D Wiklund



nature

7,263 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 | 1,031 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](#)

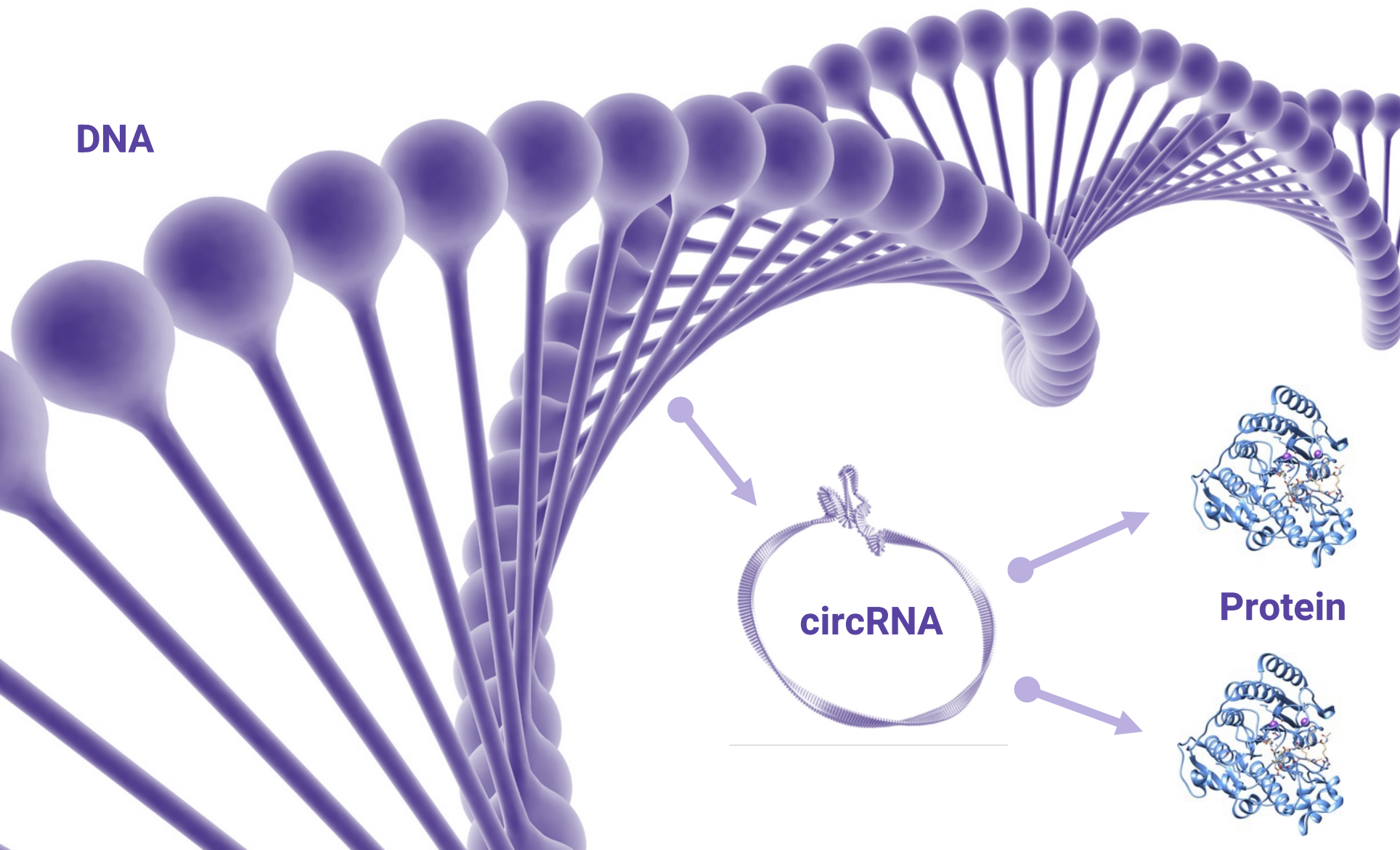
nature reviews genetics | 3,224 citations

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](#)

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








circVec
DNA or viral
vector

Inject

circRNA
biogenesis

Enhanced and
durable protein
expression

The circVec platform is technologically differentiated and creates novel possibilities for circRNA

		<i>Expression durability</i>	<i>Main opportunity in vaccines</i>	<i>Suitable for gene therapy</i>	<i>Delivery system</i>	<i>Existing CDMO manufacturing</i>
	circVec vector approach	months to years	✗	✓	Viral or DNA-LNP	✓
 	Synthetic circRNA	7-10 days	✓	✗	circRNA-LNP	✗
 	Synthetic mRNA	2-3 days	✓	✗	mRNA-LNP	✓

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

Increased expression level

Prolonged durability

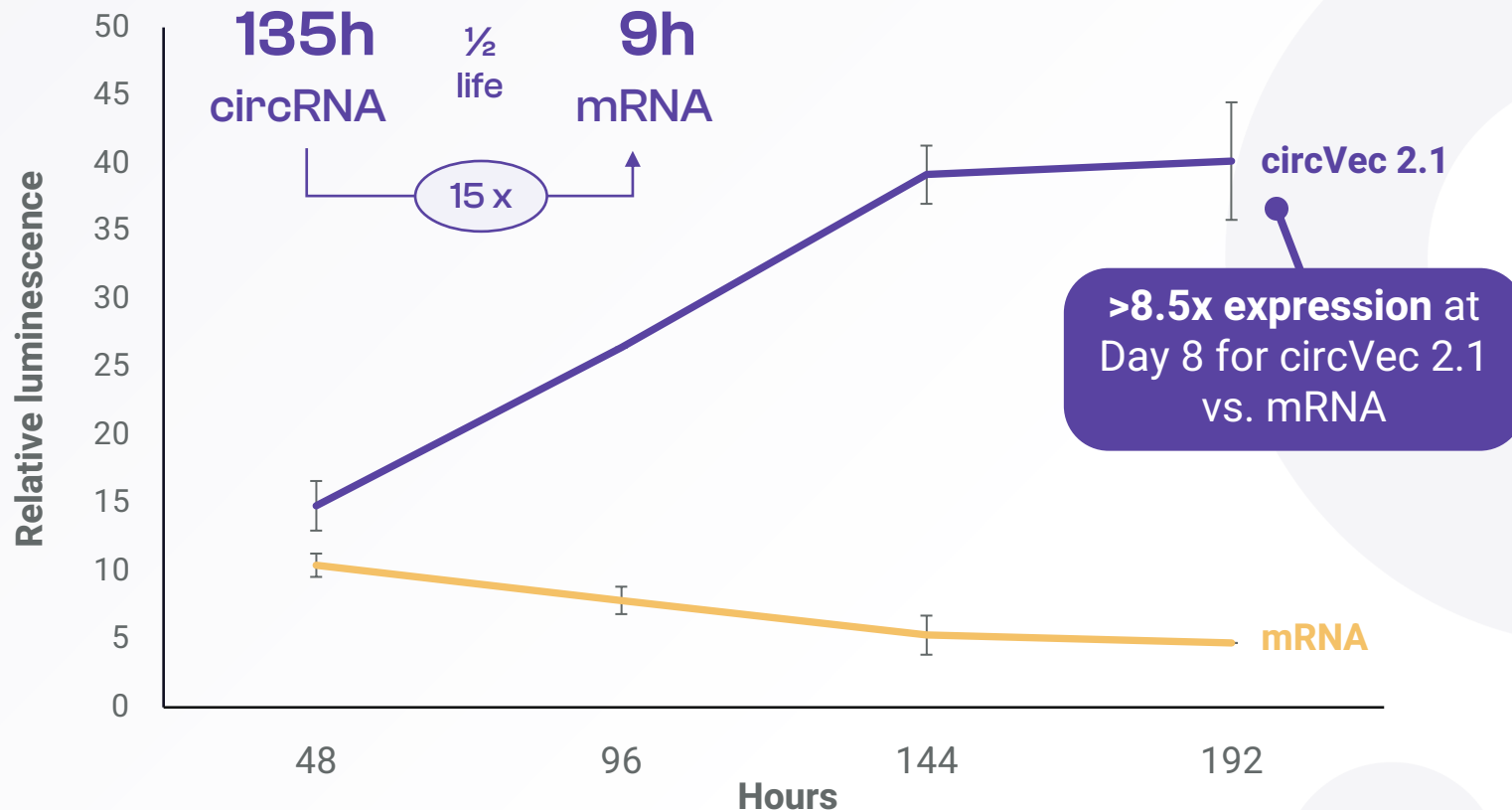
Enhanced therapeutic potency

“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

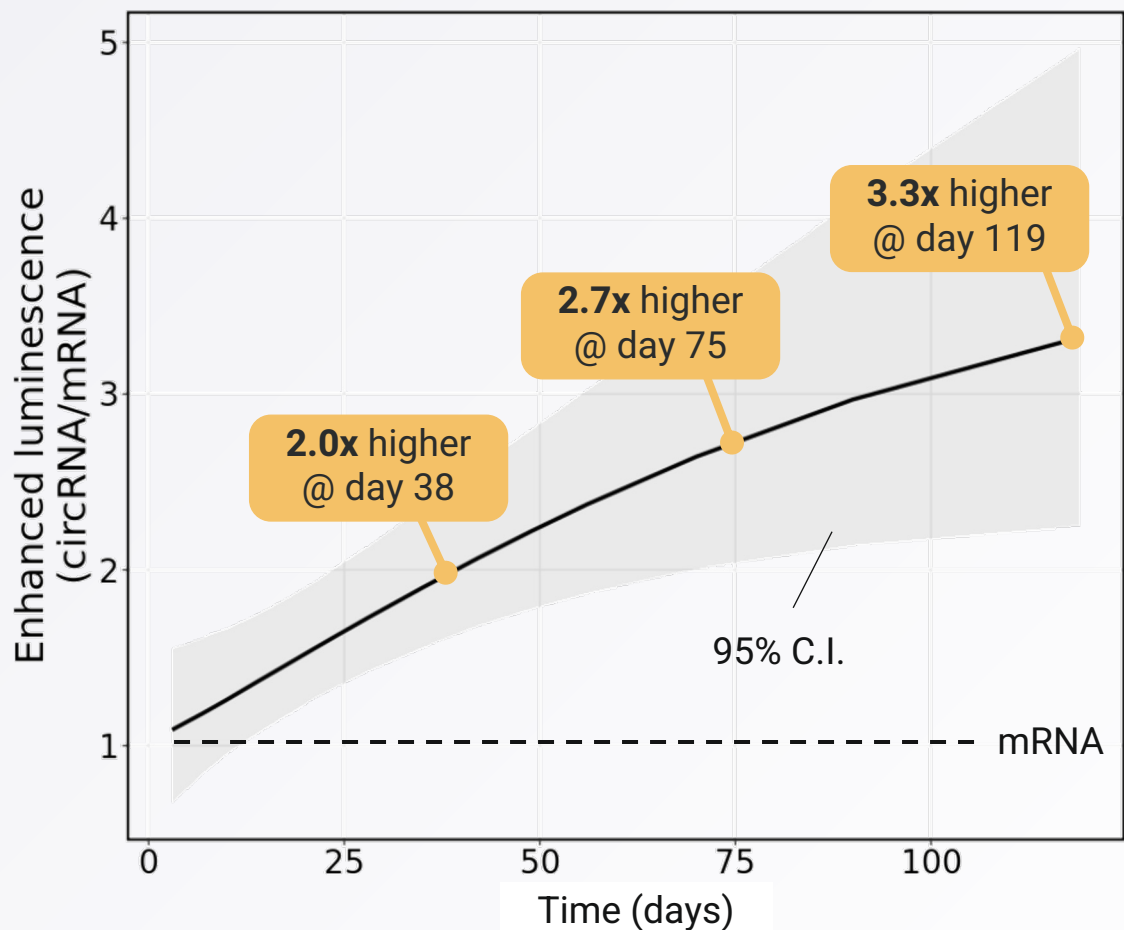
Scientific founder
oRNA Therapeutics

circVec vs. mRNA luciferase reporter expression; time course

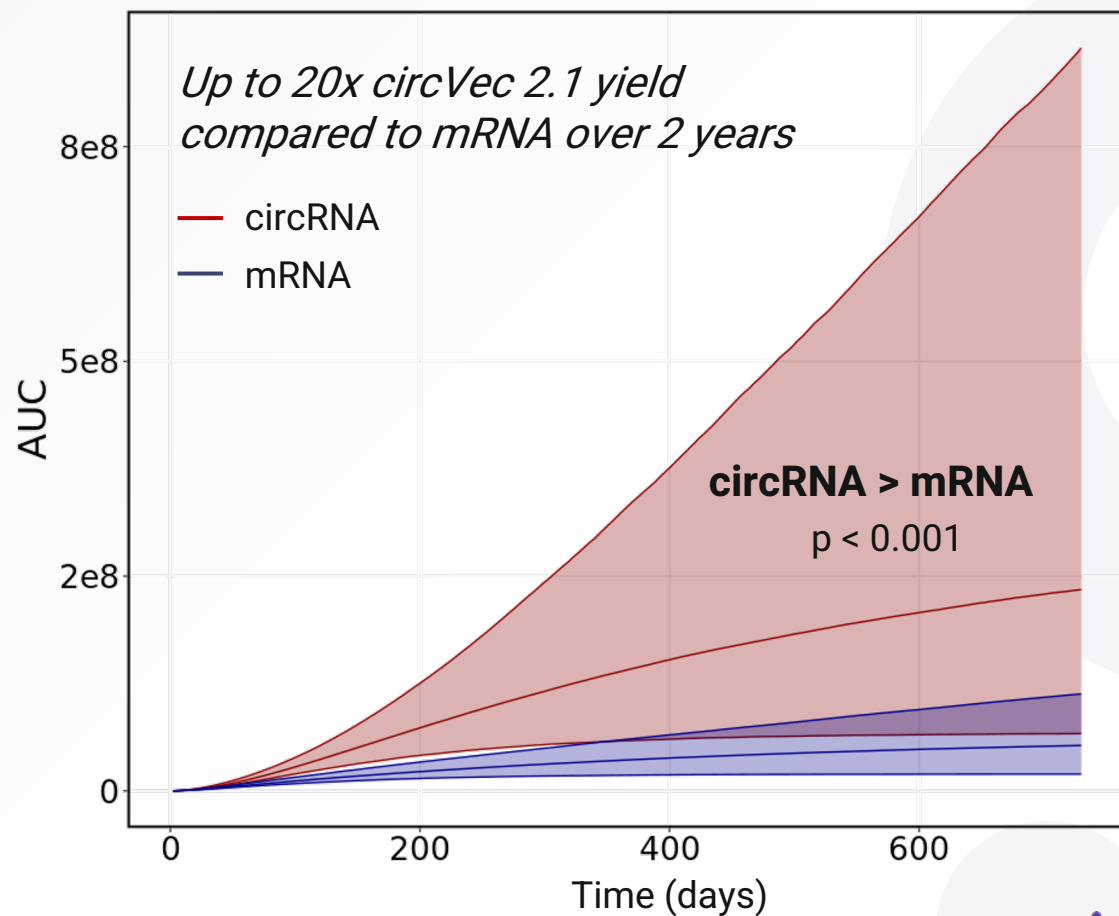


Statistical analysis of in vivo data demonstrates significant advantage vs. mRNA increasing over time

Luciferase signal in vivo, -fold change
circVec 2.1 vs. mRNA pDNA vector expression



Statistical modelling of long-term expression
circVec 2.1 vs. mRNA expression dynamics, 2 years



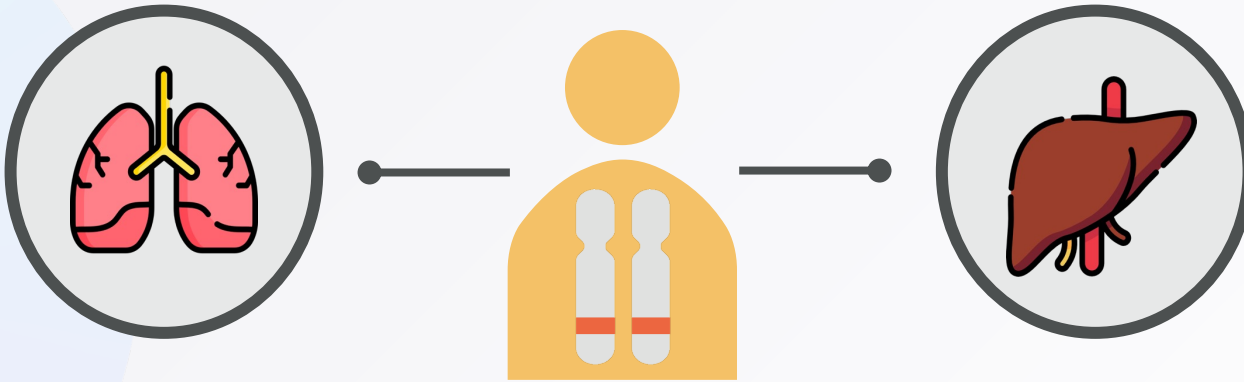
3

Therapeutic application of circVec

4. Summary & finance

Lead indication: Alpha-1 antitrypsin deficiency (AATD)

AATD is a genetic disease manifested in liver and lung



- Lack of functional AAT protein
- Emphysema and/or chronic bronchitis

- Toxic accumulation of mutant form of protein
- Cirrhosis

Number of patients:

120K in EU

75K in US

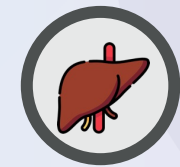
No satisfactory treatment options → Major unmet medical need
Significant commercial opportunity

Current treatment options



Lung-associated AATD

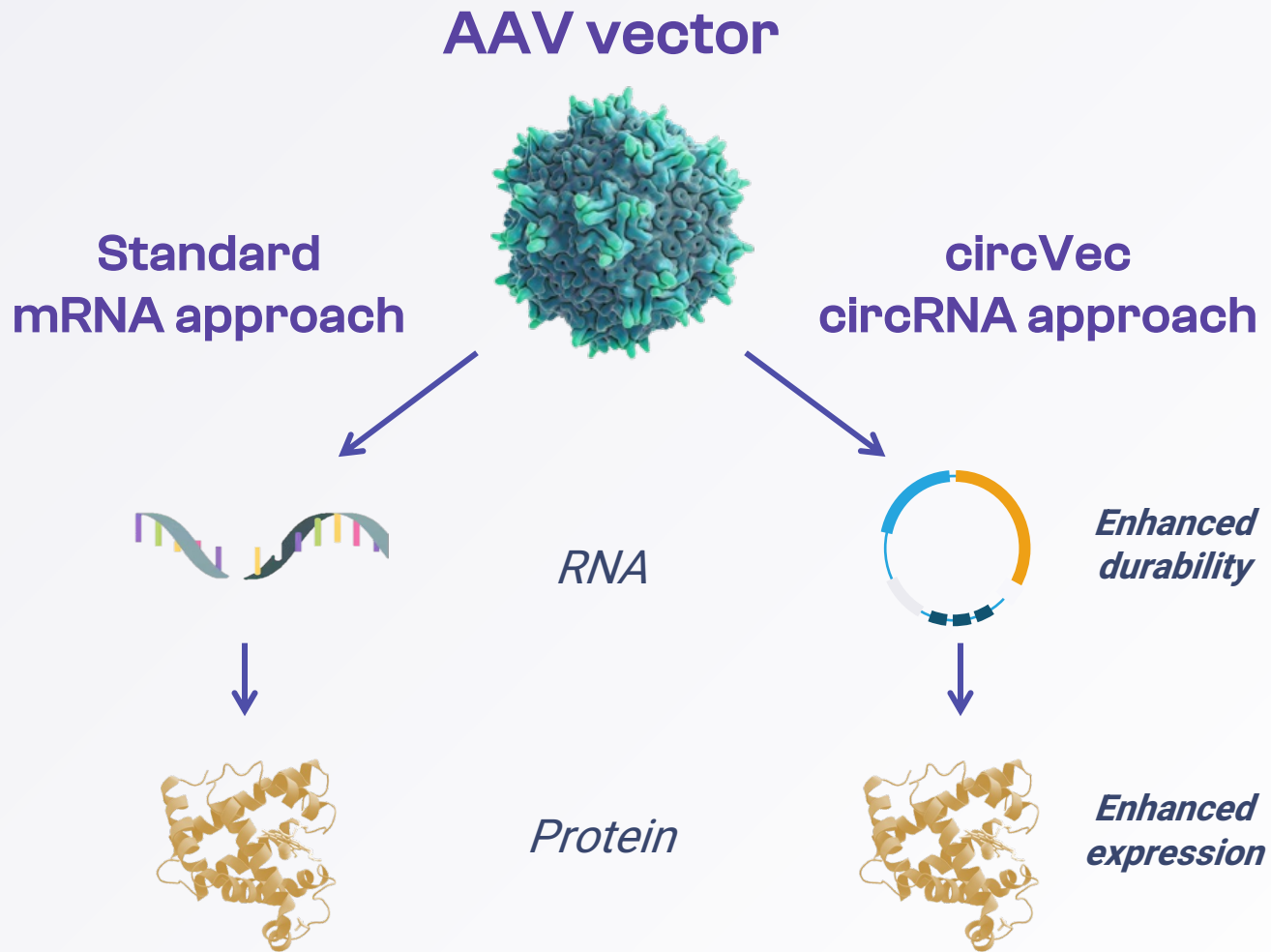
- Replacement therapy with an alpha-1 proteinase inhibitors
- Weekly IV infusions
- Bronchodilators and inhaled steroids used for mild symptoms



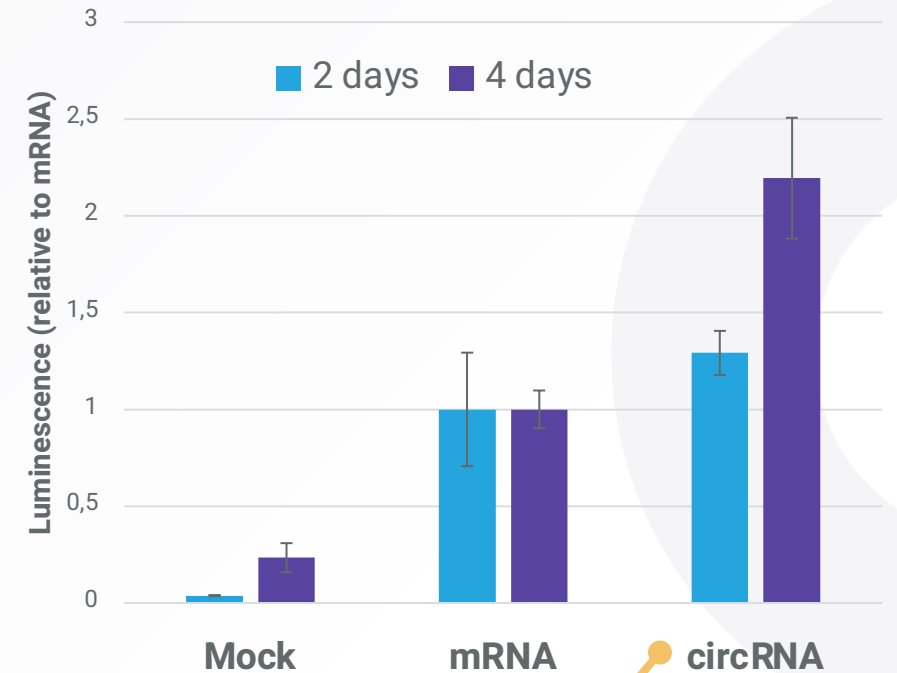
Liver-associated AATD

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

circVec-AAV gene therapy for AATD



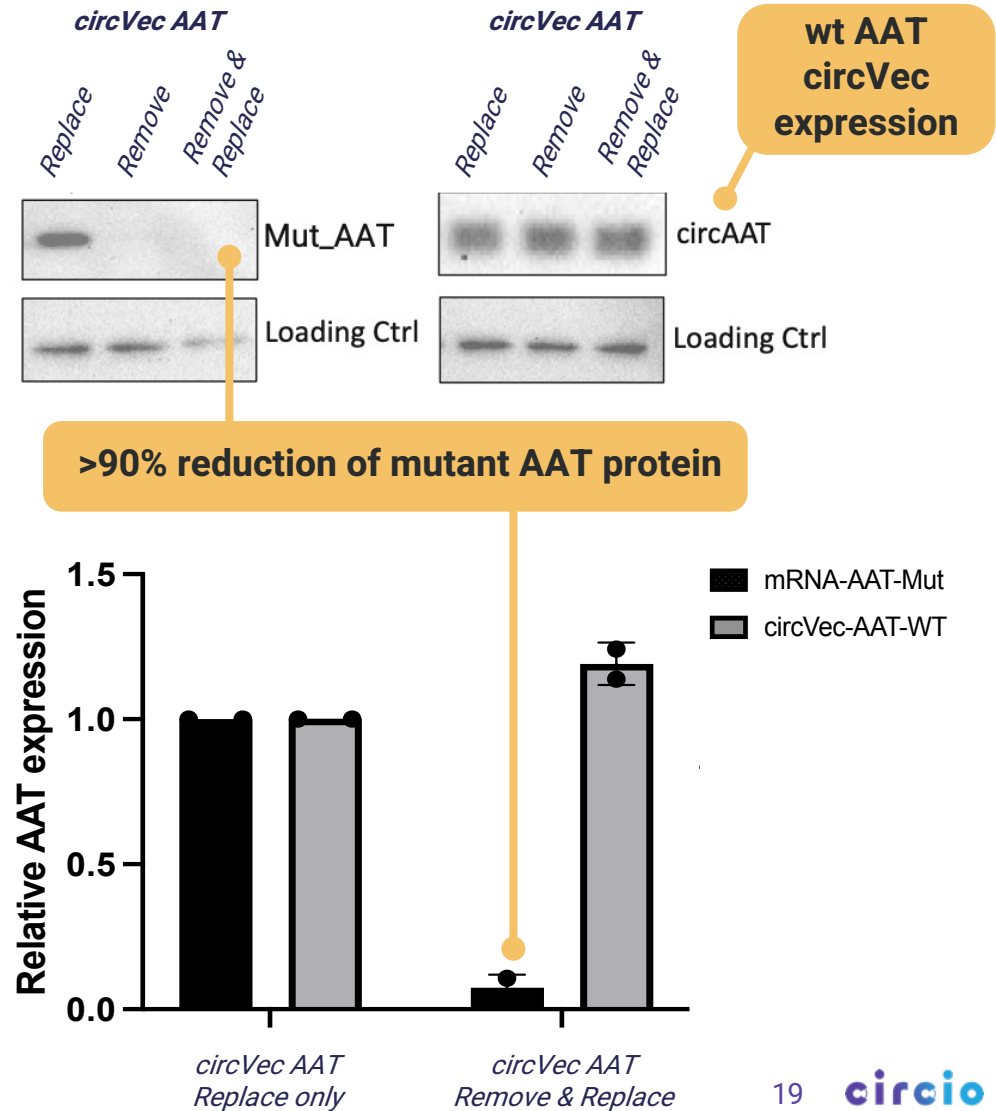
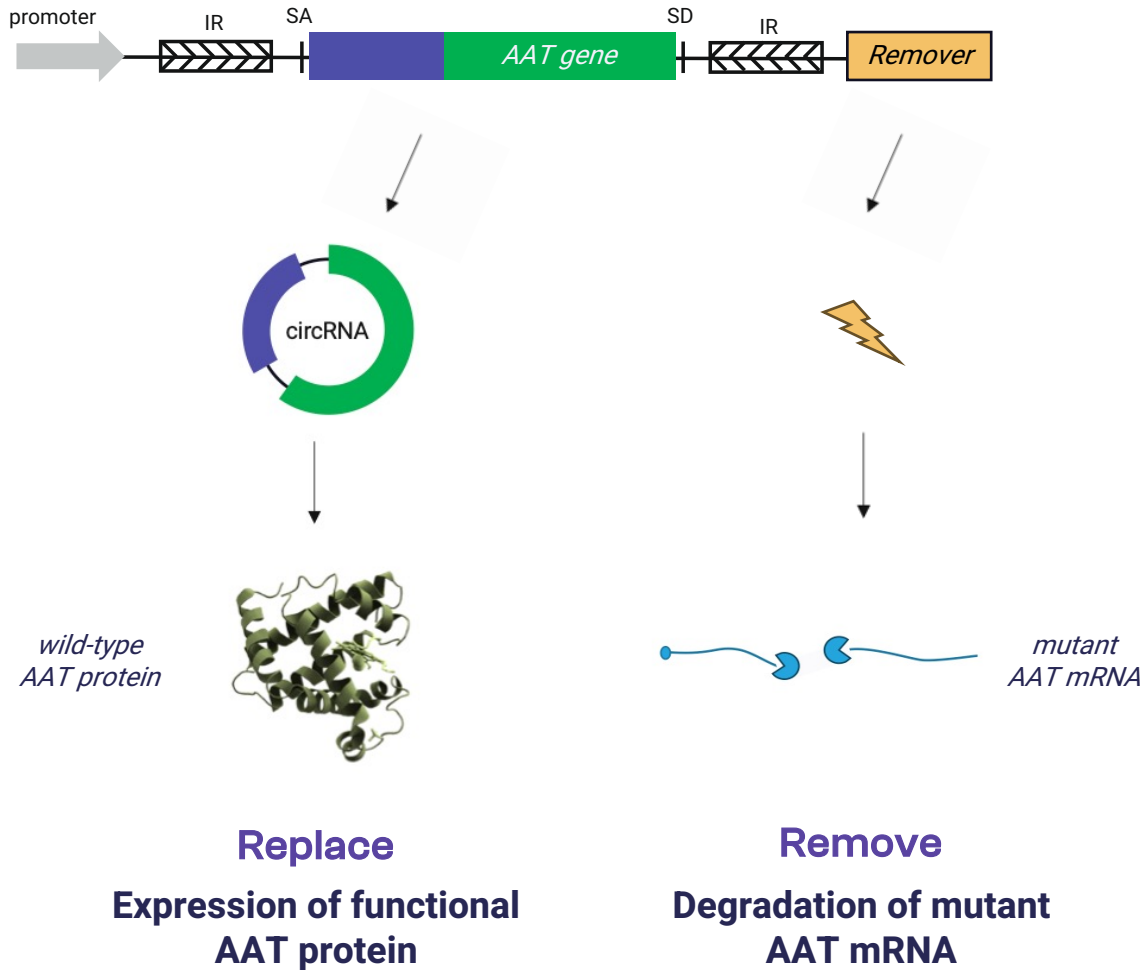
AAV protein expression, luminescence



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

Lead circVec gene therapy program: Differentiated 'Remove-&-Replace' concept for AATD

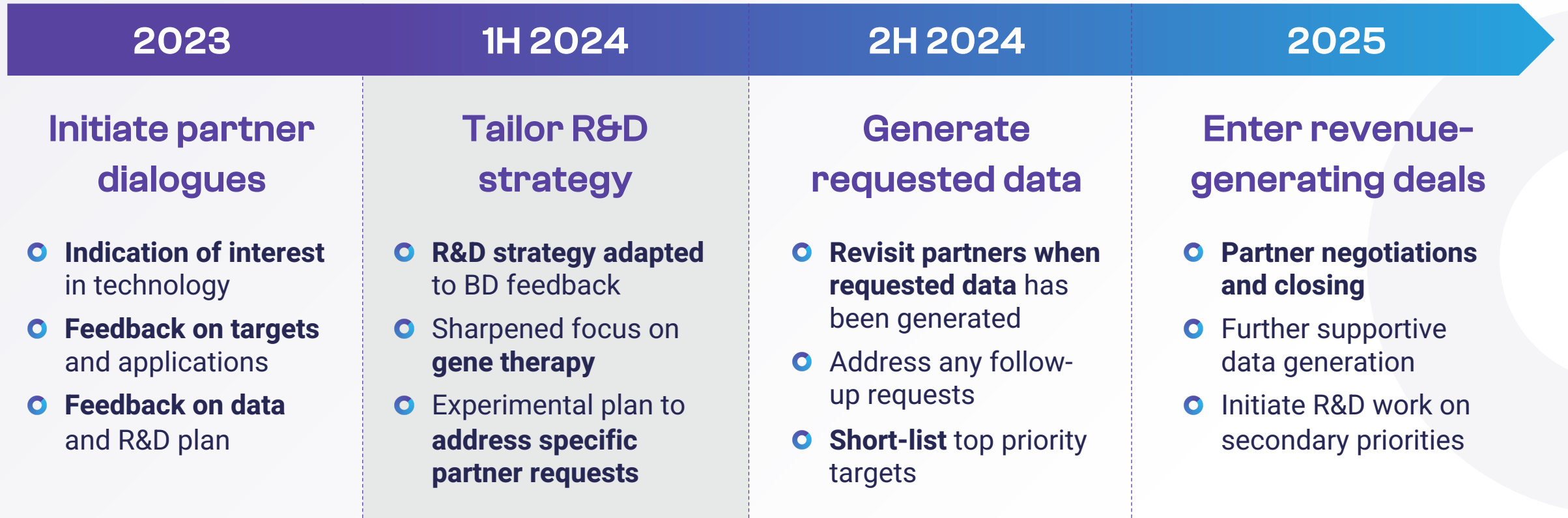
AAV-circVec2.0 AATD R&R design



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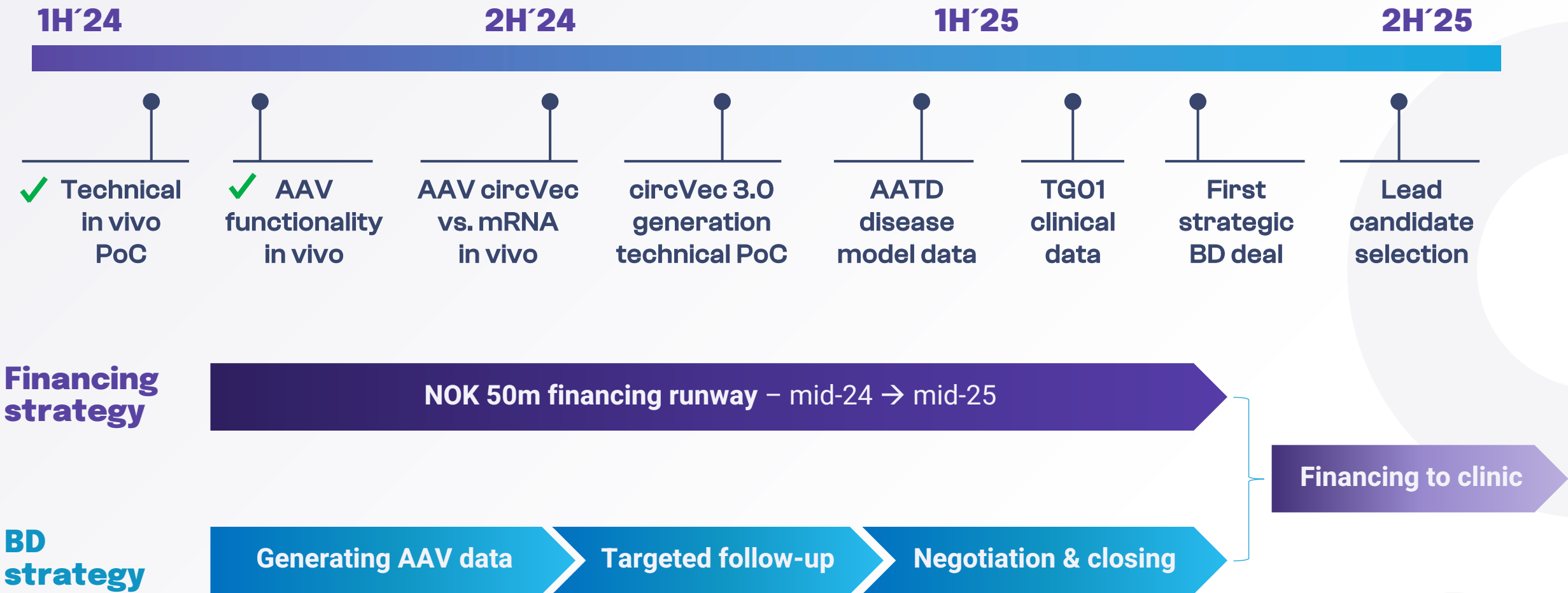
Summary & finance

Active strategy to develop shareholder value through revenue-generating partnerships



100+ prospective partners contacted – 30+ requested follow-ups – 10 CDAs entered to date

R&D & BD value inflection points: Targeting first partnering deal during 1H '25



Main terms of planned NOK 52m rights issue

Subscription price ○ NOK 2.5

Subscription period ○ 24 June – 8 July

Warrants

- 1:1 against subscribed shares
 - Exercise period 4-18 December 2024
 - 30% discount to WVAP, with floor at NOK 0.6
-

Pre-commitment

- NOK 9.4m (+ 12 month financing commitment from Atlas)
 - Compensated with 17% fee paid in units
 - 1 unit = 1 share + 1 warrant
-

Subscription rights

- Pro-rata, record date 21 June
- The subscription rights will be tradeable during the subscription period