## Repotentiating Beta Lactam antibiotics

The most common form of resistance to ß-lactam antibiotics is the expression of ß-lactamase enzymes. These bacterial enzymes are capable of inactivating ß-lactam drugs by hydrolyzing their ß-lactam ring, rendering them ineffective. Co-administration of a ß-lactam antibiotic with a ß-lactamase inhibitor is a recognized strategy to circumvent this type of bacterial resistance, yet the number of compounds that have actually made it to clinical application so far is extremely limited. The aim of this project is to discover and characterize new molecules of botanical origin that selectively inhibit ß-lactamases, yielding new lead compounds. Natural products from plants serve as rich resources for drug development, and the enormous structural diversity of plant derived compounds suggests that they may hold many more interesting pharmacological constituents. As a source of finding new ß-lactamase inhibitors however, they have remained largely unexplored. New ß-lactamase inhibitors will be obtained by systematically screening the PECKISH library (Plant Extract Collection in Kiel in Schleswig-Holstein). PECKISH is a standardized library containing more than 4600 unique aqueous, ethanolic and other extracts from > 860 different plant species (~190 different plant families) and 11 different plant tissues. The screening strategy involves miniaturized agar-diffusion growth inhibition assays based on a range of modified ***E. coli*** bacteria expressing different (types of) ß-lactamases. Extracts showing ß-lactamase inhibitory activity will be profiled and a selection of the most promising extracts will be subjected to further isolation, identification and structural confirmation of the bioactive compound. After verification of the inhibitory capacity of the new compounds, design and synthesis of analogues will be initiated. Full characterization of the newly identified inhibitors and analogues using biochemical and crystallographic studies will be carried out. Ultimately this project should yield the identification of new lead compounds for the development of clinical ß-lactamase inhibitors.

**Keywords**: beta-lactamases, inhibitors, PECKISH library

**Coordinator**: Mariel Pikkemaat, RIKILT – Wageningen UR, as part of stichting DLO, Netherlands
**Partners**:
Natalie Strynadka, Univerisity of British Columbia, Canada

Fredrik Almqvist, Umeå University, Sweden