My laboratory has had a long-standing interest in the design, synthesis and analysis of peptides and peptidomimetics that target opioid receptors, with the goal of advancing compounds for the potential treatment of pain and substance abuse. We have recently been focusing on the exploration of the pharmacology and structure-activity relationships (SAR) of macrocyclic tetrapeptides based on the natural product CJ-15,208 (cyclo[Phe-D-Phe-Phe-Trp]). These macrocyclic peptides are promising lead compounds because they are not degraded by proteolytic enzymes, are active after systemic, including oral, administration and can cross the blood-brain barrier to reach targets in the brain. We have identified analogs with a range of opioid activity profiles that have potential application in the treatment of pain and substance abuse. Examples will be presented highlighting these diverse activity profiles and their potential advantages in terms of improved safety profiles. We have identified other therapeutic areas where these macrocyclic tetrapeptides also exhibit promising activity, including decreasing the proliferation of cancer cells, opening up additional potential therapeutic applications for these peptides.