Abstract: P96

Supramolecular hydrogel for local cardiac delivery of antimiR therapeutics

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Background/Introduction?
In an average myocardial infarction, approximately 1 billion cardiomyocytes are lost. As adult cardiomyocytes are post-mitotic cells, these cardiomyocytes will not be regenerated but instead be replaced by a fibrotic scar. Furthermore, the loss of contractility will cause adverse cardiac remodeling and puts the patient at risk of developing heart failure later in life.

MicroRNAs (miRs) are short RNAs (±22 nucleotides), that inhibit protein synthesis by binding to their target mRNAs. The miR-15 family (miRs 15a/b, 16, 195 & 497) targets cell cycle genes. Upregulation of the miR-15 family has been implicated in the loss of proliferative capacity of cardiomyocytes during the early postnatal period and the miR-15 family is further upregulated after myocardial infarction. Therapeutic inhibition of the miR-15 family using synthetic miR inhibitors (antimiRs) has shown promise for inducing cardiac regeneration. However, the delivery of these antimiRs is still a challenge as systemic delivery causes the majority of the injected compound to end up in the liver and kidneys.

Local delivery opportunities for antimiR therapeutics can increase the efficacy and decrease delivery to off-target organs.

Purpose
Here we aim to test whether we can improve cardiac delivery of antimiRs by using intramyocardial injections with a supramolecular hydrogel based on ureido-pyrimidinone units and poly(ethylene glycol) (UPy-PEG) as delivery vehicle to get local sustained release delivery, thereby increasing efficacy in the heart and protecting off-target organs.

Methods
To assess safety of UPy-PEG, healthy mice received intramyocardial injections of UPy-PEG and response was measured at multiple time points by echocardiography, histology and qPCR for stress marker expression. ELISA was used to assess spread of UPy-PEG to other tissues. To assess efficacy, mice were subjected to ischemia-reperfusion injury (IR) and subsequently received intramyocardial injections of PBS or UPy-PEG with antimiR-195, or either vehicle alone. Hearts were collected for RNA-isolation and histology 3 days after injection.

Results
Intramyocardial injections of UPy-PEG by itself did not significantly alter cardiac function, geometry or stress marker expression. RNA-sequencing showed that injection of antimiR-195 in UPy-PEG resulted in stronger target derepression than antimiR-195 in PBS, indicating enhanced efficacy of antimiR-195 when using the UPy-
PEG hydrogel.

Conclusion
UPy-PEG is a safe and effective vehicle to improve the local cardiac delivery of antimiR therapeutics.