GMP Circular RNA LNP: Process Development and Manufacturing Innovations for the Next Frontier of ATMPs



Presenter
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Presenter
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CSO & Board Member
Circurna



Genetic Medicine Innovator & Entrepreneur
Peter Weinstein, Ph.D., J.D.
Founder & CEO
Circurna

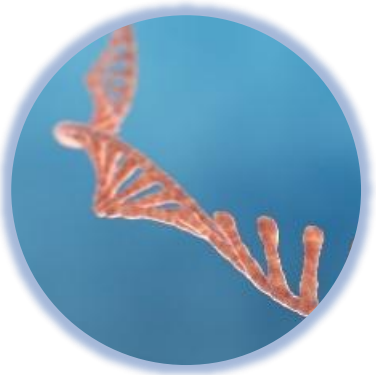


Moderator
Jeff Hung, Ph.D.
VP of Commercial Strategy
uBriGene

Logistics:

- You will be put on mute during the webinar
- We welcome you to ask questions using the “Q&A” on the top right corner of the platform
- Your questions will be addressed after the presentation

Agenda





01 Introductions

02 uBriGene's RNA manufacturing platform

03 Circurna: Design & Application of circRNA

04 Fireside Chat: circRNA Trends, Challenges, & Opportunities

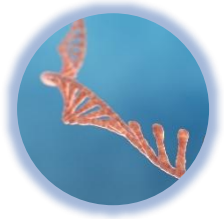
05 Q&A

uBriGene – Cell and Gene Therapy CDMO

Plasmids



Non-Viral Platform (RNA-LNP)

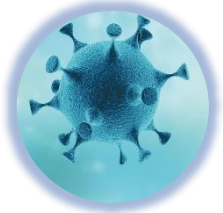


circRNA, mRNA, saRNA



Encapsulation into LNP

Viral Vectors



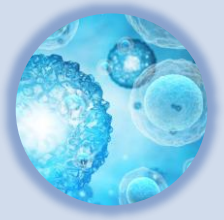
AAV, LVV, Retrovirus, Oncolytic virus

Quality Control



***EX VIVO* CGT**

Cell Therapies



CAR-T/-NK, TIL, iPSC, MSC

Cell isolation, reinfusion

***IN VIVO* CGT**

Direct injection

Patient



uBriGene's RNA Manufacturing Platform

Plasmid DNA Production

- Master cell banking
- pDNA production
- pDNA linearization

Production of DS

- *In vitro* transcription (IVT) ± circularization
- Purification
- DS release (mRNA, circRNA and saRNA)

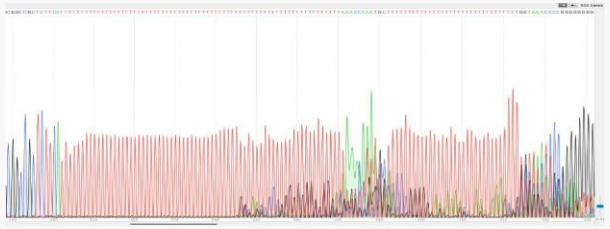
Production of DP

- RNA-LNP formulation PD
- RNA-LNP DP manufacturing

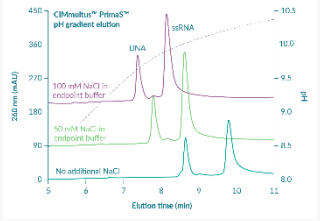
Analytics

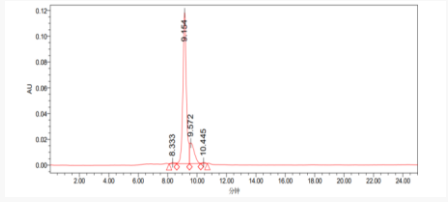
- Aseptic filling
- DP release testing

Plasmid Stability



Process Development
Analytical Development

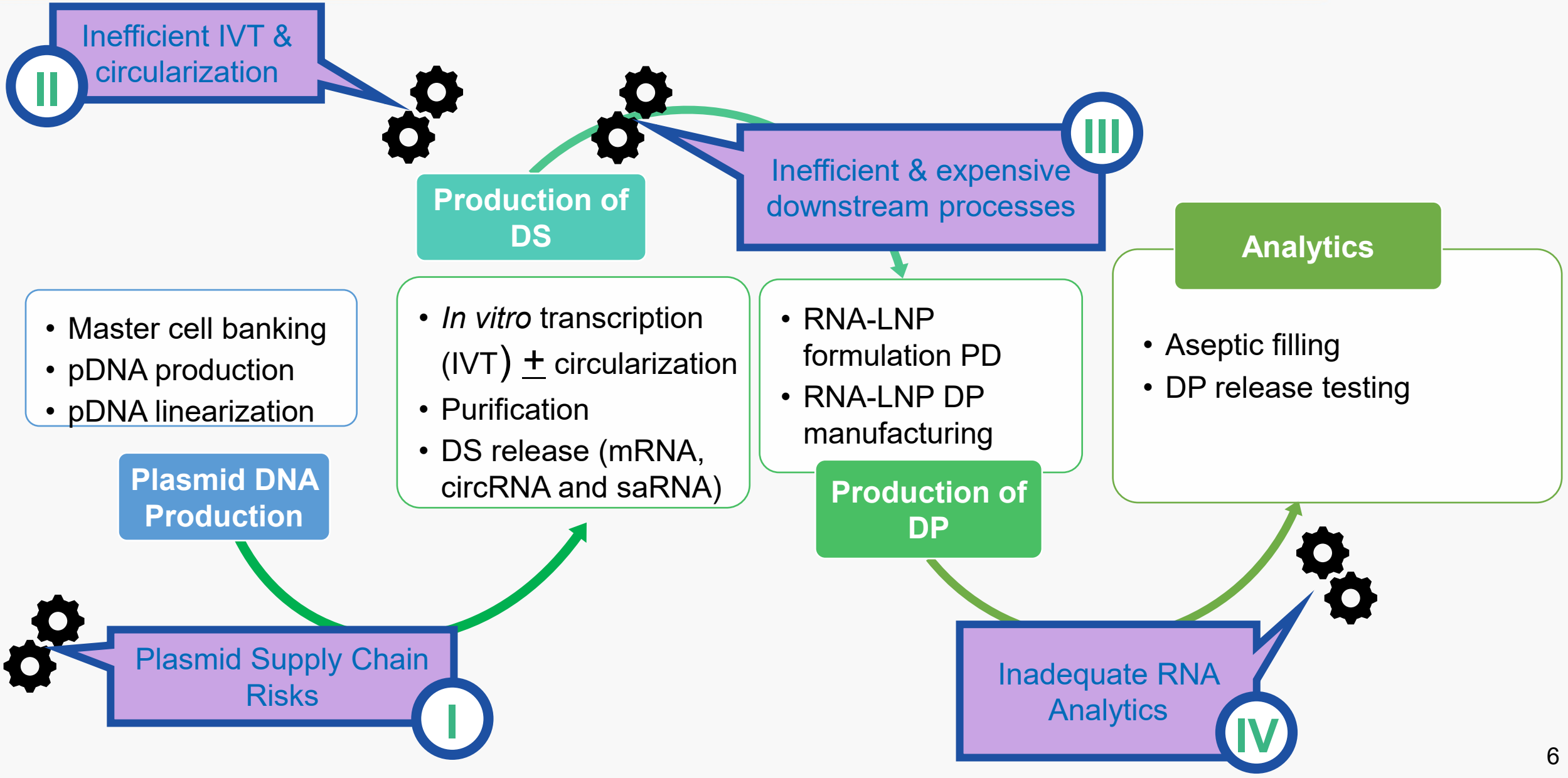




DS/DP Stability



circRNA Manufacturing Bottlenecks



Trustworthy GMP Plasmid Supply Chain



Upstream Process Innovations

- Single-use fermenters
- Fermentation yields > 1g/L
- Animal component- & antibiotic-free process
- Scalable to 200L

Downstream Process Innovations

- Two-step chromatography
- Effective impurities removal
- >95% supercoiled plasmid
- High recovery rates (40-50%)



Clinical Track Record

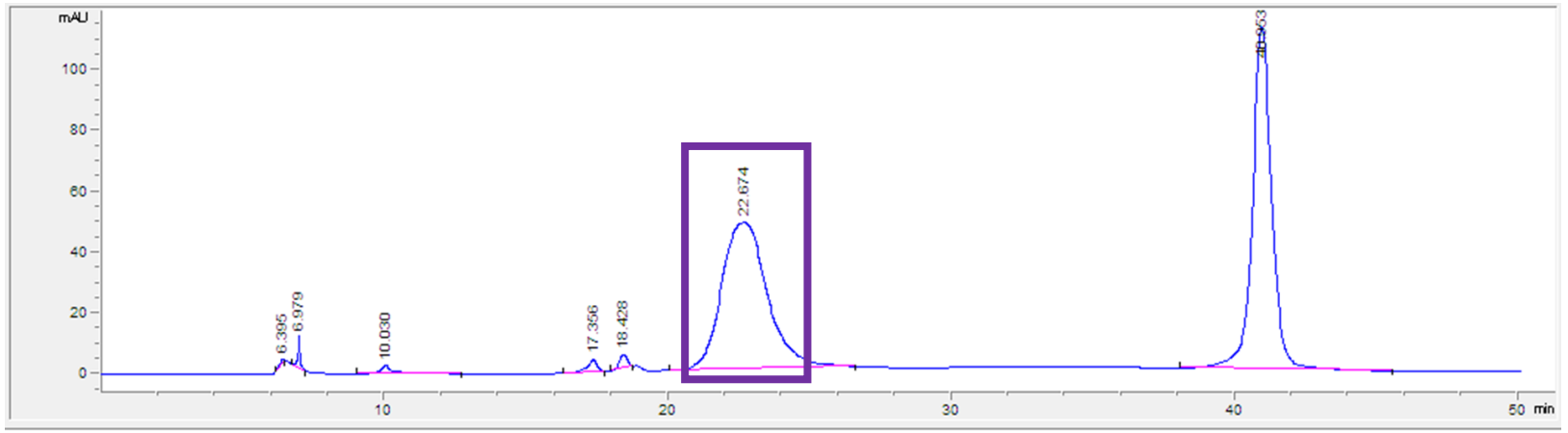
- Manufacture 100+ GMP plasmid batches annually
- Multiple manufacturing sites ensure supply chain security
- FDA DMFs in place for plasmids
- uBriGene plasmids have supported 20+ global INDs

High efficiency RNA IVT and circularization

IVT / Circularization condition	% circRNA
P1	**50**
P2	ND
P3	34
P4	36
P5	ND
P6	ND
P7	43
P8	28
P9	49
P10	44

Excellent Process, Excellent Product

- 2 mg/ml IVT RNA
- High fidelity RNA Pol minimizes dsRNA
- 50%+ circularization rate
- Scalable process (10ug – grams circRNA)



RNA analysis by RP-HPLC

Scalable, Enzyme-free circRNA Purification

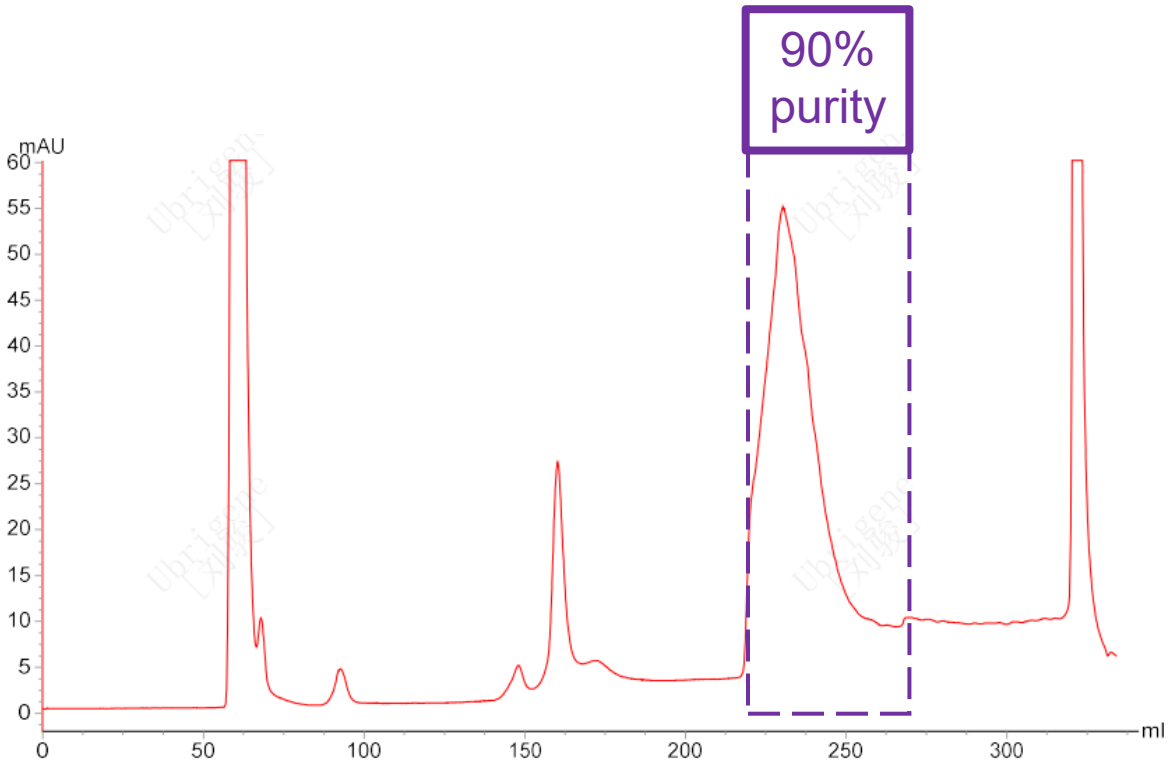
Current enzymatic circRNA purification process bottlenecks:

- GMP enzyme sourcing challenges
- Scaling is technically challenging
- Scaling is exorbitantly expensive

This is THE BIGGEST HURDLE to circRNA commercialization

uBriGene Purification Innovations:

- Enzyme independence
- Scalability
- Cost-effectiveness



Preparative column circRNA purification

IV circRNA Analytics for circRNA Purity & Integrity (1/2)

circRNA Analytics Challenges

circRNA manufacturing workflows can introduce many process-related contaminants:

- **Enzymes** – RNA Pol, DNAse, ligases, ribozymes, etc.
- **Structural heterogeneity** – circRNA, linear, nicked linear, fragmented RNA
- **Unreacted nucleotides**
- **Chemical byproducts**

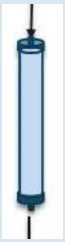
Analytics Platform Limitations

Size Exclusion Chromatography (SEC)



- Effectively separates circRNA from small contaminants & NTPs
- **Unable to distinguish circRNA from linear RNA of similar sizes**

Capillary Electrophoresis (CE) limitations



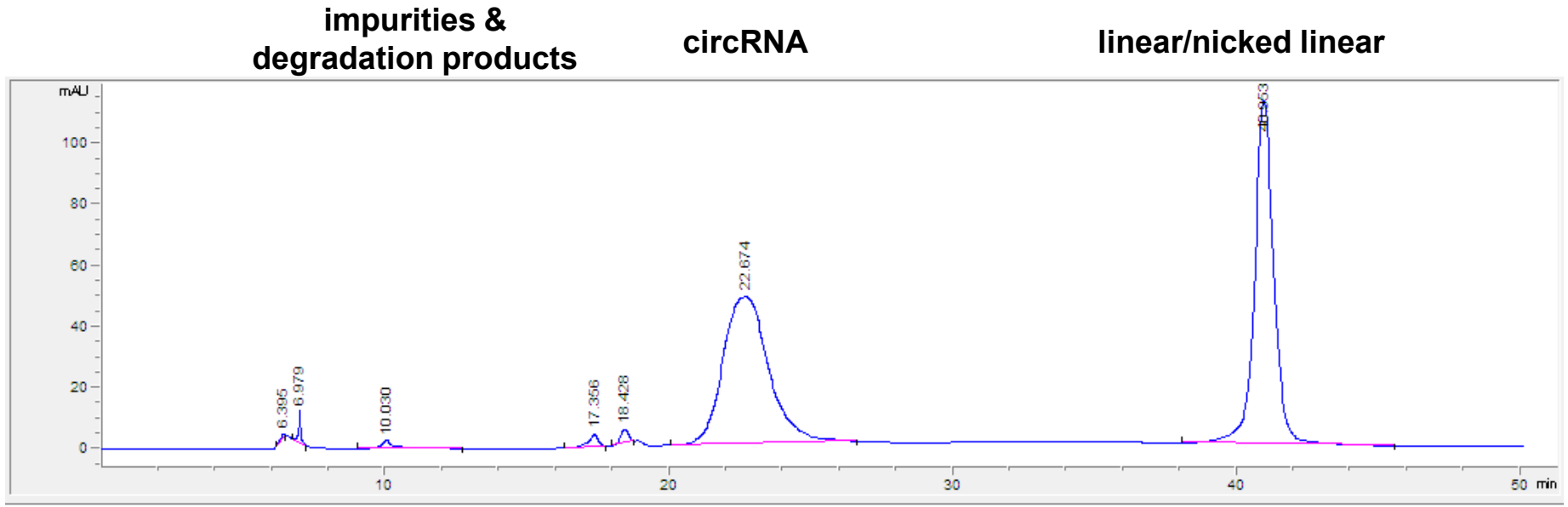
- Can distinguish small contaminants, degradation products, & linear precursor RNA
- **Unable to distinguish circRNA from nicked linear RNA**

Data-driven use case: See uBriGene QC team's 2025 World Vaccine Congress poster

IV circRNA Analytics for circRNA Purity & Integrity (2/2)

The uBriGene RP-HPLC QC assay solution

- circRNA is quantitatively resolved from small impurities, degradation products, linear & nicked linear RNA
- Cleanest and most quantitative circRNA analytics platform to-date

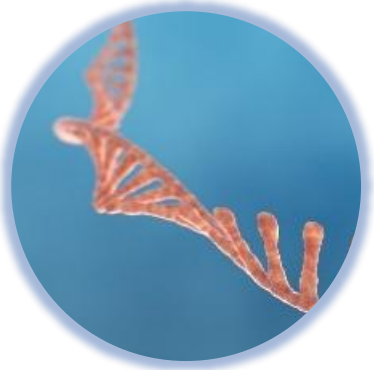


Data-driven use case: See uBriGene QC team's 2025 World Vaccine Congress poster

uBriGene's circRNA CMC platform solutions

Client's Challenges		uBriGene's circRNA CMC Solution
Unreliable plasmid supply	I	**Industry-leading plasmid quality & reliability**: >100 GMP plasmid batches annually
Inefficient IVT and Circularization	II	**Scalable upstream process**: Consistently high RNA yields with 50%+ circularization efficiencies
Ineffective & expensive downstream processes	III	**Efficient enzyme-free downstream process:** No GMP enzyme dependencies means reliable, scalable, & cost-effective purification
Lack of quantitative circRNA analytics	IV	**Quantitative RNA species-specific QC assays:** Qualified HPLC assay for circRNA quantitation

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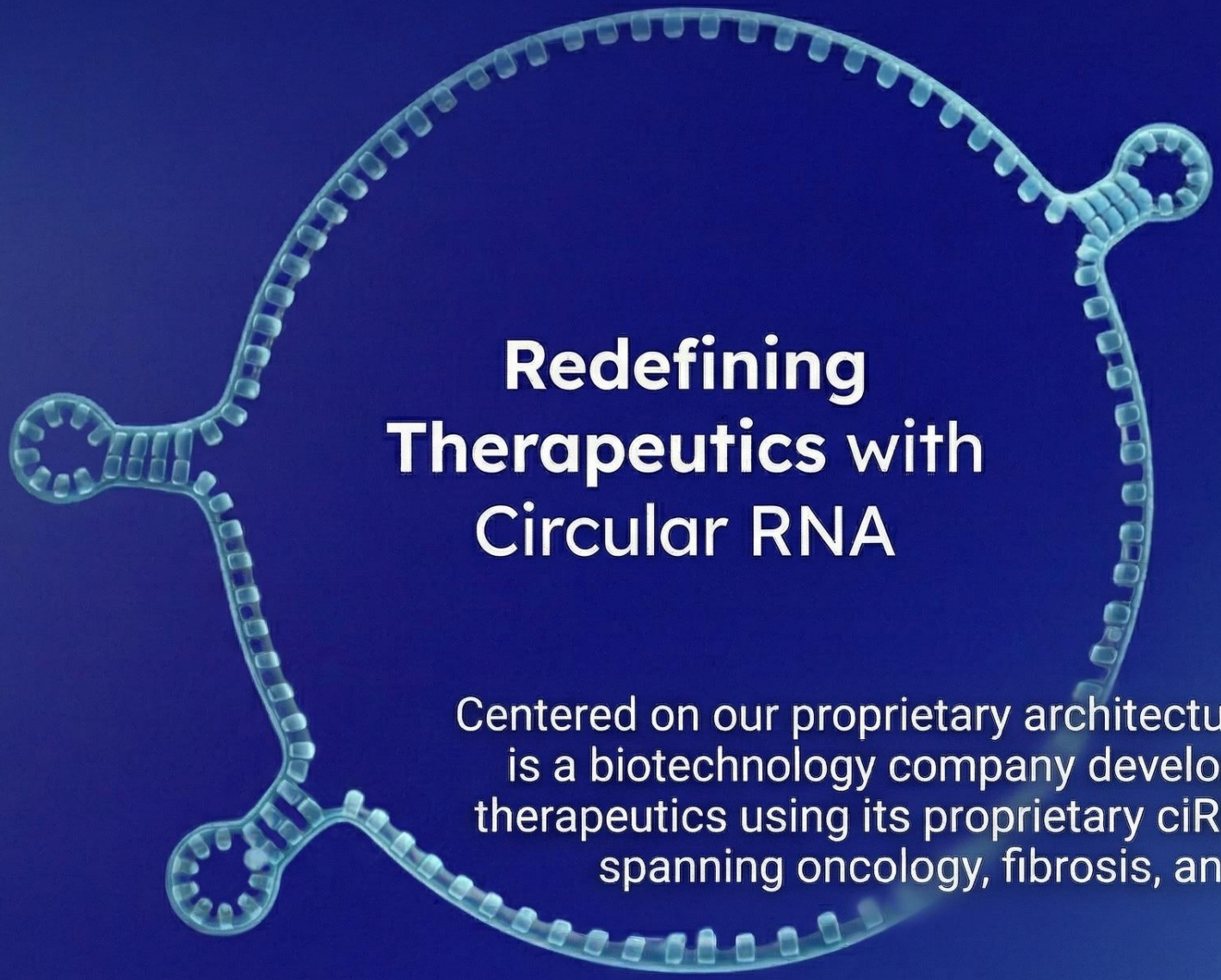
03 **Circurna: Design & Application of circRNA**

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05 Q&A

Circurna

The New Architecture for Therapeutics



Redefining Therapeutics with Circular RNA

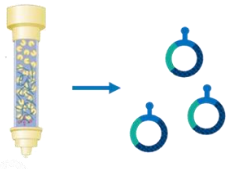
Centered on our proprietary architecture for therapeutics, Circurna is a biotechnology company developing next-generation RNA therapeutics using its proprietary ciRNA™ circular RNA platform, spanning oncology, fibrosis, and chronic conditions.

CiRNA™ RNA PLATFORM
SAFE, THERMOSTABLE AND NEEDLE-FREE

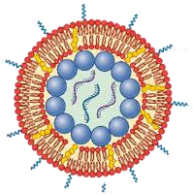
Genetic Elements



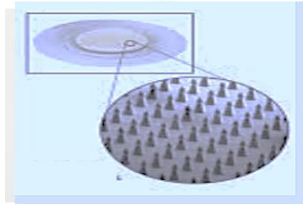
Purification



Thermostable LNP



Microneedle Patch



Protein Production

ciRNA generates robust and sustained protein production *in vivo*

Thermostable Nanoparticles

Stable at room temperature, removing the need for cold storage



CIRCULAR RNA IS STABLE INSIDE CELLS

Microneedle Patch Delivery

Painless self-administration improves compliance and ease of use

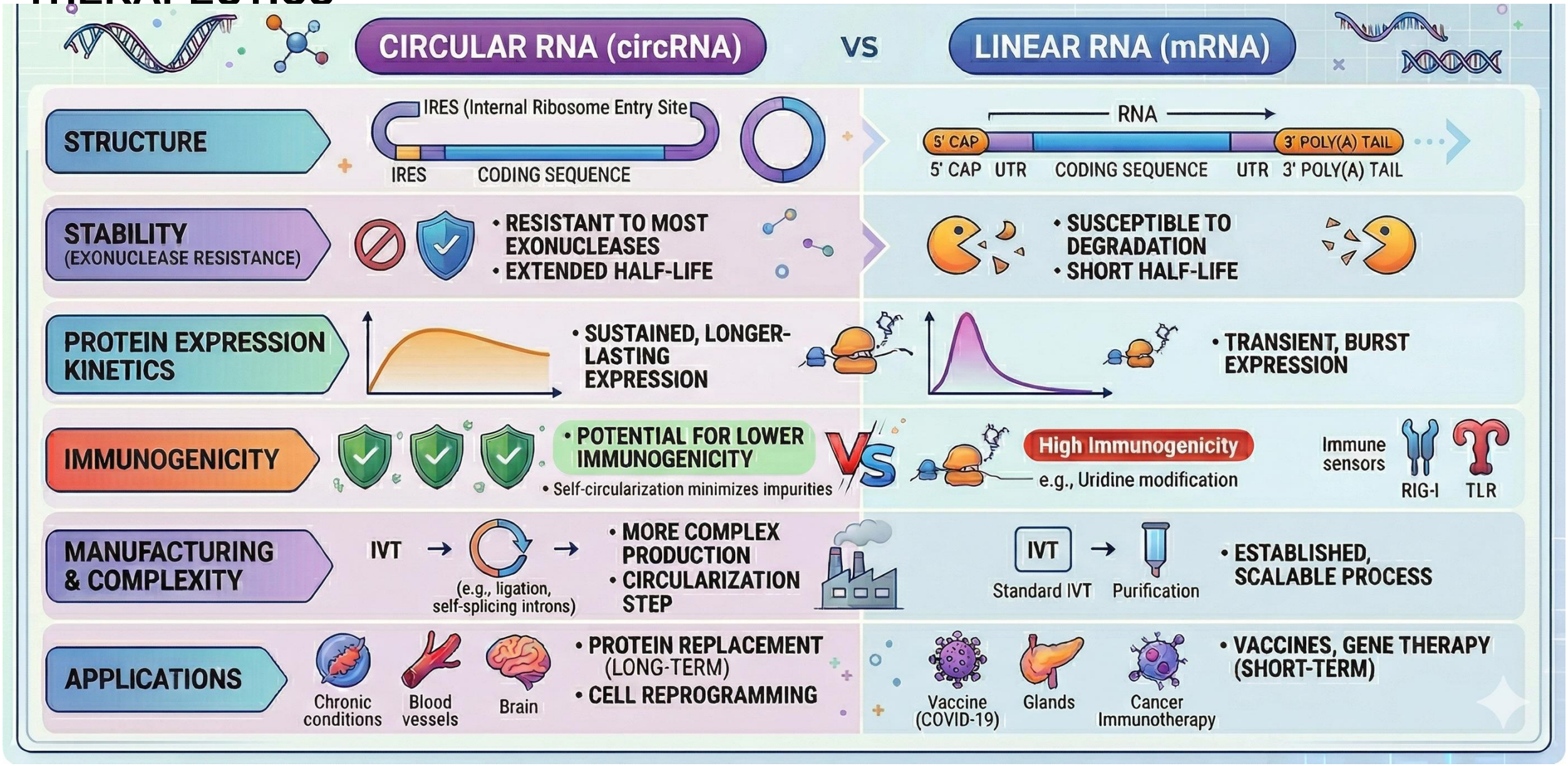
Rapid Scalability Easily adaptable

Novel therapeutics, powered by AI for accelerated development

Circurna owns all components of its ciRNA platform with no royalty obligations other than a royalty to Kindeva for the microneedle patch

COMPARISON OF LINEAR RNA VS CIRCULAR RNA PLATFORMS FOR THERAPEUTICS

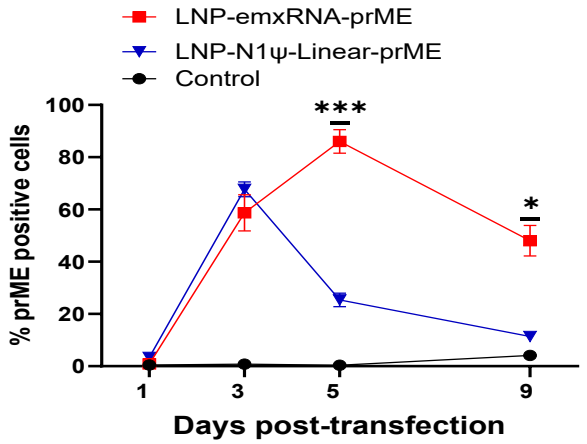
Circurna



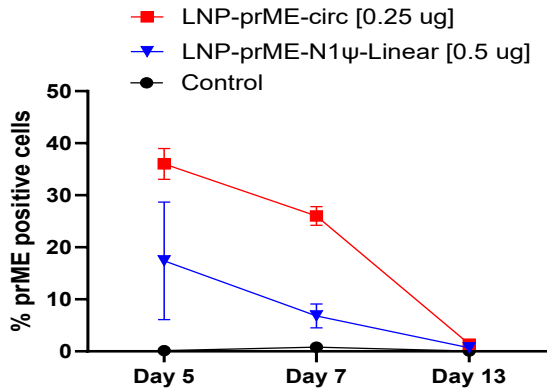
ciRNA SUSTAINS HIGHER PROTEIN EXPRESSION AND ANTIBODY LEVELS IN VIVO RELATIVE TO LINEAR mRNA

In Vitro Cell Culture Expression

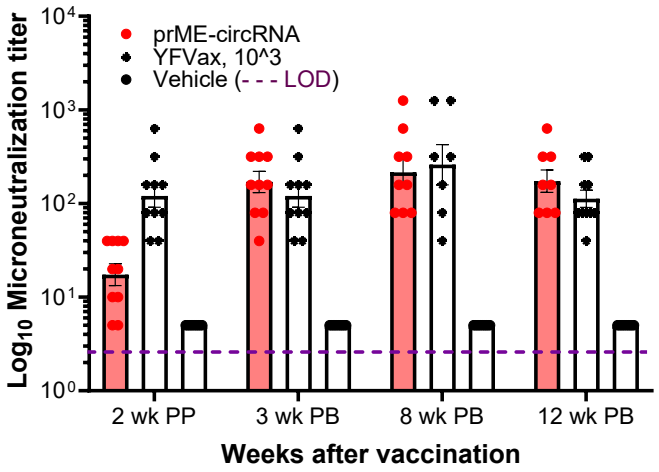
A549 cells

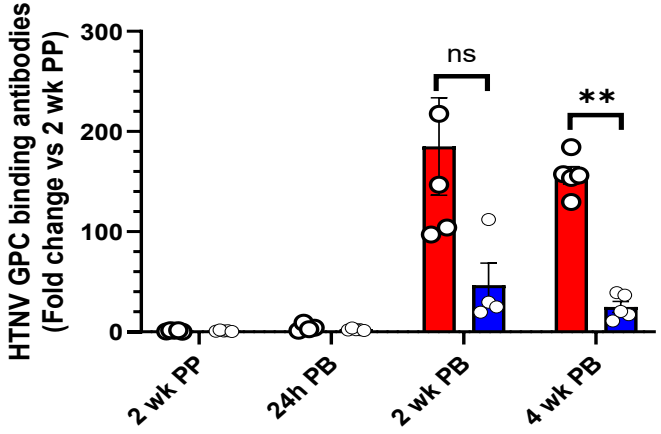


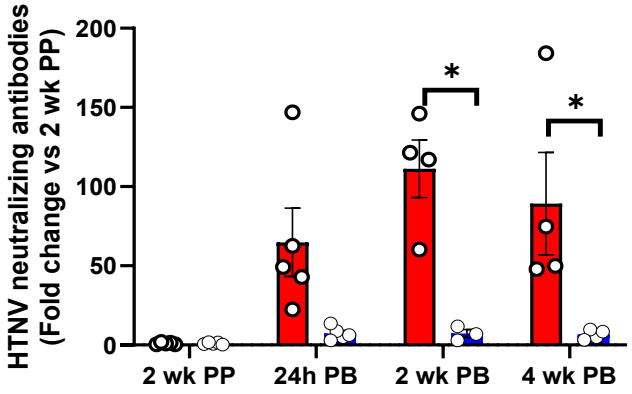
Human Monocyte Derived Cells



In Vivo Antibody Titers

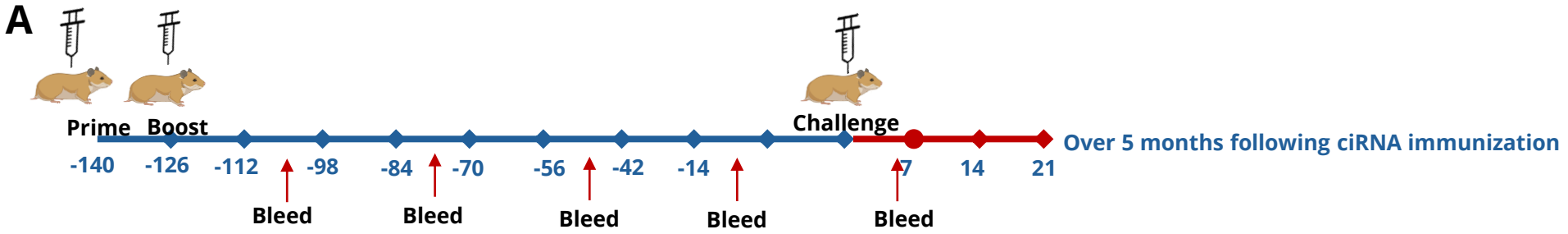


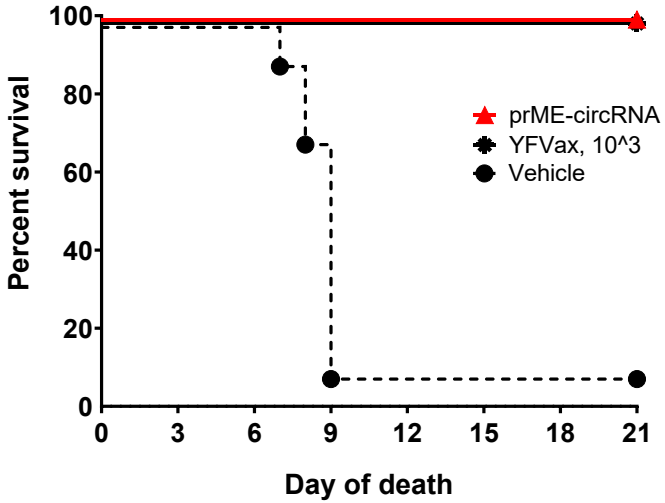


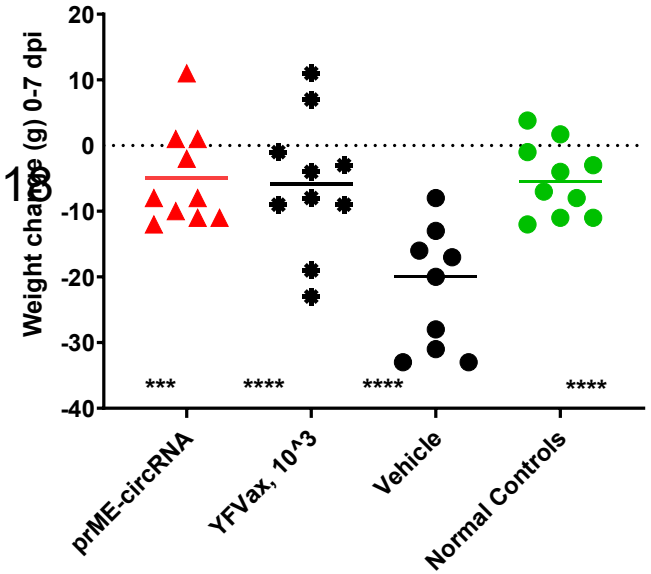


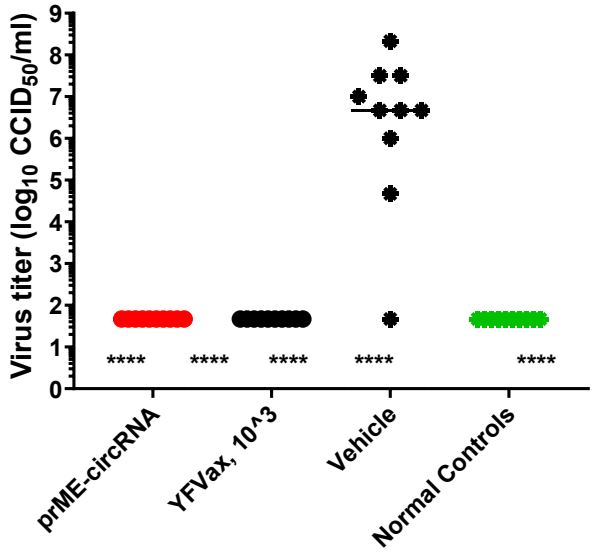
Red - Circular RNA, Blue - Linear RNA
prME = yellow fever proteins, HTNV = Hantaan virus

IMMUNIZATION WITH ciRNA PROVIDES DURABLE IMMUNITY AND COMPLETE (100%) PROTECTION AGAINST A LETHAL CHALLENGE IN HAMSTERS



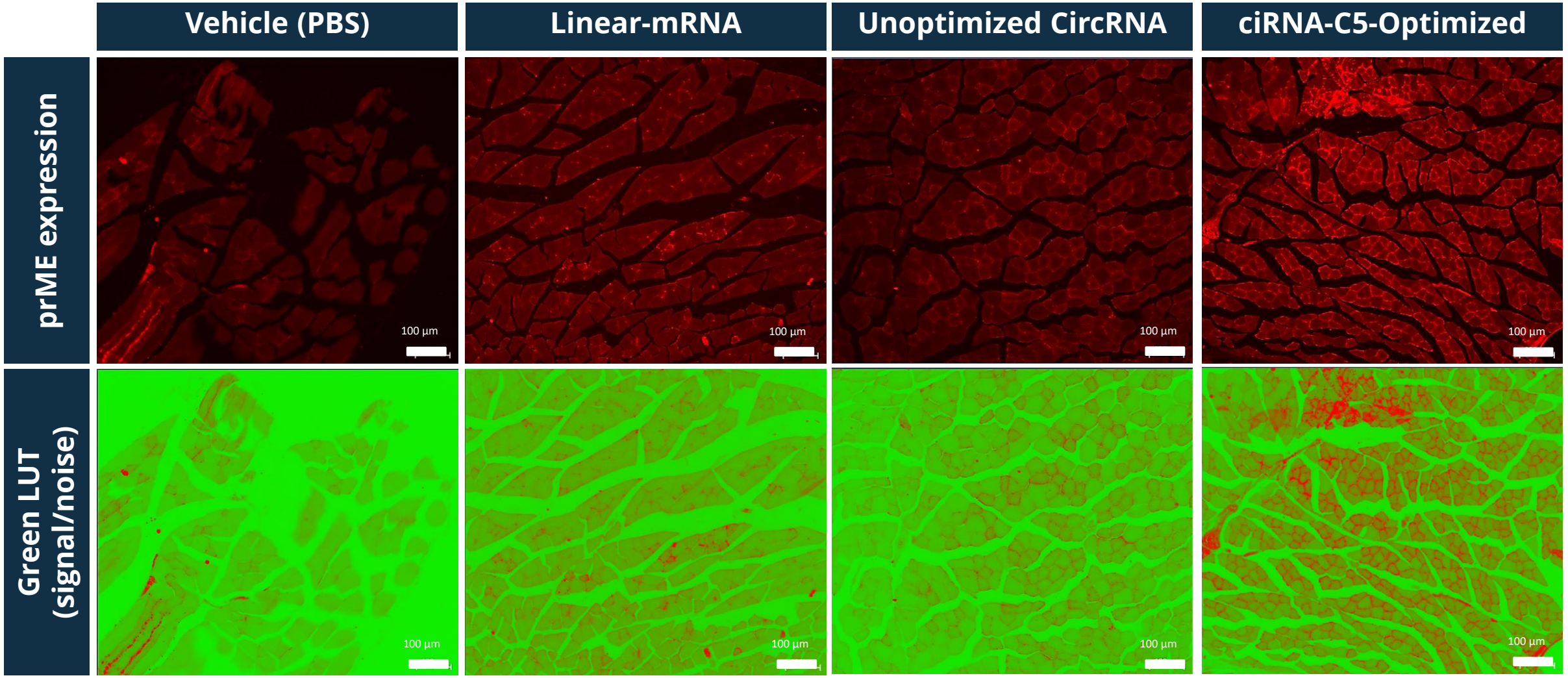






PROTEIN EXPRESSION IN MUSCLE 1 DAY AFTER INJECTION

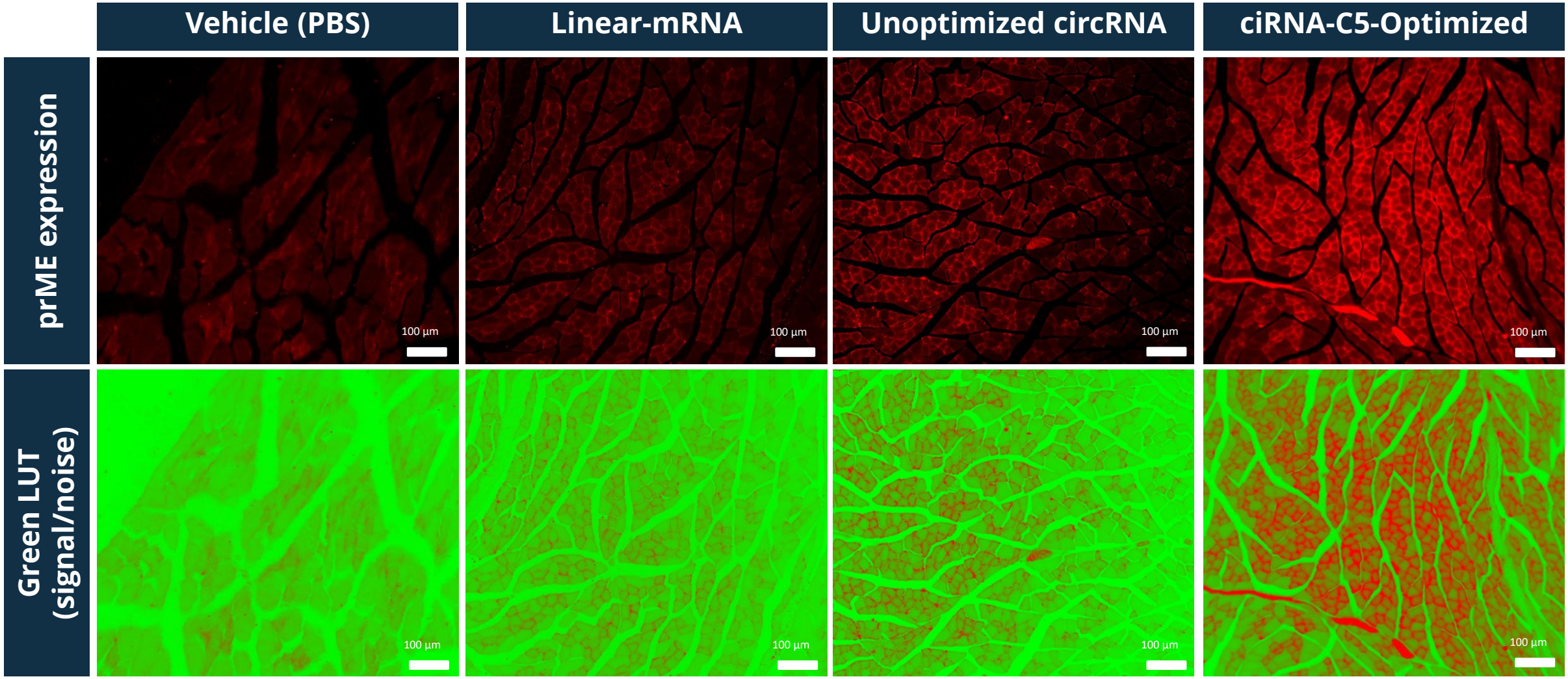
Circurna's Optimized C5 ciRNA Produces Significantly More Protein Than Linear mRNA *In Situ*



All samples used same LNPs and expressed the same protein
Red color identifies cells producing protein

PROTEIN EXPRESSION IN MUSCLE 4 DAYS AFTER INJECTION

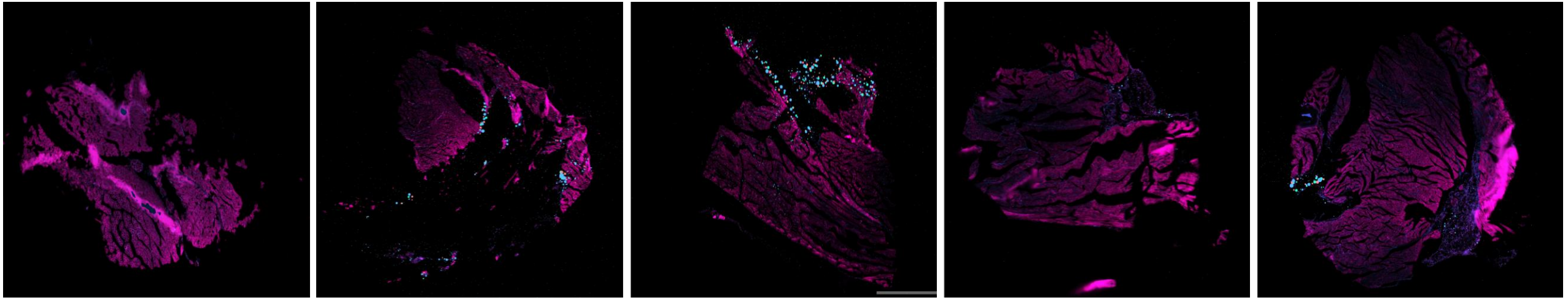
Circurna's Optimized C5 ciRNA Continues to Produce Significantly More Protein Than Linear mRNA *In Situ*



All samples used same LNPs and expressed the same protein
Red color identifies cells producing protein

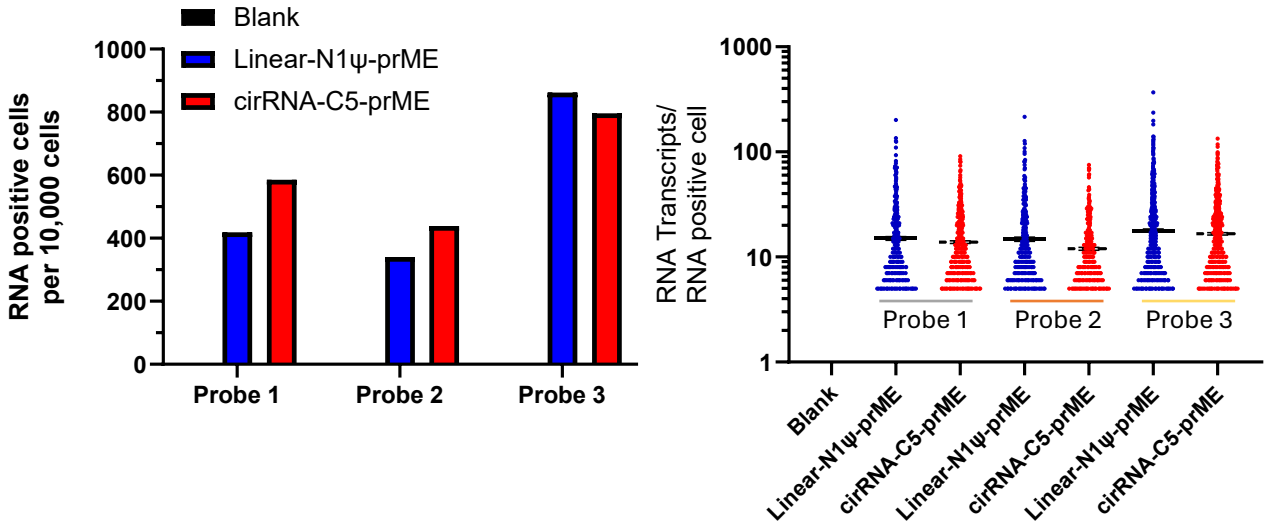
PROLONGED IN SITU STABILITY OF circRNA VACCINE VECTOR OUTPERFORMS LINEAR RNA COUNTERPARTS

Circurna

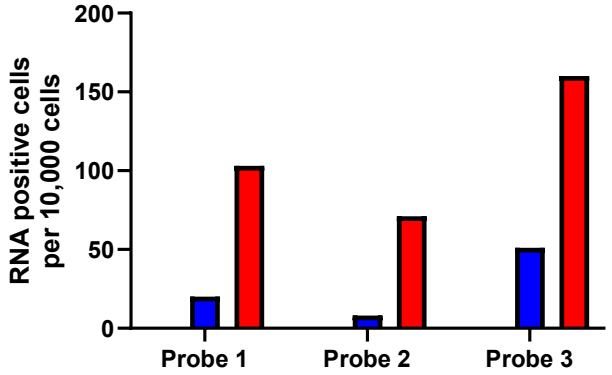


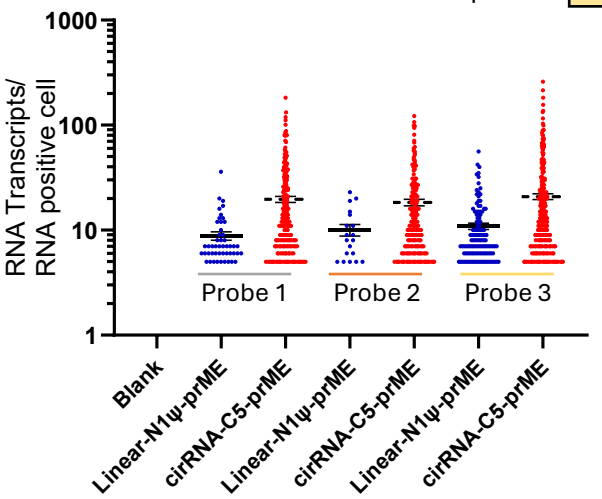
Cell membrane stain
Nuclear stain
RNA probe 1
RNA probe 2
RNA probe 3

Day 1 post-vaccination

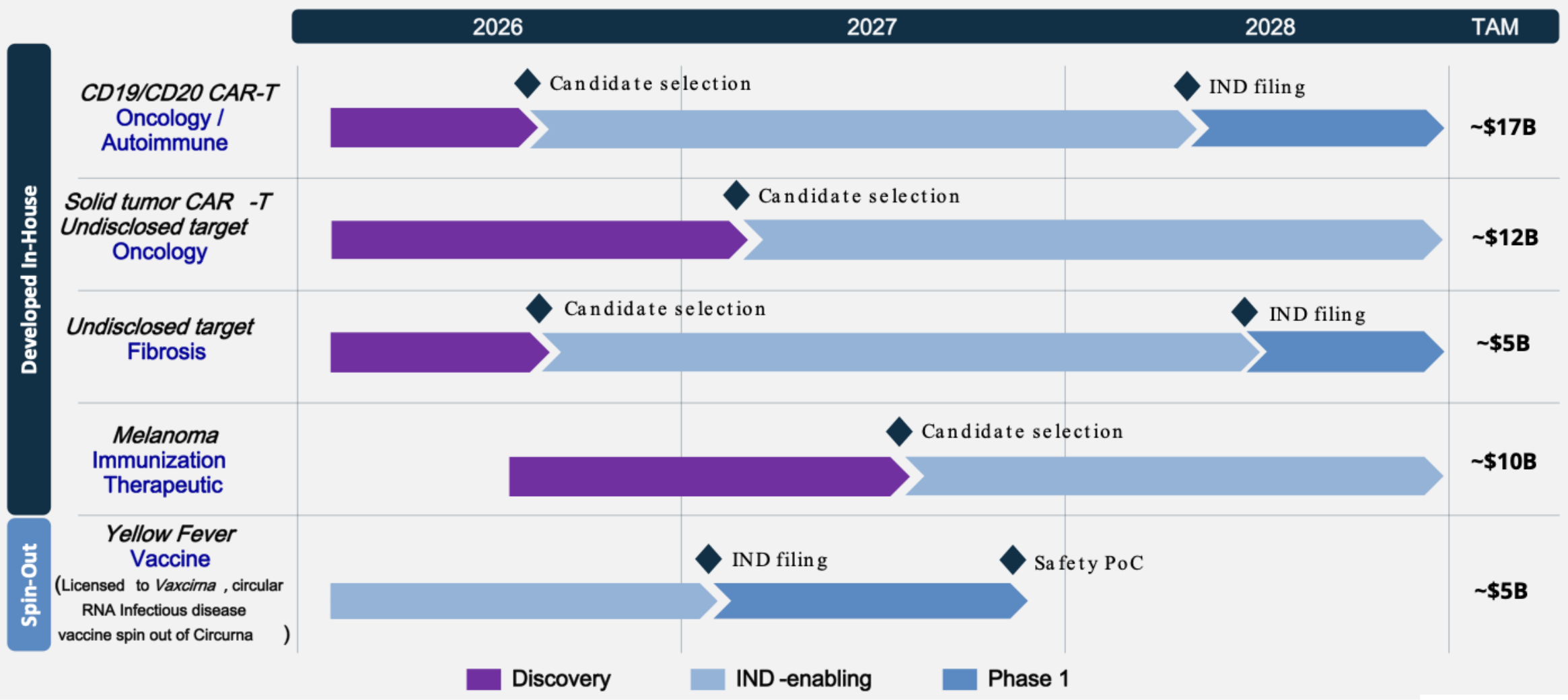


Day 4 post-vaccination





PLATFORM ENABLES STRONG PIPELINE MOMENTUM ACROSS MULTIPLE THERAPEUTIC AREAS



Notably shorter time to advance drug candidates into clinical trials

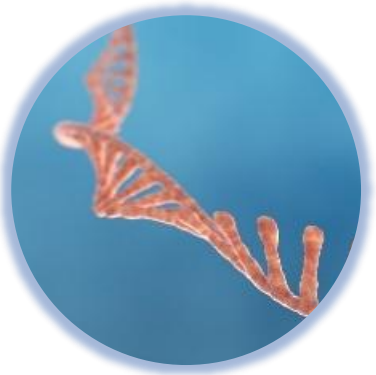
Circurna

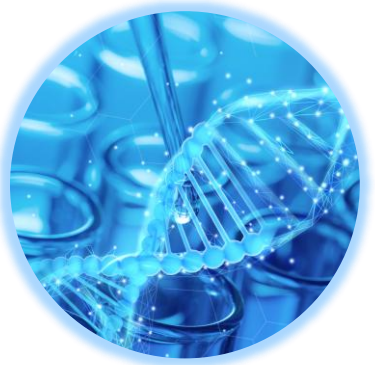
CiRNA™ - A platform poised for broad and rapid development

- **Disease and therapeutic area agnostic**, driving innovation beyond in vivo CAR-T (oncology, autoimmune, CNS, gene editing)
- AI-assisted **proprietary sequence optimization** and **next gen LNP** development for cell/tissue targeting
- Rapid development (2-3 years to IND filing) at **low cost of goods**
- **Receptive regulatory environment** to work with FDA in developing platform solutions (section 506K of the FD&C Act)
- Opportunity for **target-specific partnerships** with external parties

Circurna

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04 **Fireside Chat: circRNA Trends, Challenges, & Opportunities**

05 Q&A

circRNA Trends, Challenges & Opportunities Fireside Chat

Jeffrey Hung, Ph.D.
VP, Commercial Strategies

Peter Weinstein, Ph.D., J.D.
Co-Founder and CEO