OMEGA™ THERAPEUTICS

Pioneering a New Class of Programmable Epigenomic Medicines

December 2024

Disclaimer and Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding: our anticipated cash runway; our prioritization of certain preclinical programs and platform efforts; potential strategic partnership opportunities; our competitive market position and market opportunity; our expectations surrounding the applicability and potential of our product candidates and programs, development timelines; anticipated timing of regulatory submissions and filings and introduction of development candidates; and expectations regarding our programs and pipeline, including our priorities and anticipated milestones, trial design, initiation of preclinical studies and our goal of declaring additional EC development candidates. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: the novel technology on which our product candidates are based makes it difficult to predict the time and cost of preclinical and clinical development and subsequently obtaining regulatory approval, if at all; the substantial development and regulatory risks associated with epigenomic controllers due to the novel and unprecedented nature of this new category of medicines; our limited operating history; the incurrence of significant losses and the fact that we expect to continue to incur significant additional losses for the foreseeable future; our need for substantial additional financing; volatility in capital markets and general economic conditions; our investments in research and development efforts that further enhance the OMEGA platform, and their impact on our results; uncertainty regarding preclinical development, especially for a new class of medicines such as epigenomic controllers; potential delays in and unforeseen costs arising from our clinical trials; the fact that our product candidates may be associated with serious adverse events, undesirable side effects or have other properties that could halt their regulatory development, prevent their regulatory approval, limit their commercial potential, or result in significant negative consequences; difficulties manufacturing the novel technology on which our EC candidates are based; our ability to adapt to rapid and significant technological change; our reliance on third parties for the manufacture of materials; our ability to successfully acquire and establish our own manufacturing facilities and infrastructure; our reliance on a limited number of suppliers for lipid excipients used in our product candidates; our ability to advance our product candidates to clinical development; and our ability to obtain, maintain, enforce and adequately protect our intellectual property rights. These and other important factors discussed under the caption “Risk Factors” in our most recent Quarterly Report on Form 10-Q and our Annual Report on Form 10-K for the year ended December 31, 2023, and our other filings with the SEC could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management’s estimates as of the date of this presentation. While we may elect to update such forward-looking statements at some point in the future, we disclaim any obligation to do so, even if subsequent events cause our views to change.

OUR VISION

Harness the power of epigenetics to develop an unrivaled class of transformative medicines

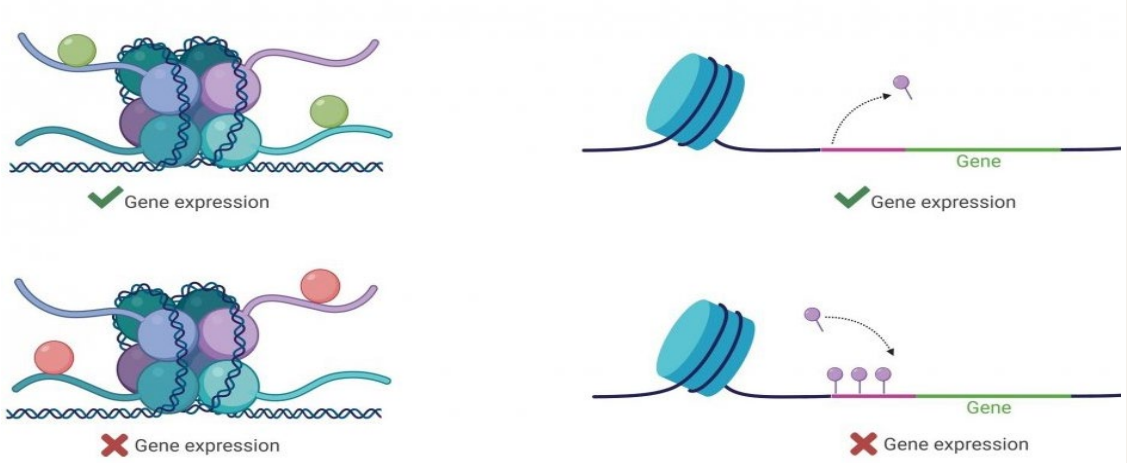
OMEGA™ THERAPEUTICS

Epigenomic Modulation Leverages Nature's Innate Mechanisms to Precisely Control Gene Expression

Versatile Features of Epigenomic Control

- **Tunable**
  - Control over the magnitude of changes
- **Pre-transcriptional**
  - Drives gene control at the source
- **Heritable**
  - Propagation of changes to daughter cells
- **Reversable**
  - Changes can be recalibrated since DNA sequence is not altered
- **Cell fate deterministic**
  - Ability to assign desired biological identity

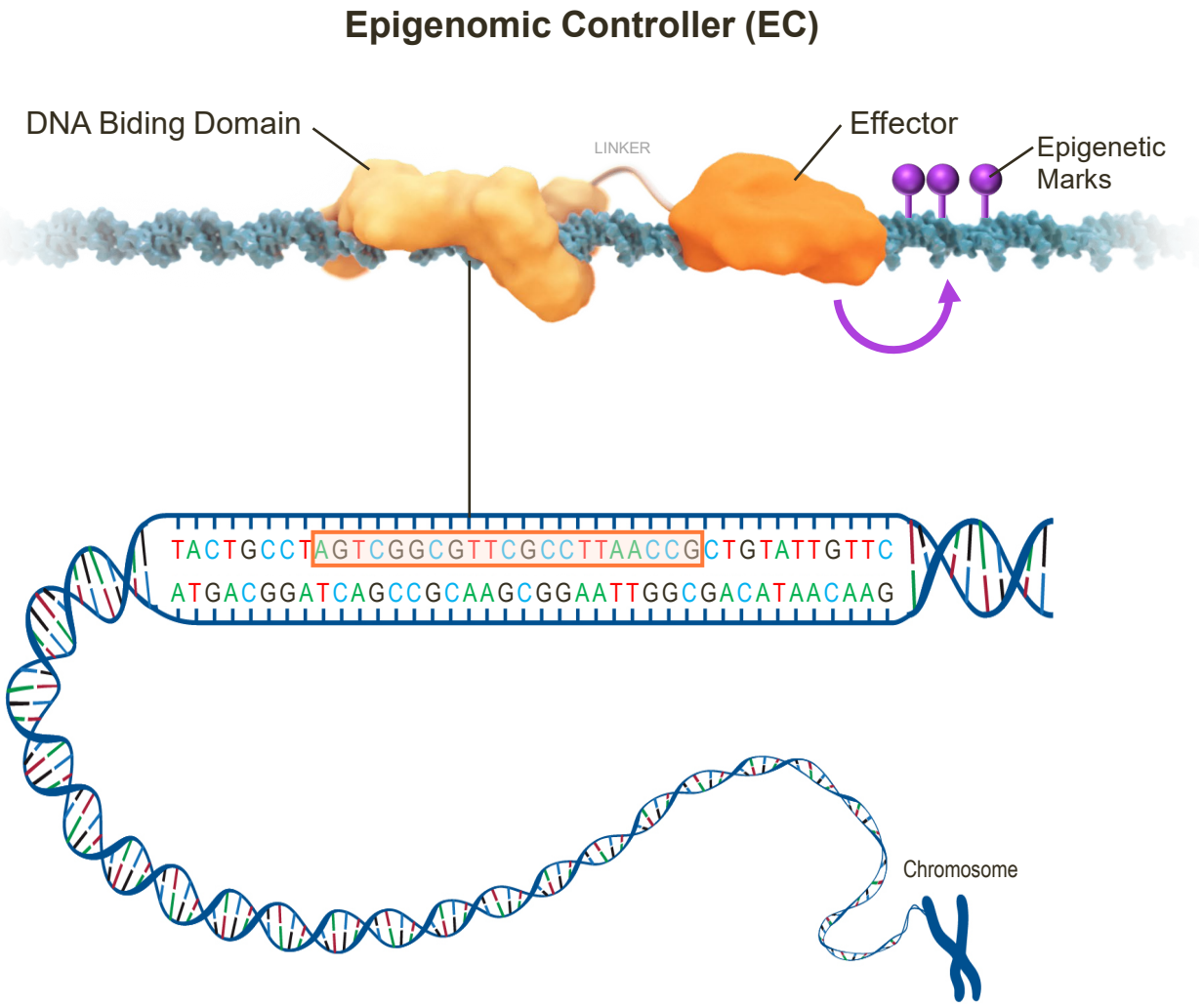
Precise Targeted Control



Genome-wide Change

Targeted Change

Omega's Platforms Engineers Programmable Epigenomic Medicines



Highly-specific DNA Binding Domain

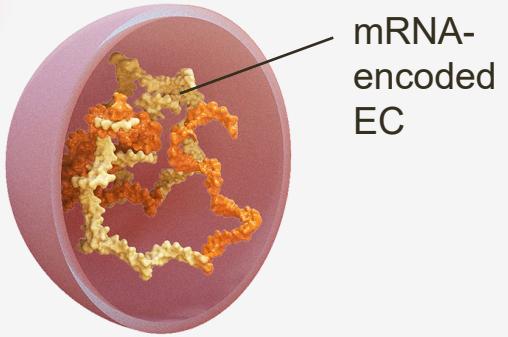
Target genome-wide unique 21-base pair DNA sequences as precise drug targets

Modular Effectors

Leverages full spectrum of epigenetic mechanisms available in nature to enable controlled tunability and durability

Customized Delivery

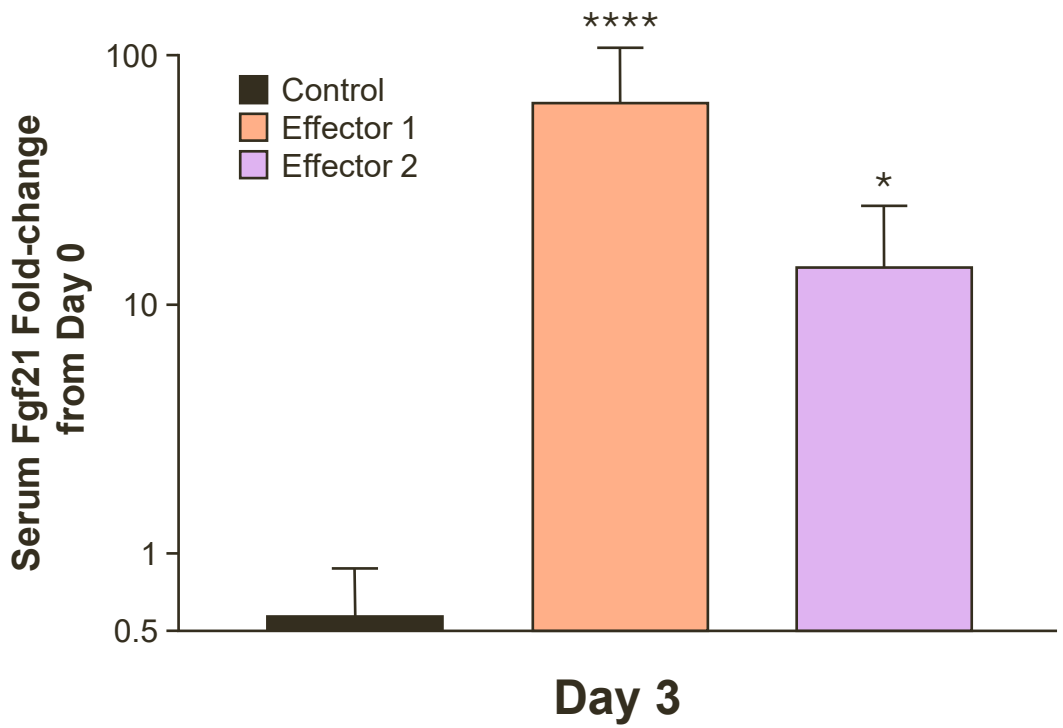
First wave of candidates delivered as mRNA-encapsulated lipid nanoparticles (LNPs)



Unparalleled Control of Gene Expression

Disease-relevant Level of Gene Modulation in the Appropriate Cell and Tissue Types

FGF21 Upregulation *In Vivo*



* p<0.05, **** p< 0.0001

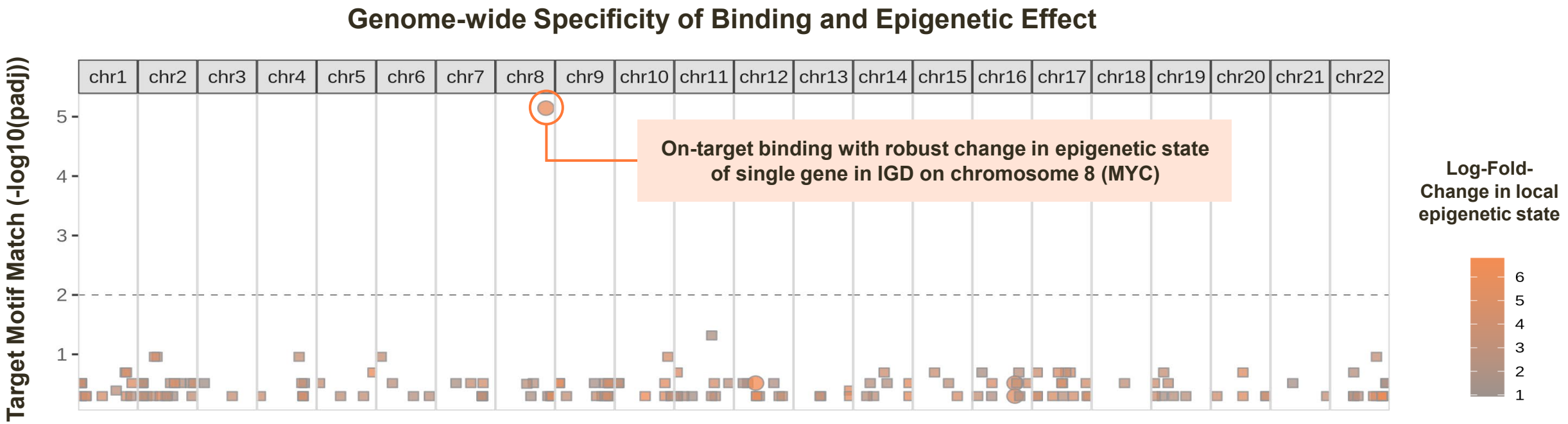
- **Broad applicability**: Proprietary, modular database of epigenomic effectors and DNA binding domains enable targeting of nearly every gene in the genome
- **Exquisite specificity**: Highly-specific targeting to precise drug targets without changing genomic architecture
- **Controlled tunability**: Bi-directional (up or down) modulation of gene expression optimized to intended therapeutically-relevant levels
- **Ability to multiplex**: Efficient and tunable up- or down-regulation of multiple genes with a single therapeutic
- **Tailored durability**: Transient expression of drug substance with engineered durability tailorable to last days, weeks or months

Demonstration of Omega Platform's Capabilities

OMEGA™ THERAPEUTICS

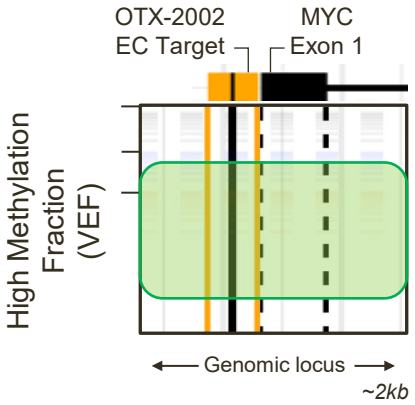
Exquisite Specificity

Highly-Specific Binding to Unique DNA Target Sequence with Intended Epigenetic Effect



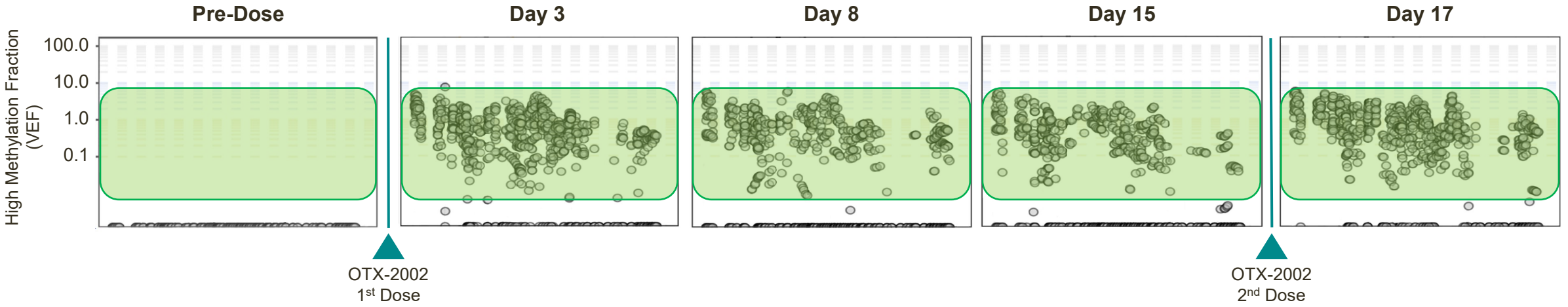
Controllers ensure epigenetic change is local to a single target as intended, and nowhere else in the genome

Clinical Demonstration of Highly-Specific Target Engagement and Persistent Epigenetic State Change



MYC methylation assessed across OTX-2002 target site and surrounding sequences in the MYC promoter

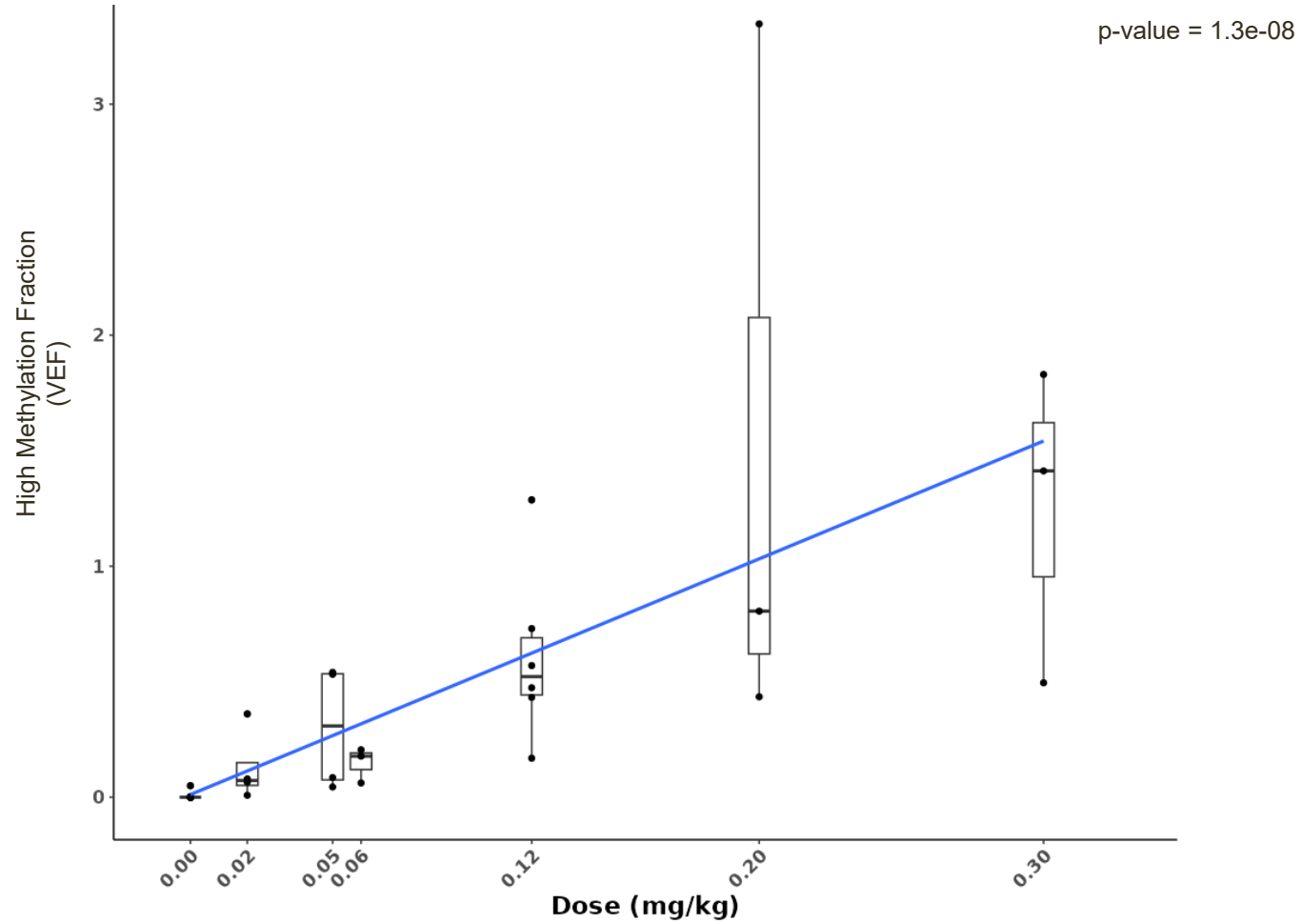
Persistent increase in cell-free DNA MYC methylation signature observed between doses (DL4, 0.12 mg/kg)



*Data represent aggregate methylation for n=4 patients in Cycle 1 of Dose Level 4 (0.12 mg/kg)

Clinical Demonstration of Dose-Dependent Increase in MYC Methylation in cfDNA From Patient Plasma

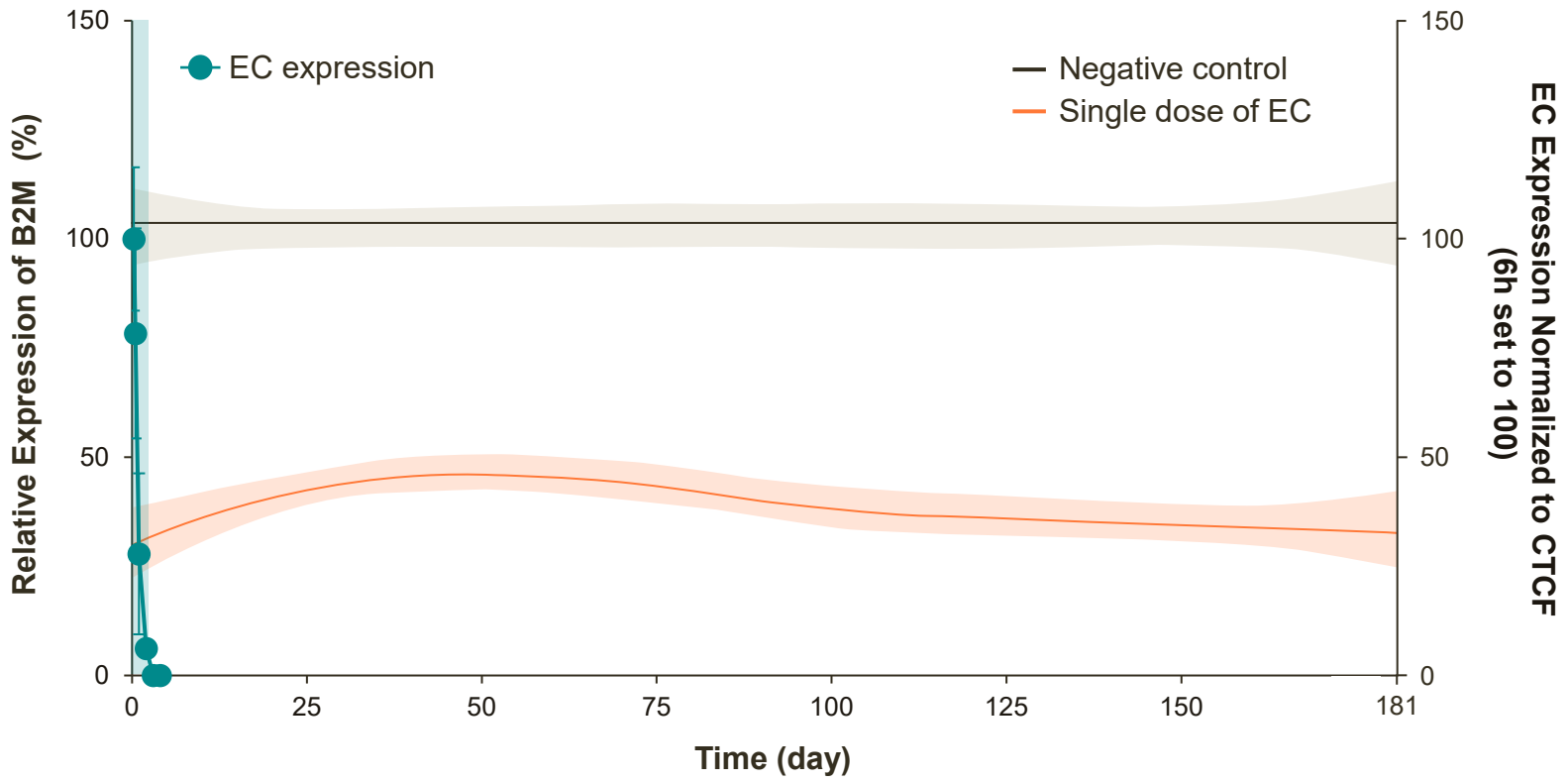
Patient plasma (48 hours post-single dose)



Tailored Durability

Epigenomic Effect Programmed to Last Days, Weeks or Months

Transient EC Expression with Durable Epigenomic Effect

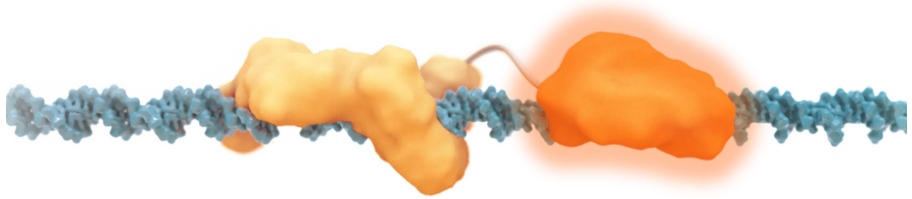


- Rapid degradation of drug within 2-3 days, yet durable intended epigenomic effect
- Decoupled approach offers potential for favorable safety profile; derisks off-target toxicity especially in chronic use setting

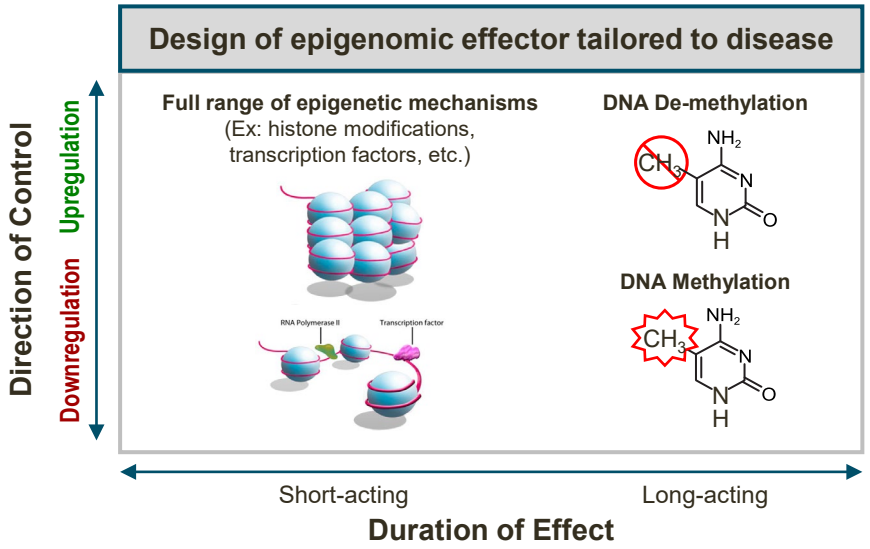
Controlled Tunability

Epigenomic Controllers Designed to Precisely Upregulate or Downregulate Gene Expression

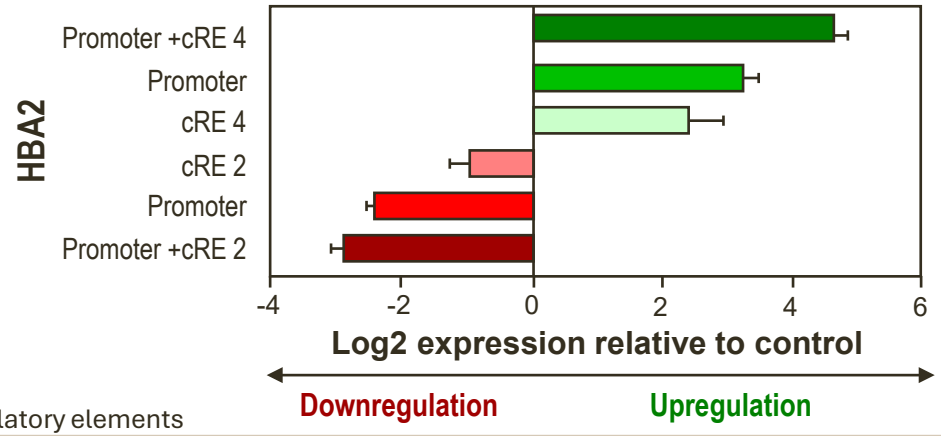
Epigenomic Effector



Programmed for controlled bi-directional tunability and tailored durability of effect

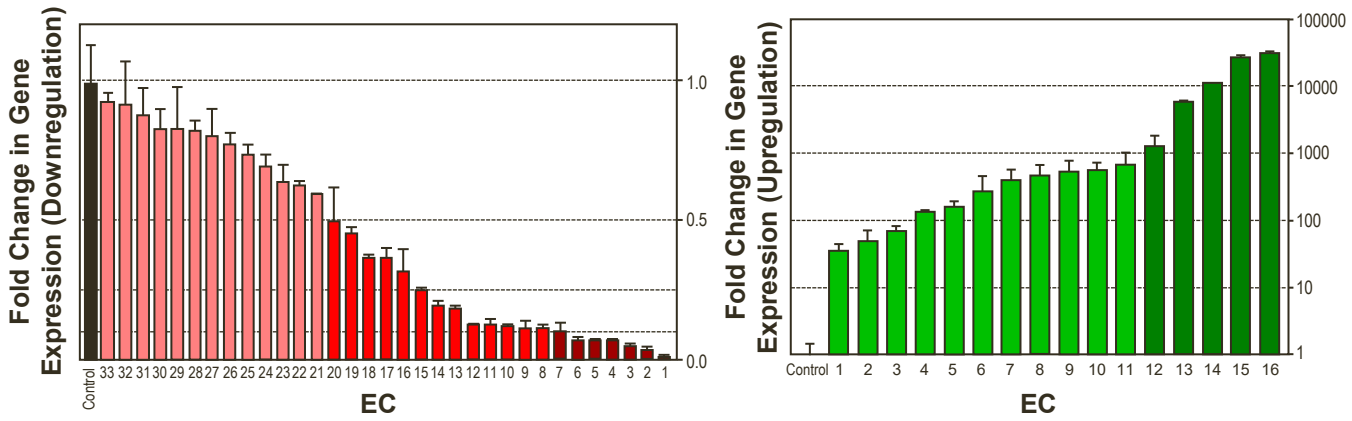


Bi-directional Tuning



cRE: cis-regulatory elements

Exquisite Tunability Achieved via DNA-binding and Effector Selection

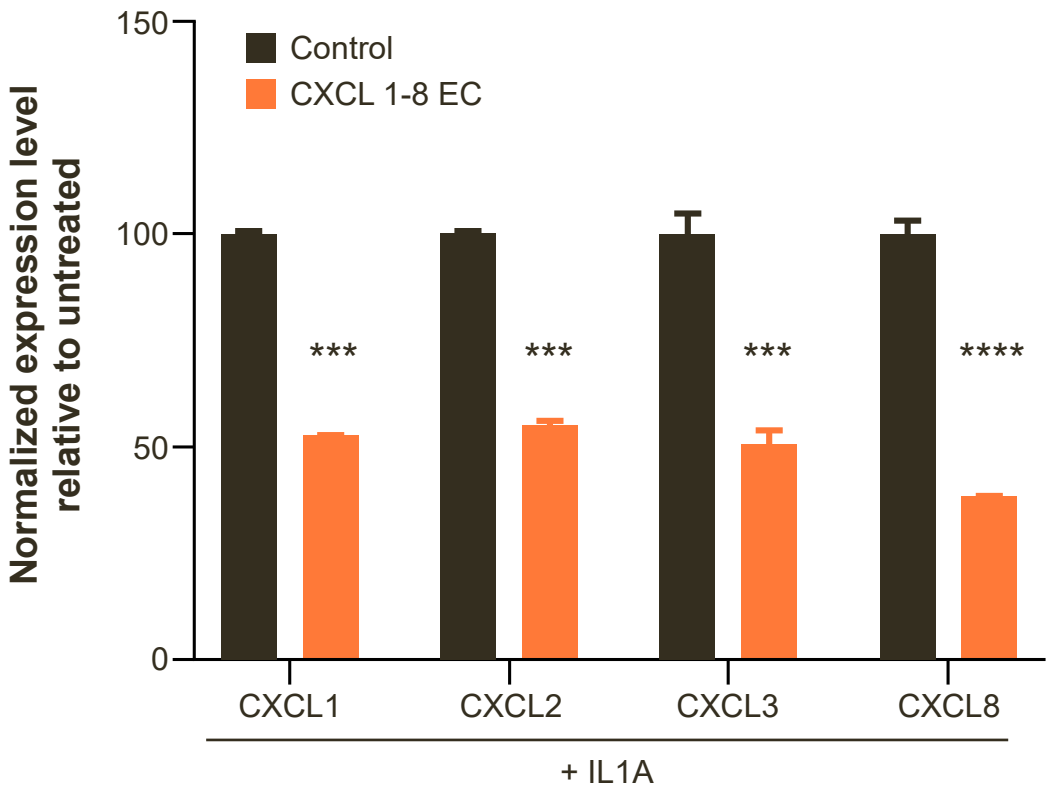


DBD: DNA binding domain

Efficient & Effective Multiplexing

Coordination of Gene Activities to Reach Healthy State

Coordinated Downregulation of mRNA Expression

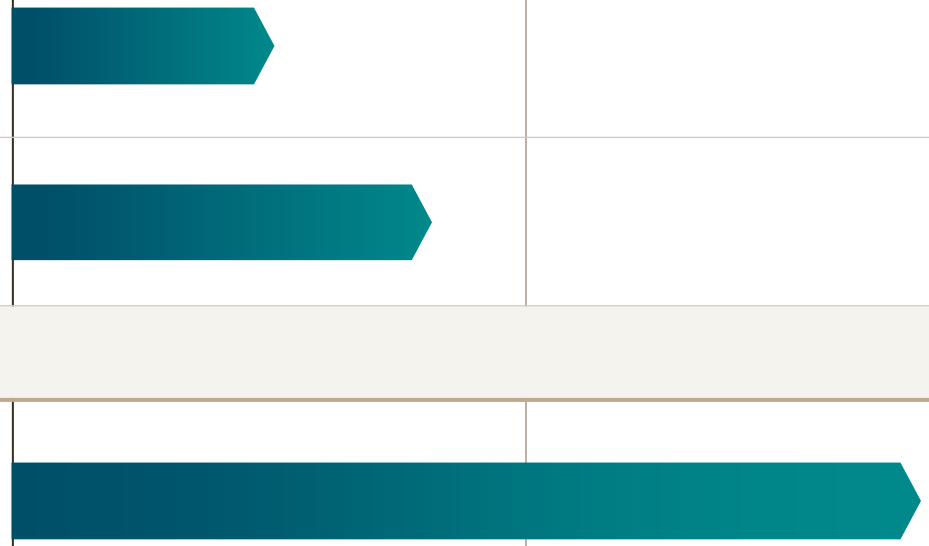


***p<0.001, ****p<0.0001

- Regulation of multiple target genes individually with a single drug
- Potential to modulate the expression of different target genes in different directions or levels
- Targeting key nodes of multiple pathways involved in the same disease biology
- Address potential redundancies, gene compensation, and resistance barriers that would overwhelm other modalities

With Clinical Proof-of-Platform Established, Omega is Advancing a Focused Pipeline of High-Value Programs

TARGET GENE(S)	INDICATION	DISCOVERY	LEAD OPTIMIZATION	IND-ENABLING	PARTNER
Metabolic					
FGF21	Multi-Indication Opportunities				
Undisclosed	Obesity				novo nordisk®
Regenerative Medicine					
HNF4A	Fibrosis / Liver regeneration				



Additional gene targets under evaluation for strategic partnering or internal development via disciplined, stage-gated process for program advancement

Thermogenesis Research Collaboration with Novo Nordisk

Opportunity For Orthogonal and Transformative Innovation In Obesity

- **Trans-differentiation of human adipose tissue:** Transitioning the epigenetic state of white to metabolically active brown fat
- **Potential first-in-class program:**
  - Epigenomic controller that regulates "browning" of human white adipose tissue
  - LNP to adipose tissue
  - Complementary to existing GLP1-related approaches

- **Collaboration validates broad applicability of the OMEGA platform**
- **Strategically complements** our internal efforts and expands our pipeline into cardiometabolic / obesity
- **Novo reimburses all R&D costs**

Program advancing with epigenomic controller design, optimization, and formulation

FGF21 Program

Physiological Relevance of FGF21

- FGF21 is a hepatocyte-derived hormone involved in energy homeostasis, and implicated in multiple metabolic indications
- Acts as an endocrine regulator of glucose and lipid metabolism and whole-body energy homeostasis that increases insulin sensitivity
- Reduces cellular stress by increasing mitochondrial capacity, inducing antioxidant pathways, and restoring proteostasis
- In adipose tissue, FGF21 stimulates glucose uptake, suppresses lipolysis in the fed state, and enhances adiponectin secretion
- Recombinant/overexpressed FGF21 has demonstrated alleviation of hyperlipidemia, and a significant effect on NASH resolution and fibrosis clinically and in preclinical models

Targeting FGF21 Upregulation in Liver Benefits Adjacent Indications

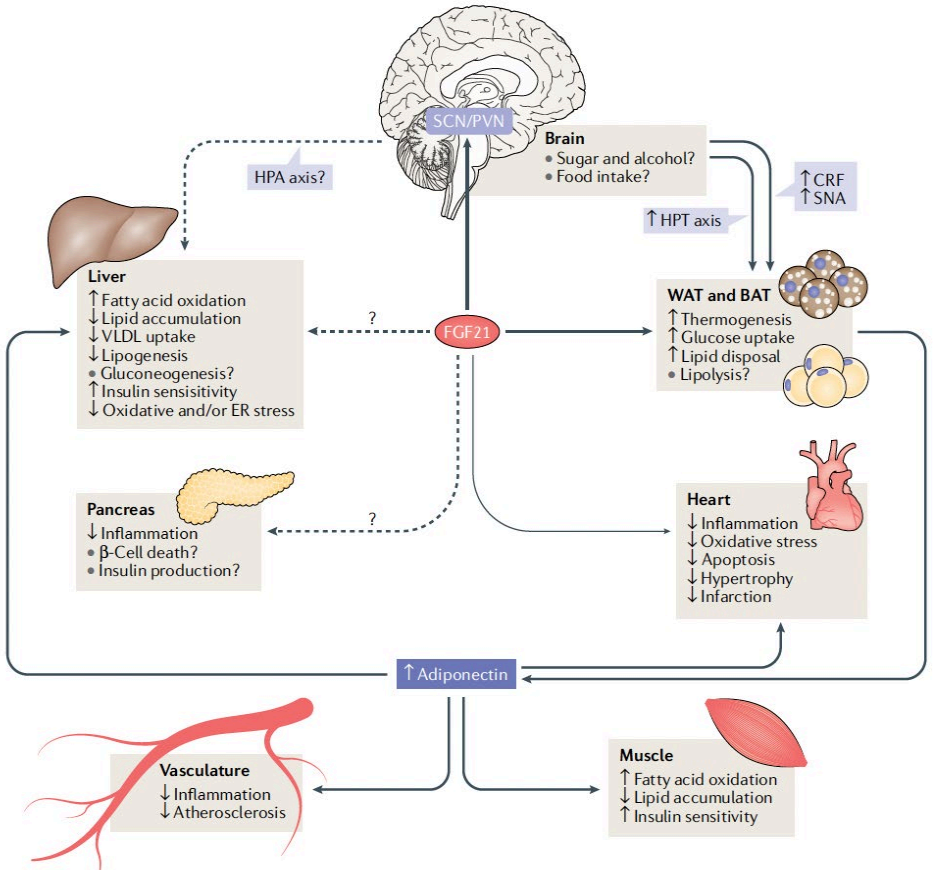
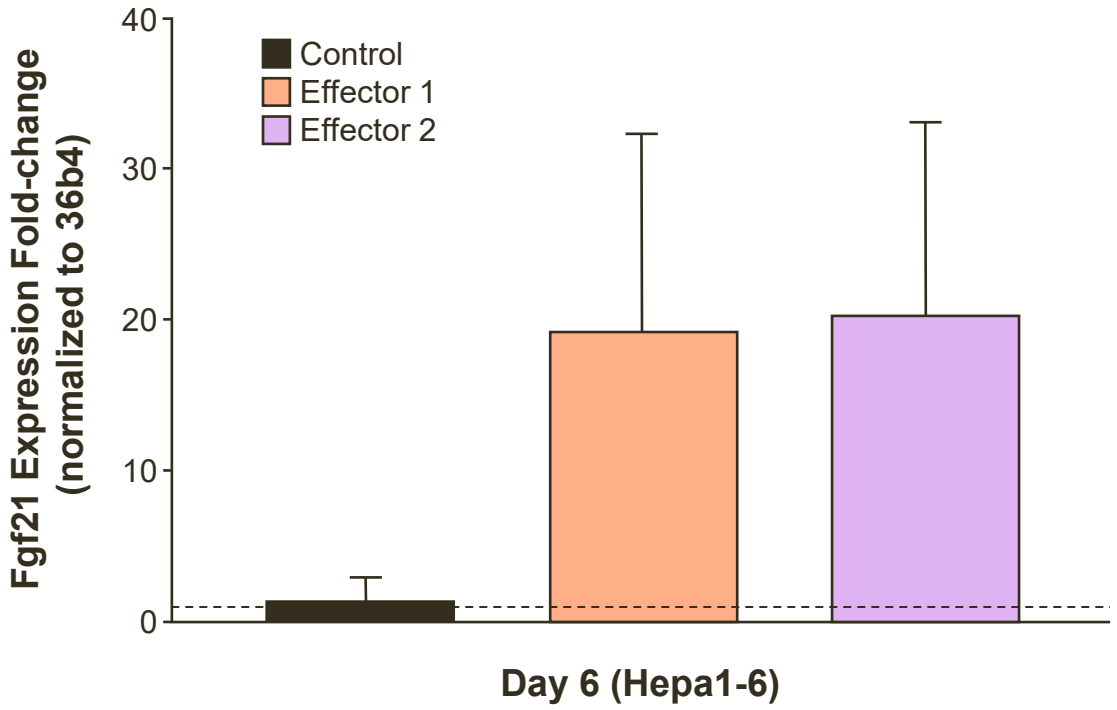


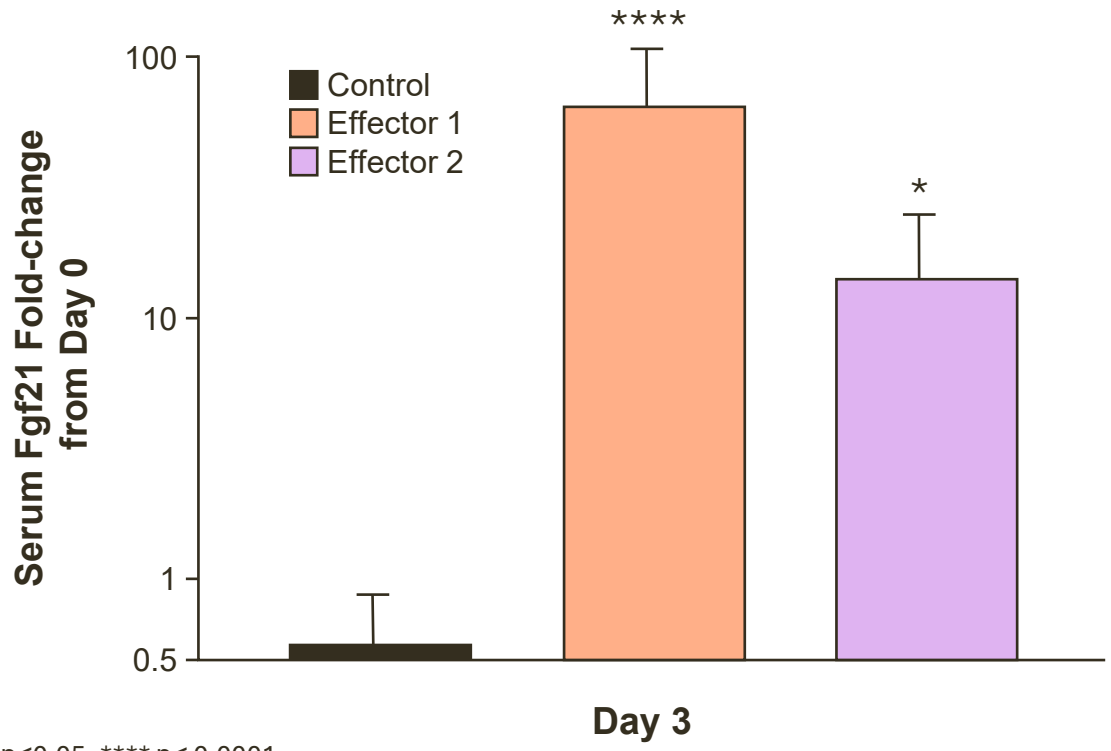
Image from: Geng *et.al.*, Nature Reviews Endocrinology, 2020

FGF21 Upregulation PoC Demonstrated *In Vitro* and *In Vivo*

In Vitro Upregulation Observed Across Multiple Epigenomic Effectors



FGF21 Upregulation *In Vivo*

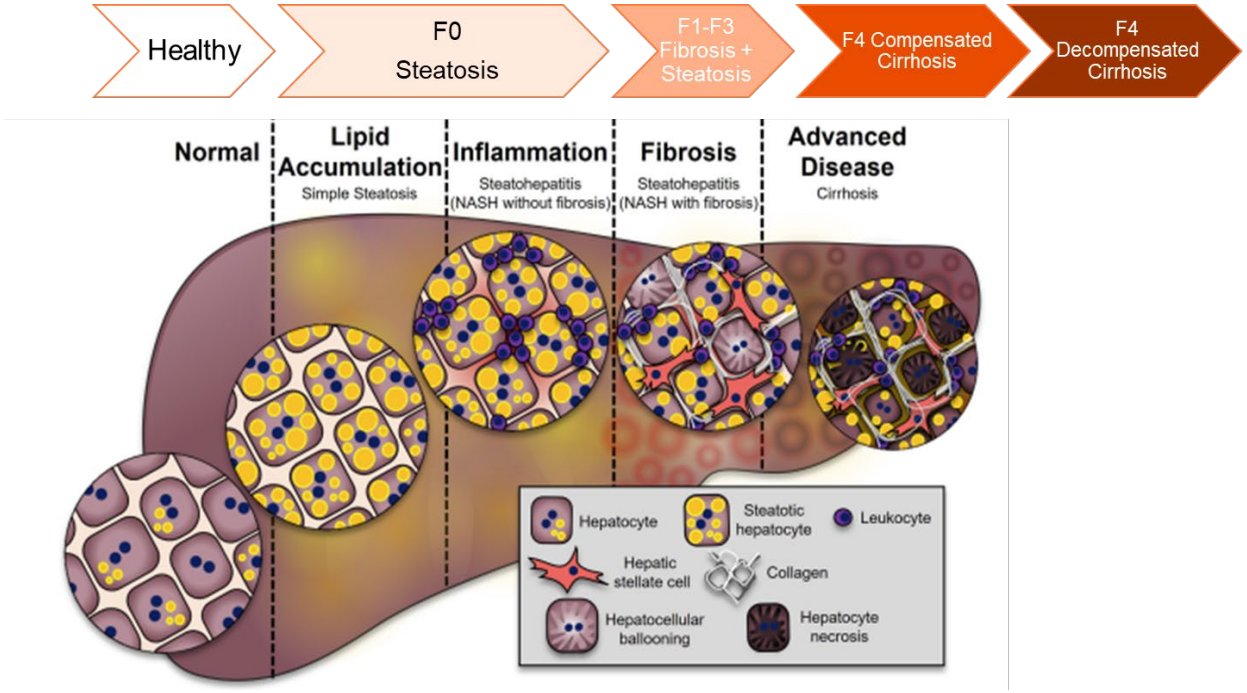


* p<0.05, **** p< 0.0001

Planning for DC in Q4 2025 and IND mid-2027

MASH and ESLD Encompass Advanced Stages of Inflammation, Fibrosis, and Eventually Cirrhosis

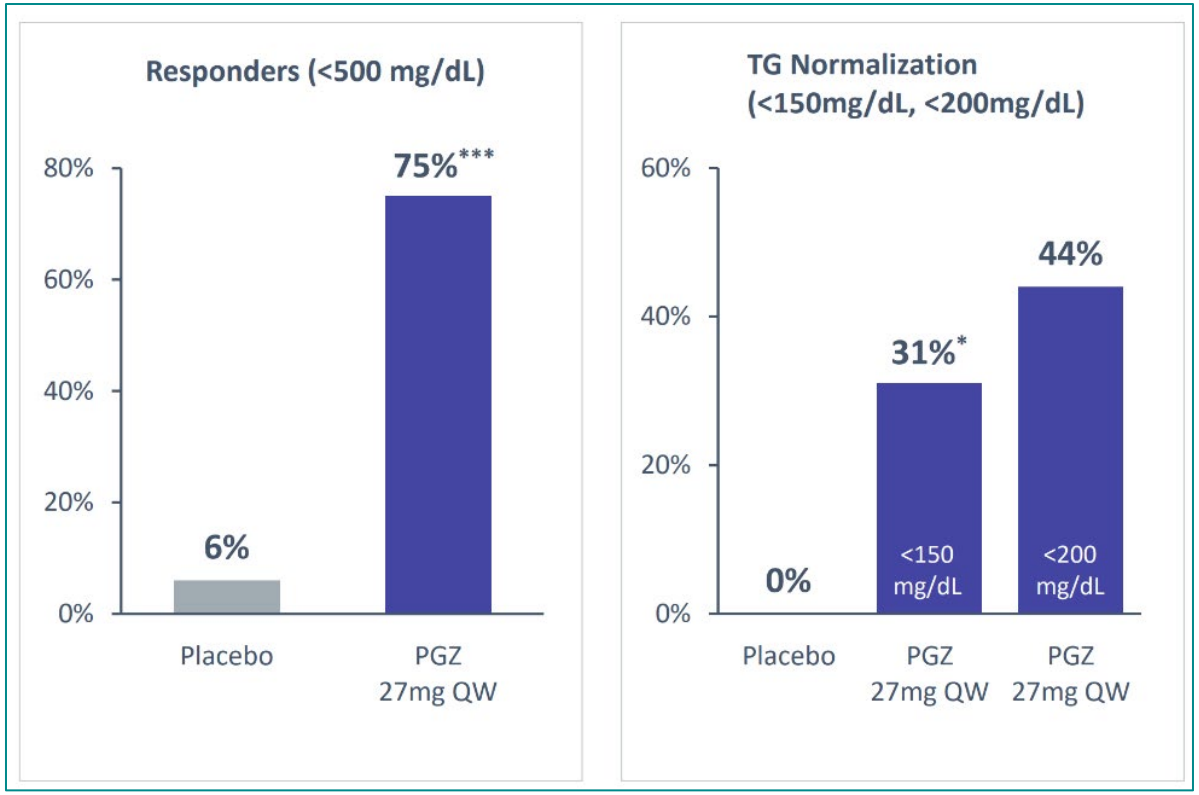
- MASH is a complex and progressive disease involving:
  - Lipid accumulation in the liver
  - Inflammatory processes associated with metabolic dysfunction
  - Fibrotic changes and eventually cirrhosis in advanced stages of the disease
- Unmet need remains for new therapies that offer stabilization of metabolic dysfunction, including reduction of liver lipid accumulation to effectively slow or reverse fibrosis
- In ESLD, highest unmet need for therapies which can effectively slow progression to decompensated cirrhosis and reverse fibrotic changes in the liver



FGF21 plays an important role in metabolic regulation and has anti-inflammatory and anti-fibrotic effects, potentially addressing multiple components of MASH and ESLD

Severe Hypertriglyceridemia

- Severe hypertriglyceridemia (sHTG): fasting serum TG levels > 500 mg/dL
- More than 2 million Americans estimated to have sHTG, not optimally controlled despite use of statins or other LDL cholesterol-lowering medication
- Commonly associated with metabolic syndrome, obesity, Type 2 diabetes
- High unmet need – uncontrolled sHTG is associated with increased risk of ASCVD events and coronary complications
- 89Bio's pegozafermin (FGF21) has shown moderate reduction of TGs in Ph2 trial; less than half of patients achieved TG normalization
- Opportunity for therapies that achieve lipid normalization in greater percentage of patients, with less frequent dosing



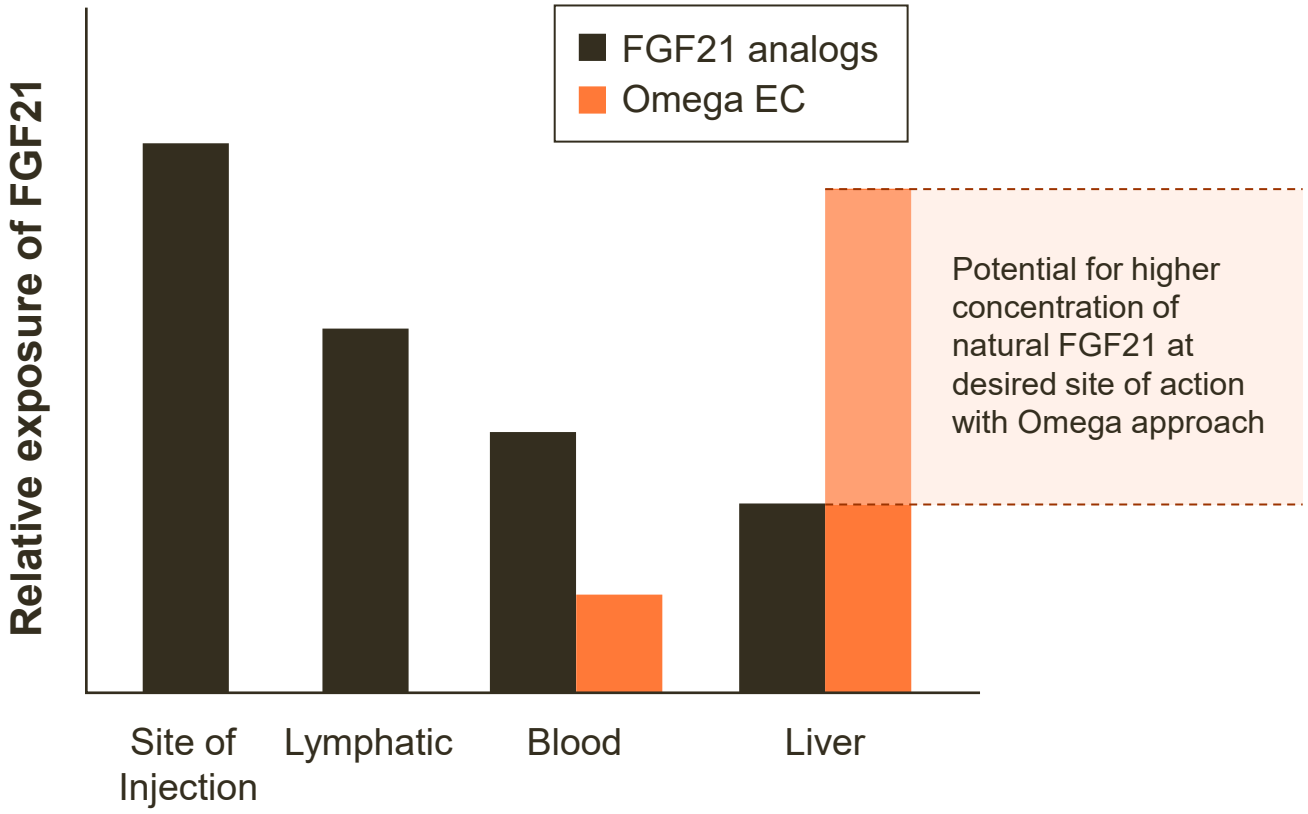
89Bio Phase 2 trial, pegozafermin in sHTG

Sources: Fan 2019; Ganda et al., 2018; UpToDate: Hypertriglyceridemia in adults; 89Bio corporate presentation, November 2024

Omega Differentiation: Upregulation of FGF21 Where and How Nature Intended

Potential Advantages

- ☑ **Expression concentrated in natural tissue/cell type**
  - Potential for higher efficacy
  - Potentially avoids off-target effects
- ☑ **Lower long-term risk of immune reactions/drug resistance**
- ☑ **Less frequent dosing**



For illustrative purposes only

Market Opportunity and Development Pathways

F4 MASH / ESLD

- Unmet need: Potentially several million patients in U.S. with F4 cirrhosis due to MASH
- This is patient segment in MASH with highest unmet need due to severity, morbidity/mortality and high cost of care for patients with cirrhosis
- Multiple attempts to develop drugs specific to F4 patient population have failed to show results and have been discontinued
- FGF21 is one of few remaining MOAs showing promise in late-stage clinical development for F4 compensated cirrhosis

F2-F3 MASH

- The F2-F3 patient segment in MASH is largest clinically-relevant subgroup, potentially ~10 million patients in U.S.
- Clinically, there is a strong desire to treat MASH in these intermediate stages, as opposed to waiting until F4
- With one currently approved drug and several expected approvals in near-term, disease awareness and identification will grow and demand for novel therapies will increase

SHTG

- More than 2 million individuals in the U.S. have severe hypertriglyceridemia (Tgs>500 mg/dL)
- There is significant unmet need for patients with SHTG despite use of existing hyperlipidemia treatments (e.g. statins), owing to increased risk of coronary heart disease in patients with elevated triglycerides
- The SHTG market is poised for indication-specific growth within the large hyperlipidemia space, due to anticipated launches of targeted drugs (plozasiran and olezarsen)
- Anticipated approvals in SHTG for these drugs will provide development precedent

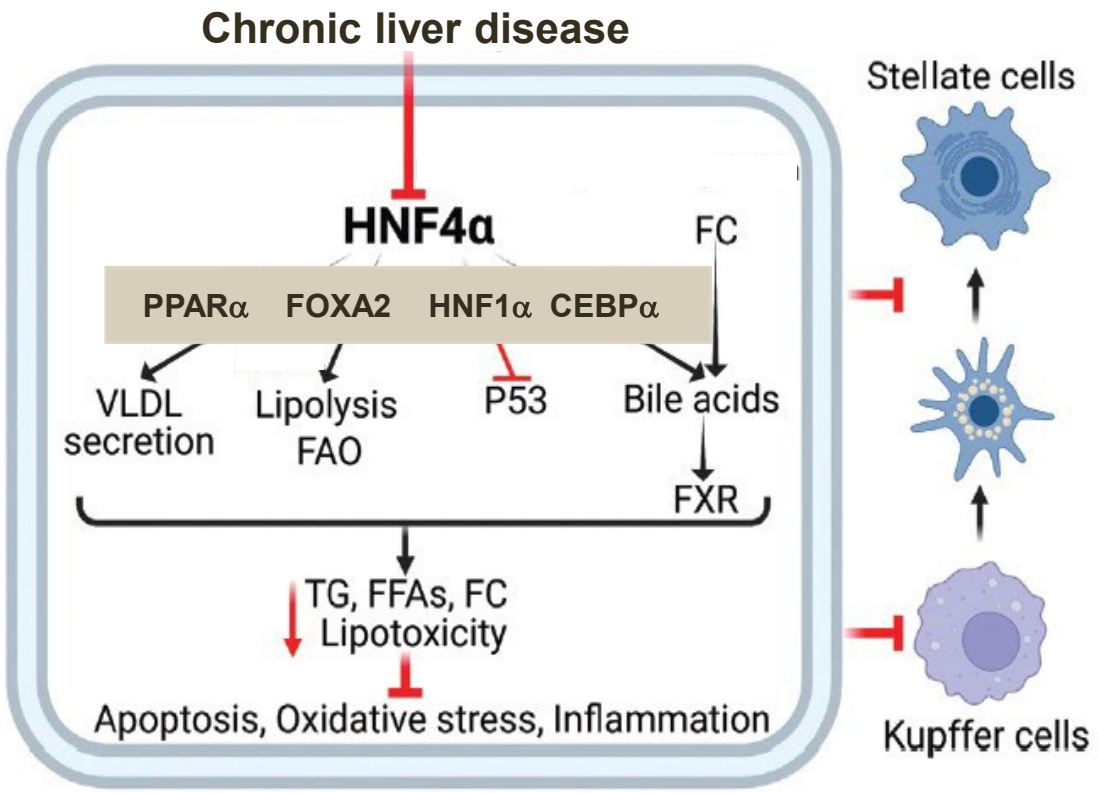
- MASH Global Market Size (all stages of disease) estimated > $30B by 2030
- Although competitive landscape is crowded, multiple MOAs are likely needed to satisfy unmet need
- FDA guidance for drug development in MASH with and without cirrhosis and approved drugs provide clear clinical development paths

Sources: Evaluate Pharma; Tapper et al., 2023; Fishman et al, 2024; Fan 2019; American College of Cardiology, 2018

HNF4A Program

Physiological Relevance of HNF4A

- HNF4A is a critical transcriptional regulator of hepatocyte differentiation and function; expression is dysregulated in fibrotic liver diseases
- Reduced HNF4α expression observed in clinical samples from patients with NAFLD, NASH, cirrhosis and HCC
- In animal models, forced re-expression of HNF4A upregulates expression of hepatocyte differentiation and function, and can revert ESLD
- HNF4A interacts with both the DNA sequences and the proteins of validated clinical targets (FGF21, PPARa, THRb) providing multiple opportunities to select effective combination strategies



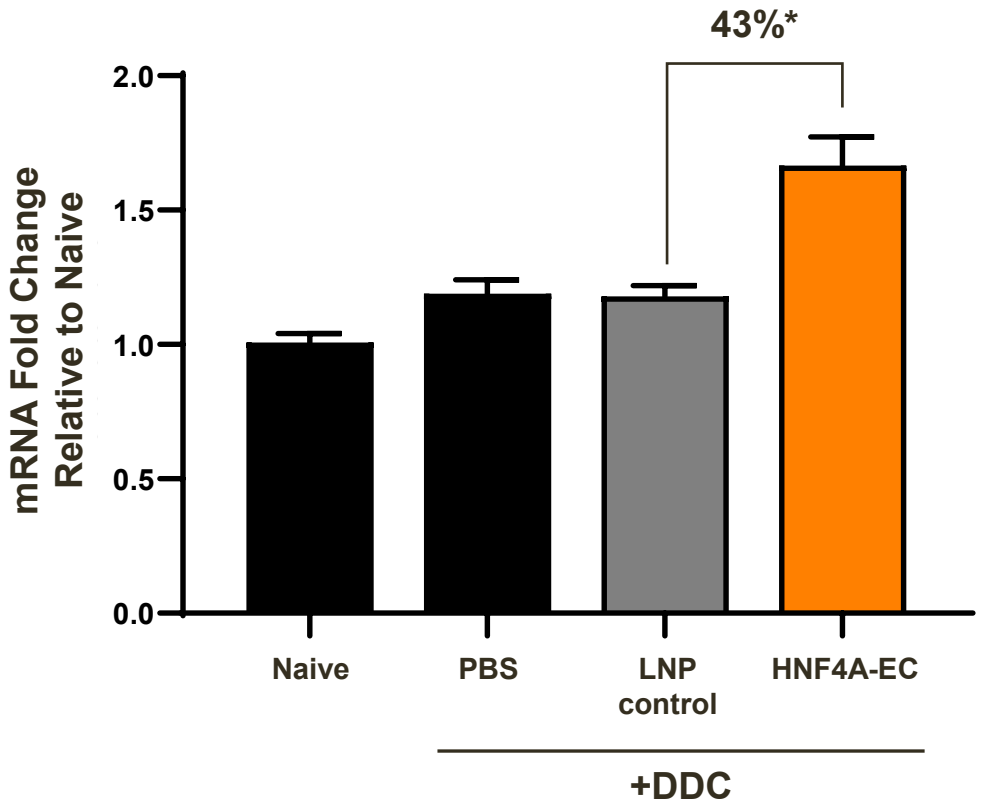
Re-expression of HNF4A has potential to impact multiple pathways important in MASH/ESLD, diabetes and obesity and may improve liver and overall metabolic health

Figure adapted from: Pan and Zang, *Chinese Medical Journal*, 2022

HNF4A: Potential Opportunity in Fibrotic Liver Diseases

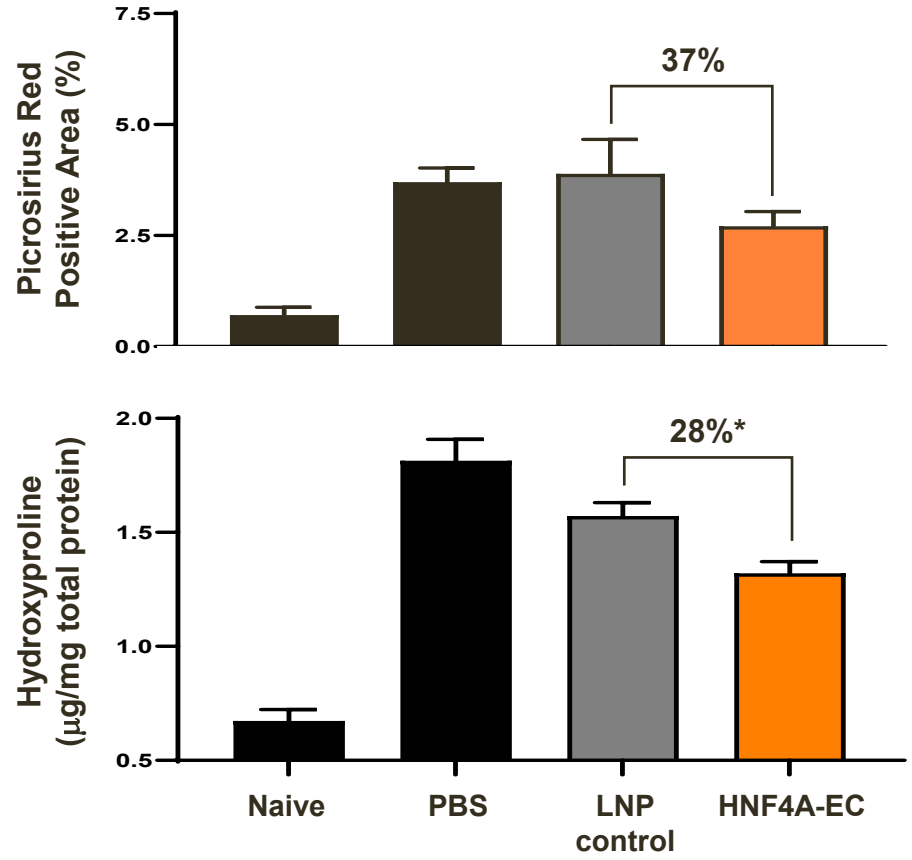
EC Significantly Upregulated Gene Expression and Reduced Key Fibrosis Measures *In Vivo*

HNF4α Expression



*p<0.001

HNF4α Induction Improves Collagen Deposition

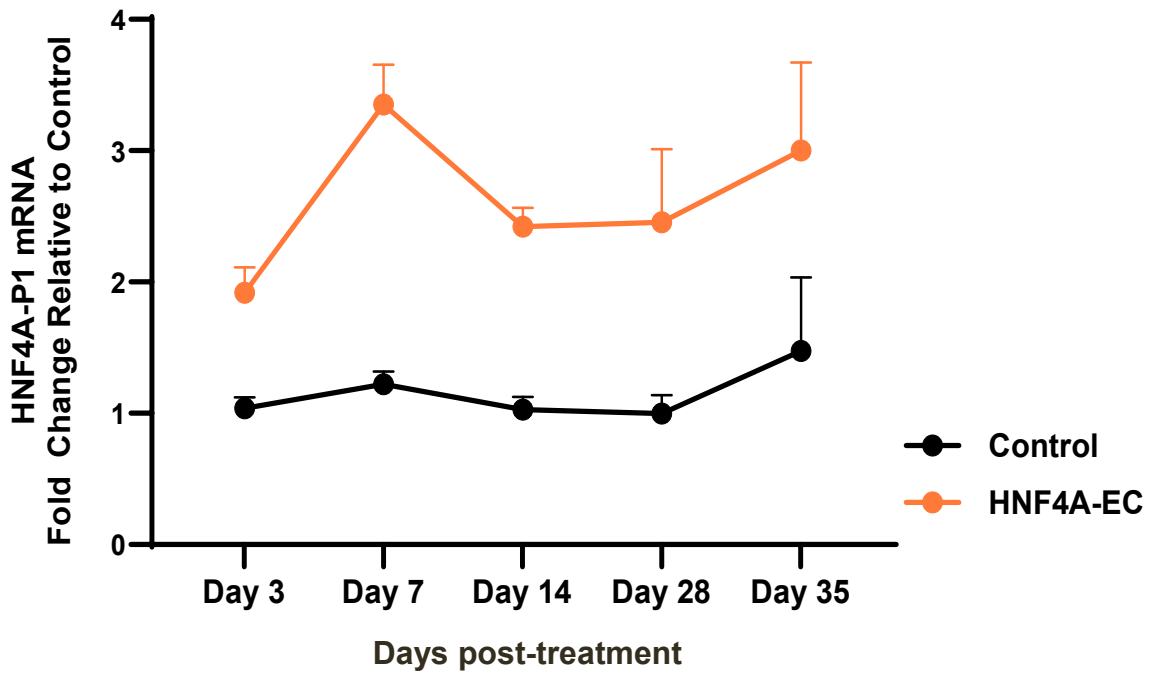


*p<0.05

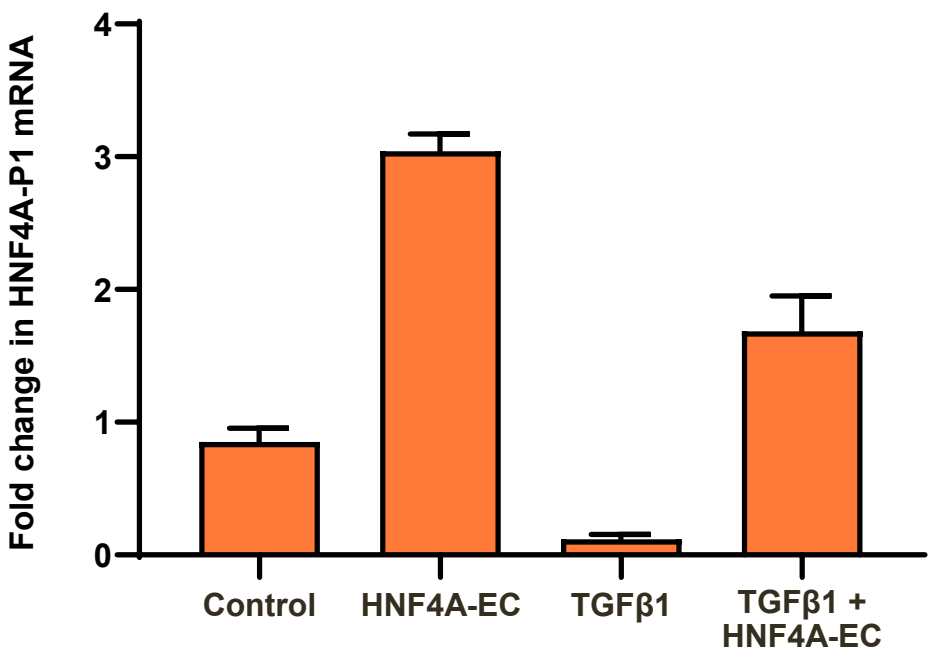
Source: Data presented at AASLD 2023. DC: development candidate

HNF4A-EC Selectively and Durably Upregulated P1 Isoform and Restored Dysregulated Expression Caused by TGFβ Signaling *In Vitro*

HNF4A-EC Treatment Increased HNF4α-P1 Isoform Expression for 35 Days in Primary Human Hepatocytes



HNF4A-EC Treatment Rescued TGFB1-induced HNF4α-P1 Downregulation in Primary Human Hepatocytes

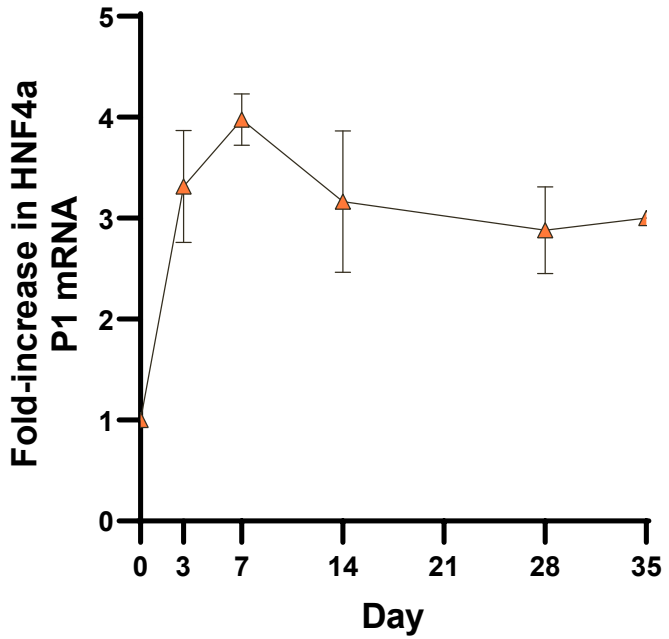


Planning for DC in Q2 2025 and IND in Q1 2027

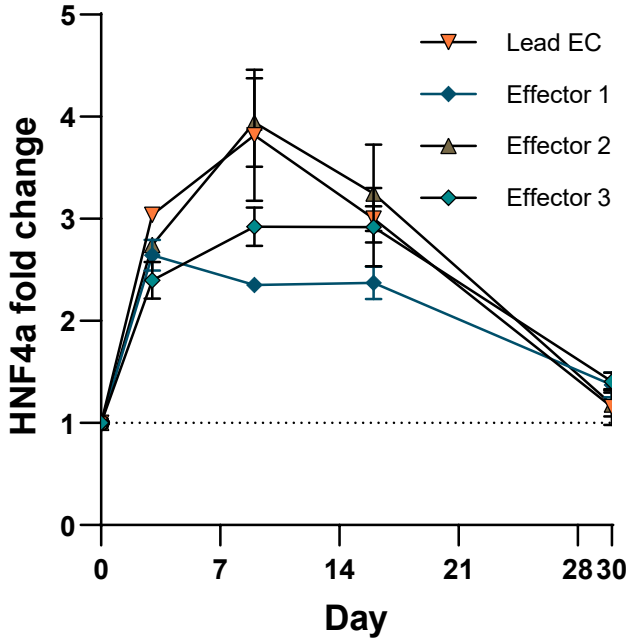
Source: Data presented at AASLD 2024.

HNF4A Human EC Demonstrated *In Vitro* Durability of at Least Three Weeks

Current Human EC
(n=4 human donors)



New Human Single ECs
(n=1 human donor)

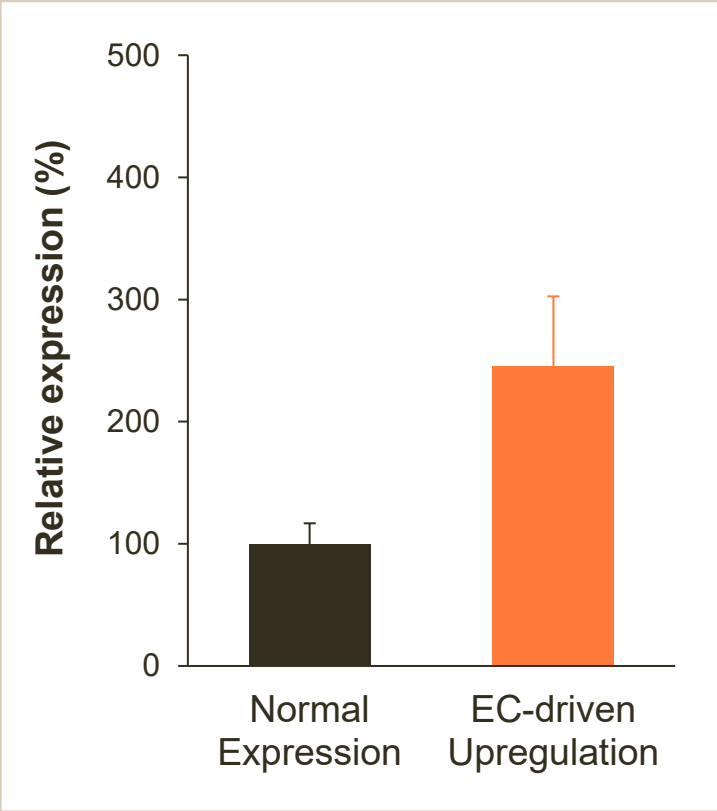


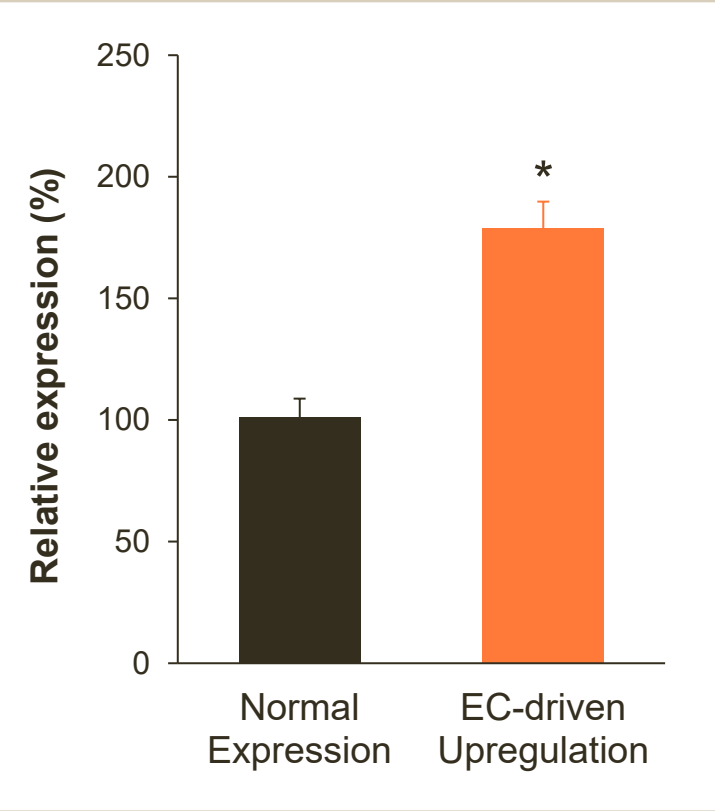
The current lead human EC upregulates HNF4A for up to 35 days *in vitro* (the limit of the assay)

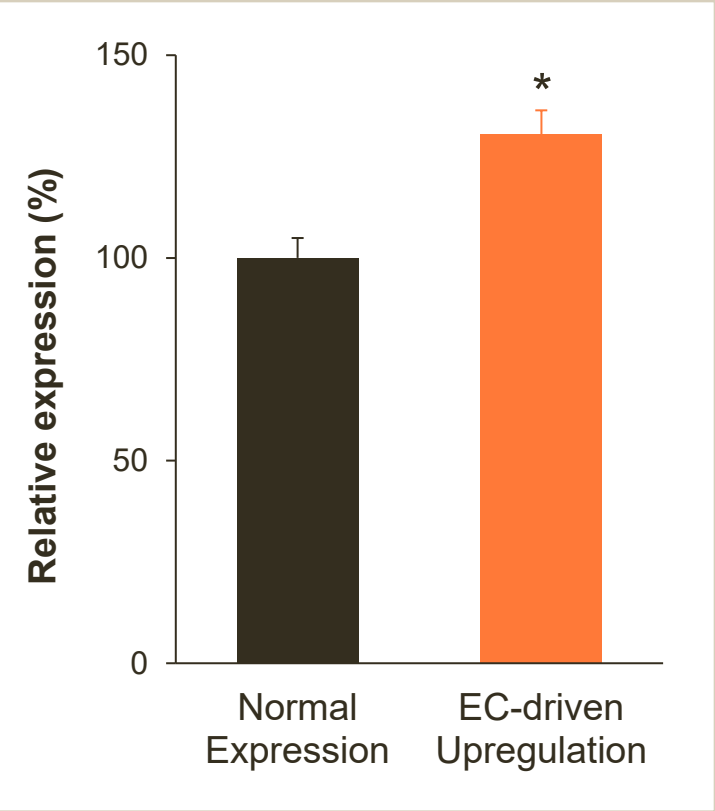
HNF4A-EC Robustly Upregulated HNF4α Expression Across Species

Increased HNF4α Expression in Healthy Liver Tissues (Over and Above Normal Expression)

Species	Mouse	Nonhuman primate	FRG Mouse
Liver Cells	Mouse (48h)	Nonhuman primate (24h)	Human (24h)







* Significant, paired t-test p<0.05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