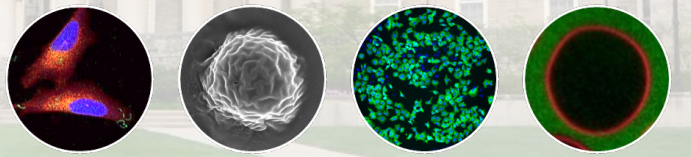
38th EPS European Peptide Symposium
6-11 September 2026, Vienna, Austria

https://doi.org/10.17952/38EPS.2026.O53

Retro-Inverted Host Defense Peptides as Inhalable Antitubercular Therapies

Diptomit Biswas,
Ph.D. Student
Sep. 9th, 2026

the Medina Group
Precision Therapeutics and Bioresponsive Materials Lab

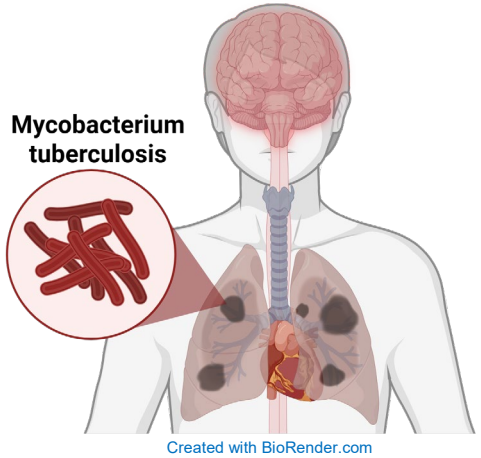


PennState Huck Institutes of the Life Sciences

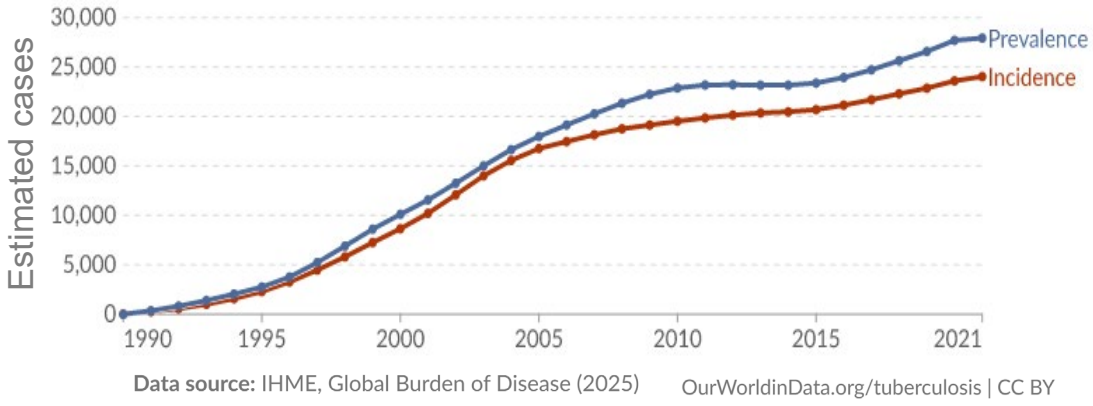
Dr. Scott Medina, Associate Professor,
Department of Biomedical Engineering, PSU

PennState College of Engineering

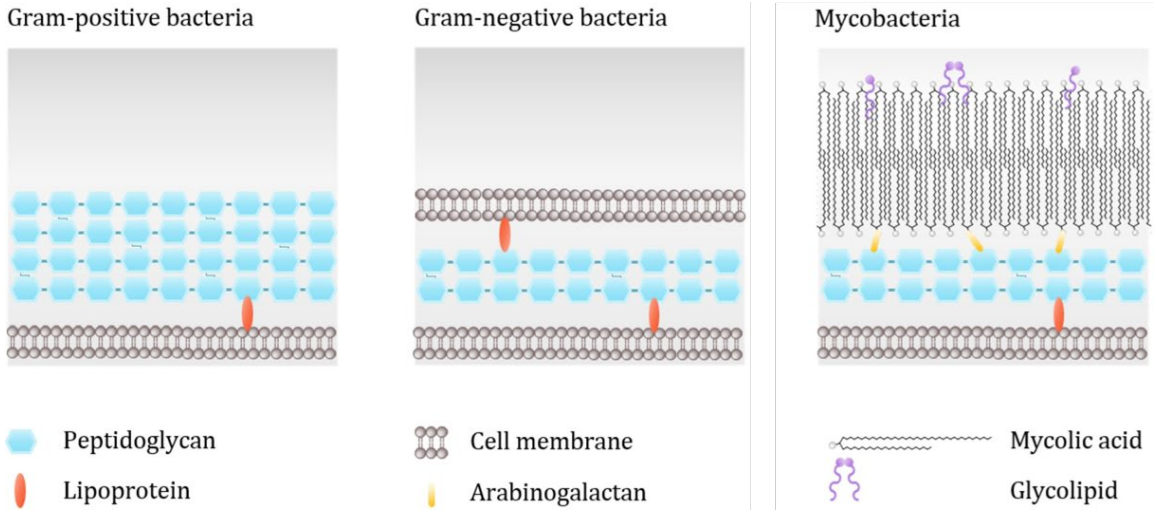
Drug Resistant Tuberculosis (TB) remains a serious global health concern



Despite modern diagnostic and therapeutic successes, drug-resistant TB cases continue to emerge and spread across the world.



1. Thick hydrophobic Outer Membrane



2. Residence inside Macrophages within Granulomas

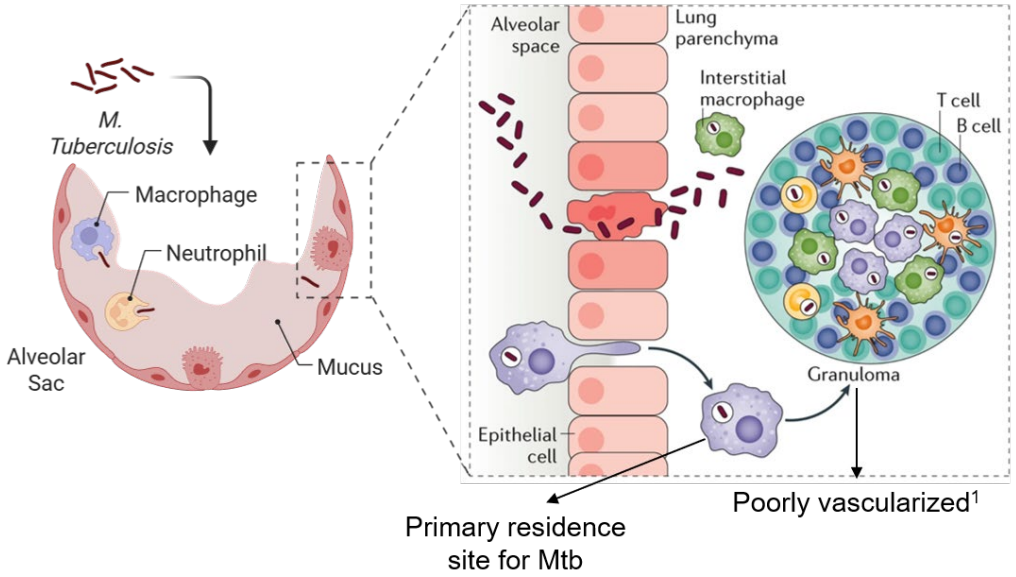


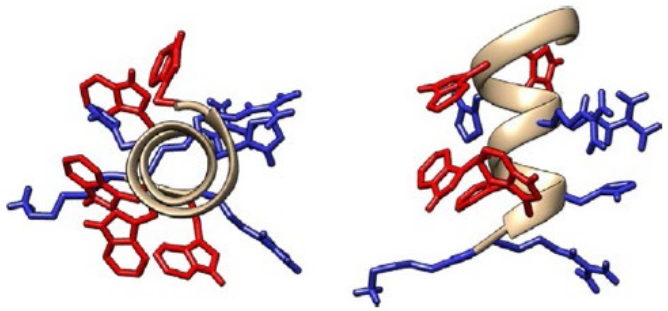
Fig. (bottom left) Djik J.H.M.V, et al. *Chem. Rec.*, 2021.; (bottom right) Pai M, et al. *Nat Rev Dis Primers*, 2016.; (1) Polena H, et al. Sci Rep, 2016

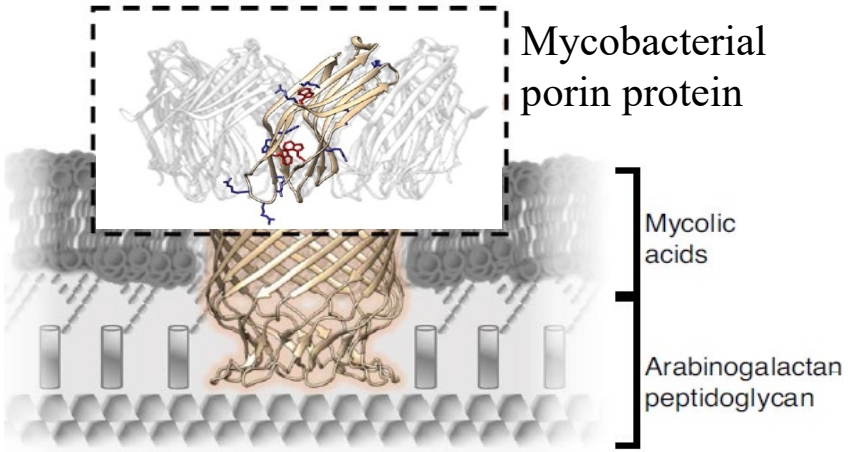
De novo synthetic host defense peptide showed specific inhibitory activity against Mycobacteria

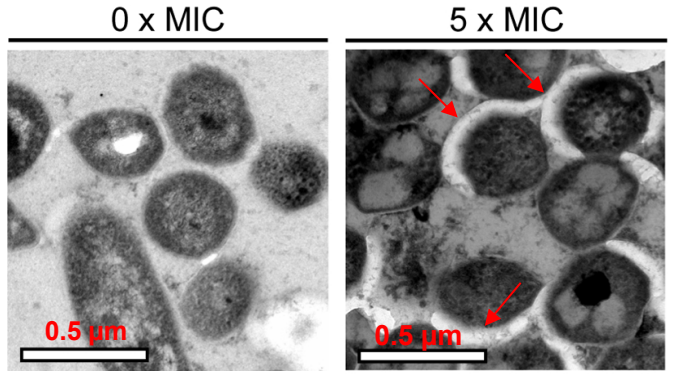
Previous Work from our Lab

(Simonson AW, et al. *Nat Biomed Eng*, 2021)

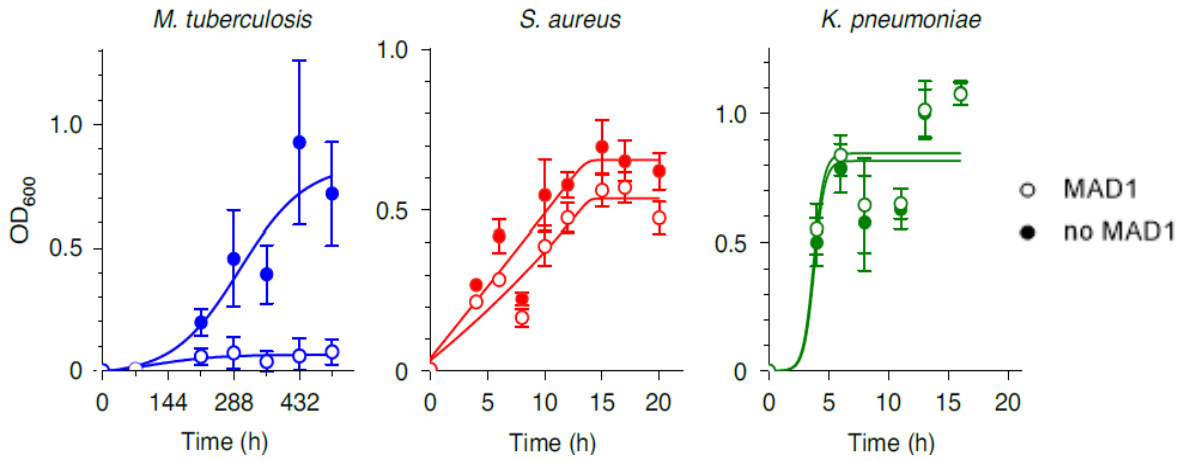
MAD1 peptide
(KRWHWWRRHWVVW-CONH$_2$)

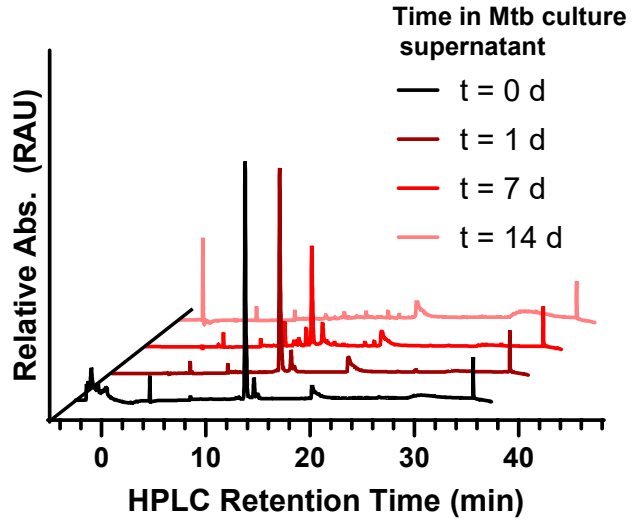






TEM Images showing MAD1-driven membrane effects



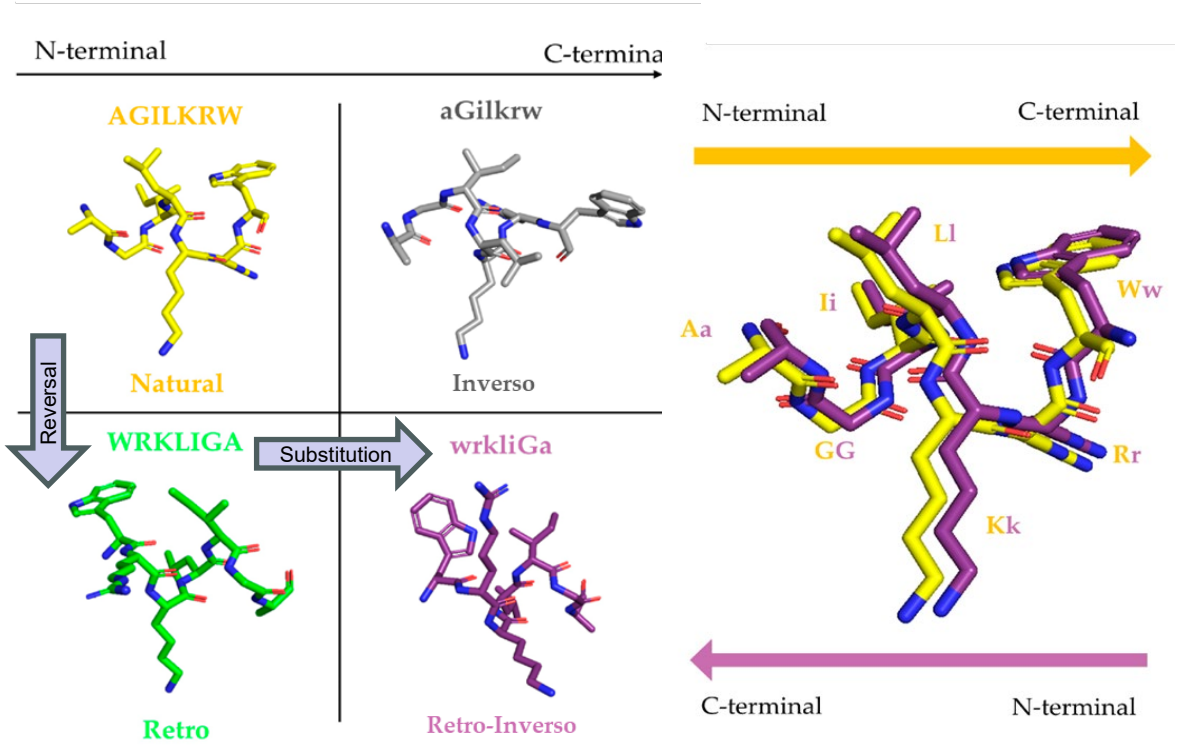


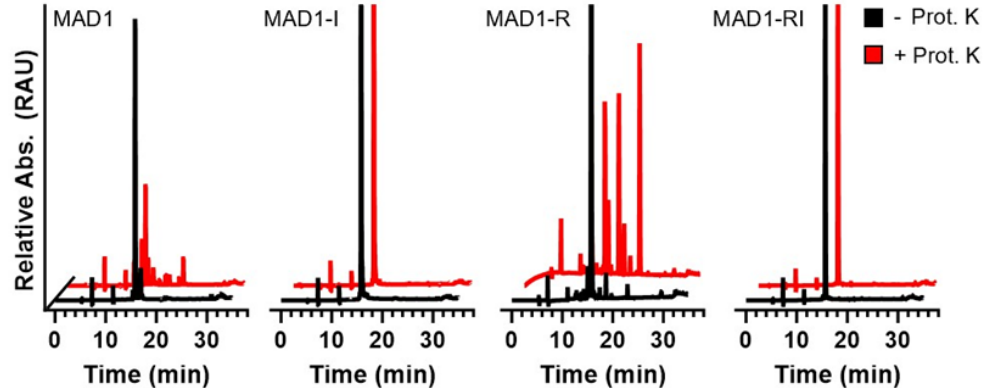
However, proteolytic instability makes them clinically unfeasible.

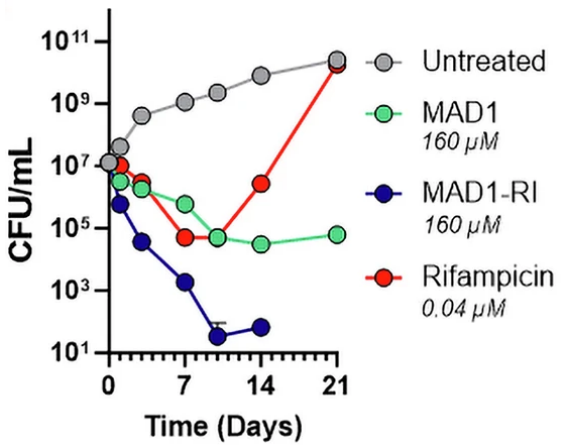
Fig. (bottom right) Glossop H.D, et al. *Nat. Comms.*, 2025.

MAD1 Retro-inversion improved proteolytic stability, enhanced anti-TB potency while retaining synergistic activity with second line TB antibiotic Moxifloxacin

Retro-inversion flips the peptide backbone but preserves the spatial orientation of amino acids as shown below with this example-







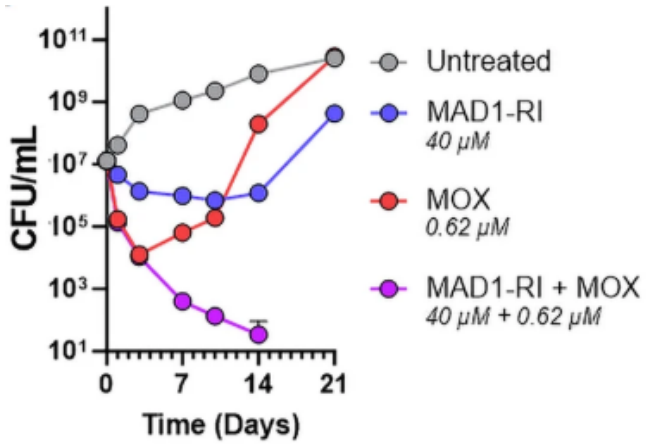
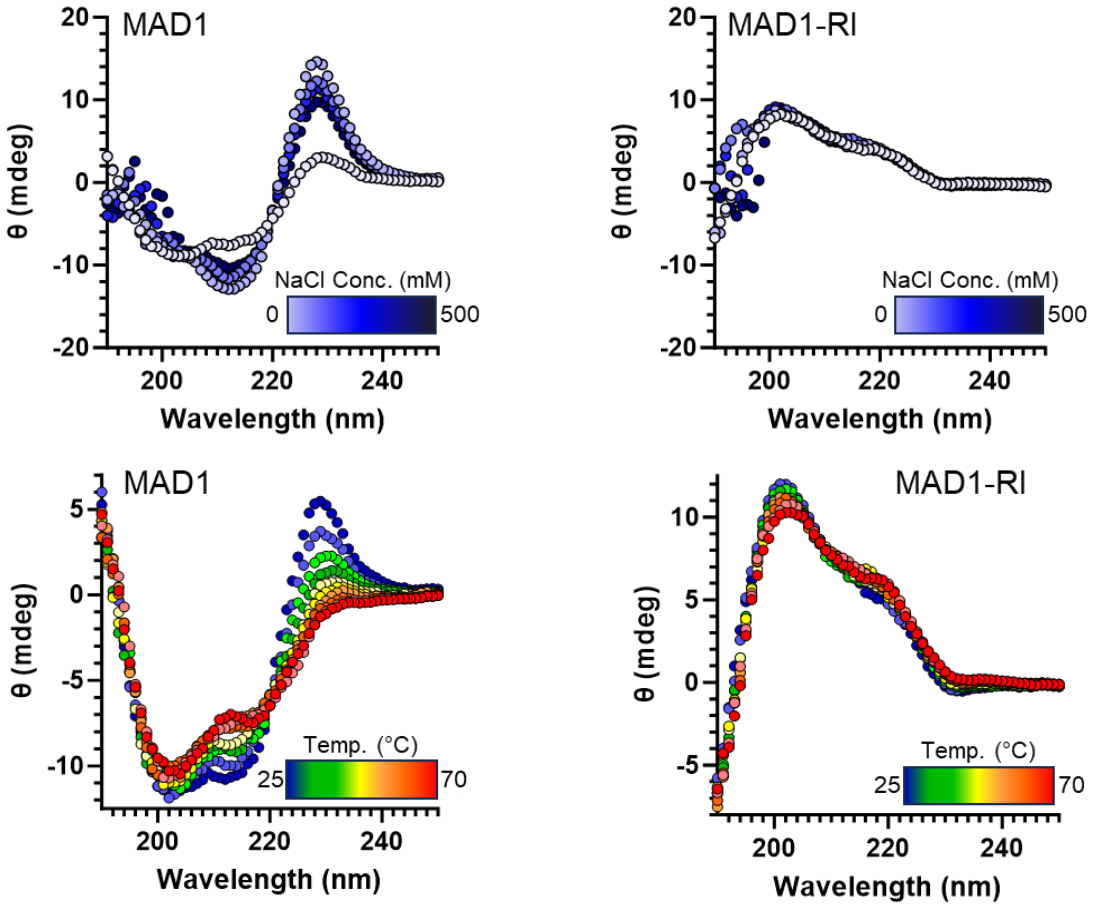


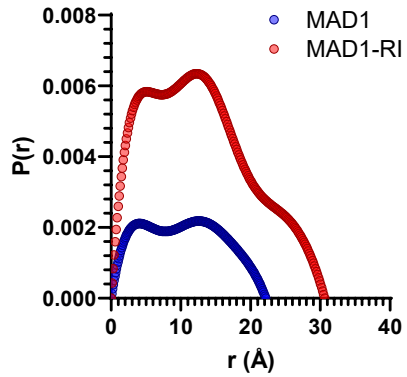
Fig. (Left) Carrera-Aubesart A, et al. *Pharmaceutics*, 2023.; Fig. (Right top and bottom) Glossop H.D, et al. *Nat. Comms.*, 2025.

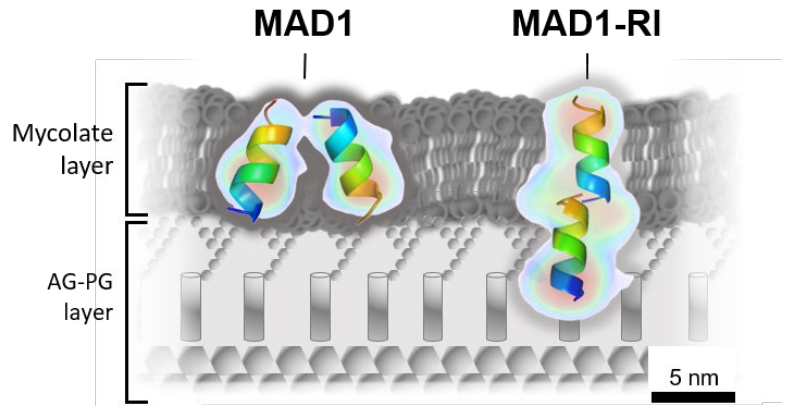
Retro-inverted MAD1 adopts a more elongated conformationally rigid assembly relative to MAD1

Circular Dichroism studies



Small-Angle X-ray Scattering-Analytical Ultracentrifugation studies





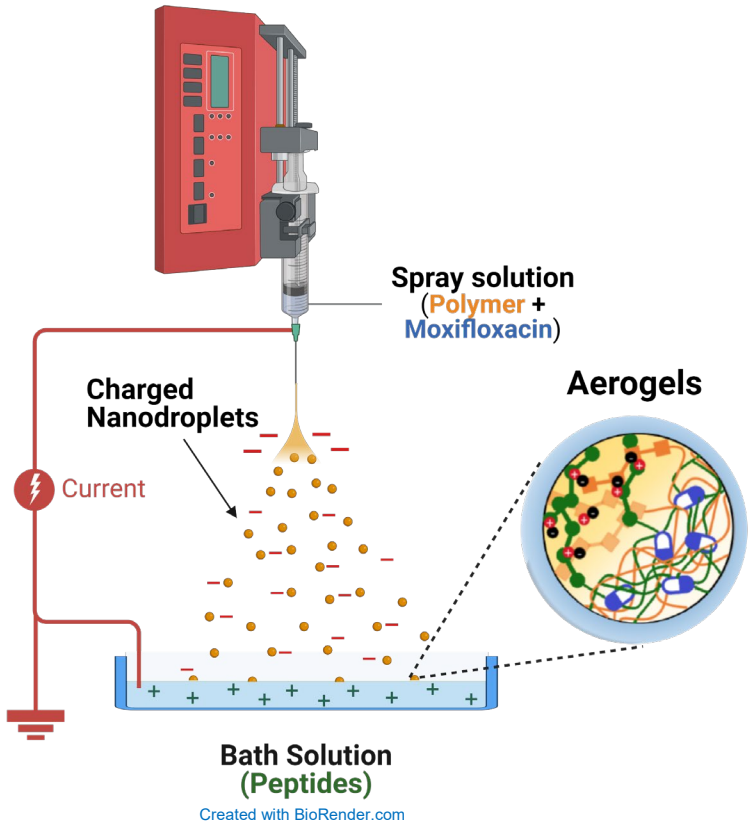
These features potentially lower the entropic barrier for interpolation and assembly of MAD1-RI within the mycomembrane, further contributing to improved anti-TB potency

All figures: Glossop H.D, et al. *Nat. Comms.*, 2025.

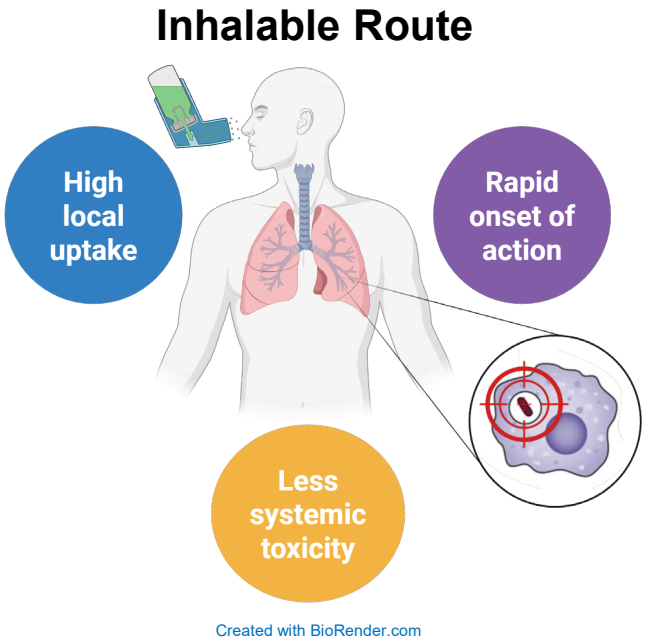
Targeting anti-TB drugs to infected lung macrophages using biocompatible anionic polymers

Previous Work from our Lab

(Simonson AW, et al. *Biomaterials*, 2021)



Anionic carbohydrate-based polymers can be complexed with cationic peptides like MAD1 to form nano-sized aerosolizable particles loaded with moxifloxacin.





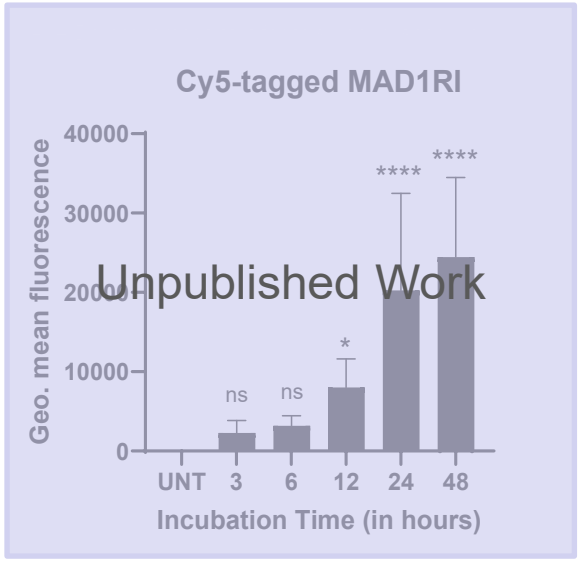
Different ratios of polymers and peptides were tested to optimize size of aerogels and ensure maximal loading of therapeutics

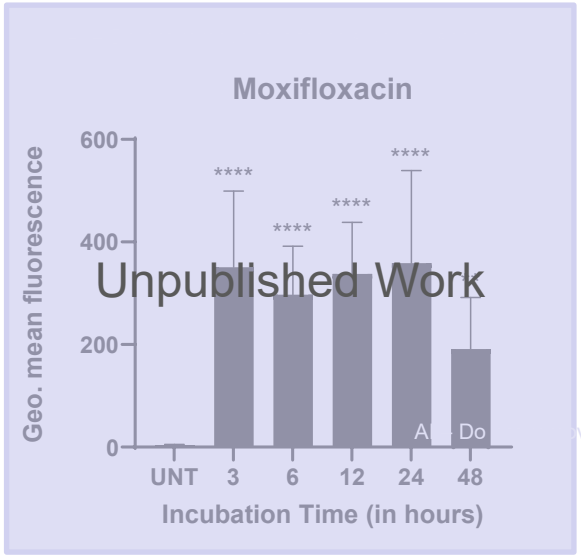


Figs. (right) *Unpublished work*

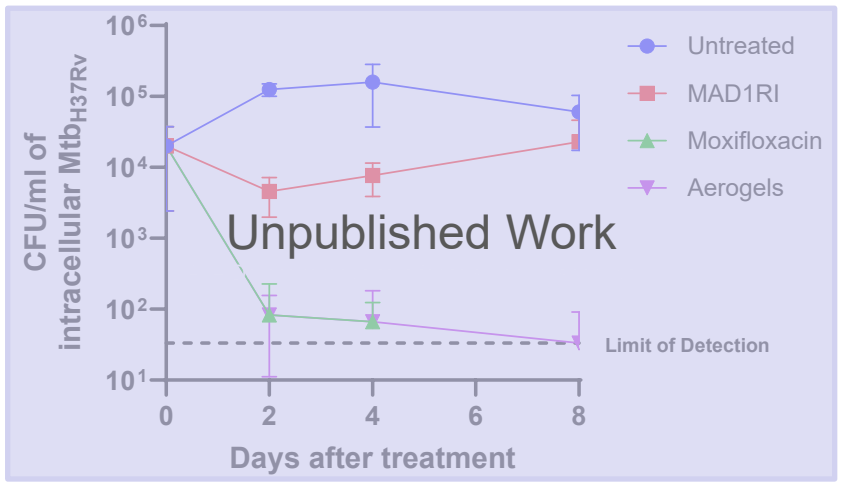
Aerogels efficiently deliver therapeutics to Macrophages to clear TB persisters

Uptake, Localization and Effect of Aerogel Cargo on THP1 macrophages



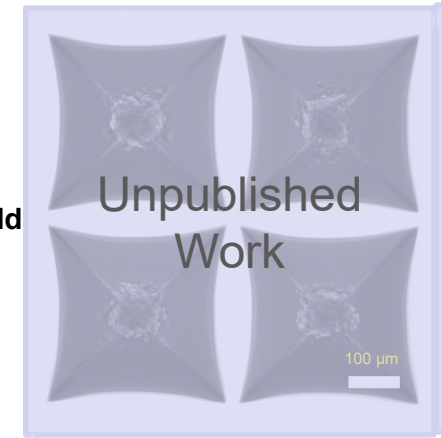


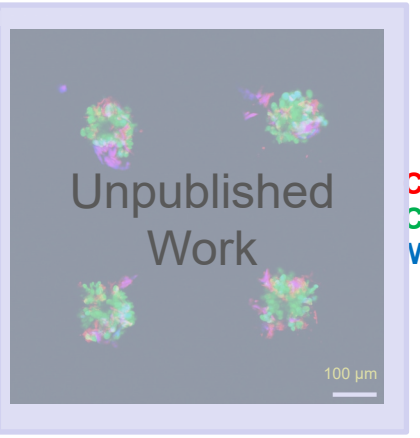




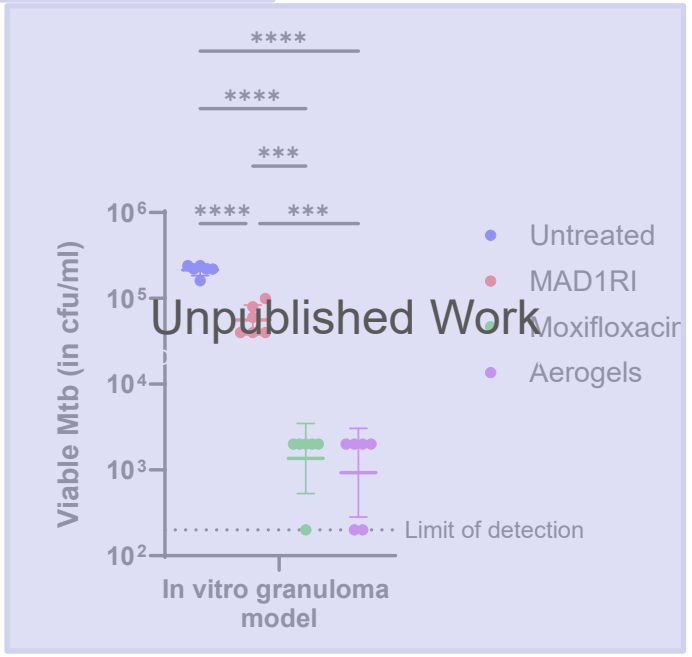
Penetration of Aerogel Cargo into in vitro THP1 spheroids and clearance of intracellular Mtb

Brightfield



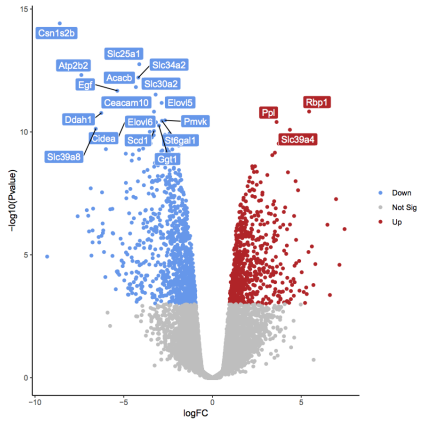


Cy5-MAD1-RI,
Calcein AM,
Moxifloxacin

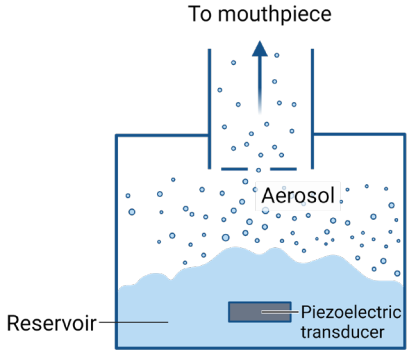


Ongoing and Future Experiments

- Gene expression analysis of uninfected macrophages treated with different polymer-based aerogels loaded with MAD1-RI.



- Post-Aerosolization size and stability of aerogels.

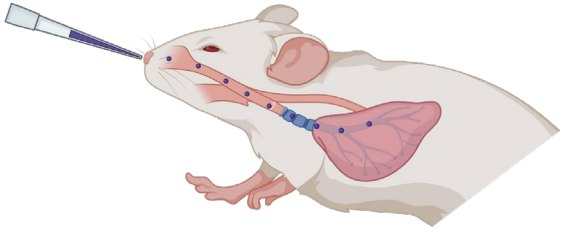


Ultrasonic nebulizer



Microspray aerosolizer

- *In vivo* efficacy and biocompatibility of MAD1-RI and Moxifloxacin-loaded aerogels in mice models of TB infection.



Acknowledgements



Dr. Hugh Glossop,
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PSU



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CWRU



Dr. Scott Medina,
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Dr. Anthony D. Baughn,
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UMN



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PennState Huck Institutes of the Life Sciences

NIH National Institutes of Health

PennState College of Engineering

To know more about this work and other ongoing research in our lab, please visit -

Hugh D. Glossop, et al. Retro-inversion imparts antimycobacterial specificity to host defense peptides, *Nature Communications*, **2025**, 17, 469, doi:10.1038/s41467-025-67162-0.

Lab Website: https://sites.psu.edu/medinalabgroup/

Email Address: dzb5866@psu.edu

Thank you for your attention!

Questions?