UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of report (Date of earliest event reported): December 31, 2023

Omega Therapeutics, Inc.

(Exact Name of Registrant as specified in its charter)

Delaware	**001-40657**	**81-3247585**
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

140 First Street, Suite 501
Cambridge, Massachusetts 02141
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (617) 949-4360

N/A
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbols	Name of each exchange on which registered
Common Stock, $0.001 par value per share	**OMGA**	**The Nasdaq Global Select Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 1.01. Entry into a Material Definitive Agreement.

On December 31, 2023, Omega Therapeutics, Inc. (the "Company") entered into a Research Collaboration Agreement (the "Agreement") with Novo Nordisk A/S ("Novo Nordisk"), Pioneering Medicines 08, Inc. ("PM SpinCo"), and, with respect to certain provisions set forth in the Agreement, Pioneering Medicines (NN), LLC ("Shareholder") and PM (NN) Explorations, Inc. ("PMCo" and together with PM SpinCo and Shareholder, the "PM Entities"). PM SpinCo, Shareholder and PMCo are entities affiliated with Flagship Pioneering, a significant stockholder of the Company. Christian Schade, Michelle C. Werner, and John Mendlien, Ph.D., JD. are each a member of the Company's Board of Directors and Growth Partner, CEO-Partner, and Executive Partner, respectively, of Flagship Pioneering.

Under the terms of the Agreement, the Company granted to Novo Nordisk an exclusive, royalty-bearing, transferable license, with the right to grant sublicenses through multiple tiers, for certain of the Company's intellectual property to conduct research and development activities under an agreed-upon research and development plan, together with the PM Entities, relating to a product candidate, or program target, for the prevention, treatment or control of a cardiometabolic disease, including diabetes, in humans throughout the world (the "Territory").

In connection with the Agreement, Novo Nordisk will have the right to exercise its irrevocable option to purchase from Shareholder all of the outstanding equity securities of PM SpinCo (the "Option") pursuant to the terms of a separate option agreement (the "Option Agreement") and a separate share purchase agreement (the "Share Purchase Agreement"). Certain provisions in the Agreement are triggered in connection with the exercise of the Option pursuant to the Option Agreement (the "Program Handoff Date") and the closing of the Option pursuant to the Share Purchase Agreement (the "Closing Date"), but the Company is not a party to the Option Agreement or Share Purchase Agreement. Following the Program Handoff Date, subject to certain exceptions set forth in the Agreement, Novo Nordisk will take over responsibilities for development, manufacturing and commercialization of the product candidate in accordance with the terms of the Agreement.

During the term of the Agreement (and for a period of time thereafter if the Agreement is terminated prior to the Closing Date), and subject to certain exceptions set forth in the Agreement, the Company is prohibited from, alone or with any third party, directly or indirectly, exploiting any product that (a) uses the same (i) epigenomic controller included in the licensed product candidate in the Territory or (ii) custom lipid nanoparticle component included in the licensed product candidate in the Territory for the prevention, treatment or control of a cardiometabolic disease (including diabetes) in humans or (b) is directed to (i) with respect to the initial program target, the initial program target or (ii) if a backup target replaces the initial program target, the selected program target for the prevention, treatment or control of a cardiometabolic disease (including diabetes) in humans. The Company is also prohibited from exploiting the program target or any of the potential backup program targets during the period in which Novo Nordisk has a right to replace the initial program target with a backup target for the prevention, treatment or control of a cardiometabolic disease (including diabetes) in humans.

In connection with the execution of the Agreement, Novo Nordisk agreed to make an upfront cash payment of $10 million, up to $522 million in future development and sales milestone payments, and mid and high-single digit to low double digit percentage royalties on net sales of the licensed product. These payments will be shared approximately equally between the Company and Shareholder. Novo Nordisk's obligations to pay royalties with respect to a licensed product and country will expire upon the latest of ten years following first commercial sale of a licensed product in such country, the expiration of the last-to-expire of certain valid patent claims applicable to such licensed product in such country, and the expiration of regulatory exclusivity for such licensed product in such country (the "Royalty Term"), subject to certain royalty reduction and step-down provisions set forth in the Agreement.

Following the Closing Date and upon Novo Nordisk's request, the Company and Novo Nordisk have agreed to negotiate in good faith and on commercially reasonable terms, for Novo Nordisk to buyout its future payment obligations under the Agreement (but neither the Company nor Novo Nordisk is obligated to enter into any such buyout arrangement).

The Agreement includes customary terms and conditions, including mutual representations and warranties and covenants, and indemnification, insurance, intellectual property, dispute resolution and confidentiality and publication provisions. Unless earlier terminated, the Agreement will terminate on a country-by-country and licensed

product-by-licensed product basis upon the expiration of the last Royalty Term in the Territory for such licensed product. Upon expiration of the Royalty Term for a given licensed product in a given country in the Territory, the licenses granted to Novo Nordisk pursuant to the Agreement under the Company's licensed intellectual property survive and become perpetual, irrevocable, fully paid-up and royalty free with respect to such licensed product in such country. Subject to certain limited exceptions, the Agreement will automatically terminate in the event that (a) the Option Agreement expires in accordance with its terms without Novo Nordisk having exercised its option to acquire the outstanding equity interests of PM SpinCo or (b) the Option Agreement and the Share Purchase Agreement otherwise terminate in accordance therewith. Novo Nordisk may also terminate the Agreement in its entirety for convenience upon prior written notice as set forth in the Agreement. Both the Company and Novo Nordisk may terminate the Agreement upon written notice in the event of a material breach by the other party that has not been cured within a specified cure period. Both the Company and Novo Nordisk may also terminate the Agreement upon written notice if the other party undertakes certain bankruptcy, reorganization, liquidation or receivership proceedings or the assignment of a substantial portion of its assets for the benefit of creditors. The Company and PM SpinCo may terminate the Agreement upon certain patent challenges by Novo Nordisk with respect to each such party's intellectual property, subject to certain exceptions and limitations set forth in the Agreement.

Item 7.01. Regulation FD Disclosure.

On January 4, 2024, the Company issued a press release announcing the entry into the Agreement. A copy of the press release is being furnished as Exhibit 99.1 to this Current Report on Form 8-K.

The Company plans to present a corporate update on January 8, 2024 at the 2024 J.P. Morgan Healthcare Conference. A copy of the presentation that will be used is furnished as Exhibit 99.2 to this Current Report on Form 8-K.

The information contained in this Item 7.01 (including Exhibit 99.1 and Exhibit 99.2) shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Press Release, dated January 4, 2024
99.2	Corporate Presentation by Omega Therapeutics, Inc., dated January 2024
104	Cover Page Interactive Data File - the cover page XBRL tags are embedded within the Inline XBRL document.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Omega Therapeutics, Inc.

Date: January 5, 2024

By: /s/ Mahesh Karande

Mahesh Karande

President and Chief Executive Officer

Omega Therapeutics Announces Research Collaboration with Novo Nordisk to Develop a Novel Therapeutic for Obesity Management

- *Collaboration will leverage Omega's proprietary platform to develop an epigenomic controller designed to increase metabolic activity and support obesity management –*

CAMBRIDGE, Mass., January 4, 2023 -- Omega Therapeutics, Inc. (Nasdaq: OMGA) ("Omega"), a clinical-stage biotechnology company pioneering the development of a new class of programmable epigenomic mRNA medicines, today announced a research collaboration with Novo Nordisk, a leading global healthcare company, to develop a novel therapeutic for obesity management. The collaboration will leverage Novo Nordisk's expertise in research and development within cardiometabolic diseases and Omega's proprietary platform technology to develop an epigenomic controller designed to enhance metabolic activity as a part of a potential new treatment approach for obesity management.

"By harnessing the body's innate mechanisms to control cellular identity and gene expression, we believe that our epigenomic controllers offer an opportunity to therapeutically modulate genes linked to metabolism in a precise way," said Mahesh Karande, President and Chief Executive Officer of Omega Therapeutics. "We look forward to leveraging our OMEGA platform and pursuing this ambitious strategy with Novo Nordisk to advance transformative developments for people living with obesity."

Uli Stilz, Head of Novo Nordisk's Bio Innovation Hub, added, "As the population of people living with obesity grows, it is vitally important that we seek out next generation therapeutic solutions to address the unmet need. Much of the scientific advancement in this area has been focused on appetite regulation, but by looking at new ways to increase energy expenditure, including through controlled epigenomic modulation, there is an opportunity to unlock a new path for intervention. We look forward to working together with Omega and leveraging our complementary capabilities to advance much needed new treatments."

Globally, there are more than 800 million adults living with obesity[1]. Many of the existing therapeutic interventions for weight management have focused on appetite regulation. Thermogenesis, the production of heat within tissues to raise body temperature, is a natural metabolic function that critically regulates overall energy balance. By seeking to harness this naturally occurring metabolic function, Omega's proprietary platform has the potential to create an epigenomic controller that can intervene in a unique way to possibly affect energy expenditure. This may ultimately lead to an alternative, and potentially more durable, approach to weight management.

This agreement was signed under the existing framework collaboration between Flagship Pioneering and Novo Nordisk to develop a portfolio of transformational medicines. Omega, Flagship's Pioneering Medicines initiative, and Novo Nordisk will jointly advance this obesity management program through preclinical development and conduct foundational activities, after which point Novo Nordisk could further advance the program including through human proof-of-concept studies.

Under the terms of the agreement, Novo Nordisk will reimburse R&D costs and has the right to select one target to advance for clinical development. Omega and Pioneering Medicines are

[1] World_Obesity_Atlas_2023_Report.pdf (worldobesityday.org)

eligible to receive up to $532 million in upfront, development and commercial milestone payments, as well as tiered royalties on annual net sales of a licensed product.

About Omega Therapeutics

Omega Therapeutics is a clinical-stage biotechnology company pioneering the development of a new class of programmable epigenomic mRNA medicines to treat or cure a broad range of diseases. By pre-transcriptionally modulating gene expression, Omega's approach enables precision epigenomic control of nearly all human genes, including historically undruggable and difficult-to-treat targets, without altering native nucleic acid sequences. Founded in 2017 by Flagship Pioneering following breakthrough research by world-renowned experts in the field of epigenetics, Omega is led by a seasoned and accomplished leadership team with a track record of innovation and operational excellence. The Company is committed to revolutionizing genomic medicine and has a diverse pipeline of therapeutic candidates derived from its OMEGA platform spanning oncology, regenerative medicine, multigenic diseases including immunology, and select monogenic diseases.

For more information, visit omegatherapeutics.com, or follow us on X and LinkedIn.

About the OMEGA Platform

The OMEGA platform leverages the Company's deep understanding of gene regulation, genomic architecture and epigenetic mechanisms to design programmable epigenomic mRNA medicines that precisely target and modulate gene expression at the pre-transcriptional level. Combining a biology-first approach and world-class data science capabilities with rational drug design and customized delivery, the OMEGA platform enables control of fundamental epigenetic processes to correct the root cause of disease by returning aberrant gene expression to a normal range. Omega's modular and programmable mRNA medicines, called epigenomic controllers, target specific genomic loci within insulated genomic domains with high specificity to durably tune single or multiple genes to treat and cure diseases through unprecedented precision epigenomic control.

Omega Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding the research collaboration with Novo Nordisk and the development of a programmable epigenomic mRNA candidate designed to increase metabolic activity and support weight management; the potential of the OMEGA platform to engineer programmable epigenomic mRNA therapeutics that successfully regulate gene expression by targeting insulated genomic domains; and expectations surrounding the potential of our product 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; 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; 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 epigenomic controller 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 Quarterly Report on Form 10-Q for the quarter ended September 30, 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 press release. Any such forward-looking statements represent management’s estimates as of the date of this press release. 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.

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OMEGA™ THERAPEUTICS

Transforming Medicine Through Precision Epigenomic Control

Programmable mRNA Therapeutics

January 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, 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

CLINICAL PROOF-OF-PLATFORM ESTABLISHED

Preliminary data for lead program in HCC showed site-specific and controlled epigenomic modulation of c-MYC oncogene in 8/8 patients*

UNLOCKING HIGH-VALUE TARGETS

Pre-transcriptional gene expression modulation offers potential to treat historically 'undruggable' targets

BROAD APPLICABILITY TO ALL GENES

Diverse pipeline spanning oncology, regenerative medicine, cardio-metabolic, inflammation/immunology, monogenic and other multigenic diseases

WORLD-CLASS LEADERSHIP

Deeply experienced team focused on operational excellence

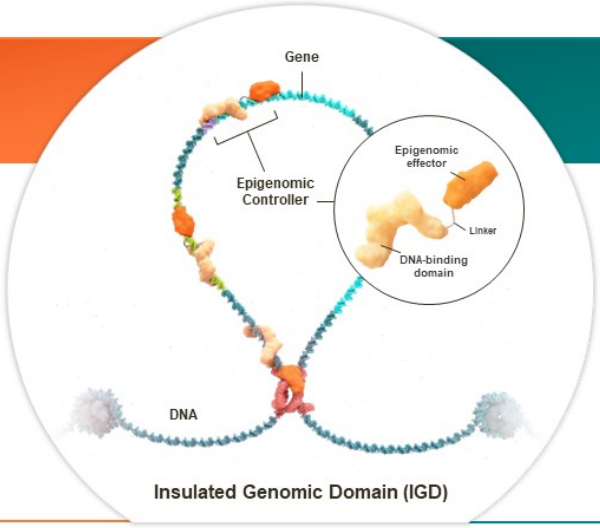
Delivering on the Promise of Epigenetics

*Preliminary data from first two cohorts of ongoing MYCHELANGELO™ I trial announced Sept. 26, 2023.

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

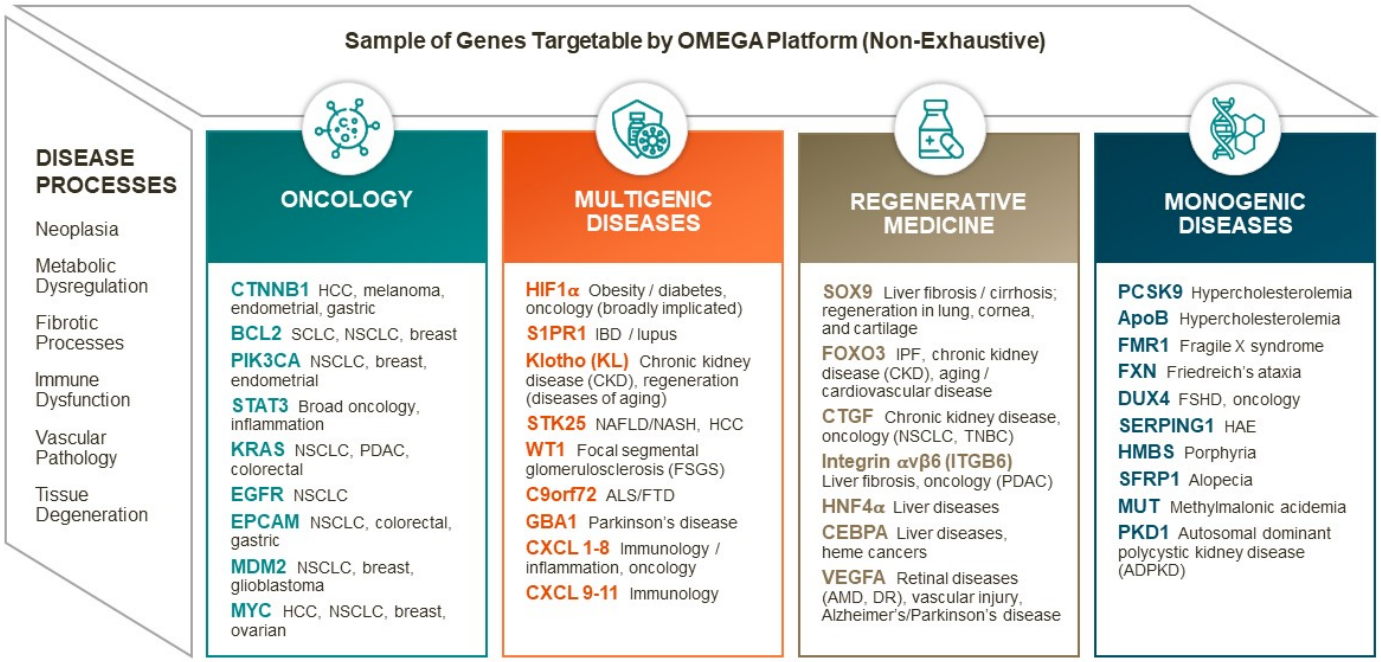
- Restricted to druggable target structures
- Can only address narrow therapeutic areas
- Constrained to direct PK/PD relationship with associated concerns for safety / therapeutic index

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



Preclinical Proof-of-Concept Established 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*				
	Undisclosed	Multiple					
Multigenic Diseases	**CXCL 1-8**	Inflammation / immunology					
	Undisclosed	Idiopathic pulmonary fibrosis					
	Undisclosed	Obesity					novo nordisk®
Regenerative Medicine	**HNF4A**	Liver regeneration					
	Undisclosed	Multiple					
Monogenic Diseases	**SFRP1**	Alopecia					

Additional gene targets across multiple disease processes screened and characterized; Ready to enter early development

Lead Program Overview

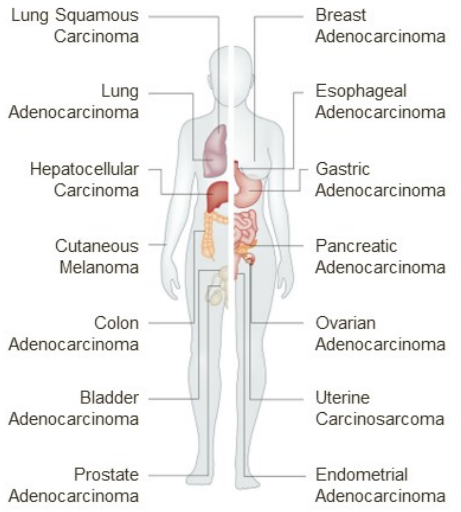
OTX-2002 for MYC-HCC

OMEGA™ THERAPEUTICS

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



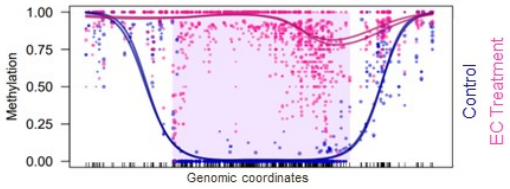
Reference: Dhanasekaran R, et al. *Nat Rev Clin Oncol*. 2022 Jan;19(1):23-36.

OTX-2002 Mechanism of Action

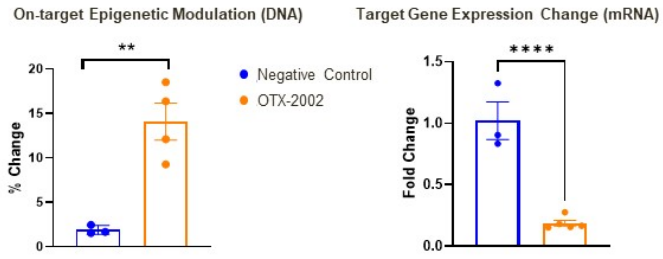
Preclinical Data Confirms Proof-of-Concept Through Epigenetic Modulation of MYC

1 Site-specific target engagement

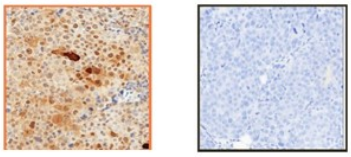
2 Site-specific epigenetic state change (*in vitro*)



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

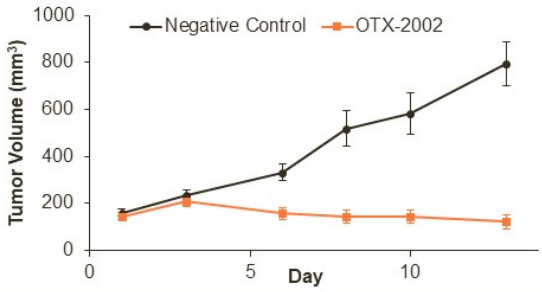


4 Biomarker changes in tissue (*in vivo* change in protein)

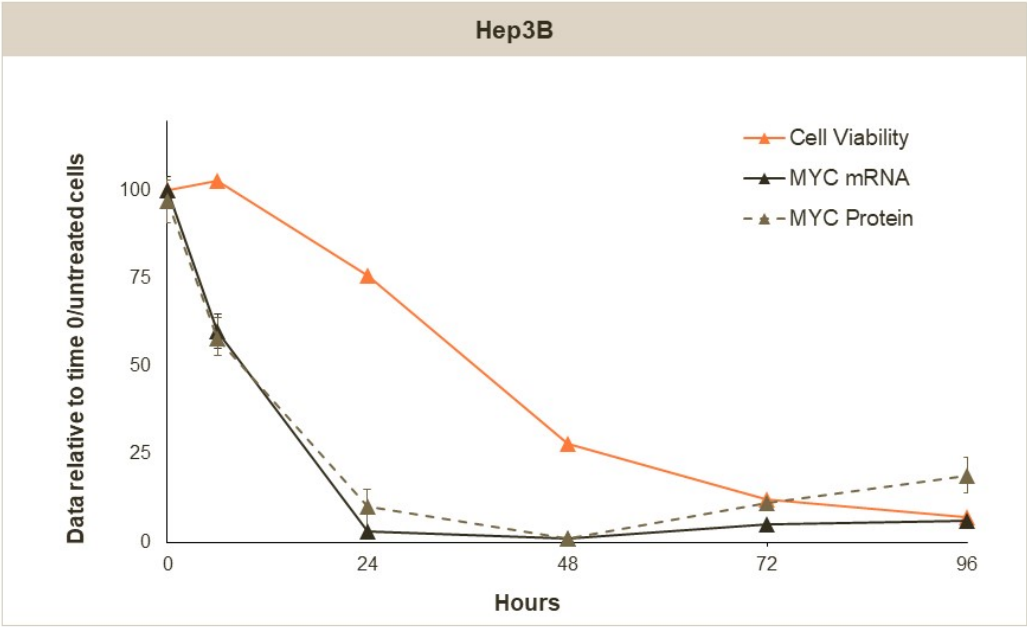


Negative control OTX-2002 treated

5 *In vivo* efficacy



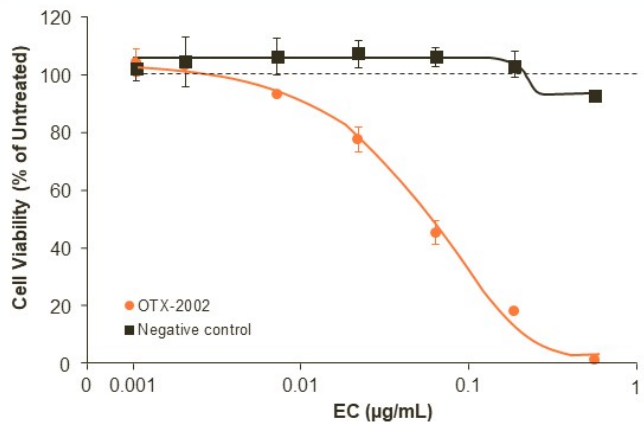
OTX-2002 Results in Rapid and Durable Downregulation of MYC Expression and Reduces Viability of HCC Cancer Cells Preclinically



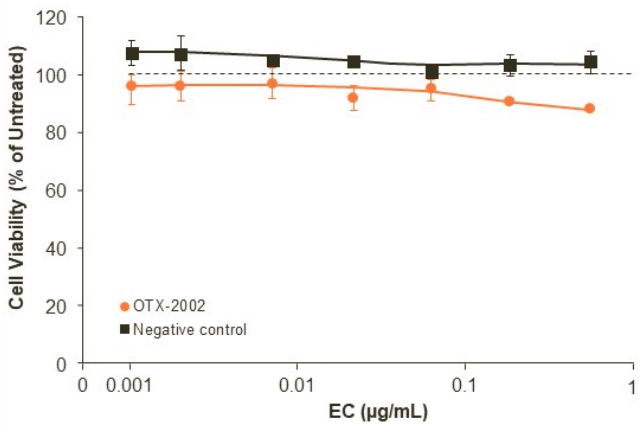
- OTX-2002 is designed to target a specific EpiZip in order to downregulate MYC expression
- Rapid and durable downregulation of MYC mRNA and protein levels demonstrated following treatment with OTX-2002 preclinically
- Lowered MYC protein primes "MYC-addicted" HCC cancer cells to undergo apoptosis

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

Cancer cells



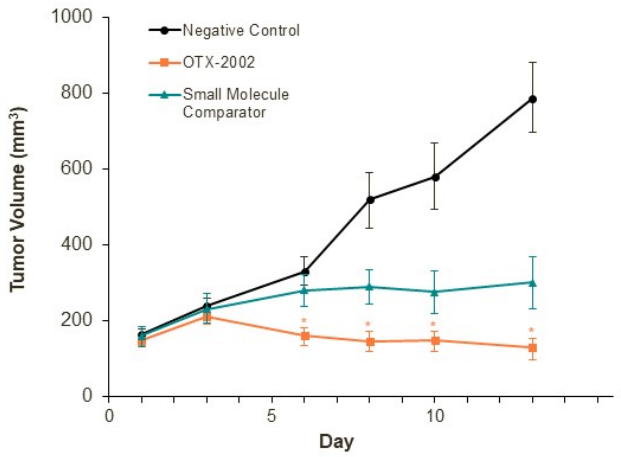
Normal cells



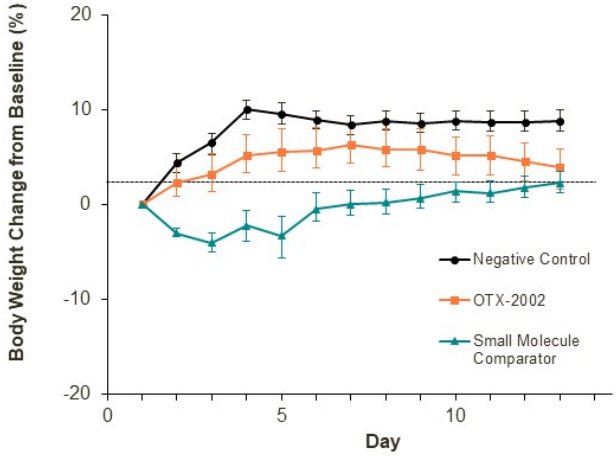
OTX-2002 is designed to controllably tune down MYC expression to levels that lead to cancer cell death while sparing healthy cells and avoiding autoregulation

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

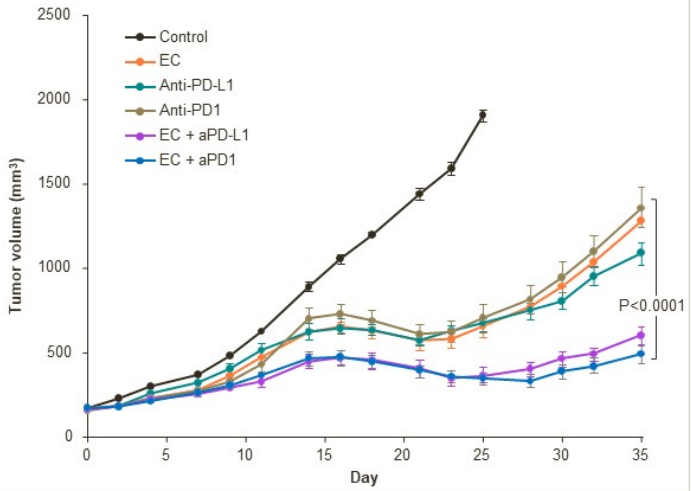


Similar anti-tumor activity and tolerability observed in HCC orthotopic tumor model (Hep3B)

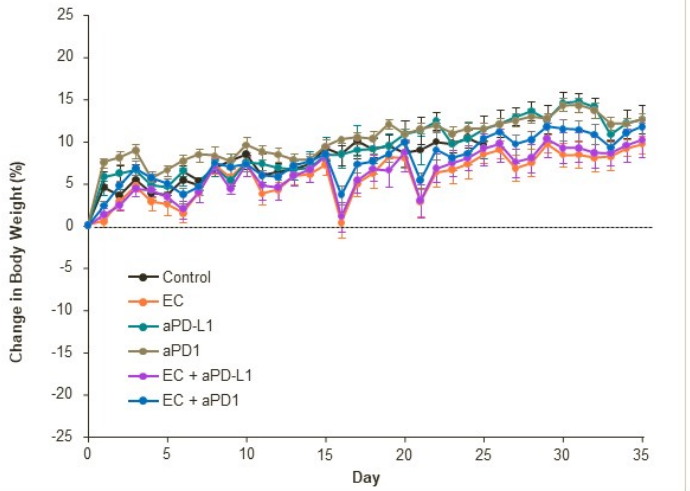
*Statistically significant vs negative control, t-test p<0.05 starting on Day 6. OTX-2002 dosed IV every 5 days

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

HCC Tumor Model (Hepa1-6)



No Significant Impact on Body Weight in Mice



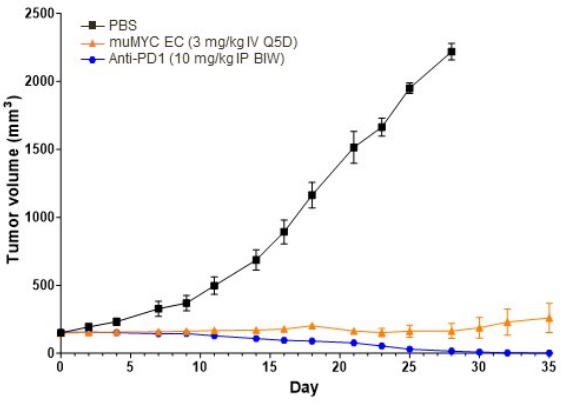
Statistically significant combination benefit in immune competent mice with *a*PD1 or *a*PD-L1

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).

MYC-Targeting EC Conferred Long-Term, Tumor-Specific Immune Memory as Monotherapy and in Combination with Anti-PD1 in Preclinical Models

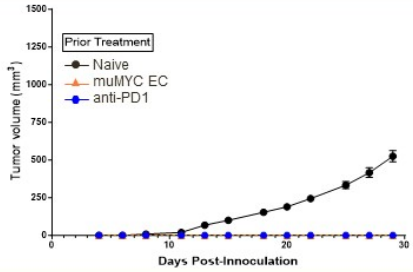
Immunocompetent HCC Subcutaneous Tumor Model (Hepa 1-6)



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

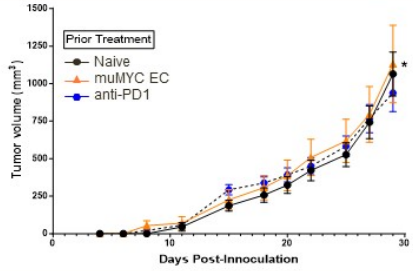
Tumor-free mice rechallenged ~70 days after last dose

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.

MYCHELANGELO™ I

Preliminary Clinical Data for OTX-2002

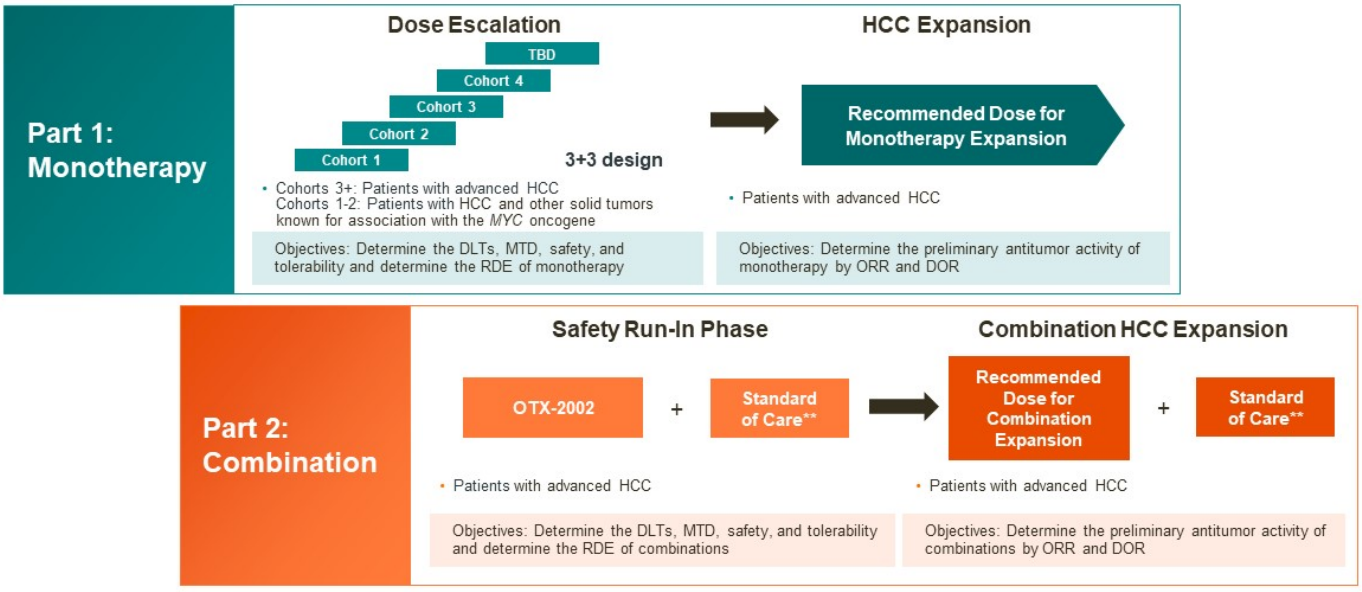
Announced September 2023

OMEGA™ THERAPEUTICS

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



* 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 From First Two 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 (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

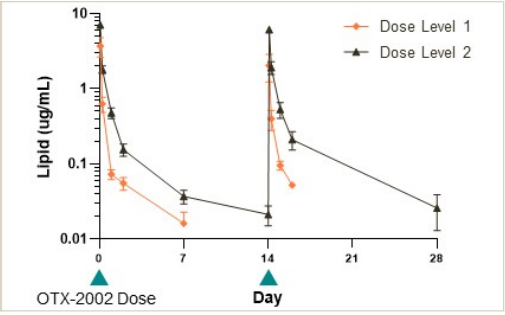
- OTX-2002 was generally well tolerated with no DLTs; MTD not reached
- Majority of AEs were grade 1 or 2 (87%)
- Most common treatment-related AEs were infusion-related reactions (26%); generally consistent with known profile of other FDA-approved LNP-delivered therapeutics
- One grade 4 AST elevation 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

*Data cut-off date of September 18, 2023. **Patient remains on treatment as of January 2, 2024.

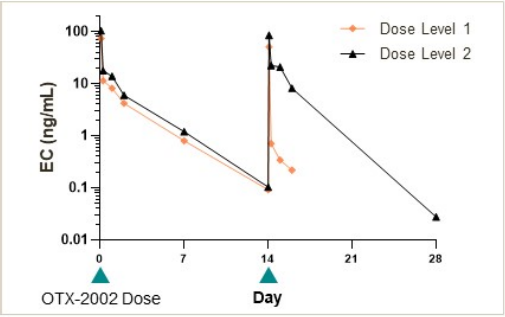
Predictable Pharmacokinetics with Rapid Clearance of Drug Product Observed

Clinical Pharmacokinetics and Lack of Immunogenicity Directly Translate from Preclinical Experience

LNP



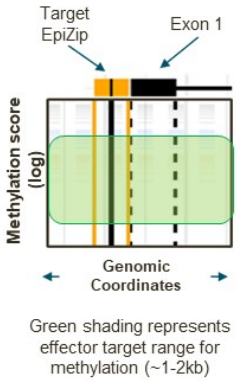
Epigenomic Controller mRNA



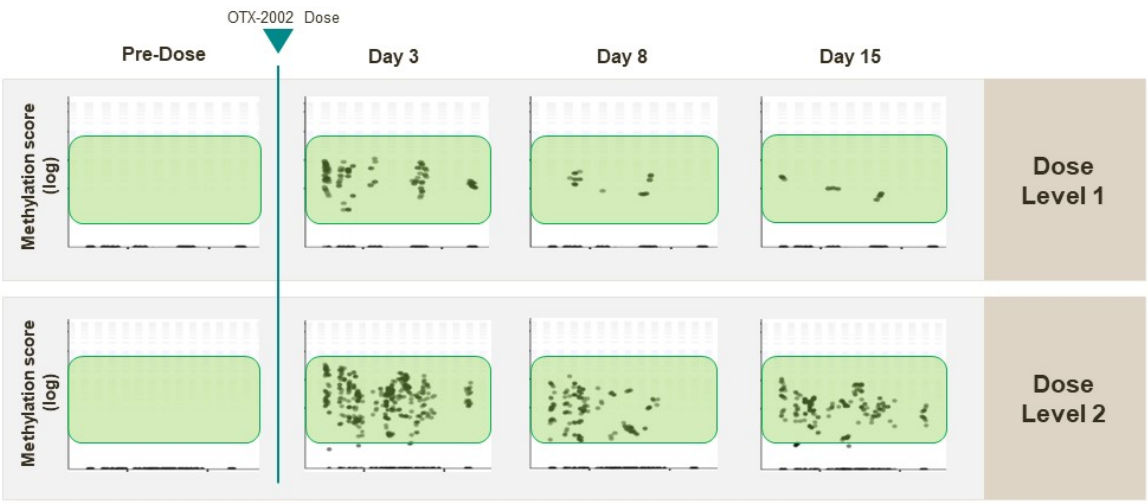
- OTX-2002 was cleared rapidly from systemic circulation
- No accumulation observed with repeat doses
- Low levels of immune response; no related adverse events or impact on PK observed
- PK profile of both LNP and mRNA components of OTX-2002 were consistent overall between patients across both cohorts

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



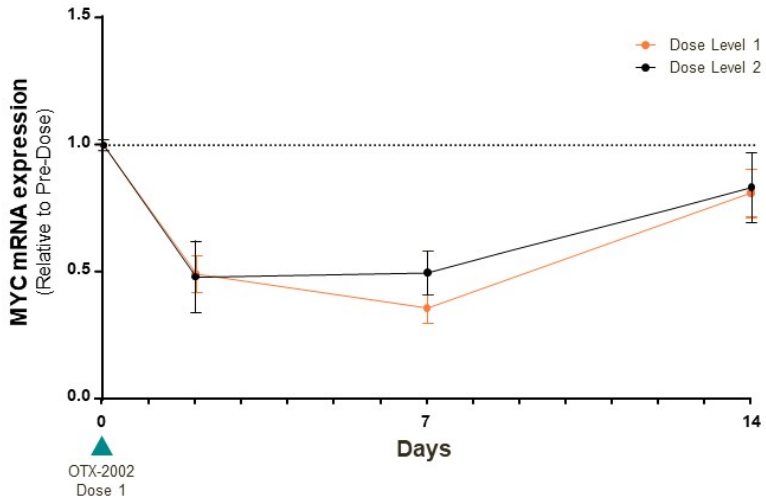
Green shading represents effector target range for methylation (~1-2kb)



*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

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)

Clinical Data Show Promising Potential of Controlled Epigenomic Modulation

8/8 Patients Treated with OTX-2002 in Dose Levels 1 & 2 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

Building Value Through the OMEGA Platform

Sample Data from Other Pipeline Programs

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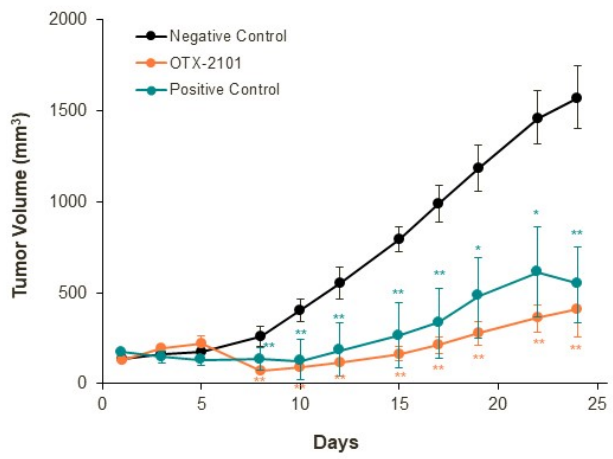
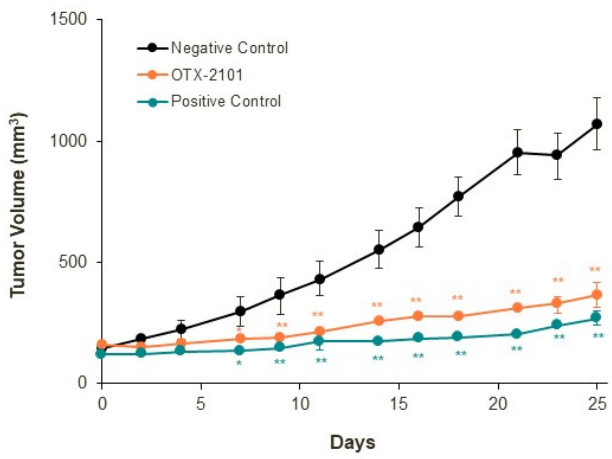
In vivo Proof-of-Concept Data in Oncology Program: MYC-NSCLC

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

H460



H2009

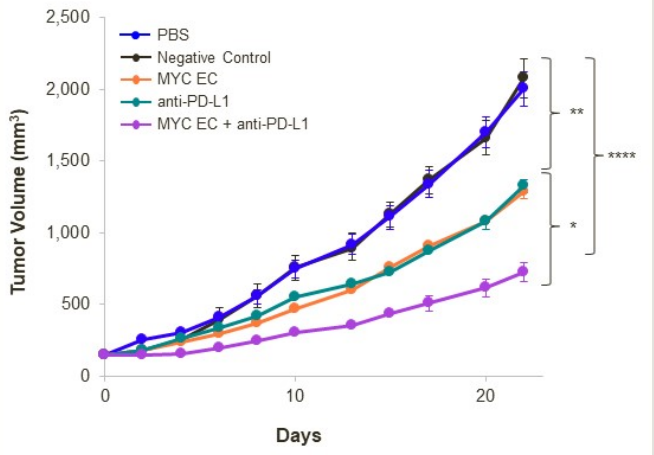


*p<0.05; **p<0.01
OTX-2101 dosed every five days

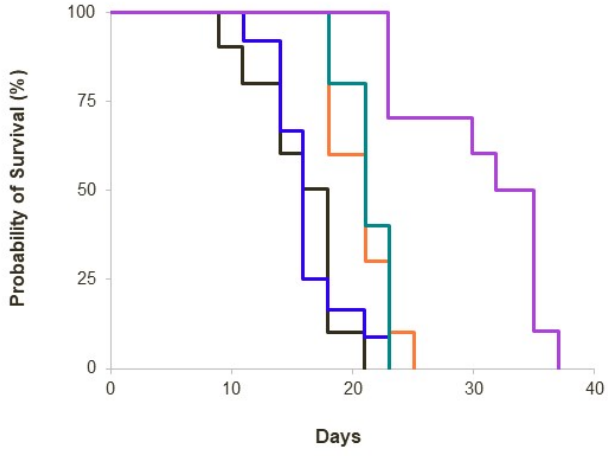
Source: Data presented at ASGCT 2023.

Combination of MYC-Targeting EC with Immune Checkpoint Significantly Enhanced Anti-Tumor Activity in Syngeneic Mouse Model of NSCLC

Lewis Lung Carcinoma Subcutaneous Tumor Model



Survival

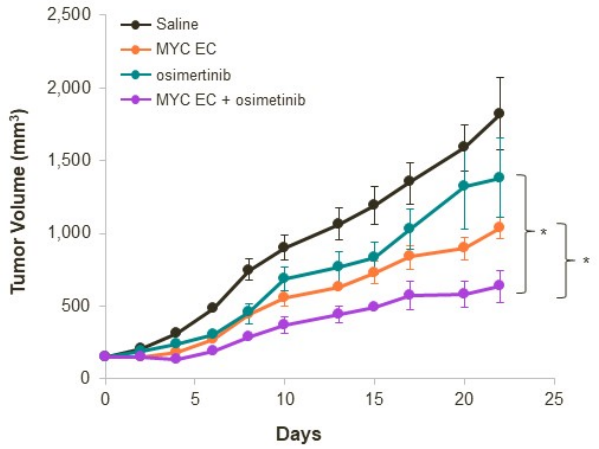


*p<0.05, **p<0.01, ****p<0.0001
MYC EC dosed every five days

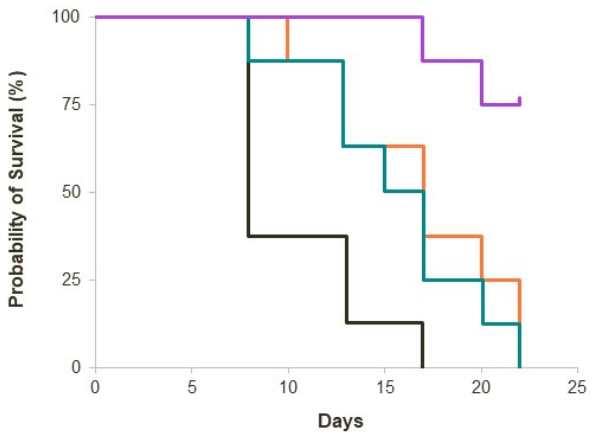
Source: Data presented at AACR-NCI-EORTC 2023.

Combination of MYC-Targeting EC with EGFR Inhibitor Significantly Enhanced Anti-Tumor Activity in Human Xenograft Model of NSCLC

H1975 Subcutaneous Tumor Model



Survival

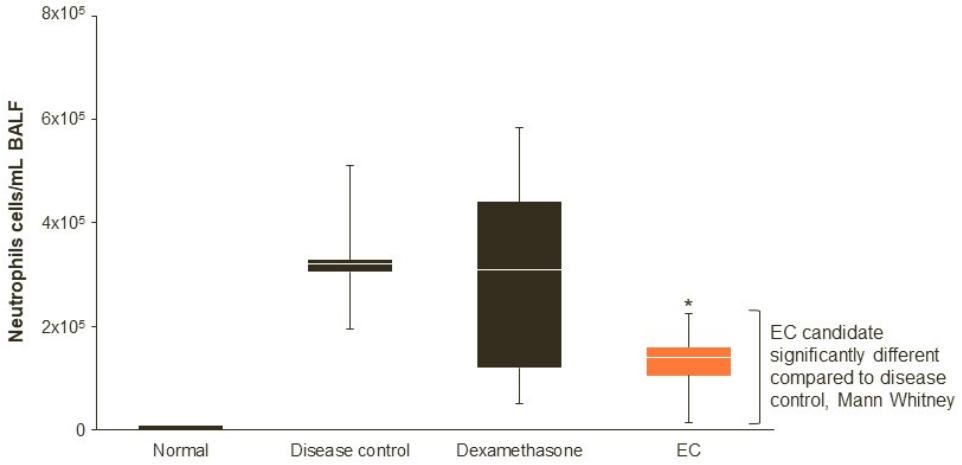


*p<0.05, **p<0.01
MYC EC dosed every five days

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

CXCL 1-8-Targeting EC Significantly Decreased Neutrophil Infiltration in Inflamed Lung *In Vivo*

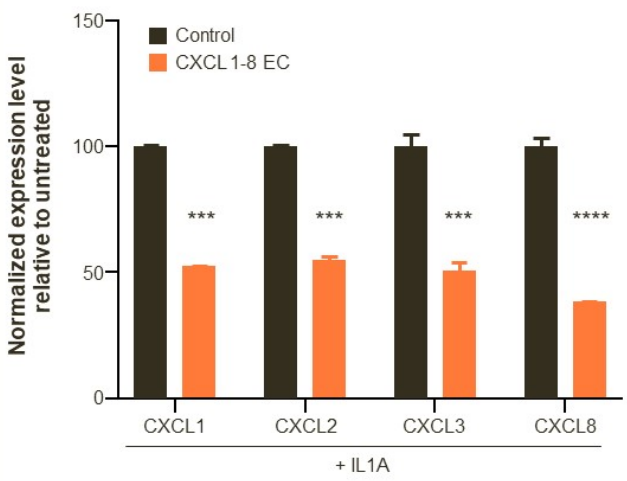
Measurement of Cellular Penetration Into Inflamed Lung



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

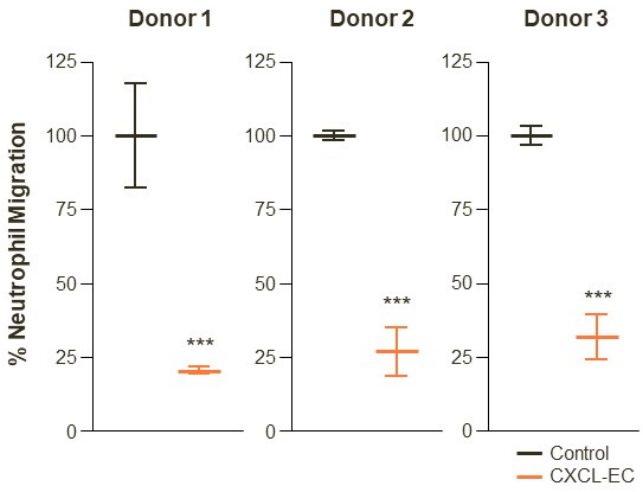
Multigenic Targeting of CXCL1-8 Downregulated Chemokine mRNA Expression and Reduced Neutrophil Migration in Donor Lung Fibroblasts *In Vitro*

Coordinated Downregulation of mRNA Expression



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

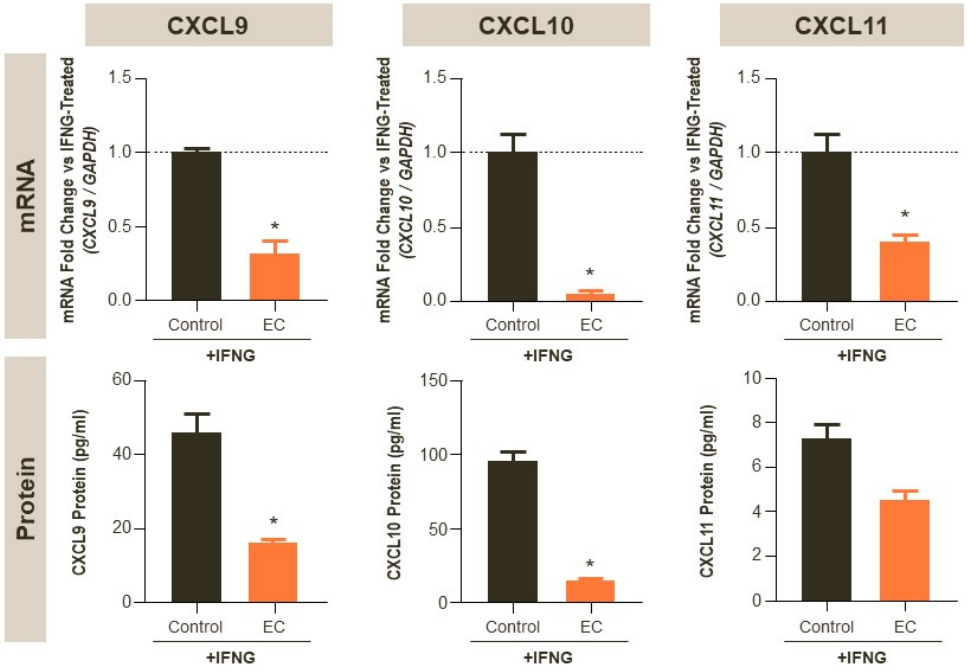
Significant Decrease in Neutrophil Migration

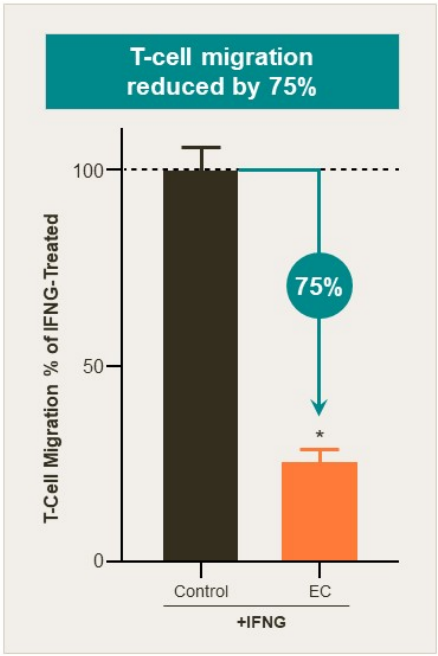


Supernatants from IMR90 cells stimulated with IL1A; ***p<0.001

Source: Data presented at International mRNA Health Conference 2023.

CXCL 9-11-Targeting EC Reduced mRNA Expression and Protein Levels in IFNG-Stimulated Primary Human Hepatocytes

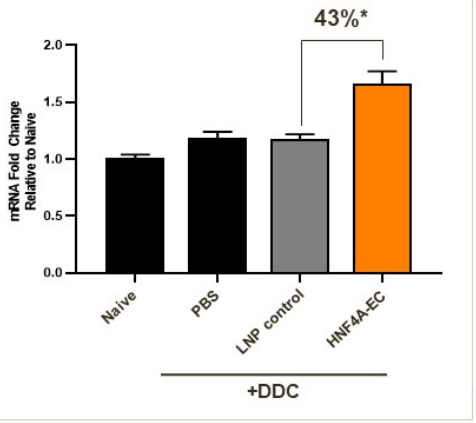




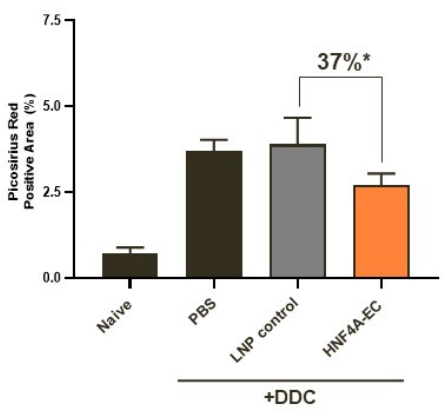
Source: Data presented at AASLD 2023. *p<0.05

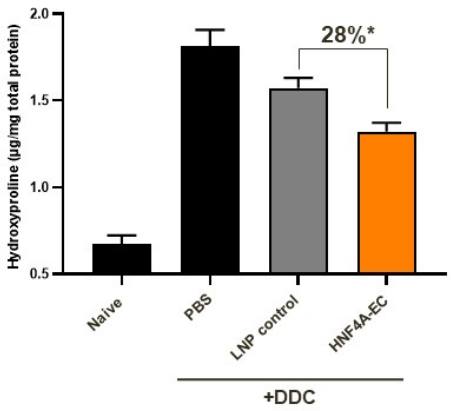
HNF4A-Targeting EC Significantly Upregulated HNF4α Gene Expression and Reduced Key Measures of Fibrosis

HNF4α Expression



HNF4α Induction Conferred Protection in DDC Fibrosis Model



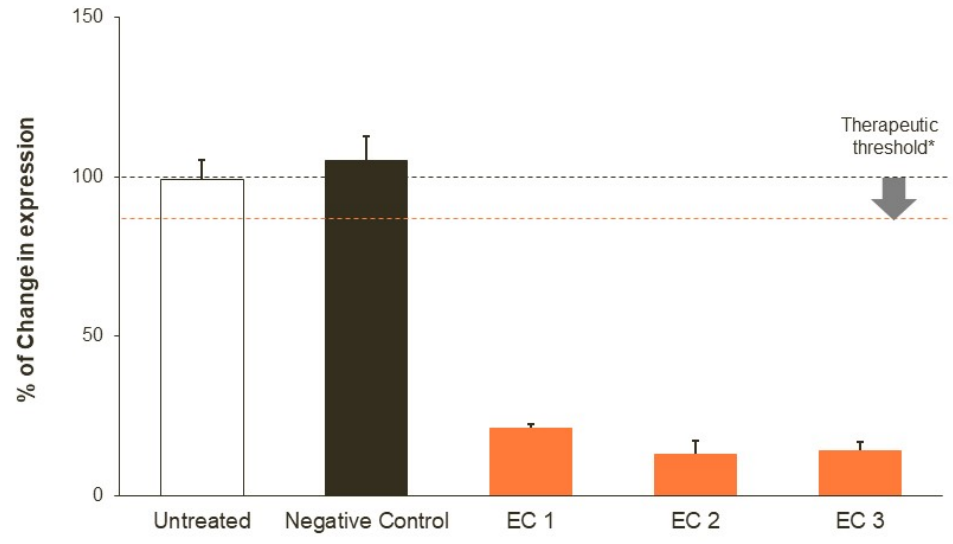


Source: Data presented at AASLD 2023. *p<0.05

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

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

Primary Human Hair Follicle Dermal Papilla (HFDP) Cells



- 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.

Understanding the OMEGA Platform

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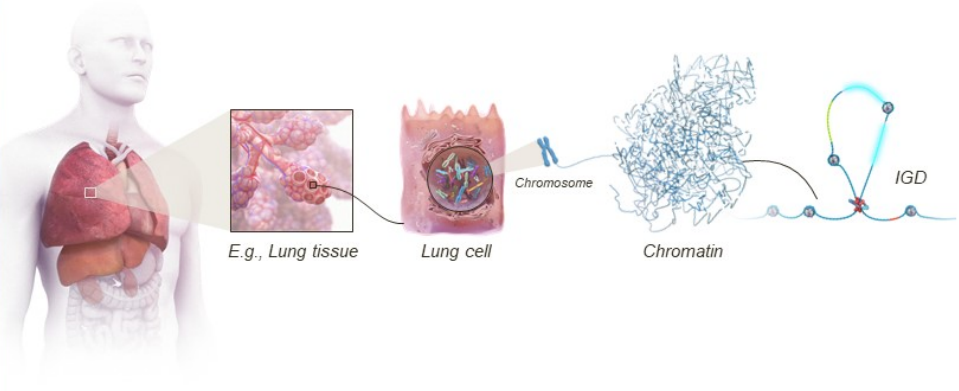
Insulated Genomic Domains Are Nature's Control System to Regulate Gene Expression

IGDs are the fundamental structural and functional units for gene control

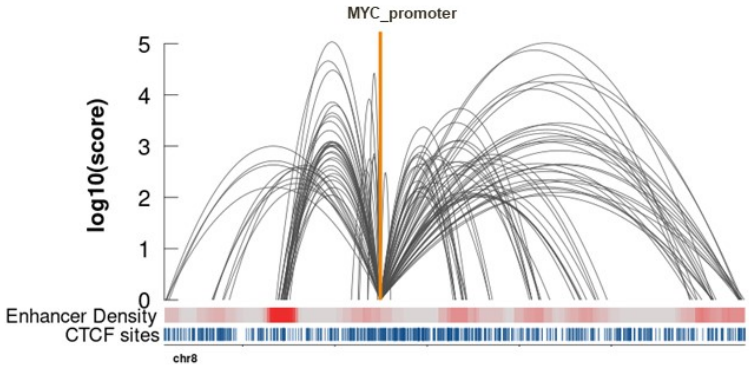
Nature organizes genes in evolutionarily conserved 3D loops of chromatin called Insulated Genomic Domains (IGDs)



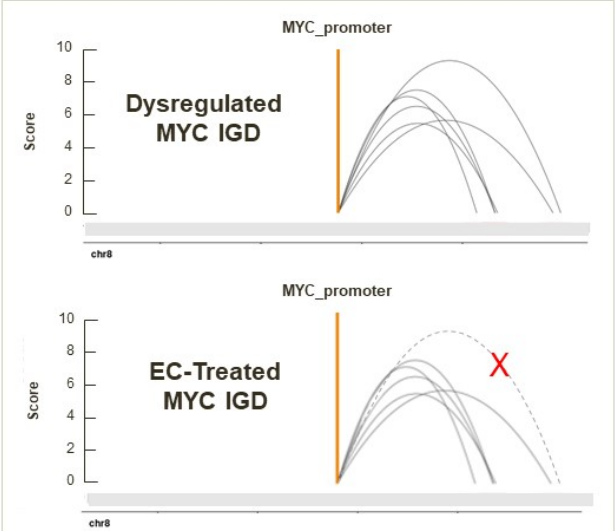
- Insulated from outside transcription by CTCF, each IGD contains 1-10 genes & their regulatory elements
- Regulators have unique DNA-sequences (**Epi**genomic **Zip**codes, "EpiZips"); can be used as drug targets
- Most diseases are caused by aberrant gene expression driven by epigenetic changes within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



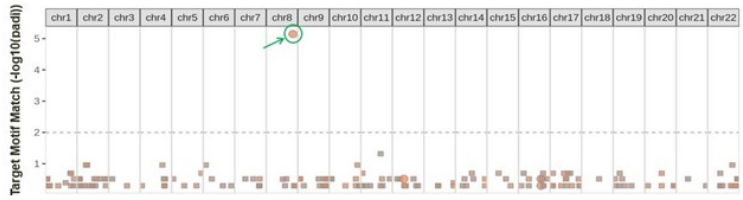
MYC IGD is controlled through many different looping interactions across cell types and is dysregulated differently across diseases

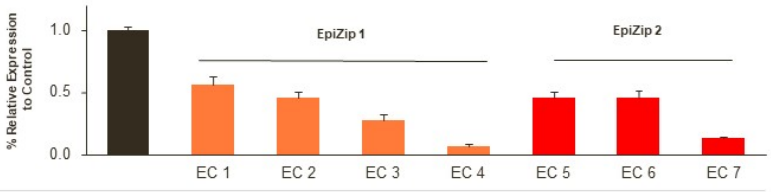


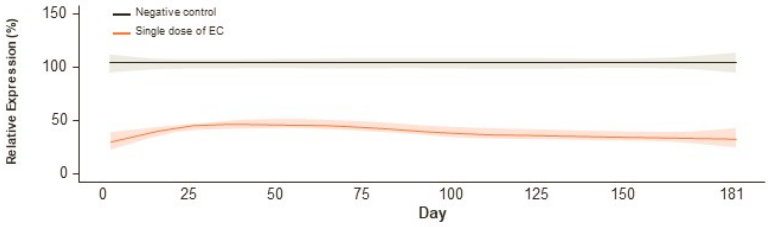
Treatment with EC restores dysregulated IGD to pristine state

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



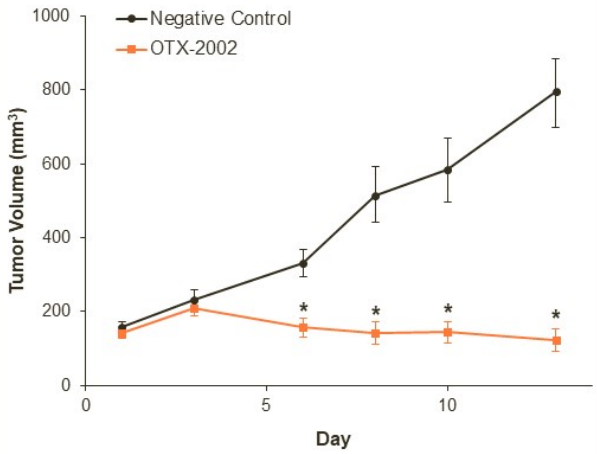




Proof-of-Concept Demonstrated Across Diverse Set of Disease Areas

Oncology (MYC HCC)

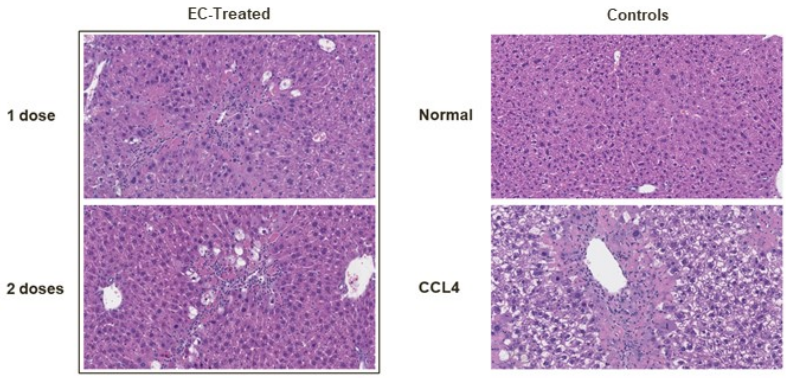
Statistically significant inhibition of HCC tumor growth *in vivo* through direct targeting of c-MYC



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

Liver Regeneration (HNF4a)

Significant improvement in liver histology in murine model of fibrosis



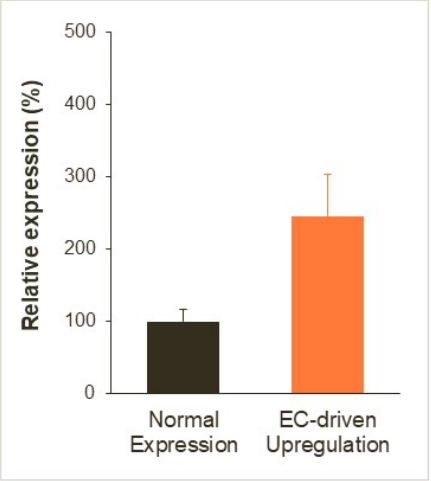
EC ameliorates CCL4-induced hepatic fibrosis in C57BL/6J mice

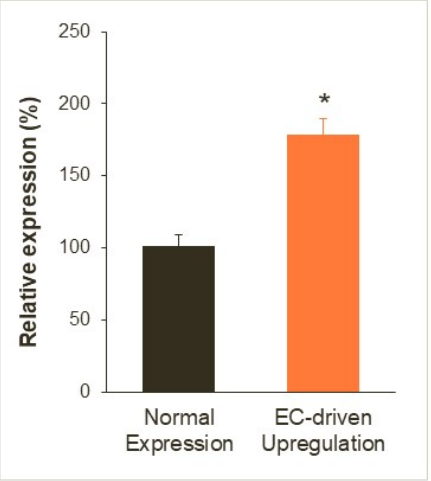
Translation Across Species Demonstrated for EC Mechanism

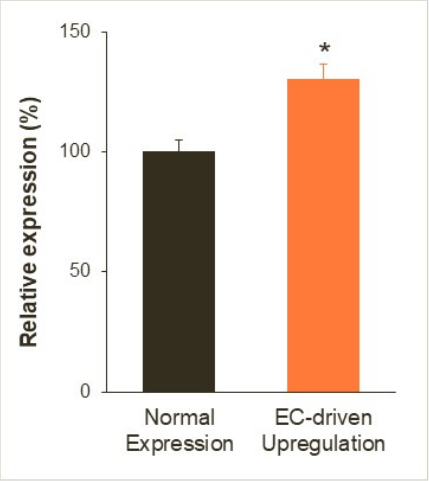
In-House Data for Both Up and Down Regulation

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)

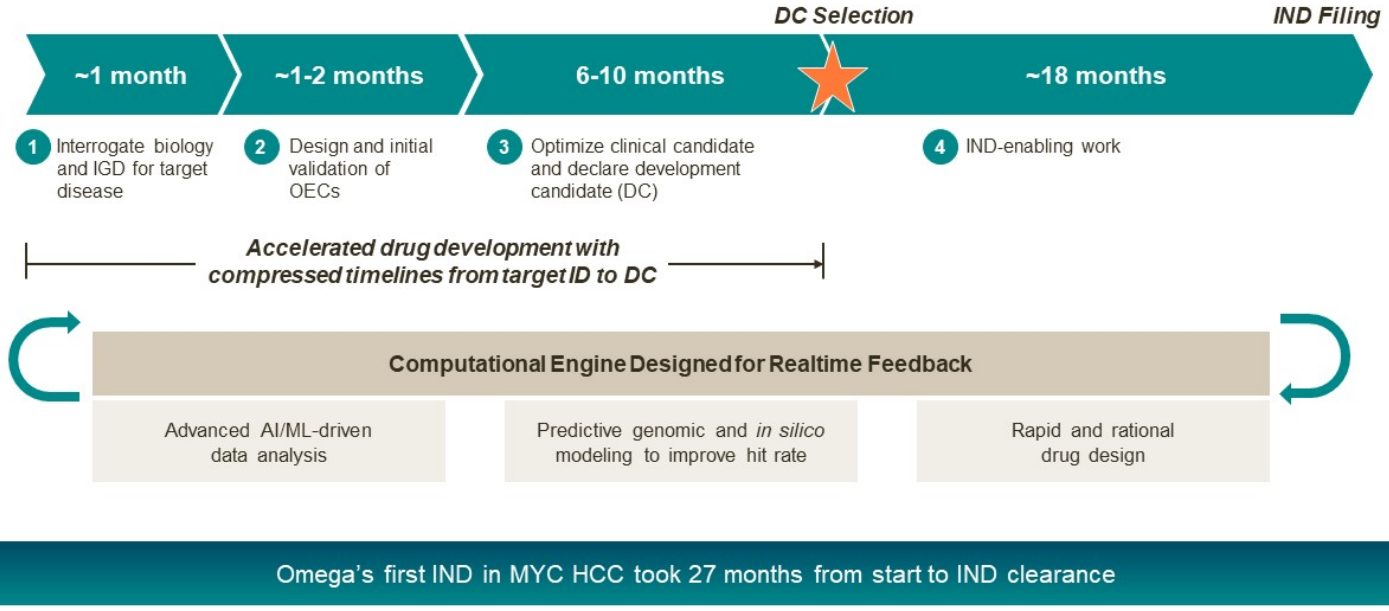






* Significant, paired t-test p<0.05

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



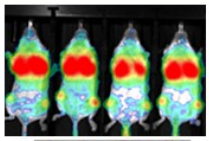
Omega's first IND in MYC HCC took 27 months from start to IND clearance

Initial Programs Leverage Validated LNP Delivery Technologies

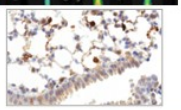
OMEGA Platform is Delivery Agonistic; Evaluation Expanding into Other Delivery Modalities

Internal Development Efforts to Develop Proprietary LNPs and Expand into Additional Tissues

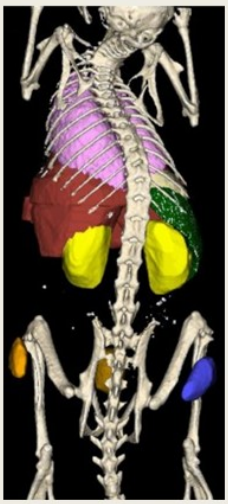
Lung



Systemic

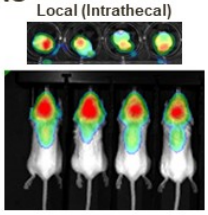


Local
Intratracheal
Double positive cells

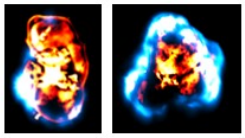


CNS

Local (Intrathecal)



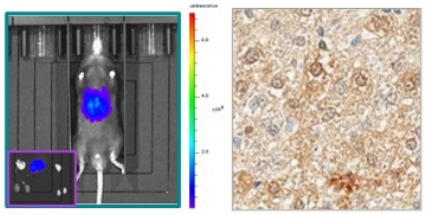
Solid Tumor (extrahepatic)



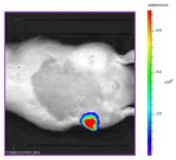
Orthotopic Lung Tumor

Subcutaneous Tumor

Liver

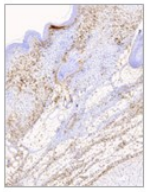


Joint



Intraarticular administration

Dermis



- Spleen
- Bone Marrow
- Cutaneous Tissue
- Immune Cells

Corporate Summary

OMEGA™ THERAPEUTICS

A World-Class Team to Deliver on Our Vision

Leadership

Mahesh Karande
President & CEO

Thomas McCauley
CSO

Yan Moore
CMO

Joshua Reed
CFO

Ling Zeng
CLAO

Siva Sakhamuri
SVP Tech Ops & Quality

Tony Mullin
Chief People Officer

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

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 preliminary data provides clinical proof-of-platform***

Elite investor syndicate; **balance sheet of $89.3 million** as of September 30, 2023

Diverse pipeline with therapeutic potential across broad range of diseases

World-class leadership focused on operational excellence

*Announced September 26, 2023.

2024 Priorities and Anticipated Milestones

LEAD PROGRAM: OTX-2002

- ☑ Continue monotherapy dose escalation in HCC patients
  - ☑ Cohort 3 (0.06 mg/kg): Completed 28-day DLT window
  - ☑ Cohort 4: Commence enrollment in January 2024; dose to be selected within range of 0.09 - 0.125 mg/kg
  - ❑ Protocol provides flexibility to further escalate to higher doses in future cohorts
- ❑ Announce additional updates from monotherapy dose escalation in 1H 2024
- ❑ Plan for monotherapy / combination expansion cohorts mid-2024

PIPELINE & PLATFORM

- ❑ OTX-2101: Advance IND-enabling work and novel lung-targeting LNP formulation
- ❑ HNF4A: Advance through discovery and lead optimization activities
- ❑ CXCL 1-8: Advance through discovery and lead optimization activities
- ☑ Expand pipeline into additional high-value opportunities (Obesity collaboration with NVO)
- ❑ Delivery: Progress internal LNPs in other tissues; Expand into other technologies
- ❑ Present data at medical meetings supporting OMEGA platform's diverse capabilities


OMEGA™
THERAPEUTICS
Thank You