DBPR116

A next generation opioid analgesic with novel mode of action and fewer adverse reactions

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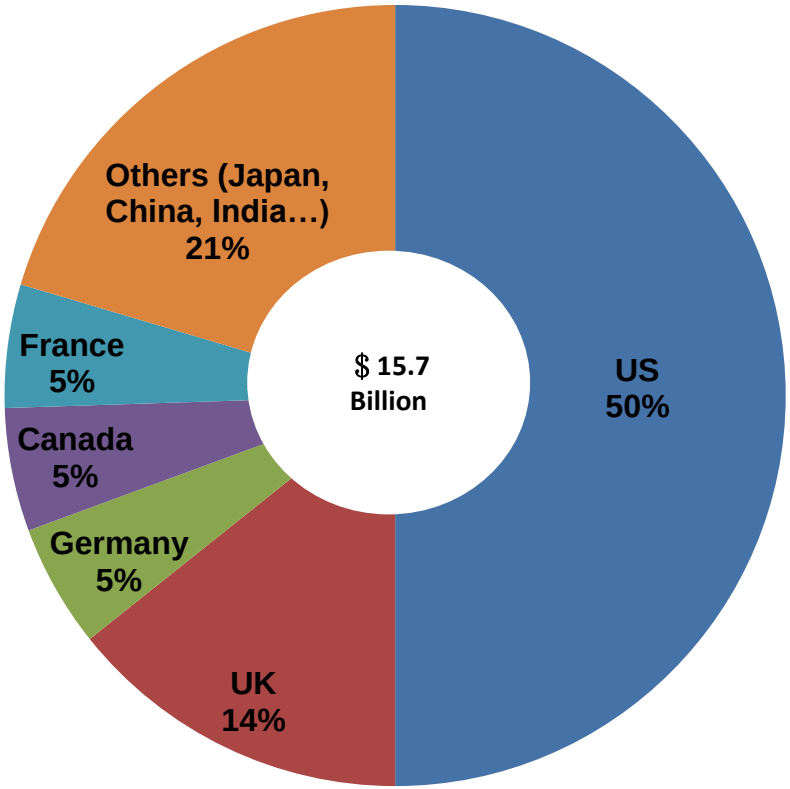
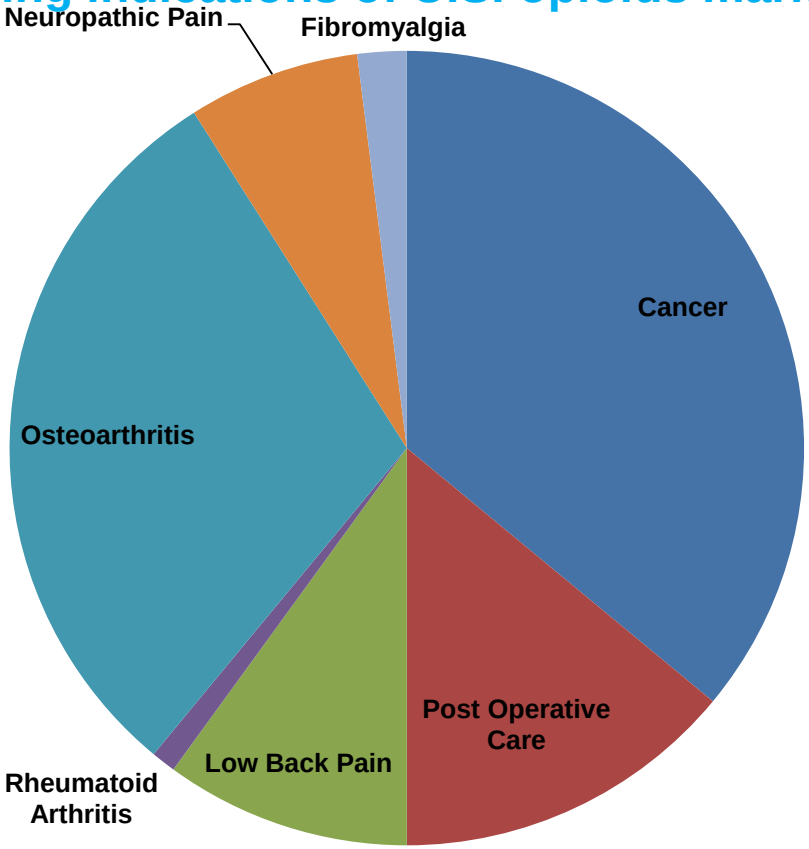
Overview (1)

Opioids are substances that act on the nervous system in a similar way to opiates such as morphine and codeine---- activation of mu-opioid receptor (MOR), delta-opioid receptor (DOR) or kappa-opioid receptor (KOR).

2014 Global Opioid Market



7 leading indications of U.S. opioids market



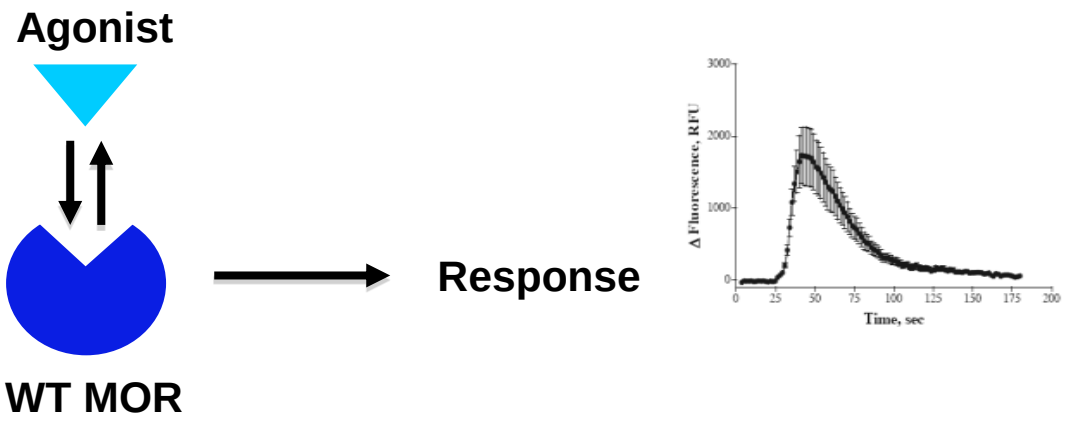
GBI Research. Opioids Market to 2017. June 2011
CBR Pharma Insights. Opioids Overview to 2021 - An Assessment of Pain Management and Dependence . August 2015

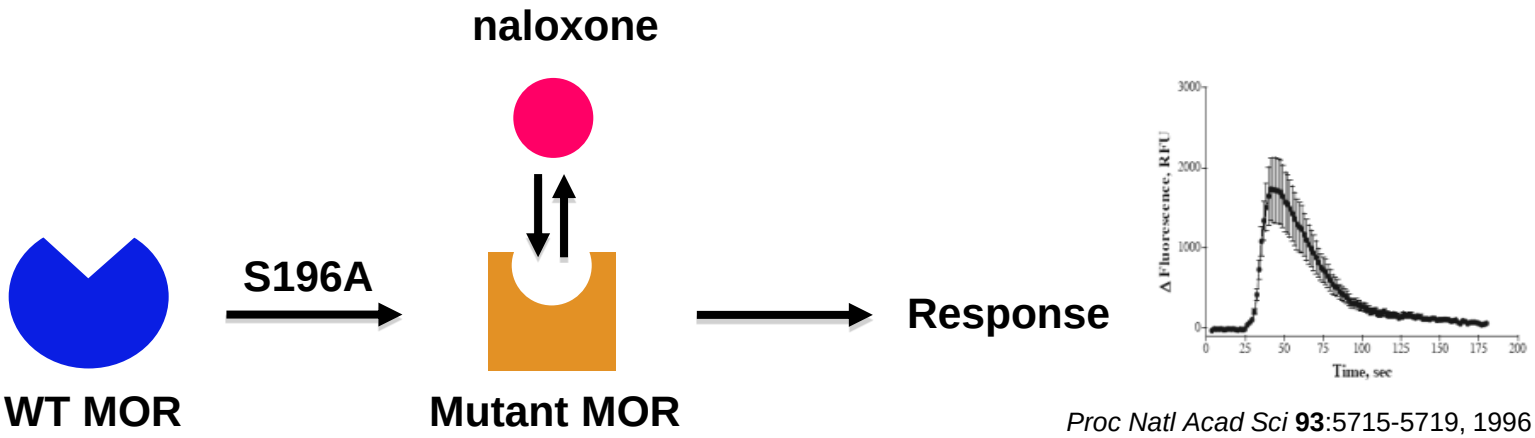
Overview (2)

Pain Severity	Class	Compounds	Advantages	Disadvantages
Mild	Acetaminophen		Antipyretic properties; oral; no opioid AEs	Only effective for mild pain; short acting
	NSAIDs	Ketorolac, ibuprofen, aspirin	Mild to moderate analgesia; oral; no opioid AEs	Bleeding risk; GI and renal complications; short acting
Moderate	Sodium channel blockers	Bupivacaine, lidocaine	Use directly at pain site; mostly perioperative	Limited duration of action; some are concerned about local tissue impact
Moderate to severe	Long-acting preferential COX-2	IV/IM meloxicam (Recro Pharma)	Long acting; fast onset; high pain relief; less constipation	Bleeding risk; GI and renal complications
	Alpha 2 agonists	Dexmedetomidine (Recro Pharma)	Good pain relief; anxiolytic properties; no respiratory depression, impaired GI or addictive properties	In development-potential for first in class to be approved for post-operative pain
	Opioids	Morphine, Hydrocodone, fentanyl	Good pain relief	Respiratory depression; sedation; constipation; frequent nausea and vomiting; abuse/addiction potential; tolerance

Overview (3)

A specific mutation (S196A) on the wild type MOR can confer agonistic activity (and thus pain relief effect) to classical opioid antagonist (naloxone).





Proc Natl Acad Sci **93**:5715-5719, 1996

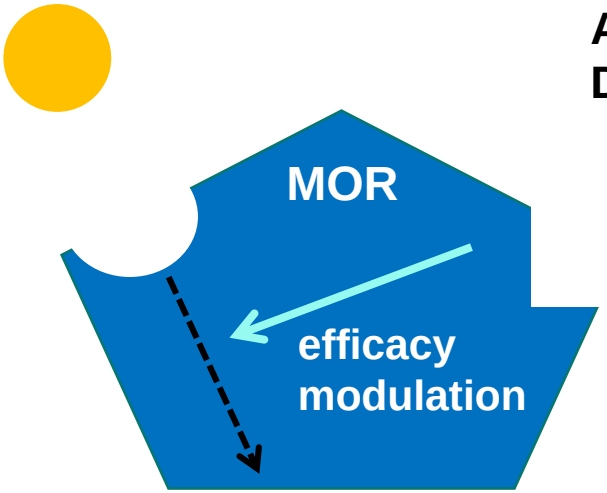
Proc Natl Acad Sci **100**:2117-2121, 2003

Proc Natl Acad Sci **104**:20096-20101, 2007

DBPR116: Mechanism of Action

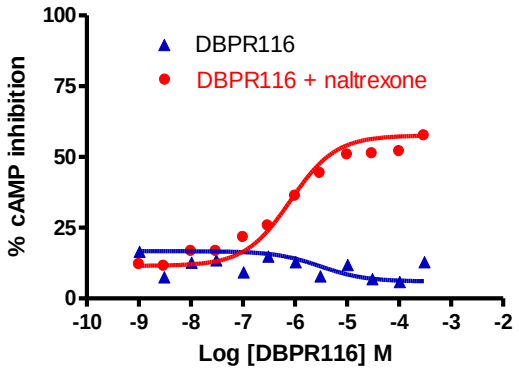
Small molecular antagonist:
Naloxone or Naltrexone

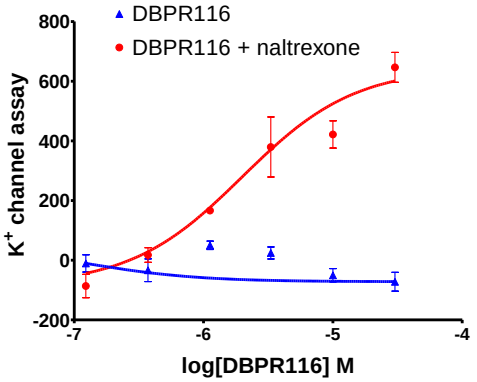
Allosteric modifier:
DBPR116



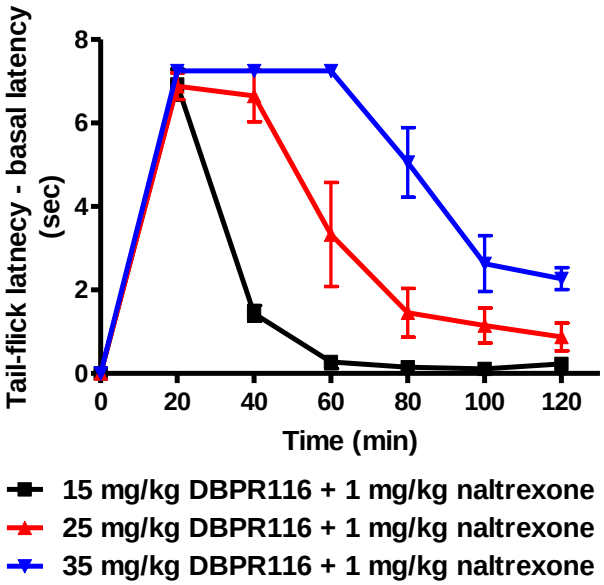
G protein-dependent signaling (cAMP, K^+ channel)

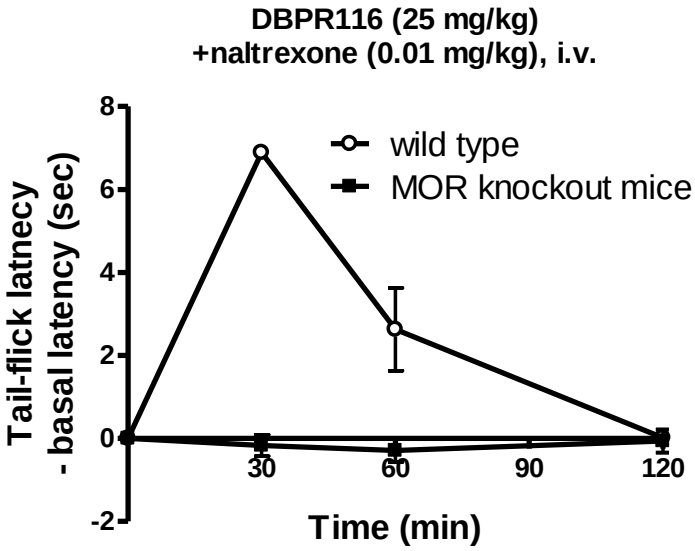
Functional response





DBPR116

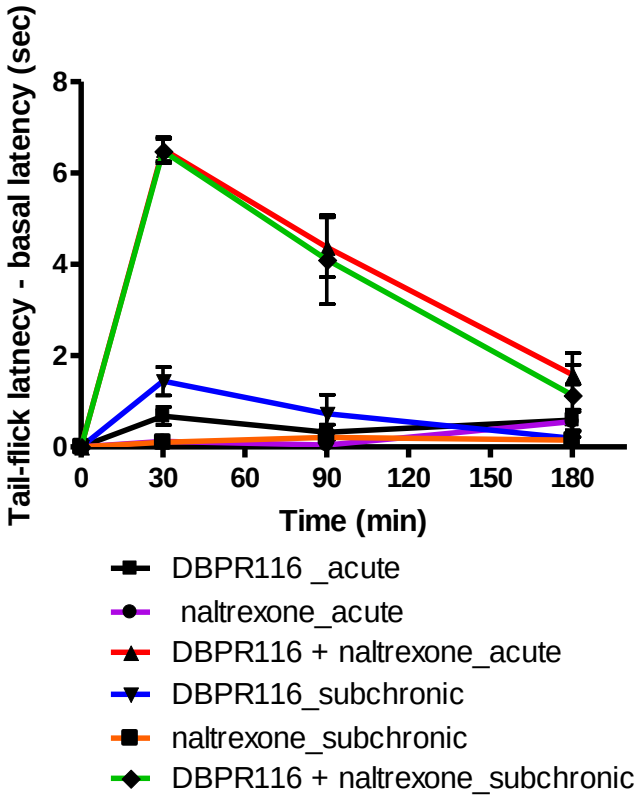


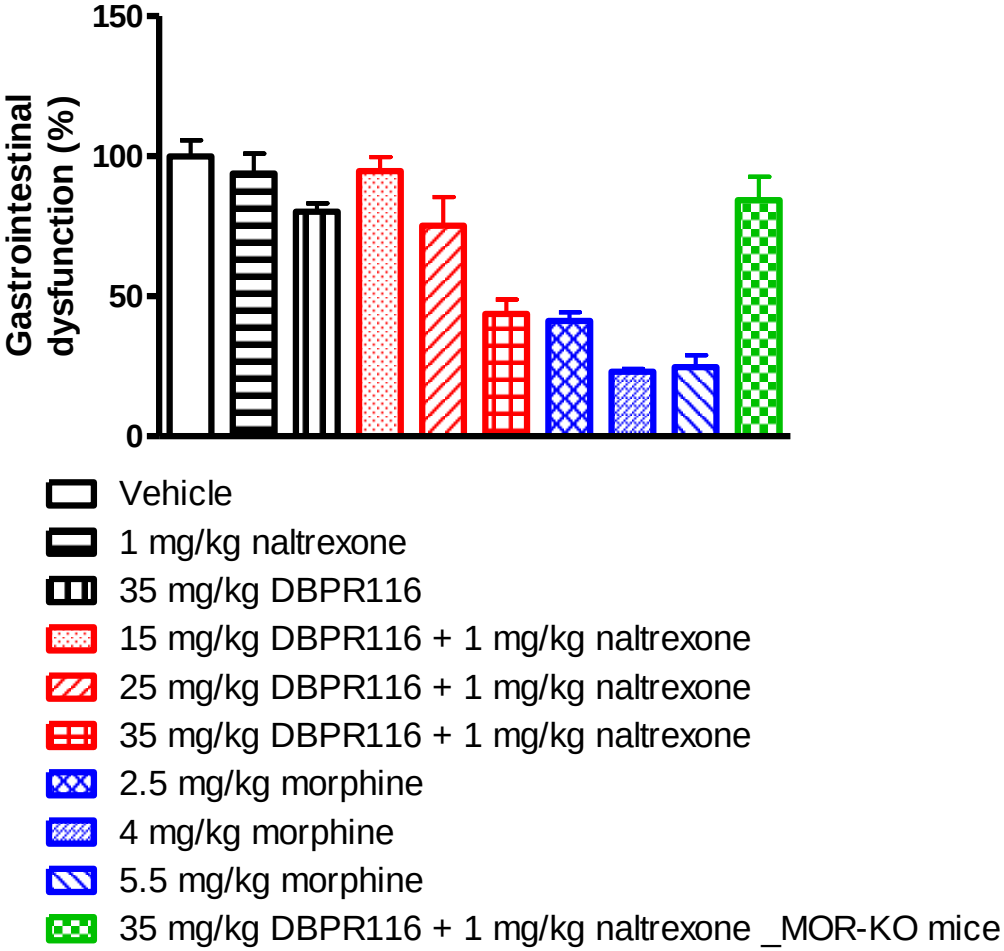


DBPR116 (with 1 mg/kg naltrexone; i.v.)
Formulation: DMA/Solutol/5%Captisol in H_2O (5/5/90)

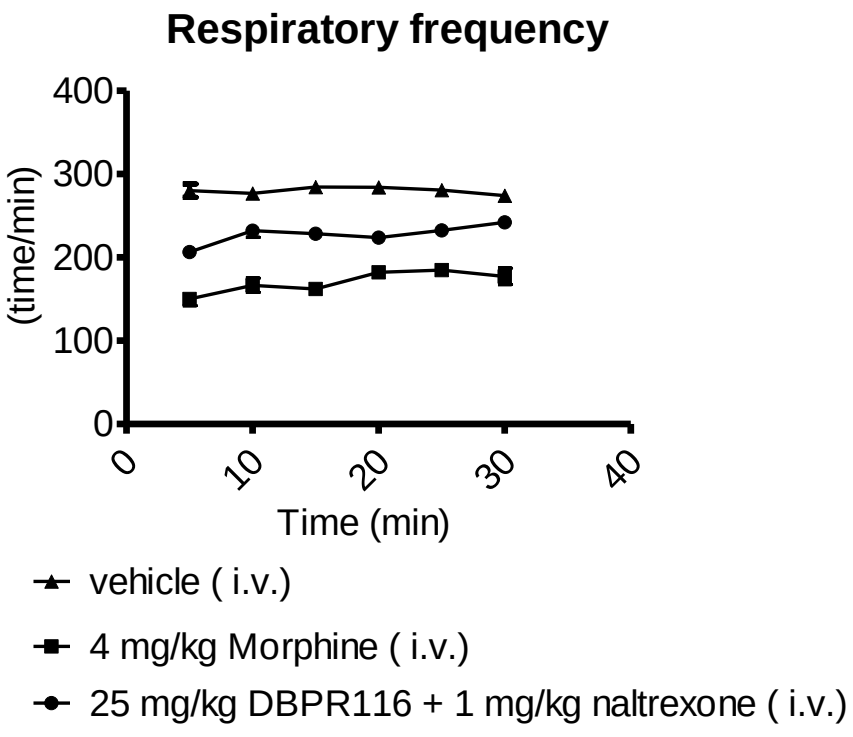
ED_{50} : 11.9 ± 1.7 mg/kg
Maximum Tolerated Dose (MTD) : 40-50 mg/kg

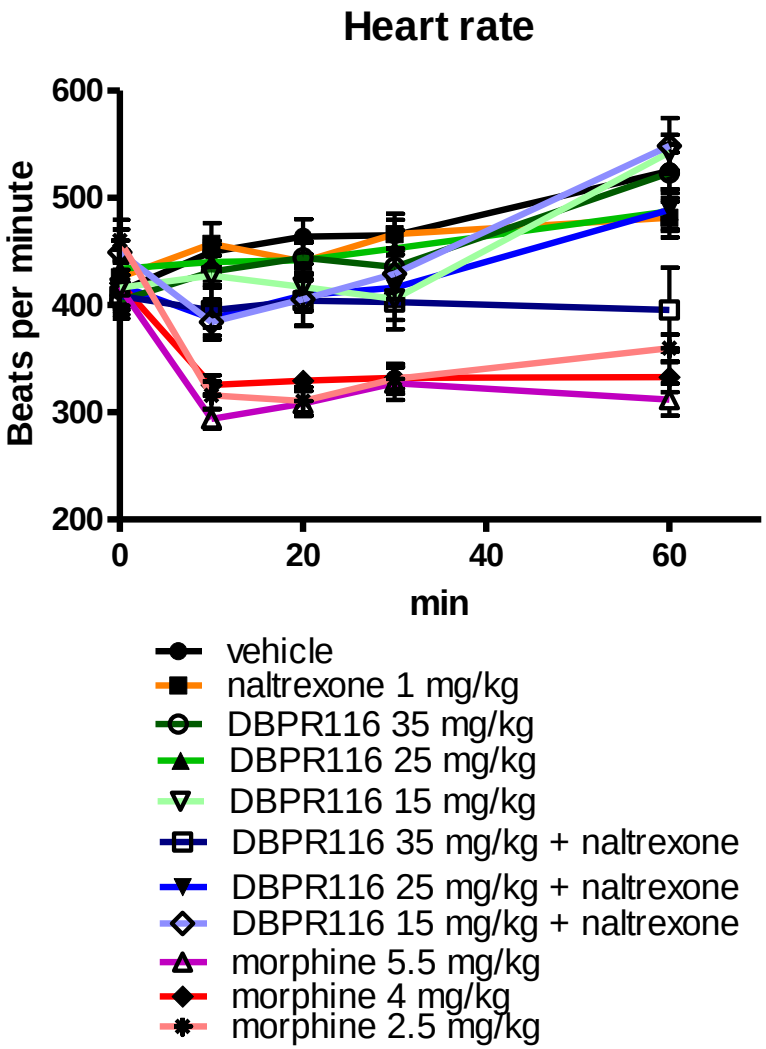
Side Effects (1)



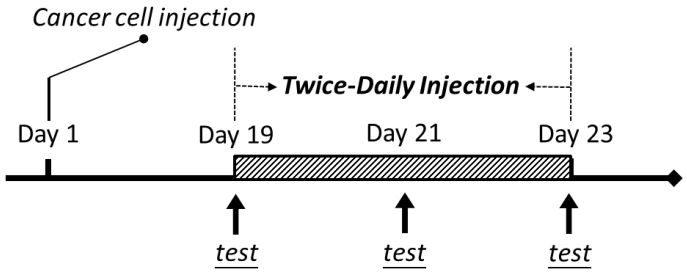


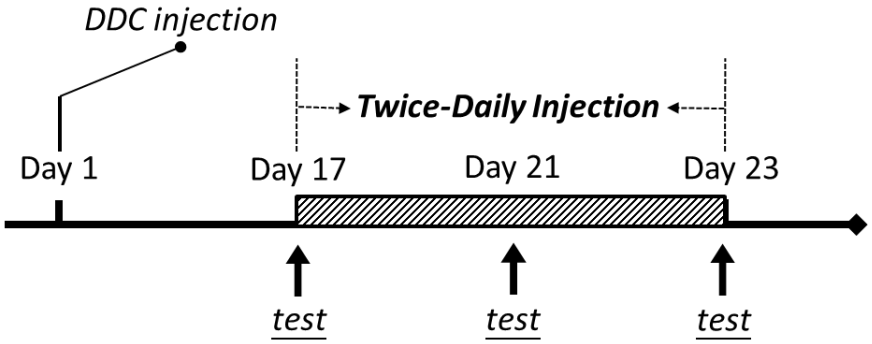
Side Effects (2)



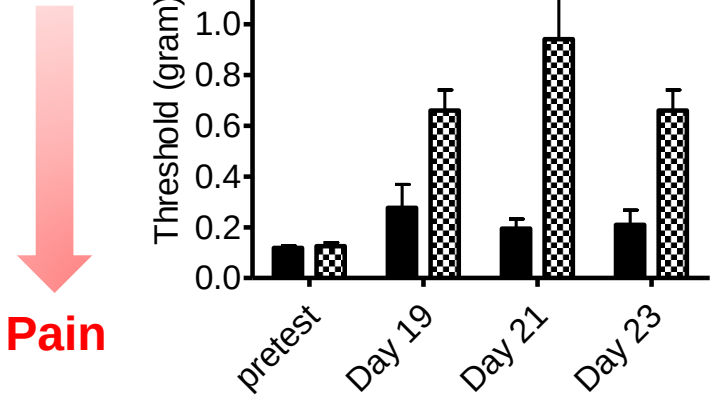


Animal models of disease-related pain





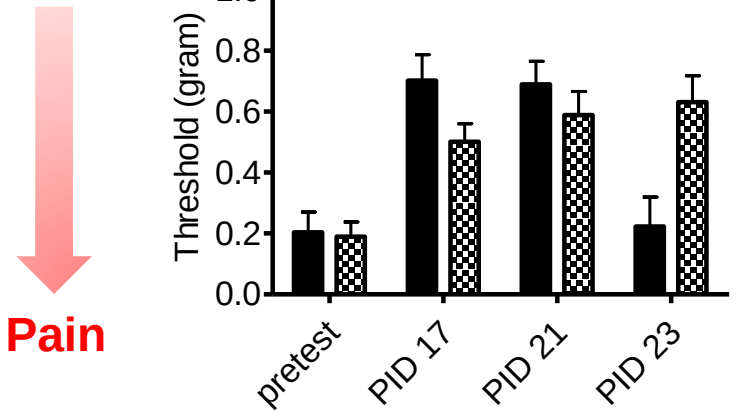
Cancer pain



4 mg/kg morphine (twice daily; i.v.)

25 mg/kg DBPR116 +
1 mg/kg naltrexone (twice daily; i.v.)

Dideoxycytidine (ddC)-induced neuropathic pain



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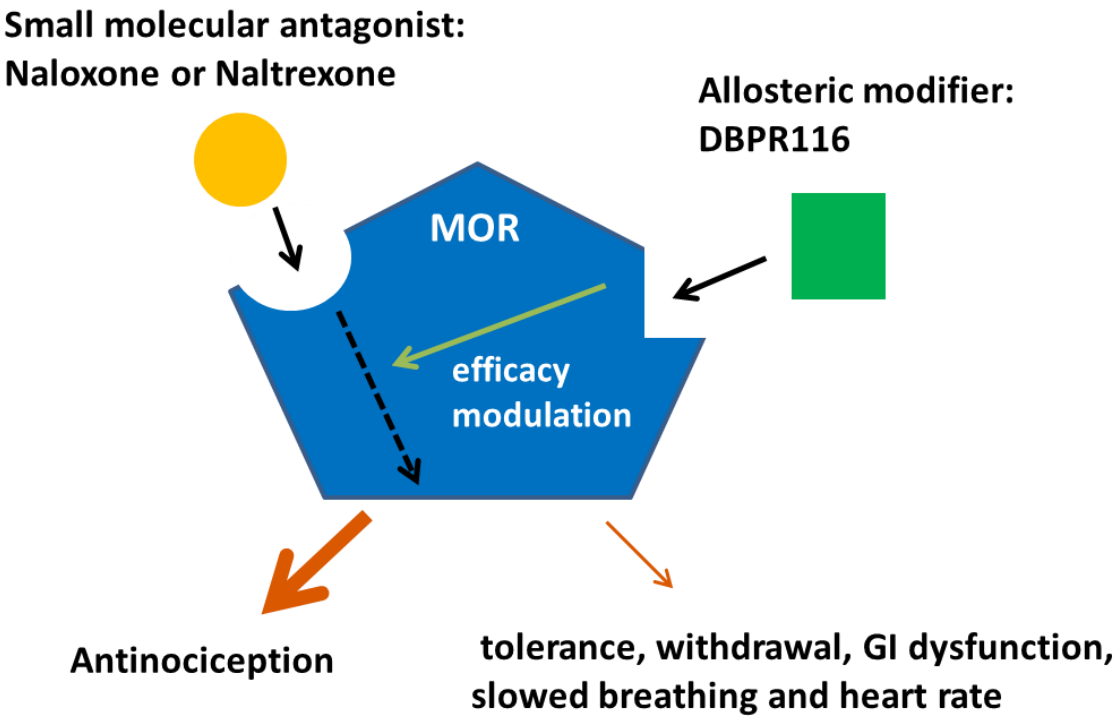
Summary

- **Identification of a novel antagonist-to-agonist allosteric modifier (AAM) of MOR: First-in-class pain relief agent without the unwanted side effects of opioids**



Major Advantages and Differentiation of DBPR116

DBPR116:

- DBPR116 is a novel "First-in-Class" AAM which can combine effectively with MOR antagonist (such as naloxone or naltrexone) and produce impressive anti-nociception effects in tail-flick pain model (mice)
- DBPR116/naltrexone combination also exhibit better tolerance in cancer pain and efficacy in neuropathic pain models
- AAM/MOR antagonist combination also exhibited significant less adverse effects (compare to morphine) on:
  - ✓ Constipation (measured by GI inhibition)
  - ✓ Respiratory suppression
  - ✓ Addiction
  - ✓ Tolerance
  - ✓ Sedation
- DBPR116 represents a potential breakthrough therapy for the world acute and chronic pain medication market ($15~30 B USD)