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Development of Cyclized L-RNA Aptamer and Application Thereof

Health & Wellness

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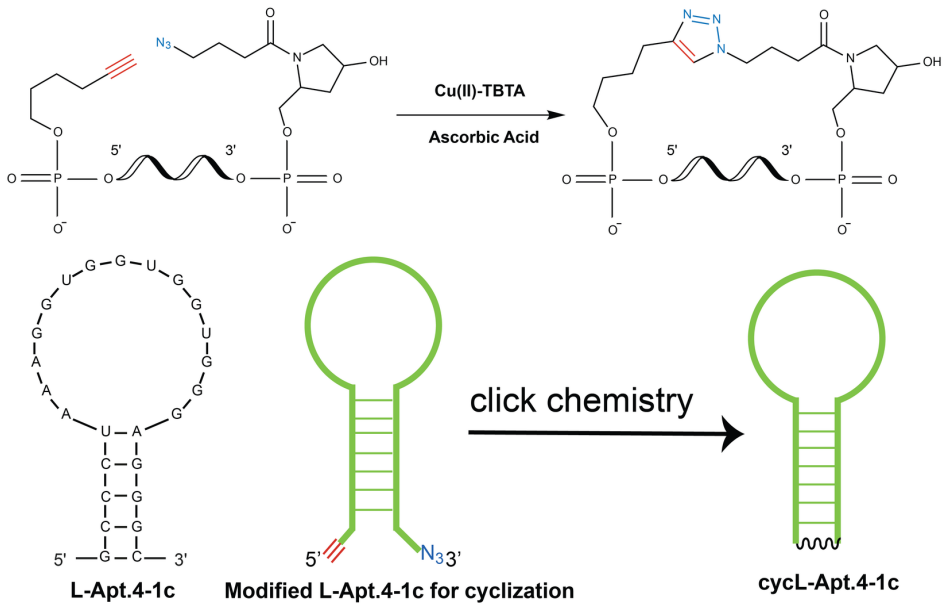

Figure 1: A general strategy for L-RNA aptamer cyclization.

IP Status
Patent filed

Technology Readiness Level (TRL) ? 5

Inventor(s)
Prof. KWOK Chun Kit
Dr. JI Danyang
Enquiry: kto@cityu.edu.hk

Opportunity

Over the past few decades, antibodies have been the most popular products for molecular recognition of bio-targets. They are used across broad domains, including life and health sciences, as well as in clinical settings. The estimated market for antibodies was roughly 85 billion USD in 2015 and is expected to grow to 140 billion USD in 2024.

Given the widespread use of antibodies, there is an opportunity to develop more efficient alternatives. Aptamer, an emerging tool, can also tap into the same domains as antibodies but as a better alternative. Compared with antibodies, aptamer can typically be generated in weeks instead of months, and can be stored and applied in a broader range of conditions. L-RNA aptamer (Spigelmer), one of the most advanced and promising technologies to generate nuclease-resistant aptamer, is expected to quickly penetrate into the existing antibody and aptamer market. Thus, the opportunity exists to provide a universal, simple, and robust strategy for L-RNA oligos cyclization.

Technology

This invention provides a universal, easy-to-operate method of cyclizing L-RNA oligos with mild reaction conditions and high efficiency. This click chemistry, reaction-based method synthesizes L-RNA oligos to functionalize with a 3'-azido residue and a 5'-hexynyl residue, which can simply introduce a

5' terminal alkyne group. The 5'-alkyne and 3'-azide of L-RNA are ligated through intramolecular copper(I)-catalyzed azide-alkyne cycloaddition with high efficiency. This method can be applied to functional L-RNA oligos, like L-RNA aptamer, for further application.

The inventors successfully demonstrated this strategy by cyclizing L-Apt.4-1c, an L-RNA aptamer for human telomerase RNA component G-quadruplex (hTERC rG4). The cyclized L-Apt.4-1c (cycL-Apt.4-1c) keeps the core structure intact for target binding and exhibits stronger binding affinity and higher conformation stability. The improved properties of cycL-Apt.4-1c allow it to effectively interfere with hTERC rG4-protein binding interactions and inhibit telomerase activity. This invention demonstrates that the head-to-tail cyclization can be an effective way to strengthen the function of L-RNA aptamer, which enables its applications in buffer or complex biological conditions.

Advantages

- This method does not require any enzymes or template DNA/RNA oligos. It is more cost-effective and simpler compared to traditional ligase-based methods.
- The cyclized L-RNA product (cycL-Apt.4-1c in this invention) shows 10-times stronger binding affinity to hTERC rG4 than the linear form (L-Apt.4-1c) and higher conformation stability. CycL-Ap4-1c also inhibits telomerase activity and has much greater ability to inhibit hTERC rG4-protein binding.
- Typically, aptamers can be generated in weeks, compared with months for antibodies.
- Aptamers can be stored and applied in a broader range of conditions compared with antibodies.

Applications

- Aptamers can be used in the same broad domains as antibodies, including life and health sciences, as well as in clinical settings.
- Potential markets include the aptamer and oligonucleotide synthesis market; the diagnostic and therapeutics market that currently uses antibody-based approaches; and the L-RNA structure analysis (e.g., crystallographic studies, NMR spectroscopy) market.
- This invention will not only be applicable to aptamer studies, but also potentially to other functional L-RNAs, especially L-RNA hairpins, which easily unfold when conditions change.
- This invention can be used to cyclize L-RNAs for function optimization, such as cyclized L-RNA aptamers.
- CycL-Apt.4-1c can be applied to interfere with hTERC rG4-protein binding; inhibit telomerase activity; and detect, image, or pull down hTERC rG4.