# Responsive Polymer Conjugates of Cyclic Peptide Nanotubes as Smart Antibiotics

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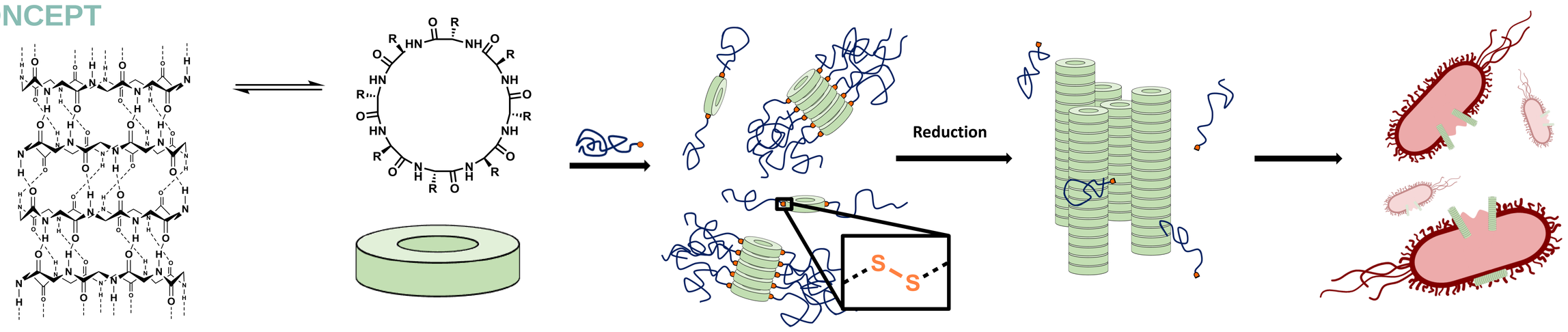
WARWICK
INTEGRATE ANTIMICROBIAL RESISTANCE

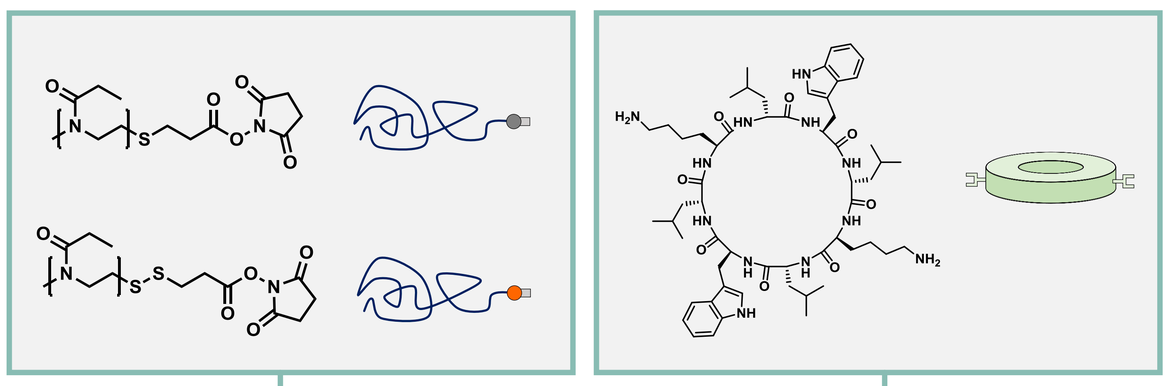
## INTRODUCTION

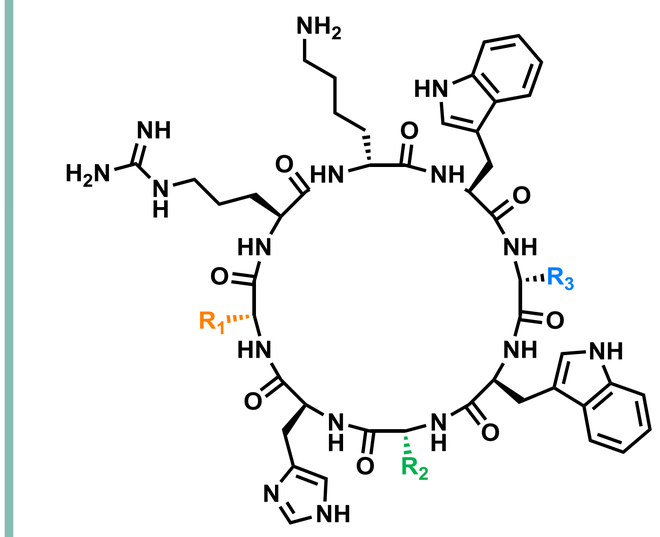
The alarming rate of the development of multi resistant bacteria strains,[1] so called "super bugs" was addressed recently by the WHO and labelled an "increasingly serious global threat to public health".[2] As the number of newly approved antibiotics is decreasing steadily, in particular for the treatment of gram negative bacteria[3] humanity is steering into a "post antibiotic era" endangering the advances of modern medicine. A possible way to counteract these developments is the design of new antibiotics, which are less likely to be challenged by bacterial resistance.[4] A promising candidate are cyclic peptide nanotubes (CPNT) as first described by Ghadiri et al. in 1993.[5] These supramolecular polymers show great potential as antimicrobial agents as they interact with bacterial membranes, which leads to the formation of pores or membrane disruption. However, their tendency for lateral aggregation results in solubility restrictions and their lacking selectivity between bacterial and mammalian cell membranes leads to undesired toxicity. By the reversible conjugation of biocompatible polymers to the outside of CPNT we present a potential strategy to overcome these issues and establish CPNT as next generation antibiotics.

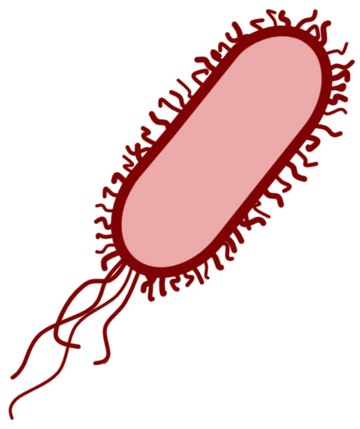
## CONCEPT




## PROOF OF CONCEPT

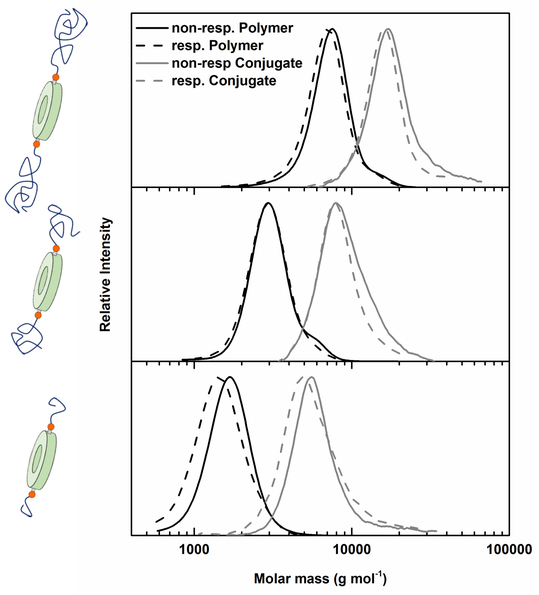




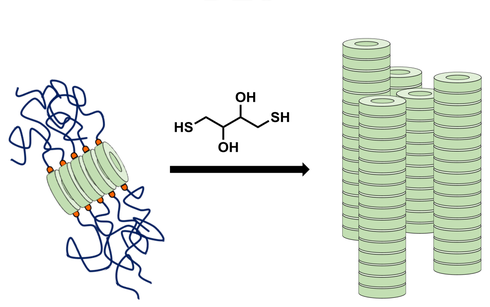

| | R1 | R2 | R3 | P. aeruginosa | K. Pneuminiae | S. aureus | E. Coli | S. pyogenes |
|---|---|---|---|---|---|---|---|---|
| **CP1** | Lys | Lys | Lys | >128 | >128 | 8 | >128 | 32 |
| **CP2** | Lys | Leu | Lys | 128 | 32 | 4 | 16 | 2 |
| **CP3** | Lys | Leu | Leu | >128 | >128 | 2 | 64 | 4 |
| **CP4** | Arg | Ley | Leu | 64 | 64 | 2 | 16 | 4 |
| **CP5** | Arg | Leu | Leu | >128 | 16 | 2 | 16 | 1 |

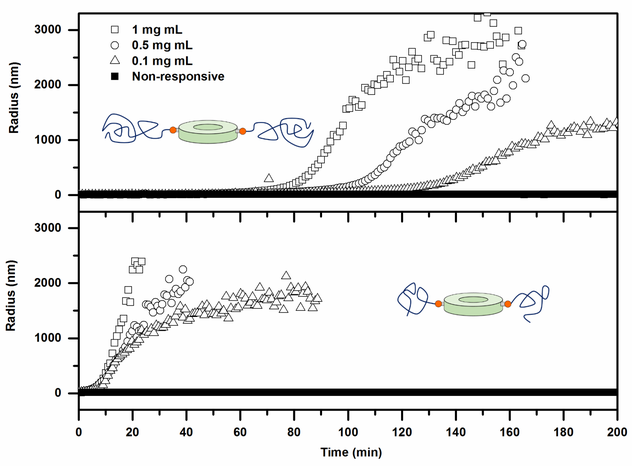
### GPC



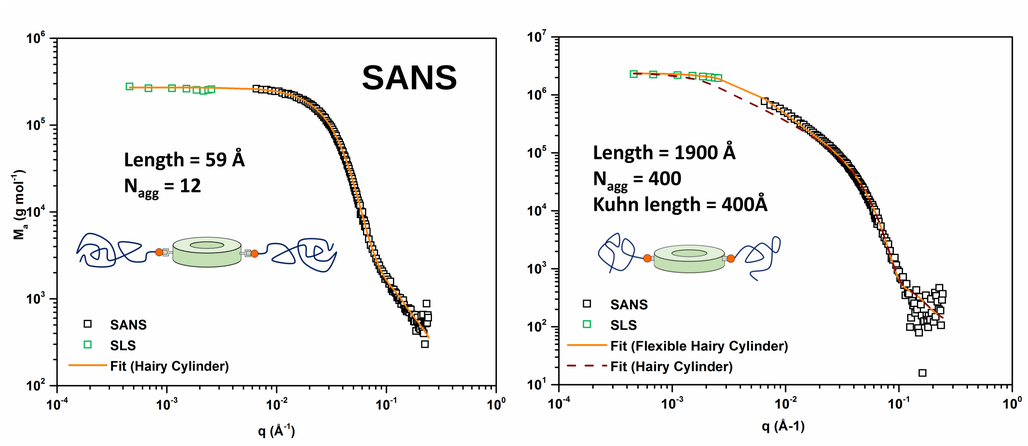

| Sample | DP | SLS Mw | SLS $N_{agg}$ | SANS $N_{agg}$ |
|---|---|---|---|---|
| non resp. | 45 | 320,000 | 32 | |
| resp. | 45 | 340,000 | 34 | |
| non resp. | 20 | 440,000 | 88 | |
| resp. | 20 | 1,400,000 | 278 | |
| non resp. | 10 | - | - | Not water soluble |
| resp. | 10 | - | - | |

### DLS

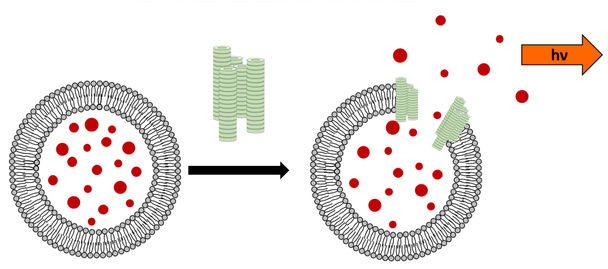


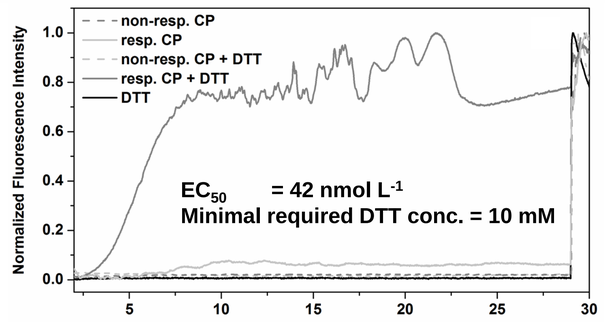




### SANS




### DYE LEAKAGE




## OUTLOOK

It has been shown that the stacking of cyclic peptides (CP) to form nanotubes can be induced on demand be the detachment of a polymer from CP-conjugates. The next goal is to use bactericidal CP and conjugate them to polymers using a cleavable peptide sequence able to respond to the presence of pathogenic bacteria.

[1] C. A. Arias , B. E. Murray *New Engl. J. Med.* **2009**, *360*, 439-443.
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[3] J. H. Lee, S. H. Jeong, S.-S. Cha, S. H. Lee, *Nat. Rev. Drug Discov.* **2007**, *6*.
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[5] M. R. Ghadiri, J. R. Granja, R. A. Milligan, D. E. McRee, N. Khazanovich, *Nature* **1993**, *366*, 324-327.

## ACKNOWLEDGEMENT

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DFG Deutsche Forschungsgemeinschaft