



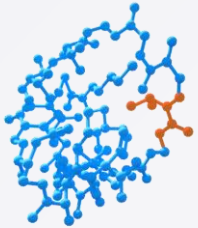
circio

Disruptive circRNA technology for genetic medicine

Dr. Erik Digman Wiklund - CEO

**Redeye Fight Cancer Event
24 January 2024**

Circio is developing a unique portfolio of cancer vaccines and next generation RNA therapeutics



TG01 Clinical stage cancer vaccine

- Targets KRAS mutations, found in 30% of all cancer patients
- Clinically validated target, both by industry and academia
- Potential upcoming USD 3m milestone from Chinese partner



Circular RNA Innovative pipeline

- Circular RNA (circRNA) is a next generation mRNA format
- Potential to disrupt the genetic medicine and vaccine fields
- Versatile platform with broad commercial opportunities

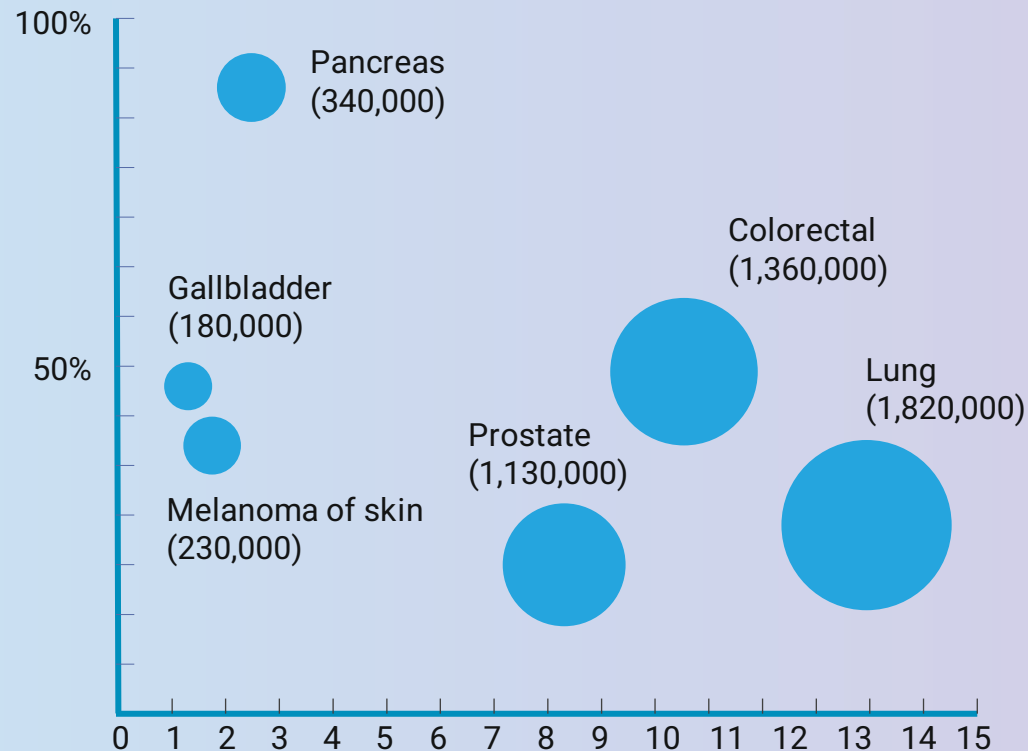
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KRAS cancer vaccine program

The RAS gene is mutated in 30% of all cancers

Frequency of RAS mutations

Global cancer incidents per 10,000
(xx) = no. of cancer patients



- RAS is the most frequently occurring cancer driver mutation
- RAS is a clinically validated shared neoantigen
- RAS mutations likely to become a future “genetic marker” indication

Phase 1 study completed with TG01 cancer vaccine in pancreatic cancer

Pancreatic Cancer
chemotherapy combination

Phase 1
post-surgery
n = 32 patients

BJC
British Journal of Cancer

www.nature.com/bjc



ARTICLE

Clinical Study

TG01/GM-CSF and adjuvant gemcitabine in patients with resected RAS-mutant adenocarcinoma of the pancreas (CT TG01-01): a single-arm, phase 1/2 trial

Daniel H. Palmer^{1,2}, Juan W. Valle^{3,4}, Yuk Ting Ma^{5,6}, Olusola Faluyi², John P. Neoptolemos¹, Trine Jensen Gjertsen⁷, Berit Iversen⁷, Jon Amund Eriksen⁷, Anne-Sophie Møller⁷, Anne-Kirsti Aksnes⁷, Robert Miller⁷ and Svein Dueland⁸

- TG01 targets seven different RAS mutations in parallel
- Mutant RAS immune response detected in 94% of patients
- Six month survival benefit vs. chemotherapy

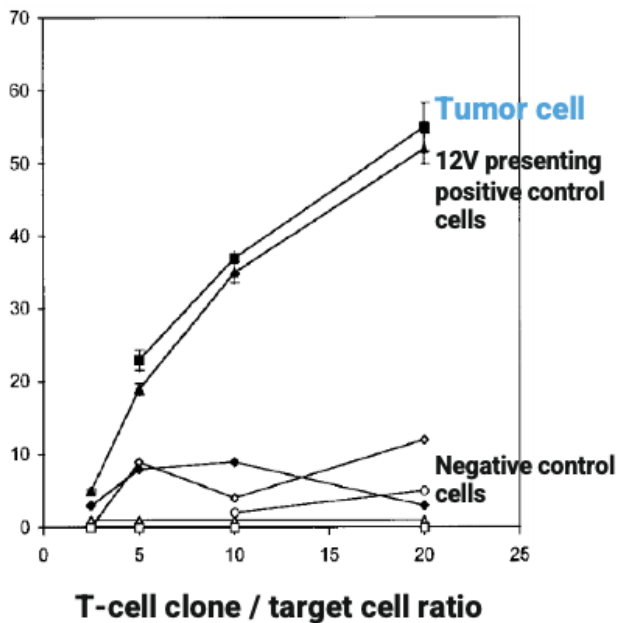
TG01 drives robust anti-RAS T-cell immune responses



CD4+ T-cells

mutRAS specific CD4+ T-cells isolated from vaccinated patient

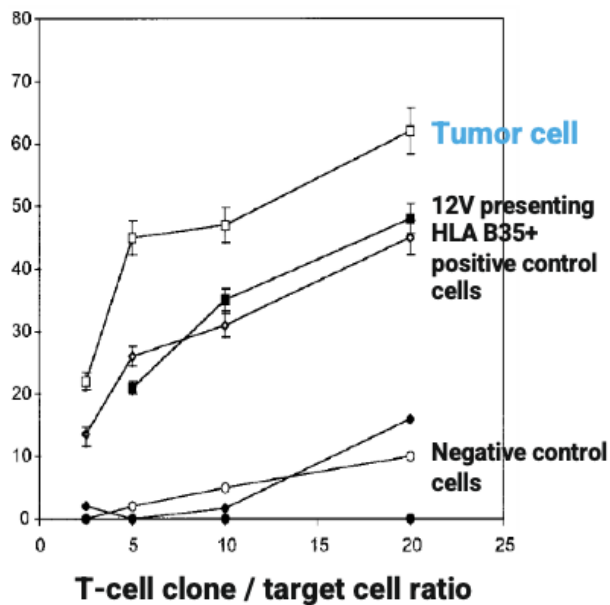
% CD4+ T-cell clone cytotoxicity



CD8+ T-cells

mutRAS specific CD8+ T-cells isolated from vaccinated patient

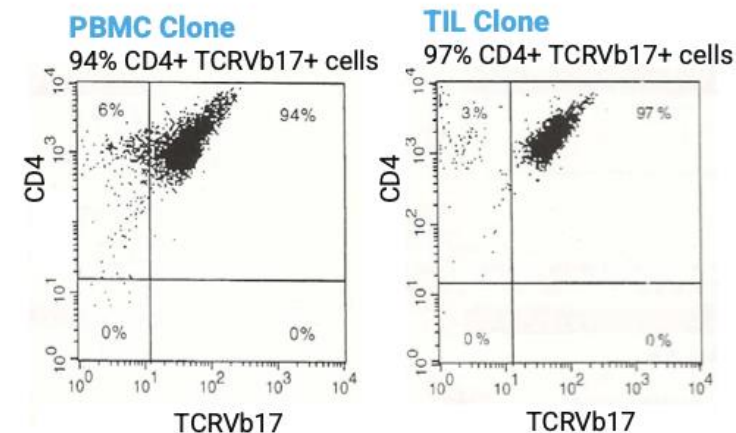
% CD8+ T-cell clone cytotoxicity



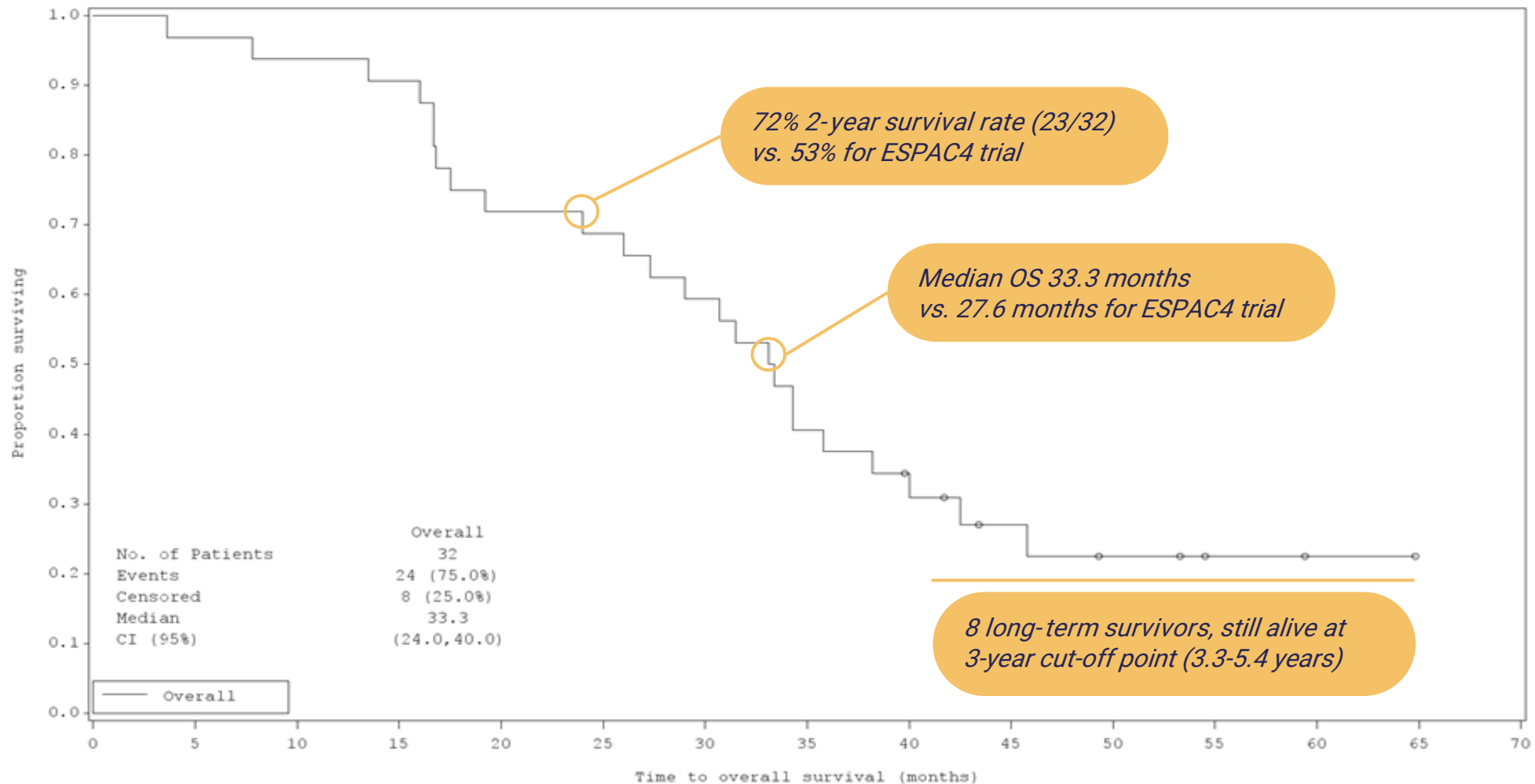
CD8+ TILs

mutRAS specific CD8+ T-cells isolated from the tumor of vaccinated patient

The same CD8+ T-cell clone found both in circulation and in the tumor



TG01 RAS immune responses were associated with six month survival benefit in pancreatic cancer



Cancer vaccine data presented at ASCO 2023 provides external proof-of-concept for KRAS vaccination

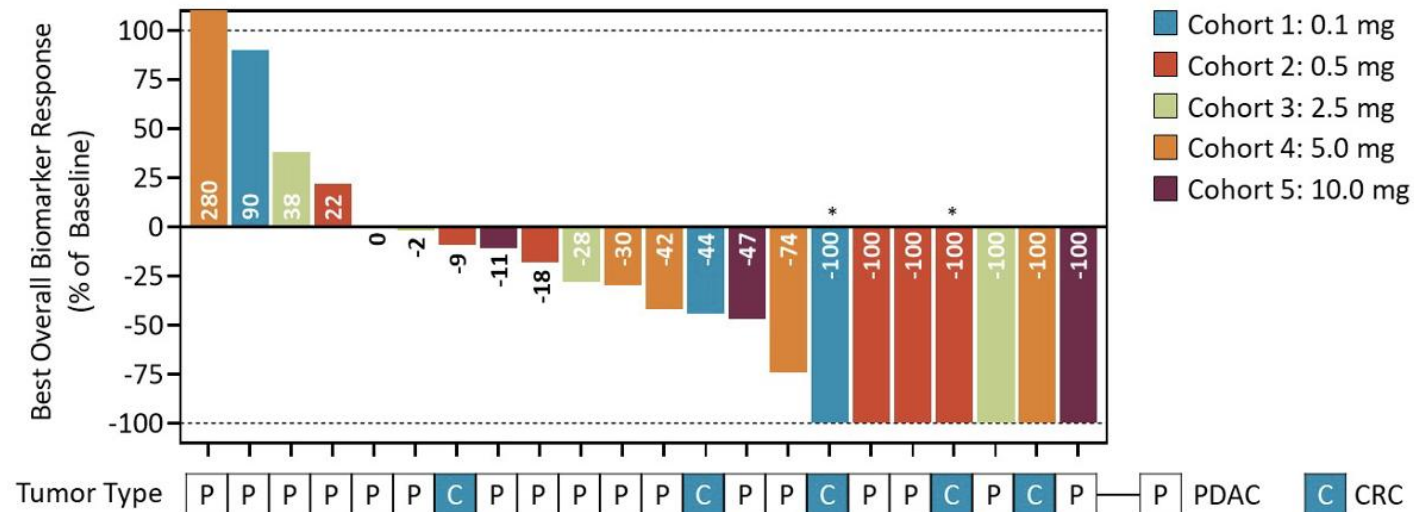
AMPLIFY-201 Waterfall Plot: Biomarker Reduction/Clearance

Reduction = % decrease from baseline

➤ 17/22 (77%)

Clearance = 0 MTM/mL on ctDNA assay

➤ 7/22 (32%)



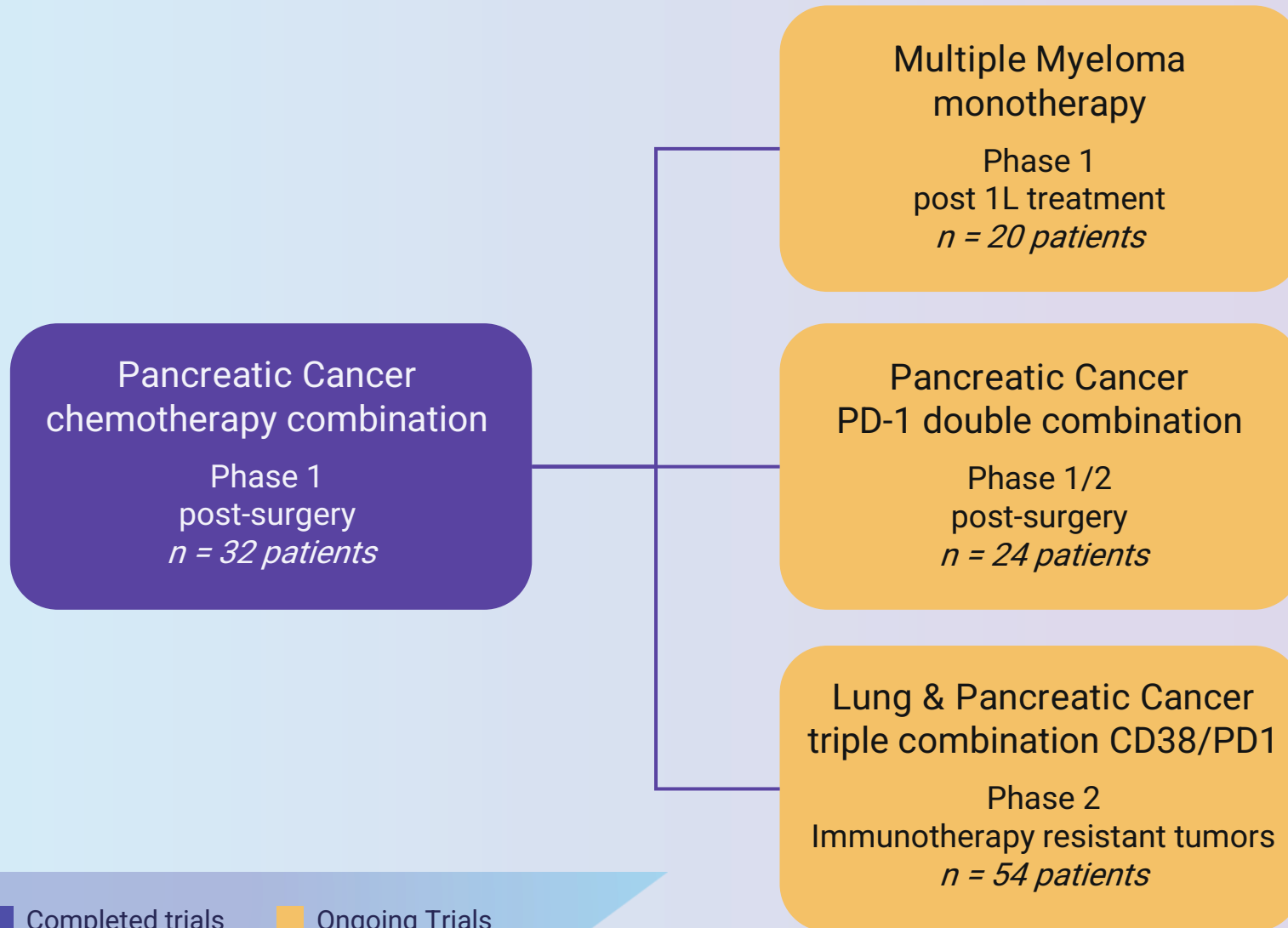
- Product: ELI-002 KRAS vaccine
- KRAS 12D + 12R mutations only
- Monotherapy only, no PD1 combo

2023 ASCO[®]
ANNUAL MEETING

circio

- Product: TG01 KRAS vaccine
- Covers 7 KRAS mutations
- Monotherapy & IO combinations

Next steps: TG01 program expanded into multiple cancer settings



Sponsored by:



THE UNIVERSITY OF KANSAS
CANCER CENTER

agenus



Georgetown University



Johnson & Johnson

TG01: Additional opportunity in China

Pancreatic Cancer
chemotherapy combination

Phase 1
post-surgery
n = 32 patients



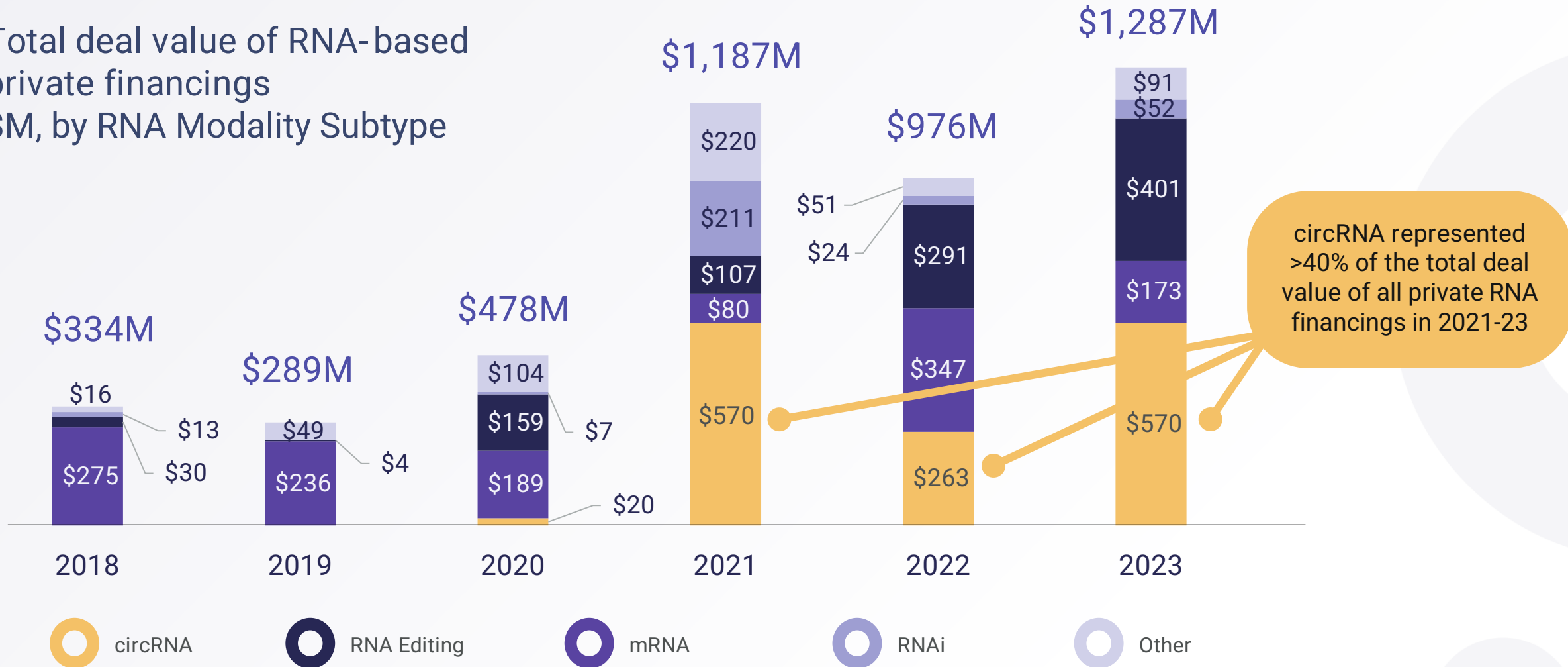
- License option for TG01 in China
- IND-review in process for two clinical studies in China
- USD 3m milestone payable upon IND approval

2

Circular RNA pipeline program

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

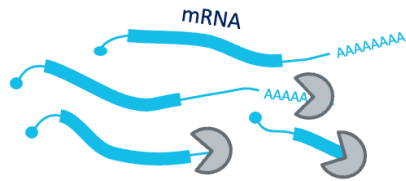
Total deal value of RNA-based private financings \$M, by RNA Modality Subtype



Circular RNA (circRNA) is a novel disruptive RNA format

Extended RNA durability

15x half-life vs. mRNA



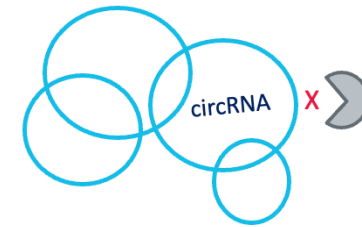
microRNA sponging

mRNA is destabilized by microRNAs

**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

Circio leadership established the circRNA field



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](#)

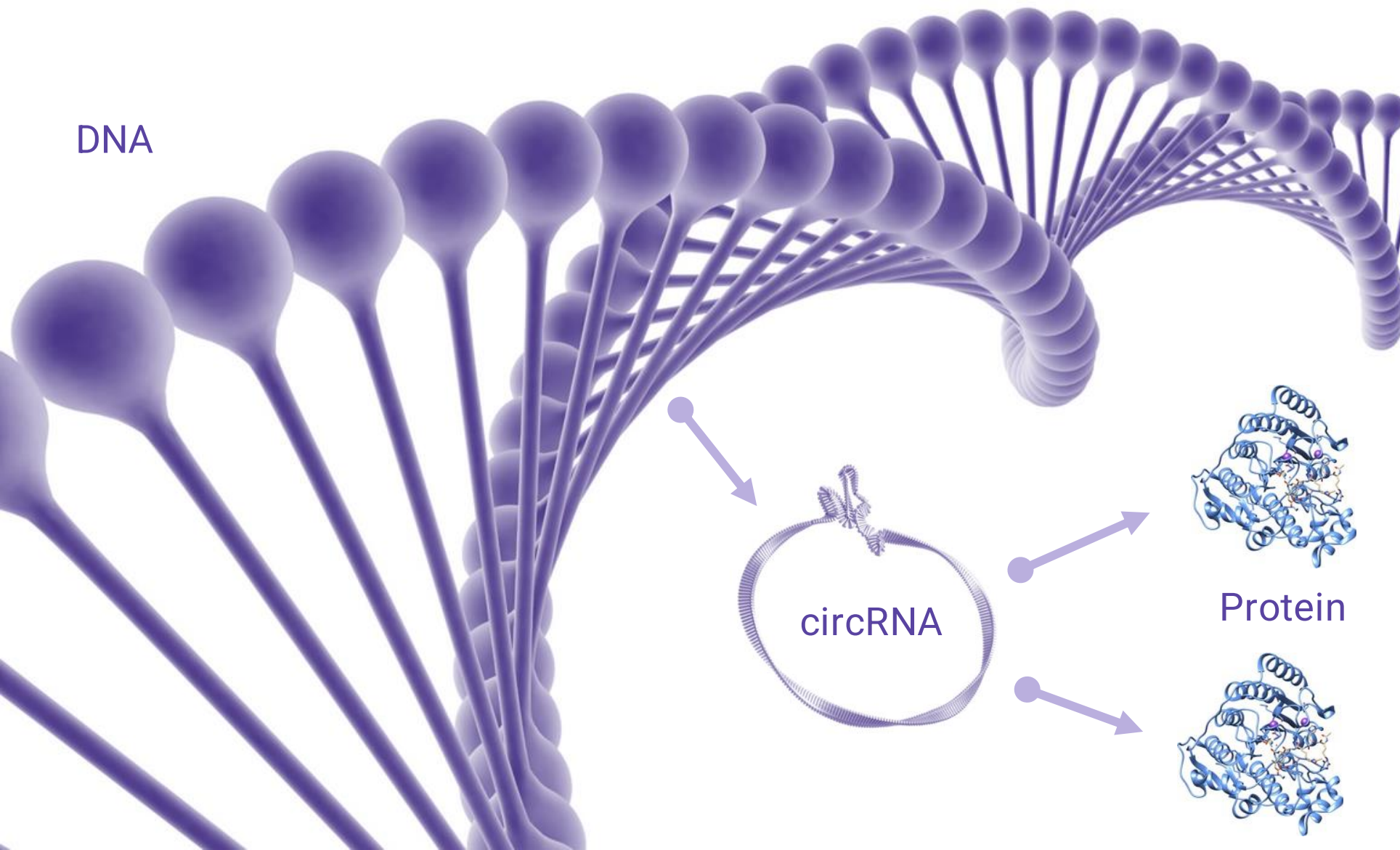
nature reviews genetics 2,291 citations

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](#)

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



circVec
DNA or viral
vector

Inject

circRNA
biogenesis

Intra-cellular
protein expression

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

Increased expression level

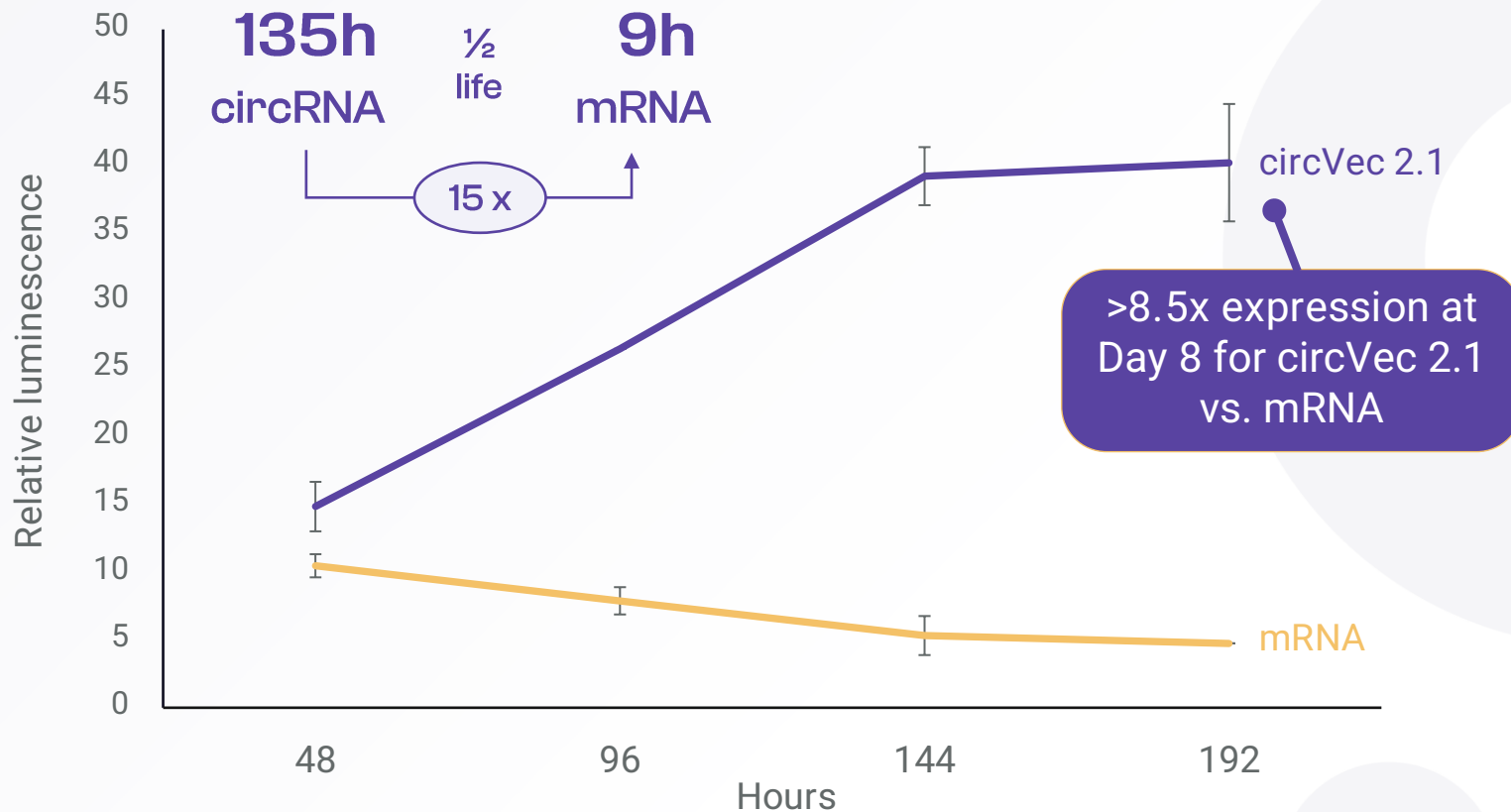
Prolonged durability

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 substantially outperforms mRNA durability

circVec 2.1- *Luciferase*

mRNA-vector- *Luciferase*

Left hindleg

Right hindleg

Monitor expression over time



Day 1

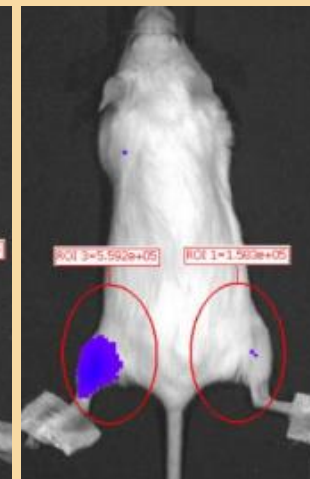
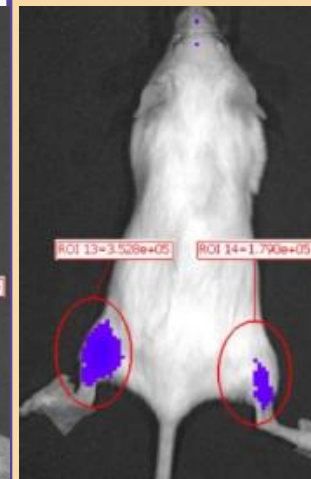
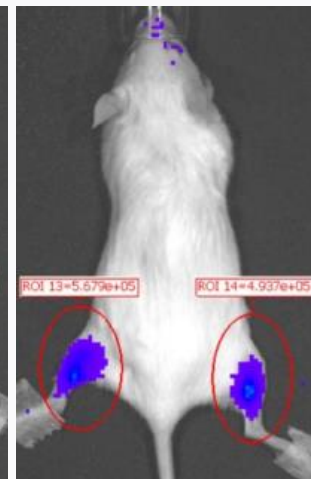
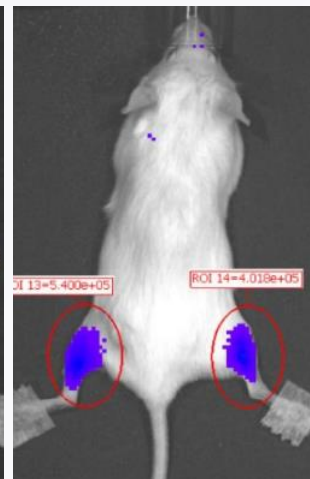
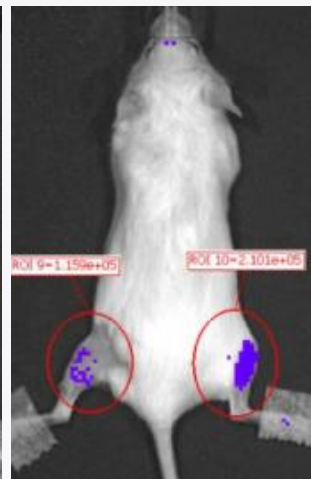
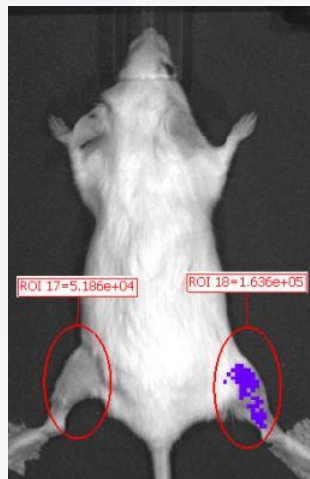
Day 8

Day 14

Day 21

Day 28

Day 35



circRNA mRNA

circRNA mRNA

circRNA mRNA

circRNA mRNA

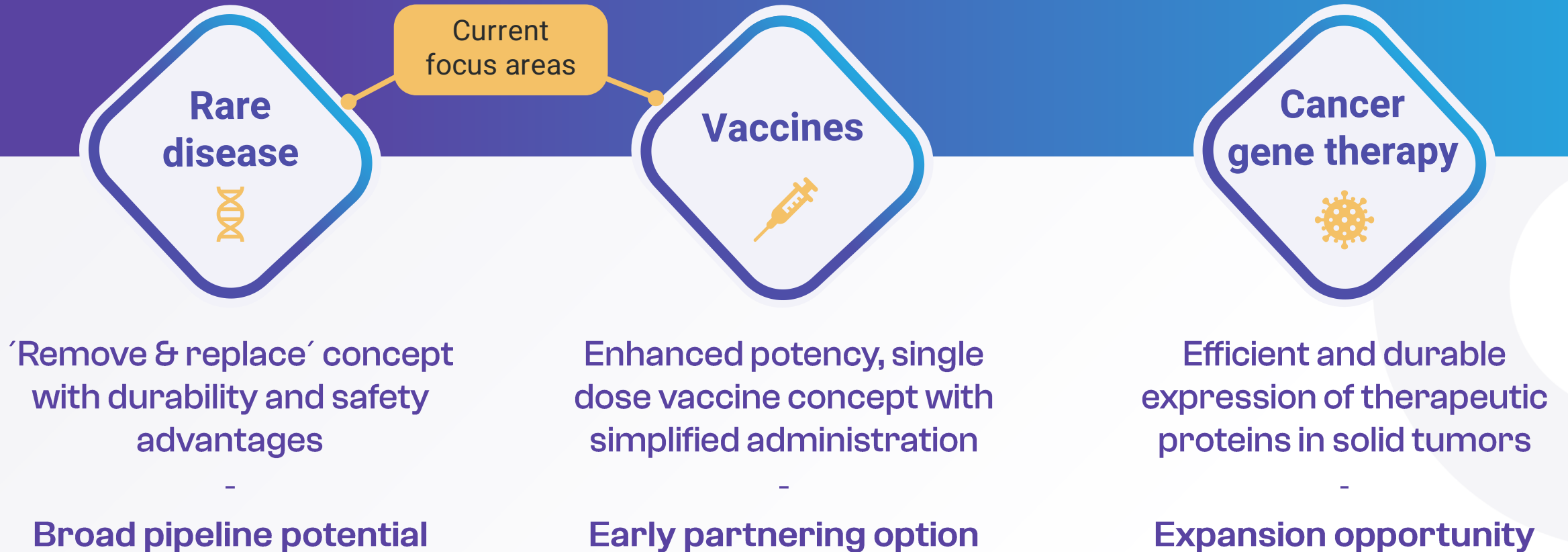
circRNA mRNA

circRNA mRNA

Real-time monitoring ongoing

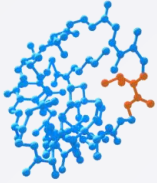
Increasing circVec expression: highest at Day 35, mRNA lowest at Day 35

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



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

Circio investment case – executive summary



Clinical stage cancer vaccine

- Ongoing phase 2 program creates multiple shots on goal
- Low cost, financed through partnerships and grants
- Potential upcoming USD 3m milestone from Chinese partner



Unique circRNA pipeline

- Deep expertise: the discoverers of circRNA work for Circio
- Differentiated approach, substantially improved durability
- Platform potential, lead applications in gene therapy and vaccines



Value drivers

- TG01 out-licensing following strong phase 2 data package
- Aiming for several circRNA partnering deals during 2024-2025