Harnessing Nature's Defences to Treat Gut Biofilms

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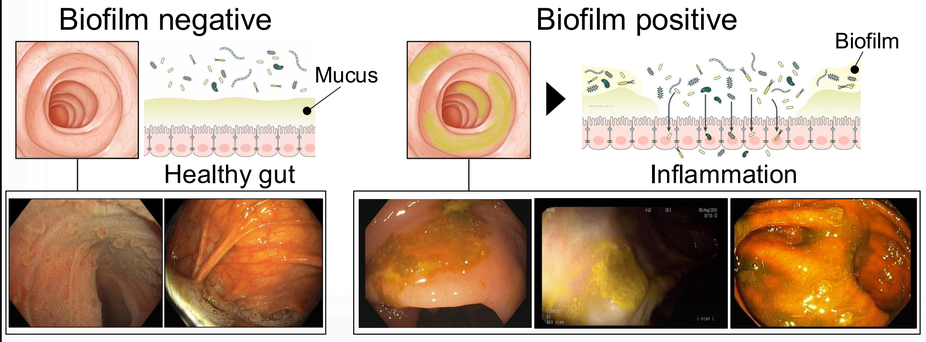
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Gut Biofilms – A New Drug Target

Irritable bowel syndrome (IBS) and **inflammatory bowel diseases** (IBD, including **Crohn's disease** (CD) and **ulcerative colitis** (UC)) are increasingly prevalent chronic gastrointestinal disorders **affecting over 10% of the global population**.[1,2] These gastrointestinal disorders can lead to severe complications (i.e., chronic inflammation, abdominal pain, intestinal bleeding, anaemia) with annual associated costs at €115 billion in Europe, $75 billion in the USA and €1.5 billion in Austria.[1] In a recent clinical study with over 1,100 participants, we observed that gut biofilms are macroscopically visible and highly prevalent in **IBS (57%)**, **UC (34%)** and **CD (22%)** patients but less in **healthy individuals (6%)**, indicating that gut biofilms could be a new drug target for the treatment IBS and IBD.[1,2,3]

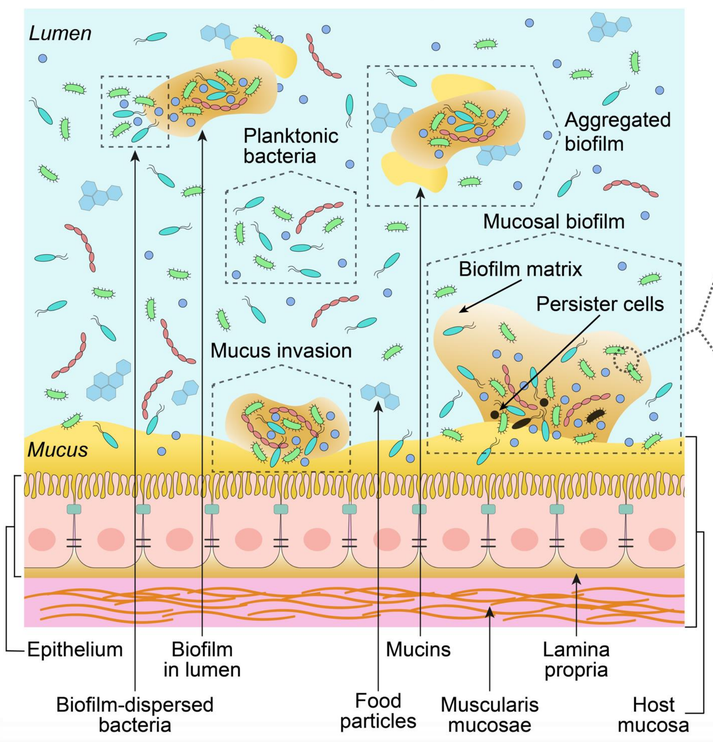


Biofilm occurrence

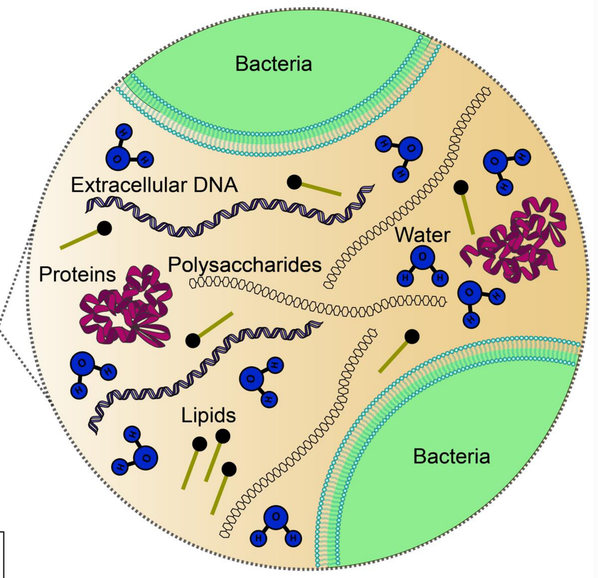
57% in IBS
34% in UC
22% in CD



Gut bacteria arrangement



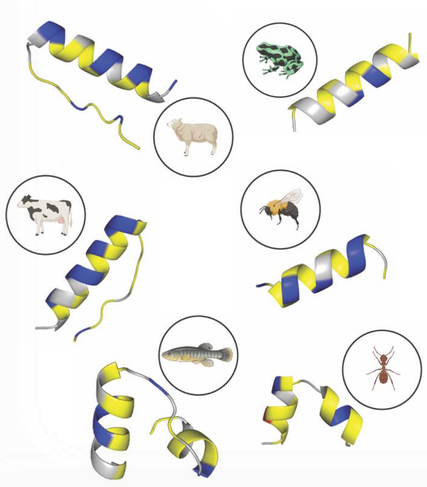
The biofilm matrix



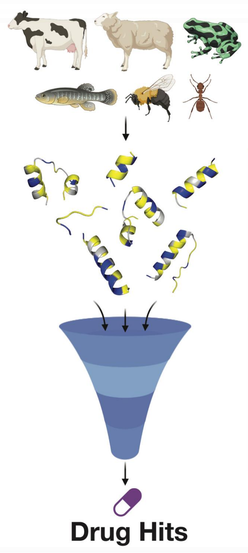
Components	Regulatory systems
Extracellular DNA	Quorum sensing
Polysaccharides	Stringent response
Proteins	Second messengers
Water	

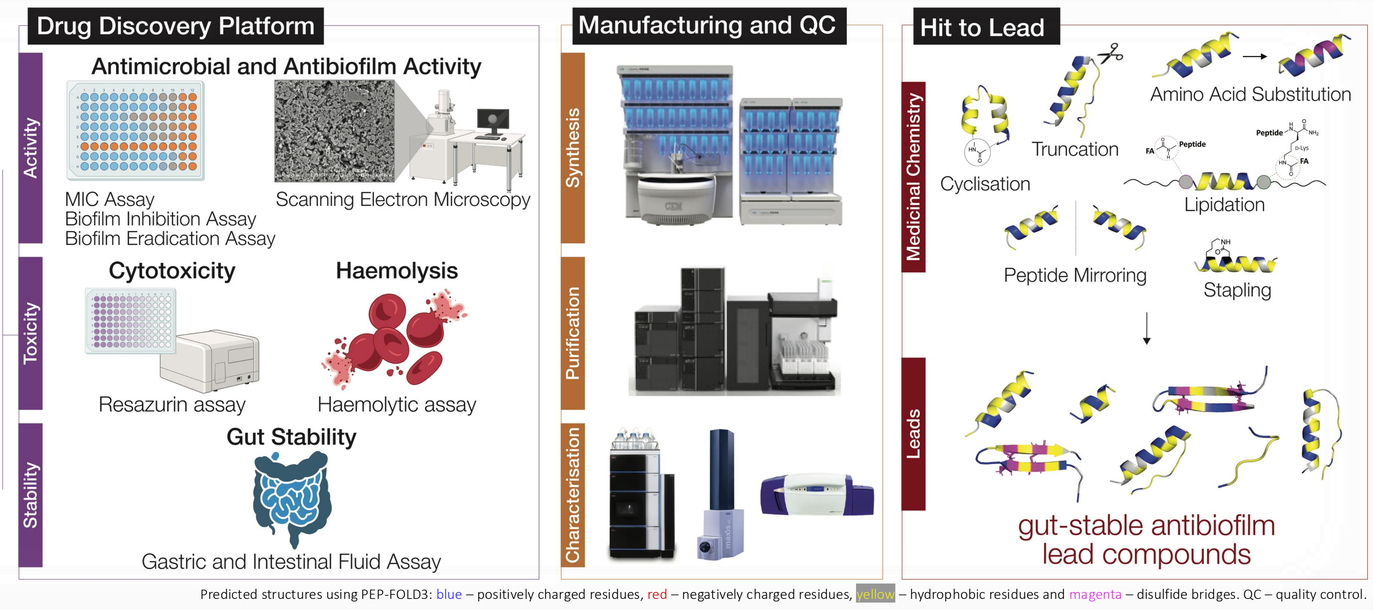
Drug Discovery and Development Platform

Nature's molecular defences



Our drug discovery strategy builds on nature's molecular defences by focusing on animals that routinely encounter biofilms, including ants, bees, cows, fish, frogs, pigs, sea urchins, sheep, and wasps. Building on this concept, we established the first gut-biofilm-targeted drug discovery and development platform that harnesses nature-derived antimicrobial peptides (AMPs) and integrates clinical biofilm samples from IBS patients, aiming to develop highly stable oral antibiofilm therapeutics.





Predicted structures using PEP-FOLD3: blue – positively charged residues, red – negatively charged residues, yellow – hydrophobic residues and magenta – disulfide bridges. QC – quality control.

Highly-stable Antibiofilm Peptides

Hit screen. We synthesised 31 AMPs *via* Fmoc-solid-phase peptide synthesis and evaluated their inhibition of planktonic and biofilm growth, eradication of mature biofilms and cytotoxicity against HEK-293 cells (**Figure 1**). This screen used two clinical isolates from biofilm-positive IBS patients and two biofilm-forming control strains.

Hit-to-lead development. MMBJ018 and MMBJ020 were identified as hit compounds due to their broad-spectrum antimicrobial and antibiofilm activity. Both AMPs underwent hit-to-lead optimisation using state-of-the-art medicinal chemistry guided by structure-stability-activity relationship data which produced D-MMBJ055 and D-MMBJ059 as highly stable antibiofilm leads (**Figure 2**). We also applied circular dichroism to analyse the peptides' secondary structure and scanning electron microscopy to evaluate antibiofilm activity and biofilm penetration capacity.

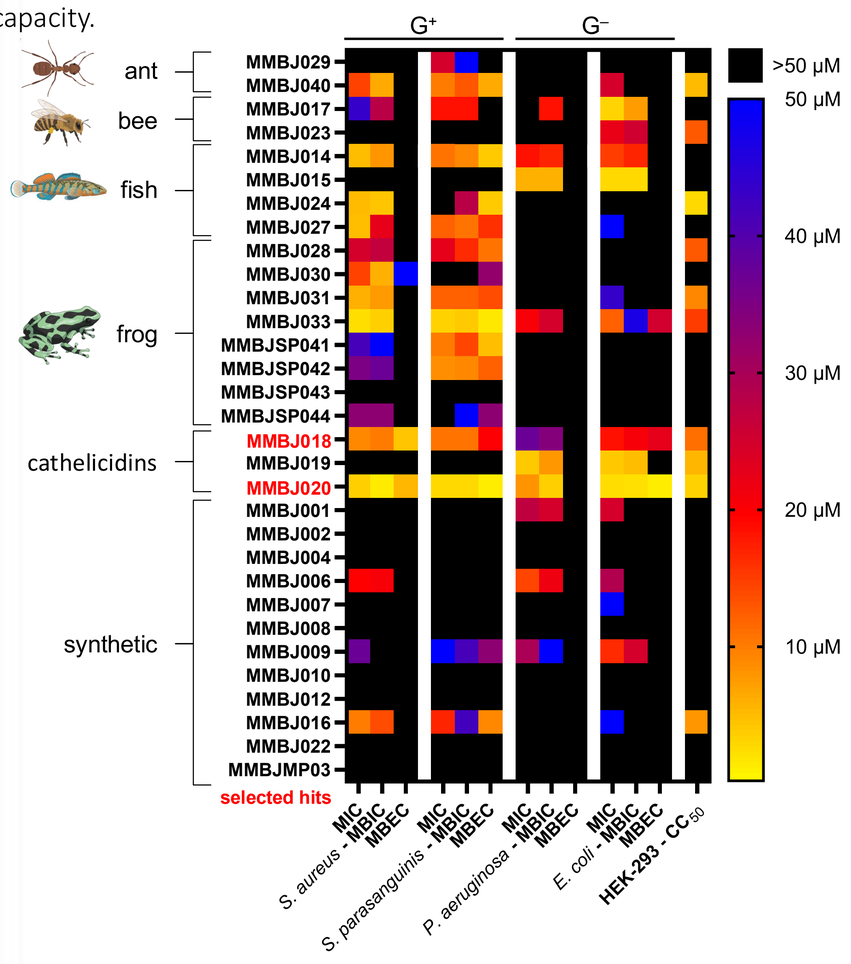


Figure 1. Heat map displaying the results of the antimicrobial, antibiofilm and cytotoxicity screen. MIC – minimum inhibition concentration; MBIC – minimum biofilm inhibition concentration; MBEC – minimum biofilm eradication concentration; CC_{50} – half-maximal cytotoxic concentration; G^+ – Gram-positive; G^- – Gram-negative.

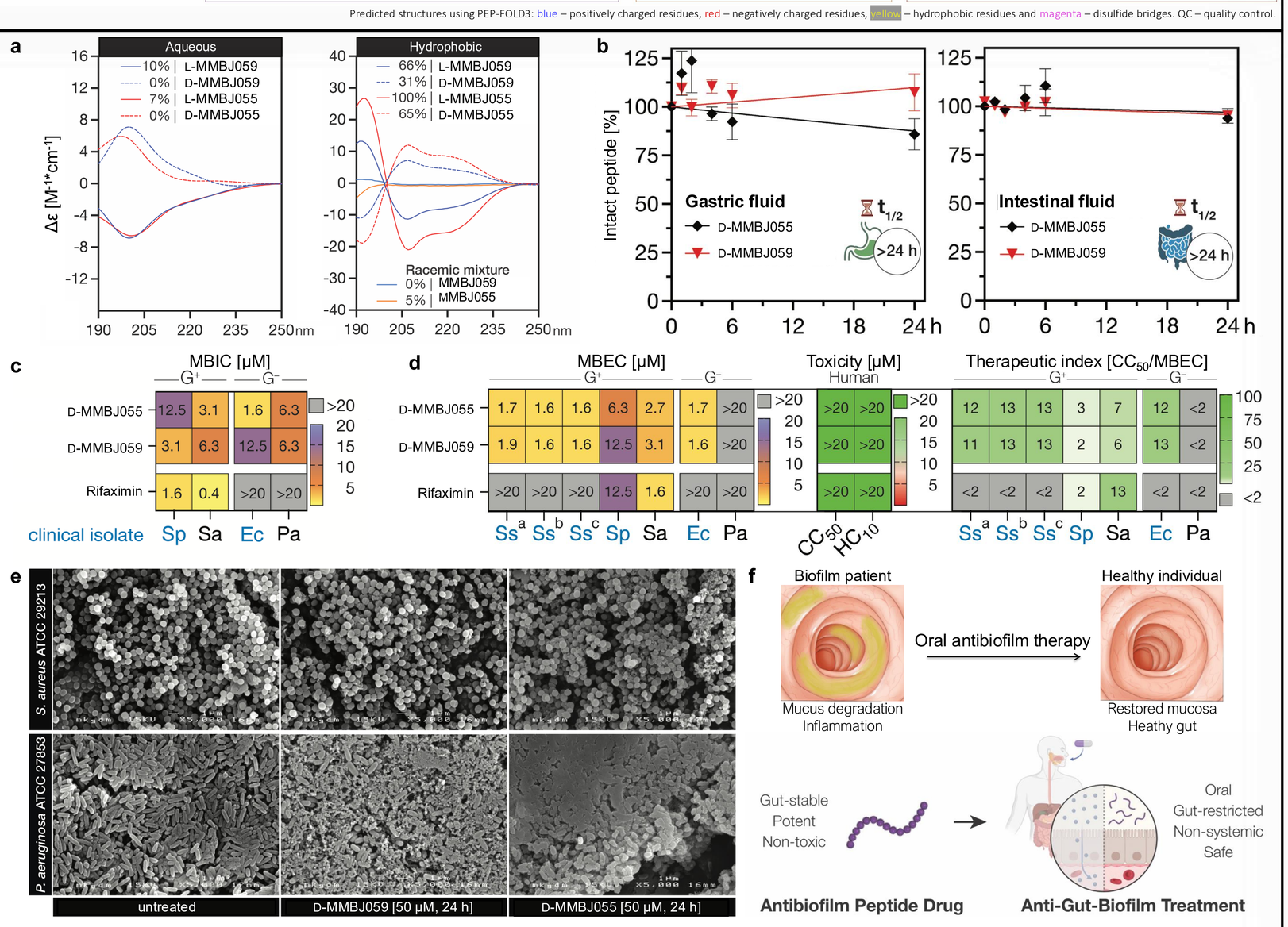


Figure 2. Hit-to-lead development. a) Circular dichroism analysis. b) Stability in gastric and intestinal fluid. c) Biofilm inhibition activity. d) Biofilm eradication activity, cytotoxicity, haemolytic activity and therapeutic indices. e) Scanning electron microscopy images of mature biofilms. f) Therapeutic strategy. Ss, *Streptococcus salivarius* [a] – R22-K2¶ / [b] – R22-K3¶ / [c] – R30-K3¶; Sp, *Streptococcus parasanguinis* 102-K3/3¶; Sa, *Staphylococcus aureus*; Ec, *Escherichia coli*; Pa, *Pseudomonas aeruginosa;* ¶ – in-house patient ID; CC_{50}, half-maximal cytotoxic concentration; HC_{10}, 10% of maximal haemolytic concentration; G^+ – Gram-positive; G^- – Gram-negative.

Conclusion

We present a novel antibiofilm peptide drug discovery platform for the development of gut-specific oral therapeutics for patients with gut biofilms. Nature proved to be a rich source of potent antibiofilm compounds, evolved to penetrate and eradicate mature biofilms, including patient-derived isolates. Our approach resulted in two strong drug leads, D-MMBJ055 and D-MMBJ059, for gut-biofilm-targeted therapy. Both peptides are fully gut stable and have potent biofilm eradication activity (MBEC=1.6–12.5 µM) with favourable therapeutic indices (TI_{MBEC}=2–13) against clinical biofilm isolates. This work established the first nature-inspired drug discovery platform and delivered an initial set of highly stable antibiofilm drug leads for further development as oral treatments for patients with gut-biofilm-associated chronic gut disorders.

Reference

(1) Intestinal biofilms – Pathophysiological relevance, host defence and therapeutic opportunities. Jandl B et at., *Clinical Microbiology Reviews* 2024.
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(3) Mucosal biofilms are an endoscopic feature of irritable bowel syndrome and ulcerative colitis. Baumgartner M et. al., *Gastroenterology* 2021.

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