

# An orally available $\mu$ -opioid receptor biased ligand is analgesic with reduced constipation in rodents

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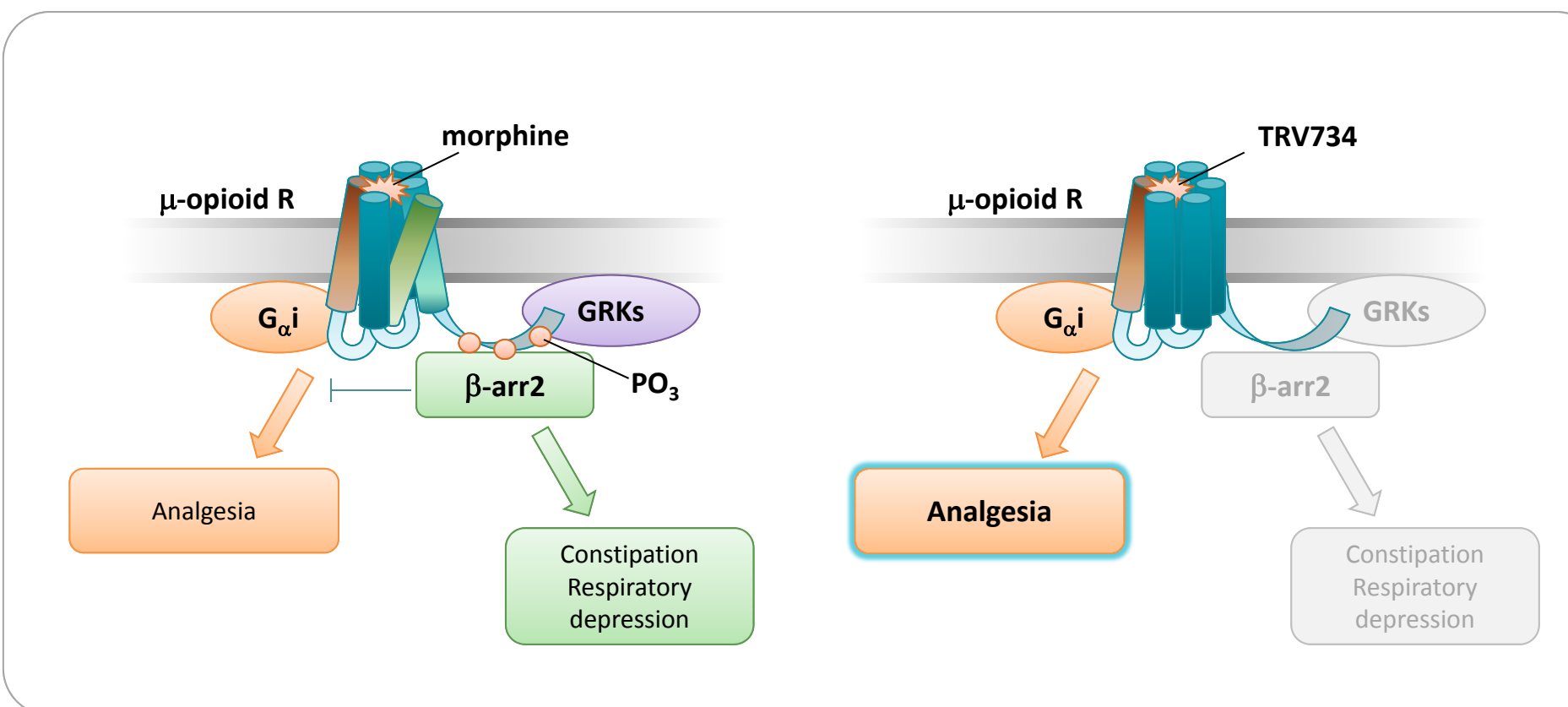


Biased ligands. Better drugs.

## Introduction

- Morphine elicits both analgesia and treatment-limiting adverse effects, including constipation and respiratory depression, through the  $\mu$ -opioid receptor.
- Morphine exerts increased analgesia but decreased constipation and respiratory depression in  $\beta$ -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  $\mu$ -opioid receptor ligand will avoid  $\beta$ -arrestin-mediated constipation and respiratory depression to deliver safer, better tolerated analgesia than morphine

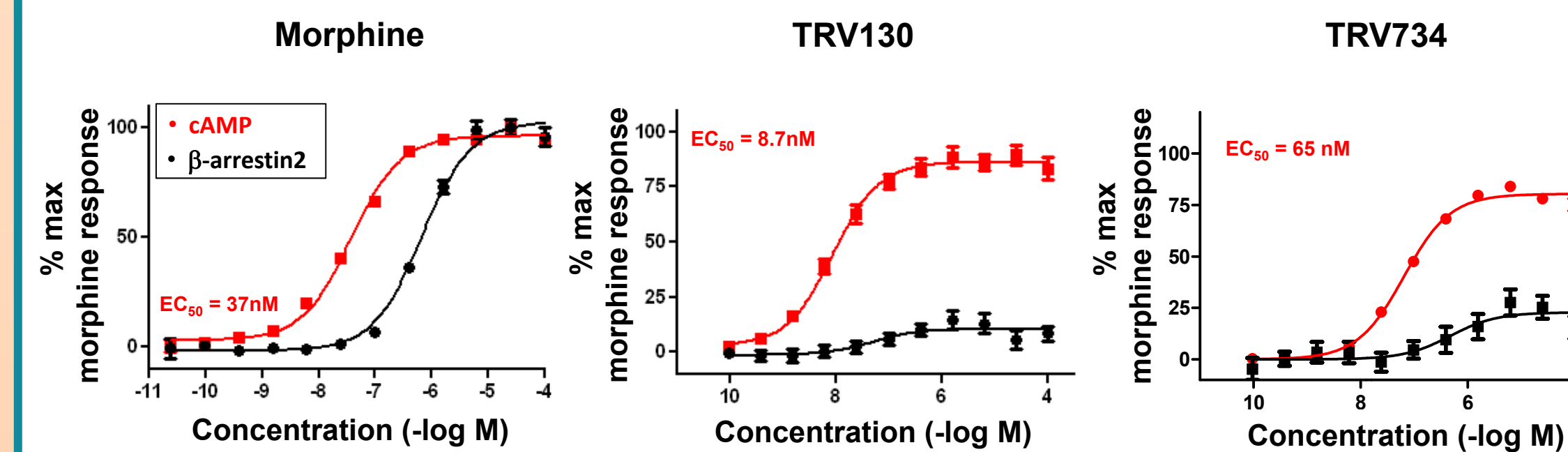


## Approach

- 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

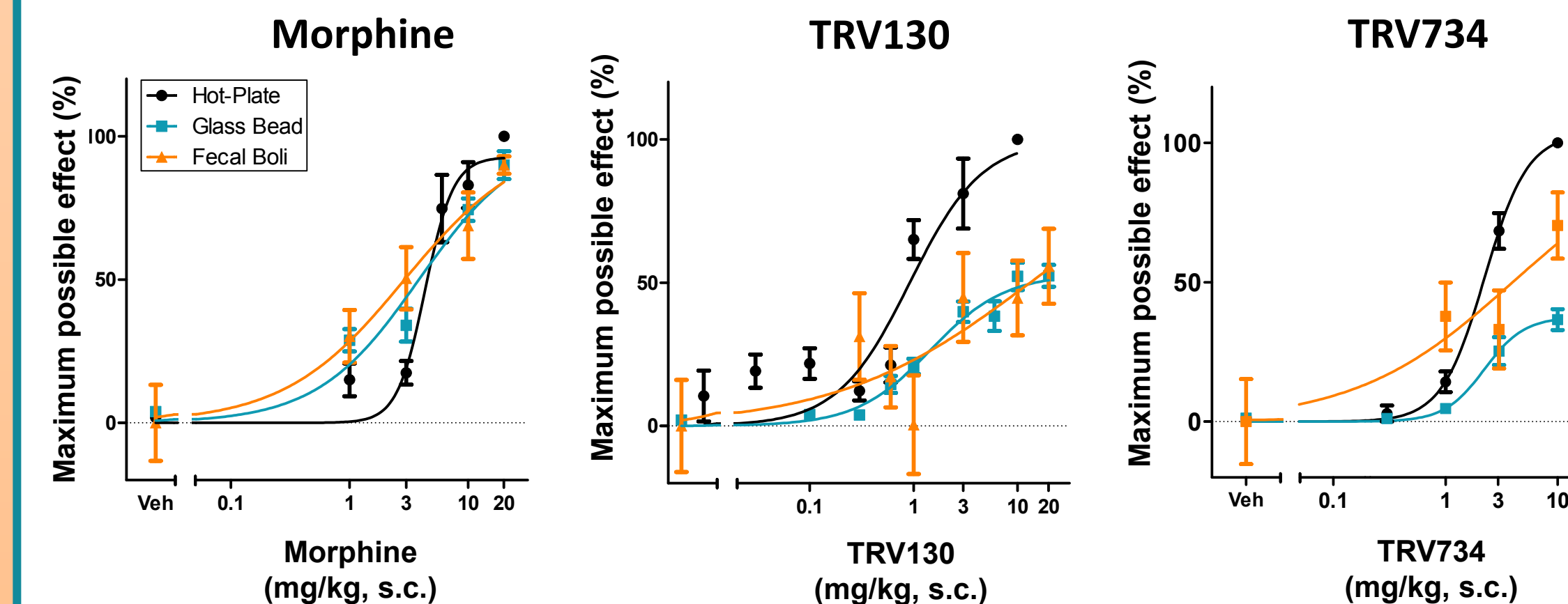
### TRV130 and TRV734 are potent opioids with reduced $\beta$ -arrestin recruitment vs. morphine



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

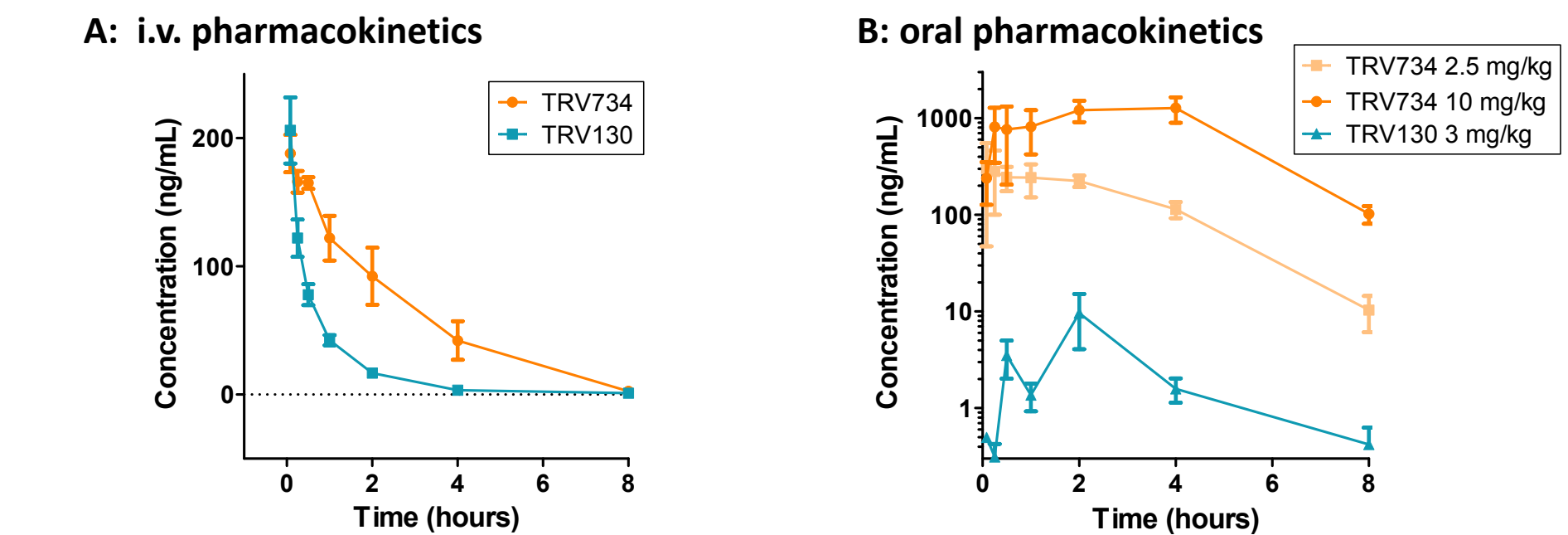
**Figure 1.** Ligand-stimulated G protein coupling and  $\beta$ -arrestin recruitment at the human  $\mu$ -opioid receptor were measured for morphine and TRV130; G protein coupling is measured by inhibition of forskolin-stimulated cAMP accumulation (red);  $\beta$ -arrestin2 recruitment is measured by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

### TRV130 and TRV734 cause less constipation than morphine in mice



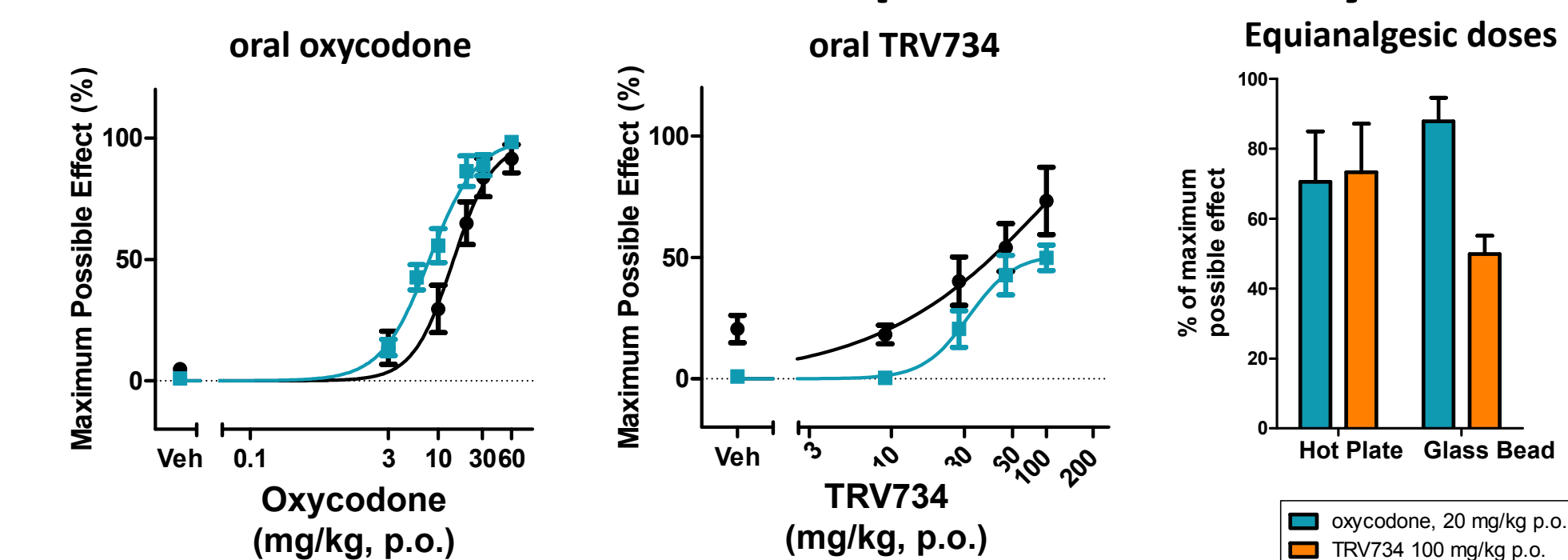
**Figure 2.** Mice were administered morphine, TRV130, or TRV734 by subcutaneous bolus, followed by testing 30 minutes later. Maximum possible effect = 30 second latency in 56° hot plate, 240 minute retention in glass bead assay, and zero fecal boli production, all compared to values in vehicle-treated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

### TRV734 has good oral PK in non-human primates



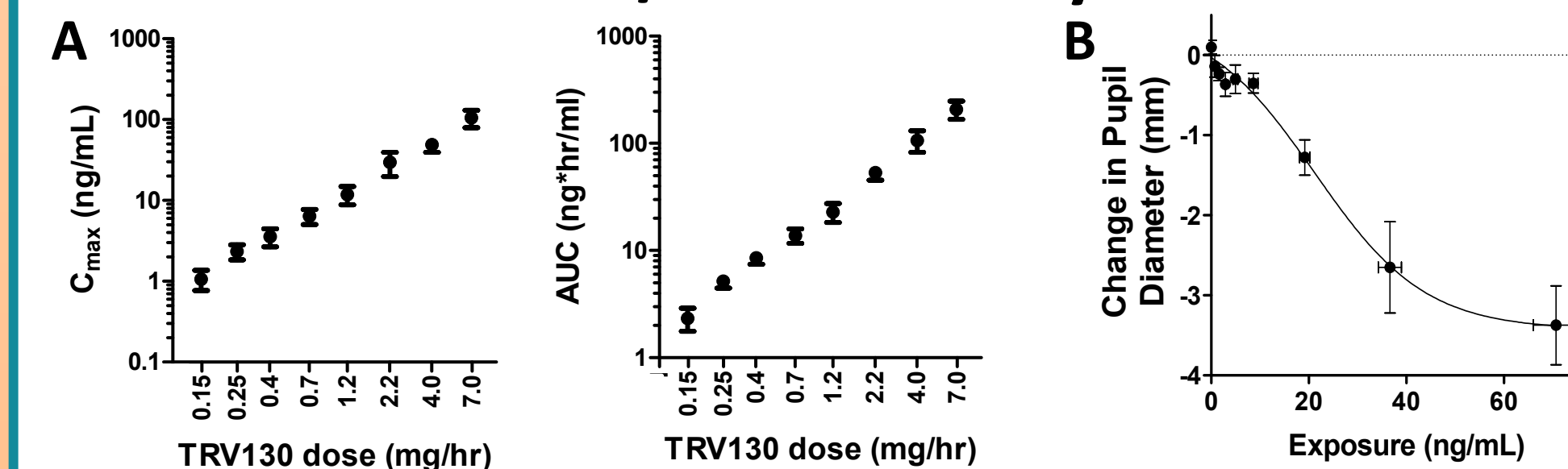
**Figure 3.** Pharmacokinetics in cynomolgous monkey. **A.** Intravenous bolus reveals slower clearance for TRV734 (0.5 mg/kg) than TRV130 (0.3 mg/kg). **B.** Oral dosing of 2.5 and 10 mg/kg TRV734 shows a good pharmacokinetic profile, with oral availability of 43±8% and 72±13%

### 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  $\pm$  s.e.m. ClinicalTrials.gov identifier: NCT01514578.

## Conclusions

- TRV130 and TRV734 are novel, potent, and selective G protein-biased  $\mu$ -opioid receptor ligands.
- TRV130 and TRV734 robustly engage G protein coupling with efficacy and potency comparable to morphine, but display dramatically reduced  $\beta$ -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.<sup>4</sup>
- TRV734 is in preclinical development for the treatment of acute and chronic pain.
- 25 ng/mL TRV130 in plasma at ED<sub>50</sub> 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

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