19 de noviembre de 2025

NRF2 Activation: Pharmacological Innovation against Fatty Liver Disease

SERVATRIX

Antonio Cuadrado

MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES
AGENCIA ESTATAL DE INVESTIGACIÓN
MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española
farmaindustria

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Summary

01 The problem

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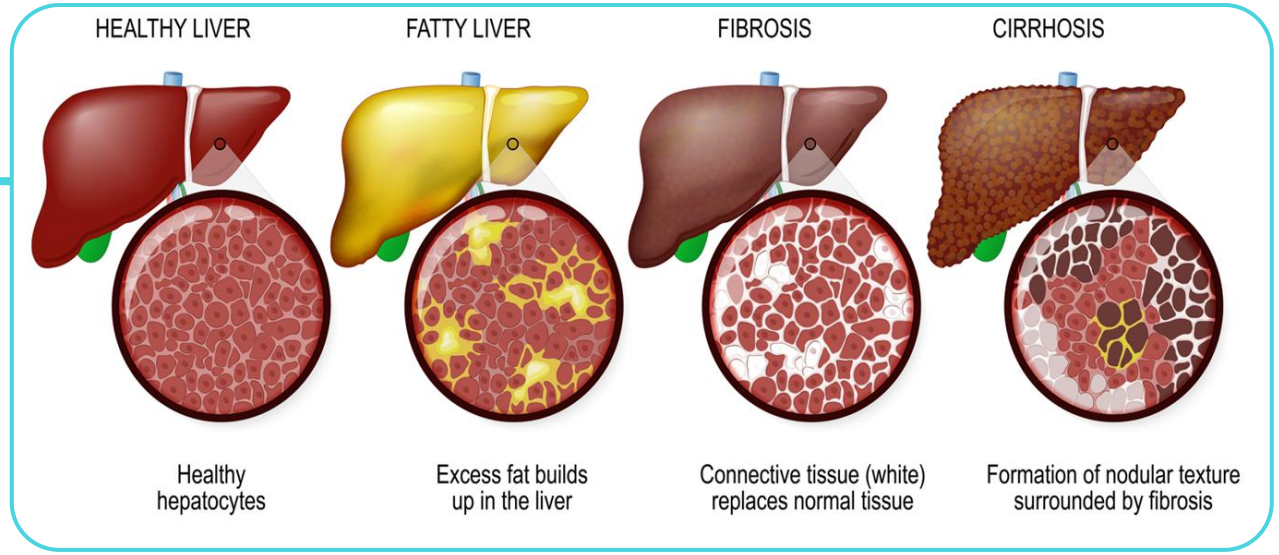
The disease



THE DISEASE

Non-alcoholic fatty liver may develop inflammation and fibrosis and may progress towards a very **dangerous disease** termed non-alcoholic steatohepatitis (NASH) or Metabolic dysfunction-associated steatohepatitis (MASH).

NASH/MASH

MASH is characterized by loss of liver function and fibrosis, ultimately leading to cirrhosis.
MASH increases the risk of liver-related morbidity and mortality, while promotes chronic kidney disease, cardiovascular disease, and cancer.

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MASH

- Killing 2M+ people per year & Causing 70M+ of prevalent cases evolving to cirrhosis
- There's only one provisionally approved therapy
- Current potential solutions present very high costs, low efficacy, and still uncertain side-effects
- Associated with high health care costs ($13k+ / year per patient*)

Rapidly becoming the leading cause of liver transplantation in the U.S

02 Our company

03 Our team

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SERVATRIX Biomed S.L. is a spin-off of Universidad Autónoma de Madrid

Our team

Antonio Cuadrado

CSO

Biochemistry Professor (UAM)

>100 publications on NRF2

>6 M€ in research-funded grants

Several contracts with Biopharma

Chair of EU Network on NRF2 with 35 countries/380 participants

+35 years of experience

Alejandro Expósito

CEO

Director of Innovation/ Digital/ Commercial Excellence

MERCK / MCDONALD´S / KODAK / DANKA / PC CITY / …

+ 35 years of experience

Jorge Cuadrado

COO

Innovation Manager/ Global Strategy & Operations Manager

EDP /SGS GROUP & PWC

Entrepreneur / Investor / M&A Manager / Business Development

+10 years of experience

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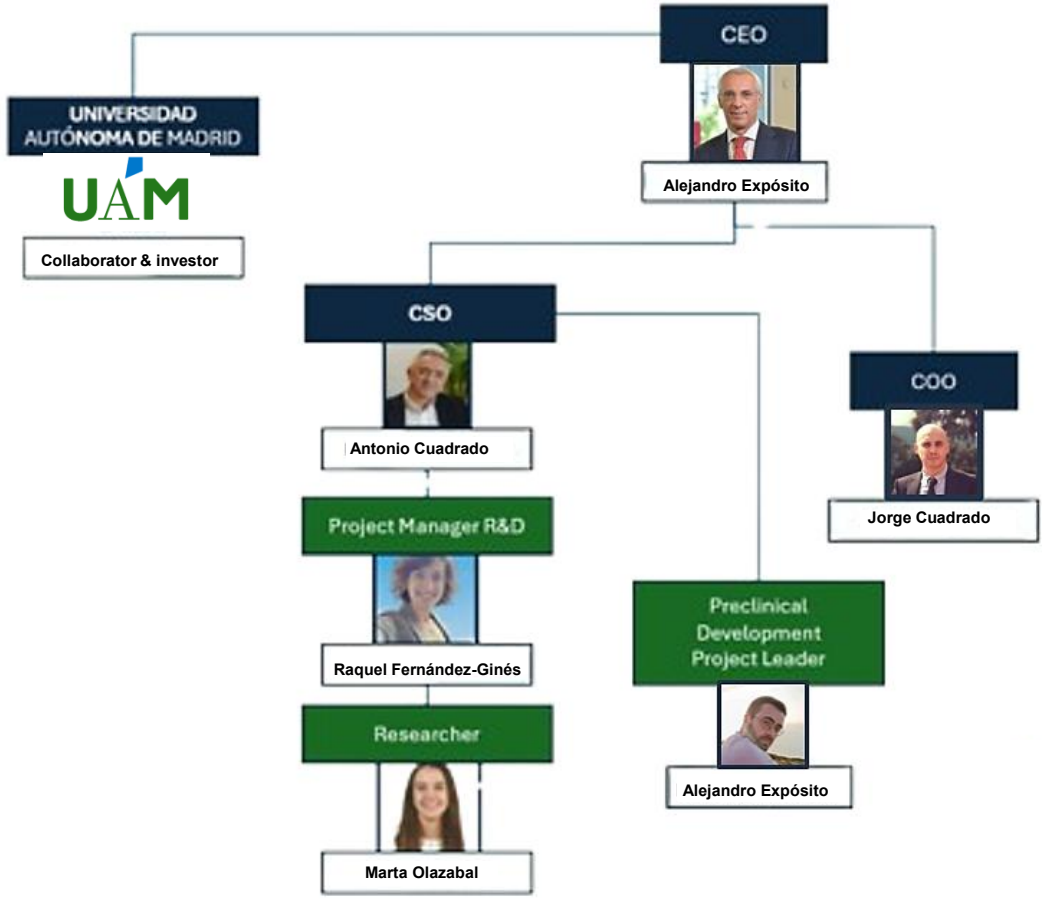
Team & Partnerships & Network



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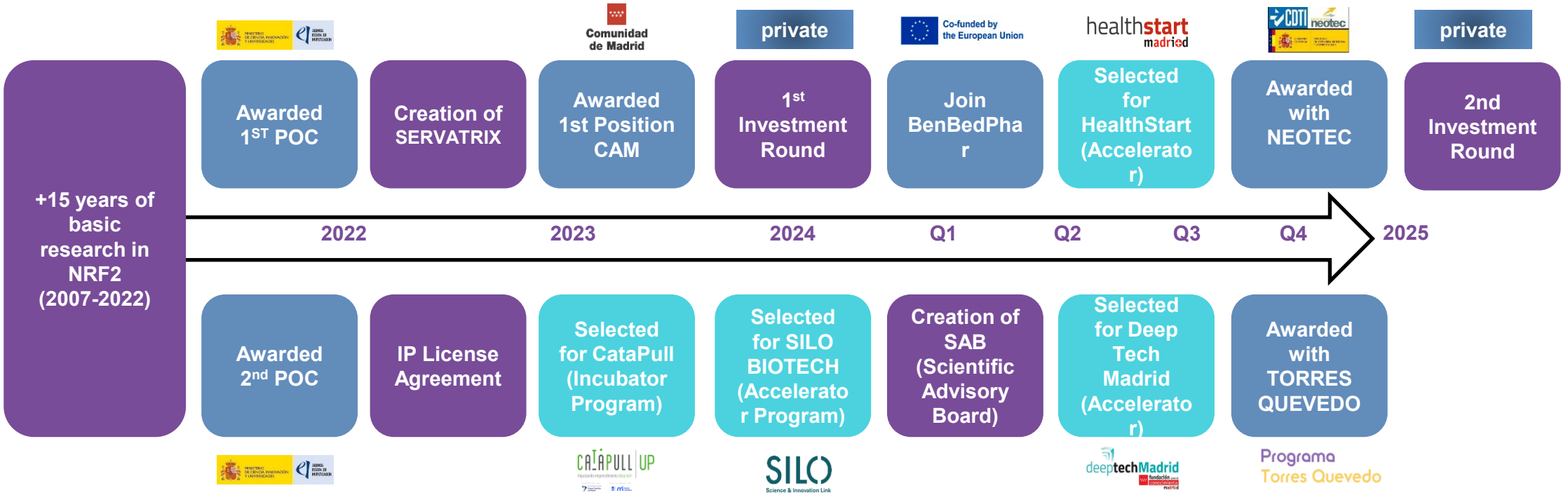
Highlights & Company Milestones

Since its creation (Nov 2022) the company has executed a robust strategy based on:

- IP Generation
- Partnerships with key institutions & entities
- Creation of a robust entrepreneurial team
- Leverage on public & private funding **+900k EUR**



04 Market & competitors

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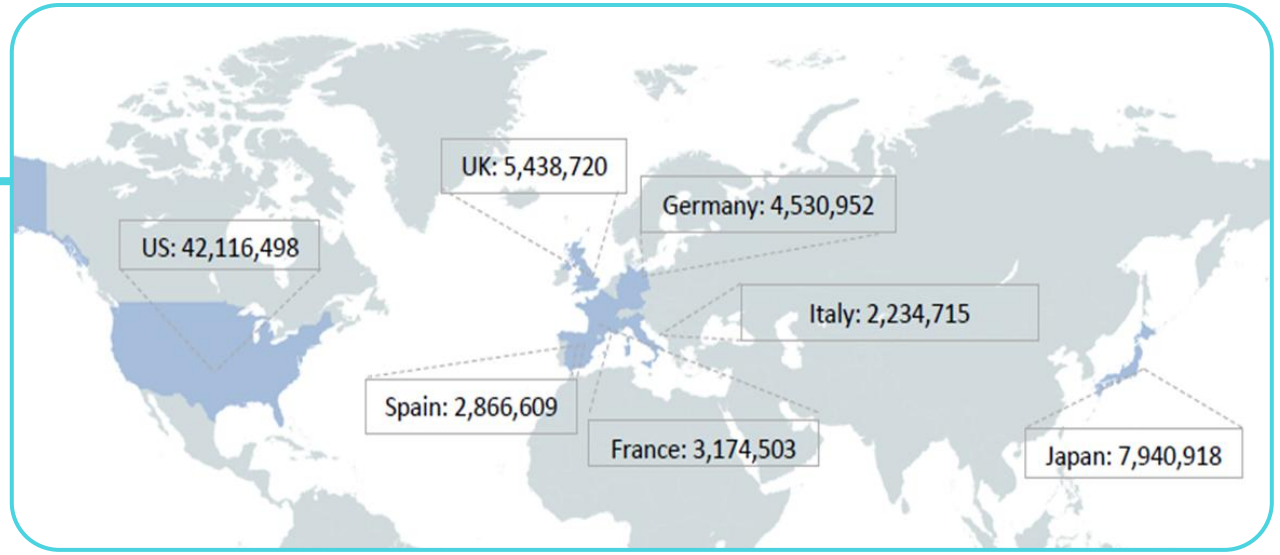
A relevant market opportunity

Prevalence of MASH diagnosed cases by region



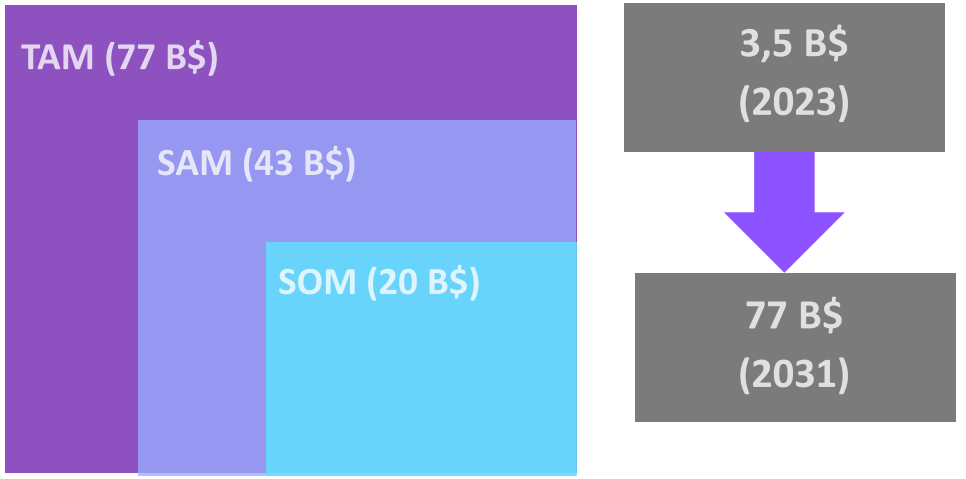
* Source/ Global Data: Non-Alcoholic Steatohepatitis NASH Opportunity Analysis and Forecasts to 2029

MARKET OPPORTUNITY

Liver fibrosis in the form of MASH is the most common liver disorder worldwide, **will affect approximately 25% of world´s population** (1 in 4)

- **Intensive growth of diagnosed cases worldwide**
- **Only provisional approval of one drug for MASH**
- **A huge unmet medical need**

CAGR 47%



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Current landscape of drugs for MASH

Currently, only Rezdiffra (resmeritrom) from Madrigal has received provisional FDA approval for MASH after 1 year of clinical trial.

Concerns: results after completion of the 5-year clinical trial / optimization of dosing and timing / long term safety / very expensive / not covered by Health Systems for a chronic treatment

		No-to-mild Fibrosis	Moderate to Advanced Fibrosis	Cirrhosis *(Compensated)*	Cirrhosis *(Decompensated)*
Fibrosis Stage		F0-F1	F2-F3	F4	F4
% of US Patients by 2030		~50%	~40%	~10%	<5%
Key Treatment Goal		Manage co-morbidities	Halt or improve fibrosis	Prevent liver failure	Transplant
Potential Treatment Setting		GP / Specialist *(Hep, GI, Endo)*	Specialist *(Hep / GI)*	Specialist *(Hep / Surgeon)*	Specialist *(Hep / Surgeon)*
Example MoAs in Late-stage Development *(Non-exhaustive)*	THRβ		Madrigal VIKING		*Anticipated expansion[1]*
	GLP-1R[2]		novo nordisk Lilly		
	Pan-PPAR		inventiva		
	FGF21		akero 89bio		
	FXR / ACC			GILEAD	

Metabolic modulators

Antifibrotic drugs

Source: Blue matter William Jonsson, Mike Gottlieb. June 28th, 2024

05 Our products & results

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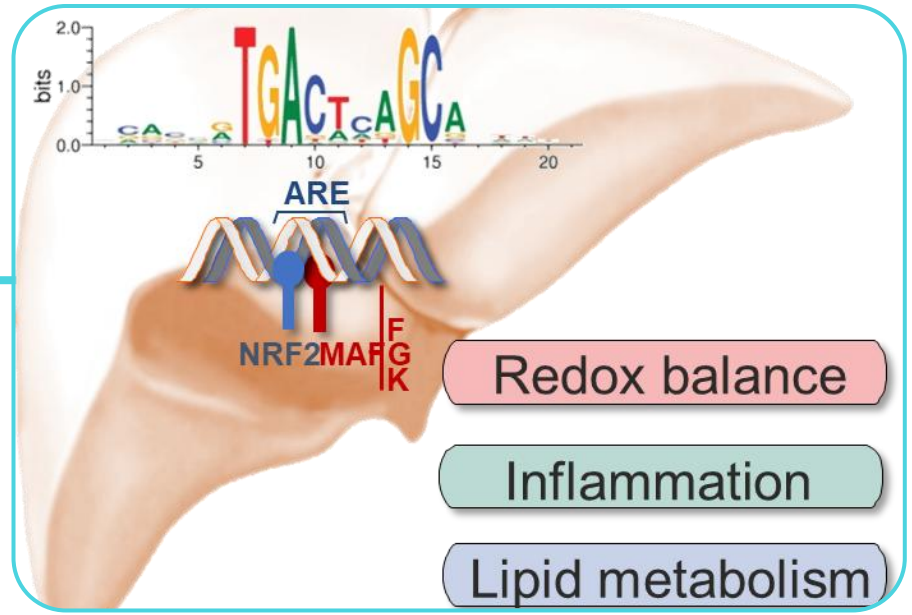

Our VIEW:

NRF2 as a new and successful therapeutic target

Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that **regulates the expression of multiple defensive genes**.

NRF2 makes heterodimers with small MAFs and activates genes containing the Antioxidant response Element (ARE).

Redox balance
HMOX1, NQO1, TrxR, cGS, GCLc, GCLm, Gpx, GR ...

Purine metabolism
PPAT, MTHFD2

Pentoses metabolism
G6PDH, PGD, IDH1, ME

Lipid metabolism
ACC1, FAS, SCD1 ACL...

Inflammation
MARCO, CD36, IL17D

Proteostasis
Gpx8, PSMB7, SQSTM, CALCOCO2, ULK1.....

Modified from Cuadrado et al Pharmacol Rev 2018

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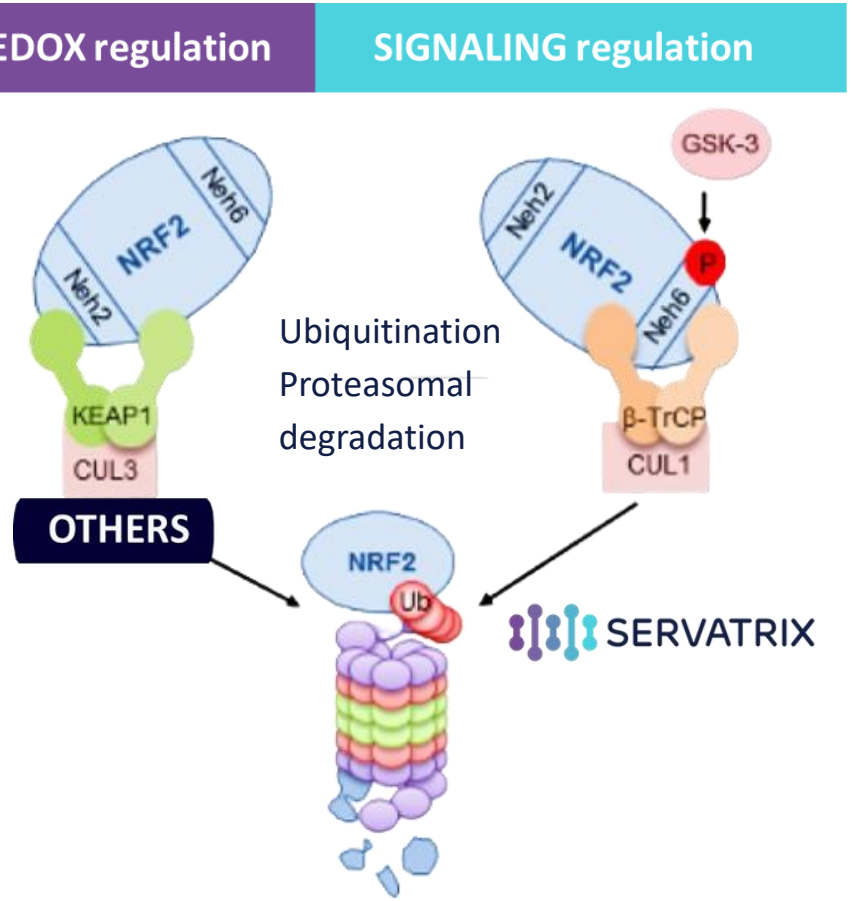
Our VIEW:

NRF2 as a new and successful therapeutic target

Two physiological mechanisms of NRF2 regulation at the level of protein stability:

- KEAP1: redox sensor
- Beta-TrCP: phospho-sensor

Targeting the KEAP1 and beta-TrCP repressors is a pharmacological strategy for activation of NRF2



Modified from Cuadrado et al Pharmacol Rev 2018

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CLINICAL EVIDENCE

that NRF2 is druggable

1rst case of success: Tecfidera-Vumerity

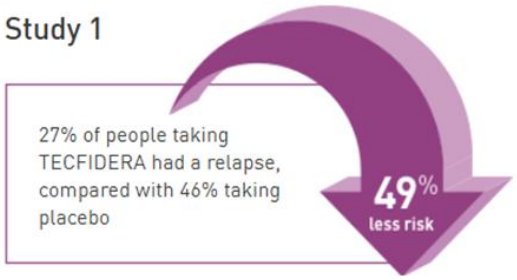
Developed by Biogen.

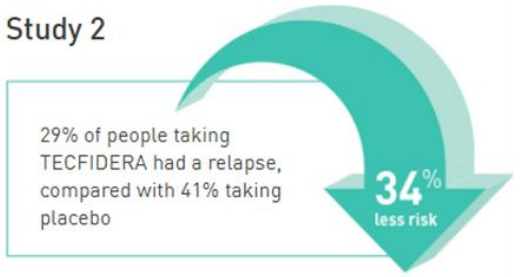
Tecfidera (dimethyl fumarate) and Vumerity (diroxymel fumarate) target KEAP1, leading to NRF2 activation.

Approved by FDA and EMA for treatment of multiple sclerosis and psoriasis.

Biogen

— TECFIDERA ● VUMERITY





Source: Biogen: https://www.tecfidera.com/en_us/home/about/benefits.html

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CLINICAL EVIDENCE

that NRF2 is druggable

2nd case of success: Skyclaris-Omeveloxolone

Developed by Reata Pharmaceuticals

Extremely potent inhibitor of KEAP1, leading to NRF2 activation

Approved by FDA for treatment of Friedrich ataxia

Orphan drug exclusivity, providing seven years of market protection from potential genercic competitors

Reata was acquired by Biogen for 7,300 B $

Biogen

REATA PHARMACEUTICALS

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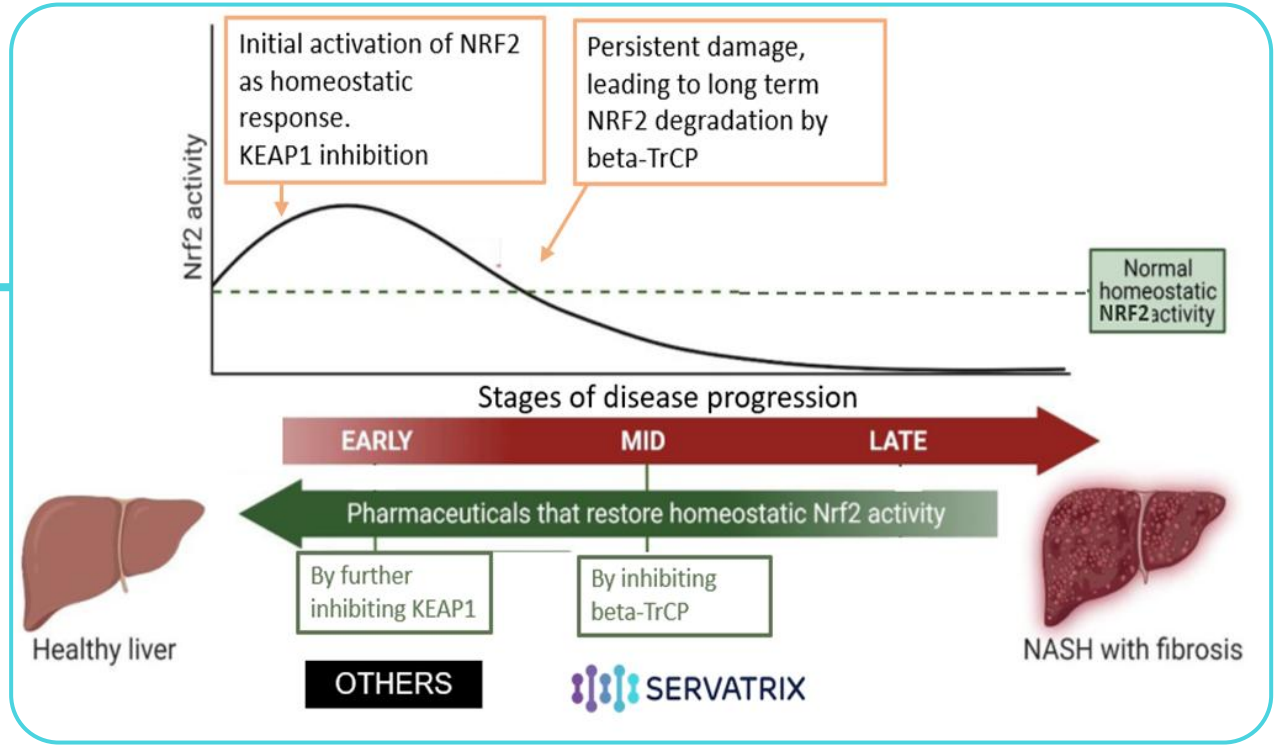
THE GREAT COMPETITIVE ADVANTAGE

Targeting Beta-TrCP



Our completely **novel approach to NRF2** activation is the development of molecular disruptors that prevent the interaction of NRF2 with beta-TrCP.

No evidence of significant off-target effects (molecular target selectivity)

Our compounds exert a mild activation of NRF2, close to physiological levels, **allowing prolonged treatment in chronic diseases** (safe)

Although NRF2 is ubiquitously expressed, our compounds target it **only in liver** (organ selective)

Modified from Batish et al, Free Radic Biol Med. 2022

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HIT COMPOUNT (PHAR)

Beta-TrCP

PUBLICATIONS

Fernández-Ginés et al, 2022 Redox Biology, 65: 102396.

Fernández Ginés et al, 2024. Redox Biology, 69: 103027.

García-Yagüe et al, 2025. J Biomed Sci, 32: 65.

Fernández Ginés et al, 2026 in preparation

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HIT CHARACTERIZATION (PHAR)

COMPLETED

Discovery Phase — 500k EUR

1. **Target Identification**: Selection of a biological target associated with the disease (e.g., NASH).
2. **Biochemical assays:** for target validation.
3. **Hit Identification**: Computational modeling to identify hit compounds. 1M+ compounds. SBDD (Molecular docking and structure-based drug design).
4. **Hit Validation**: Biochemical and cellular assays to confirm activity of HIT candidates.
5. **Initial ADMET Profiling**: Early assessments for absorption, distribution, metabolism, excretion, and toxicity of selected HIT (PHAR).
6. **Hit-to-Lead Transition**: Refinement of our HIT with preliminary efficacy and safety profiles.
7. **Early *IN VITRO* and *IN VIVO* pharmacokinetics.**

HIT COMPOUND (PHAR)	Tasks	2022				2023				2024			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Proof of concept	1. In silico docking to beta-TrCP												
	2. ADMET prediction												
	3. Chemical synthesis and characterization												
	4. Activation of NRF2 reporter(Luciferase)												
	5. Increase of NRF2 protein levels												
	6. Activation fo NRF2 target genes												
	7. Toxicity in cell culture												
Patent (PCT) submission and approval	8. Submission												
	9. Approval												
Preclinical in vitro (non-GLP)	10. Solubility												
	11. Plasma stability												
	12. Plasma protein binding												
	13. Microsomal stability												
	14. Caco-2 permeability												
	15. Metabolism.												
	16. Off-targets (Eurofins).												
	17. Off targets (RNAseq)												
Preclinical in mouse	18. Target organ liver/plasma/brain												
	19. Bioavailability/PK												
	20. Toxicity. Body weight												
	21. Locomotor activity and external examination												
	22. Toxicity. Blood analysis												
Preclinical in rat (no-GLP)	23. Validation of analytical method in rat plasma												
	24. Prelimianry pharmacoinetics (Tmax, Cmax, AUC)												
Preclinical in dog (no-GLP)	27. Validation of bioanalitical method in dog plasma												
	28. Preliminary pharmacokinetics (Tmax, Cmax, AUC)												

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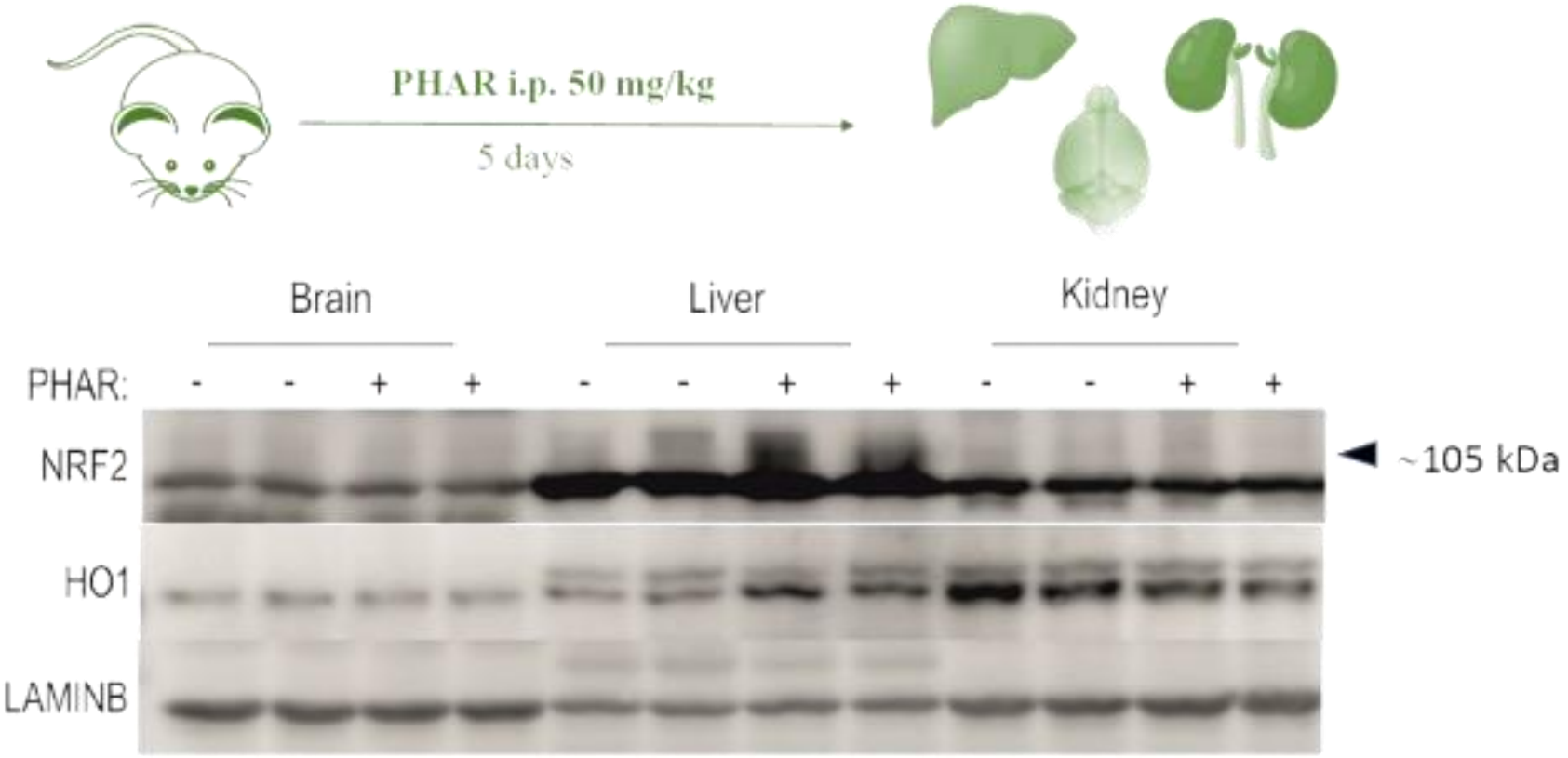
PHAR successfully activate NRF2 in mouse liver



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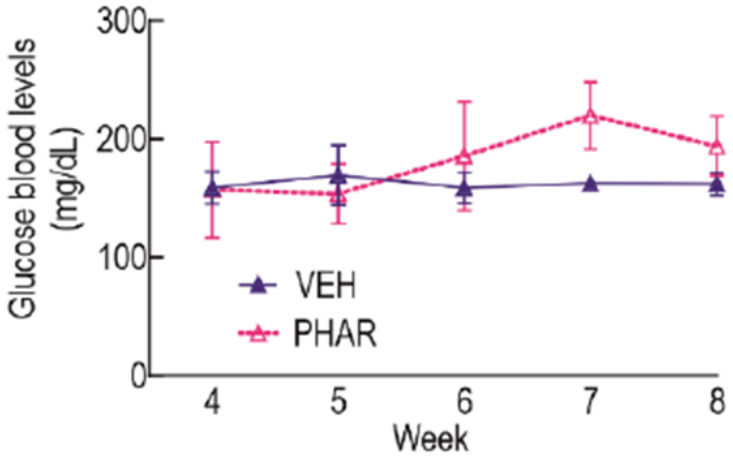
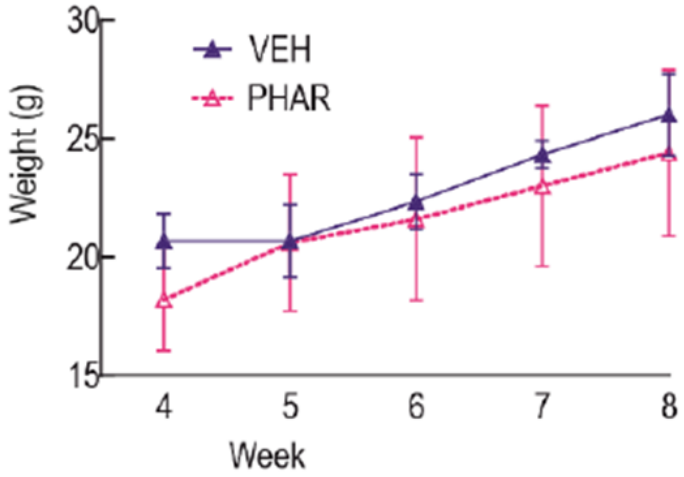
PHAR successfully deliver preliminary safety results

SAFETY

Groups	Alb (g/L)	ALT (U/L)	AST (U/L)	AP (U/L)	TP (g/L)	Total bilirrubin (mg/dL)	Direct bilirrubin (mg/dL)
CTRL-VEH	33.0 ± 0.58	56.5 ± 21.7	576.2 ± 387.1	91.3 ± 23.5	65.8 ± 3.2	3.3 ± 1.4	<0.01
CTRL-PHAR	31.8 ± 1.26	51.7 ± 30.2	517.4 ± 231.2	109.8 ± 39.6	67.3 ± 2.2	4.0 ± 1	<0.01





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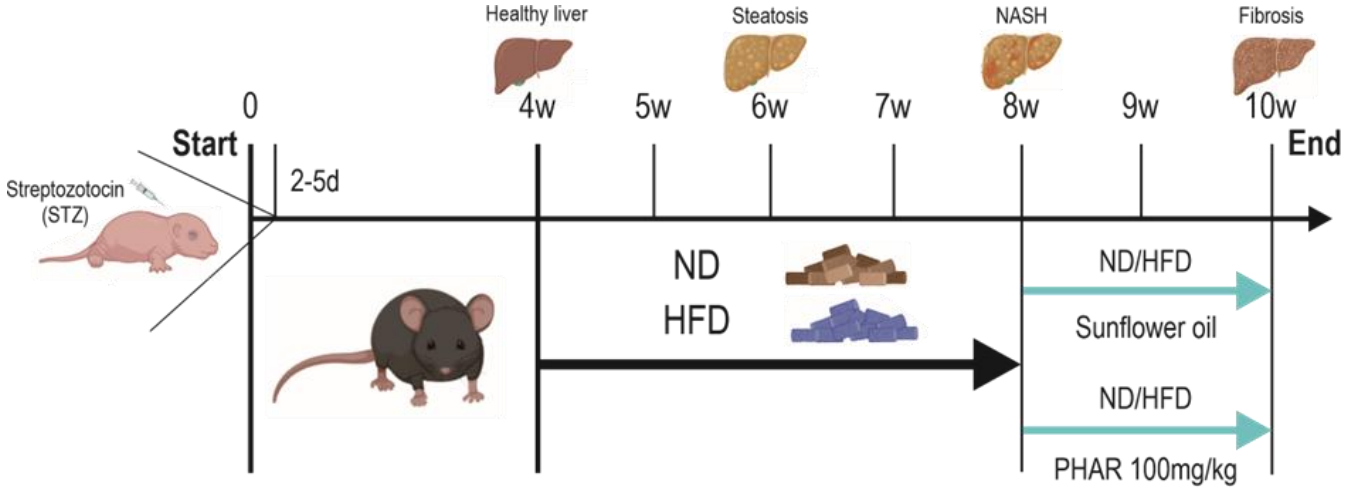
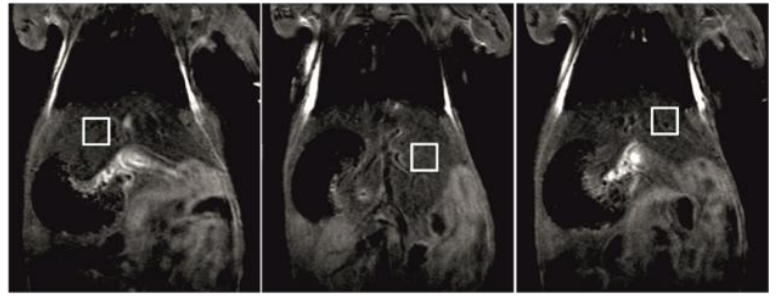
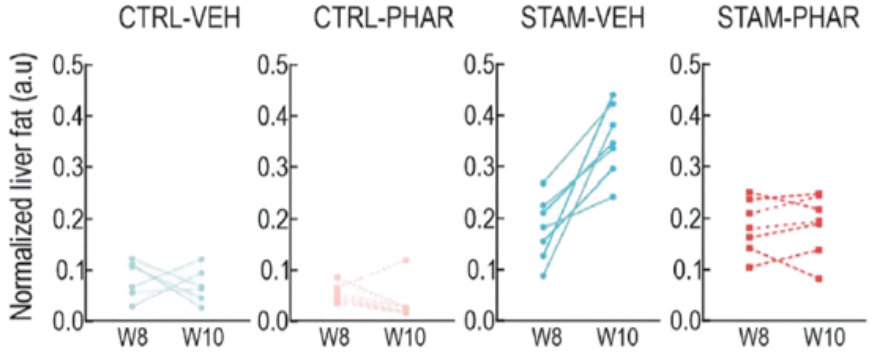
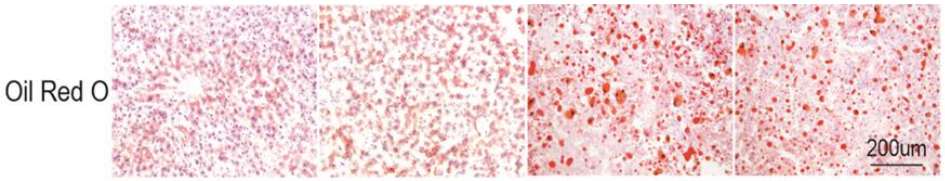
PHAR successfully delivers preliminary efficacy results (in vivo)

Efficacy in fat reduction in the STM mouse model of NASH/MASH









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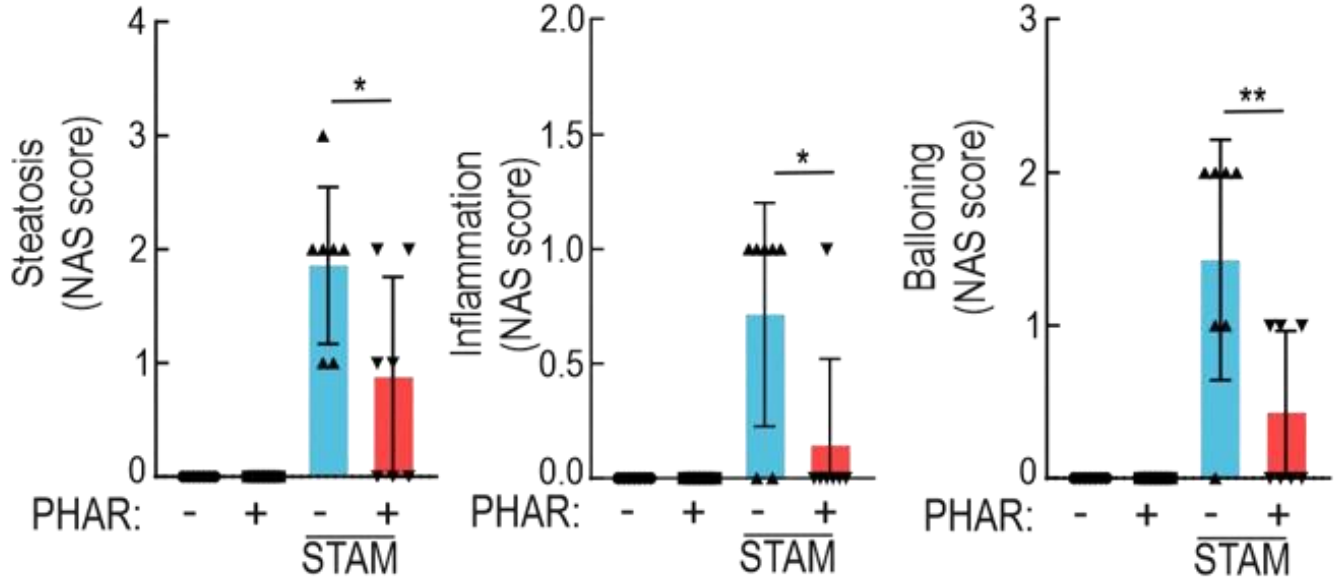

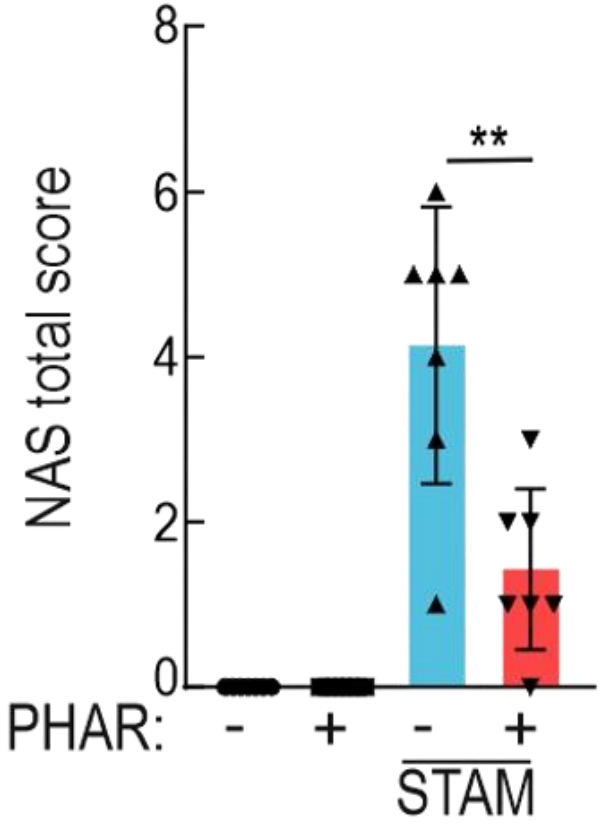

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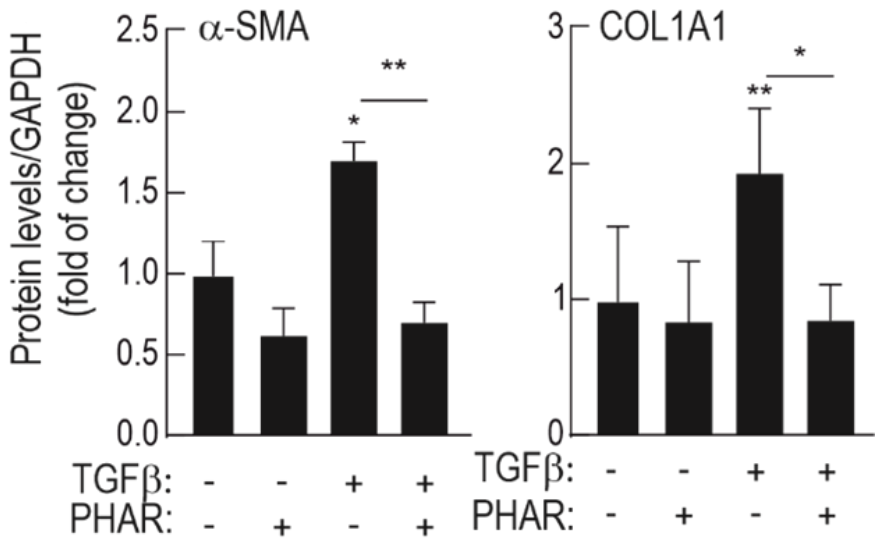
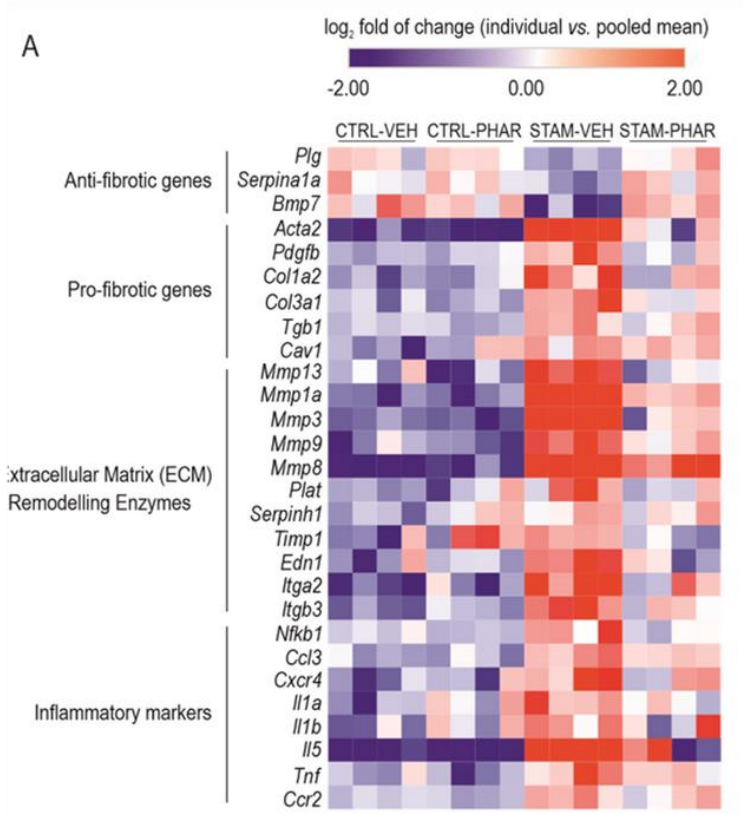
PHAR successfully deliver preliminary efficacy results (in vivo)

Efficacy in reduction of inflammation and fibrosis

ESTELLATE CELLS



MOUSE LIVER



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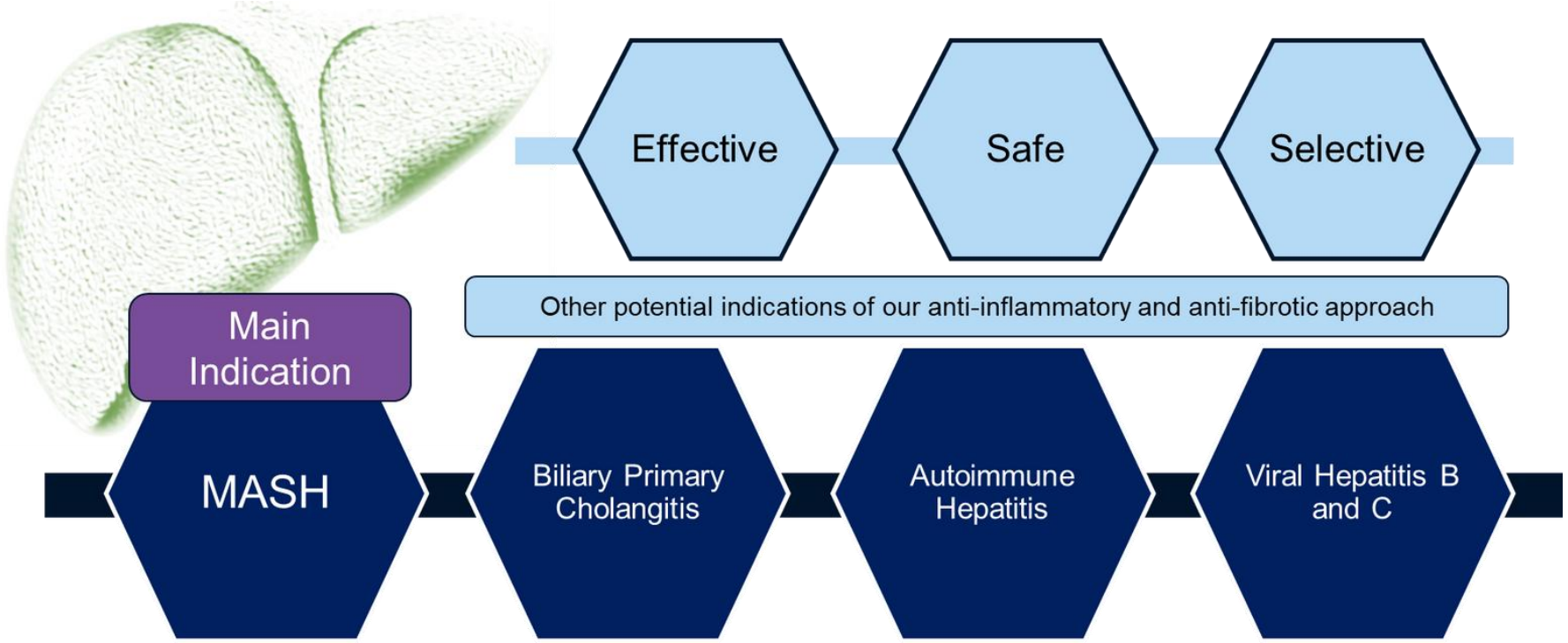
Our therapeutic target and hit compound present relevant potential in liver fibrosis diseases



Next step in our roadmap -> Lead compound optimization (Hit-to-Lead)

06 IP strategy

A proven IP Strategy

Intellectual property:

European patent: date of priority January 2021

PCT/EP2022/050657. Date of priority: January 2022

New additional IP under development for:

Extension of original scope

New applications and diseases

07 Business model

Business model

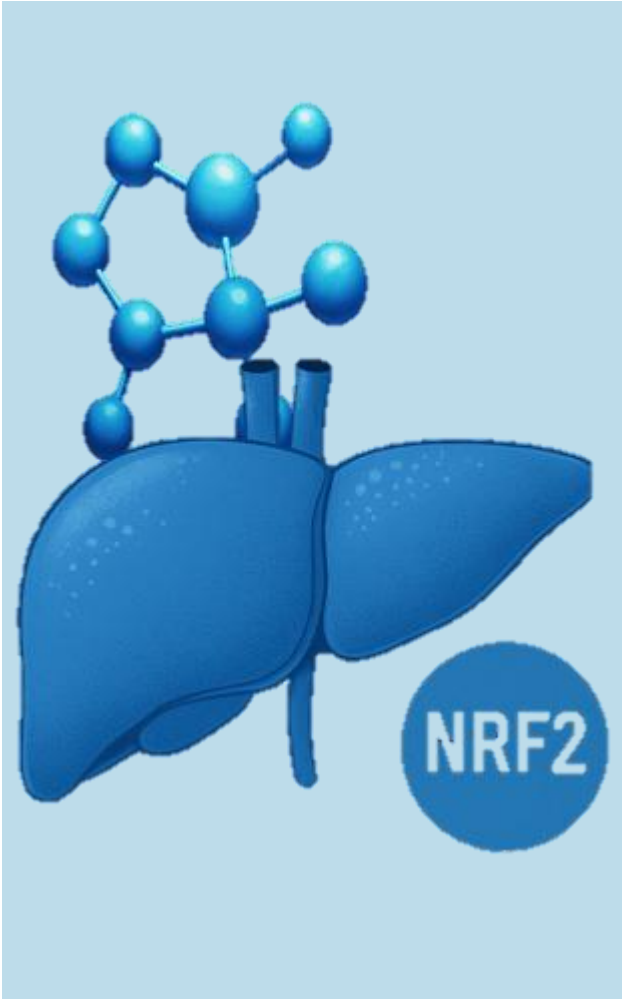
Dual strategic focus:

1. **Development of proprietary drug candidates, with PHAR as the lead asset.**
   - PHAR is a first-in-class molecule inhibiting NRF2-β-TrCP interaction
   - Target therapeutic indication: (NASH). Clinical Phase I entry expected in 2027, marking a key inflection point for licensing or acquisition.

2. **Biomarker. Kit companion of drug response and target engagement**

3. **Offer of specialized scientific services to pharma, biotech, and academic clients.**
   - B2B offerings built on Servatrix's deep NRF2 expertise. Services include: computational screening, molecular modeling, dynamic simulations. Also offers omics data analysis (transcriptomics and lipidomics). Supports in vitro validation in collaboration with FUAM lab.
   - Validated through contracts with Kinjirushi (Japan) and University of Bern (Switzerland).

4. **Digital infrastructure underpins both segments for efficiency and scalability.**
   - Digital workflows reduce time and cost of development. Massive structural iterations via high-throughput computation.
   - AI assists in efficacy prediction, target selection, toxicity minimization.
   - Advanced process increases success probability in preclinical and clinical phases.



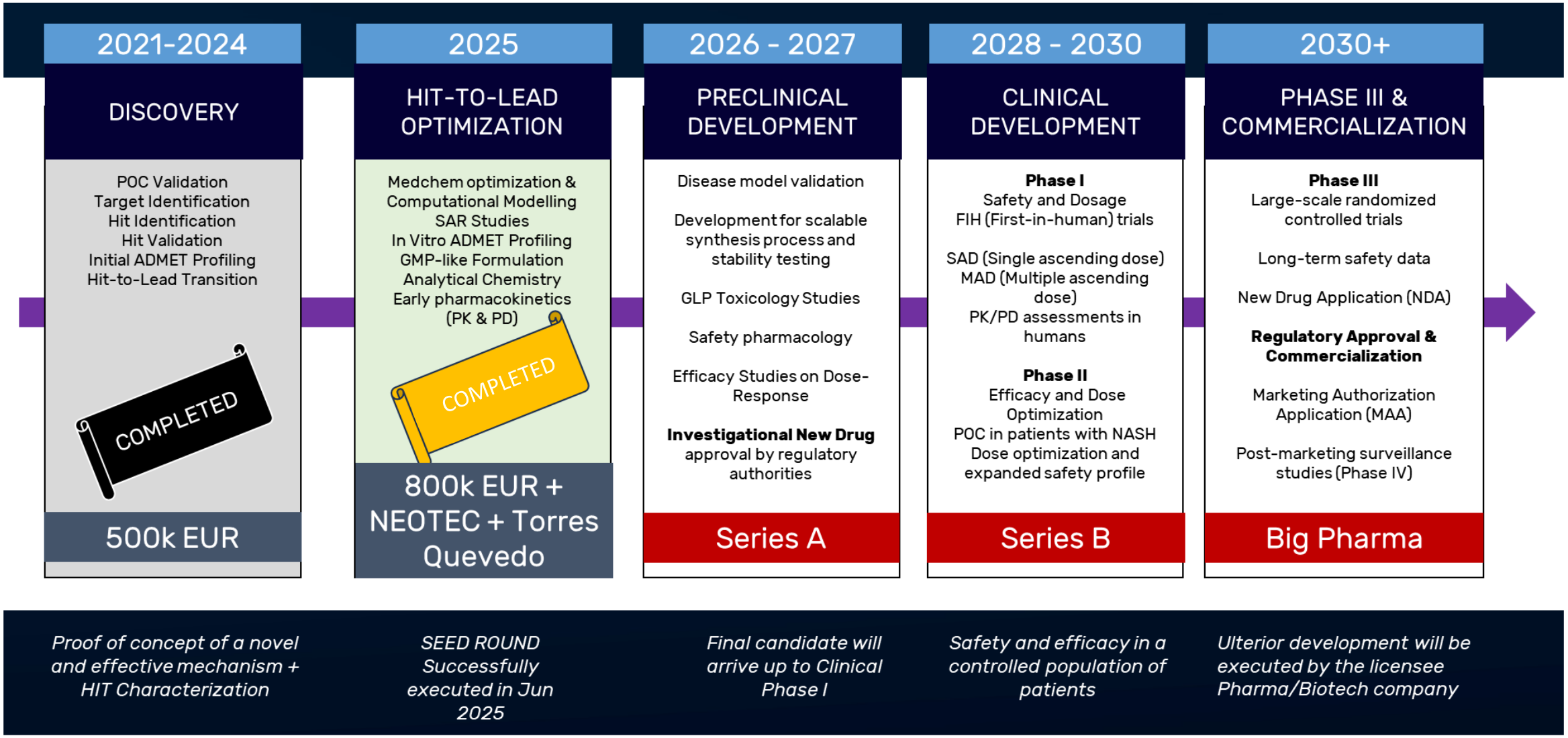
International growth

- **Priority markets: US, EU, and Japan.**
  - EU unitary patent PCT/EP2022/050657 already validated.
  - National extensions in Switzerland, UK, and Spain.
  - US and Japanese patent filings submitted for strategic coverage.
  - Entry strategy: alliances with pharma leaders in metabolic and neuroinflammatory fields.

- **Mixed growth model:**
  - Direct asset monetization (PHAR through licensing or co-development).
  - Indirect revenue via B2B services and platform licensing.
  - Service portfolio: Kinjirushi LTD, Univ. of Bern,
  - Strategic collaborations ENAMINE, Galchimia, INNOQUA Toxicology, CSIC
  - Participation in COST Action CA20121 involving 440+ NRF2 researchers across 40 countries

08 Financial & strategic roadmad

Scientific roadmap & milestones



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Thank You So Much

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