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Enhanced pDNA Delivery Mediated by Backbone-Degradable RAFT Copolymers

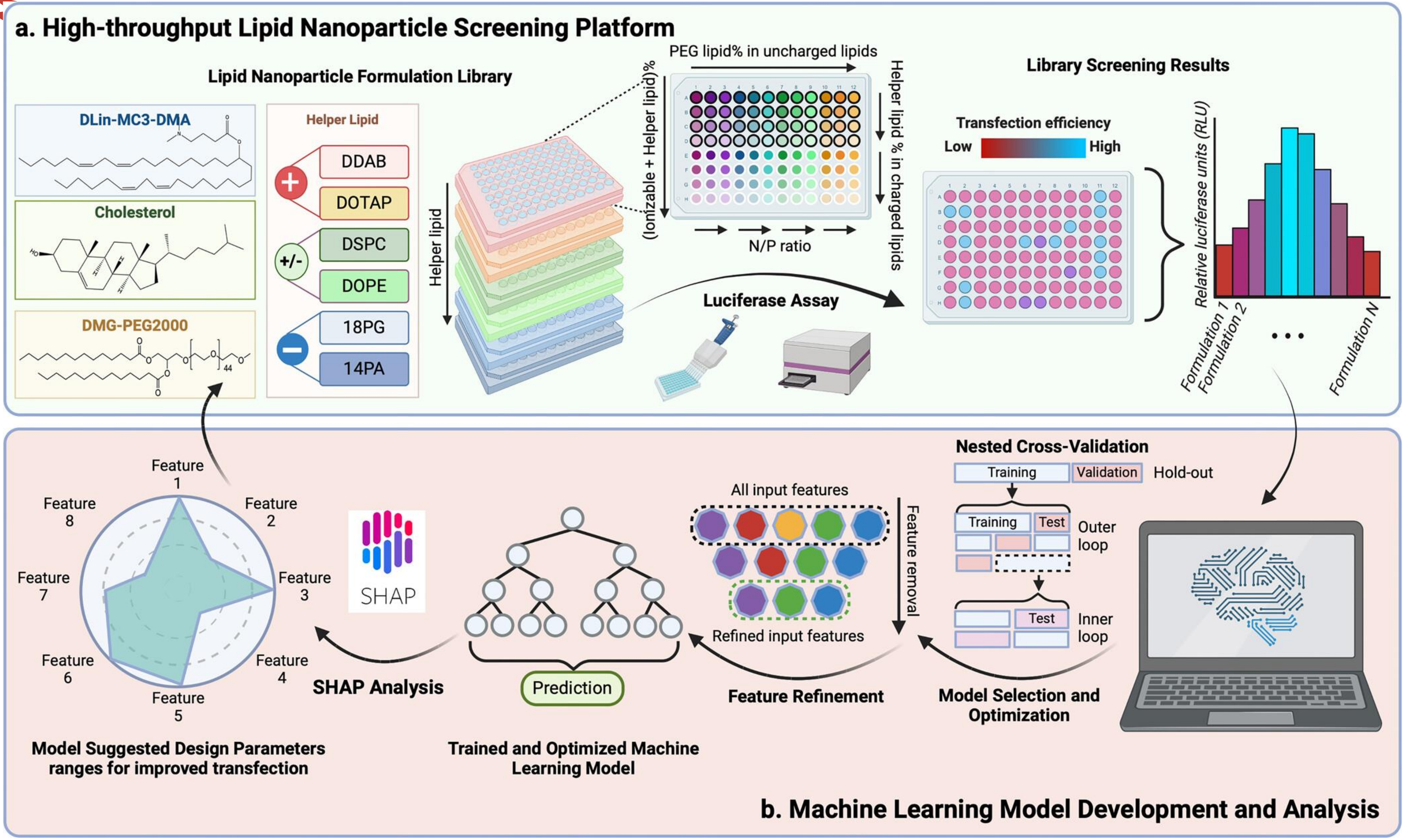
Adam J. Gormley

Associate Professor, Biomedical Engineering, Rutgers University

July 16th, 2025

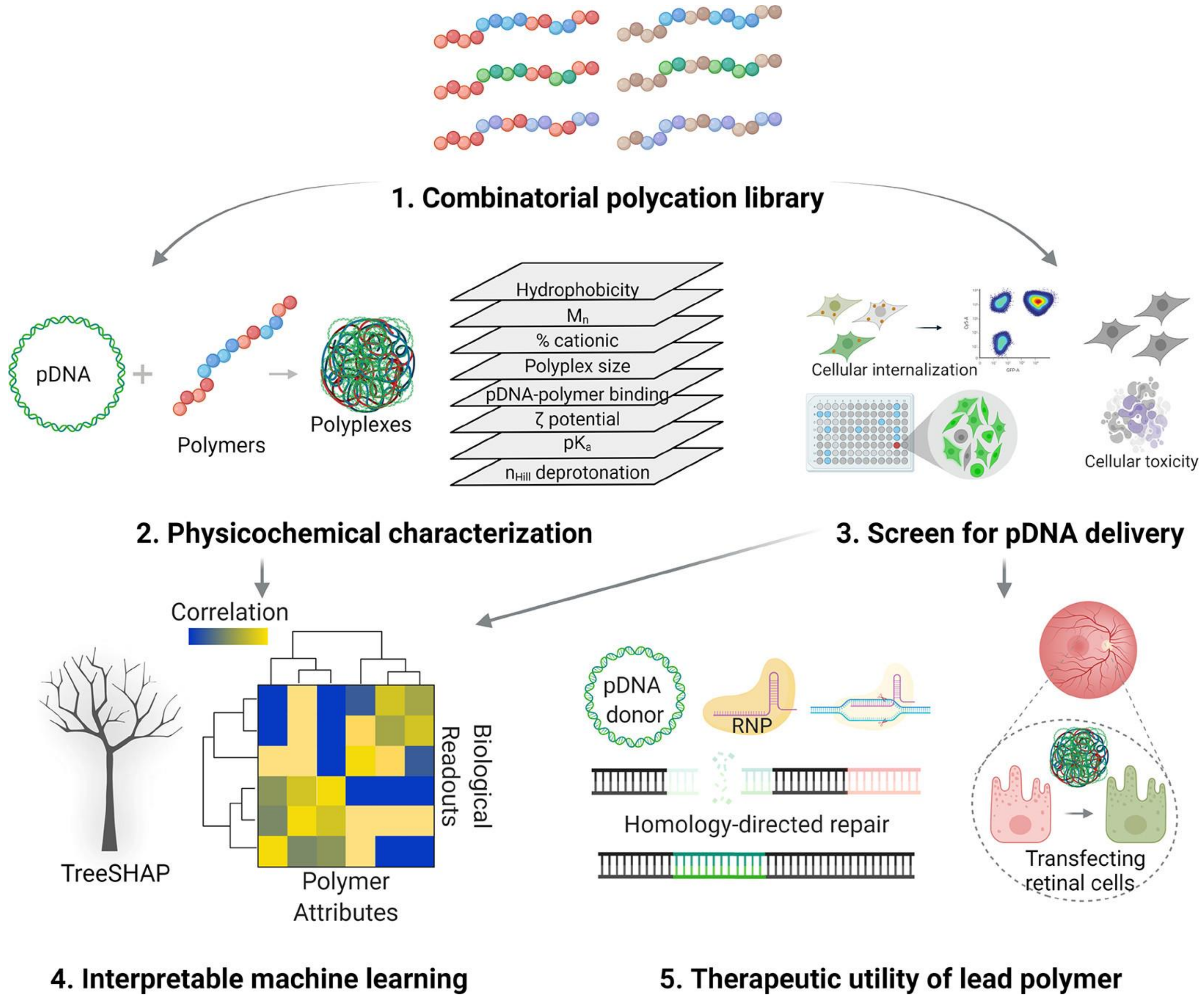
Gene Delivery and Gene Editing II, CRS 2025 Annual Meeting & Exposition, Philadelphia, PA

High Throughput Experimentation in Gene Delivery: Lipids



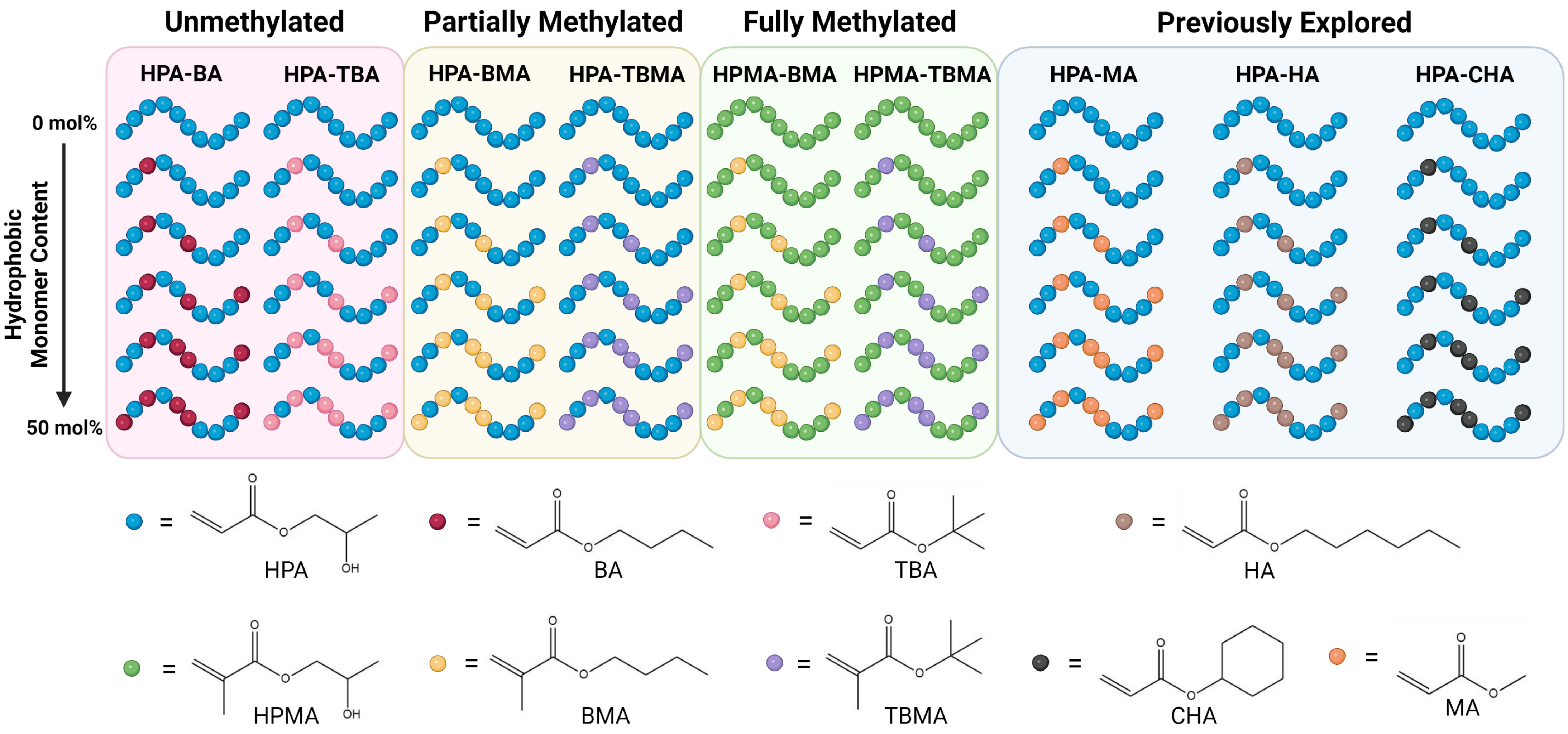
Ramya Kumar, Hai-Quan Mao, et al., 2024. Machine Learning Elucidates Design Features of Plasmid Deoxyribonucleic Acid Lipid Nanoparticles for Cell Type-Preferential Transfection. **ACS Nano**. 18: 28735-28747

High Throughput Experimentation in Gene Delivery: Polymers



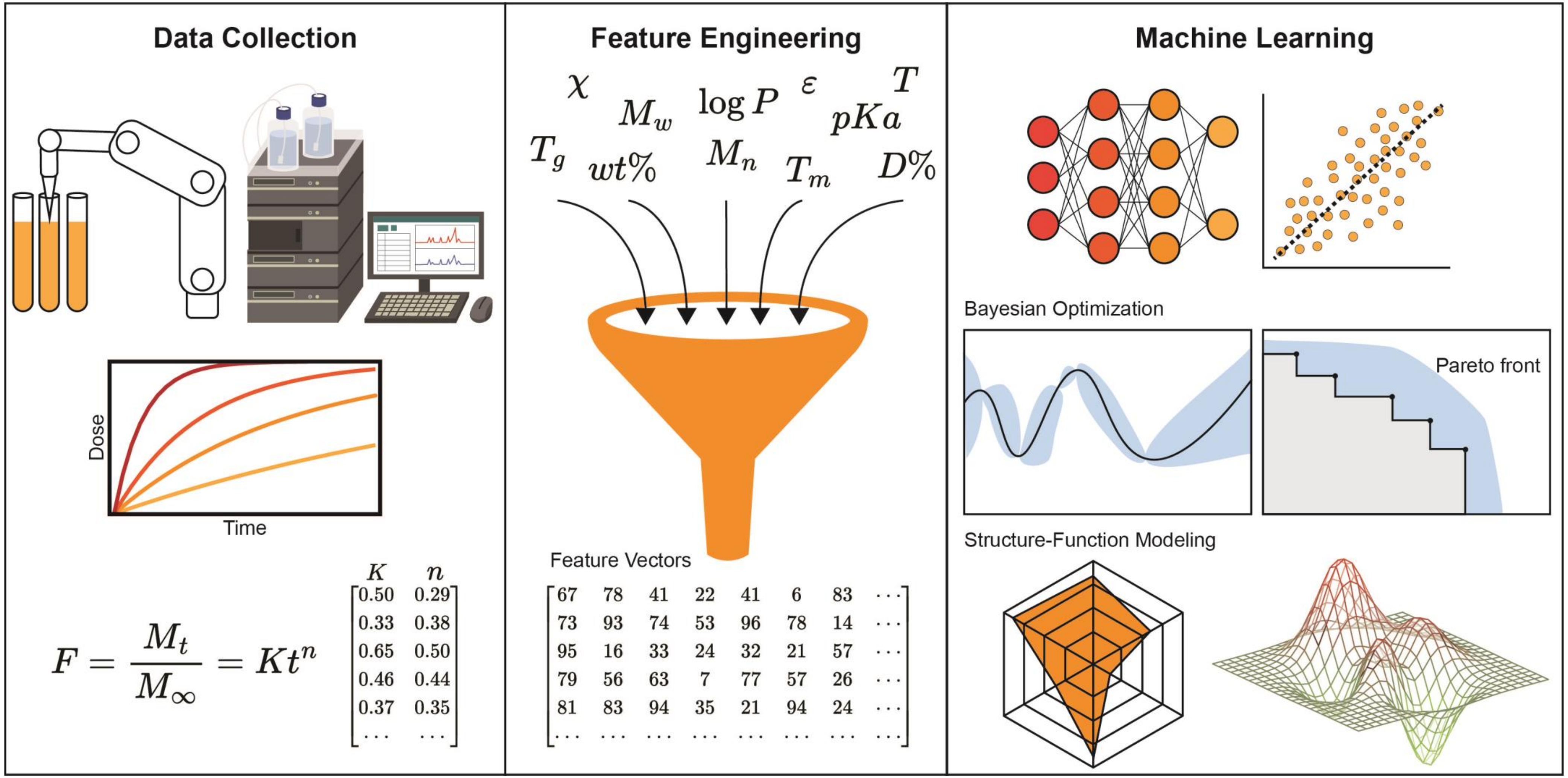
Ramya Kumar, Theresa Reineke, et al., 2022. Combinatorial Polycation Synthesis and Causal Machine Learning Reveal Divergent Polymer Design Rules for Effective pDNA and Ribonucleoprotein Delivery. **JACS Au**. 2: 428-442

Large Libraries of RAFT Copolymers



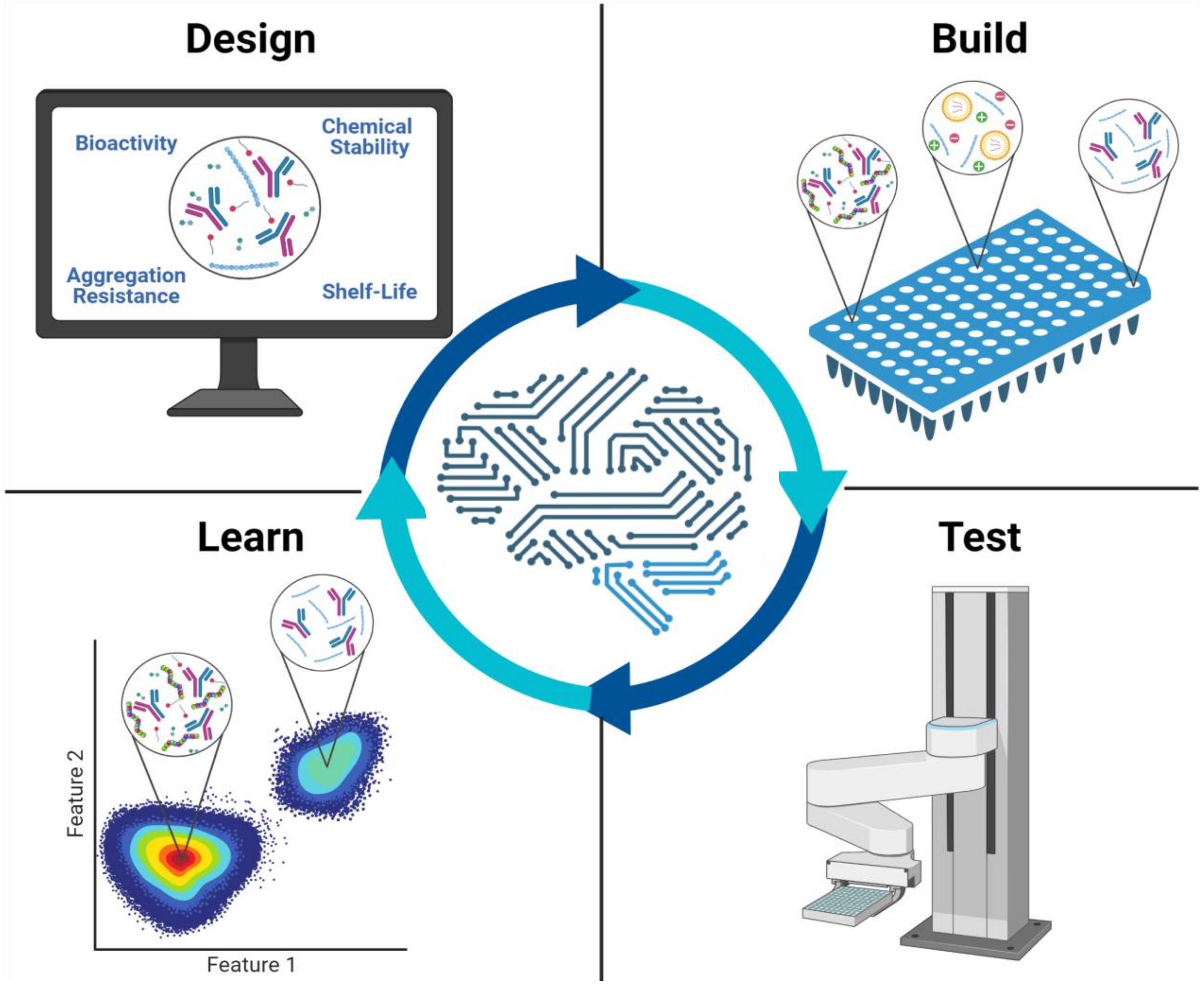
Di Mare, E., et al., 2024. Data-driven design of novel polymer excipients for pharmaceutical amorphous solid dispersions. **Bioconjugate Chemistry**. 35: 1363-

Machine Learning to Understand Structure-Function Behavior



A.J. Gormley, 2024. Machine learning in drug delivery. **Journal of Controlled Release**. 373: 23-30

AI and Robotics for Autonomous Materials Discovery

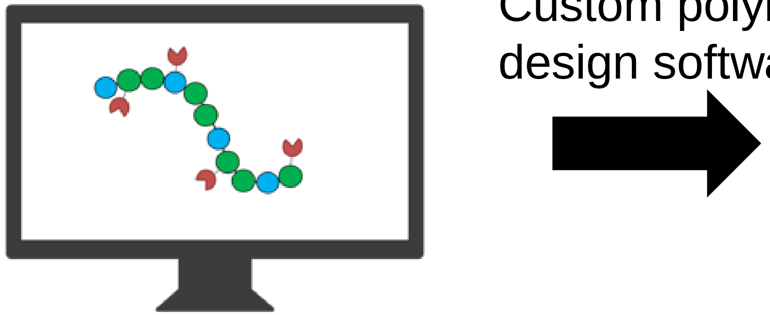


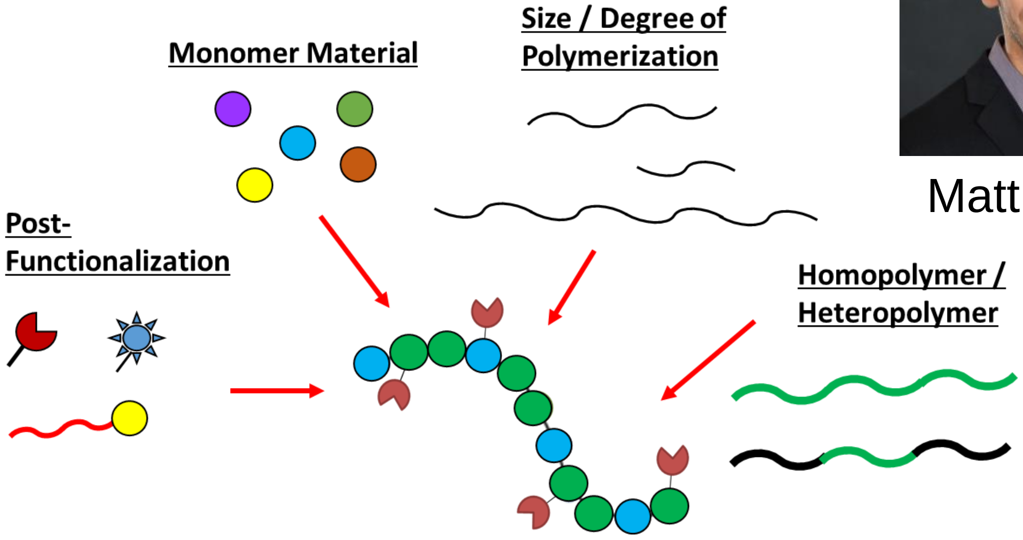
M.J. Tamasi & A.J. Gormley, 2022. Biologic formulation in a self-driving biomaterials lab. **Cell Reports Physical Science**. 3: 101041

M. Tamasi, et al, 2022. Machine learning on a robotic platform for the design of polymer-protein hybrids. **Advanced Materials**. 34: 2201809.

Automated Polymer Synthesis

Matt Tamasi



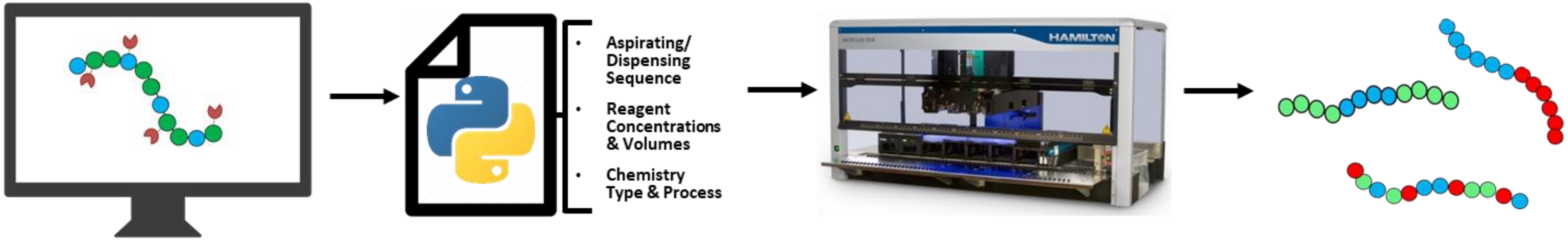


Inputs
Polymer characteristics such as Monomer, DP, and CTA are loaded into Python.

Script Creation
Python software generates the reagent handling process specific to inputs.

Reagent Handling
A Hamilton MLSTARlet mixes and dispenses reagents in 96-well plates

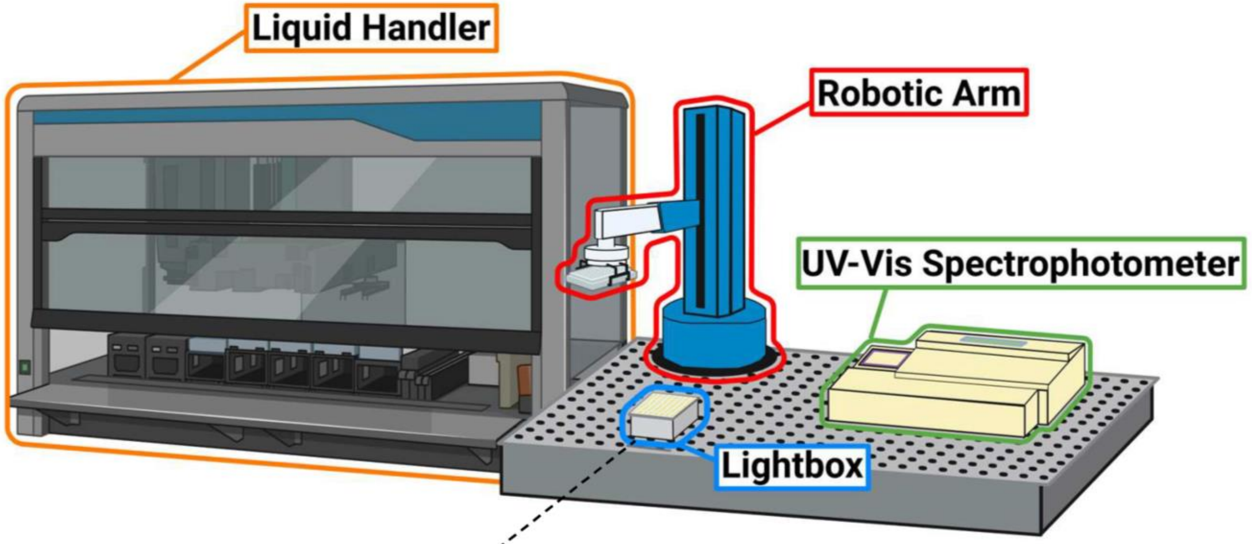
Polymer Synthesis
Polymerization occurs in well plates by photoinitiation or thermal initiation



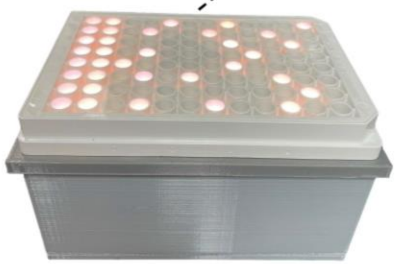
M. Tamasi, et al., 2020. Automation of controlled/living radical polymerization. **Advanced Intelligent Systems**. 2:

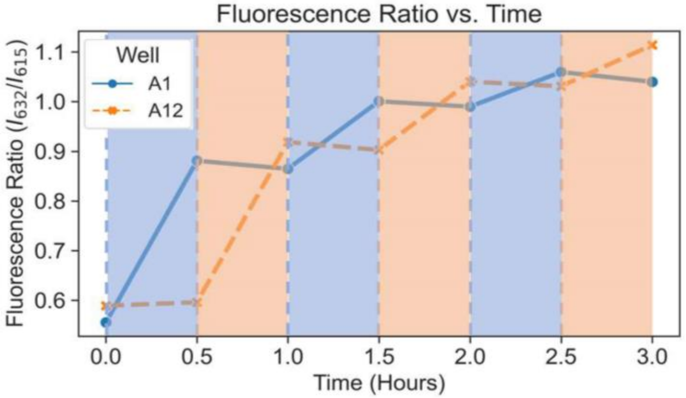
Fully Automated Python Control with Reaction Monitoring

Jules Lee



Custom built 96 LED array for multiplex lighting

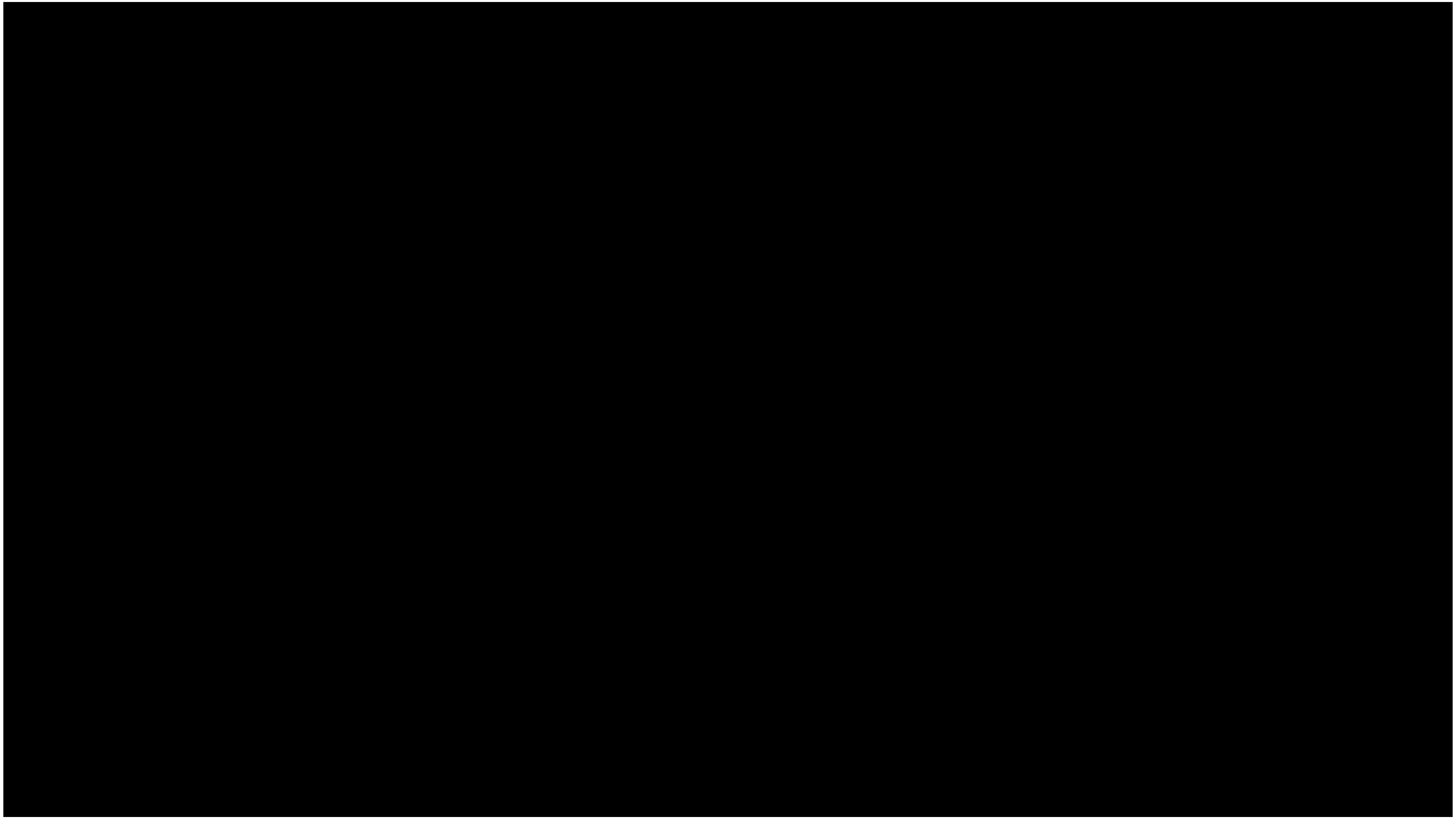




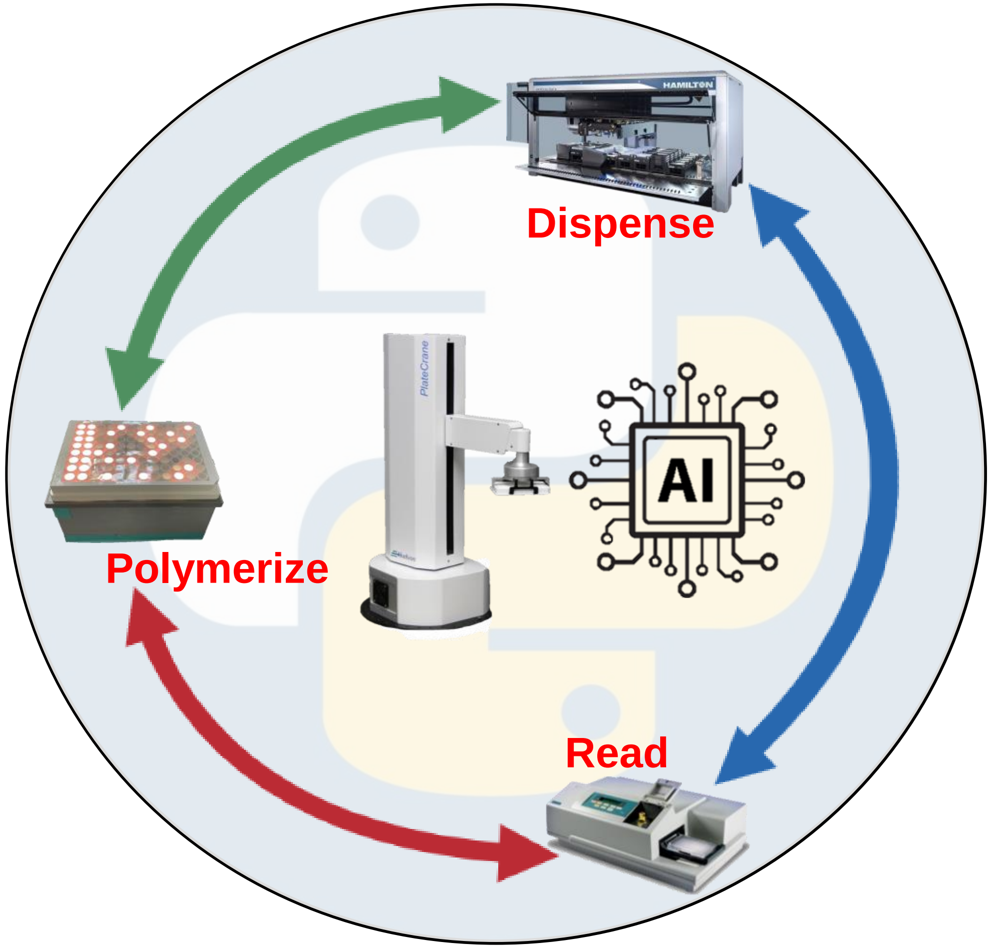
We have closed the hardware and software loop for a fully automated discovery workflow using a custom-built Python interface

Lee, J., et al., 2023. A fully automated platform for photoinitiated RAFT polymerization. **Digital Discovery**. 2: 219-233

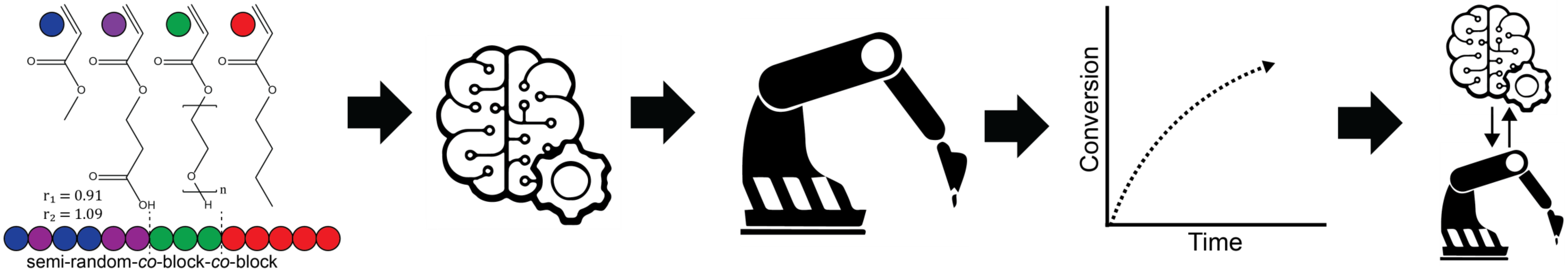
Automated Platform



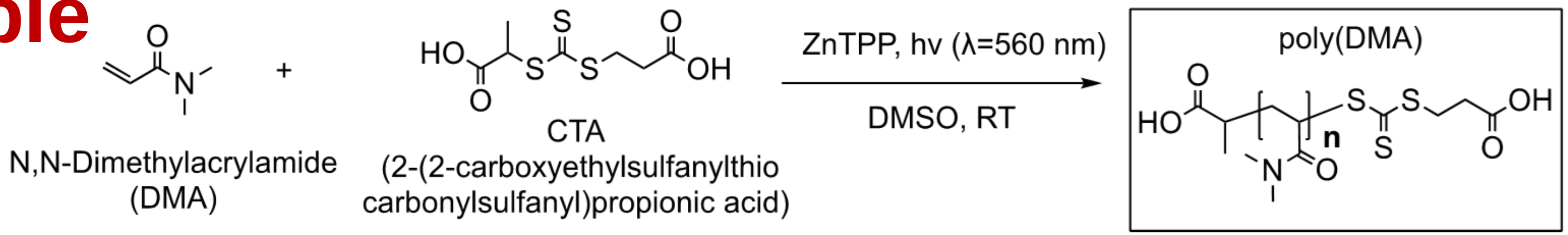
Sequence-Level Control in Combinatorial Libraries

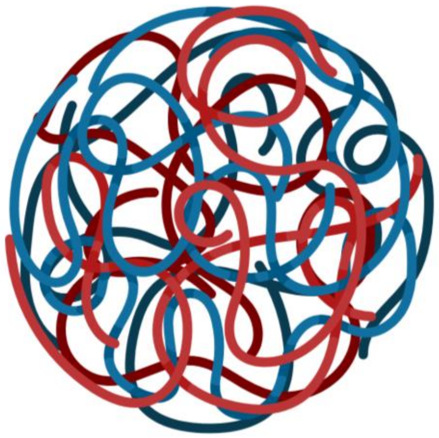


Might this allow for statistical sequence-level control by strategic monomer additions within an automated environment?

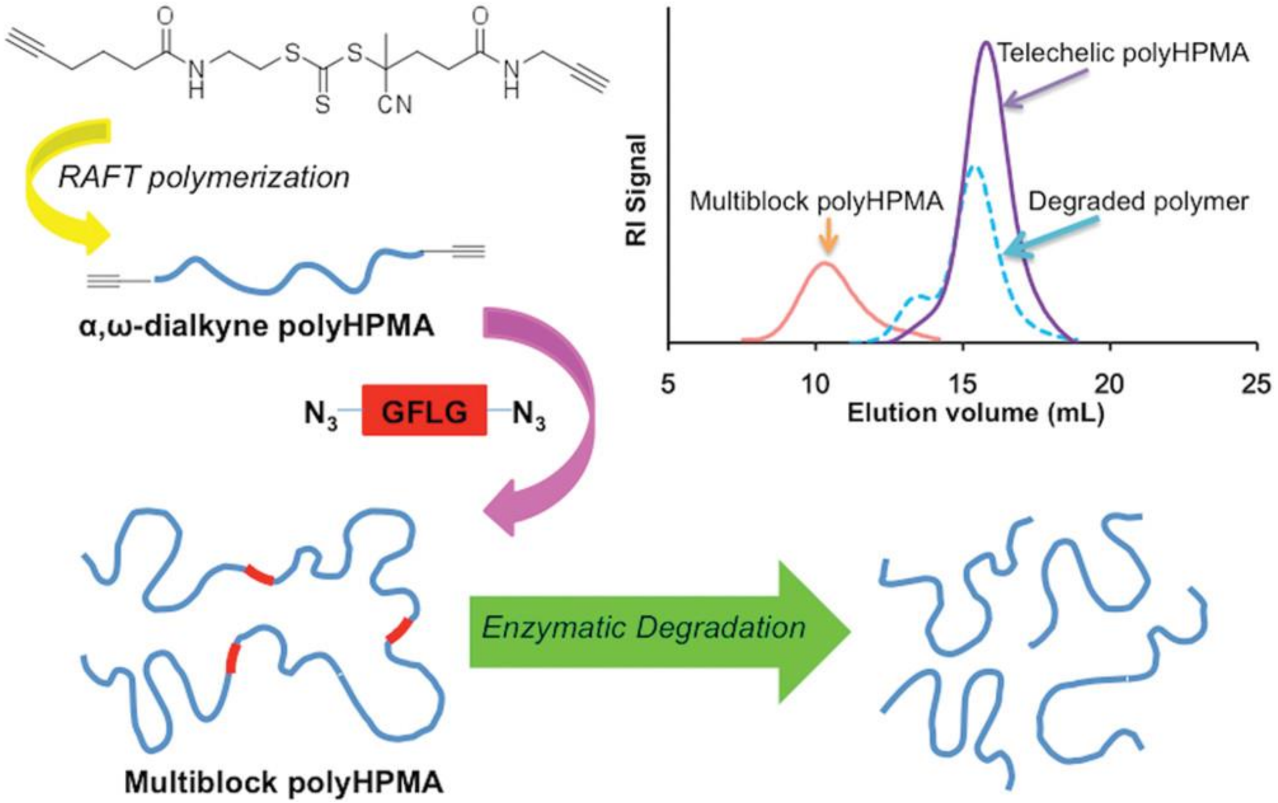


Drawback of RAFT: Polymers are Non-Degradable



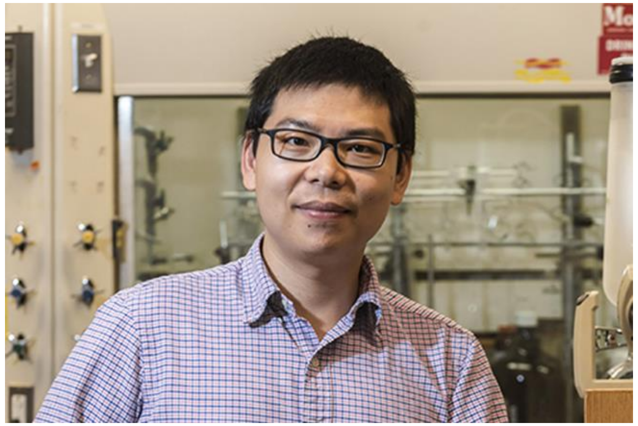


Entanglement likely limits disassociation



J. Kopecek, et al., 2011. Biodegradable Multiblock Poly[N-(2-hydroxypropyl)methacrylamide] via Reversible Addition−Fragmentation Chain Transfer Polymerization and Click Chemistry. **Macromolecules**. 44: 2481-2488

Radical Ring-Opening Cascade Copolymerization (rROCCP) to Incorporate Ester Groups into RAFT Polymers



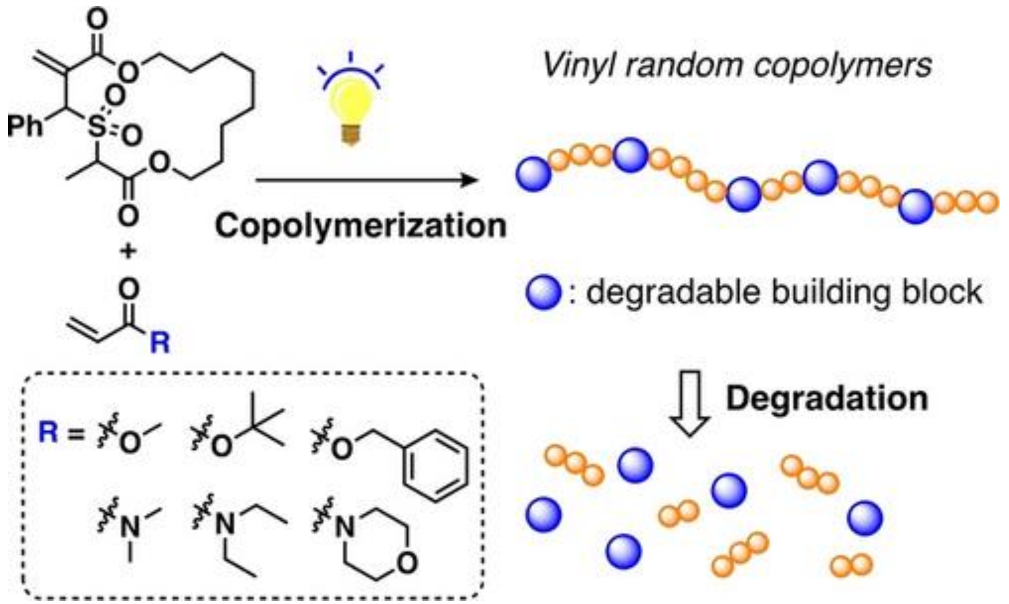
Jia Niu
Associate Professor of Chemistry
Boston College

Copolymerization

How to cite: *Angew. Chem. Int. Ed.* **2022,** *61,* e202113302
International Edition: doi.org/10.1002/anie.202113302
German Edition: doi.org/10.1002/ange.202113302

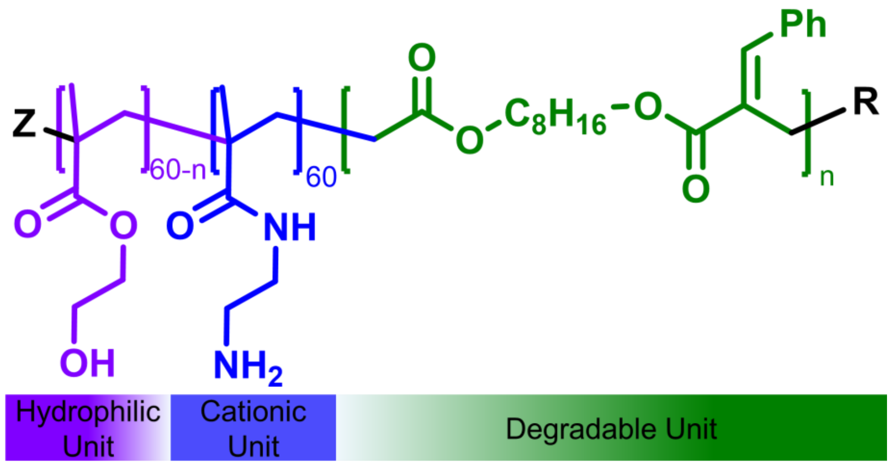
Degradable Vinyl Random Copolymers via Photocontrolled Radical Ring-Opening Cascade Copolymerization**

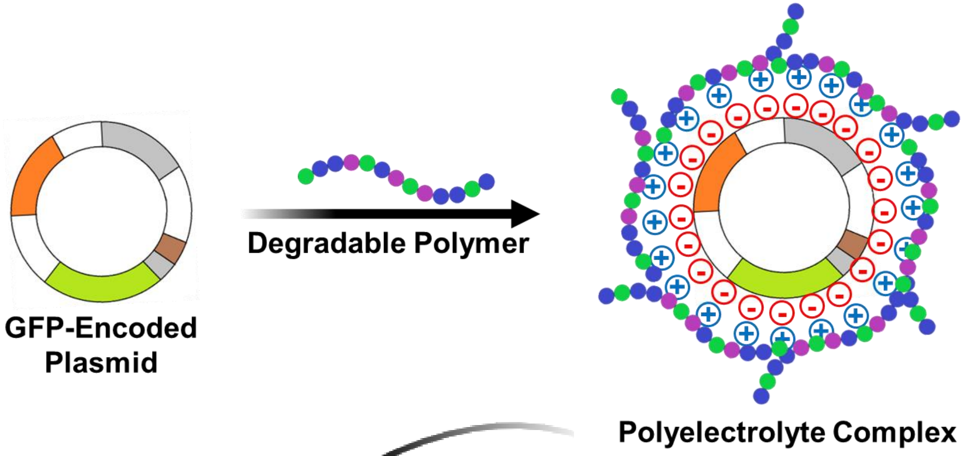
*Wenqi Wang, Zefeng Zhou, Devavrat Sathe, Xuanting Tang, Stephanie Moran, Jing Jin, Fredrik Haeffner, Junpeng Wang, and Jia Niu**

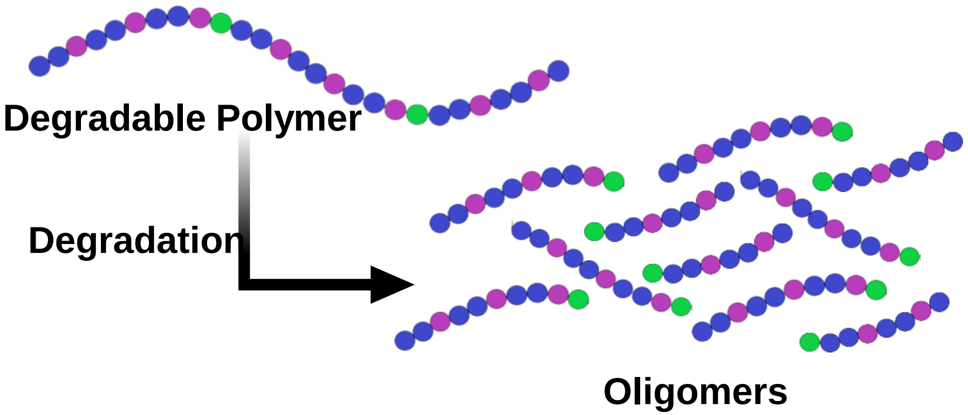


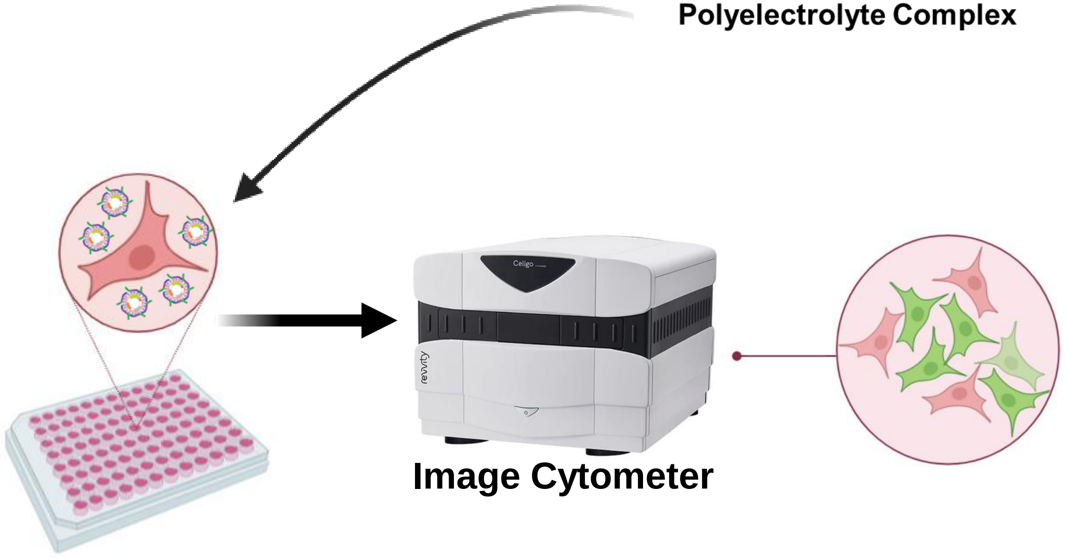
Goal: Use photocontrolled rROCCP to incorporate degradability into cationic polymers and evaluate their potential as gene delivery vectors

Biodegradable Precision Polycations for Gene Delivery









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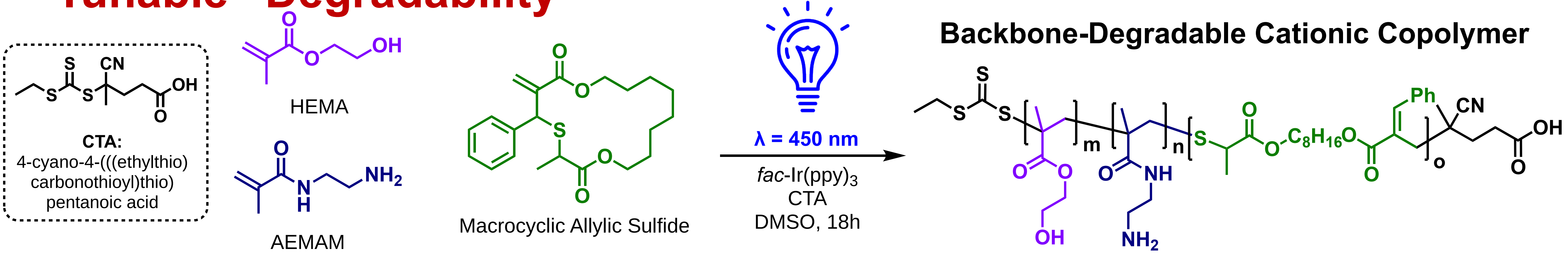
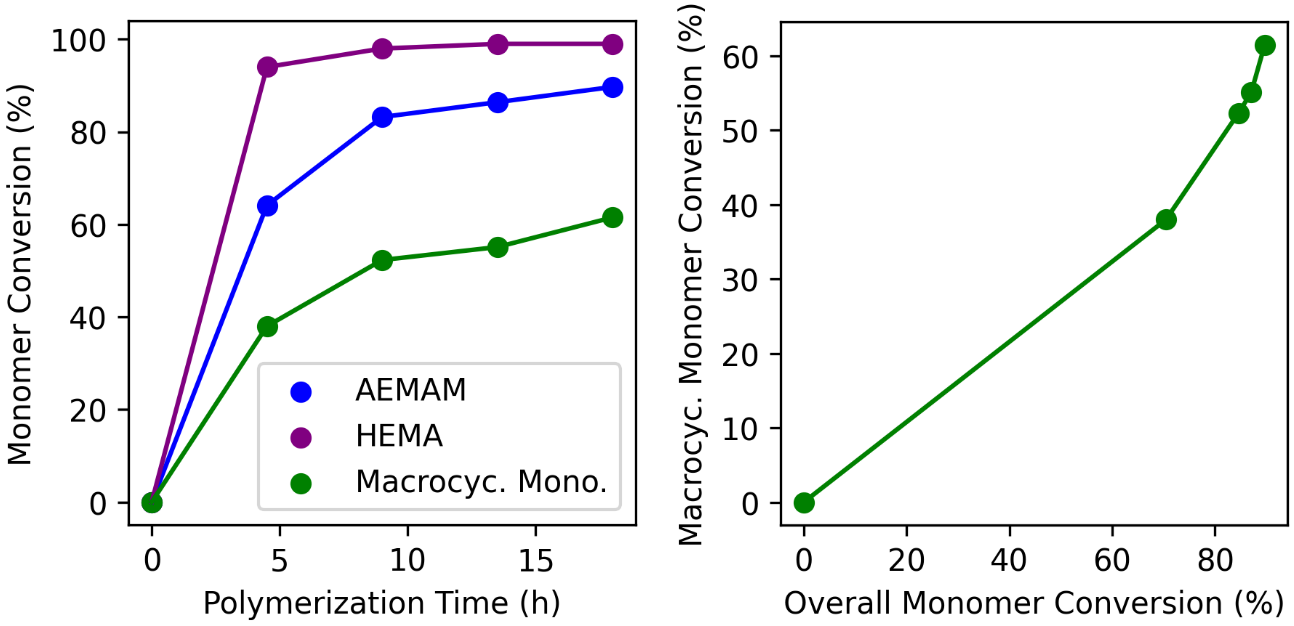
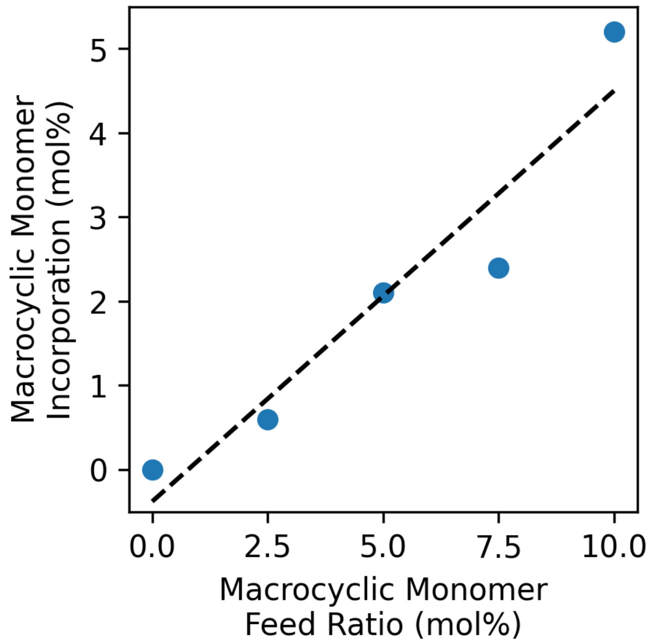
rROCCP Enables Synthesis of Cationic RAFT Copolymers with "Tunable" Degradability



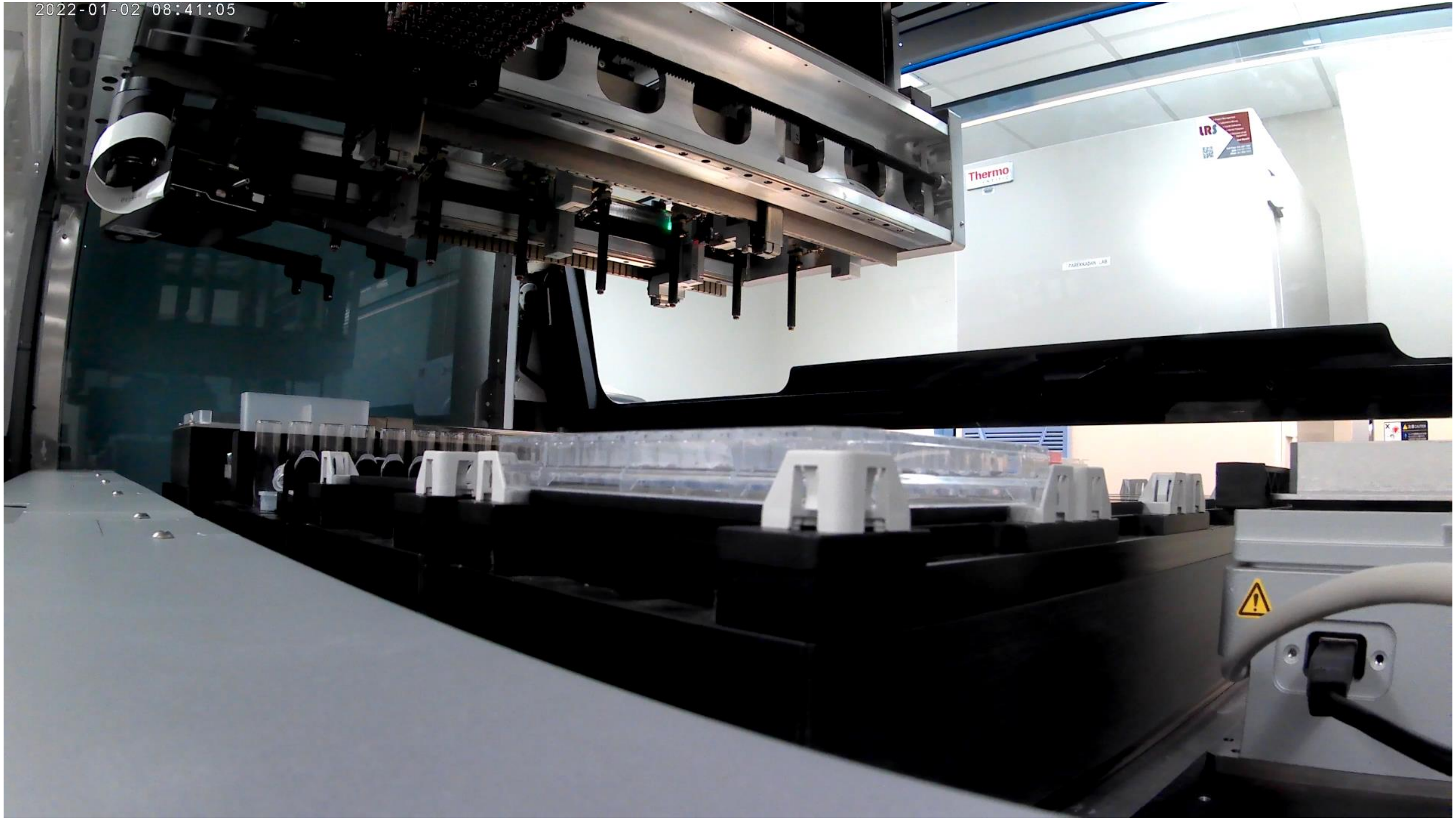
Reaction Kinetics Demonstrate Incorporation of Degradable Sequence Throughout Polymer Chain



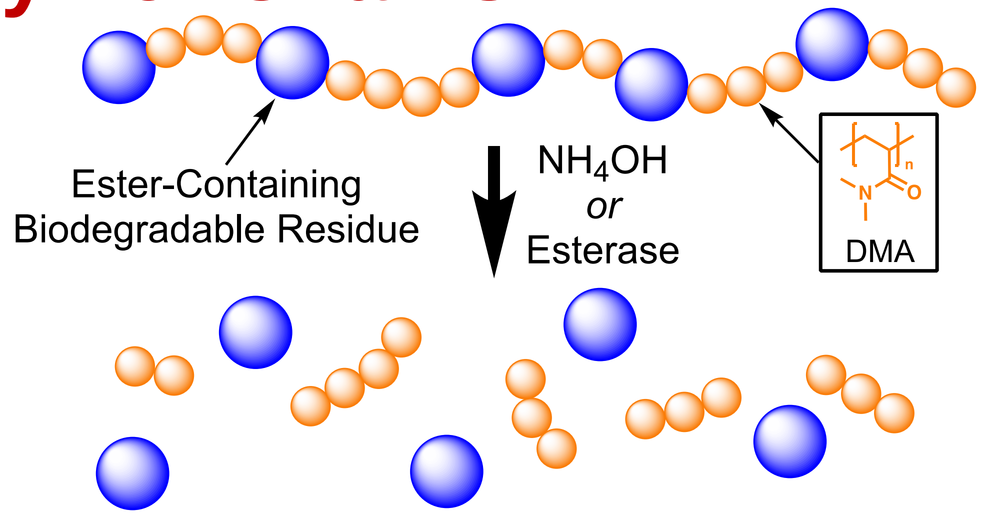
Frequency of Degradable Group in Backbone Scales with Feed Ratio of Macrocyclic Monomer

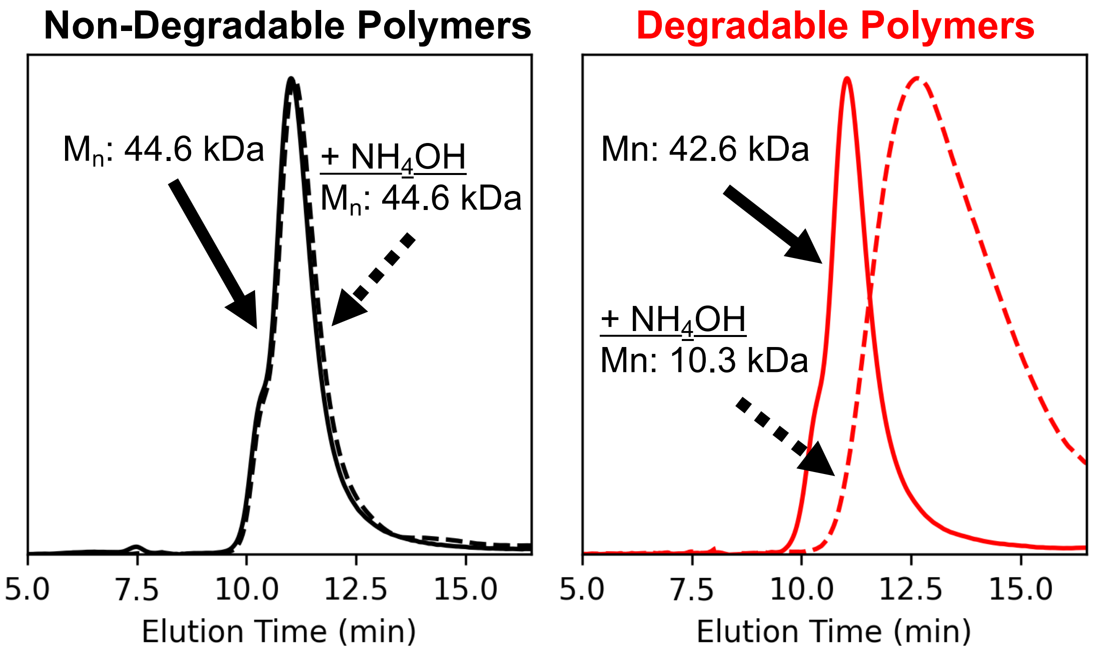


Automating Degradable Polycations



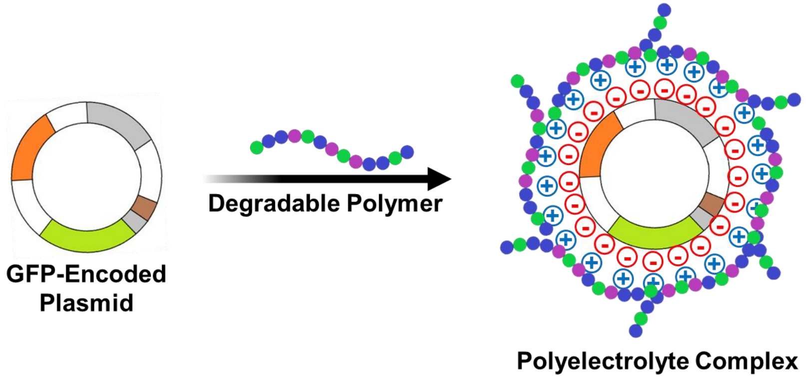
Ester Incorporation via rROCCP Yields Biodegradable Polymer Chains



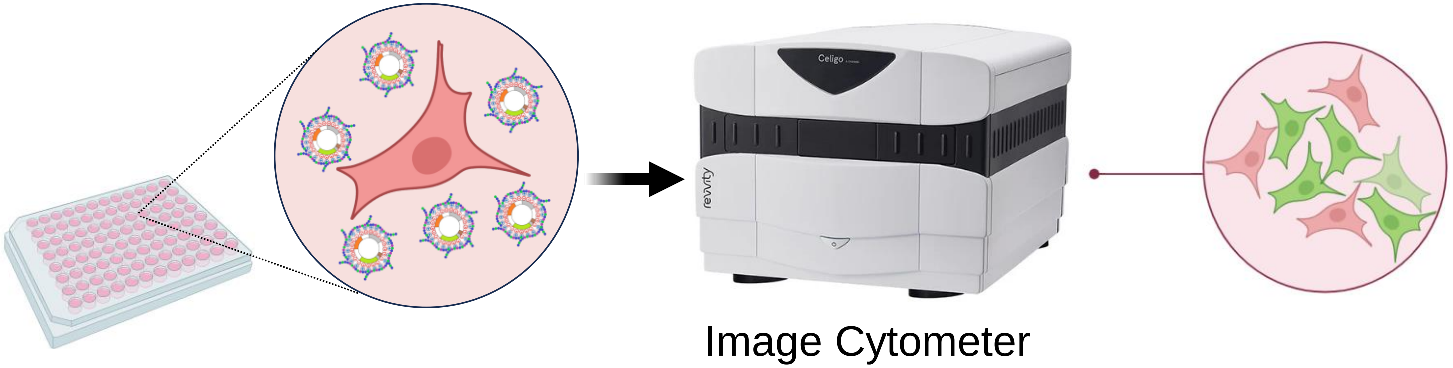


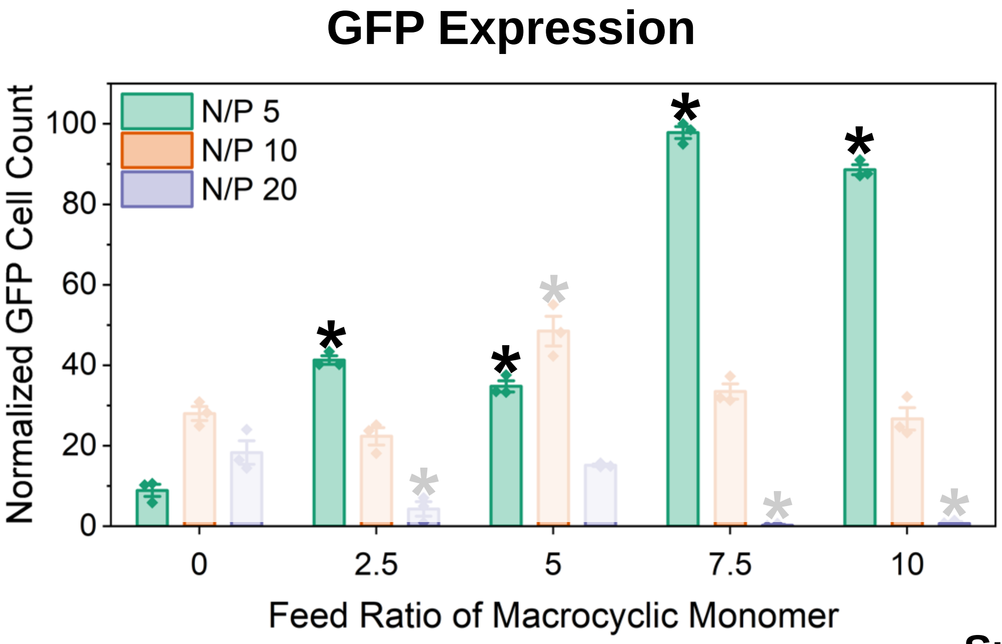
Degradability Enhances Transfection without Increasing Cytotoxicity

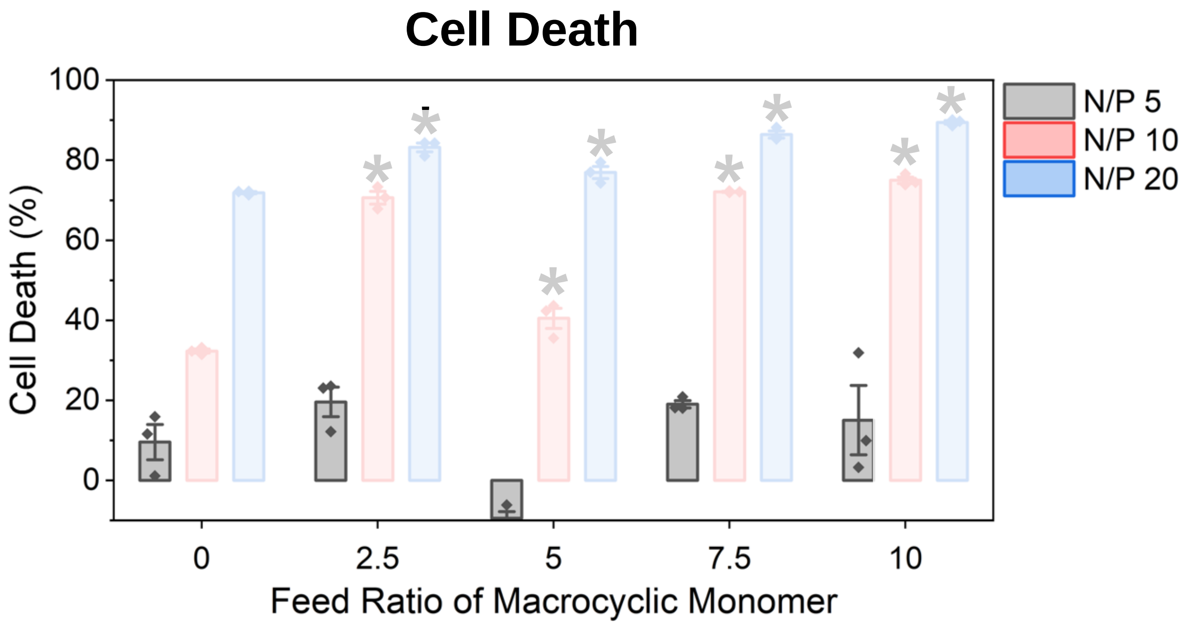
Polyplex Formation with GFP Plasmid



Transfection Efficiency and Cytotoxicity Evaluation







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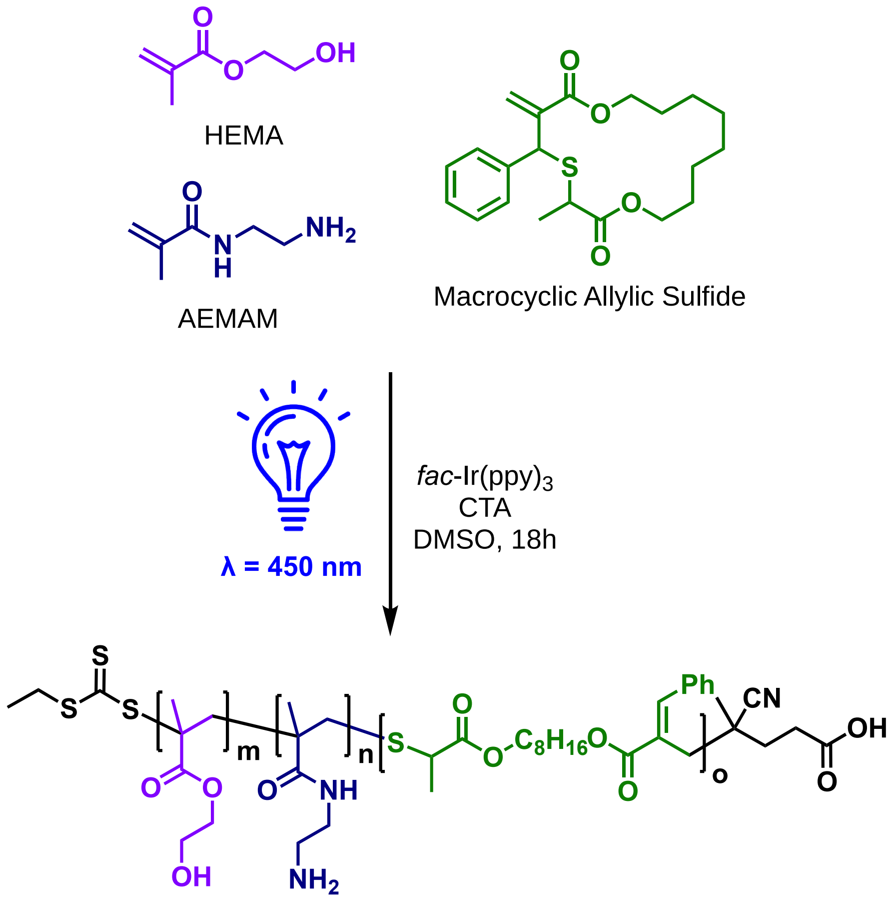
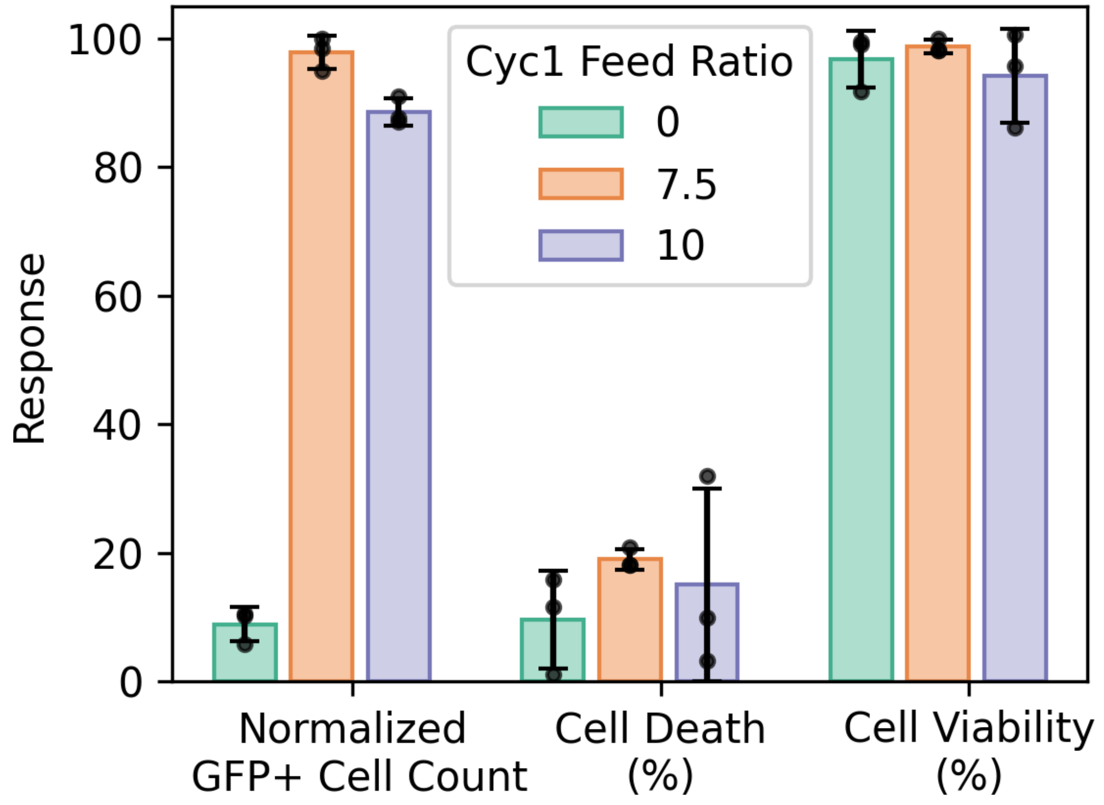
Conclusions

Novel rROCCP chemistry enables single-step synthesis of backbone-degradable polymers via automated PET-RAFT



Incorporation of backbone degradability yields polymers with improved transfection efficiency while maintaining low cytotoxicity



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Acknowledgements

Collaborators

Jia Niu, Boston College
Mike Webb, Princeton
Sanjeeva Murthy, Rutgers

Students and Postdocs

Chris Radford
Cesar Ramirez
Elena Di Mare
Eugene Cheong
Eman Ahmed
Gabriela Tirado-Mansilla
Weronika Wasniowska
Cristian Lopez
Alexander Suponya
Apostolos Maroulis
Dylan Waynor
Maria Goncalv
Eric Quartey

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CBET #2009942
CBET #2309852
DMREF #2118860
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State of New Jersey Commission on Spinal Cord Research

NIH NIGMS

Maximizing Investigators Research Award (MIRA)
R35GM138296

NIH National Institute of Biomedical Imaging and Bioengineering

R01EB037022
R21EB035260

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