circio

Disruptive circRNA technology for genetic medicine

Company presentation
December 2023

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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.

Circio investment case – executive summary

Disruptive technology

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

Unique position

- Circio has a unique approach to circRNA, differentiated from all other major circRNA players
- Proprietary circVec expression system has platform potential
- Deep expertise: the discoverers of circRNA work for Circio

Value drivers

- Opportunity for multiple circRNA BD deals during 2024-2025
- Aim to enter the clinic with AATD program in 2026
- Additional TG01 partnering opportunity with positive data from collaboration studies in 2024-25

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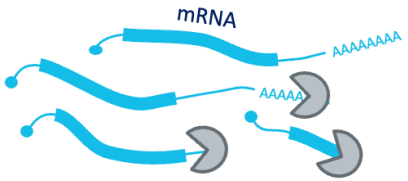
circRNA introduction

2. circVec R&D strategy
3. TG01 KRAS program

circRNA will disrupt gene therapy and vaccines by improving potency and adding novel functionality

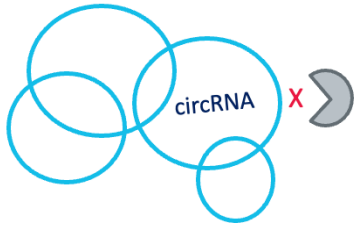
Extended RNA durability



microRNA sponging

circRNA has dramatically prolonged half-life vs. mRNA within cells

Enhanced protein expression



Regulatory functionality

The discoverers of circRNA work for Circio

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

CURRENT ISSUE ABOUT INFORMATION ARCHIVE ALERTS SUBMIT

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

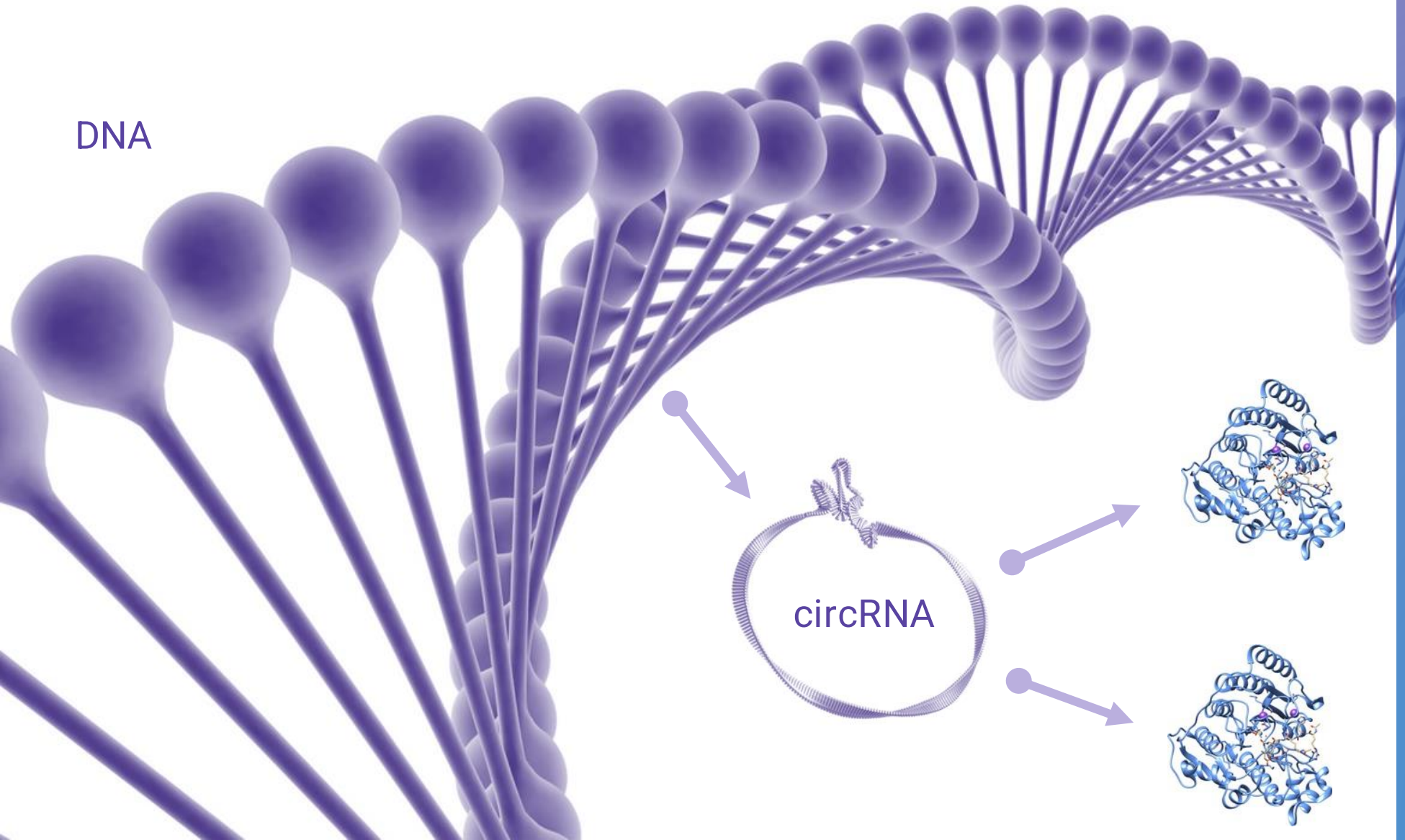
nature reviews genetics 2,291 citations

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

circVec – a differentiated and highly efficient system for intra-cellular circRNA production



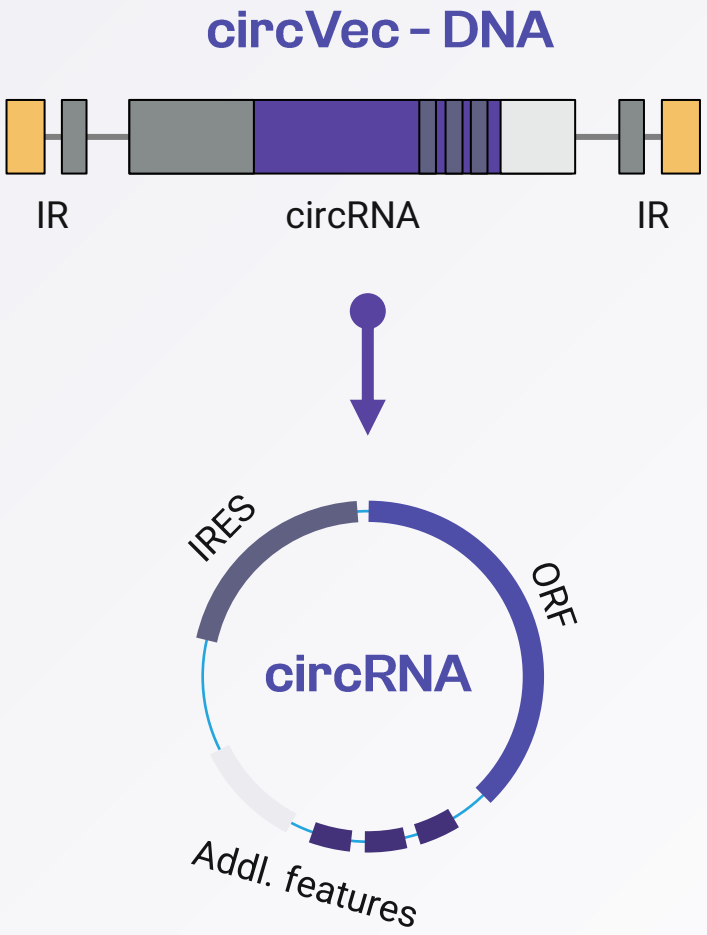
circVec
DNA or viral vector

Inject

circRNA biogenesis

Intra-cellular protein expression

circVec is a modular genetic cassette for intra-cellular circRNA biogenesis and protein expression



Genetic cassette

- Best known circRNA biogenesis rate
- In-built RNAi functionality
- Vector agnostic – viral or DNA
- IP protected

+

Multi-functional circRNA

- 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

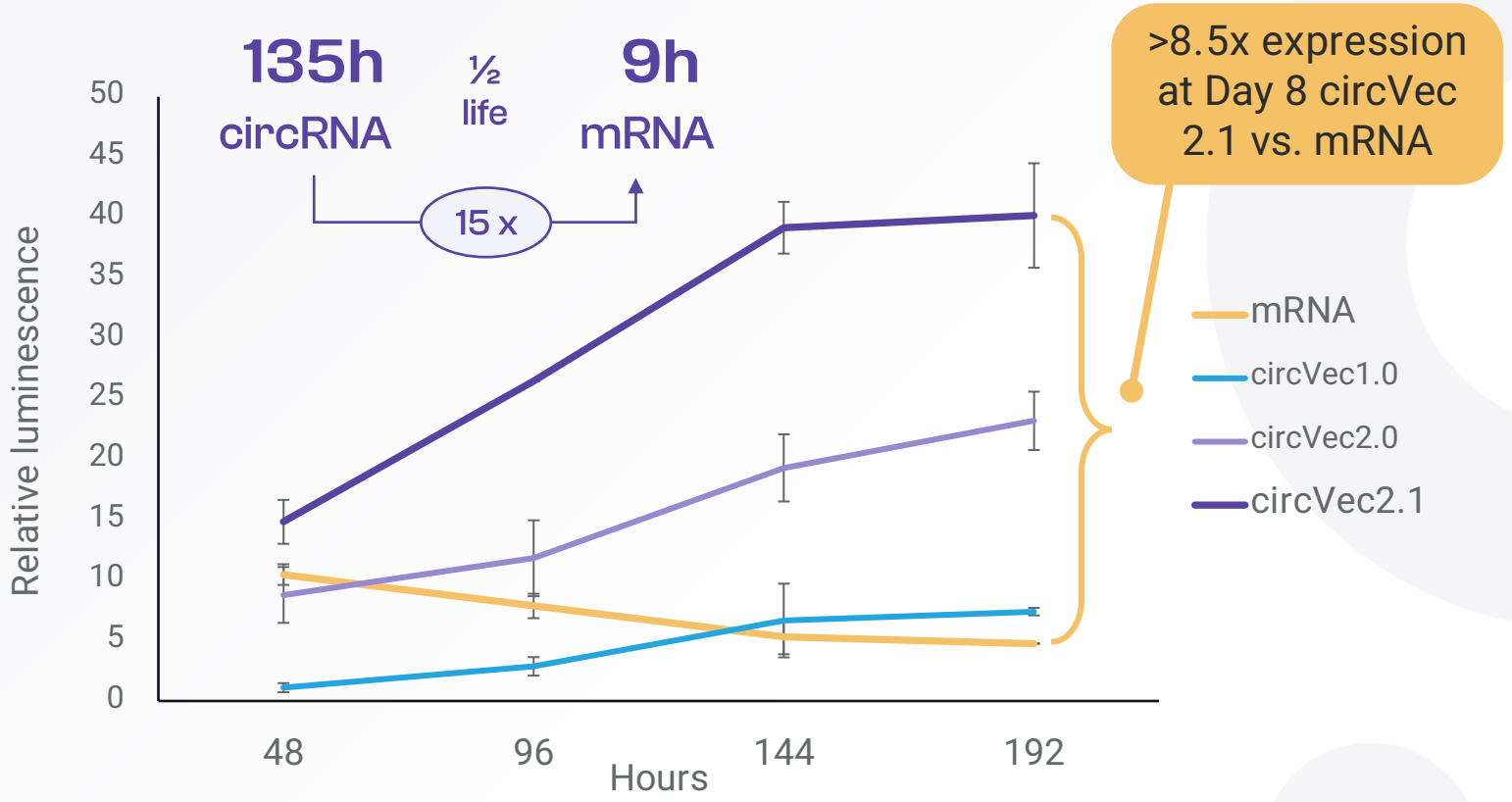
Enhanced therapeutic potency

"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"

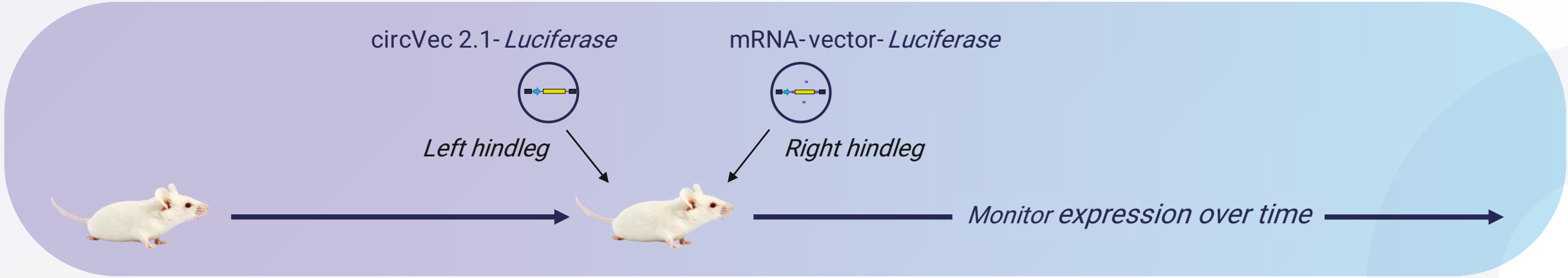
Dr. Alex Wesselhoeft

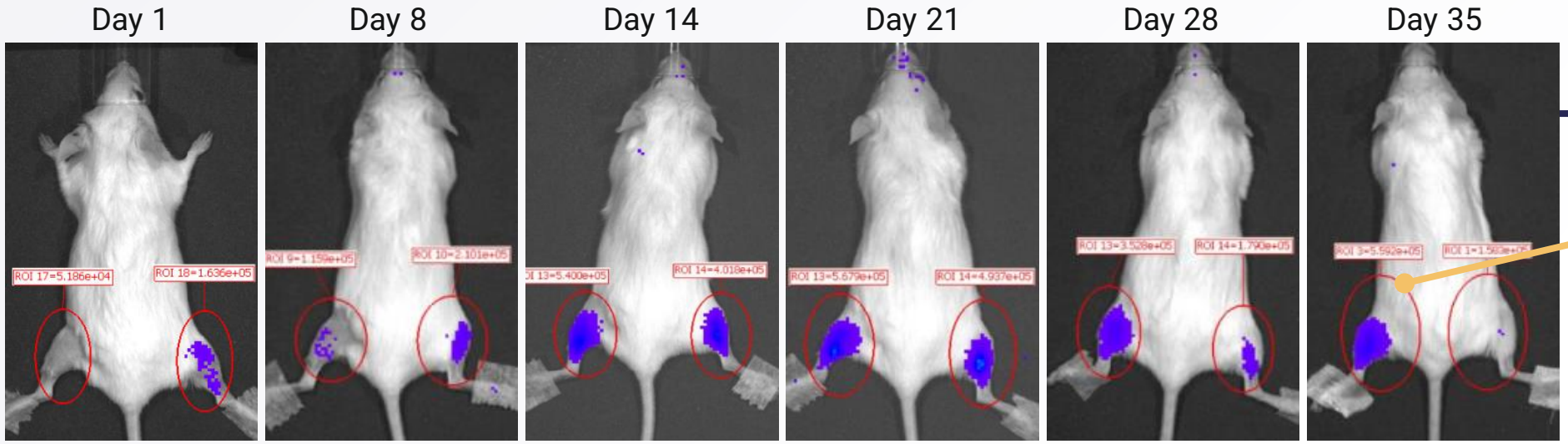
Scientific founder
oRNA Therapeutics

circVec vs. mRNA luciferase reporter expression; time course



ONGOING PILOT STUDY: circVec 2.1 shows increasing durability at Day 35 post injection





Real-time monitoring ongoing

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

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circVec R&D Strategy

3. TG01 KRAS program

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

Current focus areas

Rare disease

"Remove-and-replace" concept with durability and safety advantages

-

Major long-term 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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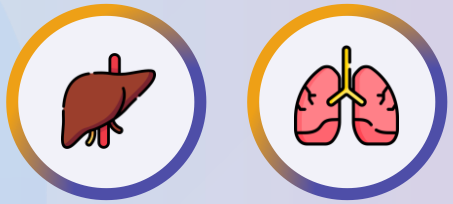
Unique oncology concept

Designed for intra-cellular circRNA supply, durable protein expression and targeted regulatory functionality

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

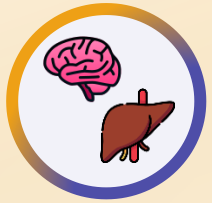
Lead Indication



Alpha-1 Antitrypsin Deficiency

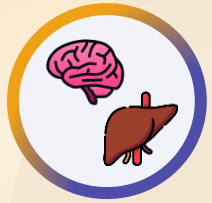
AATD

Second priority



Ornithine Transcarbamylase Deficiency (OTCD)

Citrullinemia Type I (CTLN1)



Argininosuccinate Synthetase Lyase Deficiency (ASLD)

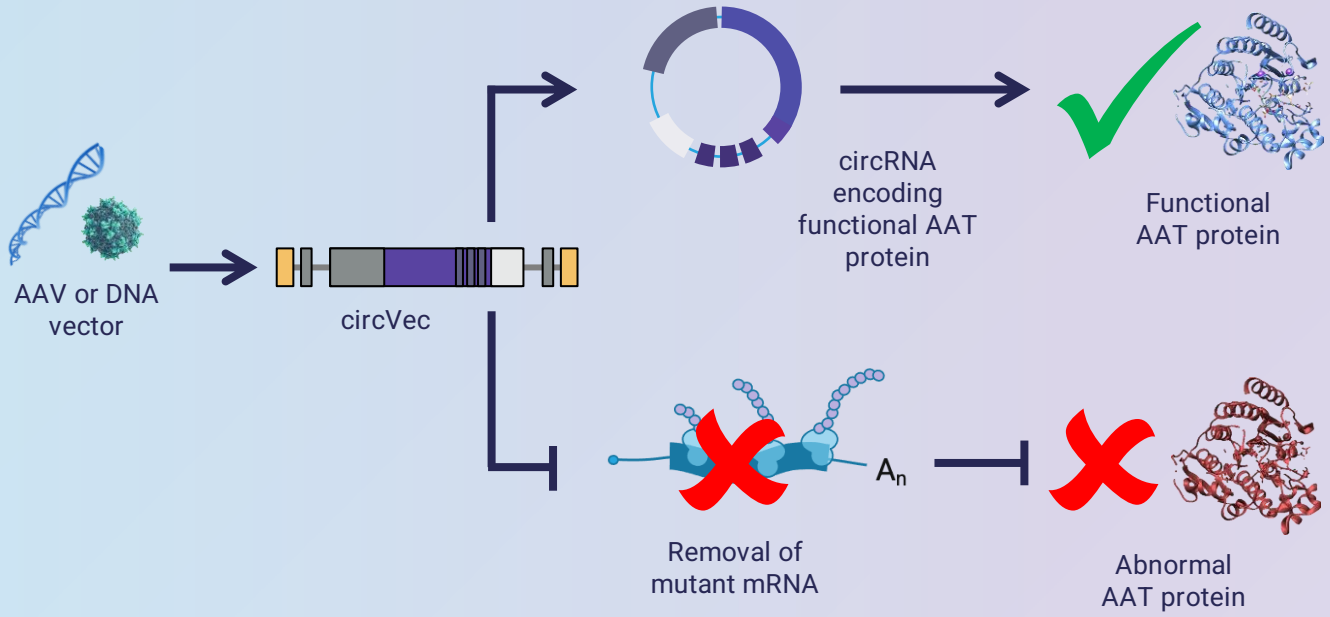
Urea Cycle Disorders (UCDs)

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

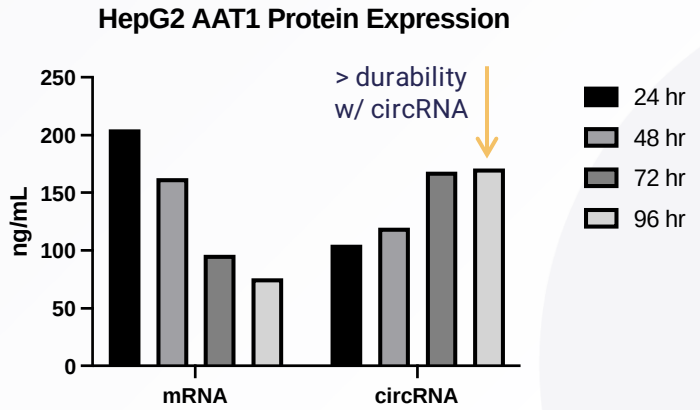
Unique ”Remove-and-Replace” concept for AATD

Depleting mutant form and replenishing functional protein by circVec

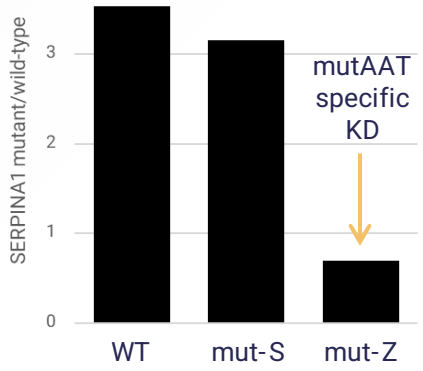
- *reverses toxic protein accumulation in liver and restores normal function in lung*



circVec v1.0 AAT expression in liver cells



circVec mutAAT knock-down

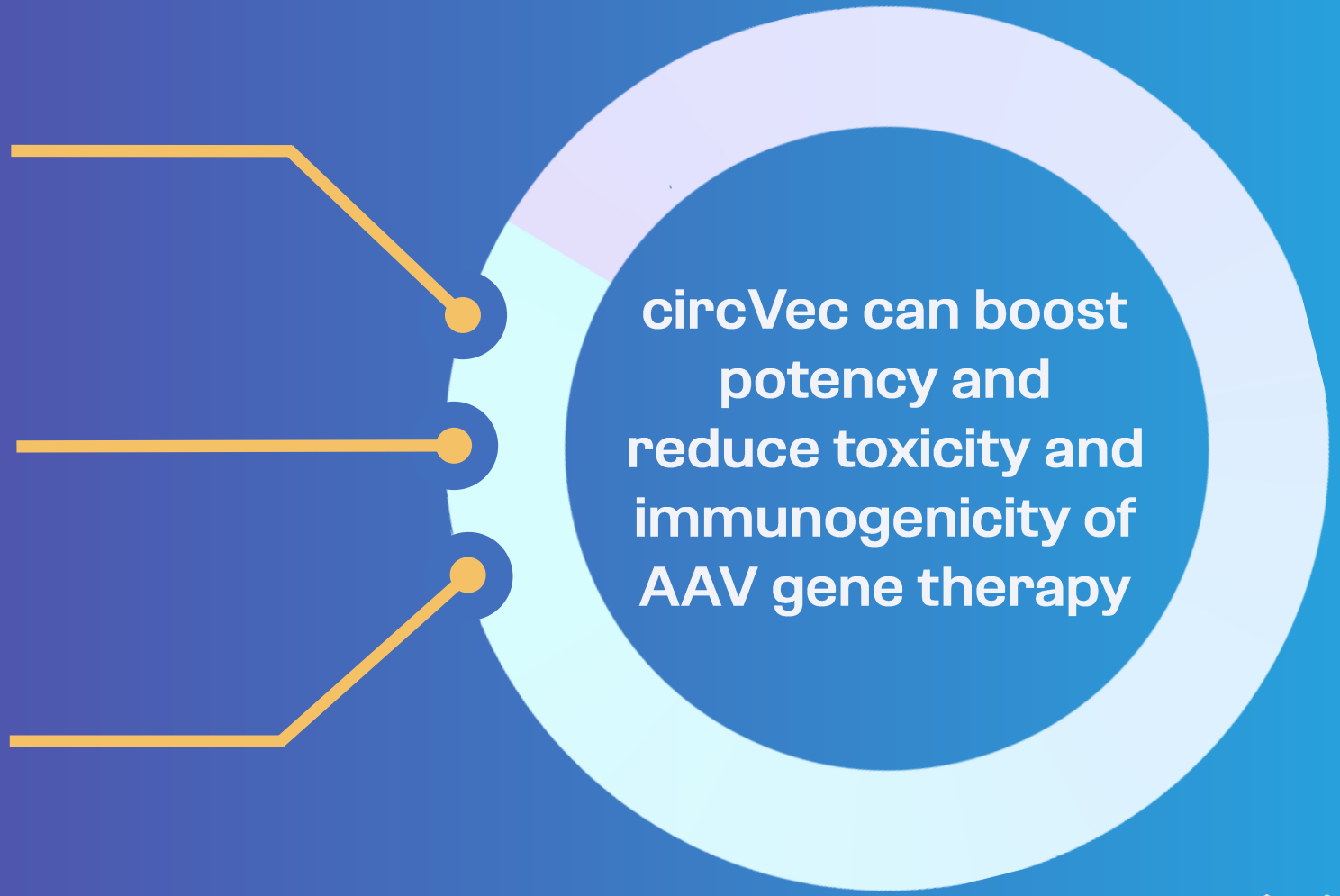


High dosing requirement is a substantial shortcoming for current AAV-based gene therapy

Safety issues
Liver toxicity, innate immunity

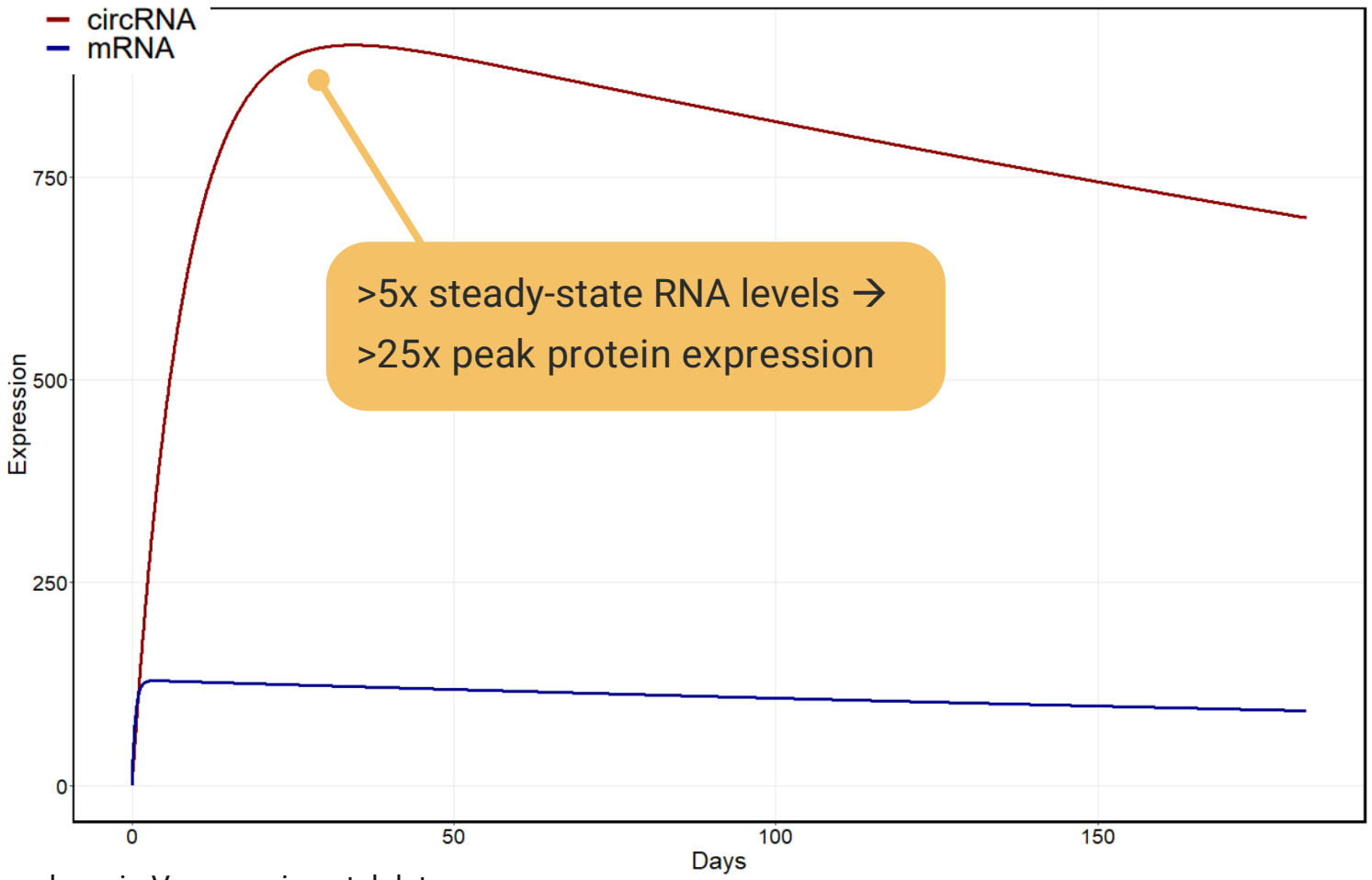
High dose = high immunogenicity
No repeat dosing

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 for out-licensing

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

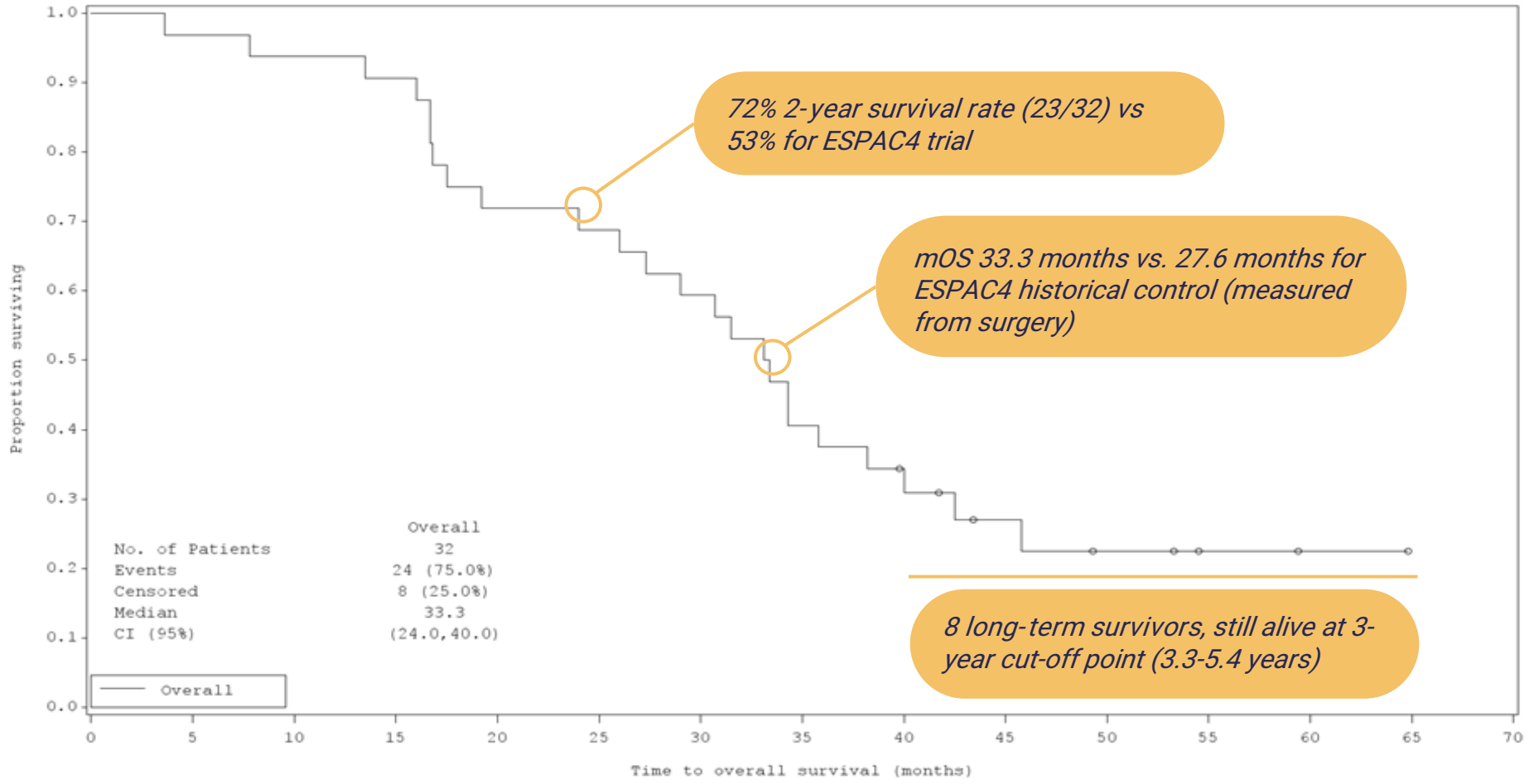
- Vector-expressed circRNA has the potential to become the preferred format for any DNA-based therapeutic in the future
  - *Just as synthetic circRNA is expected to become the preferred format for long RNA-based therapeutics in the future*

3

TG01 KRAS program

Legacy clinical program: Mutant RAS cancer vaccine TG01 has shown promising efficacy in previous studies

TG01 + gemcitabine phase 1/2 study – Post-surgery pancreatic cancer (n=32)



Source: Palmer et al. Br J Cancer, 2020, Neoptolomus et al, Lancet 2017

Three studies ongoing with new enhanced TG01 cancer vaccine

Pancreatic Cancer
Phase 1/2

Combination w/chemotherapy
post-surgery
n = 32 patients

Pancreatic Cancer
Phase 1/2

Combination w/anti-PD1
post-surgery
n = 24 patients

Multiple Myeloma
Phase 1/2

Monotherapy
post 1L treatment
n = 20 patients

Lung & Pancreatic Cancer
Phase 2

Triple therapy w/anti-CD38 & anti-PD1
Immunotherapy resistant patients
n = 54 patients

Completed trials Ongoing Trials

Sponsor / collaboration:

The University of Kansas Cancer Center

agenus

Oslo University Hospital

Georgetown University

Bristol Myers Squibb

Johnson & Johnson

circio

Strong international senior management team with deep scientific and drug development experience

Dr Erik D Wiklund

Chief Executive Officer

Co-discoverer of circRNA, Pharma consultant at McKinsey & Co and various commercial and R&D roles in biotech, Previously CFO and CBO of Targovax

PhD Cancer epigenetics and RNA biology

Dr Lubor Gaal

Chief Financial Officer

BD and finance industry executive with 25 years experience from big pharma and biotech, incl. BMS, Bayer, Almirall and Locust Walk

PhD Molecular and cell biology

Dr Victor Levitsky

Chief Scientific Officer

Deeply experienced tumor immunology scientist from academia and industry, incl Karolinska Institute, John´s Hopkins, Roche and Molecular Partners

MD, PhD Virology and tumor biology

Dr Thomas B Hansen

VP & Head of Research

World-leading pioneer and co-discoverer of circular RNA; 10 years as group leader at Aarhus University in RNA biology and bioinformatics

PhD Molecular and RNA biology

Ola Melin

VP & Head of CMC

25 years experience in Biologics development, manufacturing, and supply, most recently as Director of Technical Operations at OxThera AB.

BS Biochemical engineering

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