Docket #: S18-350

GENERATION AND SCREENING OF NON-NATURAL APTAMER LIBRARIES

Researchers at Stanford, supported in part by the Chan Zuckerberg Biohub, have developed an integrated system for the automated generation, screening, and characterization of base-modified aptamers.

High affinity binding reagents have revolutionized biology and medicine. One class of synthetic affinity reagents, called aptamers, are DNA or RNA oligonucleotides typically composed of naturally occurring nucleotides. The performance of "natural" aptamers can be improved through site specific incorporation of chemically modified, non-natural nucleotides. So-called non-natural aptamers greatly improve the binding repertoire and utility of these affinity reagents. However, previous methods to characterize non-natural aptamers (e.g., binding affinity and/or specificity) are inefficient and burdensome.

Stage of Research

The inventors have developed an integrated "non-natural aptamer array" (N2A2) system to generate and characterize binding of base-modified aptamers. The inventors have modified a benchtop high-throughput DNA sequencing instrument to directly synthesize clusters of unique sequence-defined aptamers, generate base-modified nucleotides with desired functional groups through click conjugation, and perform target binding assays in situ. Available custom software directly links an aptamer's sequence and binding characteristics for use in downstream machine learning applications to generate aptamer libraries predicted to have desired binding properties for the target molecule.

Stage of Development

Research - *in vitro*

Applications

- Integrated and automated workflow for the parallel screening of unique base-modified aptamer candidates in terms of both affinity and specificity.

Advantages

- Create stable affinity reagents for molecules for which the generation of monoclonal antibodies remains difficult, such as small-molecule drugs, metabolites and carbohydrates.
- Easily screen a variety of different functional group modifications to identify the best chemical modification for optimal target binding.
- Assess target specificity with negative screening.
- Identify high-affinity aptamers with a machine learning model by exploring sequence space that is currently inaccessible to traditional in vitro methods.

Publications

- Wu D, Feagin T, Mage P, Rangel A, Wan L, Li A, Coller J, Eisenstein M, Pitteri S, Soh HT. Automated platform for high-throughput screening of base-modified aptamers for affinity and specificity. bioRxiv (2020).

Patents

- Published Application: WO2019236548
- Published Application: 20210324374

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