Injectable thermosensitive hydrogel for cardiac delivery of therapeutics

Session: Long-Acting Drug Delivery Formulations I

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CONTROLLED RELEASE SOCIETY
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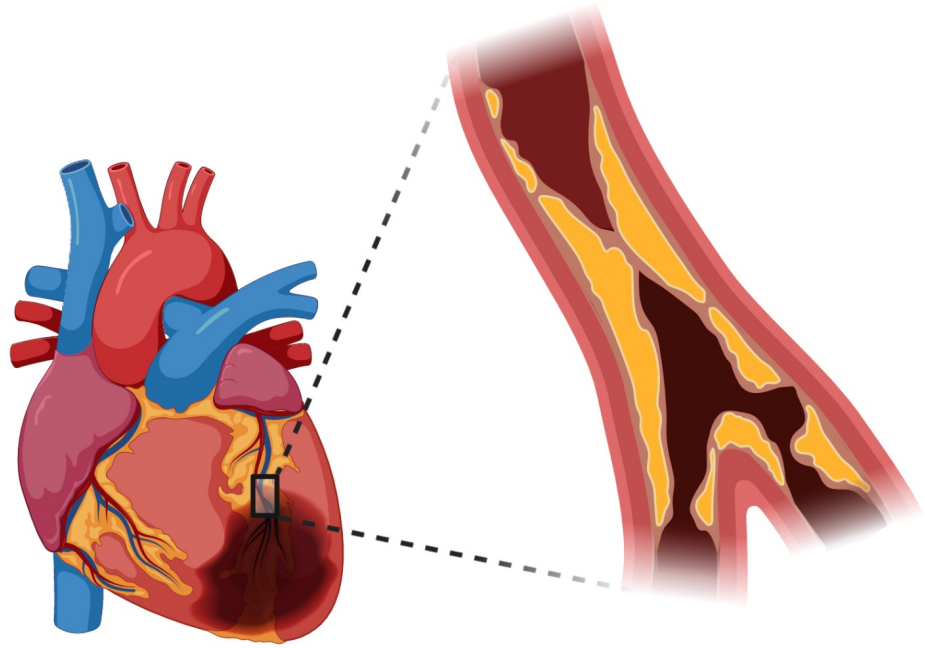
INTEGRATING
Delivery Science
ACROSS DISCIPLINES

World Health Organization

- Cardiovascular diseases are the leading cause of death globally (representing 32% of all global deaths)
- Of these deaths, 85% were due to heart attack and stroke



Myocardial infarction

Myocardial infarction occurs when blood flow decreases or stops to a part of the heart, causing damage to the heart muscle.

Conventional therapies

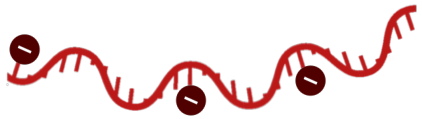
- Surgical intervention
- Pharmacological treatments (aspirin, thrombolytics, etc.)

Heart regeneration

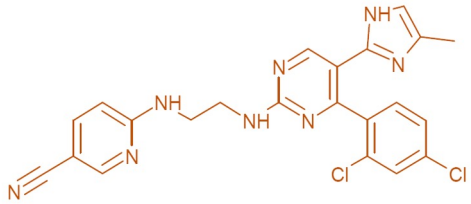
Cardiac regeneration

Many genes and pathways have been indicated to play essential roles during heart regeneration

- manipulation of these pathways using mRNAs



- small molecules such CHIR99201 (GSK3 inhibitor and Wnt agonist)

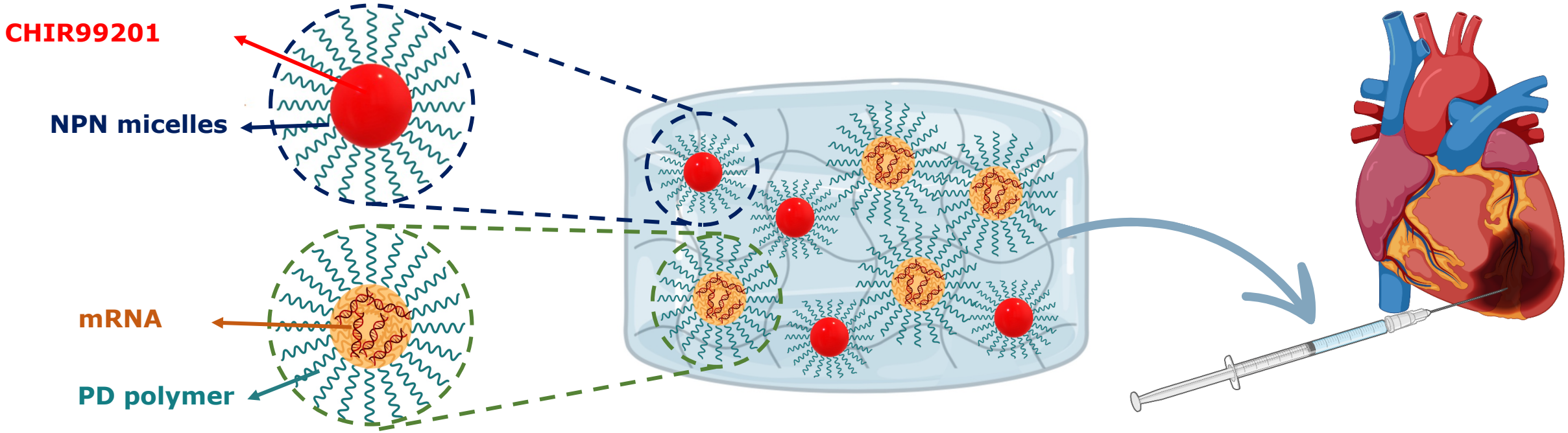


Damaged heart

Healthy heart

Aim of the project

Local treatment for myocardial infarction

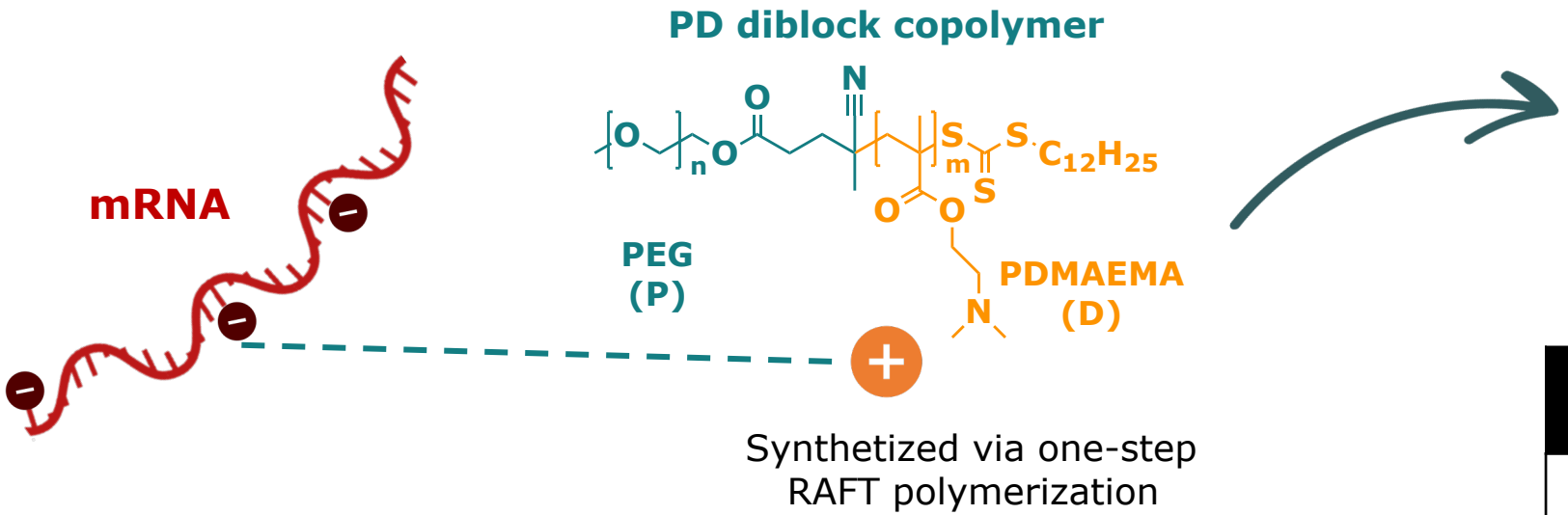


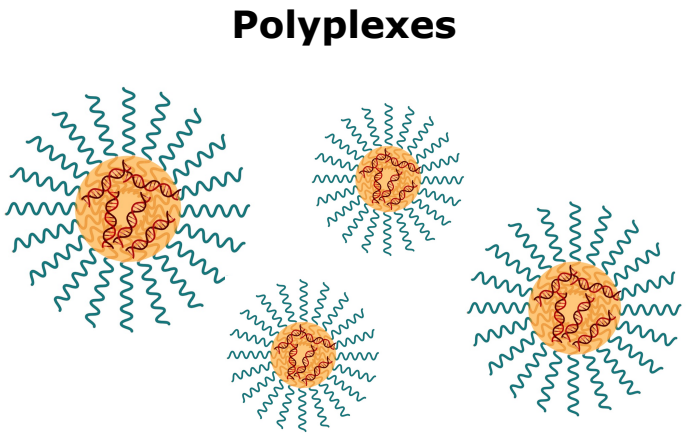
mRNA polyplexes and CHIR-loaded thermosensitive hydrogel

Challenges in mRNA delivery

Unfavorable mRNA physiochemical properties

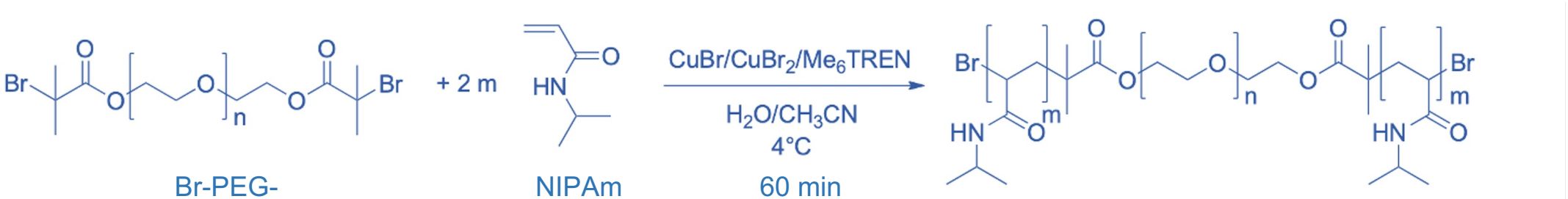
- High negatively charged density and high MW
- Poor cellular uptake
- Degradation by nucleases

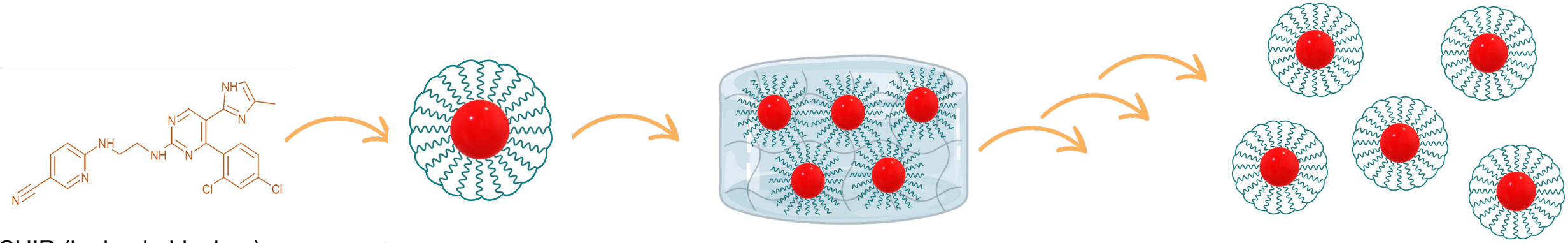




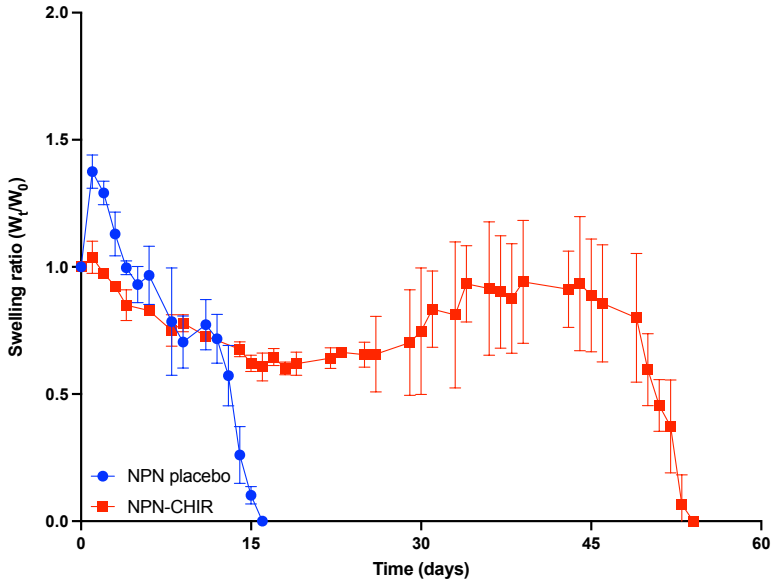
N/P ratio	Size (nm)	ζ-potential (mV)
5	125 ± 10	9.2 ± 0.4
10	146 ± 11	10.1 ± 0.3

NPN-CHIR system

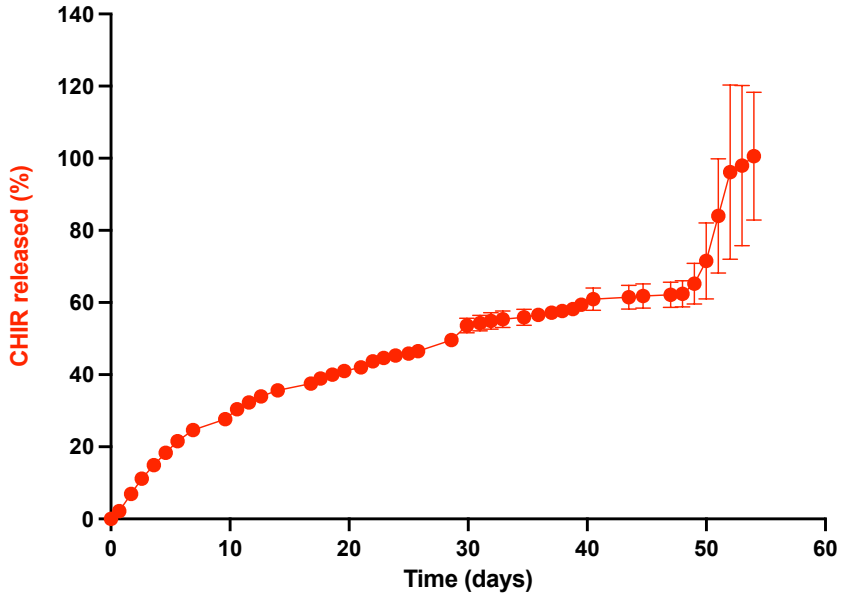


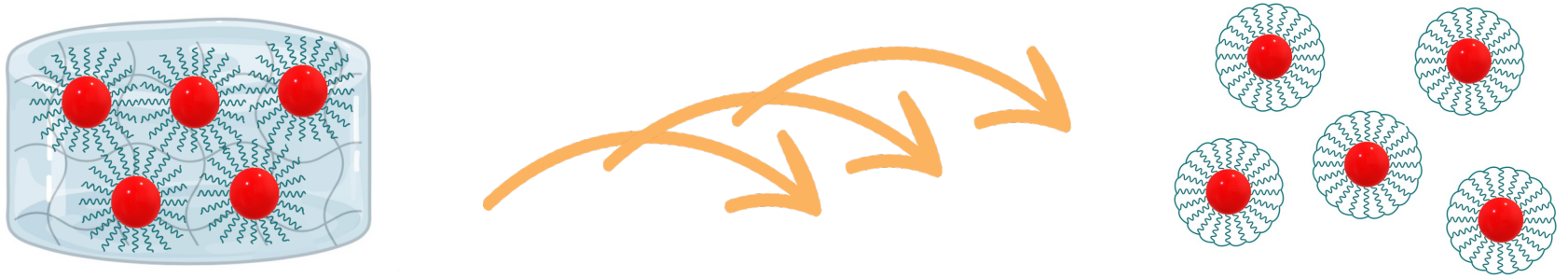


Hydrogel swelling and degradation

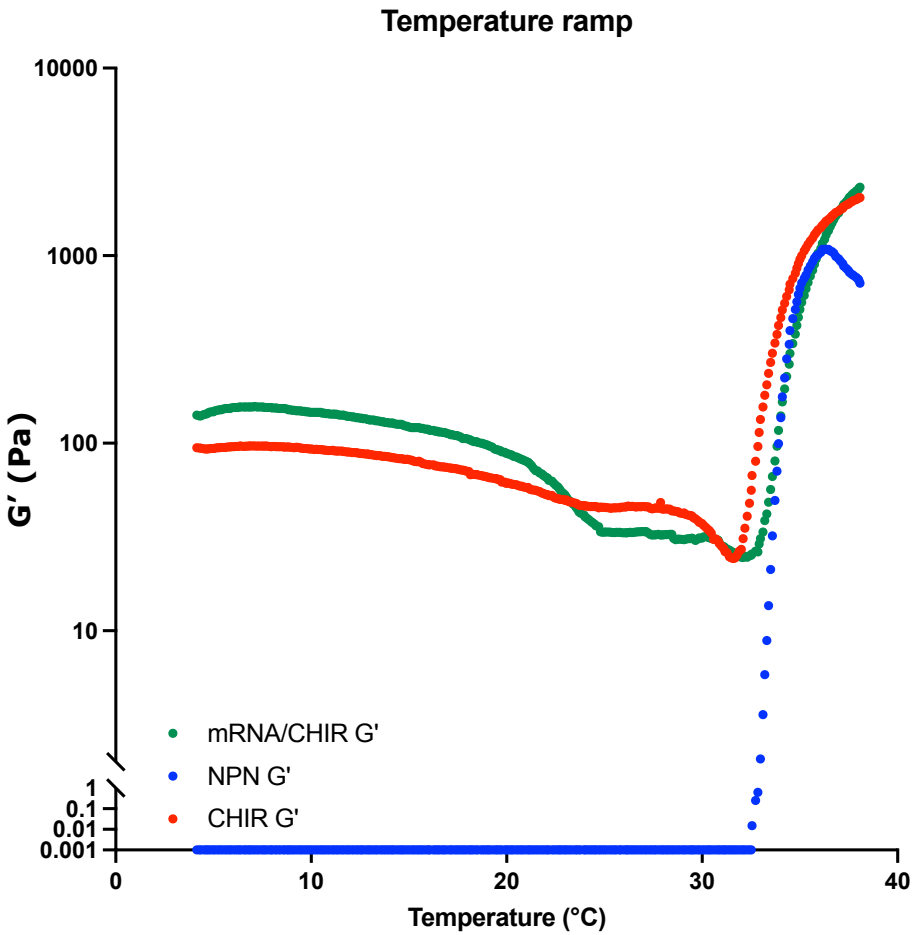


CHIR release

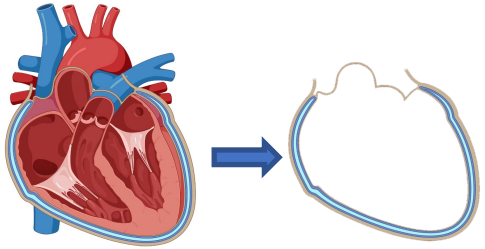




Rheological measurements

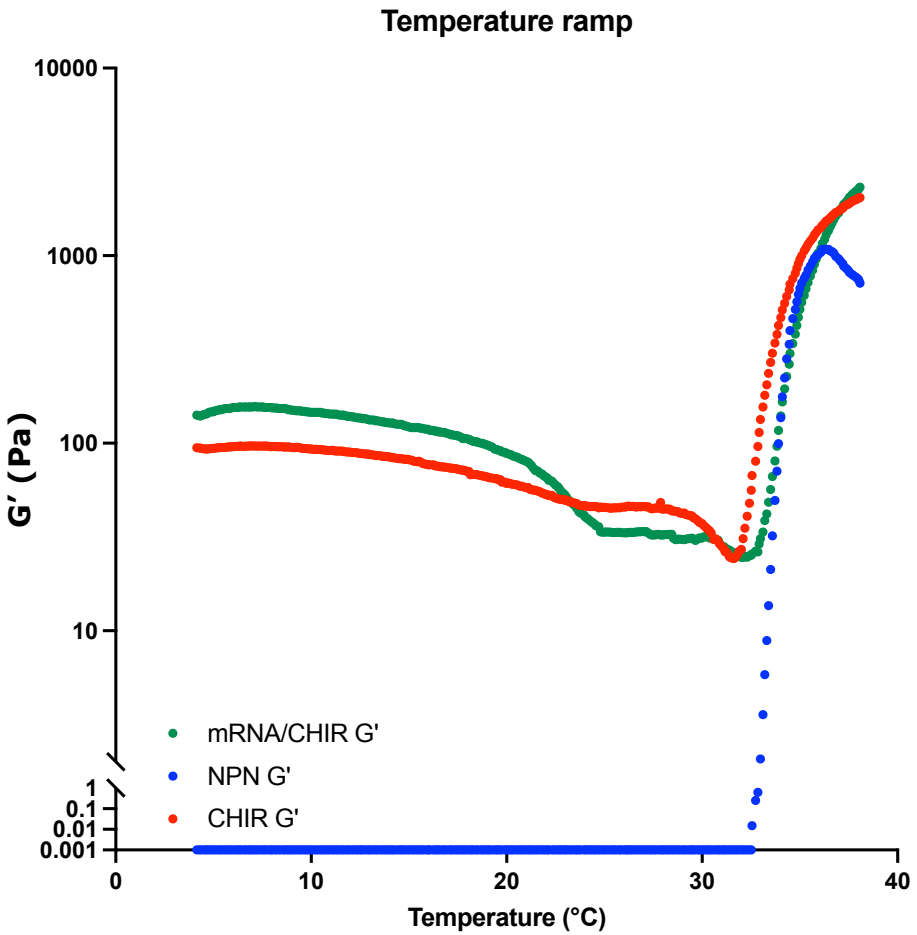


Injectability



Heart section Pericardial cavity

Rheological measurements



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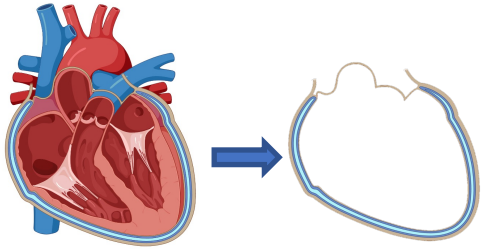
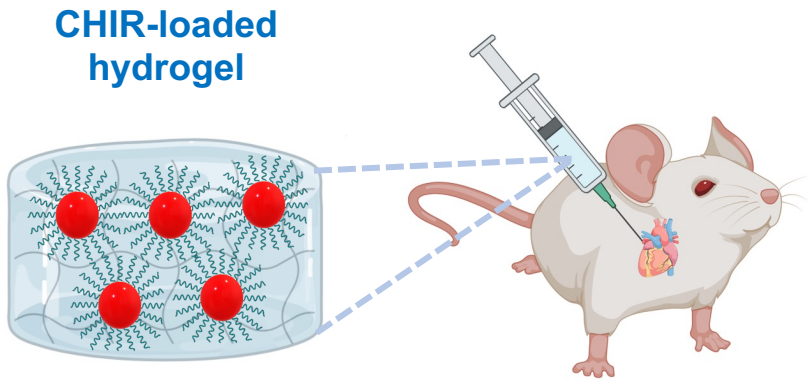
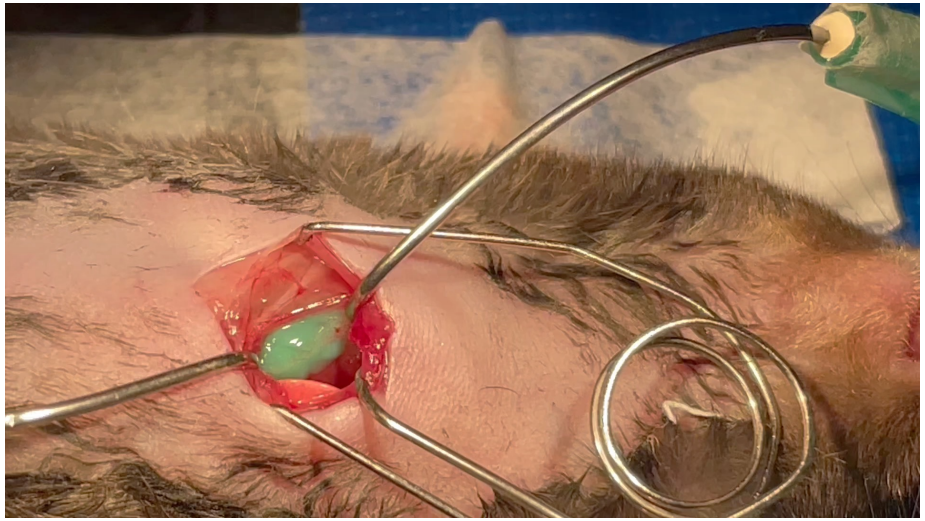
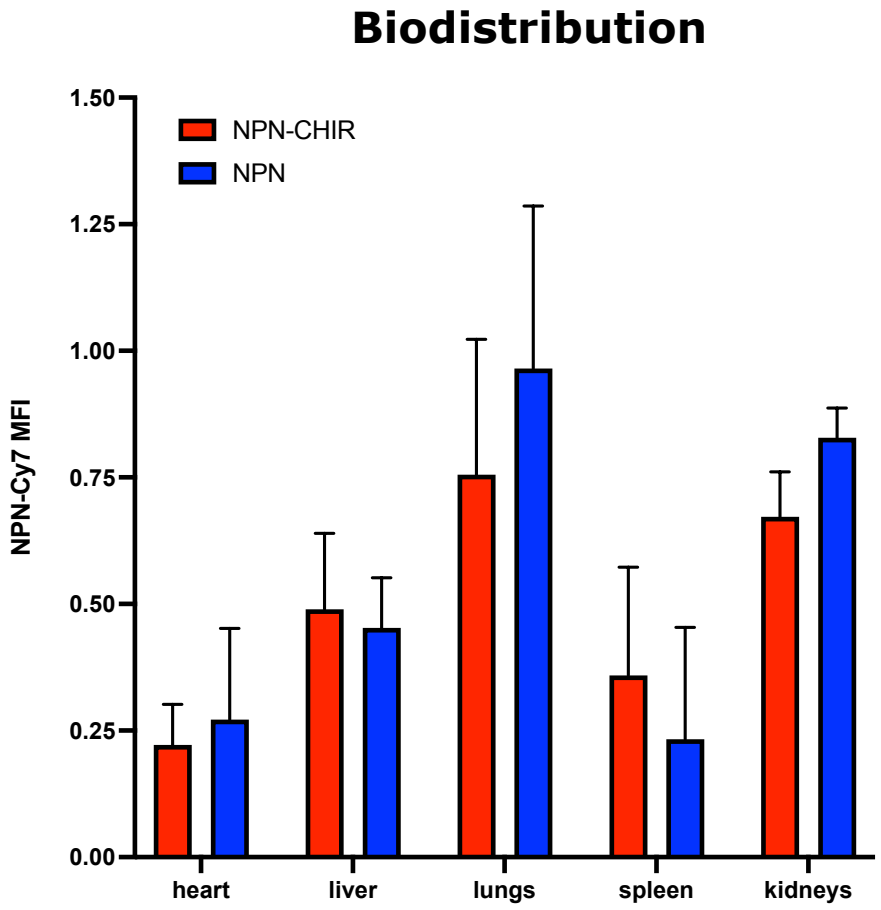


Heart section Pericardial cavity

In vivo pilot study - Pericardial cavity



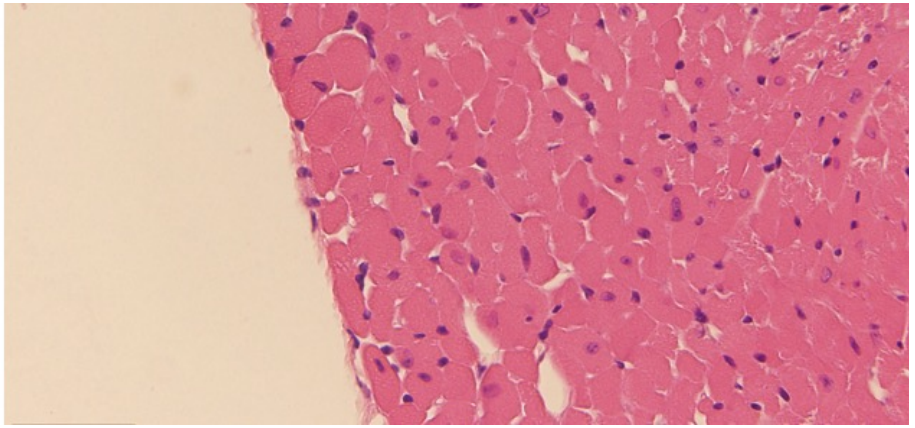


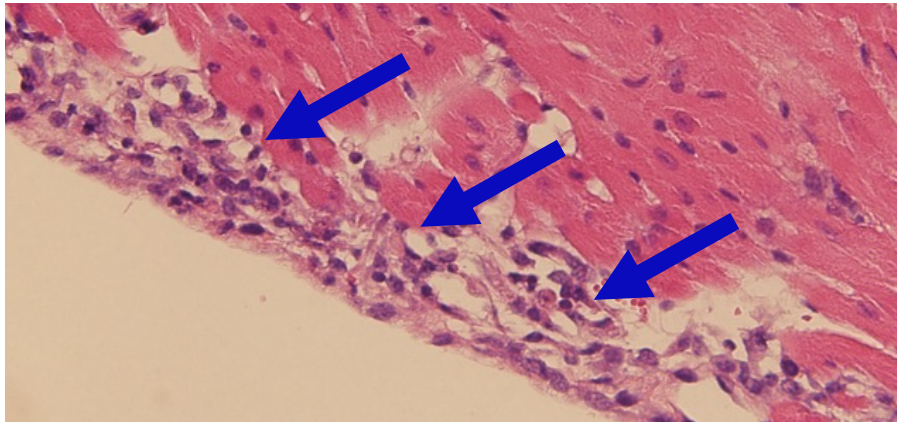


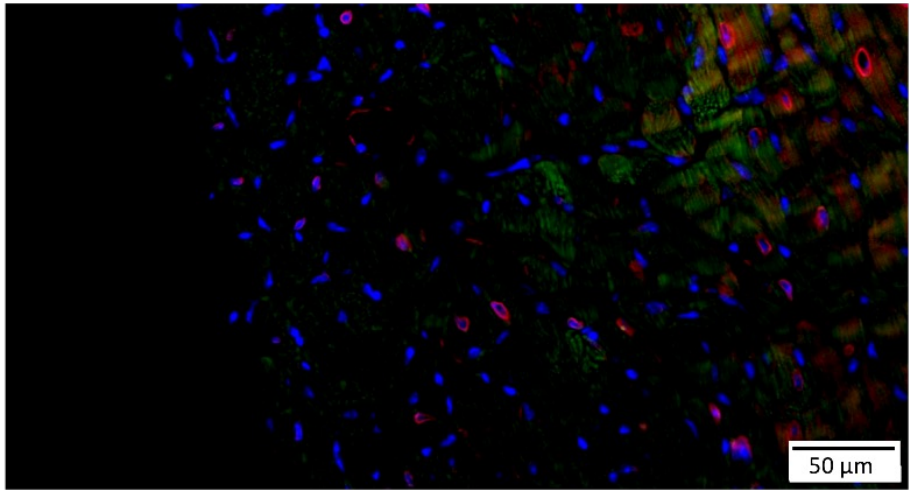
In vivo pilot study - Pericardial cavity

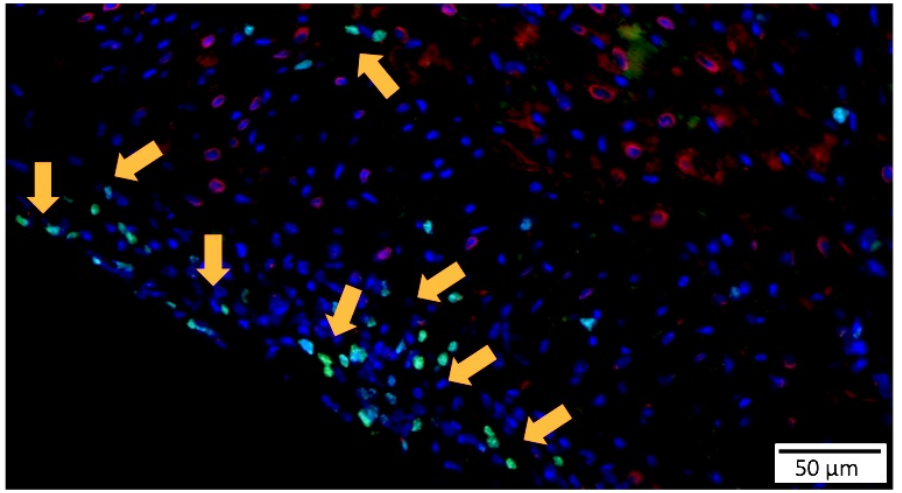
Mouse treated with placebo

Mouse treated with mRNA-CHIR hydrogel





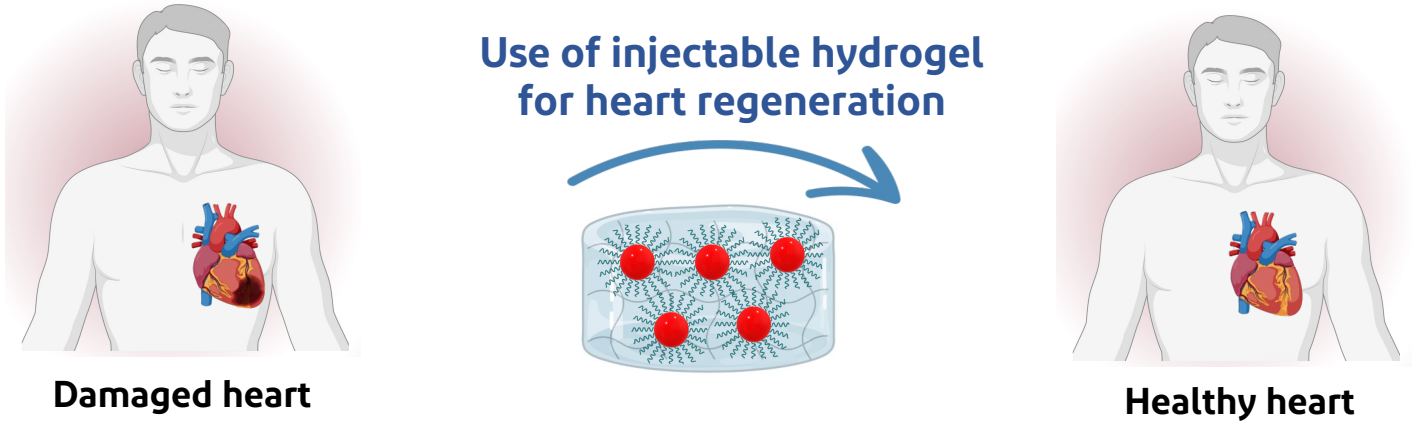




Findings

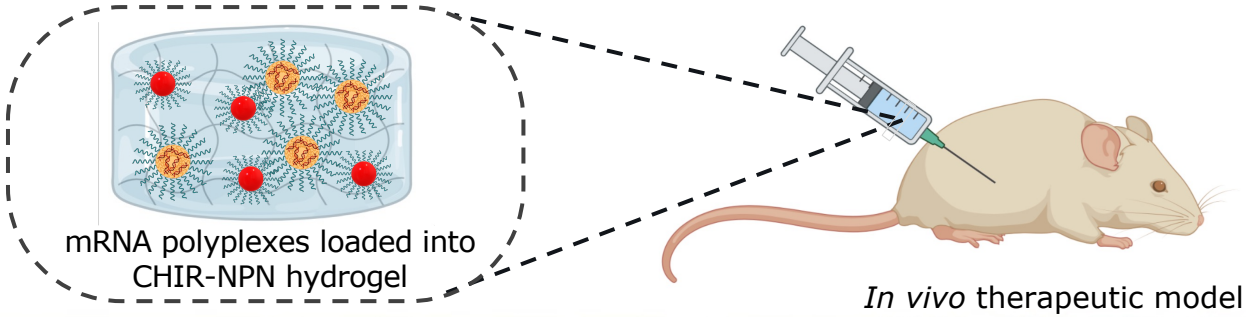
✓ NPN thermosensitive hydrogel is a potent candidate for cardiac delivery thanks to its erosion-dependent releasing characteristics and injectability

✓ Synergistic release of mRNA polyplexes and CHIR-NPN micelles offers a promising therapy for myocardial regeneration



Prospective

• *In vivo* dual delivery system as a tool for local treatment for myocardial infarction



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