FISCHELL DEPARTMENT OF BIOENGINEERING
RESPIRATORY NANO BIOENGINEERING LAB

Engineering synthetic mucus biomaterials for local therapeutic delivery

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Fischell Department of Bioengineering
University of Maryland

Respiratory Nano Bioengineering (RnB) Laboratory

We engineer new tools to understand and better treat respiratory disease

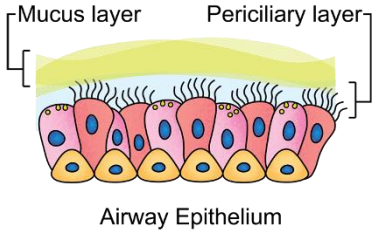
OUR RESEARCH

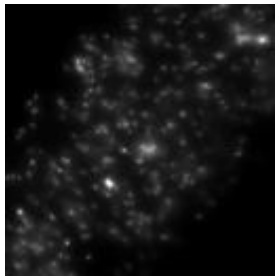
Airway clearance

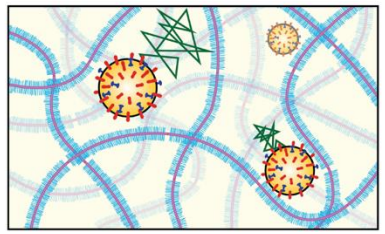
Respiratory infection

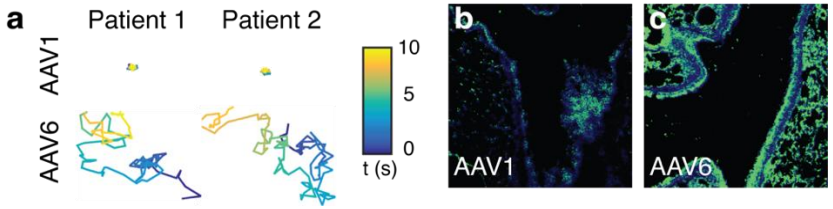
Biomaterials

Drug/Gene Delivery









OUR GOALS

Understand the lung airway microenvironment

Identify new biophysical mechanisms of infection

Overcome biological barriers to drug & gene delivery

Train scientists & engineers from diverse backgrounds

FISCHELL DEPARTMENT OF BIOENGINEERING

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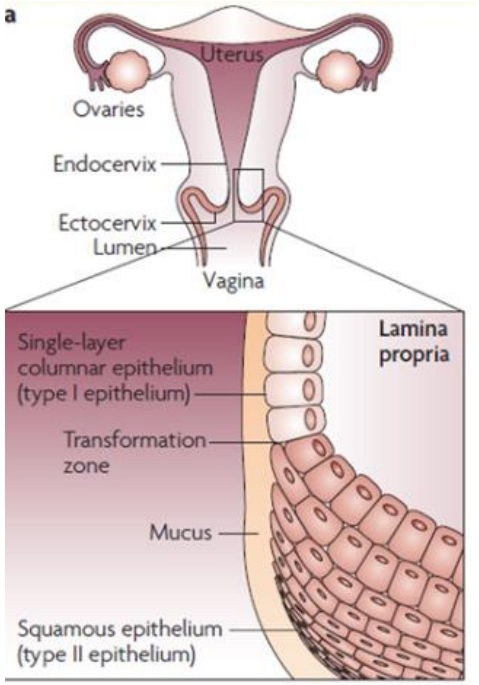
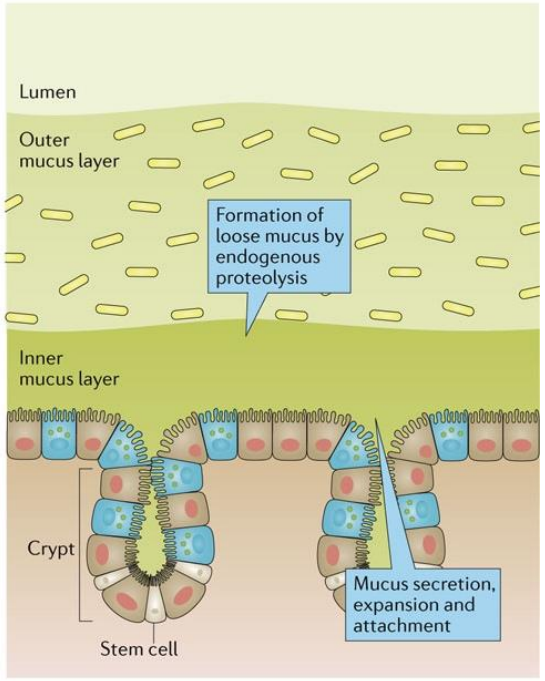
Mucus has diverse, tissue-specific functions

Mucus acts to protect epithelial surfaces and shape the microenvironment

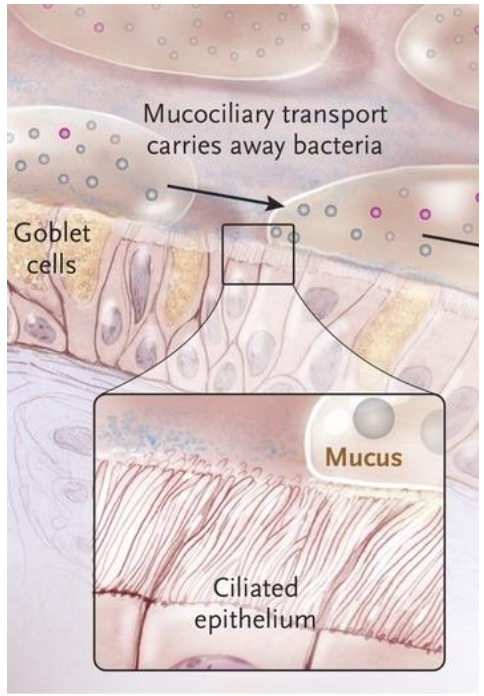
Reproductive tract[1]



Intestinal tract[2]



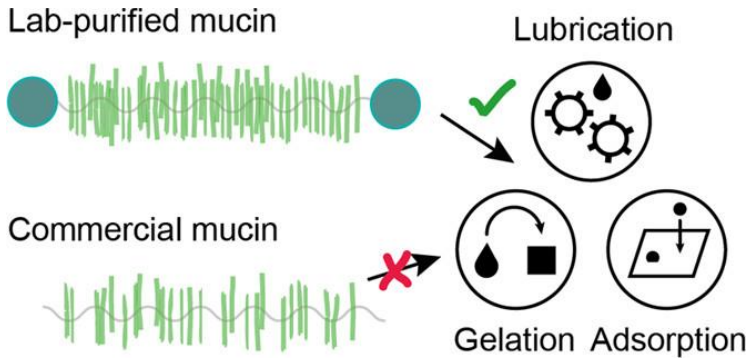
Respiratory tract[3]

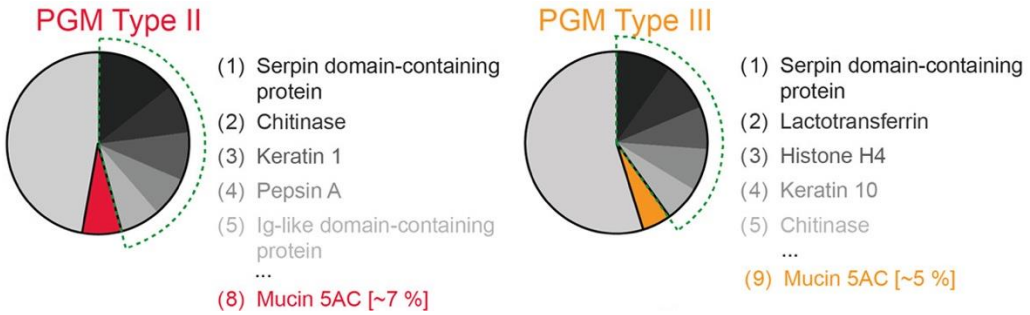


1. Iwasaki, *Nature Reviews Immunology* (2010)
2. Johansson & Hansson, *Nature Reviews Immunology* (2016)
3. Stoltz et al, *New England Journal of Medicine* (2015)

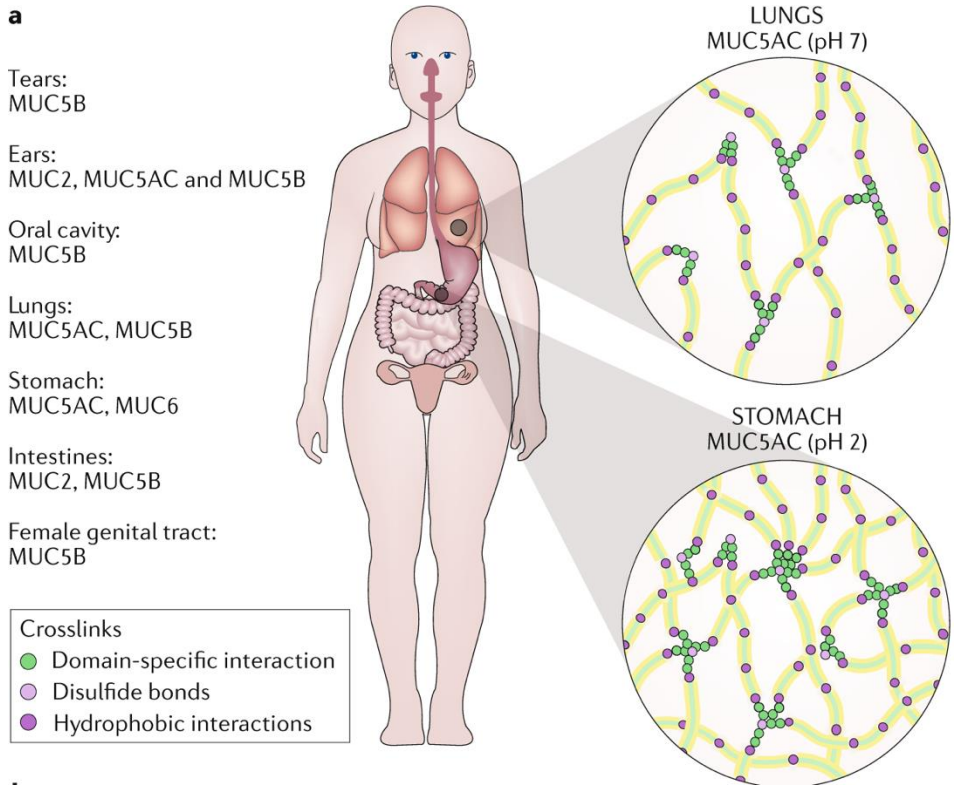
Disclaimer: Not all mucins are the same

Commercial mucins are imperfect





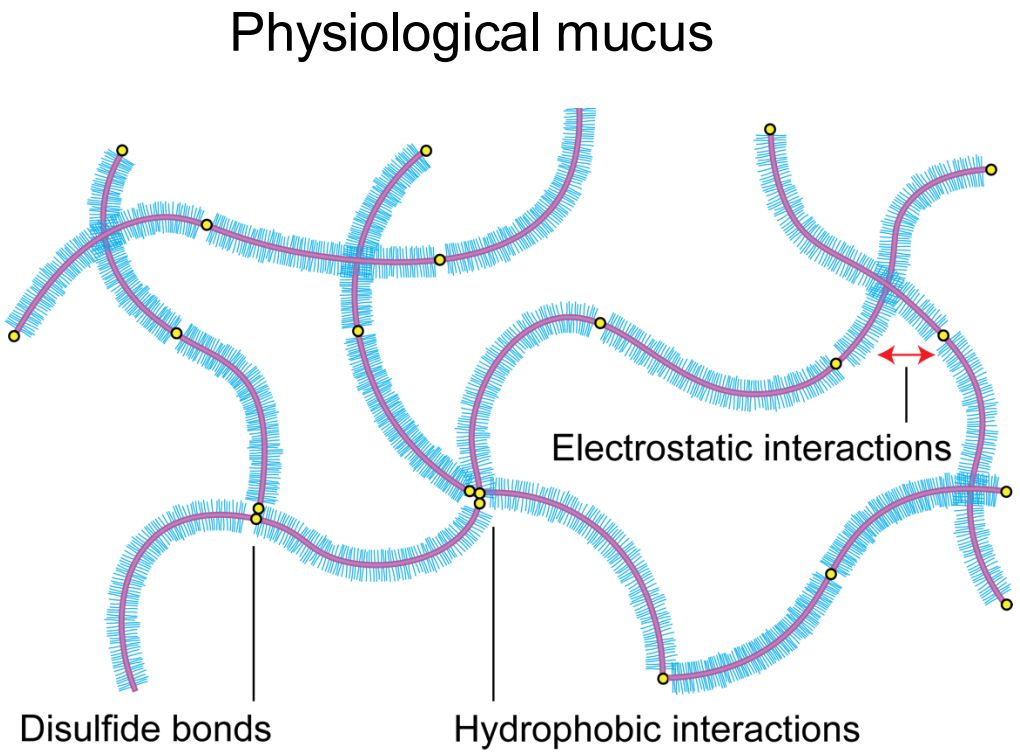
Mucus composition varies from tissue to tissue



Marczynski et al, *Biomacromolecules* (2021)
Werlang et al, *Nature Reviews Materials* (2019)

From mucins to mucus

Mucins organize via disulfide bonds, non-covalent interactions, and entanglements



5% porcine gastric mucin (PGM)

Human mucus

Crude mucins at physiological concentration and buffer conditions do not form mucus gels

Song et al, *Langmuir* (2020)

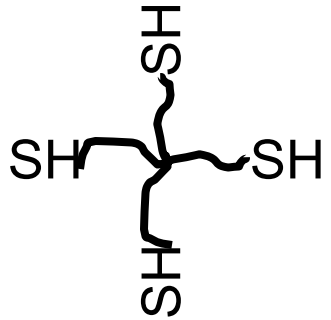
Engineering mucin-based hydrogels

Mucin-based hydrogel formed via 4-arm PEG thiol crosslinker

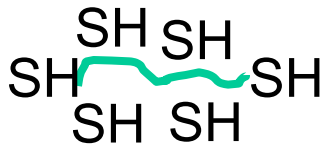
Crosslinkers (CL) tested:

PEG-2SH

PEG-4SH

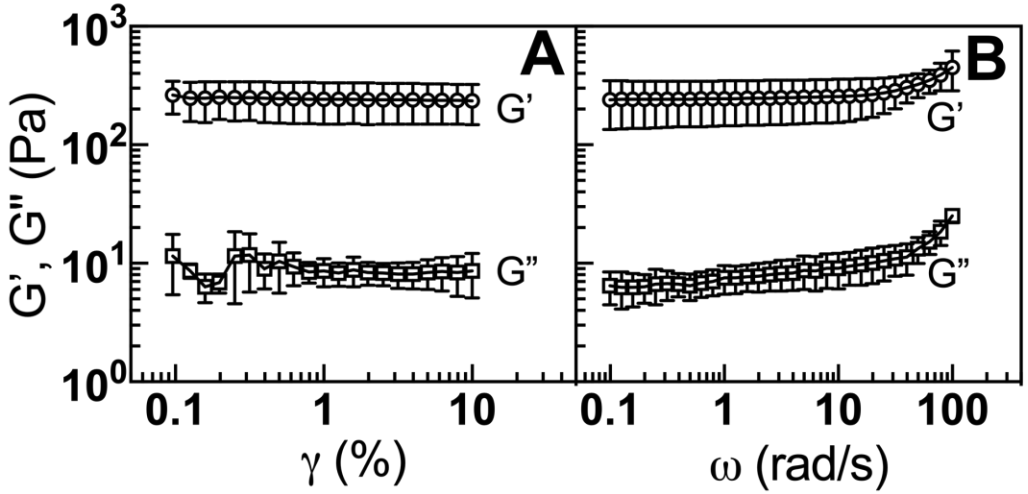


dextran-SH



Strain sweep at 1 rad/s

Frequency sweep at 1% strain



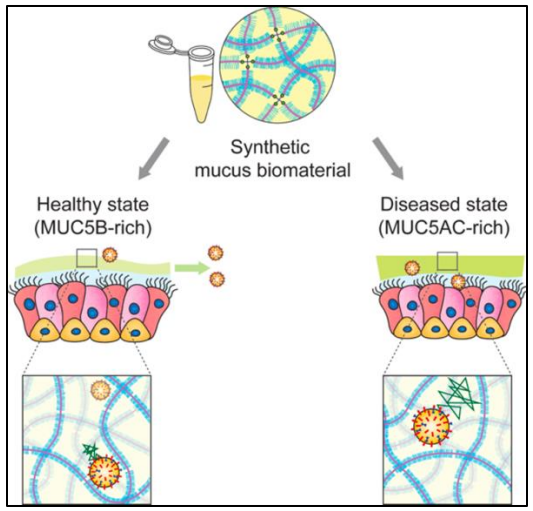
Mucin hydrogel crosslinked with 4-arm PEG-thiol

Joyner & Song et al, *Soft Matter* (2019)

Synthetic mucus biomaterials

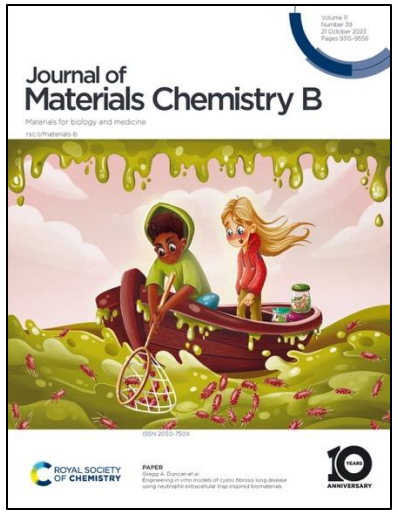
Synthetic mucus biomaterials as models of lung dysfunction

Asthma



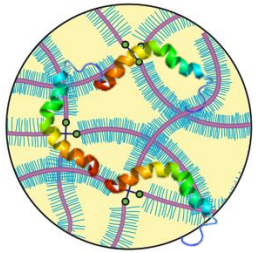
Song et al,
ACS Biomaterials Sci (2021)

Cystic Fibrosis

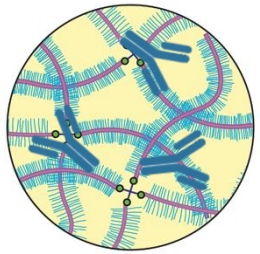


Boboltz et al,
J Mat Chem B (2023)

Synthetic mucus biomaterials as platform for drug delivery



Antimicrobial delivery
Yang et al, JBMR Part A (2023)
Yang et al, Adv Ther (2025)

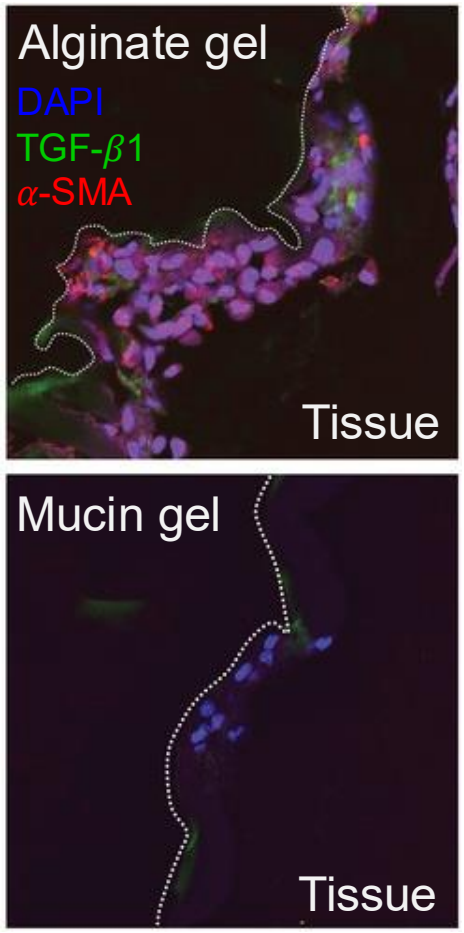


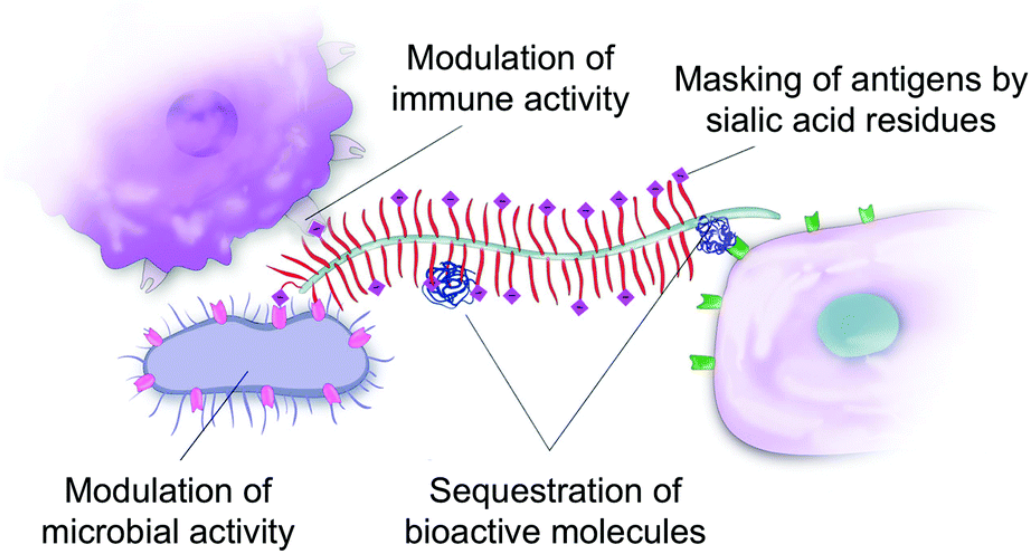
Monoclonal antibody delivery
Yeruva & Yang et al, In Prep

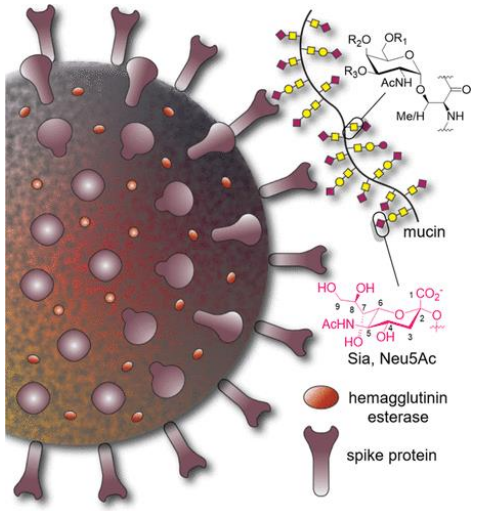
Key collaborator: Katharina Maisel

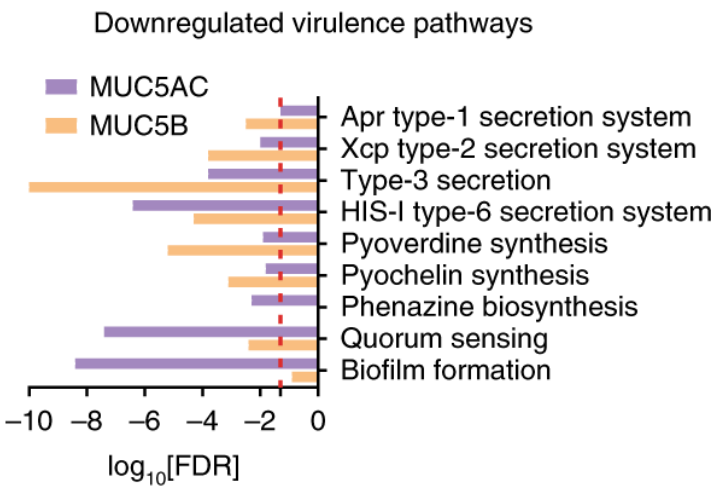
Recapitulating the antimicrobial and immunological functions of native mucus

Mucus and its constituents are key legislators of host-pathogen interactions





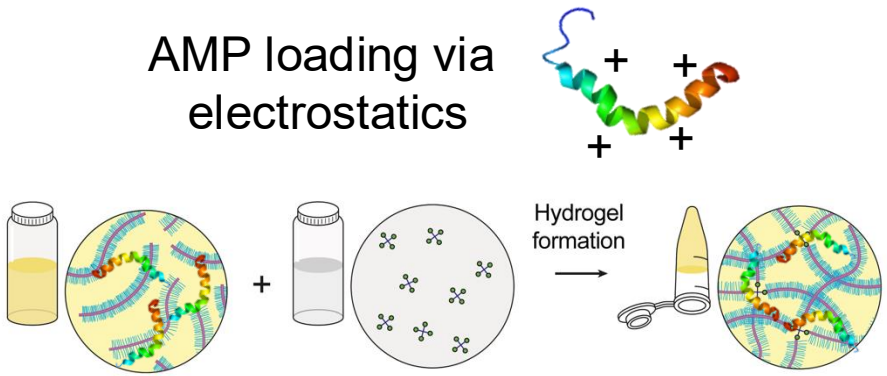


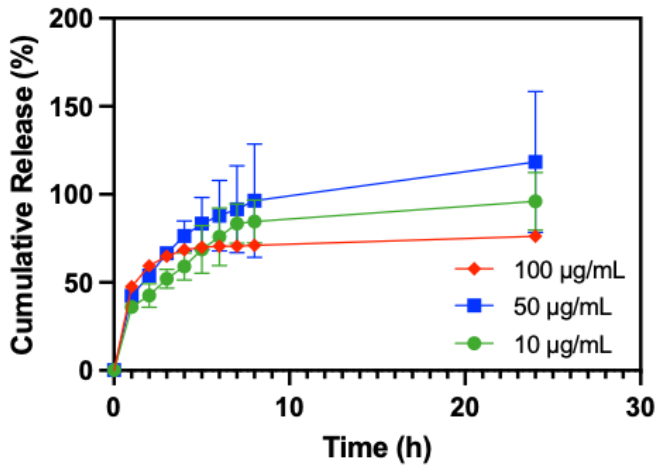


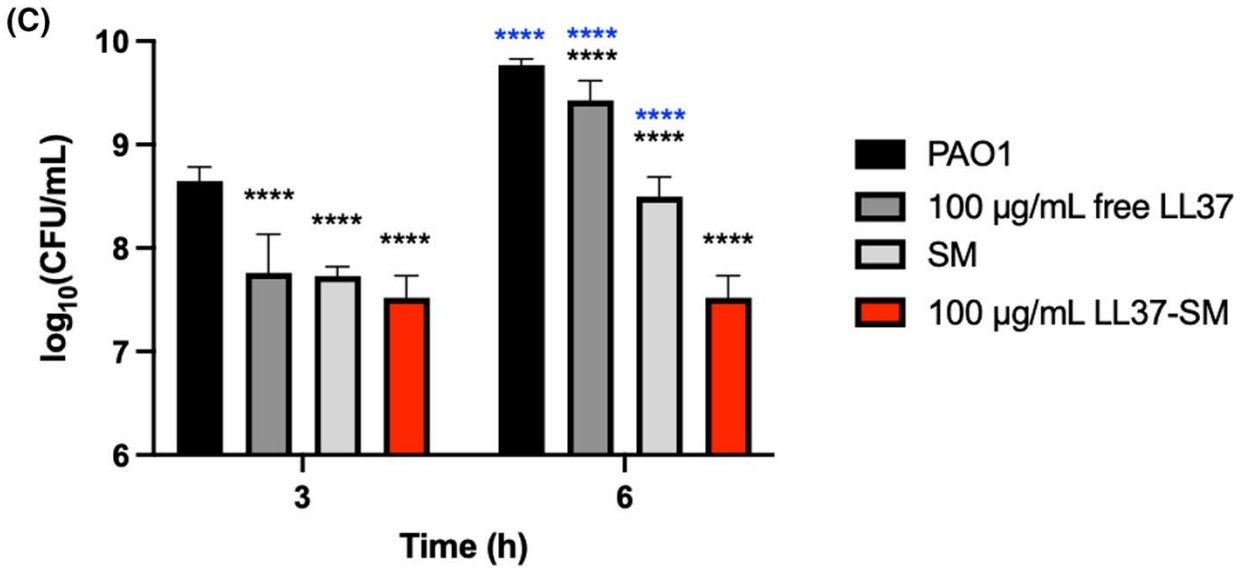
Petrou et al, *Biomaterials Science* (2018)
Wheeler et al, *Nature Microbiology* (2019)
Yan et al, *Advanced Functional Materials* (2019)
Wardzala et al, *ACS Central Science* (2022)

Antimicrobial peptide (AMP) loaded synthetic mucus (SM) biomaterials

Synthetic mucus sustains the bactericidal activity against *P. aeruginosa* GFP







Yang et al, *J Biomed Mater Res* (2023)

Biofilms and antimicrobial resistance

Antibiofilm agents (e.g. DNase, amylase) used to improve antimicrobial efficacy against biofilm-associated infections

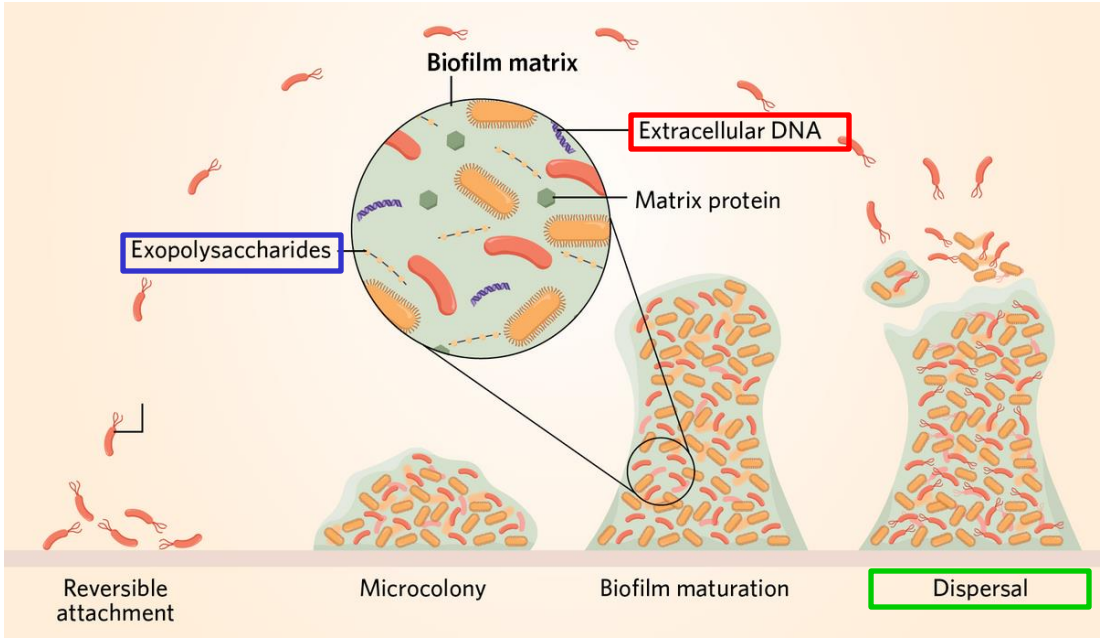
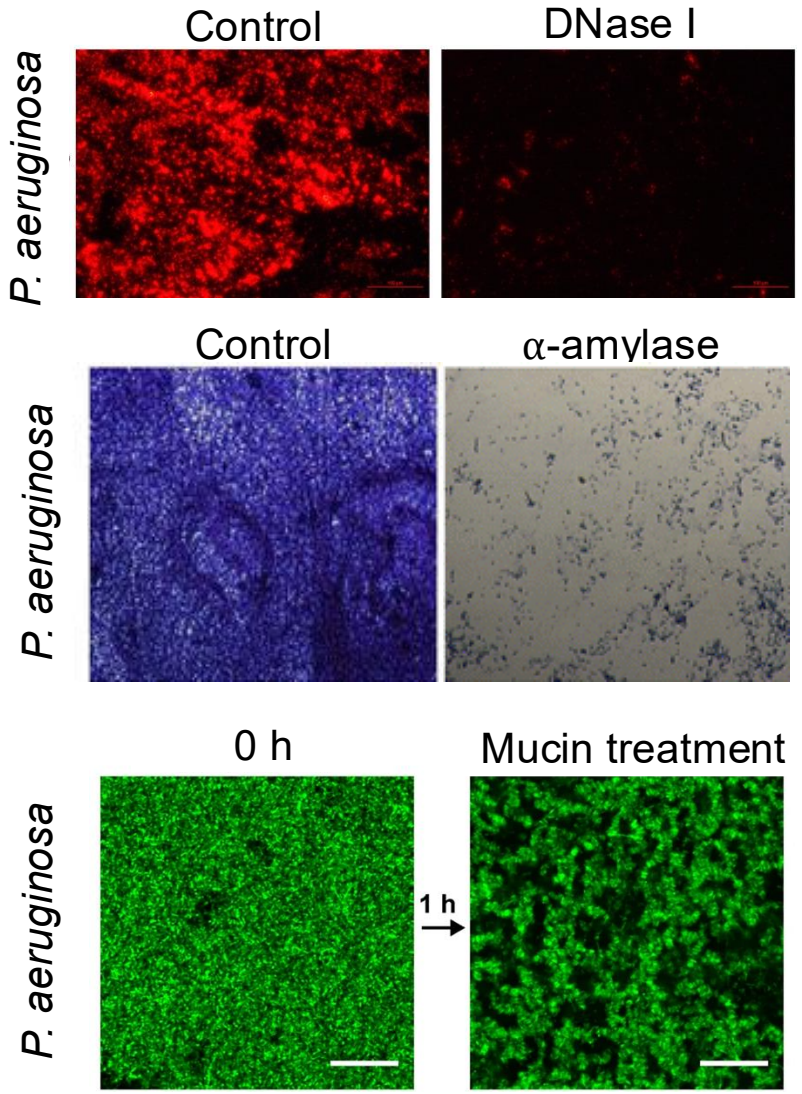


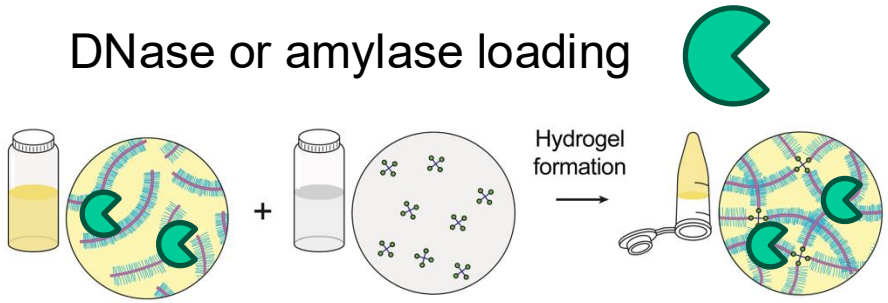
Image Credit: The Scientist

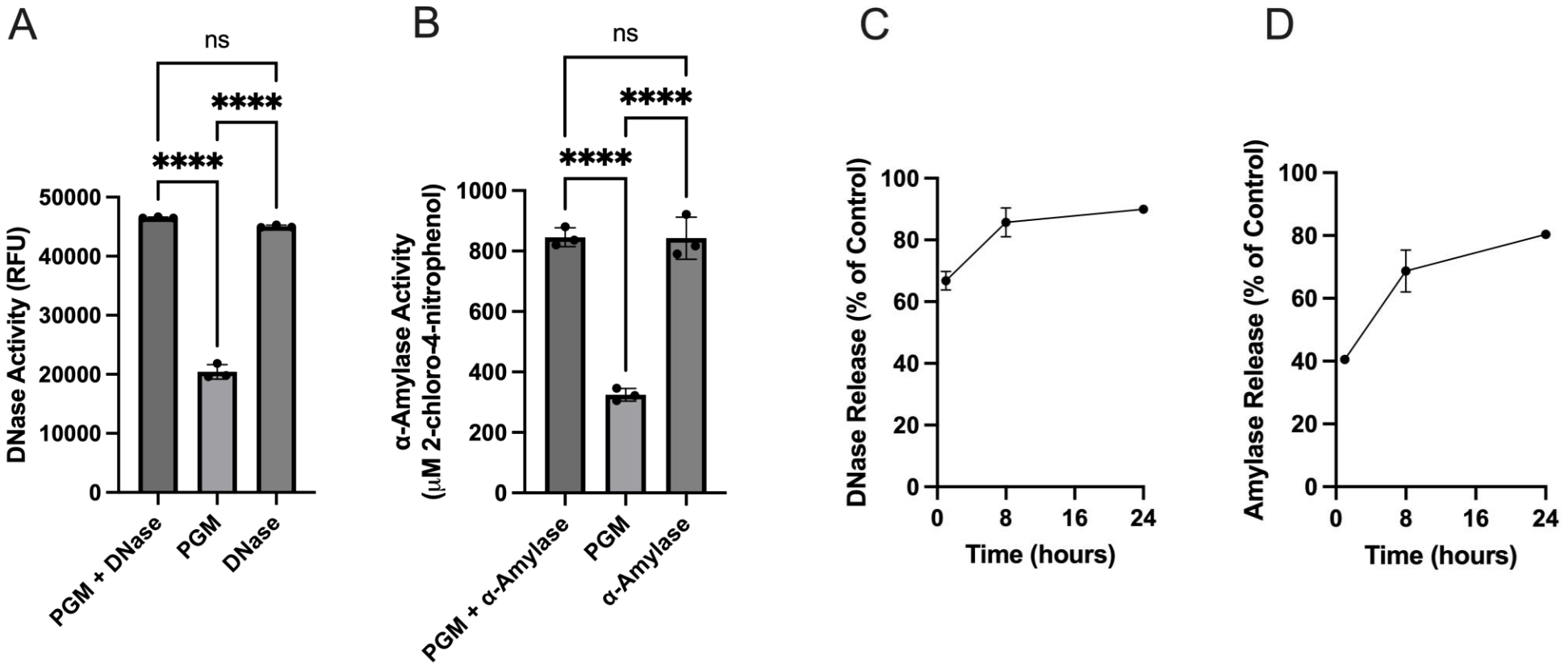


Sauer et al., *Nature Rev Microbio* (2022)
Deng et al., *Front Cell Front Microbio* (2012)
Kalpana et al., *App Biochem Biotech* (2012)
Co et al, *npj Biofilms and Microbiomes* (2018)

DNase / amylase loaded SM hydrogels

Antibiofilm agents loaded in SM hydrogels as combination treatment for *P. aeruginosa* biofilms

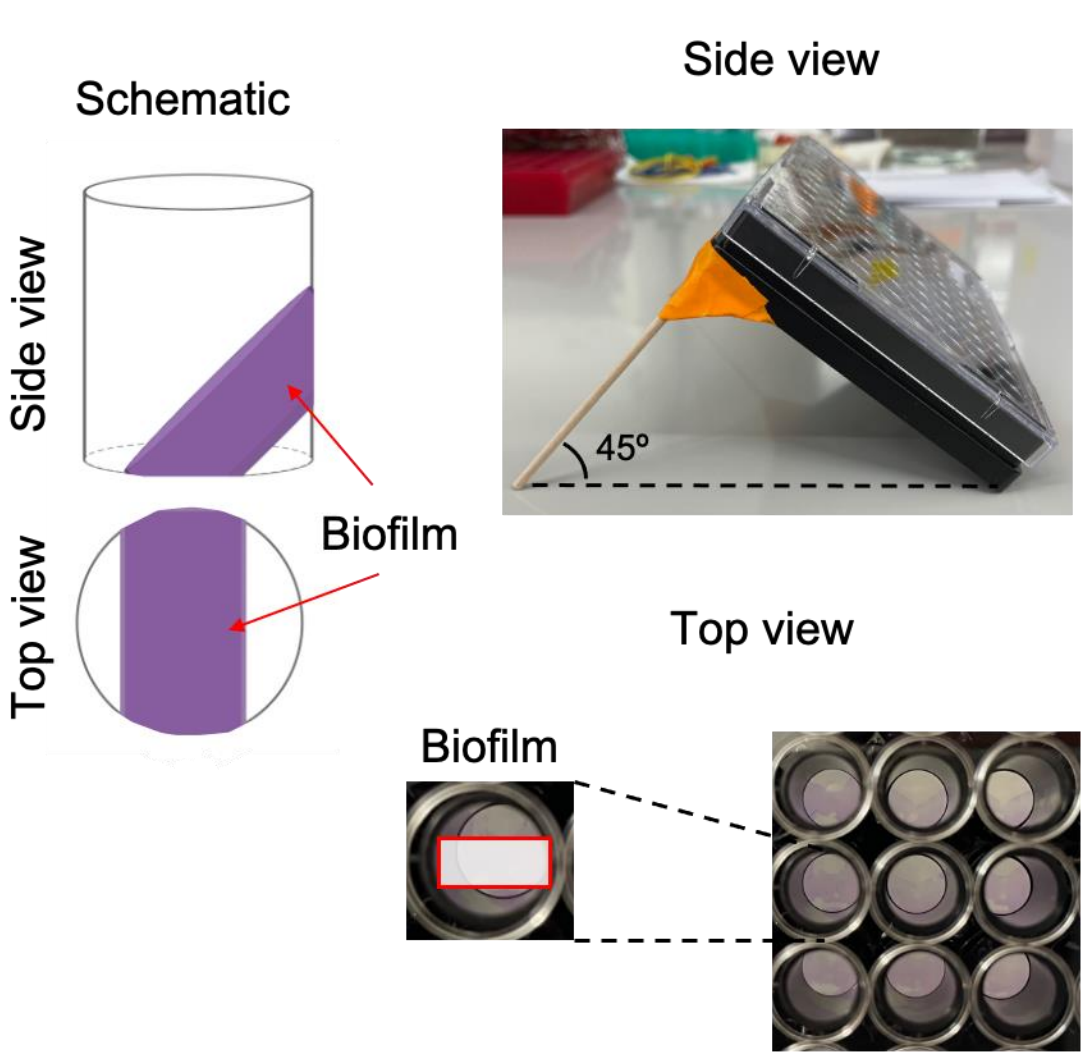


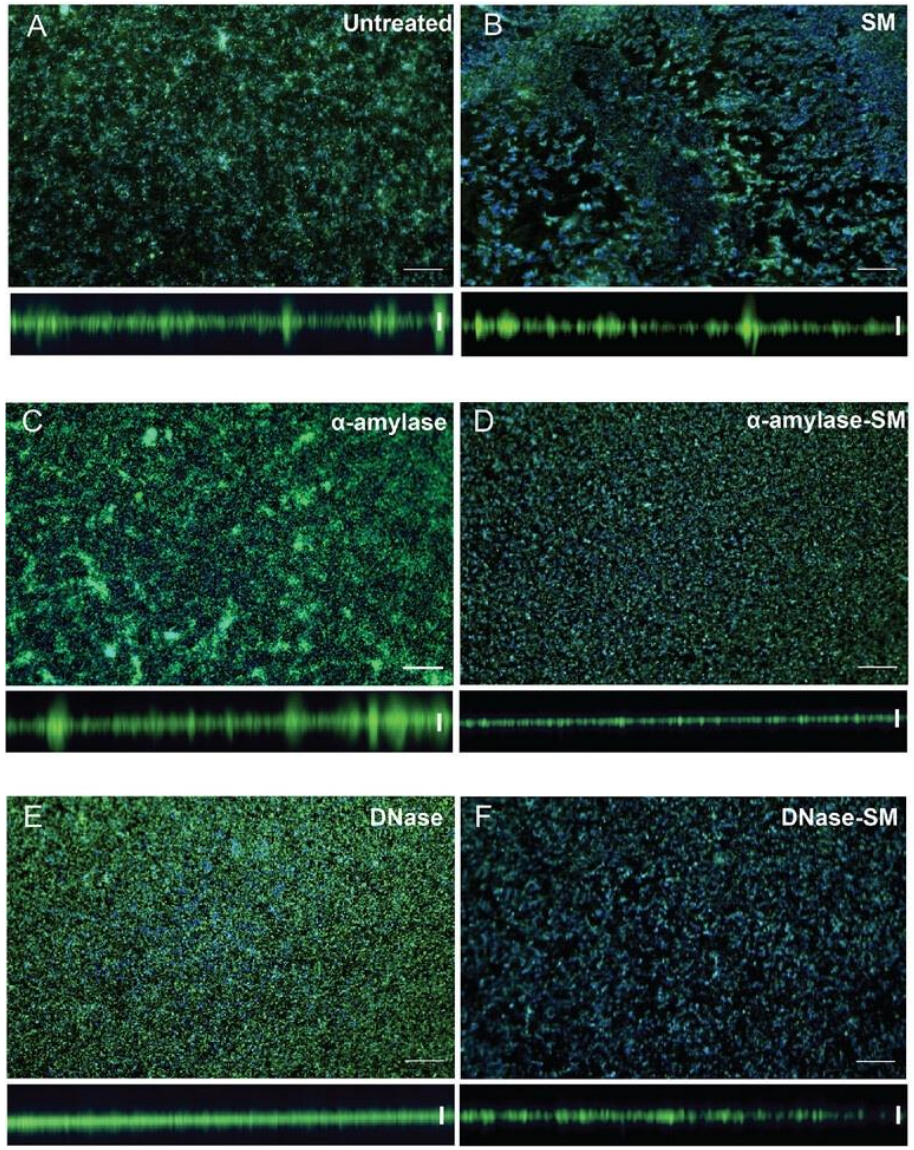


Yang et al, *Advanced Therapeutics* (2025)

Biofilm architecture following treatment with antibiofilm agents and synthetic mucus biomaterials

Significant reductions in biofilm surface area and thickness following amylase/DNase loaded SM treatment

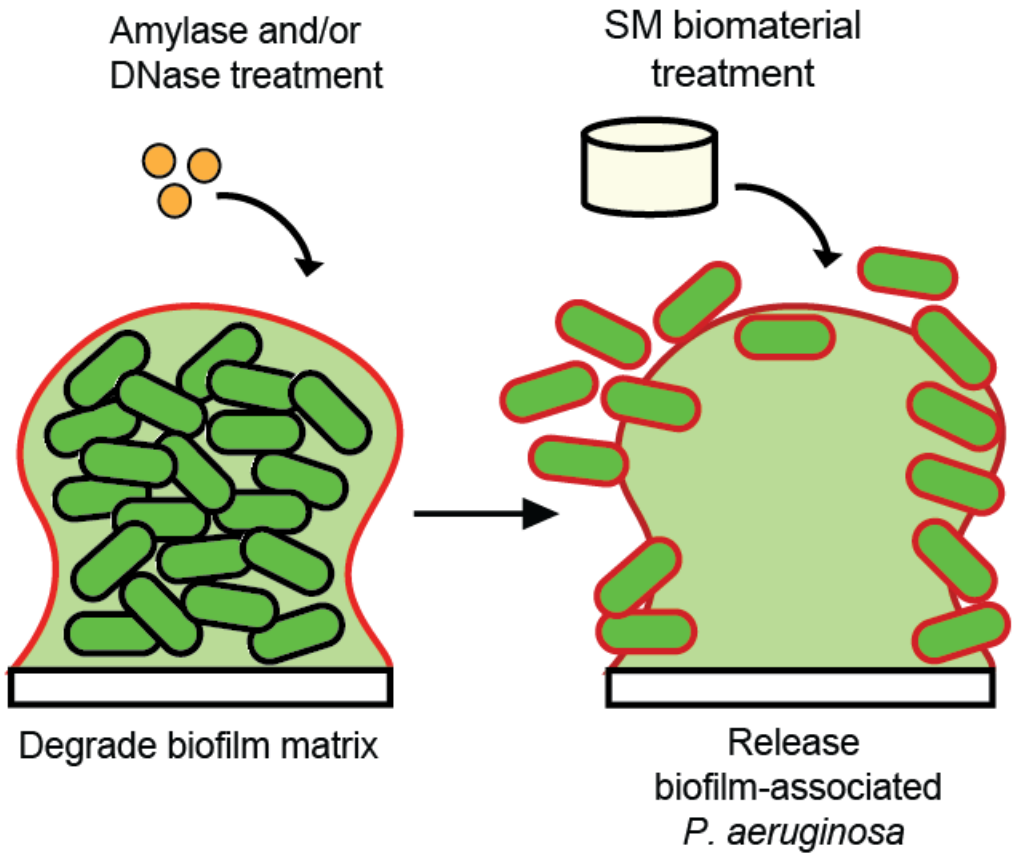


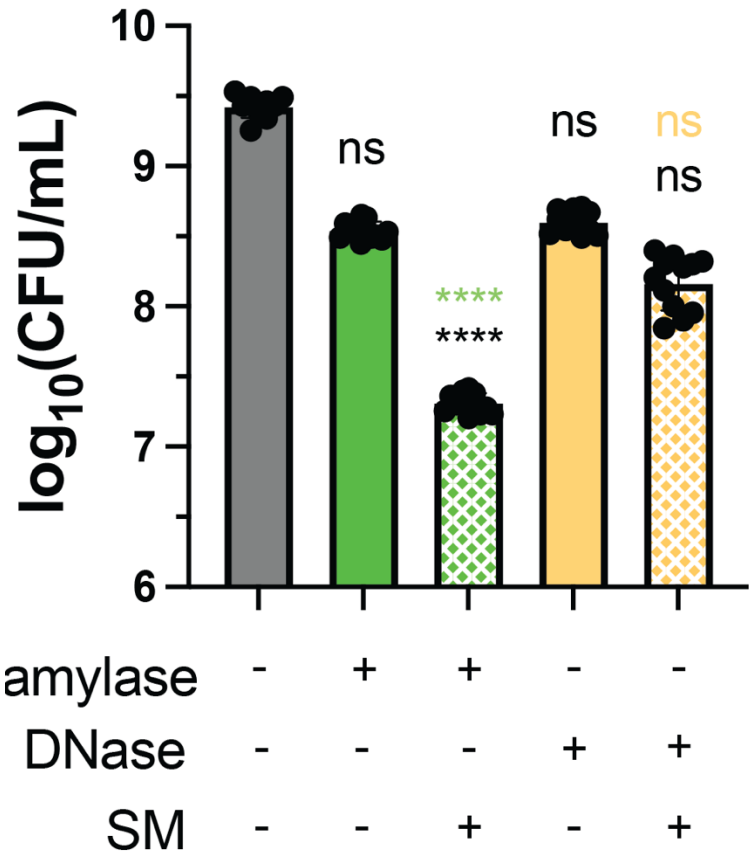


Yang et al, *Advanced Therapeutics* (2025)

Sequential treatment improve synergistic effect of antibiofilm agents with synthetic mucus biomaterials

~2-log reductions in biofilm viability following sequential amylase and synthetic mucus biomaterial treatment

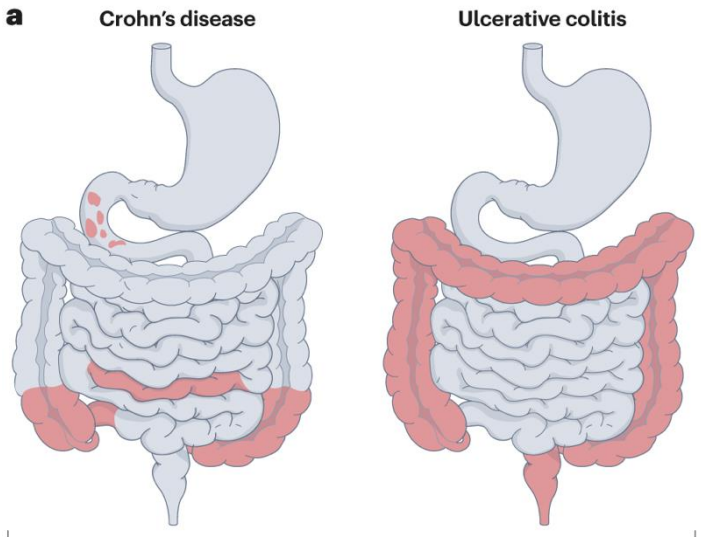


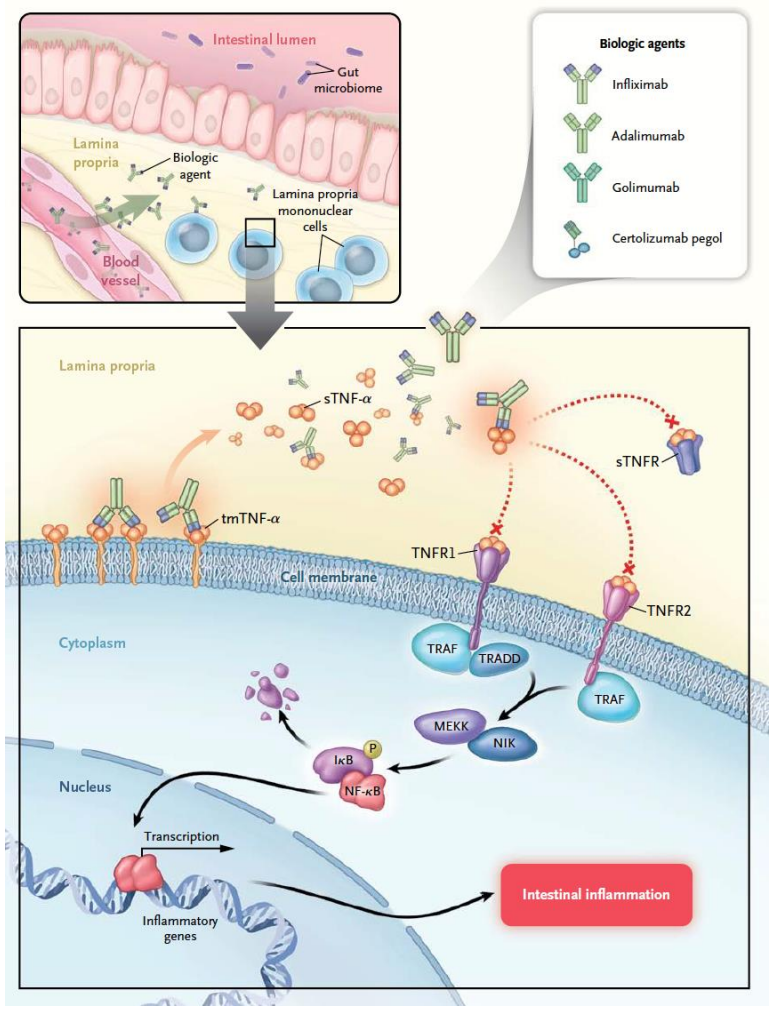


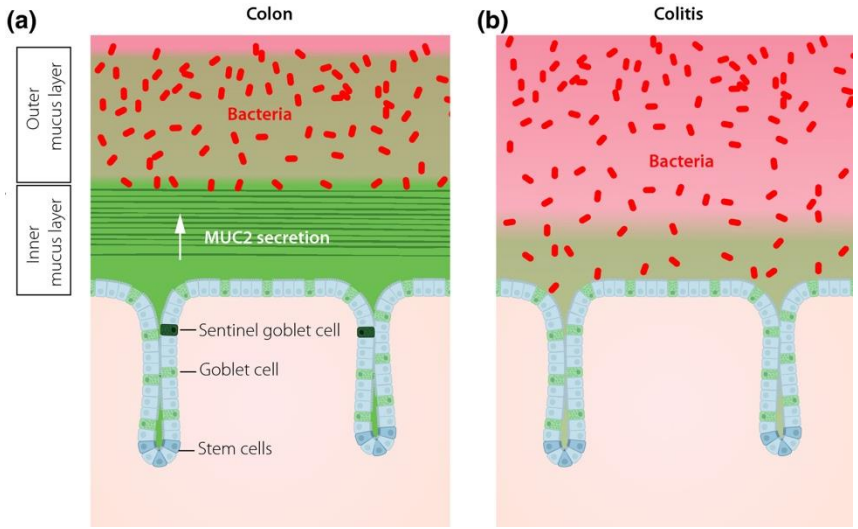
Yang et al, *Advanced Therapeutics* (2025)

Inflammatory Bowel Disease (IBD)

For many patients who do not respond to glucocorticoids, TNF inhibitors are an important treatment option



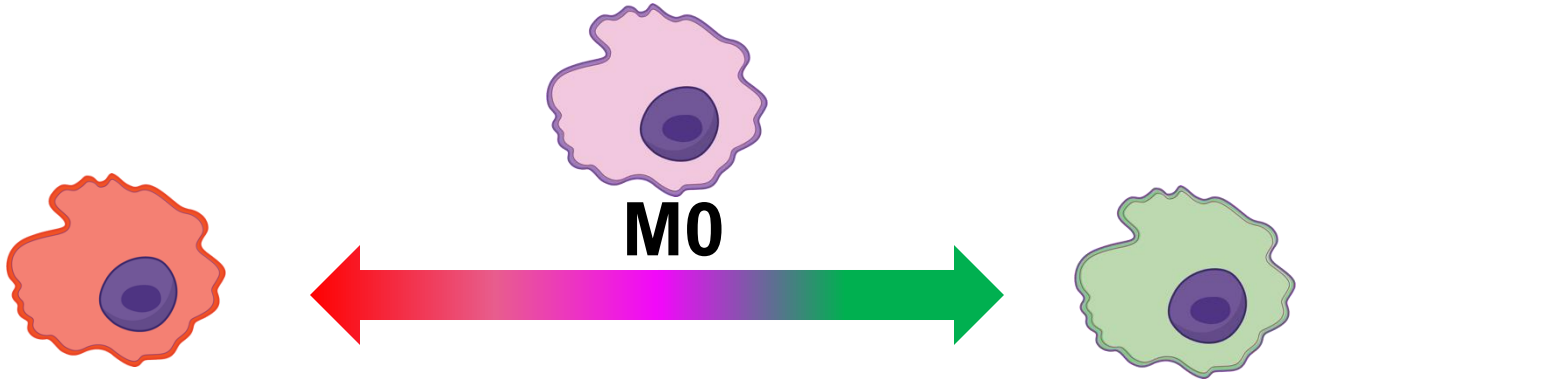




Neurath et al, *Nature Immunology* (2024)
Nielsen & Ainsworth, *NEJM* (2013)
Johansson et al, *Gut* (2012)
Hansson, *J Internal Med* (2019)

Immunomodulatory function of synthetic mucus biomaterials

Can mucins on their own skew macrophage phenotypes?



M1

Pro-Inflammatory

Tissue Injury

↑CD80

↑TNF- α

M2

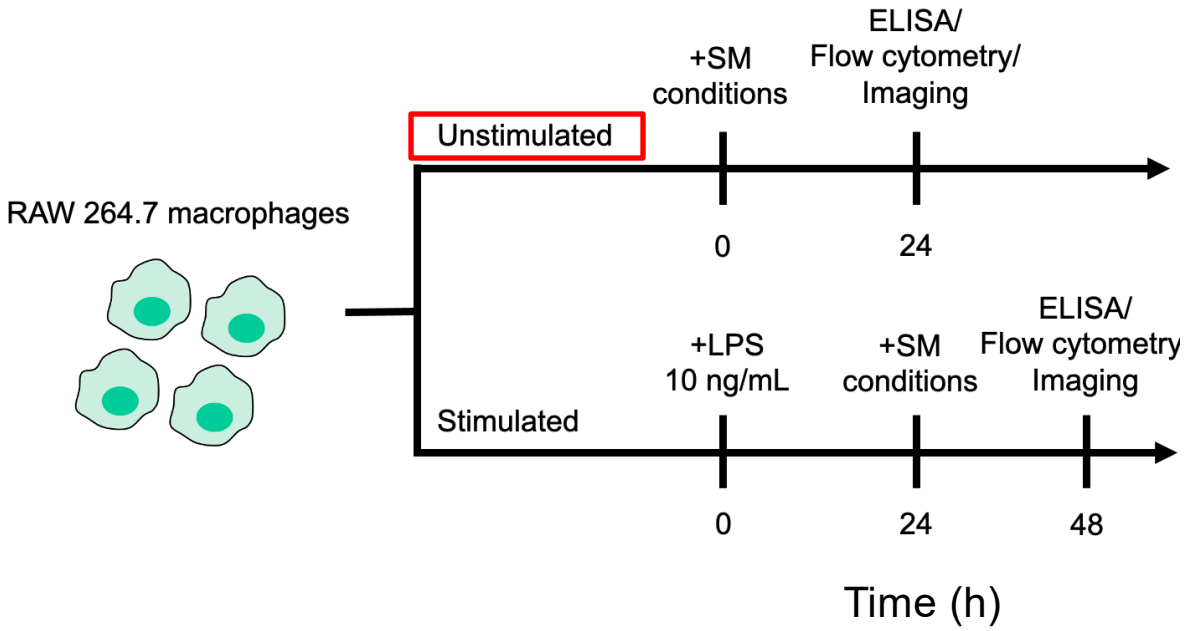
Anti-Inflammatory

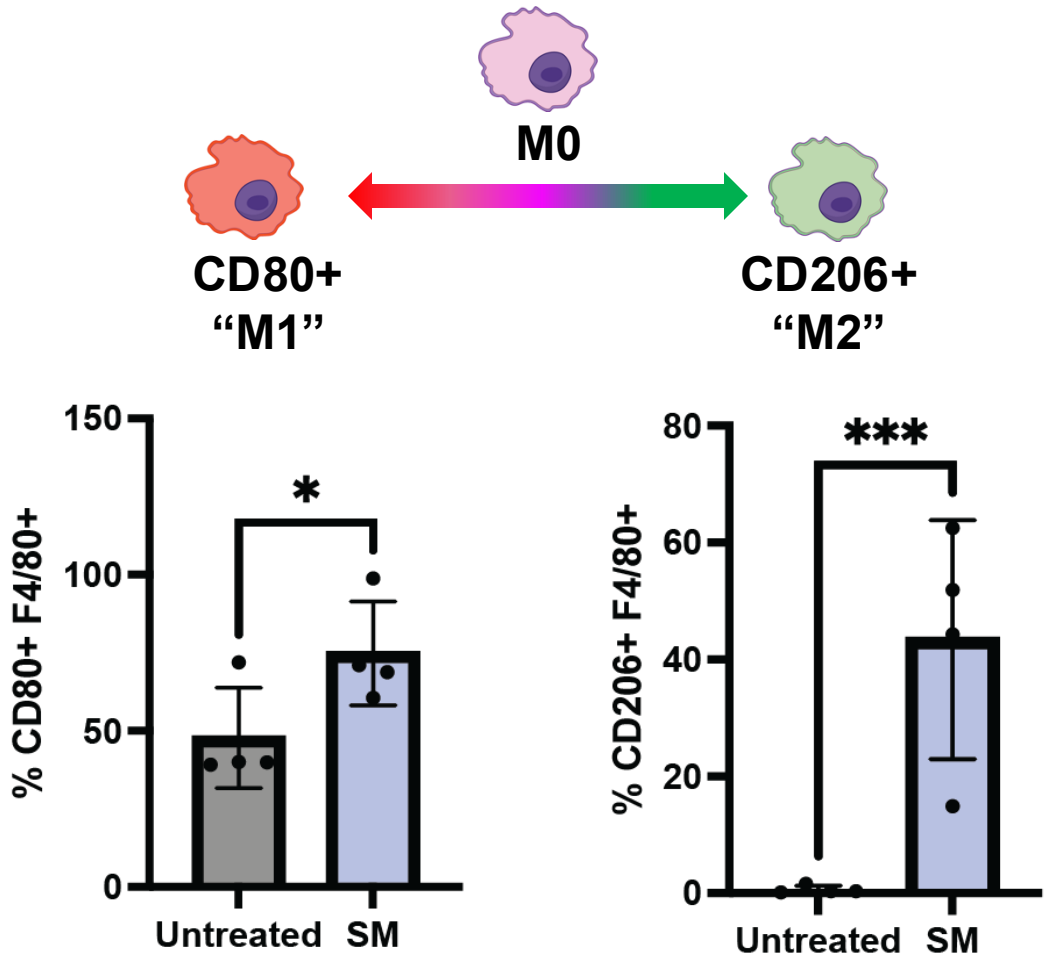
Tissue Remodeling

↑CD206

Immunomodulatory function of synthetic mucus biomaterials

Can mucins on their own skew macrophage phenotypes?





Yeruva & Yang et al, In Prep

Immunomodulatory function of synthetic mucus biomaterials

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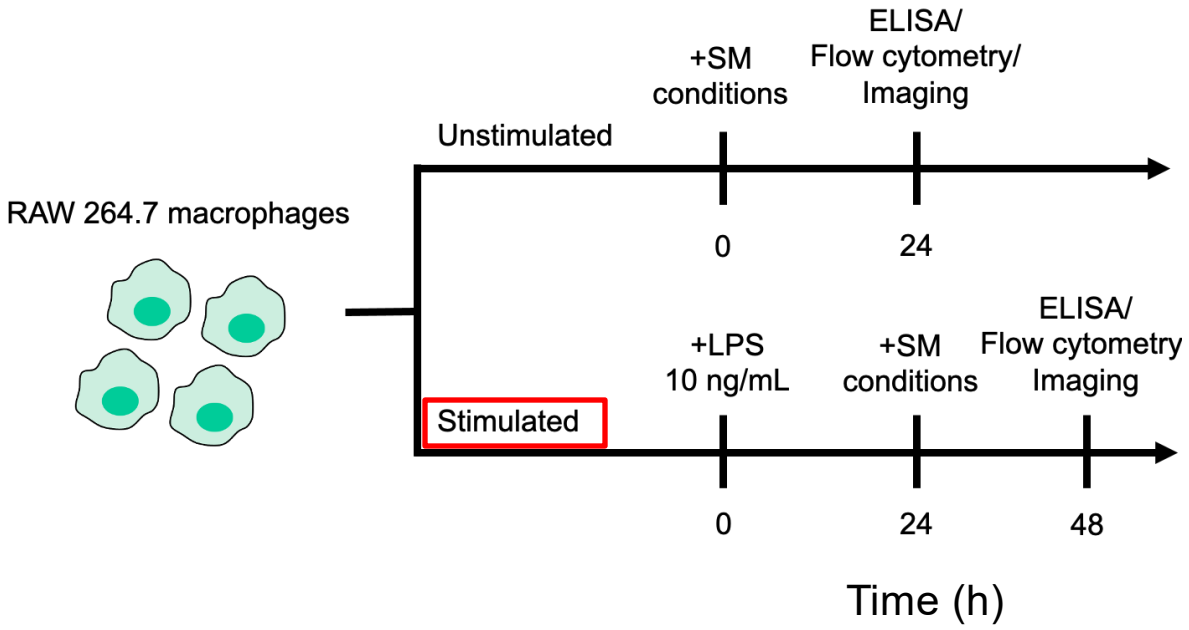
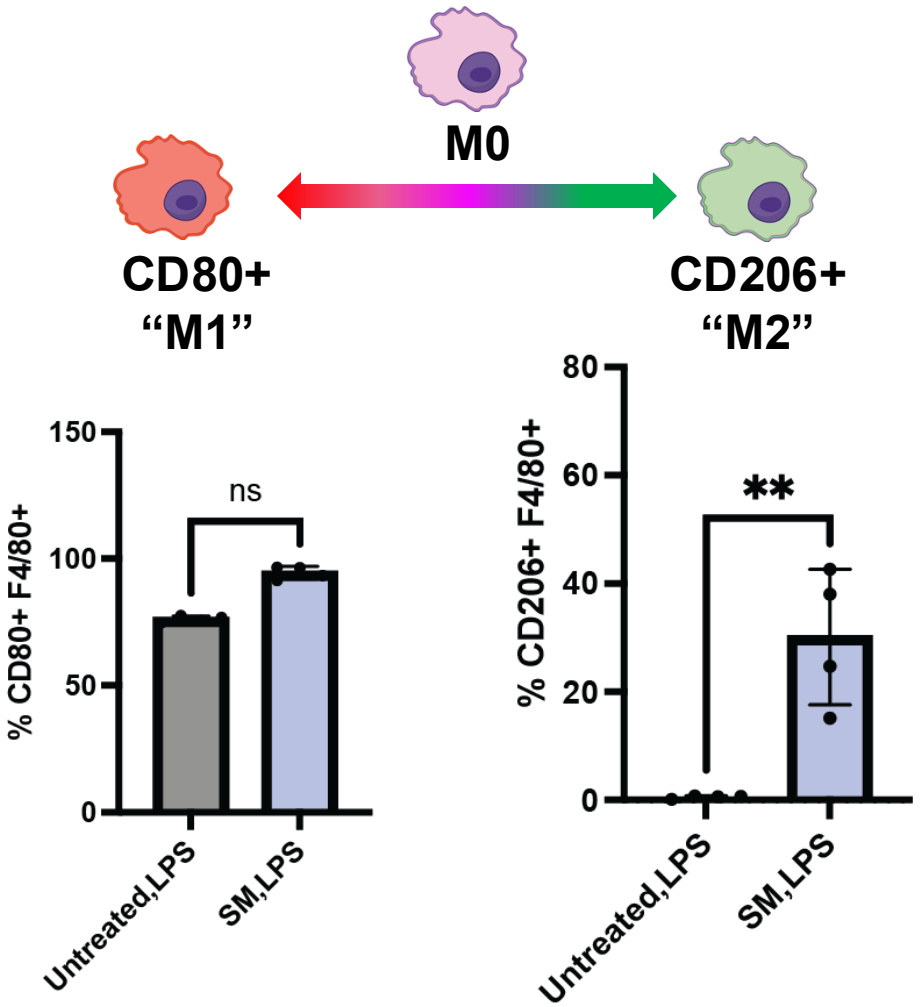
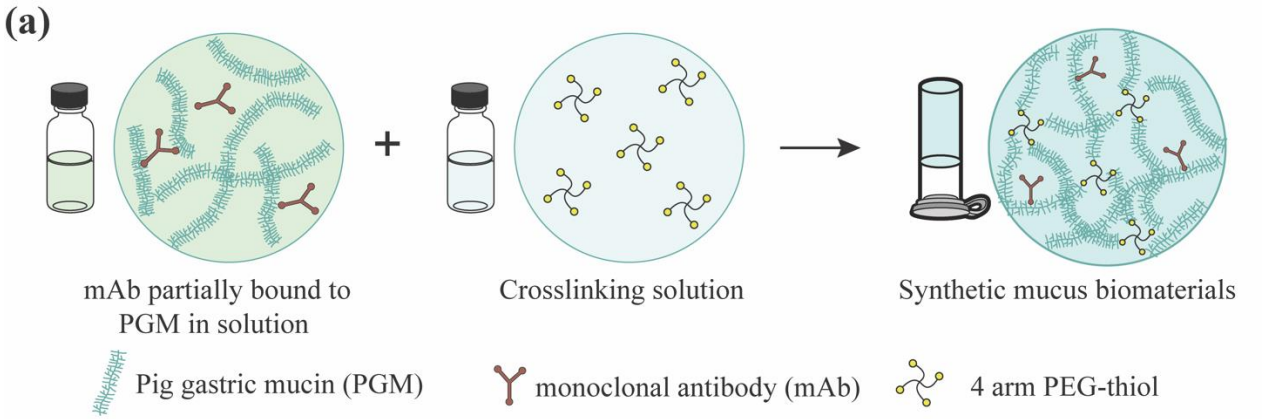


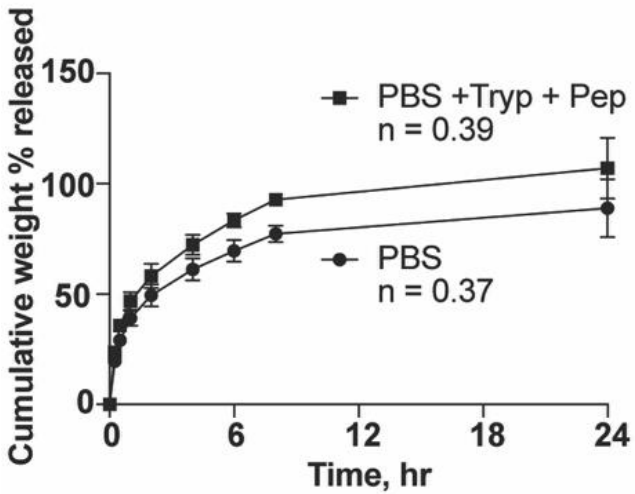


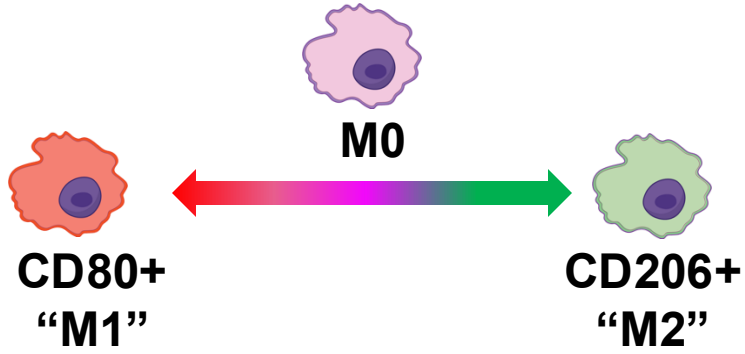
Yeruva & Yang et al, In Prep

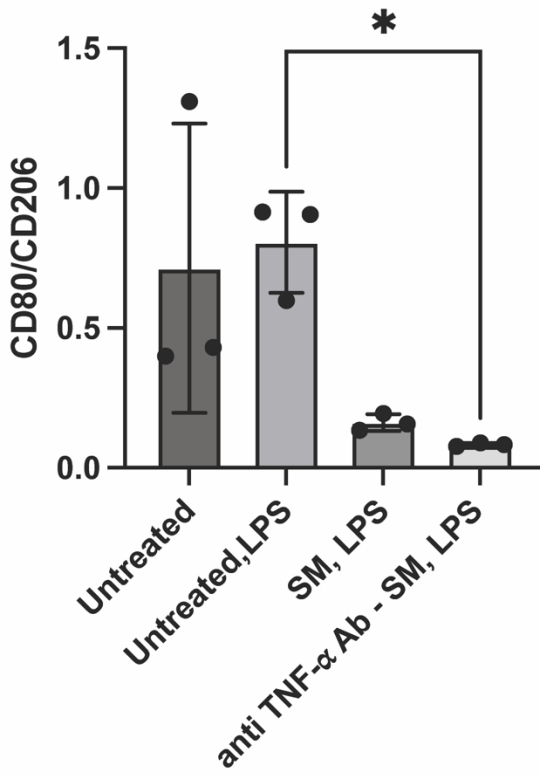
Immunomodulatory function of TNF mAb-loaded synthetic mucus biomaterials

Anti-TNF retains activity in synthetic mucus biomaterials





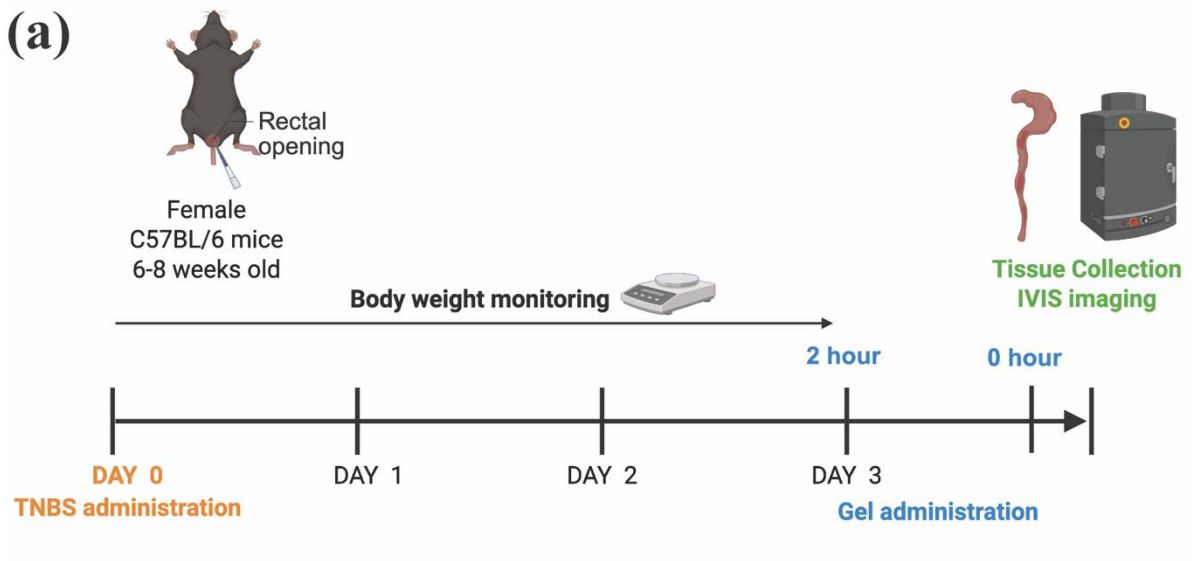




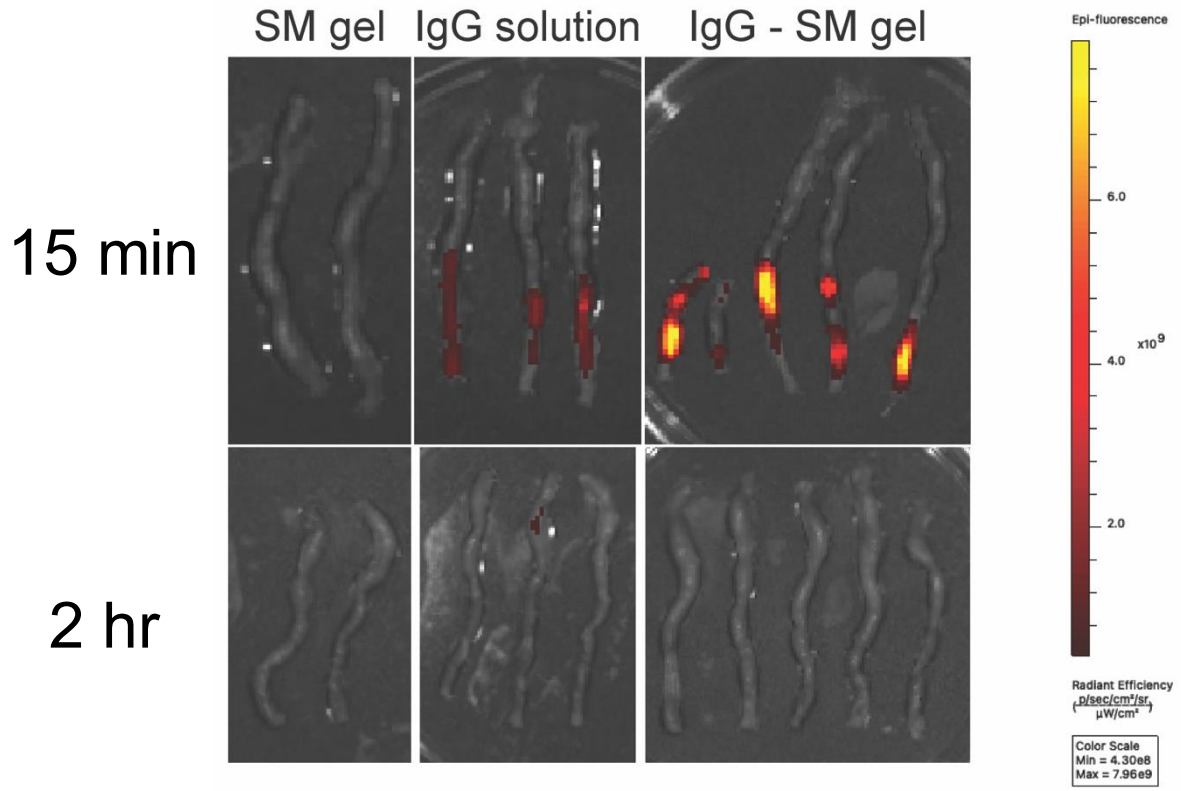
Yeruva & Yang et al, In Prep

Local intrarectal delivery of synthetic mucus biomaterials

Greater adsorption of IgG when loaded in synthetic mucus biomaterial



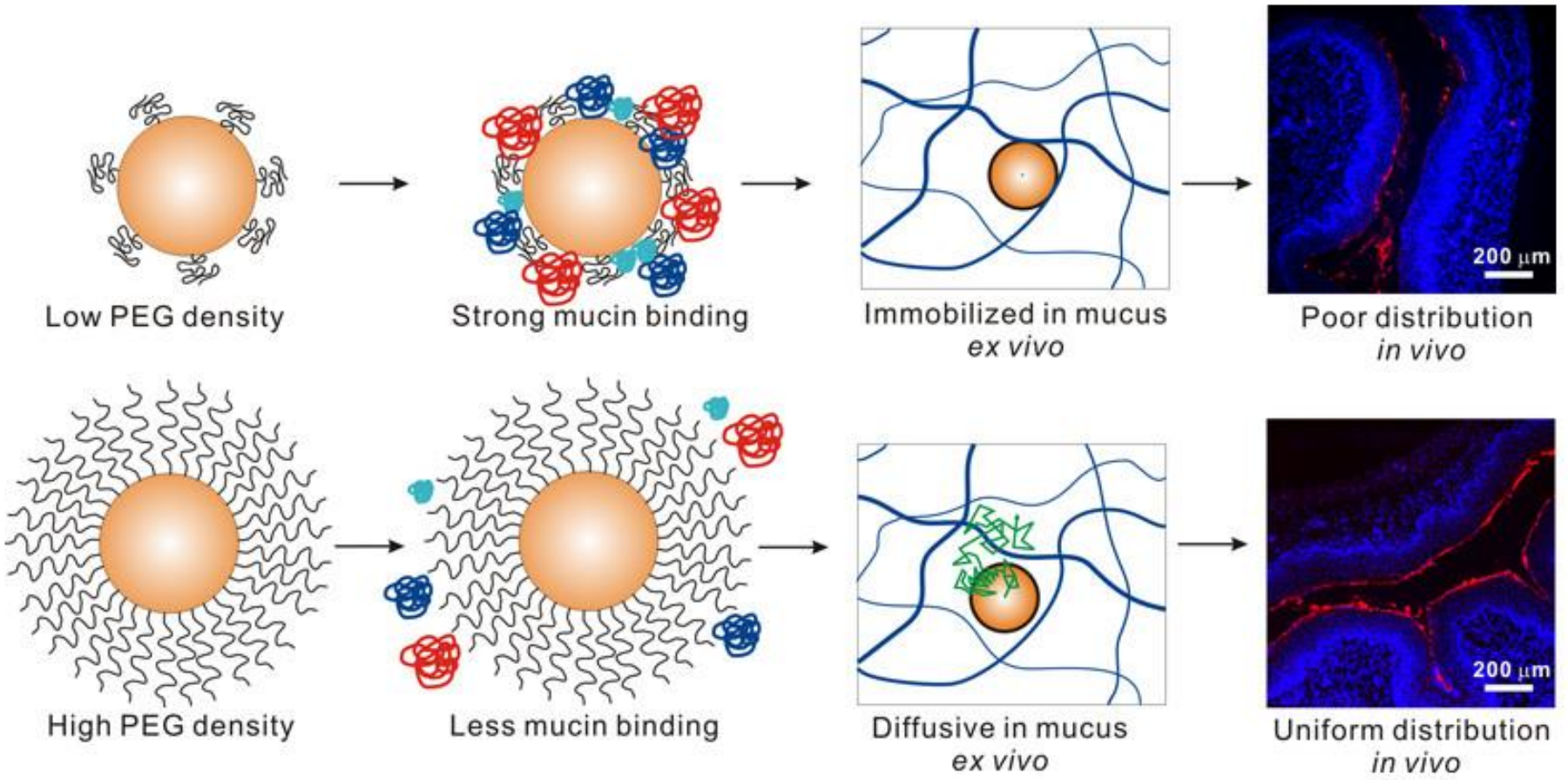
Note: mice showed no weight loss, decreases in colon length or obvious signs of disease



Yeruva & Yang et al, In Prep

Overcoming the mucus barrier to nanoparticle drug delivery

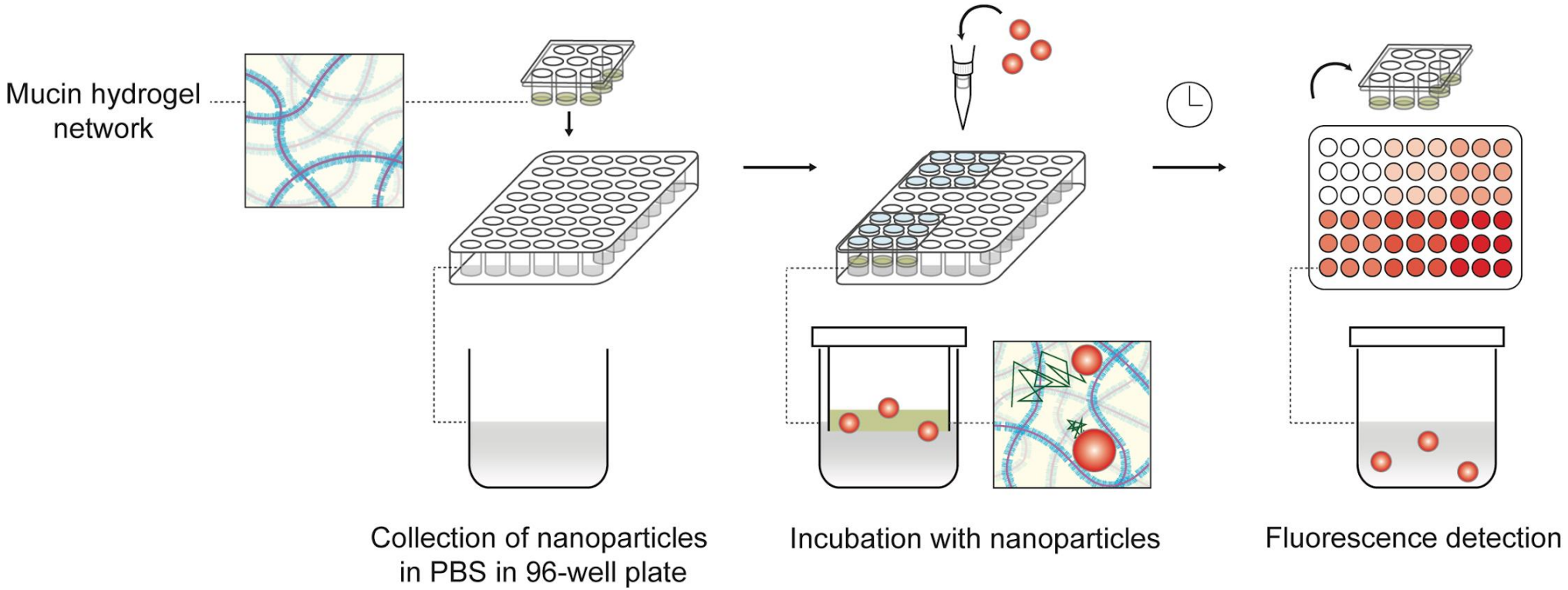
Dense polyethylene glycol (PEG) coatings improve mucus penetration



Xu et al, *ACS Nano* (2015)

Synthetic mucus barrier arrays as a nanoparticle formulation screening platform

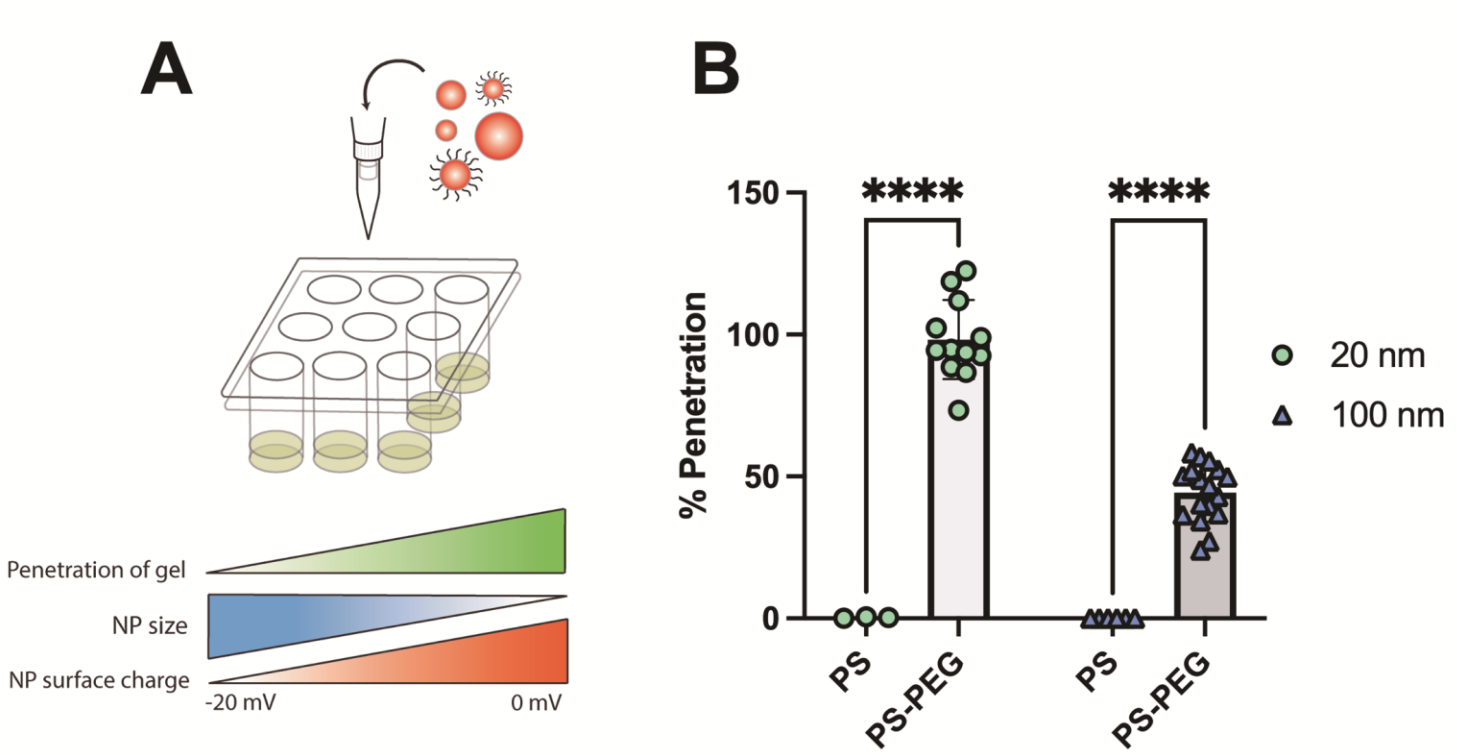
New simple method to rapidly screen and optimize nanomedicines used for mucosal drug delivery



Zou & Boboltz et al, *RSC Pharmaceutics* (2024)

Synthetic mucus barrier arrays as a nanoparticle formulation screening platform

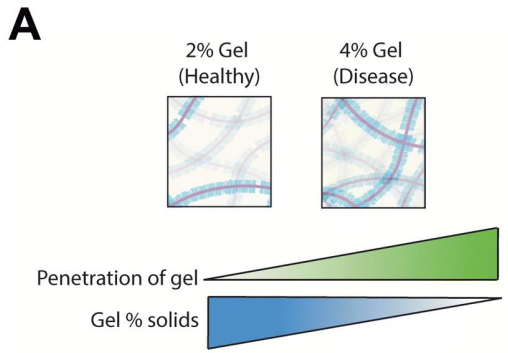
Consistent with literature, small (≤ 100 nm) PEGylated nanoparticles penetrate synthetic mucus barrier

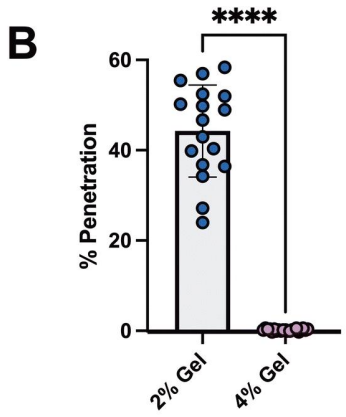


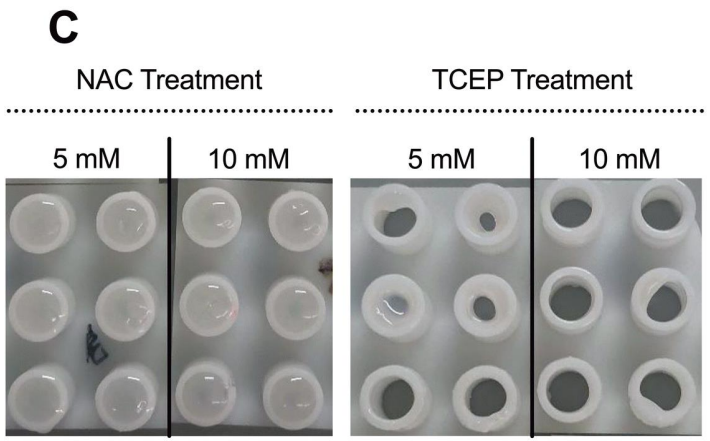
Zou & Boboltz et al, *RSC Pharmaceutics* (2024)

Evaluating mucolytics as nanoparticle permeation enhancers using synthetic mucus barrier arrays

TCEP greatly improves nanoparticle penetration through “airway disease-like” synthetic mucus barriers







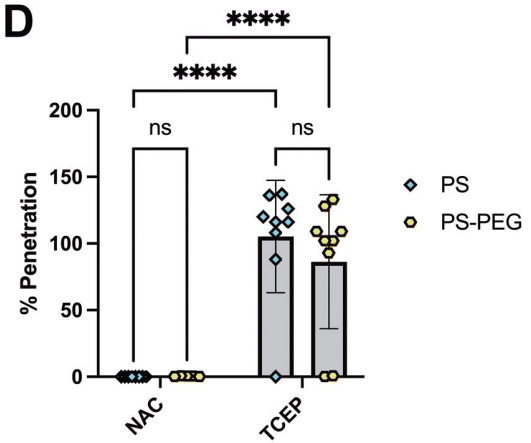
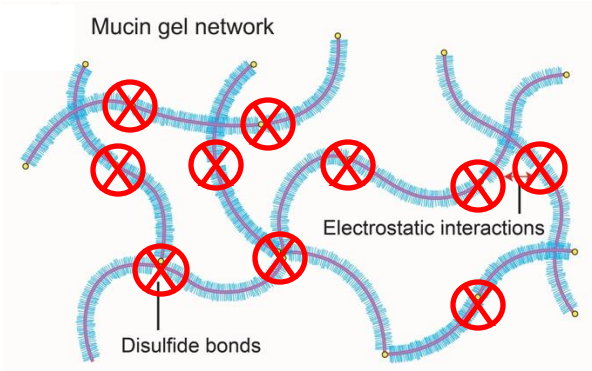
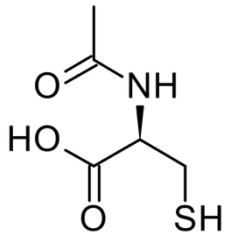
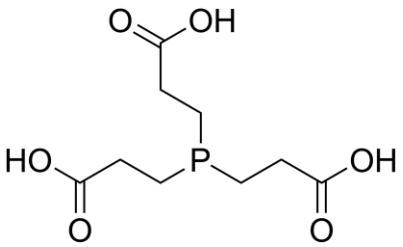


Image: aegisshield.com





N-acetyl cysteine (NAC)



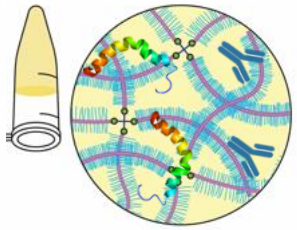
Tris(2-carboxyethyl) phosphine (TCEP)

Zou & Boboltz et al, *RSC Pharmaceutics* (2024)

Conclusions

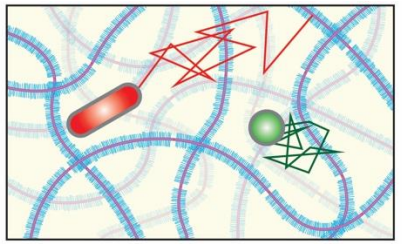
Synthetic mucus biomaterials for therapeutic delivery

Synthetic mucus biomaterials may be useful for biologic drug delivery to treat infectious and inflammatory diseases.

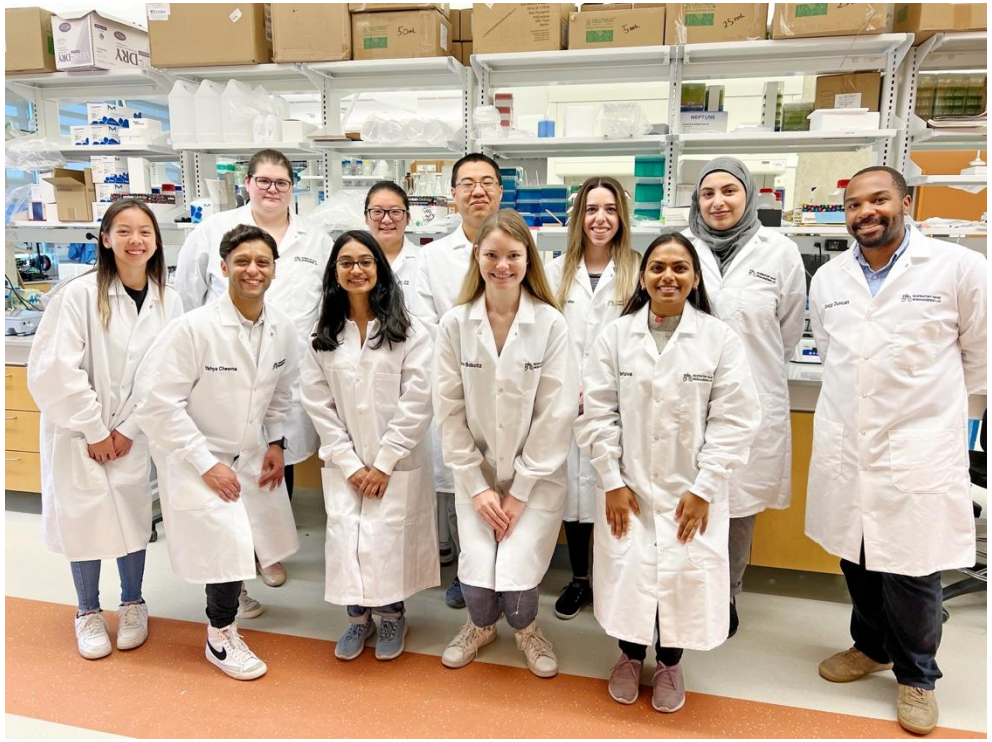


Optimizing nanoparticle formulations to overcome the mucus barrier

Synthetic mucus barrier arrays can be used as screening tools to identify the strongest candidates for mucosal drug delivery.



Acknowledgements



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GRAND CHALLENGES GRANTS
GC18 Team Grant

Stay tuned for more from our lab at CRS!

Tech Session I: Skin and Mucosal Delivery (10am-12pm)
Tuesday, July 14th at 11:05am

Rapid In Situ Forming Hydrogels for Mucosal Drug Delivery

Taj Yeruva

Tech Session III: Skin and Mucosal Delivery (10am-12pm)
Wednesday, July 16th at 11:27am

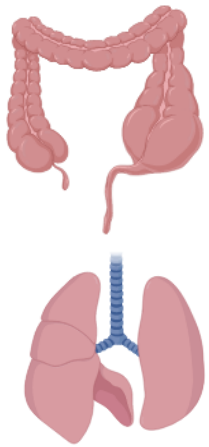
Branched PEGylation as a strategy to overcome the mucus barrier to aerosolized nanomedicine

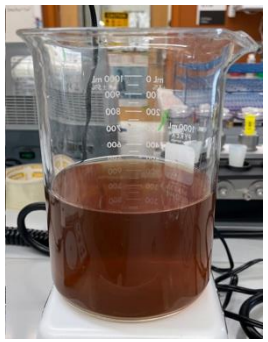
Alexa Stern

Tissue-specific synthetic mucus biomaterials

Mucins extracted from whole tissue for integration into hydrogel platform

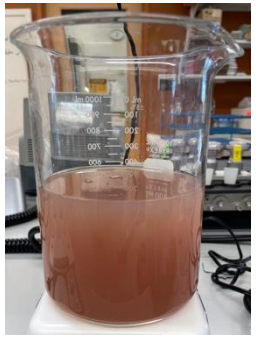
Harvest mucus from tissue





Solubilized in 0.1M NaOH

pH 4 gel phase



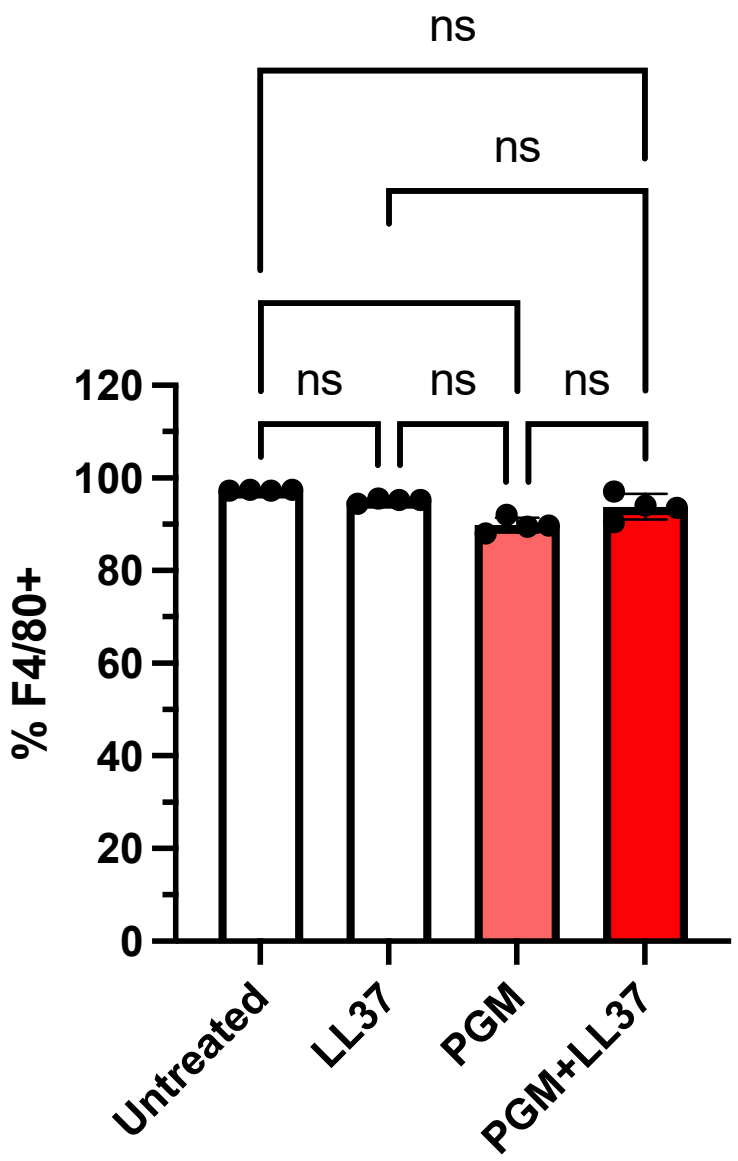
pH 8 sol phase

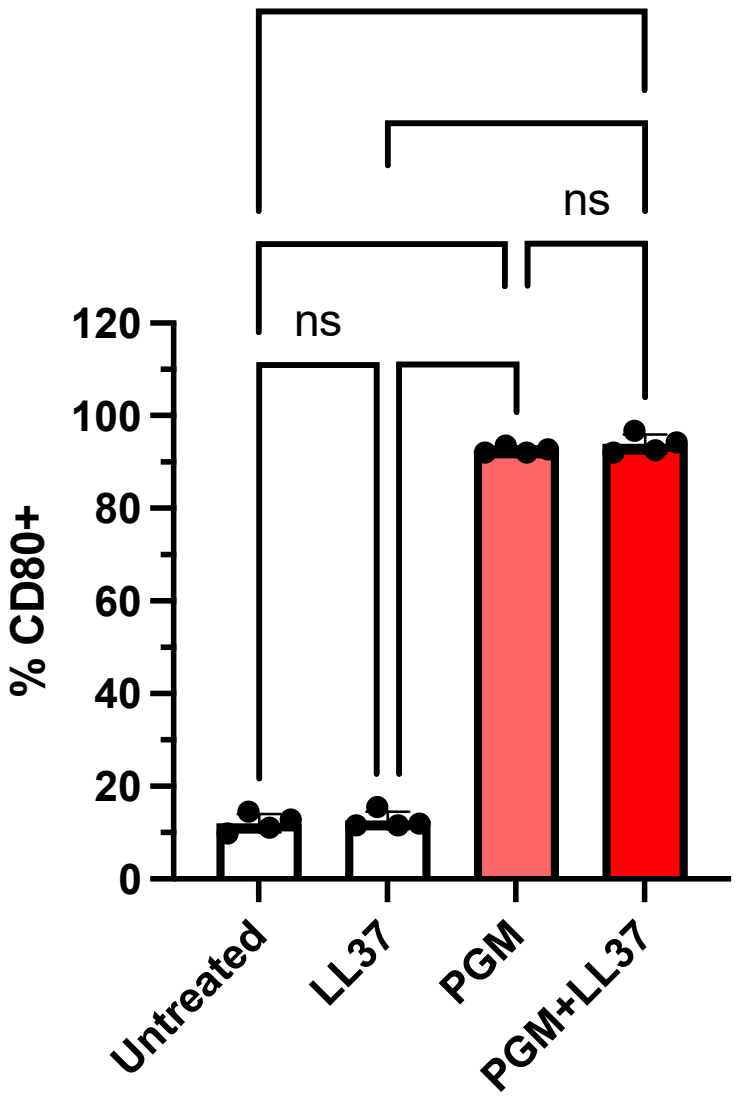
Lyophilized Mucin Extract

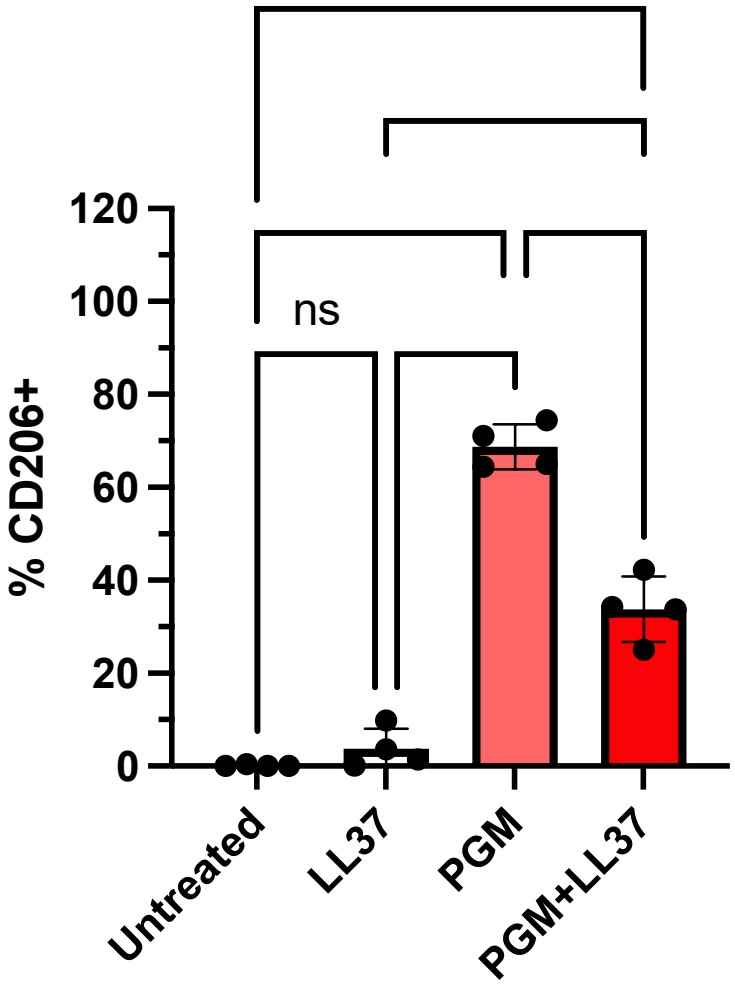
Benefits:

- Gentler procedure without protease treatment
- Batch-to-batch quality control
- Can integrate mucins from specific tissues (e.g. airway, GI, reproductive)

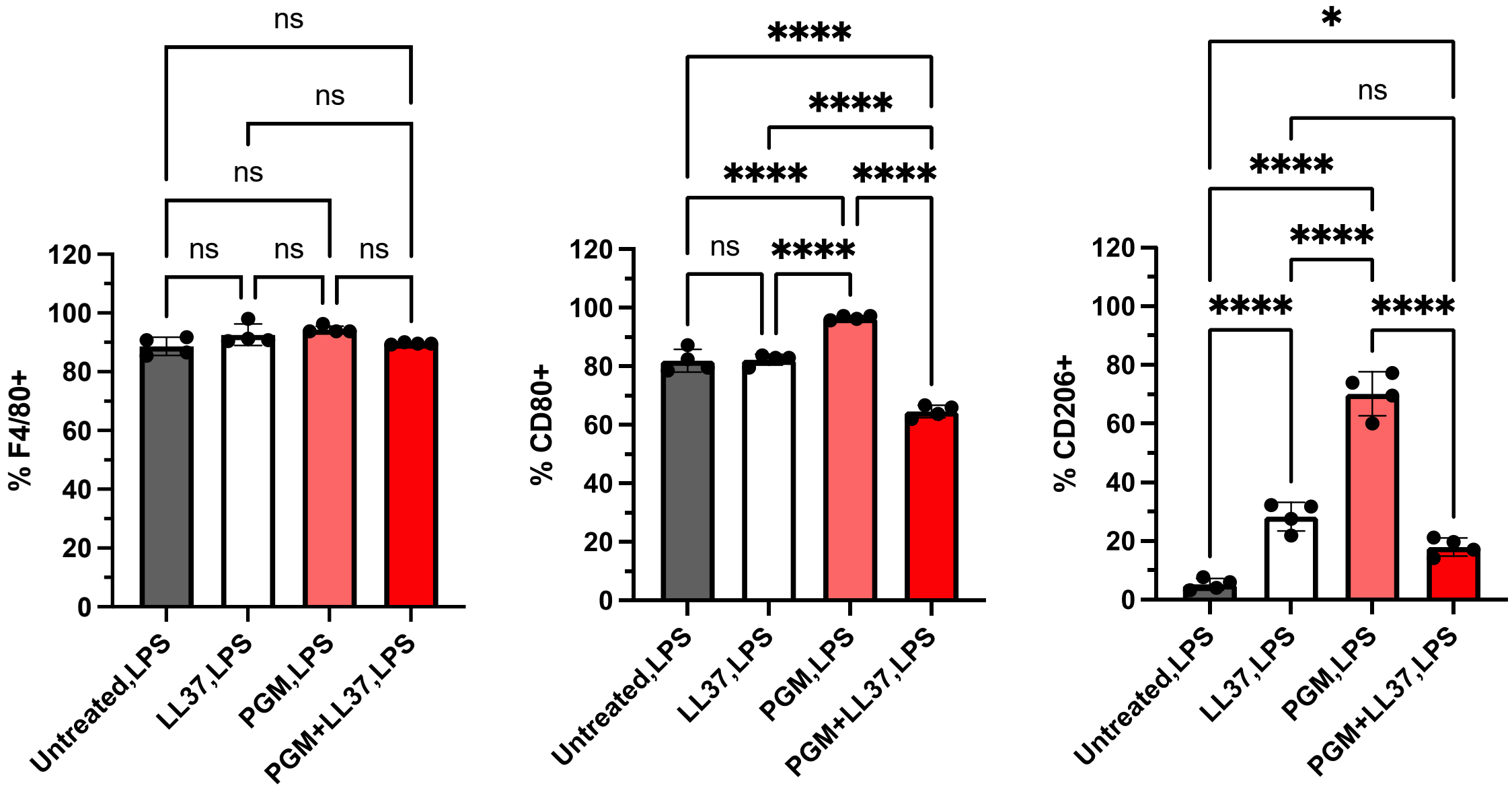
Surface markers: Mucin treatment of unstimulated (-LPS) macrophages







Surface markers: Mucin treatment of stimulated (+LPS) macrophages



CD80 and CD206 co-expression after SM treatment