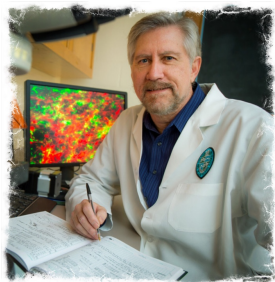


# Pain Therapeutics



## Zadina Lab Research and Innovation

The lab of **James Zadina** studies opioids and their role and mechanisms of action in alleviating pain and inducing side effects, particularly drug abuse. Current focus is on development of novel, safer analgesics based on modifications of naturally occurring opioids (endomorphins). One compound is in clinical trials and a second generation of analogs has been shown in animal models to provide analgesia equal to or greater than morphine with substantial reduction or absence of several major side effects. These include: reduced risk of abuse, respiratory depression, tolerance, pro-inflammatory responses, and side effects of particular importance for older adults (including motor and cognitive impairment).

## Motivation and Development

Opioid prescription painkillers are the gold standard for alleviating pain but are associated with several adverse side effects. Abuse liability is particularly important as it results in major medical, societal, and economic problems that have led to an epidemic of abuse and a quadrupling of painkiller overdoses since 2000. In addition, respiratory depression is the cause of death from overdose, and tolerance complicates treatment and increases the risk of side effects. Motor and cognitive impairment are especially problematic for older adults. Fear of these side effects has contributed to a large proportion of the population (39 million, 19%) suffering from inadequate relief of moderate to severe pain. Separation of analgesia from unwanted effects has long been an unmet goal of opioid research, but the most commonly used opioids besides morphine are still based on oxycodone and hydrocodone, discovered nearly 100 years ago. A new approach and new painkillers are desperately needed.

In 1997 naturally occurring peptides were discovered (endomorphins, EMs) in the brain that act potently and selectively at the mu (morphine) opioid receptor to alleviate pain (Zadina et al., Nature 386:499, 1997). Because the natural EMs are rapidly metabolized, we have developed metabolically stable **EM analogs for use as therapeutics**, that provide analgesia equal or greater than that of morphine, and show significant reduction of side effects. This program has been highly successful.

## Lead Compound Identified

We have identified a lead compound with a favorable profile in multiple tests. At doses providing equal or greater pain relief relative to morphine in the rat, our lead EM analog showed **significantly reduced**: a) respiratory depression, b) impairment of motor coordination, c) impairment of cognitive function, d) tolerance, e) inflammation/glial activation associated with tolerance and pain hypersensitivity and f) abuse liability in several complementary tests that correlate well with human results, indicating that it is **highly unlikely to be abused**. The analog is very effective at relieving pain in multiple pain models in animals. The results indicate that this EM analog could provide the **gold standard pain relief** typical of currently used opioids like morphine, but with a **remarkably safer profile of major side effects**.

## Publications

Zadina et al., *Endomorphin Analog Analgesics with Reduced Abuse Liability, Respiratory Depression, Motor Impairment, Tolerance, and Glial Activation Relative to Morphine*. *Neuropharmacology* 105:215-227, 2016. doi:10.1016/j.neuropharm.2015.12.024

Feehan, A.K....Zadina, *Novel Endomorphin Analogs are More Potent and Longer-Lasting Analgesics in Neuropathic, Inflammatory, Postoperative, and Visceral Pain Relative to Morphine*. *Journal of Pain* 18:12, 1526-1541, 2017.

[http://www.jpain.org/article/51526-5900\(17\)30698-3/pdf](http://www.jpain.org/article/51526-5900(17)30698-3/pdf)

## Intellectual Property & Development Plan

These compounds are patented under a VA-Tulane University cooperative agreement, and patents should expire no earlier than July 8, 2031. Additional term extensions may be available and will be filed for at the appropriate times.

Transition to clinical trials is being coordinated in a cooperative effort of the Tulane School of Medicine and Office of Technology Transfer and Intellectual Property Development and the VA. This Technology has been licensed and efforts are underway to fund FDA-required preclinical studies and Phase I clinical trials.

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