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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		Improving delivery of RNA therapeutics
Name		Dr Ken Pang
Award Received		2019 RACP Fellows Career Development Fellowship
Report Date		September 2020
Administering Institution		Murdoch Children's Research Institute
Funding Period	Start Date:	January 2019
	Finish Date:	December 2019

PROJECT SUMMARY

RNA interference (RNAi) is a fundamental biological process by which gene activity is regulated. Since its discovery twenty years ago, substantial efforts have been made to develop RNAi-based therapeutics for human disease. However, despite numerous clinical trials across a wide range of diseases, including diabetes, hypercholesterolemia, hepatitis, melanoma and ovarian cancer, only a single RNAi therapeutic has been approved for clinical use. This lack of success is due to a common problem: namely, ineffective delivery of RNAi therapeutics into cells.

My team previously discovered that a little-studied protein, known as SIDT2, recognises and transports viral RNAs into cells (and is critical for the body's ability to mount a robust defence against different viruses).

Our recent data indicate that SIDT2 can recognise RNAi therapeutics as well. This led us to hypothesise that optimising SIDT2's natural RNA transport activity may be important in achieving more effective RNAi therapeutic delivery into cells.

With the support of the RACP, we have now determined that recognition of RNAi therapeutics by SIDT2 is impaired by the use of specific chemical modifications that are commonly used in clinical trials to improve the stability of these drugs.

These findings therefore suggest that more judicious selection of chemical modifications is required if SIDT2's natural RNA transport activity is to enable more effective delivery of RNAi therapeutics.

PROJECT AIMS / OBJECTIVES

The aim of this study was to determine which chemical modifications commonly used in RNAi therapeutic drug design are permissive for SIDT2-mediated transport.

To address this aim, we used a unique range of molecular, cellular and microscopy-based tools to characterise the interaction between SIDT2 and various RNAi therapeutics, each of which incorporated a different set of chemical modifications.

SIGNIFICANCE AND OUTCOMES

As a naturally-occurring RNA transporter capable of efficiently bringing RNA into cells, SIDT2 offers a potential solution to the long-standing challenge of how to effectively deliver RNAi therapeutics into cells. Our discovery that chemical modifications commonly used in clinical trials to improve the stability of these drugs abolish the ability of SIDT2 to recognise RNAi therapeutics suggests that the use of such modifications must be re-considered.

Looking ahead, more judicious design of RNAi therapeutics is required if they are to reach their full clinical potential. Specifically, it will be important to take into consideration the impact of chemical modifications on SIDT2 recognition and transport if SIDT2's natural RNA transport activity is to be exploited to more effectively deliver RNAi therapeutics.

PUBLICATIONS / PRESENTATIONS

Our initial findings have recently been published:

Smith, B.R.S., Nguyen TA, Pang KC. (2020) Bulky chemical modifications of siRNAs impair interaction with the SIDT2 endosomal RNA transporter. Science Matters. Accepted May, 2020.

ACKNOWLEDGEMENTS

The RACP was duly acknowledged in the above publication.