Nano-mupirocin for the Treatment of Resistant Gonorrhea

#122

Ahuva Cern[1,2], Ann E. Jerse[3], Kristie L. Connolly[3], Guy Cinamon[1] & Chezy Barenholz[1,2]

1. RebioticsRx LTD, Jerusalem, Israel; 2. Membrane and Liposome Research Lab, Hebrew University Hadassah Medical School, Jerusalem, Israel; 3. Dept. of Microbiology & Immunology, Uniformed Services University, Bethesda, MD

Background

Nano-mupirocin (NM) is a PEGylated nano-liposomal formulation of mupirocin for parenteral administration. Mupirocin has a unique MoA: inhibition of isoleucil tRNA synthase, which is not shared by other antibiotics. Yet, due to rapid metabolism in vivo and high protein binding, its current use is limited to topical administration.

Our formulation overcomes this limitation; The liposomal formulation protects mupirocin in the circulation and passively targets it to infected tissues as was previously demonstrated in several animal models (pneumonia, osteomyelitis, endocarditis, necrotizing fasciitis). Thus, it enables the systemic use of mupirocin, resulting in a new parenteral antibiotic de facto with a unique MoA, and favorable PK and safety profiles.

Mupirocin spectrum of activity consists of most gram-positive bacteria and certain gram-negative ones. In particular, N. gonorrhea, for which resistance for all marketed antibiotics is emerging, was found to be affected by mupirocin. Due to its unique MoA, no cross resistant with currently used antibiotic is expected. We thus started in vitro and in vivo studies to support the development of IM nano-mupirocin for the treatment of MDR gonorrhea.

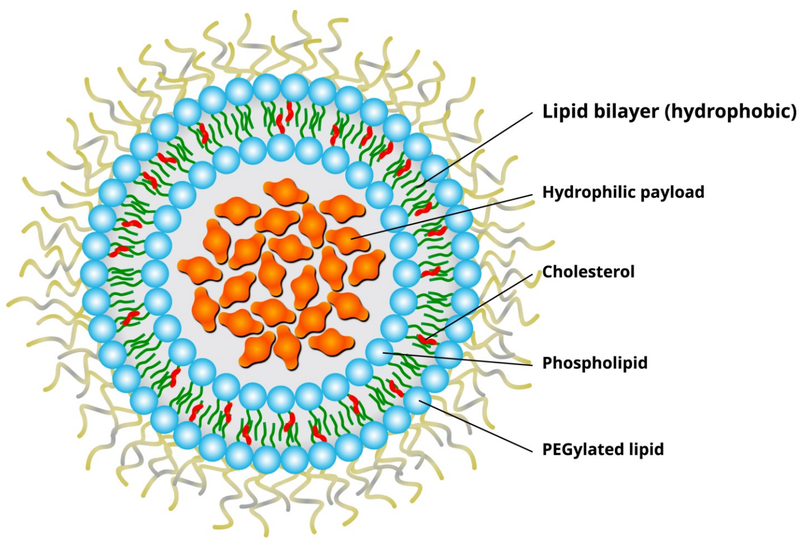
Methods

Mupirocin MIC against clinical isolates of N. gonorrhea was determined by the agar dilution method. The first part of the study was performed at Southern Research (SR) using gonorrhea isolates, received from the CDC. The second part of the study was performed at Uniformed Services University (USU) with three gonorrhea isolates, which have different antibiotic resistant profiles.

PK data of mupirocin in rats were obtained from the Tox studies (see below). The PK profile of NM in mice was tested inhouse.

Tox studies were done in rats by ITR laboratories (Canada). NM was administered 3 times per week for 2 weeks (total of 6 doses). In addition, the persistence, delayed onset or reversibility of any changes were assessed following a 7-day recovery period.

Fig. 1. **Nano-mupirocin structure**



Results

Table 1. **Mupirocin is highly active against gonorrhea with a very low MIC**

A

Compound	MIC_{90} (µg/ml)	MIC_{50} (µg/ml)	MIC range (µg/ml)	EUCAST breakpoint (R>) (µg/ml)	No. of isolates with MIC above the breakpoint	Number of isolates tested
Mupirocin	0.031	0.031*	0.0039 to 0.0625	NA	NA	94
Azithromycin	8	0.5	0.0156 to >16	0.5	21	96
Cefixime	0.25	0.125	0.0039 to 0.5	0.125	31	95
Ceftriaxone	0.063	0.031	0.0039 to 0.125	0.125	0	94
Ciprofloxacin	16	16*	<0.0156 to >32	0.06	71	96
Penicillin	2	1	0.0156 to 8	1	43	95
Tetracycline	2	2*	0.0156 to 16	1	55	96

*No difference between MIC_{90} and MIC_{50} value due to sharp susceptibility breakpoint across all isolates

B

Strain	Mupirocin MIC (µg/ml)	Resistance profile
MS11	0.05	Resistant to macrolide antibiotics
NG886	0.013	Resistant to tetracycline, penicillin, and ciprofloxacin
H041	0.05	Resistant to ceftriaxone, cefixime, other beta-lactam antibiotics, fluoroquinolones, macrolide antibiotics, and tetracycline

Cern A, Connolly KL, Jerse AE, Barenholz Y. In vitro susceptibility of Neisseria gonorrhoeae strains to mupirocin. An antibiotic reformulated to parenteral nano-liposomal antibiotic. Antimicrob Agents Chemother. 2018; 62:e02377-17

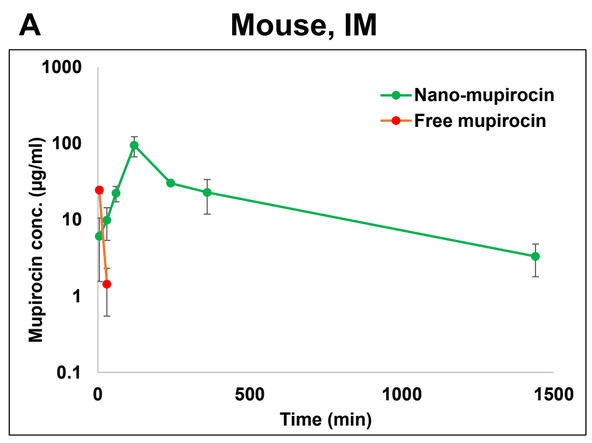
(**A**) Mupirocin MIC against 94 isolates of gonorrhea was tested and exhibited **strong antibacterial activity (MIC_{90} of 0.03ug/ml).** Mupirocin activity against these isolates was compared to 6 other antibiotics and **no cross-resistance** with mupirocin was detected. (**B**) Gonorrhea isolates, with different antibiotic resistance profiles, were found to be sensitive to mupirocin. Notably, strain H041, which is resistant to both cefixime and ceftriaxone, had MIC of 0.05µg/ml.

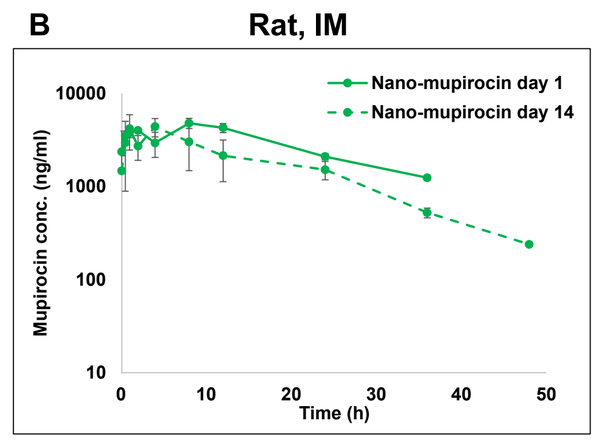
Table 3. **Early Tox study depicts no significant AEs for nano-mupirocin in rats**

Group No.	Group Designation	Dosing Route	Dose Level (mg/kg/ dose)
1	Control	IV	0
2	Low Dose	IV	10
3	Mid Dose	IV	30
4	High Dose	IV	100
5	Max feasible dose	IM	2.6 mg/animal

Rat toxicology study for NM demonstrated **a favorable safety profile** with NOAEL of at least 100mg/kg/dose for slow IV, and 10.5mg/kg for IM, both being the highest doses tested.

Fig. & Table 2. **NM results in a favorable mupirocin PK profile upon IM administration**





	C_{max} (ug/ml)	T_{max} (min)	C_{24h} (ug/ml)	AUC_z (min*ug/ml)
Nano-Mupirocin	94.6	120	3.3	28,991
Free Mupirocin	24.5	5	BLOQ	386

Day	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (µg/ml)	AUC_{0_Tlast} (hr*µg/ml)
1	13.5	8.0	4.8	105.7
14	9.0	4.0	4.4	77.2

PK of mupirocin upon IM administration of nano- and free-mupirocin showed superior PK profile for NM in (**A**) mice(*) (25 mg/kg, n=4), and (**B**) rats (10.5 mg/kg, n=3). Additionally, the data show that **mupirocin exposure is highly above gonorrhea's MIC**, and that the AUC/MIC ratio is 16,000 and 2,000 times above the MIC for mice and rats, respectively, at the doses tested.

(*) Cern A, Michael-Gayego A, Bavli Y, Koren E, Goldblum A, Moses AE, Xiong YQ, Barenholz Y. Nano-mupirocin: enabling the parenteral activity of mupirocin. Eur. J. Nanomed. 2016; 8:139–149

Conclusions

- We have strong preclinical data demonstrating mupirocin **activity against multiple gonorrhea isolates** including MDR ones
- Our liposomal formulation supports **a good mupirocin PK profile upon IM administration**, which should allow adequate systemic exposure in terms of C_{max}, AUC, and C_{trough} levels in humans, per gonorrhea's MIC
- NM has **a good safety profile**
- While NM is yet to be tested for in vivo efficacy in a gonorrhea model (to start soon), it showed **robust anti-bacterial effects** in many other mice models of infections
- Taken together, we consider **nano-mupirocin a promising candidate for development against gonorrhea in humans**

Acknowledgements

- Yaelle Bavli, Laboratory of Membrane and Liposome Research, Department of Biochemistry, IMRIC, The Hebrew University Hadassah Medical School, Jerusalem, Israel
- The study was supported by the National Institutes of Allergy and Infectious Diseases (NIAID), National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN2722011000121
- The authors would like to thank Dr. Stefan Richter and John D. Anderson from SR for their work on the MIC data of mupirocin. Dr. Thomas Hiltke and Kimberly Murphy from the NIAID are acknowledged for their help in the study

RebioticsRx
www.rebioticsrx.com