An orally available μ-opioid receptor biased ligand is analgesic with reduced constipation in rodents

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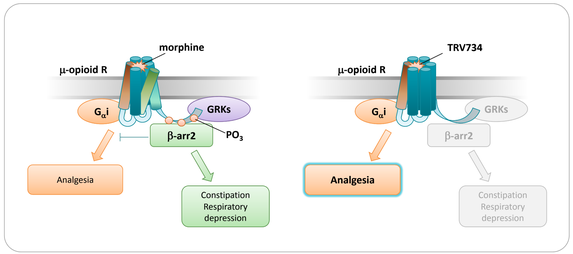
Biased ligands. Better drugs.

Introduction

- Morphine elicits both analgesia and treatment-limiting adverse effects, including constipation and respiratory depression, through the μ-opioid receptor.
- Morphine exerts increased analgesia but decreased constipation and respiratory depression in β-arrestin2 knockout mice (1, 2).
- "Biased ligands" selectively engage subsets of receptor signals and unlock the potential for novel, improved GPCR-targeted therapeutics (3).

Hypothesis: a G protein-biased μ-opioid receptor ligand will avoid β-arrestin-mediated constipation and respiratory depression to deliver safer, better tolerated analgesia than morphine

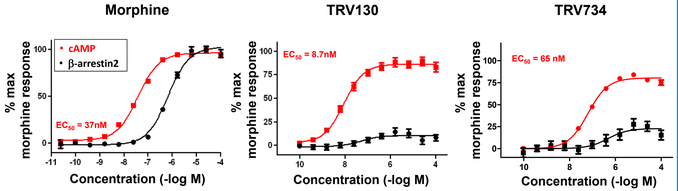


Approach

- Trevena's small molecule library was screened for novel opioid receptor ligands
- Hits were optimized for potency, efficacy, bias, selectivity, and pharmacokinetics.
- Pharmacology tested in a battery of standard rodent models of opioid action.

Results

TRV130 and TRV734 are potent opioids with reduced β-arrestin recruitment vs. morphine



Not shown: in a screen of 130 GPCRs, ion channels, transporters, and enzymes, TRV130 and TRV734 were highly selective (>100-fold) for the μ-opioid receptor.

Figure 1. Ligand-stimulated G protein coupling and β-arrestin recruitment at the human μ-opioid receptor were measured for morphine and TRV130; G protein coupling is measured by inhibition of forskolin-stimulated cAMP accumulation (red); β-arrestin2 recruitment is measured by enzyme complementation in the same cells (black).

TRV130 and TRV734 cause less constipation than morphine in mice

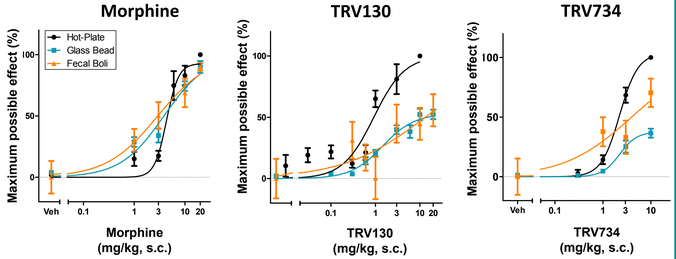


Figure 2. Mice were administered morphine, TRV130, or TRV734 by subcutaneous bolus, followed by testing 30 minutes later. Maximum possible effect = 30 second latency in 56° hot plate, 240 minute retention in glass bead assay, and zero fecal boli production, all compared to values in vehicle-treated animals.

TRV734 has good oral PK in non-human primates

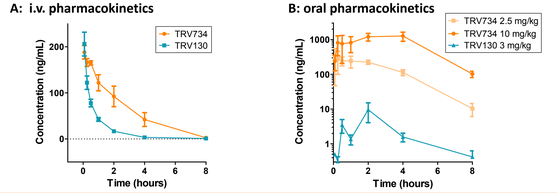


Figure 3. Pharmacokinetics in cynomologous monkey. **A.** Intravenous bolus reveals slower clearance for TRV734 (0.5 mg/kg) than TRV130 (0.3 mg/kg). **B.** Oral dosing of 2.5 and 10 mg/kg TRV734 shows a good pharmacokinetic profile, with oral availability of 43±8% and 72±13%

TRV734 causes less constipation than oxycodone

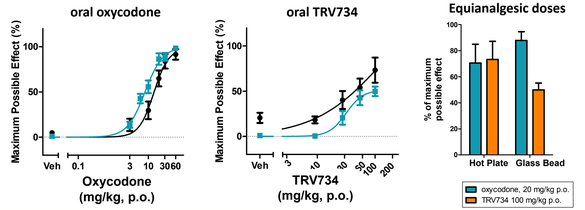


Figure 4. Mice were administered oxycodone or TRV734 by oral gavage, followed by testing 30 minutes later. Maximum possible effect = 30 second latency in 56° hot plate or 240 minute retention in glass bead assay, all compared to values in vehicle-treated animals.

TRV130 PK/PD in healthy volunteers

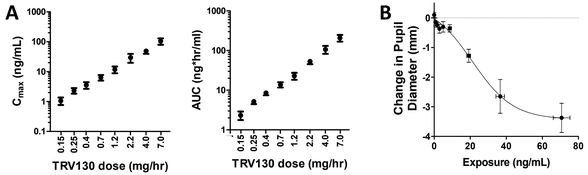


Figure 5. Healthy volunteers (6 per dose group) were infused with TRV130 for 1 hour. Doses ≤4 mg were well tolerated, with nausea and vomiting dose-limiting at 7 mg. **A:** TRV130 C_{max} and AUC were dose linear; half-life was approximately 2 hours. **B**: Pupil size change at 70 minutes in relationship to TRV130 exposure at 60 minutes shows a dose-response relationship consistent with established opioid pharmacology. Data are mean ± s.e.m. ClinicalTrials.gov identifier: NCT01514578.

Conclusions

- TRV130 and TRV734 are novel, potent, and selective G protein-biased μ-opioid receptor ligands.
- TRV130 and TRV734 robustly engage G protein coupling with efficacy and potency comparable to morphine, but display dramatically reduced β-arrestin coupling.
- In rodents, TRV130 and TRV734 are potently analgesic, but display reduced gastrointestinal dysfunction compared to morphine.
- The improved therapeutic index of TRV130 and TRV734 could allow safer, more effective pain management by removing key barriers to effective opioid therapy.
- TRV130 also has reduced impact on respiratory suppression compared to morphine, and is in development for treating post-operative pain.[4]
- TRV734 is in preclinical development for the treatment of acute and chronic pain.
- 25 ng/mL TRV130 in plasma at ED_{50} for pupil constriction in healthy volunteers suggests efficacious exposure of TRV734 of 100-150 ng/mL based on extrapolation of *in vitro* and rodent potencies.

i.v. TRV130 and oral TRV734 may offer safer, more tolerable relief than is achievable with current opioids

References

1) Bohn LM, Lefkowitz RJ, Gainetdinov RR, Peppel K, Caron MG, Lin FT. Enhanced morphine analgesia in mice lacking beta-arrestin 2. *Science* 1999; 286(5449): 2495-2498
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3) Violin JD, Lefkowitz RJ. Beta-arrestin-biased ligands at seven-transmembrane receptors. *Trends Pharmacol Sci.* 2007; 28(8): 416-422
4) DeWire et al, A G protein-biased ligand at the μ-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine. *J Pharmacol Exp Ther.* 2013; 344(3):708-717