



circio

Company update

Erik Digman Wiklund - CEO
15 June 2023

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.



1

Highlights

2. circRNA program
3. TG01 KRAS program
4. HR update

2022 year-to-date highlights



Strategic shift to prioritize and accelerate development of the circRNA platform

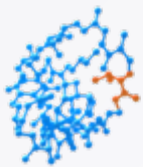
- New company name **Circio Holding ASA**, with OSE ticker: **CRNA**
- Staff reduction of **40%** - scientific operations at Karolinska Institutet in Stockholm



Circular RNA

Key IP filed and proof-of-concept data generated for circRNA platform

- 15x longer half-life demonstrated for circRNA versus linear mRNA *in vitro*
- Filed patent application extending coverage of circVec technology
- Three focus areas defined: cancer gene therapy, rare genetic diseases and vaccines



KRAS

Two investigator-sponsored studies opened for enrolment in the USA and Europe

- First patient dosed in **pancreatic cancer trial** at Kansas University Cancer Center to test TG01 in combination with PD1 CPI balstilimab from collaboration partner Agenus
- First patient enrolled in **TG01 trial** in multiple myeloma at Oslo University Hospital

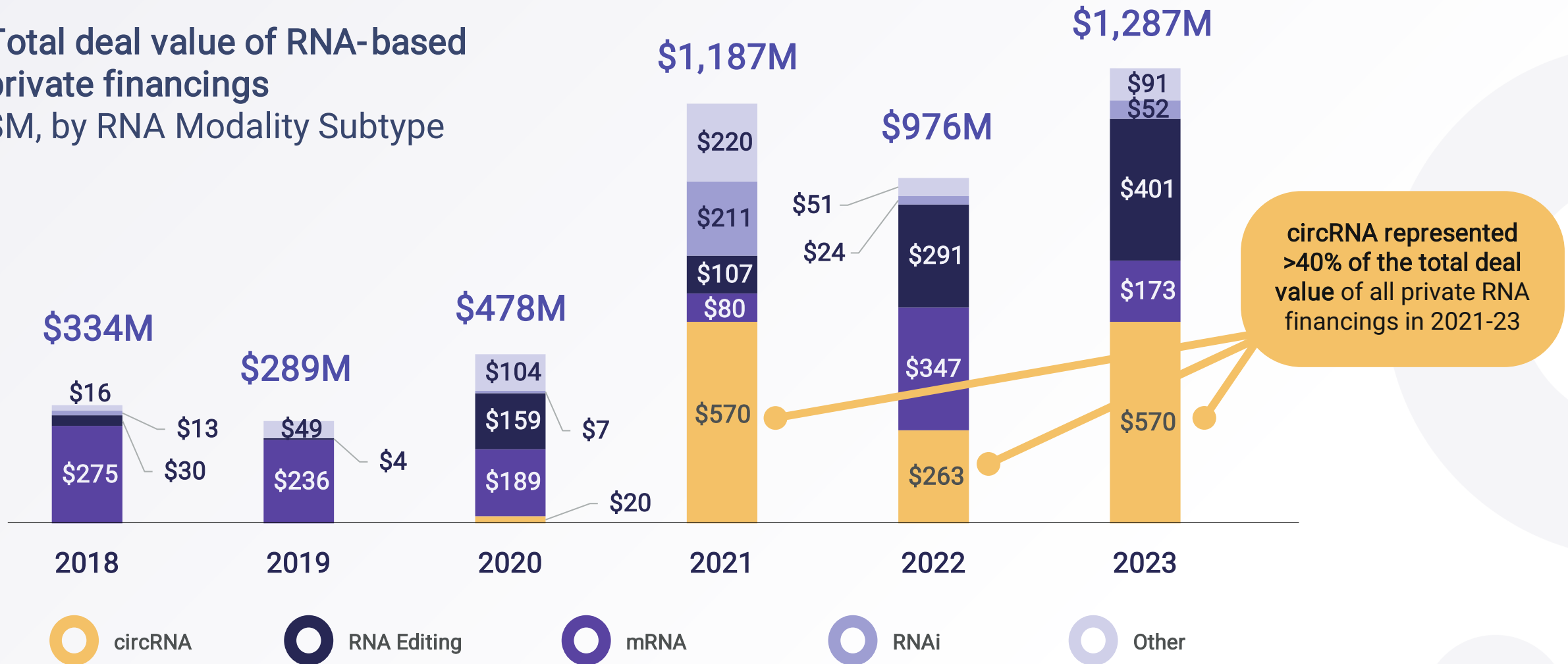
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circRNA program

- 3. TG01 KRAS program
- 4. HR update

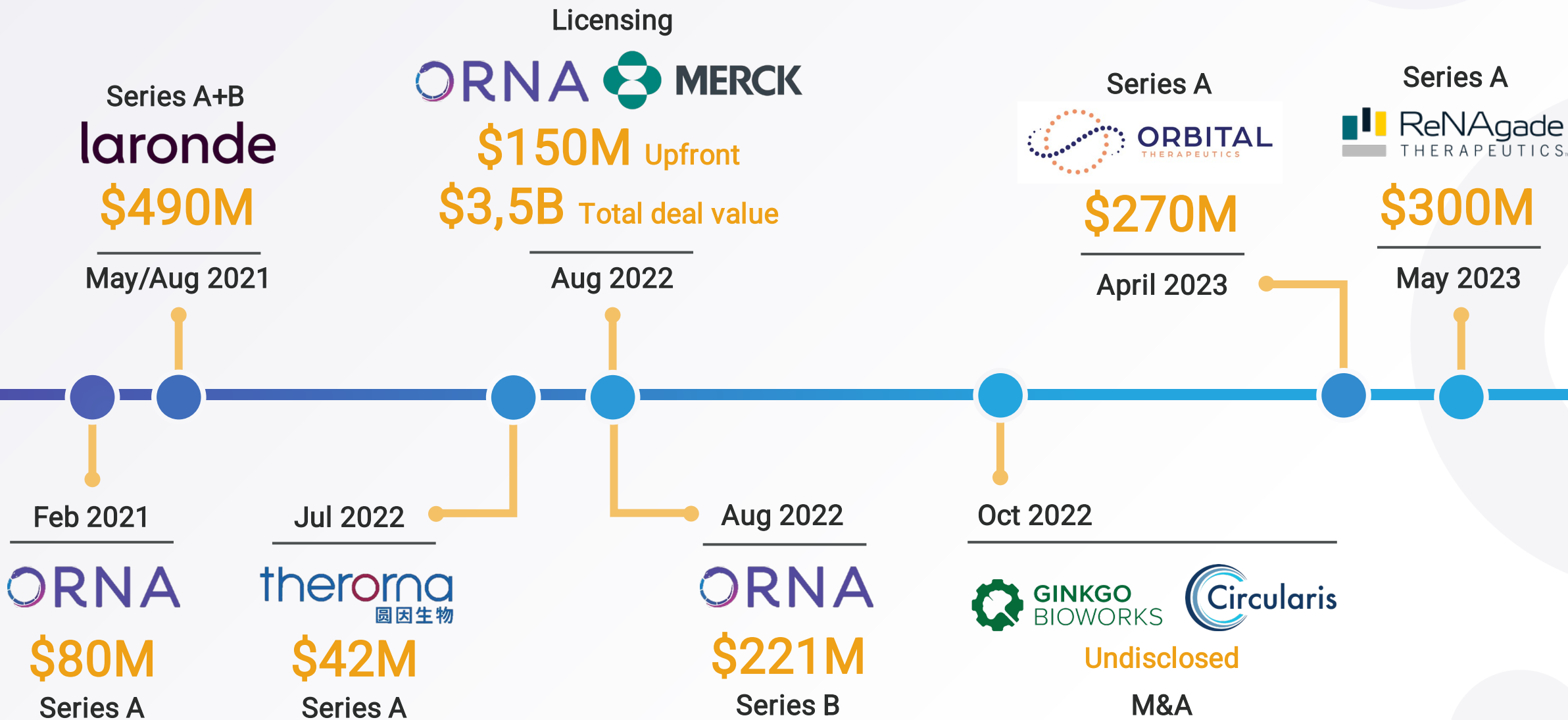
Despite tough market conditions, RNA-based financings increased sharply during 2021-23

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

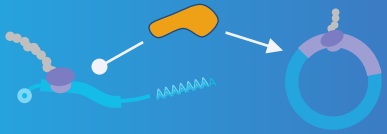


- circRNA
- RNA Editing
- mRNA
- RNAi
- Other

circRNA is gaining momentum as a superior mRNA platform

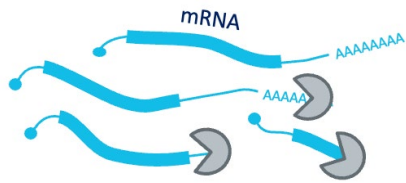


circRNA provides a toolbox to create a novel class of medicines



Enhanced protein expression

Extended RNA durability

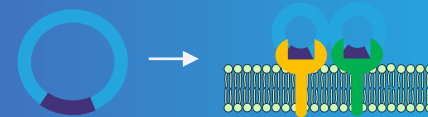


microRNA sponging

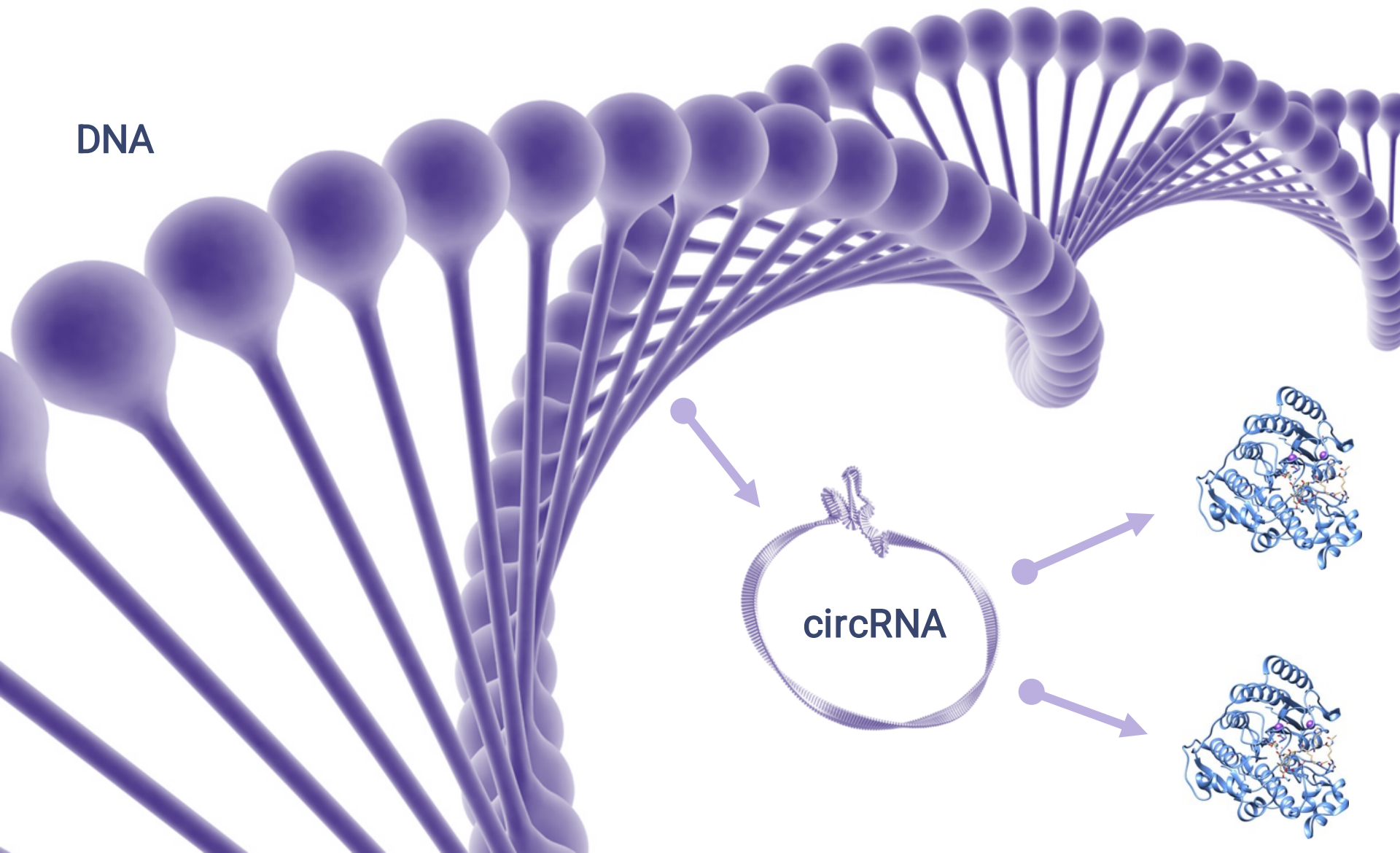
CircRNA is resistant to exonuclease degradation, leading to vastly increased half-life



Regulatory functionality



circVec – Circio's proprietary vector system for intra-cellular protein expression



DNA

circRNA

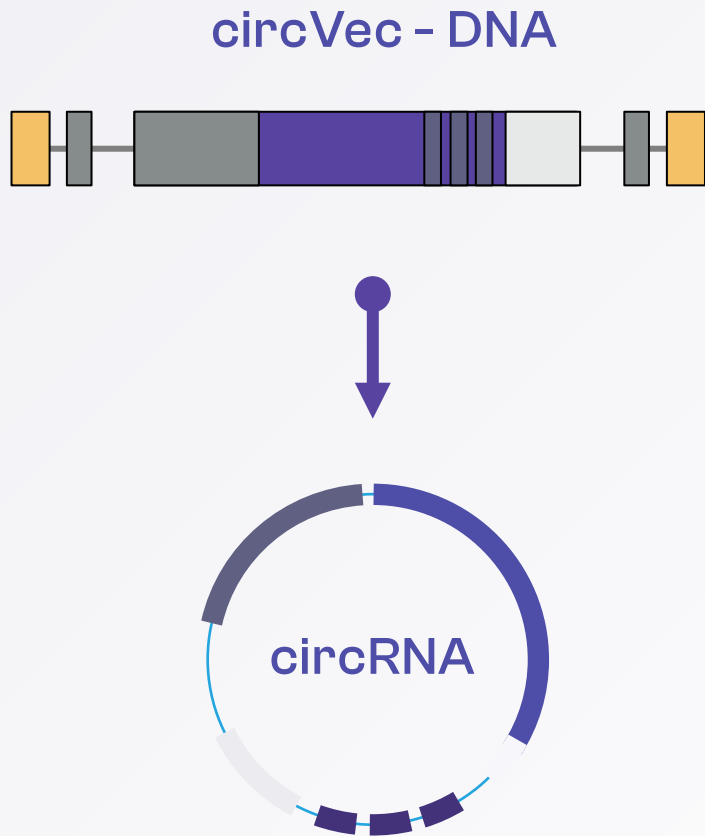
circVec
DNA vector

Inject

circRNA
biogenesis

Intra-cellular
protein expression

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



Genetic cassette design

+

Multi-functional circRNA design

- Modular structure
- Efficient circRNA biogenesis
- In-built RNAi
- Core circVec design IP filed 4Q'22
- Vector agnostic – IP filed 1Q'23 for use in adenoviral vectors

- Long-half life
- Enhanced protein expression
- microRNA sponging
- Regulatory functionality

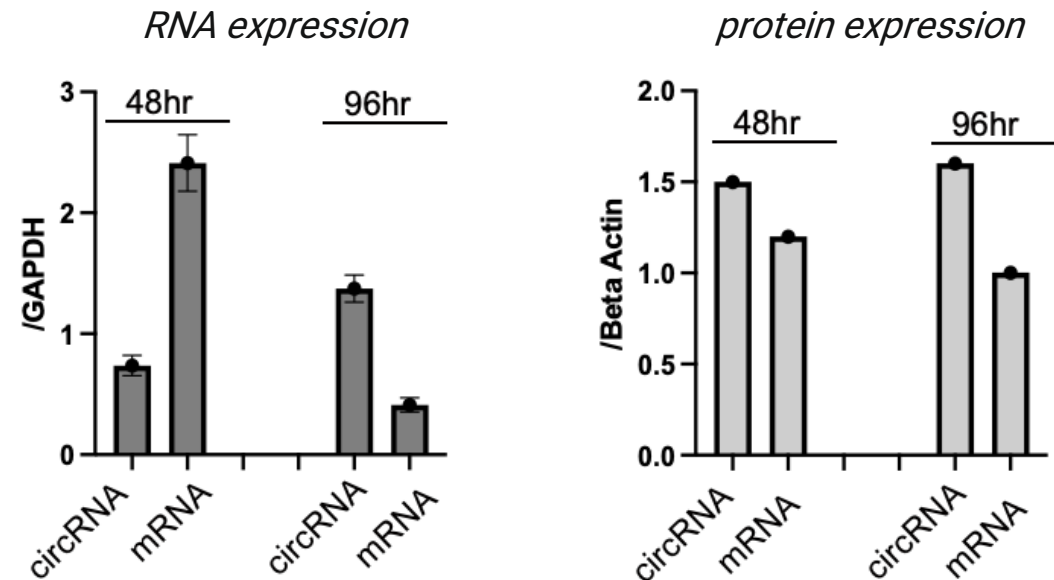
circVec achieves 15x prolonged circRNA half-life and increased protein expression vs. mRNA *in vitro*

circVec RNA stability
RT-qPCR, nascent vs. total RNA

135h vs. 9h
circRNA mRNA

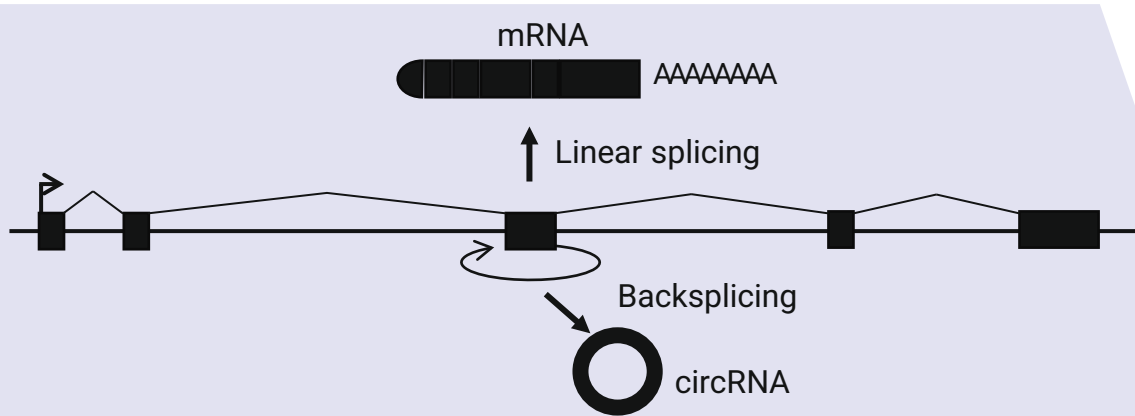


Accumulation of circVec circRNA and protein payload over time, RT-PCR and Western blot

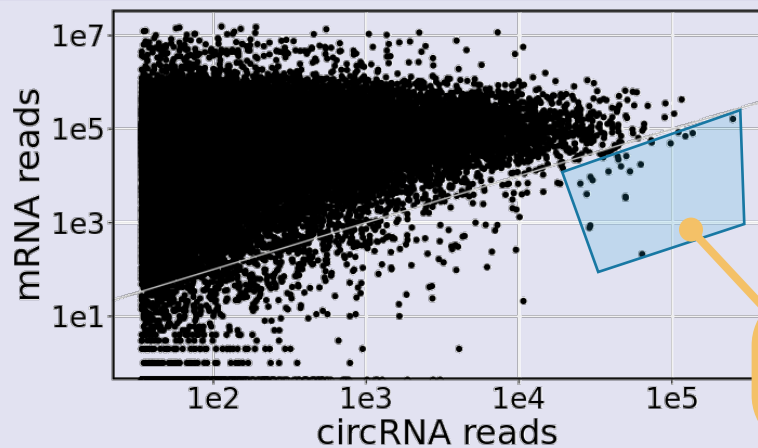


circRNA outperforms mRNA in vitro – confirmatory in vivo experiments ongoing

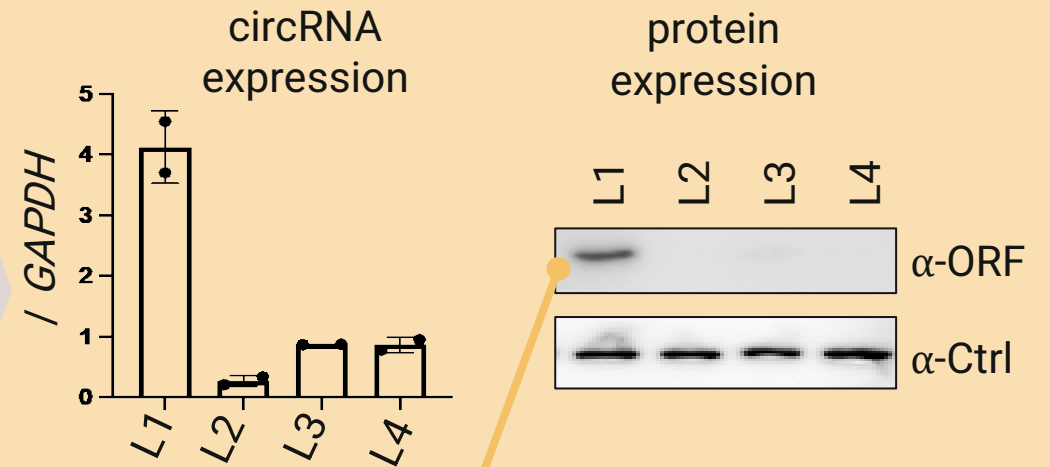
circVec starting point is based on nature's best design



Expression of endogenous circRNA
NGS analysis of 300+ RNAseq datasets



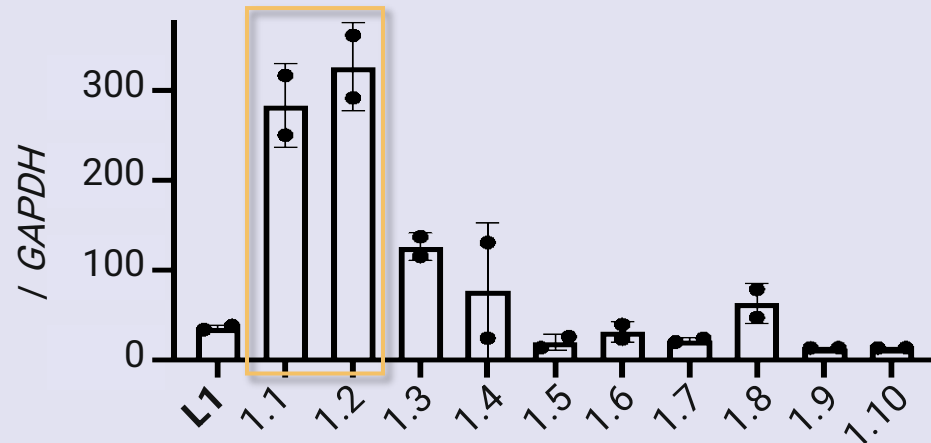
Screening of most effective circRNA-producing sequences invented by nature



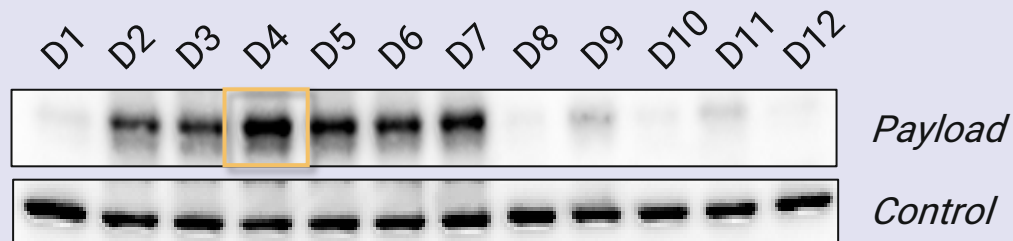
L1 cassette design shows most efficient circRNA biogenesis

circVec design has been systematically optimized for circRNA biogenesis and protein expression

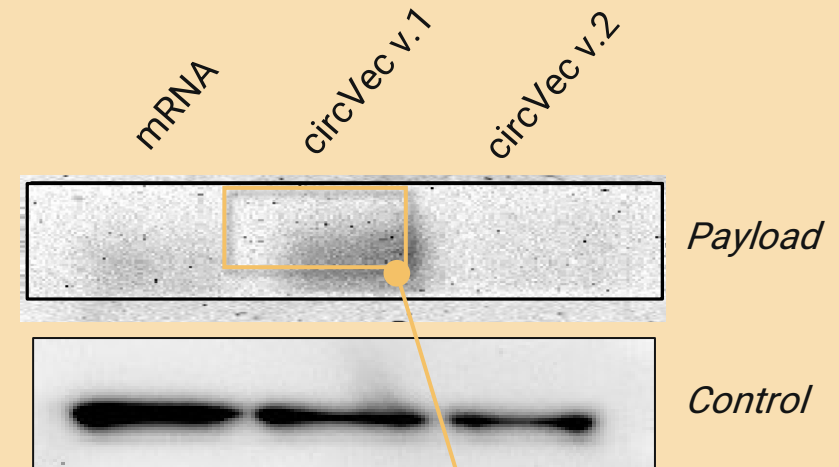
Design optimization for circRNA biogenesis
circRNA-specific RT-PCR



Design optimization for protein expression
Western blot, circRNA protein payload



Efficient circRNA designs outperform mRNA
Western blot, protein expression



circVec v.1 superiority over mRNA achieved by optimal combination of features

circVec data summary: broad technical proof-of-concept established



circRNA biogenesis

- Design optimized for highly efficient circRNA biogenesis in cells
- 10x improvement on “nature’s best design”
- 15x extended half-life vs. mRNA *in vitro*

Vector functionality

- DNA and virus -based circRNA biogenesis
- Replicating and non-replicating AdV, multiple insert sites identified
- Ability to express up to 5kb circRNAs

Protein expression

- Enhanced and more durable protein expression vs. mRNA
- Validated for multiple protein types
- Modular design optimized for high efficiency

Regulatory functions

- Robust miRNA sponging activity confirmed
- Additional regulatory functionality established
- “Hi-jacking” of host cell protein expression machinery

○ *Next step: validate findings in vivo*

○ *Next step: screening of additional vector types*

○ *Next step: validate durability in vivo*

○ *Next step: combine functionalities*

circVec can overcome limitations of synthetic RNA approaches and open new opportunities for circRNA

Cancer gene therapy



Efficient and durable expression of therapeutic proteins in solid tumors

-

Fastest path to clinic

Vaccines



Enhanced potency, single dose vaccine concept with simplified administration

-

Early partnering option

Rare disease



Durable protein replacement, without need for genome integration or LNP delivery

-

Major long-term potential

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

Circio has a unique edge in the emerging circRNA field



World-leading experts in-house with over 10 years experience in circRNA biology

- Led by circRNA discoverer and pioneer Dr. Thomas B Hansen



Differentiated vector delivery platform opening new therapeutic areas for circRNA

- Efficient circRNA biogenesis and superiority vs. mRNA established in vitro
- In vivo PoC studies initiated – first validation of a vector-delivered circRNA
- Technological fit in cancer gene therapy, rare genetic disease and vaccines



Opportunity for quick route to clinic in cancer gene therapy

- Building on clinical validation and existing manufacturing capability for in house adenoviral vector platform

3

TG01 KRAS program

4. HR update

The two TG01 investigator-initiated trials are open for enrolment in the USA and Norway

Sponsor



Clinical Design

- Pancreatic cancer
- Post-surgery TG01 vaccination
- TG01 monotherapy & PD1 combo
- Clinical benefit by ctDNA tracking
- 24 patients

Milestones

- US IND approved
- Actively enrolling
- First patient dosed March 2023



- Multiple myeloma
- TG01 vaccination following 1L therapy
- TG01 monotherapy only
- Clinical benefit by MRD tracking
- 20 patients

- NOMA approved
- Actively enrolling
- First patient enrolled June 2023

Phase 1 data presented at ASCO provides proof-of-concept for KRAS vaccination post-surgery

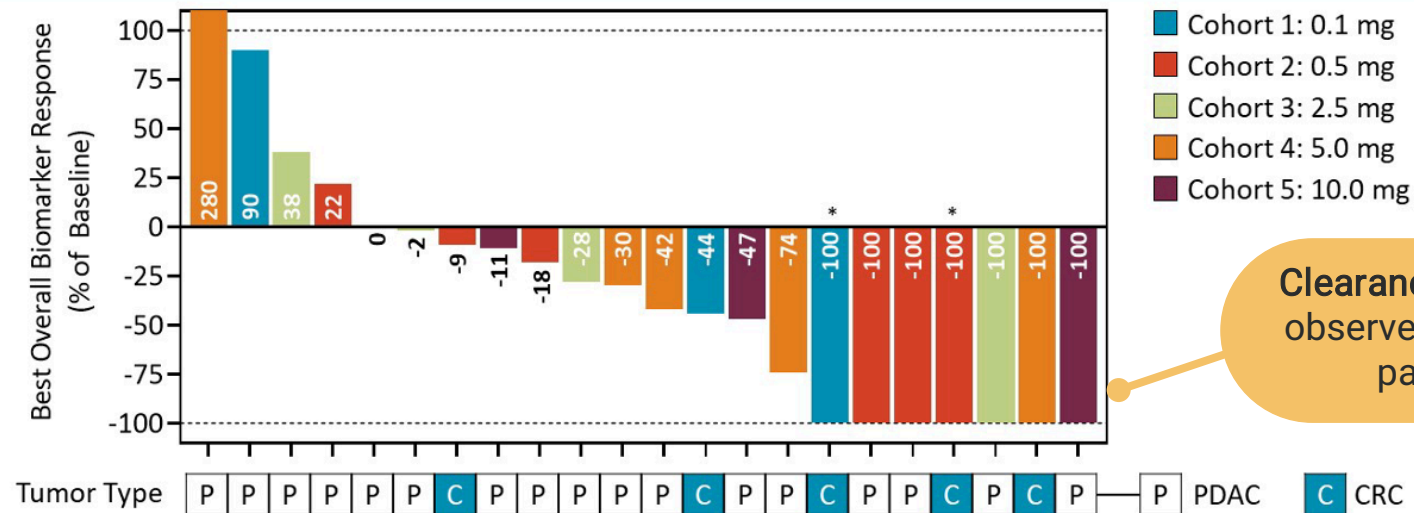
AMPLIFY-201 Waterfall Plot: Biomarker Reduction/Clearance

Reduction = % decrease from baseline

➤ 17/22 (77%)

Clearance = 0 MTM/mL on ctDNA assay

➤ 7/22 (32%)



- Product: ELI-002 KRAS vaccine
- KRAS 12D + 12R mutations only
- Monotherapy only, no PD1 combo

2023 ASCO
ANNUAL MEETING



- Product: TG01 KRAS vaccine
- Covers 7 KRAS mutations
- Monotherapy & PD1 combo

4

HR update

The senior management team has been adapted to increased preclinical circRNA platform focus



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



Margrethe Sørgaard
VP & Head of Clinical Development

Clinical development and PV expert with 30 years experience from big pharma and biotech. Previously Head of unit for PV and safety assessment at **NOMA**

MSc Biology



Ola Melin
VP & Head of Manufacturing

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

BS Biochemical engineering



“

circRNA is gaining strong momentum and Circio has a unique approach and delivery system that opens up novel therapeutic areas for circRNA, led by a high-caliber team aiming to build the leading circRNA biotech

Dr Erik D Wiklund – CEO ”