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Editorial

From HIV to Inflammation: How RNA Biology Redefined Drug Discovery

RNA biology has reshaped drug discovery over the past three decades, revealing unexpected therapeutic connections between viral infection and inflammation. The rise of RNA medicine has bridged molecular biology with pharmacological innovation. From the first antisense oligonucleotides correcting splicing defects[(p1)] to mRNA vaccines enabling rapid pandemic responses,[(p2)] RNA-based drugs[(p3)] have become a cornerstone of biomedical progress. Yet these achievements reveal only part of RNA's potential. Beyond coding transcripts and gene silencing lies an intricate universe of non coding RNAs and RNA–protein complexes that orchestrate cellular life. Harnessing this complexity requires not only biological insight but also chemical ingenuity (Figure 1).

The story of obefazimod began in an unexpected place—the study of HIV RNA splicing. In the early 2000s, efforts to inhibit viral replication by modulating RNA processing uncovered an unforeseen dialogue between viral and host RNA metabolism.[(p4)] Screening programs for small molecules that influenced this process identified a quinoline derivative—later named obefazimod—as a potent modulator. Initially explored as an antiviral agent, obefazimod proved safe and well tolerated in patients with HIV, while reducing residual viral reservoirs under antiretroviral therapy.[(p5)] These early clinical findings validated the concept that pharmacological control of RNA splicing could be therapeutically therapeutic impact.

At the CNRS–University of Montpellier, the search for the molecular target of obefazimod led to the Cap Binding Complex (CBC), a key player in early RNA processing. The CBC, composed of NCBP1 and NCBP2, works with its cofactor ARS2 to connect nascent transcripts to multiple RNA maturation pathways.[(p6),(p7)] Obefazimod was found to stabilize the CBC–ARS2 interaction, thereby enhancing the processing of a long non coding RNA precursor encoding the anti inflammatory microRNA miR 124.[(p6),(p7)] Importantly, obefazimod did not globally alter mRNA splicing; rather, it selectively promoted the splicing and maturation of pri miR 124,[(p5),(p6)] resulting in its robust induction in immune cells. The consequence was striking: a molecule designed to block viral RNA now reprogrammed immune function by amplifying an endogenous anti inflammatory pathway.

This scientific pivot—from infection to inflammation—transformed a virology project into a therapeutic paradigm. Preclinical studies in models of colitis and arthritis demonstrated broad anti inflammatory effects,[(p8)] prompting a pilot clinical trial in ulcerative colitis. The encouraging outcomes led to a randomized, placebo controlled Phase 2b study that confirmed obefazimod's efficacy and safety, paving the way for pivotal Phase 3 trials successfully completed in 2025.[(p9),(p10)] These results established obefazimod as the first small molecule to demonstrate clinical benefit through modulation of RNA biogenesis.

Mechanistically, this discovery opened a new frontier in drug discovery. Unlike antisense or siRNA strategies that act directly on RNA sequences, obefazimod modulates the endogenous machinery that governs RNA processing. By stabilizing a protein–protein interface within a nuclear RNA–protein complex, it enhances the natural biogenesis of a regulatory RNA molecule. This concept—pharmacologically tuning RNA biogenesis—extends RNA therapeutics beyond correction or inhibition toward the orchestration of cellular regulation itself.

The implications reach far beyond inflammation. Similar mechanisms could be exploited to correct RNA dysregulation in neurodegenerative disorders, cancer, autoimmunity, or viral persistence. Systematic mapping of RNA–protein complexes and long non coding RNA precursors amenable to smallmolecule stabilization will dramatically expand the druggable landscape. The integration of RNA targeted small molecules with biologics, RNA vaccines, or gene editors could create synergistic therapeutic platforms unimaginable a decade ago.

The trajectory of obefazimod underscores the power of curiosity driven science. What began as a study of viral splicing evolved into a demonstration that small molecules can act upon

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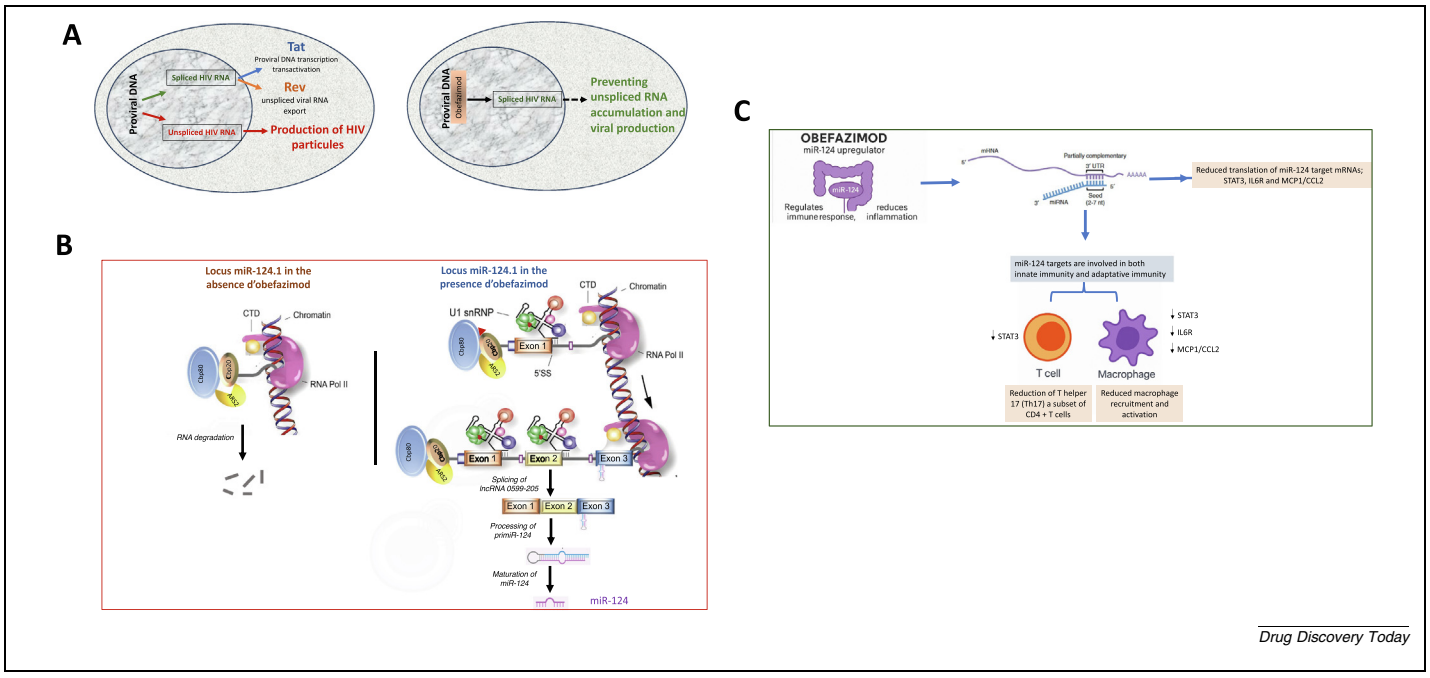

FIGURE 1

A. Obefazimod enhances HIV RNA splicing and prevents viral particle production. In HIV infected cells, transcription from integrated proviral DNA generates primary viral transcripts that are alternatively spliced to produce essential regulatory proteins such as Tat and Rev. Tat promotes efficient transcription of viral RNA, while Rev allows the nuclear export of unspliced viral RNA required for the assembly of new viral particles (left panel). Unspliced viral RNAs are normally unstable and need Rev to escape nuclear degradation and be exported to the cytoplasm for virion production. Obefazimod enhances the splicing of HIV RNA, leading to the depletion of unspliced transcripts and preventing the synthesis and export of the full-length viral RNA (right panel). As a consequence, viral particle formation is abolished. **B. Obefazimod stabilizes CBC–ARS2 to enhance miR-124 biogenesis.** Obefazimod (in red) binds at the interface of Cbp 80 and Cbp20 and stabilizes the Cap Binding Complex (CBC) and strengthening its interaction with ARS2, a nuclear RNA–protein complex that functions as a gatekeeper for RNA processing. This stabilization promotes splicing of the long non-coding RNA precursor lncRNA 0599-205, which contains the sequence of pri-miR-124 within its third exon (right panel). Enhanced splicing prevents degradation of the transcript (left panel) and facilitates its maturation through the canonical microRNA biogenesis pathway, leading to increased expression of miR-124. The figure also shows U1 snRNP, which recognizes the 5′ splice site and participates in intron removal as part of the spliceosome. RNA Pol II (RNA Polymerase II) with its CTD (carboxy-terminal domain) is included to indicate co-transcriptional recruitment of RNA processing factors. CBC, Cap Binding Complex; ARS2, Arsenite resistance protein 2; lncRNA, long non-coding RNA; miR, microRNA. **C. miR-124 mediates anti-inflammatory reprogramming of macrophages and T cells.** Up-regulation of miR-124 by obefazimod elicits broad anti-inflammatory effects across innate and adaptive immune compartments. MiR-124 acts by base-pairing with 3′ UTRs of target mRNAs, leading to translational reduction. In **macrophages**, miR-124 downregulates expression of key pro-inflammatory mediators—including **STAT3**, **MCP-1/CCL2**, and **IL-6 receptor (IL-6R)**—thereby reducing downstream cytokines such as **TNF-α** and **IL-6**. In **T cells**, miR-124 modulates lineage commitment by attenuating **STAT3-dependent Th17 differentiation** while favoring regulatory T-cell phenotypes. The combined repression of STAT3-driven transcriptional programs in both macrophages and T cells dampens effector inflammation and promotes immune resolution. Together, these actions explain how pharmacological induction of a single microRNA network can rebalance immune homeostasis and account for the clinical efficacy of obefazimod in ulcerative colitis. **Abbreviations:** miR, microRNA; TNF-α, tumor necrosis factor-α; IL, interleukin; Th, T-helper cell subset. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the regulatory architecture of RNA itself. By uniting infection biology, RNA chemistry, and immunology, this journey revealed that restoring immune balance[(p9)] may depend not only on inhibiting proteins or cytokines but on reprogramming the RNA networks that control them.

The emergence of RNA biogenesis modulation as a therapeutic principle highlights a broader lesson: transformative innovation often arises at disciplinary crossroads. As the first in class enhancer of miR 124 biogenesis, obefazimod embodies the promise of a new generation of medicines—those that fine tune our endogenous RNA systems to achieve durable immune and physiological harmony.

Declaration of competing interest

Professor Jamal Tazi is the scientific founder of Splicos Therapeutics and Abivax SA. He holds equity in Abivax and has contributed to the discovery and early development of obefazimod. The scientific work leading to obefazimod's identification and mode of action originated in his academic laboratory at IGMM, CNRS–University of Montpellier, in collaboration with the Curie Institute. No other conflicts of interest are declared.

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Data availability

No data was used for the research described in the article.

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Jamal Tazi is Professor Emeritus at the University of Montpellier and Research Director at CNRS (IGMM). A pioneer in RNA biology, he has authored over 130 scientific publications and several patents. He co-founded Splicos Therapeutics and Abivax, where his discoveries on RNA splicing and RNA biogenesis led to the development of obefazimod, the first small-molecule modulator of RNA biogenesis to achieve Phase III clinical success in inflammation. His research bridges fundamental RNA mechanisms and translational medicine, defining RNA biogenesis as a new frontier for drug discovery. Professor Tazi's work has been honored with the Académie de Médecine Prize, the Académie des Sciences Prize, the ARRI Innovation Award, the CNRS Innovation Medal, and a nomination for the 2025 Prix Galien.

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