Biophysical characterization and structural studies of Small Multidrug Resistance family of transporters

The Small Multidrug Resistance (SMR) family of membrane proteins is known for conferring resistance to a wide range of antibiotics and xenobiotic compounds in bacteria. Moreover, their small size and rare dual topology architecture have made them a suitable model system for studying membrane protein mechanism and evolution. Despite many years of research on multidrug exporters in the SMR family, the family’s main function has remained a mystery. We show for the first time, using phylogenetic studies and membrane transport assays, that the majority members of this family are not drug exporters. Instead, they mediate the export of guanidinium, a small cationic metabolic byproduct produced by bacteria. Guanidinium exporters, which we term Gdx proteins, are highly selective for guanidinium and mono-substituted guanidinyl compounds and share an overlapping set of non-canonical substrates with drug exporter EmrE. We also recently determined the X-ray crystal structure of Clo, a representative member of SMR family to 2.3 Å resolution. Our studies pave the way to better understand the evolutionary process by which multidrug exporters emerged.