# Bringing precision therapy to mental disorders

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### **Translational Therapeutics**



**Osler's** "Broken Machine"

**Garrod's** "Maladapted Evolutionary Product"

**Florey's** "Transformational Intervention" *and* 

Schultz's "Science Changing Life"



## **Intelligent Intervention**

"... the mechanisms of disease are quite open to intelligent intervention and reversal whenever we learn more about how they operate...

Lewis Thomas, 1974

With Professor Ed Roberts in the Sierras planning Navacaprant



Use the power of chemistry and genetics to define and alter Nodal Points of Control in disease



Chemistry

#### Selective Kappa opioid receptor antagonists

Rapid in vivo efficacy

Surviving Multiple Near Deaths

**Advantages of Scripps** Research Leadership

- Minds
- Infrastructure
- Pathway depth
- Powers of persistence

**Administrative & Technical** 

mage Science and Analysis Laboratory, NASA-Johnson Space Center. 03/27/2011 09:46:43.

Human Safety and Efficacy



## What is anxiety?

- Anxiety is a feeling of fear and dysphoria (feeling bad) that mimics the feelings of fight or flight, that occurs in a non-physically threatening setting
  - It has mental components (fear or dysphoria)
  - It has physical components resulting from the overproduction of stress hormones in the periphery such as adrenaline
  - Sympathetic nerves get input from the brain, via spinal nerves, and innervate organs such as the adrenal glands
  - Catecholamines (adrenaline and noradrenaline) are overproduced
  - Heart pounds, hear rate speeds up, blood pressure is elevated, hyperventilation occurs, we blow off CO2, plasma pH rises, ionized Ca2+ drops, hands and toes claw up in cramps
- Triggers can be social, fear of failure, exams
- The behaviors can become autonomous (learnt) over time (Generalized Anxiety Disorder)



## What is depression (according to the APA)

- Depression (major depressive disorder) is a common, serious but TREATABLE medical illness that negatively affects how you feel, the way you think and how you act.
- Depression causes feelings of sadness and/or a loss of interest in activities you once enjoyed (ANHEDONIA)
  - Changes in appetite weight loss or gain unrelated to dieting
  - Trouble sleeping or sleeping too much
  - Loss of energy or increased fatigue
  - Increase in purposeless physical activity (e.g., inability to sit still, pacing, handwringing) or slowed movements or speech
  - Feeling worthless or guilty
  - Difficulty thinking, concentrating or making decisions
  - Thoughts of death or suicide



## **Unmet Needs in Psychiatry:**

Diseases with thought disorders



#### Mental stress-related and developmental disorders are undertreated and have high prevalence

- 18.4% of US adults have life-time diagnosis of depression (n=392,746) MMWR 72:644-50 (2023)
- 2.8% of US adults had a past-year prevalence of bipolar disorder (National Comorbidity Survey Replication 2001-2003)
- Schizophrenia prevalence ranges from 0.25-0.64% (*Biol Psychiatry*. 2005 Oct 15;58(8):668-76)

#### **Common Side Effects:**

• Sedation, abnormal movements, gynecomastia, weight gain, cognitive impairment, sexual dysfunction, dry mouth, difficulty urinating

#### Unmet Medical Needs ~50% of schizophrenic patients are nonadherent to therapy

- Even though 80% will be stabilized by first-line antipsychotics
- Non-adherence factors include newly started treatment, younger or older age of treatment onset, substance misuse, poor social and familial support
- Disease-related drivers include cognitive impairment, poor insight and psychotic paranoia
- Medication drivers include side-effects and complex treatment regimens
- Provider factors include poor therapeutic alliance between psychiatrist and patient/caregivers



### The Ying-Yang Seesaw of endorphins and dynorphins

- Endogenous Opioids are short peptides, often cleaved from larger proteins, that activate opioid receptors
- Endorphins activate the Mu Opioid receptor, the target of morphine and heroin
- Endorphins stimulate the pleasure centers of the brain delivering a sense of happiness and well being
- Dynorphin is an endogenous opioid peptide produced by the stress response
- It is elevated in anxiety and depression
- It activates the Kappa Opioid Receptor and induces anxiety, agitation, bad feelings (dysphoria), impaired executive decision making, and hallucinations
- When produced by chronic stress, dynorphin may convert anxiety into depression



## What is a cell-surface receptor?

- These are protein integrated within the cell surface membrane
- They bind specific molecules like morphine with high affinity (ligands)
- Receptors are the sensing switches of the cell
  - Recognize the ligand
  - They change shape or conformation (ON)
  - They transduce a signal that AMPLIFIES
  - Receptors then terminate signaling (OFF)
- Ligands that activate the receptor are AGONISTS (**ON**)
- Ligands that block the receptor are ANTAGONISTS (**OFF**)





## **G-protein coupled receptors**

- **Opioid receptors are a family of** four G protein-coupled receptors
- The first family member, MOR, • was initially found as the receptor for morphine, heroin, fentanyl
- **Cloning the family in the early** • 90s defined Delta, Kappa and the Opioid Related receptor.
- No discrete physiological ulletfunctions are known for DOR or OPRL1



## Kappa Opioid Receptor:

#### Good for escaping Saber-toothed tigers, but very bad for modern life



PFC	Prefrontal cortex	
ACC	Ant. Cingular cortex	
S	Striatum	
Α	Amygdala	
DRM	Dorsal raphe nucleus	
LC	Locus ceruleus	
HYP	Hypothalamus	
PAG	Periaqueductal gray	
PPG	Pedunculopontine nucleus	
K	KOR	

**NA, VTA** are dopaminergic, and regulate pleasure, i.e., sex, drugs and rock and roll

**DRN** is serotonergic and site of SSRI action

**KOR** regulates neuronal circuits impacting emotion, cognition, addiction, stress and dysphoria



## Kappa Opioid Receptor: Disease mechanisms



#### **Receptor Mechanism**

- KORs are G-Protein Coupled Receptors activated by the endogenous ligand Dynorphin (DYN)
- DYN is produced in brain in response to stress
- KOR activation by DYN inhibits presynaptic dopamine release (BAD!!)
- Dopamine release is essential for pleasure, satisfaction, motivation, normal movement

#### **Disease Relevance**

• DYN is up-regulated in response to stress in brain regions associated with mood, reward

#### Activation of KOR is BAD!!

 Induces dysphoric , anxiety, depression and hallucinations (auditory and visual) in both humans and animal models

#### Blocking KOR is GOOD!!

 Disruption of KOR signaling through gene knockouts or the use of KOR blockers have anti-depressant and anxiolytic effects in animal models



## Warning: some lines of scientific evidence....

- Arise from people doing stupid and extremely dangerous things!!
- Do NOT try this at home
- The line from social experimentation to addiction or psychiatric illness can be very short in some individuals



## Salvinorin A (hallucinogen from Salvia Divinorum) activates KOR with mind-bending effect



#### What is its effect on the mind?

- Psychic effects include perceptions of bright lights, vivid colors, shapes, and body movement, as well as body or object distortions.
- Salvia divinorum may also cause fear and panic, uncontrollable laughter, a sense of overlapping realities, paranoia, and hallucinations.
- Users typically experience rapid onset of intense hallucinations that can impair judgment and disrupt sensory and cognitive functions.
- Salvinorin A is the principal ingredient responsible for the psychoactive effects of Salvia divinorum.

DEA Drug Facts

White, K. L. and B. L. Roth (2012). "Psychotomimetic effects of kappa opioid receptor agonists." <u>Biol Psychiatry</u> **72**(10): 797-798. Abi-Dargham, A. (2021). "Relevance of the Kappa Dynorphin System to Schizophrenia and Its Therapeutics." <u>J Psychiatr Brain Sci</u> **6**. Clark, S. D. and A. Abi-Dargham (2019). "The Role of Dynorphin and the Kappa Opioid Receptor in the Symptomatology of Schizophrenia."<u>Biol Psychiatry</u> **86**(7): 502



#### Controlled clinical trial evidence that Kappa Receptor activation induces psychosis

- Enadoline was a highly potent selective Kappa activator developed for pain relief
- Tiny doses were tested in man from 15ug-160ug
- The starting dose is 1/33,333 of a Tylenol table
- At a dose of 25ug and above, subjects reported dysphoria, anxiety and abnormal thinking
- Dosing had to be stopped at 160ug because of all of the test subjects were hallucinating



Reece, P. A., et al. (1994). J Clin Pharmacol 34(11): 1126-1132.



## **Therapeutic hypothesis**

#### Selective blocking of Kappa Opioid Receptor should:

- Block anxiety
- Be non-sedating
- Disrupt the progression between chronic anxiety and depression
- Interrupt processes involved in psychotic behaviors

#### The plan:

• Test this directly by making a reversible blocker of the KOR



## So where did we start (10 years ago!!)? Don't overthink – interrogate chemical space





Guerrero M, Urbano M, Brown SJ, Cayanan C, Ferguson J, Cameron M, Devi LA, Roberts E, Rosen H. Optimization and characterization of an opioid kappa receptor (OPRK1) antagonist. 2013 Apr 15 [updated 2014 Sep 18]. In: Probe Reports from the NIH Molecular Libraries Program [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2010–. PMID: 24479196.



## The wizardry of chemistry

- Our compounds all have the prefix CYM
- This is a reference to Ed Roberts origins as a proud Welshman (Cymru)
- The mythical magician Merlin had his origins in Wales where he was known as Myrddin Wyllt
- The secret to therapeutics is to have the right magician leading the chemistry



#### The starting hit, that most people would not take seriously ③



## RaMP (Rational Multi Parameter) Optimization Shortcomings of compound





## Every potential drug has to survive near death!!

+

## This process is very difficult

+

We have to be robust enough to weather the "death zone"

#### Funding Risk

Withering on the vine – lack of funding

#### Hypothesis Risk

You don't know what you don't know

#### **Technical Risk**

+

Some properties are rational and can be resolved by inductive logic (potency, selectivity)

Distribution to brain and efflux can be more random

#### Success requires finding the inductive path to a good solution



## **Turning near death into resurrection**

- Mutagenicity is an unacceptable cancer risk
- We test it in both bacteria (the Ames test) and in mammalian cells (micronucleus assay)
- Our lead was Ames positive on a single strain
  - Investors run the other way
  - Companies stop development
  - Scripps Research scientists ask questions
- The positive strain suggested an insertion mutation

Is the solution random or rational?

Can the answer be deduced or is brute force the only hope?







## Inductive logic and chemistry solve the dilemma

- Insertion mutants require DNA minor groove binding
- The methyl-quinilino-amine metabolite predisposes to minor groove binding
- Change the chemistry in a subtle way to kick the molecule out of the minor groove and retain excellent receptor activities





## For a molecule to be a drug, it must work every time it comes off the shelf!!



Automated, high-throughput 384 well-format Highly reproducible, precise and rapid





### Navacaprant: It must also work in every assay format



Functional Assay	IC <sub>50</sub>
hKOR (U-50,488 agonist)	0.8 nM
hKOR (Dynorphin A agonist)	6.1 nM
hKOR (β-Arrestin)	3.1 nM
hMOR (DAMGO agonist)	0.1 µM
hDOR (SNC80 agonist)	6.5 µM

120-fold selective vs. OPRM1 >4500-fold selective vs. OPRD



### Navacaprant: It must work in every animal experiment



The secret for success: Rapid, easy in vivo efficacy looking for inhibition of Prolactin release 3-4 days for all receptor and in vivo assays

#### No wasted time!!!

For compound to work, it must be absorbed orally and cross the Blood-Brain Barrier



## Discovering early good compounds can happen in academia

- Developing them into drugs takes hundred of millions of dollars
  - Preclinical optimization
  - Selectivity studies
  - Preclinical toxicology
  - Investigational New Drug filing
  - Clinical trials
    - Phase 1: Ascending single and multiple dose safety for dose choice
    - Phase 2a: Efficacy proof-of-concept (binded)
    - End of Phase 2 meeting with FDA to agree development plan for potential approval
    - Phase 3: Safety and efficacy demonstration in multiple trials (blinded, usually placebo, sometime active comparator)



## At that time - we had only one option

Company formation: Scripps Research Out-licensed the relevant patent estate to a spin-out BlackThorn Therapeutics (now acquired by Neumora Therapeutics)

- This allowed much additional work that:
- 1. Taught us more about the wiring diagram, and
- 2. Progressed the compound through early clinical development



Kristina Burow, ARCH Ventures



## Prefrontal Cortical (PFC) networks, working memory (WM) and stress

- The PFC affects decision making, planning, abstract thought and goal-directed behaviors
- KOR is found in the PFC
- Ventral and medial regions regulate emotion
- Dorsal and lateral regions influence working memory
- Prefrontal cortex projects towards the amygdala and hypothalamic "pleasure centers"
- Acute stress reduces neuronal firing and impairs cognitive abilities (we get flustered)
- The effects of acute stress can be readily measured
- Our collaborators at BlackThorn (Tanya Wallace and Bill Martin) were able to interrogate this system

Arnsten, Nat Rev Neurosci.: 10(6): 410–422, 2009; Nat Neuro. 18(10), 1376-85, 2015. Wallace, T.L Neurobiol Stress 2022: 21:100493. doi: 10.1016/j.ynstr.2022.100493.





## How can one acutely and reversibly induce stress?

Valium or Xanax as sedating anxiolytics (benzodiazepines) that act as positive allosteric modulators of GABA-A receptor

## FG-7142 is a benzodiazepine analog that is a partial inverses agonist of GABA-A and drives anxiety i.e., it is anxiogenic

- FG-7142 increases DA turnover in the PFC, but not non-PFC regions
- PFC dopamine response to stress is mimicked by FG7142 (Tam and Roth, 1985, 1990; Roth and Tam, 1987; Deutch and Roth, 1990)
- DA response is blocked by anxiolytic benzodiazepine receptor agonists (Tam and Roth, 1990)
- FG-7142 impairs prefrontal cortical-dependent, tasks in rats and monkeys (Murphy et al., 1994, 1996)



### KOR is non-sedating, acts down-stream of benzodiazepines and preserves Working Memory



- GABAergic signaling is inhibitory (sedating, treatment of epilepsy)
- Blockage of GABA-A receptors induces anxiety
- Removal of GABA-A inhibition stimulates
  Dynorphin production
- Activation of Kappa is a final common pathway for feeling dysphoria

#p<0.05 vs Vehicle \*p<0.05 vs FG7142

#### BTRX-335140 (Navacaprant) protects against stress-induced WM deficit Wallace TL, Martin WJ, Arnsten AFT. Neurobiol Stress. 2022 Sep 24;21:100493.

BlackThorn Therapeutics Collaboration w/Amy Arnsten (Yale)



## Pharmacological evidence supporting the useful effects of navacaprant in stress and dysphoria

- Xie, J. Y., et al. (2017). "Kappa opioid receptor antagonists: A possible new class of therapeutics for migraine prevention." <u>Cephalalgia</u> **37**(8): 780-794.
- Ito, H., et al. (2023). "Chronic pain recruits hypothalamic dynorphin/kappa opioid receptor signaling to promote wakefulness and vigilance." <u>Brain</u> 146(3): 1186-1199.

## Navacaprant restores REM sleep in chronic pain i.e., resolution of sleep disturbances

Sleep disturbance is a symptom of anxiety, depression and schizophrenia It is also a tough side-effect of first line therapies such as SSRIs



## Navacaprant: Phase 2a trial design

Amendments included expanding enrolment criteria to allow patients with moderate-to-severe MDD



 Patients with a baseline HAMD-17 total score that received at least one dose of study drug and had at least one post-baseline HAMD-17 assessment
 Baseline HAMD-17 score <u>></u>22



#### Neumora Amended to Fit With MDD Studies

Product Candidate	MDD Severity Criteria
SAGE-217	HAMD-17 <u>&gt;</u> 24
PRAX-114	HAMD-17 <u>&gt;</u> 23
Aticaprant	MADRS <u>&gt;</u> 25
MD-120	HAMD-17 <u>&gt;</u> 20
Lumateperone	MADRS <u>&gt;</u> 24

Phase 3 trials posted to clinicaltrials.gov after Jan 1, 2020, and have been completed or currently enrolling, excludes trials without disclosed criteria

#### **Neumora Amendments to Optimize Trial**

- Increased HAMD-17 inclusion to focus on moderate-to-severe patients (baseline HAMD-17 range 22-30)
- Increased target enrollment to 204 (40 sites)

#### **Study Endpoints**

#### **Primary Endpoint:**

 Δ from Baseline to WK 8 on the HAMD-17 (depression)

#### NMRA Prespecified Subgroup Analysis of Primary Endpoint

 Δ from Baseline to WK 8 on the HAMD-17 ≥22 at baseline

#### Secondary Endpoints:

- % of HAMD-17 responders (≥50% ↓)
- Δ from Baseline in SHAPS (anhedonia)
- Δ from Baseline in HAM-A (anxiety)

#### **Final Efficacy Population:**

- N=171 patients<sup>1</sup>
- N=100 moderate-to-severe MDD<sup>2</sup>

https://ir.neumoratx.com/static-files/76b4fd4e-566f-4c27-976e-0d74da1b0391c



## **Navacaprant:** Established proof-of-concept for treatment of depression and anhedonia in patients with moderate-to-severe MDD

## HAMD-17 A complex scoring of psychological and physical symptoms of depression

SHAPS: scoring ANHEDONIA



Note: Graphs depict prespecified statistical sensitivity analysis for moderate-to-severe patients (n=100; baseline HAMD-17 > 22)

https://ir.neumoratx.com/static-files/76b4fd4e-566f-4c27-976e-0d74da1b0391



### Pivotal studies designed to evaluate potential benefits of Navacaprant monotherapy in MDD

**Pivotal Efficacy Studies** 

#### **KOASTAL**



\*Safety Assessments include Change in Sexual Functioning Questionnaire (CSFQ-14)

CGI-I = Clinical Global Impression-Improvement scale; CGI-S = Clinical Global Impression-Severity scale; EQ-5D 5L = EuroQoI-5D 5L; HAM-A = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; PHQ-9 = Patient Health Questionnaire-9; QD = once daily; SDS = Sheehan Disability Scale; SHAPS = Snaith-Hamilton Pleasure Scale; wk = week; WPAI-GH = Work Productivity and Activity Impairment Questionnaire – General Health.



moderate-to-severe MDD

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## Other areas of potential therapeutic application

- Significant decreases alcohol consumption (Zorilla/Roberto)
  - Mechanistic studies in progress at Scripps Research
- Restoration of REM sleep in neuropathic pain (Porreca)
  - Sleep disturbance is an important symptom complex in both MDD and BPD
  - It is a very common side effect of SSRI/SNRI
- Withdrawal from substance abuse (opiates, methamphetamine)
- PTSD



## Potential for broad applicability of navacaprant beyond MDD includes Bipolar Depression

## Strong rationale for efficacy in Bipolar Depression (BPD):

- Anhedonia is a highly prevalent and clinically relevant symptom in BPD, and there is a growing body of research in the pathophysiologic underpinnings of anhedonia in BPD
- Given that navacaprant studies have demonstrated meaningful improvements in anhedonia symptoms in patients with moderateto-severe MDD, we believe it may also be effective in treating anhedonia related to BPD
- The primary endpoint for evaluating efficacy in bipolar depression is MADRS
- Currently approved therapies (e.g., atypical antipsychotics) have significant limitations

Signal-seeking study in patients with BPD enables decisionmaking on advancing navacaprant to proceed to pivotal program in BPD





## Paying it forward: Impact on patients and fundamental research





### Dr. Schultz's Vision: "Science Changing Life" made real

The Roberts and the Rosen labs have successfully used RaMP to invent, discover and develop Ozanimod and Navacaprant

We also have NMRA-511 about to enter Phase 2 clinical trials for agitation in Alzheimer's Disease

We remain committed to improving the lives and dignity of patients and those that care for them through the discovery of disease mechanisms and agents for their amelioration. We are now building the future within Scripps Research and Calibr-Skaggs

#### Calibr-Skaggs at Scripps Research provides a paradigm-shifting infrastructure and skillset to:

- Navigate the "death-zone"
- Manage Hypothesis and Technical Risk
- Leverage Scripps Research ingenuity and pathway depth
- Find the imaginative and inductive paths to great solutions for patients



### Scripps Research

• Ed Roberts, PhD

- Steve Brown, PhD
- Nora Leaf, BS
- Miguel Guererro, PhD

Hugh Rosen, MD, PhD

• Sean Riley, BS

- Seokjun Jo, PhD
- Fiona O'Murphy, BS

#### University of Arizona

• Frank Porreca, PhD

#### **BlackThorn Therapeutics**

- Bill Martin, PhD
- Lori Jean Van Orden, PhD
- Mariangela Urbano, PhD
- Tanya Wallace PhD

#### <u>Support</u>

- Blueprint Neurosciences/NINDS 1UH2 NS093030-01 (Edward Roberts, Hugh Rosen, Frank Porreca)
- Molecular Libraries Initiative/NIHM U54 MH084812 (Hugh Rosen)
- BlackThorn Therapeutics



