Transforming Medicine Through Precision Epigenomic Control
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 OEC 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 OEC 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 OEC 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 is Pioneering the Next Generation of Medicine

Evolution of Drug Development

1849 1976 2010 2013 2017

Small Molecules Biologics mRNA and ncRNA Gene Therapy Genome Editing

Programmable Epigenomic mRNA Medicines

Central Dogma of Biology
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 all human genes**, including historically undruggable and difficult-to-treat targets
- **No editing or changes** to native nucleic acid sequences
Omega Therapeutics was Founded to Harness the Power of Epigenetics

What if…

- … Epigenetics worked through a central control system?
- … We could interrogate that system and design therapeutics to precisely regulate gene expression?
- … We could safely and effectively correct gene dysregulation pre-transcriptionally, and thereby treat or cure diseases?

Epigenetics is nature’s fundamental mechanism for gene regulation

Founded by Flagship Pioneering
Insulated Genomic Domains Are Nature’s Control System to Regulate Gene Expression

It turns out that...

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

IGDs are the fundamental structural and functional units for gene control

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

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 disease 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 Programmable mRNA Medicines

Omega Epigenomic Controllers (OECs)

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

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

**DNA-binding domain**

**Epigenomic effector domain**

Design of epigenomic effector tailored to disease

Full range of epigenetic mechanisms (Ex: histone modifications, transcription factors, etc.)

- DNA De-methylation
- DNA Methylation

Direction of Control

- Down
- Up

Regulation

Duration of Effect

- Short-acting
- Long-acting
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
The OMEGA Platform

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

World-Class Computational Genomics & Data Science
Accelerated drug development driven by:
- Deterministic, rational and rules-based drug design
- Advanced data analysis and machine learning algorithms
- Highly predictive genomic and \textit{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
# Our Pipeline of Innovative Omega Epigenomic Controllers

## Oncology

<table>
<thead>
<tr>
<th>Target Gene(s)</th>
<th>Indication</th>
<th>OEC</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYC</td>
<td>Hepatocellular cancer</td>
<td>OTX-2002*</td>
<td>Phase 1/2 MYCHELANGELO™ Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYC</td>
<td>Non-small cell lung cancer</td>
<td>OTX-2101</td>
<td>IND-Enabling Studies Ongoing</td>
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<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>Small cell lung cancer</td>
<td></td>
<td></td>
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</table>

## Multigenic Diseases

<table>
<thead>
<tr>
<th>Target Gene(s)</th>
<th>Indication</th>
<th>OEC</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCL 1-8</td>
<td>Potential franchise of programs**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>Idiopathic pulmonary fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Regenerative Medicine

<table>
<thead>
<tr>
<th>Target Gene(s)</th>
<th>Indication</th>
<th>OEC</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF4A</td>
<td>Liver regeneration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undisclosed</td>
<td>Corneal regeneration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Monogenic Diseases

<table>
<thead>
<tr>
<th>Target Gene(s)</th>
<th>Indication</th>
<th>OEC</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFRP1</td>
<td>Alopecia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 OEC include neutrophilic asthma, acute respiratory distress syndrome (including COVID-related), dermatological and rheumatological indications, and oncology
MOA Video

- Click here to view our Mechanism of Action video
Platform Overview
MYC IGD is controlled through many different looping interactions across cell types and is dysregulated differently across diseases.

Treatment with OEC restores dysregulated IGD to pristine state.
OECs Provide 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

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

*Statistically significant vs control, t-test p<0.05 starting on day 6
Translation Across Species Demonstrated for OEC Mechanism
In-House Data for Both Up and Down Regulation

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

<table>
<thead>
<tr>
<th>Species</th>
<th>Mouse</th>
<th>Nonhuman primate</th>
<th>FRG Mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Cells</td>
<td>Mouse (48h)</td>
<td>Nonhuman primate (24h)</td>
<td>Human (24h)</td>
</tr>
</tbody>
</table>

![Graphs showing relative expression of HNF4α in different species](image)

- * 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

Systemic

Local (joint)

Brain

Lung

Liver

Joint

Lung Tumor

SubQ Tumor

Local (intrathecal)
MYC: Master Oncogene Contributes to Genesis of Many Human Cancers

- MYC is a pleiotropic transcription factor important in many aspects of the cell cycle
- MYC dysregulation is implicated in over 50% of human cancers
- Previously thought of as an “undruggable” target due to its disordered protein structure masking epitopes to target
- Omega Epigenomic Controllers target MYC via its IGD and regulate gene expression pre-transcriptionally

MYC is central to cell cycle progression, proliferation, growth, adhesion, differentiation, apoptosis & metabolism.
OEC Mechanism of Action
Highly Specific On-Target Binding Leads to Intended Epigenetic Effect

Site-specific target engagement

Site-specific epigenetic state change (in vitro)

OEC treatment induces site-specific epigenetic change and reduces mRNA levels (in vivo)

Biomarker changes in tissue (in vivo change in protein)

In vivo efficacy

PBS: Phosphate buffered saline (negative control)
OTX-2002 Results in Rapid and Durable Downregulation of MYC Expression and Reduces Viability of HCC Cancer Cells

• 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

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

**HCC Subcutaneous Tumor Model (Hep3B)**

<table>
<thead>
<tr>
<th>Day</th>
<th>Tumor Volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>10</td>
<td>600</td>
</tr>
<tr>
<td>15</td>
<td>800</td>
</tr>
<tr>
<td>20</td>
<td>1000</td>
</tr>
</tbody>
</table>

- **Negative Control**
- **OTX-2002**
- **Small Molecule Comparator**

**No Significant Impact on Body Weight in Mice**

<table>
<thead>
<tr>
<th>Day</th>
<th>Body Weight Change from Baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

- **Negative Control**
- **OTX-2002**
- **Small Molecule Comparator**

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

HCC Tumor Model (Hepa1-6)

- Control
- OEC
- Anti-PDL1
- Anti-PD1
- OEC + aPDL1
- OEC + aPD1

Statistically significant combination benefit in immune competent mice with αPD1 or αPD-L1. Both αPD1 and αPD-L1 combinations well tolerated with no significant impact on body weight during the study.

Change in Body Weight (%)

- Control
- OEC
- aPD-L1
- aPD1
- OEC + aPD-L1
- OEC + aPD1

OEC dosed IV every 5 days (last dose on Day 25). αPD1 or αPD-L1 dosed intraperitoneally once-weekly (last dose on Day 14).
MYCHELANGELO™ I: Ongoing Phase 1/2 Clinical Trial of OTX-2002 as Monotherapy and in Combination with Standard of Care for HCC*

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

**Dose Escalation**

<table>
<thead>
<tr>
<th>Part 1: Monotherapy</th>
<th>HCC Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>TBD</td>
</tr>
<tr>
<td>Cohort 2</td>
<td></td>
</tr>
</tbody>
</table>

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

**3+3 design**

**Objectives:**
- Determine the DLTs, MTD, safety, and tolerability and determine the RDE of monotherapy
- Determine the preliminary antitumor activity of monotherapy by ORR and DOR

**Safety Run-In Phase**

<table>
<thead>
<tr>
<th>Part 2: Combination</th>
<th>Combination HCC Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTX-2002 + SOC**</td>
<td>SOC** + SOC**</td>
</tr>
</tbody>
</table>

- Patients with advanced HCC

**Objectives:**
- Determine the DLTs, MTD, safety, and tolerability and determine the RDE of combinations
- Determine the preliminary antitumor activity of combinations by ORR and DOR

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* 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)
Sample Data from Other Pipeline Programs
**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

OTX-2101 dosed every five days

**p**<0.05; **p**<0.01

OTX-2101 dosed every five days

---

**H460**

- Negative Control
- OTX-2101
- Positive Control

**Tumor Volume (mm³)** vs **Days**

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**H2009**

- Negative Control
- OTX-2101
- Positive Control

**Tumor Volume (mm³)** vs **Days**

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p<0.05; **p**<0.01
Measurement of Cellular Penetration Into Inflamed Lung

- OEC candidate administration prior (-2h) to challenge and at peak of inflammation (8h)
- Significantly decreased neutrophil infiltration in bronchoalveolar lavage (BALF) at 72 hrs
Ex vivo Proof-of-Concept in Monogenic Disease Program: Alopecia
Downregulation of SFRP1 at 7 Days Post-Treatment With OEC 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

Primary Human Hair Follicle Dermal Papilla (HFDP) Cells

![Graph showing % of Change in expression for untreated, negative control, and different OEC candidates.]

*Hawkshaw et. al. 2018 PLOS Biology 16(5): e2003705.
Our Differentiation
Therapeutic Potential Across Nearly All Human Genes

**Omega Epigenomic Controllers (OECs)**

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

**Disease Areas**
- Oncology ($100B+)
- Multigenic diseases ($150B+)
- Regenerative medicine ($25B+)
- Monogenic diseases (Table Stakes for Gene-Based Therapies)

**Diseases (Examples)**
- Pan-Essential Oncogenes
  - Hepatocellular carcinoma
  - Non-small cell lung cancer
  - Pancreatic cancer
  - Glioblastoma multiform
- Respiratory diseases
- Obesity
- Neutrophilic asthma
- Inflammatory bowel disease
- Congestive heart failure
- Idiopathic pulmonary fibrosis
- Regeneration of Liver, Pancreas, Heart, Cornea
- T-cell programming
- Alopecia
- Hypercholesterolemia
- Rare Diseases (Fragile X, Friedreich's ataxia)
Our Approach Has Differentiated and Distinct Advantages

**Leverages Innate Epigenetic Mechanisms**
Harnessing fundamental biology and IGD-level targeting provides complete control of gene expression

**Broad Applicability to Nearly All Disease Areas**
Unlocks previously undruggable targets across broad range of diseases

**Rapid Prosecution and Scalability**
Highly predictive *in silico* modeling combined with rational, modular drug design enables rapid prosecution of new targets to *in vivo* PoC in ~3-6 months

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**Favorable Therapeutic Profile**
- No editing or changes to nucleic acid sequence
- Separation of PK and PD:
  - Transient pharmacokinetics provides favorable safety profile
  - Programmed, durable pharmacodynamic effect without drug resident in body
- Pre-transcriptional tuning addresses current limitations (e.g., autoregulation in oncology)
- IGD-level targeting renders individual driver mutations irrelevant
Corporate Summary
A World-Class Team to Deliver on Our Vision

Leadership

Mahesh Karande
President & CEO

Joshua Reed
CFO

Ling Zeng
CLAD

Noubar Afeyan
Co-Founder Chairman
Flagship, Founder & CEO

Luke Beshar
NPS Pharma

Rainer Boehm
Novartis

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

Mary Szela
Trisalus Life Sciences, CEO

Elliott Levy
Amgen, BMS

John Mendlein
Executive Partner,
Flagship

Mahesh Karande
President & CEO

Thomas McCauley
CSO

Yan Moore
CMO

Siva Sakhamuri
SVP Tech Ops & Quality

Ramola Bhandarkar
VP Regulatory Affairs

Richard A. Young
Founding Scientific Advisors

David Berry,
Founder

Founded by Flagship Pioneering

Noubar Afeyan,
Chairman & Founder

MIT & Whitehead Institute

Rudolf Jaenisch

Joshua Reed

Flagship Pioneering

Rudolf Jaenisch

David Berry,
Founder
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 expected in 2023

Preclinical proof-of-concept data generated across a broad pipeline spanning 4 uncorrelated 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 $136.8 million as of March 31, 2023.
Thank You
Specificity
OECs Demonstrate Exquisite Specificity of Binding with Intended Epigenetic Effect

Genome-wide Specificity of Binding and Epigenetic Effect

On-target binding with robust change in epigenetic state of single gene in IGD on chromosome 8

OEC candidates precisely target and control expression of a single gene or IGD genome-wide
Tunability
Designed to Precisely and Controllably Tune Gene Expression

Bi-directional tuning ability

Precision tuning through choice of EpiZips and OEC MOA
Durability
Decoupling PK from PD May Lead to Favorable Safety and Tolerability

- OECs have transient residence in the body and are rapidly degraded with 2-3 days, however intended epigenomic effect is durable
- OECs are designed for controlled durability that can be tailored to last days, weeks or months
- We believe our approach may lead to a favorable safety benefit by decoupling PK (transient) from PD (durable)

PK: Pharmacokinetics; PD: Pharmacodynamics