



**circio**

# Building next generation RNA therapeutics

**Erik D Wiklund - CEO**

**ABGSC Cancer Vaccine seminar  
28 August 2023**

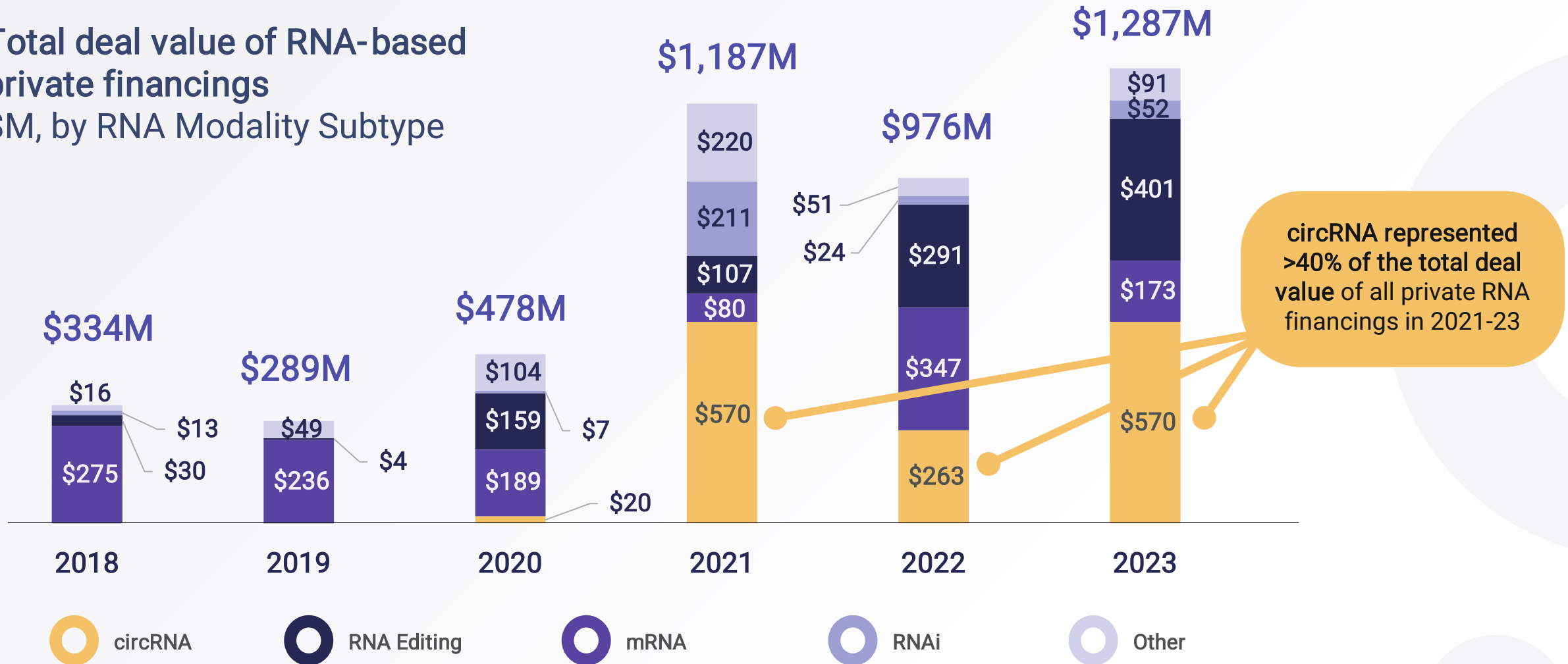
# Important notice and disclaimer

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.

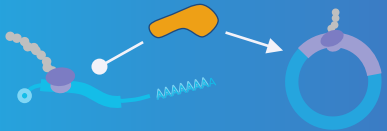
# Despite tough market conditions, RNA-based financings have increased sharply during 2021-23

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



# circRNA provides a toolbox to create a novel class of medicines

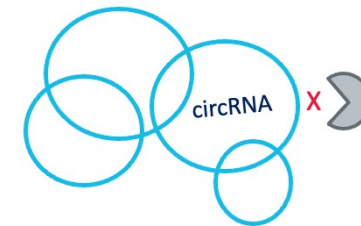
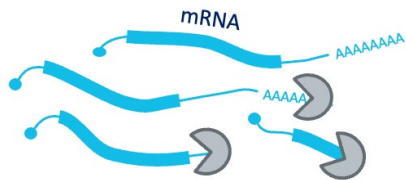
Enhanced protein expression



Extended RNA durability



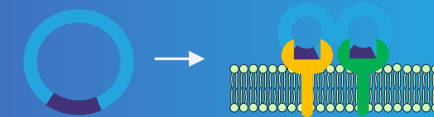
circRNA is resistant to exonuclease degradation, leading to significantly improved half-life vs. mRNA



microRNA sponging



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

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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](#)

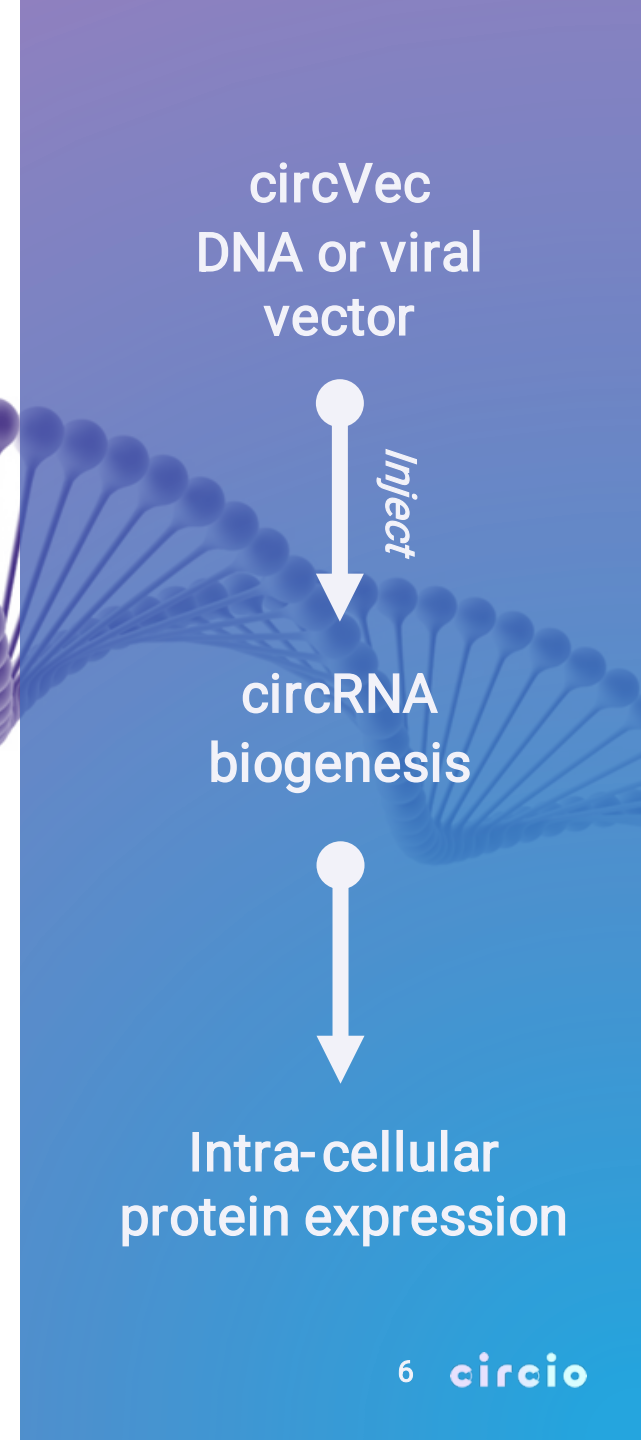
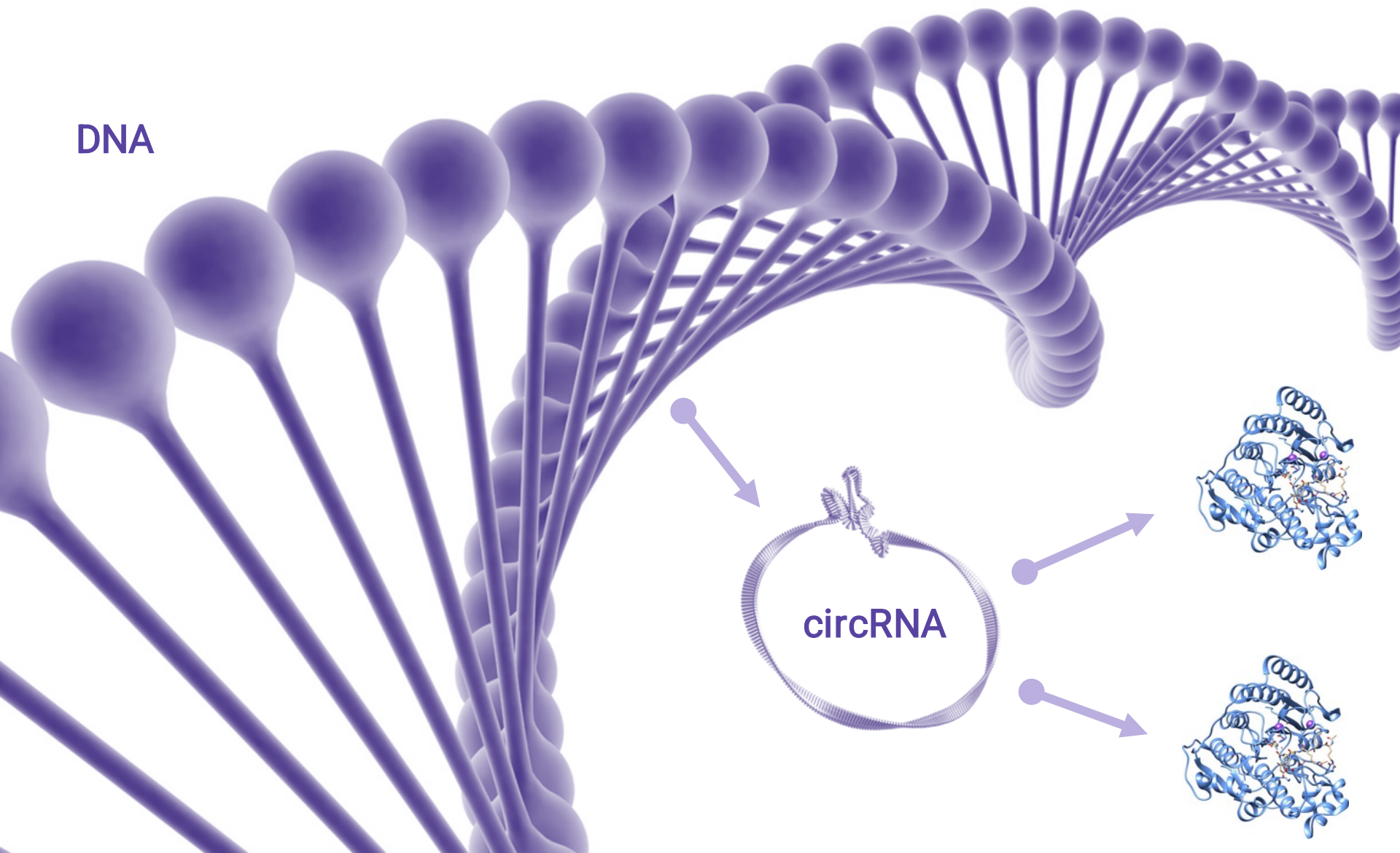
**nature reviews genetics** | 2,291 citations

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](#)

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



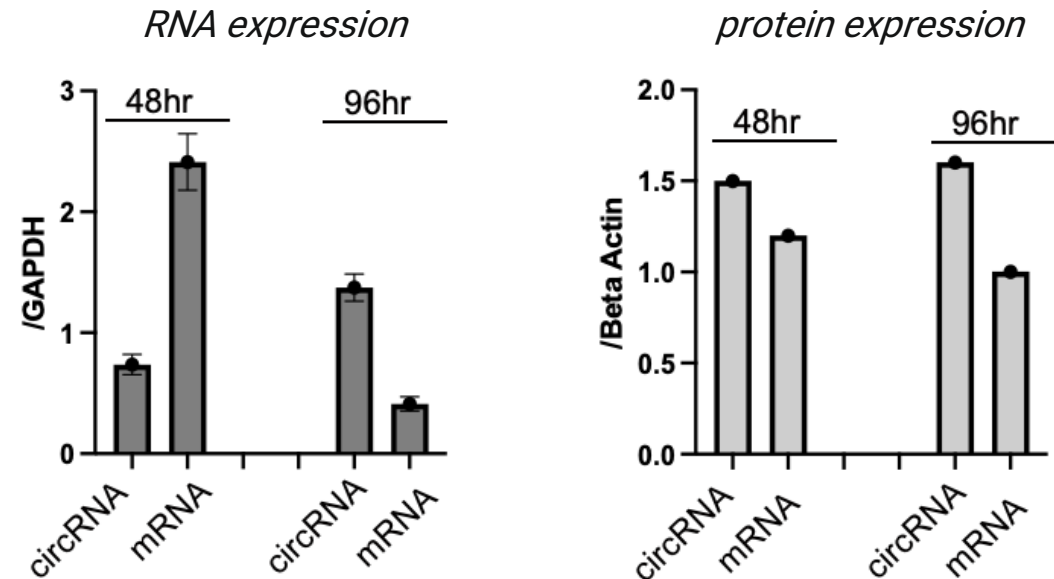
# circVec achieves 15x prolonged circRNA half-life and increased protein expression vs. mRNA *in vitro*

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 offers clear advantages in multiple therapeutic areas, and opens new opportunities for circRNA

**Rare disease**



“Remove-and-replace”  
concept with durability and  
safety advantages

Major long-term potential

**Cancer  
gene therapy**



Efficient and durable  
expression of therapeutic  
proteins in solid tumors

Fastest path to clinic

**Vaccines**



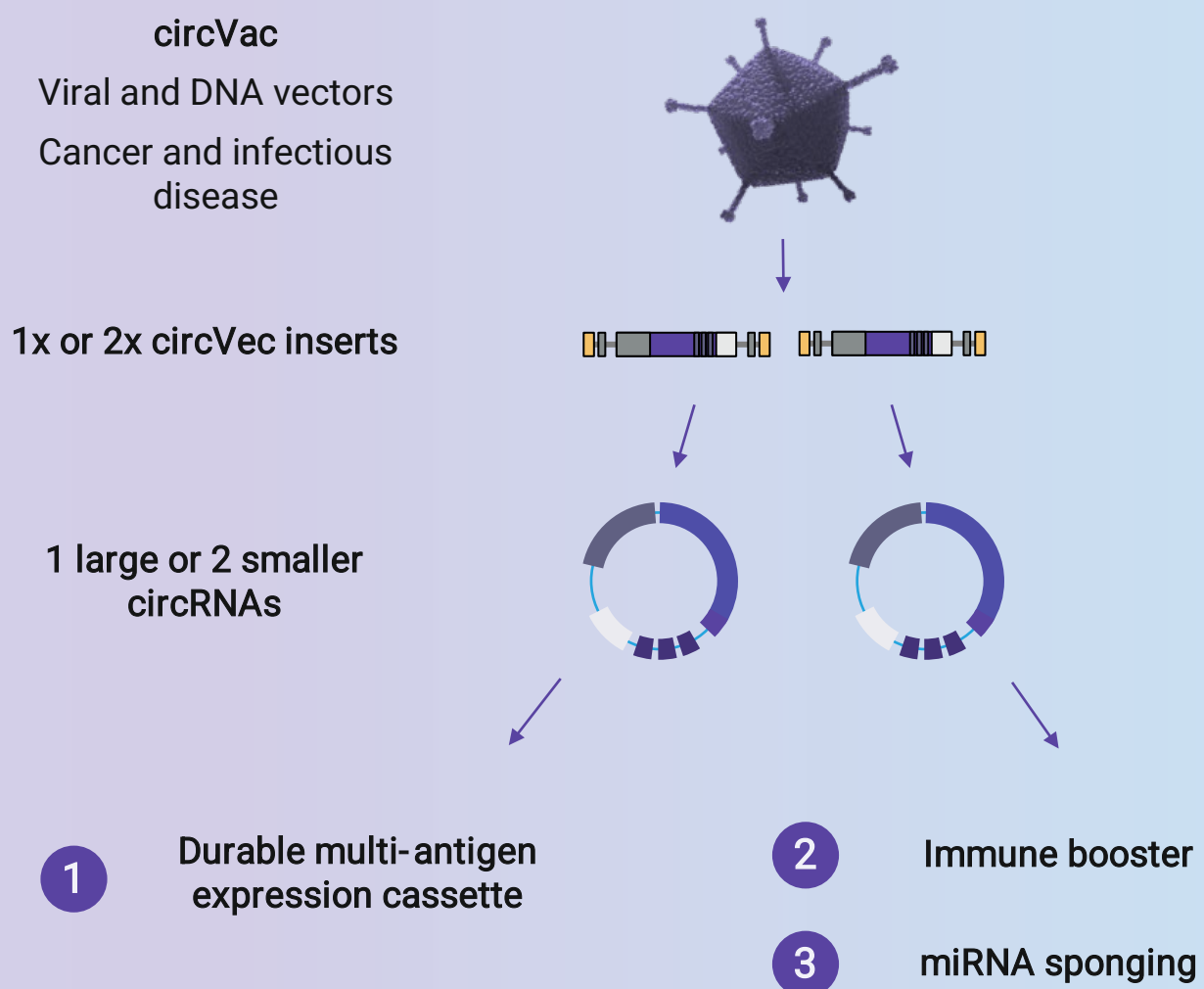
Enhanced potency, single  
dose vaccine concept with  
simplified administration

Early partnering option

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



# Establishing circVac proof-of-concept with aim to out-license for clinical development



## Development plan & target indication

- Cancer and infectious diseases, incl. influenza, shingles, malaria
- Out-license technical concept for clinical development following pre-clinical PoC with model disease antigens

## Project status

- Optimization of antigen expression level and durability for model antigens
- Evaluation of immune booster options

## Upcoming milestones

- 3Q'23: Comparative *in vivo* immune data
- 4Q'23: Vector / construct optimization
- 1H'24: *In vivo* data w/ disease and cancer antigens

# KRAS cancer vaccine program: mutant KRAS T-cells can recognize and eliminate tumors



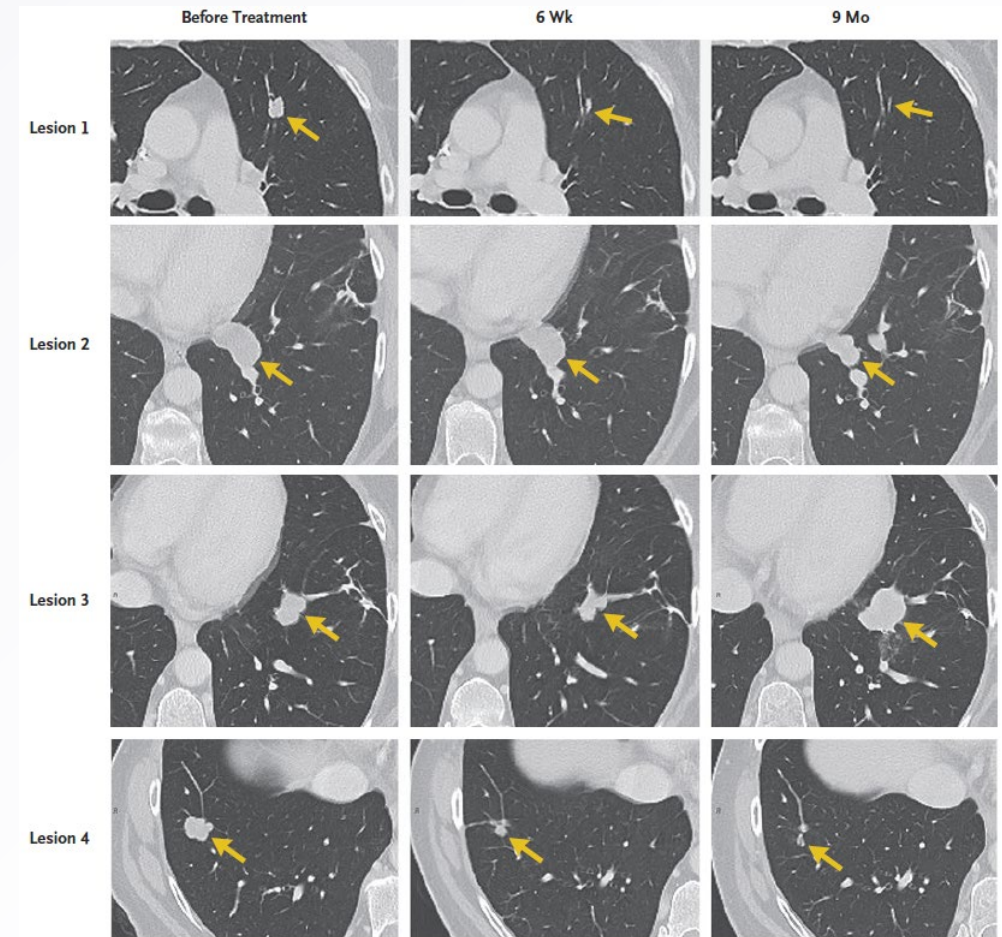
1

Endogenous CD8+ tumor-infiltrating lymphocytes (TIL) recognizing the G12D RAS mutation were isolated from a colorectal cancer patient

2

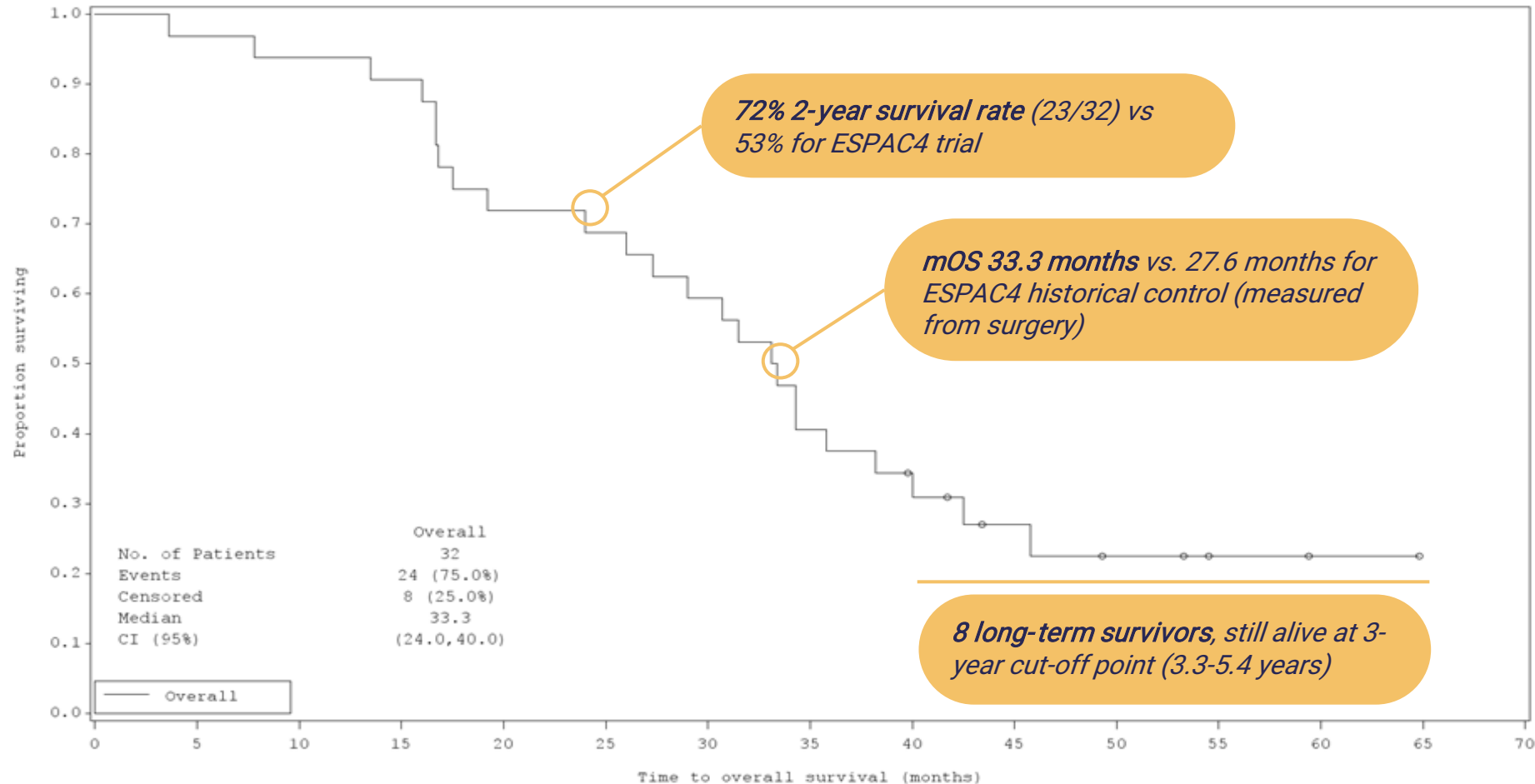
The G12D mutRAS CD8+ T-cells were expanded *ex vivo* and transfused back into the patient (single infusion of  $1.48 \times 10^{11}$  cells)

- All seven lung metastases detected in the patient showed regression (pictured on the right)
- One lesion (#3) progressed after 9 months of therapy, due to loss of the HLA locus
- Proof-of-concept for spontaneous T-cell response to mutant RAS in patients



# Legacy KRAS cancer vaccine TG01 has shown promising activity in phase 1 study in pancreatic cancer

PDAC PI/II Adjuvant Therapy



# The TG01 vaccine has been enhanced to drive stronger immune responses and further improve efficacy

## First generation TG01

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### Promising clinical activity

- 6 month survival benefit in pancreatic cancer
- mutRAS immune response in >90% of patients

### However, several factors complicate usage

- Sub-optimal treatment format
- Too many injections required
- Narrow immune response

## Second generation TG01

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### New adjuvant – QS21 (Stimulon) from Aenus

- Stronger and broader immune response
- Co-formulated adjuvant and vaccine
- Simplified dosing regimen

### Early-stage combination treatment strategy

- Combination with PD1 checkpoint inhibitor
- Improved opportunity to boost immune responses and clinical benefit

# Two TG01 investigator-initiated trials are enrolling patients in the USA and Norway

## Sponsor

THE UNIVERSITY OF KANSAS  
CANCER CENTER

Collaboration  
partner:

agenus

## Clinical Design

- Surgically removed pancreatic cancer
- Minimal residual disease postadjuvant therapy then TG01 vaccination
- TG01 monotherapy & PD1 combo
- Clinical benefit by ctDNA tracking
- N=24 patients

## Milestones

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

 Oslo  
University Hospital



- Multiple myeloma with persistent disease post 1L treatment
- TG01 monotherapy
- Clinical benefit by ORR criteria
- N=20 patients

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

# Circio has a unique edge in circRNA and immunotherapy



**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**

- Potential applications in rare disease, cancer gene therapy and vaccines
- Efficient circRNA biogenesis and H2H superiority vs. mRNA demonstrated in vitro
- Unique, multifunctional "remove-and-replace" therapeutic concept for rare disease



**Clinical stage KRAS cancer vaccine in clinical testing in multiple settings**

- Externally sponsored collaborative studies at low cost to Circio
- Early stage settings, higher likelihood of success