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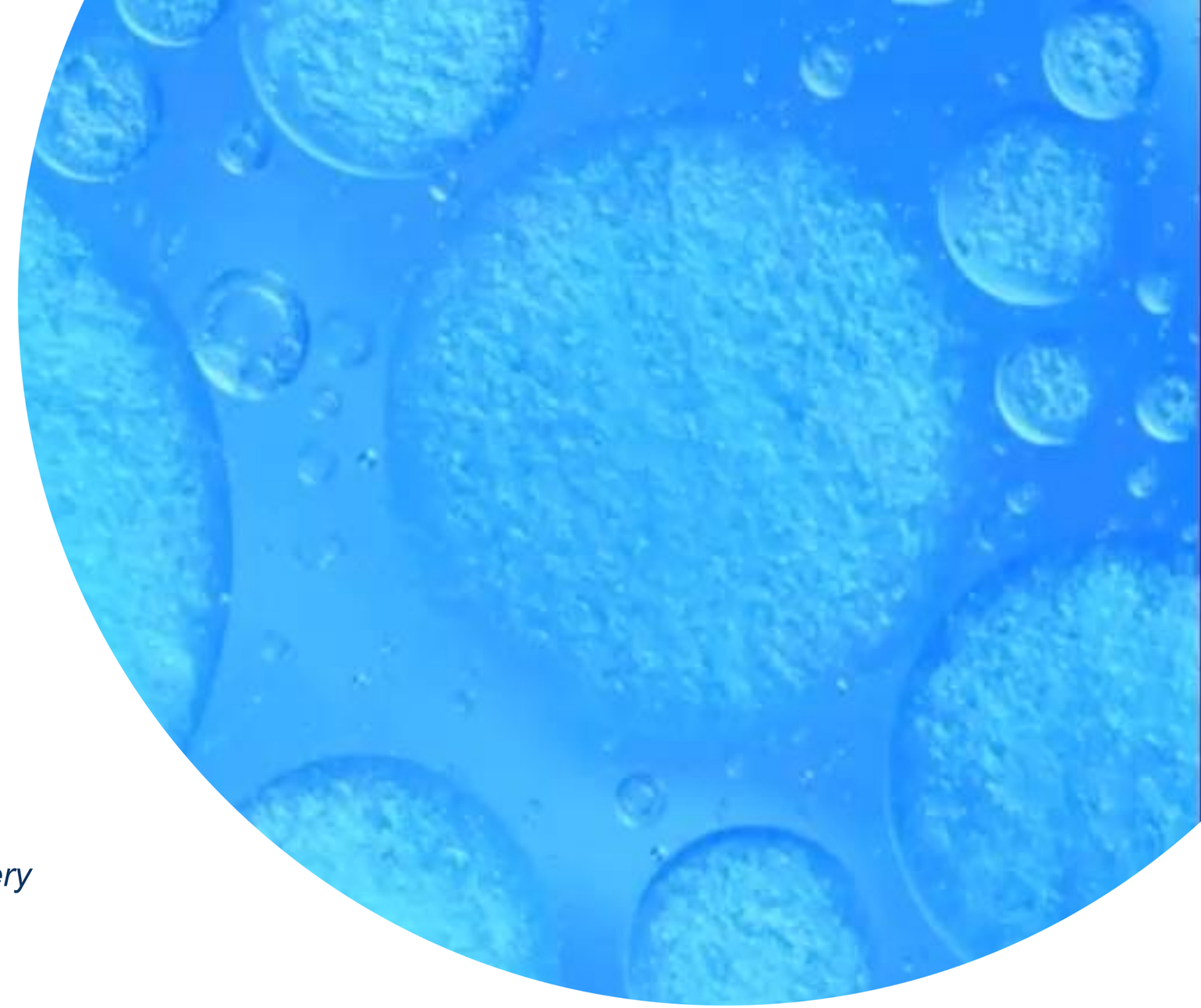


TARGETED ONCOLOGY THERAPEUTICS

The Platform Behind the Pipeline

Phospholipid Ethers

Precision Carriers for Next-Generation Drug Delivery

NASDAQ: CLRB

Educational Webinar

August 2026

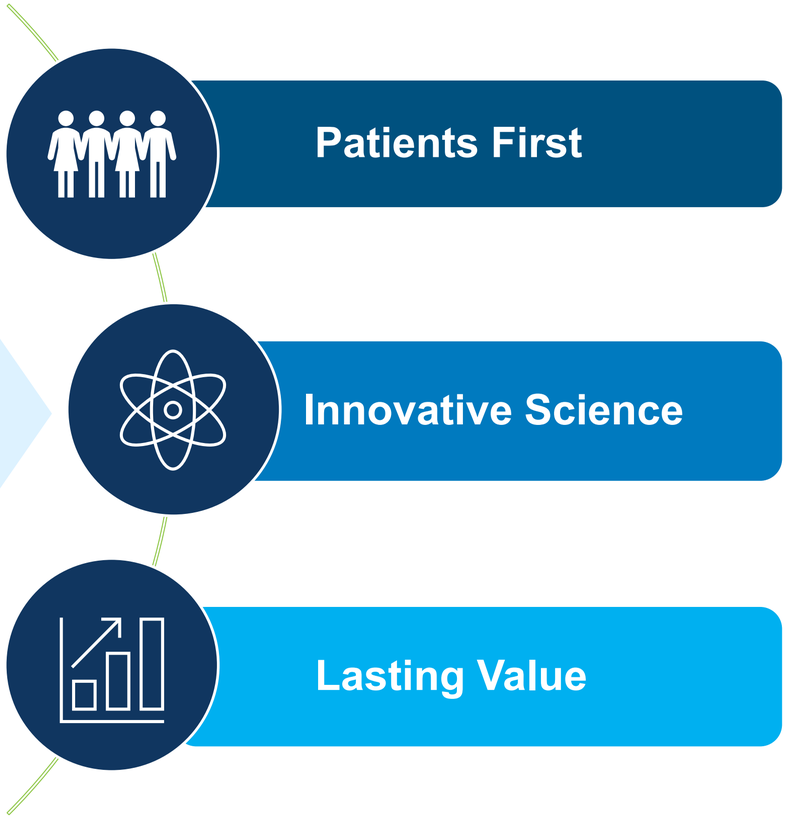
Forward-Looking Statements and Disclaimers

This presentation contains forward-looking statements. Such statements are valid only as of today, and we disclaim any obligation to update this information. These statements are only estimates and predictions and are subject to known and unknown risks and uncertainties that may cause actual future experiences and results to differ materially from the statements made. These statements are based on our current beliefs and expectations as to such future outcomes. Factors that might cause such a material difference include our ability to pursue strategic alternatives; our current views with respect to our business strategy, business plan and research and development activities; the progress of our product development programs, including clinical testing and the timing of commencement and results thereof; our projected operating results, including research and development expenses; our ability to continue development plans for CLR 121225, CLR 121125, CLR 1900 series, CLR 2000 series, and iopofosine I 131 (also known as CLR 131 or iopofosine); our ability to continue development plans for our Phospholipid Drug Conjugates (PDC); our ability to maintain orphan drug designation in the U.S. for iopofosine as a therapeutic for the treatment of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia multiple myeloma, neuroblastoma, osteosarcoma, rhabdomyosarcoma, and Ewing's sarcoma, and the expected benefits of orphan drug status; any disruptions at our suppliers; our ability to advance our technologies into product candidates; our enhancement and consumption of current resources along with ability to obtain additional funding; our current view regarding general economic and market conditions, including our competitive strengths; uncertainty and economic instability resulting from conflicts, military actions, terrorist attacks, natural disasters, public health crises, including the occurrence of a contagious disease or illness, cyber-attacks and general instability; the future impacts of legislative and regulatory developments in the United States on the pricing and reimbursement of our product candidates; our ability to meet the continued listing standards of Nasdaq; assumptions underlying any of the foregoing; any other statements that address events or developments that we intend or believe will or may occur in the future; our ability to receive NDA approval for our iopofosine I 131 program and our ability to commercially manufacture and launch our product candidate if we receive regulatory approval. A complete description of risks and uncertainties related to our business is contained in our current and periodic reports filed with the Securities and Exchange Commission, including our Form 10-K for the year ended December 31, 2024, and our subsequent reports on Form 10-Q.

This presentation includes industry and market data that we obtained from industry publications and journals, third-party studies and surveys, internal company studies and surveys, and other publicly available information. Industry publications and surveys generally state that the information contained therein has been obtained from sources believed to be reliable. Although we believe the industry and market data to be reliable as of the date of this presentation, this information could prove to be inaccurate. Industry and market data could be wrong because of the method by which sources obtained their data and because information cannot always be verified with complete certainty due to the limits on the availability and reliability of raw data, the voluntary nature of the data-gathering process, and other limitations and uncertainties. In addition, we do not know all of the assumptions that were used in preparing the forecasts from the sources relied upon or cited therein.

Cellectar Biosciences Mission

To deliver better outcomes for patients facing serious cancers while creating meaningful long-term value through innovative science and a scalable technology platform



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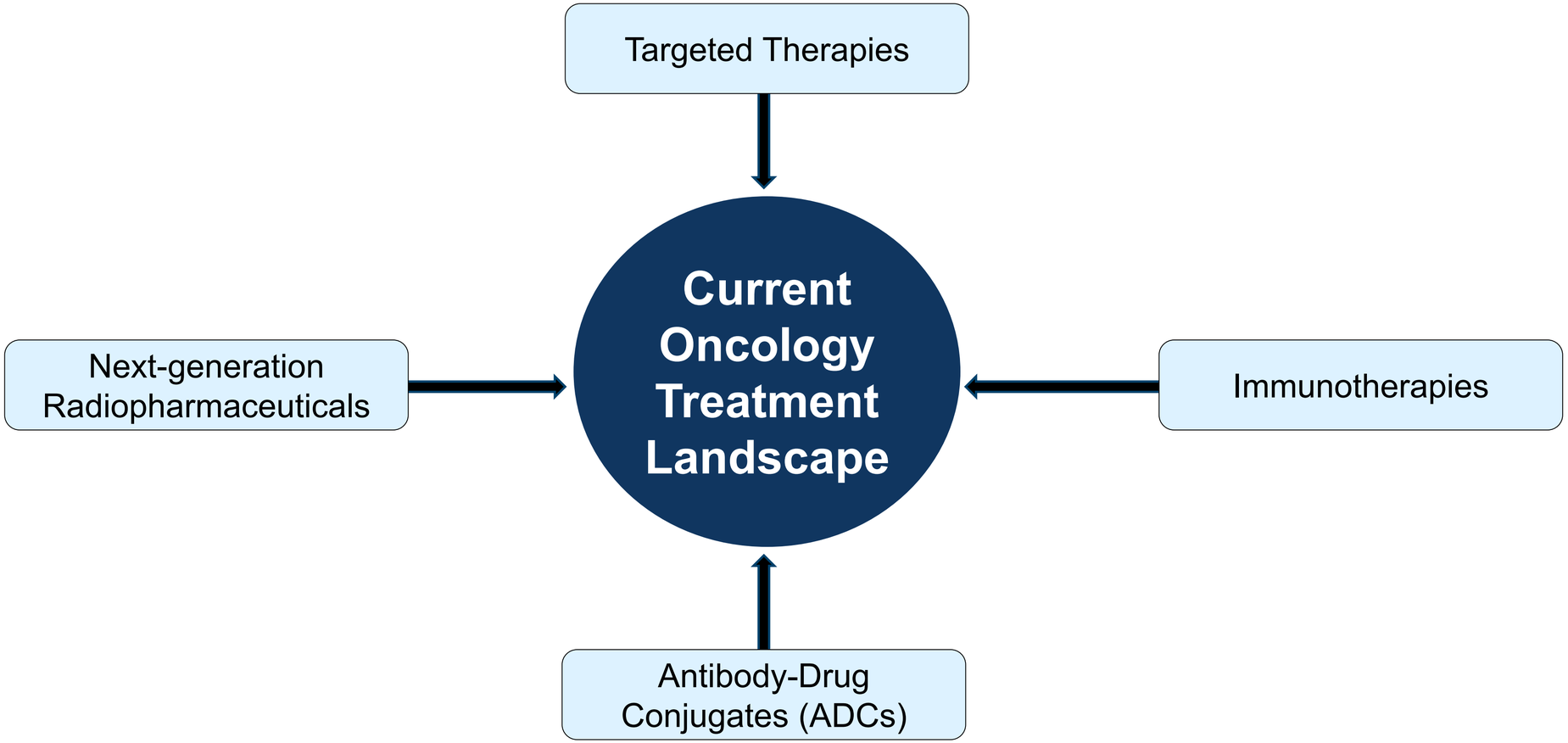
Current Oncology Innovations Represent the Beginning of Future Therapeutic Opportunities



Cellectar is Advancing Beyond Current Therapies

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PDC Platform: Expanding Opportunities Beyond Waldenström Macroglobulinemia

Compound	Disease State	Preclinical	Phase 1	Phase 2	Phase 3
Iopofosine I 131 Iodine-131 β-emitting radioconjugate	Waldenström macroglobulinemia			Clover WaM Phase 2 Study r/r WM	CONDITIONAL MARKET AUTHORIZATION APPROVAL ACCELERATED APPROVAL
	b-cell Malignancies			DLBCL, MM & NHL	
	Pediatric High-grade Glioma		Phase 1b		
CLR 121125 Iodine-125 Auger-emitting radioconjugate	Solid Tumor - TNBC		Phase 1b/2		
CLR 121225 Actinium-225 α-emitting radioconjugate	Solid Tumor - Pancreatic	Phase 1a/b Ready			
Early Pipeline	Alpha Emitters (^{211}At, ^{212}Pb, ^{223}Ra)	Phase 1 Ready			
	Beta Emitters (^{177}Lu, ^{90}Y, ^{67}Cu)	IND Enabling			

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Tumor Targeting

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Why Tumor-Selective Delivery Is Still Hard

The Unmet Need in Solid and Hematologic Tumors

Targeted therapies, antibody–drug conjugates, and immunotherapy have advanced rapidly — yet most solid tumors resist durable response. The barrier is delivery, not just biology.

Intratumoral heterogeneity
Variable, downregulated, or spatially restricted antigens defeat receptor-directed agents.

Abnormal vasculature & high pressure
Elevated interstitial pressure and uneven perfusion limit therapeutic penetration.

Stromal & microenvironment barriers

Dense stroma and TME adaptations blunt reach and drive resistance.

THE SHIFT

Target what every tumor shares — not a single antigen.

Phospholipid ethers exploit a near-universal feature of malignant transformation — remodeled, cholesterol-rich membrane microdomains — rather than discrete surface receptors.

Antigen-independent · broadly applicable

The Barrier Is Delivery — Target a Universal Property of Cancer

What Is a Phospholipid Ether (PLE)?

Anatomy and Defining Properties of the Scaffold

Anatomy of the Scaffold

Polar phosphocholine headgroup

Ether bond: metabolically stable, resists phospholipases

Long hydrophobic alkyl chain

inserts into the lipid bilayer; embeds in cholesterol-rich, ordered domains, transported into cytoplasm, delivered to the mitochondria and nucleus

Metabolic stability

The ether linkage resists enzymatic degradation, so the scaffold persists in vivo far longer than ester phospholipids.

Tumor-selective retention

High-affinity partitioning into malignant membranes followed by slow efflux → durable intratumoral residence.

Modular payload platform

One vector can carry radioisotopes, small molecules, mRNA, siRNA, degraders, or peptides as conjugates.

A Metabolically Stable, Tumor-Seeking, Payload-Agnostic Vector

Three Generations of Ether-Lipid Therapeutics

Evolution of the Field

1

Drug-only ether lipids

Edelfosine · Miltefosine

Proof that membrane-active lipids are clinically deliverable and active. Limited by GI toxicity (oral) and hemolysis (IV).

2

Optimized analogs

Perifosine · Erufosine

Improved plasma stability, longer half-life, reduced hemolysis, BBB crossing — but anti-tumor activity insufficient for solo use.

3

Targeting scaffolds & conjugates

CLR1404 · Iopofosine I-131 · PDCs

Eliminated IV hemolysis; re-engineered as multi-payload vectors with a wide therapeutic index.

From Toxicity-Limited Drugs to Engineered Multi-Payload Vectors

Mechanism of Tumor Targeting

How phospholipid ethers find, bind, and persist inside cancer cells

Lipid rafts · membrane partitioning · durable retention

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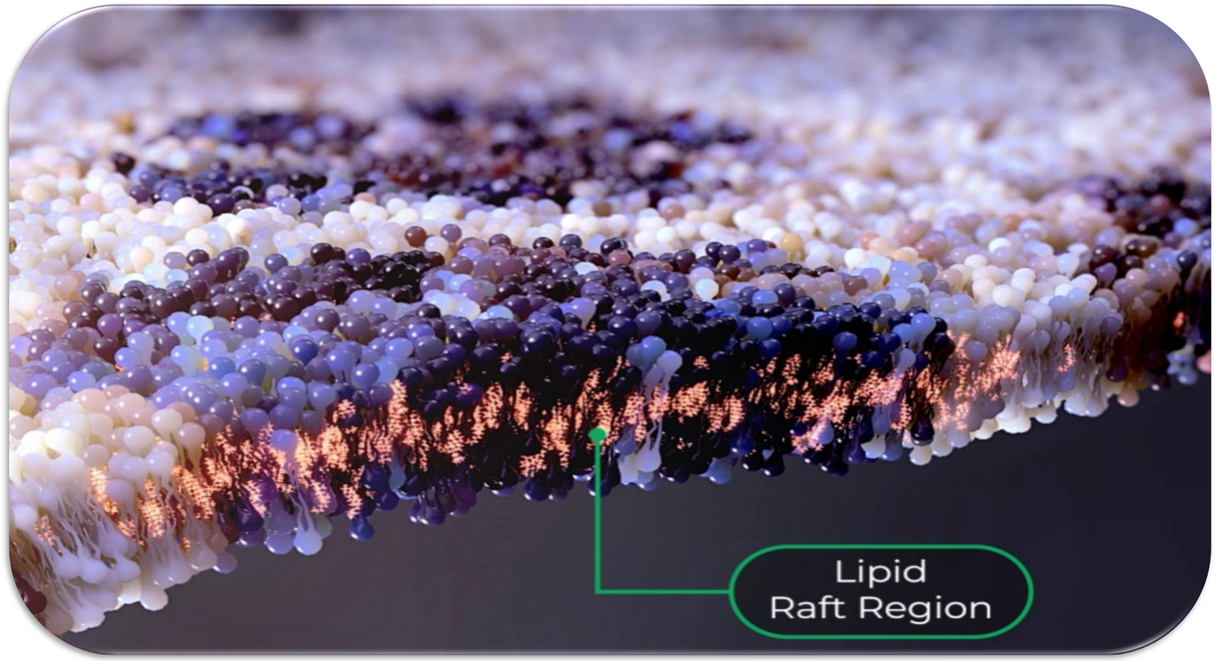
Lipid Rafts: The Biological Target

Mechanism · Part 1



Lipid rafts are cholesterol- and sphingolipid-rich membrane microdomains that organize signaling. In cancer, metabolic reprogramming makes them larger, more abundant, and persistent; creating a physical signature PLEs can identify.

Normal Cell Rafts

- Small, transient, tightly regulated
- Assemble & disassemble rapidly & on demand
- Balanced cholesterol homeostasis
- Spatially restricted (≈ nanometer scale)

Tumor Cell Rafts

- Expanded, stabilized, persistent
- Sterol reg. element binding protein / FASN-driven lipid synthesis
- Concentrate key receptors; TKR, GPCR, etc (i.e. EGFR, HER2, PI3K/Akt, MAPK)
- Enlarged platforms (up to micrometer scale)

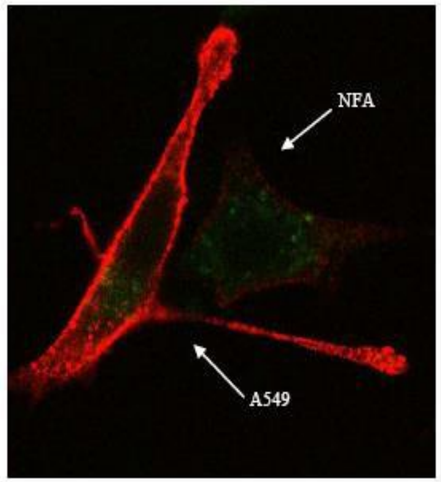
Tumor Rafts Are the Physical Signature PLEs Exploit

Lipid Rafts: The Biological Target

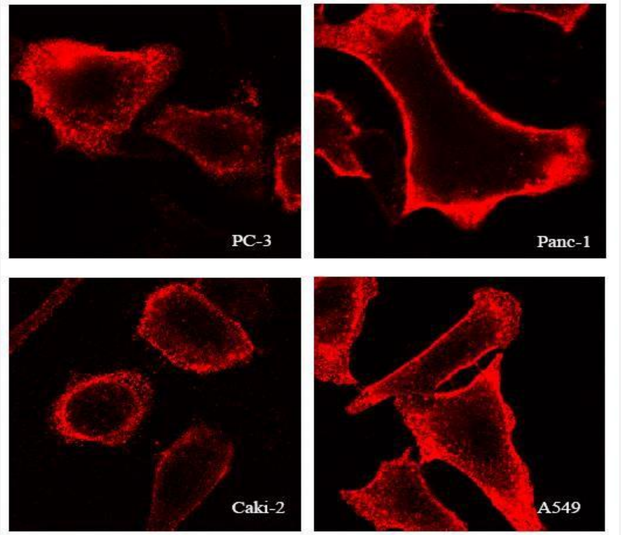
Mechanism · Part 1, cont.

Lipid Rafts Fluorescent-labeled with Cholera Toxin Subunit

A549 labeling vs Fibroblast Co-cultured



Prostate **Pancreatic**



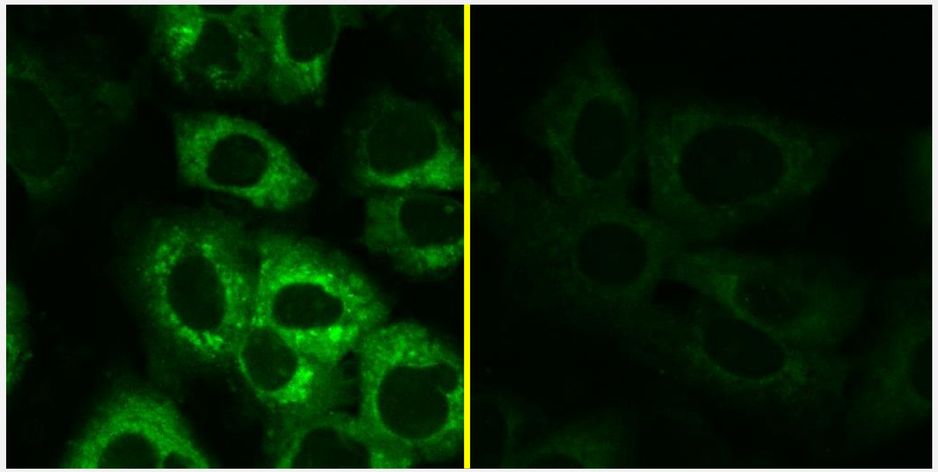
Kidney **Lung**

Red = labeled lipid rafts

Overabundance of lipid raft on tumor cells

Methyl-β-cyclodextrin (MBCD) Selectively Disrupts Lipid Rafts

A549 NSCLC



No MBCD pretreatment
Intact lipid rafts

MBCD pretreatment
Disrupted lipid rafts
Uptake decreased by ~60%

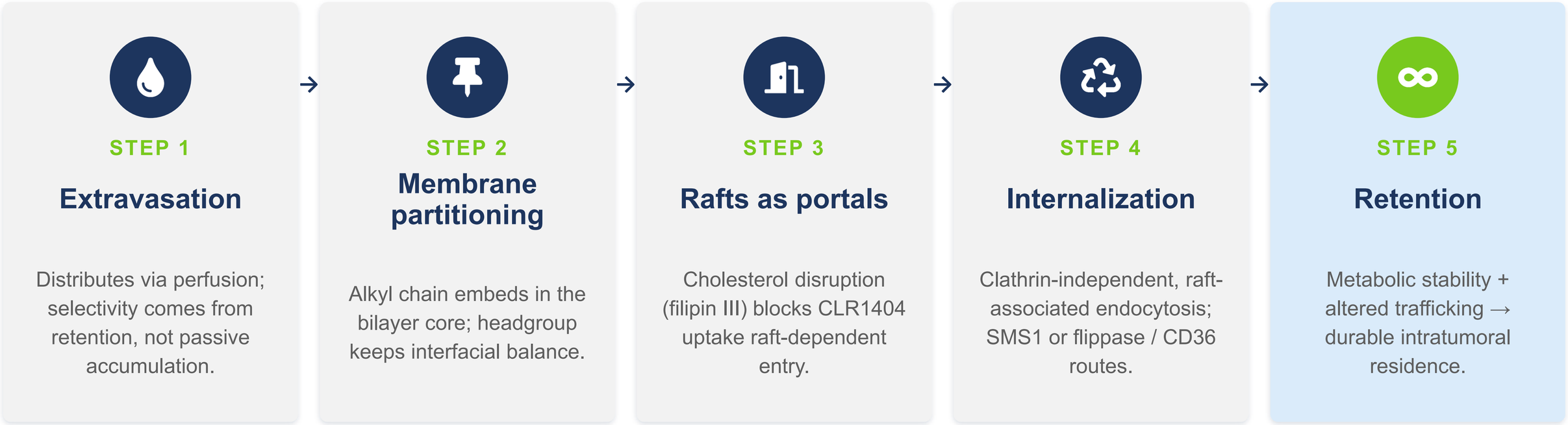
Green = fluorescent tagged PDC

Knock-down of lipid rafts = loss of uptake

Targeting, Binding & Cellular Entry

Mechanism · Part 2

Targeting is membrane biophysics, not ligand–receptor docking. “Binding” means thermodynamically favorable partitioning into ordered, cholesterol-rich domains.



Key consequence: tumor uptake is antigen-independent — no homogeneous surface target required, broadening reach across heterogeneous tumors.

Raft-Mediated, Antigen-Independent Uptake and Durable Retention

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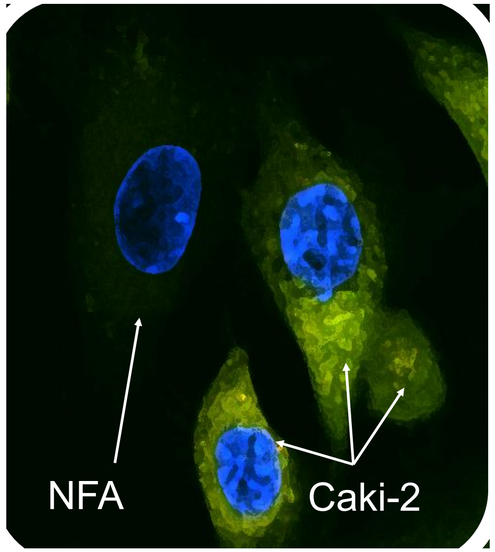
Targeting, Binding & Cellular Entry

Mechanism · Part 2, cont.

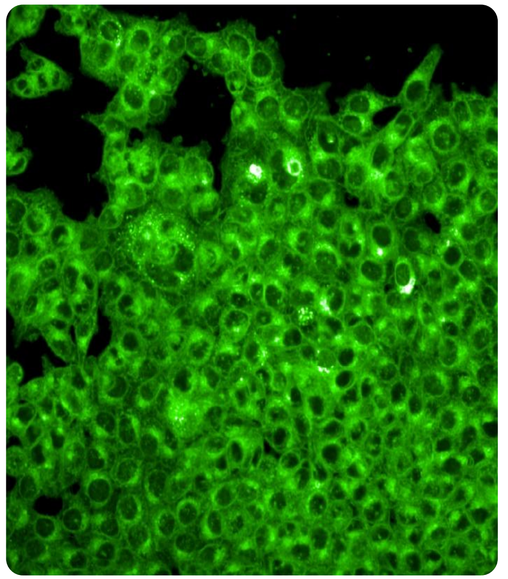
Phospholipid Ethers (PLEs)

- Mimetic of long chain fatty acid; takes advantage of the metabolic reprogramming of tumor cells
- Cellectar's PLEs/APLs designed for enhanced targeting of tumor lipid rafts and demonstrate preferential uptake
- Lipid rafts conserved across tumors, resulting in near uniform uptake (potential to target 100% of tumor cells)
- PLEs do not need to escape endosome – increases functionality
- PLEs retain in tumor for weeks

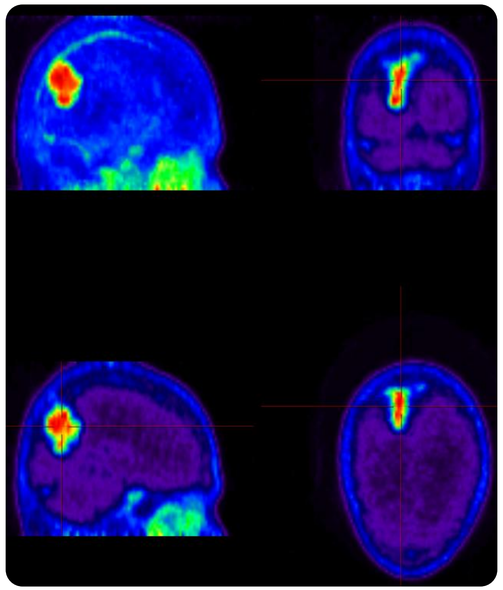
SPECIFIC UPTAKE



UNIFORM DELIVERY



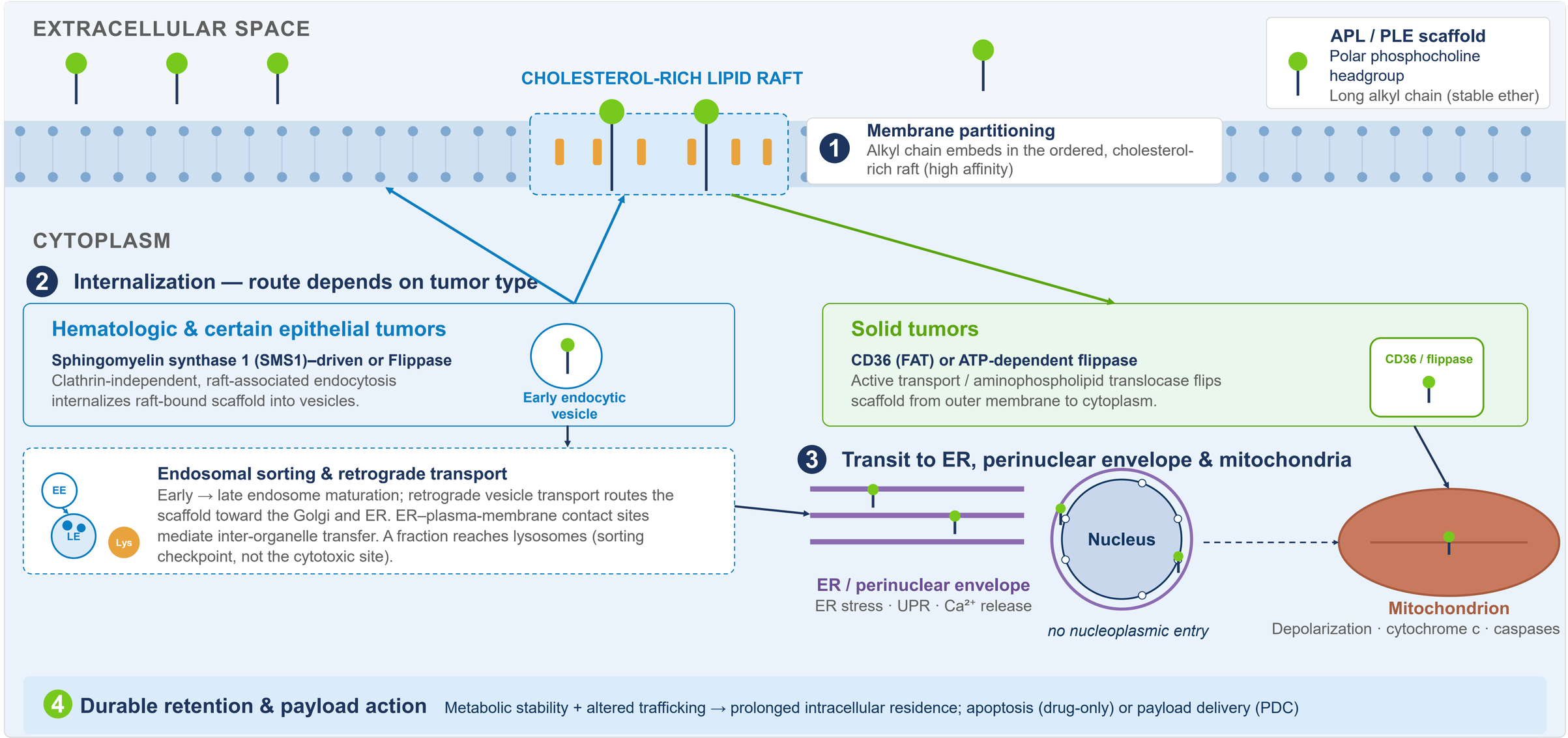
SPECIFIC TARGETING



Pre-clinical and Clinical Validation of Tumor Specificity, Uptake and Retention

Cellular Uptake, Endosomal Sorting and Organelle Targeting of APLs / PLEs

PDC Platform MOA · Raft-Mediated Entry · Endosomal Trafficking · ER / Perinuclear & Mitochondrial Targeting



Raft Binding → Endosomal Sorting → ER / Perinuclear & Mitochondrial Targeting → Durable Retention

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The Microenvironment Reinforces the Target

Mechanism · Part 3

The tumor microenvironment actively expands and stabilizes lipid rafts — deepening the very signature that phospholipid ethers exploit.

Hypoxia & acidity

Stress drives cholesterol and GM1 ganglioside accumulation, reinforcing raft structure and stabilizing EGFR / HER2.

Sustained signaling

Compartmentalization shields receptors from phosphatases, locking in PI3K/Akt and MAPK/ERK growth signals.

Lipid scavenging

CD36-mediated uptake pulls fatty acids from circulation, adipocytes (CAAs) and fibroblasts (CAFs) to fuel growth.

Immune evasion

Raft manipulation exhausts CD8+ T and NK cells and polarizes macrophages toward a pro-tumor M2 phenotype.

The TME Doesn't Just Permit the Target — It Amplifies It

Targeting by Phospholipid Ethers

Selective Tumor Uptake Is Intrinsic to the Scaffold — Independent of Payload or Radioisotope

WHY TARGETING WORKS — DETERMINANTS OF SELECTIVE UPTAKE

Raft & cholesterol abundance

Tumor membranes carry 5–10× more cholesterol-rich rafts; the alkyl chain partitions into them with high affinity. Disrupting rafts cuts uptake — selectivity is causal, not coincidental.

Akt / PTEN-loss biology

Lipid-avid, PI3K/Akt-driven tumors stabilize rafts and accumulate cholesteryl esters, deepening the membrane signature the scaffold reads.

Stem-cell & proliferation state

Raft content is enriched in cancer stem cells and proliferating tumor cells, while normal resting cells and marrow are comparatively spared.

HOW IT ENTERS — TWO RAFT-DEPENDENT ROUTES BY LINEAGE

Hematologic / lymphoid

Raft-dependent endocytosis (SMS1-driven). Recruits Fas/CD95 and displaces Akt from rafts → apoptosis.

Carcinoma / solid

Active transport via the ATP-dependent CDC50A / P4-ATPase flippase, translocating the scaffold inward.

Both routes are raft-dependent and antigen-independent — no surface receptor required, so targeting reaches heterogeneous tumors that defeat ligand-directed agents.

WHERE TARGETING IS STRONGEST

Hematologic malignancies
Myeloma · MCL / CLL · leukemia — strongest, most selective uptake; spares normal lymphocytes

Akt-driven solid tumors
Prostate · pancreatic · squamous head & neck · ovarian · breast · Ewing sarcoma

Stem-cell-high / recurrent
Raft-rich CSC compartments that drive resistance and relapse

Targeting is intrinsic to the scaffold. Pan-tumor imaging breadth and CNS / blood–brain-barrier delivery are unique to the CLR1404 radioconjugate platform; the selective-uptake mechanism depicted earlier belongs to the alkylphospholipid class itself.

Pharmacokinetics, Biodistribution & Safety

A Distinctive Class Profile

A Distinctive PK Signature

- **Membrane-driven distribution** — low free plasma levels; accumulation in remodeling membranes
- **High protein binding** — increases accumulation in tumor microenvironment
- **Minimal metabolism** — resists phospholipases; little CYP450 involvement
- **Slow elimination** — biliary / fecal clearance, largely intact compound
- **Prolonged retention** — half-lives of days–weeks; effect outlasts plasma levels

Efficacy Tracks Membrane Exposure, Not Plasma Concentration

Phospholipid Radioconjugate (PRC) Platform

The theranostic core: one scaffold, multiple therapeutic isotopes:
CLR1404 · Iopofosine I-131 · CLR 125 · CLR 225 · Others

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The Theranostic Platform: CLR1404 / NM404

Third Generation

One scaffold, multiple isotopes. Durable tumor retention lets a diagnostic isotope predict the therapeutic dose.

IMAGE

Iodine-124

PET imaging quantifies tumor uptake and retention kinetics before treatment — enabling patient selection and dosimetry.

TREAT

Iodine-131

The β-emitter delivers cytotoxic radiation inside tumor cells, causing DNA damage while sparing most normal tissue.

Weichert et al. established broad-spectrum tumor targeting with the alkylphosphocholine analog CLR1404 — the foundation for the iopofosine program and every downstream conjugate.

Imaging Predicts Therapy: The Theranostic Logic

Iopofosine I-131 (CLR 131)

Lead Clinical Asset Provides Validation of Platform

A Targeted Radiotherapeutic PDC

Iopofosine I-131 couples the PLE tumor-targeting scaffold to the β-emitting radioisotope iodine-131. Preferential raft association and internalization concentrate the radiolabel inside malignant cells and their progenitors, giving prolonged intracellular retention and delivering β-radiation directly inside the tumor while sparing most normal tissue.

First-in-class **Radioconjugate** **Antigen-independent**

Approved WM options are limited and the disease remains incurable — the rationale for a novel mechanism.

Clinical Program at a Glance

Waldenström macroglobulinemia
Pivotal CLOVER-WaM — lead indication

Multiple myeloma & B-Cell malignancies
CLOVER-1 Phase II, relapsed/refractory

Pediatric high-grade glioma
CLOVER-2 Phase 1b

Head & neck cancer
Combination with external-beam RT

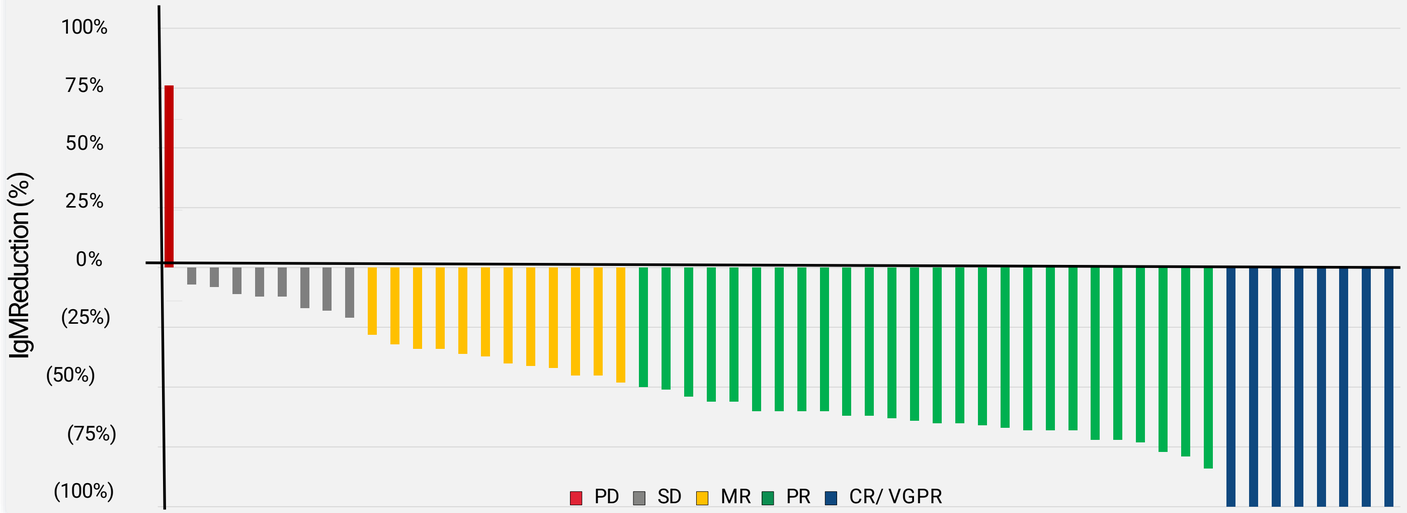
First-in-Class, Antigen-Independent Targeted Radiotherapy

CLOVER-WaM: Waldenström Macroglobulinemia

Clinical Evidence · Pivotal Phase 2b

83.6%	61.8%	14.5%	17.8 mo	98.2%
Overall response rate	Major response rate	VGPR/CR rate	Median duration of response	Disease control rate

Best Response by r/r WM Patient (n=55)



What It Means

- Primary endpoint (MRR ≥ 20%) far exceeded
- High rate of VGPR & CR in refractory patients
- Active even after prior BTK inhibitors
- Responses held across MYD88, CXCR4, TP53 genotypes
- Hematologic AEs predominate, manageable

Exceeded Primary Endpoint; Durable Responses Despite Highly Refractory Patients

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Activity Across B-Cell Malignancies

Clinical Evidence · Beyond Waldenström’s macroglobulinemia

Multiple myeloma

CLOVER-1 Phase II

32% ORR at >60 mCi; 50% ORR in quad-class refractory and post-BCMA relapse — heavily pretreated, high-risk patients.

Diffuse Large B-Cell Lymphoma

CLOVER-1 Phase II

30% ORR and 10% CR in patients with median >3 prior lines

Other NHL (R/M)

CLOVER-1 Phase II

50% ORR in median 3rd line patients. >70% clinical benefit with median tumor volume reduction of >25%

Breadth Across Hematologic, CNS and Solid Tumors

Activity Beyond Hematologic Malignancies

Clinical Evidence · CNS & Solid Tumors

Pediatric high-grade glioma

CLOVER-2 Phase 1a and b

Multi-dose PFS ~8.1 months and OS ~11.5 months; all evaluable patients achieved disease control with manageable toxicity.

Head & neck (R/M)

Iopofosine + EBRT

Combination with external-beam radiation was tolerable, with no unexpected safety signals and expected hematologic toxicity.

Breadth Across Hematologic, CNS and Solid Tumors

CLR 125: Auger Emitter (^{125}I)

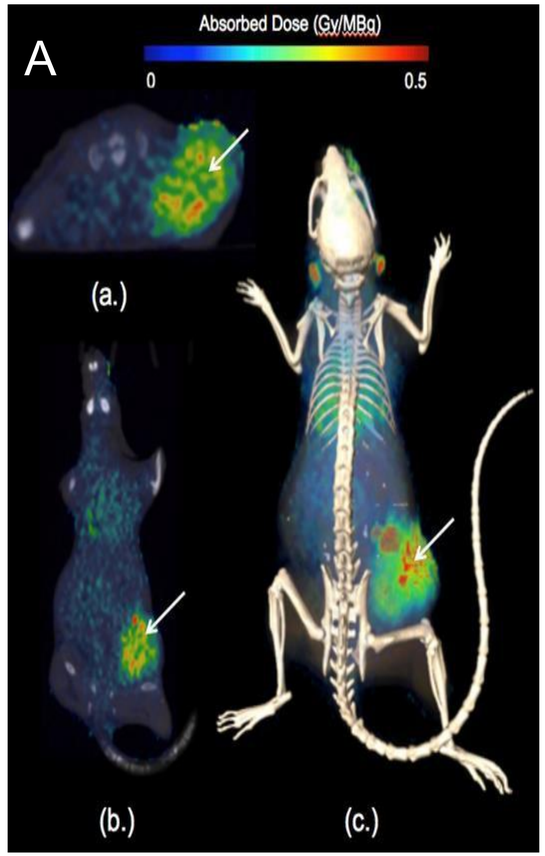
TNBC - Observed Statistically Significant Activity and Well Tolerated In Vivo

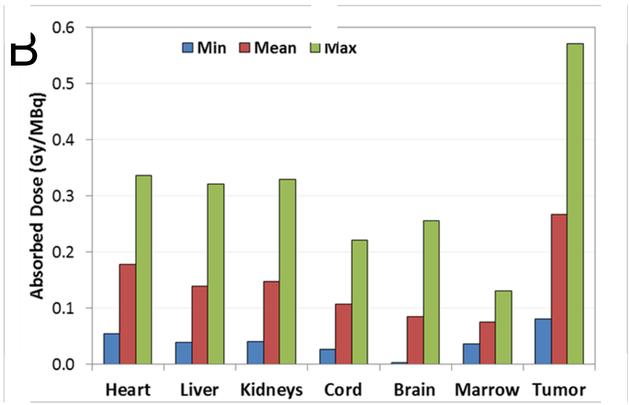
CLR 125 structurally identical to iopofosine I 131; potentially reduced development risk

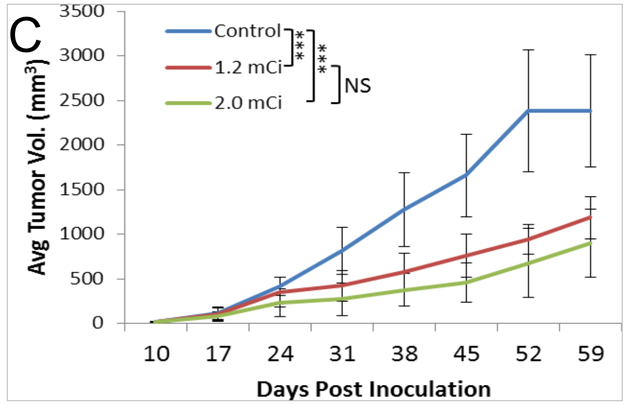
CLR 125 tested in MDA-MB-231 triple negative breast cancer

- Observed significant tumor uptake (images A & B)
- Single infusion resulted in growth inhibition at both tested doses (1.2mCi and 2mCi) – Image C
- Observed statistically significant activity at 2mCi dose - data not shown

No signs of end-organ toxicity, including hematologic toxicity







Validated Intracellular Delivery with CLR 121125

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CLR 125: Auger Emitter (^{125}I)

Phase 1b Dose Finding Study in Relapsed Triple Negative Breast Cancer

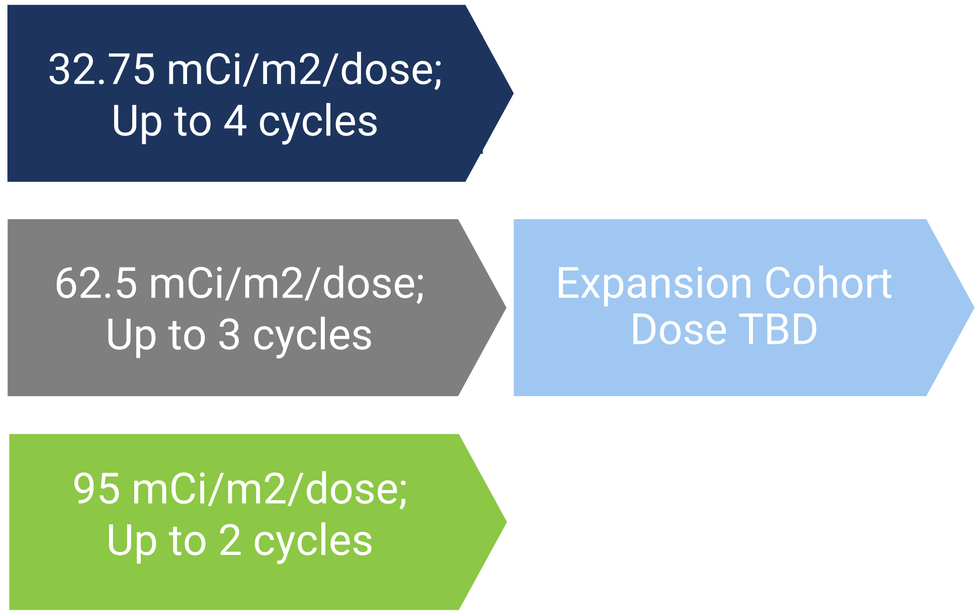
Phase 1 Study Overview

- Imaging and therapy study
- Population: TNBC patients with progressive disease and no treatment option
- Primary Endpoint: Recommended Phase 2 dose
- Secondary Endpoints: Safety & tolerability; initial response assessment (RECIST v1.1 and PFS); distribution
- Dose determination based upon preclinical data and imaging results

Key Inclusion/Exclusion Criteria

- Confirmed TNBC
- Relapsed from at least 1 prior treatment
- At least 1 measurable lesion of >10mm
- No ongoing Grade 2 or greater adverse events
- At least 2 weeks since prior antitumor treatment

Study Schematic
2 doses per cycle: 15 patients per arm



Mayo Clinic Network to Lead Clinical TNBC Study

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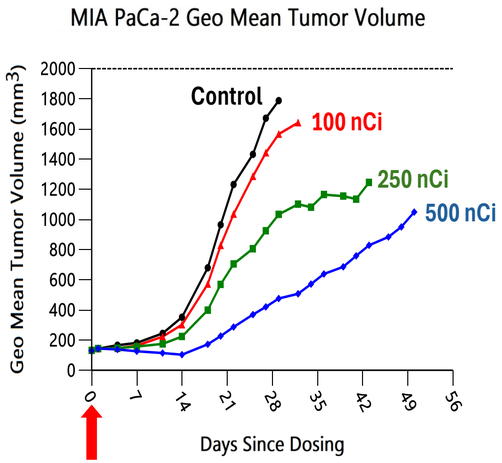
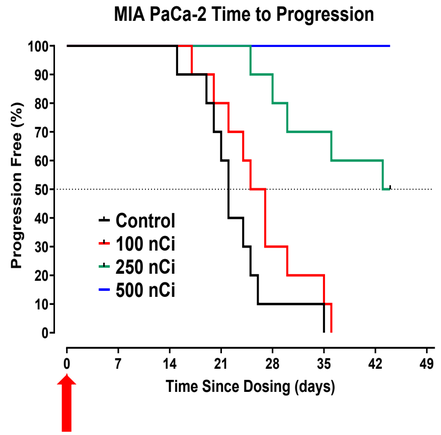
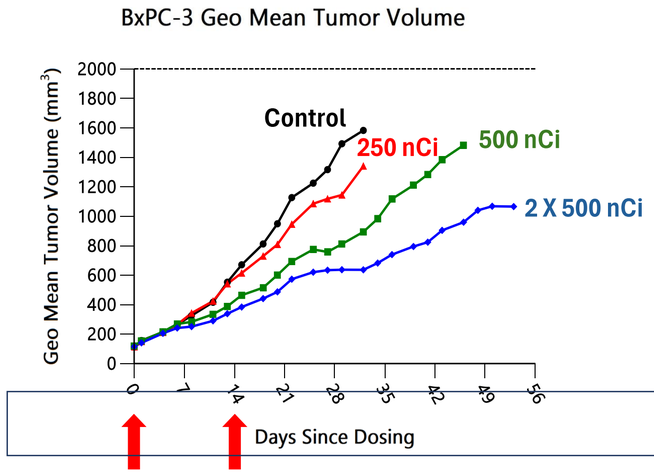
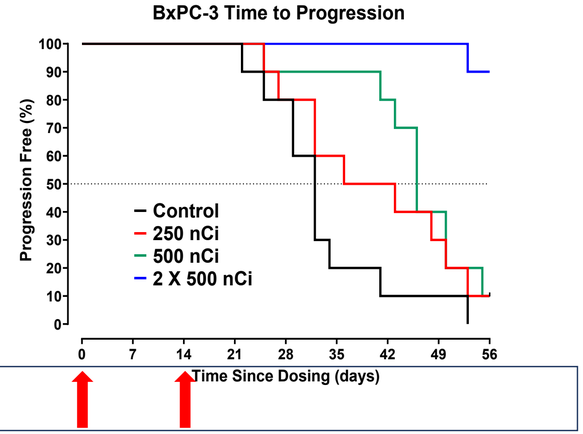
CLR 225: Alpha Emitter (^{225}Ac)

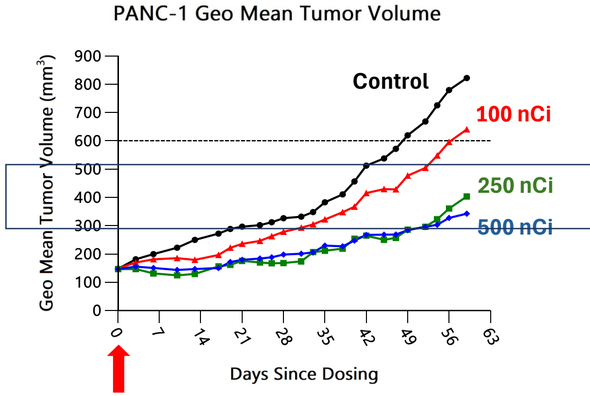
Tumor Volume Reduction and Survival Benefit in Pancreatic Cancer

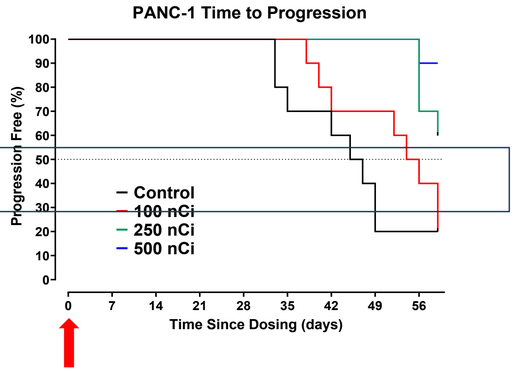


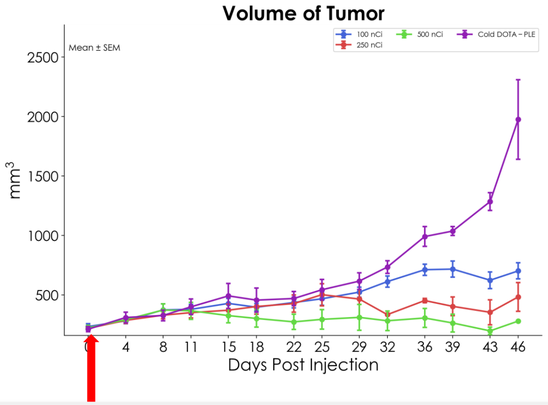


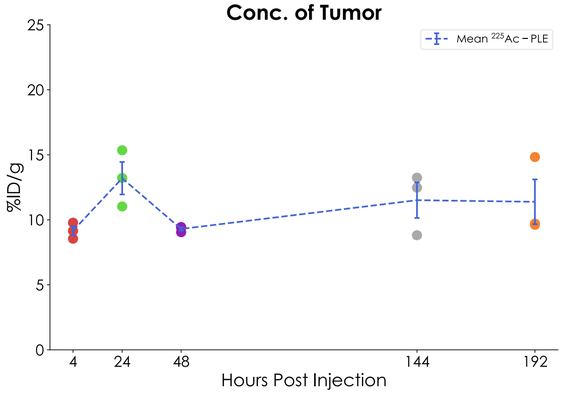












- 3 xenograft models of pancreatic cancer
- Dose response exhibited in all models (Cold, 100nCi, 250nCi and 500nCi)
- All doses well tolerated

Tumor Volume Reduction and Survival Benefit Observed in Every Model

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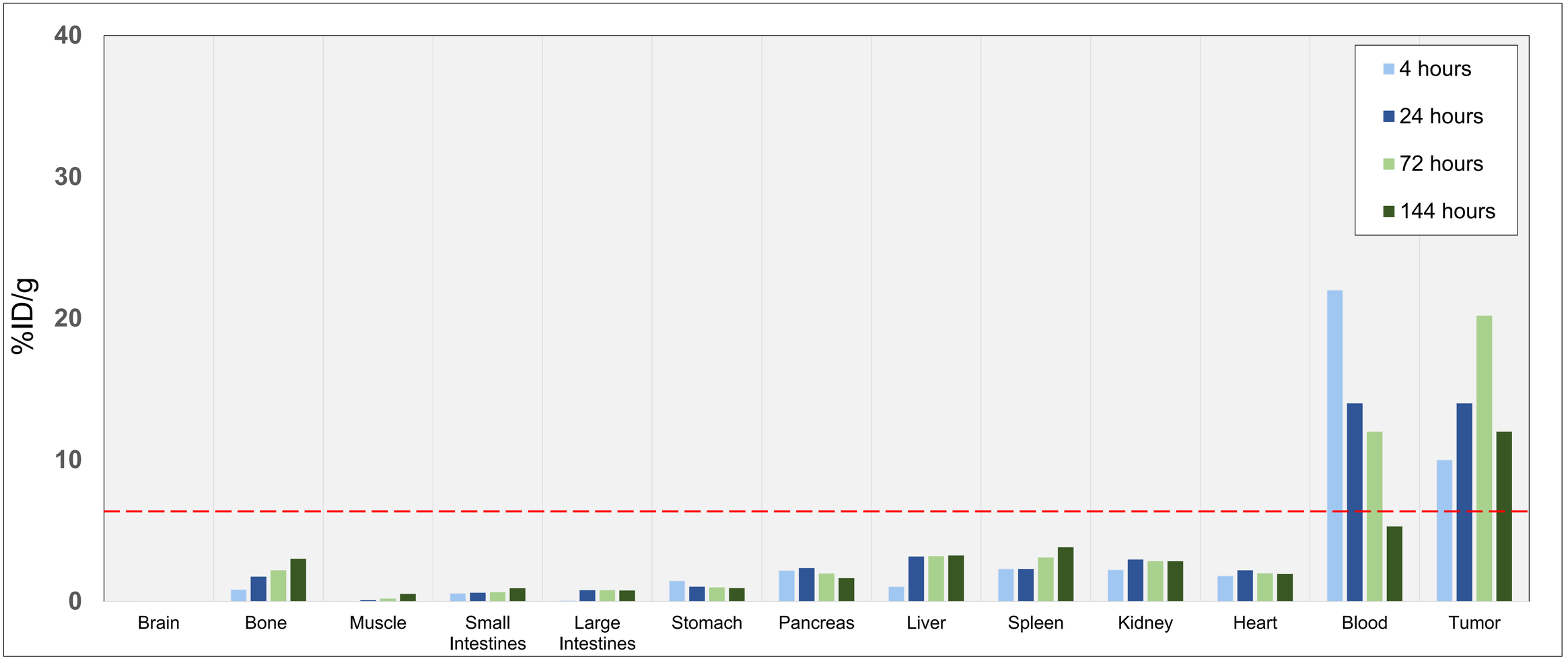
CLR 225: Alpha Emitter (^{225}Ac)

Biodistribution in Pancreatic Model



High and Prolonged Tumor Uptake; Low Normal Tissue Uptake

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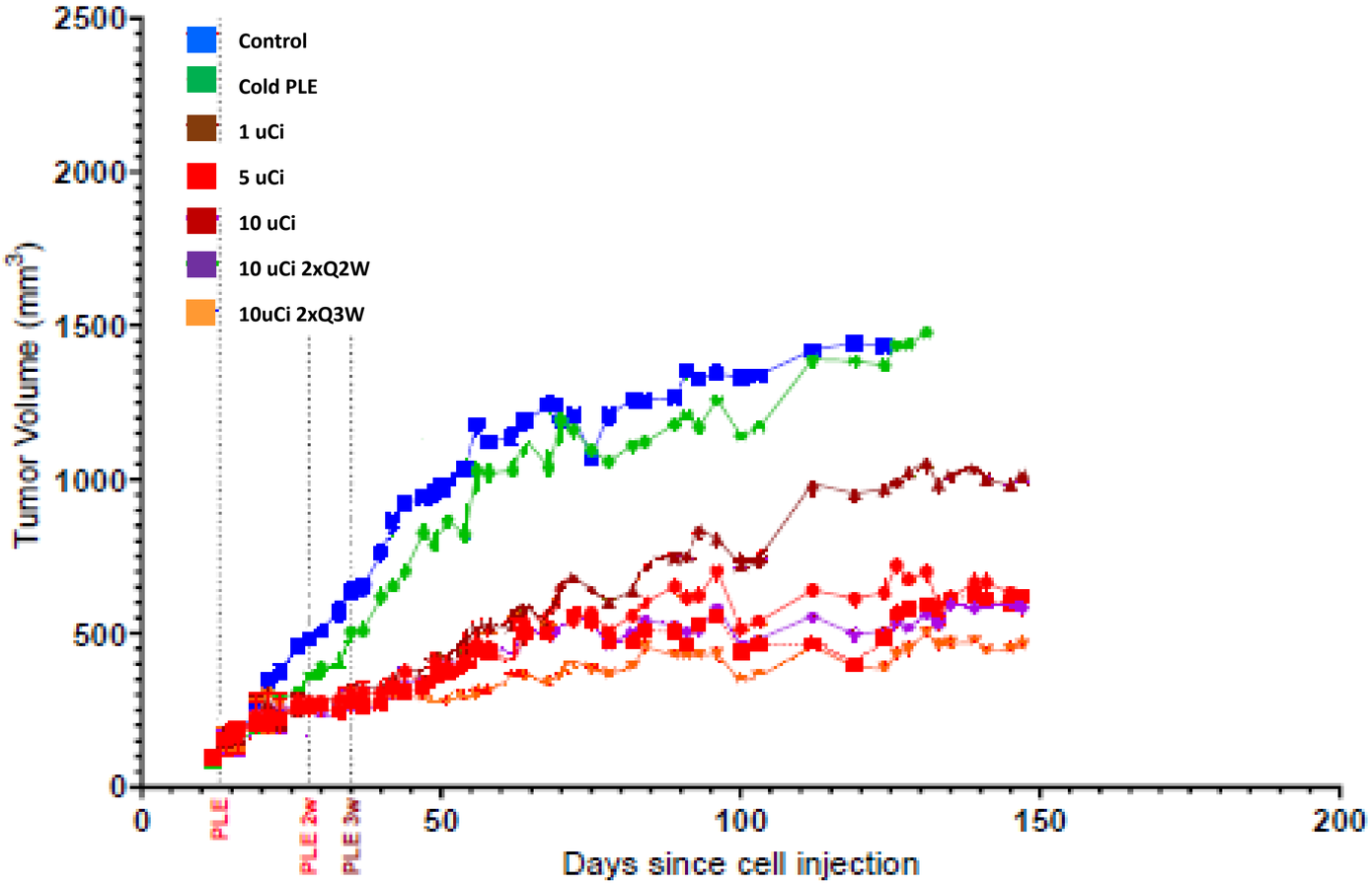
CLR 121: Astatine (^{211}At)

Efficacious and Well Tolerated in Triple Negative Breast Cancer Model (HCC70)



- A variety of doses and dosing regimens tested
- Tumor volume at dosing ~150mm3
- All treatment doses show some tumor volume reduction and growth delay
- Optimum response achieved with 2 doses given 3 weeks apart (20uCi total) or high specific activity at 10uCi given 2 weeks apart
- Dosing optimization continues

CLR 211 Expected to Provide Tumor Eradication at Doses of ~40 uCi

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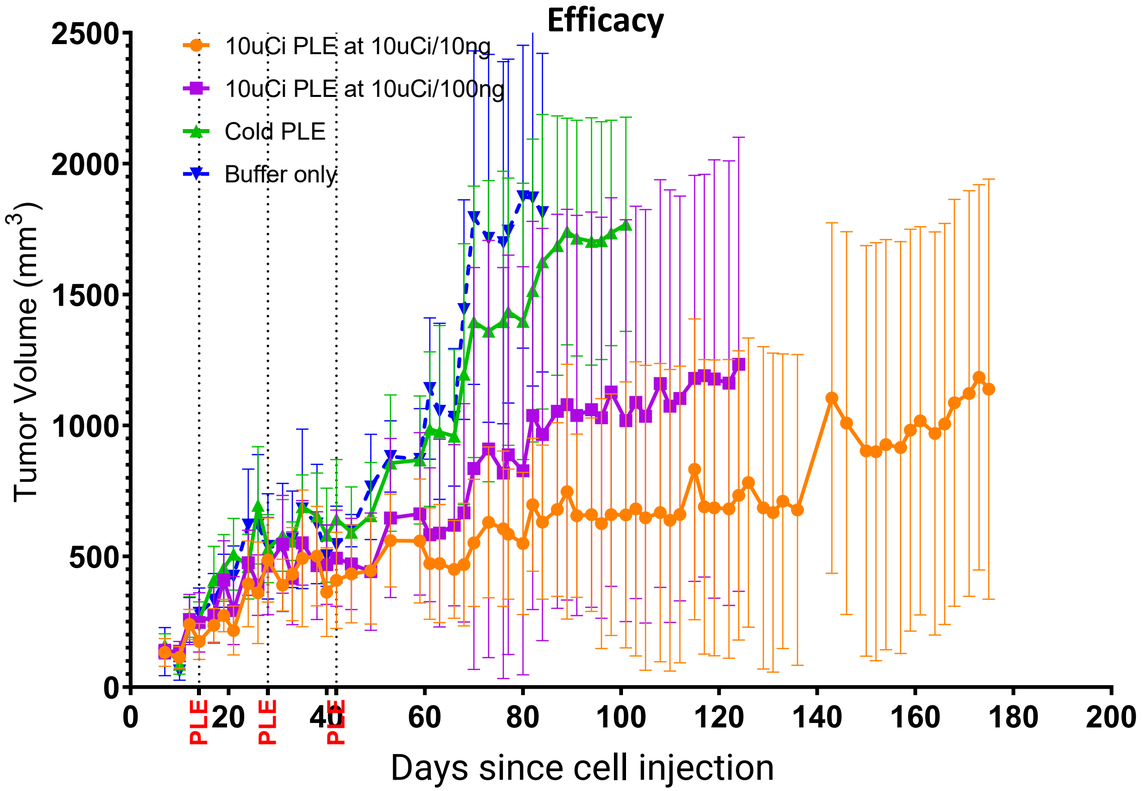
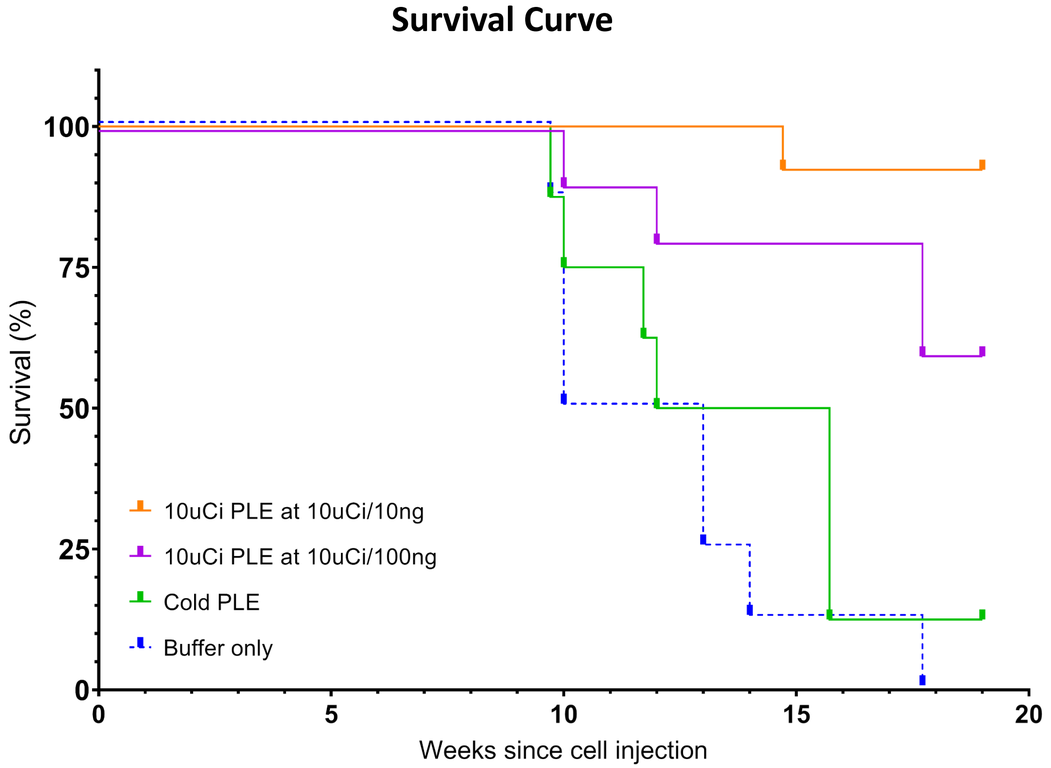
CLR 212: Lead (^{212}Pb)

Efficacious and Well Tolerated





CLR 121212 tested in HCC70 triple negative breast cancer

- Growth inhibition with both doses tested
- Observed survival benefit with high specific activity dose
- All doses well tolerated

	10uCi PLE at 10uCi/10ng	10uCi PLE at 10uCi/100ng	Cold PLE	Buffer only
Median Survival (weeks)	Not reached	Not reached	13,8571	11,5

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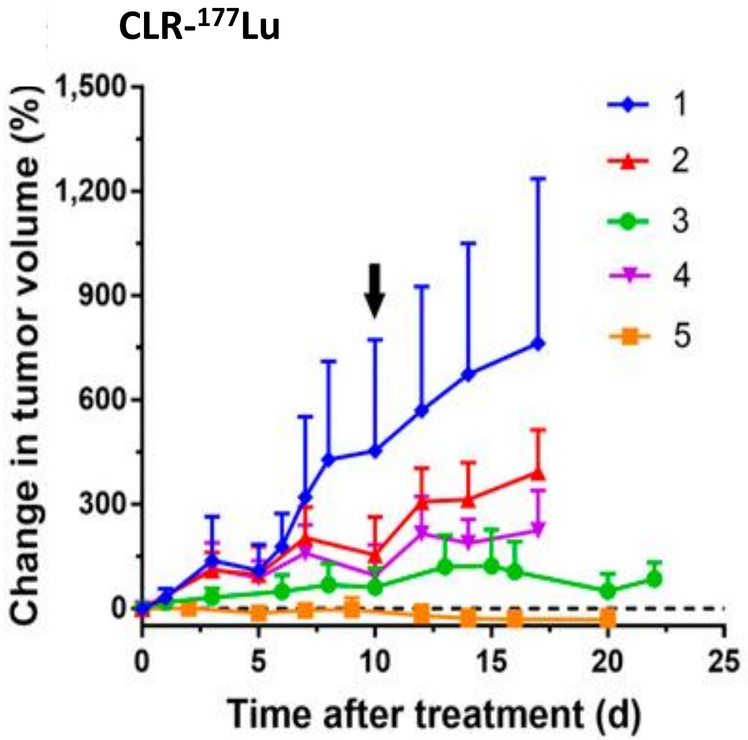
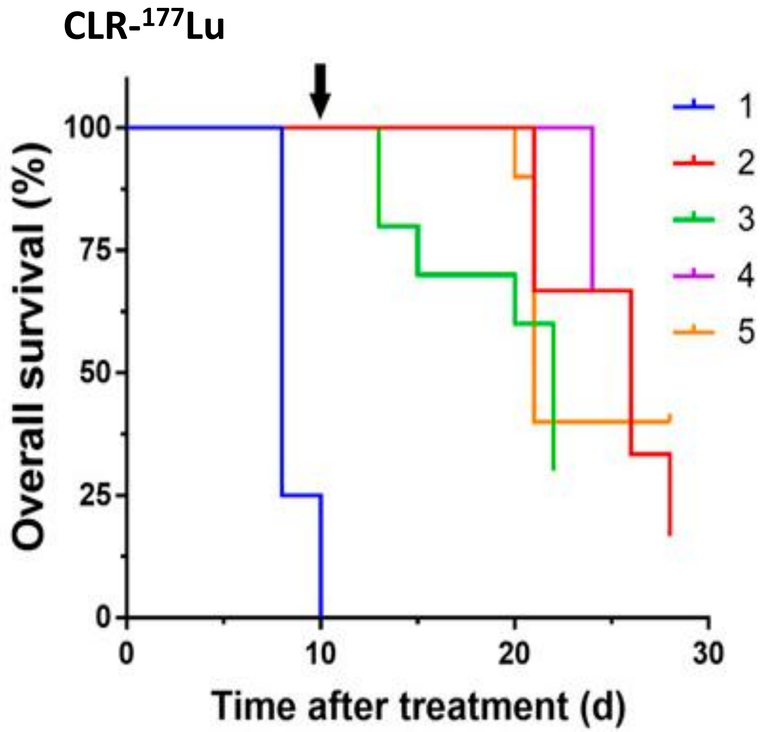
CLR 177: Lutetium (^{177}Lu)

Activity in Breast Cancer





1. control: 2. 9.25MBq: 3. 18.5MBq: 4. fractionated 18.5MBq (2 x 9.25): 5. 3 x 9.25MBq

- Lutetium and Yttrium – PLEs tested in 4T07 (uptake) & 4T1 (efficacy) breast cancer xenograft model
- Tumors achieved 200 mm^3 prior to dosing

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Beyond Radioisotopes: A Multi-Payload Platform

The same tumor-targeting scaffold can carry diverse therapeutic cargoes: Small molecules · mRNA · siRNA · degraders · peptides

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One Scaffold, Many Payloads

Phospholipid Drug Conjugate (PDC) Modalities

Membrane-partitioning delivery is intrinsically payload-agnostic: the PLE vector concentrates and internalizes cargo in tumor cells regardless of the payload's mechanism — expanding from radioisotopes to five additional therapeutic classes.

Small molecules

Cytotoxins & targeted inhibitors

Tumor-concentrated delivery widens the therapeutic index of potent payloads that are too toxic systemically.

mRNA

Expression of therapeutic proteins

Intracellular routing supports cytoplasmic translation — tumor antigens, immunomodulators, or replacement proteins.

siRNA

Gene silencing of oncodrivers

Raft-mediated entry delivers duplexes to the cytoplasm to knock down otherwise undruggable targets.

Degraders

Targeted protein degradation

PROTAC / molecular-glue cargo co-opts the ubiquitin–proteasome system after tumor-selective uptake.

Peptides

Targeting & functional cargo

Stapled or cyclic peptides — including epitopes and signaling disruptors — delivered intracellularly.

Receptor-Independent Delivery Is Payload-Agnostic

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Small-Molecule & Peptide Conjugates

Multi-Payload Platform · Cytotoxins, Inhibitors & Peptides

Small molecules

- Potent cytotoxins (e.g. tubulin or topoisomerase poisons) delivered tumor-selectively
- Targeted inhibitors concentrated intracellularly to raise local exposure
- Cleavable linkers borrow ADC chemistry for tumor-specific payload release
- Goal: widen therapeutic index for payloads too toxic for free systemic dosing

Peptides

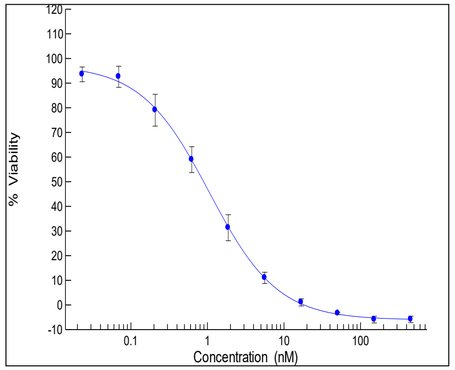
- Stapled / cyclic peptides stabilized against proteolysis
- Intracellular disruptors of protein–protein interactions (otherwise membrane-impermeant)
- Antigenic epitopes for in-situ vaccination or immune engagement
- Conjugation must preserve scaffold amphiphilicity for raft partitioning

Tumor-Selective Delivery Widens the Therapeutic Index

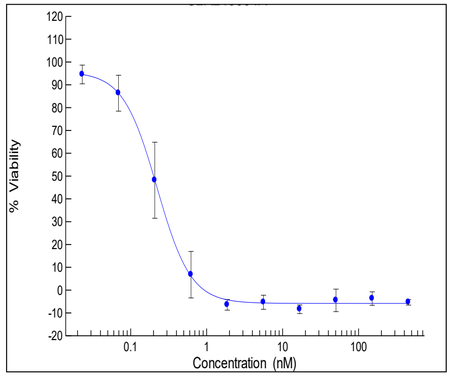
Small-Molecule & Peptide Conjugates

Multi-Payload Platform · Small Molecule Cytotoxin

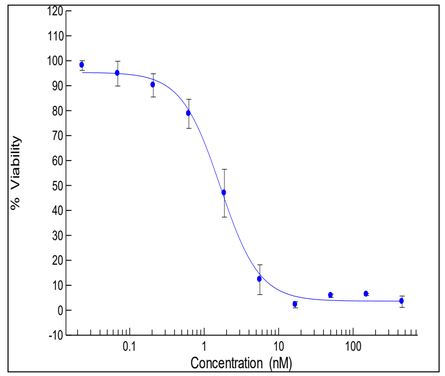
JIMT – 1 Invasive ductal breast



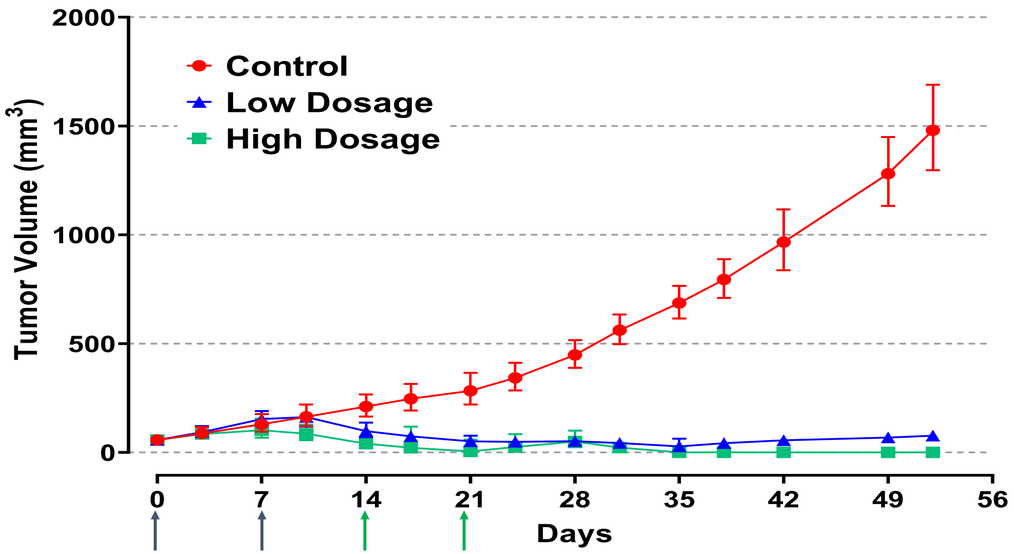
SKBR 3 Her2+ Breast



HS 578T Triple negative breast



JIMT-1 Xenograft



- Demonstrates broad utility across all solid tumor cell lines tested; breast, kidney, colon, lung and ovarian
- In-vitro activity demonstrated across multiple cancer cell lines
  - ~150pM – 5nM activity depending cell line
  - >3uM for normal tissue
- Breast cancer demonstrated the greatest variation in vitro (pM to nM) but activity against cell lines tested
- In vivo activity seen at both low and high doses (2mg/kg per dose)
- Full tumor regression and no regrowth post treatment

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In vitro and In vivo Validation of Platform Utility with Non-radioactive Payloads

Nucleic-Acid Cargo: mRNA & siRNA

Multi-Payload Platform · Cytoplasmic Delivery

Lipid-based, raft-mediated entry is naturally suited to nucleic acids — the challenge that limits most oligonucleotide therapeutics is exactly the tumor-selective cytoplasmic delivery the PLE scaffold provides.

mRNA

- Encodes therapeutic proteins translated in the tumor cytoplasm
- Applications: tumor neoantigens, immunostimulatory cytokines, tumor-suppressor restoration
- Lipid scaffold protects the transcript and aids endosomal escape
- Tumor-restricted expression limits off-target protein production

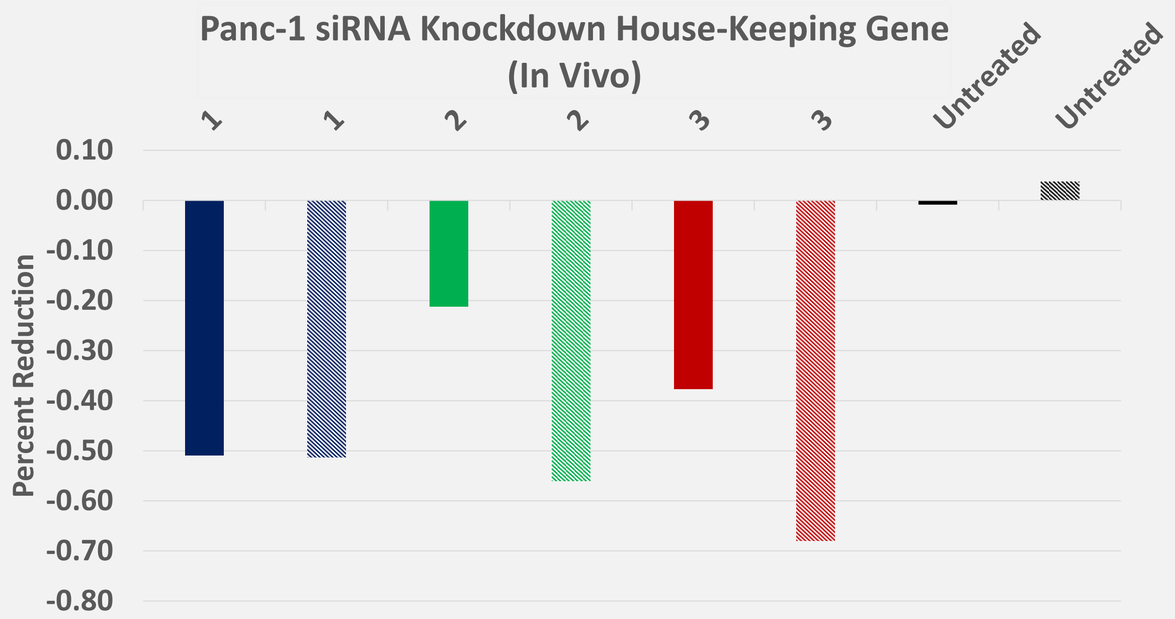
siRNA

- Sequence-specific knockdown of otherwise undruggable oncodrivers
- Targets transcription factors, fusion oncogenes, resistance mediators
- Chemically stabilized duplexes resist nuclease degradation
- Raft entry delivers cargo to the RISC machinery in the cytoplasm

A Lipid Vector Solving the Cytoplasmic-Delivery Bottleneck

Nucleic-Acid Cargo: siRNA

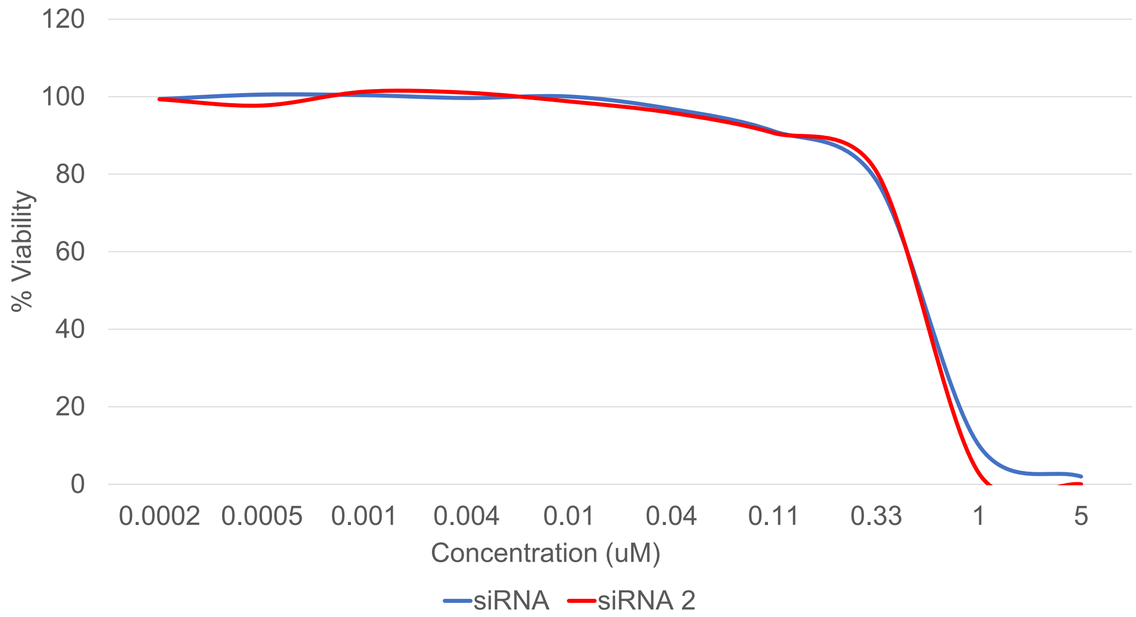
Multi-Payload Platform · Cytoplasmic Delivery



- Three variations of XD-33934 tested in vivo
  - Single tail vein infusion, assessed at 24 & 72 hours
  - Knock-down in the tumor 20% - 70%
  - No knock-down in non tumor cells

IC50s (μM)

	OCILY3	SUDHL-2	Raji	MiaPaCa-2
siRNA1	> 5 μM	0.633	0.501	> 5 μM
siRNA2	0.740	0.620	0.463	> 5 μM



In vivo Targeted Activity with Non-Cytotoxic siRNA & Nanomolar In vitro Cytotoxic Activity

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Targeted Protein Degraders

Multi-Payload Platform · PROTACs & Molecular Glues

Degraders eliminate target proteins catalytically rather than merely inhibiting them — but their size and physicochemistry challenge cell entry. Tumor-selective lipid delivery directly addresses that limitation.

Event-driven pharmacology

A single degrader molecule triggers repeated rounds of target ubiquitination and proteasomal destruction — sub-stoichiometric, catalytic activity.

Reaches “undruggable” targets

Removes scaffolding proteins and transcription factors that lack a classical inhibitor binding pocket.

Overcomes resistance

Degradation can bypass mutations that confer resistance to occupancy-based inhibitors.

Solves the entry problem

PROTACs and molecular glues are large and often poorly permeable; raft-mediated uptake delivers them tumor-selectively into the cytoplasm.

Catalytic Target Removal, Delivered Where Permeability Fails

Design Principles for Every Payload

Phospholipid Drug Conjugates · Cross-Modality Rules

Whether the cargo is a radioisotope, small molecule, mRNA, siRNA, degrader, or peptide, the same biophysical discipline governs success.

Preserve the biophysics

Chain length, amphiphilicity and balanced polarity drive raft affinity. Bulky, highly polar, or charged payloads can break membrane insertion.

Engineer linker & release

Borrow ADC discipline: plasma stability, tumor-specific release, intracellular routing — payload hydrophobicity dominates clearance and tolerability.

Re-map biodistribution

Any conjugate can shift PK and tissue distribution — integrated structure–activity–distribution studies are essential, not optional.

Conjugation Must Not Compromise the Targeting Mechanism

A Platform, Not Just a Drug

Conclusions

Receptor-independent targeting

PLEs exploit cholesterol-rich lipid rafts — a near-universal feature of malignancy — giving broad, antigen-independent reach.

Three eras of progress

From toxicity-limited drug-only ether lipids, through optimized analogs, to engineered targeting scaffolds and conjugates.

Clinical validation

Iopofosine I-131 delivers durable responses in r/r Waldenström with manageable, isotope-driven hematologic toxicity.

A multi-payload modality

The same scaffold extends to small molecules, mRNA, siRNA, degraders and peptides — payload-agnostic, dosimetry-guided delivery.

Antigen-Independent, Multi-Payload, Dosimetry-Guided Delivery

Thank You

Phospholipid Ethers
Precision Carriers for Next-Generation Drug Delivery

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