Dipeptidic Phosphonates: Potent Inhibitors of *Pseudomonas aeruginosa* Elastase B Showing Efficacy in an in vivo Murine Keratitis Model

Lukas Hiller[a,b,c], Alexander F. Kiefer[a,b], Christian Schütz[a,b], Colya N. Englisch[d], Dominik Kolling[e], Andreas M. Kany[a,b], Roya Shafiei[a,b,c], Ahmad Aljohmani[f], Niklas Wirschem[a,b,c], Daniela Yildiz[f], Katharina Rox[b,g], Jesko Köhnke[e], Tim Berger[h], Markus Bischoff[d], Berthold Seitz[h], Jörg Haupenthal[a,b] and Anna K. H. Hirsch*[a,b,c,i]

Affiliation(s)

[a] Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Campus E8.1, 66123 Saarbrücken, Germany; Helmholtz Centre for Infection Research (HZI), Inhoffenstraße 7, 38124 Braunschweig, Germany
[b] German Center for Infection Research (DZIF) Inhoffenstraße 7, 38124 Braunschweig, Germany
[c] Department of Pharmacy, Saarland University, Campus E8.1, 66123 Saarbrücken, Germany
[d] Institute of Medical Microbiology and Hygiene, Saarland University, Kirrbergerstraße 100, 66421 Homburg/Saar, Germany
[e] Institute for Food Chemistry, Callinstraße 5, 30167 Hannover, Germany
[f] Institute of Experimental and Clinical Pharmacology and Toxicology, PZMS, ZHMB, Saarland University, Kirrbergerstraße 100, 66421 Homburg/Saar, Germany
[g] Department of Chemical Biology, Helmholtz Centre for Infection Research (HZI), Inhoffenstraße 7, 38124 Braunschweig, Germany
[h] Department of Ophthalmology, Saarland University Medical Center (UKS), Kirrberger Straße 100, 66424 Homburg/Saar, Germany
[i] Helmholtz International Lab for Anti-Infectives, Campus E8.1, 66123 Saarbrücken, Germany

The ubiquitous opportunistic pathogen *Pseudomonas aeruginosa* (*PA*) is responsible for severe infections of diverse organs like the lungs, skin and eyes. Notoriously known for acquiring antimicrobial resistance, it has been acknowledged by the WHO as a high priority pathogen urgently requiring new treatment methods.[1] Due to its role in microbial keratitis, being one of the main reasons for blindness worldwide, the eyes are an important treatment target.[2],[3]

A promising approach in this context involves the inhibition of the bacterium's extracellular elastase, LasB – a zinc-dependent protease. As a main driver of *PA*'s pathogenicity, it has a wide spectrum of substrates ranging from structural proteins like elastin and collagen (causing tissue damage) to cytokines and antibodies (helping the bacteria evade the host's immune system).[4],[5] Therefore, targeting LasB will mitigate the harm to infected individuals and improve their capability to combat the pathogen themselves, while reducing the selection pressure for resistant mutants by not killing it directly.[6]

Within a medicinal chemistry–driven hit-to-lead optimization campaign, new highly potent dipeptidic phosphonates and derivates thereof were designed and synthesized following a structure–based drug discovery approach. In vitro and in vivo evaluation reveal beneficial pharmacokinetic profiles, excellent selectivity over human off-targets and good tolerability in murine toxicity studies. Ultimately, the scaffold presented demonstrates promising in vivo efficacy in a murine *PA* keratitis model in combination with the antibiotic meropenem (Figure 1A & B).[7]

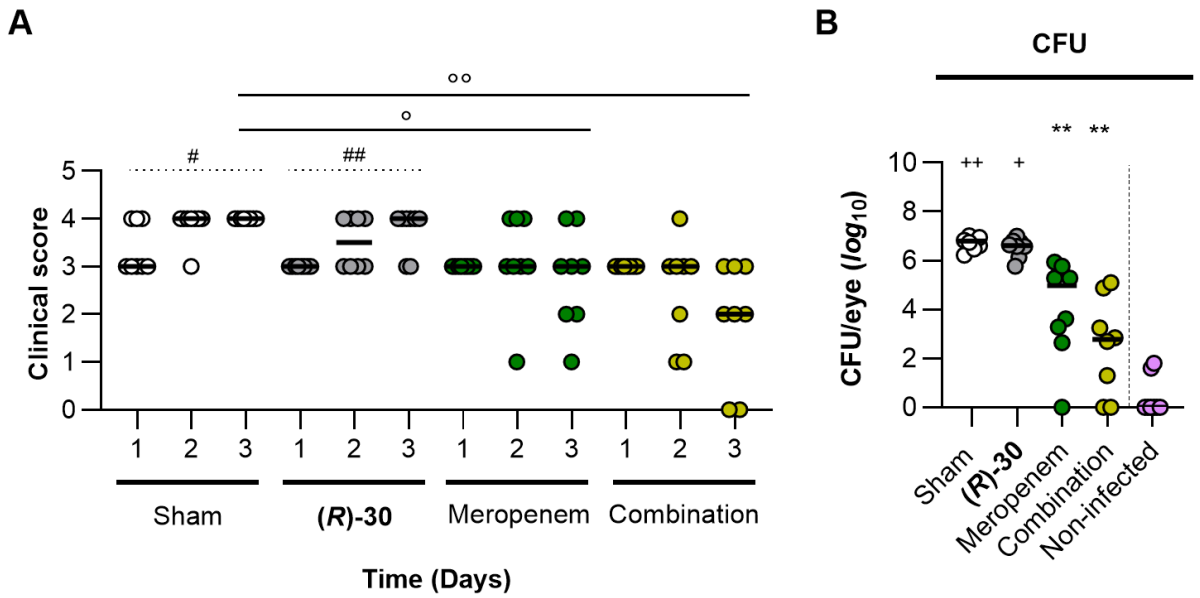

Figure 1: Impact of different treatment methods on keratitis development in C57BL/6N mice after infection with strain PA54. (**A**): Evolution of clinical score from day 1 to day 3 (n = 8 per group) after treatment with LasB inhibitor **(*R*)-30**, Meropenem or a combination of both. (**B**) Determination of bacterial loads in whole-eye homogenates at 3 days post infection in respect to the treatment methods (n = 8 per group).[7]

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