

Engineered Circular RNA: A Stable and Versatile Therapeutic Platform Transforming mRNA Medicine

Introduction

Circular RNAs (circRNAs) have emerged as a significant innovation in therapeutic RNA research, profoundly reshaping the pharmaceutical landscape previously dominated by linear messenger RNA (mRNA). Unlike traditional linear RNAs, circRNAs exhibit remarkable stability due to their covalently closed circular structures, eliminating susceptibility to exonuclease degradation and extending their half-life in biological environments (Wang et al., 2017). Recently, engineered circRNAs have attracted extensive attention, particularly as novel vaccine platforms and cancer therapies (Cao et al., 2023; Zhang et al., 2023). These engineered circRNAs demonstrate lower immunogenicity, efficient translation capability, and persistent protein expression, positioning themselves as superior alternatives to conventional linear mRNA approaches. Despite considerable potential, engineered circRNA technology still faces hurdles related to manufacturing efficiency, delivery specificity, and regulatory considerations. This essay will critically analyze the pharmaceutical implications of engineered circRNAs, emphasizing their transformative roles in cancer therapy and vaccine development. It will argue that while engineered circRNAs offer substantial advantages in stability and therapeutic efficacy, challenges in scalability and delivery systems must be effectively addressed.

Innovation Overview and Mechanism

Engineered circRNAs represent a sophisticated evolution in RNA medicine, designed primarily through back-splicing methods involving intronic sequences and RNA-binding proteins to form stable closed-loop structures (Wang et al., 2017). Unlike linear mRNAs, circRNAs lack terminal ends, thereby gaining inherent resistance to RNA-degrading enzymes. Additionally, engineered circRNAs frequently incorporate internal ribosome entry sites (IRES) or N⁶-methyladenosine (m⁶A) modifications, enabling efficient cap-independent translation of encoded proteins (Cao et al., 2023). Cao et al. (2023) highlight multiple strategies for optimizing circRNA expression efficiency, including sequence optimization and structural refinement, underscoring their adaptability as versatile drug delivery platforms.

This robustness makes circRNA ideal for sustained therapeutic protein expression, especially in chronic diseases or conditions demanding persistent immune responses. For instance, engineered circRNAs encoding therapeutic antigens have been successfully applied in vaccine development, notably the SARS-CoV-2 vaccine, demonstrating prolonged antigen presence compared to traditional linear mRNA

vaccines (Zhang et al., 2023). Such prolonged antigen expression contributes significantly to sustained and potent immune responses, enhancing the overall effectiveness of vaccination programs. Zhang et al. (2023) further demonstrated that circRNA vaccines administered via lipid nanoparticles (LNPs) offer enhanced thermal stability, significantly improving their logistical feasibility for global distribution. Thus, the sophisticated design and unique mechanisms of engineered circRNAs establish them as powerful tools capable of overcoming limitations inherent in traditional RNA-based therapies.

Advantages in Pharmaceutical and Clinical Applications

Engineered circRNAs hold substantial advantages, particularly in the contexts of vaccine development and cancer treatment. One of their most notable benefits is their enhanced stability, which directly translates to sustained therapeutic protein expression. This characteristic is particularly critical in vaccine platforms, where prolonged antigen presence can amplify immune responses. According to Zhang et al. (2023), circRNA-based vaccines not only showed robust antigen expression but also elicited durable humoral and cellular immune responses in animal models. These responses persisted significantly longer compared to those induced by linear mRNA vaccines, showcasing circRNA's potential for creating effective long-term immunity.

Furthermore, circRNAs' lower immunogenicity relative to conventional mRNAs reduces the likelihood of adverse immune reactions, enabling safer repeated dosing strategies. This reduced immunogenicity is especially advantageous for chronic therapeutic interventions, such as cancer therapies or protein replacement therapies, where long-term administration is required. Additionally, circRNAs have been demonstrated to effectively function as miRNA sponges, modulating gene expression pathways integral to cancer progression and metastasis (Wang et al., 2017). The multifunctional nature of circRNAs, including their capability to encode therapeutic peptides and modulate gene expression through microRNA inhibition, expands their therapeutic potential significantly.

Cao et al. (2023) have also emphasized engineered circRNAs' applicability in regenerative medicine, highlighting their use in promoting cellular differentiation and tissue regeneration. Such versatility further enhances their attractiveness as comprehensive pharmaceutical platforms, able to address diverse therapeutic challenges across multiple clinical contexts.

Current Challenges and Limitations

Despite substantial promise, engineered circRNAs encounter significant hurdles limiting their widespread clinical adoption. A critical challenge involves their efficient synthesis and scalability. CircRNAs' production typically relies on complex enzymatic

or autocatalytic processes, which can be resource-intensive and yield variable results (Cao et al., 2023). The current methodologies for circRNA synthesis, although sophisticated, generally present lower circularization efficiencies compared to linear RNA synthesis, posing substantial barriers to large-scale manufacturing necessary for clinical applications.

Moreover, the translation efficiency of engineered circRNAs largely depends on internal regulatory elements like IRES or m6A modifications. Placement, structure, and sequence optimization of these elements require precise engineering, complicating the design process. Additionally, the selection of appropriate delivery vectors, such as lipid nanoparticles (LNPs), remains an ongoing area of research. Although LNPs effectively facilitate RNA delivery, their targeting specificity and biodistribution remain suboptimal for certain tissues, potentially limiting therapeutic effectiveness and increasing off-target effects (Zhang et al., 2023).

Regulatory uncertainty represents another critical challenge. Given the novelty of engineered circRNA therapeutics, standardized guidelines for their quality control, clinical evaluation, and approval pathways remain undeveloped. Establishing comprehensive regulatory frameworks is essential to facilitate clinical translation and commercialization. Addressing these barriers demands significant advancements in circRNA manufacturing technologies, delivery mechanisms, and international regulatory cooperation.

Conclusion

Engineered circRNA technology is emerging as a revolutionary therapeutic modality, poised to substantially enhance the landscape of RNA-based pharmaceuticals. Its unique attributes, such as superior stability, sustained protein expression, and multifunctionality, underscore its potential as a transformative platform in vaccine development and cancer therapy. Clinical evidence supports circRNAs' promise, demonstrating their effectiveness in generating prolonged and robust immune responses and facilitating precise modulation of cancer-related pathways.

However, translating engineered circRNA from laboratory to clinical settings will require surmounting considerable technical and regulatory challenges. Enhancing circRNA synthesis methods for greater efficiency, optimizing translation control elements, and refining targeted delivery systems are paramount to maximizing therapeutic efficacy and safety. Additionally, establishing clear regulatory pathways will facilitate circRNAs' clinical acceptance and market entry.

In summary, engineered circRNAs hold profound promise in pharmaceutical innovation. Continued research and development in this field are expected to address current limitations, fostering the realization of circRNAs' full therapeutic potential and marking a significant advancement in modern medicine.

