



# Promotion of RNA-targeted small molecule drug discovery

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## Abstract

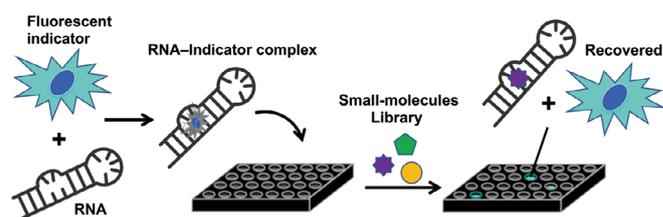
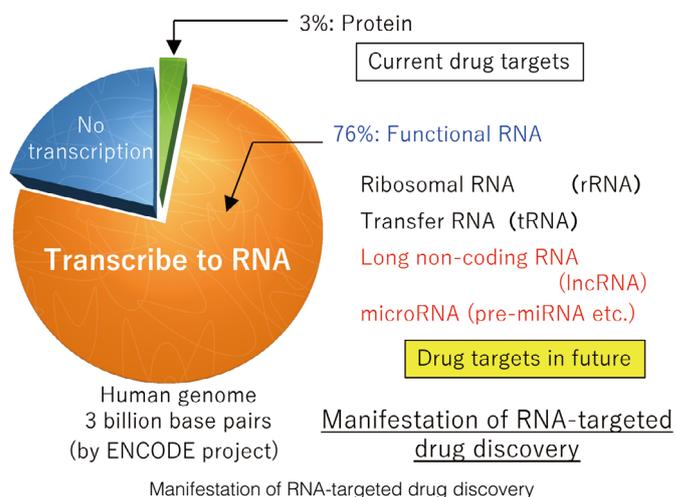
In recent years, drug discovery research targeting RNA has accelerated. A small molecule drug Evrysdi™ (lisdipram) was approved by the U.S. FDA and in Japan as the first oral drug to improve and maintain motor function and survival in patients with Spinal Muscular Atrophy (SMA). The function of the drug is to improve pre-mRNA splicing of the Survival Motor Neuron 2 (SMN2) gene. The ENCODE project, which has been studied after completion of the human genome, has shown that most of the human genome is involved in sustaining our lives as non-coding RNAs. The development of drug discovery research targeting non-coding RNAs, in addition to that targeting mRNA shown in Evrysdi™, will enable the regulation of the expression and function of a wide variety of functional RNAs in the cell, and will lead to therapeutic strategies that are different from the conventional regulation of protein expression and function. In this study, we developed an RNA-binding fluorescent dye, ANP77, for use in the fluorescent dye displacement assay, one of the screening methods for small molecule compounds that bind to RNA, and selected RNA motifs that could be used in the assay.

## Background & Results

Pharmaceutical companies have accumulated know-how in small molecule drug discovery and a diverse library of organic small molecule compounds, but it has been said that the conventional drug discovery targeting proteins with small molecules has reached its limits. Screening of compounds that bind to target RNA is essential for small molecule drug discovery. In the Fluorescent Indicator Displacement assay (FID assay), a fluorescent dye is pre-bound to RNA, and the binding of the compound to RNA is evaluated by the amount of change in fluorescence when a library compound is added. The newly developed ANP77 is a molecule that binds with high affinity to the C/CC inner loop in RNA, and its fluorescence is quenched when it binds to RNA. When library compounds displace ANP77, the fluorescence of the free ANP77 is used to determine which compound has bound to the RNA.

## Significance of the research and Future perspective

The use of non-coding RNA as a drug target in addition to mRNA will enable drug discovery not only for conventional protein-targeted drug discovery, but also for drug discovery in cases where the target protein does not exist.



Screening of RNA-binding small molecules using fluorescent indicator displacement assay

### Patent

### Treatise

### URL

### Keyword

Das, Bimolendu; Murata, Asako; Nakatani, Kazuhiko. A small-molecule fluorescence probe ANP77 for sensing RNA internal loop of C, U, and A/CC motifs and their binding molecules. *Nucleic Acids Res.* 2021,49, 8462-8470. doi: 10.1093/nar/gkab650<https://www.sanken.osaka-u.ac.jp/labs/rbc/index.html>

RNA, small molecules, drug development, drug screening