# Stony Brook University
# The Graduate School

Doctoral Defense Announcement

## Abstract

"Development of modified microRNAs as cancer therapeutics"

**John Yuen**

MicroRNAs (miRNAs) are pleiotropic post-transcriptional modulators of gene expression whose dysregulation has been increasingly highlighted in a variety of diseases, including cancer. Each miRNA can bind and regulate multiple target genes. Their inherently pleiotropic nature make them strong candidates for the development of cancer therapeutics, as it may be difficult for cancer cells to develop resistance compared to targeted therapies.

We developed a novel approach to modify miRNAs by replacing the uracil bases with 5-fluorouracil (5-FU) in the guide strand of tumor suppressor miRNAs, thereby combining the therapeutic effect of 5-FU with tumor suppressive effect of miRNAs to create a multi-targeted therapeutic molecule. We hypothesized that this modification strategy does not alter its native RNA interference (RNAi) function and that there will be an increased efficacy at killing cancer cells compared to its unmodified counterparts. To test our hypotheses and to demonstrate the general applicability of this approach to other tumor suppressive miRNAs, we screened a panel of 12 novel miRNA mimetics in several cancer types including leukemia, breast, gastric, lung, and pancreatic cancer. Our results show that the miRNA activity is preserved and that 5-FU-modified miRNAs have increased potency in inhibiting cancer cell growth and that these mimetics can be delivered into cancer cells without delivery vehicle both *in vitro* and *in vivo*. This work demonstrates the potential of nucleic acid modifications that can be broadly applicable and may serve as a platform technology for future miRNA and nucleic acid-based therapeutics.

To further refine this modified-miRNA approach, we focused on miRNA modifications with other chemotherapeutic drugs that may be more tailored to a specific cancer type. We focused on miR-15a and replaced the cytidine bases with gemcitabine (GEM) and evaluated its ability to treat pancreatic cancer. Our results show that GEM-modified miR-15a has a similar preservation of miRNA activity and has an increased potency compared to the 5-FU-modified miR-15a. Overall, this work expands our understanding of the therapeutic potential of miRNAs and different miRNA modification approaches that can be improved and optimized to create cancer therapeutics.

**Date**: April 26, 2023 **Program**: Genetics
**Time**: 1:00 PM **Dissertation Advisor**: Jingfang Ju
**Place**: Basic Sciences Tower Level 8 Room 180