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# Harnessing the Power of the Epigenome

***Pioneering a New Class of Programmable mRNA Therapeutics***

May 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 expectations surrounding the potential of our product candidates, including our lead epigenomic controller (EC) candidate OTX-2002; development timelines; anticipated timing of regulatory submissions and filings; and expectations regarding our pipeline, including our 2024 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; 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; 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; the impact of increased demand for the manufacture of mRNA and LNP based vaccines to treat COVID-19 on our development plans; 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” 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.

# Omega Therapeutics: A Clinical-Stage Company

Precision Epigenomic Control of Nature's Fundamental Mechanisms for Gene Regulation and Cellular Function

**Our Vision is to Treat and Provide Cures for Patients Suffering from Serious Diseases by Pioneering Programmable Epigenomic mRNA Medicines**

**Mapped >1M unique drug targets**

Interrogated 1K *in silico; in vitro / in vivo* data on >100

**Pioneers of epigenomic controllers**

Based on foundational genomic insight from world experts in epigenetics

**Built robust R&D engine**

Designed for expedited prosecution of new targets

**Potential applicability to nearly all human genes**

>100 targets validated *in silico / in vitro / in vivo* across disease areas

**Pipeline focused on value creation opportunities**

Preclinical proof-of-concept data across diverse therapeutic areas

**Clinical proof-of platform established**

Target engagement observed in previously undruggable target

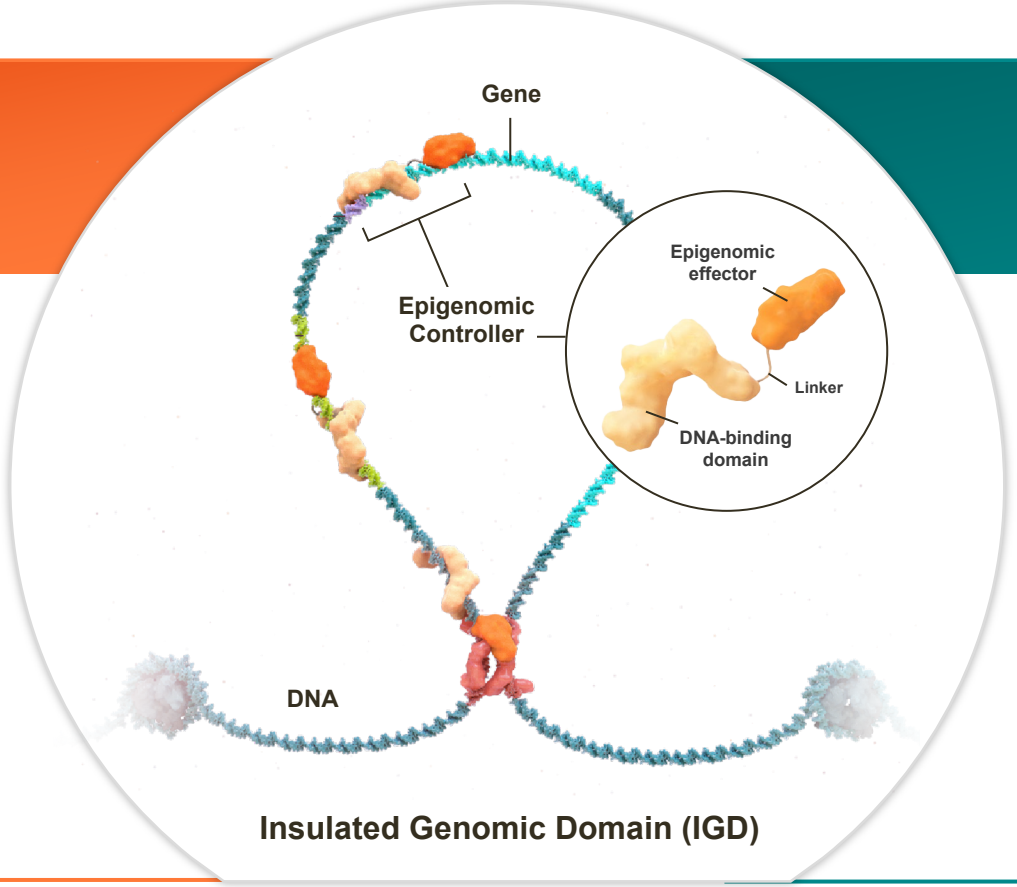
**Internal liver and lung LNP delivery efforts**

Exploring other high-value tissues and additional technologies

# OMEGA Platform Engineers Programmable mRNA Therapeutics

## BIOLOGY
New Drug Targets

- Insulated genomic domains (IGDs): Contain genes and their controlling regulators
- EpiZips: Unique regulatory sequences as precise drug targets



Insulated Genomic Domain (IGD)

## TECHNOLOGY
Epigenomic Controllers

- mRNA expresses a fusion protein consisting of:
  - DNA-binding domain for site-specific targeting
  - Epigenomic effector for controlled and durable gene modulation

Pre-transcriptional control of gene expression leveraging nature's control system

# Omega's Controlled Epigenomic Modulation Approach is a Significant Technological Advance

## Existing modalities have limitations

- Restricted to druggable target structures
- Can only address narrow therapeutic areas
- Constrained to direct PK/PD relationship with associated concerns for safety / therapeutic index

Wide opportunity space in drug development remains

## Pre-transcriptional approach addresses multiple challenges in drug development

- Independent of structure, chemistry or location of target; addresses undruggable/inaccessible targets
- Uncouples PK and PD for potential safety benefit
- Capable of both up or down regulation for therapeutic benefit
- Avoids liabilities of permanent genetic alterations
- Applicable to any human gene or disease process

# Broad Applicability Across Nearly All Diseases and Human Genes

## Sample of Genes Targetable by OMEGA Platform

***Validated Via Initial In Silico and In Vitro Work***

**DISEASE PROCESSES**

- Neoplasia
- Metabolic Dysregulation
- Fibrotic Processes
- Immune Dysfunction
- Vascular Pathology
- Tissue Degeneration

### ONCOLOGY

- **CTNNB1** HCC, melanoma, endometrial, gastric
- **BCL2** SCLC, NSCLC, breast
- **PIK3CA** NSCLC, breast, endometrial
- **STAT3** Broad oncology, inflammation
- **KRAS** NSCLC, PDAC, colorectal
- **EGFR** NSCLC
- **EPCAM** NSCLC, colorectal, gastric
- **MDM2** NSCLC, breast, glioblastoma
- **MYC** HCC, NSCLC, breast, ovarian

### MULTIGENIC DISEASES

- **HIF1α** Obesity / diabetes, oncology (broadly implicated)
- **S1PR1** IBD / lupus
- **Klotho (KL)** Chronic kidney disease (CKD), regeneration (diseases of aging)
- **STK25** NAFLD/NASH, HCC
- **WT1** Focal segmental glomerulosclerosis (FSGS)
- **C9orf72** ALS/FTD
- **GBA1** Parkinson's disease
- **CXCL 1-8** Immunology / inflammation, oncology
- **CXCL 9-11** Immunology

### REGENERATIVE MEDICINE

- **SOX9** Liver fibrosis / cirrhosis; regeneration in lung, cornea, and cartilage
- **FOXO3** IPF, chronic kidney disease (CKD), aging / cardiovascular disease
- **CTGF** Chronic kidney disease, oncology (NSCLC, TNBC)
- **Integrin αvβ6 (ITGB6)** Liver fibrosis, oncology (PDAC)
- **HNF4α** Liver diseases
- **CEBPA** Liver diseases, heme cancers
- **VEGFA** Retinal diseases (AMD, DR), vascular injury, Alzheimer's/Parkinson's disease

### MONOGENIC DISEASES

- **PCSK9** Hypercholesterolemia
- **ApoB** Hypercholesterolemia
- **FMR1** Fragile X syndrome
- **FXN** Friedreich's ataxia
- **DUX4** FSHD, oncology
- **SERPING1** HAE
- **HMBS** Porphyria
- **SFRP1** Alopecia
- **MUT** Methylmalonic acidemia
- **PKD1** Autosomal dominant polycystic kidney disease (ADPKD)

# Power of OMEGA Platform: Potential to Treat or Cure Diseases

**By leveraging the full spectrum of epigenetic mechanisms available in nature, epigenomic control allows us to tackle diseases in potentially two ways:**

| | | Non-exhaustive Sample of Gene Targets |
|---|---|---|
| **Disease Treatment** | **Restorative:** return to normal epigenetic state<br>**Corrective:** epigenetic control over disease cause<br>**Augmentive:** gain of function | • MYC (pan-oncology), HIF1a (obesity/diabetes), FMR1 (Fragile X Syndrome), DUX4 (FSHD)<br>• KRAS (NSCLC, CRC, PDAC), PCSK9/ApoB (hypercholesterolemia), VEGFA (vascular disease)<br>• SOX9 (regenerative disease in liver, lung, eye), CEBPA (liver disease, heme cancers), FXN (Friedreich's ataxia) |
| **Disease-Modification** | **Transdifferentiation:** reprogramming of cellular state and function | • MYC – Modulating the tumor microenvironment<br>• HNF4a – Restoring cellular and organ system function<br>• Thermogenesis – Cellular reprogramming of adipocytes from white to metabolically active brown state |

# Clinical Proof-of-Platform Established in Lead Program; Preclinical In Vivo Proof-of-Concept Across Diverse Therapeutic Areas

| | TARGET GENE(S) | INDICATION | DISCOVERY | PRECLINICAL | CLINICAL | | PARTNER |
|---|---|---|---|---|---|---|---|
| | | | | | Phase 1 / 2 | Phase 3 | |
| **Oncology** | **MYC** (OTX-2002*) | Hepatocellular carcinoma | *Phase 1/2 MYCHELANGELO™ I Study* | | | | |
| | **MYC** (OTX-2101) | Non-small cell lung cancer | *IND-Enabling Studies Ongoing* | | | | |
| **Multigenic Diseases** | **CXCL 1-8** | Inflammation / immunology | | | | | |
| | **Undisclosed** | Obesity | | | | | novo nordisk® |
| **Regenerative Medicine** | **HNF4A** | Liver regeneration | | | | | |

Additional gene targets across multiple disease processes assessed with *in silico*, *in vitro* and *in vivo* data; Ready to enter early development

*In November 2022, OTX-2002 received Orphan Drug Designation from the FDA for the treatment of hepatocellular carcinoma

# Broad Applicability of OMEGA Platform to Drug Development May Unlock Tremendous Value Across the Disease Spectrum

## Tractable Disease Processes in Large Total Addressable Markets*

| | |
|---|---|
| ONCOLOGY $100B+ | Neoplasia |
| MULTIGENIC DISEASES $150B+ | Tissue degeneration<br>Vascular pathology |
| REGENERATIVE MEDICINE $25B+ | Immune dysfunction<br>Fibrotic processes |
| MONOGENIC DISEASE $120B+ | Metabolic dysregulation |

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## Existing Modality-Focused Companies Market Cap, $

| | | |
|---|---|---|
| mABs Small Molecules | Roche Genentech $222B | NOVARTIS $212B |
| RNA Medicines | moderna $38B | Alnylam PHARMACEUTICALS $21B |
| DNA-Altering Therapies | Beam $2.2B | CRISPR THERAPEUTICS® $5.3B |

Source: Evaluate Pharma, Internal Analysis; *2026 projections. Market caps as of Feb. 6, 2024

# Lead Program Overview

Clinical Development Program:
OTX-2002 in MYC-HCC

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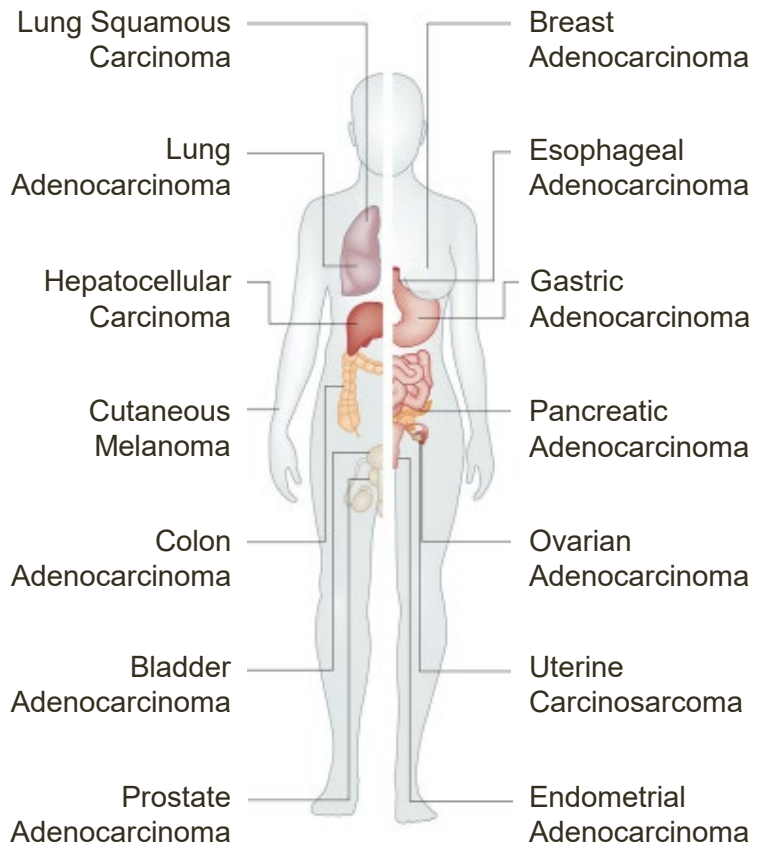
# MYC: The Holy Grail of Master Oncogenes

- Primary driver of cancer growth and immune evasion in **>50%** of human cancers
  - Strongly correlated with metastases and poor patient prognosis
- Precision epigenomic control is the potential solution
  - OTX-2002 in development for treatment of HCC (70% MYC-associated); Designed to:
    - **Restore** c-MYC to normal epigenetic state
    - **Correct** aberrant MYC overexpression
    - Access historically **intractable** target

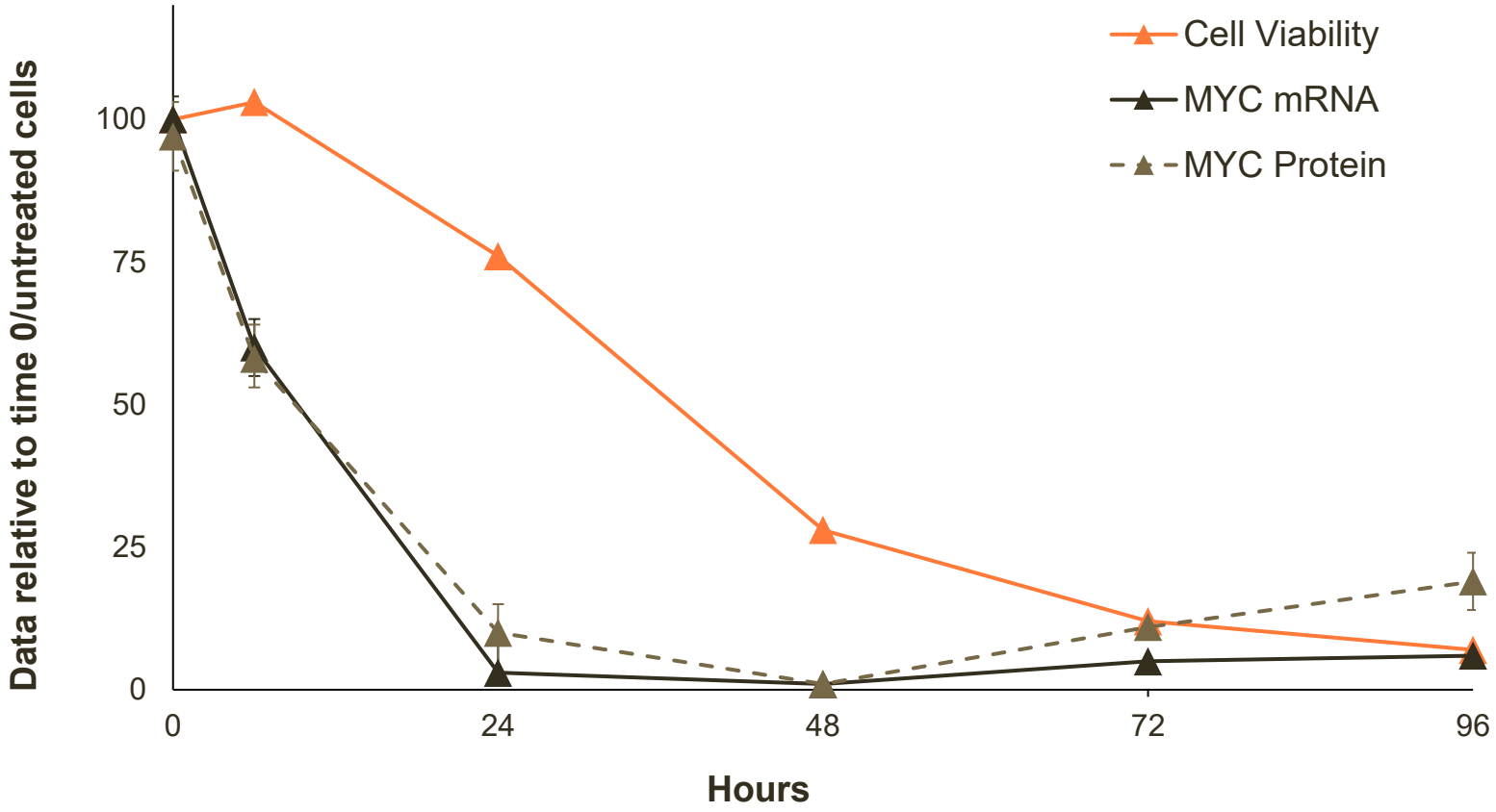
**MYC is a master oncogene that contributes to many human cancers**




Reference: Dhanasekaran R, et al. *Nat Rev Clin Oncol*. 2022 Jan;19(1):23-36.

# OTX-2002 Results in Rapid and Durable Downregulation of MYC Expression and Reduces Viability of HCC Cancer Cells Preclinically

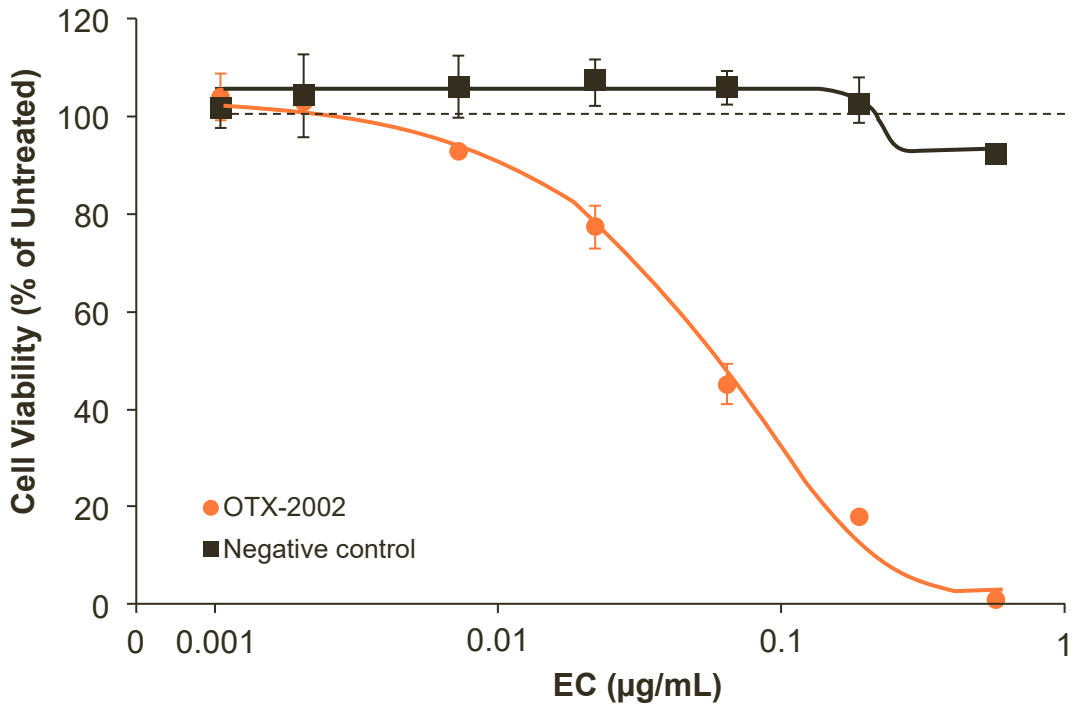
**Hep3B**



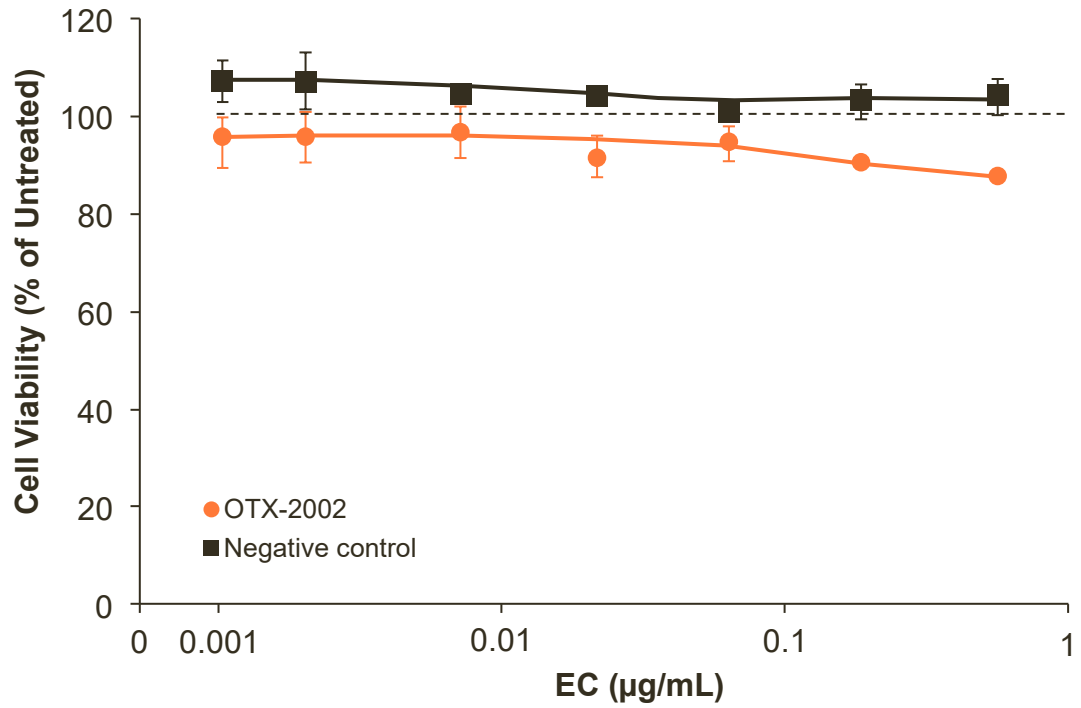

- OTX-2002 is designed to target a specific EpiZip in order to downregulate MYC expression
- Rapid and durable downregulation of MYC mRNA and protein levels demonstrated following treatment with OTX-2002 preclinically
- Lowered MYC protein primes “MYC-addicted” HCC cancer cells to undergo apoptosis

# OTX-2002 Selectively Modulates Cancer Cells without Impacting Normal Primary Cells in Preclinical Models

## Cancer cells




## Normal cells




OTX-2002 is designed to controllably tune down MYC expression to levels that lead to cancer cell death while sparing healthy cells and avoiding autoregulation

# MYCHELANGELO™ I: Ongoing Phase 1/2 Clinical Trial of OTX-2002 in HCC*

## Global Two-Part Study of OTX-2002 as Monotherapy and in Combination with Standard of Care**

OTX-2002: IV dosing, once-every-two-weeks; Patients to be enrolled across U.S., Asia, and Europe

### Part 1: Monotherapy

**Dose Escalation** (3+3 design)

- 0.3 mg/kg
- 0.12 mg/kg ✓
- 0.06 mg/kg ✓
- 0.05 mg/kg ✓
- 0.02 mg/kg ✓

HCC only

All comers w/ MYC-associated solid tumors

**HCC Expansion**

**Recommended Dose for Monotherapy Expansion**

Objectives: Determine the DLTs, MTD, safety, and tolerability and determine the RDE of monotherapy

Objectives: Determine the preliminary antitumor activity of monotherapy by ORR and DOR

### Part 2: Combination

**Safety Run-In Phase**

**OTX-2002** + **Standard of Care****

**Combination HCC Expansion**

**Recommended Dose for Combination Expansion** + **Standard of Care****

Objectives: Determine the DLTs, MTD, safety, and tolerability and determine the RDE of combinations

Objectives: Determine the preliminary antitumor activity of combinations by ORR and DOR

* Patients with HCC who progressed, relapsed, refractory or intolerant of >1 prior systemic therapy and without available subsequent SOC

** Tyrosine kinase inhibitors, and checkpoint inhibitors including anti-PD-1 and anti-PD-L1 monoclonal antibodies. Dose of SOC in accordance with approved dose in local region.

Definitions: HCC (hepatocellular carcinoma); RDE (recommended dose for expansion); ORR (objective response rate); DOR (duration of response); SOC (standard of care)

In November 2022, OTX-2002 received Orphan Drug Designation from the FDA for the treatment of hepatocellular carcinoma

# Encouraging Emerging Safety Profile for OTX-2002 From First Three Cohorts*

Phase 1 Study Enrolled Difficult-to-Treat, Heavily Pretreated Population

| Dose Level | Demographics | Cancer Type at Initial Diagnosis | # Prior Lines of Therapy |
|---|---|---|---|
| **Dose Level 1** 0.02 mg/kg | 78 / F / White | Soft Tissue Sarcoma | 3+ |
| | 51 / M / Asian | HCC | 3+ |
| | 70 / M / White | Colorectal Cancer | 3+ |
| | 69 / F / Asian | Sarcoma | 2 |
| **Dose Level 2** 0.05 mg/kg | 46 / F / Asian | Cervical Cancer | 2 |
| | 68 / M / White | Pancreatic Cancer | 3+ |
| | 56 / M / Asian | HCC | 3 |
| | 66 / M / Asian** | HCC | 2 |
| **Dose Level 3** 0.06 mg/kg | 71 / M / Asian | HCC | 2 |
| | 39 / F / Asian | HCC | 3+ |
| | 76 / F / Asian | HCC | 2 |

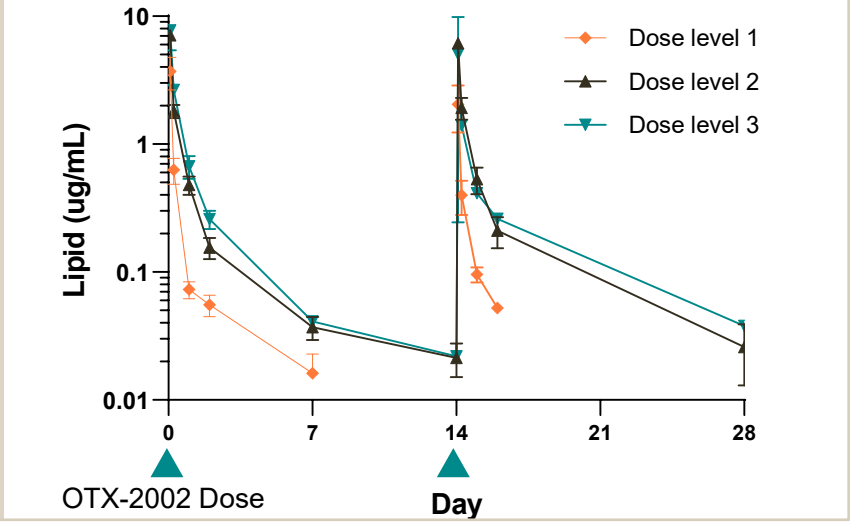
- OTX-2002 was generally well tolerated with no DLTs; MTD not reached
- Majority of AEs were grade 1 or 2 (87%)
- Most common TRAEs were infusion-related reactions (53%); generally consistent with known profile of other FDA-approved LNP-delivered therapeutics
- Three SAEs of AST elevation were reported in BCLC stage C HCC patients (one grade 4 in dose level 2; two grade 3 in dose level 3)
  - Resolved with minimal intervention (supportive care)

*Data cut-off date of March 24, 2024. **Patient remains on treatment as of March 24, 2024.

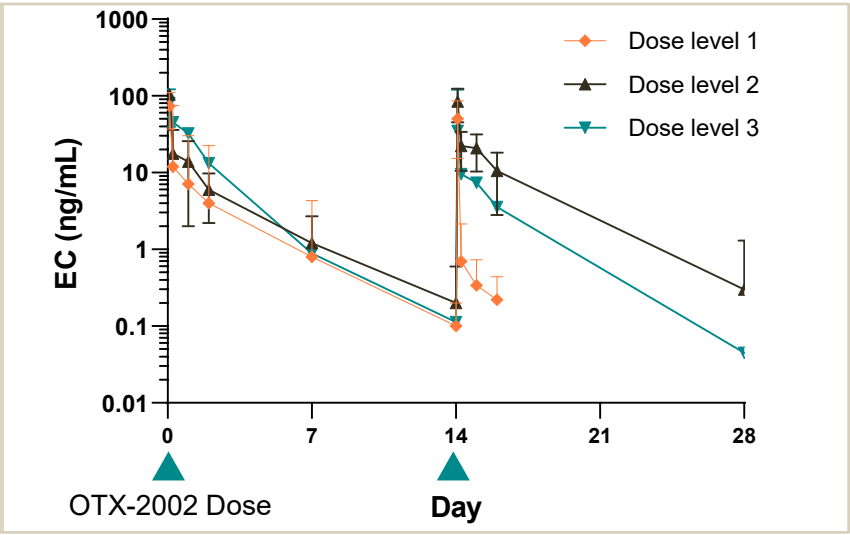
# Predictable Pharmacokinetics with Rapid Clearance of Drug Product Observed

## Clinical Pharmacokinetics and Lack of Immunogenicity Directly Translate from Preclinical Experience

**LNP**



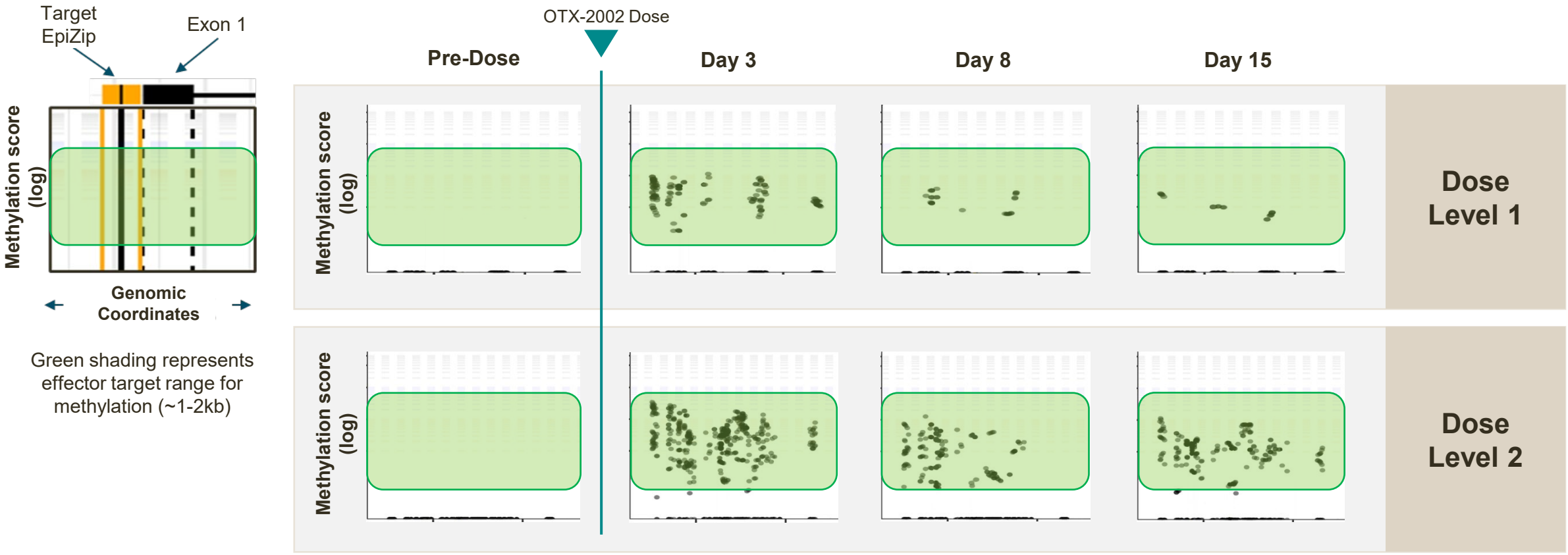

**Epigenomic Controller mRNA**




- Predictable and consistent PK profile, in line with our preclinical experience
- OTX-2002 was cleared rapidly from systemic circulation
- No accumulation observed with repeat doses
- Low levels of immune response; no related adverse events or impact on PK observed
- Low degree of variability in the PK profiles of both the LNP and mRNA components; consistent both within and between patients as well as across dose levels

# Highly-Specific Target Engagement and Intended Epigenetic State Change at Target Genomic Loci within MYC IGD Observed

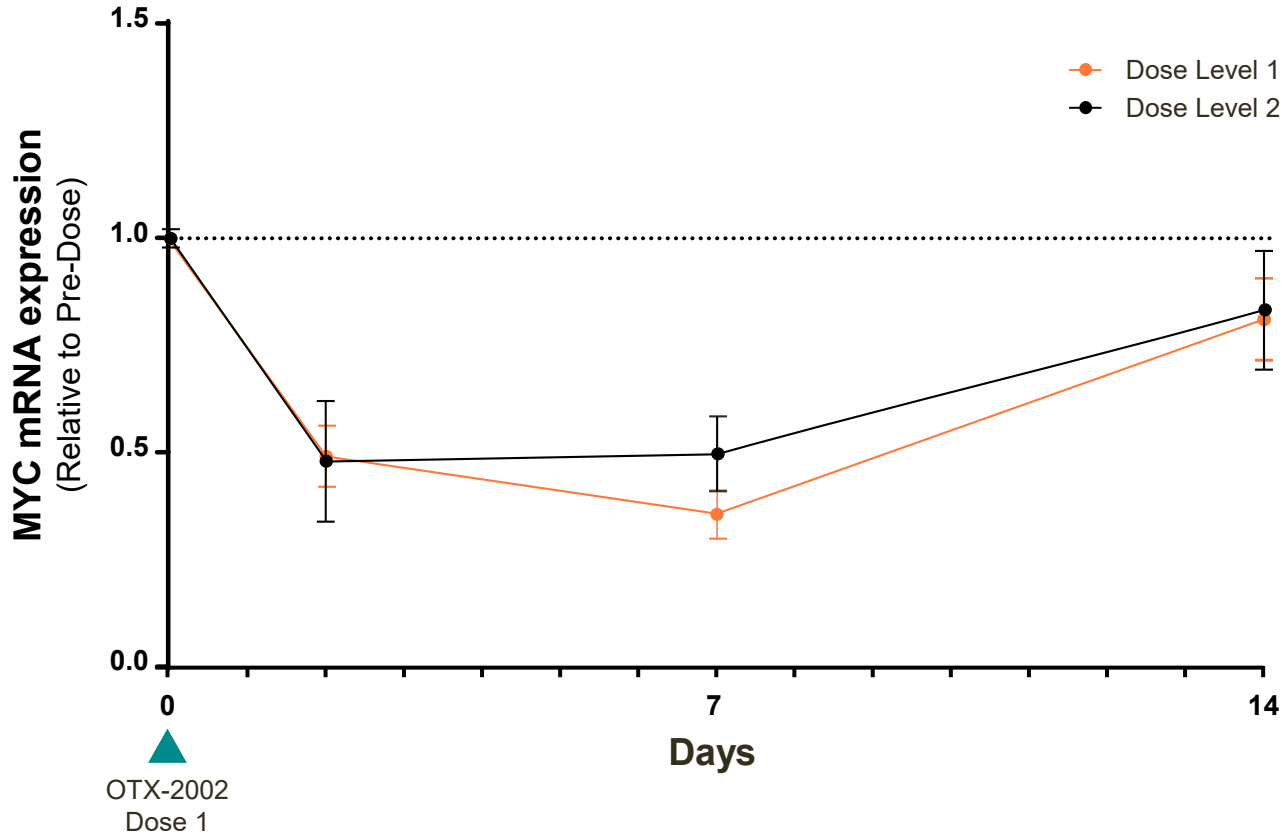
## Dose-dependent, on-target increase in cell-free DNA MYC methylation signal; persistent over two-week dosing cycle




*Data represent aggregate methylation for all patients in each cohort (dose level 1, n=4; dose level 2, n=4)

# Rapid, Robust & Durable Downregulation of MYC mRNA Expression Observed

**First Dose Cycle**




- OTX-2002 reduced MYC mRNA levels in all 8 patients across dose levels 1 and 2
  - Clinical MYC downregulation consistent with levels that led to robust anti-tumor efficacy in preclinical settings
- Mean curves represent averaged downregulation across transfected and non-transfected cells, across all tissues, as measured in exosomal mRNA in blood samples
  - Transfection rate expected to increase with higher doses; to be confirmed through tissue biopsies

*Data represent mean expression data for all patients in each cohort (dose level 1, n=4; dose level 2, n=4)

# OTX-2002: Interim Monotherapy DCR Data are Encouraging

| Best Overall Response | Participants with Non-HCC Solid Tumors (Dose Levels 1 & 2: 0.02-0.05 mg/kg) N = 5 | Participants with HCC (Dose Levels 1-3: 0.02-0.06 mg/kg) N = 5* | Total N = 10* |
|---|---|---|---|
| Complete Response (CR) | 0 | 0 | 0 |
| Partial Response (PR) | 0 | 0 | 0 |
| Stable Disease (SD) | 2 (40%) | 4 (80%) | 6 (60%) |
| Progressive Disease (PD) | 3 (60%) | 1 (20%) | 4 (40%) |
| Objective Response Rate (ORR = CR + PR) | 0 | 0 | 0 |
| Disease Control Rate (DCR = CR + PR + SD) | 2 (40%) | 4 (80%) | 6 (60%) |

Range of completed Phase 1 trials for TKIs and PD-1 monotherapies† in HCC: DCR (29-65%)

Interim data date of March 24, 2024. Patients who withdrew from the study for any reason other than progression were censored at date of last assessment. For participants with HCC, response assessed using mRECIST criteria.

*5 efficacy-eligible HCC patients from Cohorts 1-3. One patient in Cohort 3 discontinued treatment prior to their 6-week scan.

†We have not conducted head-to-head trials with any other therapeutic candidates and the design and endpoints of such trials may not be comparable to our protocol for OTX-2002.

Phase 1 trials for sorafenib, lenvatinib and nivolumab: https://classic.clinicaltrials.gov/ct2/show/results/NCT00044512; https://pubmed.ncbi.nlm.nih.gov/17470685/; https://pubmed.ncbi.nlm.nih.gov/28434648/; https://pubmed.ncbi.nlm.nih.gov/34051329/; https://doi.org/10.1158/1078-0432.CCR-15-1354.

# OTX-2002:
# Development Strategy

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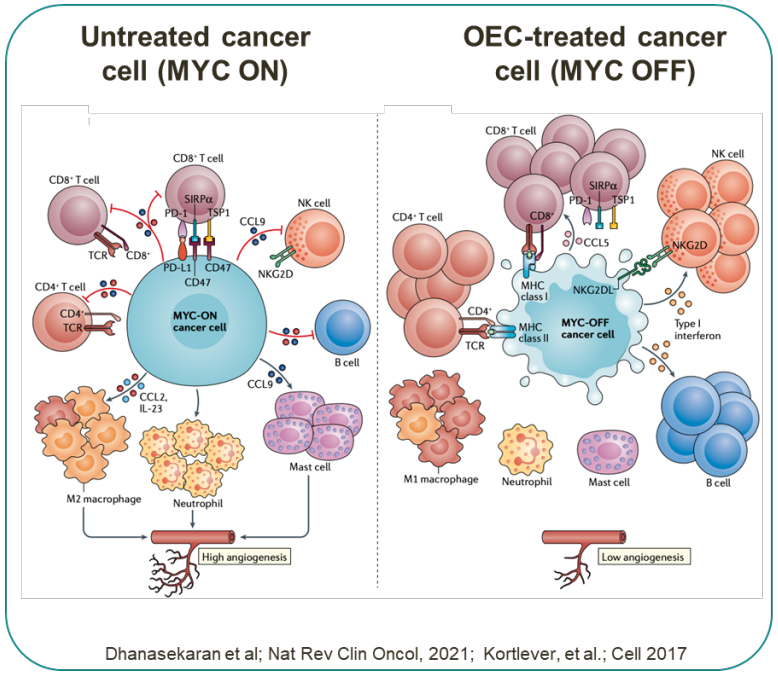
# MYC-Targeting ECs Have Potential to Reverse Mechanisms of Checkpoint Inhibitor Resistance; Believe Will Show Benefit in Combination

- MYC acts at both cell-intrinsic and TME / host adaptive immune response levels to suppress immune surveillance, drive tumor growth
  - Drives lack of response and rapid generation of resistance to TKIs and CPIs
- **MYC-targeting EC attacks cancer in 2 orthogonal ways:**
  - **Cell-intrinsic** – e.g., inducing tumor cell apoptosis, neoantigen release
  - **Host adaptive immune response** – e.g., downregulating PD-L1 to recruit CD8+T and NK cells, "warm up" immunologically cold tumors
- OTX-2002 MoA is complementary to and overlapping with MoAs of both SOC agents but with non-overlapping exposure/safety profiles



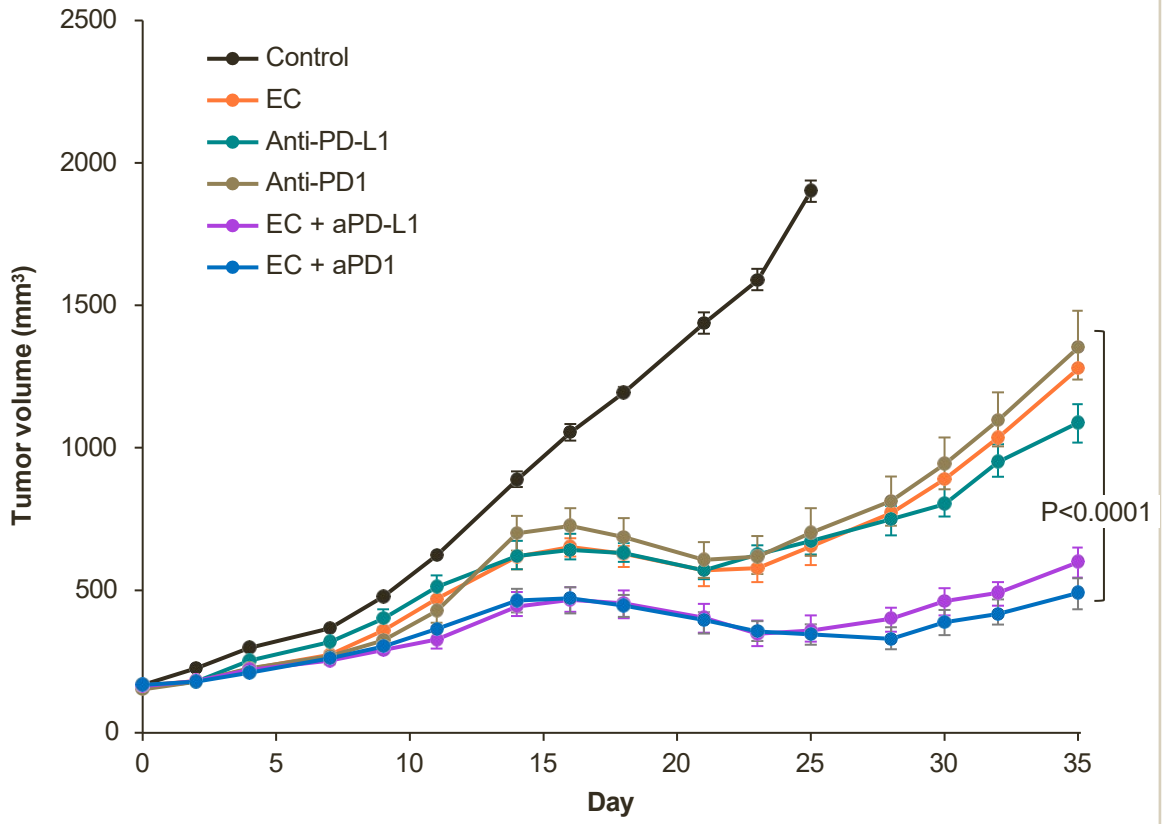

Dhanasekaran et al; Nat Rev Clin Oncol, 2021; Kortlever, et al.; Cell 2017

**Potential to effectively treat CPI-resistant or refractory tumors clinically***

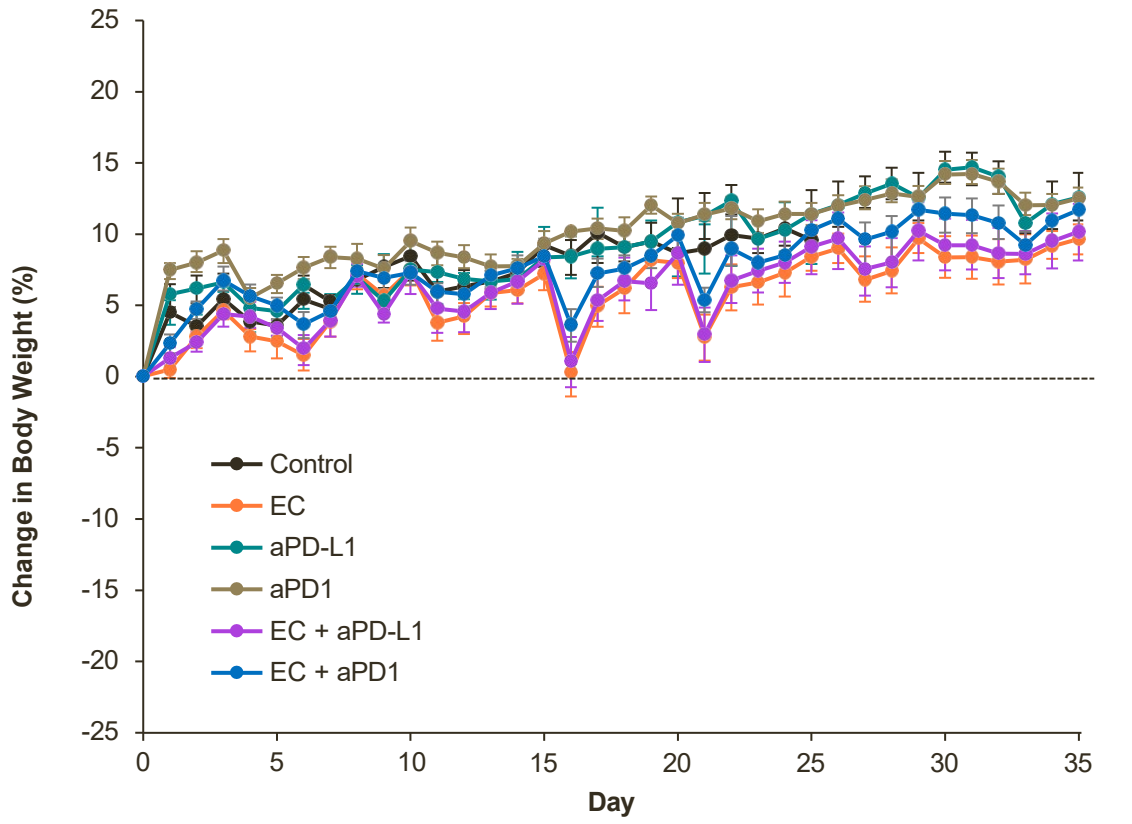
*Significant unmet need in 1L; no post-CPI agents approved in 2L; no approved therapies in 3L

# MYC-Targeting EC Demonstrated Significant Combination Benefit with Checkpoint Inhibitors in Preclinical Models of HCC

## HCC Tumor Model (Hepa1-6)




## No Significant Impact on Body Weight in Mice



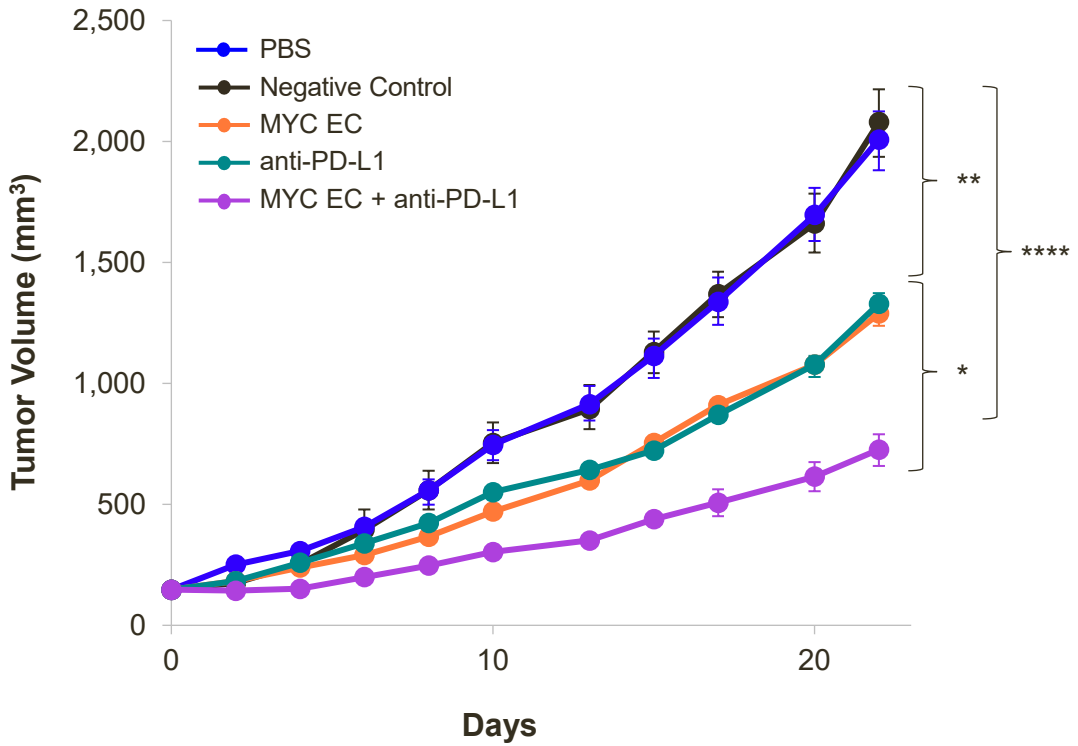

Statistically significant combination benefit in immune competent mice with *a*PD1 or *a*PD-L1

Both *a*PD1 and *a*PD-L1 combinations well tolerated with no significant impact on body weight during the study

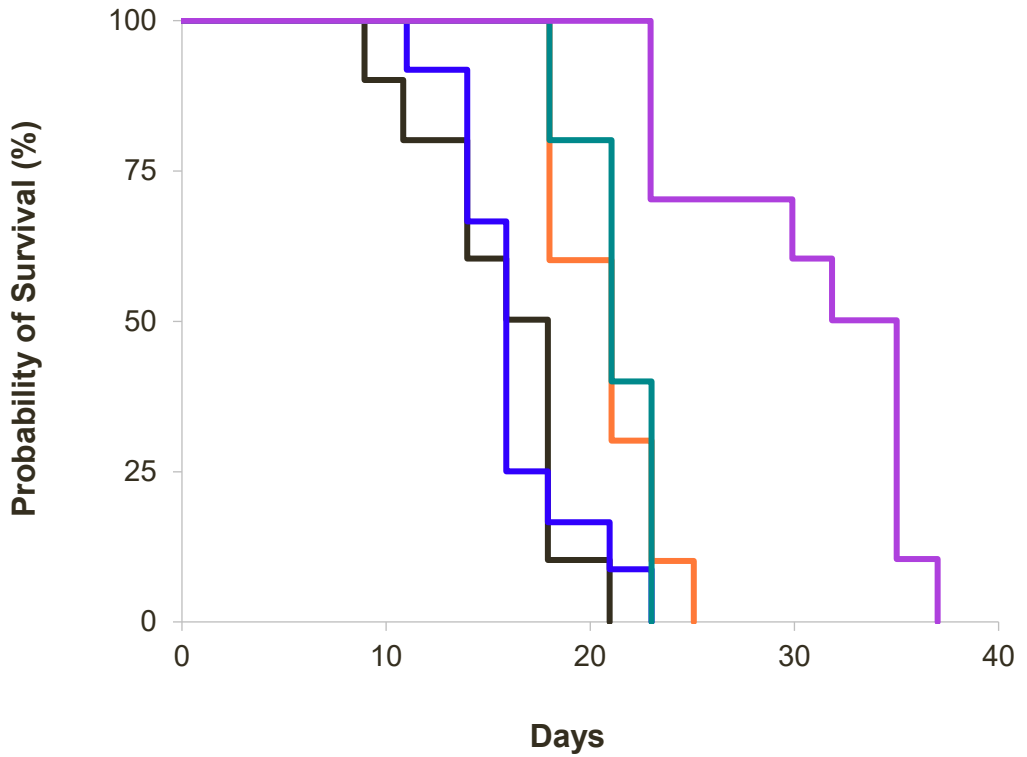
EC dosed IV every 5 days (last dose on Day 25). aPD1 or aPD-L1 dosed intraperitoneally once-weekly (last dose on Day 14).

# MYC-Targeting EC Demonstrated Significant Efficacy as Monotherapy and in Combination with Anti-PD-L1 in CPI-Refractory Preclinical Lung Cancer Model

## Lewis Lung Carcinoma Subcutaneous Tumor Model




## Survival

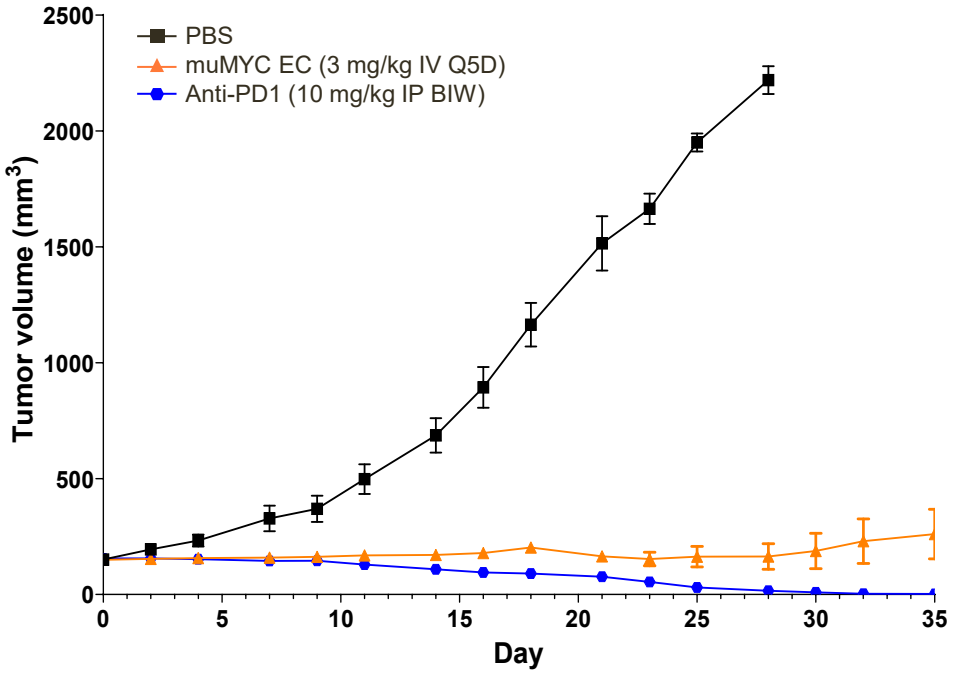



*p<0.05, **p<0.01, ****p<0.0001
MYC EC dosed every five days

Source: Data presented at AACR-NCI-EORTC 2023.

# MYC-Targeting EC Conferred Long-Term, Tumor-Specific Immune Memory in Preclinical Models of HCC

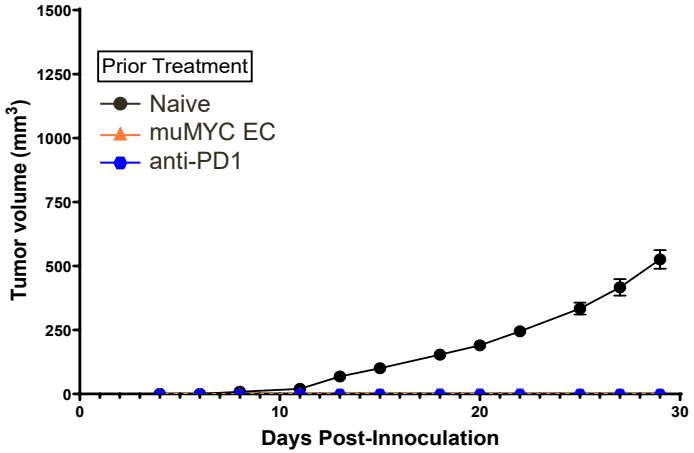
## Immunocompetent HCC Subcutaneous Tumor Model (Hepa 1-6)




- Anti-PD1: 19/20 (95%) mice tumor-free by day 35
- MYC EC: 14/20 (70%) mice tumor-free by day 35

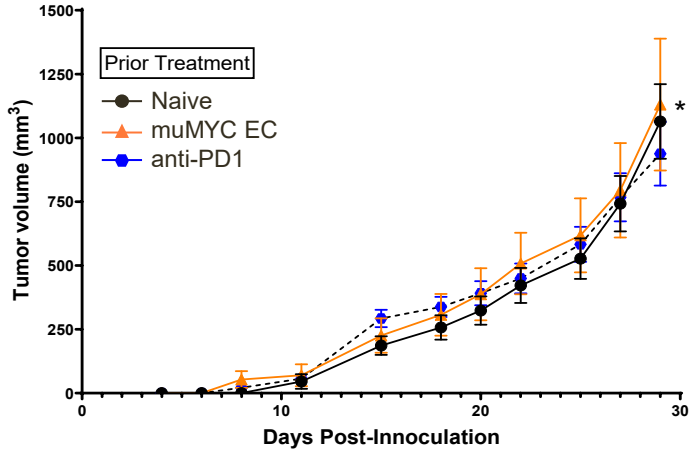
Tumor-free mice rechallenged ~70 days after last dose

## Hepa 1-6 Rechallenge




No Hepa1-6 tumor growth in mice previously treated with MYC EC or anti-PD1

## LL/2 Rechallenge




LL/2 tumor growth in mice previously treated with MYC EC or anti-PD1

Source: Data presented at ASCO 2023.

# Building Value Through the OMEGA Platform and Pipeline

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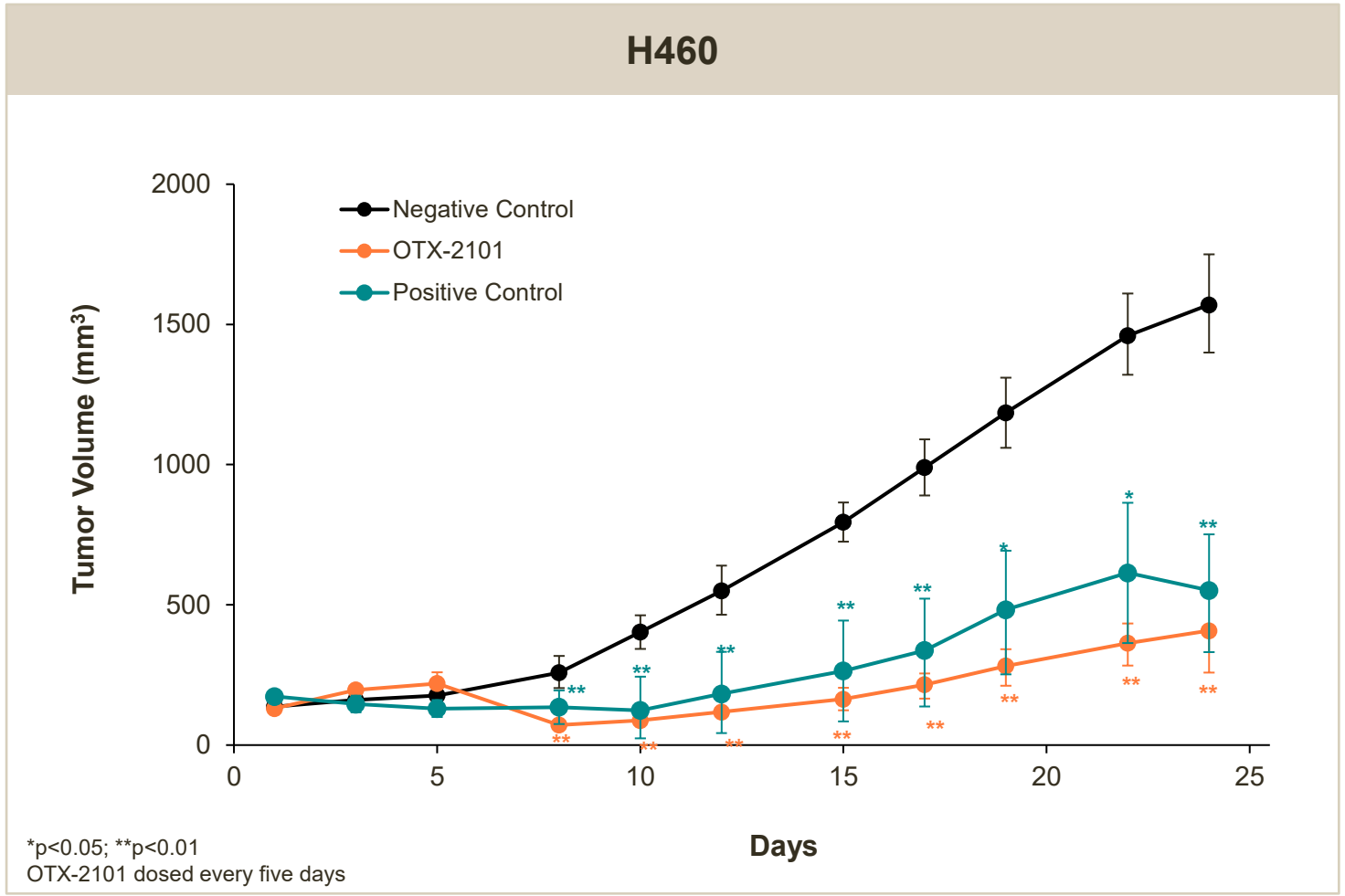
# MYC-Targeting EC, OTX-2101, Led to Statistically Significant Inhibition of Tumor Growth in *In Vivo* NSCLC Xenograft Tumor Model

- Pan-mutational approach leverages a novel lung-targeting LNP delivery technology
- NSCLC accounts for ~85% of lung cancer cases in U.S.*
- MYC overexpression is present in approximately 60% of NSCLC**
- Currently being evaluated in IND-enabling studies

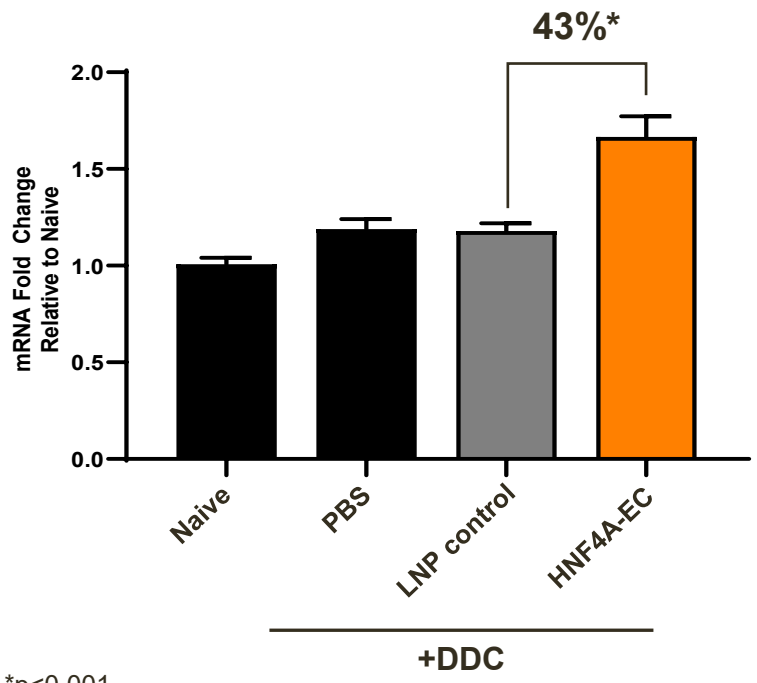



Source: Data presented at ASGCT 2023. *Mayo Clin Proc. 2008 May; 83(5): 584–594. **J Cancer Res Clin Oncol, 2019 Nov; 145(11): 2663-2674.

# HNF4A-Targeting EC Significantly Upregulated Target Gene Expression and Reduced Key Measures of Fibrosis

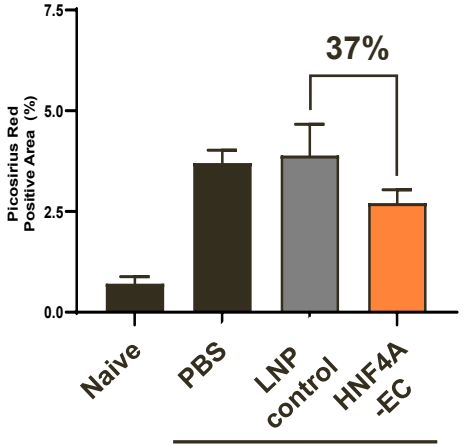
- Pioneering program in liver/liver function regeneration
- HNF4α is a critical transcriptional regulator of hepatocyte differentiation and function
- Expression of HNF4α is dysregulated in fibrotic liver disease; upregulation has been shown to improve hepatocyte function

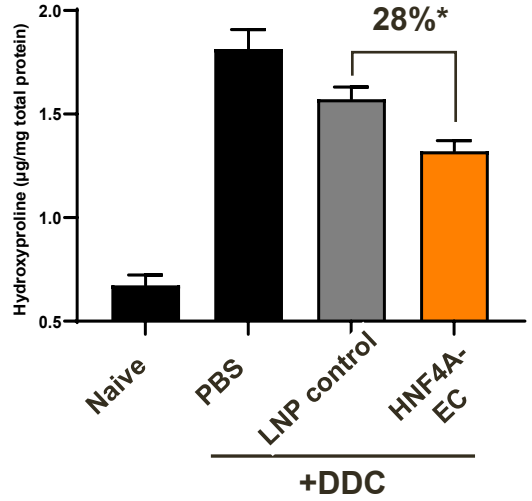
## HNF4α Expression




*p<0.001

## HNF4α Induction Conferred Protection in DDC Fibrosis Model



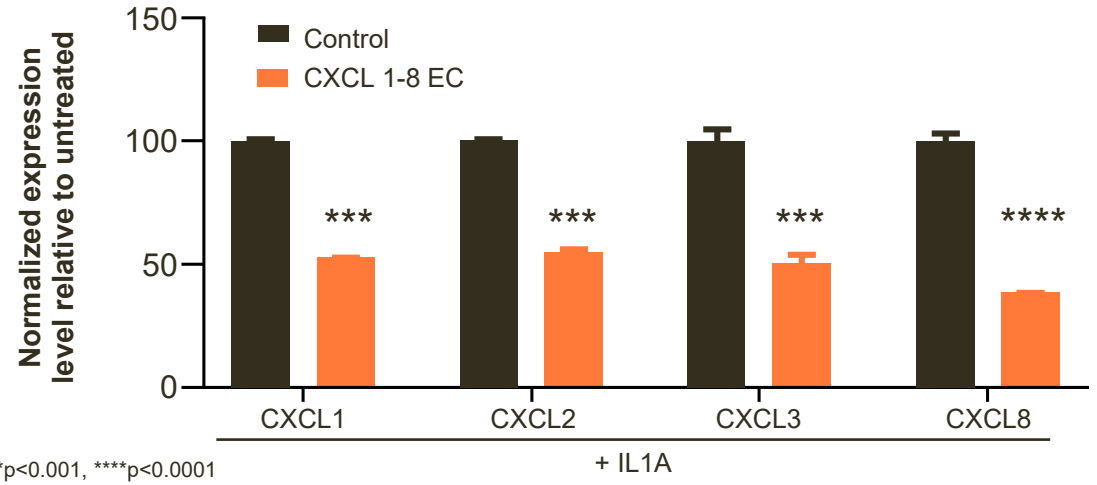

*p<0.05

Source: Data presented at AASLD 2023.

# Multiplexed Modulation of CXCL 1-8 Gene Cluster: Inhibition of Neutrophil Migration Achieved w/ Single EC in Preclinical Models of Inflammatory Lung Disease

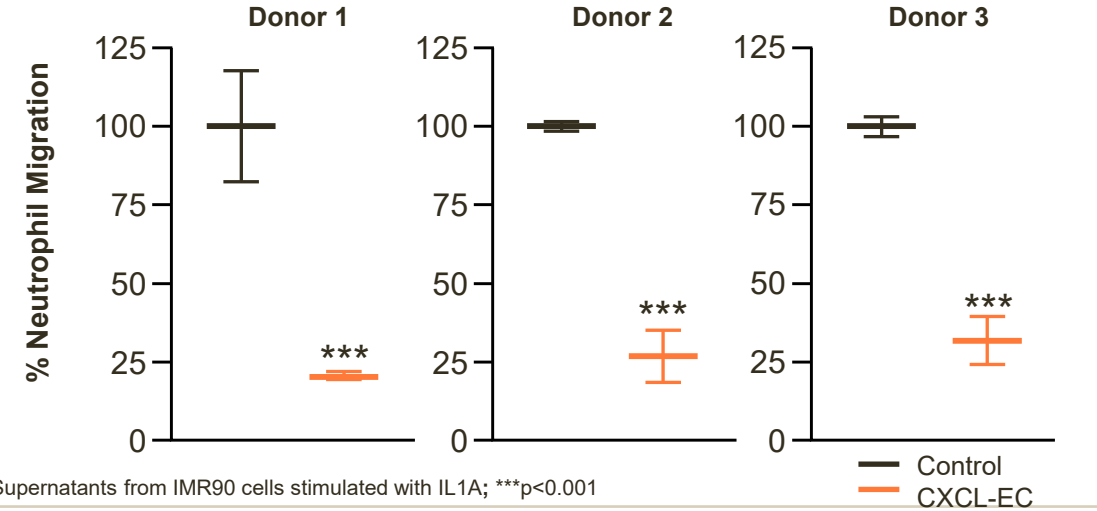
- Demonstrates OMEGA platform's ability to multiplex gene regulation with a single construct
- Dysfunction of these chemokines implicated in wide array of inflammatory disorders, including:
  - neutrophilic asthma
  - acute respiratory distress syndrome (ARDS)
  - dermatological indications
  - rheumatological indications

## Coordinated Downregulation of mRNA Expression




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

## Significant Decrease in Neutrophil Migration




Supernatants from IMR90 cells stimulated with IL1A; ***p<0.001

Source: Data presented at International mRNA Health Conference 2023.

# Opportunity For Orthogonal and Transformative Innovation In Obesity

## Thermogenesis Research Collaboration with Novo Nordisk

- **Transdifferentiation of human adipose tissue:** Transitioning the epigenetic state of white to metabolically active brown fat
- **Aspiration for potential first-in-class program:**
  - Epigenomic controller that regulates "browning" of human white adipose tissue
  - LNP to adipose tissue

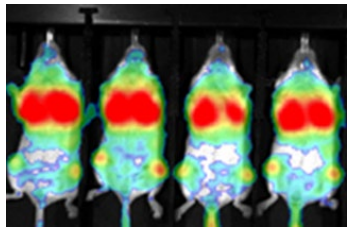
- **Collaboration validates broad applicability of the OMEGA platform**
- **Strategically complements** our internal efforts and expands our pipeline into cardiometabolic / obesity
- **Novo to reimburse all R&D costs**

Project initiated in Q1 2024 with epigenomic controller design, discovery, and formulation

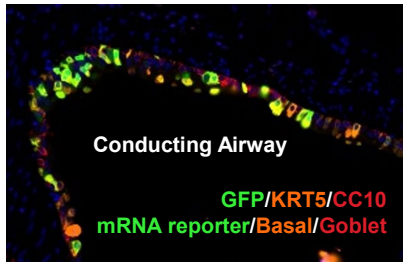
# Omega Has Extensive Internal Liver and Lung Delivery Efforts

## Additional Proprietary LNPs Targeting CNS, Joints, Skin and Adipose in Development

### Lung (Inhaled, Systemic)



Systemic

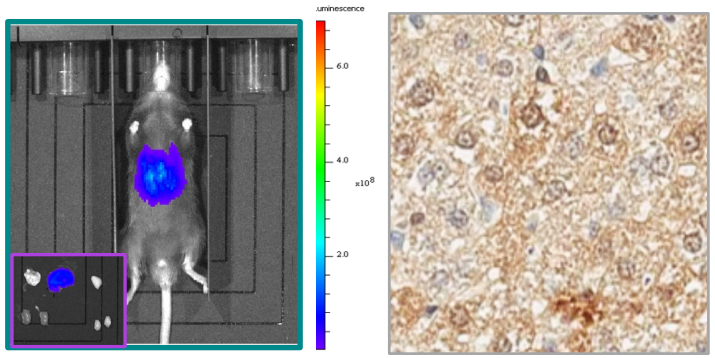



Local
Intratracheal
Double positive cells

**Developed and funded in partnership with CF Foundation**

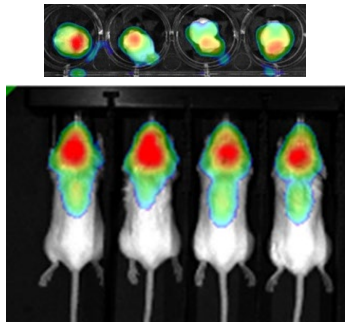
CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

### Liver

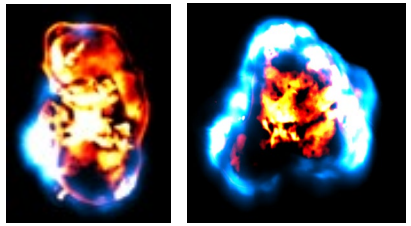


### CNS

Local (Intrathecal)



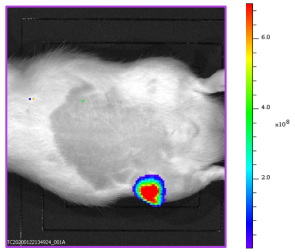
### Solid Tumor (extrahepatic)



Orthotopic Lung Tumor

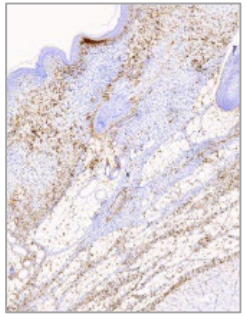
Subcutaneous Tumor

### Joint



Intraarticular administration

### Dermis



- Spleen
- Bone Marrow
- Cutaneous Tissue
- Immune Cells

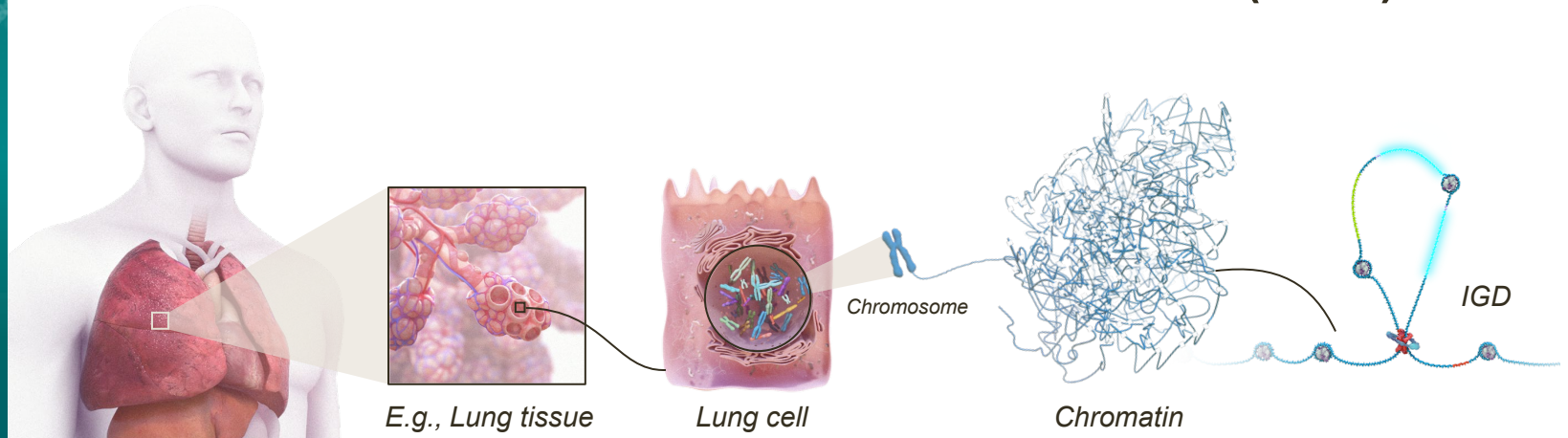
# Understanding the OMEGA Platform

OMEGA™ THERAPEUTICS

# Insulated Genomic Domains Are Nature's Control System to Regulate Gene Expression

**IGDs are the fundamental structural and functional units for gene control**

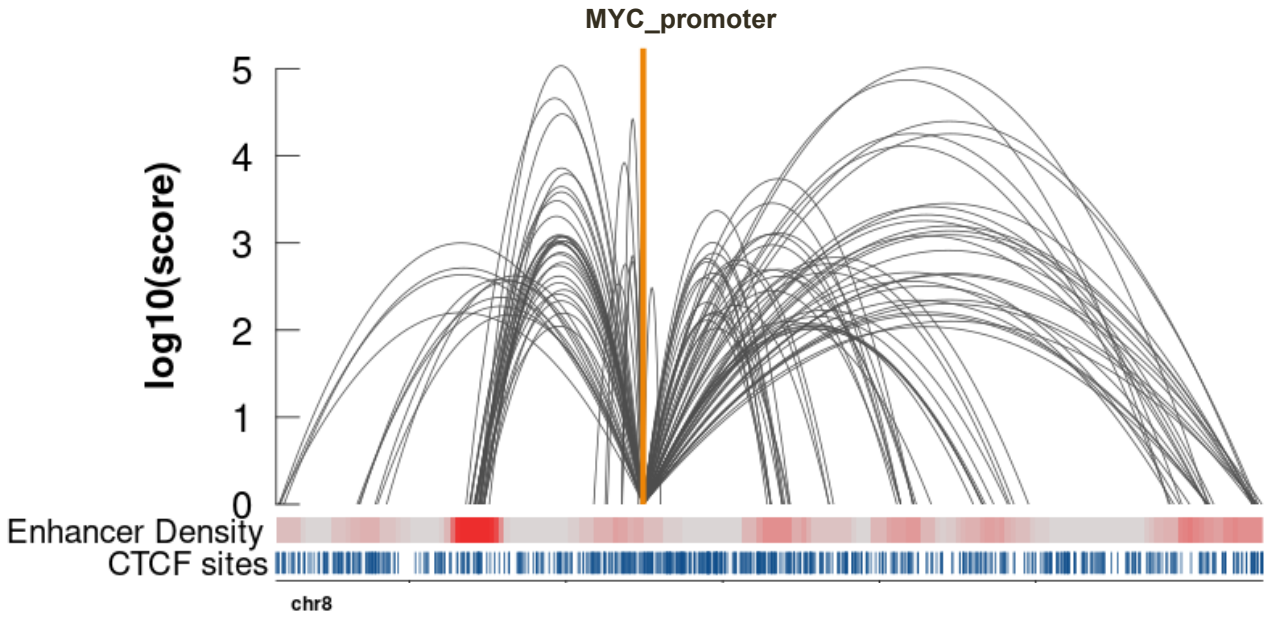
## Nature organizes genes in evolutionarily conserved 3D loops of chromatin called Insulated Genomic Domains (IGDs)



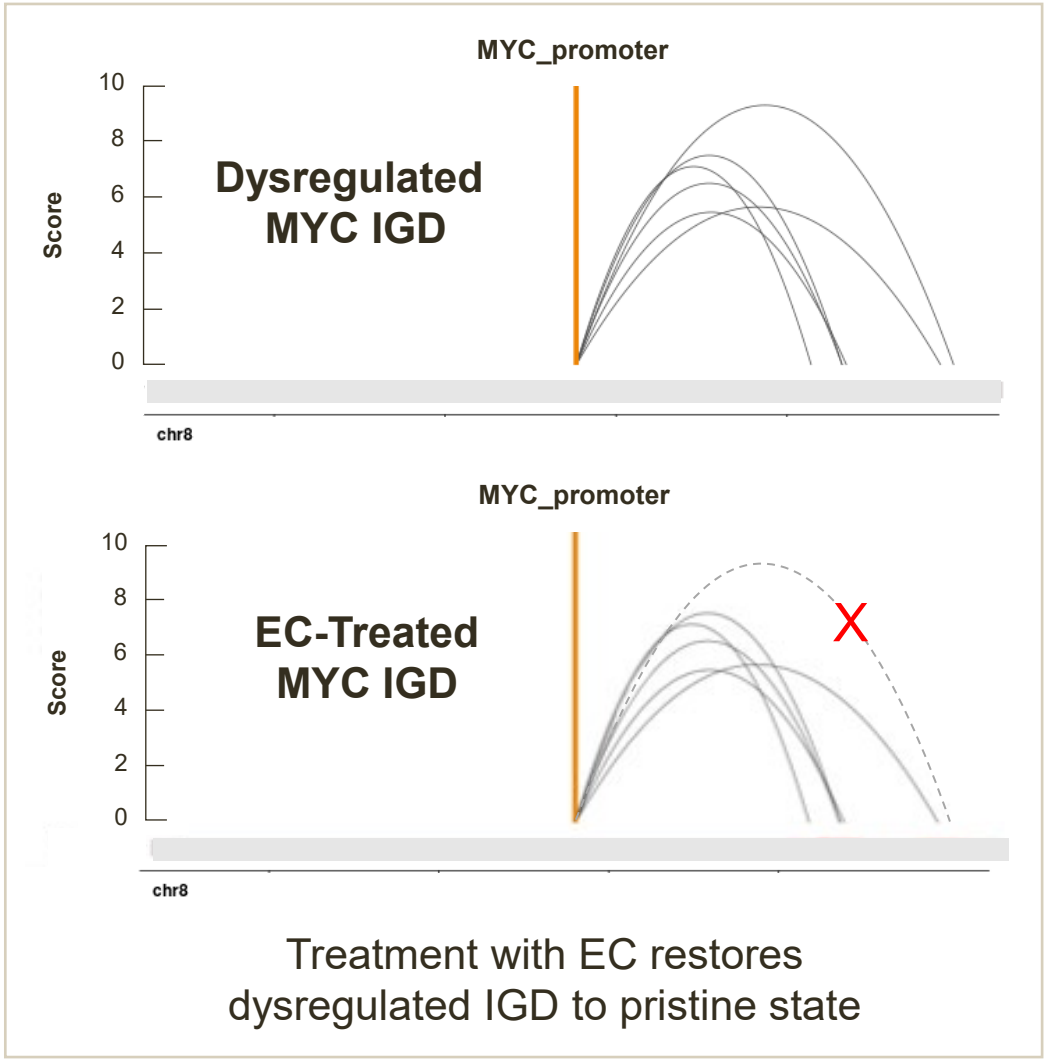

- Insulated from outside transcription by CTCF, each IGD contains 1-10 genes & their regulatory elements
- Regulators have unique DNA-sequences (**Epi**genomic **Zip**codes, "EpiZips"); can be used as drug targets
- Most diseases are caused by aberrant gene expression driven by epigenetic changes within IGDs

Source: Hnisz, D., Day, D.S., Young, R.A. *Cell.* Vol. 167, Issue 5, p1188-1200 (2016).

# OMEGA Platform Prospectively and Comprehensively Interrogates IGD Intervention Points to Determine Optimal Approach




MYC IGD is controlled through many different looping interactions across cell types and is dysregulated differently across diseases

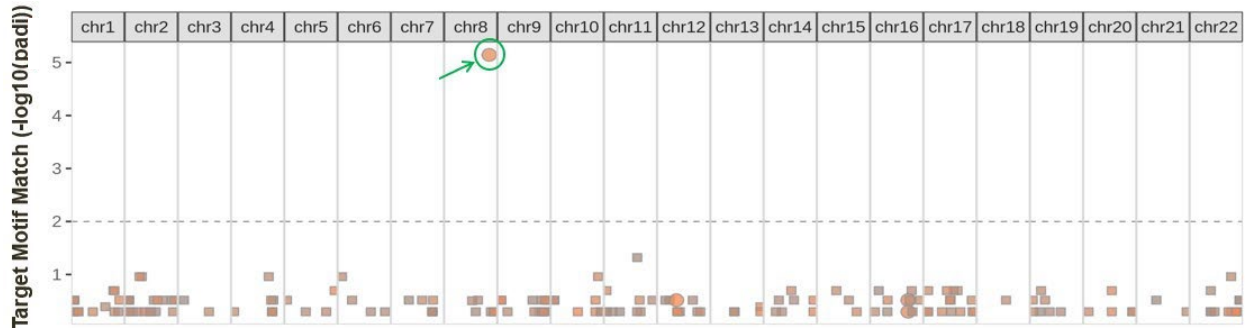



Treatment with EC restores dysregulated IGD to pristine state

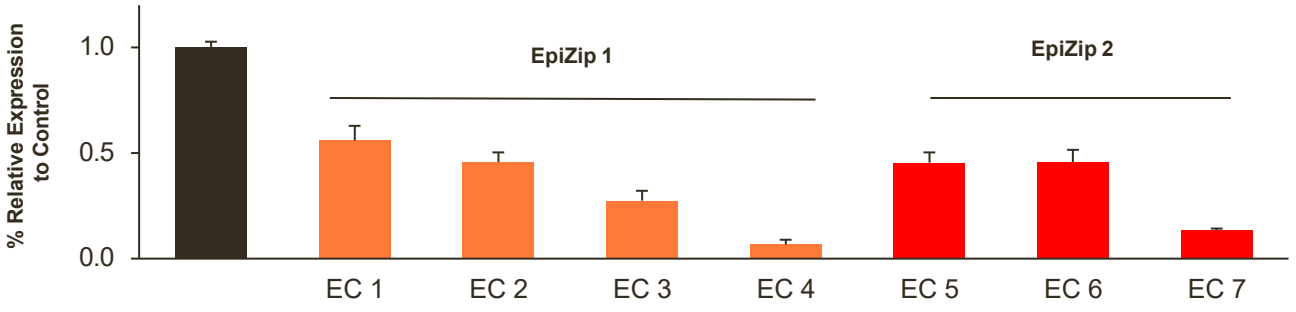
# Unique Epigenomic Control at Pre-transcriptional Level

| | |
|---|---|
| **Exquisite Specificity** | Precise binding to ~21 base pair sequence(s) to target a single gene or IGD genome-wide |
| **Controlled Tunability** | Bi-directional tuning and precise control on magnitude of expression |
| **Tailored Durability** | Transient PK with prospectively engineered durability tailorable to last days, weeks or months |

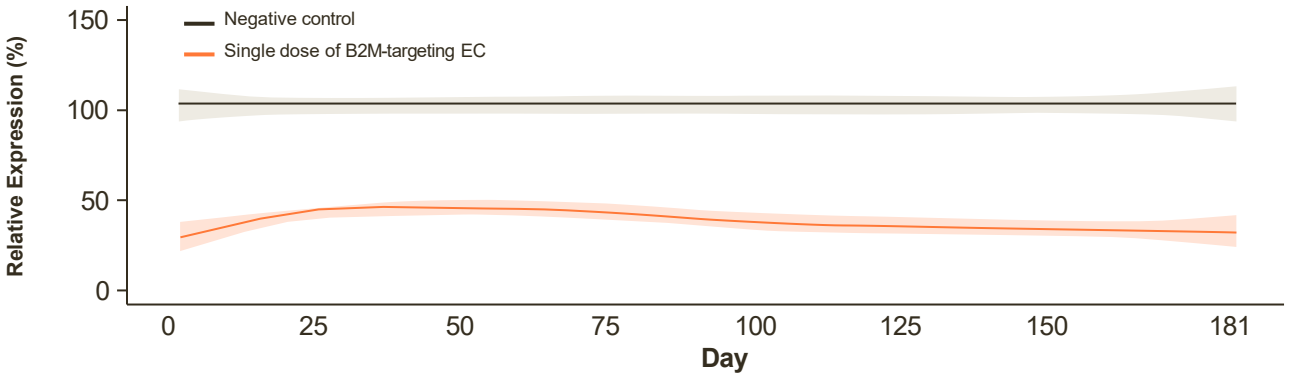
**MYC**




**MYC**




**B2M**



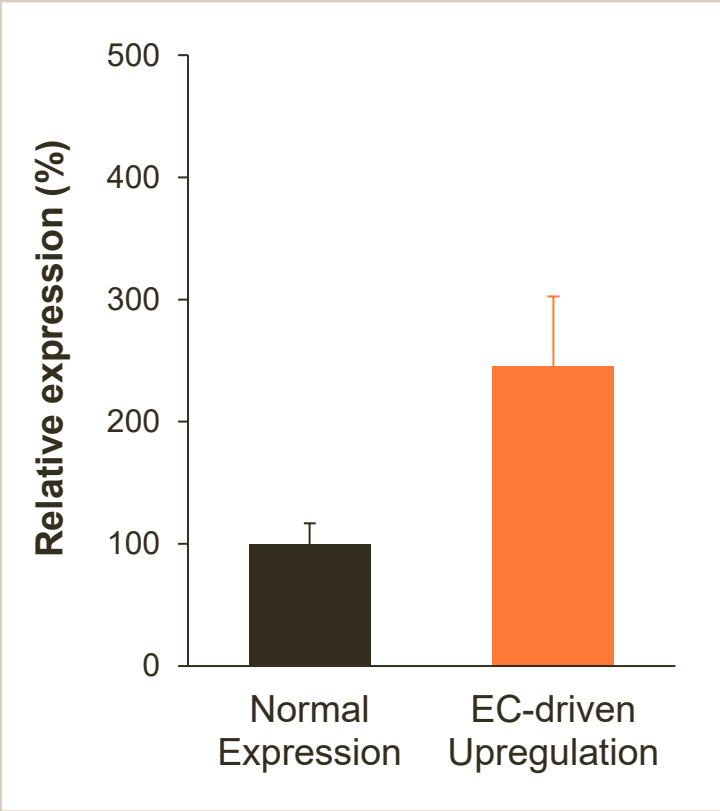

Specificity: In vitro immunoprecipitation ChiP data
Tunability and Durability: In vitro qPCR

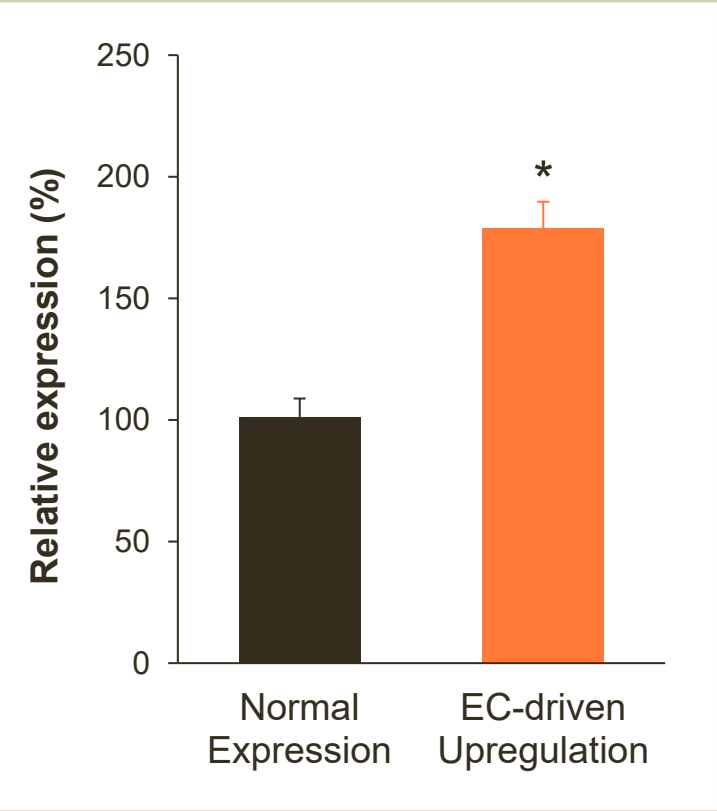
# Translation Across Species Demonstrated for EC Mechanism

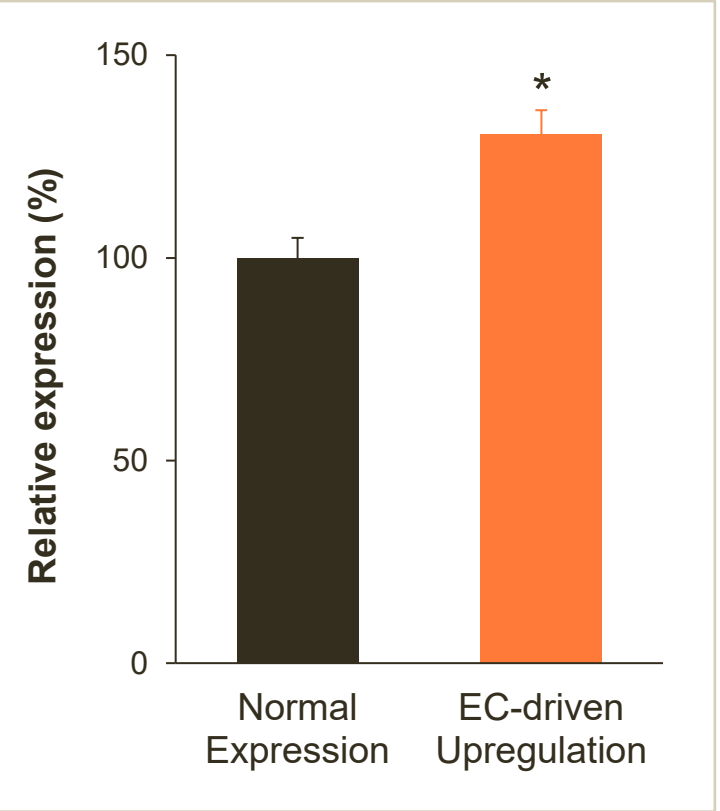
In-House Data for Both Up and Down Regulation

## Increase in 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) |

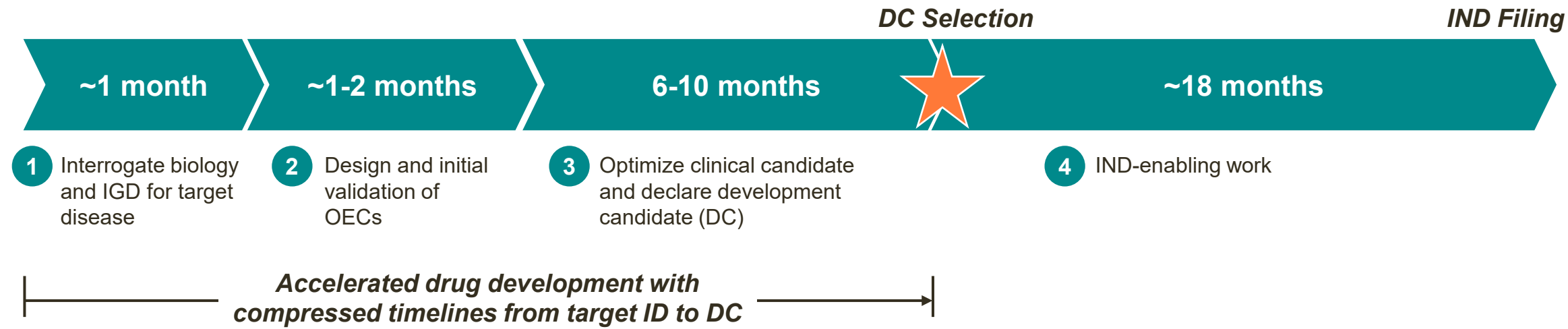



* Significant, paired t-test p<0.05

# Computation-Driven Approach to Expedite Prosecution of New Targets to IND




**Computational Engine Designed for Realtime Feedback**

| | | |
|---|---|---|
| Advanced AI/ML-driven data analysis | Predictive genomic and *in silico* modeling to improve hit rate | Rapid and rational drug design |

Omega's first IND in MYC HCC took 27 months from start to IND clearance

# Corporate Summary

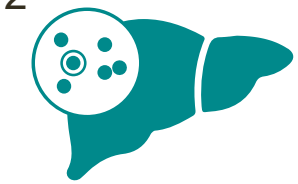
# Omega Therapeutics

## A Clinical-Stage Company Pioneering a New Class of Programmable Epigenomic mRNA Medicines

**Programmable epigenomic mRNA medicines** designed for pre-transcriptional gene modulation

**Platform enables rapid prosecution** of new targets and IGD biology driven by data science and advanced computational genomics

Lead program, OTX-2002, in Phase 1/2 MYCHELANGELO™ study for HCC; **Promising interim data provides clinical proof-of-platform**



**Cash runway into Q1 2025;** Balance sheet of $60.0 million as of March 31, 2024

**Pipeline focused on value creation opportunities;** therapeutic potential across broad range of diseases

**World-class leadership** focused on operational excellence

# 2024 Priorities and Milestone Opportunities

## LEAD PROGRAM: OTX-2002

- Complete monotherapy dose escalation in HCC patients, select recommended dose(s) for expansion; mid-2024
- Present additional updated clinical data from monotherapy dose escalation in mid-2024
- Present completed Phase 1 dose escalation data; Q4 2024
- Planning for expansion into monotherapy and combination settings in mid-2024

## PIPELINE & PLATFORM

- Establish additional partnerships (ex: oncology, cardiometabolic, regenerative, respiratory, other therapeutic areas)
- OTX-2101: Advance IND-enabling work and novel lung-targeting LNP formulation
- HNF4A: Advance lead optimization activities
- Advance obesity program in collaboration with Novo Nordisk
- Delivery: Progress internal LNPs in lung and other high-value tissues*; explore other delivery technologies

*Liver, CNS, Joints, Skin and Adipose.


OMEGA™
THERAPEUTICS