The opioid crisis is a national public health crisis that directly affects millions of Americans and indirectly impacts countless more. Indeed, in the State of Oklahoma, 100,000 individuals struggle with addiction to opioids, amounting to costs in excess of $500 million dollars that the state estimates it will cost to fight the crisis for 1 year. This crisis is fueled by diversion and misuse of prescription opioid analgesics, which includes oxycodone (OxyContin®) and hydrocodone (Vicodin®), mu opioid receptor (MOPr) agonists that cause tolerance, dependence, and life-threatening respiratory depression. To counteract this crisis, therapeutic alternatives lacking this adverse effect profile are critically needed. We approach this unmet need by designing bifunctional ligands that exhibit pharmacologic effects at two OPr targets simultaneously. In this seminar, we will discuss the rational development of bifunctional ligands possessing a MOPr agonist/delta (DOPr) antagonist pharmacologic profile. We will first present 7-E-benzylideneoxymorphone (BOM), which is a MOPr partial agonist/DOPr antagonist that is remarkably effective in controlling visceral pain and lacks reinforcing effects in rats. Then, we will discuss how we improved the MOPr efficacy of BOM to generate MOPr agonist/DOPr antagonist with morphinelike efficacy and potency that is active in antinociception tests in mice. Finally, we will show how these compounds are predicted to bind MOPr via a binding pose that engages a region of the receptor active site that is seldom targeted by available analgesics. We hope that these studies will lead to the development of new analgesics that lack tolerance, dependence, and life-threatening respiratory depression.

About Dr. Cunningham: Chris earned his BS, with honors, in Chemistry and Germanic Studies from the University of Maryland, College Park, and was a doctoral fellow at the University of Maryland, Baltimore, School of Pharmacy where he earned his Ph.D. in Pharmaceutical Sciences under the direction of Dr. Andy Coop. He completed postdoctoral training at the University of Kansas, where he worked under the direction of Dr. Jeffrey Aubé with the Specialized Chemistry Center and Dr. Tom Prisinzano in the Department of Medicinal Chemistry. He began his independent career at Concordia University Wisconsin School of Pharmacy in 2011, and is currently Associate Professor of Pharmaceutical Sciences and Director of the Center for Structure-Based Drug Design and Development.