OMEGA™ THERAPEUTICS

Transforming Medicine Through Precision Epigenomic Control

Programmable mRNA Therapeutics

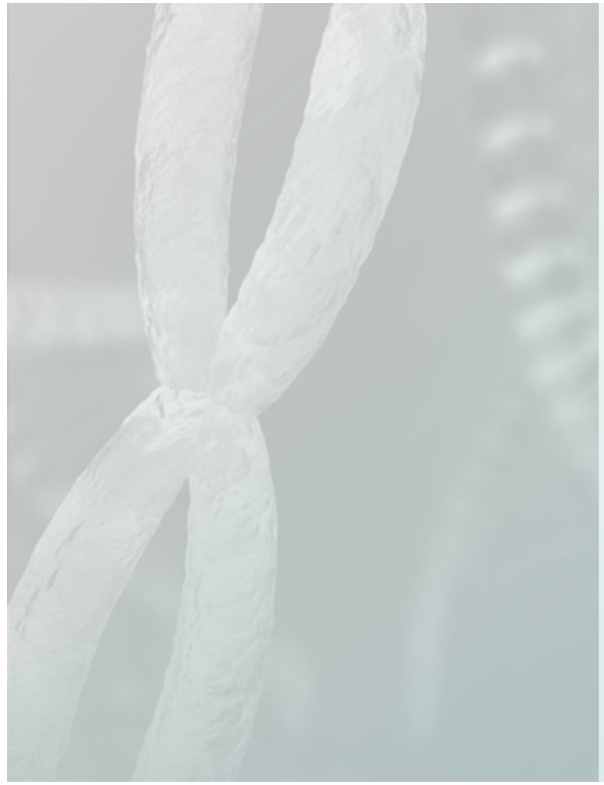
October 2023

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 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, 2022, 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 Pioneering a New Class of Programmable Epigenomic mRNA Medicines

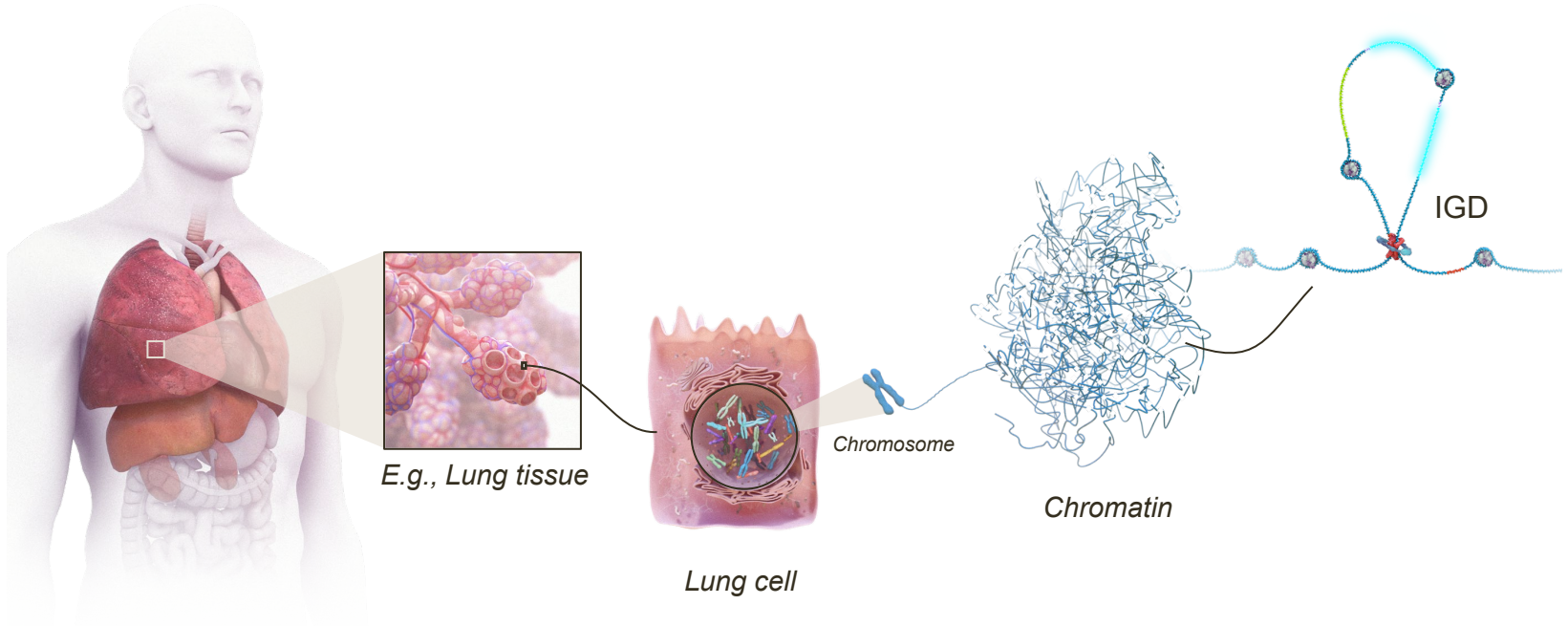


- OMEGA platform **leverages nature's innate epigenetic mechanisms** for regulating gene expression to treat or cure diseases
- **Broad applicability to nearly all human genes**, including historically undruggable and difficult-to-treat targets
- **No editing or changes** to native nucleic acid sequences

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)*

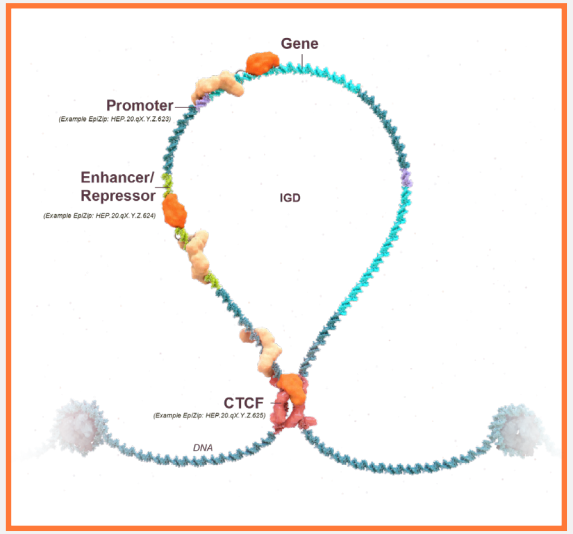


- Insulated from outside transcription by CTCF, each IGD contains 1-10 genes & their regulatory elements
- Regulators have unique DNA-sequences (**Epi**genomic **Zip**codes, "EpiZips"); can be used as drug targets
- Most diseases are caused by aberrant gene expression driven by epigenetic changes within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

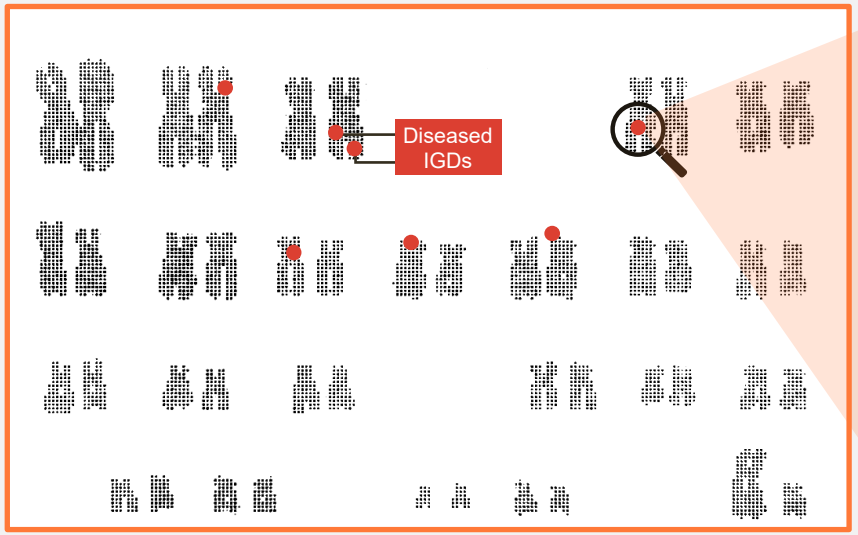
*Hnisz, D., Day, D.S., Young, R.A. *Cell.* Vol. 167, Issue 5, p1188-1200 (2016).

Precision Mapping of Unique Epigenomic Drug Targets

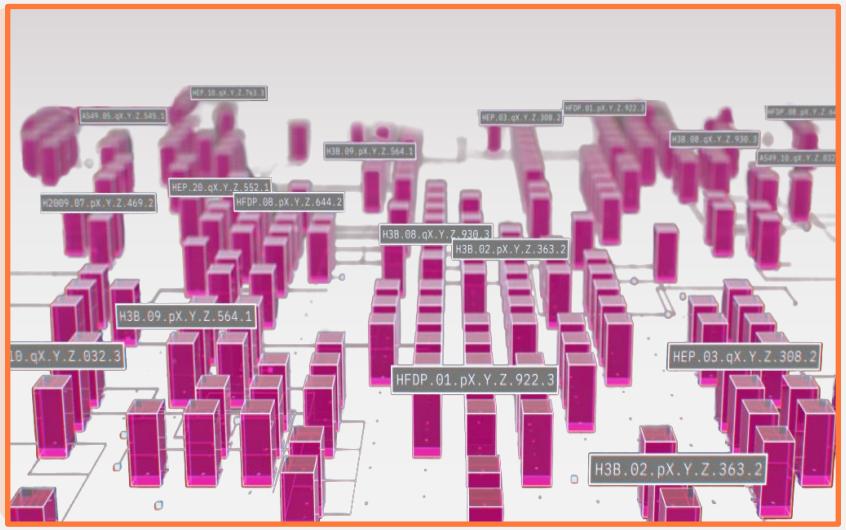
Powered by Our Deep Understanding of Genomic Architecture and Disease Biology



We have **identified key IGDs** and genes critical to disease pathology via *in silico* and cellular data…



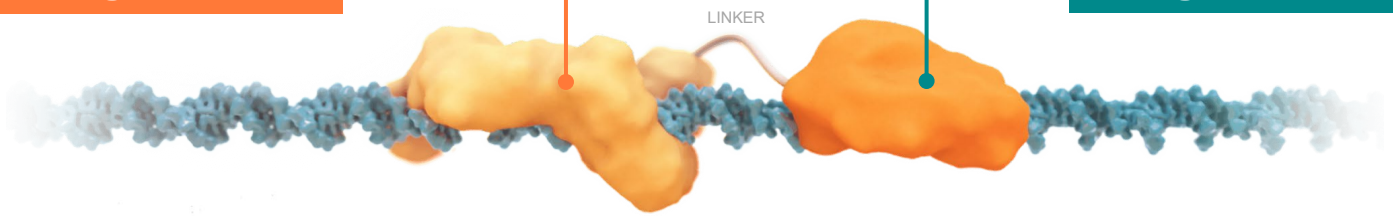
…**mapped the spatial network** of ~15,000 IGDs in both healthy and diseases states across the human genome…

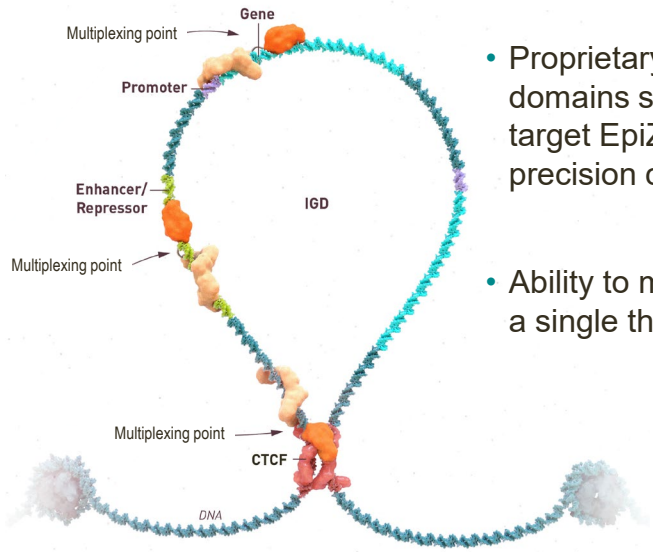


..and **built a proprietary database of precise drug targets** with thousands of unique, 21-basepair EpiZips to pre-transcriptionally control gene expression.

Proprietary Technology to Engineer Epigenomic Controllers

DNA-binding domain

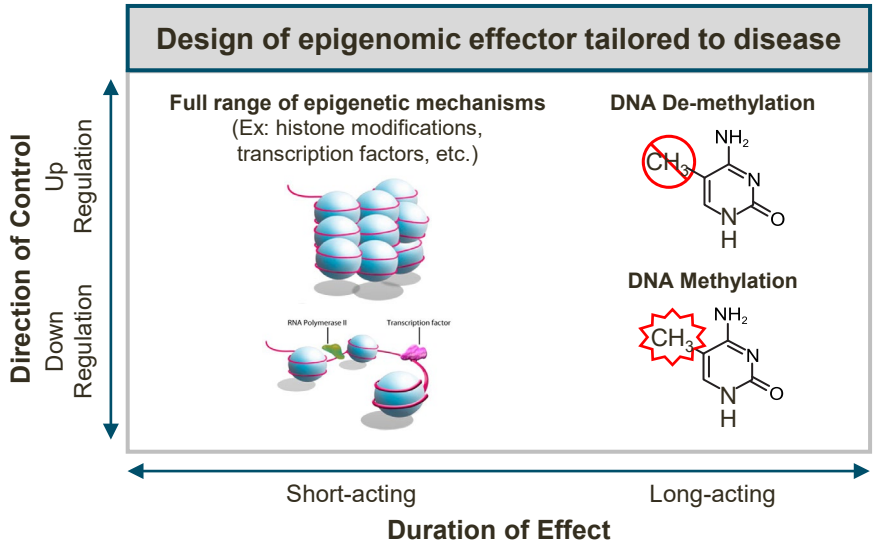




- Proprietary DNA-binding domains site-specifically target EpiZips with precision control
- Ability to multiplex in a single therapeutic

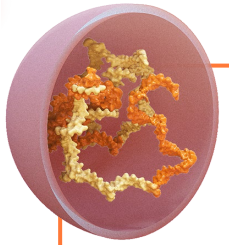
Epigenomic effector domain

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



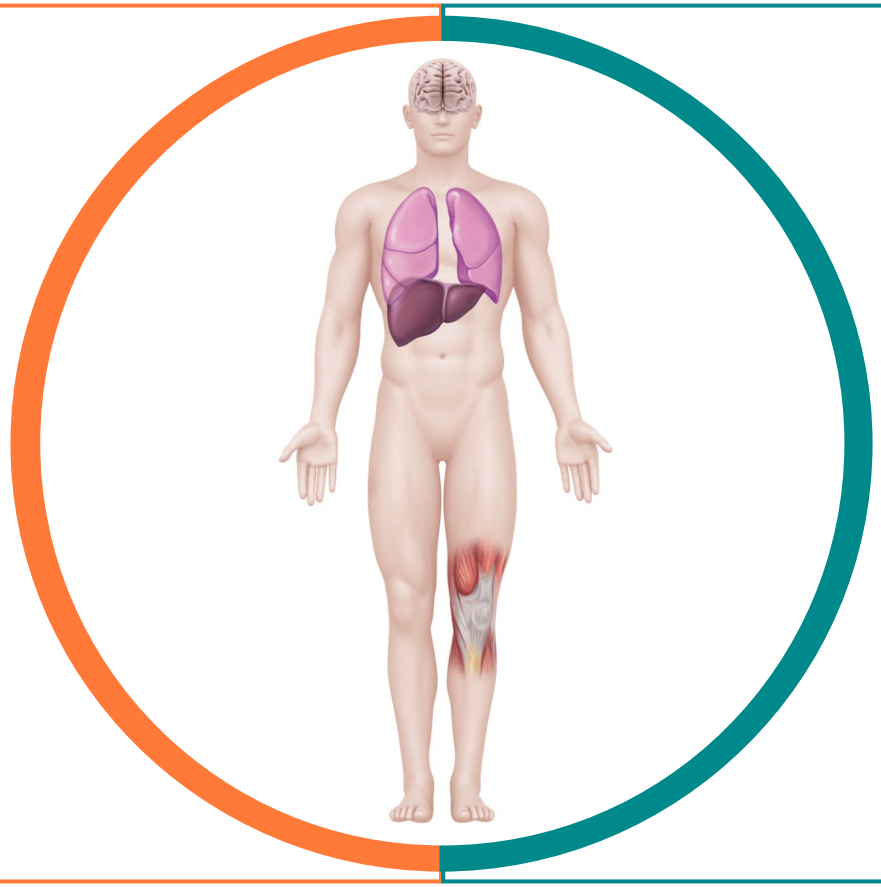
Initial Programs Leverage Validated LNP Delivery Technologies

Internal and External Approach to Unlock Full Potential of mRNA Medicine



Liver and Lung LNPs Clinic-Ready

License agreements for our lead programs, OTX-2002 (liver) and OTX-2101 (lung)



Internal Efforts to Unlock New Tissues

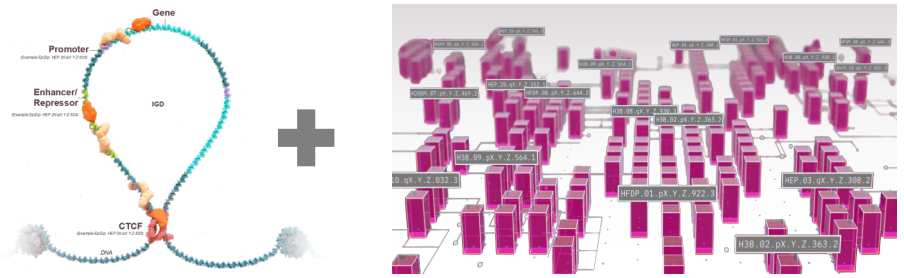
Internal development efforts ongoing for proprietary LNPs to extra-hepatic, extra-pulmonary tissues

LNP: Lipid Nanoparticle

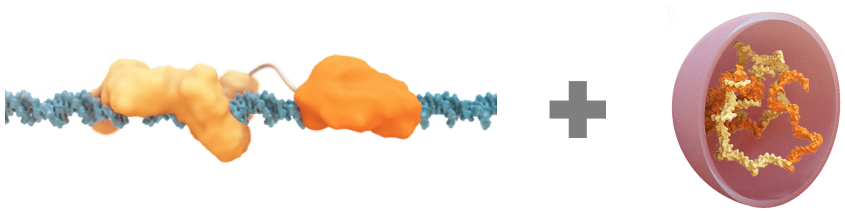
The OMEGA Platform

Leverages In-House Capabilities to Rapidly Design and Prospectively Engineer Programmable mRNA Medicines

Biology



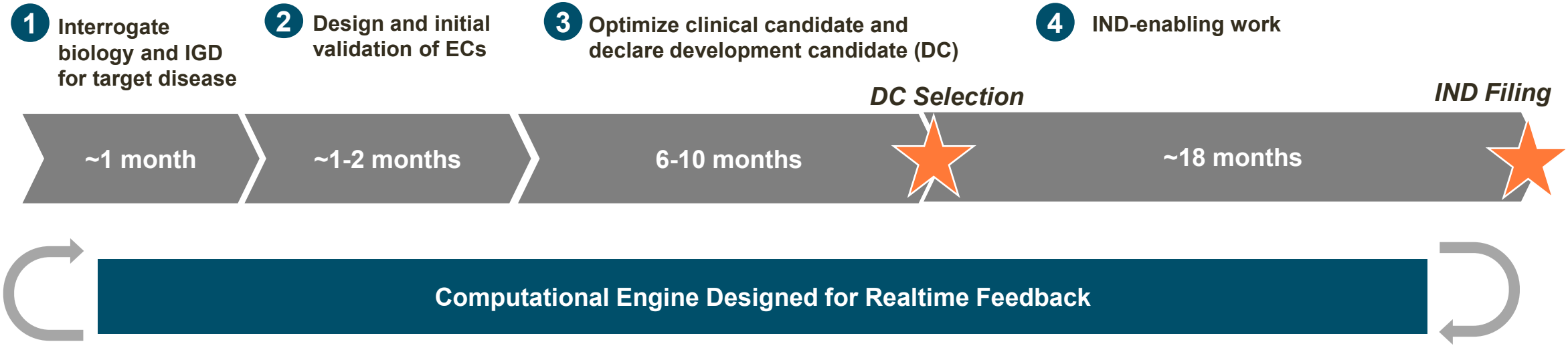
Technology



World-Class Computational Genomics & Data Science

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

Our First IND in MYC HCC Took 27 Months from Start to IND Clearance



Accelerated drug development driven by:

- Deterministic, rational and rules-based drug design
- Advanced data analysis and machine learning algorithms
- Highly predictive genomic and *in silico* modeling
- Modular, engineered nature of platform

Transformative benefits of our approach:

- Accelerated drug development with compressed timeline from target ID to DC
- We believe our approach offers the potential for improved outcomes in the clinic, due to our rational design approach

Robust Pipeline Across Diverse Therapeutic Areas

	Target Gene(s)	Indication	EC	Discovery	Preclinical	Clinical		
						Phase 1	Phase 2	Phase 3
Oncology	**MYC**	Hepatocellular carcinoma	OTX-2002*	*Phase 1/2 MYCHELANGELO™ Study*				
	MYC	Non-small cell lung cancer	OTX-2101	*IND-Enabling Studies Ongoing*				
	Undisclosed	Small cell lung cancer						
Multigenic Diseases	**CXCL 1-8**	Potential franchise of programs**						
	Undisclosed	Idiopathic pulmonary fibrosis						
Regenerative Medicine	**HNF4A**	Liver regeneration						
	Undisclosed	Corneal regeneration						
Monogenic Diseases	**SFRP1**	Alopecia						

Route of Administration (top to bottom): IV (HCC), IV (NSCLC), IV (SCLC), IV/Pulmonary, IV/Pulmonary (IPF), IV (Liver Regeneration), Topical (Corneal Regeneration), Topical (Alopecia)
*In November 2022, OTX-2002 received Orphan Drug Designation from the FDA for the treatment of hepatocellular carcinoma
**Potential indications for CXCL-targeting EC include neutrophilic asthma, acute respiratory distress syndrome (including COVID-related), dermatological and rheumatological indications, and oncology

Clinical Data Showcase Potential of Controlled Epigenomic Modulation

Preliminary Data from Initial 2 Cohorts of MYCHELANGELO I Trial Announced September 2023

8/8 Patients Treated with OTX-2002 Showed:

- ✓ Highly-specific binding at target genomic loci
- ✓ Intended epigenetic state change with on-target increase in methylation signature
- ✓ Rapid, robust and durable downregulation of MYC expression
- ✓ Encouraging safety and consistent PK profile

First known clinical observation of pre-transcriptional epigenetic control of gene expression

Unlocks potential for MYC, a historically 'undruggable' target

Establishes clinical proof-of-platform

Validates epigenomic controllers as a new class

Platform Overview

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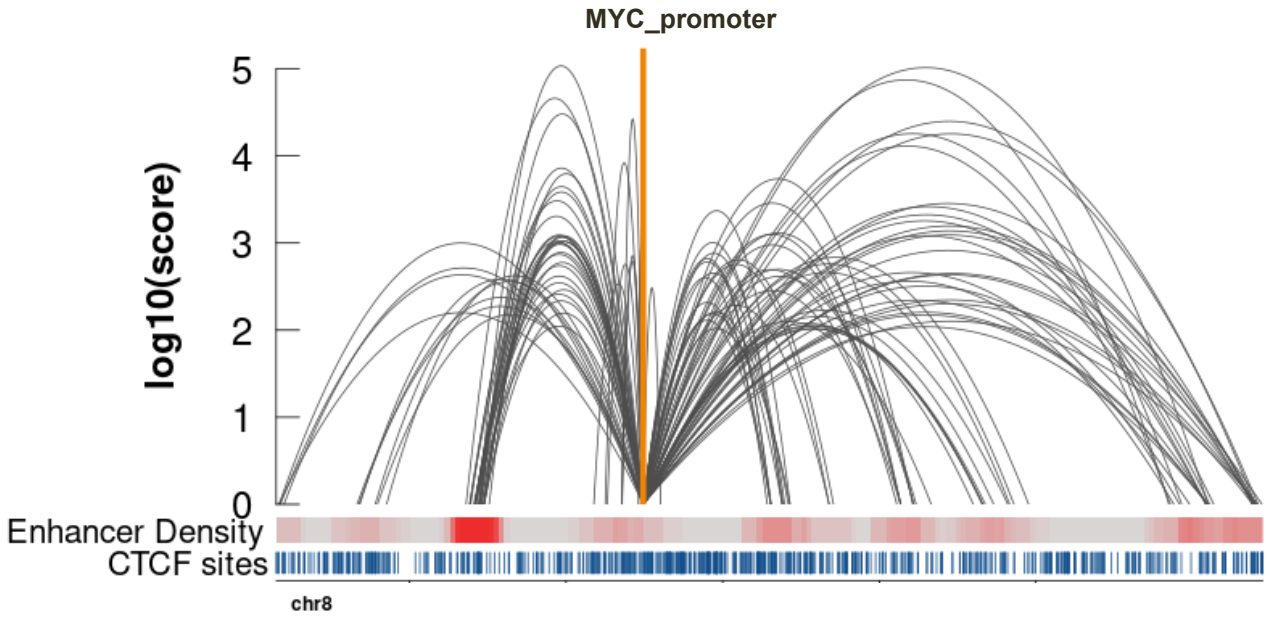
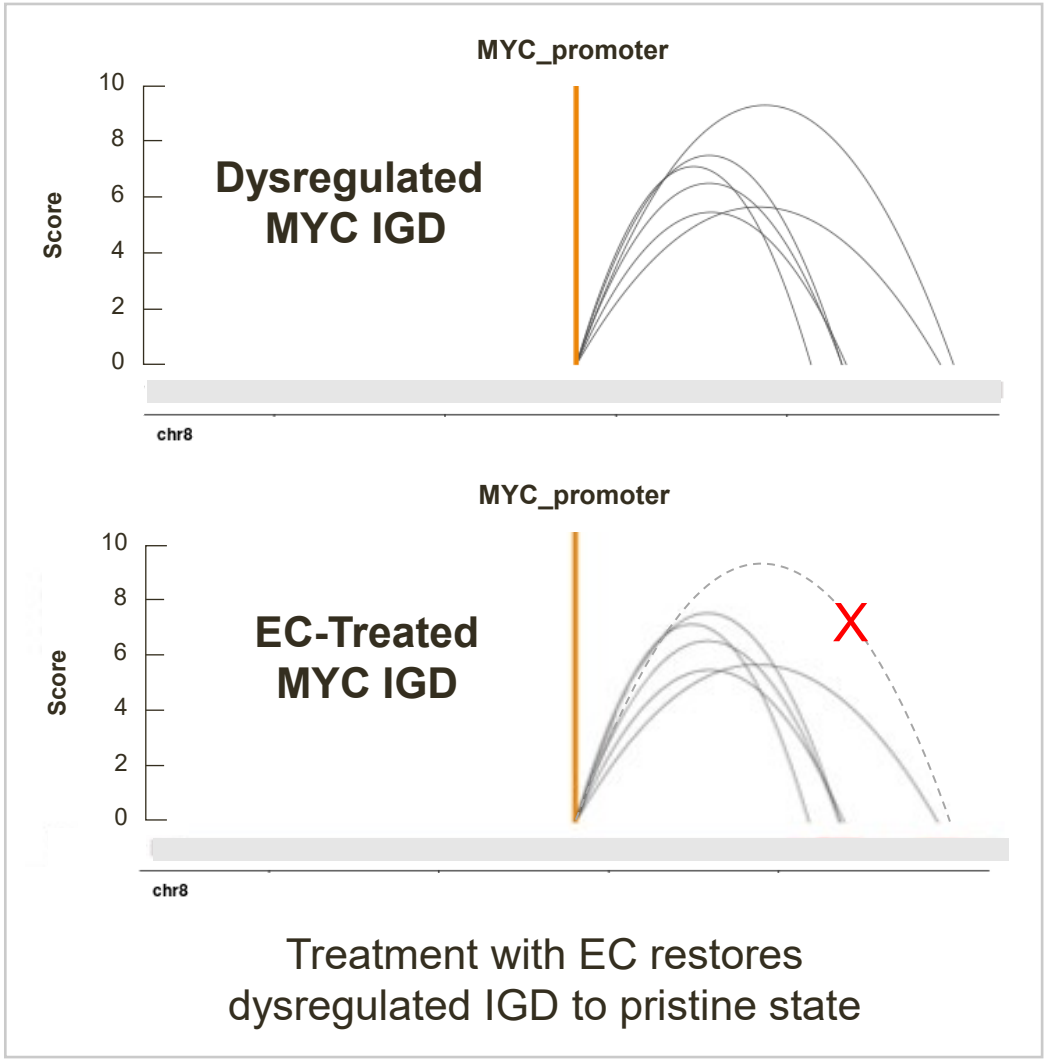
OMEGA Platform Prospectively and Comprehensively Interrogates IGD Intervention Points to Determine Optimal Approach



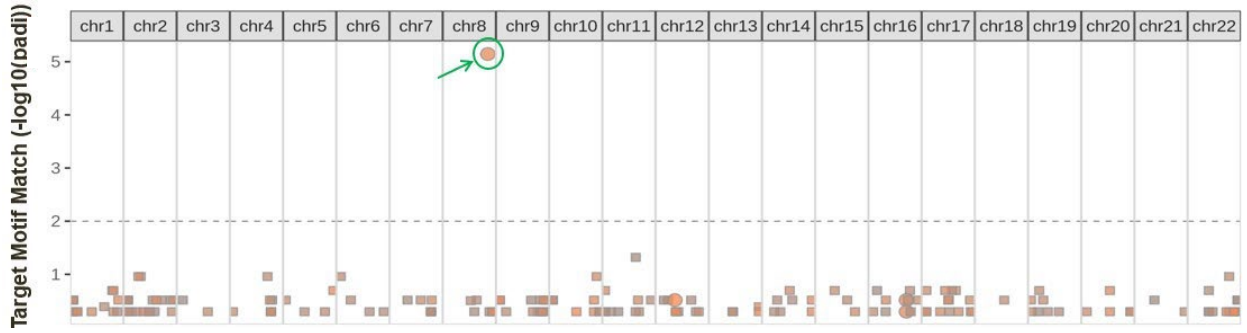
MYC IGD is controlled through many different looping interactions across cell types and is dysregulated differently across diseases

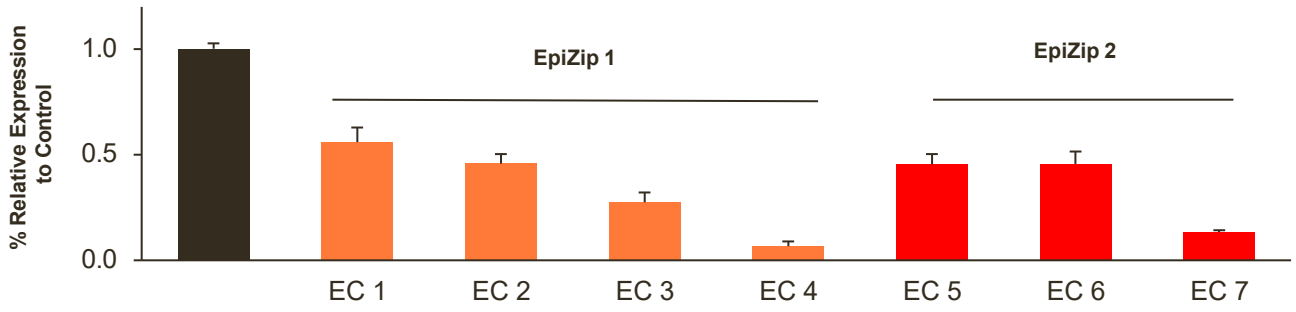


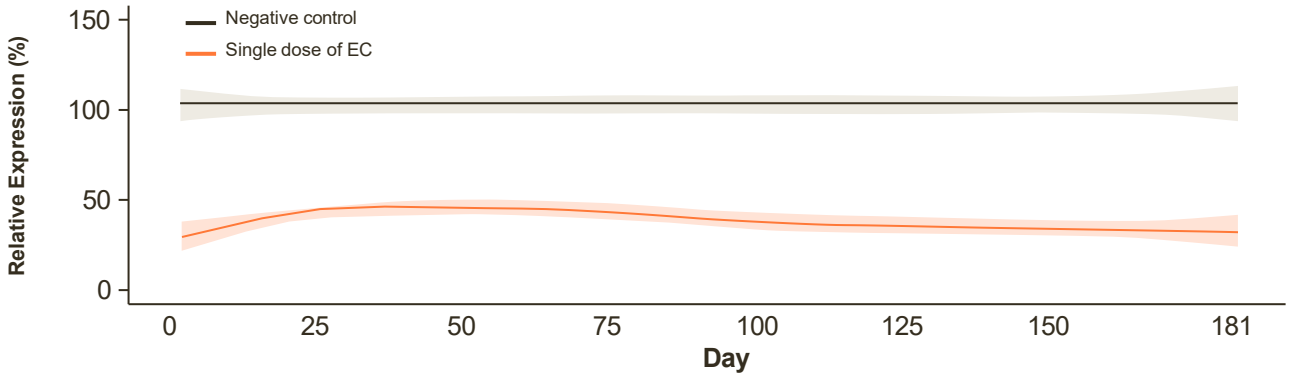
Treatment with EC restores dysregulated IGD to pristine state

Unprecedented Epigenomic Control at Pre-transcriptional Level

Exquisite Specificity	Precise targeting of a single gene or IGD genome-wide to produce robust change in gene expression
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



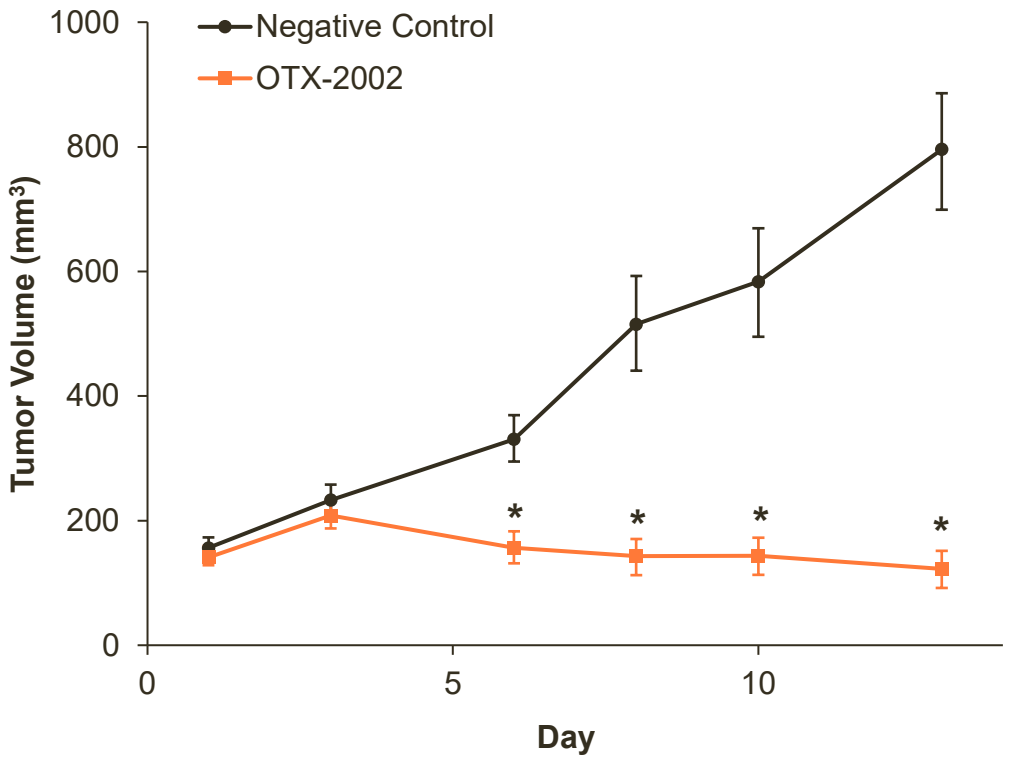




Proof-of-Concept Demonstrated Across Diverse Set of Disease Areas

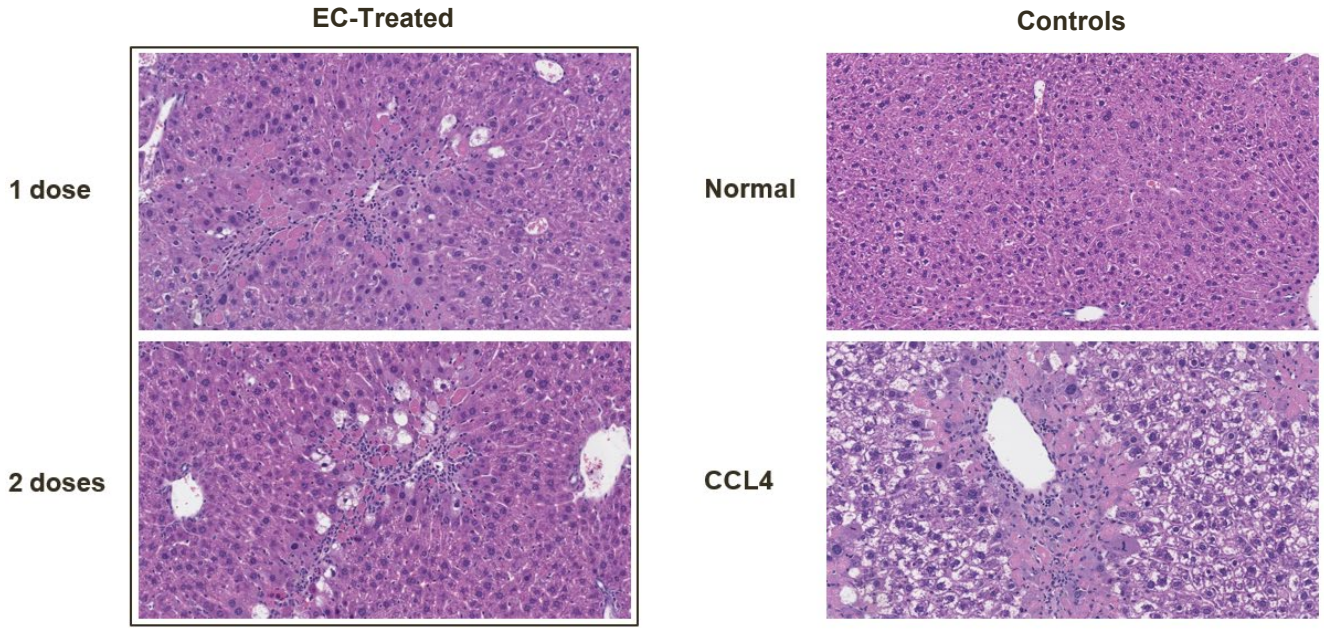
Oncology (MYC HCC)

Statistically significant inhibition of HCC tumor growth *in vivo* through direct targeting of c-MYC



Liver Regeneration (HNF4a)

Significant improvement in liver histology in murine model of fibrosis



EC ameliorates CCL4-induced hepatic fibrosis in C57BL/6J mice

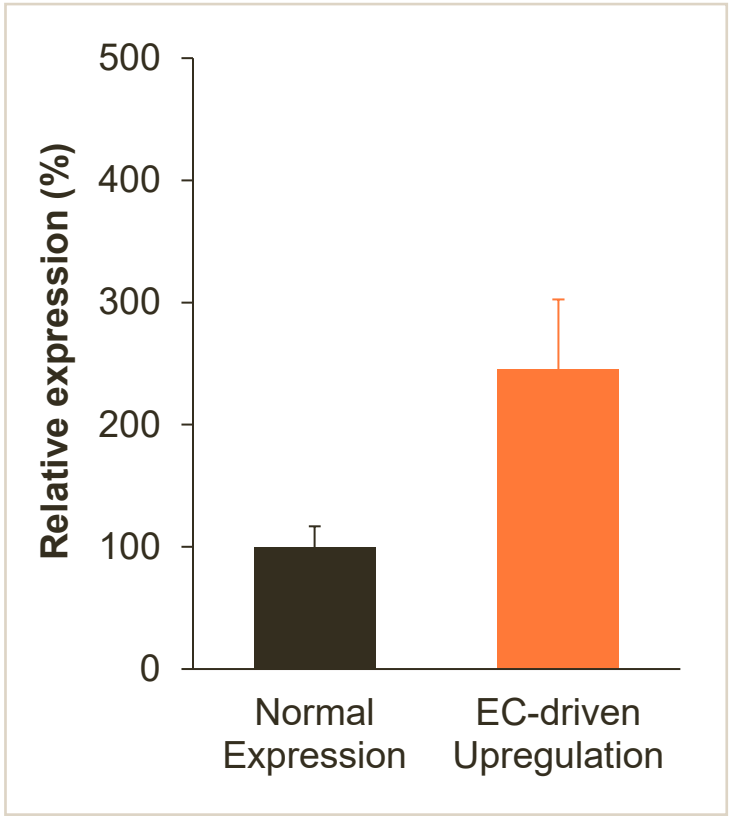
*Statistically significant vs negative control, t-test p<0.05 starting on day 6

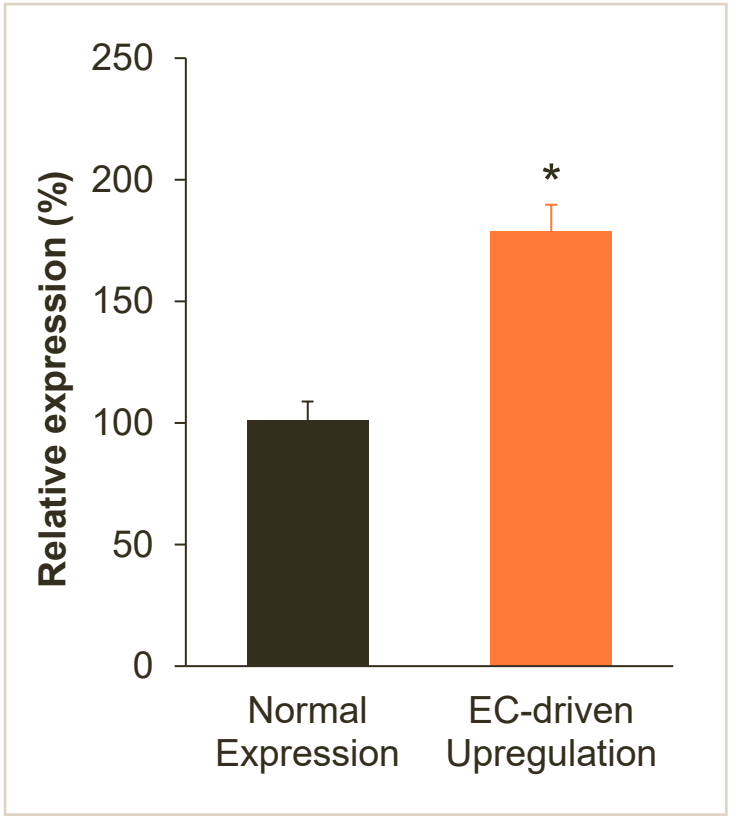
Translation Across Species Demonstrated for EC Mechanism

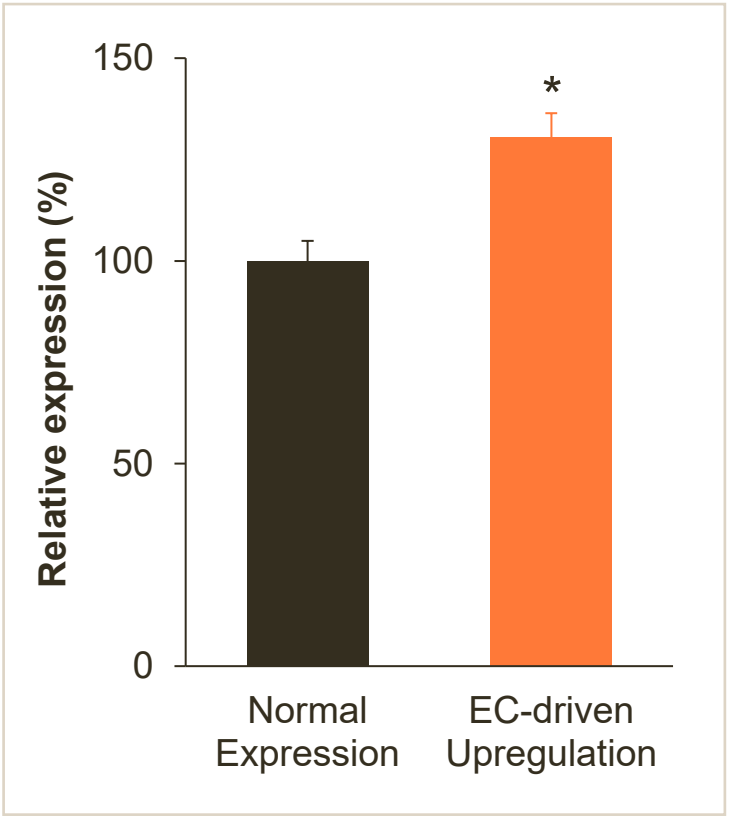
In-House Data for Both Up and Down Regulation

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)





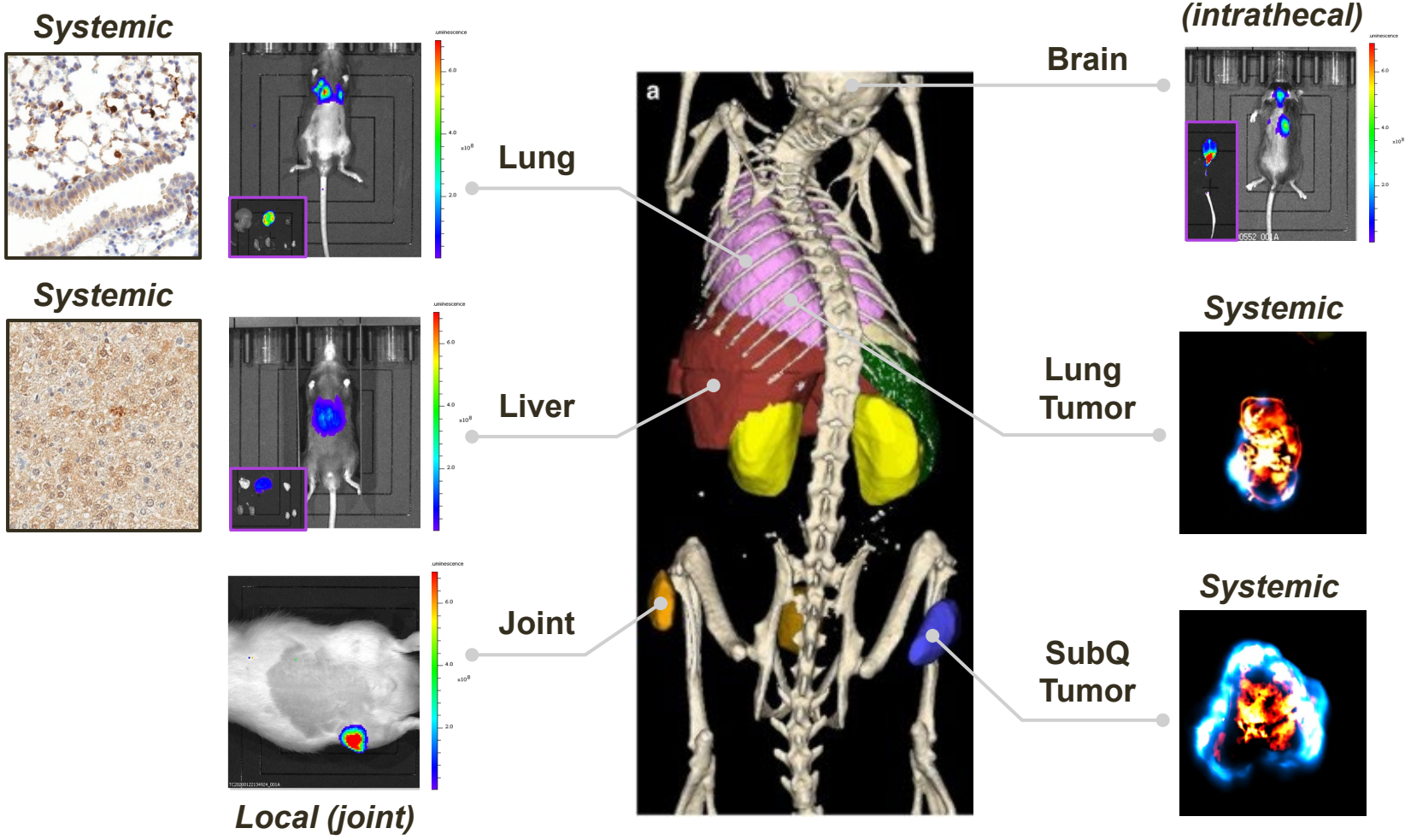


* Significant, paired t-test p<0.05

Delivery

Liver and Lung LNPs Clinic Ready; Expanding into Additional Tissues Through Internal Development Efforts

Internal LNP Development Efforts



Therapeutic Potential Across Nearly All Human Genes

Epigenomic Controllers Have Broad Applicability

Epigenomic Controllers (ECs)

Disease Processes	Disease Areas	Diseases (Examples)
Neoplasia Metabolic Dysregulation Fibrotic Processes Immune Dysfunction Vascular Pathology Tissue Degeneration	**Oncology ($100B+)**	Pan-Essential Oncogenes • Hepatocellular carcinoma • Non-small cell lung cancer • Pancreatic cancer • Glioblastoma multiform
	Multigenic diseases ($150B+)	• Respiratory diseases • Obesity • Neutrophilic asthma • Inflammatory bowel disease • Congestive heart failure • Idiopathic pulmonary fibrosis
	Regenerative medicine ($25B+)	• Regeneration of Liver, Pancreas, Heart, Cornea • T-cell programming
	Monogenic diseases (Table Stakes for Gene-Based Therapies)	• Alopecia • Hypercholesterolemia • Rare Diseases (Fragile X, Friedreich's ataxia)

Lead Program Overview

OTX-2002 for MYC-HCC

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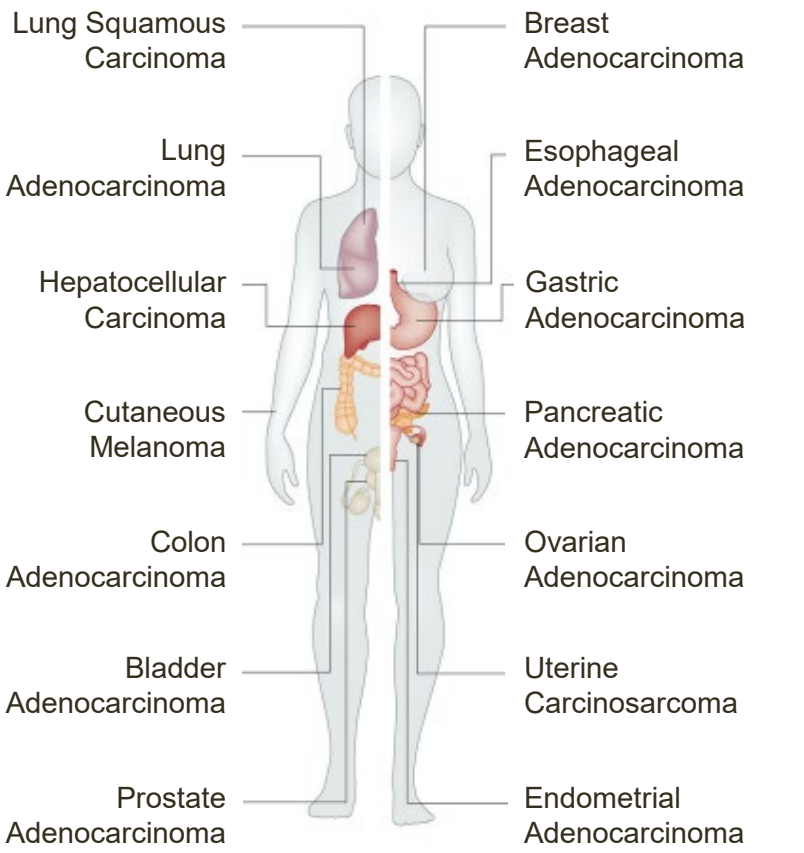
MYC: The Holy Grail of Master Oncogenes

- Primary driver of cancer growth and immune evasion in more than 50% of human cancers
- Strongly correlated with metastases and poor patient prognosis
- Historically ‘undruggable’ due to its disordered protein structure and autoregulation
- Potential solution: Controlled epigenomic modulation
  - OTX-2002 in development for treatment of HCC (70% MYC-associated)

MYC is a master oncogene that contributes to many human cancers



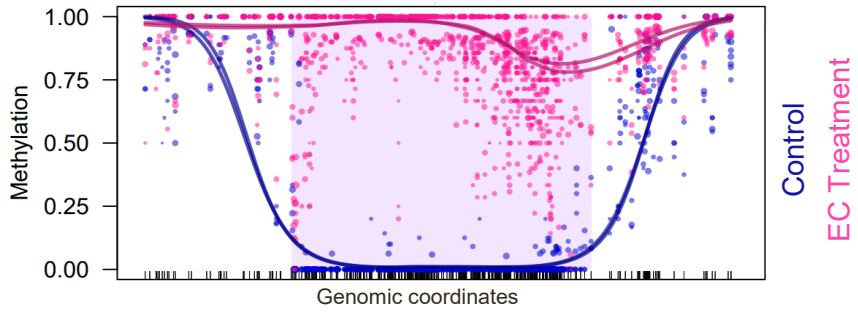
Reference: Dhanasekaran R, et al. *Nat Rev Clin Oncol*. 2022 Jan;19(1):23-36.

OTX-2002 Mechanism of Action

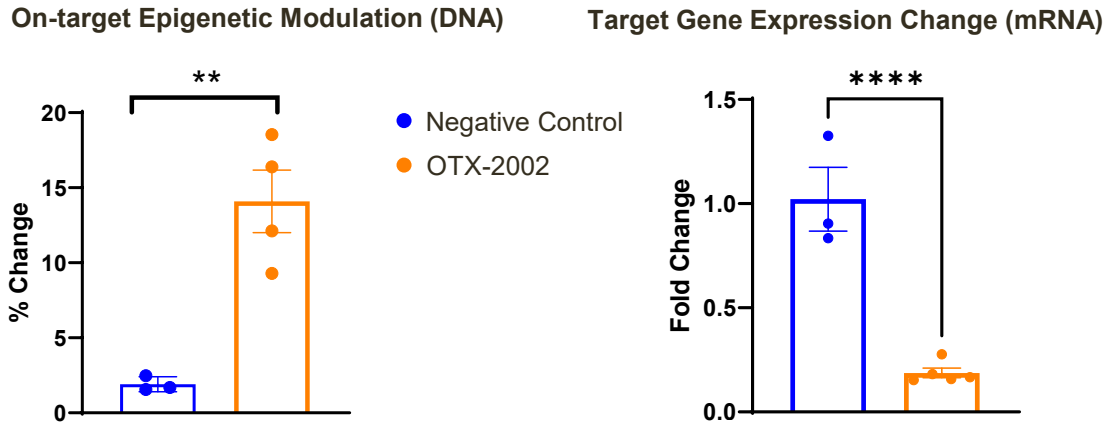
Preclinical Data Confirms Proof-of-Concept Through Epigenetic Modulation of MYC

1 Site-specific target engagement

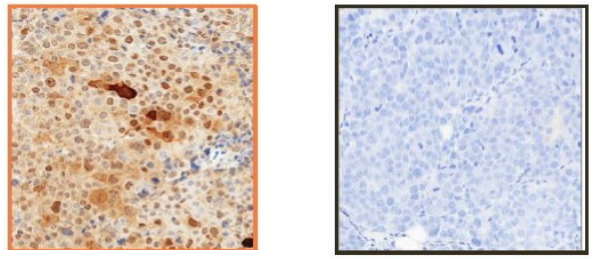
2 Site-specific epigenetic state change (*in vitro*)



3 Site-specific epigenetic change and reduction in mRNA levels (*in vivo*)



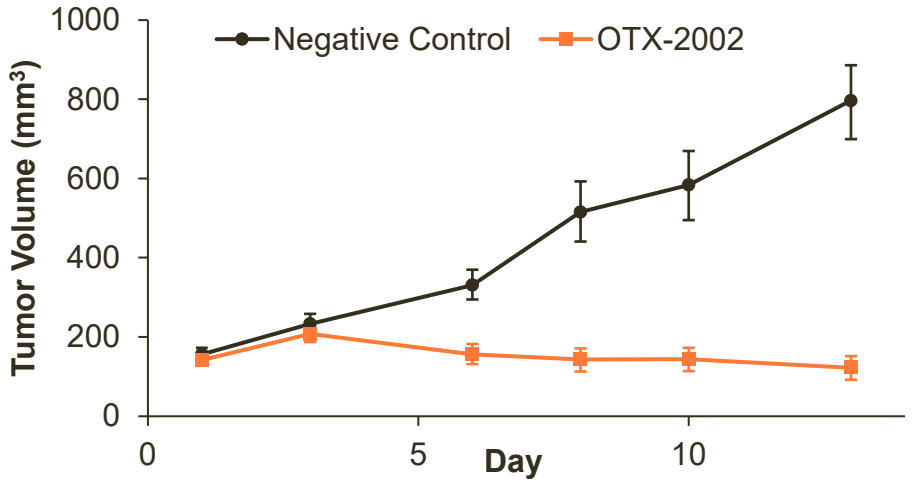
4 Biomarker changes in tissue (*in vivo* change in protein)



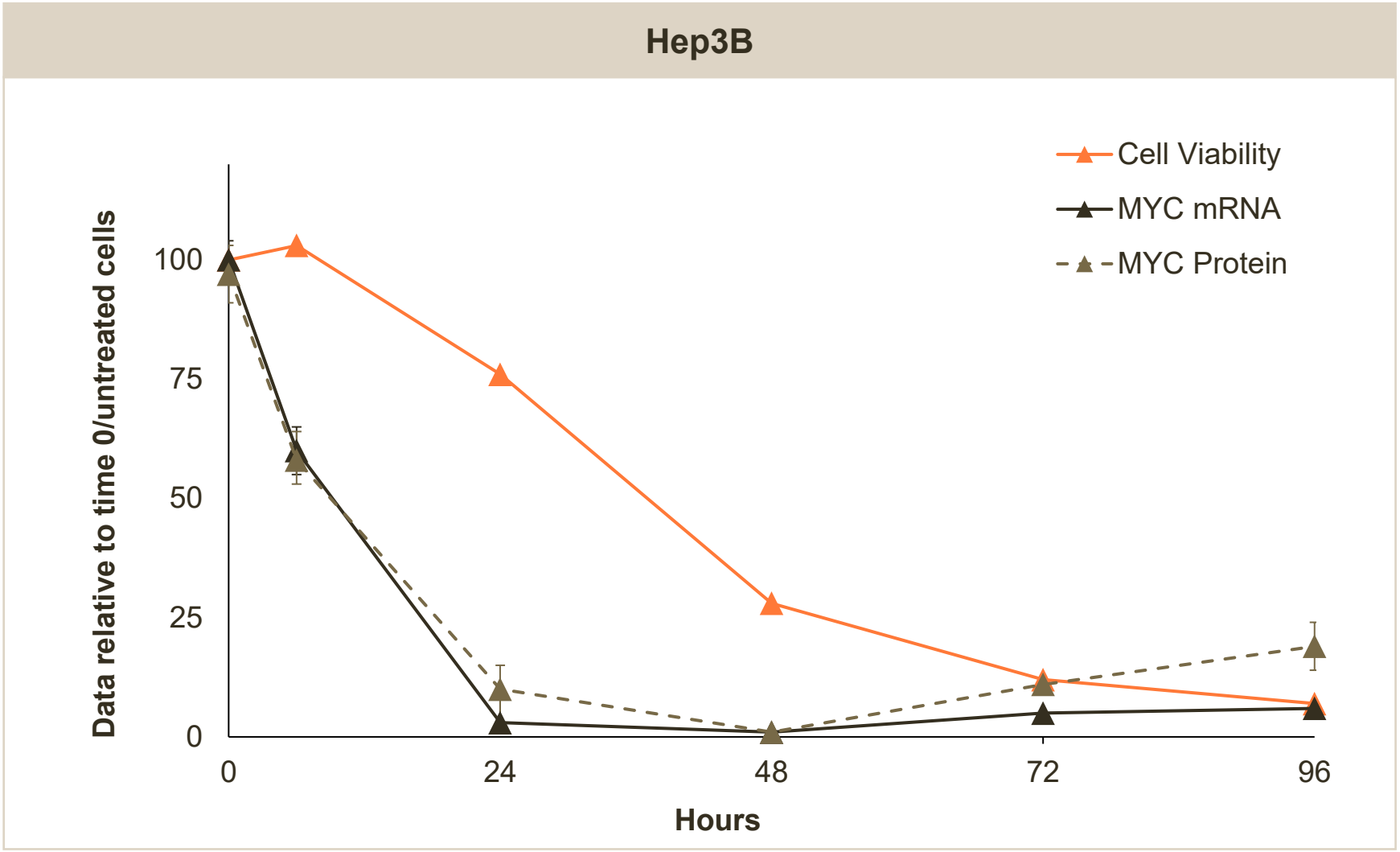
Negative control

OTX-2002 treated

5 *In vivo* efficacy



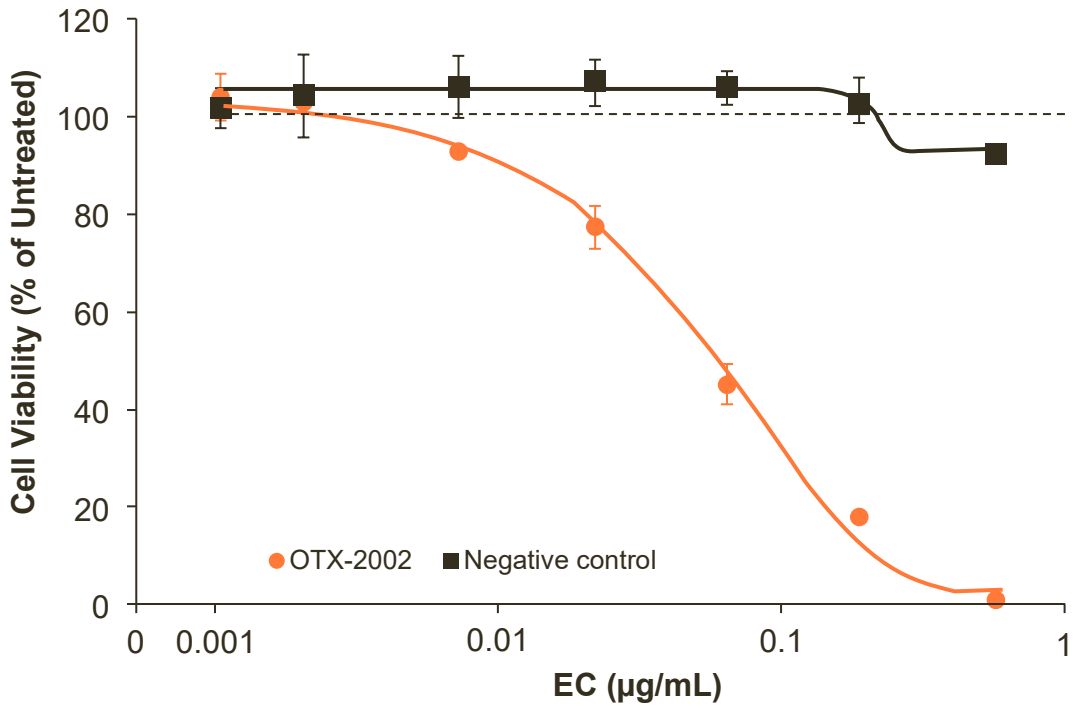
OTX-2002 Results in Rapid and Durable Downregulation of MYC Expression and Reduces Viability of HCC Cancer Cells Preclinically



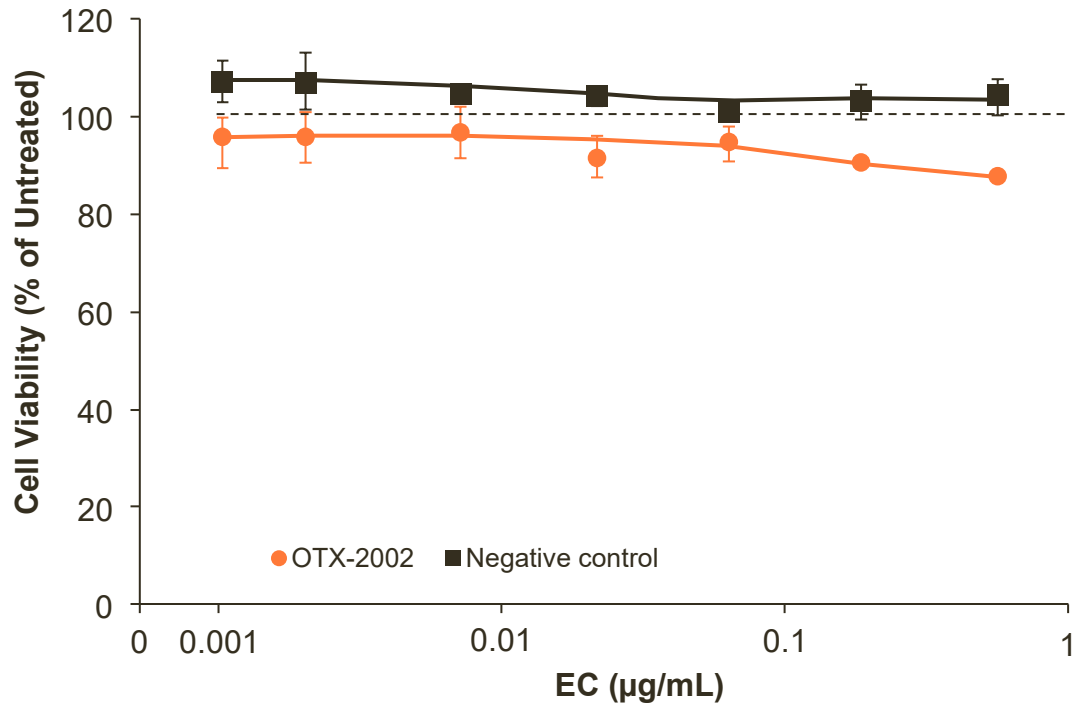
- OTX-2002 is designed to target a specific EpiZip in order to downregulate MYC expression
- Rapid and durable downregulation of MYC mRNA and protein levels demonstrated following treatment with OTX-2002 preclinically
- Lowered MYC protein primes “MYC-addicted” HCC cancer cells to undergo apoptosis

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

Cancer cells



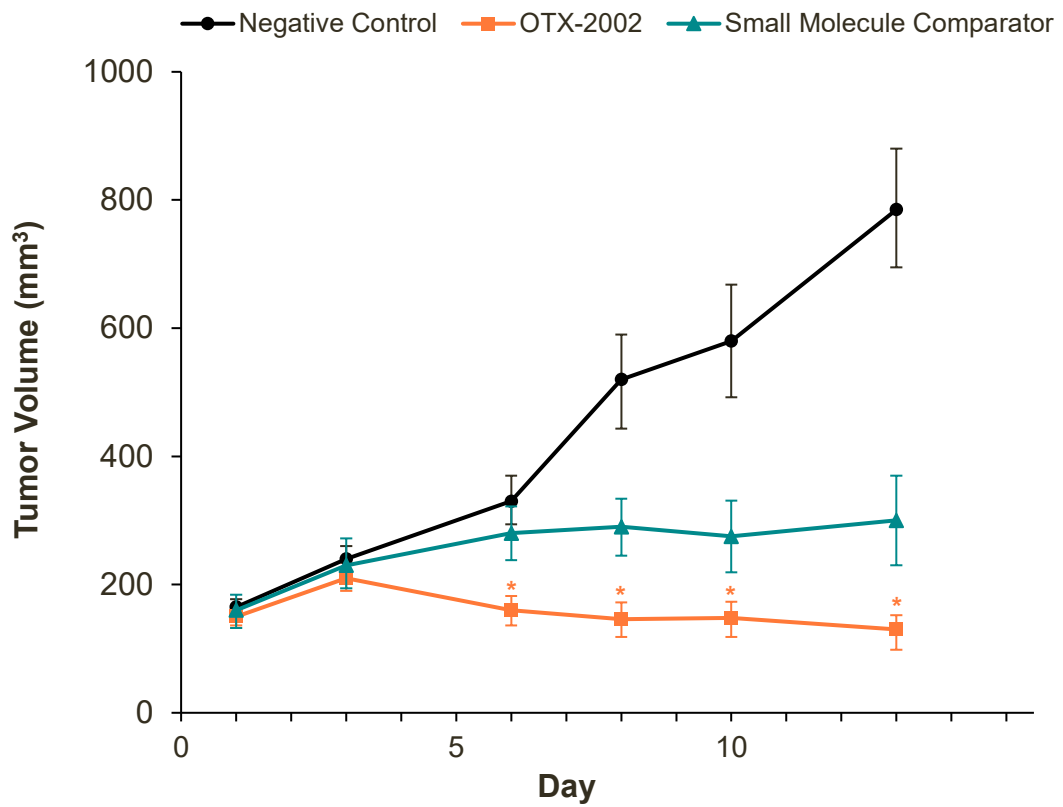
Normal cells



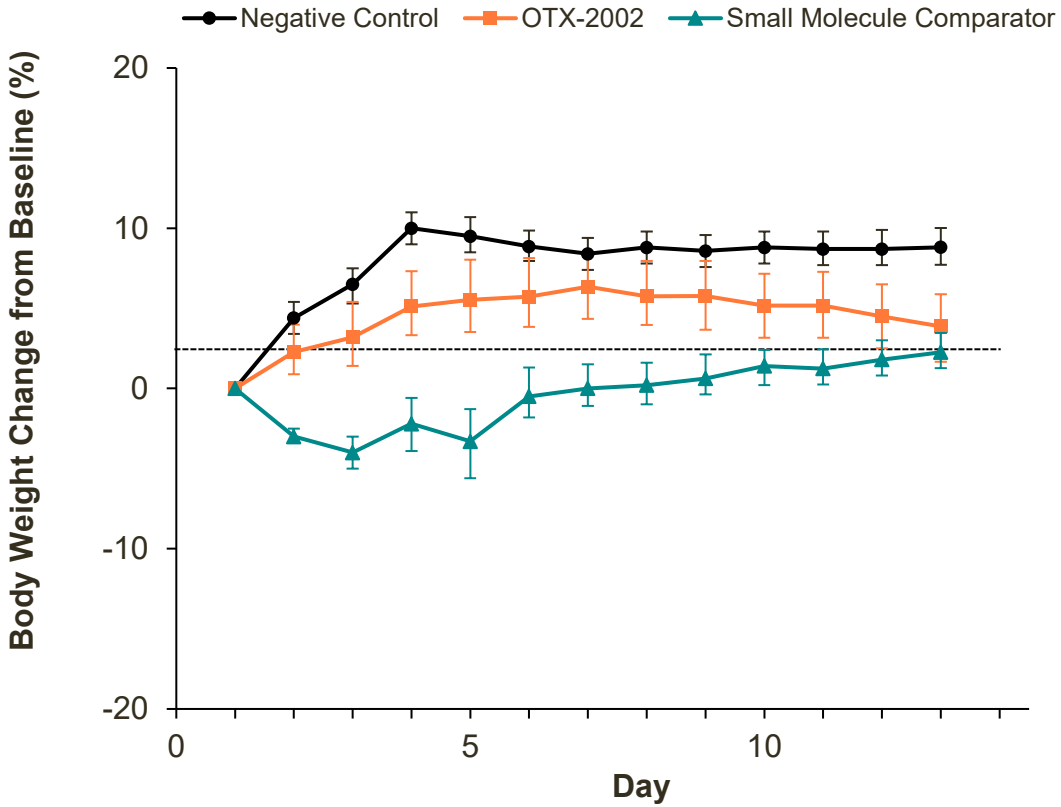
OTX-2002 is designed to controllably tune down MYC expression to levels that lead to cancer cell death while sparing healthy cells and avoiding autoregulation

OTX-2002 Demonstrated Statistically Significant Inhibition of Tumor Growth in Preclinical Models

HCC Subcutaneous Tumor Model (Hep3B)



No Significant Impact on Body Weight in Mice

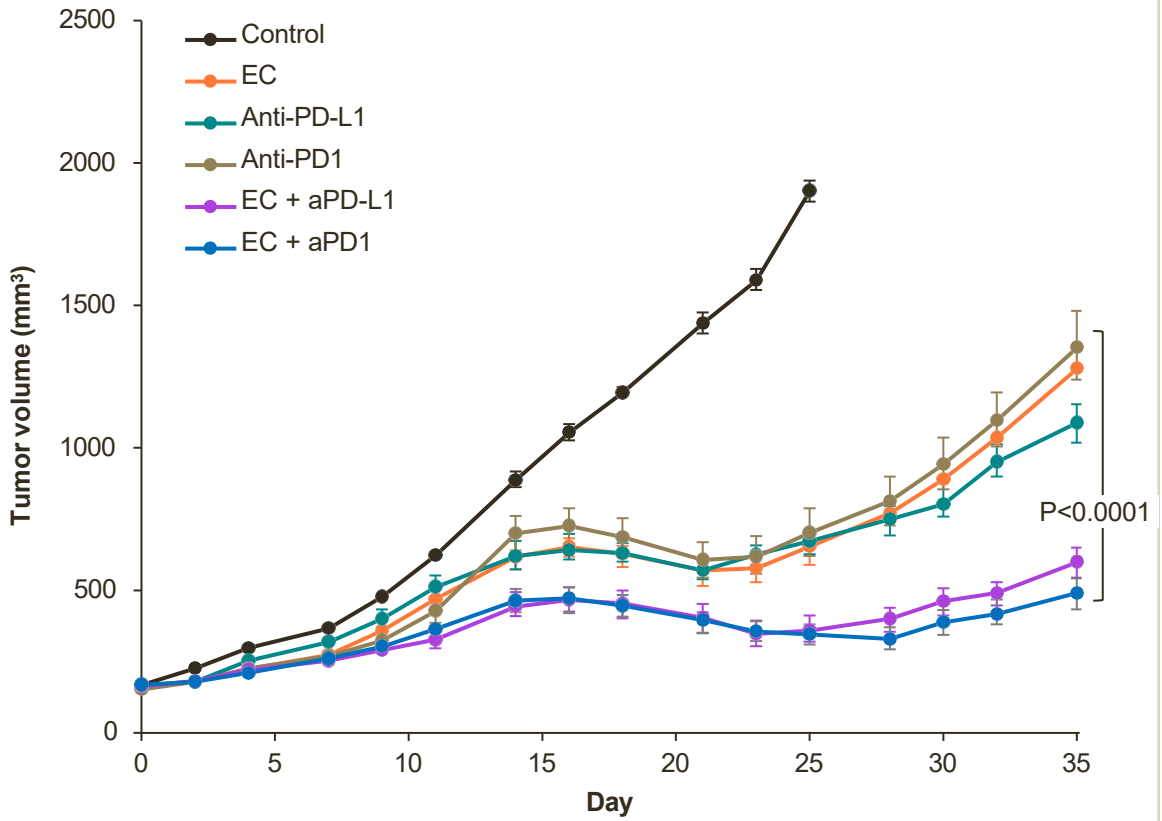


Similar anti-tumor activity and tolerability observed in HCC orthotopic tumor model (Hep3B)

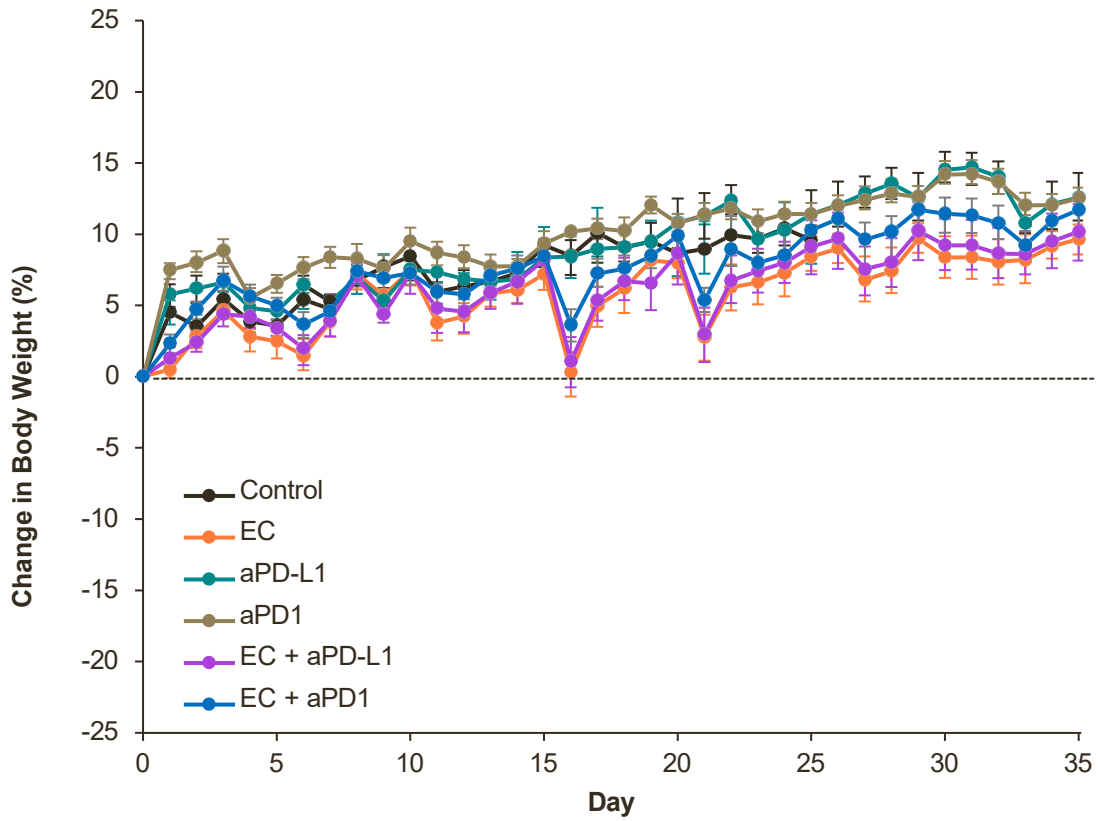
*Statistically significant vs negative control, t-test p<0.05 starting on Day 6. OTX-2002 dosed IV every 5 days

OTX-2002 Demonstrated Combination Benefit with Checkpoint Inhibitors in Preclinical Models

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).

MYCHELANGELO™ I

Preliminary Clinical Data for OTX-2002

Announced September 2023

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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

TBD
Cohort 3
Cohort 2
Cohort 1

3+3 design

- Patients with HCC and other solid tumors known for association with the *MYC* oncogene

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

HCC Expansion

Recommended Dose for Monotherapy Expansion

- Patients with advanced HCC

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

Part 2: Combination

Safety Run-In Phase

OTX-2002 + Standard of Care**

- Patients with advanced HCC

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

Combination HCC Expansion

Recommended Dose for Combination Expansion + Standard of Care**

- Patients with advanced HCC

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)

Encouraging Emerging Safety Profile for OTX-2002*

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 (Oct 2015)	3+
	51 / M / Asian	HCC (Feb 2020)	3+
	70 / M / White	Colorectal Cancer (Sep 2016)	3+
	69 / F / Asian	Sarcoma (Mar 2022)	2
Dose Level 2 0.05 mg/kg	46 / F / Asian	Cervical Cancer (Jan 2014)	2
	68 / M / White	Pancreatic Cancer (Oct 2021)	3+
	56 / M / Asian	HCC (Apr 2020)	3
	66 / M / Asian**	HCC (Aug 2015)	2

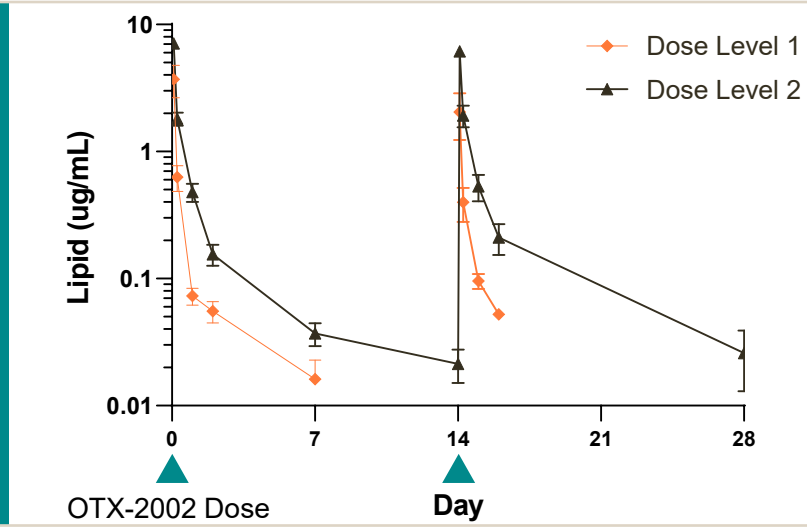
- OTX-2002 was generally well tolerated with no DLTs; MTD not reached
- Majority of AEs were grade 1 or 2 (87%)
- Most common treatment-related AEs were infusion-related reactions (26%); generally consistent with known profile of other FDA-approved LNP-delivered therapeutics
- One grade 4 AST elevation SAE was reported after end of DLT period (Dose Level 2); resolved within 4 days with minimal intervention (supportive care); no clear etiology or causality
- No dose interruption or modification due to treatment-related AEs

Preliminary data from Cohorts 1 and 2. *Data cut-off date of September 18, 2023. **Patient remains on treatment as of data cut-off date.

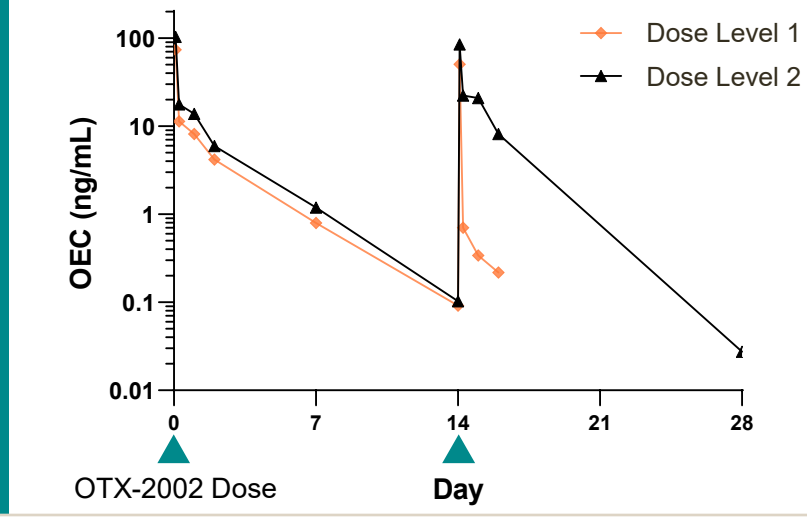
Predictable Pharmacokinetics with Rapid Clearance of Drug Product Observed

Clinical Pharmacokinetics and Lack of Immunogenicity Directly Translate from Preclinical Experience

LNP



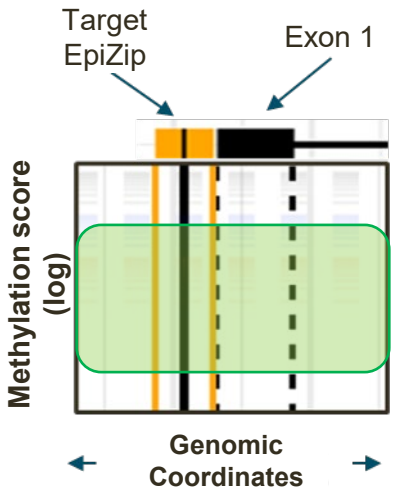
Epigenomic Controller mRNA



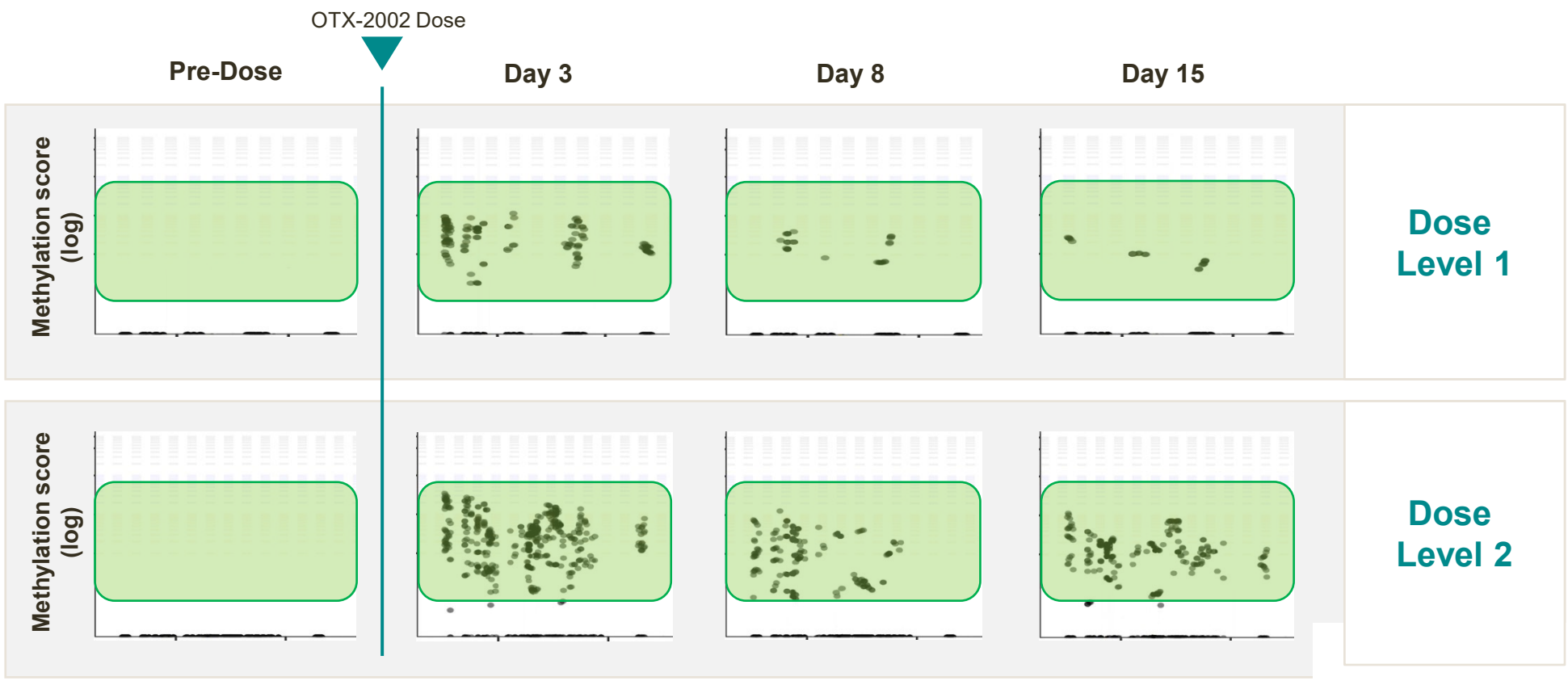
- OTX-2002 was cleared rapidly from systemic circulation
- No accumulation observed with repeat doses
- Low levels of immune response; no related adverse events or impact on PK observed
- PK profile of both LNP and mRNA components of OTX-2002 were consistent overall between patients across both cohorts

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

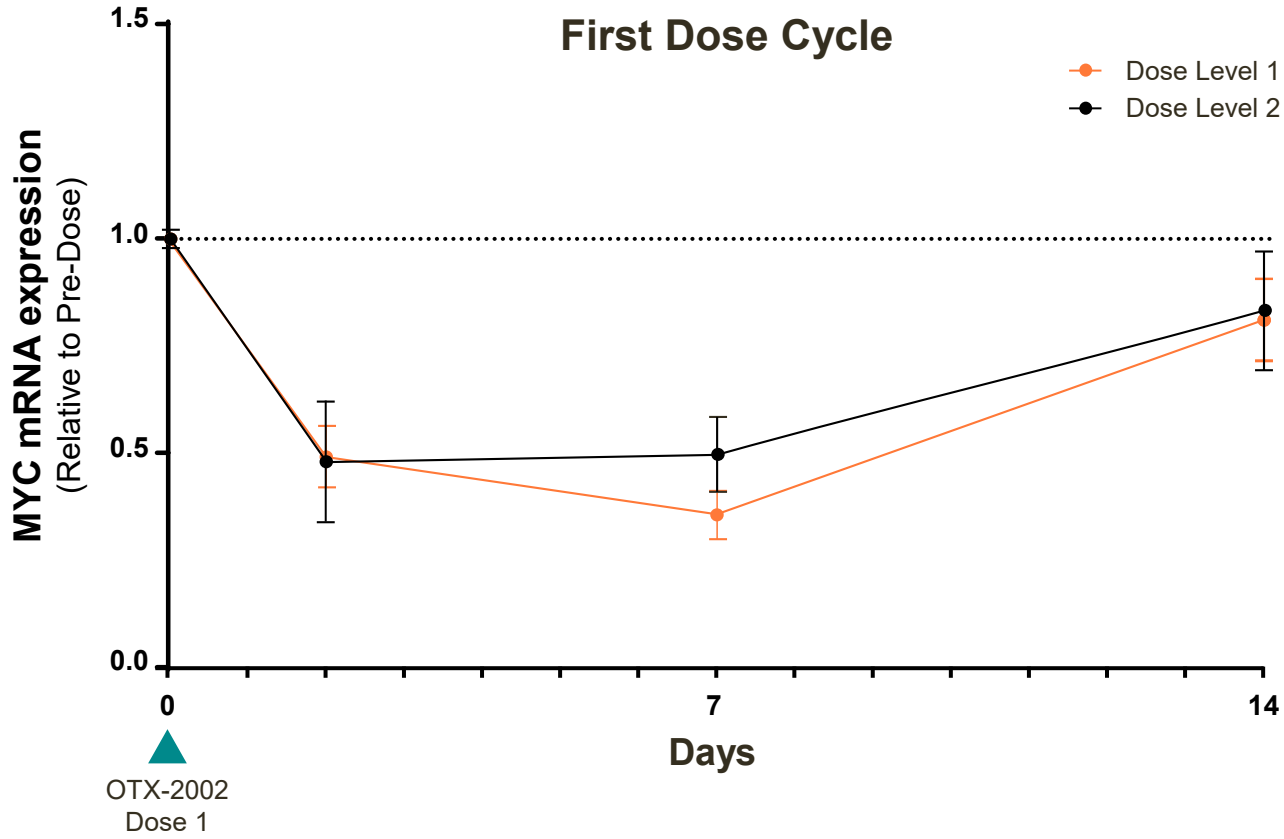


Green shading represents effector target range for methylation (~1-2kb)



*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



- 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)

Preliminary Data Show Promising Potential of OTX-2002 and MYC Modulation

Key Takeaways

- ✓ First known clinical observation of pre-transcriptional control of gene expression using a programmable mRNA development candidate
- ✓ OTX-2002 directly targeted and therapeutically controlled historically 'undruggable' MYC in 8/8 patients
- ✓ Rapid, robust and durable downregulation of MYC expression to levels therapeutically relevant in literature and preclinical settings
- ✓ Encouraging safety, predictable PK and demonstration of intended epigenetic effects support continued development of OTX-2002

Next Steps

- ✓ Continue monotherapy dose escalation
- Provide additional updates on clinical data
- Select recommended dose for expansion
- Initiate monotherapy expansion and combination with standard of care

Preliminary data support overall translation of preclinical experience to clinical performance

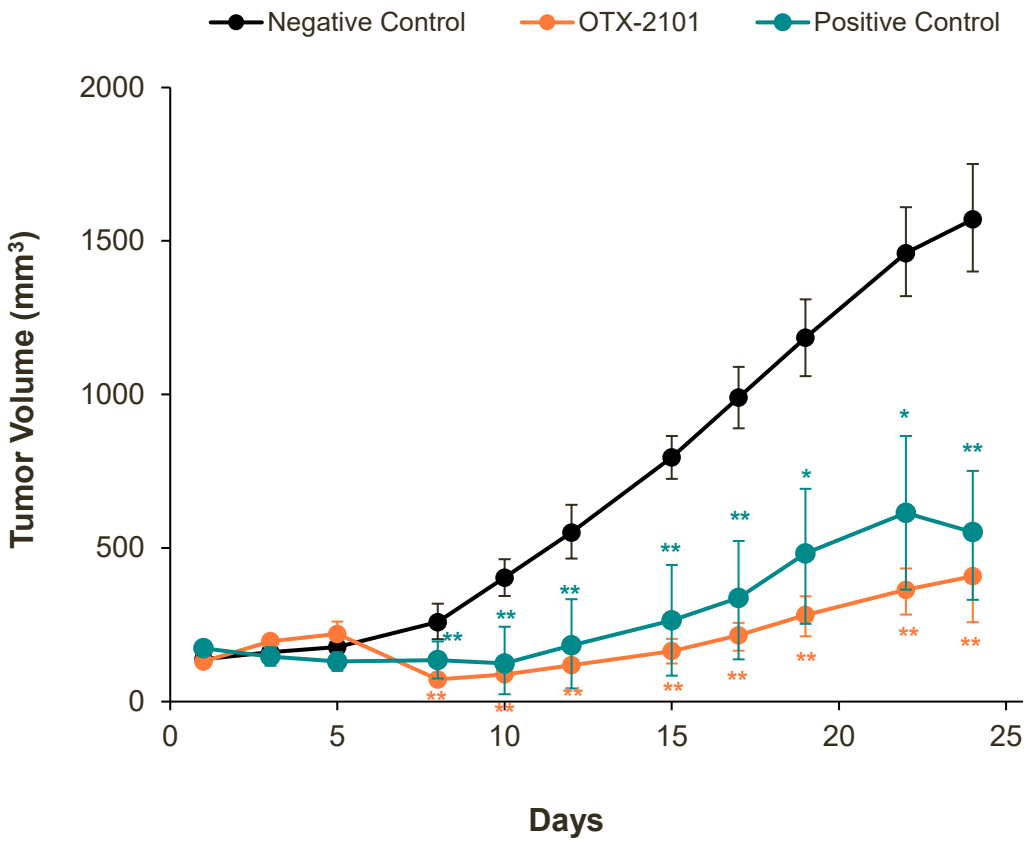
Sample Data from Other Pipeline Programs

OMEGA™ THERAPEUTICS

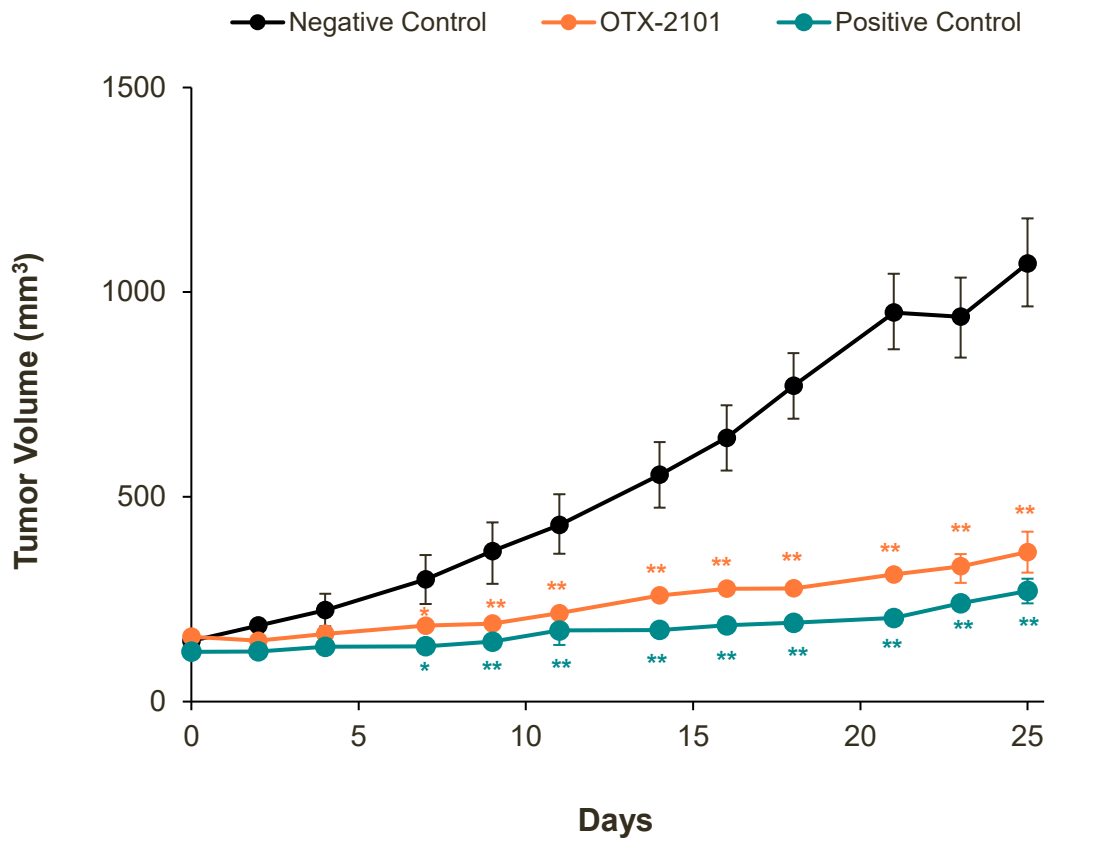
In vivo Proof-of-Concept Data in Oncology Program: MYC-NSCLC

OTX-2101 Led to Statistically Significant Inhibition of Tumor Growth in NSCLC Xenograft Tumor Models

H460



H2009

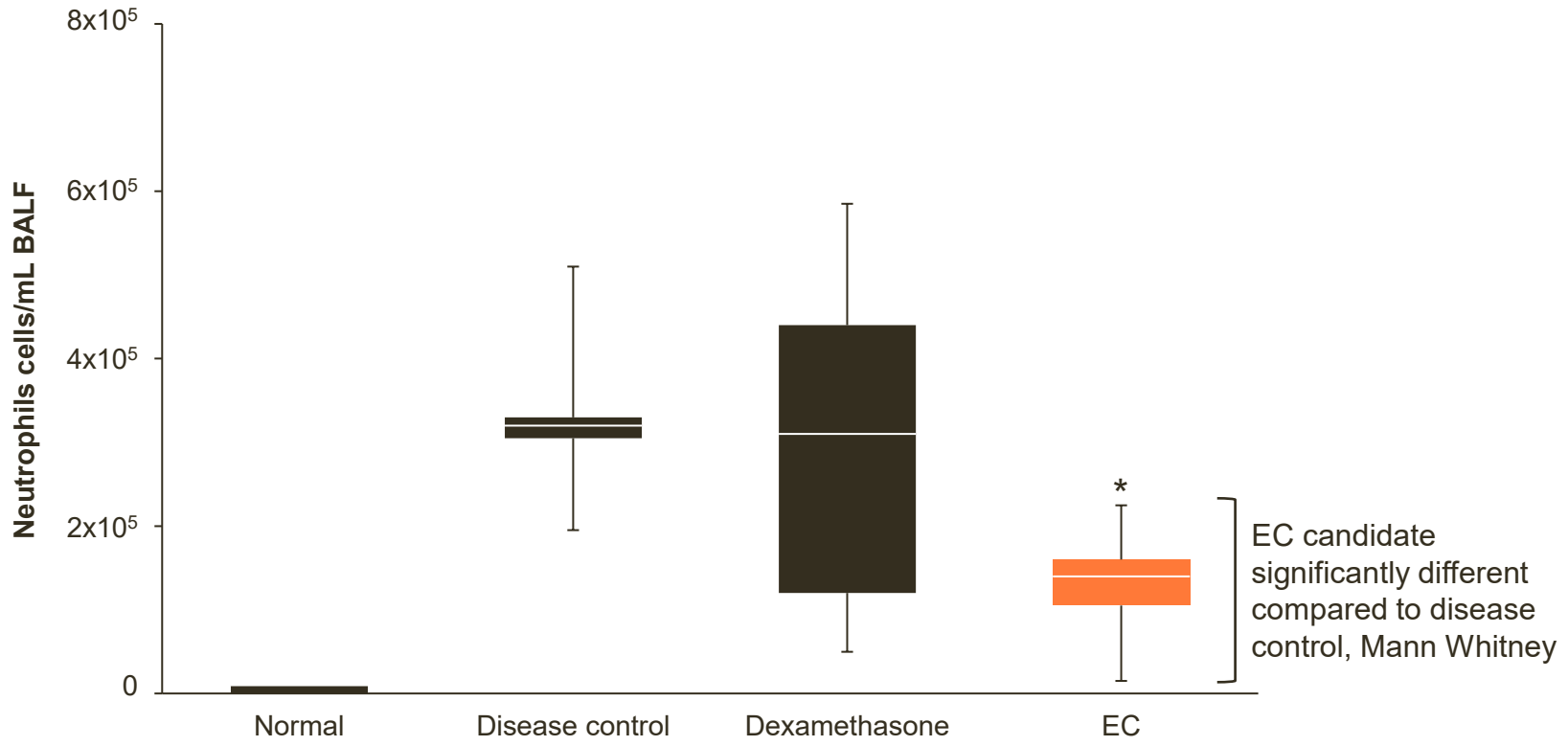


p<0.05; **p<0.01
OTX-2101 dosed every five days

In vivo Proof-of-Concept in Complex Multigenic Disease Program: CXCL-ARDS

Systemic Administration of EC Candidate in Lung-targeting LNP Significantly Decreased Neutrophil Infiltration in Inflamed Lung

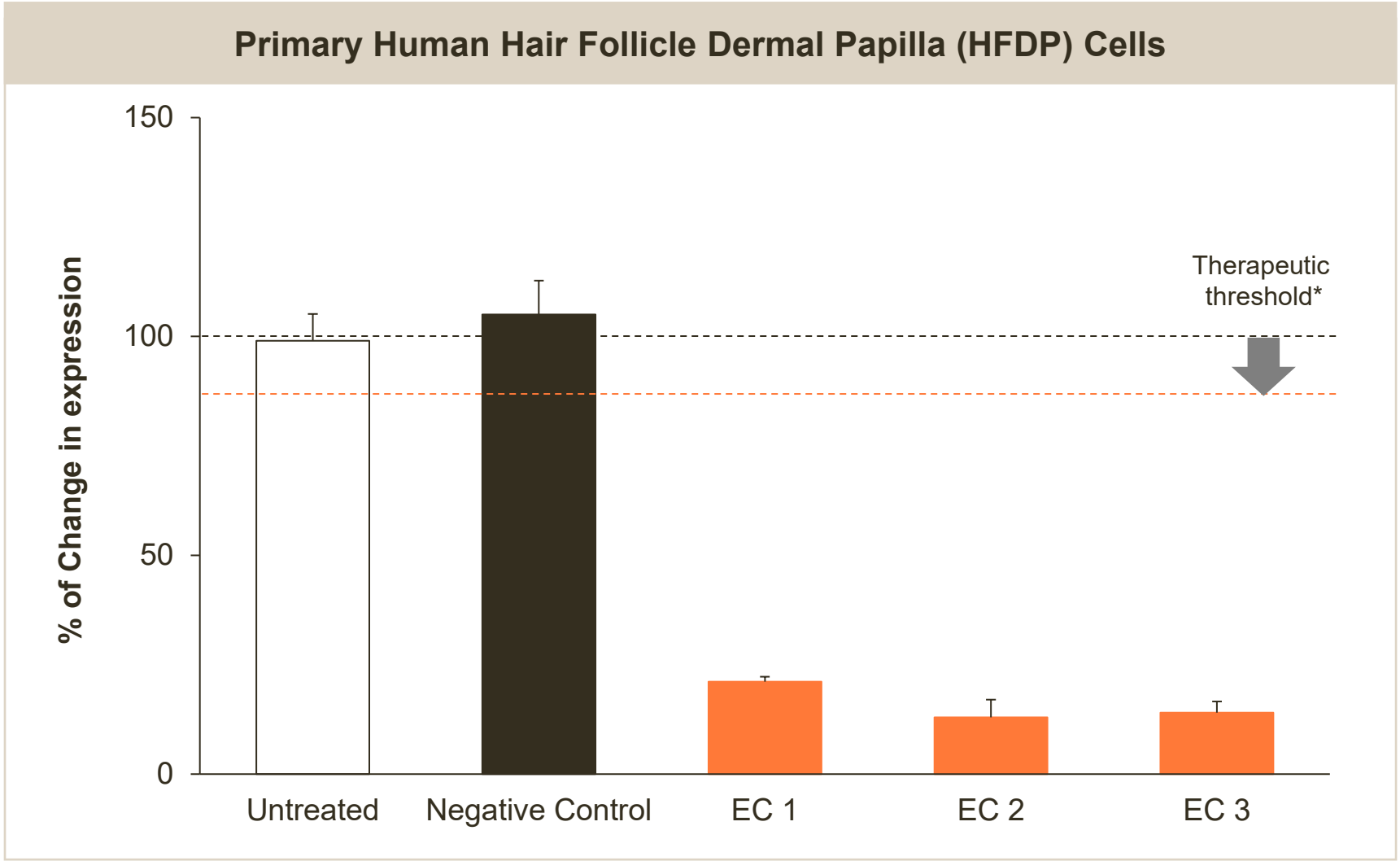
Measurement of Cellular Penetration Into Inflamed Lung



- EC candidate administration prior (-2h) to challenge and at peak of inflammation (8h)
- Significantly decreased neutrophil infiltration in bronchioalveolar lavage (BALF) at 72 hrs

Ex vivo Proof-of-Concept in Monogenic Disease Program: Alopecia

Downregulation of SFRP1 at 7 Days Post-Treatment With EC Candidate



- SFRP1 regulates intrafollicular canonical Wnt/β-catenin activity in the human hair bulb
- Inhibiting SFRP1 activity has the potential to enhance hair shaft production, hair shaft keratin expression

*Hawkshaw et. al. 2018 PLOS Biology 16(5): e2003705.

Corporate Summary

A World-Class Team to Deliver on Our Vision

Leadership

Mahesh Karande
President & CEO

NOVARTIS
MACROLIDE PHARMACEUTICALS
McKinsey & Company

Joshua Reed
CFO

JPMorgan Chase & Co.
aldeyra
Bristol Myers Squibb

Ling Zeng
CLAO

Dicerna
Bosch
NOVARTIS

Thomas McCauley
CSO

Shire
TranslateBIO
RaNA Therapeutics
Archemix

Yan Moore
CMO

SANOFI
IPSEN
GlaxoSmithKline
Bristol Myers Squibb

Siva Sakhamuri
SVP Tech Ops & Quality

Alnylam
ALEXION

Ramola Bhandarkar
SVP Regulatory Affairs

bluebirdbio
immunogen
Cephalon

Board of Directors

Chris Schade
Chairman;
Growth Partner, Flagship

Luke Beshar
NPS Pharma

Rainer Boehm
Novartis

Mahesh Karande
President & CEO

Elliott Levy
Amgen, BMS

John Mendlein
Executive Partner, Flagship

Mary Szela
Trisalus Life Sciences, CEO

Michelle Werner
CEO, Alltrna;
CEO Partner, Flagship

Rick Young
MIT, Professor of Biology;
Whitehead Institute, Member

Founded by Flagship Pioneering

Noubar Afeyan, Co-Founder

David Berry, Co-Founder

Founding Scientific Advisors

MIT & Whitehead Institute

Rudolf Jaenisch | **Richard A. Young**

Omega Therapeutics

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

World-class team focused on operational excellence

- Programmable epigenomic mRNA medicines designed for pre-transcriptional gene modulation to achieve target specificity, controlled tuning, and durability of effect
- Lead program, OTX-2002, in Phase 1/2 MYCHELANGELO™ study for HCC and other solid tumors associated with c-MYC oncogene overexpression; Preliminary data announced in September 2023
- Robust pipeline spanning diverse disease processed and therapeutic areas, including oncology, multigenic diseases, regenerative medicine, and select monogenic diseases
- Platform enables rapid prosecution of new targets and IGD biology driven by data science and advanced computational genomics
- Elite investor syndicate and strong balance sheet*

*Cash, cash equivalents and marketable securities of $113.0 million as of June 30, 2023.

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Thank You

MOA Video

- Click here to view our Mechanism of Action video

Omega's Controlled Epigenomic Modulation Approach Is a Significant Technological Advance

Existing modalities have limitations

- Restricted to druggable target structures or can only address narrow therapeutic areas
- Constraints of direct PK/PD relationship with associated concerns for safety / therapeutic index
- Wide opportunity space in drug development remains

Epigenomic controllers solve multiple challenges in drug development

- Independent of structure, chemistry or location of target
- Address undruggable or inaccessible targets
- Uncoupled PK and PD for potential safety benefit
- Both up or down regulation for therapeutic benefit
- Avoid liabilities of permanent genetic alterations
- Applicable to any human gene or disease process
- Speed to development candidates and INDs