



Weill Cornell Medicine

Opto-Opioids: Light-Activated Compounds for Locally-restricted and Reversible Pain Management

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Background & Unmet Need

- Approximately 2.5 million people in the U.S. have Opioid Use Disorder, with over 80,000 opioid-related overdose deaths occurring in the US annually
- Opioid receptors are widely expressed across the nervous system, with central opioid receptors present in the CNS and peripheral opioid receptors present in the peripheral nervous system
- Given that many opioid-driven side effects, including respiratory depression and addiction, are centrally mediated in the brain, peripherally-restricted opioids provide a promising strategy for safer analgesia
- Light-activated ligands offer a promising approach for restricting the actions of opioids to the site of pain
- **Unmet Need:** New techniques that harness the analgesic power of opioids without the risk of addiction or respiratory depression

Technology Overview

- **The Technology:** Opioid analgesic compounds that can be locally and reversibly activated and deactivated with light, reducing addiction potential
- **The Discovery:** The inventors developed a morphine-based compound, *azo-morphine-3* (AM-3), which has substantially stronger agonism for the mu-opioid receptor in the light-activated *cis* form than in the relaxed *trans* configuration
- **PoC Data:** Administration of *cis*-AM-3, but not *trans*-AM3, increased paw withdrawal latency (PWL) in the radiant-heat test with identical effect size to morphine ($P > 0.001$ vs. vehicle)
- In vivo activation of AM-3 via paw illumination increased PWL in the same test ($P > 0.05$), and demonstrated reversible and repeatable analgesic effects in the spared nerve injury model (SNI) of chronic neuropathic pain ($P < .001$)
- *cis*-AM-3 does not promote hyperlocomotion in the open field test, demonstrating lack of CNS activation

Inventors:

Joshua Levitz
Dirk Trauner
Vsevelod Katritch

Patents:

[PCT Filed](#)

Publications:

[Posa et al. bioRxiv. 2025.](#)
(preprint)

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Technology Applications

- Topical and self-inactivating treatment for local control of acute pain
- Replacement for commonly prescribed opioids with less addiction potential

Technology Advantages

- Low penetration of the CNS, reducing potential for addiction and central side effects such as respiratory depression
- Avoids gut-based side effects seen with other peripheral opioids (e.g. loperamide)
- Pain relief is localized to pain site and is reversible
- Precursor compound, naltrexone, is not subject to controlled substance regulation

Supporting Data / Figures

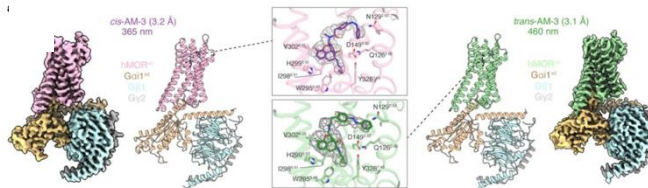
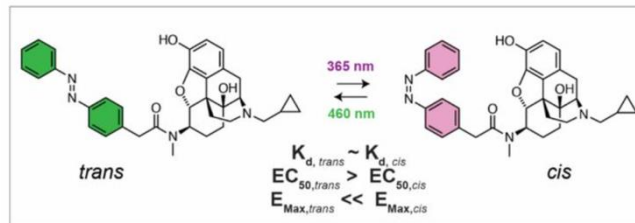


Figure 1: AM-3 is a photochromic mu opioid receptor (MOR) agonist which enables reversible efficacy switching. **Top:** Overview of AM-3 switching mechanism **Bottom:** Cryo-EM reconstructions of *cis*-AM-3 and *trans*-AM-3 in complex with MOR:G protein heterotrimer.

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Cultured Cells

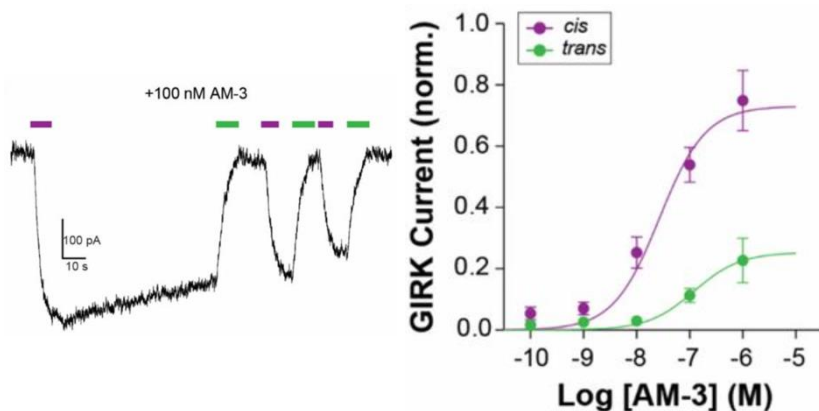
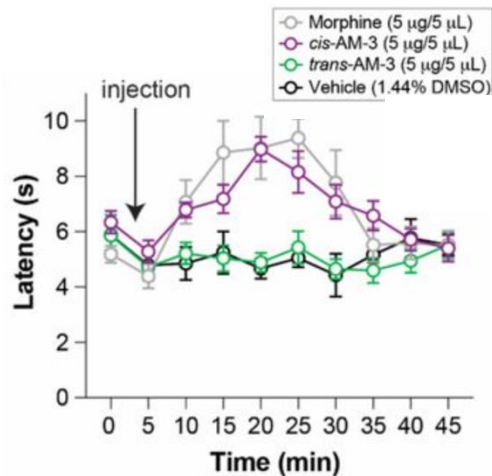


Figure 2: Left: Representative trace showing bistable, reversible, and repeatable photo-activation of MOR via AM-3 in a HEK 293 cells. Middle: Dose-response curve showing enhanced GIRK current by cis-AM-3. Right: Time course of paw withdrawal latency in the radiant heat test following intraplantar (i.pl.) injection of cis-AM-3 vs morphine.

In Vivo



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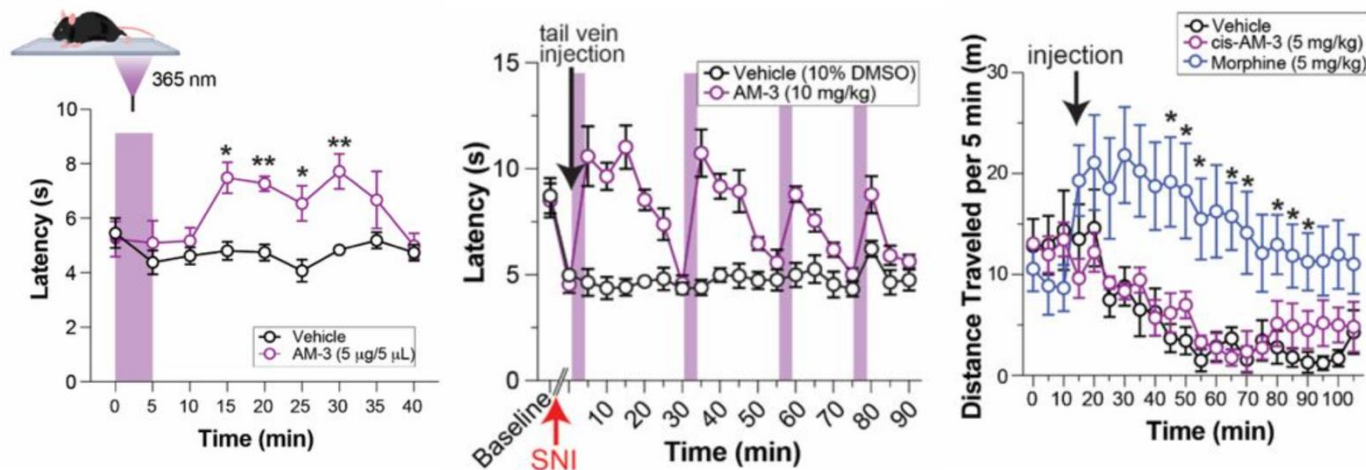


Figure 2: Left: Time course of paw withdrawal latency shows in vivo activation of AM-3 via paw illumination (i.pl. administration) Middle: Reversible in vivo activation via paw illumination following systemic administration in a spared nerve injury (SNI) model of chronic neuropathic pain Right: Open field test comparing locomotion in mice administered morphine vs. pre-illuminated cis-AM-3, demonstrating that cis-AM-3 does not drive adverse central effects (i.v. administration).

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