# Tuned Upregulation of Diverse Gene Targets using Programmable Epigenomic Controllers

Jeremiah D. Farelli, Chevaun Morrison-Smith, Houda Belaghzal, Marcus Gibson, Mayur Gurnani, Prachi Dhanania, Steve Siecinski, Yaoyu Wang, Justin Chen, Adam Katz, Sam Mildrum, Giuliana Coatti, Charles W. O'Donnell, Thomas McCauley

Omega Therapeutics, Cambridge, MA, USA

ASGCT Annual Meeting 2024
Abstract # 697

## Programmable Epigenomic Modulation

Therapeutic modulation of the epigenome presents significant opportunities to leverage natural mechanisms to control and resolve gene dysregulation pre-transcriptionally. Omega Therapeutics, a clinical-stage biotechnology company, is designing programmable epigenomic mRNA therapeutics through an innovative platform capable of specifically, controllably and durably modifying epigenetic chromatin state to correct aberrant gene expression and treat disease.

Leveraging 3D chromatin architecture, we identify Insulated Genomic Domains (IGDs), target sequences driving epigenetic gene control within these IGDs, and rationally design Epigenomic Controllers (ECs), mRNA-encoded therapeutic proteins (Fig. 1). Using endogenous modifications, ECs induce changes processed by cellular machinery to tune expression levels of one or more genes.

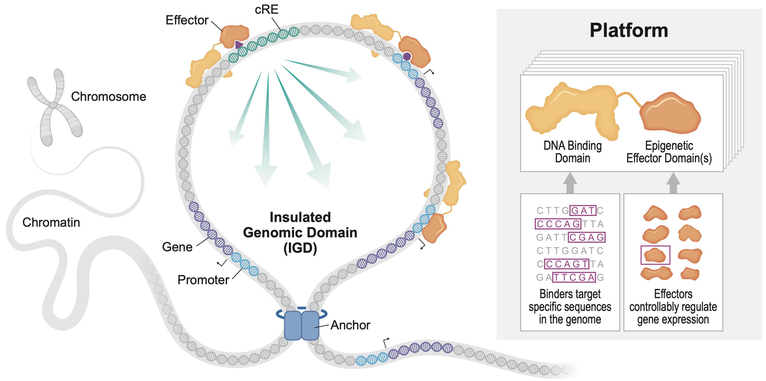


**Figure 1.** Composition and Mechanism of Action of Epigenomic Controllers

## Durable Epigenetic Effect Through Decoupled PK/PD

Optimized mRNA drug product is delivered via LNP, and the translated EC protein rapidly degrades within days (Fig. 2(a)) after modulating the targeted epigenetic state (Fig. 2(b)) and altering gene transcription (Fig. 2(c)). This results in a functional decoupling of pharmacokinetics and pharmacodynamics. Regulation of gene expression can be designed to last for weeks or months.

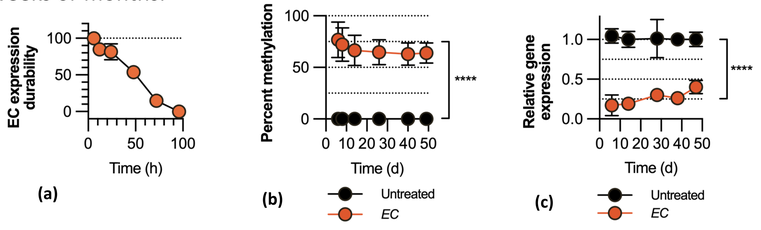


**Figure 2.** EC expression profile, durability of transcriptional and epigenetic effects after treatment with an EC targeting a specific gene.

## Tunable Gene Regulation with Programmable Epigenomic Controllers Across a Diverse Set of Genes

We demonstrate platform capabilities to upregulate (green) and downregulate (red) gene expression to a wide range of levels; this enables the ability to select ECs tuned to the desired therapeutic effect (Fig. 3). Upregulation is possible across a diverse set of gene types, spanning a broad spectrum of conditions, including (1) genes that are inactive in a cell type of interest, (2) genes that are expressed but whose further upregulation leads to therapeutic benefit, and (3) genes that are inactive or lowly-expressed but are in a poised state, ready for high activation upon pathway engagement or stimulation. This further includes the reactivation of a downregulated gene.

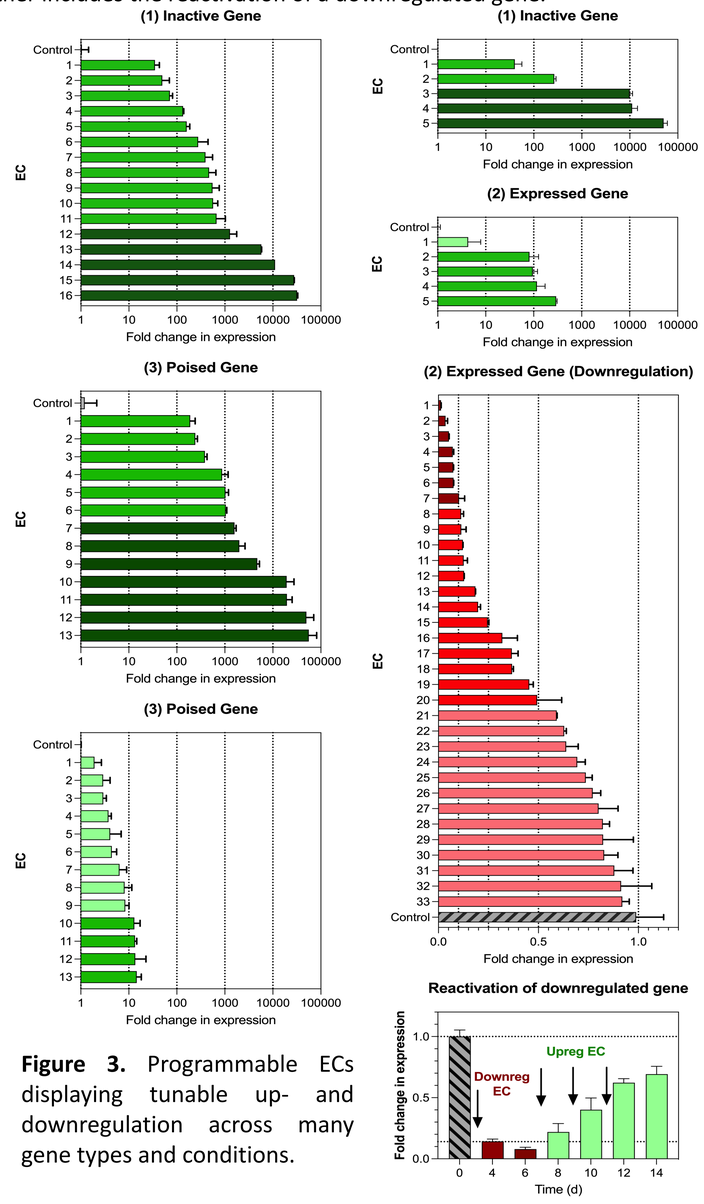


**Figure 3.** Programmable ECs displaying tunable up- and downregulation across many gene types and conditions.

## Durable Upregulation with Epigenomic Controllers

ECs can be designed to impart durable gene expression upregulation with different levels and temporal profiles following a single dose (Fig. 4). Such effects can last weeks to months.

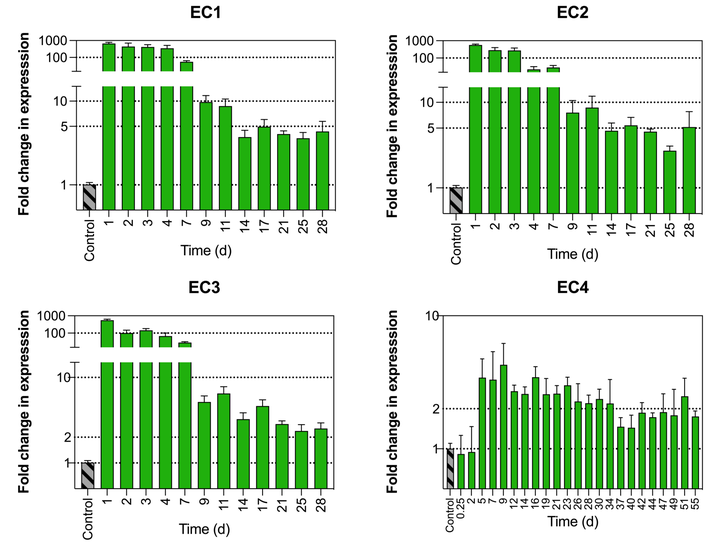


**Figure 4.** Programmable ECs displaying tunable and durable upregulation across a broad range of gene types and cellular conditions.

## Precision and Multi-Gene Control via Epigenetic Target Selection

Gene expression is naturally regulated via elements such as Promoters, cis-Regulatory Elements (cREs), and IGD anchors. Similarly, ECs can tune expression through identification and combinatorial targeting of different regulatory elements and types. The IGDs regulating *RHBDF1/HBA1/HBA2* contain several elements whose targeting with ECs demonstrate a diversity of possible control (Fig. 5): (a) Different levels of upregulation is achieved by targeting different types (Promoter, cRE, or Anchor-driven re-wiring), (b) Single or multi-gene control can be achieved through choice in cRE targeting, and (c) the same element can be used for both up- and downregulation, with the combination showing additive effects in both cases.

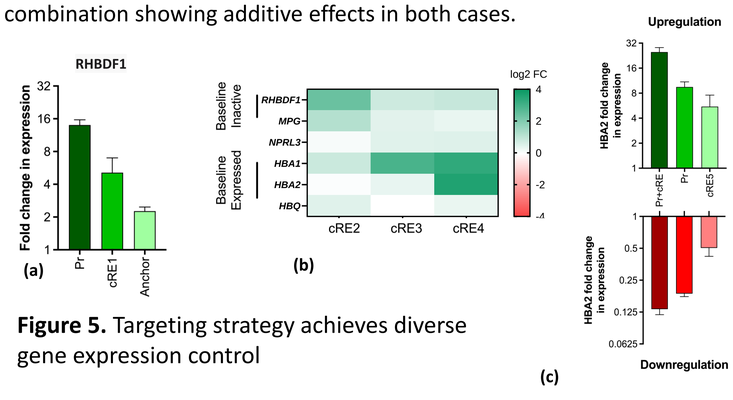


**Figure 5.** Targeting strategy achieves diverse gene expression control