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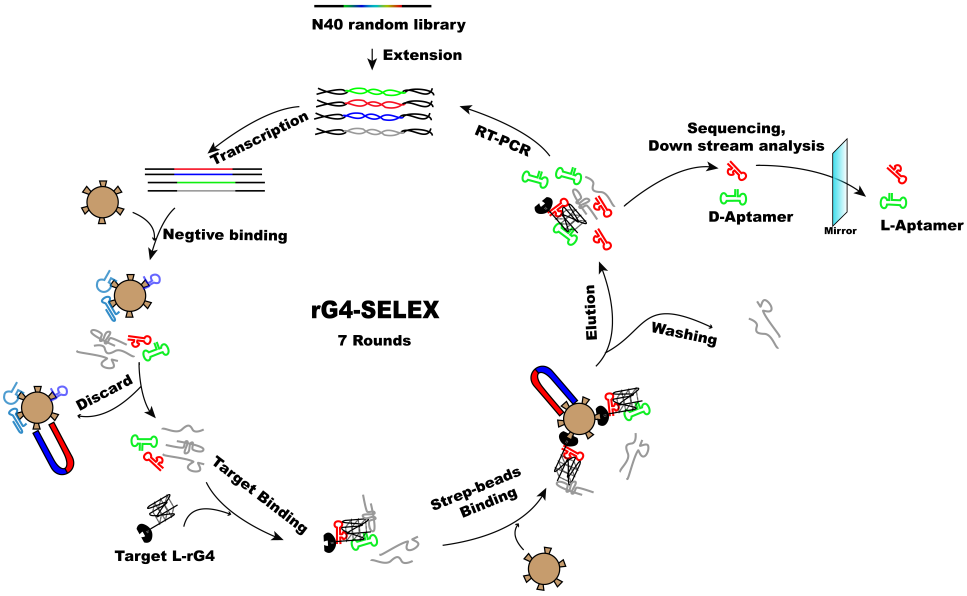
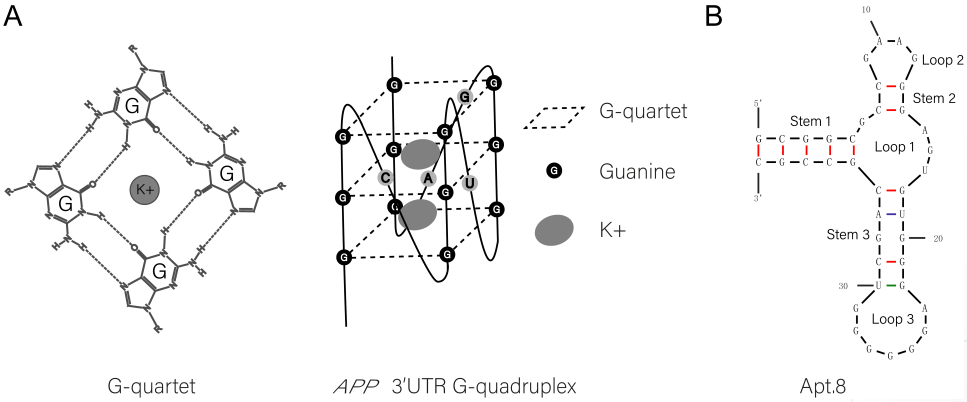
RNA G-quadruplex Targeting L-RNA Aptamer and Application Thereof

Health & Wellness

Biomedical and Genetic Engineering



Schematic flowchart of rG4-SELEX



Structure of G-quartet, APP 3'UTR G-quadruplex, and Apt.8 aptamer

IP Status
Patent filed

Technology Readiness Level (TRL) 5

Inventor(s)

Prof. KWOK Chun Kit

Enquiry: kto@cityu.edu.hk

Opportunity

Amyloid precursor protein (APP) is an Alzheimer's disease related gene, which can produce amyloid β (Aβ) peptides and with the accumulation at last leading to Alzheimer's disease. Controlling APP and Aβ level can control the development of disease. The earlier research indicated that RNA G-quadruplex (rG4), one non-canonical RNA secondary structure motif, can regulate the expression of APP. Therefore, rG4 is considered as good target for the regulation of APP and further diseases. However, traditional approaches available to target rG4 such as small molecules, peptides, proteins are with limitation on the specificity, side immune response and drug administration. Earlier study has shown L-RNA aptamer (single-

stranded DNA or RNA) can be evolved to target rG4 structure tightly and specifically. Therefore, an efficient rG4 binding L-aptamer is with great potential to be developed to target APP/ Aβ for potential disease therapy.

Technology

The invention developed an APP rG4 binding L-aptamer, Apt.8, to specifically and strongly target APP rG4 by using rG4 systematic evolution of ligands by exponential enrichment (rG4-SELEX). To get a smaller aptamer, the aptamer has been minimized and the redundant part has been removed resulting in the final aptamer Apt.8f with strong binding affinity in sub-nanomolar. The processed Apt.8f was proved containing a thermostable and parallel G4 motif through structural analysis. Binding assays showed that it only bounds APP rG4 while not other rG4s, DNA G-quadruplexes (dG4s) and non-G4s (DNA and RNA hairpin, poly rA, poly rU and poly rC), suggesting its specific binding and the binding was enantiomeric-, magnesium ion-, and potassium ion-dependent. L-Apt.8f was applied to control reporter gene expression by targeting natural APP rG4 motif for the first time. Taken together, a promising tool L-aptamer has been developed to target APP rG4 and control its gene expression.

Advantages

- The developed L-aptamer, Apt8, is with great binding specificity and tightness to APP rG4.
- The developed L-aptamer, Apt8, will not activate immune response.
- The developed L-aptamer, Apt8, is resistant to nucleases degradation, making it potentially suitable for drug administration.

Applications

- This invention provides a new and important platform for evolving and selecting L-RNA aptamer for targeting specific transcript that contains RNA G-quadruplex in vitro and in cells.
- The method used to develop and produce Apt.8 could be further applied to other L-aptamers development.
- The developed L-RNA aptamer, like L-Apt.8f, could be used for controlling gene expression.
- The L-RNA aptamer such as L-Apt.8f could be applied to regulate APP translation and potentially disease therapy.