RNA Therapeutics: Clinical and technology advancements & deal activity

Kristine Dorward in Pullan's Pieces #221, January 2026

kristine@pullanconsulting.com

Industry-wide advancement in RNA drug development was on full display at this month's JPM conference, with emphasis on compelling clinical progress, expanding delivery technologies and an accelerating pace of partnerships and licensing deals.

HIGHLIGHTS FROM JPM 2026 CONFERENCE PRESENTATIONS

Wave Life Sciences outlined how its chemistry innovation enables a single molecule to both silence and edit genes.

- Management is prioritising WVE-007 in obesity (Phase 2a INLIGHT study) and RNA-editing assets WVE-006 (AATD) and WVE-008 (PNPLA3)
- WVE kicks off 2026 with US$602M cash runway, carrying the company comfortably into Q3, 2028

Novartis estimates an addressable RNA therapeutics market to reach ~US$36B by 2030 (per Evaluate Pharma).

- Novartis' advanced RNA technology platforms involve a range of approaches, further expanded by their recent acquisition of Avidity Biosciences which includes microRNA late-stage candidate farabursen

Arrowhead's proprietary TRiM platform has demonstrated ability to deliver RNAi to **7** tissue types (liver, lung, skeletal muscle, CNS, adipose, ocular, cardiomyocytes)

- ARWR aims to unlock a new cell type every ~ 18 months

IONIS provided updates on its corporate performance and portfolio progress, announcing that revenues of antisense oligonucleotide *TRYNGOLZA* (olezarsen) reached US$105M for 2025

- FDA has granted Breakthrough Therapy Designation to IONIS' **zilganersen** for treating Alexander disease
- Ziglanersen is an investigational ASO designed to stop the production of excess glial fibrillary acidic protein

Also at JPM '26, Sino Biopharmaceutical outlined its xRNA technologies and capabilities, achieved through multiple acquisitions & integrations

- Sino is pursuing a 10-platform strategy and predicts highly differentiated launches across oncology, respiratory and metabolic diseases over the next 3 years, facilitated by new global BD plans

Biogen & Stoke Therapeutics announced accelerated timelines for achieving complete enrollment and Phase 3 data readout of the EMPEROR study evaluating zorevunersen

- Zorevunersen is a first-in-class, potentially disease-modifying treatment for Dravet syndrome with FDA Breakthrough Therapy Designation
- Zorevunersen increases functional NaV1.1 protein production from non-mutated (WT) copy of the SCN1A gene

Other JPM '26 highlights included Tessera Therapeutics' announcement regarding FDA clearance of their IND to initiate recruitment for their Phase 1/ 2 trial with TSRA-196 in AATD

- TSRA-196 uses in vivo target-primed reverse transcription (TPRT), based on RNA, to correct the *SERPINA1* gene mutation

Lilly's partner ProQR Therapeutics released preliminary safety and pharmacokinetics results for AX-0810 earlier this month

- AX-0810 is ProQR's lead investigational editing oligonucleotide targeting NTCP, which is being developed for the treatment of

cholestatic diseases, such as primary sclerosing cholangitis and biliary atresia

- Initial AX-0810 data show no safety signals after 4 weeks of dosing and PK consistent with pre-clinical data; target engagement data expected in H1 2026, followed by inclusion of an active patient cohort
- AX-0810 is part of the multi-target discovery and development collaboration with Lilly; PRQR has recently received > $4.5M in milestone payments from LLY, extending its cash runway to mid-2027

In its collaboration with Sirius, **CRISPR Therapeutics** has expanded beyond their foundational CRISPR/Cas9, DNA gene editing platform, to include an siRNA pillar to their corporate platform.

- Lead program CTX611 (Factor XI) will target a range of thromboembolic and clotting-related indications and represents a multi-billion-dollar market opportunity, including arterial fibrillation (AF), venous thromboembolism (VTE), ischemic stroke, cancer-associated thrombosis, CKD, PVD, and CAD
- For these indications, siRNA is believed to be a preferable approach, versus DNA gene editing which may not match the therapeutic profile, flexibility of reversibility and potential for biannual dosing

THE EVOLVING LANDSCAPE IN RNA THERAPEUTICS

RNA-based medicines are increasingly derisked, demonstrate expanding clinical relevance and strong commercial promise

New targeting technology should broaden the range of conditions that can be treated as RNA therapeutics move beyond rare diseases to include a range of common conditions

Extrahepatic targeting is the new wave in RNA therapeutics; achieving tissue-specific delivery is a key focus in 2026 and beyond

Many approved RNA-based therapeutics, when conjugated, have been targeted to the liver via GalNAc-ASGPR – this method is extremely effective for diseases of the liver but limits eligible indications and prevents therapeutic targeting in neurology and other vital organ systems

Design solutions, now well advanced in the clinic, include use of newer targeting mechanisms such as the transferrin receptor (TfR) or C16 conjugates, which improve precision CNS targeting and expand target feasibility to include lung and eye tissue. Denali and Alnylam both have proprietary, advanced BBB shuttle technologies.

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Preclinical mechanisms such as megalin (LRP2) provide compelling promise in targeting solid organs such as the kidney

Judo Bio recently released NHP data demonstrating that a single subQ administration of its

megalin-STRIKERs therapy resulted in increased excretion of disease-related solute levels lasting for at least 2 months

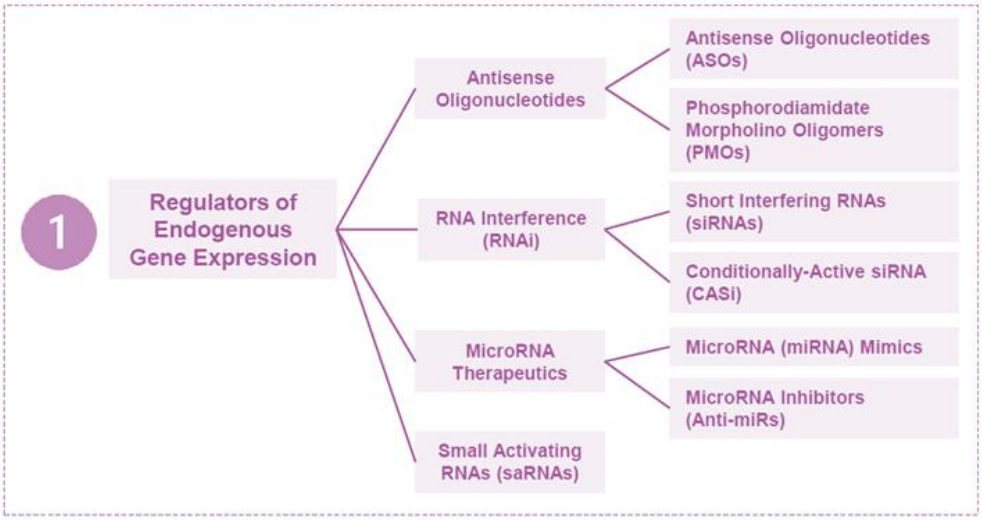
The next wave of RNA therapies to launch will provide greater convenience, ease of administration and less invasive delivery; these features have become table steaks for next generation RNA therapies to gain a competitive commercial foothold

First-generation RNA therapies were typically given via IV or intrathecally, however 8 of the last 10 approved RNA medicines have been subQ administration

HIGH LEVEL OVERVIEW OF RNA THERAPEUTIC MODALITIES

Classifying RNA medicines according to their function

1) **Regulators of Endogenous Gene Expression**



Regulators of endogenous gene expression include ASO, RNAi, miRNA, saRNA

Antisense Oligonucleotides include ‘classic’ ASOs, single-stranded oligos with DNA/RNA-like backbones that bind a target RNA; included are RNase H gapmer ASOs and steric-block ASOs

PMOs (phosphorodiamidate morpholino oligomers) are a chemically distinct (i.e., morpholino backbone) sub-class of ASOs; PMOs act mainly as steric blockers (example, as exon skippers in DMD)

Short interfering RNA comprises ~21-23-mer dsRNA duplexes which are loaded into a RISC; the guide strand directs the cleavage of complementary mRNA and ‘silences’ gene expression

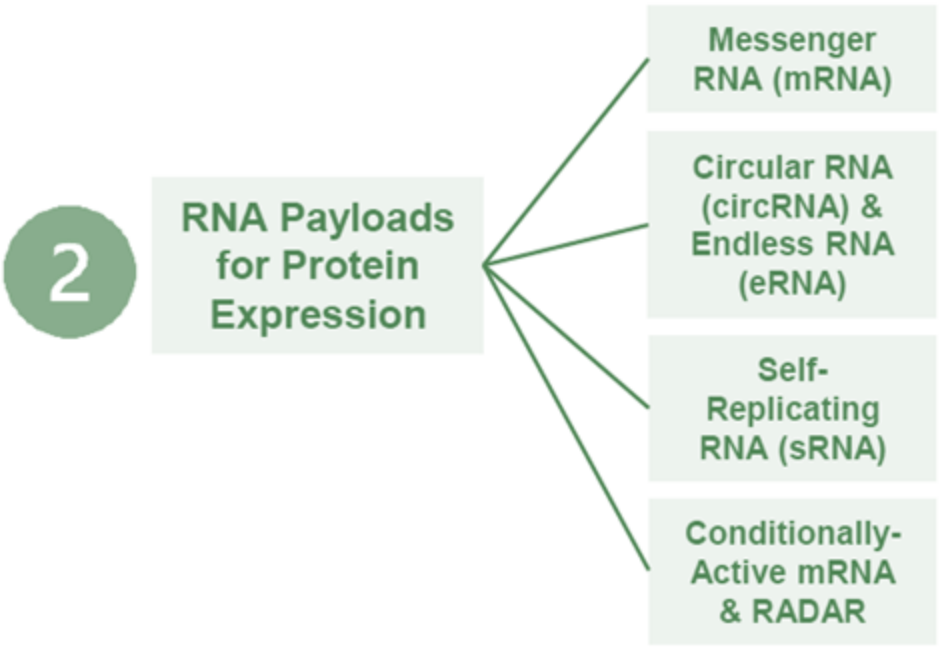
Conditionally activated siRNA encompasses a platform-level subtype of siRNA in which the siRNA is inactive or masked until a specific stimulus (e.g. pH, protease, microRNA, etc.) releases it

Engineered microRNAs (miRNA) mimic dsRNA-like structures, and can restore or rescue the function of a lost or weakly-expressed, naturally occurring, endogenous miRNA and repress its target

MiRNA inhibitors (Anti-miRs) are single-stranded antisense-like oligos that block function of a specific miRNA to de-repress its target

Small Activating RNAs (saRNAs) are short dsRNAs that induce gene expression by targeting promoter/enhancer regions to recruit transcriptional apparatus

2) RNA Payloads for Protein Expression



Conventional mRNA therapeutics are linear, capped, polyadenylated mRNA that encode proteins of interest (e.g. antigens for a vaccine or enzymes for protein replacement)

Circular RNA (circRNA) are covalently closed RNA circles that can encode proteins when engineered with IRES and other translational elements

Circular RNA represents an alternate format to mRNA and typically provide higher stability (also termed oRNA & endless RNA (eRNA)

Self-Replicating RNA (srRNA) are also known as self-amplifying RNA; srRNA include both the mRNA strand and the replicase/replicon elements (often from alphaviruses) to replicate

Within the cell, the RNA amplifies the replication machinery to increase the RNA and protein output from a much smaller initial RNA dose

Conditionally or context-activated mRNA are engineered genetic logic circuits, including stop codons, to control timing, location, and magnitude of mRNA expression

3) Translation Machinery Modulators

Engineered tRNAs can suppress premature termination (stop) codons to enable protein translation read-through

tRNA therapies do not regulate RNA or encode for proteins, but rather act at the ribosome level of the translation apparatus

4) RNA Ligands & Scaffolds

The category of RNA ligands and scaffolds is primarily comprised of RNA Aptamers

RNA aptamers are structurally folded ssRNAs that are selected for their high-affinity binding to proteins, small molecules, or cells

These can be thought of as “chemical antibodies” that can act as ligands, antagonists, agonists, targeting molecules, or decoys

RNA aptamers may also be conjugated with other oligos (e.g., siRNA, ASO) or fully differentiated payload types, such as toxins

5) RNA-Guided Editing & Recoding

RNA editing and recoding involves use of RNA guides to recruit or encode editing enzymes that chemically-modify the nucleotides in the target RNA to produce a transient effect, unlike permanent gene (DNA) editing

ADAR-based A-to-I editing is a frequently used platform

RNA Gene Writers exploit mobile genetic elements (MGEs) to make virtually any edit to the genome

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M&A, COLLABORATION AND LICENSING DEAL ACTIVITY IN THE RNA MEDICINES SPACE

RNA-focused transactions have generated **~ US$60B** in deal value over the last 5 years (2020-2025), which includes **~ US$21B** in acquisition deal value and **~US$39B** in licensing deal value

~74% of M&A value in the RNA space came from Novartis' acquisition of Avidity for $12B in October 2025 as well as Novartis' prior antibody-oligo conjugation deals

There were ~ US$15.3B in licensing deals during the 2020-2025 period and ~$23.8B in R&D collaborations

Many of these transactions were extensively milestone-based and/or included earnouts/contingencies that could significantly increase overall deal values, if future thresholds are achieved

The RNA deal landscape has transitioned over the past five years

R&D collaborations and licensing deals comprised a majority, 66%, of all RNA deal value from 2020 – 2022

However, the pace of acquisitions subsequently increased, comprising ~ 43% of all RNA transaction deal value from 2023 through 2025

Notable licensing and acquisition deals involving RNA medicines and delivery technologies in the past year

Sarepta Therapeutics' licensing agreement with Arrowhead Pharmaceuticals for up to US$10.825B (February 2025)

Novartis' licensing agreement with Argo Biopharma (Private) for ~$5.4B (September 2025)

GSK's agreement with ABL Bio for ~$2.8B (April 2025)

Novartis' licensing agreement with Arrowhead Pharmaceuticals for $2.2B (October 2025)

Vertex and Orna's 3-year strategic R&D collaboration for $700M, with additional option rights value >$3.65B (January 2026)

Bausch & Lomb and City Therapeutics' strategic collaboration agreement (January 2026)

GSK & CAMP4 Therapeutics forge strategic collaboration for $417M (December 2025)

Vir grants Norgine an exclusive commercial license for € 550M (December 2025)

Bristol Myers Squibb's acquisition of Orbital Therapeutics for $1.5B in October 2025

BioNTech's acquisition of CureVac for $1.25B (June 2025)

Novartis' acquisition of Avidity Biosciences for $12B (October 2025)

AbbVie's acquisition of Capstan Therapeutics for $2.1B (August '25)

Sino Biopharmaceutical's acquisition of Hygieia Pharmaceuticals for RMB 1.2B or ~ US$167M