Engineering Blood-Brain Barrier Penetrant and P-gp Efflux Deficient Compounds for the Treatment of Brain Metastasis

Rachel E. Schaaf and Paul J. Hergenrother

Brain metastases are one of the major causes of premature death from many cancers, yet many of the current approved therapeutics have limited to no blood-brain barrier (BBB) penetrance. It is estimated that 98% of small molecule drugs cannot cross the BBB. Even for drugs that can traverse the BBB, many suffer from efflux liabilities causing poor accumulation and the inability to properly treat the metastasis. Thus, patients with brain metastases have more dismal survival rates than those without brain metastases. P-glycoprotein (P-gp) efflux liability is a major concern for drugs used to central nervous system (CNS) diseases and one that has not been fully addressed in a streamlined-manner. However, there is precedent for installation of a simple function group to reduce P-gp efflux liability and thus this gap in the clinic can be fulfilled by engineering efflux out of drug scaffolds through incorporation of this functional group and its bioisosteres to decrease the efflux liabilities of these drugs while maintaining potency and selectivity.