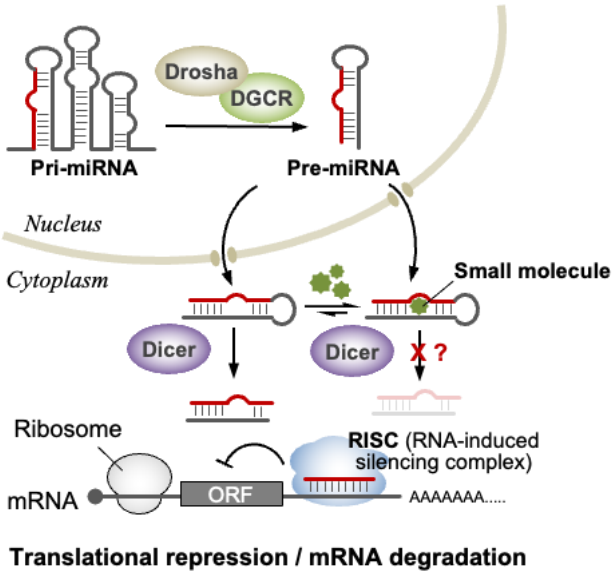
Our Research (Asako Murata, Ph.D.)

Regulation of RNA function by small molecules

RNA is more than just a messenger carrying genetic information for making proteins. The ENCODE (Encyclopedia Of DNA Element) project revealed that about 76% of the human genome is transcribed to RNA but is not translated to protein. Among these non-protein-coding RNAs (ncRNAs), some classes (miRNA, lncRNA, snRNA, snoRNA, circRNA, etc.) have particular functions and play important roles in biological processes.

In response to the increasing interest in the ncRNA-related topics, small molecules targeting ncRNAs have attracted considerable attention from researchers in various research fields, including chemistry, chemical biology, biotechnology, and medicine. I have been exploring and developing small molecules targeting RNAs.

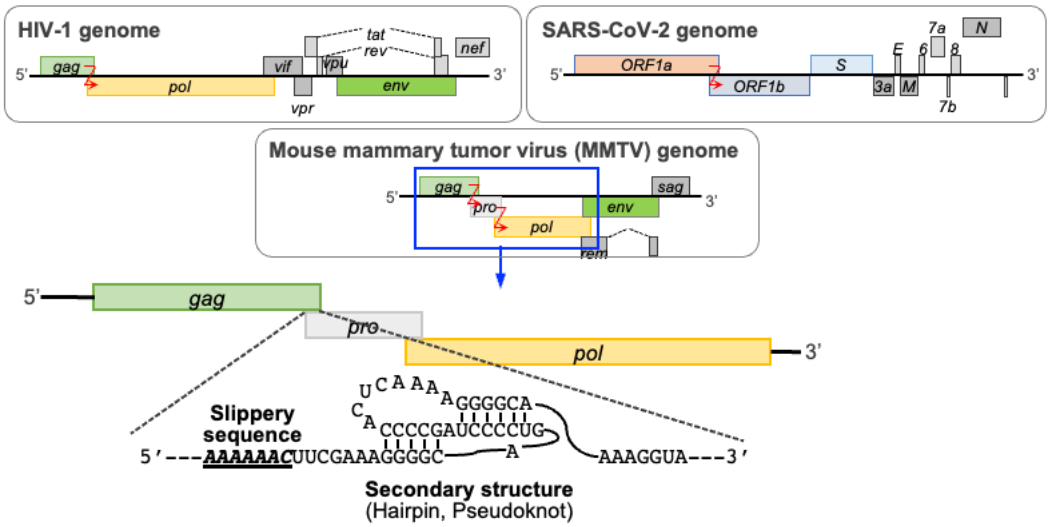
Topic 1: Targeting miRNA biogenesis by small molecules



Translational repression / mRNA degradation

MicroRNAs (miRNAs) are involved in many biological processes including development, differentiation and carcinogenesis through translational repression by binding to their target mRNA. miRNAs are produced from their precursor called pre-miRNA by cleavage of the enzyme Dicer. A small molecule that can modulate this miRNA biogenesis will provide the biological tool for elucidating mechanisms of miRNA-mediated gene regulation and can be the drug lead for miRNA-associated diseases. Our group aims to develop small molecules that can recognize the secondary structures in a pre-miRNA and modulate the Dicer-mediated processing of the pre-miRNA.

Topic 2: Small-molecule modulators of programmed –1 ribosomal frameshifting



Many RNA viruses, including SARS-CoV-2 (the causative virus of COVID-19), use a translational recoding mechanism called programmed –1 frameshifting (–1 PRF) to produce two proteins from a single transcript at a fixed stoichiometric ratio. –1 PRF is typically triggered by two *cis*-acting signals of mRNA signals, a slippery sequence and a downstream secondary structure. The secondary structure formed in the mRNA impedes the movement of the ribosome and stalls the ribosome on the slippery sequence, which stimulates a backward shift by one nucleotide. The ribosome resumes translation by unfolding the secondary structure. Since –1 PRF mechanism is essential for viral replication, modulating –1 PRF efficiency can be a potential anti-viral strategy. Our group has been exploring and developing small-molecule tools to alter –1 PRF efficiency.

Topic 3: Development of a method for comprehensively analyzing small molecule-RNA pairs

Small molecules targeting functional RNAs have attracted much attention from academics and pharmaceutical companies as they are orally availavle and amenable to chemical modifications. However, there are issues in the development of small molecules that can specifically target a druggable RNA: there is not enough number of known small molecules for target RNAs of interest and therefore there exists only a few design strategies for small molecules harboring desired binding and functional properties required for targeting RNAs.

To solve these issues, we are trying to develop a facile and efficient method to analyze the inter action of a given small molecule with various RNA sequences. With a large data set of RNA-sm all molecule interactions that will be obtained by applying the method to various small molecule s, data mining of small molecules will be carried out to obtain the chemical structures of small m olecules important for binding to the target RNAs. (URL: https://projectdb.jst.go.jp/grant/JST-PROJECT-20352888/)

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