Synthetic mRNA-Guided Cell Engineering to Modulate the Implant-Tissue Interface

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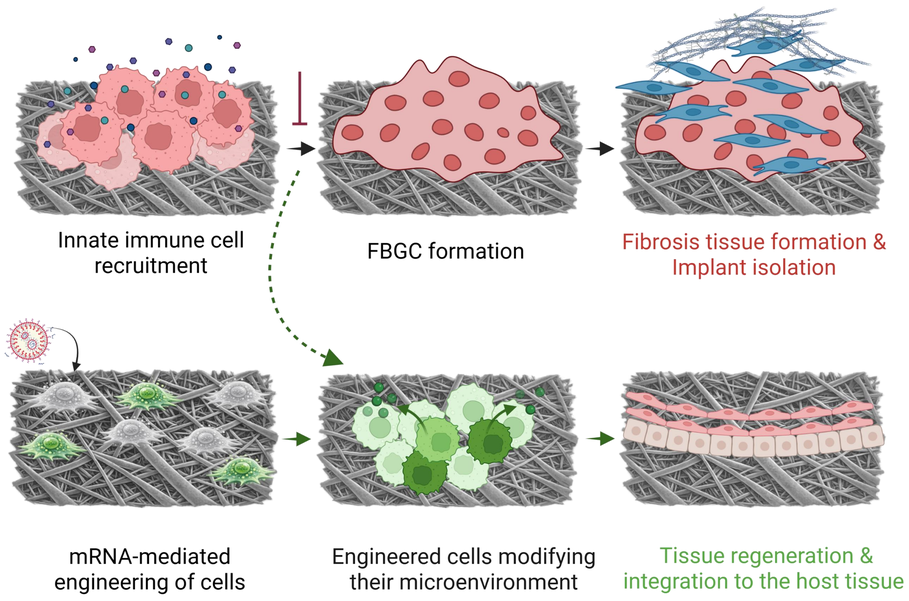
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Background & Motivation

- The increasing use of biomedical implants is limited by poor long-term integration
- The foreign body response (FBR) drives chronic inflammation and fibrotic encapsulation
- Macrophages are key regulators of inflammation at the implant-tissue interface
- Controlling macrophage behavior is critical to promote constructive tissue integration

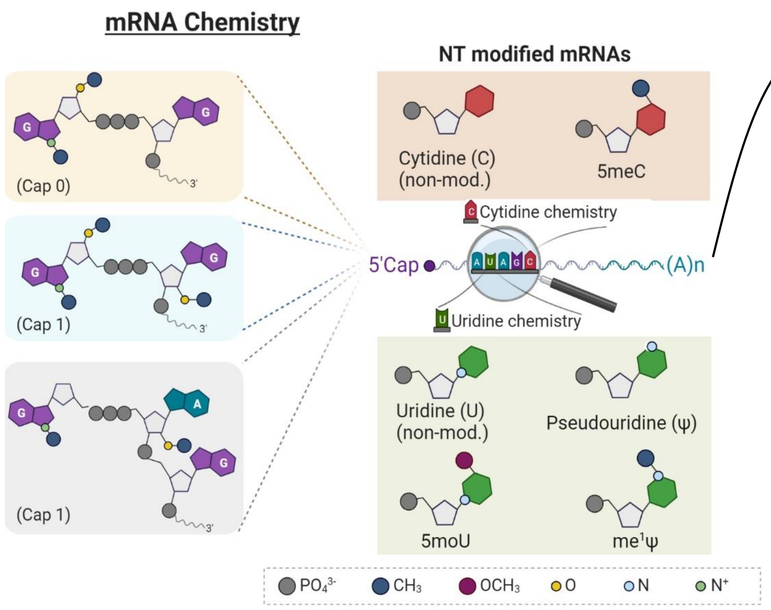
Objective

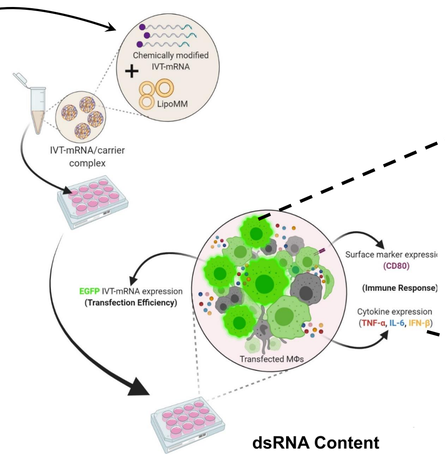
- To engineer macrophages using synthetic mRNA for localized immunomodulation
- To identify mRNA chemistries that enable expression without triggering immune activation

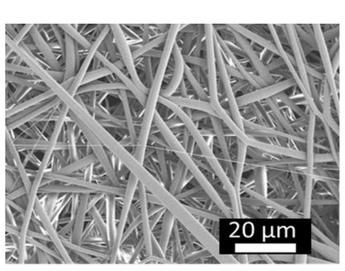


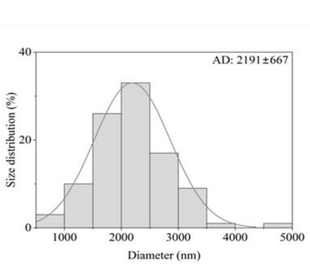
Approach

- Designed and synthesized chemically modified mRNA variants
- Delivered mRNA into macrophages (e.g., via transfection/LNPs)
- Evaluated:
  - ✓ Transgene expression efficiency
  - ✓ Immune activation (co-stimulatory markers)
  - ✓ Cytokine secretion (pro-inflammatory & antiviral)









- Electrospun meshes as a platform for local release of mRNA formulations

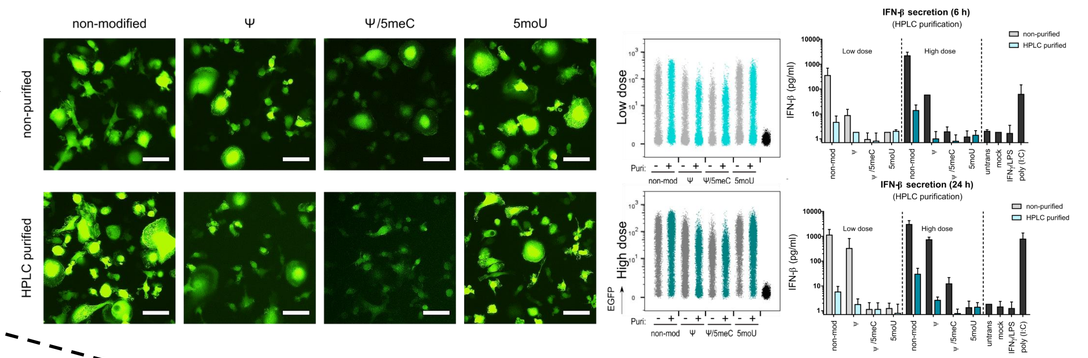
Results

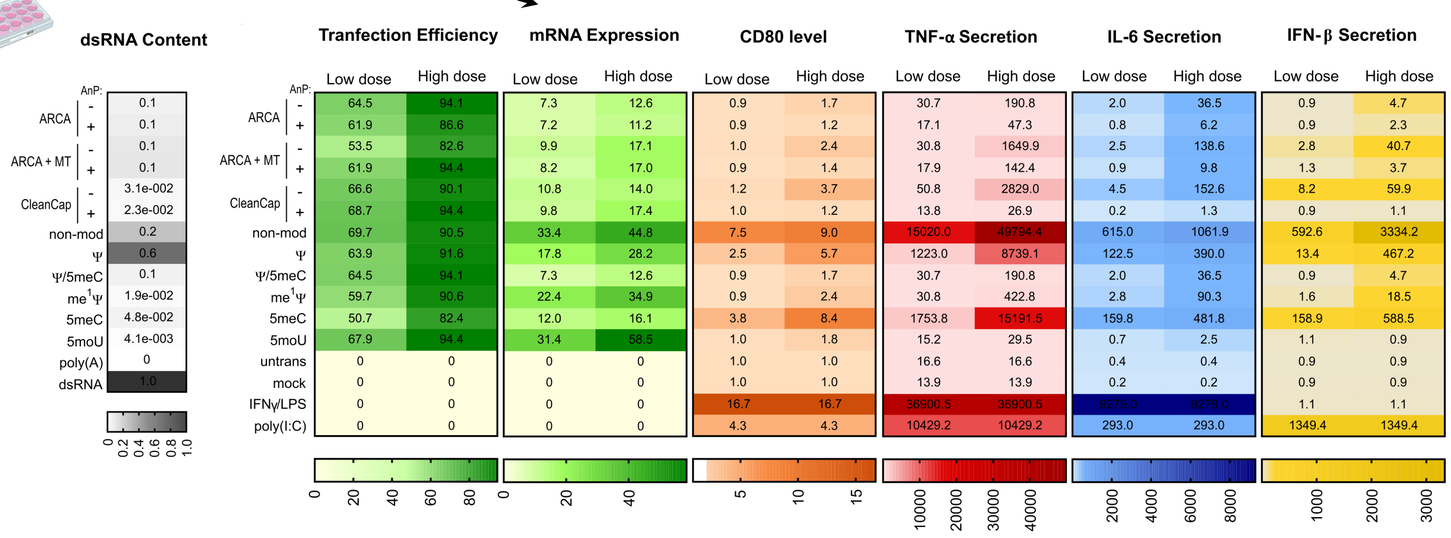
mRNA triggers immune activation in macrophages

- Unmodified mRNA induces strong innate immune responses
- Increased expression of co-stimulatory markers and cytokines

Chemical modification reduces immunogenicity

- Uridine modifications significantly attenuate immune activation
- Reduced pro-inflammatory and antiviral signaling
- 5-methoxyuridine (5moU) completely abrogates immune activation in transfected macrophages





Conclusion

- mRNA chemistry is a key determinant of immune compatibility
- 5moU-modified mRNA enables non-immunogenic macrophage engineering
- Provides a platform for programmable immunomodulation at implant sites

Future work

- LNP incorporation into implant coatings
- Localized delivery at biomaterial interface
- Validation of immune modulation using advance in vitro models

Impact

- Enables next-generation immuno-instructive implants
- Bridges RNA therapeutics and biomaterials engineering

References

1. Moradian, H., Roch, T., Anthofer, L., Lendlein, A., Gossen, M., 2022. Molecular Therapy - Nucleic Acids 27, 854–869.. doi:10.1016/j.omtn.2022.01.004
2. Moradian, H., Dunne C.M.,Gossen, M., Hartlieb, M. 2026. Advanced Science, 13(4):e12653. doi: 10.1002/advs.202512653.

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