Engineering Intrinsically Self-Assembling RNA NanoStructures for Improved Precision Delivery of Cancer Therapeutics

James Carroll, President & CEO

January 28, 2026

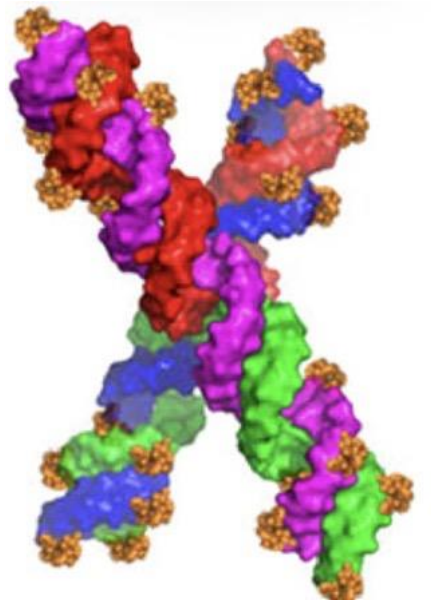
The Future of Oncology: Targeted Combination Therapies & RNA-Based Medicines

“Most cancers will not be controlled with single agents. Rationally designed combination therapies are required to address resistance and tumor heterogeneity.”
— Fabrice André — Nat Rev Clin Oncol (2020)

“Cancer drug development is increasingly focused on combination strategies rather than monotherapies.”
— Richard Pazdur — FDA OCE (2019–2021)

“RNA-based therapeutics provide access to disease drivers that are not reachable with conventional small molecules or biologics.”
— National Cancer Institute — RNA Therapeutics Workshop (2021)

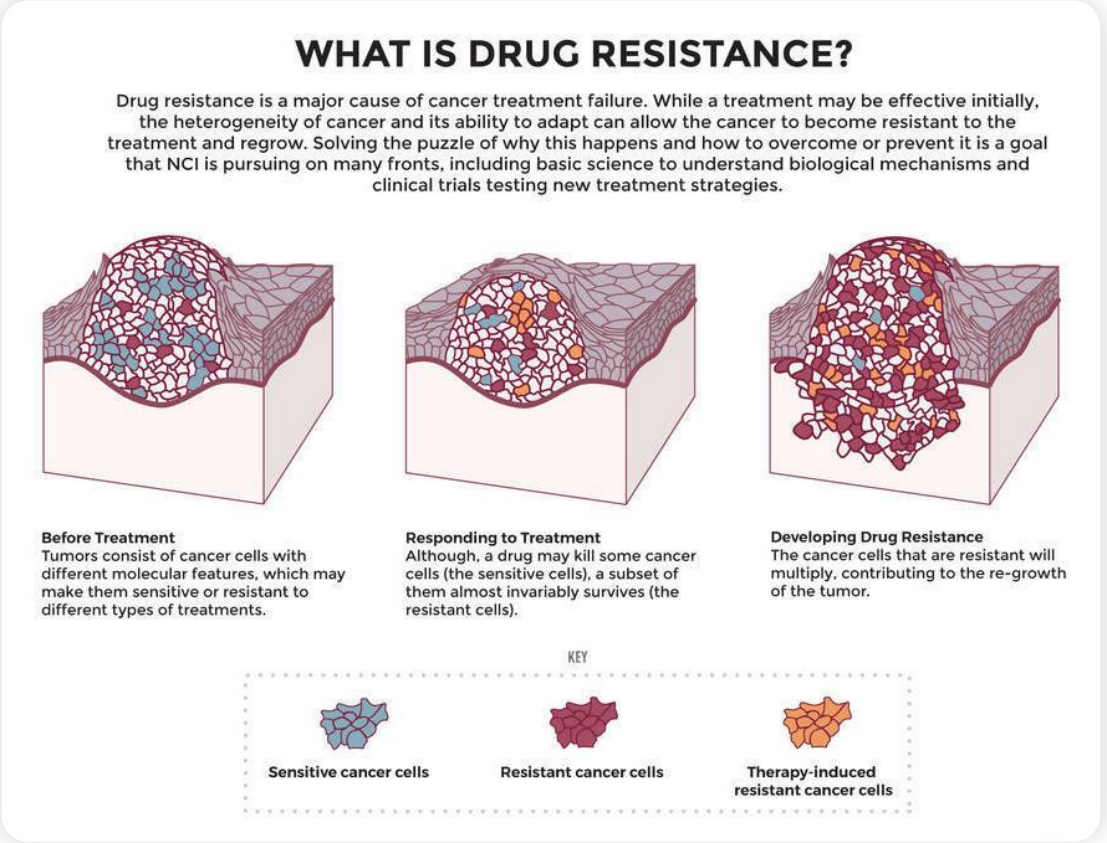
“RNA interference has clear potential in oncology, particularly when paired with effective delivery systems and used in combination regimens.”
— Craig Mello — CSHL Symposium (2019)



Oncology is converging on targeted, multi-mechanism combination therapies — RNA expands the drug-able space; delivery determines success.

The Current Challenges In Cancer Treatment

- **Cancer is adaptive, heterogeneous, and spatially complex, particularly in advanced disease.**
- **Therapies must be targeted to cancer cells, capable of supporting multiple mechanisms of action, and overcoming resistance.**
- **Delivering drugs with sufficient precision across heterogeneous tumors and to the correct intracellular location remains a fundamental challenge.**
- **The industry has pursued combination and targeted approaches, but most have tradeoffs and limitations.**
- **Many promising therapies fall short because of how, where, and when they act.**



THE OPPORTUNITY

RNA NanoBiotics has developed a modular platform built on a programmable, RNA architecture.

- **Each arm of the scaffold is independently engineered and can function as:**
  - **A targeting RNA aptamer, or**
  - **A therapeutic payload (e.g., small-molecule drugs, radioligands, RNA-based therapies)**
- **Modules are designed independently and then assembled into a single, chemically synthesized molecule**
- **The platform's behavior is driven by molecular architecture, not formulation or encapsulation**

This enables:

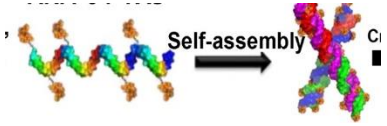
- Precise tumor and intracellular delivery
- Greater flexibility to support combination therapies
- Faster design/build/test cycles that antibody-based approaches cannot match
- Scalable foundation for multiple therapeutic programs

Why it matters:

- Preclinical data demonstrate encouraging safety and biodistribution profiles with no evidence of long-term organ accumulation or dose-limiting toxicities.
- By focusing on architecture, precision, and speed, RNA NanoBiotics is building the infrastructure needed to make targeted, and ultimately multi-mechanism, cancer therapies more practical.

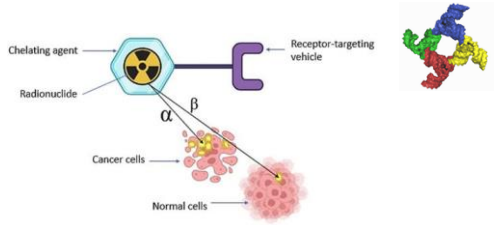
RNA NanoBiotics Platform Designs

Exclusive Licensed Patent Portfolio Covers All Applications



4WJ RNA Nanoparticles + Click Chemistry

- Enhance its cancer cell targeted delivery efficiency to > 5% , vs traditional nanotechnology <0.7%
- Extraordinary PK profiles and low accumulation to VITAL ORGANS
- Increased solubility of chemical drugs, e.g., Increased Paclitaxel solubility by 32,000 folds



4WJ RNA Nanoparticles for Radiation Therapy

- Conjugate chemical drugs to RNA nanoparticles to enhance the solubility and reduce the toxicity, include RNAi drug and an alpha emitting radioisotope in the complex for complete cytotoxicity to cancer cells

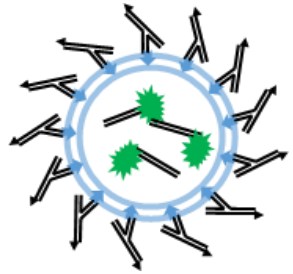
CURRENT FOCUS

RNA Micelles

- Fully Synthetic, non-lipid nanoparticles formed by self-assembly of amphiphilic RNA Conjugates
- Core-shell architecture: hydrophobic core for small molecule drugs
- Proven in vivo delivery of RNAi and chemotherapeutic payloads with proven safety
- Chemically defined and reproducable

4WJ Bispecifics

- Dual targeting of two aptamers or ligands to bind to tumor + T cell receptor or two tumor antigens for enhanced specificity
- Therapy + Immune engagement to target tumor antigen and immune stimulant or checkpoint inhibitor RNAi.

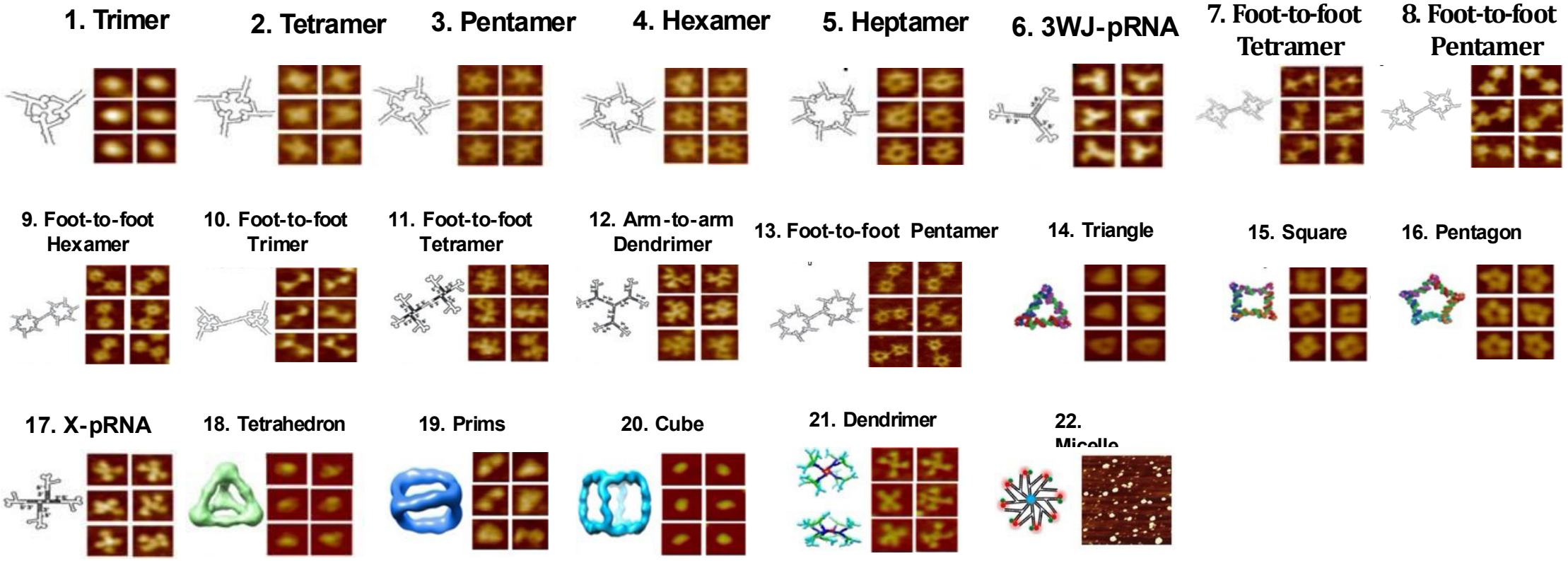


RNA/Exosome

- Display RNA on exosome to make it negatively charged, minimize nonspecific binding
- Display aptamer or chemical ligand onto exosomes for efficient targeting
- Delivers siRNA to cell's cytoplasm to escape from endosome trapping

SECONDARY PLATFORMS

RNA Nano Structures Initially Evaluated



Shu Y, et al, RNA, 2013; Khisamutdinov E, et al, Nucleic Acid Res, 2.14,42:9996-100004; Xu C. et al, Nano Research, 2019: 12:41; Yin H, et al, ACS Nano; 13(1): 706-717

Exclusive, Broad and Defensible IP Estate

- **Worldwide exclusive licenses to > 10 foundational RNA nanotechnology patents (Ohio State University, University of Kentucky and the University of Cincinnati)**
- **Broad compensation-of-matter coverage: RNA nanostructures, targeting aptamers, RNAi and RNA therapeutics, chemotherapeutics, imaging and radiotherapeutic payloads**
- **Multiple delivery modalities covered: RNA Nanoparticles, targeted RNA exosomes, and RNA micelle-based systems**
- **Platform-level claims: cover design, targeting, payload flexibility, and therapeutic use across solid and liquid tumors**
- **Manufacturing and scalability IP included: methods for synthesis, assembly and production of RNA Nanostructures**
- **Continuously expanding portfolio: ongoing academic research adds new drugs, technologies, and patent filings**

>$50M invested in platform R&D across licensed institutions

Executive Team

James Carroll

President, CEO and Board Chairman

25+ years in Executive Management, strategy, corporate and business development, and investments

- President of Wharton Alumni Angels
- Led RNA/DNA Nucleotide drug production and development efforts at Millipore/Waters
- Several Acquisitions, Turnarounds and Exits
- ExonanoRNA, Remedium Bio, Edulis, Bionostics, BioRad, Repligen, Harvard Medical School

Dr. Krystle Karoscik

Chief Technology Officer

Technology, Operations and Strategy Executive

- Niche in Translational Research and Clinical & Commercial Strategy
- Serial entrepreneur in therapeutics and med-tech
- Led >20 early-stage clinical programs
- Managing Director of Life Sciences, Wharton Alumni Angels
- VP BoD Penn Club of Boston; Co-Chair of Women in Leadership fostering development in STEM and finance

Wharton University of Pennsylvania

Penn University of Pennsylvania

Wharton Alumni Club Alumni Angels

Scientific and Legal Advisors

Peixuan Guo, PhD

Inventor, Advisor and Chairman of Scientific Advisory Board

Professor, Sylvan G. Frank Endowed Chair Pharmaceutics and Pharmacology, Ohio State University

- 2021 Innovator Of The Year Ohio State University
- Fellow of the National Academy of Inventors (NAI)
- Director of Center for RNA Nanobiotechnology and Nanomedicine
- President of International Society of RNA Nanotechnology and Nanomedicine
- International Society of RNA Nanotechnology and Nanomedicine

Jennifer Fang

Partner, Wilson Sonsini Specialty Biotech Corporate Law

- Focus on Cutting-Edge Life Science Companies
- J.D., University of Pennsylvania Law School, 2009Internet Editor, University of Pennsylvania Journal of International Law
- M.Eng., Biological Engineering, Massachusetts Institute of Technology, 2006
- B.S., Biology, Massachusetts Institute of Technology, 2005

Penn
University of Pennsylvania

Corporate Board

James J Carroll, MBA
Chairman

Highly committed business operations, sales, marketing, business development, turnaround management, life science start-up, operations, and finance executive with in-depth understanding of biotechnology, life science instrumentation, in vitro diagnostic, and medical device product development, commercialization, and strategic financing.

Ildiko Csiki, MD, PHD
Board Member

- Pioneered strategic initiatives in drug development, leading to significant advancements in cancer treatment and patient care.
- Spearheaded the development and commercialization of groundbreaking therapies, overseeing research, business development, and licensing.
- Expert in clinical trial design

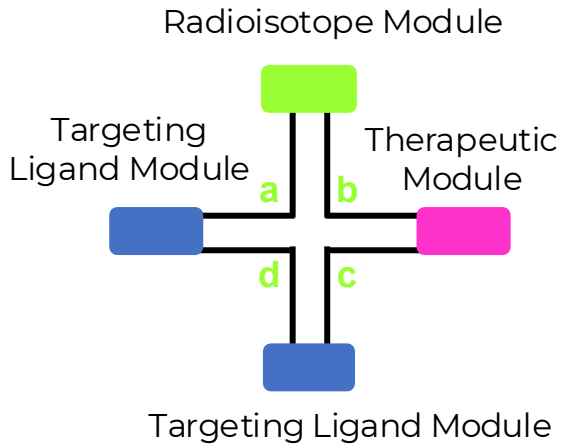
Cynthia Cai, PhD, MBA
Board Member

- Executive & Investor with 25+ years in healthcare and life sciences, experienced in equity investment, board governance, marketing, and business development.
- Board Member of Spectral AI (NASDAQ: MDAI), Arthrosi Therapeutics, Amberstone Biosciences, Basking Biosciences, HAYA Therapeutics, and the Science History Institute.

Wharton
University of Pennsylvania

Engineering an RNAi Module: Programmable Release from 4WJ RNA Nanostructures

Four Engineered Modules Combine



Targeting Ligand – Aptamer sequences engineered into module

Therapeutic Module – RNA and or Nucleoside Drugs engineered into module

Radioisotope Module – Radioisotopes attached via proprietary ligand technologies

Core Principle (Guo, Nature Protocols 2026): RNAi compatibility is governed by engineered release, not payload identity.

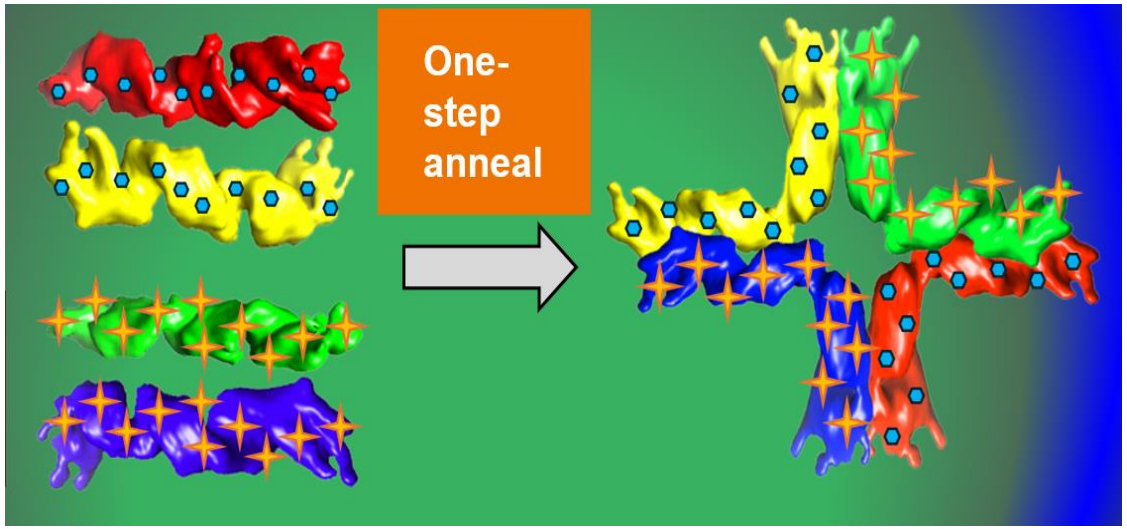
- **RNAi Payload Encoding: siRNA/shRNA/miRNA encoded as a functional arm; sequence-level strand and duplex control.**
- **Engineered Release Junction (Critical): Programmable linker with flanking sequence tuning preserves 4WJ folding while enabling enzymatic cleavage.**
- **Cytosolic Processing: Intact nanostructure reaches cytosol; RNAi released locally and processed by Dicer → RISC (no endosomal escape).**
- **Universality & Multiplexing: Same 4WJ backbone supports all RNAi classes and multiple independent RNAi arms via linker design.**

AI End-to-End System Architecture

- Target module: Literature + trial mining → aptamer targets.
- Design module: Generative LLM for aptamers + 4WJ scaffolds.
- Payload module: siRNA + miRNA optimizer..
- Drugs Synthesized. Screened in Cell Culture and on to Animal Testing

Cycle time: Weeks instead of months

Like “LEGO Assembly”: Modular Arm Design Allows Combination Drugs or Retargeting



Arm Design Choices:

- Non-Active Stability Arms - Standardized
- Targeting Ligand – Aptamer sequences engineered into Arm or chemical agents
- Chemo Arm: SN38, Taxol, and others
- siRNA Drug Arm
- microRNA Drug Arm
- Nucleoside Drugs Like FUDR or GEM Arm
- Radioisotope Chelator Arm

Modular System Simplifies Drug Design and Approval as Individual Arms Approved And Allowing Hundreds of Targeted Combination Drug Therapies

4WJ Modular Platform: Loaded Assets & Regulatory Strategy

All 4WJ arms carry real, loaded payloads with in-vivo efficacy and safety data.
Radiopharma capability is linker-enabled, not isotope-restricted.

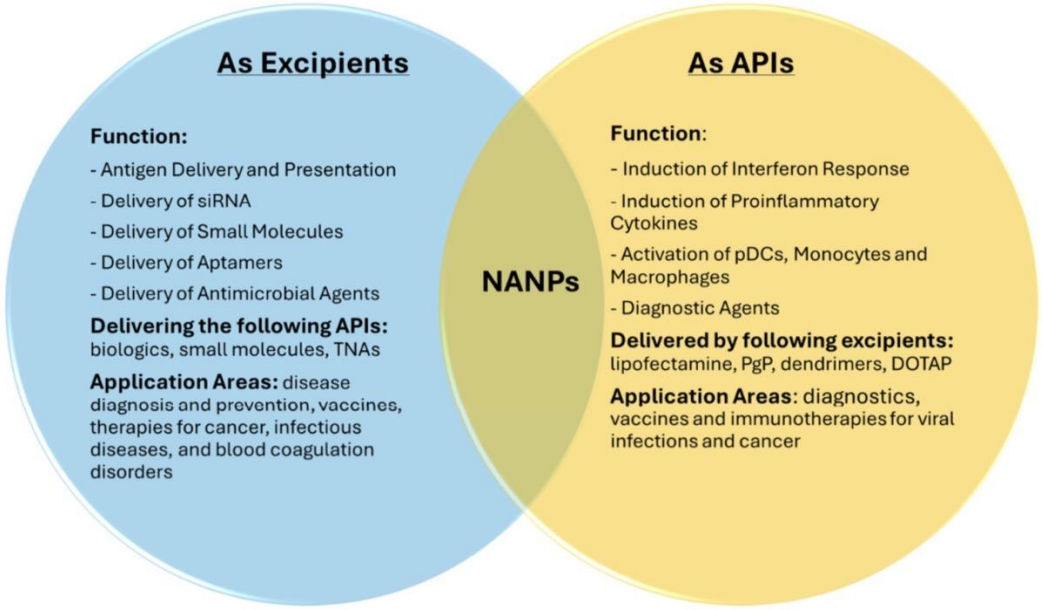
4WJ Arm	Loaded / Demonstrated Assets	Release / Function	Regulatory Path
Targeting Arm	EpCAM aptamer (CRC Lead), TNBC aptamer, leukemia aptamer...several	Binding only	CMC component internal sequence only changes, if aptamer.
Stability Arm	Chemically stabilized RNA motifs	No release	CMC / PK / tox
Chemotherapeutic Arm	SN-38 (lead), Paclitaxel (Taxol), Cisplatin...	Cleavable linkers	**505(b)(2) if preapproved**
Nucleoside Drug Arm	FUDR, Gemcitabine	Intracellular activation	**505(b)(2) if preapproved**
siRNA Arm	KRAS and oncogenic drivers	Cytosolic RNAi release	505(b)(1) RNA Sequence Changes
miRNA Arm	Anti-miR-21, tumor suppressor miRNAs	Cytosolic release	505(b)(1) RNA Sequence Changes
Radiopharma Arm	Gallium (validated) → Pb / Lu / Ac via linker	Typically non-releasing	Radiopharma pathway

Regulatory Implications of RNA Nanostructures

4WJ platform can be an API, an excipient, or both — depending on context

"***Nucleic acid nanoparticles can serve as active pharmaceutical ingredients (APIs) and excipients and can even combine both functions simultaneously, depending on their intended therapeutic mechanism of action and formulation context.***"
— ACS Nano Medicine (Afonin et al.)

"Traditional binary classification as either API or excipient does not fully capture the regulatory reality of nucleic acid nanostructures."
— ACS Nano Medicine Perspective

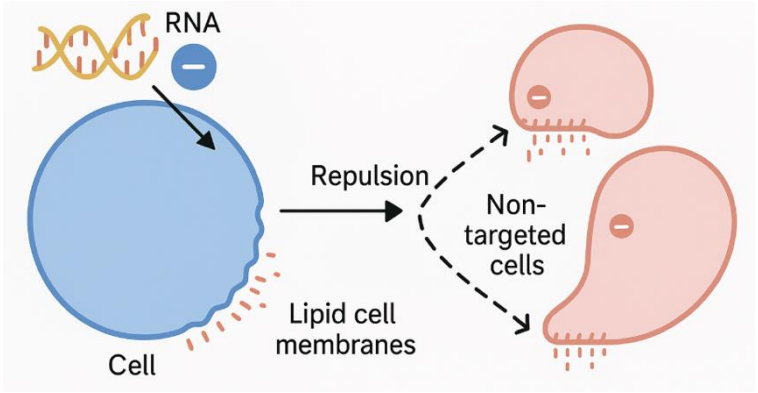


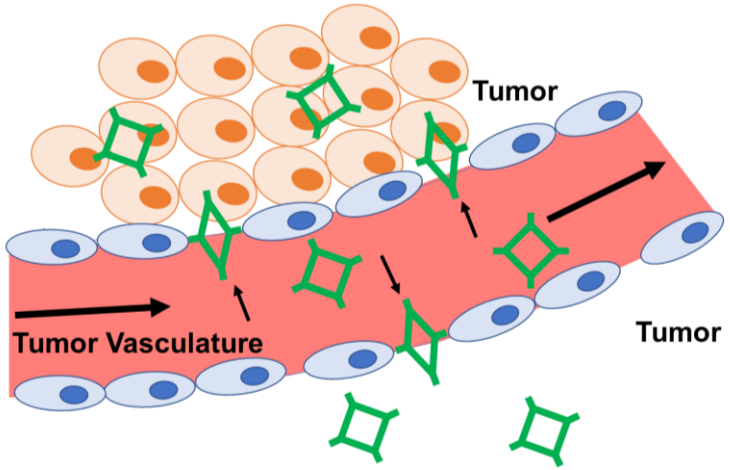
Implications for RNA NanoBiotics:

- **4WJ scaffold classification is payload- and context-dependent**
- **Enables 505(b)(2) paths for small molecules and nucleosides**
- **RNAi / miRNA arms align with established RNA therapeutic frameworks**
- **Shared platform CMC and toxicology with payload-specific deltas**

Reference: Kozlov S. et al. Nucleic Acid Nanoparticles Redefine Traditional Regulatory Terminology. ACS Nano Medicine, 2025.

Intrinsic 4WJ RNA Nanostructure Properties Enable Precise Deep Tumor Penetration





The amoeboid rubbery property of RNA nanoparticles make them penetrate more efficiently into tumors as they can easily clear the 5nm glomerulus kidney filter intact

The negative charge of RNA prevents entry into non-targeted cells or accumulation in vital organs.

Combined result is greatly enhanced tumor targeting and accumulation in solid tumors as compared to significantly larger ADCs.

Aptamers Also Confer Precise Recognition of Tumor Cells- Ensuring Minimal Uptake by Healthy Tissues

RNA NANO-PARTICLES FOR TARGETED RADIATION THERAPY

Global targeted radiotherapy market projected to exceed $15B by 2030

RNA NanoMed (Aug 2025) published proof-of-concept for targeted radiotherapeutics using modular RNA nanoparticles

Platform Highlights:

4WJ RNA nanoparticles retain chemical & targeting behavior of 3WJ core

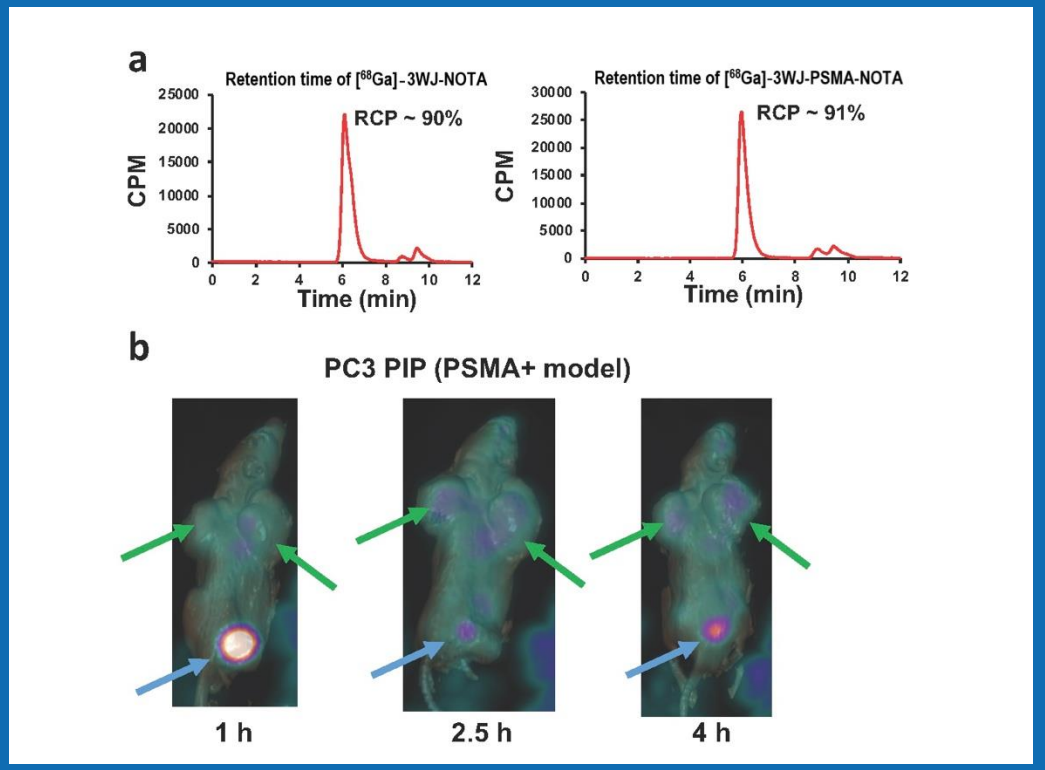
- Rapid tumor uptake: 1–4 h; rapid clearance from non-tumor tissues
- Plug-and-play design: swap targeting ligand & chelator strand without altering core
- Diagnostic ^{68}Ga easily replaced with therapeutic α/β emitters
- Single GMP & regulatory backbone supports multiple products

Alpha Emitter Priorities

- ^{212}Pb / TCMC strand – Best PK match; clean drop-in for therapy
- ^{225}Ac / DOTA or macropa strand – Straight substitution; manage daughter recoil

Theranostic Options

- Therapeutic: ^{212}Pb, ^{225}Ac, ^{211}At
- Diagnostic: ^{68}Ga, ^{18}F, ^{64}Cu



^{68}Ga-Labeled RNA Nanoparticle (3WJ-PSMA-NOTA) for Medical Imaging Proof of Concept

Green Arrow - Tumor

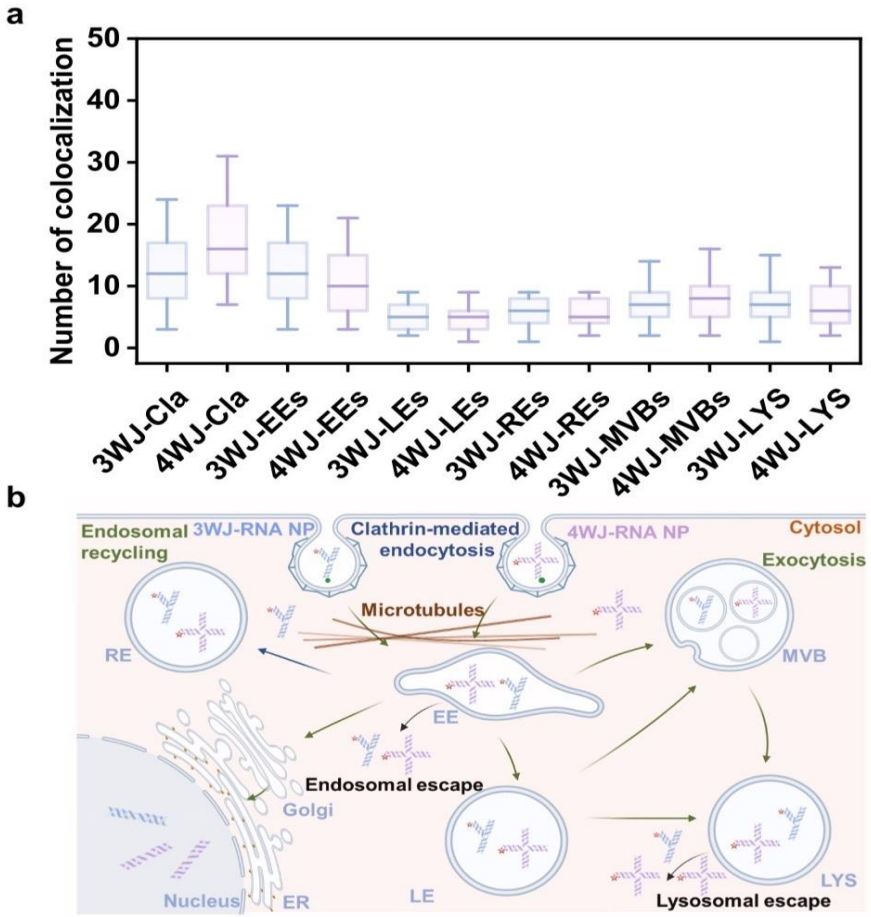
Blue Arrow – Bladder (showing excretion)

RNA 3WJ vs 4WJ Nanostructures: Delivery Mechanisms

- 3WJ and 4WJ share identical pRNA-derived chemistry, uptake routes, and biodegradation → safety data is transferable
- The 3WJ and 4WJ Nanostructures remain intact in the blood stream and do not release payloads outside of target
- Both enter via clathrin-mediated endocytosis and traffic or microtubules
- Key limitation of ADCs: inefficient endosomal escape → payload trapped or degraded
- 4WJ exhibits faster membrane translocation and sustained directed intracellular diffusion
- 4WJ demonstrates higher endosomal and lysosomal escape efficiency with preserved structural integrity
- Result: RNA payload reaches the cytosol at the correct intracellular location to be biologically effective

Strategic implication: 4WJ solves the dominant intracellular delivery failure mode seen with ADCs and many LNP systems

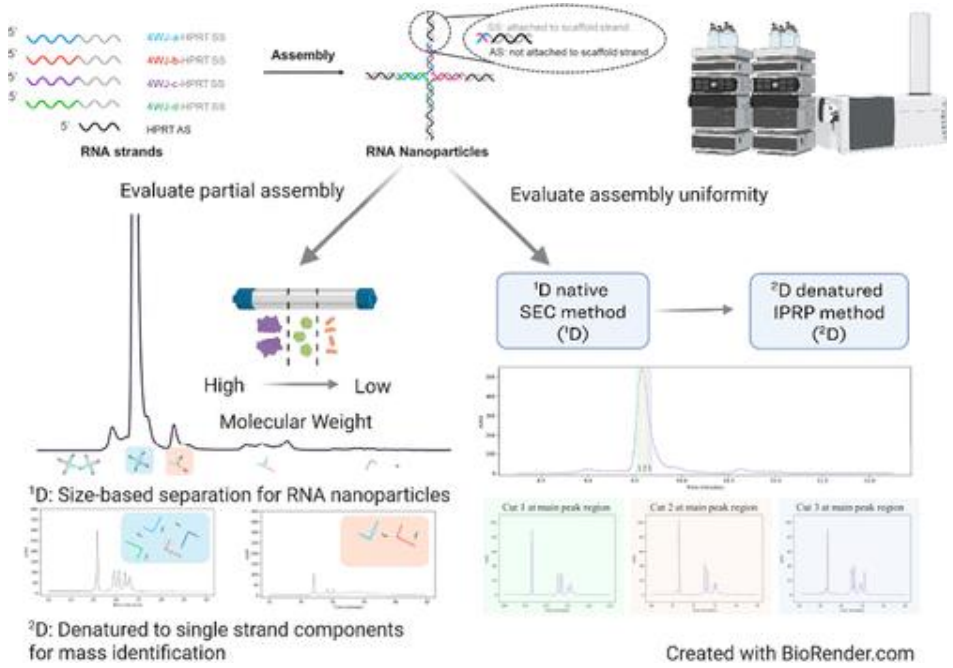
Reference: H. Wang et al., Chemical Engineering Journal 526 (2025) 171092



Intracellular delivery fate of RNA NPs. (a) The colocalization number in each cell for 3WJ-RNA NPs and 4WJ-RNA NPs (b) Schematic of the intracellular delivery pathway of RNA NPs. EE-early endosome, LE-late endosome, RE-recycle Endosome, MVB-multivescular bodies, LYS-lysosome

Industrial-Grade CMC & Assembly Validation for 4WJ RNA Nanostructures: Independent Eli Lilly

- **Third-Party Pharma Endorsement: Validated at Eli Lilly Institute of Genetic Medicine and Lilly Research Laboratories, demonstrating pharma-grade CMC transferability.**
- **Manufacturing Transferability: Uses standard SEC, IPRP, MALS, and HRMS workflows already deployed in industrial CMC labs for scale-up, batch consistency, and release testing.**
- **Assembly Control: SEC × IPRP 2D-LC resolves fully assembled RNA nanostructures from intermediates and free strands, confirming defined stoichiometry and uniformity.**
- **Formulation Stability: SEC × SEC thermodynamic testing in PBS shows no strand dissociation under formulation conditions, supporting clinical readiness.**
- **Orthogonal Validation: Native SEC-MS confirms intact mass (101.7 kDa, <25 ppm error). SEC-MALS shows narrow MW distribution. In vitro knockdown potency unchanged.**



Wu et al., ACS Applied Bio Materials, 2025 | Eli Lilly Institute of Genetic Medicine & Lilly Research Laboratories | DOI: 10.1021/acsabm.5c01565

Intrinsic Safety Profile of the 4WJ RNA Nanostructure

Cross-study, payload-agnostic toxicology and immunogenicity summary

- **Evaluated across >15 independent in vitro and in vivo studies, including external laboratories**
- **No acute or chronic systemic toxicity in repeat-dose murine studies**
- **No weight loss or histopathologic changes (liver, kidney, spleen, heart, lung)**
- **Minimal innate immune activation — no significant IL-6, TNF-α, IFN-γ elevation**
- **Normal clinical chemistry and hematology (ALT, AST, BUN, creatinine, CBC)**
- **Tumor-selective uptake with rapid renal clearance due to small, non-cationic architecture**

The 4WJ RNA nanostructure exhibits intrinsic, payload-agnostic safety at the delivery-system level.

ADC’s VS 4WJ RNA Nanoparticles

	ADCs	4WJ RNA Nanoparticles
Targeting specificity	❌ Off-target risk	✅ Programmable precision
Payload versatility	❌ Limited (mainly cytotoxics)	✅ Multiple payload types (siRNA, miRNA, drugs, imaging)
Size & tumor penetration	❌ Bulky, limited diffusion	✅ Small, tunable, better penetration
Manufacturing	❌ Complex antibody + conjugation	✅ Self-assembling, reproducible
Circulation stability	❌ Risk of premature release	✅ Chemically stabilized RNA
Immunogenicity	❌ Potential immune activation	✅ Low immunogenicity (engineered)
Controlled release	❌ Linker-dependent	✅ Smart release (pH, enzymes, miRNA triggers)
Cost & scalability	❌ Expensive biologics	✅ Low-cost, scalable synthesis

4WJ RNA Nanoparticle Key Advantages

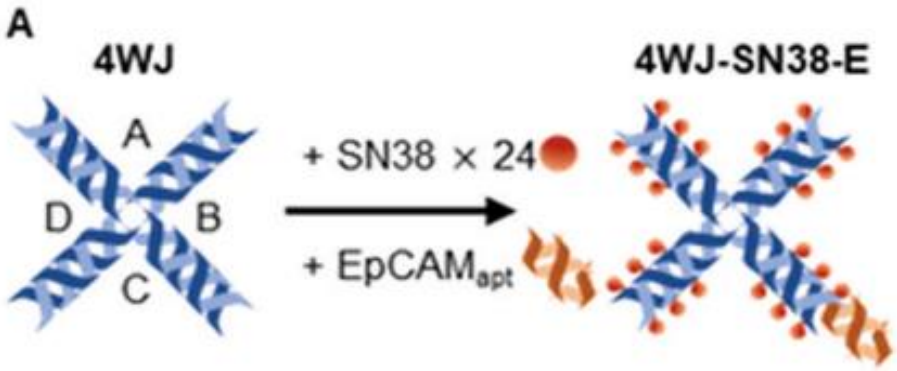
- Engineering Simplicity - 4WJ RNA nanoparticles avoid antibody discovery and conjugation, allowing faster iteration by simply changing RNA sequences. This makes the platform more agile than ADCs.

- Tumor Penetration & PK (Size) - Size is decisive: ADCs (~10-20nm) struggle to penetrate solid tumors, while 4WJs (functionally <5nm and clear glomerulus) diffuse throughout tumor tissue, improving therapeutic reach.

- Immunogenicity - Unlike ADCs, which can trigger immune responses, 4WJs with modified nucleosides show minimal immunogenicity, supporting repeat dosing.

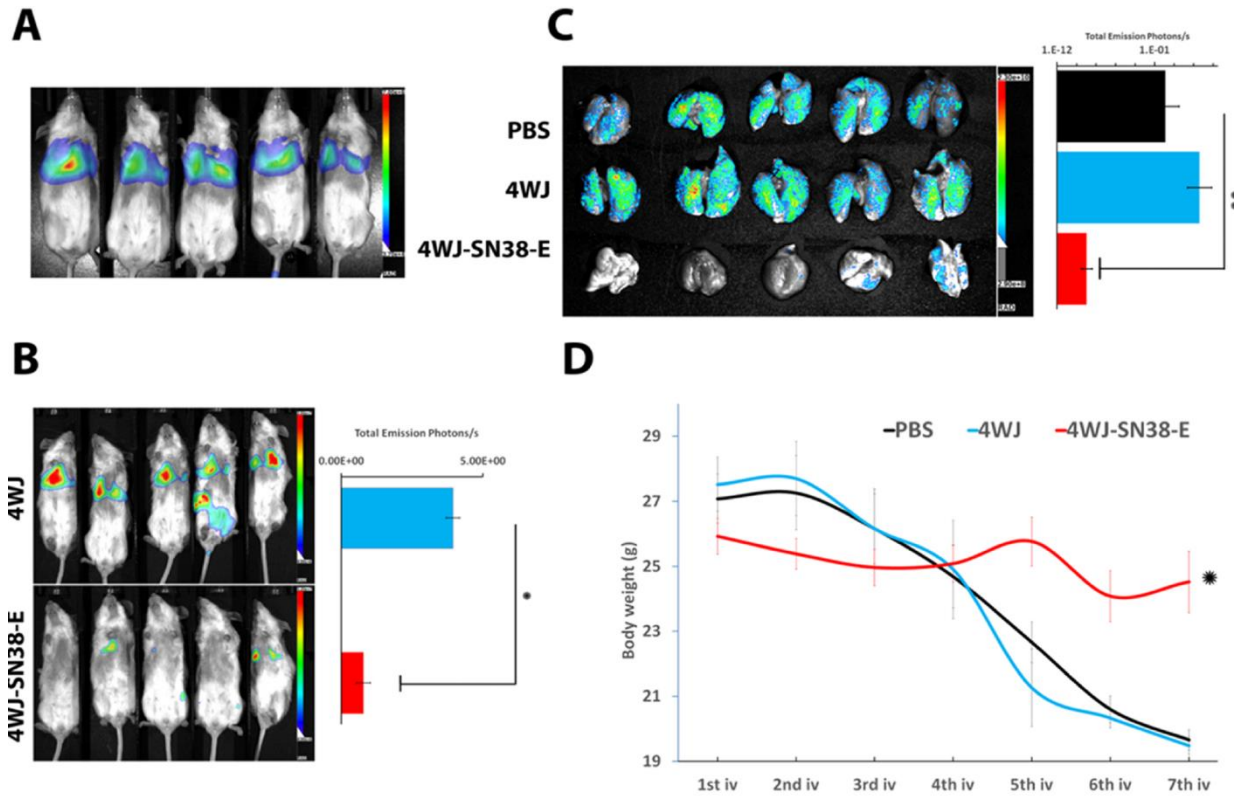
Lead Clinical Drug Candidate (end of 2026)
4WJ-SN38 Design with Targeting EpCAM Aptamer

SN-38 Pursued Under 505 (b) (2), Referencing Irinotecan to Reduce Development Risk, Time and Cost



EpCAM is overexpressed **(70-90%)** in numerous cancers

- **Dramatic reduction of metastatic lung burden**
- **In vivo and ex vivo imaging show near-eradication of lesions**
- **Achieved with excellent tolerability and no weight loss**



ig. 6. *In vivo* colorectal cancer lung metastasis model inhibition of 4WJ-SN38-E. (A) Lago imaging to confirm metastasis establishment 5 days after IV injection. (E
ioluminescence to compare metastasis *in vivo* between 4WJ and 4WJ-SN38-E groups. The mice in the PBS control group were so sick (see D) and cannot survive ti
ne whole body imaging. (C). GFP imaging to compare metastasis *ex vivo* between PBS, 4WJ, and 4WJ-SN38-E groups. (D). Mice weight changes on day 5, 8, 11, 14
7, 20, and 23.

PRECLINICAL POC DATASET 4WJ EpCAM SN38

Key Requirement	RNA NanoBiotics Result	Benchmark Met
Drug Loading Efficiency	24 SN38 molecules per 4WJ-RNA nanoparticle	✅
In Vitro Apoptosis / Cytotoxicity	31.6% apoptosis in HT29 cells (4WJ-SN38-EpCAM)	✅
In Vivo Tumor Volume Reduction	85–90% tumor volume reduction at 2 mg/kg SN38 (x5 doses)	✅
Targeting Benefit over Non-Targeted NP	20.4% greater tumor reduction with EpCAM-targeted NPs	✅
Maximum Tolerated Dose (MTD) Margin	No observable toxicity at effective dose; safe at 2 mg/kg × 5 doses	✅
Systemic Toxicity (weight, organs)	No weight loss, no histopathologic changes in liver, kidney, spleen, heart, lung	✅
Cytokine Induction (e.g., TNF-α, IL-6)	No significant TNF-α or IL-6 elevation at 100 nM (comparable to PBS control)	✅
Hemolysis / Plasma Compatibility	<5% hemolysis, no platelet aggregation, complement activation, or abnormal coagulation	✅
Biodistribution / Clearance	Tumor-targeted accumulation; fast renal clearance; undetectable off-target accumulation	✅
RNA Nanoparticle Stability	Stable >12 hrs in human serum; maintains shape and function	✅

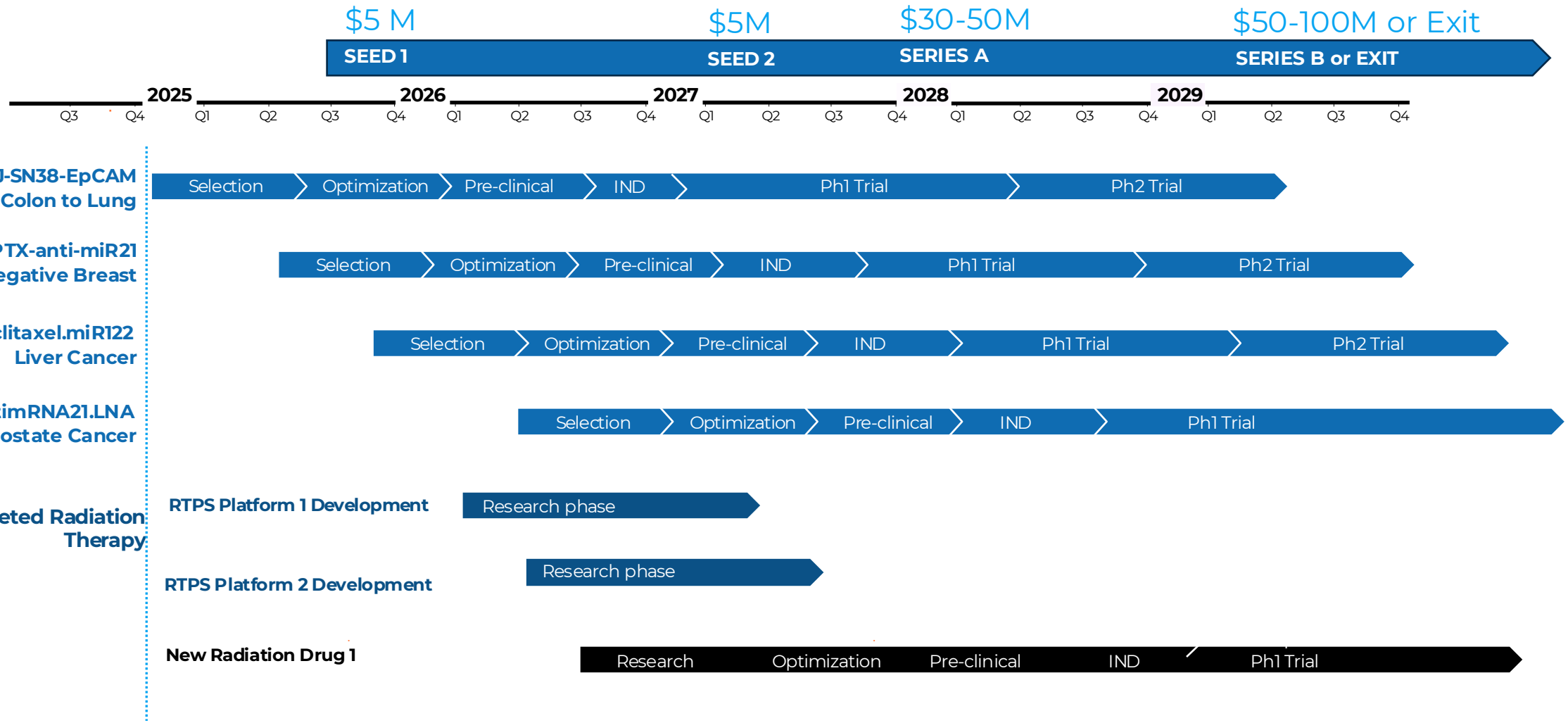
CURRENT DRUGS IND SUBMISSION TIMELINES*

	Target	Payload	Cancer Type	Ready to Initiate IND Program	Planned IND	505 (b) (2)
1	**EpCAMapt**	**4WJ-SN38**	**mCRC – Liver/Lung**	✓	**2026**	✓
1A	EpCAMapt	4WJ-CPTH-FUDR or 4WJ-CPTH-FUDR-FTD	mCRC-Liver/Lung	(secondary combination assets)	2026	✓
2	**EGFRapt**	**4WJ-X-24PTX-anti-miR21**	**Triple Negative Breast Cancer**	✓	**2027**	**?**
2	**EGFRapt**	**4WJ-X-24PTX-anti-miR21**	**Head and Neck Esophagual**	✓	**2028**	**?**
3	HTLs	4WJ-GalNex-Paclitaxel.miR122	Liver Cancer	Animal data	2028	✓
4	PSMAapt	4WJ-anti-mRNA21-LNA	Prostate Cancer	Animal data	2028	X

Several Additional Drug Candidates Identified by AI for: Gastric/GEJ, Ovarian, Pancreatic, Endometrial, Lymphoma,...

* Priorities/dates may be re-ranked based on new data and review. Platform related work can continue until priority decision.

RNA NanoBiotics Drug Pipeline Timeline



Ongoing Research at OSU may present more advanced drugs that may lead to reprioritization (5+ papers to be published)

Strategic Partnering and Exit Landscape – Top Targets

Company	Strategic Fit	Partnering Rationale	Relevant Deals / Why It Matters
Roche / Genentech	ADC leader; deep oncology presence	Aggressive dealmaker, proven external innovation appetite	Spark ($4.3B, 2019); multiple ADC deals >$1B; Entrada IPO $570M
Pfizer / Seagen	Oncology & ADC strength; RNA interest	Large acquisitions; RNA expertise post-COVID	Seagen ($43B, 2023); Array ($11.4B, 2019); RayzeBio ($4.1B, 2023)
Bayer (Radiopharma)	Radioligand leader (Pluvicto, Xofigo)	Active acquirer/licensor in radiopharma space	Ratio $745M; Aktis $175M raise; Noria/PSMA acquisition
Novartis (Radioligand Therapy)	Oncology powerhouse; radioligand expansion	Open to early partnerships; acquisitive	Mariana $1B upfront (2023); Endocyte $2.1B; AAA $3.9B; Alpha9 $175M

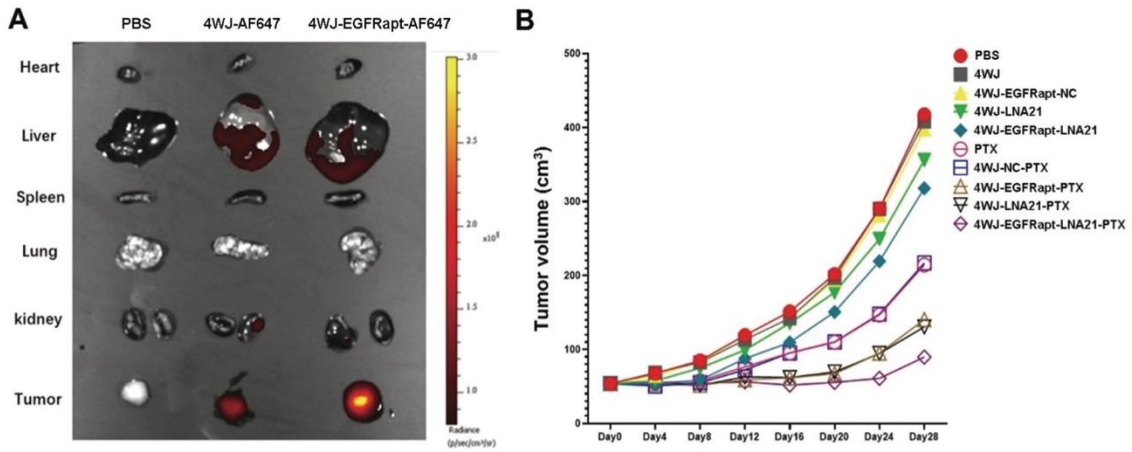
Combination Chemotherapy + RNAi via Single RNA 4WJ

Therapeutic design

- RNA4WJ nanostructure co-delivering paclitaxel (PTX) and anti-miR-21-5p
- EGFR-targeted delivery to head & neck squamous cell carcinoma (HNSCC) also (TNBC)
- Single nanoparticle enables simultaneous chemo + RNAi therapy

Key result

- Combination therapy shows superior tumor suppression vs monotherapies
- Demonstrated in both in vitro and in vivo tumor models



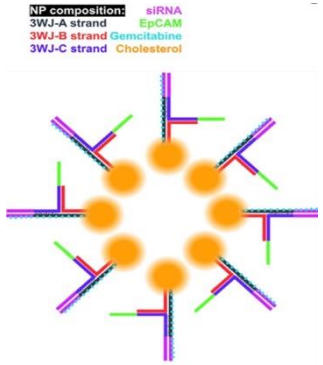
In vivo validation of combination chemo–RNA therapy using RNA4WJ nanoparticles.

Panel (A) demonstrates tumor-selective accumulation of targeted RNA4WJ nanoparticles by IVIS imaging following systemic administration.

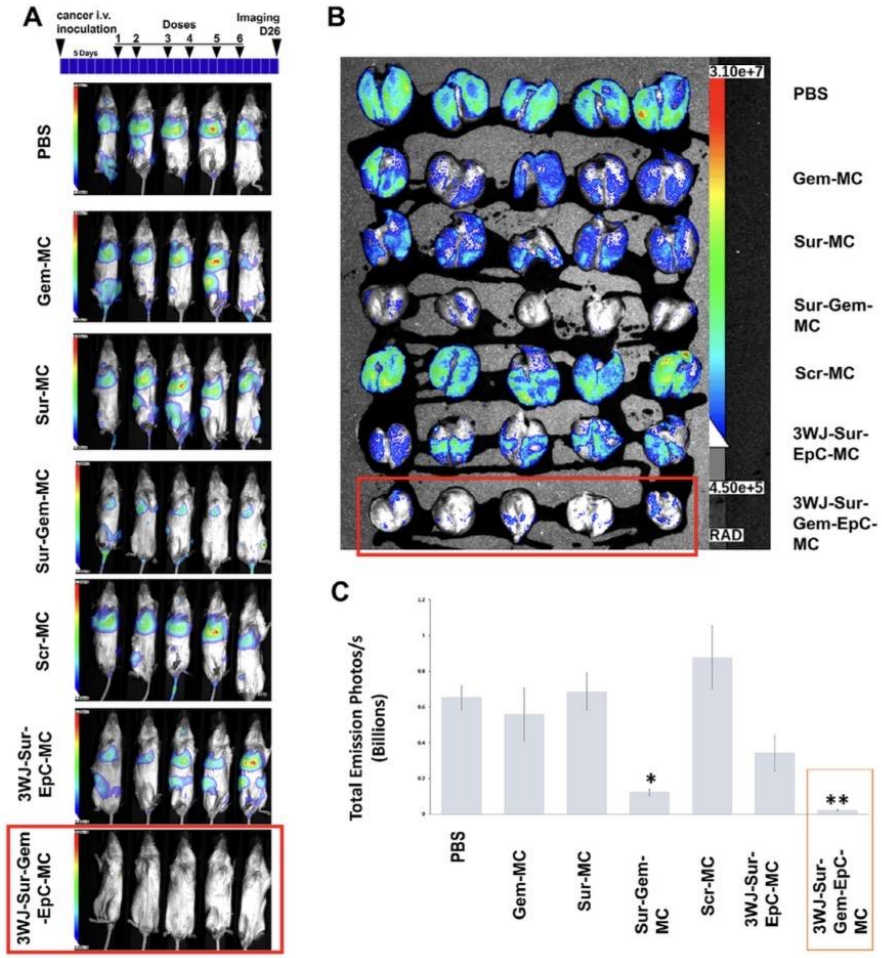
Panel (B) shows tumor volume reduction over time in HNSCC xenografts, where RNA4WJ nanoparticles with combination loading profiles achieve greater antitumor efficacy than free paclitaxel or single-loaded controls at matched PTX dosing.

Key takeaway: RNA nanostructures enable true chemo–RNAi combination therapy with synergistic tumor suppression.

RNA-Micelle–Based Delivery of Synergistic Combination Therapy of RNAi and Chemotherapy for Metastatic CRC

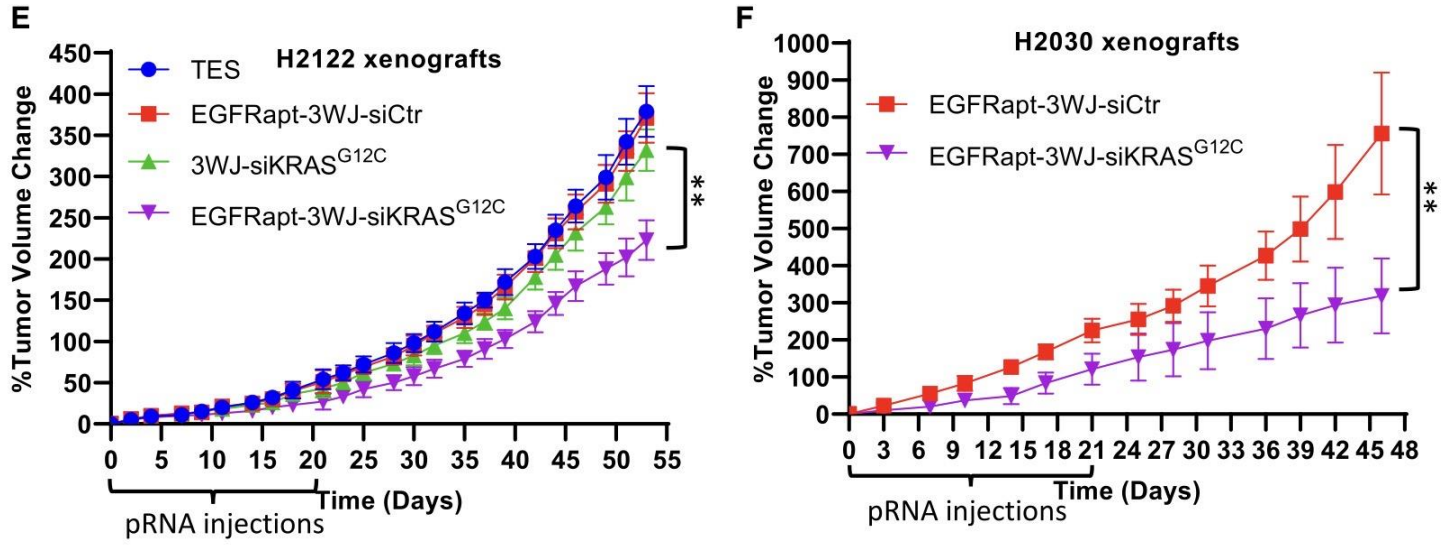


- **Distinct RNA delivery architecture: cholesterol-driven RNA-micelle self-assembly (not 3WJ/4WJ)**
- **Single RNA vehicle delivers survivin siRNA + high-payload gemcitabine to the same cell**
- **Intracellular synergy by design: RNAi disables resistance → chemotherapy induces apoptosis**
- **Represents a complementary RNA platform another mechanistically distinct way to attack mCRC**
- **RNA-micelle therapy achieves near-complete suppression of CRC lung metastases (Fig. 5A–C)**



Jin et al., Advanced Functional Materials (2026) — RNA-Micelle platform for synergistic RNAi + chemotherapy delivery

KRAS siRNA Delivery Suppresses NSCLC Tumors In Vivo

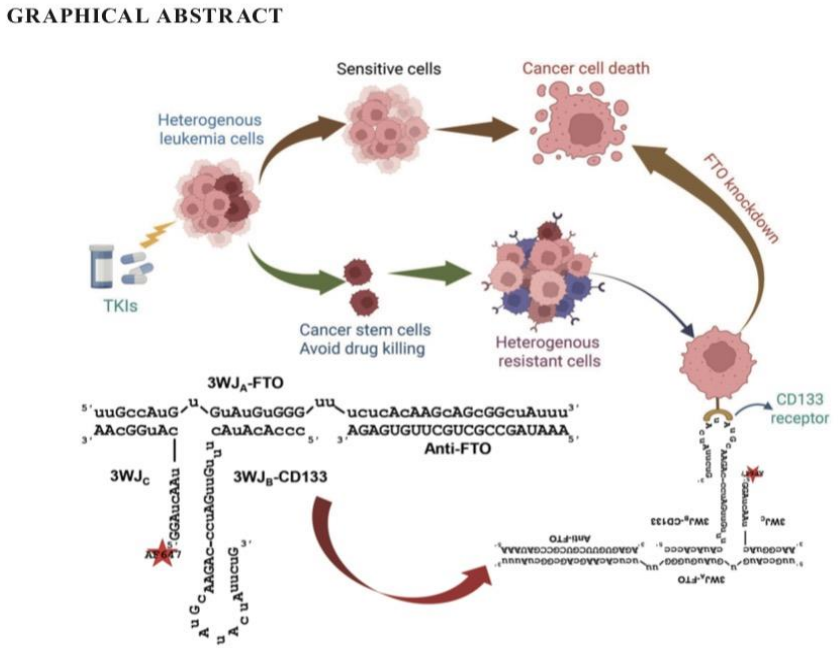


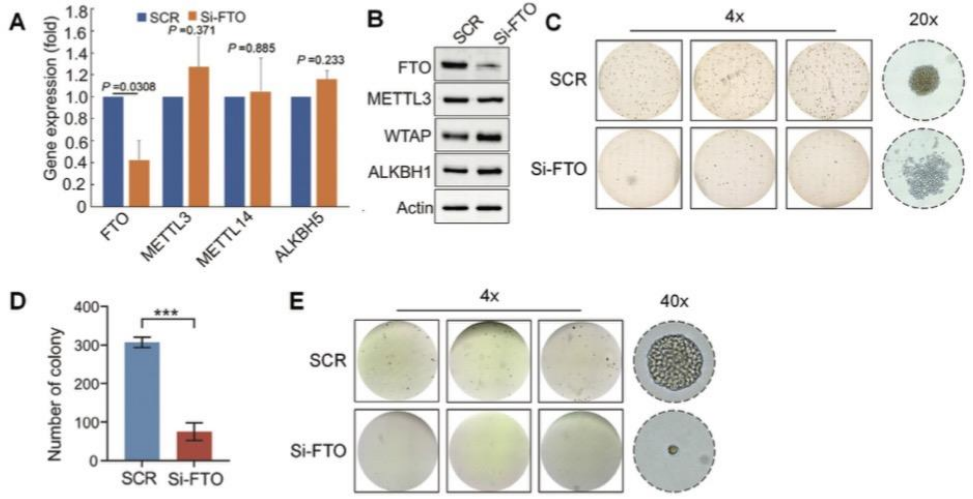
EGFR-aptamer–targeted pRNA-3WJ nanostructures delivering KRASG12C siRNA suppress tumor growth in NSCLC xenografts (H2122, H2030).

- **Systemic IV delivery of KRASG12C siRNA using pRNA-3WJ nanostructures**
- **EGFR aptamer–mediated tumor-selective uptake**
- **Significant suppression of NSCLC tumor growth versus controls**

Li et al., Molecular Therapy – Nucleic Acids, 2023. EGFR-aptamer–targeted pRNA-3WJ nanoparticles delivering KRASG12C siRNA suppress NSCLC tumor growth in vivo.

Case Western Reserve University: CD133-Guided 3WJ Delivery of FTO siRNA to Overcome TKI Resistance (Leukemia)





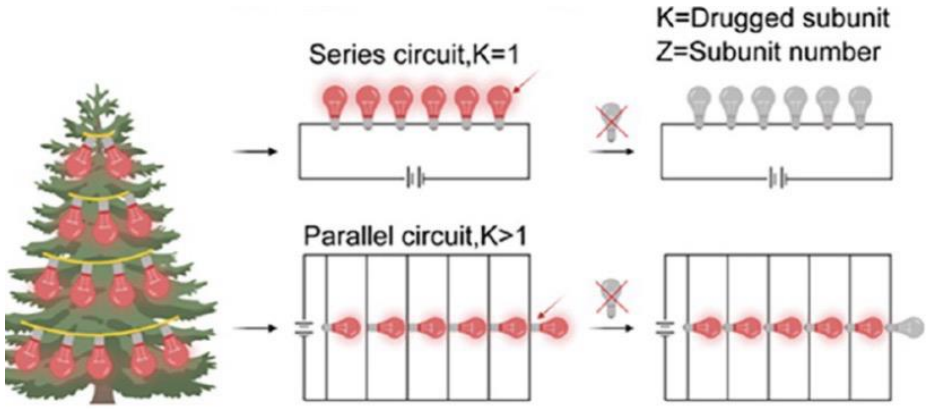
(A,B) FTO mRNA and protein knockdown by CD133-targeted siRNA.
(C,D) Colony formation markedly reduced vs control.
(E) Spheroid growth suppressed in resistant K562 cells.

CD133-guided 3WJ-siFTO significantly reduces colony formation Key takeaways:

- RNA therapeutic: FTO siRNA (2'-F pyrimidine stabilization; guide strand unmodified) delivered on phi29 pRNA-3WJ scaffold; targeting via CD133 RNA aptamer (B19 > A15 binding).
- Mechanism: CD133-high TKI-resistant K562 cells show markedly higher binding/uptake of CD133-3WJ constructs, enabling gene-specific FTO knockdown without broad disruption of other m6A regulators.
- Functional outcome: CD133 and spheroid growth in nilotinib-resistant cells versus scrambled control—supporting RNAi as a route to override drug-tolerant/stem-like leukemia populations.

Reference: Bian H, Zhou C, Koyama H, et al. "CD133-Guided RNA Nanoparticle Delivery of FTO siRNA Impairs Leukemia Resistance to Tyrosine Kinase Inhibitor Therapy." RNA NanoMed. Oct 2025;2(1):70–?.

Why Multi-Target RNAi Is Necessary: The "Christmas Tree" Concept



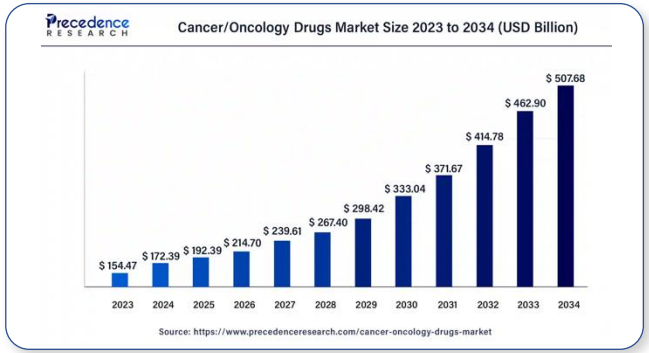
Conceptual takeaway: turning off one light does not shut down the system — multiple connections must be silenced simultaneously.

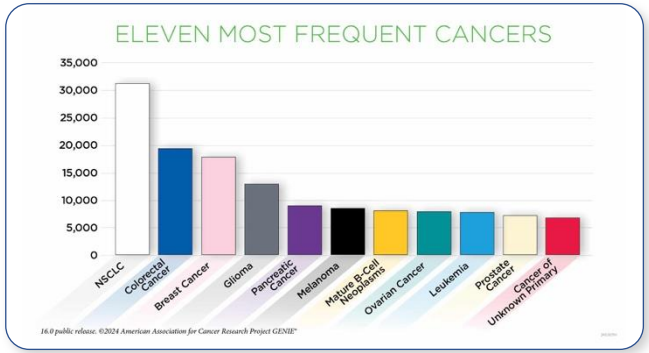
- **Chemoresistance is driven by RNA-regulated ABC drug efflux systems**
- **Efflux requires multiple RNA-controlled components to function:**
  - **transporter expression (e.g., ABCB1/P-gp)**
  - **ATP binding and hydrolysisconformational cycling and membrane transport**
- **Silencing a single RNA target allows rapid biological compensation**

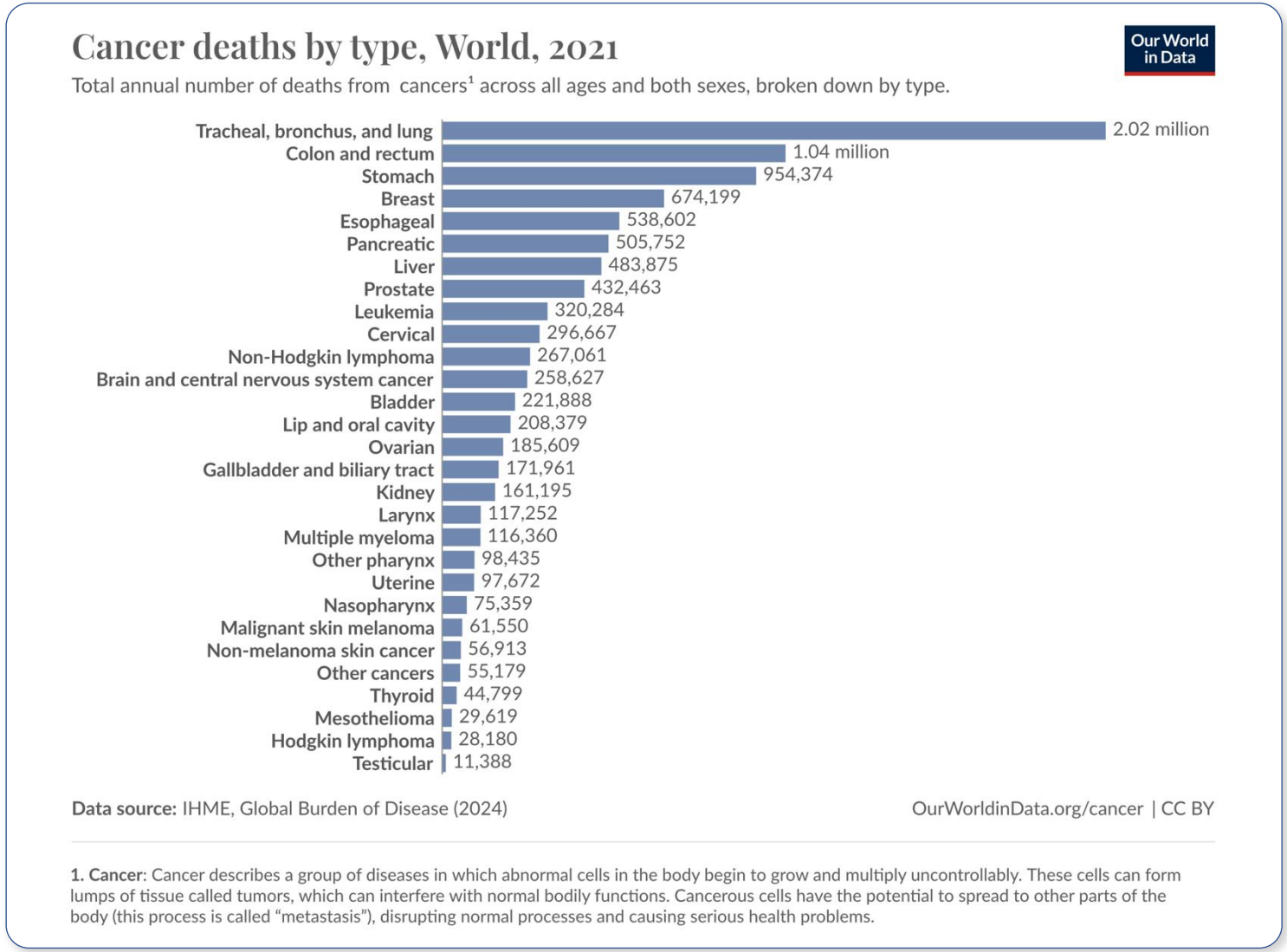
- **Cancer signaling networks are redundant and adaptive, not linear**
- **Silencing a single gene often triggers pathway rerouting or compensation**
- **Multiple RNAi agents acting in parallel are required to overcome pathway compensation and resistance**
- **RNA nanostructures enable coordinated delivery of multiple RNAi payloads**

Yudhistira T, Yunker B, Dhir L, Ho YS, Liu S, **Guo P**. Developing Potent Therapeutics for Liver Cancer Chemoresistance via an RNA Nanotech and Series-Circuit-Christmas-Bulb Mechanism Targeting ABC Transporters. Mol. Pharmaceutics, 2025

Cancer Occurrence, Therapeutics, and Market Size







THANK YOU!

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