TUNE THERAPEUTICS

FIRST-IN-CLASS IN VIVO EPIGENOME SILENCING FOR CHRONIC HEPATITIS B: ACCELERATED CMC DEVELOPMENT STRATEGIES

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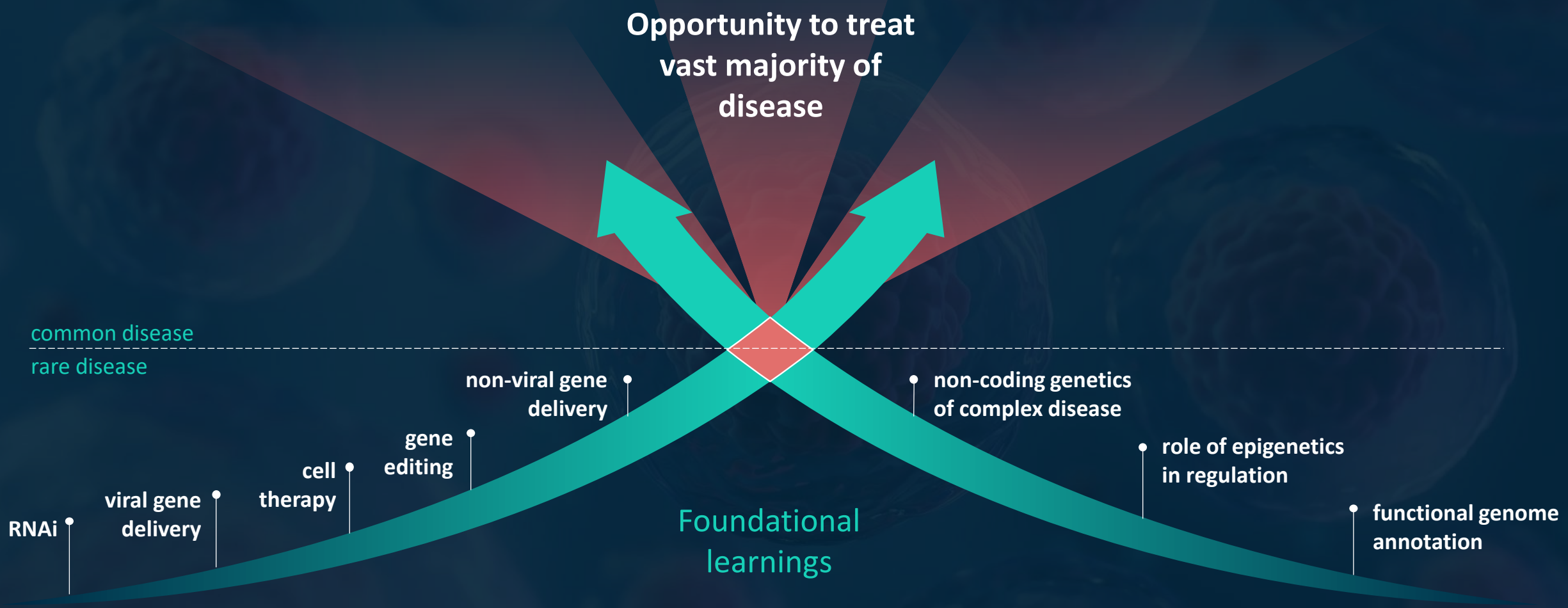
June 10th 2026

Disclaimer

The views, opinions, and conclusions expressed in this presentation are my own, and not necessarily those of Tune Therapeutics, Inc.

Genetic medicine is at a tipping point

Complex and common diseases are finally within reach of genetic medicine



The new frontier

Epigenomic therapies will transform the treatment of disease

protein-coding genes

epigenomic control

- Only a fraction of the genetics associated with disease involves changes in protein-coding genes.
- The vast majority of human disease is the result of changes in gene expression, driven by epigenomic regulators that control cell state and fate.

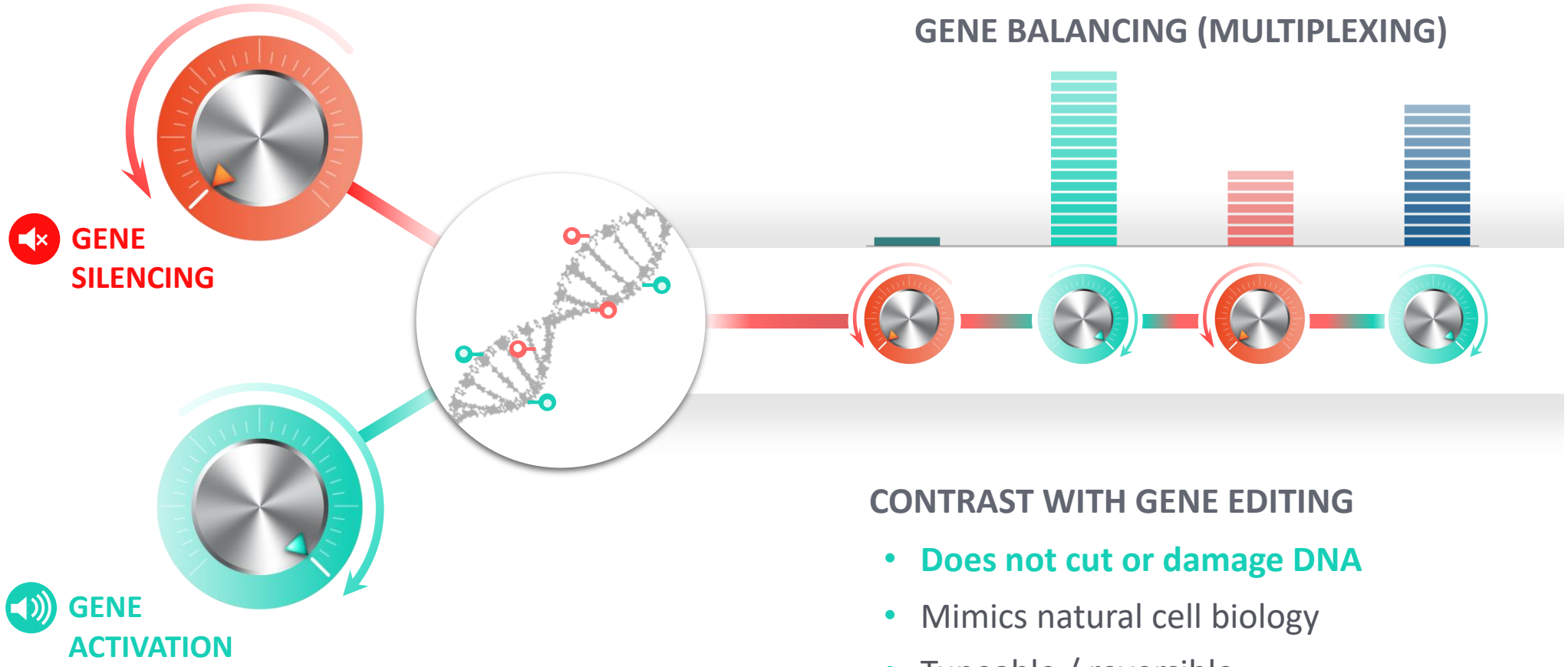
Genetic tuning will unlock our ability to

change cell states at will, without damage to DNA sequence –

transforming the treatment of common and complex diseases

Controlling Genes Without Cutting

Epi-editing allows us to durably fine-tune gene output for therapeutic effect



CONTRAST WITH GENE EDITING

- **Does not cut or damage DNA**
- Mimics natural cell biology
- Tuneable / reversible

Chronic Hepatitis B is a Significant Unmet Need

~240 million
living with chronic HBV infection worldwide

No approved curative treatment

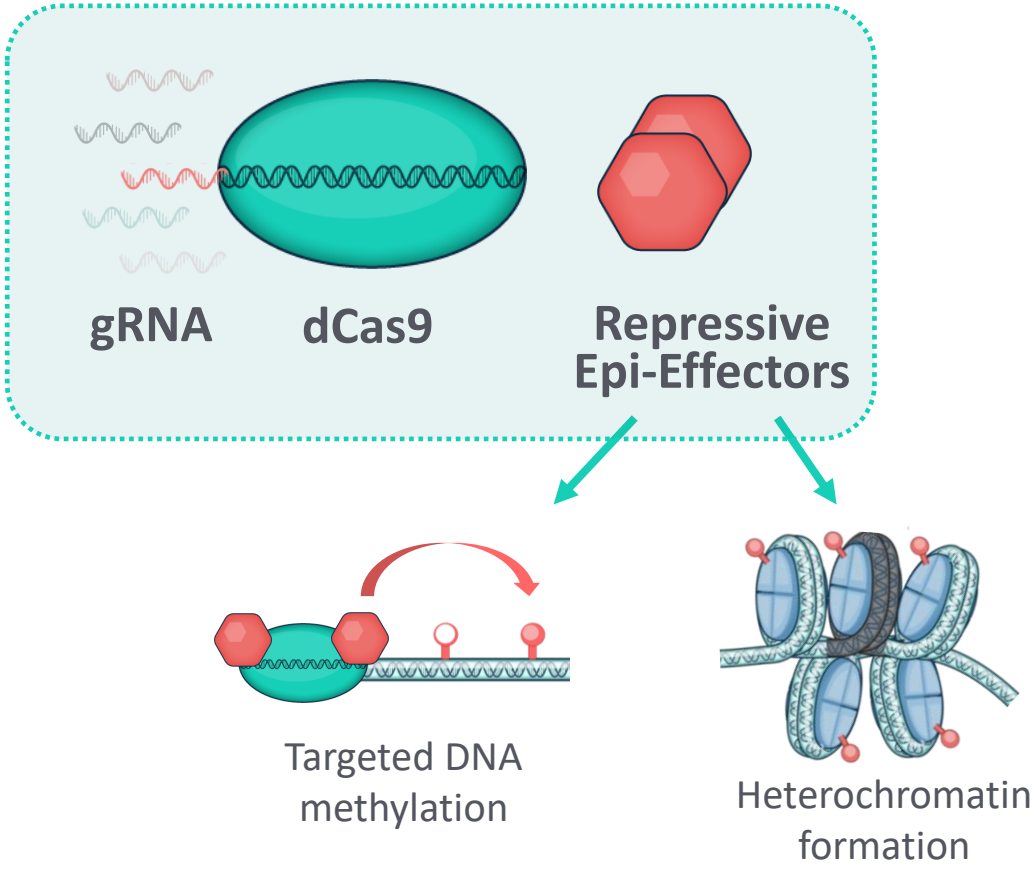
Existing therapies are suppressive and life-long, relapse off treatment is near universal

25-40% will develop cirrhosis or liver cancer, making HBV the **7th leading cause** of death worldwide

Tune-401 LNP-RNA Platform

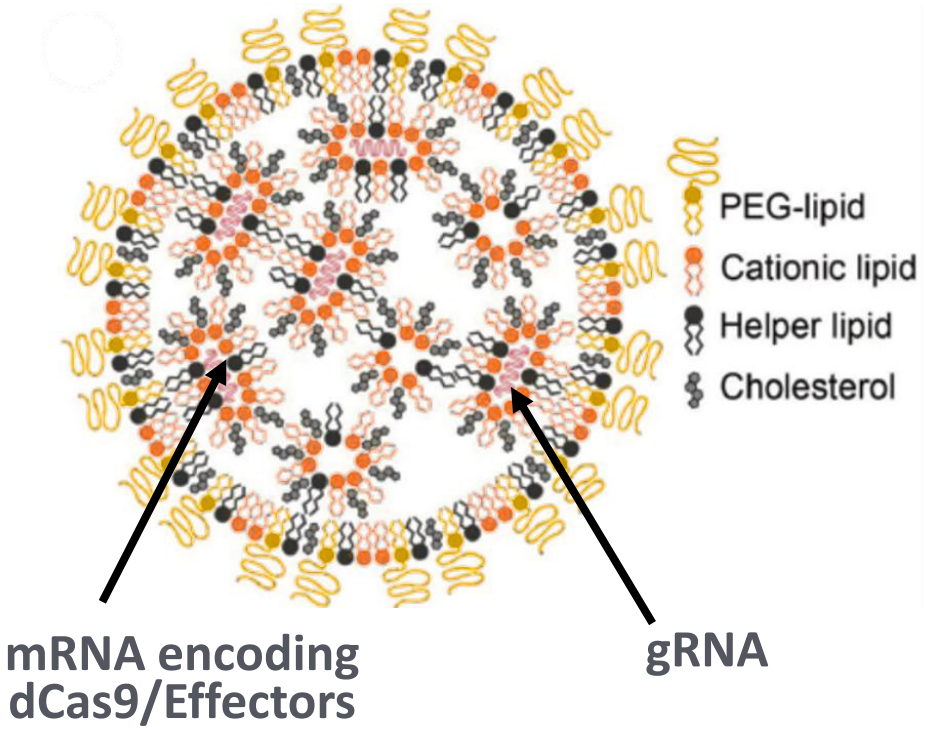
Epigenetic Silencer

LNP-delivered mRNA encoding dCas9 DNA-binding protein, virus-targeting guide RNA, and engineered effector proteins



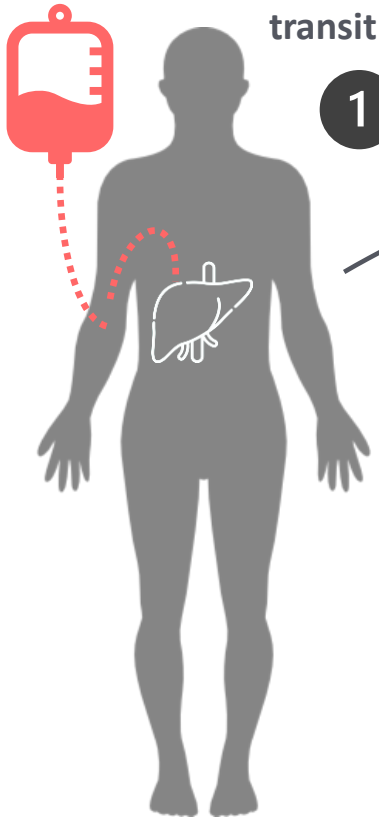
LNP Delivery System

- Ionizable lipid formulation, designed for liver tropism
- Established manufacturing platform



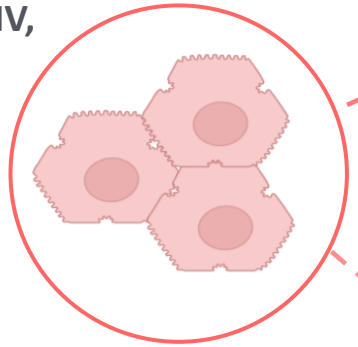
The lipid nanoparticle for TUNE-401 is licensed from Acuitas Therapeutics Inc.

Tune-401 Mechanism of Action



LNPs administered by IV, transit to liver cells

1



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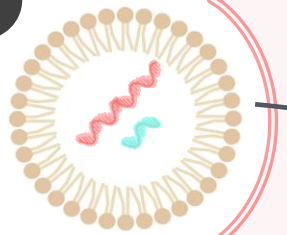
LNPs enter cells (endocytosis)



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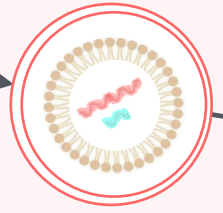
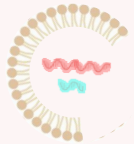
Endosome release, translation of mRNA





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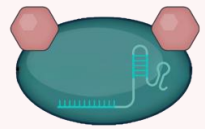
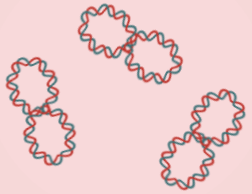
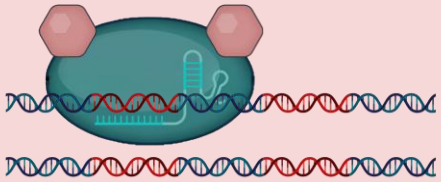


TEMPO epi-editing protein enters nucleus...



...binds to viral cccDNA

5

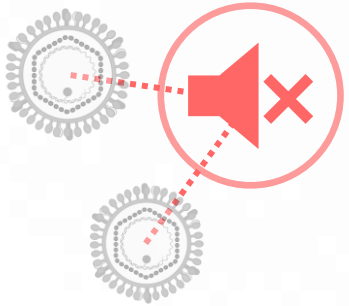


...binds to genome-integrated viral DNA (intHBV)

...and adds methyl groups, silencing viral DNA

Reduction in all viral proteins (core, capsid, Pol)

6



HepB silenced throughout the liver, with potential for functional cure

TUNE-401: a first-in-class epigenetic silencer of HBV demonstrates deep and durable antiviral activity in the phase 1b/2a proof of concept Tune-401-001 study

MAY 30, 2026 | EASL 2026, BARCELONA

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The Core CMC Challenge: Quality, Speed, & Scale

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QUALITY

Regulatory Confidence

Complex systems require robust CQA identification and control strategies that satisfy global regulatory expectations.

Key Tension:
Large global population indications require robust planning, strategy, and resourcing

SPEED

Rapid Patient Access

Phase-appropriate development accelerates timelines. Early alignment on QTPP enables the team to maintain focused and aligned execution

Key Tension:
Early decisions lock in process design — late redesigns are costly

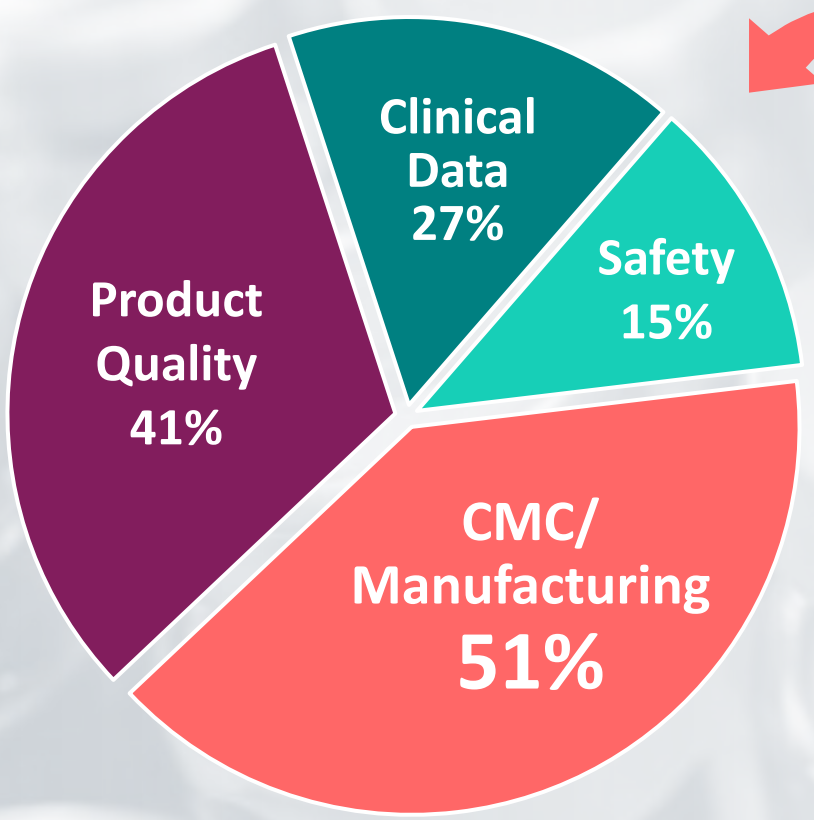
SCALE

Commercial Manuf.

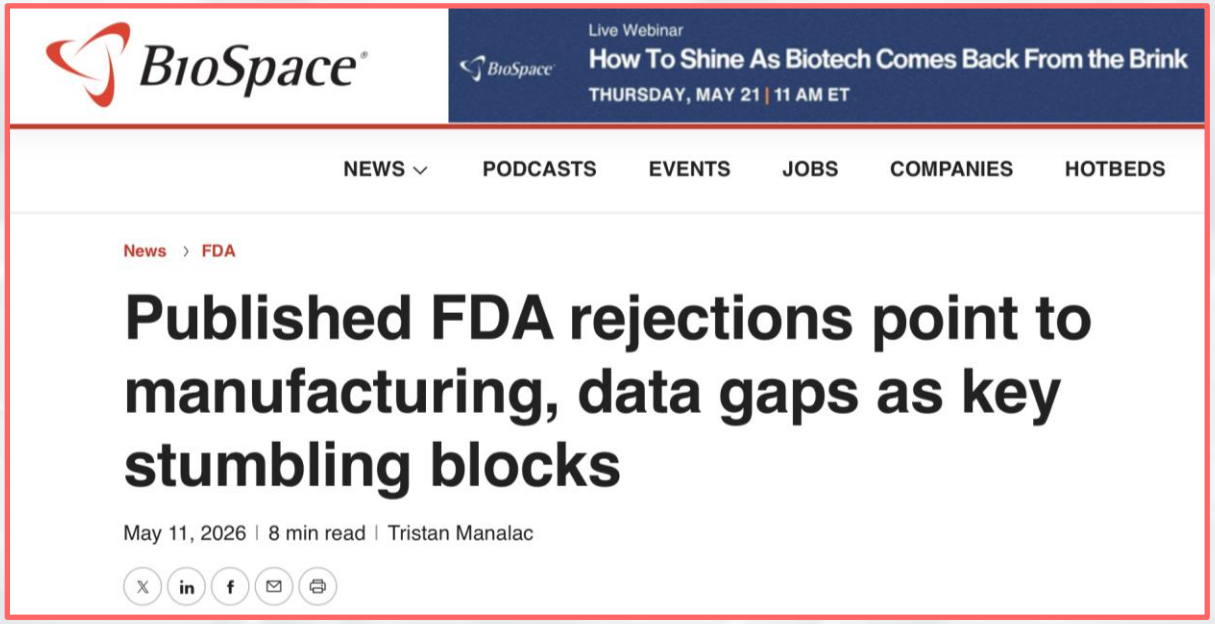
Cost of goods and supply chain robustness must be designed in early development.

Key Tension:
Scale up vs Scale Out

The Core CMC Challenge: Quality, Speed, & Scale



Reasons for FDA Rejections
(Analysis: Jeffries, 2026)


BioSpace

Live Webinar
How To Shine As Biotech Comes Back From the Brink
THURSDAY, MAY 21 | 11 AM ET

NEWS PODCASTS EVENTS JOBS COMPANIES HOTBEDS

News › FDA

Published FDA rejections point to manufacturing, data gaps as key stumbling blocks

May 11, 2026 | 8 min read | Tristan Manalac

"More than half of FDA rejections come down to concerns with manufacturing, according to a recent analysis of complete response letters made public by the agency."

Source: Biospace, May 11 2026 (*www.biospace.com/fda/published-fda-rejections-point-to-manufacturing-data-gaps-as-key-stumbling-blocks)*

A CMC Development Framework: Four Integrated Pillars

An integrated strategy linking materials, process, analytics, and commercial readiness from Phase 1 through BLA

1 Raw Materials & Supply

- Critical Material Attributes (CMAs) defined early
- Supplier qualification scaled to commercial demand
- Establishing vendor relationship and projections early and often

2 Process Development

- Define pCPPs early; leverage platform where possible
- Simplicity and scalability from the start
- Design-of-experiment approach to build process knowledge

3 CQA Identification & Control

- Established characterization assays early to gain understanding of product and process early
- Risk-based approach (ICH Q8 and Q9) to classify CQA impact
- Evolving control strategy as analytics and process understanding matures

4 Scaling Drug Supply

- Comparability strategy across process changes
- COGs optimization for large patient populations
- PPQ design representative of commercial process
- Lifecycle management built into development plans

Leveraging Risk-Based Regulatory Frameworks

Regulatory frameworks for gene therapy (OTP guidance, ICH Q8/Q9/Q10/Q12) provide a flexible, science-based foundation

Phase-Appropriate Development

Phase 1:

Start building product understanding.
Start process characterization.
Core control system to ensure safety.

Phase 2:

Initiate process characterization studies.
Build CQA/CPP linkage.
Formalizing QTPP.

Phase 3:

Linking CPP and CQA.
Confirm control strategy.
Validate BLA enabling analytical methods and lock commercial process

Post Approval:

Proactively filing post-approval change management protocols (PACMPs).

Earlier CMC development to enable fast to clinic and fast to market plans

Technical Development from Ph1 to Ph2: The Ideal Opportunity for Process & Analytical Improvements

A proactive, pre-planned **method equivalency, comparability, and change control strategy** is the cornerstone of **efficient clinical development.**

Process Comparability

Yields deeper process performance confidence and understanding of potential future PPQ design.

Method Equivalency

Improving early phase analytical methods to support deeper product and process performance understanding

Performed properly with regulatory agency alignment could:

- Enable continued use of existing Phase 1b material in the Phase 2 expanded study
- Drive faster time-to-clinic without wasting any Drug Product batch

Case Study 1: Technical Development

Method Equivalency

= *Qualification of the new method per ICH guidelines, followed by a comparison of representative batch results generated by both methods against pre-defined acceptance criteria.*

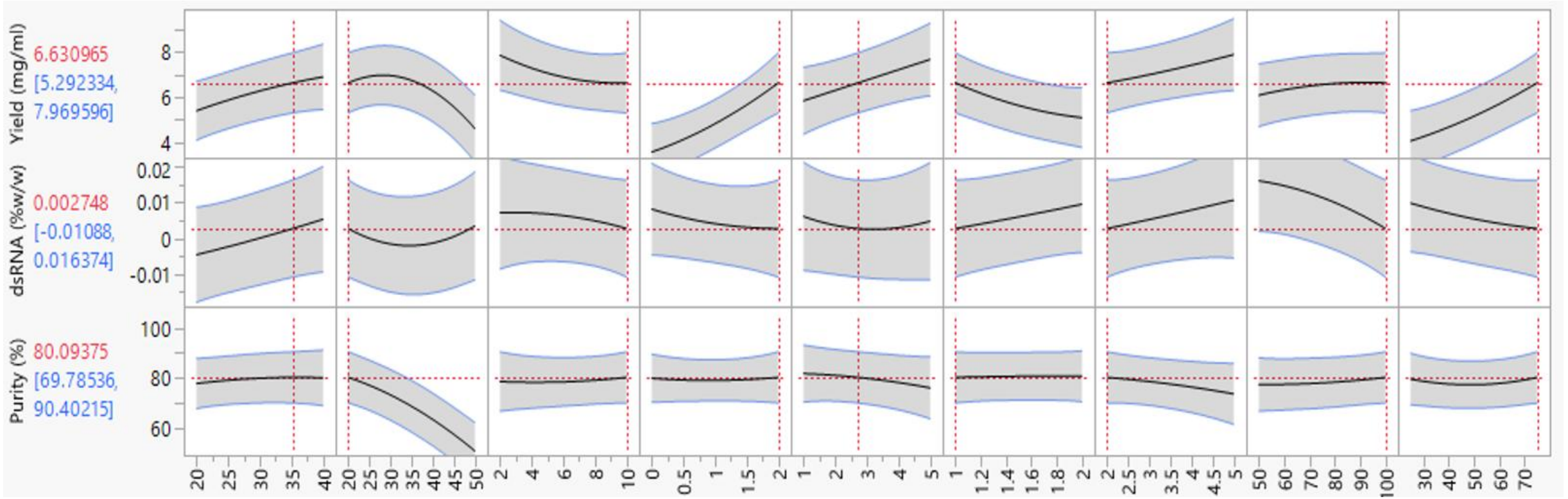
Comparability = *Establishment of new process improvements through design of experiments, followed by risk assessment and the identification of potentially impacted product quality attributes to identify analytical testing strategy*

Level of Impact and Risk of Process Changes Justify Comparability Activities

- *Tier 1: Analytical Comparability*
- *Tier 2: In Vitro Potency/Bridging*
- *Tier 3: Nonclinical/Clinical Bridging*
  - *Establishing core process early allows for avoiding costly Tier 3 process/comparability activities*

Case Study 2: Critical Reagent Sourcing

Design of Experiments = ***Understand how critical material sourcing may impact process performance and product quality across a design space***



A Framework for Common-Disease Genetic Medicines

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Tune-401's CMC development for HBV aims to lay a path in collaboration with global regulatory agencies for a replicable blueprint for other epigenome editing programs targeting common and chronic diseases

Design for Scale from Day 1

Invest in Analytical Development to Support Process Understanding

Use Regulatory Flexibility Strategically

CMC Strategy Determines Patient Access

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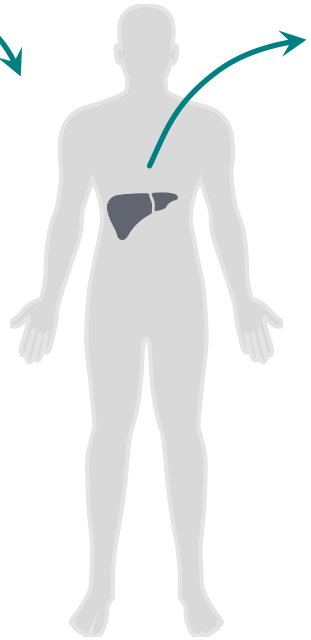
THANK YOU

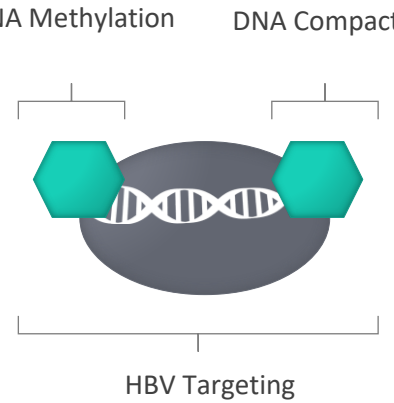
Tune-401: A first-in-class epigenetic silencer of HBV

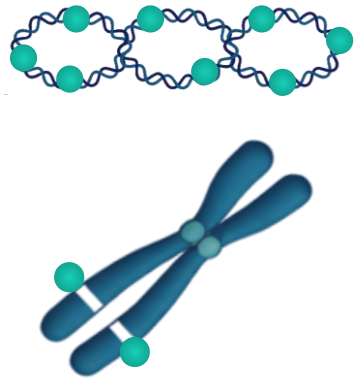
1. **Tune-401** LNP is delivered IV
2. Tune-401 is **translated** into an HBV **silencing protein** in liver
3. Tune-401 specifically **methylates integrated HBV** and **cccDNA**
4. **Virus** and associated **biomarkers** are silenced

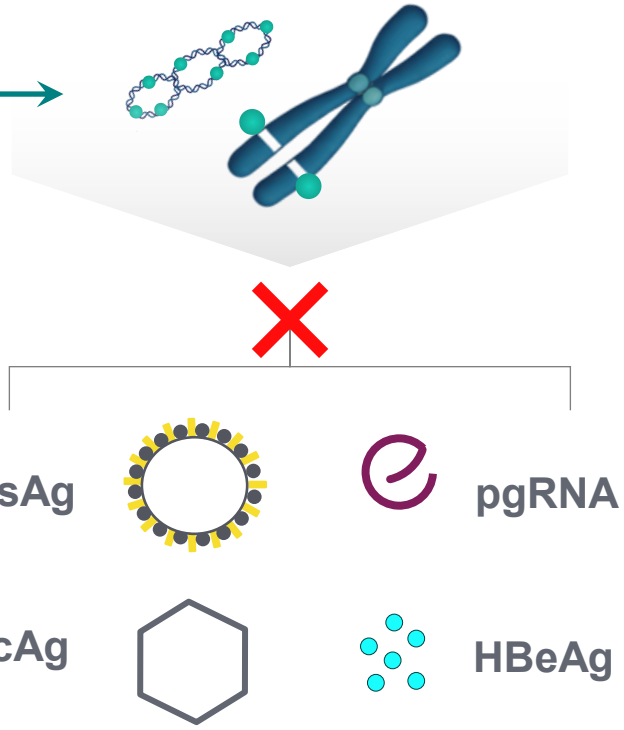
Epigenetic silencer mRNA

HBV guideRNA









The Tune-401 **target site** is conserved in 98% of HBV genome sequences

Proactive Ph2 Planning

1) Establish Process Validation Master Plan
2) Refine our selection, performance, and justification of analytical methods across our release and characterization panels
3) Deepen Process Understanding
4) Fortify Supply Chain and Materials
5) Align with Regulators and CDMOs Early

COGs, PPQ & Commercial Launch Readiness

240M patients
= unique COGs challenge

 # PPQ batches
at commercial scale

Day 0 inventory
ready at approval

COGS

- Expansion of ecosystem to support global markets
- Cost of Goods directly impacts patient access

PPQ Design Principles

- Prioritize Scale-out over Scale-up
- Establish data driven pooling strategies
- Embed Process Analytical Tech (PAT)
- Build redundancy in PPQ to survive single line points of failure

BLA CMC Priorities

- Validated analytical methods (ICH Q2)
- Ensure adequate stability data
- Characterization of CQA criticality with QTPP linkage
- Manufacturing batch record summary across development lots