First-in-Human Intra-Articular Endolysin (LYSG101) Therapy for Treatment-Refractory Prosthetic Joint Infection: Expanded-Access Clinical Experience

Julian Maamari[1], Assaf Raz[2], Bryan Li[2], Mark J. Spangehl[3], Brennan J. Boettcher[4,5], Jacob L. Sellon[4,5], Raymond Schuch[2*], Gina A. Suh[1*]

KEY MESSAGE • In two patients with limb-threatening, treatment-refractory prosthetic joint infection (PJI), intra-articular LYSG101 was feasible and generally well tolerated; one patient had rapid symptom improvement and microbiologic clearance with intensified dosing regimen.

BACKGROUND & AIM

- Staphylococcal PJI can be difficult to eradicate given its propensity to develop biofilms.
- Endolysins are bacteriophage-derived hydrolases with rapid bactericidal activity and anti-biofilm activity.
- LYSG101 (formerly ClyO) is an investigational anti-staphylococcal endolysin designed for local intra-articular delivery.
- We report the first-in-human intra-articular use of LYSG101 in two patients who had exhausted standard surgical, antimicrobial, and prior bacteriophage options.

METHODS

- Two patients with chronic total knee arthroplasty PJI received ultrasound-guided intra-articular LYSG101 injections under single-patient expanded-access investigational protocols.
- Both had persistent infection despite multiple surgeries, prolonged antimicrobials, and prior bacteriophage therapy; amputation was the only remaining standard option.
- Serial clinical assessments (including analgesic use), inflammatory markers, synovial leukocyte counts, and cultures were used to evaluate safety and treatment response.

PATIENT 1 | 70-year-old female with MRSE

- Multiply recurrent methicillin-resistant *Staphylococcus epidermidis* (MRSE) PJI after seven prior surgical procedures.
  - Initial arthroplasty > 2-stage exchange > 2-stage exchange > DAIR x2 > DAIR + intra-articular and intravenous lytic phage
- Three ascending intra-articular LYSG101 doses over three consecutive days (dose escalation protocol); no local or systemic adverse events.
- Rapid improvement after two doses with near-complete pain resolution and discontinuation of daily analgesics.
- Synovial culture became negative at day 30 before recurrence 50 days later consistent with persistent chronic biofilm-associated infection.
- Repeat LYSG101 treatment with intensified dosing schedule paired with intensified antimicrobials with dalbavancin and rifampin:
  - Week 1: Doses 1-5 given once every 24 hours
  - Week 2: Doses 6-8 given once every 48 hours
  - Week 3: Dose 9
  - Week 7: Dose 10
  - Week 11: Dose 11
  - Week 15: Dose 12

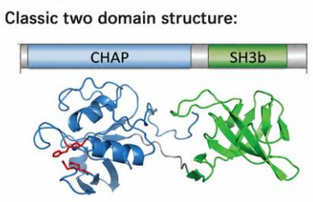
PATIENT 2 | 78-year-old female with *S. lugdunensis*

- Chronic *Staphylococcus lugdunensis* PJI with four draining sinus tracts in the setting of post-surgical lymphedema and no remaining surgical options.
  - DAIR > 2-stage exchange > intra-articular and intravenous lytic phage
- Four intra-articular doses of LYSG101 were administered over two weeks; treatment was generally well tolerated.
- A transient self-limited systemic reaction followed the first dose and did not recur.
- Infection parameters remained microbiologically positive during early follow-up.

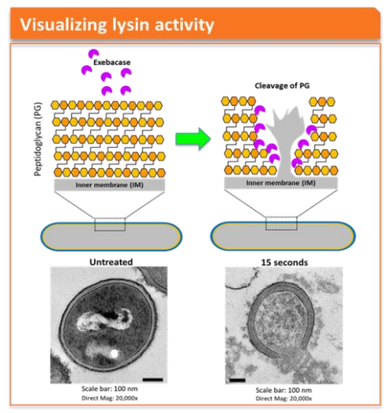
LYSG101 STRUCTURE AND KINETICS

LYSG101

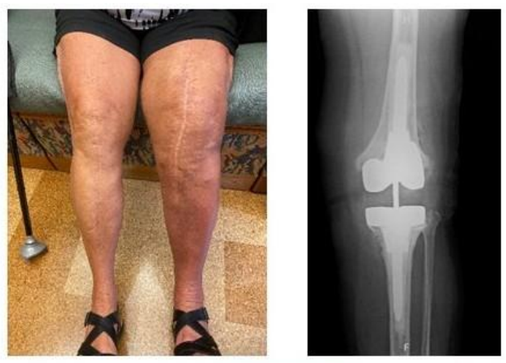
- 28.6 kDa, N-Met processed
- Engineered
- Putative D-alanyl-L-glycyl endopeptidase
- Well behaved CMC
- Broad patent protection
- Classic two domain structure:

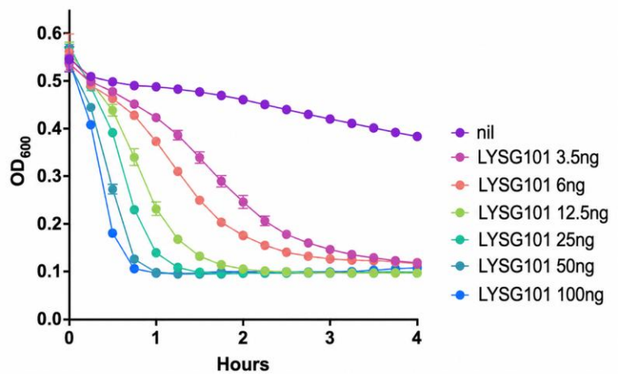


Visualizing lysin activity



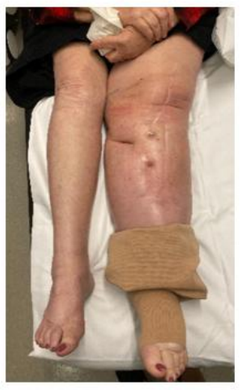
Panel A: Patient 1

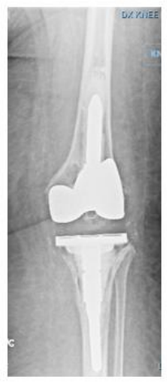


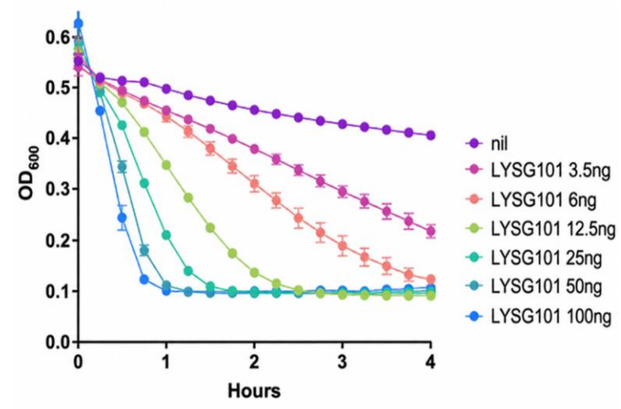


Synovial Culture	MRSE	MRSE	MRSE	MRSE	NEGATIVE	MRSE	MRSE	NEGATIVE	
Synovial WBC (cells/mm3)	25,400	24,802	82,324	37,295	12,680	20,540	78420	15070	--
CRP (mg/L)	48	37.6	56.7	79	13.9	19.3	53.4	29.5	18.4
Dosing	Baseline	Dose 1	Dose 2	Dose 3	Day 30	Day 80	Dose 1	Day 23	Day 71
Pain/Analgesic Use	Daily analgesics (Acetaminophen 4g/day)				Analgesics discontinued		Gradual recurrence	Intensified dosing	

Panel B: Patient 2







Synovial Culture	*S. lugdunensis*	*S. lugdunensis*	*S. lugdunensis*	*S. lugdunensis*	
Synovial WBC (cells/mm3)	129,030	152,600	56,705	119.847	Not obtained
CRP (mg/L)	70.9	109.6	81.2	86.9	100
Dosing	Baseline	Dose 1	Dose 2	Dose 3	Day 30
Pain/Drainage	Moderate	Unchanged	Unchanged	Unchanged	Unchanged

CONCLUSIONS

• First-in-human local LYSG101 therapy was feasible and generally well tolerated in patients lacking standard limb-salvage options.

• Microbiologic clearance and rapid symptom improvement in one patient support biologic activity of locally delivered endolysin therapy despite chronicity of biofilm-associated infection.

• Findings support prospective investigation as an adjunctive strategy for device-associated musculoskeletal infection.

Affiliations

[1]Division of Public Health, Infectious Diseases and Occupational Medicine, Mayo Clinic, Rochester, MN, USA.
[2]Precisio Biotix Therapeutics, Dover, DE, USA.
[3]Department of Orthopaedic Surgery, Mayo Clinic Arizona, Phoenix, AZ, USA.
[4]Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, MN, USA.
[5]Division of Sports Medicine, Department of Orthopedic Surgery, Mayo Clinic, Rochester, MN, USA.
* These authors contributed equally

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