Paul Ehrlich’s Magic Bullet – A Vision Comes True: Synthesis and Evaluation of Drug Conjugates for Targeted Therapy

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Biosketch: Norbert Sewald obtained his PhD degree in Organic Chemistry ("New Strategies for the Synthesis of Trifluoromethyl Substituted Heterocycles, Amino Acids, and Hydroxy Acids") in the group of Prof. Klaus Burger at the Technical University Munich. He was a postdoc in the group of Prof. Jack E. Baldwin at the Technical University Munich. In 1998 he finished his habilitation at the University of Leipzig ("Peptides Containing β-Amino Acids: Asymmetric Synthesis, Solid Phase Peptide Synthesis, and Conformational Analysis by NMR Spectroscopy"). Since 1999 he is a Professor for Organic and Bioorganic Chemistry at the University of Bielefeld. His research interests comprise Biocatalysis (Enzymatic Halogenation) and Chemocatalysis, Bioconjugation (Drug Conjugates), Peptides and Peptidomimetics, and Natural Product Chemistry. He was/is coordinator of the Bilateral Bielefeld-Yaoundé Graduate School YaBiNaPA (2018–2023) and the Marie Skłodowska-Curie Training Networks MAGICBULLET (2015–2018) and Magicbullet::reloaded (2020–2023). He has supervised 72 MSc and 60 PhD students. Currently 16 PhD students are working with him. 3 former PhD students have been awarded Marie Curie postdoctoral fellowships. The group hosted 22 guest scientists on the postdoctoral level from 13 countries (among them 4 Marie Curie fellows and 9 Alexander von Humboldt fellows). Norbert Sewald currently is the President of the European Peptide Society.

Abstract: Cryptophycins, natural occurring cyclic depsipeptides, show high cytotoxicity against several cancer cell lines, even towards multi-drug resistant (MDR) cancer cell lines [1,2]. These characteristics made the synthetic analog cryptophycin-52 (LY355703) a promising drug for cancer treatment. However, clinical trials had to be discontinued because of neurotoxic side effects and lacking efficacy in vivo. Selectivity issues may be tackled with in a directed therapy approach. The lack of an addressable functional group in cryptophycin-52 hampers the conjugation to a homing device. We developed efficient strategies for the total synthesis of cryptophycins and their analogues taking specific emphasis on the synthetically most challenging unit A [1,2]. Structure–activity relationship (SAR) studies have been done aiming at the introduction of a new functional group for bioconjugation while maintaining the high biological activity of the parent compound [3]. In addition, cryptophycin conjugates with peptides and antibodies have been developed for targeted delivery in tumour therapy [4].

References: