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# From the desk of Editor-In-Chief

## *Are we ready for using RNAi in lab medicine: looking into its major challenges*

*RNAi was first discovered in the Petunia plants when Craig Mello and Andrew Fire revealed how the purple colour in the Petunia flowers were converted into faded or white coloured flowers instead of darker ones after the RNAs responsible for the purple colours were introduced into their cell nucleus. Discovery and elucidation of this interference mechanism by RNAs inside the cells took a long period of 8 years from 1990 to 1998, and the whole process was identified as a different mechanism from gene silencing and was named as RNA interference or RNAi. The outcomes of the experiments in Petunia flowers were re-inforced when further experiments in the C. elegans proved that this silencing was mediated by a dsRNA through an evolu¬tionarily preserved natural process that is the hall mark of RNA interference by small RNAs. After discovery, this mechanism has proved its utility through its application in functional genomics, gene target validation methods and a useful tool for gene knockdown model. Gradually, the RNAi replaced the anti-sense gene silencing technology and ribozyme mediated techniques for its more specific and robust methodology and output. Despite this, many issues remain to be solved before this technique can be utilised for consideration as a routine laboratory method for benefit of patients. Firstly, the inconsistent stability and fragile nature of the dsRNA need to be addressed for improving its functional stability and effective silencing effect inside the cell. Accordingly, addressing this issue, several companies have developed modified siRNA molecules by altering some crucial nucleotides that significantly increased the stability of the siRNA molecules from minutes to days.*

*The second major limitation was related to the successful delivery of the RNAi molecules into their target cell. Till now the entry of siRNAs into their target cells depend mainly on the quantity of the siRNA to be injected. This experimental evidence in animal models are producing a great restraint for their use in human beings as injection of large quantities of any foreign matter is not possible in humans. This problem has been circumvented by incorporation of siRNAs into cationic lipo¬somes composed of polyethylenimine or synthetic car¬diolipin analogue that enhance the penetration power of siRNAs into their cognate target cells significantly. The negatively charged siRNAs, when covered by the cationic lipid vesicles can enter their target cells using endocytosis. These cationic molecules containing the specific siRNAs have been already developed by several biotechnogical companies and have smoothened the entry of specific siRNAs into their target cells with minimum side effects. Incorporation of the complementary ligand molecules for specific cell receptors and use of viral vectors are making the delivery of siRNAs into their target cells more specific and accurate. Use of viral vectors are novel in this field regarding the fact that they contain siRNA transcribing machinery like RNA polymerase III pro¬moter in their DNA inserts and can enter into the non dividing cells as neurons. Due to this enormous advantage, viral vectors are now being used as therapeutic agents against HIV, hepatitis C virus (HCV) and muscular dystrophy. The third major problem about the effective and beneficial function of siRNAs inserts are their capability to silence non targeted important genes. These limitations are being minimized by using the microarray analysis to ensure the stringency and fidelity of binding of the siRNAs to their target regions only exclusively.*

*Lastly, the chances of stimulating the innate immune system of the host is another major disadvantage of siRNA techniques which can be minimized by more accurate scanning of the whole siRNA sequence for any possible immunostimulatory se¬quences and eliminating them during designing the final siRNA segment.*

*Removing these obstacles can lead to a much smoother pathway for using the siRNA technology to prevent or cure human diseases now and in future with much more effectivity and lesser side effects.*

***Professor (Dr) Anindya Dasgupta***

***Editor in Chief,***

***Journal of Applied Biochemistry and Lab Medicine.***