The Influences of Circular RNA Design Based on Computer Algorithms on the Future

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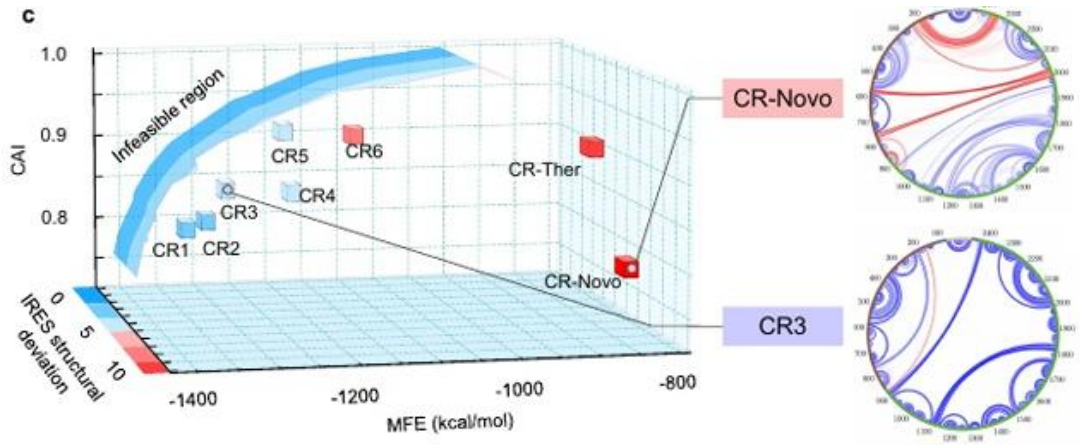
Introduction

Recently, RNA therapeutics has became the new tendency for treatment. In this case, circRNAs has been attracted great attention due to their unique covalently closed-loop structures, which can enhanced stability, and prolonged protein expression compared to conventional linear mRNAs.[2] (Cao, X., Cai, Z., Zhang, J., & Zhao, F. (2024). Engineering circular RNA medicines.). Here, we are going to talk about a new technology whose name is circdesign which can solve the problem of the rational design of a circRNA sequence to jointly improve its stability and protein coding potential. In this approach, a specific IRES sequence is selected for ensuring effective translation. The entire design space, integrating minimum free energy (MFE), codon adaptation index (CAI), and IRES structural deviation are all taken into consideration in the design of the CDS region which can contribute to design circRNA with improved stability, and translatability. It was developed by Liang Zhang's team at the Hangzhou Institute of Medicine, Chinese Academy of Sciences, and further experimentally validated by Congcong Xu's group from Soochow University.[1](Xu et al., 2025) Our assay is aimed at discussing the influences of circDesign in the future application of drug design. We will talk about it from the following perspectives like its advantages and disadvantages.



Proven Benefits

The circDesign algorithm greatly prolongs the expression time of proteins by designing more stable CDS and select IRES in circRNA. In traditional linear RNA

systems, the structure is instable and easy influenced by enzymatic degradation, so protein expression is often influenced. However, circDesign algorithm solve these problems by careful computational optimization. The algorithm strategically selects internal ribosome entry sites (IRES) and coding sequences (CDS) to reduce structural influence. In this way, it prolongs the translational time of circRNAs. For example, a experiment demonstrated that circRNAs designed by circDesign showed higher expression levels in cell-based assays compared to traditional linear RNAs and other common circRNA[2] (Xu et al., 2023). To be exact, circRNAs optimized by circDesign had a translational efficiency of 233.7 units, which was better than the 159.9 units reached by conventional methods [2](Xu et al., 2023).What is more, this enhancement is reached through structural modifications that retain optimal IRES integrity and reduce minimal free energy (MFE). This is very important for efficient translation[2](Xu et al., 2023). This structural optimizations greatly improve circRNA's translational ability, making proteins express stable and long. This will benefit a lot to therapeutic applications. To sum up, circDesign's computational strategy overcomes the traditional problems about circRNA translation. The innovation makes it an advanced key in protein therapeutics, vaccine development and gene editing technologies. CircDesign makes great progress in RNA-based pharmaceutical innovation. It can achieve more efficient and sustained protein production than before.

Expect from protein expression, circDesign also greatly improves the stability of circRNA, significantly enhancing vaccine efficacy and therapeutic ability. Nowadays, stability is one of the most difficult problems for RNA-based therapeutics because RNA molecules are rapidly degraded in human bodies. CircDesign solve the problem by optimizing the circRNA secondary structures. This can minimize the sensitivity of RNA to enzymatic degradation. Experimental data shows that circRNAs designed by circDesign greatly improve half-lives both in the body and outside the body compared to linear RNAs and other common circRNA. For example, circDesign-generated circRNAs showed extended half-lives of 24.56 ± 5.2 hours in blood samples, which was dramatically better than linear RNAs that degrade in 16.4 hours [2](Cao et al.,

2025). Furthermore, in vivo studies highlighted stable and sustained expression of antigens encoded by circDesign RNAs. It can maintain effective condition for over one week after consumption [2](Cao et al., 2025). This long-lasting stability will improve vaccine potency. Animal studies shows that circRNA vaccines designed by circDesign have more persistent immune responses. It includes many elevated neutralizing antibody titres and can improve cellular immunity. They emphasized circRNA's anti-exonucleases ability due to its circular shape. Then they combined it with algorithm-driven optimization to improve this advantage. Therefore, circDesign not only improve circRNA stability but also make a contributions to effective vaccines. Its stability extend antigenic activity and reduce dosage frequency. To sum up, circDesign is a advanced technology for solving stability challenges in RNA therapeutics and vaccine development. It is a outstanding innovation in the field of pharmaceuticals.

Possible or Proven Downsides

Despite the significant advantages that have been achieved, there are still several challenges and limitations. First of all, one of the major limitations is that mRNA expression is influenced by several factors, including tertiary structure, codon usage bias, untranslated regions , and cellular context [3](Mo et al., 2025). This means that optimizing only a single part, such as the coding sequence, is insufficient for maximizing translation efficiency. Additionally, current research is focused on CDS and IRES, without considering other special regions of mRNA that influence significantly to function and stability [1](Xu et al., 2025). It may reduce the stability and translation efficiency of mRNA due to the ignorance of some special codon. Besides, another critical limitation is not incorporation of modified nucleotides in current circRNA design strategies[1](Xu et al., 2025). Modified nucleotides such as pseudouridine or 5-methylcytidine have been shown to improve mRNA stability and translation. The ignorance of it will significantly restrict the full therapeutic and functional potential of circRNA application. If future designs can integrate modified nucleotides based on empirical evidence, the applications of circRNA in therapeutic

protein expression and gene regulation could be significantly broadened.

Conclusion

All in all, designing RNA drugs with computer algorithms will become the mainstream in the future. Even if it is not yet perfect, the circDesign algorithm is bound to leave a significant mark in history. In the main text, we mentioned that the expression level of RNA designed by this algorithm is much higher than that of ordinary RNA. Of course, in the future, we will also continuously improve this algorithm to make its functions more complete and its structural predictions more accurate. We are currently considering using artificial intelligence deep learning algorithms to generate IRES fragments with the smallest structural deviation in the interaction with a given CDS. Of course, in the future, we will also take into account factors such as epigenetics and the differences in modified nucleotides.

Reference

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