

## Opioid Receptor Knockout Mice

### Background

Morphine, endogenous opioid peptides and certain opioid drugs exert a pleiotropism of biological effects ranging from stress response to pain, reproductive behavior, and feeding behavior through binding to endogenous receptors called opioid receptors. There are three major types of well characterized opioid receptors:  $\delta$ ,  $\kappa$ , and  $\mu$ . Many of the opiate analgesics modulate pain perception through  $\mu$ opioid receptor. However, their use is limited by side effects such as constipation and the potential to develop dependence on opioids.  $\delta$  receptor agonists modulate pain perception without the development of dependence and thus, these receptors are useful targets in the development of novel analgesics.

**Thus, there is significant unmet medical need for the development of non-opioid analgesics that can overcome the limitations of opiates currently in clinical use. Animal models that can be used to uncover novel pathways and targets for the development of agents capable of modulating stress response, pain and feeding habit would serve to advance the current body of knowledge in opiate research toward the development of novel analgesics.**

### Description of the Technology

Knockout mice with disruptions in the  $\delta$ ,  $\kappa$ , and  $\mu$  opioid receptors and two genes that encode several opioid receptor ligands were generated. Certain  $\mu$  and  $\delta$  receptor agonists have been shown to exert analgesic effects in both  $\delta$  and  $\mu$  receptor single knockouts as well as in mice with disruptions in both these receptors suggesting that there are additional pathways that mediate analgesia. Additionally, studies with  $\delta$  knockout mice identified a novel pathway that modulates pain perception without the development of analgesic tolerance. These novel pathways represent additional targets for the development of non-opioid analgesics for the management of chronic pain as well as to overcome analgesic tolerance and thus the potential for their abuse.

In another set of experiments, these mutant mice were used to study agents that affect food intake and obesity. These studies have revealed that an intact opioid system is necessary for the effective management of feeding behavior. Thus, opioid system could serve as target for the control of feeding behavior, and management of obesity and obesity related diseases.

### Advantages

- Currently available analgesics such as morphine induce tolerance and consequently there is potential for opiate abuse. The opioid knockout mice can be used to develop non-opioid agents that can overcome these limitations.
- Antagonists to receptors are non-specific in their effects.

### Deliverables

#### I. Receptor Knockout Mice

- $\delta$  receptor knockout mice
- $\kappa$  receptor knockout mice
- $\mu$  receptor knockout mice

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## II. Opioid Receptor Ligand knockout Mice

- Enkephalin knockout mice
- Prepro-Orphanin FQ knockout mice

III. Single and combinatorial knockout mice involving the receptors and ligands are also available.

### **Applications**

- To study the role of opioid receptors in pain perception, drug abuse, and alcohol abuse
- To identify novel targets for non-opioid analgesics
- To identify compounds or agents that modulate appetite, stress, anxiety and pain.
- To develop assays or systems to test therapeutic agents for chronic pain, CNS diseases, spinal chord injury, and reproductive behavior

### **Patent Status**

- Unpatented technology

### **Licensing Opportunity**

- This technology is available for non-exclusive license.

### **Contact**

Peter Golikov, MS, MBA  
Director, Ventures and Licensing  
University of Medicine and Dentistry of New Jersey  
335 George Street  
New Brunswick, NJ 08901  
Direct Phone: (732)-235-9355  
Main Office Phone: (732)-235-9350  
Facsimile: (732)-235-9358  
golikope@umdnj.edu

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