Platform for the development of MurJ and FtsW inhibitors to treat antimicrobial resistance

KEY ACHIEVEMENTS

- Development of a method based on fluorescence anisotropy to measure MurJ and FtsW activities.
- In house production of proteins and substrates (not commercially available).

KEY COMPETITIVE ADVANTAGES

Method allows to develop first-in-class MurJ and FtsW inhibitors, which will work by novel mechanisms of action and therefore will be valuable tools to treat antimicrobial resistance to existing antibiotics.

ONGOING ACTIVITIES

Adaptation of method for high-troughput screening.

INTELLECTUAL PROPERTY

- Method has been published (Boes A. et al., Sci Rep 2020).
- Synthesis of reagents and set-up of method is based on in-house know-how.

PARTNERSHIP SOUGHT

Collaboration agreements to implement this method to high-throughput drug discovery campaigns to develop novel MurJ and FtsW inhibitors.

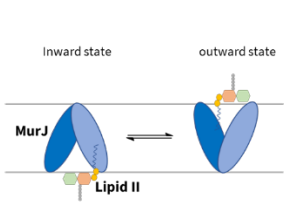
The use of existing antibacterials has been met with antimicrobial-resistant (AMR) strains. As a result, in 2013 in the US 23,000 people died from these infections. Additionally, the cost to treat these infections exceeds $20 billion per year. Globally, in the absence of new antibacterial agents, annual mortality rates could exceed 10 million by 2050.

Antibiotics recently approved or in clinical trials are analogs of existing drugs. Due to their structural and mechanistic similarities, it is likely that resistance mechanisms that inactivate the old drugs will affect newer analogs. Therefore, new antibacterial agents with novel mechanisms of action must be developed.

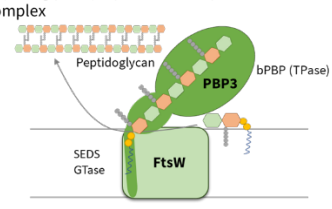
Most antibacterials target Peptidoglycan (PG) cell wall synthesis, an essential constituent of both Gram-positive and Gram-negative bacterial cell envelopes. Therefore, all biochemical steps in PG biosynthesis are considered major antibacterial targets to tackle the resistance to existing antibiotics.

The team of Dr. Mohammed Terrak at the University of Liège has developed specific and sensitive methods to measure the activities of the bacterial proteins, lipid II flippase MurJ and cell division specific GTase FtsW, both involved in the synthesis of PG and essential for bacterial viability (Boes A. et al., Sci Rep 2020). To date, there are no approved or clinical-stage drugs targeting none of them. Notably, there is a lack of relevant in vitro assays for the screening of compounds targeting either FtsW or MurJ.

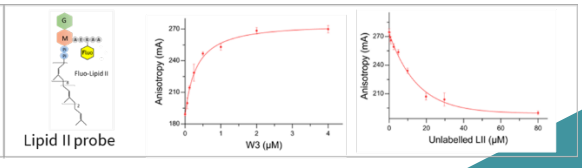
Lipid II transport across the cytoplasmic membrane by the lipid II flippase MurJ



Peptidoglycan polymerization by a FtsW/bPBP complex



Fluorecence anisotropy assay for screening of inhibitors against lipid II binding proteins (FtsW & MurJ)



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