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Circular RNA-based therapy for treating incurable diseases

nOctuRNA THERAPEUTICS

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CEO

Content

1. The Institution: NoctuRNA Therapeutics
2. The Product: circular RNAs
   a) Target Indications
   b) Innovative mechanisms of action
   c) Differential features facing the market
   d) Current status of development
   e) IPR protection
   f) Pitfalls & Risks to be considered
3. Partnering Opportunities

1. The Institution: NoctuRNA Therapeutics

Circular RNA-based therapy for treating incurable diseases

Spin-off from Universitat Pompeu Fabra Barcelona

TEAM

Miriam Corredor, PhD / MBI
CEO & cofounder
+10y experience in the biotech entrepreneurial ecosystem
Management and leadership skills

Marc Talló, PhD
CSO & cofounder
RNA Biology and circRNA expert

Ivan Dotu, PhD
VP Research & cofounder
Expert in RNA structure and computational design of synthetic RNAs

Monica Mendoza, PhD
Researcher
CNS and Mol. Biology expert

Flor Alonso, PhD
Researcher
circRNA production and molecular biology expert

Advisory Board

Juana Díez Anton, PhD
Scientific advisor & cofounder
Full Professor Microbiology, UPF
Expert in virus biology and antiviral treatments
2017 ICREA Academia Prize Research Excellence

Amadís Pagès, PhD
Business advisor & cofounder
Entrepreneur in the Biotech sector with 7 years as a CEO. Tech transfer expert

Juan Pablo Horcajada, PhD, MD
Clinical advisor
Head of the Dep. Of Infectious diseases at Hospital del Mar (Barcelona)

Miguel Angel Rubio, PhD, MD
Clinical advisor
Coordinator of the Neuromuscular Diseases area at Hospital del Mar (Barcelona)

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AWE Academy for Women Entrepreneurs

SILO · acelera startups · sector: biotecnología · ASEBIO

nature reviews genetics

ChemoStart Innovative projects in health

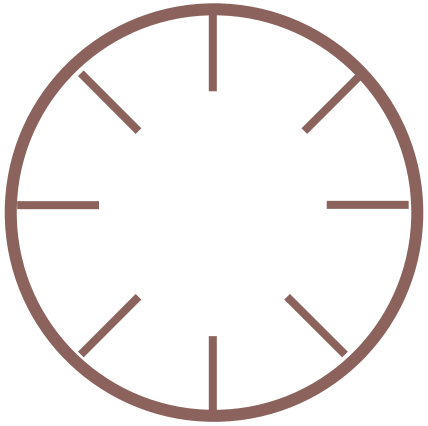
IRSUDPHARMA

nOctuRNA THERAPEUTICS

2. The Product: Target Indications

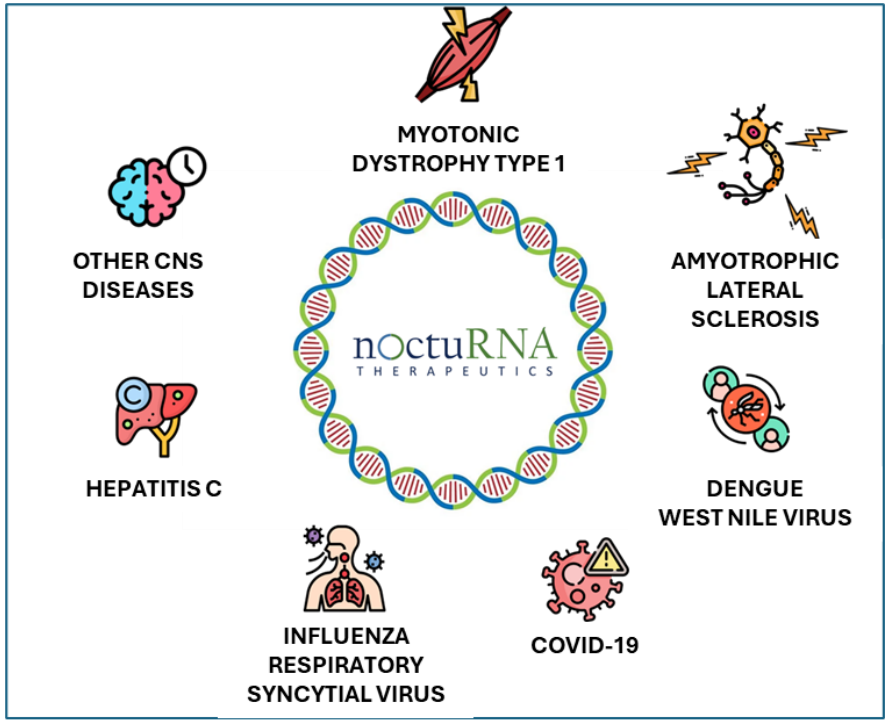
2. The Product: circular RNAs & Innovative MoA

We use circular RNAs (circRNA) that disrupt pathogenic **RNA secondary structures**



FIRST-IN-CLASS THERAPY

New and disruptive mode of action

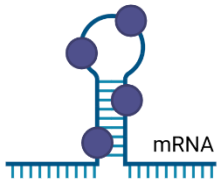


2. The Product: circular RNAs & Innovative MoA

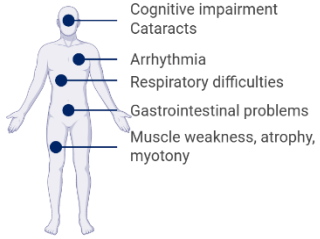
DISRUPTIVE MODE OF ACTION

(using Steinert disease as an example)

Genetic expansion in the DMPK gene

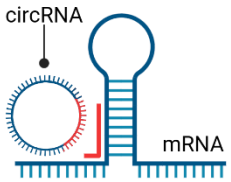


Sequestration of RNA- binding proteins and RNA foci formation

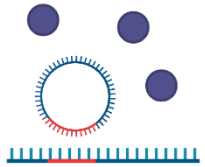


Steinert disease

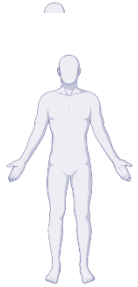
Causes of death include respiratory failure, cardiovascular disease, arrhythmia, and neoplasms



circRNA recognizes and hybridizes with nearby region

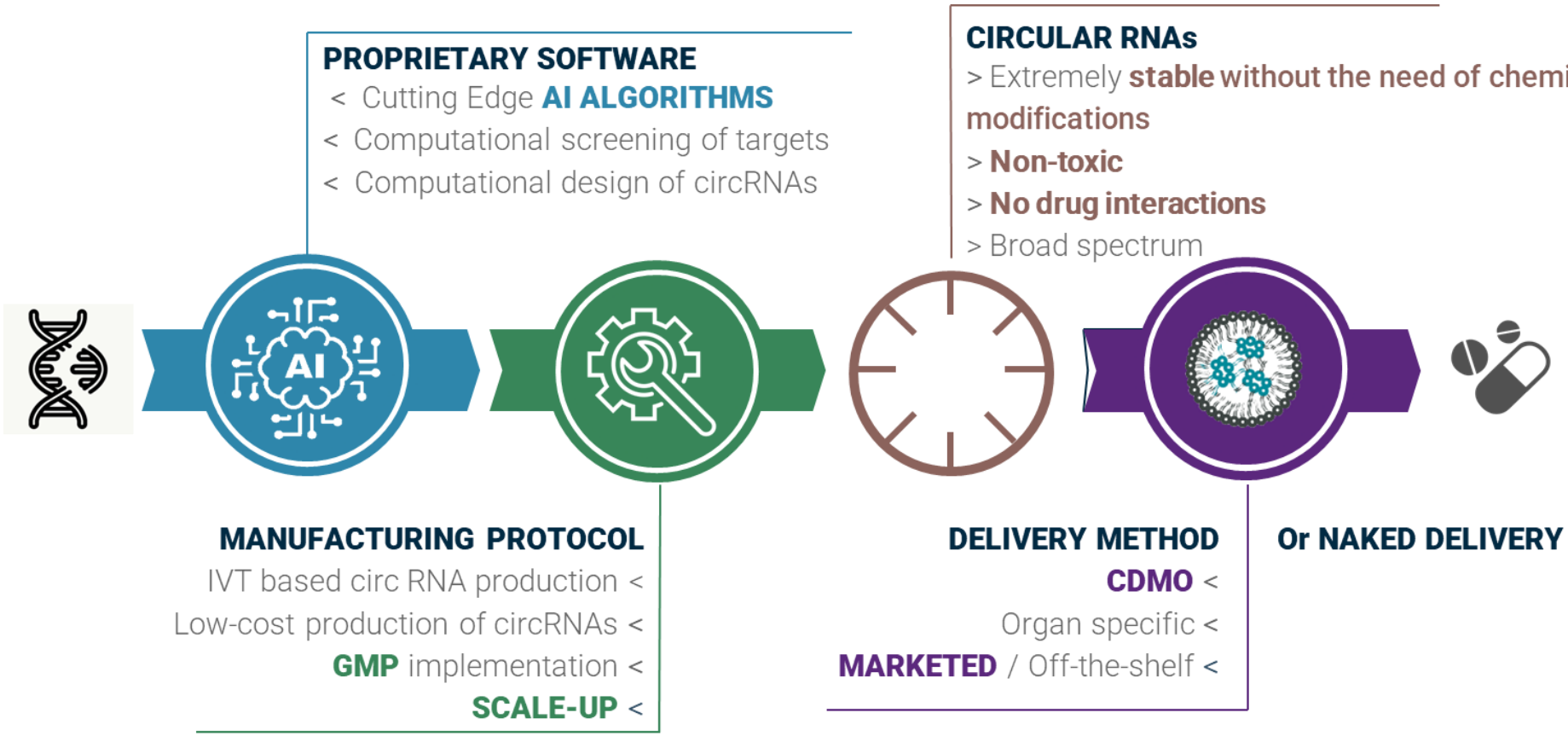


circRNA disrupts the secondary structure of the expanded mRNA



Normal function

2. The Product: Differential features



2. The Product: Differential features

- ✓ **1st in CLASS** therapy
- ✓ **HIGH STABILITY** due to circular RNA nature
- ✓ As antivirals: increased **DIFFICULTY OF RESISTANCE STRAINS,** applicable to **multiple viral diseases, BROAD SPECTRUM activity**
- ✓ **COMPLETE REDUCTION OF INFECTION** in 48h
- ✓ Novel approach to attack **undruggable targets** (i.e. genetic diseases)
- ✓ Optimized **LOW-COST PRODUCTION** of circRNA
- ✓ **ULTRA FAST DEVELOPMENT -** Effective Lead candidates obtained in **3-4 weeks**

2. The Product: Differential features

Steinert' competitors (DM1):

There is currently no company with a drug on the market

Some candidates for DM1 in clinical phases aim to increase the amount of unsequestered MBNL1 by modulating the expression of a gene. In contrast, our circRNA disrupts the structure of DMPK, which sequesters MBNL1, without affecting the expression of any other gene.

This makes it a much safer therapy.

COMPANY	PROGRAM/ LEAD CANDIDATE	MODALITY	DM SUBTYPE	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	DRUG TARGET/ MECHANISM
AMO Pharma Ltd	Tideglusib	Small Molecule	CDM					Glycogen synthase kinase 3 beta (GSK3β)
Harmony Biosciences	Pitolisant	Small Molecule	DM1					Histamine-3 receptor (H3R)
Lupin Neurosciences	Mexiletine	Small Molecule	DM1 / DM2					Sodium Channels
Avidity Biosciences	AOC 1001	Antibody Conjugated Oligonucleotide	DM1					DMPK
Dyne Therapeutics	Dyne 101	Antibody Fragment Conjugated Antisense Oligonucleotide	DM1					DMPK
Vertex	VX-670	Peptide Conjugated Oligonucleotide	DM1					DMPK
PepGen	PGN-EDODM1	Peptide Conjugated Antisense Oligonucleotide	DM1					DMPK
Arrowhead Pharmaceuticals	ARO-DM1	Investigational RNA interference (RNAi) Therapeutic	DM1					r(CUG) of DMPK
ARTHEx Biotech	ATX-01	Antisense microRNA Oligonucleotide	DM1 / DM2					MBNL and DMPK via miR-23b
Expansion Therapeutics	DM1 (CUG)	Small Molecule	DM1					r(CUG) of DMPK
Juvena Therapeutics	JUV-161	Stem Cell-Secreted Proteins	DM1					--
Rgenta Therapeutics	PMS1	Small Molecule	DM1					r(CUG) of DMPK
Sanofi	--	miRNA Technology in Adeno-Associated Virus	--					DMPK
Astellas Gene Therapies	AT466	Adeno-Associated Viral Antisense	DM1					DMPK
GrittGene Therapeutics	--	--	DM2					--
Enzerna Biosciences	--	Artificial Site Specific RNA Endonucleases (ASREs)	DM1					r(CUG) of DMPK
Design Therapeutics	--	Gene Targeting Chimera Small Molecule	DM1					r(CUG) of DMPK
Dewpoint Therapeutics	--	Biomolecular Condensates	DM1					DMPK
Kate Therapeutics	--	--	DM1					--
Prime Medicine	--	--	--					--
Denali Therapeutics		--	DM1					DMPK

Main actors/competitors in the market for Myotonic Dystrophy and their pipeline. Adapted and modified from Myotonic Dystrophy Foundation.
CDM: Congenital Myotonic Dystrophy, DM1: Myotonic dystrophy type 1 (Steinert Disease),DM2: Myotonic dystrophy type 2

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2. The Product: Differential features

ALS competitors:

- **Biogen (USA)** leads with **Tofersen**, an ASO targeting SOD1 mutations. It received FDA accelerated approval.
- **Ionis Pharmaceuticals**, a pioneer in ASO development, collaborates with Biogen and others on ALS programs: BIIB078 TERMINATED
- **Wave Life Sciences** develops **stereopure ASOs** with clinical-stage candidates for CNS disorders, including ALS: WVE-004 TERMINATED
- **Amylyx Pharmaceuticals** received US and Canada approval for **Relyvrio** (a non-genetic small molecule combo)
- **Treeay (Netherlands)** is developing **oral therapies** for ALS.
- **QurAwlis (USA)** and similar startups focus on **molecular subtype-specific approaches**.

C9ALS and ASO Limitations

In **C9ALS**, ASOs targeting mutant sense transcripts reduce RNA foci and dipeptide repeat proteins (DPRs) **in preclinical models**. However, current ASOs only target the **sense strand**, allowing antisense-derived DPRs and RNA foci to persist.

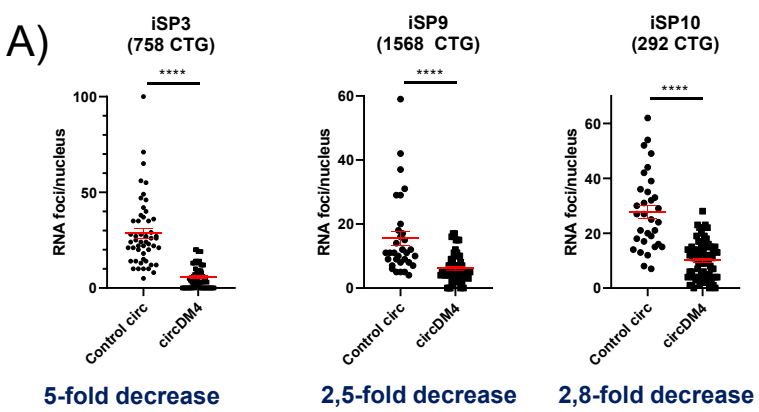
This limitation contributed to the **termination of BIIB078 and WVE-004** (2022–2023), due to limited efficacy despite early safety and tolerability.

Need for innovative therapies targeting both sense and antisense transcripts for meaningful clinical impact

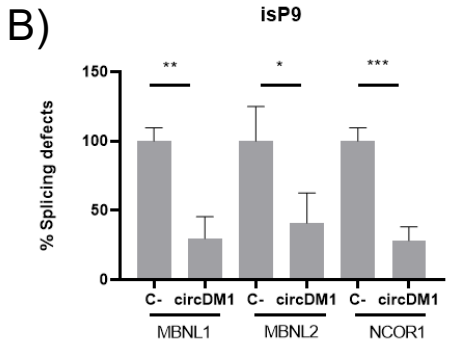
2. The Product: Development Status

STEINERT DISEASE (DM1)

In vitro EFFICACY studies



Reduction of nuclear aggregates in myocytes



Results of splicing correction in a patient cell line

In vivo EFFICACY studies

Drosophila Model:

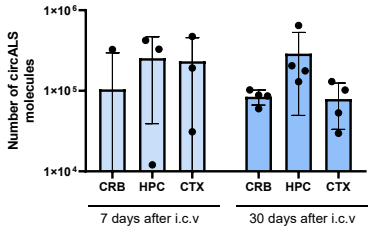
- Treatment with a specific circRNA improved **83% of flies** (25/30)
- Improvement measured by phenotypic changes in eyes expressing pathological RNA

Mice Model experiments ongoing

NEURODEGENERATIVE DISEASES

CircRNA candidates for other neurodegenerative diseases (**ALS, FTD, Huntington's disease, SCA8, FXTAS**) have been successfully validated ***in vitro***

ALS *in vivo* Biodistribution / Toxicity studies



circALS1 molecules are detected **30 days** after i.c.v injection

Maximum dose determined without toxicity throughout the 30 days

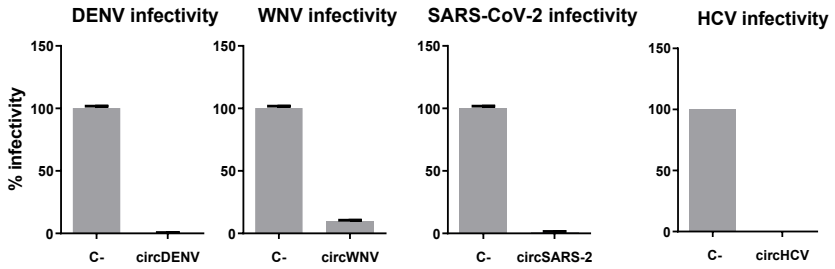
2. The Product: Development Status

INFECTIOUS DISEASES

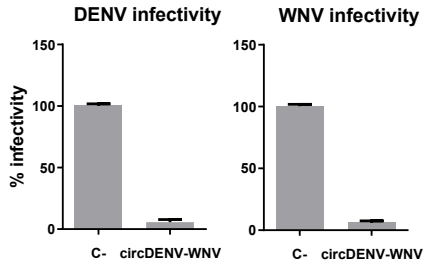
Experimental results of dengue (DENV), west Nile virus (WNV), SARS-CoV-2, hepatitis C (HCV) and the broad-spectrum circ-RNA for DENV and WNV in cell culture

EFFICACY in cell culture after 48 hours

VIRUS-SPECIFIC

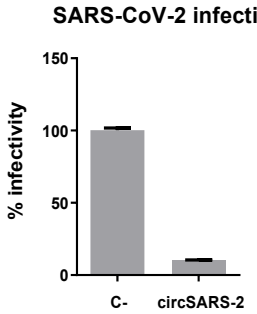


BROAD-SPECTRUM



90-100% of effectiveness in cell culture

IN VIVO EFFICACY STUDIES of the SARS-CoV-2 circRNA



90% viral load reduction

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2. The Product: IPR Protection

✓ **Therapeutic technology based on circRNA**

- **PCT / EP2021/067756**
  EU, USA, Canada, Brazil, Mexico, Israel, China, Japan, South Korea, Australia
- **ISR without concerns**

✓ **circRNA Design software**

✓ **circRNA manufacturing protocol** → **EP24382561 May 2024**

✓ **Artificial RNA targeting repeat expansion disorders** → **EP24382889 Aug 2024**

2 Positive FTOs

- **FTO in Europe regarding the production method of circRNAs**
- **Global FTO regarding the use of circRNAs**

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2. The Product: Pitfalls & Risks

1) **Financial Constraints:**

One of the primary challenges is securing sufficient funding to support the development of all our research lines. This is why we have prioritized our projects to focus resources on the most promising candidates. We'll combine public and private funding as this is key for the continued development and expansion of our platform.

2) **Technological development:**

Our design platform for circRNA is built to automatically generate a set of candidates targeting one or more specific RNA secondary structures. However, due to the complexity and specificity of certain targets, **full automation may not always be possible**. In such cases, manual intervention may be required, involving multiple steps and iterative redesigns, which could slow down the scalability of our platform.

Developing an effective **delivery system** for circRNAs tailored to each specific disease is another critical hurdle. To date, we have tested various lipid nanoparticles (LNPs) for encapsulation, and ongoing trials will determine if further optimization is necessary.

3) **Regulatory Challenges:**

Currently, there are no approved circRNAs by regulatory agencies, and therefore no specific guidelines exist. This makes it essential to engage with regulatory bodies to pave the way for future clinical trial approvals. Nocturna's circRNAs has been classified as **Gene Therapy by the Committee for Advanced Therapies** and we also achieved the SME classification by the EMA.

3. Partnering Opportunities

BUSINESS MODEL: LICENSE OF DIFFERENT ASSETS

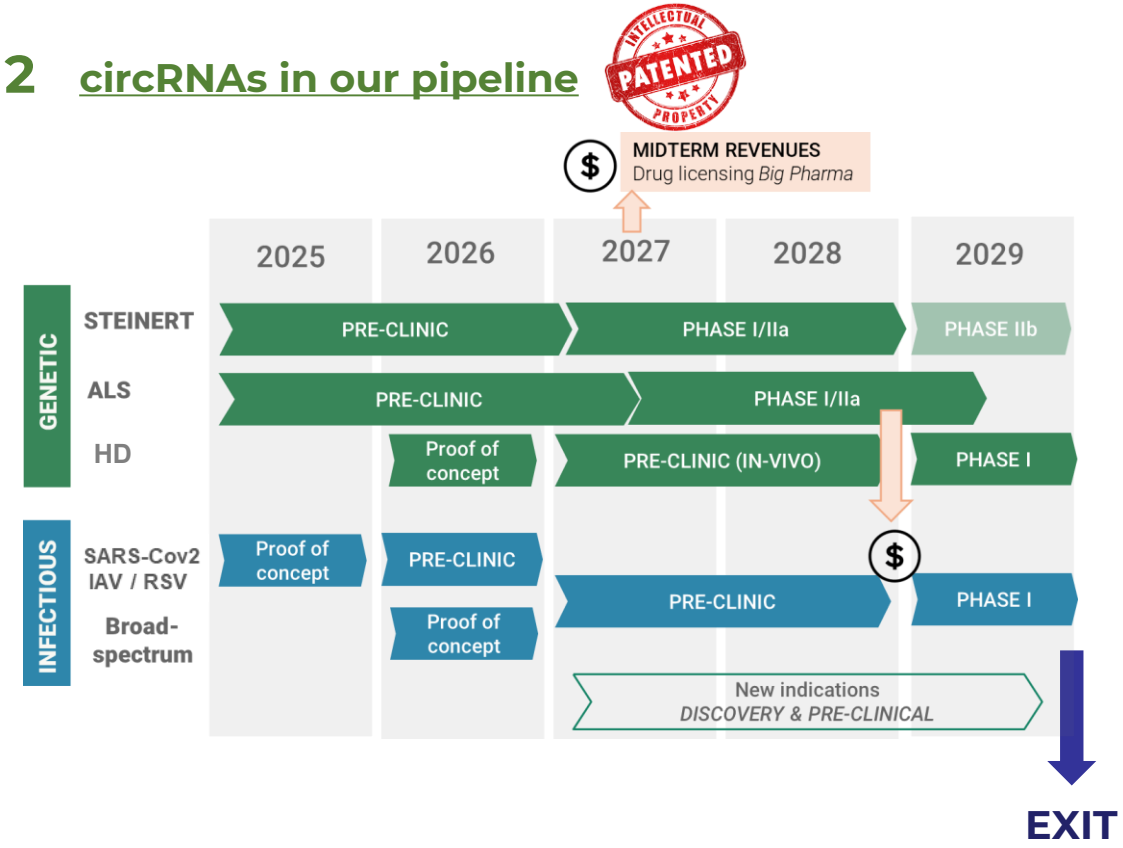
1 circRNAs production method

Licencing of our circRNA production protocol to an RNA MANUFACTURER

- Novel IVT based circRNA production
- **HIGH-YIELD (>85%)** production
- GMP implementation and scalable

SHORT TERM REVENUES

2 circRNAs in our pipeline



We are open to collaboration on our current pipeline or new Project proposals

Revolutionizing treatment: synthetic circular RNA strategy for neurodegenerative and infectious diseases

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