

## **Abstract**

Pain and addiction are two of the most devastating medical, social, and economic problems in modern society. Morphine is the most widely used analgesic in the world, while methadone is a cornerstone therapy of opiate dependence, and cancer pain. Maintenance of predictable brain concentrations of both drugs is confounded by considerable interindividual variability in pharmacokinetics, pharmacodynamics, and susceptibility to drug interactions. Potential consequences include inadequate treatment and adverse events (withdrawal, respiratory depression, death). It is increasingly recognized that the blood-brain barrier contains numerous drug transport proteins, which determine drug access into the brain. Recent cellular and animal studies suggest that the ABC-type xenobiotic efflux transporter P-glycoprotein (P-gp) is a major determinant of brain opioid access. Nevertheless, the role of P-gp in human brain opioid penetration is unknown.

This proposal tests the hypothesis that morphine and methadone are substrates for P-gp in humans, and that P-gp activity influences brain opioid penetration, pharmacodynamics, and clinical effects. The Specific Aims are to determine the role of P-gp in human blood-brain barrier transport, brain access, and clinical effects of morphine and methadone. Clinical studies in healthy volunteers will use tracer  $^{11}\text{C}$ -morphine and  $^{11}\text{C}$ -methadone, and positron emission tomography (PET), to visualize brain opioid concentrations. Comparison of brain opioid uptake and plasma concentration-effect relationships in pharmacologic dose experiments, both with and without P-gp inhibition using a newly validated in vivo inhibitor probe (cyclosporine), will test the hypothesis. The proposed study utilizes an interdisciplinary approach of anesthesiology, medicinal chemistry, and radiology, to implement first-in-man studies.