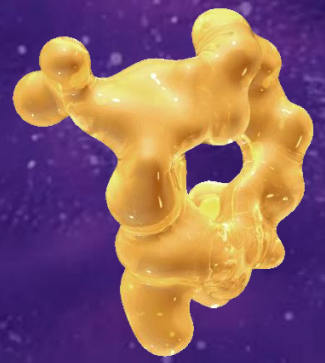
HEPION PHARMACEUTICALS

A BETTER APPROACH TO DRUG DEVELOPMENT **FOR LIVER DISEASES**

June 2021 | INVESTOR PRESENTATION



smart drug
smart technology
smart development

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THE NEED AND OPPORTUNITY
IN NASH DRUG DEVELOPMENT

NASH is a Healthcare Crisis

No drugs are approved for treating NASH

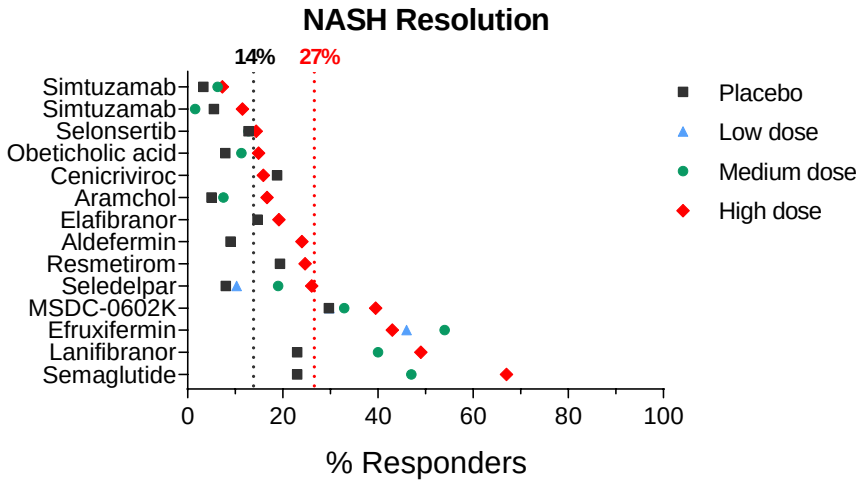
NAFLD
non-alcoholic fatty liver disease

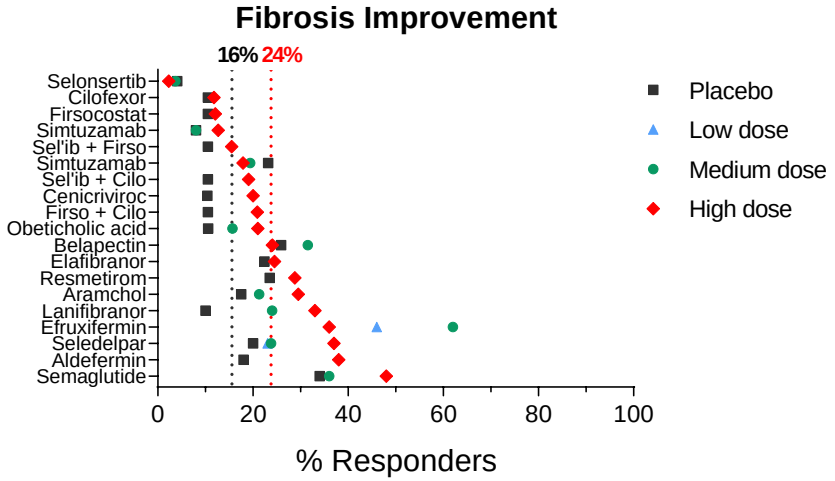
- “Fatty liver” disease associated with obesity, diabetes, hypertension, etc.
- Approx. 25% of global population (up to 100 million in U.S.)

NASH
non-alcoholic steatohepatitis

- A more severe form of NAFLD, with inflammation and liver scarring (fibrosis)
- 1.5 – 6.5% globally (up to 17 million in U.S.)

THE CHALLENGES OF NASH DRUG DEVELOPMENT





Regulatory agencies require regression of several indices of liver disease by histological analysis:

- Fatty deposits, cell death, inflammation and/or liver scarring (fibrosis)

Most study outcomes have been disappointing:

- High placebo responses
- Low responses from most candidate drugs
- Several drug candidates discontinued

New approaches to developing NASH therapeutics are needed

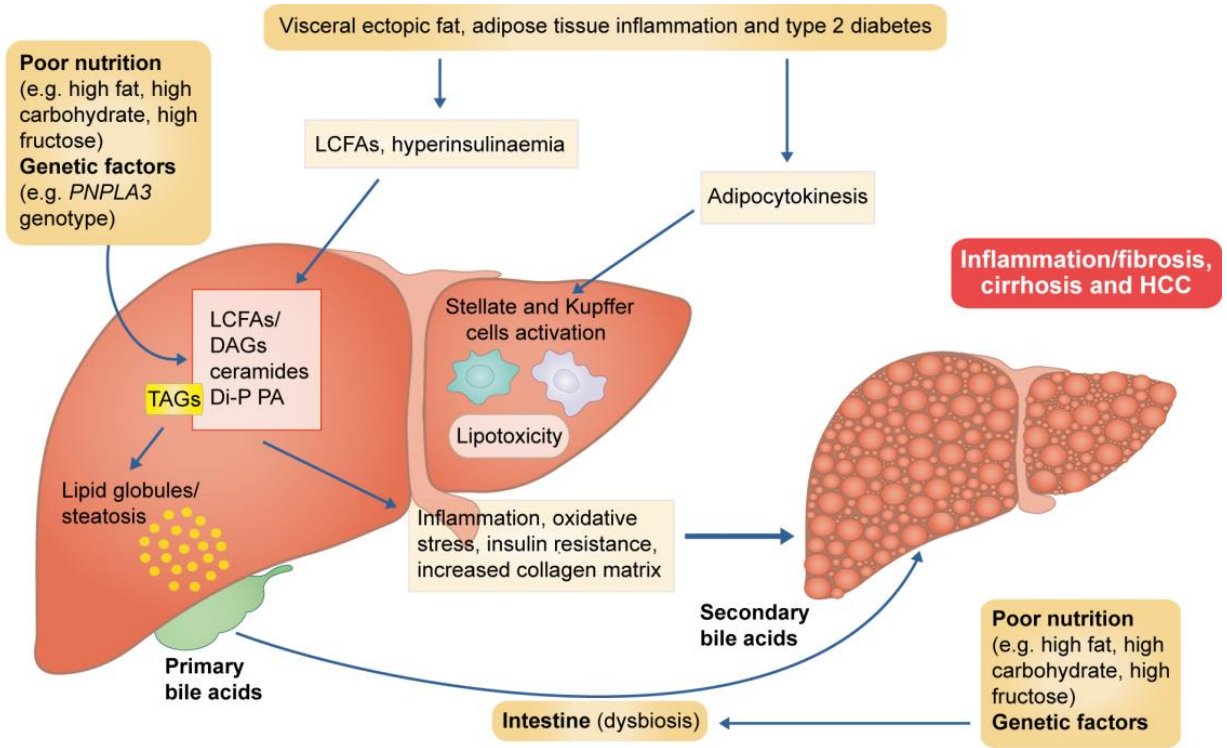
HEPION'S **APPROACH**

SMART STRATEGY #1

Target Multiple Disease Processes With a Single Agent

toxic lipids

cell death



inflammation

fibrosis

liver cancer

NAFLD: A multi system disease by Pablo Echeverria

HEPION'S APPROACH

SMART STRATEGY #2

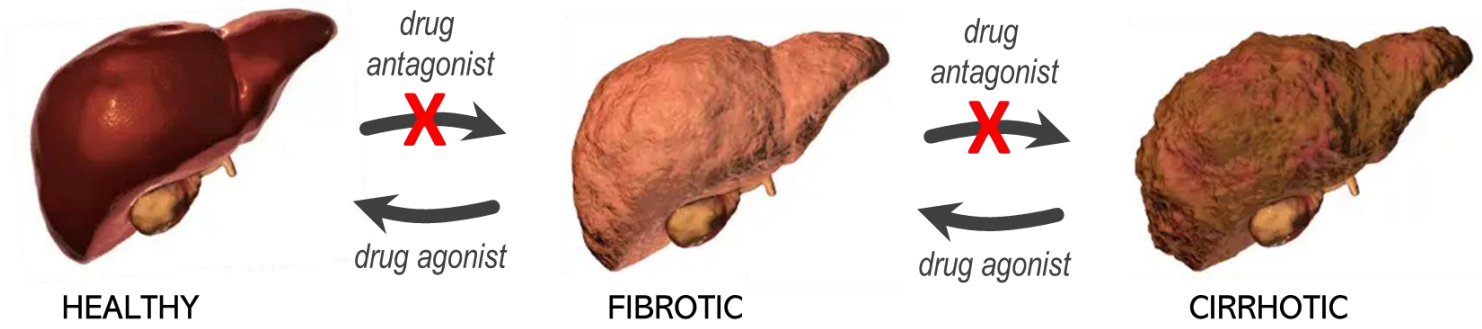
Attenuate Disease Drivers

Most NASH drug candidates are agonists that <u>amplify</u> homeostatic processes to help regress disease

PPAR agonists
FGF agonists

FXR agonists
GLP-1 agonists

THRβ agonists



Cyclophilin inhibitors <u>reduce</u> harmful processes that drive disease progression

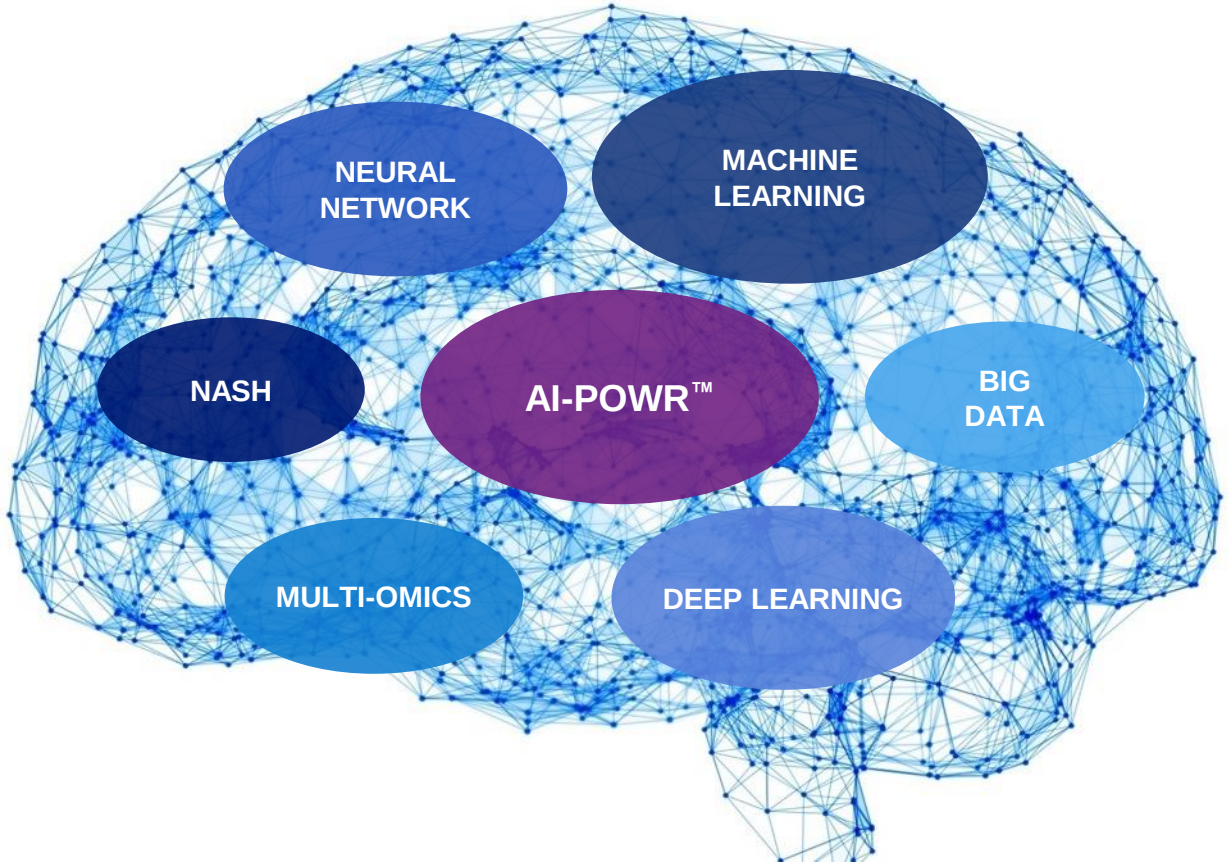
HEPION'S APPROACH

SMART STRATEGY #3

State-of-the-art Bioinformatics and Artificial Intelligence

AI-POWR™

- Understand disease mechanisms
- Identify biomarkers
- Track disease progression and regression
- Predict drug responders
- Precision medicine

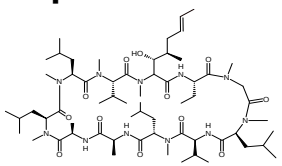
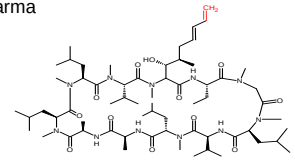
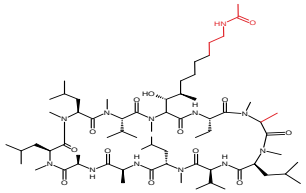
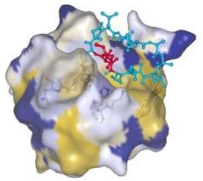


PIPELINE

Program	Pre-Clinical	Phase 1*	Phase 2	Phase 3	NDA Submission
NASH	IND 142904				**Projected NDA filing** **2025/26**
COVID-19	IND 151344		**Will proceed if externally funded**		
HBV	IND 1376787		**Open to partnerships**		

*Separate Phase 1 programs were not conducted for each separate indication. The Phase 1 program was comprised of Single and Multiple Ascending Doses, and a Drug-Drug Interaction study.

GENESIS OF HEPION PHARMACEUTICALS CRV431

Theory	Prediction and Experimentation		Findings
Modifying Cyclosporine A can greatly change its binding and functional properties	Modifications that increase calcineurin binding and immunosuppression (voclosporin) Modifications that decrease calcineurin binding and immunosuppression, and increase cyclophilin binding and inhibition (CRV431)		Inhibition of each cyclophilin isoform produces distinct therapeutic effects
Cyclosporine A  Nearly 40 years of clinical use as immunosuppressive drug for organ transplantation and autoimmune diseases	**Voclosporin** Aurinia Pharma  Modifications increase affinity for calcineurin and **increase immunosuppression potency**	**CRV431**  Modifications increase affinity for cyclophilins (13-fold) and **eliminate immunosuppression**	 CRV431 binds potently (Ki≈1 nM) to around 10 of 17 cyclophilin isoforms in the human body

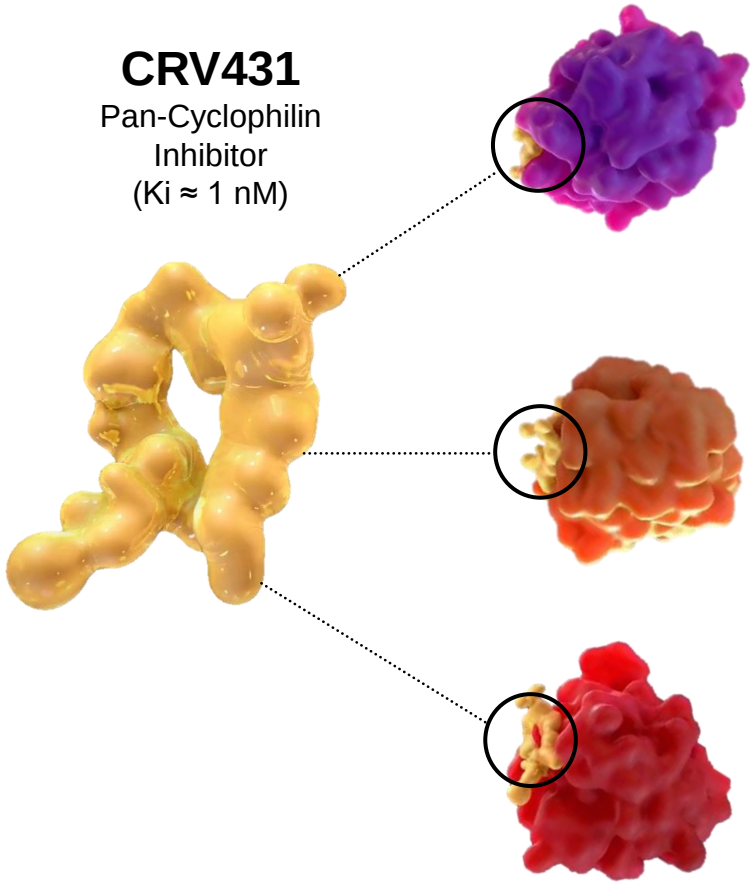
Why Target Cyclophilins?

Cyclophilins shown to play deleterious roles in:

Viral Hepatitis • Cancers • Acute and Chronic Lung Injury • Myocardial Infarction • Stroke • Arthritis • Atherosclerosis • Thrombosis • Aortic Aneurysm • Coronary Artery Disease • Pulmonary Arterial Hypertension • ALS • Alzheimers Disease • Multiple Sclerosis • Muscular Dystrophies • Traumatic CNS Injury

MULTIPLE THERAPEUTIC ACTIONS
THROUGH CYCLOPHILIN INHIBITION

CRV431
Pan-Cyclophilin Inhibitor
(Ki ≈ 1 nM)



Cyclophilin A
(cytosol and secreted)

Secreted from injured cells and acts as proinflammatory cytokine by binding to CD147

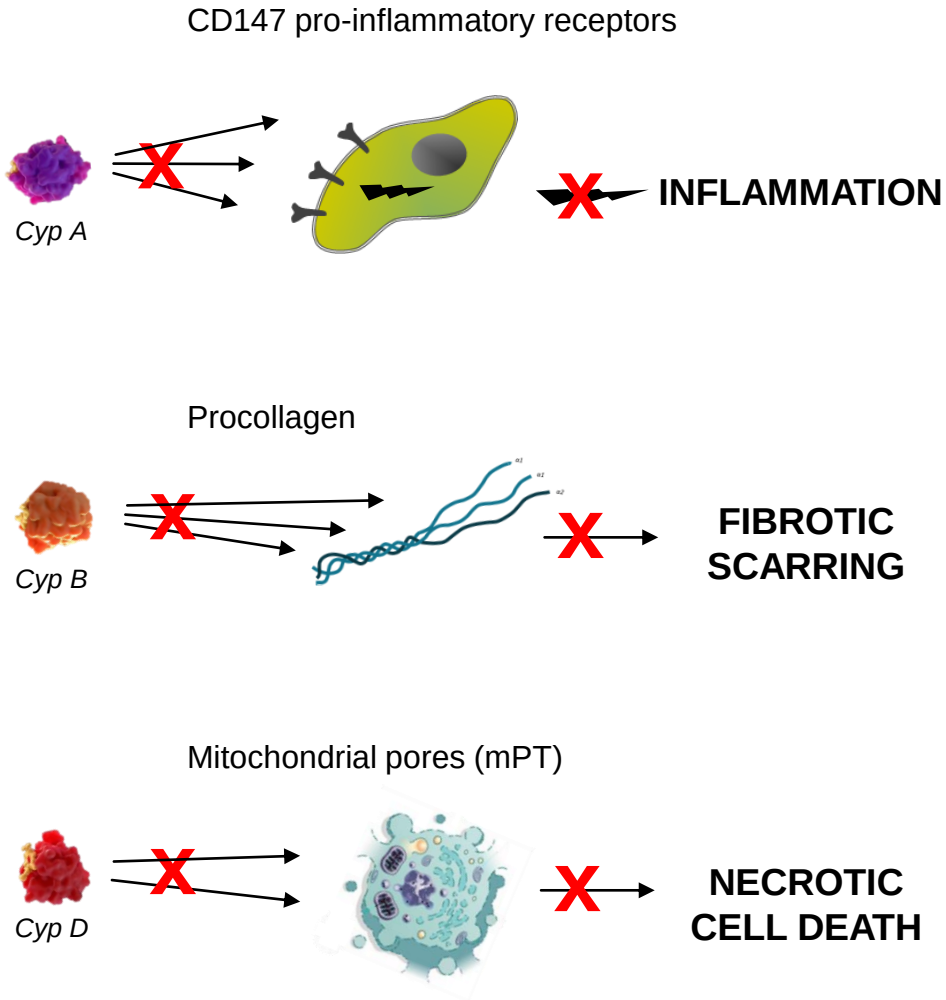
Cyclophilin B
(endoplasmic reticulum)

Promotes fibrotic scarring by controlling collagen production

Cyclophilin D
(mitochondria)

Regulates mitochondrial metabolism

Promotes mitochondrial pore opening leading to mitochondrial and necrotic cell death



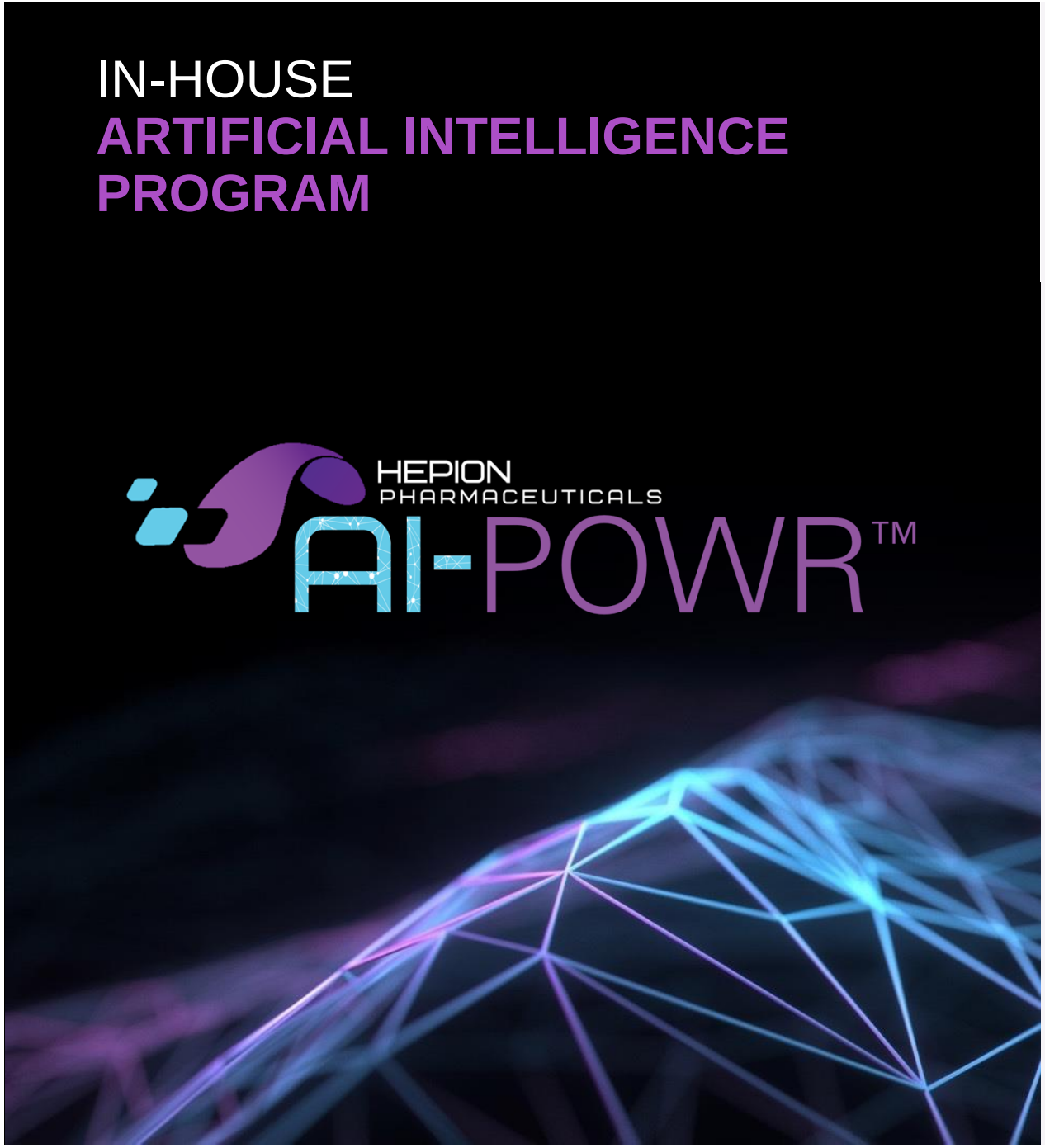
ANTIFIBROTIC AND OTHER PRECLINICAL ACTIVITIES

Human Cell Cultures		CRV431 Effects
Hepatic stellate cells, fibroblasts (multiple organs)	TGFβ or endogenous stimulation	▼fibrotic gene expression ▼procollagen and fibronectin secretion
Blood platelets	Collagen and thrombin stimulation	▼procoagulant platelet formation

Human Tissue Explants (Precision Cut Slice Cultures)		CRV431 Effects
Liver explants (4 donors)	TGFβ+PDGF-BB or endogenous stimulation	▼ inflammatory/fibrotic gene expression ▼ inflammatory/fibrotic protein secretion ▼ tissue fibrosis
IPF lung explants (1 donor)	Endogenous stimulation	

Animal Models		CRV431 Effects
Mice (NASH)	Western diet + carbon tetrachloride	82%▼ fibrosis; ▼weight gain
Mice (NASH)	High fat diet + early STZ (4 studies)	37-57%▼fibrosis; ▼weight gain; 50%▼liver tumors
Mice (liver fibrosis)	Carbon tetrachloride	44%▼ fibrosis
Mice (kidney fibrosis)	Unilateral ureter obstruction	42%▼ fibrosis
Rats (liver fibrosis)	Thioacetamide	48%▼ fibrosis; prevented cirrhosis
Mice (acute lung injury)	Lipopolysaccharide inhalation	▼BAL fluid inflammatory cytokines, neutrophils
Mice (diabetes)	High fat diet + late STZ	▼adiposity; ▼weight gain

IN-HOUSE
ARTIFICIAL INTELLIGENCE PROGRAM



- Multi-omics analyses – 25,000 data points per patient
- Identify biomarkers that predict response to CRV431
- Optimize and de-risk clinical trials through patient matching to CRV431 – precision medicine

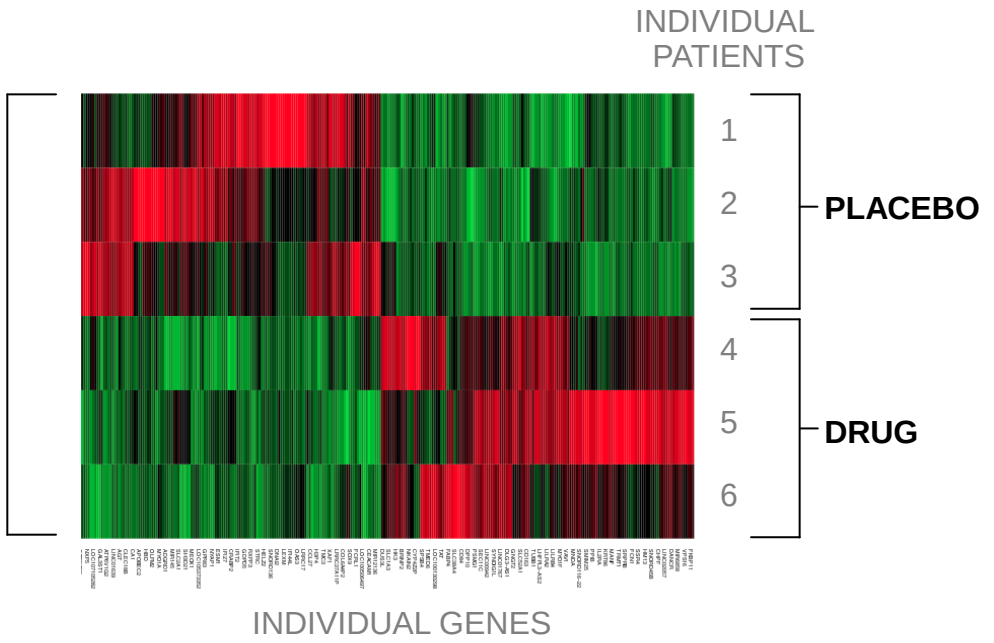
AI-POWR™
ILLUSTRATIONS

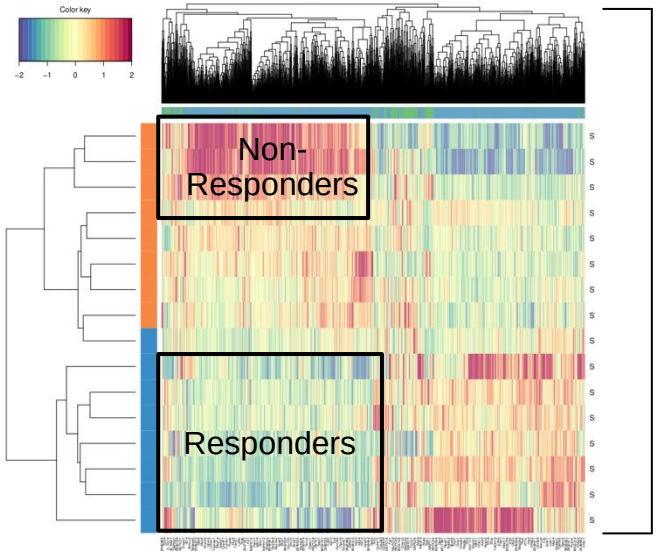
Gene Expression Analysis

NASH is heterogenous disease, underpinned by complex biochemical and pathological processes.

low expression

high expression

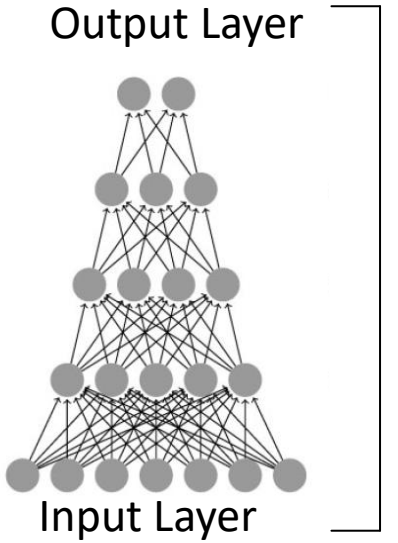




Cluster By Response

- Learn response rates for treatment and placebo
- Identify patterns predicting response
- Select patients (trial enrichment)

AI:Trained Neural Nets



- Clinical Outcomes
- Biomarkers/Patients
- Optimize & Test

NASH
CLINICAL PROGRAM

- **Phase 1** completed
- **Phase 2a** enrolment complete – data Q2 2021
- **Phase 2b** in planning – starting Q4 2021

PHASE 1
HEALTHY SUBJECTS - SAFETY, TOLERABILITY AND PK

Single Ascending Dose (SAD)

- ✓ N = 32 (24 CRV431; 8 Placebo)
- ✓ Doses: 75 mg, 225 mg, 375mg, 525 mg (single doses)
- ✓ Drug Exposure is in the range in which efficacy was demonstrated in pre-clinical models
- ✓ Pharmacokinetics are first order and support once daily dosing
- ✓ No SAE's, Mild AE's, No dose response in AE's or changes in clinical labs
- ✓ No changes in vital signs or ECG

Multiple Ascending Dose (MAD)

- ✓ N = 25 (All CRV431)
- ✓ Doses: 75 mg, 150 mg, 225 mg, 300 mg, 375 mg QD x 28 Days
- ✓ Drug Exposure starting at 75 mg QD is in the range in which efficacy was demonstrated in pre-clinical models
- ✓ Pharmacokinetics are first order and support once daily dosing
- ✓ No SAE's, Mild AE's, No dose response in AE's or changes in clinical labs
- ✓ No changes in vital signs or ECG
- ✓ Data supported initiation of Phase 2a NASH Trial

Drug-Drug Interaction (DDI)

- ✓ N= 18
- ✓ Single CRV431 375 mg Drug Interaction Study with tenofovir (TDF) 300 mg
- ✓ No SAEs, mild AEs
- ✓ No changes in vital signs or ECG
- ✓ TDF did not alter CRV431 exposure
- ✓ CRV431 increased exposure of TDF by ~32% (AUC_{0-24})

PHASE 2A
NASH SUBJECTS - SAFETY, TOLERABILITY AND PK

OBJECTIVES

- Safety and tolerability of once daily (qd) 75 mg and 225 mg doses of CRV431 in presumed NASH fibrosis stage 2 (F2)/fibrosis stage 3 (F3) patients compared to placebo control for 28 days
- Exploratory biomarkers of fibrosis and lipid metabolism: collagens, matrix metalloproteinases, lipidomics, and genomics
- Multi-omic/trait data analysis by AI-POWR™

STUDY DESIGN

- Multi-center (10 Sites), single-blind, placebo-controlled study
- Univariate Endpoints: AST, Pro-C3, ELF Score, Fibroscan

F2/F3 NASH Patients (n=36)

Cohort*	Fibrosis Stage	N	Day 1 – 28, fasted oral dosing	Day 29 - 42
A	F2/F3	12	CRV431 75 mg	Observation/Follow-up
B		6	Placebo	
C	F2/F3	12	CRV431 225 mg	
D		6	Placebo	

*randomized assignment; 2:1 – CRV431:placebo

Multivariate multi-omics-trait AI-POWR™ analysis to elucidate CRV431 activity biomarkers in F2/F3 NASH for Phase 2b Patient/Biomarker Selection

PHASE 2B
NASH SUBJECTS - EFFICACY

OBJECTIVES

- Efficacy of once daily (qd) oral dosing of CRV431 in biopsy proven NASH F2 and F3 patients compared to placebo
- 1-point reduction in fibrosis score in liver biopsies (pathologist and AI read)
- AI-POWR™ identification of biomarkers of CRV431 response from multi-omics, clinical labs, and other trait data

STUDY DESIGN**

- Multi-Center, triple-blind, placebo-controlled (2:1), study
- Liver biopsies, MRE scans, Fibroscan, ALT, AST, Pro-C3, ELF-Score, fibrosis biomarkers, lipidomics, genomics, proteomics

F2/F3 NASH Patients (n=300)

Cohort*	Fibrosis Stage	N	6-12 Months	3 Month
A	F2/F3	100	CRV431 low dose	Observation/Follow-up
B		50	Placebo	
C	F2/F3	100	CRV431 high dose	
D		50	Placebo	

*randomized assignment; 2:1 – CRV431:placebo

**final protocol in preparation, subject to change

Multivariate multi-omics-trait AI-POWR™ analysis to update CRV431 activity biomarkers in F2/F3 NASH for Phase 3 Patient/Biomarker Selection

2021 ANTICIPATED EVENTS

CRV431

- ☑ Complete Ongoing Phase 2a NASH program (Q2, 2021)
- ☑ Complete long-term animal toxicology (Q2, 2021)
- ☑ Continue to optimize and scale-up chemistry and manufacturing
- ☑ Complete additional clinical Drug-Drug (CYP3A4) Interaction study (Q2, 2021)
- ✎ Prepare for NASH Phase 2b (to start Q4 2021) using AI-POWR™ strategies

AI-POWR™

- ➡ Continue to refine and extend AI-POWR™ for NASH and possible other indications
- ➡ Continue to develop IP for additional indications and business development strategies

HIGHLIGHTS
STATUS, EXPERIENCE, RESOURCES

- Oral, once-daily, multi-modal drug candidate – CRV431
- Clinical Phase 2a NASH trial completing Q2
- Clinical Phase 2b NASH trial planned for Q4 2021 start
- Strong safety/tolerability profile in preclinical and Phase 1
- Anti-fibrotic, anti-inflammatory, cytoprotective, anti-viral, anti-cancer, and metabolic regulation - all by cyclophilin inhibition (MOA)
- Artificial Intelligence Platform (AI-POWR™)
- ~30 years experience in cyclophilin inhibitor development
- Core team discovered and developed voclosporin for transplantation and autoimmune disease (FDA approved Jan 2021)
- Robust IP (including US, Europe, Australia, Canada, China, Japan, Korea)

TWO VALUE DRIVERS

HEPION PHARMACEUTICALS CRV431

A Therapy for NASH with indications for several other conditions

HEPION PHARMACEUTICALS AI-POWR™

AI-Driven, Bioinformatic Platform

CASH

$115.4 million as of 3/31/21

76.2 million common shares outstanding

2/18/21, raised $88.4 million gross proceeds through issuance of 44.2 million common shares in a public offering

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