Optimization and early preclinical development of the antimalarial and antibacterial natural product chlorotonil

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Natural products from Myxobacteria bear an enormous potential for the development of new antiinfective drugs. Main advantages compared to synthetic small molecules include structural diversity and novel mechanisms of action. The macroloactone chlorotonil A isolated from *Sorangium cellulosum*[1,2] displays potent *in vitro* activity against several multi-drug resistant Gram positive pathogens (MIC in low to mid ng/mL range), including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci, and penicillin-resistant *Streptococcus pneumoniae*. Intriguingly, the compound class is also highly active *in vivo* as treatment with chlorotonils reduced the bacterial burden by more than 4-log in an *S. aureus* thigh infection model. Chlorotonil also acts against all blood stages of *Plasmodium falciparum* and it is highly active against chloroquine-sensitive (3D7) and chloroquine-resistant (Dd2) strains of *P. falciparum* with IC_{50} values of 9 nM and 18 nM, respectively, and an average IC_{50} of 15 nM (n = 25) on parasites isolated from patients in Lambaréné, Gabon. Additionally, chlorotonil A is active against late-stage gametocytes (IC_{50} 30 nM), in contrast to artesunate. Encouragingly, chlorotonil A is active *in vivo* after oral administration in the *P. berghei* mouse model.[3] However, although the natural product possesses many features that are required for an antibacterial or antimalarial drug development candidate, mainly its poor solubility hampers (pre-)clinical development. Current efforts utilizing semi-synthetic tools are focussed on tackling this important issue and improving chlorotonil's pharmaceutical properties.

[1] Gerth K, Steinmetz H, Höfle G, Jansen R. *Angew Chem Int Ed Engl* **2008**, *47*, 600.

[2] Jungmann K, Jansen R, Gerth K, Huch V, Krug D, Fenical W, Müller R. *ACS Chem Biol* **2015**, *10*, 2480.

[3] Held J, Gebru T, Kalesse M, Jansen R, Gerth K, Müller R, Mordmüller B. *Antimicrob Agents Chemother* **2014**, *58*, 6378.