TROY TECHNICAL

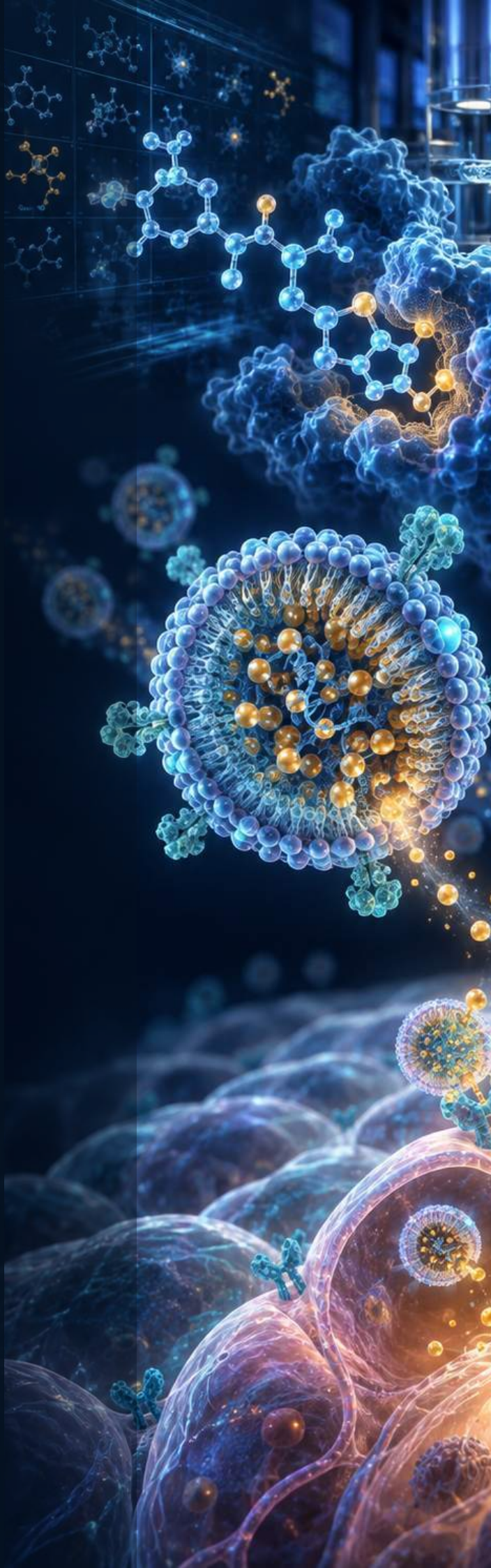
# DRUG DISCOVERY & DDS
# WEEKLY REPORT

October 31 - November 6, 2026 | Issue 2026-W44

**Target validation, translational evidence, delivery and development economics**

| 11 | 10 |
| --- | --- |
| ANALYZED ARTICLES | PRIORITY THEMES |

Issued 2026-11-06 | English edition | fixed approved cover artwork



# Drug Discovery & DDS: the boundary moved from isolated claims to qualification evidence

11 English articles were reviewed independently from the Japanese edition. Ten themes are retained for management decisions.

SIGNAL 01 | TARGET & MOLECULE

## MetaVia DA-1726: Phase 1 results for obesity and liver fat reduction

MetaVia's DA-1726 candidate demonstrated a 68% reduction in liver fat compared to placebo in a Phase 1 Part 3B interim analysis.

SIGNAL 02 | DELIVERY DESIGN

## PBGENE-HBV: Phase 1 ELIMINATE-B Data and Phase 2 Roadmap 2026

Precision BioSciences reported that PBGENE-HBV achieved undetectable pgRNA in 100% of evaluable patients at a 0.4 mg/kg dose during the Phase 1 ELIMINATE-B study.

SIGNAL 03 | PRECLINICAL PROOF

## LNP RNA Payload Quantification: TIRF and FCS Analysis 2026

Researchers used TIRF microscopy and fluorescence correlation spectroscopy (FCS) to quantify mRNA and siRNA payloads in lipid nanoparticles (LNPs).

SIGNAL 04 | CLINICAL DEVELOPMENT

## TNKS2 Inhibitor: Selective WNT Suppression via 8p Deletion

Researchers have developed a first-in-class TNKS2-selective inhibitor that targets a collateral vulnerability in cancers with chromosome 8p deletions.

DECISION

**Focus this week's management attention on target validation, translational evidence, delivery and development economics. Move only when the linked evidence can be reproduced under your own operating conditions.**

THREE MANAGEMENT MOVES

1. Buyers: separate platform promise from program-level evidence, safety and clinical differentiation.
2. Suppliers: tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.
3. Executives: track reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EVIDENCE DISCIPLINE

FACT states what the collected English source reports. BUSINESS READ and ACTION are editorial interpretations. UNKNOWN lists information that the source file does not establish. A linked article is not treated as independent confirmation of every claim.

# Five numbers or evidence anchors that require conditions

**68%**
A10

SOURCE-BOUND CONDITION
MetaVia's DA-1726 candidate demonstrated a 68% reduction in liver fat compared to placebo in a Phase 1 Part 3B interim analysis.

**100%**
A09

SOURCE-BOUND CONDITION
Precision BioSciences reported that PBGENE-HBV achieved undetectable pgRNA in 100% of evaluable patients at a 0.4 mg/kg dose during the Phase 1 ELIMINATE-B study.

**38 w**
A06

SOURCE-BOUND CONDITION
Researchers have developed ICLIST-11, a de novo designed mini-protein that binds to PACAP-38 with a $K_D$ of 4.51 nM.

**P04**
A11

SOURCE-BOUND CONDITION
Researchers have developed a first-in-class TNKS2-selective inhibitor that targets a collateral vulnerability in cancers with chromosome 8p deletions.

**P05**
A06

SOURCE-BOUND CONDITION
Researchers have developed ICLIST-11, a de novo designed mini-protein that binds to PACAP-38 with a $K_D$ of 4.51 nM.

HOW TO USE THESE NUMBERS
Each value is shown with the condition stated in the collected English article. Do not compare values across different test methods, device sizes, operating temperatures or commercial stages without normalizing those conditions.

## Where the value chain moved

Each stage combines one leading theme and one supporting theme. The report treats handoffs as evidence transfers, not decorative arrows.

1

### Target & molecule

P01/P06

MetaVia's DA-1726 candidated a 68% reduction in liver fat compared to placebo in a Phase 1 Part 3B interim.

2

### Delivery design

P02/P07

Precision BioSciences reported that PBGENE-HBV achieved undetectable pgRNA in 100% of evaluable patients at a 0.4 mg/kg dose.

3

### Preclinical proof

P03/P08

Researchers used TIRF microscopy and fluorescence correlation spectroscopy (FCS) to quantify mRNA and siRNA payloads in lipid.

4

### Clinical development

P04/P09

Researchers have developed a first-in-class TNKS2-selective inhibitor that targets a collateral vulnerability in cancers with.

5

### Access & portfolio

P05/P10

Researchers have developed ICLIST-11, a de novo designed mini-protein that binds to PACAP-38 with a $K_D$ of 4.51 nM.

EVIDENCE REQUIRED AT EACH HANDOFF

| | |
|---|---|
| Target & molecule to Delivery design | Transfer test conditions, acceptance criteria, failure data, owner and decision date. Recheck reproducibility, biodistribution, toxicity, CMC, trial design and financing. |
| Delivery design to Preclinical proof | Transfer test conditions, acceptance criteria, failure data, owner and decision date. Recheck reproducibility, biodistribution, toxicity, CMC, trial design and financing. |
| Preclinical proof to Clinical development | Transfer test conditions, acceptance criteria, failure data, owner and decision date. Recheck reproducibility, biodistribution, toxicity, CMC, trial design and financing. |
| Clinical development to Access & portfolio | Transfer test conditions, acceptance criteria, failure data, owner and decision date. Recheck reproducibility, biodistribution, toxicity, CMC, trial design and financing. |

COMMON CONTROL POINT

**No theme moves to a commercial commitment until a named owner has reproduced the relevant evidence and documented reproducibility, biodistribution, toxicity, CMC, trial design and financing.**

# Priority map: maturity and next decision locus




| | |
|---|---|
| P01 | MetaVia DA-1726: Phase 1 results for obesity and liver fat reduction<br>System / adoption \| cue: Phase 1 |
| P02 | PBGENE-HBV: Phase 1 ELIMINATE-B Data and Phase 2 Roadmap 2026<br>System / adoption \| cue: Phase 1 |
| P03 | LNP RNA Payload Quantification: TIRF and FCS Analysis 2026<br>Tech / process \| cue: no system/business cue |
| P04 | TNKS2 Inhibitor: Selective WNT Suppression via 8p Deletion<br>Tech / process \| cue: no system/business cue |
| P05 | PACAP-38 Mini-Proteins: De Novo Design of ICLIST-11 Binders<br>Tech / process \| cue: no system/business cue |
| P06 | Bispecific VSV-G Engagers: Cell-Type-Specific Viral Vector Delivery<br>System / adoption \| cue: platform |
| P07 | LPT: Bounded agentic loops for automated protein binder design<br>System / adoption \| cue: integrating |
| P08 | Ionisable Lipid Nanoparticles: pH-Dependent Mesophase Transitions<br>Tech / process \| cue: no system/business cue |
| P09 | LNP-mediated siRNA transfer: Mechanism of endosomal escape<br>System / adoption \| cue: system |
| P10 | VLPSi Nanoparticles: Tetrasulfide-Incorporated mRNA Delivery<br>Business / rules \| cue: fid |

**REPRODUCIBLE POSITIONING RULE**

Horizontal position uses five discrete stages: Research, Prototype, Joint evaluation, Product adoption and Scale. The vertical bands classify the next decision locus: Tech / process, System / adoption, or Business / rules (including supply systems). Article-title cues take precedence; the overview is used only when the title is silent. These are categories, not impact ranks. Bubble diameter reflects the editorial score.

FACT is source-bound. BUSINESS READ, ACTION and UNKNOWN are explicit editorial layers.

## P01 MetaVia DA-1726: Phase 1 results for obesity and liver fat reduction

A10 | Target & molecule | Research

2026-11-06

FACT

MetaVia's DA-1726 candidate demonstrated a 68% reduction in liver fat compared to placebo in a Phase 1 Part 3B interim analysis. The treatment also showed a 13.5% weight reduction versus placebo, indicating potential for treating obesity and metabolic-associated liver diseases.

WHY IT MATTERS

The decision relevance is target validation, translational evidence, delivery and development economics. The signal should be tested at the application and operating-system level, not accepted from a headline alone.

BUSINESS READ

For operating companies, compare the reported change with current qualification, sourcing and product-roadmap assumptions. For suppliers, tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.

ACTION

Within 30 days, separate platform promise from program-level evidence, safety and clinical differentiation; record the evidence and owner against P01.

UNKNOWN

Still unproven or incompletely stated: reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EDITORIAL SCORE 19/25 | MATURITY 1/5 | DECISION LOCUS: SYSTEM / ADOPTION

## P02 PBGENE-HBV: Phase 1 ELIMINATE-B Data and Phase 2 Roadmap 2026

A09 | Delivery design | Research

2026-11-05

FACT

Precision BioSciences reported that PBGENE-HBV achieved undetectable pgRNA in 100% of evaluable patients at a 0.4 mg/kg dose during the Phase 1 ELIMINATE-B study. The therapy demonstrated cccDNA elimination via liver biopsies and a manageable safety profile across 25 patients. These results support the program's advancement to a global Phase 2 study to evaluate viral cure rates.

WHY IT MATTERS

The decision relevance is target validation, translational evidence, delivery and development economics. The signal should be tested at the application and operating-system level, not accepted from a headline alone.

BUSINESS READ

For operating companies, compare the reported change with current qualification, sourcing and product-roadmap assumptions. For suppliers, tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.

ACTION

Within 30 days, separate platform promise from program-level evidence, safety and clinical differentiation; record the evidence and owner against P02.

UNKNOWN

Still unproven or incompletely stated: reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EDITORIAL SCORE 19/25 | MATURITY 1/5 | DECISION LOCUS: SYSTEM / ADOPTION

FACT is source-bound. BUSINESS READ, ACTION and UNKNOWN are explicit editorial layers.

## P03 LNP RNA Payload Quantification: TIRF and FCS Analysis 2026

A03 | Preclinical proof | Pilot

2026-11-06

FACT

Researchers used TIRF microscopy and fluorescence correlation spectroscopy (FCS) to quantify mRNA and siRNA payloads in lipid nanoparticles (LNPs). The study found that mRNA payload increases with LNP size according to a power law with an exponent 1.3, while siRNA/mRNA coencapsulation is competitive and constrained by diffusion.

WHY IT MATTERS

The decision relevance is target validation, translational evidence, delivery and development economics. The signal should be tested at the application and operating-system level, not accepted from a headline alone.

BUSINESS READ

For operating companies, compare the reported change with current qualification, sourcing and product-roadmap assumptions. For suppliers, tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.

ACTION

Within 30 days, separate platform promise from program-level evidence, safety and clinical differentiation; record the evidence and owner against P03.

UNKNOWN

Still unproven or incompletely stated: reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EDITORIAL SCORE 19/25 | MATURITY 2/5 | DECISION LOCUS: TECH / PROCESS

## P04 TNKS2 Inhibitor: Selective WNT Suppression via 8p Deletion

A11 | Clinical development | Pilot

2026-11-02

FACT

Researchers have developed a first-in-class TNKS2-selective inhibitor that targets a collateral vulnerability in cancers with chromosome 8p deletions. By exploiting a specific flexible loop in TNKS2, the inhibitor suppresses WNT signaling in TNKS1-deficient cells while avoiding the on-target toxicities associated with broad TNKS1/2 inhibition.

WHY IT MATTERS

The decision relevance is target validation, translational evidence, delivery and development economics. The signal should be tested at the application and operating-system level, not accepted from a headline alone.

BUSINESS READ

For operating companies, compare the reported change with current qualification, sourcing and product-roadmap assumptions. For suppliers, tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.

ACTION

Within 30 days, separate platform promise from program-level evidence, safety and clinical differentiation; record the evidence and owner against P04.

UNKNOWN

Still unproven or incompletely stated: reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EDITORIAL SCORE 19/25 | MATURITY 2/5 | DECISION LOCUS: TECH / PROCESS

FACT is source-bound. BUSINESS READ, ACTION and UNKNOWN are explicit editorial layers.

## P05 PACAP-38 Mini-Proteins: De Novo Design of ICLIST-11 Binders

A06 | Access & portfolio | Pilot

2026-11-02

FACT

Researchers have developed ICLIST-11, a de novo designed mini-protein that binds to PACAP-38 with a $K_D$ of 4.51 nM. This medium-molecular-weight binder demonstrates potent neutralizing activity against PAC1R activation, offering a potential alternative to antibody-based migraine treatments.

WHY IT MATTERS

The decision relevance is target validation, translational evidence, delivery and development economics. The signal should be tested at the application and operating-system level, not accepted from a headline alone.

BUSINESS READ

For operating companies, compare the reported change with current qualification, sourcing and product-roadmap assumptions. For suppliers, tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.

ACTION

Within 30 days, separate platform promise from program-level evidence, safety and clinical differentiation; record the evidence and owner against P05.

UNKNOWN

Still unproven or incompletely stated: reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EDITORIAL SCORE 19/25 | MATURITY 2/5 | DECISION LOCUS: TECH / PROCESS

## P06 Bispecific VSV-G Engagers: Cell-Type-Specific Viral Vector Delivery

A07 | Target & molecule | Pilot

2026-11-03

FACT

Researchers have developed reversible bispecific engagers that enable cell-type-specific delivery of VSV-G-pseudotyped lentiviral vectors. By utilizing a cell-specific ligand fused to VSV-G-binding domains of LDLR, the platform allows for targeted transduction of specific cells, including the in vivo generation of CAR T cells to control multiple myeloma tumors.

WHY IT MATTERS

The decision relevance is target validation, translational evidence, delivery and development economics. The signal should be tested at the application and operating-system level, not accepted from a headline alone.

BUSINESS READ

For operating companies, compare the reported change with current qualification, sourcing and product-roadmap assumptions. For suppliers, tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.

ACTION

Within 30 days, separate platform promise from program-level evidence, safety and clinical differentiation; record the evidence and owner against P06.

UNKNOWN

Still unproven or incompletely stated: reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EDITORIAL SCORE 19/25 | MATURITY 2/5 | DECISION LOCUS: SYSTEM / ADOPTION

FACT is source-bound. BUSINESS READ, ACTION and UNKNOWN are explicit editorial layers.

## P07 LPT: Bounded agentic loops for automated protein binder design

A08 | Delivery design | Research

2026-10-30

FACT

LPT (little protein tiger) is a framework that uses fixed orchestration of LLM stages and bounded agentic loops to automate de novo protein binder design. By integrating a curated database of approximately 14,000 papers, the system enables the autonomous identification of targets and design of candidate binders with minimal token consumption.

WHY IT MATTERS

The decision relevance is target validation, translational evidence, delivery and development economics. The signal should be tested at the application and operating-system level, not accepted from a headline alone.

BUSINESS READ

For operating companies, compare the reported change with current qualification, sourcing and product-roadmap assumptions. For suppliers, tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.

ACTION

Within 30 days, separate platform promise from program-level evidence, safety and clinical differentiation; record the evidence and owner against P07.

UNKNOWN

Still unproven or incompletely stated: reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EDITORIAL SCORE 19/25 | MATURITY 1/5 | DECISION LOCUS: SYSTEM / ADOPTION

## P08 Ionisable Lipid Nanoparticles: pH-Dependent Mesophase Transitions

A04 | Preclinical proof | Pilot

2026-10-30

FACT

Researchers have established a quantitative continuum framework to describe the pH- and temperature-dependent phase behavior of ionisable lipid nanoparticles (LNPs). The study identifies that geometric frustration from packing constraints determines mesophase stability, suggesting that metastable states are an inherent feature of the LNP core phase.

WHY IT MATTERS

The decision relevance is target validation, translational evidence, delivery and development economics. The signal should be tested at the application and operating-system level, not accepted from a headline alone.

BUSINESS READ

For operating companies, compare the reported change with current qualification, sourcing and product-roadmap assumptions. For suppliers, tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.

ACTION

Within 30 days, separate platform promise from program-level evidence, safety and clinical differentiation; record the evidence and owner against P08.

UNKNOWN

Still unproven or incompletely stated: reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EDITORIAL SCORE 19/25 | MATURITY 2/5 | DECISION LOCUS: TECH / PROCESS

FACT is source-bound. BUSINESS READ, ACTION and UNKNOWN are explicit editorial layers.

## P09 LNP-mediated siRNA transfer: Mechanism of endosomal escape

A02 | Clinical development | Pilot

2026-11-03

FACT

Researchers have developed a cell-free system using giant unilamellar vesicles (GUVs) to demonstrate that siRNA can cross endosomal membranes without causing membrane rupture. The study finds that acidification promotes siRNA translocation via lipid association while preserving the membrane's barrier function. This provides a platform to optimize lipid nanoparticle (LNP) formulations for higher efficacy and lower toxicity.

WHY IT MATTERS

The decision relevance is target validation, translational evidence, delivery and development economics. The signal should be tested at the application and operating-system level, not accepted from a headline alone.

BUSINESS READ

For operating companies, compare the reported change with current qualification, sourcing and product-roadmap assumptions. For suppliers, tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.

ACTION

Within 30 days, separate platform promise from program-level evidence, safety and clinical differentiation; record the evidence and owner against P09.

UNKNOWN

Still unproven or incompletely stated: reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EDITORIAL SCORE 18/25 | MATURITY 2/5 | DECISION LOCUS: SYSTEM / ADOPTION

## P10 VLPSi Nanoparticles: Tetrasulfide-Incorporated mRNA Delivery

A01 | Access & portfolio | Pilot

2026-11-03

FACT

Researchers have developed virus-like porous silica (VLPSi) nanoparticles incorporating tetrasulfide to overcome the cellular uptake and stability limitations of lipid nanoparticles (LNPs). The study demonstrates that tuning nanospike morphology and utilizing biodegradable silica chemistry significantly enhances mRNA expression and stability.

WHY IT MATTERS

The decision relevance is target validation, translational evidence, delivery and development economics. The signal should be tested at the application and operating-system level, not accepted from a headline alone.

BUSINESS READ

For operating companies, compare the reported change with current qualification, sourcing and product-roadmap assumptions. For suppliers, tie formulation, carriers and analytics to exposure, manufacturability and regulatory control.

ACTION

Within 30 days, separate platform promise from program-level evidence, safety and clinical differentiation; record the evidence and owner against P10.

UNKNOWN

Still unproven or incompletely stated: reproducibility, biodistribution, toxicity, CMC, trial design and financing.

EDITORIAL SCORE 18/25 | MATURITY 2/5 | DECISION LOCUS: BUSINESS / RULES

# Playbook and 0-5 year roadmap

| STAKEHOLDER | NOW \| 0-30 DAYS | NEXT \| 1-12 MONTHS | LATER \| 1-5 YEARS |
|---|---|---|---|
| **Operating companies** | separate platform promise from program-level evidence, safety and clinical differentiation | Run production-like qualification with explicit acceptance and stop criteria. | Build a portfolio and architecture that can absorb technology and supplier changes. |
| **Materials, equipment and technology suppliers** | tie formulation, carriers and analytics to exposure, manufacturability and regulatory control | Create shared reliability, process-window and failure-analysis data with customers. | Standardize interfaces, traceability, lifecycle support and recovery services. |
| **Trading, investment and legal teams** | Map reproducibility, biodistribution, toxicity, CMC, trial design and financing. | Contract for capacity, quality, change notice, liability, alternatives and exit. | Diversify regional, technical and customer concentration risk. |

ROADMAP

NOW | 0-30 DAYS
**Evidence ledger**
Owner: Strategy + quality
Deliverable: claim, source, condition, owner

NOW | 0-30 DAYS
**Risk screen**
Owner: Procurement + legal
Deliverable: unknowns, alternatives, stop

NEXT | 1-12 MONTHS
**Joint qualification**
Owner: R&D + supplier
Deliverable: process window and failure data

NEXT | 1-12 MONTHS
**Commercial gate**
Owner: Business + finance
Deliverable: unit economics and capacity

LATER | 1-5 YEARS
**Platform strategy**
Owner: Executive team
Deliverable: portfolio and interface roadmap

LATER | 1-5 YEARS
**Service layer**
Owner: Operations + channel
Deliverable: monitoring, maintenance and recovery

GO / NO-GO GATES

| GATE | OWNER | REQUIRED EVIDENCE | NO-GO CONDITION |
|---|---|---|---|
| **G1 Evidence** | **Quality** | Source, test conditions and reproducibility | No traceable evidence |
| **G2 Integration** | **R&D** | Interface, process window and failure analysis | Cannot meet system conditions |
| **G3 Commercial** | **Business** | Capacity, total cost, contract and alternatives | Economics or supply cannot be supported |
| **G4 Lifecycle** | **Operations** | Monitoring, maintenance, change notice and exit | No accountable operating plan |

## ANALYZED ARTICLES | ITEMS 01-11

Every title and URL is displayed in full. URLs wrap without shortening and remain clickable. A verified-reference label means the translated HTML did not retain its original source URL.

| ID | FULL ARTICLE TITLE | FULL SOURCE / VERIFIED REFERENCE URL - CLICKABLE |
|---|---|---|
| A01 | VLPSi Nanoparticles: Tetrasulfide-Incorporated mRNA Delivery | https://www.biorxiv.org/content/10.64898/2026.11.03.763884v1 |
| A02 | LNP-mediated siRNA transfer: Mechanism of endosomal escape | https://www.biorxiv.org/content/10.64898/2026.11.02.763664v1 |
| A03 | LNP RNA Payload Quantification: TIRF and FCS Analysis 2026 | https://www.biorxiv.org/content/10.64898/2026.11.05.763588v1 |
| A04 | Ionisable Lipid Nanoparticles: pH-Dependent Mesophase Transitions | https://www.biorxiv.org/content/10.64898/2026.10.28.762589v1 |
| A05 | ASO Chemical Conjugates: Cell-Resolved Activity vs Whole-Tissue | https://www.biorxiv.org/content/10.64898/2026.10.30.762893v1 |
| A06 | PACAP-38 Mini-Proteins: De Novo Design of ICLIST-11 Binders | https://www.biorxiv.org/content/10.64898/2026.10.30.763049v1 |
| A07 | Bispecific VSV-G Engagers: Cell-Type-Specific Viral Vector Delivery | https://www.biorxiv.org/content/10.64898/2026.11.02.763599v1 |
| A08 | LPT: Bounded agentic loops for automated protein binder design | https://www.biorxiv.org/content/10.64898/2026.10.29.762730v1 |
| A09 | PBGENE-HBV: Phase 1 ELIMINATE-B Data and Phase 2 Roadmap 2026 | https://uk.finance.yahoo.com/news/precision-biosciences-announces-breaking-pbgene-120000321.html |
| A10 | MetaVia DA-1726: Phase 1 results for obesity and liver fat reduction | https://www.yakup.com/news/?mode=view&cat=12&cat2=121&cat3=0&nid=334867 |
| A11 | TNKS2 Inhibitor: Selective WNT Suppression via 8p Deletion | https://doi.org/10.1038/s41589-026-02358-z |

# DrugDiscovery_DDS — Selected Articles

Date: 2026-11-08

Articles: 11

# Table of Contents

#01 VLPSi Nanoparticles: Tetrasulfide-Incorporated mRNA Delivery

#02 LNP-mediated siRNA transfer: Mechanism of endosomal escape

#03 LNP RNA Payload Quantification: TIRF and FCS Analysis 2026

#04 Ionisable Lipid Nanoparticles: pH-Dependent Mesophase Transitions

#05 ASO Chemical Conjugates: Cell-Resolved Activity vs Whole-Tissue

#06 PACAP-38 Mini-Proteins: De Novo Design of ICLIST-11 Binders

#07 Bispecific VSV-G Engagers: Cell-Type-Specific Viral Vector Delivery

#08 LPT: Bounded agentic loops for automated protein binder design

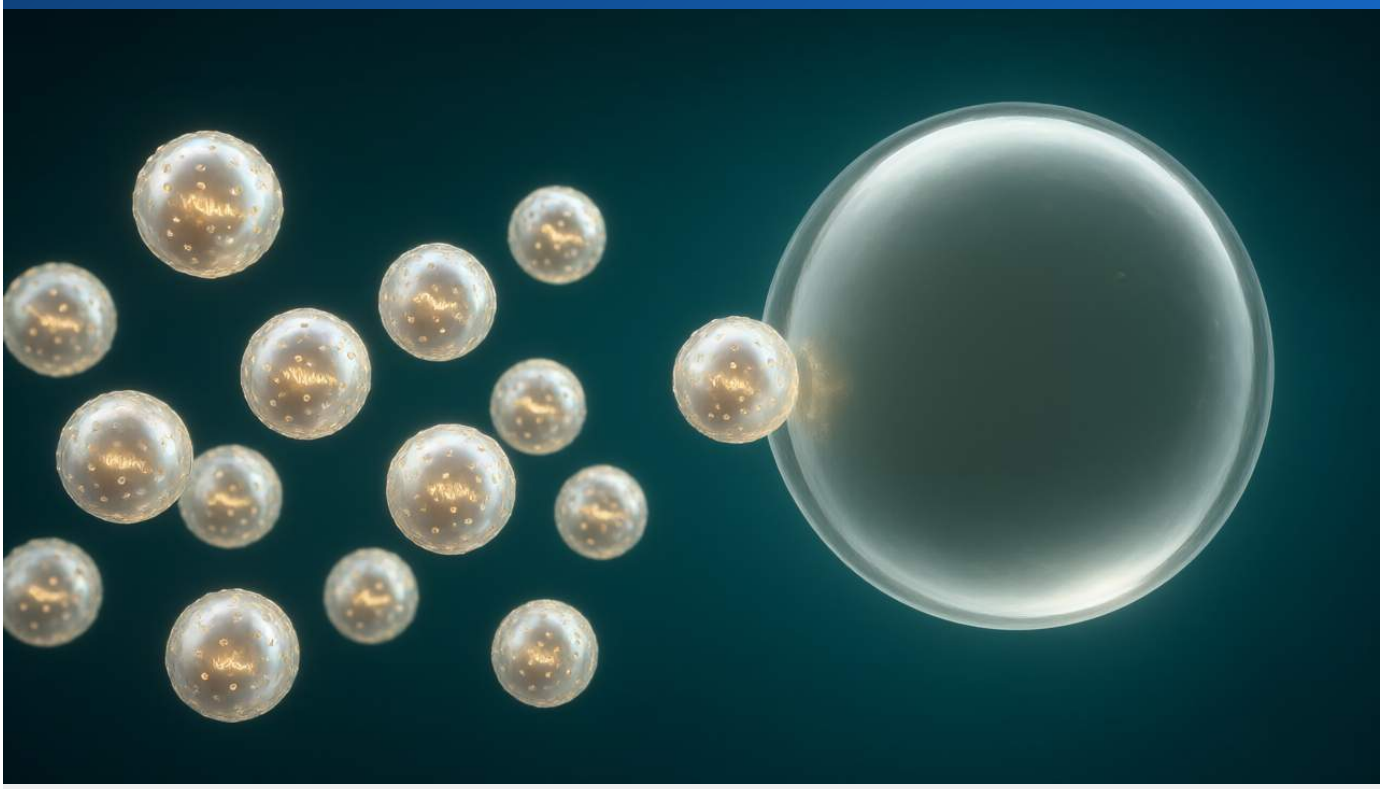
#09 PBGENE-HBV: Phase 1 ELIMINATE-B Data and Phase 2 Roadmap 2026

#10 MetaVia DA-1726: Phase 1 results for obesity and liver fat reduction

#11 TNKS2 Inhibitor: Selective WNT Suppression via 8p Deletion

# #01 VLPSi Nanoparticles: Tetrasulfide-Incorporated mRNA Delivery

Published November 03, 2026　bioRxiv (University of Eastern Finland)　フィンランド



## OVERVIEW

Researchers have developed virus-like porous silica (VLPSi) nanoparticles incorporating tetrasulfide to overcome the cellular uptake and stability limitations of lipid nanoparticles (LNPs). The study demonstrates that tuning nanospike morphology and utilizing biodegradable silica chemistry significantly enhances mRNA expression and stability.

## IN DEPTH

### Key Findings

The study identifies a direct structure-function relationship between virus-like topography, biodegradable silica chemistry, and mRNA delivery efficiency. The primary result indicates that increasing the length and number of spikes on the VLPSi surface significantly improves cellular uptake efficiency and subsequent mRNA expression.

### Technical Details

The developed platform utilizes tetrasulfide-incorporated virus-like porous silica (VLPSi) nanoparticles. By systematically tuning synthesis parameters, the researchers produced a series of nanoparticles with distinct morphologies and architectures to evaluate the specific effects of particle morphology and tetrasulfide on delivery. The performance of these nanoparticles was optimized through the evaluation of:

- Cellular uptake efficiency
- Cytotoxicity
- Transfection performance using various lipid and mRNA payloads across multiple cell types

Mechanistically, the enhancement in delivery is attributed to the combined effect of the surface nanospikes and the intracellular degradation of the tetrasulfide.

### Background & Context

Lipid nanoparticles (LNPs) are currently the most studied nanocarriers for mRNA delivery. However, their broader application is hindered by several technical bottlenecks, including suboptimal cellular uptake, low delivery efficacy, and poor stability. The VLPSi platform was designed as a safe and efficient alternative or enhancement to LNP-mediated delivery to address these specific limitations.

## Significance & Outlook

The VLPSi nanoparticles significantly enhance the stability of mRNA compared to existing methods. By providing a bioinspired nanoplatform that is both structurally tunable and biodegradable, this research offers a highly effective method for improving the delivery of genetic payloads. This framework establishes a basis for using biodegradable silica chemistry and virus-like morphology to optimize the transport of mRNA into cells.

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Source: https://www.biorxiv.org/content/10.64898/2026.11.03.763884v1

Collected: November 07, 2026 | Automated Research System (AI)

# #02 LNP-mediated siRNA transfer: Mechanism of endosomal escape

Published November 03, 2026 bioRxiv (Human Technopole)



## OVERVIEW

Researchers have developed a cell-free system using giant unilamellar vesicles (GUVs) to demonstrate that siRNA can cross endosomal membranes without causing membrane rupture. The study finds that acidification promotes siRNA translocation via lipid association while preserving the membrane's barrier function. This provides a platform to optimize lipid nanoparticle (LNP) formulations for higher efficacy and lower toxicity.

## IN DEPTH

### Key Findings

The study demonstrates that siRNA transfer from lipid nanoparticles (LNPs) across endosomal membrane mimics can occur without the detectable dissipation of the transmembrane pH gradient or membrane rupture. Using a cell-free system, the researchers found that acidification promotes LNP-membrane association and lipid redistribution, enabling siRNA translocation into the receiving lumen while maintaining the membrane's barrier function.

### Technical Details

To dissect the mechanism of delivery, the researchers employed giant unilamellar vesicles (GUVs) with a lipid composition mimicking early endosomes. The following technical observations were made:

- **Imaging:** Cryo-electron tomography revealed local interfacial lipid reorganization but no detectable membrane rupture.
- **Diffusion:** Fluorescence correlation spectroscopy showed heterogeneous diffusion of translocated siRNA, indicating the presence of both free and lipid-associated species.
- **Complexes:** Pre-formed RNA-lipid complexes exhibited pH-dependent dissociation and heterogeneous diffusion, suggesting that lipid association is a likely cause of slower luminal diffusion.
- **Inhibitors:** Preincubation with serum or apolipoprotein-E was found to reduce the translocation of siRNA into the GUV lumen.

### Background & Context

Endosomal escape is a primary limiting factor in RNA delivery via LNPs. Previous concerns suggested that if escape requires membrane rupture, productive delivery would be intrinsically linked to membrane damage and subsequent cellular toxicity. This research sought to determine if siRNA transfer could occur while the membrane barrier remains intact.

## Significance & Outlook

These findings support a model where siRNA-lipid association facilitates the crossing of the membrane without sustained loss of barrier function. By establishing this cell-free platform, the researchers provide a method to dissect LNP-mediated RNA delivery and develop new formulations that improve delivery efficacy while limiting potential membrane damage.

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Source: https://www.biorxiv.org/content/10.64898/2026.11.02.763664v1

Collected: November 07, 2026 | Automated Research System (AI)

# #03 LNP RNA Payload Quantification: TIRF and FCS Analysis 2026

Published November 06, 2026 bioRxiv (Ludwig-Maximilians-Universität München) Germany



## OVERVIEW

Researchers used TIRF microscopy and fluorescence correlation spectroscopy (FCS) to quantify mRNA and siRNA payloads in lipid nanoparticles (LNPs). The study found that mRNA payload increases with LNP size according to a power law with an exponent 1.3, while siRNA/mRNA coencapsulation is competitive and constrained by diffusion.

## IN DEPTH

### Key Findings

Fluorescence correlation spectroscopy (FCS) has been identified as a reliable method for determining RNA payload in lipid nanoparticles (LNPs), as it remains independent of fluorophore properties that may change during the encapsulation process. In tests using eGFP coding mRNA, the mRNA payload increases in relation to LNP size following a power law with an exponent 1.3. Additionally, the study found that when coencapsulating siRNA and mRNA, the siRNA fraction within the LNPs exceeds the fraction present in the initial RNA mixture.

### Technical Details

The researchers employed two primary imaging and spectroscopy techniques to analyze the vectors:

- **Total Internal Reflection Fluorescence (TIRF) microscopy:** Used to determine mRNA and siRNA/mRNA codelivered payloads.
- **Fluorescence Correlation Spectroscopy (FCS):** Used for precise payload determination.
- **Cryogenic Electron Microscopy (Cryo-EM):** Used to observe structural characteristics, revealing that blebs occur more frequently in smaller LNPs.

The study varied the PEG-lipid fraction relative to the reference ONPATTRO formulation to observe changes in payload and size. The results regarding siRNA/mRNA coencapsulation suggest that the process is competitive and limited by nucleic acid diffusion.

### Background & Context

Lipid nanoparticles are currently the most promising vectors for delivering nucleic acids to mammalian cells. As delivery strategies evolve to include multiple nucleic acid species, there is an increasing need for reliable methods to determine LNP size and the exact amount of RNA payload being delivered.

## Significance & Outlook

These findings emphasize that particle size and encapsulation kinetics are critical factors in controlling the loading and composition of RNA payloads. By providing a reliable quantification method via FCS, this research offers a pathway to better control the composition of advanced LNP-based delivery systems.

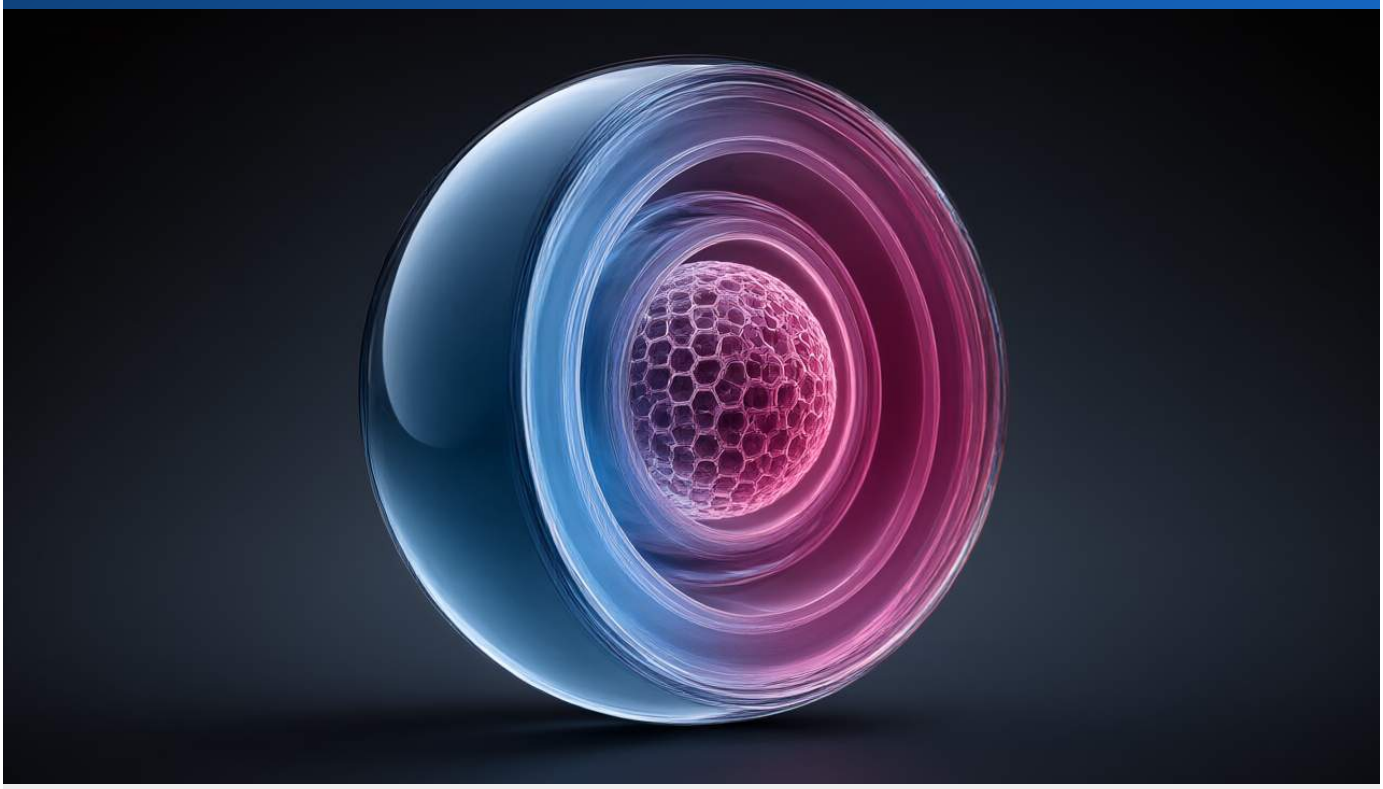
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Source: https://www.biorxiv.org/content/10.64898/2026.11.05.763588v1

Collected: November 07, 2026 | Automated Research System (AI)

# #04 Ionisable Lipid Nanoparticles: pH-Dependent Mesophase Transitions

Published October 30, 2026 bioRxiv (University of Augsburg) Germany



## OVERVIEW

Researchers have established a quantitative continuum framework to describe the pH- and temperature-dependent phase behavior of ionisable lipid nanoparticles (LNPs). The study identifies that geometric frustration from packing constraints determines mesophase stability, suggesting that metastable states are an inherent feature of the LNP core phase.

## IN DEPTH

### Key Findings

The study establishes a quantitative continuum theory for pH-dependent mesophase transitions in ionisable lipid nanoparticles (LNPs), specifically identifying the existence of kinetically trapped metastable states in the LNP core phase in response to pH changes. By combining experimental data with theoretical analysis, the researchers determined that geometric frustration resulting from packing constraints is a primary determinant of mesophase stability.

### Technical Details

The research utilized a combination of small-angle X-ray scattering (SAXS), Laurdan fluorescence spectroscopy, all-atom molecular dynamics simulations, and continuum modeling to analyze LNPs containing the ionisable lipids MC3 or ALC-0315. Key technical results include:

- Laurdan fluorescence measurements were found to report the same pH- and temperature-dependent transitions in both bulk lipid systems and LNPs.
- These transitions closely follow the inverse micellar (L II) to inverse hexagonal (H II) transitions identified via SAXS.
- The researchers parameterized a continuum model of the L II - H II transition to provide a quantitative description of stability.
- The analysis determined relevant membrane parameters, including Gaussian curvature bending rigidities and mean curvature bending rigidities, to identify the parameter ranges governing phase stability.

### Background & Context

LNPs are currently the primary delivery vehicles for RNA-based therapies. It has been proposed that pH-dependent mesophase transitions of ionisable lipids are crucial for LNP function and the process of endosomal escape. However, until this study, a consistent quantitative framework linking the thermodynamics of these transitions to molecular lipid properties was lacking.

## Significance & Outlook

By providing a quantitative link between molecular properties and mesophase thermodynamics, this framework allows for a deeper understanding of how LNP cores behave under varying pH and temperature conditions. The identification of metastable states as an inherent feature of the LNP core phase provides a theoretical basis for optimizing the delivery efficiency of RNA-based therapeutics.

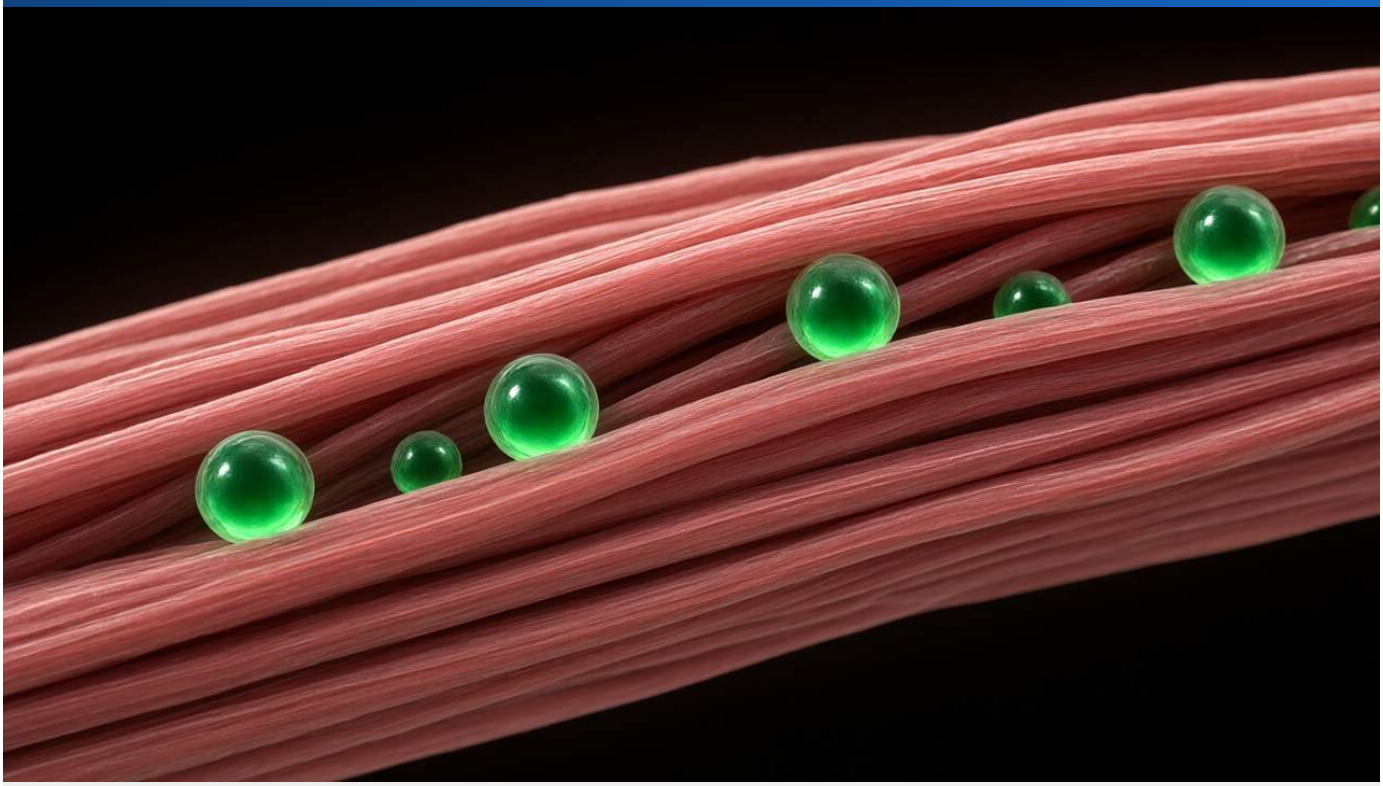
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# #05 ASO Chemical Conjugates: Cell-Resolved Activity vs Whole-Tissue

Published November 02, 2026 bioRxiv (Genetics and Genomic Medicine Research and Teaching Department)



## OVERVIEW

Researchers utilized a PDGFRα-eGFP mouse model to demonstrate that cell-resolved profiling reveals tissue- and cell-population-specific activity of antisense oligonucleotide (ASO) conjugates that whole-tissue measurements miss. Palmitate conjugation showed the broadest extrahepatic activity, specifically within PDGFRα$^{+}$ skeletal-muscle populations.

## IN DEPTH

### Key Findings

Cell-resolved pharmacodynamic profiling reveals that the activity of chemically conjugated ASOs varies significantly by tissue and conjugate chemistry. Palmitate conjugation produced the broadest extrahepatic activity and demonstrated pronounced whole-tissue activity in the heart and skeletal muscle. Crucially, cell-resolved analysis identified preferential palmitate-ASO activity specifically within PDGFRα$^{+}$ skeletal-muscle populations, a detail not fully captured by whole-tissue measurements.

### Technical Details

The study employed a platelet-derived growth factor receptor alpha-enhanced green fluorescent protein (PDGFRα-eGFP) mouse model to assess in vivo uptake in PDGFRα-expressing (GFP$^{+}$) cells. This model serves as a tool for evaluating ASO activity within mesenchymal stromal and progenitor populations, primarily tissue fibroblasts. The researchers used the knockdown of metastasis-associated lung adenocarcinoma transcript 1 (Malat1) as the pharmacodynamic readout. Following subcutaneous administration, Malat1 levels were quantified and compared between whole tissues and cell-sorted PDGFRα$^{+}$/GFP$^{+}$ and PDGFRα$^{-}$/GFP$^{-}$ populations.

### Safety Assessment

Preliminary safety evaluations indicated conjugate-dependent differences in toxicity:

- Tocopherol-ASO treatment in male mice resulted in body-weight loss and ALT elevation.
- Spleen enlargement was observed in both sexes.

## Background and Significance

While chemical conjugation is used to modulate ASO pharmacology and improve organ-specific delivery, traditional whole-tissue measurements provide limited information regarding which specific cell types are being targeted. By implementing a cell-resolved assessment, this research provides an in vivo modelling system capable of distinguishing activity between different cell populations within the same organ. This approach demonstrates the advantages of cell-resolved profiling over whole-tissue measurements for the precise evaluation of ASO conjugate efficacy and distribution.

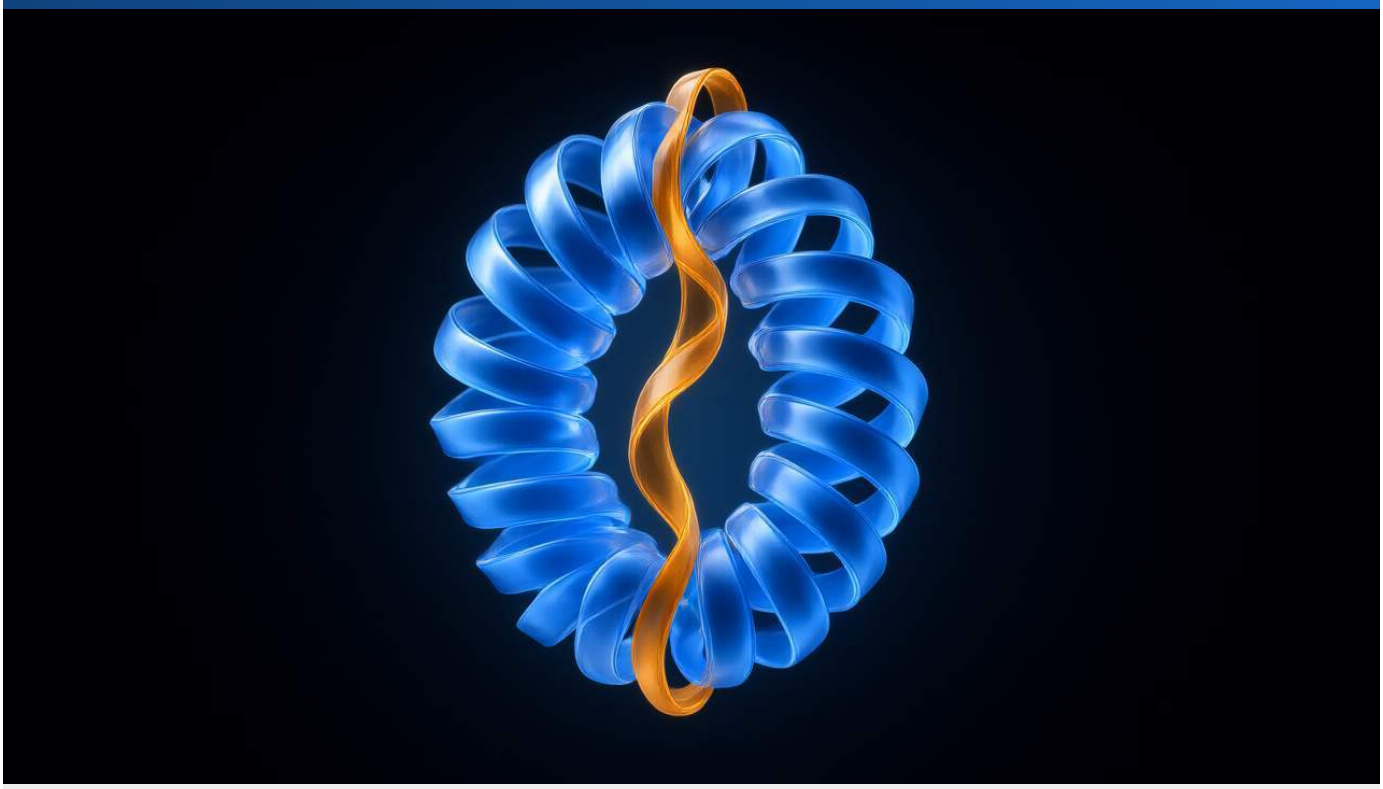
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Collected: November 07, 2026 | Automated Research System (AI)

# #06 PACAP-38 Mini-Proteins: De Novo Design of ICLIST-11 Binders

Published November 02, 2026 bioRxiv (Imperial College London) UK



## OVERVIEW

Researchers have developed ICLIST-11, a de novo designed mini-protein that binds to PACAP-38 with a $K_D$ of 4.51 nM. This medium-molecular-weight binder demonstrates potent neutralizing activity against PAC1R activation, offering a potential alternative to antibody-based migraine treatments.

## IN DEPTH

### Key Findings

The study successfully designed ICLIST-11, a mini-protein that exhibits high affinity for Pituitary adenylate cyclase-activating peptide 38 (PACAP-38) with a $K_D$ of 4.51 nM. In cell-based functional assays, ICLIST-11 showed concentration-dependent neutralizing activity against PACAP-38-induced PAC1R activation with an $IC_{50}$ of 10.6 nM, significantly outperforming the initial design, ICLIST-2.

### Technical Details

The development process utilized a computational pipeline involving Bindcraft and ProteinMPNN:

- **Initial Design:** Bindcraft was used to identify ICLIST-2, a 63-residue peptide with a $K_D$ of 26.5 nM.
- **Optimization:** Alanine scanning and structural analysis of ICLIST-2 identified residues for optimization. Using ProteinMPNN, researchers implemented nine amino acid substitutions to create ICLIST-11.
- **Stability and Affinity:** ICLIST-11 achieved a $T_m$ value 14 °C higher than its predecessor. Molecular dynamics (MD) simulations suggest that the substitution of three residues with hydrophobic residues (E30F, M31L, and R54W) contributed to this increased stability. Interaction analysis further suggests that three specific mutations were critical for enhancing binding affinity.

### Background & Context

PACAP-38 is a vasoactive peptide identified as a key mediator of migraine and a target for next-generation treatments. While antibodies against PACAP-38 have shown promising results as ligand trap medicines in clinical trials, this research explores the potential of medium-molecular-weight drugs as an alternative therapeutic modality.

## Significance & Outlook

The transition from ICLIST-2 to ICLIST-11 demonstrates the efficacy of combining de novo design tools with structural optimization to improve both the affinity and thermal stability of mini-proteins. These results establish a computational framework for the discovery of protein drugs targeting PACAP-38.

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Source: https://www.biorxiv.org/content/10.64898/2026.10.30.763049v1

Collected: November 07, 2026 | Automated Research System (AI)

# #07 Bispecific VSV-G Engagers: Cell-Type-Specific Viral Vector Delivery

Published November 03, 2026　bioRxiv (Weizmann Institute of Science)　イスラエル



## OVERVIEW

Researchers have developed reversible bispecific engagers that enable cell-type-specific delivery of VSV-G-pseudotyped lentiviral vectors. By utilizing a cell-specific ligand fused to VSV-G-binding domains of LDLR, the platform allows for targeted transduction of specific cells, including the in vivo generation of CAR T cells to control multiple myeloma tumors.

## IN DEPTH

### Key Findings

The developed bispecific engagers enable the selective delivery of viral vectors to specific cell types, overcoming the lack of specificity in standard VSV-G-pseudotyped lentiviral vectors (LVVs). A trimeric CEACAM8-based engager blocked non-specific VSV infection through LDLR with an IC50 of 16.7 pM while facilitating the lysis of CEACAM6-positive tumor cells. Furthermore, an anti-CD3-based trimeric engager demonstrated high transduction efficiency in non-preactivated T cells within human PBMCs.

### Technical Details

The platform utilizes reversible engagers composed of a cell-specific ligand or antibody fused to the VSV-G-binding domains of the LDL receptor (LDLR), which are approximately 40 amino acids in length. The mechanism operates as follows:

- The engager binds to the target cell and the VSV-G protein.
- Following endocytosis, the engager dissociates.
- Unmodified VSV-G is released to ensure the efficient delivery of the vector cargo.

Specific applications include an engager comprising the CEACAM8 N-terminal domain for the selective transduction of CEACAM6-positive epithelial cells.

### Background & Context

VSV-G-pseudotyped LVVs are highly efficient for ex vivo gene delivery because they utilize the broadly expressed LDL receptor (LDLR). However, this broad expression prevents the cell-type specificity required for effective in vivo applications. The bispecific engager platform addresses this limitation by redirecting the vector to specific cellular targets.

## Significance & Outlook

The platform has demonstrated efficacy in vivo, where engager-mediated CAR T cell generation resulted in the sustained control of human OPM2 multiple myeloma tumors in NSG mice. This technology provides a foundation for advancing in vivo gene therapies, specifically in the fields of in vivo CAR T-cell therapy and tumor-directed oncolytic virotherapy.

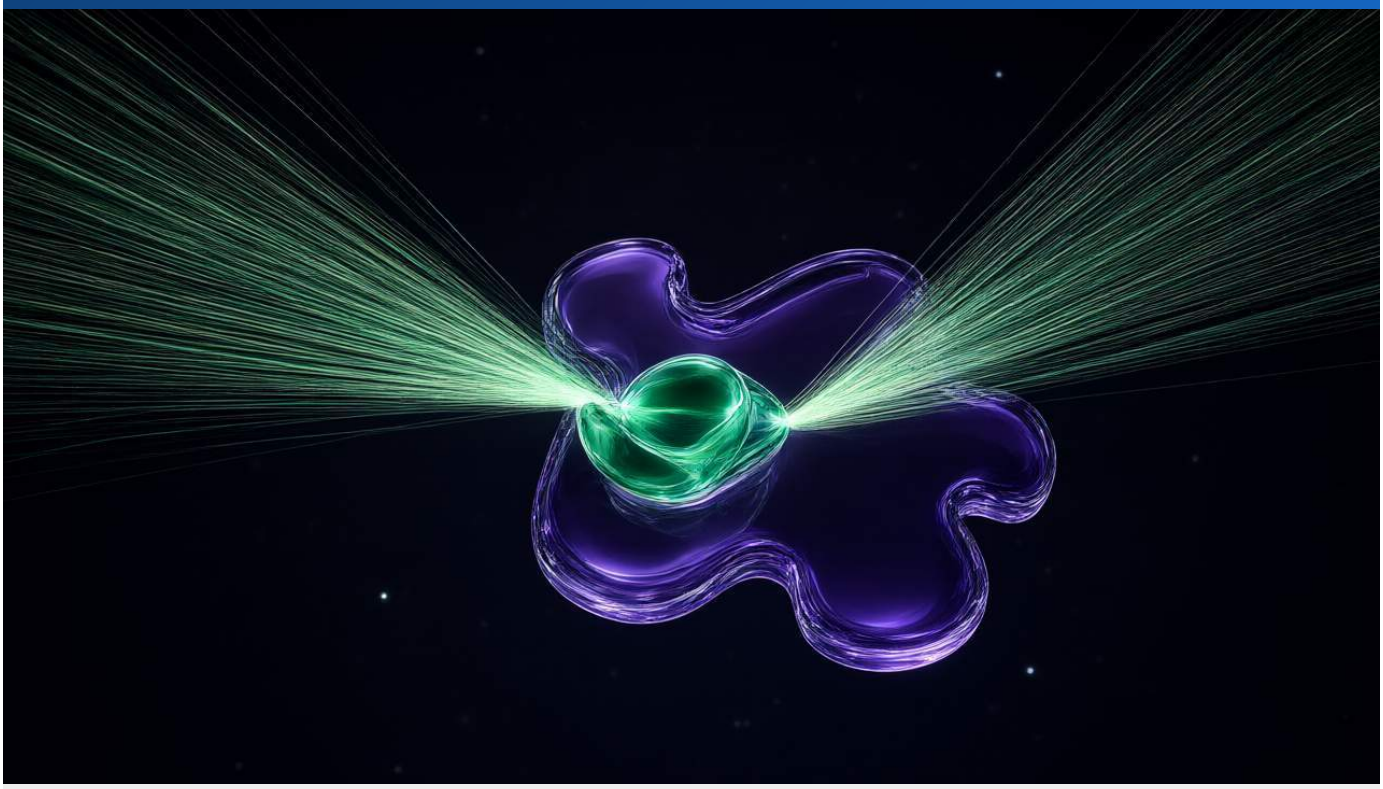
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Source: https://www.biorxiv.org/content/10.64898/2026.11.02.763599v1

Collected: November 07, 2026 | Automated Research System (AI)

# #08 LPT: Bounded agentic loops for automated protein binder design

Published October 30, 2026 bioRxiv (Hubrecht Institute)



## OVERVIEW

LPT (little protein tiger) is a framework that uses fixed orchestration of LLM stages and bounded agentic loops to automate de novo protein binder design. By integrating a curated database of approximately 14,000 papers, the system enables the autonomous identification of targets and design of candidate binders with minimal token consumption.

## IN DEPTH

### Key Findings

LPT successfully executed three end-to-end design campaigns initiated from single natural language prompts to disrupt CALCRL/RAMP1, PD-1/PD-L1, and PVR-TIGIT interactions. The framework autonomously identified design intent, selected targets, structures, and hotspot residues to design candidate binders. Cross-validation using multiple folding models indicates a high in silico success rate while maintaining low computational costs and minimal token consumption.

### Technical Details

The LPT framework employs a fixed orchestration of LLM stages, where each stage operates within a bounded agentic loop featuring custom system prompts and specific tool access. To overcome the limitations of broad or outdated LLM training data, LPT utilizes a curated literature database containing approximately 14,000 papers digested into key findings. This specialized knowledge retrieval significantly improves accuracy: in tests using questions drawn from the database, the LLM with database access answered 41/48 questions correctly, whereas the model without access answered none.

### Background & Context

Current large language models possess the ability to reason over scientific data and utilize code-based tools, but they often lack specialized knowledge and struggle with source attribution. Furthermore, unconstrained agentic workflows and unlimited tool use frequently result in the consumption of excessive amounts of tokens. LPT addresses these inefficiencies by bounding the agentic loops and providing a structured orchestration of stages.

### Significance & Outlook

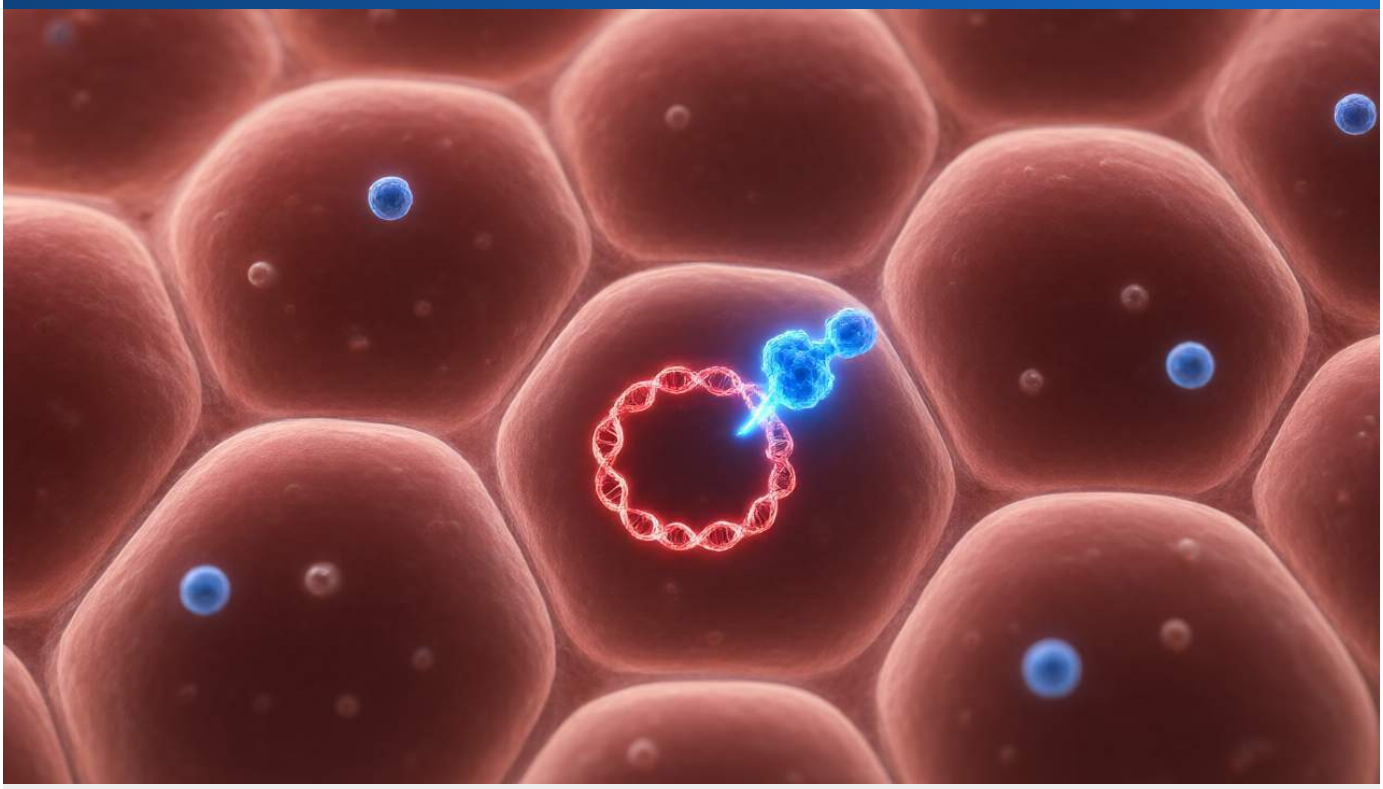
By combining bounded agentic loops with a specialized knowledge base, LPT enables the transition from a single natural language prompt to a completed protein binder design. This approach reduces the reliance on the broad, general knowledge of LLMs and minimizes the computational overhead typically associated with autonomous agentic workflows in scientific design.

Source: https://www.biorxiv.org/content/10.64898/2026.10.29.762730v1

Collected: November 07, 2026 | Automated Research System (AI)

# #09 PBGENE-HBV: Phase 1 ELIMINATE-B Data and Phase 2 Roadmap 2026

Published November 05, 2026　Precision BioSciences（Business Wire、Yahoo掲載）　USA



## OVERVIEW

Precision BioSciences reported that PBGENE-HBV achieved undetectable pgRNA in 100% of evaluable patients at a 0.4 mg/kg dose during the Phase 1 ELIMINATE-B study. The therapy demonstrated cccDNA elimination via liver biopsies and a manageable safety profile across 25 patients. These results support the program's advancement to a global Phase 2 study to evaluate viral cure rates.

## IN DEPTH

### Key Findings

PBGENE-HBV achieved pgRNA loss to undetectable levels in 100% of evaluable patients at the 0.4 mg/kg dose. This effect was durable, with 100% of patients who had at least six months of follow-up maintaining undetectable pgRNA through the September 28, 2026, data cutoff. Additionally, 100% of evaluable patients showed a treatment effect as measured by HBsAg reduction.

### Technical Details

The Phase 1 ELIMINATE-B study involved 25 patients receiving a total of 59 administrations across four dose levels. Technical highlights include:

- **pgRNA Reduction:** Out of 12 evaluable patients with detectable baseline pgRNA, 11 (92%) reached undetectable levels. One patient at 0.65 mg/kg showed a 95% reduction.
- **HBeAg-positive Efficacy:** An HBeAg-positive patient, typically difficult to treat due to higher viral loads, achieved undetectable pgRNA from a baseline of 3.7-log copies/mL (5,750 copies/mL) following the second administration at 0.4 mg/kg.
- **cccDNA Elimination:** Paired liver biopsies from two patients at the 0.4 mg/kg dose showed reductions in cccDNA of approximately 1-log (10-fold) and 1.5-log (35-fold).
- **Safety:** No dose-limiting toxicities were reported across the 59 administrations.

### Background and Context

PBGENE-HBV utilizes the proprietary ARCUS platform for in vivo gene editing. It is designed to target and eliminate covalently closed circular DNA (cccDNA), which is the root cause of chronic hepatitis B. The data was presented by lead investigator Man Fung Yuen, MD, Ph.D., at the AASLD The Liver Meeting 2026.

## Significance and Outlook

The consistency of the 0.4 mg/kg dose results provides the basis for advancing to a global Phase 2 study. The upcoming trial will evaluate cure rates—defined by sustained undetectable HBV DNA—following a finite course of treatment and the cessation of nucleos(t)ide analogs, aiming to eliminate the need for daily medication.

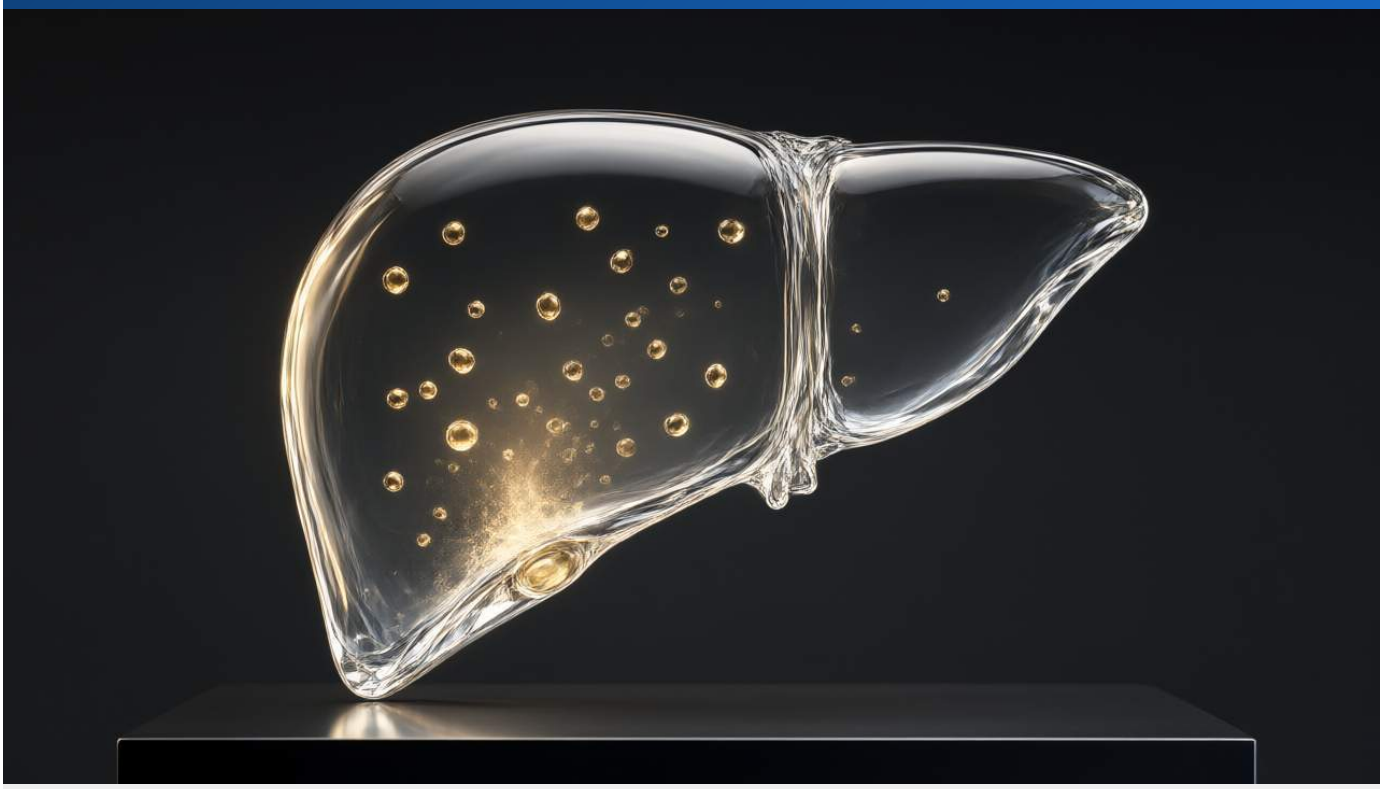
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Source: https://uk.finance.yahoo.com/news/precision-biosciences-announces-breaking-pbgene-120000321.html

Collected: November 07, 2026 | Automated Research System (AI)

# #10 MetaVia DA-1726: Phase 1 results for obesity and liver fat reduction

Published November 06, 2026 약업신문 ( Yakup.com） South Korea



## OVERVIEW

MetaVia's DA-1726 candidate demonstrated a 68% reduction in liver fat compared to placebo in a Phase 1 Part 3B interim analysis. The treatment also showed a 13.5% weight reduction versus placebo, indicating potential for treating obesity and metabolic-associated liver diseases.

## IN DEPTH

### Key Findings

In the interim analysis of Phase 1 Part 3B, DA-1726 achieved a 68% reduction in liver fat compared to the placebo group after 16 weeks of treatment. The DA-1726 group showed a 13.5% weight reduction compared to placebo, with an average weight loss of 12.19 kg (an 11.9% reduction from baseline). Using MRI-PDFF, 10 out of 12 participants (83%) in the treatment group reduced liver fat content by 30% or more from baseline. Notably, all five participants who had fatty liver at the start of the trial saw their MRI-PDFF levels drop below 5%, with average liver fat content decreasing from 8.3% to 3.0%.

### Technical Details

DA-1726 is an oxyntomodulin analogue that acts simultaneously on GLP-1 and glucagon receptors. This dual action suppresses appetite, promotes insulin secretion, and increases basal metabolic rate in peripheral tissues to induce weight loss and blood glucose control. The Phase 1 Part 3B study was a randomized, placebo-controlled trial involving 15 participants in the DA-1726 group and 4 in the placebo group. Participants received weekly subcutaneous injections for 16 weeks, with doses escalating from 16mg to 32mg and finally to a target dose of 64mg.

- **Glycemic Control:** Average HbA1c in non-diabetic participants decreased from 5.79% to 5.33%, a 0.24 percentage point reduction compared to placebo.
- **Body Composition:** Compared to placebo, visceral fat decreased by 22%, while abdominal subcutaneous fat and total adipose tissue decreased by 19%. Lean body mass and thigh muscle volume decreased by 8% and 9%, respectively.
- **Safety:** Nine of 15 participants in the treatment group experienced gastrointestinal adverse events, mostly mild to moderate. One serious adverse event involving severe vomiting was reported, though the participant recovered.

## Significance and Outlook

Based on these results, MetaVia plans to expand the development of DA-1726 to include metabolic dysfunction-associated steatotic liver disease (MetALD) and alcohol-related liver disease (ALD). MetaVia estimates there are approximately 10.7 million adult MetALD patients in the United States. The company intends to release full data for Phase 1 Part 3A and 3B in the first quarter of 2027, followed by a 48-week Phase 2 trial for up to 150 MetALD and ALD patients in the second half of 2027, utilizing a design that omits liver biopsies to reduce patient burden and costs.

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Source: https://www.yakup.com/news/?mode=view&cat=12&cat2=121&cat3=0&nid=334867

Collected: November 07, 2026 | Automated Research System (AI)

# #11 TNKS2 Inhibitor: Selective WNT Suppression via 8p Deletion

Published November 02, 2026 Nature Chemical Biology（Weill Cornell Medicine） USA



## OVERVIEW

Researchers have developed a first-in-class TNKS2-selective inhibitor that targets a collateral vulnerability in cancers with chromosome 8p deletions. By exploiting a specific flexible loop in TNKS2, the inhibitor suppresses WNT signaling in TNKS1-deficient cells while avoiding the on-target toxicities associated with broad TNKS1/2 inhibition.

## IN DEPTH

### Key Findings

The study identifies a tumor-restricted dependency on tankyrase 2 (TNKS2) in cancers characterized by the genomic loss of chromosome 8p. In these tumors, the reduction or absence of tankyrase 1 (TNKS1) creates a collateral vulnerability where WNT pathway activity is regulated primarily by TNKS2. Using structure-guided design, the researchers developed a first-in-class TNKS2-selective small-molecule inhibitor that suppresses growth in TNKS1-deleted cell and organoid models without affecting TNKS1-diploid cells.

### Technical Details

TNKS1 and TNKS2 are PARP-family enzymes that promote WNT signaling by driving the PARylation and degradation of AXIN1, a negative regulator. While broad inhibition of both enzymes stabilizes AXIN1 and downregulates WNT, it typically causes dose-limiting tissue toxicity. The researchers discovered a flexible loop in TNKS2 that allows for selective drug targeting. Data from the TCGA PanCancer Atlas and ICGC show that approximately half of lung, breast, liver, prostate, and colon cancers carry heterozygous or homozygous 8p deletions. In TNKS1 knockout (KO) and heterozygous (Het) DLD1 clones, TNKS2 silencing alone was sufficient to stabilize AXIN1, whereas 8p diploid cells required the suppression of both TNKS1 and TNKS2 to achieve the same effect.

### Background & Context

Hyperactive WNT signaling is a driver in numerous cancers, including colorectal cancer (CRC), where it is a near-ubiquitous feature. While targeting WNT has high clinical potential, previous inhibitors have been hampered by toxicity in healthy tissues. The 8p chromosome arm contains several potential tumor suppressor genes, including DLC1, FGL1, and TRIM35, but the specific loss of the TNKS1 locus creates the unique dependency on TNKS2 observed in this research.

## Significance & Outlook

This approach provides a method to achieve tumor-restricted WNT suppression, potentially overcoming the safety barriers that have limited previous WNT-targeted therapies. By targeting a cancer-specific genomic vulnerability, this modality offers a new therapeutic strategy for multiple epithelial cancer types exhibiting 8p deletions.

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Source: https://doi.org/10.1038/s41589-026-02358-z

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