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Sensors for high-throughput screening of RNA-modulating drugs

Stanford researchers have developed a method for screening RNA-modulating drugs that reports on changes to mRNA in its native cellular context.

80-90% of protein targets are thought to be undruggable by conventional approaches. Drugging mRNA therefore has the potential to vastly expand the scope of targets accessible to small molecules by modulating mRNA splicing or half-life. However, strategies to screen for mRNA-modulating drugs are lacking: small molecule-mRNA binding assays poorly predict functional changes to mRNA, while the development of reporter cell lines generally require editing or overexpression of the gene of interest and therefore may not reflect changes to mRNA in its native context.

To address this, Stanford researchers have developed modular mRNA sensors that can detect drug-induced changes to mRNA in its native cellular context. These sensors are trivial to design (relying on simple base-paring principles), can detect any arbitrary mRNA sequence, and are completely modular (facilitating the use of any reporter protein, including fluorescent and luminescent reporters). Researchers have demonstrated that these sensors can detect gene knockdown, as well as the inclusion or exclusion of specific exons. Sensors can be transiently transfected or integrated into reporter cell lines for high-throughput phenotypic screens of RNA-modulating drugs.

Stage of research
In vitro: development of sensors that can report on gene knockdown or upregulation; exon inclusion (i.e., exon 7 inclusion in SMN2 towards treatments for spinal muscular atrophy); exon exclusion (i.e., exon 20N exclusion towards treatments for Dravet syndrome)

Applications

- High-throughput screening for small molecules that act on RNA
- Evaluating other modalities that modulate mRNA, including ASOs, siRNAs, and gene editors

Advantages

- Easy-to-design for a specific RNA of interest
- Can detect specific exon inclusion and exclusion events
- Can use an arbitrary output signal, including fluorescent or luminescent reporters
- Report on functional changes to mRNA, not just small molecule binding
- Can report on changes to any RNAs, including mRNA and non-coding RNAs

Publications

- Kaseniit, K.E., Katz, N., Kolber, N.S. et al. Modular, programmable RNA sensing using ADAR editing in living cells. *Nat Biotechnol* 41, 482–487 (2023).

Patents

- Published Application: WO2024249530
- Published Application: 20260317811

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