Peptide Biomimetic Matrix offers Antibacterial Protection and Rapid Wound Closure of Refractory Diabetic Foot Ulcers

Ana Tellechea[1], Brunno Caetano[1], Trudy-Ann Grant[1], Daljit Kaur[1], Manav Mehta[1], Adam Landsman[2]

[1]Gel4Med, Inc., Lowell, MA, United States; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

BACKGROUND

Diabetic Foot Ulcers (DFUs) are the leading cause of non-traumatic lower extremity amputations and have an associated 5-year mortality rate of 50-70%[1]. Approximately 60% of DFUs become infected, substantially increasing morbidity and raising the rate of lower extremity amputations up to 90%[2]. Despite advancements in treatment, DFUs remain an unmet medical need. To tackle this issue, we designed and developed a **biomimetic matrix (BMM)** aimed at preventing infection while promoting wound healing. BMM is a **synthetic self-assembling peptide matrix** designed to (i) provide **antibacterial protection** via cationic charge and (ii) support **tissue regrowth** via a 3D scaffold with cell attachment sites that eliminates dead space. The purpose of this study was to evaluate BMM's safety and performance in refractory DFUs.

METHODS

Preclinical: Efficacy against several clinically relevant bacterial and fungal pathogens was tested by *in vitro* assays. Efficacy against 72 hour-aged *Pseudomonas aeruginosa* (PAO1) biofilms was evaluated *in vitro* and *ex vivo* [porcine skin]. In a swine model of full-thickness excisional wounds, BMM healing efficacy was tested vs. silver and collagen wound products using digital imaging and histopathology.

Clinical: 8 subjects with Wagner 1 to Wagner 3 DFUs were included in a case series to evaluate BMM safety and performance. Other comorbidities included venous stasis, Charcot neuroarthropathy, obesity, osteomyelitis, peripheral vascular disease, and a history of prior partial foot amputation. Subjects were selected based on wound chronicity and failure to respond to previous advanced treatments, including animal and human-derived matrices. After debridement, BMM was applied and the wounds were monitored for healing progress.

RESULTS

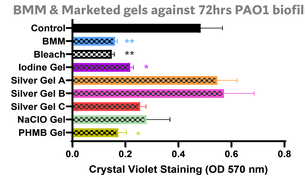
1. BMM shows broad-spectrum activity against MDROs

	Species	Full clearance (>10^6 CFU)
Gram-positive bacteria	*Enterococcus faecium**	✓
	Staphylococcus epidermidis*	✓
	Staphylococcus heamolyticus*	✓
	MRSA	✓
Gram-negative bacteria	*Pseudomonas aeruginosa**	✓
	ESBL *Escherichia coli**	✓
	ESBL *Klebsiella pneumoniae**	✓
	*Acinetobacter baumannii**	✓
Fungi	*Aspergillus fumigatus*	✓
	Cladosporium herbarum	✓
	Fusarium solani	✓
	Candida albicans	✓

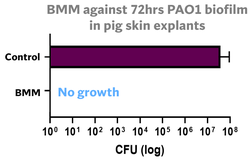
- Complete cidal activity against 10^6 CFU of Gram-positive & Gram-negative clinical isolates as well as clinically relevant fungal pathogens, all multidrug-resistant organisms (MDROs)

RESULTS

2. BMM eradicates established biofilms in skin explants



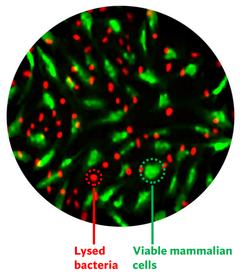
72hrs PAO1 biofilm in fresh pig skin



- Efficacy against mature PAO1 biofilms comparable to undiluted bleach
- 72h-aged PAO1 biofilm eradication confirmed in pig skin explants

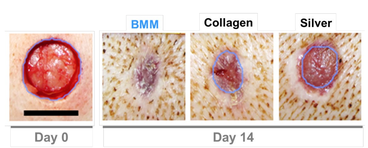
3. BMM demonstrates high compatibility with mammalian cells

BMM activity in co-cultures of MRSA & human dermal fibroblasts

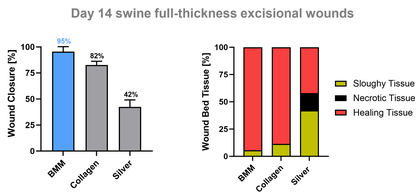


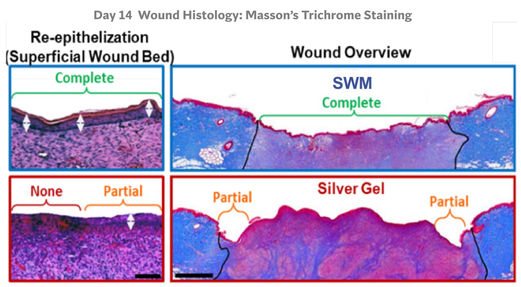
- Selective cidal activity against microbes and rescue of mammalian cells
- High mammalian cell viability, cell spreading, and cell attachment

4. BMM improves healing in a swine full-thickness wound model



Representative images of gross wounds at Day 0 & Day 14
Scale bar: 2 cm





Representative images of Masson's Trichrome stained wound sections at Day 14
Scale bar: 2 mm

BMM unique results

- ✓ Only treatment achieving full re-epithelialization by Day 14
- ✓ Only treatment resulting in wounds repleted with granulation tissue (0% necrotic tissue; 0% sloughy tissue)

- Superior healing profile compared to collagen and silver gels with greater wound closure (95% ± 5%), increased granulation tissue, increased neovascularization, and reduced inflammation
- Only treatment achieving complete re-epithelialization by Day 14 post-wounding

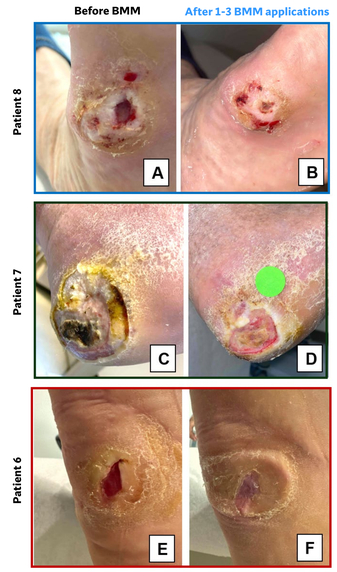
RESULTS

5. BMM achieves positive healing outcomes in refractory DFUs

Clinical Characteristics of Study Participants

#	Comorbidities (besides Diabetes)	Wound Location	Wound duration (months)	Wagner Grade
1	Neuropathy, Osteomyelitis	Heel	39	2
2	Osteomyelitis, PVD	Forefoot	30	1
3	Neuropathy	Heel	8	2
4	Neuropathy, Obesity, Osteomyelitis, Partial Amputation	Forefoot	56	1
5	Neuropathy, Osteomyelitis, PVD	Ankle	3	3
6	Charcot deformity, Neuropathy, PVD	Lateral Foot	15	1
7	Neuropathy, Obesity	Heel	8	3
8	Charcot deformity, Neuropathy	Mid-arch	13	2

- ✓ Despite prior failed treatments with advanced biologics, all wounds responded to BMM with **rapid granulation tissue formation** and progress towards healing observed after a single application.
- ✓ A mean **percent area reduction of 64%** was achieved **after 1-3 BMM applications** in DFUs originally measuring 7.5 cm^2 and present for 21.5 months on average.
- ✓ One patient achieved complete wound closure after 6 weeks following 1 BMM application.
- ✓ Odor, drainage, inflammation, and wound depth were noticeably reduced.
- ✓ No adverse events were observed.



Representative images of chronic DFUs before (left) and after (right) BMM treatment.

SUMMARY & CONCLUSIONS

BMM demonstrated broad-spectrum activity against MDROs and biofilms in preclinical studies. In the clinically relevant swine model, BMM showed superior re-epithelialization, granulation tissue formation, and inflammation resolution when compared to silver and collagen wound products. The clinical case series confirmed rapid healing progression of refractory DFUs with granulation tissue formation over exposed tissues after a single application and substantial PAR. Altogether, the data suggests benefits in hard-to-heal DFU management and a potential change in practice give the success of BMM after failure of advanced wound products. Additional studies are needed to expand the clinical findings.

References:

1. Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic Foot Ulcers: A Review. JAMA. 2023 Jul 3;330(1):62-75. doi: 10.1001/jama.2023.10578. PMID: 37395769; PMCID: PMC10723802.
2. McDermott K, Fang M, Boulton AJM, Selvin E, Hicks CW. Etiology, Epidemiology, and Disparities in the Burden of Diabetic Foot Ulcers. Diabetes Care. 2023 Jan 1;46(1):209-221. doi: 10.2337/dci22-0043. PMID: 36548709.

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