The Discovery and Initial Human Pharmacokinetics of BTRX-335140, a Selective Kappa Opioid Receptor (KOR) Antagonist

Kappa Therapeutics Conference – March 2019
Seattle

BlackThorn THERAPEUTICS

Transforming CNS Therapeutics

Disclosures

Employee and shareholder of BlackThorn Therapeutics

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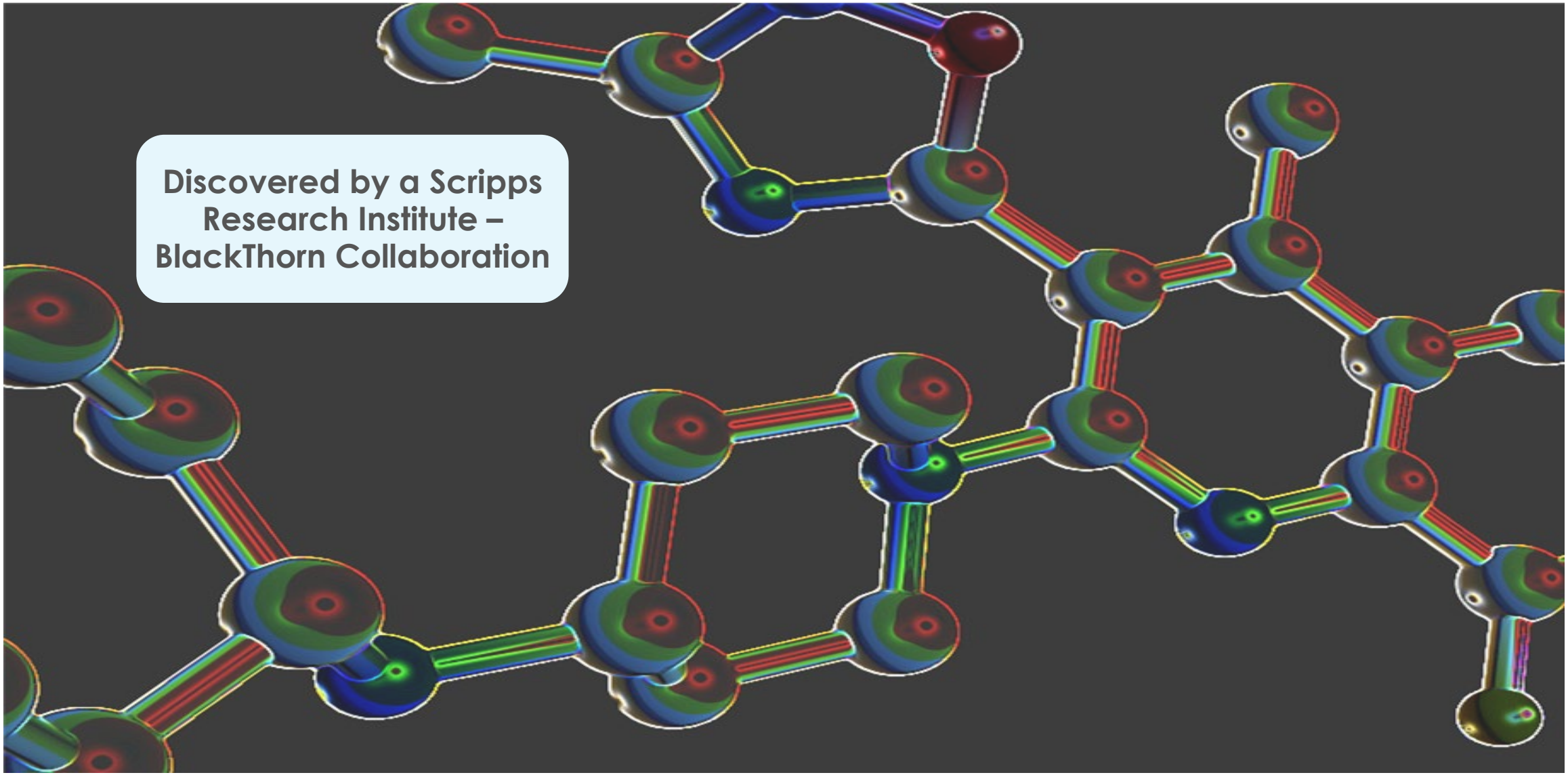
BTRX-335140 – a kappa opioid antagonist for mood and anxiety disorders



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Overview

- Interest in KOR antagonists as therapeutics
- Historical challenges in KOR antagonist drug discovery
- Identification and characterization of BTRX-335140
- Phase 1 clinical data
- Summary

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The KOR-dynorphin system in stress and neurobehavioral disorders

KOR-peptide system identified to modulate dopamine signaling in key regions of the brain resulting in stress-induced dysphoria, anhedonia, and anxiety

Van't Veer and Carlezon, Psychopharmacology 2013

The first antagonists discovered have anxiolytic properties and protect against affects of stress on mood and behavior

Carroll and Carlezon, JMedChem 2013

KOR binding potential changes tied to severity of dysphoria in trauma-exposed psychopathology

Pietrzak et al., JAMA Psychiatry 2014

Fast-MAS study - JNJ-67953964 produced ventral striatal activation occurring with reward and anticipation during the Monetary Incentive Delay Task and impacted anhedonia on SHAPS.

https://www.clinicaltrials.gov/ct2/show/NCT02218736?term=CERC-501&rank=2

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Historical challenges with the KOR antagonist chemical space

- Low brain penetration
- Poor oral bioavailability
- Long duration of action decoupled from plasma/brain exposure
- Poor selectivity for KOR vs. MOR and other GPCRs

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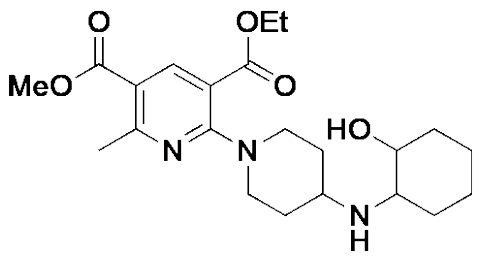
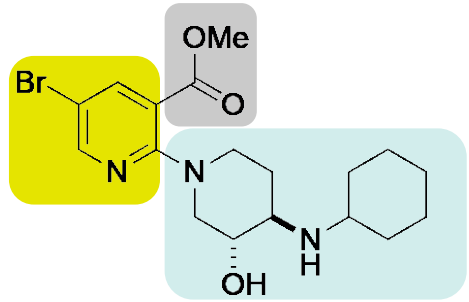
Breakthrough with chemical matter identified from the ML-SMR library

HTS Hit



IC_{50} values
KOR = 410 nM
MOR = 4590 nM
DOR = >50000 nM

MW = 419
tPSA = 100.5
cLogP = 2.3



IC_{50} values
KOR = 12.6 nM
MOR = 323 nM
DOR = 3500 nM

MW = 412
tPSA = 74.2
cLogP = 2.9

- ✓ Increased potency
- ✓ >25-fold selectivity
- ✓ Good starting point for physicochemical properties
- ✓ Short duration of action (<24 hours) in a U-69593-induced plasma prolactin mouse model

Functional potency at KOR, MOR, DOR determined by a Tango™ assay

Guerrero, et al. *J. Med. Chem.* 2019, 62, 1761-1780.
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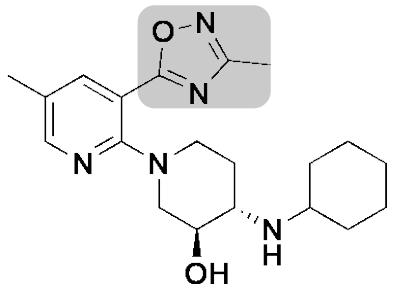
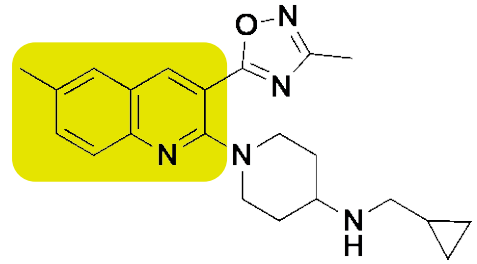
Key modifications improve potency and selectivity



IC_{50} values
KOR = 1.3 nM
MOR = 31.1 nM
DOR = 2410 nM

MW = 371
tPSA = 82
cLogP = 2.2
cpKa = 10.2



IC_{50} values
KOR = 2.2 nM
MOR = 829 nM
DOR = >10000 nM

MW = 377
tPSA = 62
cLogP = 2.9
cpKa = 10.6

Ester to oxadiazole

✓ Better hepatocyte stability and drug properties without erosion of potency or selectivity

Pyridine to Quinoline

✓ Additional potency and selectivity (>300-fold KOR vs. MOR)
X Scaffold-wide AMES signals +/- metabolic activation
X High clearance in human hepatocytes (>50 mL/min/kg)
✓ Metabolite ID facilitated identification of soft spots

Guerrero, et al. *J. Med. Chem.* 2019, 62, 1761-1780.

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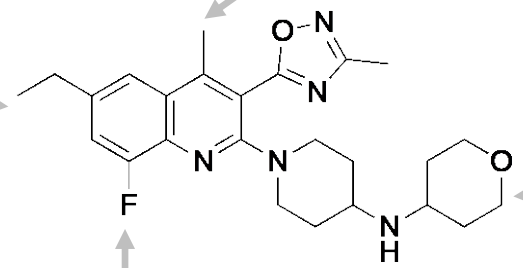
Additional modifications improve drug properties and reduce liabilities

BTRX-335140



Mitigates quinoline oxidation

Ethyl further improves potency and selectivity

Improved human hepatocyte stability

Electron withdrawing group mitigates Ames liability

IC_{50} values
KOR = 0.8 nM
MOR = 110 nM
DOR = 6500 nM

MW = 354
tPSA = 71
cLogP = 2.4
cpKa = 10.5

138-fold selectivity for KOR over MOR

Guerrero, et al. *J. Med. Chem.* 2019, 62, 1761-1780.

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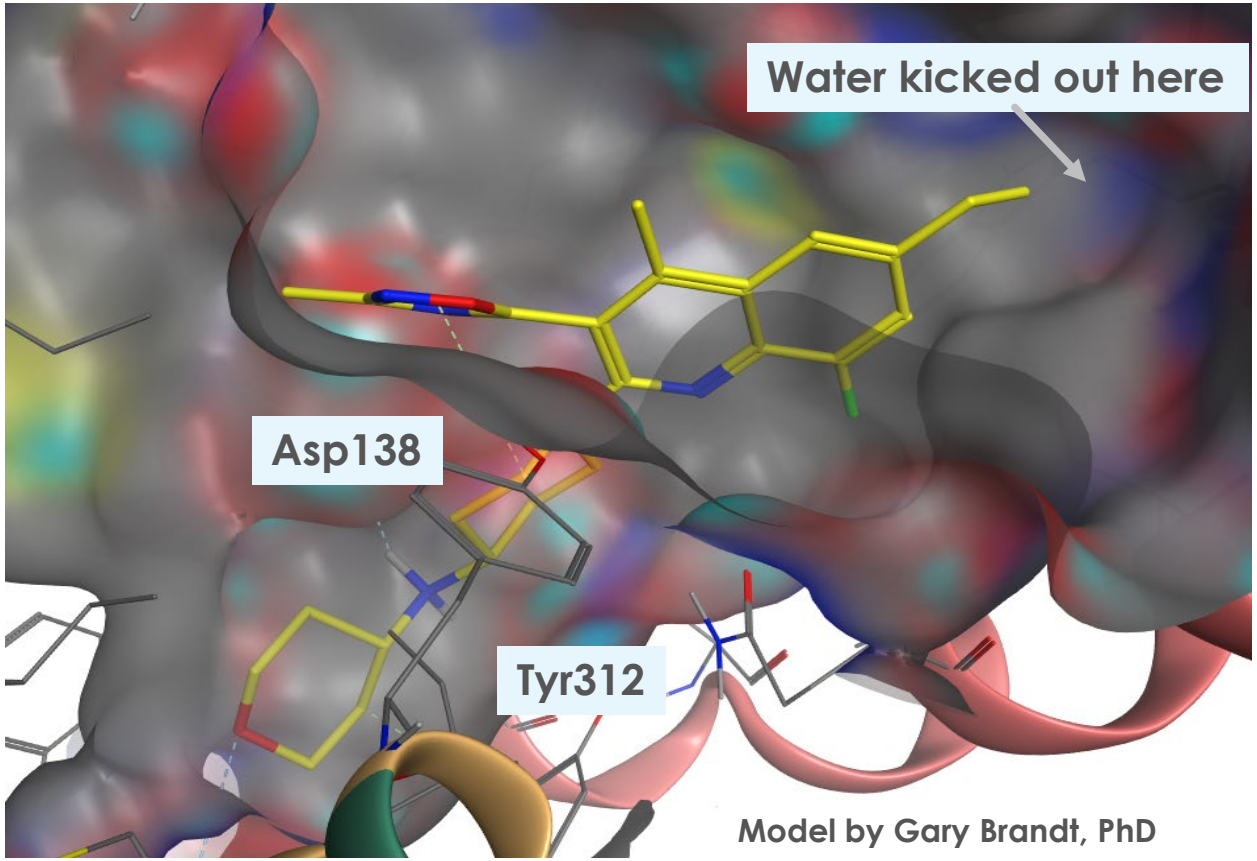
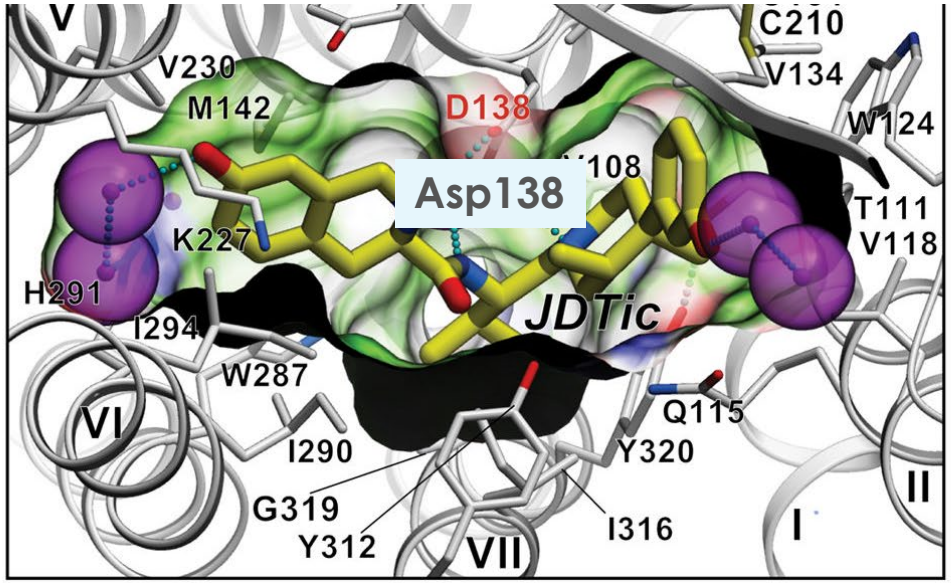
Binding model elucidates selectivity and potency increases with key interactions

BTRX-335140



Model by Gary Brandt, PhD

JDTic



Tyr312

Similar binding site but different interactions may impart different duration of action properties

Wu, et al. *Nature* 2012, 485(7398), 327-332

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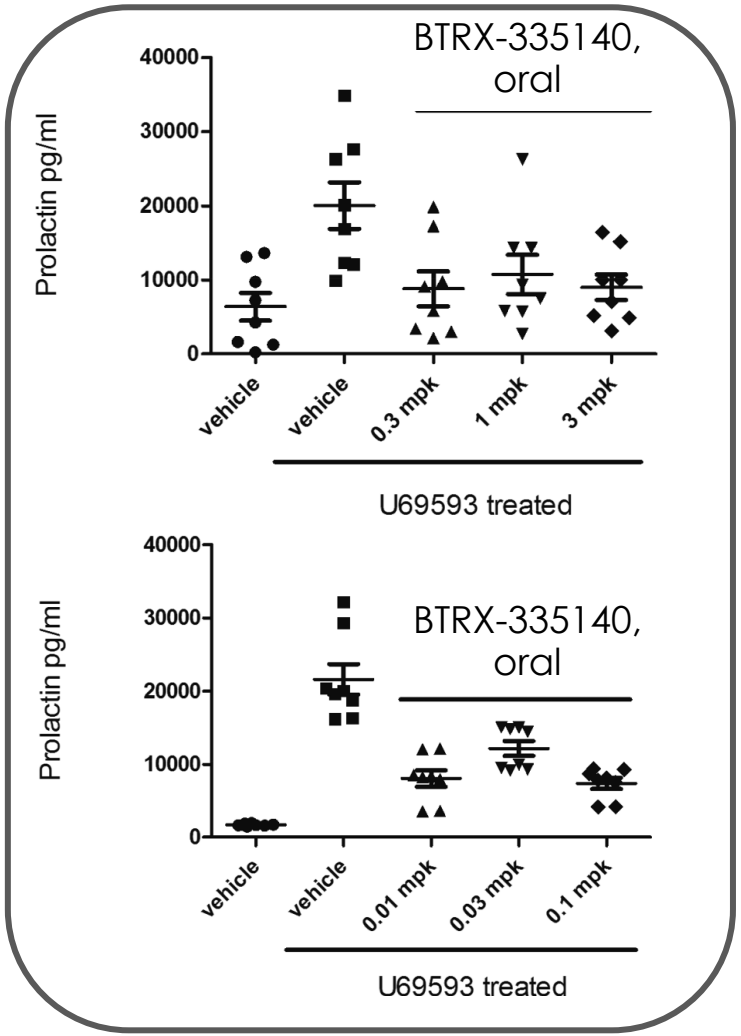
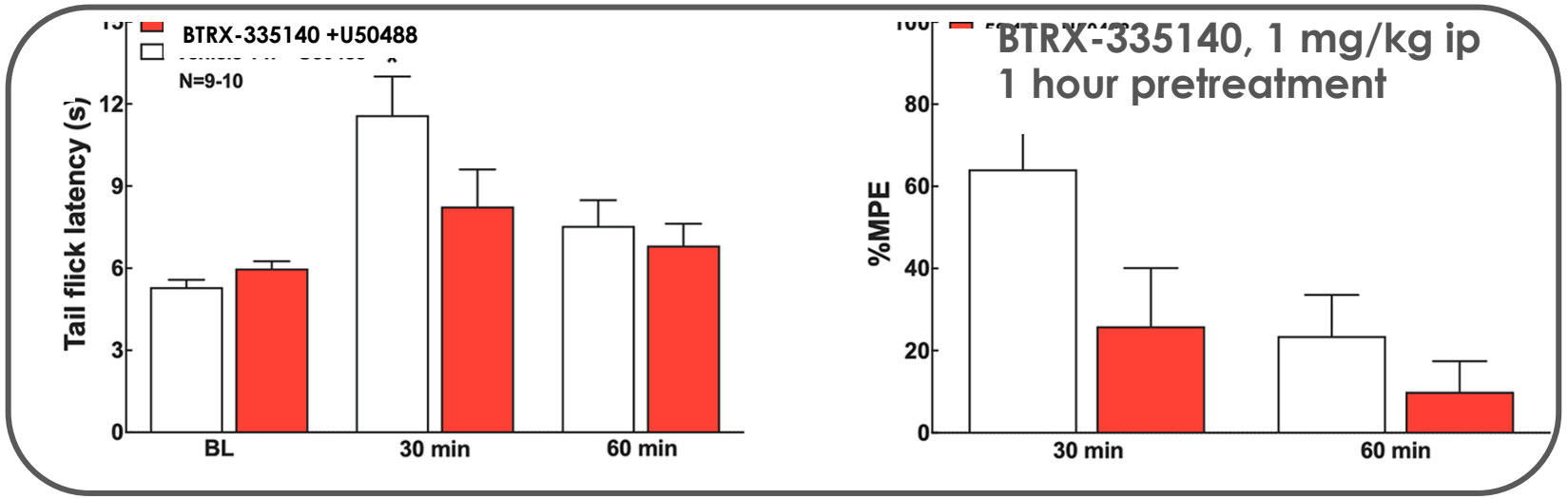
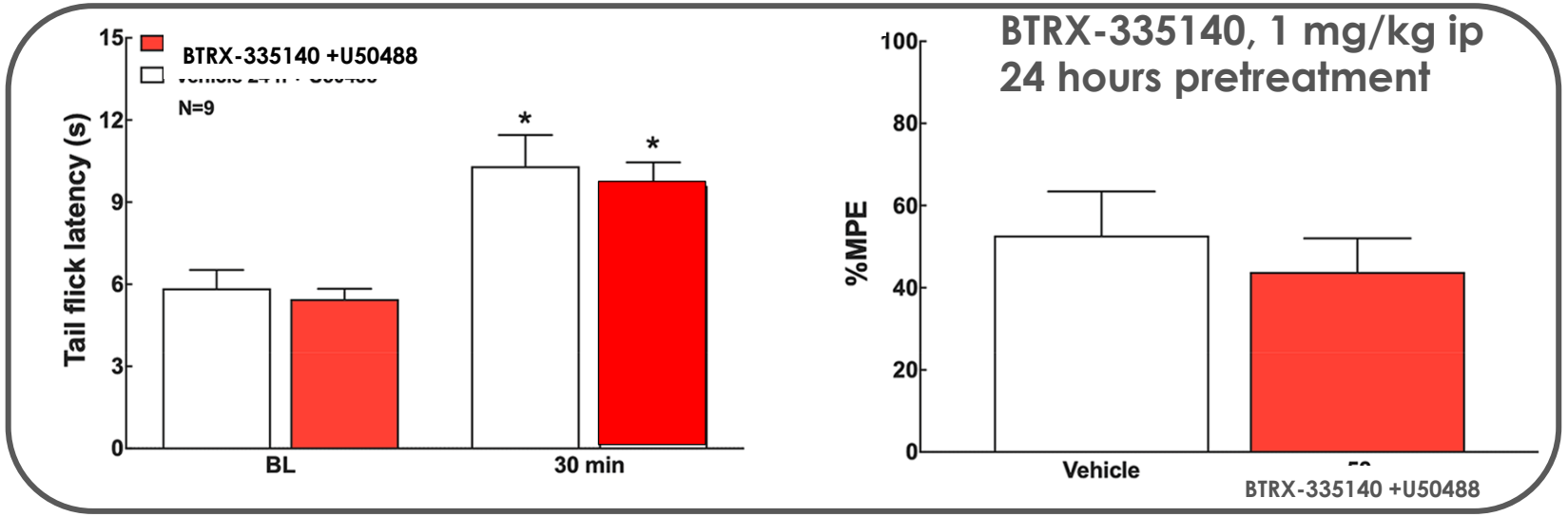
BTRX-335140 engages the KOR target and has <24 hour duration of action







Additional BTRX-335140 pharmacodynamic characterization presented by Dr. Wallace tomorrow

Studies conducted by TSRI and Frank Porreca (U of Arizona)

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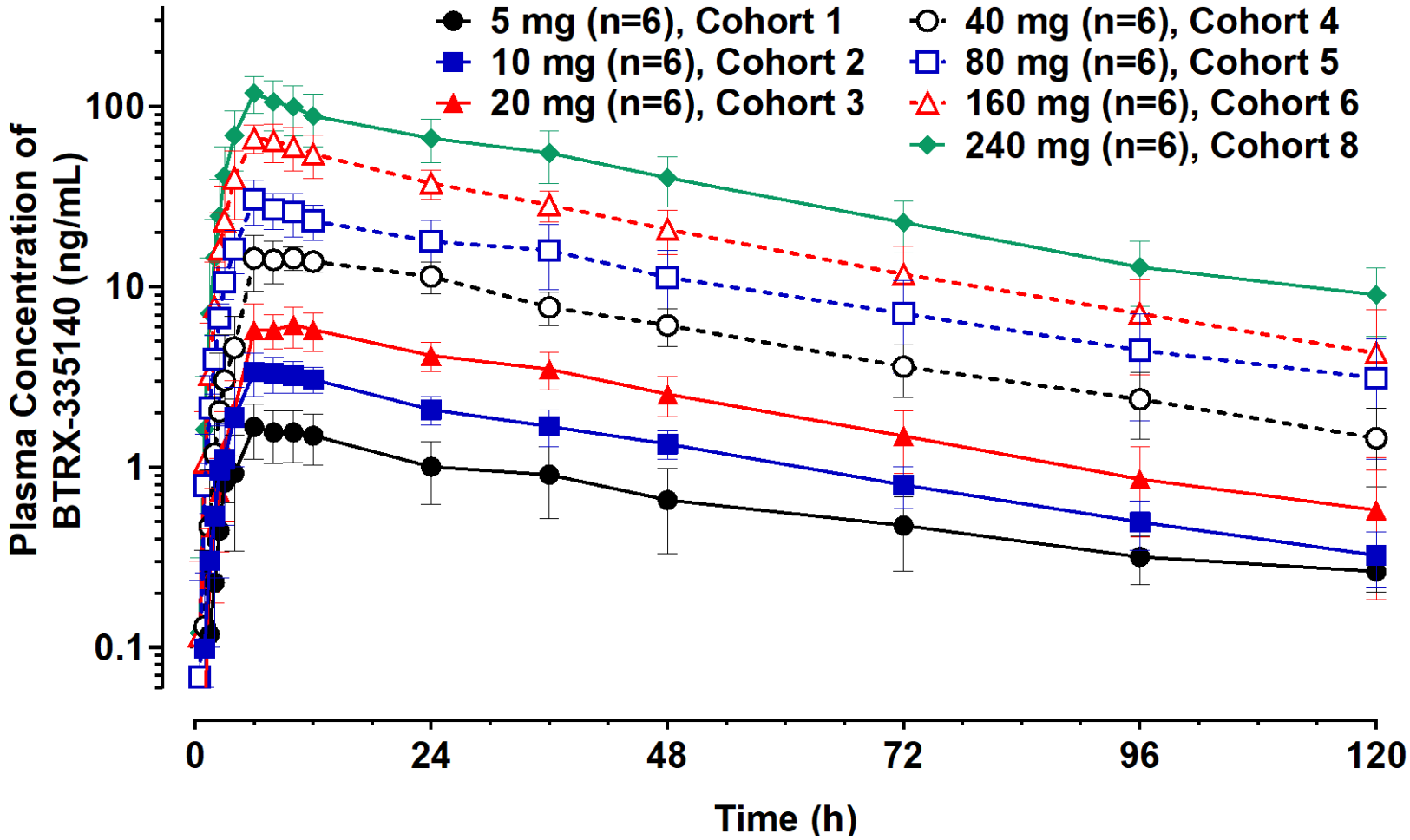
Human PK – Single oral doses



T_{max} @ 6-8 h

$T_{1/2}$ of 32 h

Exposure increases with dose, generally dose proportional
No food effect (Cohort 7)

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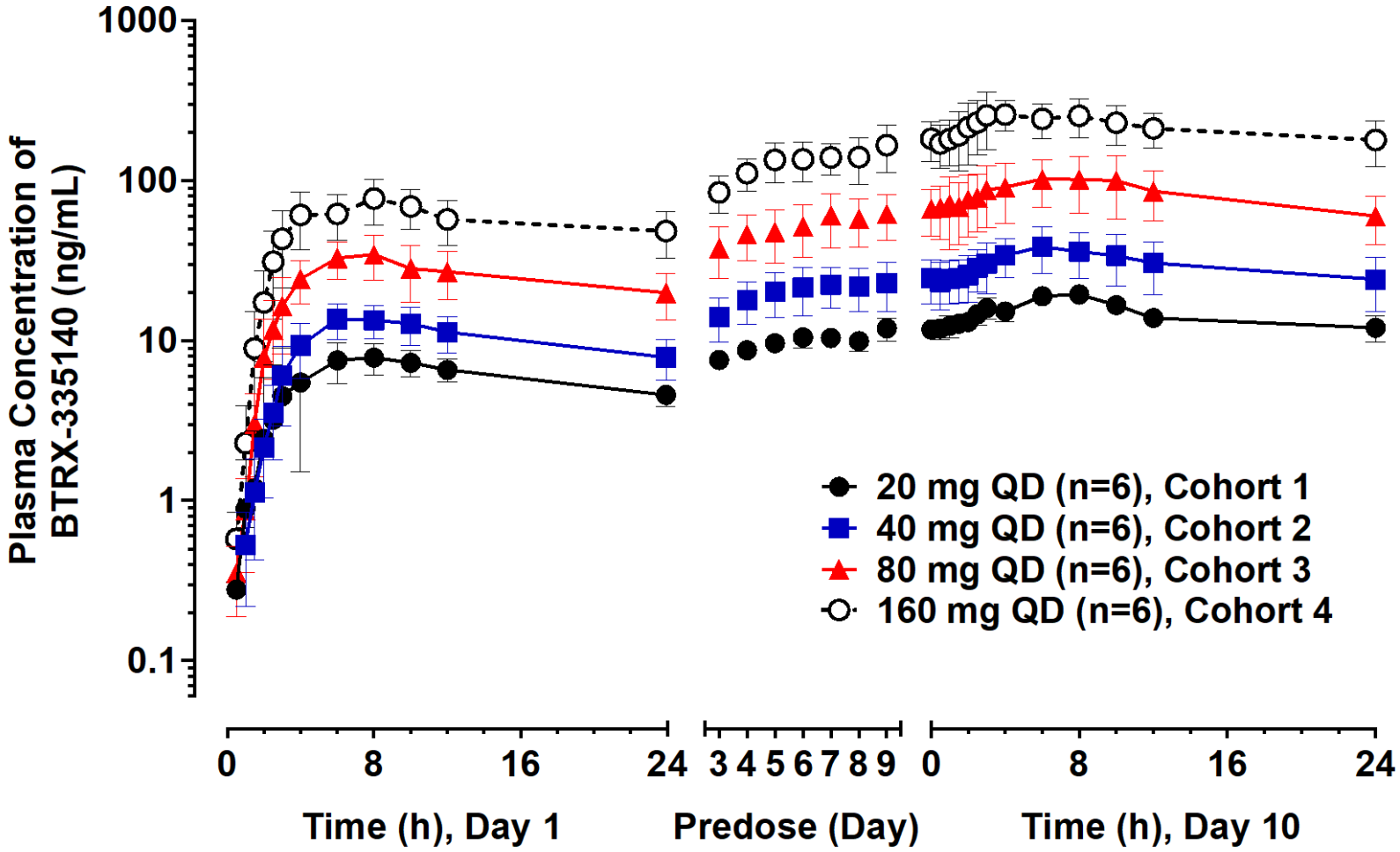
Human PK – Multiple oral doses (QD for 10 days)



2.5-4.5-fold accumulation upon repeat dosing; steady state reached by Day 9

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BTRX-335140 is well tolerated after 10 days of dosing in healthy volunteers

- ✓ No deaths or serious adverse events
- ✓ No adverse cardiac signals by EKG
- ✓ All adverse events classified as possibly related to treatment were Grade 1
- ✓ No treatment-related discontinuations

Adverse Events Occurring in >1 Subject Determined Possibly Related to Drug*

	Placebo	20 mg	40 mg	80 mg	160 mg	Overall Active
# subjects	6	6	6	6	6	24
pruritis	0	1	0	0	3	4 (16%)
headache	0	0	0	1	1	2 (8%)
fatigue	0	0	0	2	1	3 (13%)
asthenia	0	0	0	2	0	2 (8%)
abnormal dreams	0	0	1	1	0	2 (8%)

*Investigator determined

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Review of KOR antagonist BTRX-335140 attributes and timelines

✓ Highly potent, selective antagonist for KOR	2016
✓ Exhibits on-target activity in a variety of pharmacological assays	2016
✓ Excellent safety and tolerability profile in non-clinical toxicology studies	2017
✓ Favorable tolerability and pharmacokinetics in healthy volunteers in Phase 1	2018
➢ PET occupancy study and Phase 2 readiness work	2019
➢ Phase 2 studies in mood and anxiety disorders	2020

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