Submitter Name: Ying-Xian Pan
Submitted email: pany@mskcc.org

Pharmacological functions of alternatively spliced mu opioid receptor variants in conditional Oprm1 rat models generated by Easi-CRISPR

Jin Xu[1], Valerie P. Le Rouzic[1], Gavril W. Pasternak[1], Miyasaka Yoshiki[2], Tomoji Mashimo[2], Thom Saunders[3], Channabasavaiah B. Gurumurthy[4], and Ying-Xian Pan[1]

[1]Department of Neurology and Molecular Pharmacology Program, Memorial Sloan-Kettering Cancer Center; [2]Institute of Experimental Animal Sciences, Graduate School of Medicine, Osaka University; [3]Transgenic Animal Core, University of Michigan; [4]Mouse Genome Engineering Core Facility, University of Nebraska Medical Center

Background: A single-copy mu opioid receptor (OPRM1) gene generates a vast array of mu opioid receptor splice variants through extensive alternative splicing that is conserved from rodent to human. These variants can be divided into two sets: exon 11 (E11) and exon 1 (E1) associated variants. The functional differences between the E1 and E11 sets of variants have been demonstrated using gene targeted mouse models.

Rationale/Significance: While mouse models are valuable, rats have many advantages both in behavioral modeling and in vivo manipulation.

Hypothesis: E11- and E1-associated splice variants play important and distinct roles In opioid pharmacology.

Result: We have generated two conditional Oprm1 knockout (KO) models, E11-KO and E1-KO, in Sprague Dawley rats using a novel Easi-CRISPR approach. Cre-mediated E11 and E1 deletions was confirmed through breeding a CAG-Cre rat. Initial behavioral studies showed that in both E11 and E1 KO rats, buprenorphine analgesia was lost. Buprenorphine CPP was significantly reduced in E11 KO rats. Morphine analgesia was completely lost in the E1-KO rat, but intact in the E11-KO rat.

Discussion: Our results suggest that buprenorphine analgesia is dependent on both E11 and E1-associated variants, a similar scenario seen in the E11-KO and E1-KO mouse models. E11-associated variants also involved in buprenorphine reward in rat. These conditional Oprm1 KO rat models will provide valuable resources for the research community and would expand our ability explore mu opioid pharmacology with approaches and techniques not feasible in mice.

Supported in part by grants from NIH (DA040858, DA042888, DA46714 and CA08748)