Programmably Degradable Oxanorbornadiene Hydrogels for Functional Biomolecular Release

Wenting Shi
PhD. Candidate, Georgia Institute of Technology
Advisor: Prof. M.G. Finn
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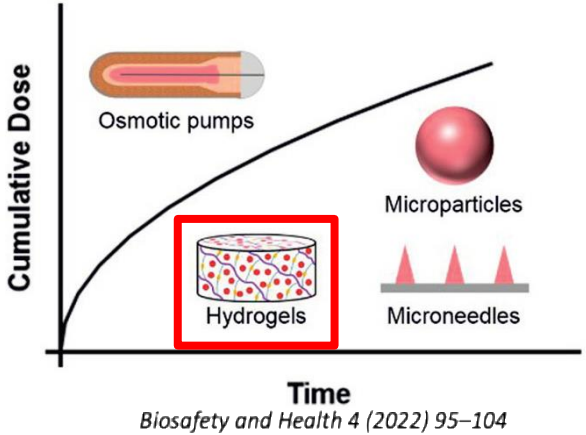
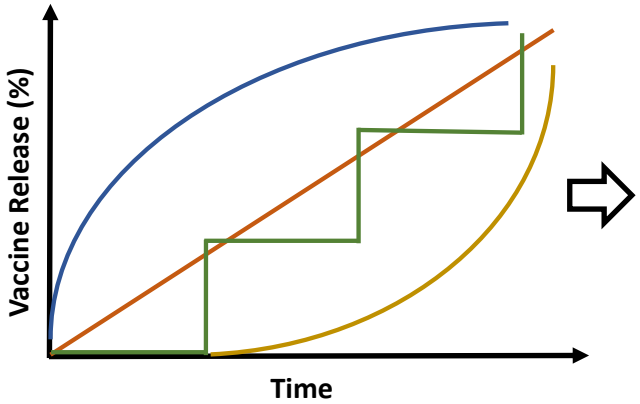
NEXT-GENERATION DELIVERY INNOVATIONS

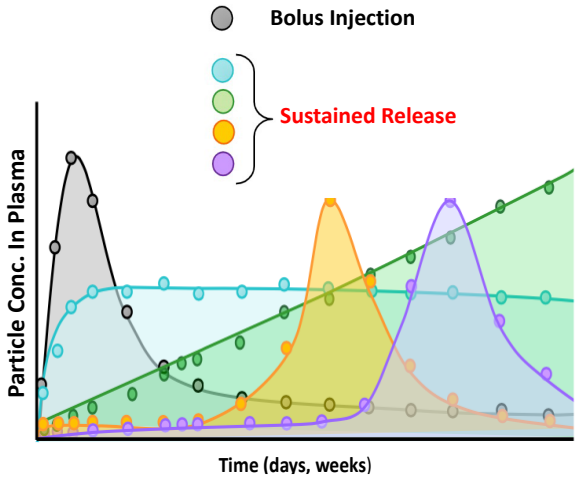
Injectable hydrogels for sustained release of biologics

- Enhance the stability of protein cargo by maintaining aqueous environment
- Sequester relatively high quantities of the cargo
- Better mimic the mechanical properties of surrounding tissues
- Provide a minimally invasive method of injection



Biosafety and Health 4 (2022) 95–104





Fine-tuning the cargo release profiles from hydrogels remains challenging (e.g., uncontrolled burst release, non-tunable pharmacokinetics).

Injectable hydrogels for sustained release of biologics

- Enhance the stability of protein cargo by maintaining aqueous environment
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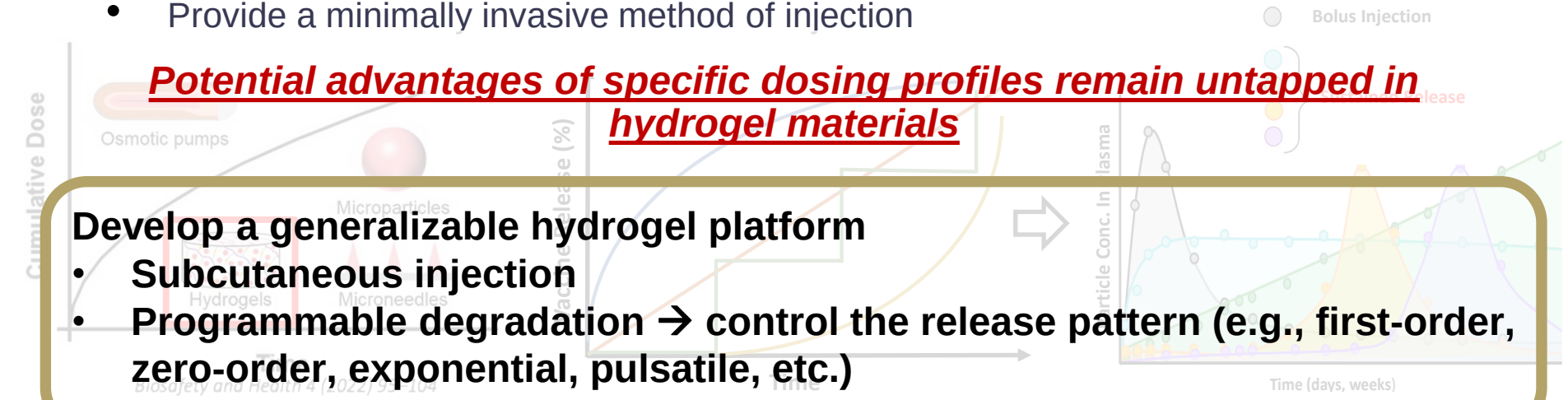
Potential advantages of specific dosing profiles remain untapped in hydrogel materials



Develop a generalizable hydrogel platform

- **Subcutaneous injection**
- **Programmable degradation → control the release pattern (e.g., first-order, zero-order, exponential, pulsatile, etc.)**

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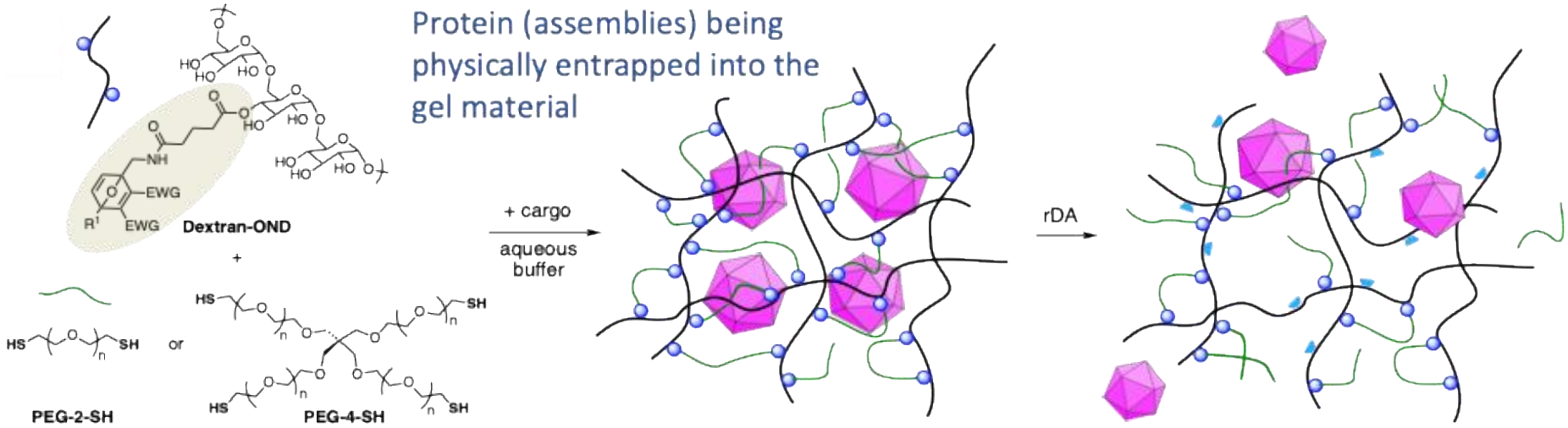
Gels created by oxanorbornadiene (OND) linkages



Oxanorbornadiene (OND) Chemistry

Michael Addition: fast gelation under mild conditions

Retro Diels-Alder: highly tunable and independent of pH or enzymes

JACS 2012, *134* (14), 6491-6497
ACS Applied Bio Materials 2020, *3* (8), 4779-4788
Adv. Funct. Mater. 2024, 2409796

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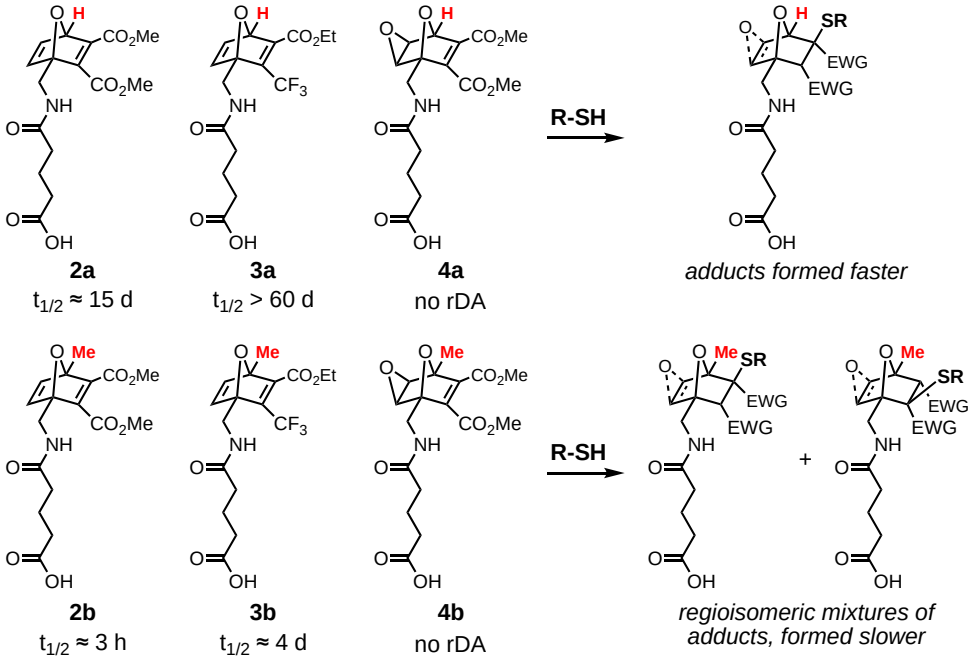

2a $t_{1/2} \approx 15$ d

3a $t_{1/2} > 60$ d

4a no rDA

adducts formed faster

2b $t_{1/2} \approx 3$ h

3b $t_{1/2} \approx 4$ d

4b no rDA

regioisomeric mixtures of adducts, formed slower

Fragmentation half-lives were tested in chloroform at RT

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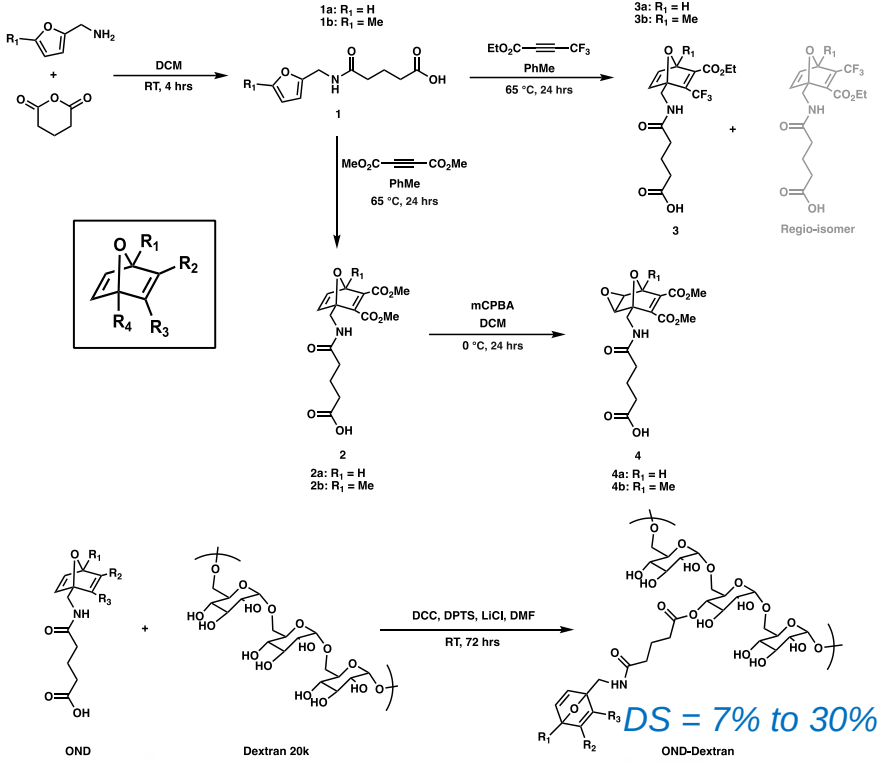

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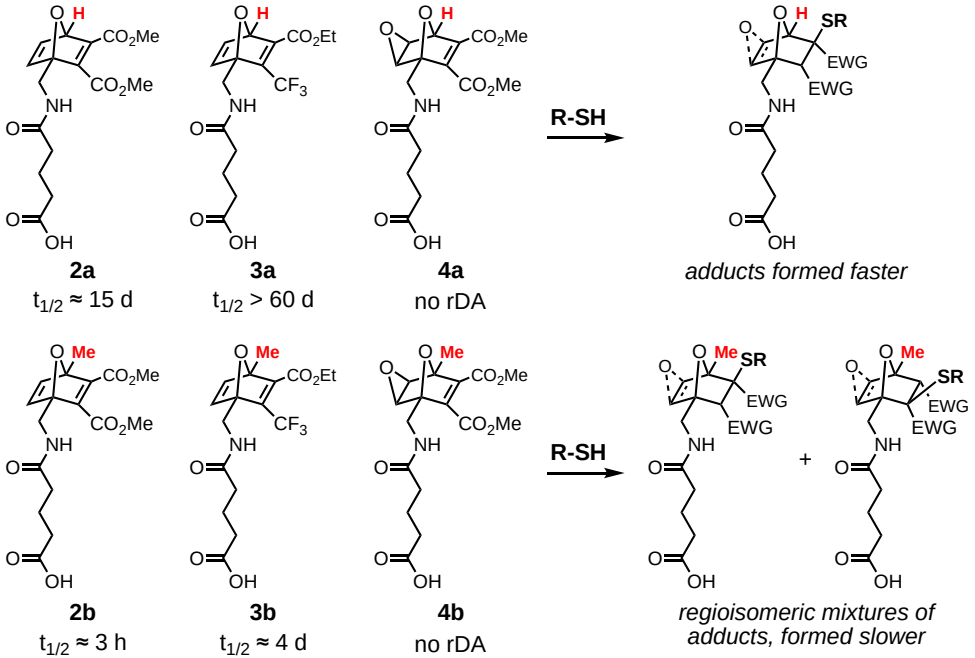

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OND entities
Ring "bridge" substitution

PEG valences
2 arm vs 4 arm PEG

pH values
Higher pH, faster gelation

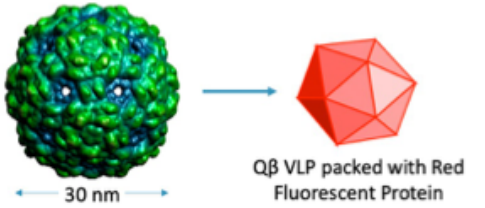
Temperature
Higher temp, faster gelation

Homogeneous and reproducible gels require > 10 s gelation time

Ready for injection: 1X PBS, pH 6.0
Gelation: 1-3 min

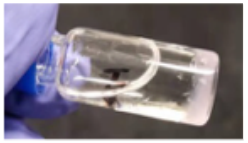
100 µL gel SubQ

Programmable release of VLP using single/combinational ONDs



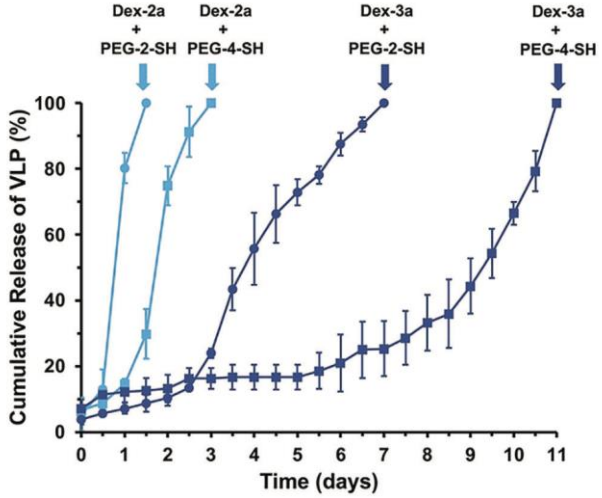
Virus-like Particles (VLPs): e.g. Qβ VLP

- Nanoparticulate subunit vaccines

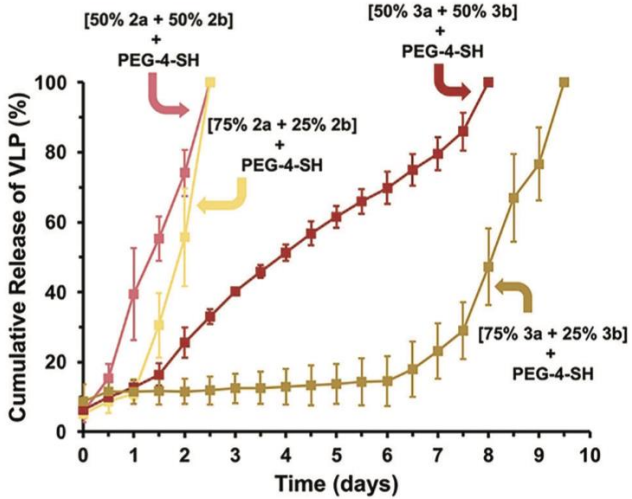


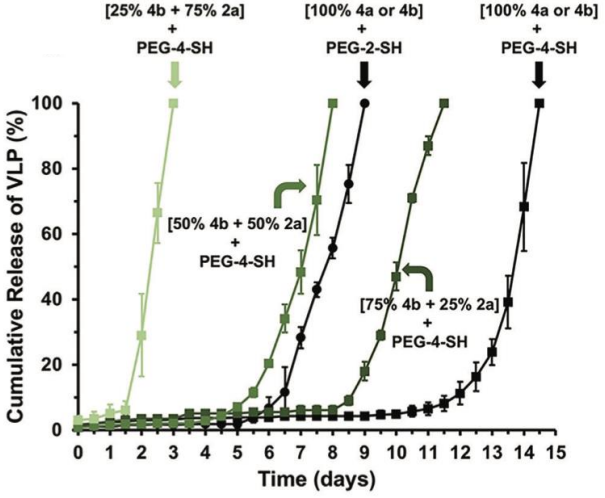
Entrapped into Dex-OND (DS = 14-15%) + PEG-thiols; 10 wt%, 1-2 mg/mL loading

Single type of ONDs



Combination of different ONDs in a same gel





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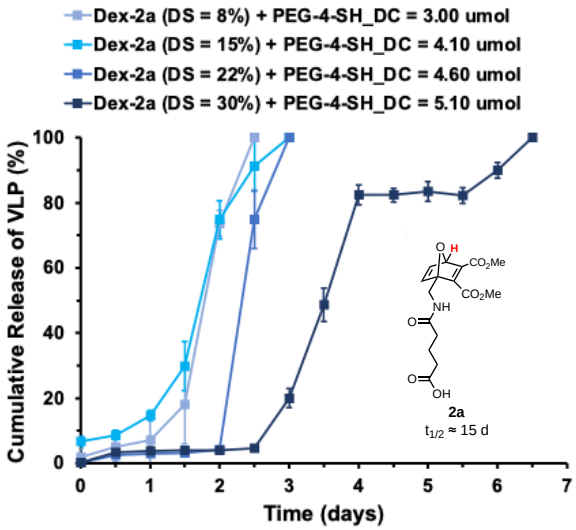
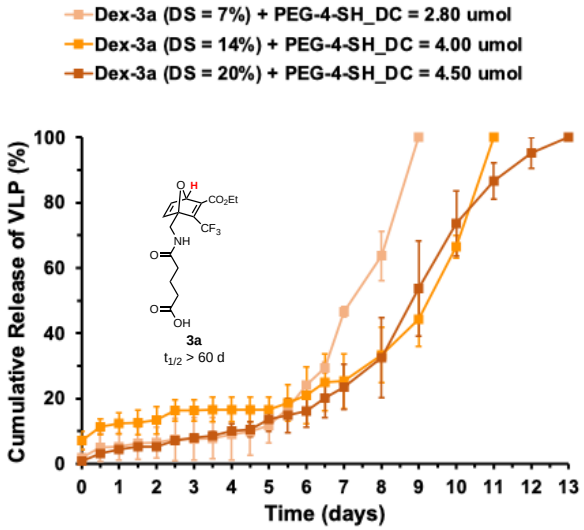
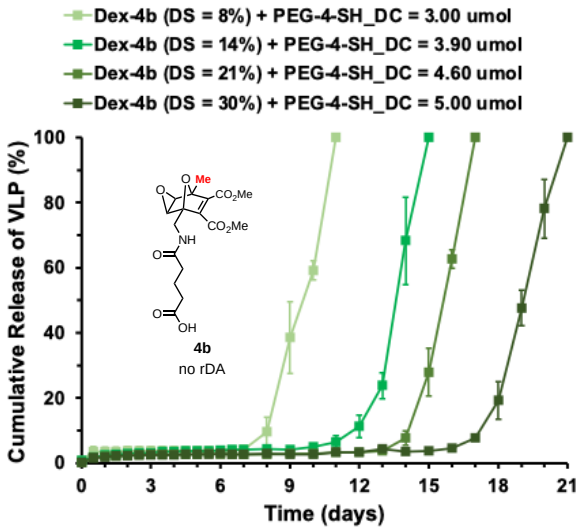
Expanding the release portfolio by optimizing degree of crosslinking (DC)

OND degree of substitution (DS) → hydrogel degree of crosslinking (DC) → material stability

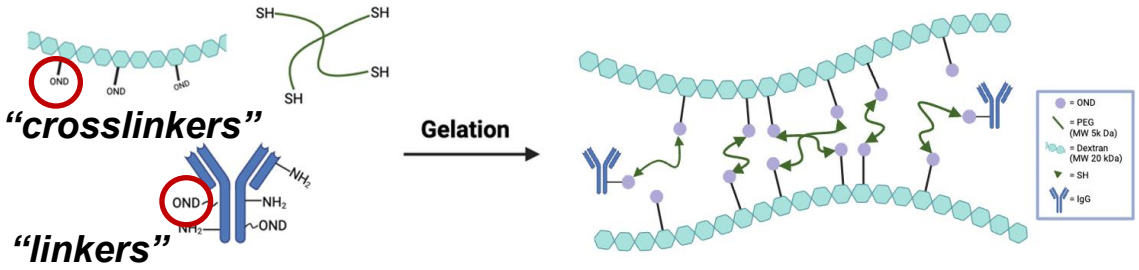




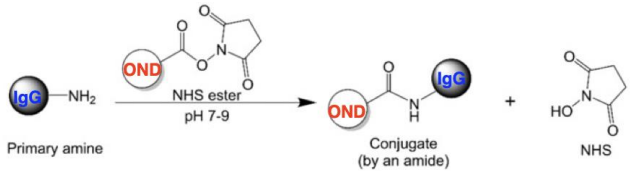


Chemistry + Topology = customized release patterns over 3 weeks: burst, linear, delayed, exponential

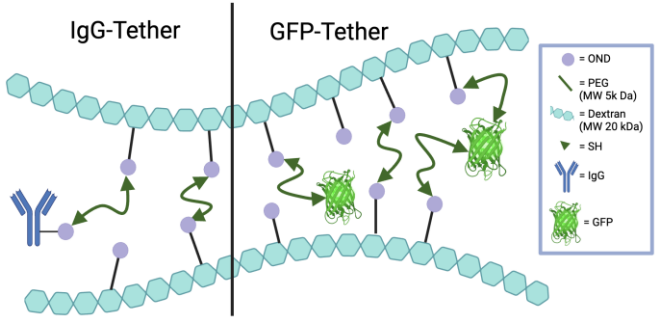
Expanding small biologic modalities: adding tethering approaches

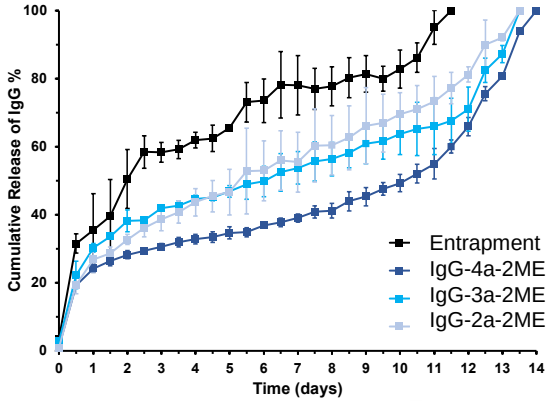


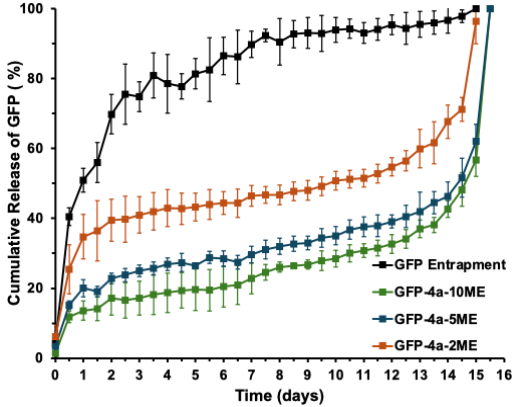
NHS-ester bioconjugation



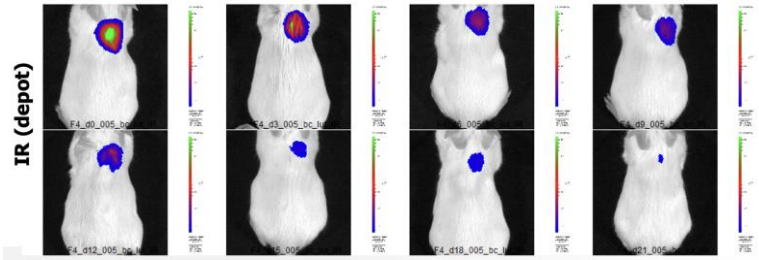
IgG (150 kDa) and GFP (30 kDa) tethered using different ONDs

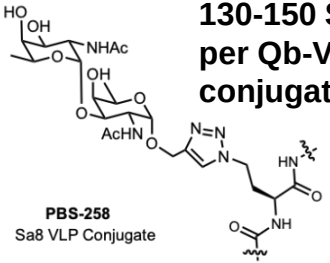






In vivo characterization & long-acting immunization



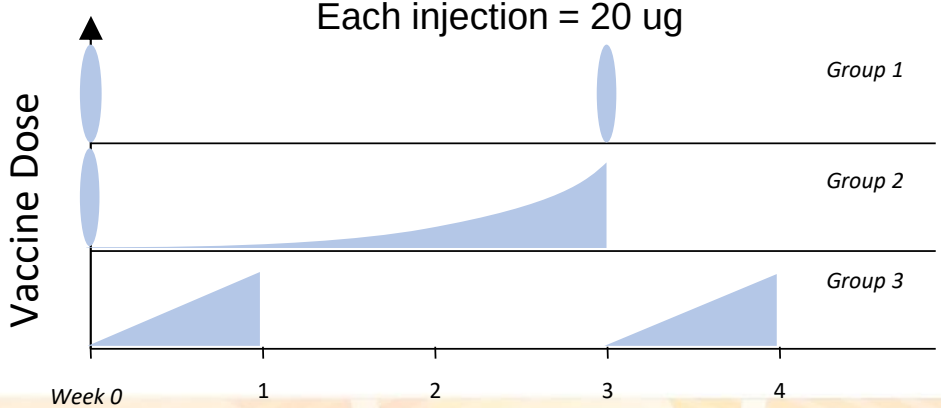


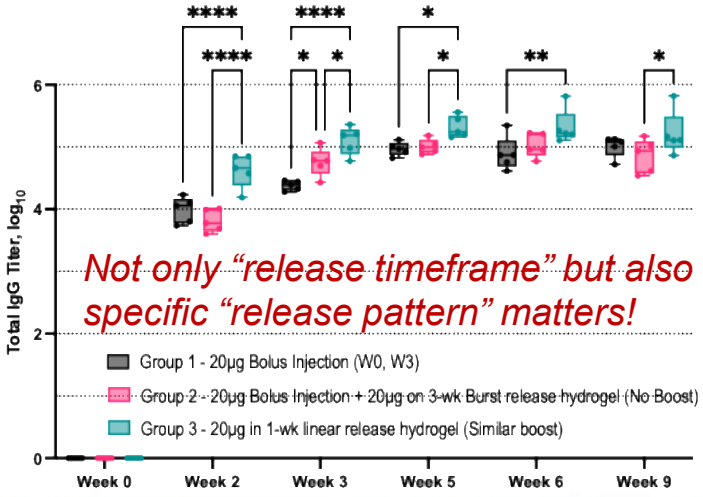
PBS-258
Sa8 VLP Conjugate

130-150 Sa8 glycan per Qb-VLP → conjugate vaccine

Staphylococcus aureus (Sa)

40 ug total over course of injections
Each injection = 20 ug

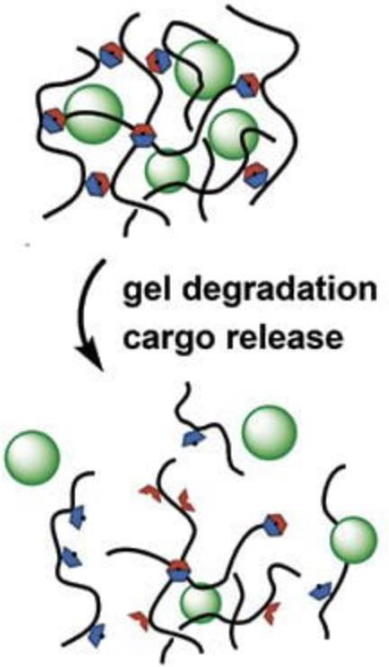




Conclusion & Takeaways

Material contains the seeds of its own destruction!

- Developed injectable hydrogels with **programmable degradation** via OND chemistry
- Enabled **precise control over release kinetics profiles**—burst, linear, delayed, exponential—for multi-scale cargo (VLPs, IgG, GFP) over 2-3 weeks
- Demonstrated **enhanced immune respons**es from sustained in vivo vaccine delivery



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Mridula Nandi, PhD
Seth Taylor, PhD

Thank you for listening!