Targeted Combination Cancer Therapeutics Designed to Improve Cancer Treatment and Reduce Side Effects

RNA nanobiotics

Engineered RNA Nanostructures enable targeted intracellular delivery of multiple therapeutic payload classes to improve treatment effectiveness while reducing effects on healthy tissues.

Lead clinical-entry program: Targeted SN38 therapy for metastatic colorectal cancer combining physiological tumor targeting with RNA aptamer-mediated specificity.

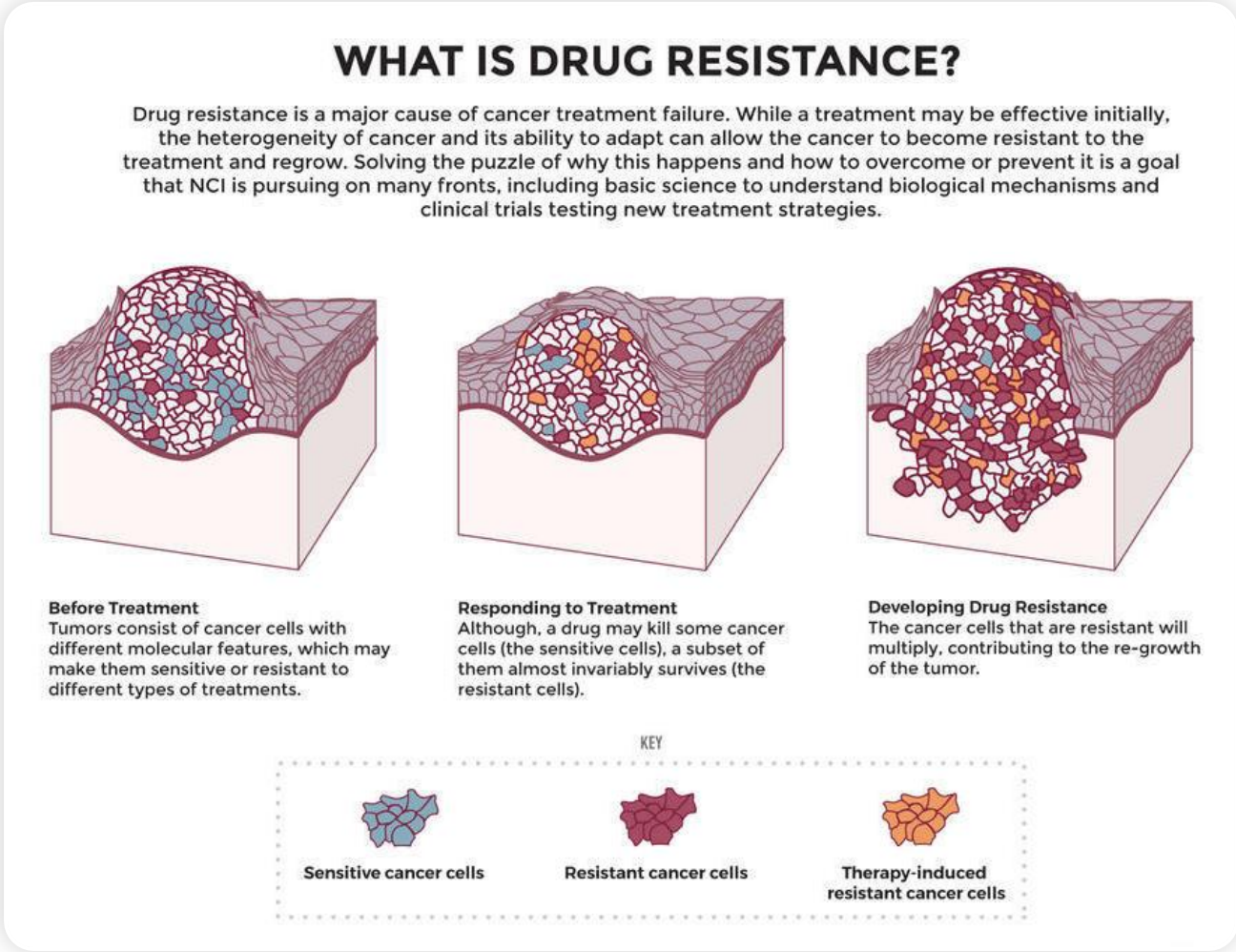
Exclusive rights to foundational RNA Nanostructure IP (4WJ and related architectures) enabling defined multidrug stoichiometry and engineered intracellular activation, supported by linker, payload and individual drug patents.

James Carroll, President & CEO

June 04, 2026

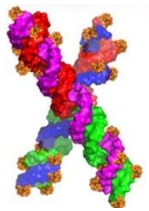
Current Challenges In Cancer Treatment

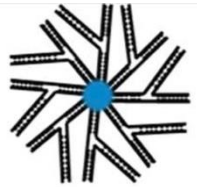
- **Cancer adapts rapidly. Tumor heterogeneity and drug resistance often limit durability of single-agent therapy.**
- **Many patients require combination regimens. Leading oncology therapies often rely on multiple drugs delivered together or in timed sequence, as improper timing may reduce synergy or increase toxicity.**
- **Delivery remains inefficient. Conventional dosing may not place enough active drug inside the appropriate tumor cells.**
- **Cancer treatment often forces a tradeoff between efficacy and toxicity. Potent drugs may be limited by damage to healthy tissue.**
- **Next-generation therapies should improve proven multidrug regimens, not just add new drugs.**

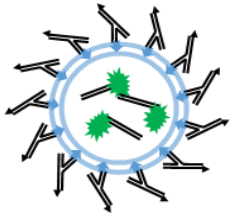


RNA NanoBiotics Combination Therapeutics Platforms

Validated Therapeutic Combinations - Exclusive Licensed Patent Portfolio Spans Multiple Therapeutic Applications





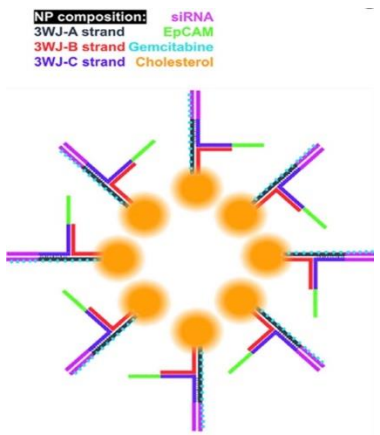


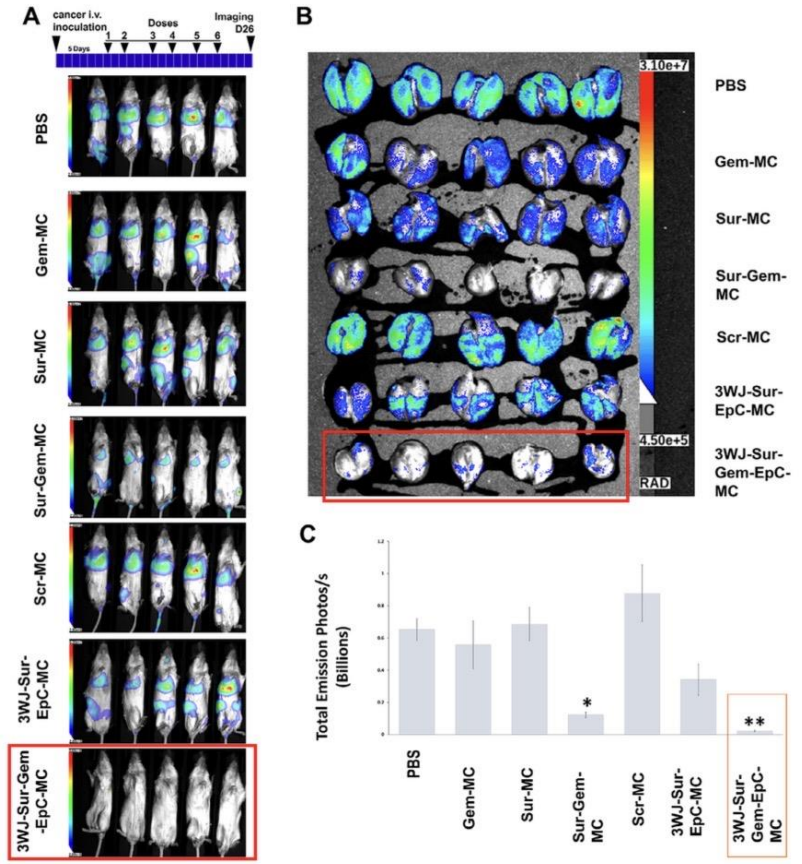
Delivery Constraint	4WJ Nanoparticles	RNA Micelles	RNA Exosome Systems
Deep Tissue Penetration	High	Moderate	Context-Dependent
Drug Load Capacity	Moderate	High	Moderate
Circulation Stability	High	Moderate	Good
CNS/Biological Access	Limited	Limited	Broad/Strong
Multi-Payload Capacity	Yes	Limited	Yes
Staged Delivery Timing	Yes	No	No
Representative Therapeutic Fit	Solid Tumors, RNA + Chemotherapy Combo	High-Burden Disease, hydrophobic Payloads	CNS Delivery, Gene/RNA Editing, mRNA

4WJ serves as the lead oncology platform, complementary architectures expanding future therapeutic opportunities.

RNA-Micelle Platform for RNAi + Chemotherapy in Metastatic CRC

- Distinct RNA delivery architecture: cholesterol-driven self-assembly (separate from 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 with a mechanistically distinct approach to metastatic CRC
- 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

RNA Junction–Engineered EV Platform

In Vivo TNBC Suppression with Reduced Chemotherapy Dosing

Orthotopic TNBC Xenograft

Treatment: CD44-targeted EV + Survivin siRNA + GEM + PTX

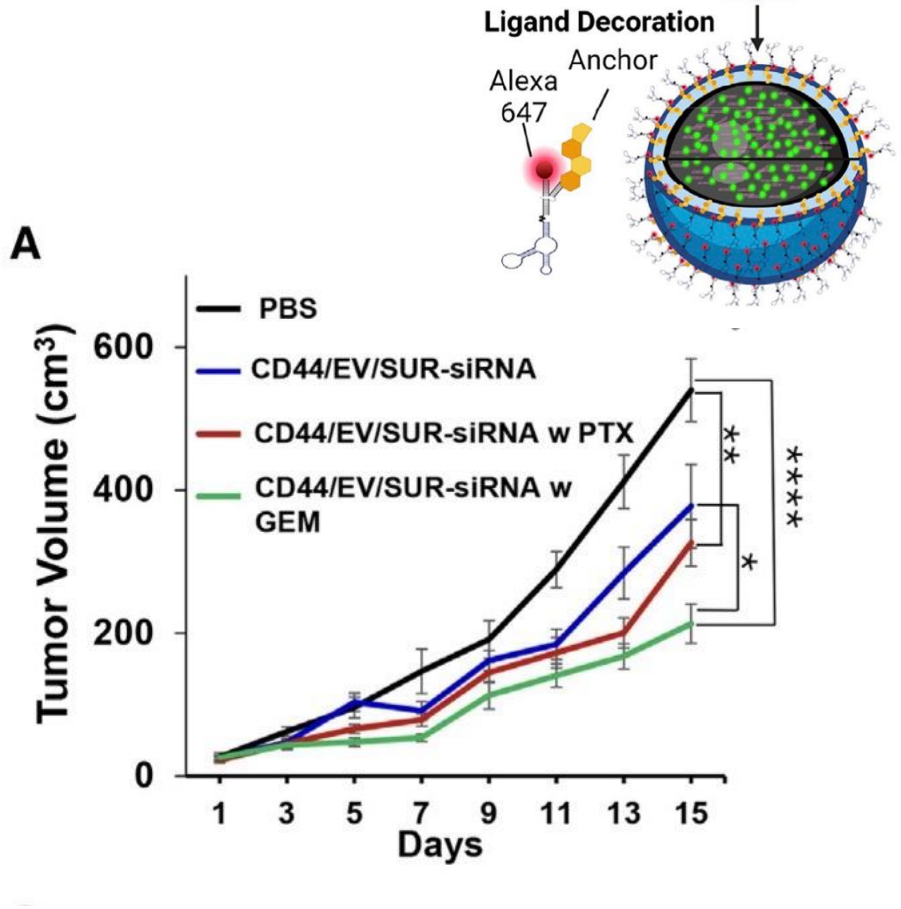
Study Dose Levels:

Gemcitabine: 2.2 mg/kg
(typical mouse dosing 50–100 mg/kg)

Paclitaxel: 5.6 mg/kg
(typical mouse dosing 10–20 mg/kg)

Outcomes:

- Significant tumor suppression vs controls
- Efficacy maintained at substantially reduced chemotherapy doses
- Targeted multi-delivery demonstrated synergistic potential



The Future of Oncology: Targeted Combination Therapy & RNA Medicines

"Most cancers will not be controlled with single agents. Rationally designed combination therapies are required to address resistance and tumor heterogeneity."

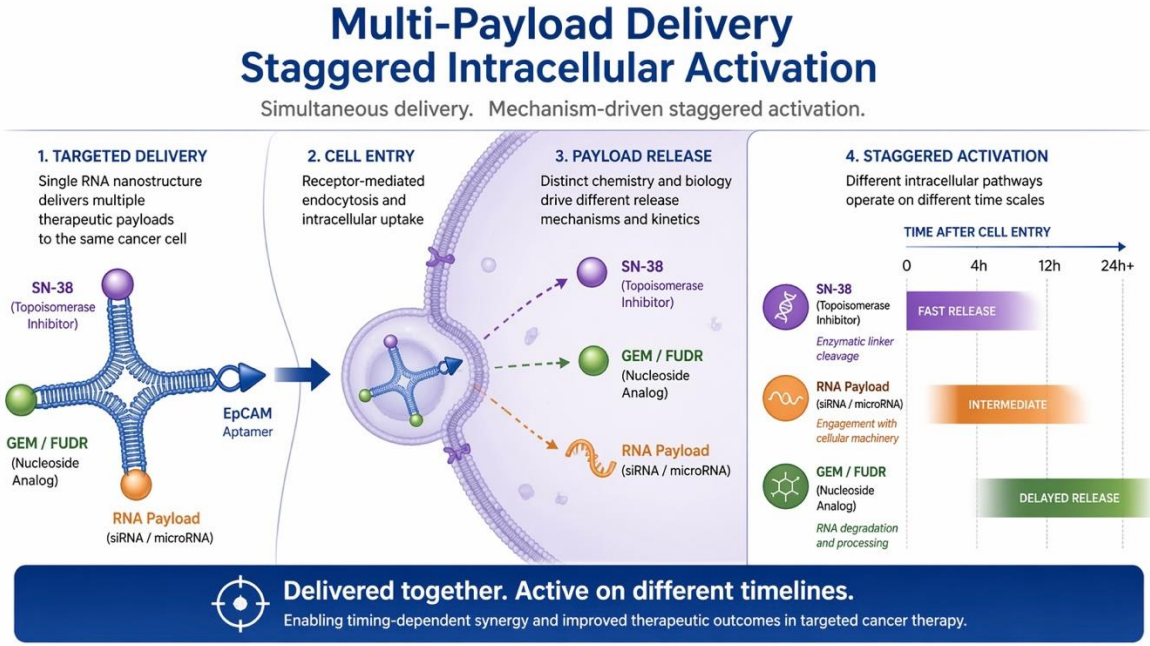
— Fabrice André — Nat Rev Clin Oncol (2020)

"Cancer drug development is increasingly focused on combination strategies rather than monotherapies."

— Richard Pazdur — FDA OCE (2019–2021)

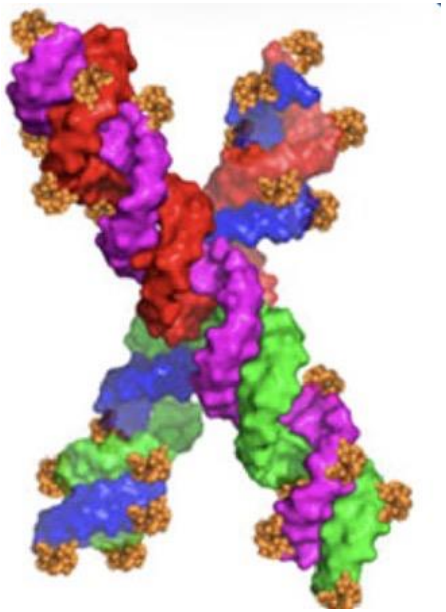
"RNA-based therapeutics provide access to disease drivers that are not reachable with conventional small molecules or biologics."

— National Cancer Institute — RNA Therapeutics Workshop (2021)



Next generation cancer therapies require targeted synergistic combination treatments with staged intracellular drug payload delivery.

4WJ RNA Nanostructures: Core Platform for Targeted Oncology Combination Therapy



Optimized 4-Way-Junction (4WJ) Nanostructure

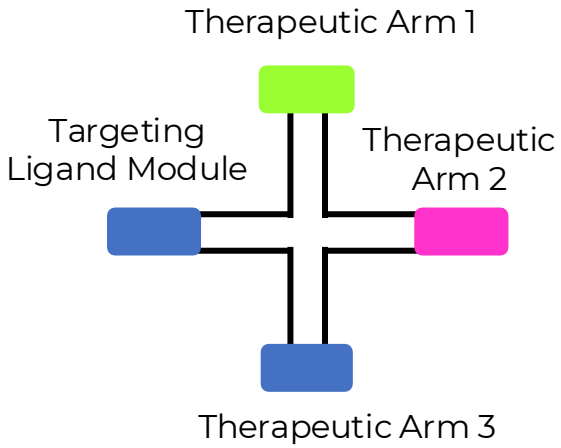
Engineered RNA architecture designed on **modularity**.

- **Defined Stoichiometry:** **Precise control of payload number and spatial positioning on each arm**
- **Multi-Payload Design:** **Simultaneous delivery of multiple therapeutic payload classes including chemotherapeutics, RNAi, radioisotopes and targeting ligands within a single construct. (Expandable to more than three payloads)**
- **Mechanism-Driven Release:** **Distinct payload classes activate via different intracellular pathways enabling, staggered intracellular drug release (e.g., linker cleavage vs RNA processing)**
- **Structural Stability**: **Rigid 4WJ architecture maintains integrity in circulation while enabling efficient cellular uptake**
- **Independent Arm Functionality:** **Each arm independently engineered for targeting, payload delivery, or release control**

Therapeutic behavior is engineered into the molecular architecture-not dependent on formulation or encapsulation.

Engineering 4WJ Release RNA Nanostructures for Precision Oncology

Four Engineered Modules Combine



Targeting Ligand Arm– Aptamer sequences engineered into module

Therapeutic Arms– miRNA, siRNA, nucleoside and chemo Drugs , and radioisotope linkers engineered into arms

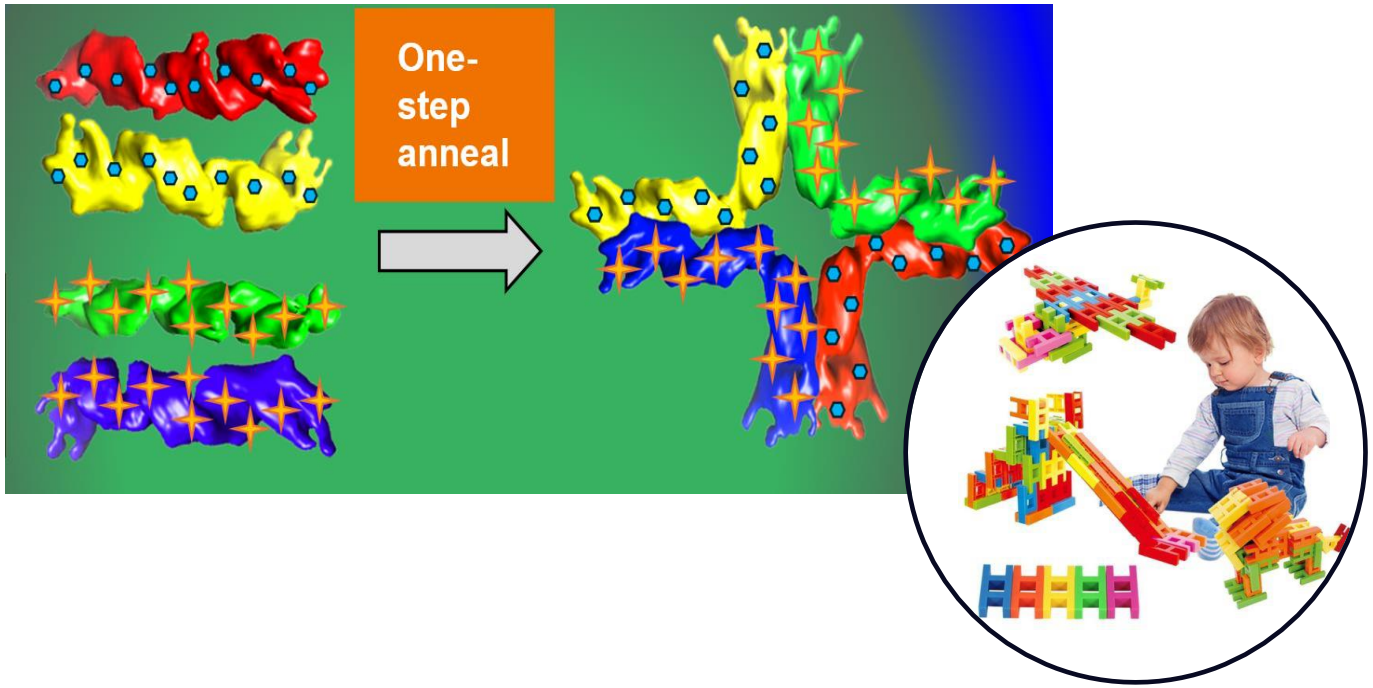
- Target cancer and identified, Literature Search, Manual Layout of Drugs
- High-affinity aptamer(s) chosen or identified via Literature and testing
- Best-fit therapeutic payload(s) selected by public availability:
  - RNAi, microRNA, Chemo, Radiation
- Click chemistry sites and best linkers selected for each drug payload
- Stabilizing modified nucleosides placed for serum durability
- Drug cleavage points ranked and mapped to linker chemistry
- Aptamer surface orientation and density optimized

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

Modular 4WJ architecture enables progression from validated single, double and triple-payload combination therapies within the same structural framework…other arms can be added to expand payloads if necessary

Like “LEGO Assembly”: Modular Arm Design Enables Rapid Combination Therapy Engineering



ARM DESIGN CHOICES:

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

Modular System Simplifies Drug Design: Rapidly enables targeted single-, double-, and multi-payload therapies with staged intracellular activation.

4WJ Modular Platform: Multi-Payload Assets, Differentiated Activation Timing & Regulatory Strategy

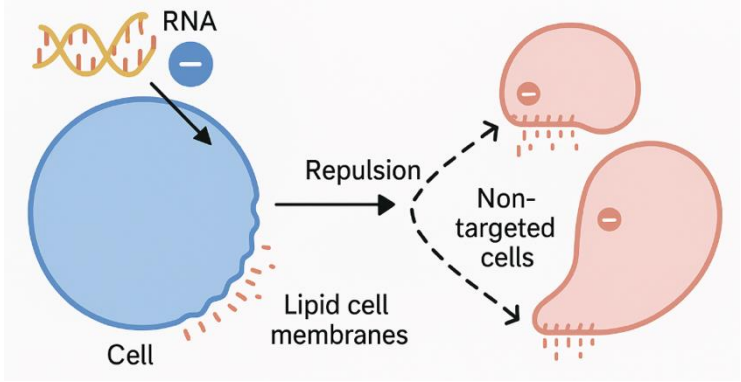
RNA nanobiotics

Distinct payload classes activate on different intracellular timelines-enabling inherent sequential drug exposure within a single nanostructure.

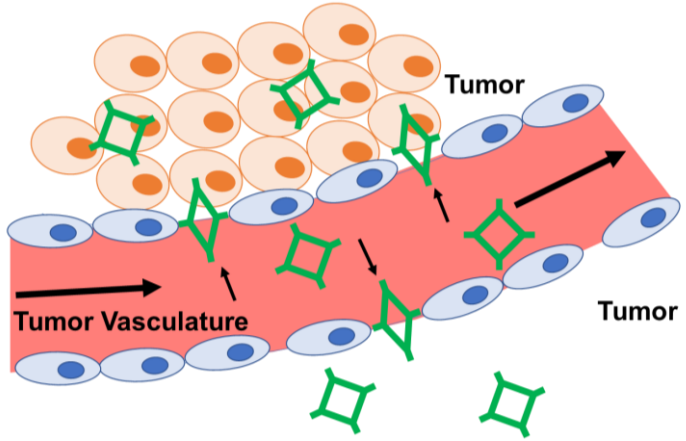
4WJ Arm	Loaded / Demonstrated Assets	Release Mechanism/ Activation Timing	Regulatory Path
Targeting Arm	EpCAM aptamer (CRC Lead), TNBC aptamer, leukemia aptamer…several	Binding only	CMC component internal sequence only changes, if aptamer.
Stability Arm	Chemically stabilized RNA motifs	No release	CMC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

Intrinsic 4WJ Physiologic Properties and RNA Aptamers Integrate Complementary Validated Tumor Targeting Mechanisms

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.

Physiological tumor targeting drives primary tumor accumulation, while RNA aptamers provide an additional layer of molecular specificity and enhanced tumor-cell uptake.

Validated Radiopharmaceutical Arm for Modular Targeted RNA Nanoparticle Therapy

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

Platform Highlights:

- Chelator/payload arm is modular-same chemistry enables substitution of diagnostic and therapeutic isotopes (e.g., ^{68}Ga -> alpha emitters).
- Rapid tumor uptake: 1–4 h; rapid clearance from non-tumor tissues
- Plug-and-play design: swap targeting ligand & chelator strand without altering core
- Chelator arm supports direct substitution of diagnostic and therapeutic isotopes without altering core structure
- Single GMP & regulatory backbone supports multiple products

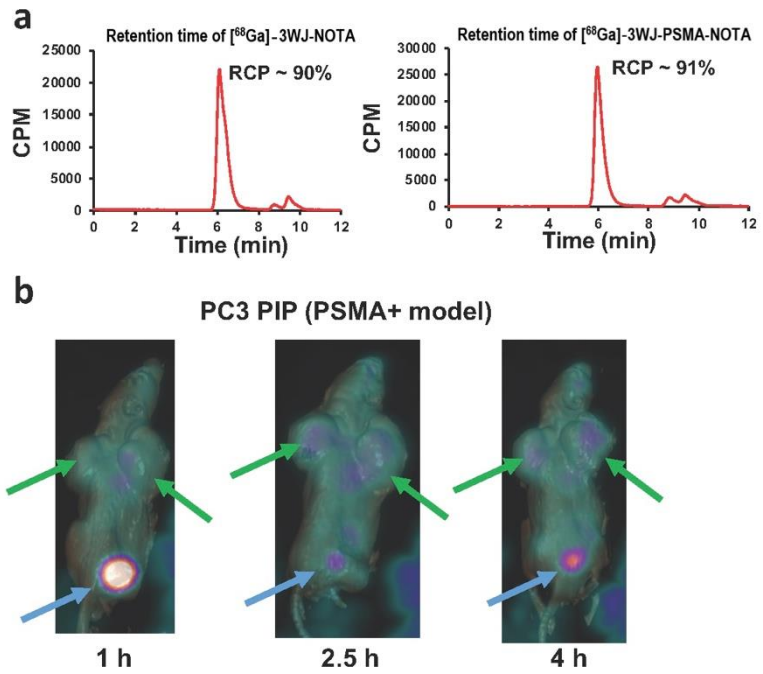
Alpha Emitter Priorities

- ^{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

RNA NanoMed (Aug 2025) published proof-of-concept



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

Green Arrow - Tumor

Blue Arrow – Bladder (showing excretion)

4WJ Cytosolic Delivery Enables Controlled Intracellular Activation and Payload Sequencing

4WJ Nanostructure Behavior
- Stable in circulation → payloads remain intact until cellular uptake

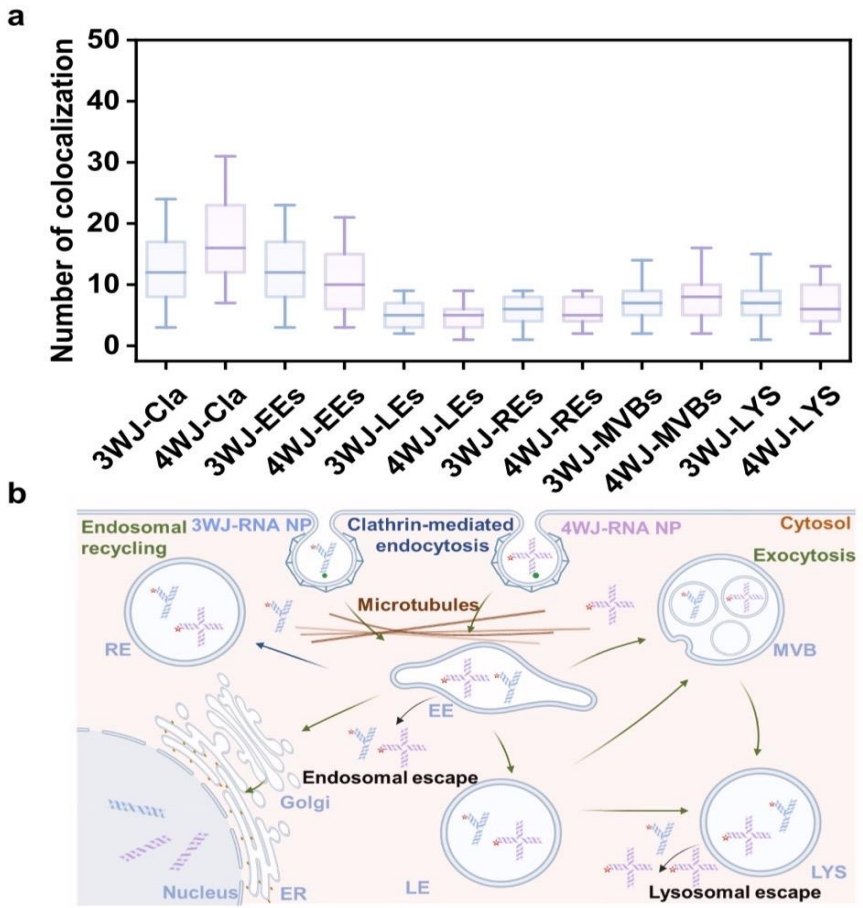
Intracellular Barrier (Industry Limitation)
- Endosomal uptake → ADC/LNP payloads trapped or degraded → reduced activity

4WJ Mechanistic Advantage
- Efficient endosomal escape → cytosolic delivery
- Payload integrity preserved → functional intracellular activity

Observed Outcome (tie directly to your SN-38 data)
- Cytosolic delivery → effective tumor cell kill observed in vivo

Strategic Implication
- Cytosolic delivery preserves payload function
- Enables differential activation across payload classes

Foundation for Clinically relevant sequential combination therapy within a single targeted delivery

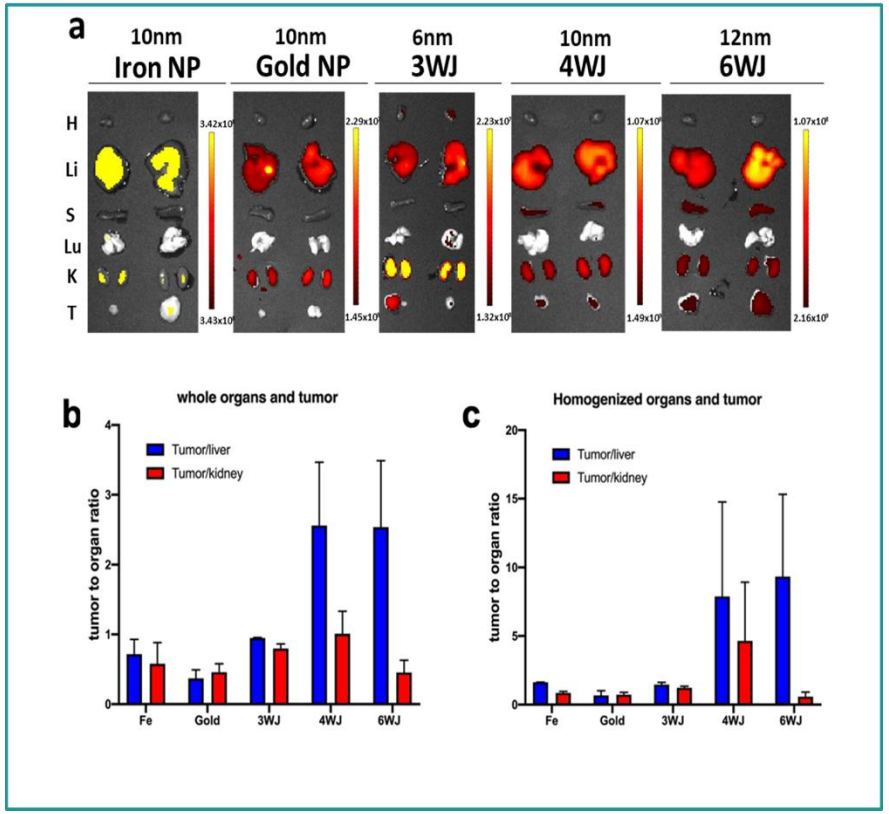


Intracellular delivery fate of RNA NPs. (a) The colocalization number in each cell for 3WJ-RNA NPs and 4WJ-RNA NPs (b) Schematic of the intracellular delivery pathway of RNA NPs. EE-early endosome, LE-late endosome, RE-recycle Endosome, MVB-multivescular bodies, LYS-lysosome

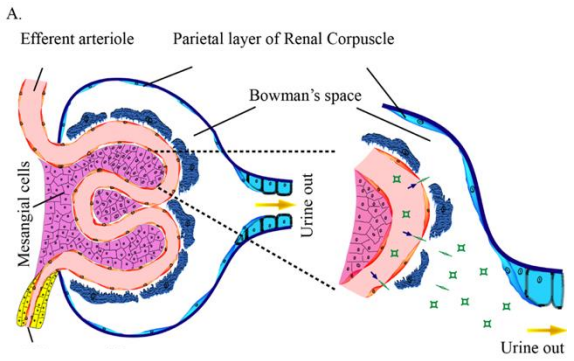
Reference: H. Wang et al., Chemical Engineering Journal 526 (2025) 171092

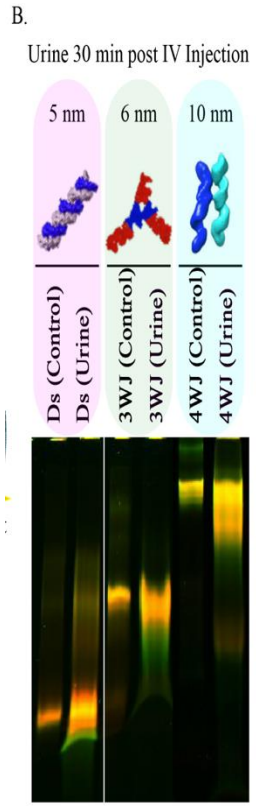
Favorable PK Profile: Rapid Clearance with Minimal Off-Target Accumulation

Intrinsic 4WJ size, deformability, and charge support tumor penetration while minimizing non-target organ accumulation.



Non-tumor-associated RNA Nanostructures rapidly clear through the kidney Glomerular Filtration Barrier, limiting off-target tissue accumulation.





Binzel D., et al. & Guo P. *Chemical Reviews 2021*

Li X., et al. & Guo P. *Advanced Drug Delivery Reviews.* 2022

Rapid renal clearance of non-bound nanostructures may support repeat dosing and reduced systemic exposure while preserving tumor accumulation.

RNA Junction Nanostructures — Consistent Payload- Agnostic Safety Across >15 Independent Studies Including Human Serum

Cross-Study Validation
- **Consistent safety across >15 independent studies, including in vivo, in vitro, human serum, and external laboratory validation**

Systemic Safety
- **No acute or chronic toxicity in repeat-dose studies at therapeutic and supra-therapeutic exposure**
- **Normal clinical chemistry and hematology**

Low Immunogenicity
- **Minimal immune activation (no significant IL-6, TNF-α, IFN-γ)**

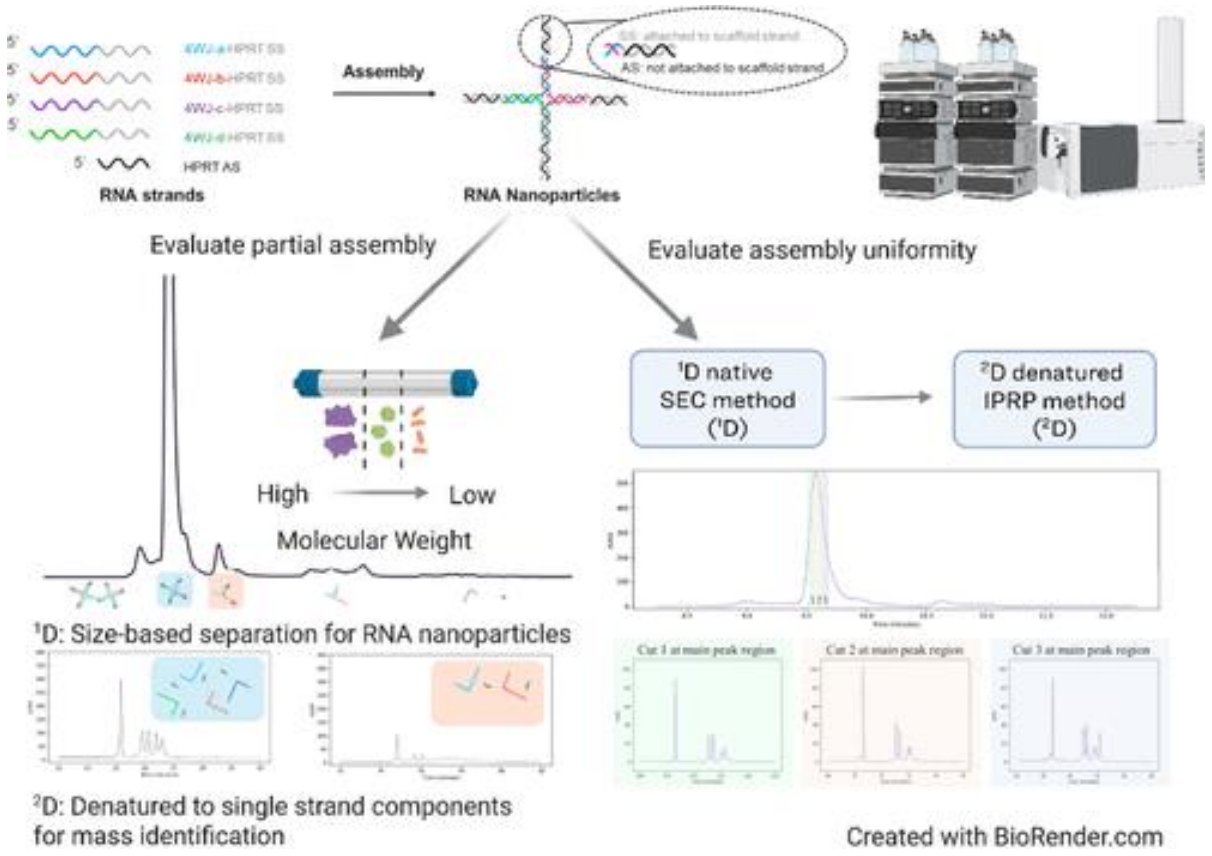
Biodistribution & Clearance
- **Tumor-selective uptake; minimal off-target accumulation**
- **Rapid renal clearance of non-bound nanostructures**

Platform Consistency
- **Safety maintained across multiple payload classes**

Bottom Line
- **Enables repeat dosing and supports multi-payload, staged therapeutic delivery**

Industrial-Grade CMC Validation of 4WJ RNA Nanostructures: Independent Eli Lilly

- **Independent validated at Eli Lilly Institute of Genetic Medicine and Lilly Research Laboratories, demonstrating pharma-grade CMC transferability.**
- **Manufacturing Transferability: standard analytical methods (SEC, IPRP, MALS, and HRMS) support scale up, batch consistency, and release testing.**
- **Assembly Control: SEC × IPRP 2D-LC confirm fully assembled RNA nanostructures confirming defined stoichiometry and uniformity.**
- **Formulation Stability: no strand dissociation under formulation conditions, supporting clinical readiness.**
- **Orthogonal Validation: native SEC-MS confirms intact mass. SEC-MALS shows narrow MW distribution. In vitro knockdown potency unchanged.**
- **Reproducible, scalable platform suitable for multi-payload therapeutic development.**
- **cGMP manufacturing capability established (ChemGenes), enabling immediate clinical supply.**



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

Engineering Synergistic mCRC Targeted Combination Therapeutics for Maximum Tumor Suppression with Favorable Tolerability

SN38

Established Clinical Backbone for mCRC

MODE OF ACTION
- Causes DNA damage in dividing cancer cells
- Prevents Cancer Cells from reproducing
- Rapid tumor-cell killing

ENGINEERING RATIONALE
- Strong irinotecan precedent
- Starpharma validates SN38 delivery
- Fastest 505(b)(2) path
- Primary tumor reduction driver

FUdR

Clinically Established Synergistic mCRC Combination

–Sequential Intracellular Timing Preserves Synergy

MODE OF ACTION
- Disrupts DNA synthesis
- Prevents surviving cells from recovering
- Suppresses continued tumor growth

ENGINEERING RATIONALE
- Strong colorectal alignment
- Timing-dependent synergy established clinically
- Staged intracellular release preserves synergy
- Expands cumulative tumor suppression

Survivin RNAi

Resistance Suppression and Durability Enhancement

MODE OF ACTION
- Reduces survivin expression in tumors
- Weakens tumor survival signals
- Makes tumors more sensitive to chemotherapy
- Increases tumor-cell death
- Reduces treatment resistant cancer cells

ENGINEERING RATIONALE
- Independent mechanism from Chemo
- Directly addresses treatment resistance
- Improves durability of response
- Addresses heterogeneous tumor populations

THERAPEUTIC ENGINEERING OBJECTIVE: Maximize cumulative tumor suppression while preserving synergy and tolerability.

Expected Therapeutic Progression: SN38: ~90% reduction (pre dose optimization)→ SN38+GEM/FUdR: near-complete inhibition → GEM/FUdR+Survivin: near-complete inhibition + improved durability

Progressive mCRC Program Evolution from Single to Triple Targeted Synergistic Drug Payloads

RNA Nanostructure Foundations — Already Engineered and Demonstrated:

• Physicochemical targeting • EpCAM enhanced targeting • Staged intracellular release timing
• Payload loading/ratio engineering • Independent therapeutic mechanisms

EpCAM–SN38

505(b)(2)

Validated:
• Human platform entry
• Human safety + CMC

Therapeutic Effect:
• ~90% tumor reduction *(pre-dose optimization)*

EpCAM–SN38 + FUdR

Expected 505(b)(2)-Expansion

Validated:
• Same-cell pharmacology
• Ratio-engineered synergy

Therapeutic Effect:
• Synergistic same-cell activity
• Near-complete inhibition

EpCAM–SN38 + FUdR + Survivin

Expected 505(b)(1) Expansion

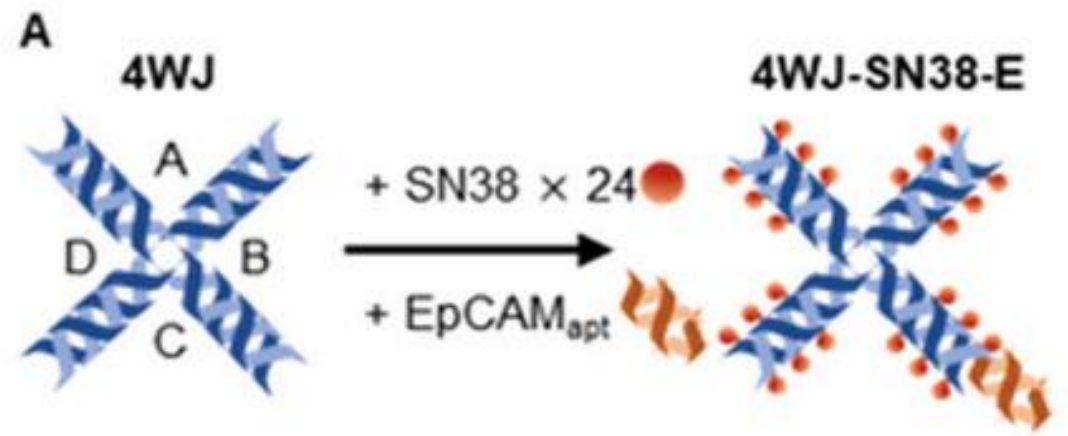
Validated:
• Resistance suppression
• Heterogeneity coverage

Therapeutic Effect:
• Near-complete inhibition
• Increased durability across heterogeneous tumors

Lead Clinical Entry Candidate: EpCAM-SN38 as the Foundation of the mCRC Targeted Therapeutic Strategy

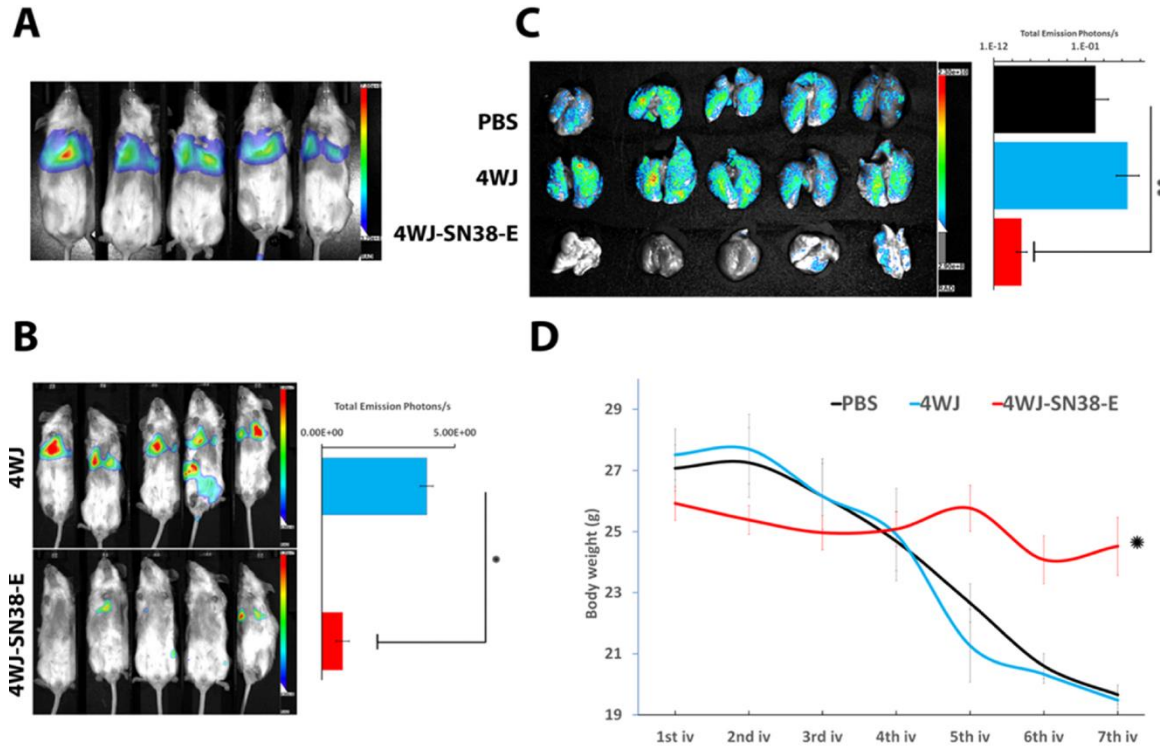
RNA nanobiotics

505(b)(2) strategy leveraging recent Starpharma/Genentech clinical validation of optimized SN38 delivery to accelerate clinical entry and establish the foundation for progressive multi-payload mCRC Targeted Drugs



mCRC Strategy Fondation Lead:

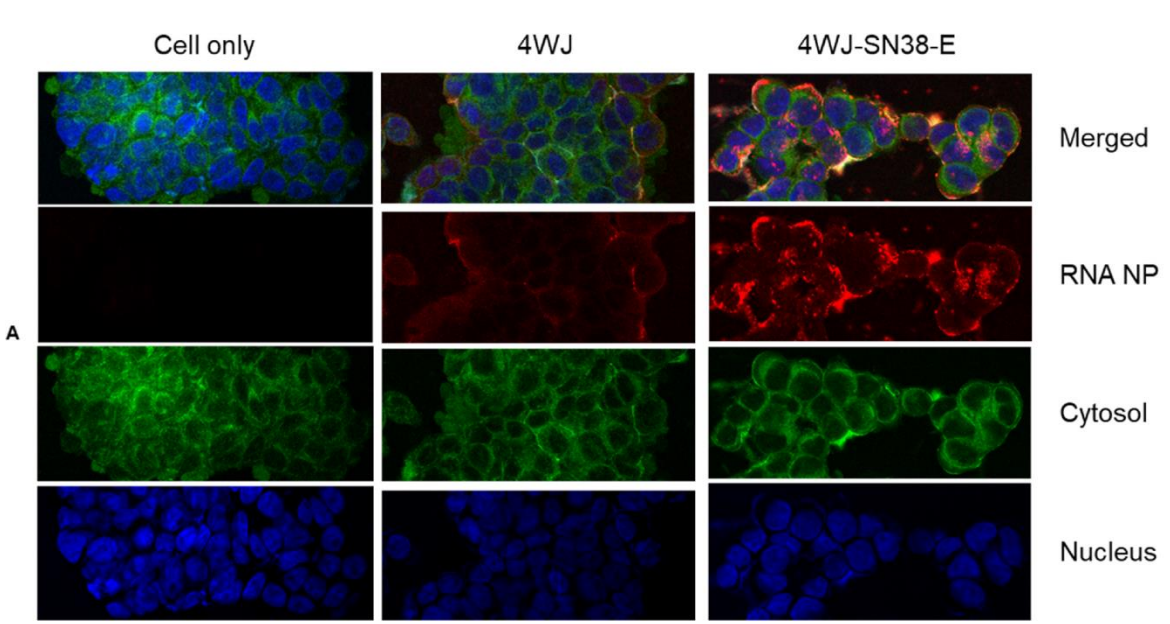
- EpCAM targeting adds ~20% tumor reduction over physicochemical targeting only
- **85-90% tumor reduction achieved prior to dose optimization**
- Strong efficacy generated at lower SN38 exposure levels with additional optimization headroom
- In vivo and ex vivo imaging show near-eradication of lesions
- Achieved with excellent tolerability and no weight loss

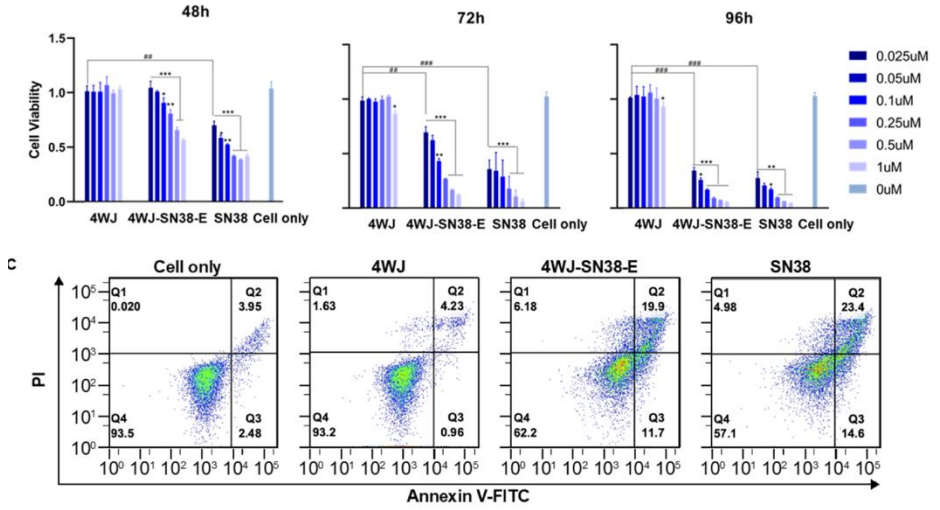


ig. 6. *In vivo* colorectal cancer lung metastasis model inhibition of 4WJ-SN38-E. (A) Lago imaging to confirm metastasis establishment 5 days after IV injection. (E ioluminescence to compare metastasis *in vivo* between 4WJ and 4WJ-SN38-E groups. The mice in the PBS control group were so sick (see D) and cannot survive ti ıe 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.

4WJ-SN38-EpCAM In Vitro Efficacy: Tumor Cell Killing & Apoptosis

- Dose-dependent tumor-cell killing confirms biological activity in colorectal cancer cells
- 4WJ-SN38-EpCAM achieves potency comparable free SN-38 by 96 hrs while enabling nanostructure-mediated delivery.
- Strong tumor-cell death induction confirms effective intracellular payload activity (~32% vs ~38% free SN-38)
- Confocal imaging confirms successful EpCAM-mediated cellular uptake and intracellular delivery



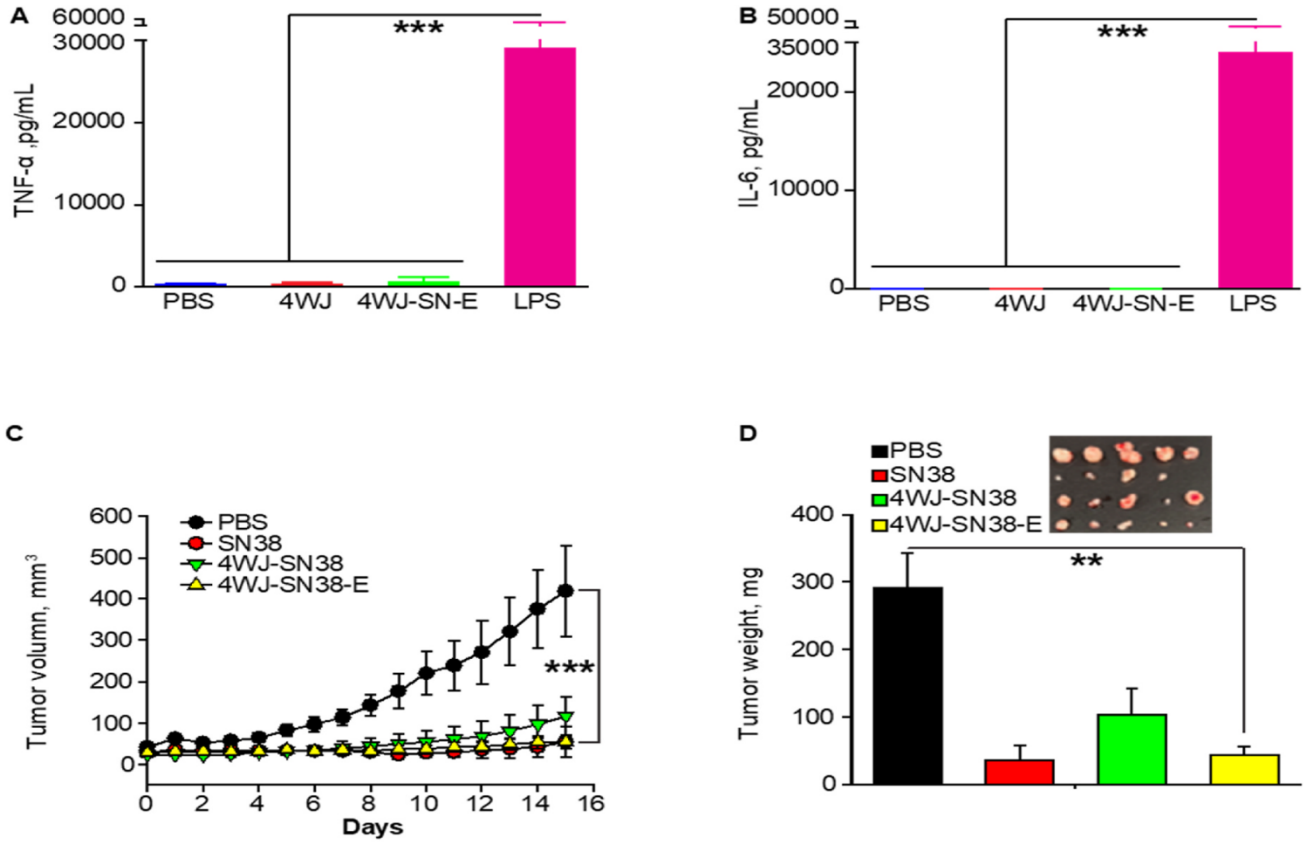


ig. 3. *In vitro* cell binding, internalization, and cancer suppression study of 4WJ-SN38-E RNA nanoparticles. (A) Confocal images of HT29 cells after incubation with BS, 4WJ, and 4WJ-SN38-E, respectively. (Blue: nucleus; Green: Cytosol; Red: RNA nanoparticle). (B) Evaluation of cell viability by MTT assay in HT29 cells ıcubated with RNA nanoparticles and SN38 for 48, 72, and 96 h, respectively. Statistics were calculated by two-tailed unpaired *t*-test presented as mean ± SEM. ignificant results compared to the RNA nanoparticle at a concentration of 0.025 μM are marked with an asterisk (*p < 0.05, **p < 0.01, ***p < 0.001). Significant esults compared to the 4WJ at a concentration of 0.025 μM are marked with an hash (##p < 0.01 and ###p < 0.001). (C) *In vitro* apoptotic effects of RNA anoparticles and SN38 by PI/Annexin V-FITC dual staining and FACS analysis (Q2 = Annexin V-FITC positive & PI positive, indicating late apoptotic and dead cells;)3 = Annexin V-FITC positive & PI negative, indicating early apoptotic cells). (For interpretation of the references to color in this figure legend, the reader is referred) the Web version of this article.)

4WJ-SN38-EpCAM In Vivo CRC Xenograft: Significant Tumor Suppression

4WJ-SN38-EpCAM

- In vivo data confirms strong translation of intracellular activity into durable tumor suppression.
- Targeted EpCAM SN38 achieved the deepest tumor suppression across treatment groups.
- ~20% additional tumor reduction beyond physicochemical targeting alone.
- 85-90% tumor reduction achieved prior to formal dose optimization.



ig. 5. *In vitro* immune response and *in vivo* tumor inhibition of 4WJ-SN38-E RNA nanoparticles. (A,B) Evaluation of TNF-α (A) and IL-6 (B) production afte ıcubating 4WJ-SN38-E with macrophage-like cells by ELISA. (C) Intravenous treatment of nude mice bearing HT29 xenografts with 4WJ-SN38-E and control group very three days for a total of 5 injections (indicated by arrows). Mice tumor size was monitored during the time course of treatments. (D) Comparison of tumc /eight and size at the endpoint (n = 5 biologically independent animals). Statistics were calculated by two-tailed unpaired *t*-test presented as mean ± SEM, **p < .01, ***p < 0.001.

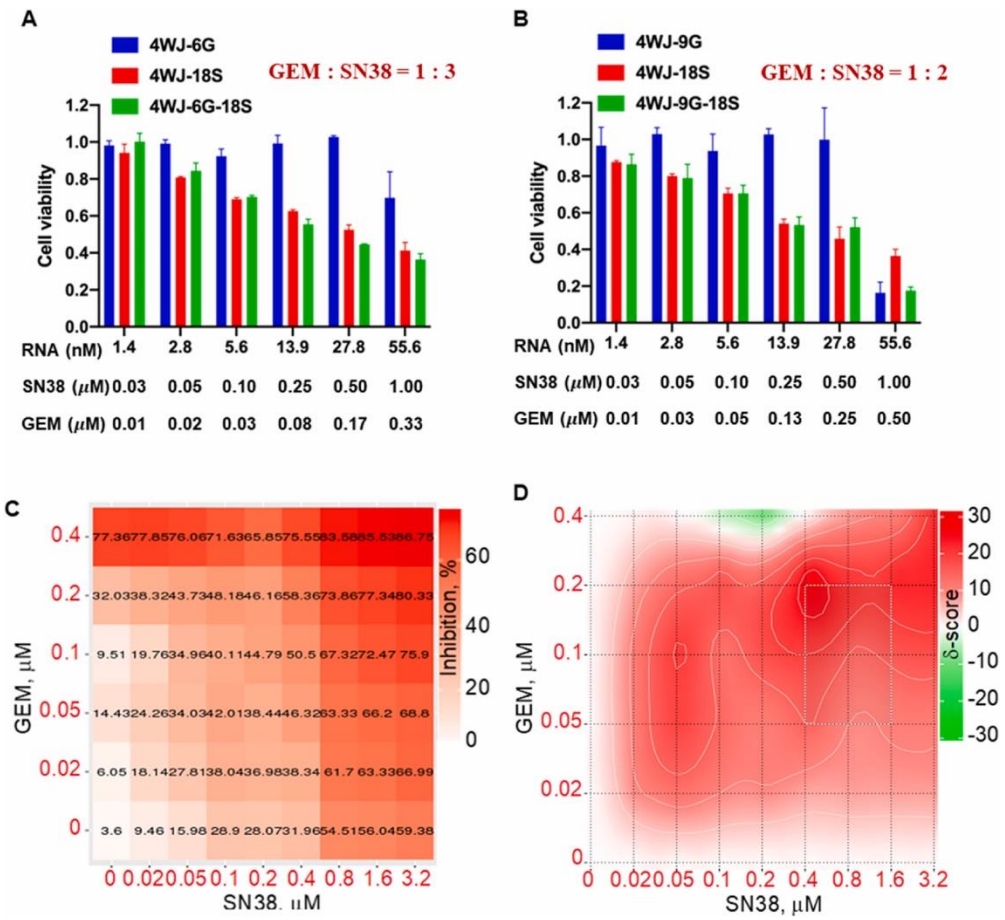
Validated Preclinical Proof-of-Concept: 4WJ EpCAM SN38 Demonstrates Efficacy and Safety

RNA nanobiotics

Key Requirement	RNA NanoBiotics Result	Benchmark Met
Drug Loading Efficiency	24 SN38 molecules per 4WJ-RNA nanostructure	Yes
In Vitro Apoptosis / Cytotoxicity	31.6% apoptosis in HT29 cells (4WJ-SN38-EpCAM)	Yes
In Vivo Tumor Volume Reduction	85–90% tumor volume reduction at 2 mg/kg SN38 (x5 doses); Lab standard and not maximum	Yes
Targeting Benefit over Non-Targeted 4WJ	20.4% greater tumor reduction with EpCAM-targeted NPs	Yes
Maximum Tolerated Dose (MTD) Margin	No observable toxicity at effective dose; safe at 2 mg/kg × 5 doses	Yes
Systemic Toxicity (weight, organs)	No weight loss, no histopathologic changes in liver, kidney, spleen, heart, lung	Yes
Cytokine Induction (e.g., TNF-α, IL-6)	No significant TNF-α or IL-6 elevation at 100 nM (comparable to PBS control)	Yes
Hemolysis / Plasma Compatibility	<5% hemolysis, no platelet aggregation, complement activation, or abnormal coagulation	Yes
Biodistribution / Clearance	Tumor-targeted accumulation; fast renal clearance; undetectable off-target accumulation	Yes
RNA Nanostructure Stability	Stable >12 hrs. in human serum; maintains shape and function	Yes

mCRC Therapeutic Program Next Step: Expanding EpCAM-SN38 into Synergistic Dual-Payload Therapeutics

Targeted Double Payload SN38 + FUdR



Preclinical Dual-Payload Synergy

- 4WJ studies demonstrate synergistic SN-38 + FUdR (and Gemcitabine) co-delivery
- Synergy observed across defined SN-38 FUdR ratios (1:2–1:3)
- Co-delivery preserves synergistic payload activity

Mechanistically Distinct Activation

- SN-38: esterase-mediated linker cleavage → rapid intracellular release
- FUdR: Incorporated into RNA Structure → release via RNA degradation
- Result: Structurally driven staggered activation timing from a single nanostructure

Resulting Activation Profile

- Non-synchronous intracellular activation driven by nanostructure design
- Inherent delay in FUdR activation relative to early SN-38 release

Clinical Relevance

- Aligns with clinically established staged administration of SN-38 and FUdR
- Sequencing is used to optimize efficacy and reduce antagonism
- The nanostructure reproduces staged intracellular exposure from a single administration
- Applies FOLFIRI-style combination logic through targeted intracellular co-delivery.

Leverages validated EpCAM-SN38 clinical entry to generate multiple mCRC combination Therapeutic candidates.

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Li X, Guo P. *Biomaterials*. **2023.**

mCRC Therapeutic Program Next Step: Engineering Synergistic Triple-Payload Targeted Intracellular Therapeutics

RNA nanobiotics

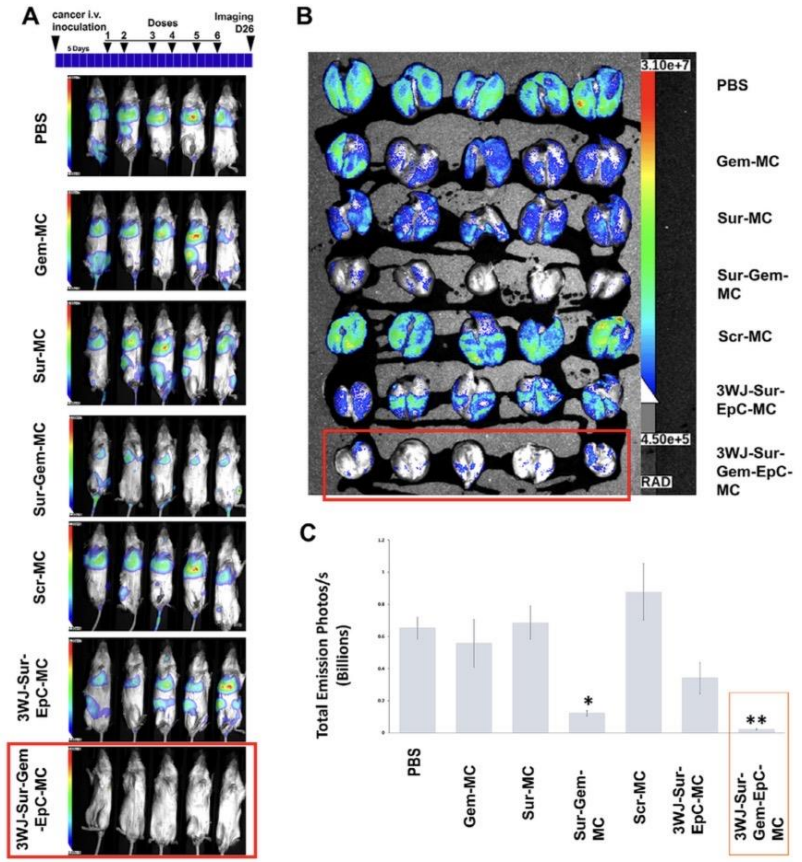
Targeted Triple-Payload Strategy: SN38 + FUdR + Survivin RNAi

Triple-Payload Therapeutic Architecture

- Survivin siRNA suppresses resistance pathways while chemotherapy induces tumor-cell death
- Independent intracellular mechanisms support synergistic multi-payload activity within the same cell
- RNAi payload activation occurs through a biologically distinct pathway from SN38 and FUdR
- Enables staged intracellular therapeutic activity from a single targeted construct
- Establishes the engineering framework for future SN38 + FUdR + surviving mCRC therapeutic candidates

Leverages validated EpCAM-SN38 clinical entry to generate targeted Synergistic multi-payload mCRC therapeutics

Near-complete suppression of mCRC lung metastases (Fig. 5A–C)



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

Clinical Entry and Progressive Multi-Payload Platform Development Roadmap

	Aptamer/Targeting Support	Therapeutic Payload	Cancer Type	Strategic Purpose	Time From Funding Start to IND	Regulatory Path
1	**EpCAMapt**	**SN38**	**mCRC (Liver/Lung Metastasis)**	**Human Safety + Platform Clinical Entry**	**9-12 months**	**505(b)(2)**
1A	EpCAMapt	SN38 + FUdR	mCRC (Liver/Lung Metastasis)	Validate Dual-Payload for Safety + Clinical Valedation	18-24 Months	505(b)(2)
1B	EpCAMapt	SN38 + FUdR + Survivin RNAi	mCRC (Liver/Lung Metastasis)	Validate Triple Payload for Safety + Clinical Valedation	24 -30 Months	505(b)(1)
2	EGFRapt	SN38 + Gemciitabine + Survivin RNAi	GI/epithelial cancers	Expand validated Multi-Payload Therapeutic	Following Clinical P Validatiom	505(b)(1)
3	RNA Micelle Platform	SN38 + FUdR + Survivin RNAi	Colon Cancer	Expand Multi-Payload Therapeutic Architecture	Following Clinical Validatiom	505(b)(1)
4	EGFRapt	SN38 + Platinum + Survivin RNAi	Advanced GI Malignancies	Expand Muti-Payload Therpies	Following Clinical Validatiom	505(b)(2)

Lead Program human validation may enable Phase II indication expansion without repeating Phase I for the same validated therapeutic construct

RNA nanobiotics

THANK YOU!

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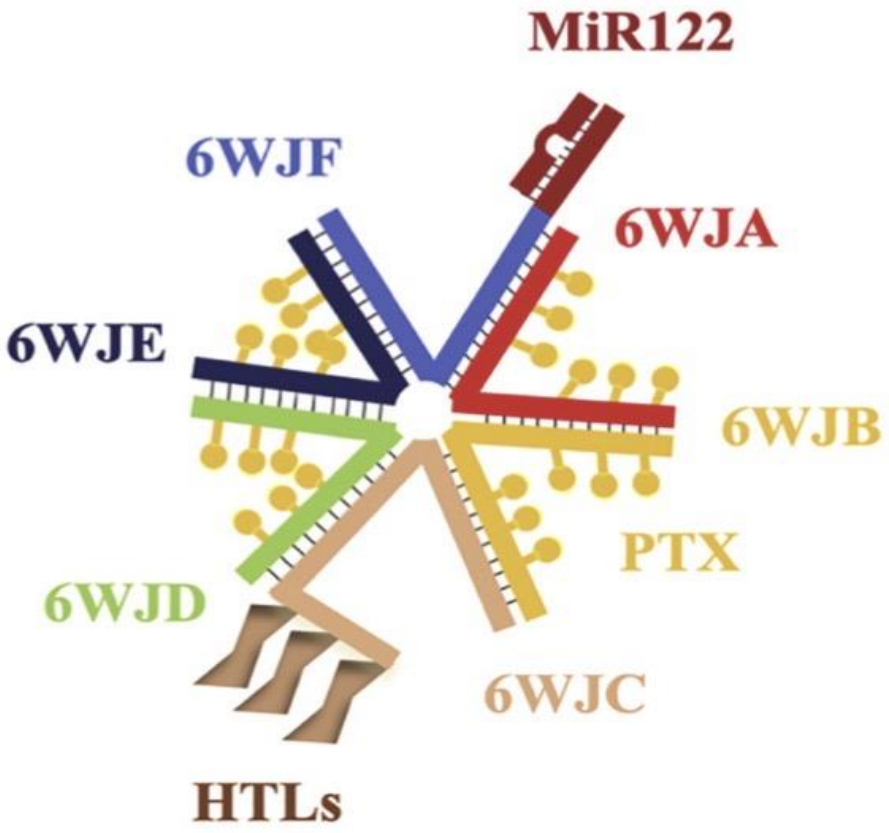
https://rnanano.osu.edu/Guo/publications.html

Beyond Triple Payload: RNA Architectures Enable >3 Payload Arms + Independent Targeting



5 Functional Payload Arms and a Dedicated Targeting Arm

- 6WJ RNA scaffold expands payload capacity beyond conventional dual- and triple-cargo systems
- 4 small-molecule loading arms + 1 RNA therapeutic arm + separate targeting ligand arm
- Demonstrated loading of **24 paclitaxel molecules** on a single programmable scaffold
- Supports future combinations of chemo + RNAi + radiotherapy + immune modulation
- Illustrates scalable architecture family extending beyond current 4WJ clinical lead designs

RNA nanostructures can exceed 3 payload arms while preserving independent targeting

Guo et al., Journal of Controlled Release 330 (2021) 173–184

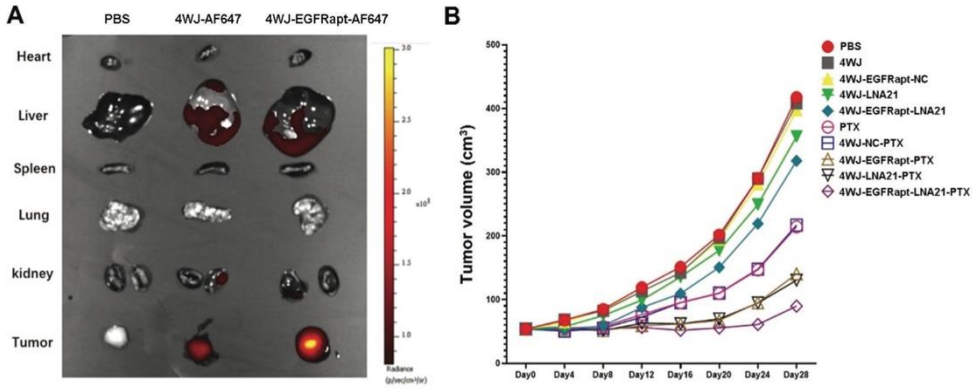
Validated Multi-Mechanism Payload: Chemotherapy + microRNA via Single RNA 4WJ

Therapeutic design

- **Enables coordinated or staged activation based on intracellular release mechanisms**
- **RNA4WJ nanostructure co-delivering paclitaxel (PTX) and anti-miR-21-5p**
- **EGFR-targeted delivery to head & neck squamous cell carcinoma (HNSCC)**
- **Modular multi-payload architecture extendable beyond two payload classes**

Key results

- **Combination therapy demonstrates superior tumor suppression vs single drugs.**
- **Validating simultaneous chemo + RNAi delivery from a single nanostructure.**
- **Validated microRNA therapeutic arm**



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.

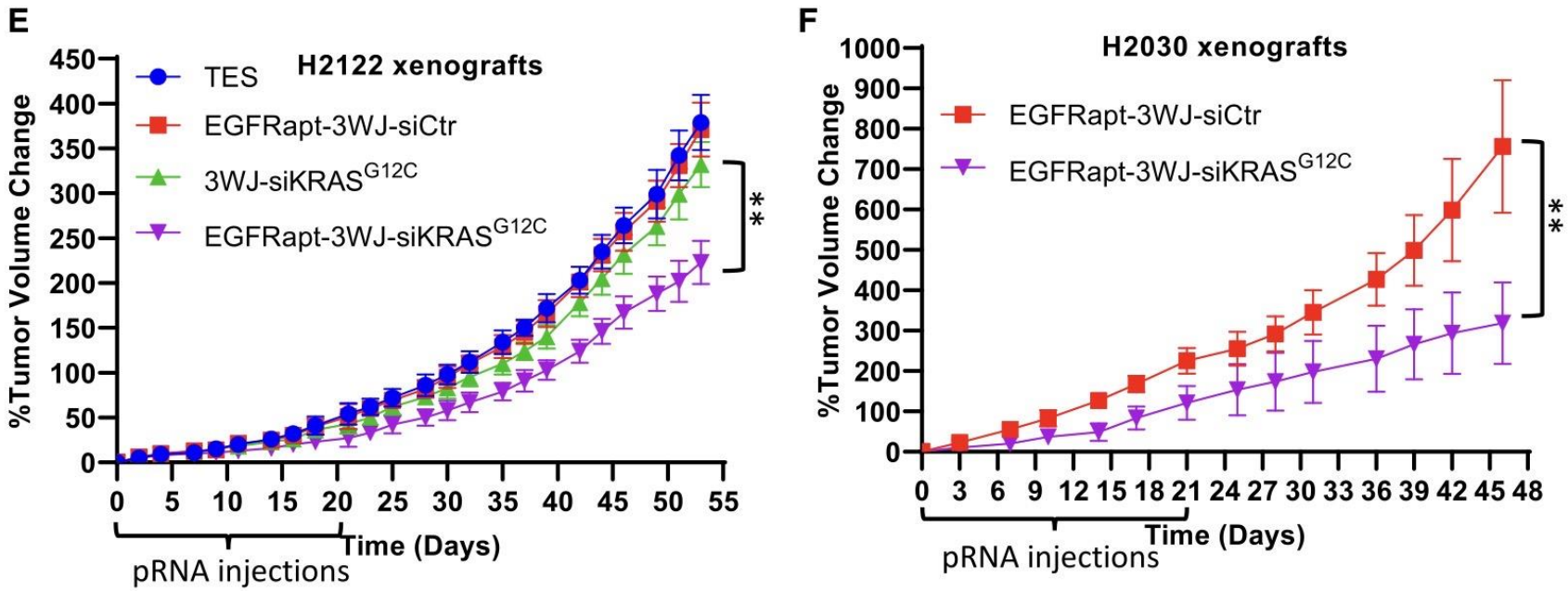
RNA nanostructures enable integrated multi-mechanism therapy (chemo + RNAi) within a single targeted nanostructure.

RNA NanoMed 2025 — RNA4WJ nanoparticles co-delivering paclitaxel and anti-miR-21 in head & neck cancer

Validated siRNA Single Therapeutic Arm: KRAS siRNA Delivery Suppresses NSCLC Tumors In Vivo

EGFR-aptamer–targeted RNA Nanostructures deliver KRASG12C siRNA with tumor-selective uptake and in vivo efficacy.

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

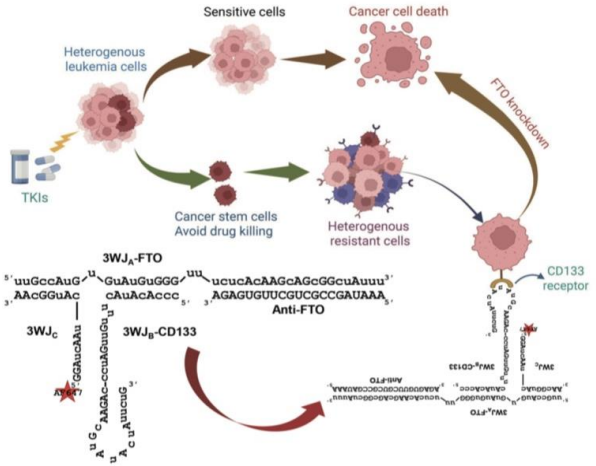


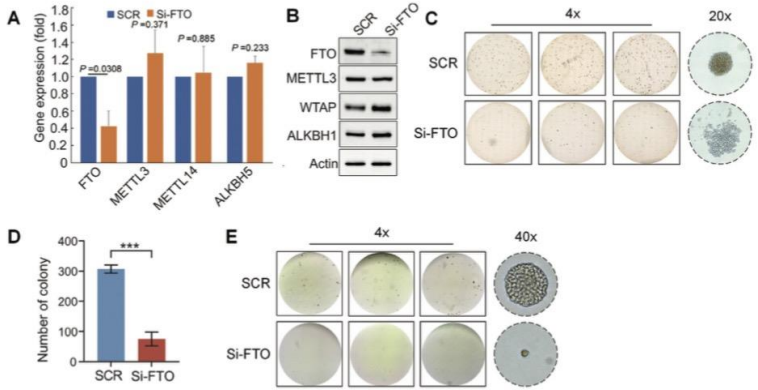
Li et al., Molecular Therapy – Nucleic Acids, 2023. EGFR-aptamer–targeted pRNA-3WJ nanoparticles delivering KRASG12C siRNA suppress NSCLC tumor growth in vivo.

Validated siRNA Arm: CD133-Targeted siRNA Delivery in Liquid Tumors (Leukemia)

CD133-targeted RNA Nanoparticle delivery of siFTO demonstrates functional knockdown and suppression of drug-resistant leukemia cells:

- 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.



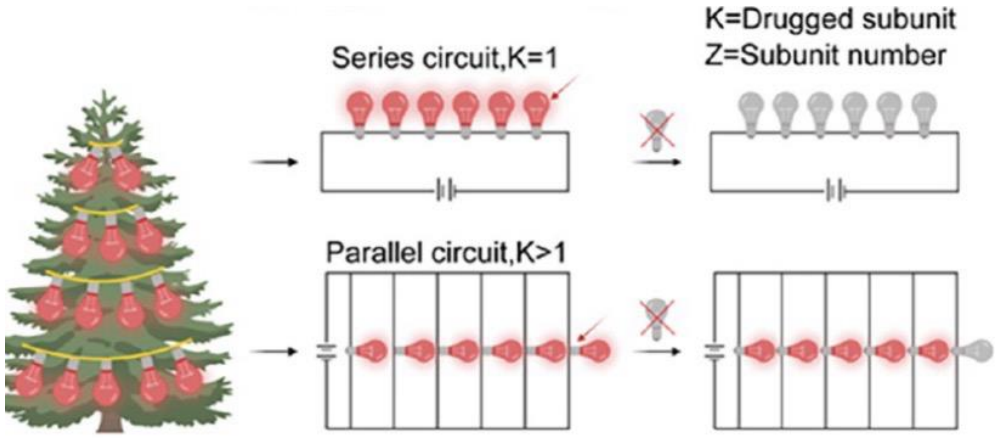


(A,B) FTO mRNA and protein knockdown by CD133-targeted siRNA.
(C,D) Colony formation markedly reduced vs control.
(E) Spheroid growth suppressed in resistant K562 cells.

Demonstrates a modular RNAi therapeutic arm complimentary to chemotherapeutic and radiopharmaceutical payloads.

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–?.

Overcoming Resistance Requires Multi-Target RNAi



- 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 hydrolysis conformational cycling and membrane transport
- Silencing a single RNA target allows rapid biological compensation

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

- 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-addressing resistance mechanisms not tractable with single-agent therapies

*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*

Regulatory Implications of RNA Nanostructures

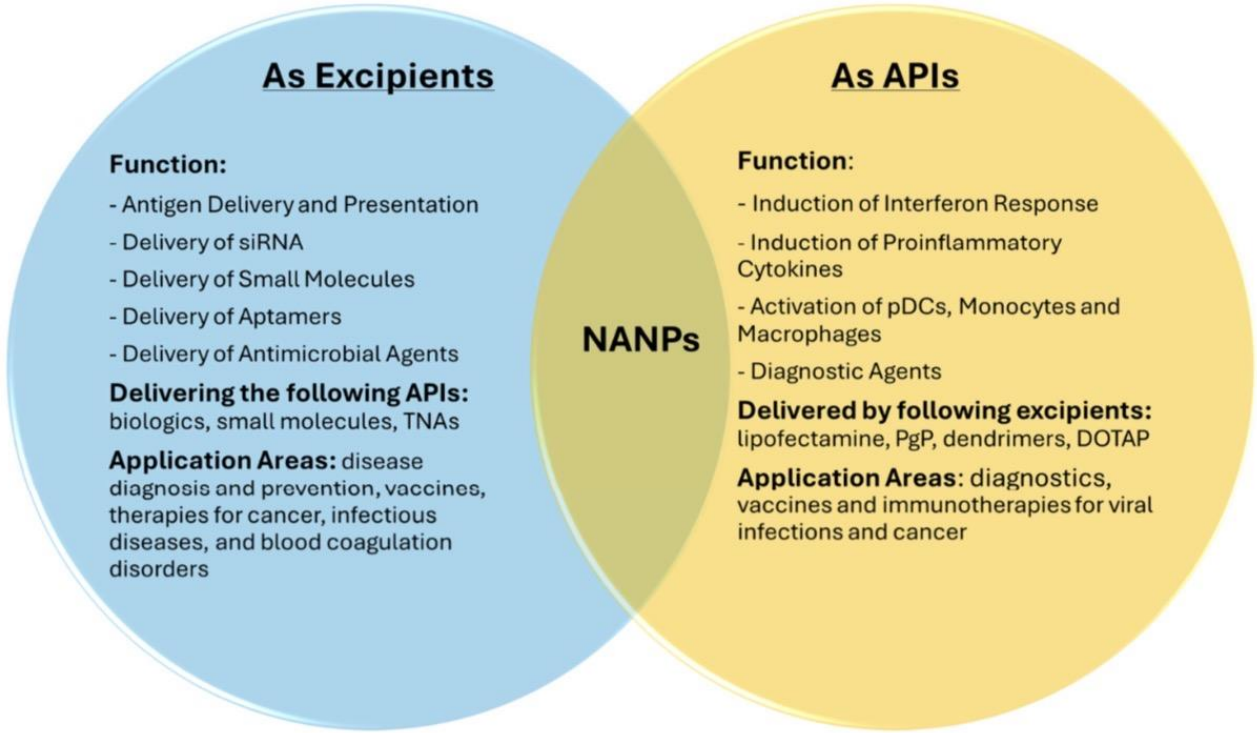
4WJ platform can be an API, an excipient, or both — depending on context

"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.