Editorial

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A lifetime with RNA: John J. Rossi and the questions that science revisits

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SUMMARY: Dr. John J. Rossi's scientific career has unfolded alongside the transformation of RNA from a biological intermediary into a programmable therapeutic modality. Beginning with catalytic RNA and anti-HIV ribozymes, his work progressed through RNA interference, expressed siRNA and shRNA, combinatorial RNA gene therapy, and aptamer-guided delivery. This Editorial uses that trajectory to examine a broader feature of modern biomedicine: discovery and delivery must advance together, and scientific progress often depends on returning to unexplained observations with better tools. Rossi's roles at City of Hope and in building the oligonucleotide therapeutics community further show that continuity is sustained not only by experiments, but also by institutions, mentorship, and collaboration. His 2026 reflection on revisiting long-standing biological questions therefore offers a timely vantage on a career spent expanding what RNA can do. The resulting history links changing concepts of RNA with persistent questions of specificity, control, delivery, safety, and clinical translation across biomedicine.

Keywords: RNA biology, RNA interference, ribozyme, RNA therapeutics, scientific continuity

1. A lifetime with RNA

On October 13, 2026, John J. Rossi, Ph.D. was honored with the Lifetime Achievement Award of the Oligonucleotide Therapeutics Society (OTS) at its 22nd Annual Meeting, held October 11–14 at the Colorado Convention Center in Denver, Colorado, USA. This recognition provides a timely opportunity to reflect not simply on a sequence of individual achievements but on a scientific career that has unfolded alongside the transformation of RNA from a biological intermediary into a programmable therapeutic modality. This recognition provides a timely opportunity to reflect not simply on a sequence of individual achievements but on a scientific career that has unfolded alongside the transformation of RNA from a biological intermediary into a programmable therapeutic modality (Figure 1).

Asked shortly before the award what he considered his greatest scientific accomplishment, Rossi pointed to the development of small therapeutics for the treatment of patients with HIV that were eventually tested in clinical trials (personal communication, August 21, 2026). The emphasis is revealing. It places the weight not on a single molecular observation but on the difficult transition from mechanism to engineering and from experimental design to clinical translation—a theme that runs through much of his scientific career.

Within this context, in a recent *BioScience Trends* Editorial Rossi reflected on a deceptively simple feature of scientific progress: new technologies do not merely generate new questions; they also allow old questions to be asked again (*1*). He illustrated this idea with two examples: the re-examination of a *Streptomyces* lectin originally studied in the 1970s using modern analytical techniques, and the investigation of ethanol responses in *Caenorhabditis elegans* using contemporary transcriptomic approaches.

This point is particularly profound when considered in light of Rossi's own scientific career. He received his PhD in microbial genetics from the University of Connecticut in 1976, completed postdoctoral training at Brown University, and began his long association with City of Hope in 1980 (*2*). Over more than four decades, his research moved through catalytic RNA, antisense strategies, RNA interference, small noncoding RNAs, combinatorial gene therapy, and targeted RNA delivery. This was not simply a succession of topics. It paralleled a transformation in biology: RNA came to be understood



Figure 1. John J. Rossi honored with the Oligonucleotide Therapeutics Society Lifetime Achievement Award. John J. Rossi at the 22nd Annual Meeting of the Oligonucleotide Therapeutics Society, held in Denver, Colorado, USA, October 11–14, 2026. *Photo*: Courtesy of OTS Oligo Meeting.

not only as an intermediary in gene expression but also as a catalyst, a regulator, an experimental instrument, and a therapeutic modality.

2. RNA becomes an active molecule

When self-splicing RNA was demonstrated in the early 1980s, it overturned the assumption that biological catalysis was exclusive to proteins (*3*). Catalytic RNA soon became both a fundamental discovery and an engineering opportunity. In 1990, Sarver, Rossi, and colleagues reported that hammerhead ribozymes precisely cleaved HIV-1 RNA in a cell-free system and reduced viral gag RNA and p24 antigen in human cells (*4*). The conceptual move was striking. RNA was no longer only the molecule to be read or measured; it could be engineered to recognize and destroy another RNA.

Feasibility in a model system, however, was not the same as therapy. Ribozymes had to find accessible targets inside cells, remain stable, be expressed at useful levels, and avoid disrupting normal cellular processes. Rossi's later assessment of therapeutic ribozymes emphasized that intracellular localization, RNA metabolism, target accessibility, and delivery were inseparable from catalytic design (*5*). By the late 1990s, anti-HIV ribozyme strategies were being examined clinically. This transition from biochemical principle to human application established a pattern that would recur throughout RNA therapeutics: discovery and delivery had to advance together.

3. From RNA interference to programmable silencing

The discovery that double-stranded RNA could induce potent and sequence-specific gene silencing in *C. elegans* sparked another conceptual chapter (*6*). The identification of short siRNA duplexes that functioned in mammalian cells made the pathway experimentally and therapeutically accessible (*7*). Rossi's group soon explored this topic. In 2002, Lee and colleagues used a mammalian polymerase III promoter to express functional siRNAs in human cells; constructs directed against HIV-1 rev inhibited viral gene expression by up to four orders of magnitude in a cotransfection system (*8*). RNA could now be programmed not only as an enzyme but also as a guide for endogenous silencing machinery.

The power of this approach also exposed new constraints. Viral escape could occur when relying on a single target, unintended seed interactions could alter other transcripts, innate immune pathways could be activated, and high-level shRNA expression could compete with endogenous microRNA processing. Rossi's 2006 review framed these issues as central to clinical development rather than peripheral technicalities (*9*); the same year, dose-dependent toxicity from oversaturation of small-RNA pathways in mice demonstrated how consequential the level of expression could be (*10*). The lesson was sobering but productive: programmable specificity did not eliminate the need for biological control.

4. From molecular recognition to clinical translation

The translational history of anti-HIV RNA therapy therefore became a history of platforms. A randomized phase 2 study of a cell-delivered anti-HIV ribozyme in 74 adults did not meet its primary viral-load endpoint, although the intervention was reported to be safe and biologically active and some secondary measures favored the ribozyme group (*11*). The result was neither a triumph nor a dead end. It clarified the gap between molecular activity and durable clinical effects.

Combination strategies were one response. In 2010, DiGiusto and colleagues transplanted autologous CD34-positive hematopoietic progenitor cells engineered to express three RNA-based anti-HIV agents: a tat/rev shRNA, a TAR decoy, and a CCR5 ribozyme (*12*). Hematopoietic engraftment was achieved in all four patients; gene-modified cells and introduced RNAs were detected, with vector-derived sequences persisting at low levels in multiple blood-cell lineages for up to 24 months. The study was not evidence of an HIV cure. Its importance lay elsewhere, that is, several generations of RNA engineering – ribozyme, decoy, and shRNA – had been assembled into one cell-based clinical platform.

A second response was to make delivery itself molecularly specific. Aptamer-siRNA chimeras combined recognition and silencing in the same RNA architecture. An anti-gp120 aptamer could both interfere with viral entry and carry an siRNA against HIV transcripts (*13*). Chemically synthesized aptamer constructs later enabled interchangeable, multiplexed siRNA delivery *in vivo*, suppressing viral and host targets while addressing the problem of escape (*14*). Subsequent receptor-targeted conjugates extended this strategy to transcriptional silencing and systemic delivery in humanized mice (*15*). Through these studies,

RNA evolved from serving as cargo to an integrated system: a recognition element, therapeutic effector, and delivery vehicle. These studies did not anticipate the exact platforms that now dominate clinical settings, but they addressed the same design problem: coupling potent RNA to a delivery system that determines where it acts (*16*). That logic is now implemented, by distinct mechanisms, in lipid nanoparticle-encapsulated patisiran and GalNAc-conjugated inclisiran (*17,18*).

RNA therapeutics cannot be described as molecular discovery alone. Potent target cleavage or silencing *in vitro* may still fail because of instability, endosomal trapping, off-target tissue uptake, toxic expression, or rapid clearance. Rossi's work repeatedly involved this interface, where an elegant mechanism had to be rebuilt as a usable therapeutic system.

5. A field rather than just experiments

Rossi's career also shows that a field consists of more than just experiments. At City of Hope, he directed the Center for RNA Biology and Therapeutics for more than two decades, while his roles in graduate education, journal editing, biotechnology, and the Oligonucleotide Therapeutics Society helped connect mechanistic biology to therapeutic development (*2,19*). These activities matter to scientific continuity because institutions and communities preserve expertise and allow different disciplines and generations to work on persistent translational problems.

Oligonucleotide therapeutics required synthetic chemistry, RNA structure, computational design, pharmacology, toxicology, vector biology, clinical medicine, and manufacturing to become mutually intelligible. The Oligonucleotide Therapeutics Society provided a forum for this exchange, and Rossi served as its founding president (*2,19*).

The intellectual scope widened as questions regarding HIV - specificity, resistance, innate immune recognition, intracellular trafficking, and selective delivery - became more pointed and more relevant to cancer, genetic disease, and other therapeutic areas. Rossi's later emphasis on RNA medicines and noncoding RNA therefore expanded on the same central problem: how can RNA's informational and structural properties be used without losing control of context, dose, or destination (*2,16*)?

By 2018, the first RNA interference drug had been approved in the US. RNAi had become a clinical modality, although targeting, endosomal escape, durability, manufacturing, and access remained challenges (*16*). Rossi's trajectory thus provides a window into how RNA biology matured through repeated cycles of mechanism, engineering, delivery, and clinical testing.

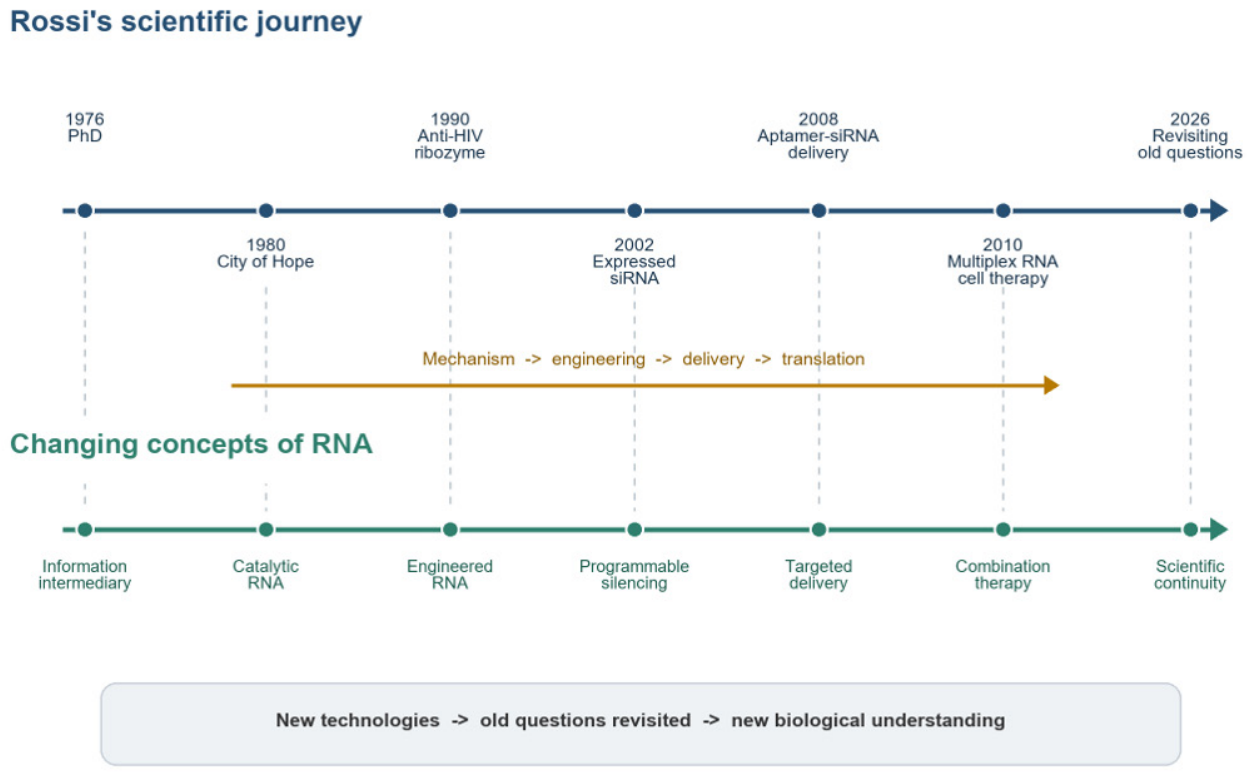


Figure 2. A lifetime with RNA: Scientific milestones and changing roles of RNA. Representative milestones in John J. Rossi's career are aligned with shifts in how RNA has been understood and used. Dotted lines indicate conceptual correspondence rather than single-cause attribution. The central arrow summarizes a recurring translational sequence: mechanism, engineering, delivery, and clinical testing.

6. Changing scientific verbs

Seen in this light, Rossi's career is also a history of changing scientific verbs. Researchers first observed RNA, then sequenced it, cleaved it, silenced it, expressed it, combined it, and attempted to deliver it selectively. Each new verb expanded the range of what could be asked. At the same time, the central questions remained remarkably consistent: How does RNA recognize its target? How is its activity controlled in a cell? How can molecular specificity be translated into clinical benefit? Figure 2 places these changing roles of RNA alongside representative milestones in Rossi's career.

This continuity explains why Rossi's 2026 Editorial looks backward without being nostalgic. The *C. elegans* study he discussed used time-resolved RNA sequencing to separate an ethanol response into early detoxification and redox programs, later DAF-16-associated gene induction, and repression of peroxisome- and development-related signaling (*20*). Earlier experiments noted a lifespan-related phenotype; contemporary transcriptomics have revealed a sequence of pathway-level responses. The aforementioned study did not merely produce more data. It changed the form of the question. The lectin example offers the complementary molecular-scale case: mass spectrometry and expanding sequence databases revealed structural features that earlier methods were unable to (*1*). Taken together, the lectin and *C. elegans* studies show the same principle from protein architecture to system-wide transcription.

This choice of subject is best understood as a vantage point rather than an endpoint. A new technique enables researchers to perform experiments that could not be performed earlier; a later advance can make the past intelligible. Observations that were previously set aside because the sequence, structure, or system-wide response could not be identified may be returned to as productive questions. Rossi's Editorial therefore reads not only as a comment on omics technologies but also as a reflection on the timescale of research itself - on what one generation observes, what it cannot yet explain, and what it leaves for another generation to reexamine.

Good questions often outlast the methods first used to investigate them. Rossi's journey from hammerhead ribozymes to targeted RNA therapeutics shows that progress is neither a straight line nor a continual abandonment of the past. It is a repeated cycle of old observations and new instruments. As technology matures, an unexplained result can be explained, and a question that appears to be settled is given new life.

That may be the most durable lesson of a lifetime with RNA: scientific continuity depends not only on moving forward but also on knowing when the tools are good enough to return to previous topics.

In closing, Rossi left us with these words: "all successful translational aspects of my research stem directly from interpreting sound basic research findings, most of which occurred in lower organisms and plants. Basic research is the foundation of all good science. We must stand on the shoulders of those whose work laid the foundations."

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