# RespireRx Pharmaceuticals Inc

OTC QB: RSPI

## Advanced Treatments for Neurological Signaling & Respiratory Pathways

**November 2020**

# Forward Looking Statements

In some cases, you can identify forward-looking statements by the following words: “anticipate,” “assume,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “ongoing,” “plan,” “potential,” “predict,” “project,” “should,” “will,” “would,” or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words, and such statements may include, but are not limited to, statements regarding (i) future research plans, expenditures and results, (ii) potential collaborative arrangements, (iii) the potential utility of the Company’s product candidates, (iv) reorganization plans, and (v) the need for, and availability of, additional financing. Forward-looking statements are not a guarantee of future performance or results and will not necessarily be accurate indications of the times at, or by, which such performance or results will be achieved. Forward-looking statements are based on information available at the time the statements are made and involve known and unknown risks, uncertainties and other factors that may cause our results, levels of activity, performance or achievements to be materially different from the information expressed or implied by the forward-looking statements contained herein. These factors include but are not limited to, regulatory policies or changes thereto, available cash, research and development results, issuance of patents, competition from other similar businesses, interest of third parties in collaborations with us, and market and general economic factors. We cannot assure you that the forward-looking statements contained herein will prove to be accurate and therefore prospective investors are encouraged not to place undue reliance on forward-looking statements. We caution investors to recognize that forward-looking statements are predictions of future results, which may not occur as anticipated. Actual results could differ materially from those anticipated in the forward-looking statements and from historical results. These forward-looking statements are based on assumptions regarding the Company’s business and technology, which involve judgments with respect to, among other things, future scientific, economic, regulatory and competitive conditions, collaborations with third parties, and future business decisions, all of which are difficult or impossible to predict accurately and many of which are beyond the Company’s control. Although we believe that the expectations reflected in our forward-looking statements are reasonable, we do not know whether our expectations will prove correct. Our expectations reflected in our forward-looking statements can be affected by inaccurate assumptions that we might make or by known or unknown risks and uncertainties. We advise investors and all other interested parties to consult any further disclosures we may make on related subjects in our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K that we file with or furnish to the SEC.

# RespireRx – A Tale of Discovery

RespireRx Pharmaceuticals Inc

*HMS Discovery*

***"The world is made up of stories Not atoms"***

Muriel Rukeyser

# RespireRx – Underlying Science

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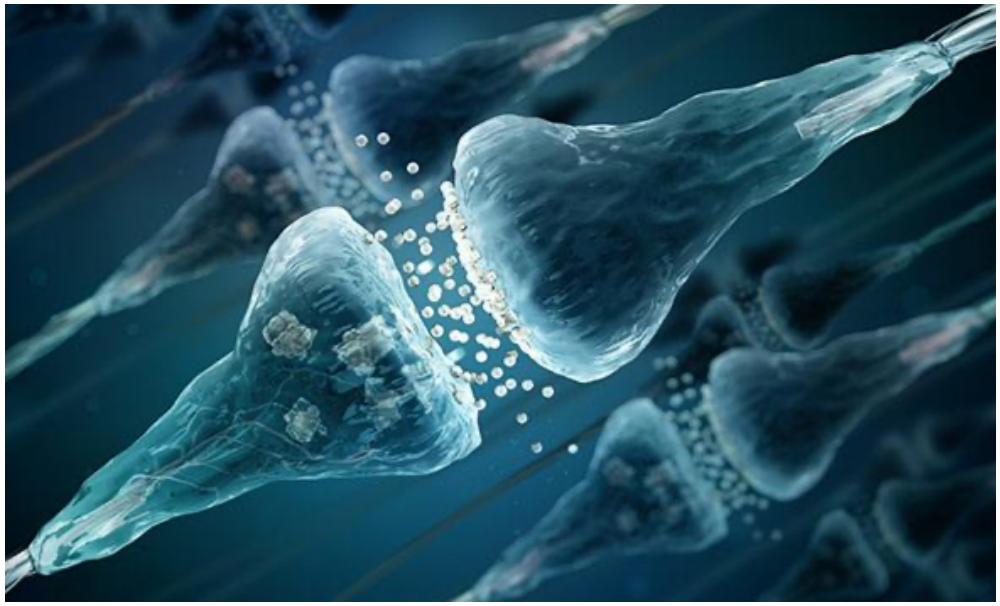
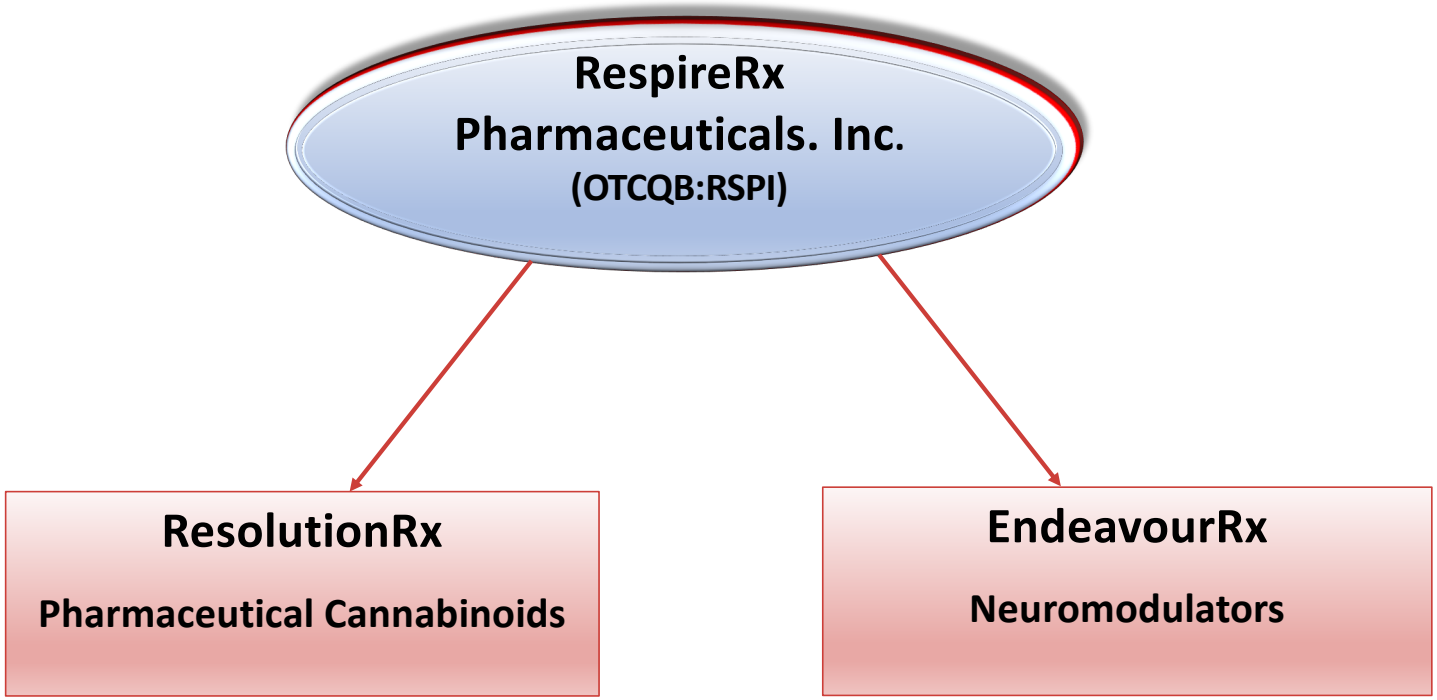
## *Neurotransmission*

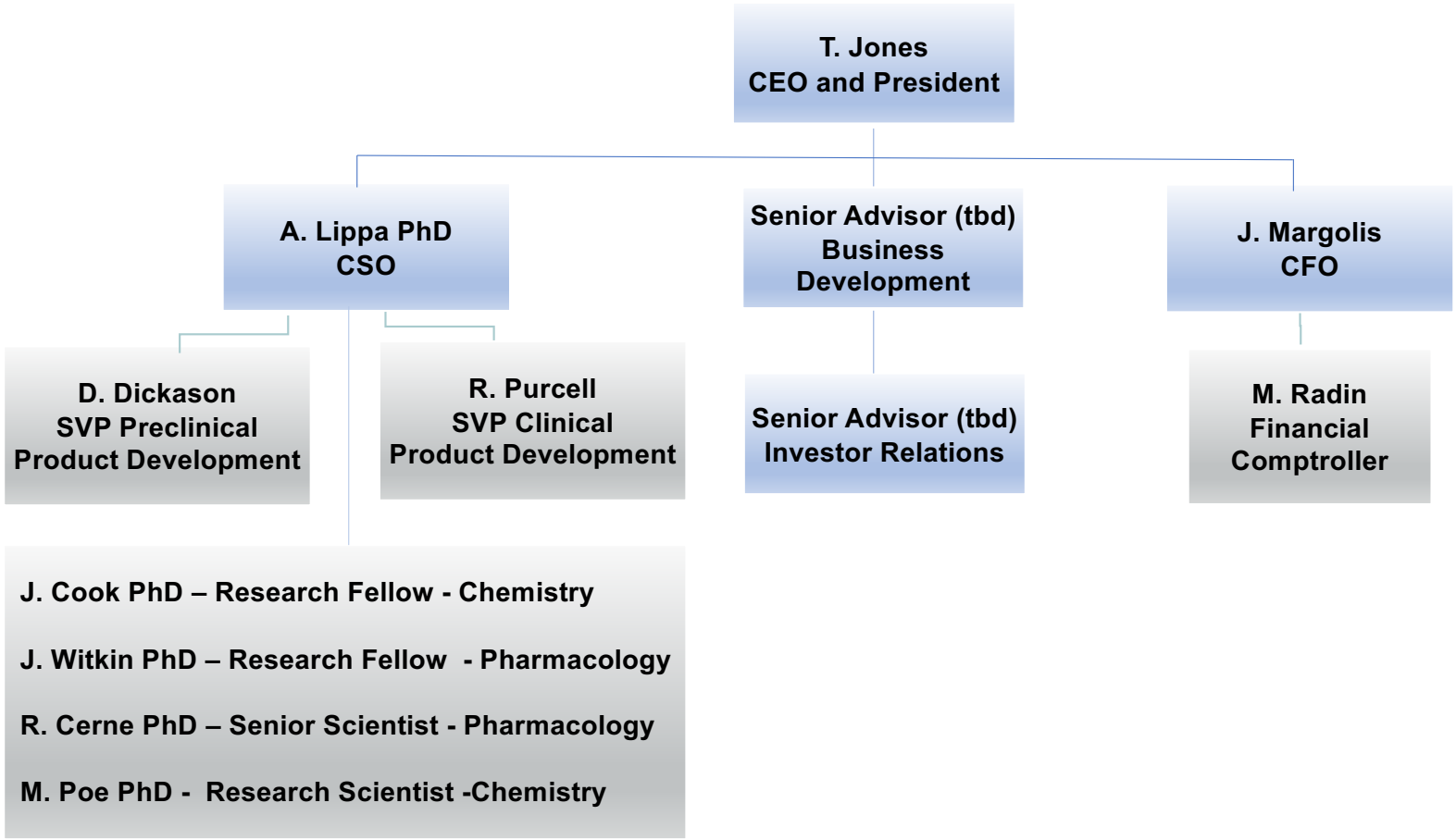


- Neurons communicate through a process of neurotransmission in which they release chemical neurotransmitters that bind to specific receptors on adjacent neurons.
- RespireRx is developing drugs to modify neurotransmission and create advanced treatments for disorders with high unmet needs.

# Corporate Re-Organization



# RespireRx - Organizational Structure



# RespireRx - Product Development Status

RespireRx Pharmaceuticals Inc

| | Preclinical | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|
| ***ResolutionRx - Cannabinoids*** | | | | |
| Dronabinol – OSA | → | → | → | |
| Dronabinol Formulation | → | | | |
| ***EndeavourRx - Neuromodulators*** | | | | |
| **AMPAkines** | | | | |
| CX717 - ADHD | → | → | → | |
| CX1739 - Spinal Cord Injury | → | → | | |
| CX1942 –follow-up compound | → | | | |
| **GABAkines** | | | | |
| KRM-II-81 – Epilepsy/Pain | → | | | |

# ResolutionRx - Pharmaceutical Cannabinoids

RespireRx Pharmaceuticals Inc

*HMS Resolution*

# ResolutionRx - Pharmaceutical Cannabinoids

RespireRx Pharmaceuticals Inc

## *Dronabinol (Δ9-THC)*

- Treatment of Obstructive Sleep Apnea (OSA)
- Potential multi-billion $ market – estimated 30 million U.S. patients, with comparable amounts in UK and Germany
- Successful Phase 2B clinical trial in OSA
- Phase 3 ready, pending completion of a new formulation and an IND meeting
- Development and supply agreement with global dronabinol manufacturer
- Broad enabling IP for dosage and novel formulations
- No approved drugs available for OSA

# ResolutionRx - Pharmaceutical Cannabinoids

RespireRx Pharmaceuticals Inc

## *Dronabinol for Obstructive Sleep Apnea*

- **Sleep Apnea**
  - Repetitive episodes of airflow cessation (apnea) or reduction (hypopnea) for more than 10 seconds during sleep
  - Three types: Obstructive, Central & Mixed

- **The Sleep Apnea Market is Large**
  - Approximately 30 million U.S. adults suffer from OSA
  - Market potential for OSA is $3 - 9 Billion/Year

- **Current Treatments**
  - CPAP device
  - Surgery
  - Dental devices

- **Clear Market Need**
  - Poor compliance with CPAP
  - No drug treatment available

# Dronabinol: A Breakthrough Treatment for OSA

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- **Mechanism of Action**
  - Dronabinol is Δ9-THC, a synthetic cannabinoid agonist at CB1 and CB2 receptors

- **Background**
  - Schedule III generic drug available by prescription, with a low risk of addiction
  - Approved in 1985 as Marinol® for the treatment of anorexia in AIDS patients and nausea and vomiting in cancer patients undergoing chemotherapy
  - Positive Phase 2A & 2B studies in the treatment of OSA
  - Phase 3 ready pending completion of novel formulation and IND meeting

- **Intellectual Property**
  - License to issued method-of-use patent in the US, UK and Germany for the use of dronabinol for treating OSA (expires 2025)
  - Pending patents on broad, enabling dosage and modified release formulations with patent life through at least 2031

# Two Successful Phase 2 Studies – Phase 3 Ready!

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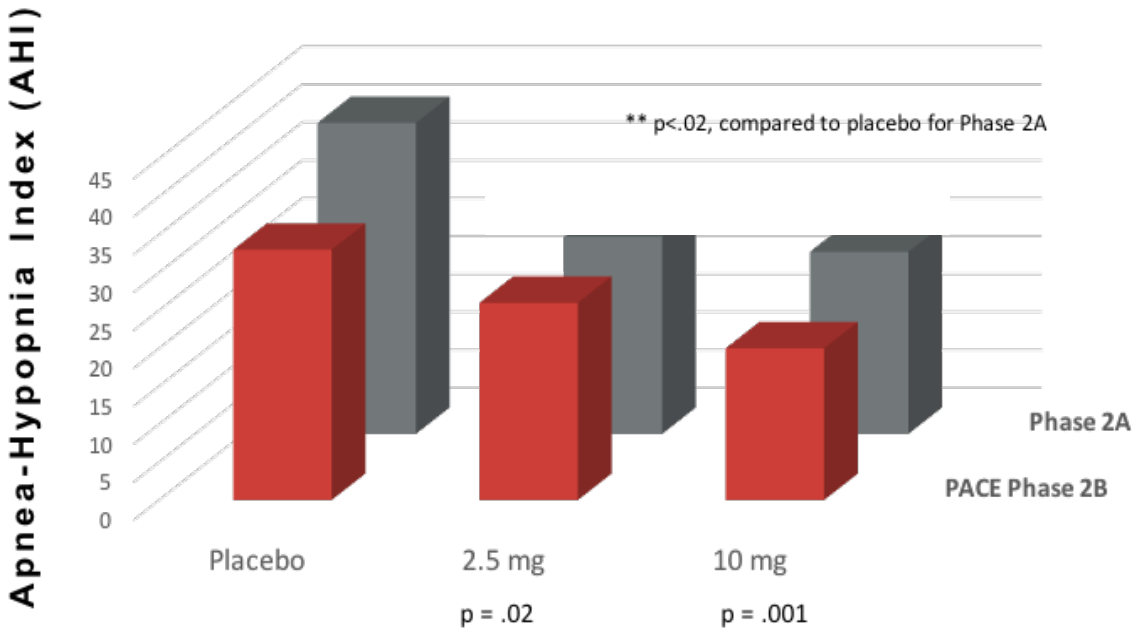


* Double blind, placebo controlled dose-ascending study in patients with OSA, n=19

**Two Phase 2 Clinical Trials Have Shown That Dronabinol Treatment Results in a Statistically Significant, Dose Related Improvement in AHI, the Primary Endpoint for FDA Approval**

# A Clinical View of the Pace Trial Results

RespireRx Pharmaceuticals Inc

***Comments by David Rapoport, MD***

**Professor of Medicine Mount Sinai School of Medicine***

"OSA may affect….long term cardiovascular and cerebrovascular health,…..memory loss and progression of Alzheimer Disease biomarkers."

"…dronabinol is effective in lowering AHI in patients with moderate obstructive sleep apnea."

"The results of the PACE trial are among the first to show sustained effect of a drug therapy targeting the behavior of the upper airway. Dronabinol is easy to take, appears to have a low side effect profile and now has been shown to be effective."

"…dronabinol "may help address the significant medical need for alternative treatments for OSA."

***RespireRx press release, November 30, 2017**

# EndeavourRx - Neuromodulators

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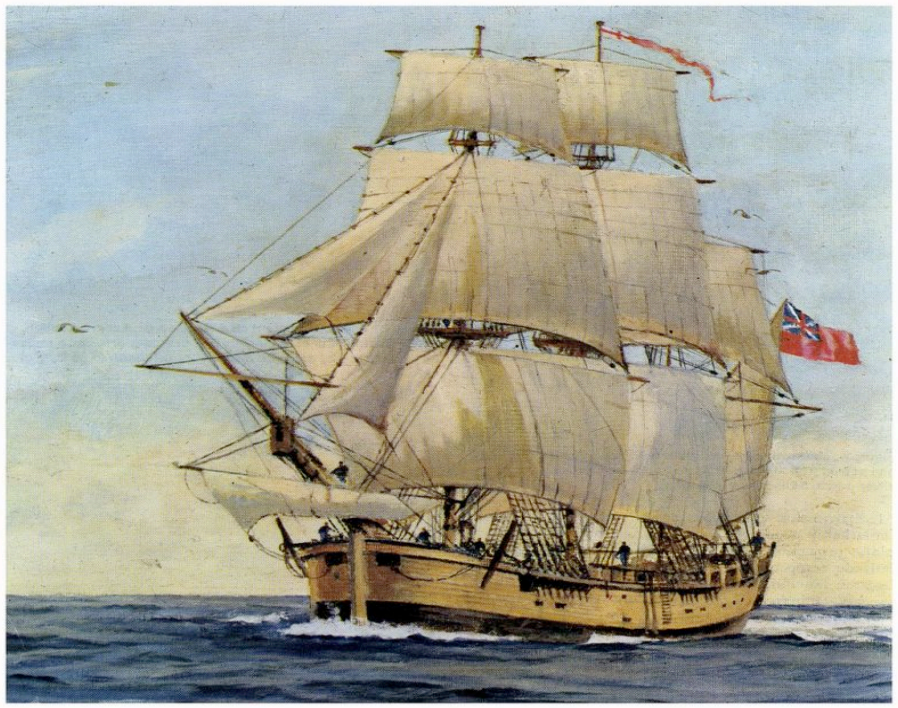

***HMS Endeavour***

# EndeavourRx - Neuromodulators

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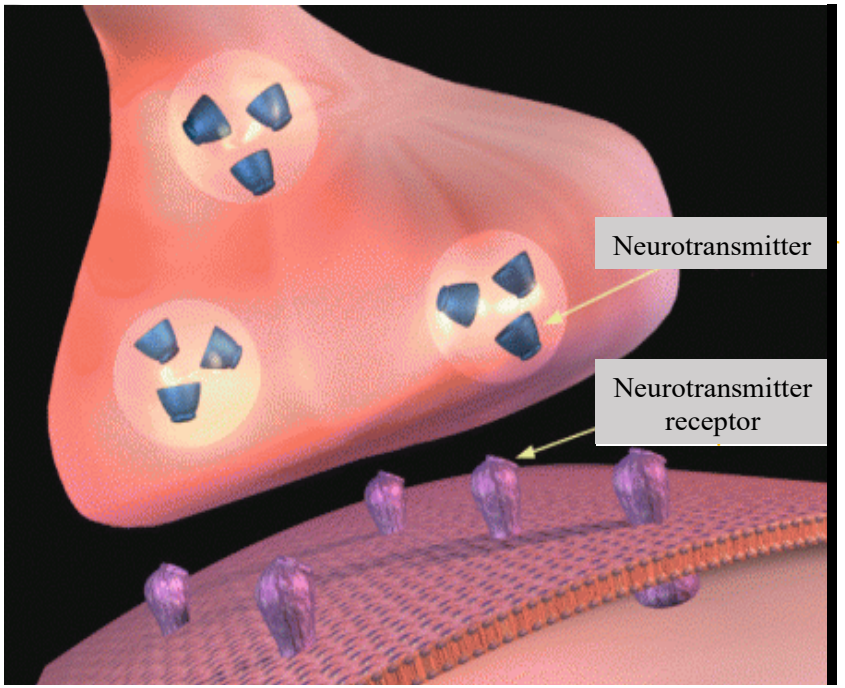
## *Neuromodulators Can Enhance Synaptic Transmission*

- Neurons communicate by releasing chemical neurotransmitters that bind to specific receptors on the adjacent neuron.
- Glutamate is the major excitatory neurotransmitter and GABA is the major inhibitory neurotransmitter.
- Neuromodulators do not act directly at the neurotransmitter binding site and have no intrinsic activity of their own, but instead act at accessory sites that enhance or reduce the actions of neurotransmitters.
- Neuromodulators offer the possibility of developing “kinder and gentler” neuropharmacological drugs with greater pharmacological specificity and reduced side effects



# EndeavourRx - Neuromodulators

RespireRx Pharmaceuticals Inc

## *Novel Brain Targeting Drugs*

### Ampakines (AMPA Glutamate Receptor Positive Allosteric Modulators)

- 3 Successful phase 2A trials for CX1739 and CX717 demonstrate target engagement
- Successful Phase 2A trial for CX717 in adult ADHD
- Successful pre-clinical studies in spinal cord injury (SCI) and Phase 2 clinical trial planned with Miami Project at Univ. Miami School of Medicine and others
- Planning Phase 2 trials in ADHD and orphan indications

### GABAkines ($GABA_A$ Receptor Positive Allosteric Modulators)

- Efficacious in multiple animal models of treatment resistant epilepsy
- Efficacy in isolated brain slices from epileptic patients
- Efficacy in animal models of neuropathic pain
- Lead is druggable and ready for pre-clinical development

# AMPA Glutamate Receptor Structure

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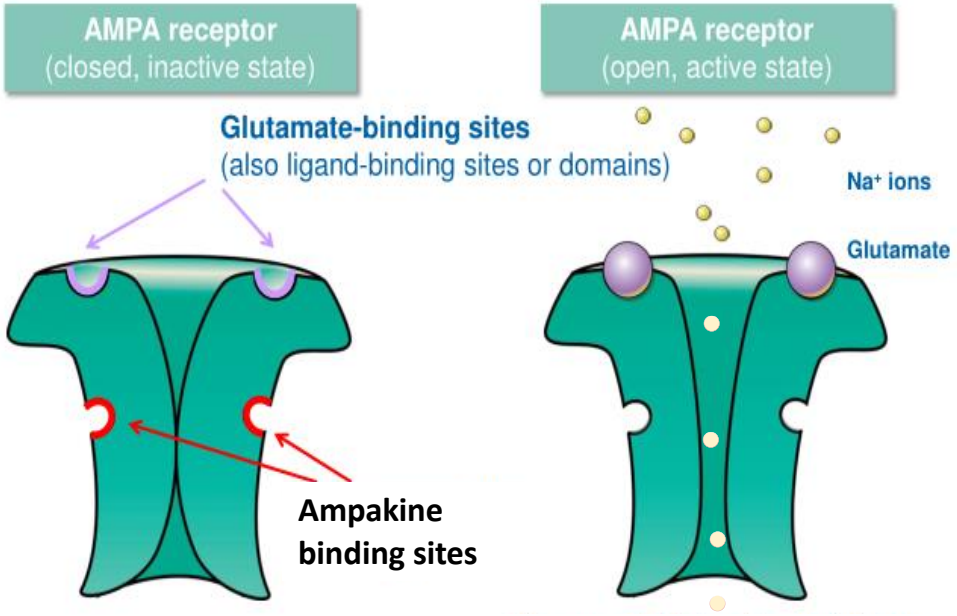
- The AMPA receptor is composed of four transmembrane proteins that form a pore, which when activated by glutamate opens and allows positive ions to enter the cell.
- Ampakine binding sites are located adjacent to the glutamate binding sites and increase the normal excitatory response to glutamate.
- As opposed to direct acting agonists that constantly bombard the glutamate binding site in a non-physiological manner, ampakines act by enhancing the natural actions of glutamate.
- ***The AMPA receptor proteins are heterogeneous and form various combinations allowing for subtype specificity and neuroanatomical and pharmacological selectivity.***




The receptors ion channel allows influx of $Na^+$ and $Ca^{2+}$ ions into the neuron

# Low Impact Ampakines: Targeting Markets with High Unmet Medical Need

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- **Attention Deficit Hyperactive Disorder (ADHD) – Phase 2B Ready**
- **Spinal Cord Injury – Phase 2A Ready**
- **Orphan Diseases – Phase 2A Ready**

**2nd and 3rd Generation Low Impact Ampakines Are Devoid of the Neurotoxicity Observed with High Impact Ampakines**

# Translational Approach: Conduct Clinical Trials

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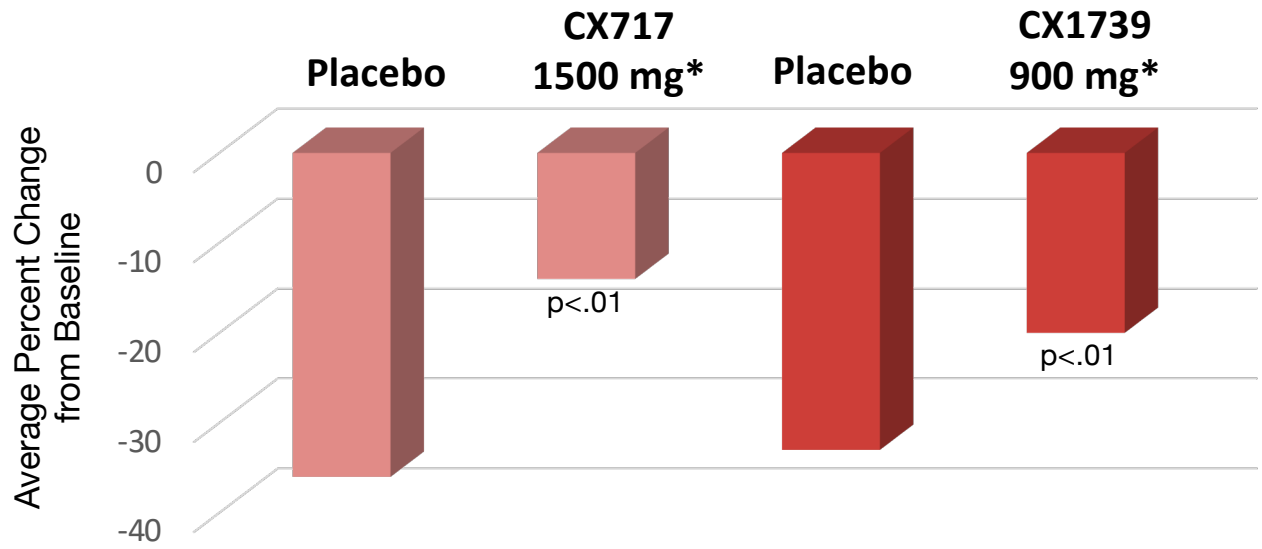
## *Ampakines Reduce Opioid-Induced Respiratory Depression in Phase 2A Clinical Trials*




*** Approximately 15 and 10 mg/kg on a weight basis, respectively; comparable to animal doses**

**Validation of Doses for Target Engagement**

# Ampakines for the Treatment of ADHD

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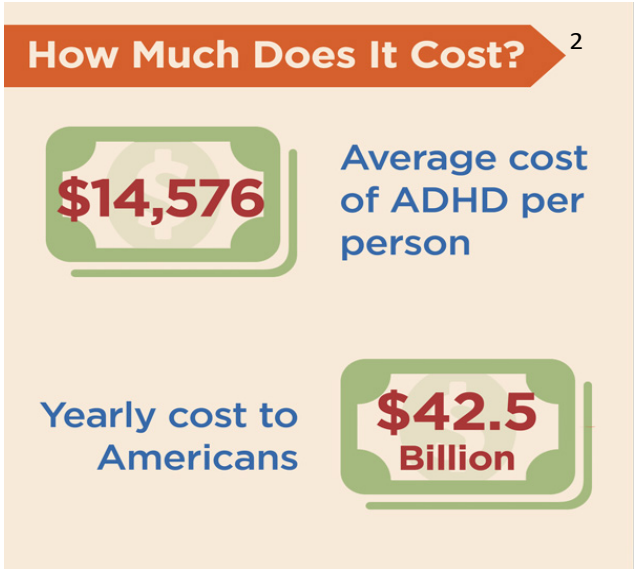
- Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.1% to 4.4% in the US. [1]
- An estimated 10 million adults have ADHD.
- ADHD in adults is characterized by symptoms of inattention, impulsivity, and restlessness, resulting in functional impairment.




[1] Kessler, Adler, Barkley. **The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication**. American Journal of Psychiatry 2006; 163(4):724-732
[2] Pelham et al. **The economic impact of attention-deficit/hyperactivity disorder in children and adolescents.** J Pediatr Psychol. 2007 Jul;32(6):711-27. Epub 2007 Jun 7

# CX717 Shows Significant Improvement in ADHD

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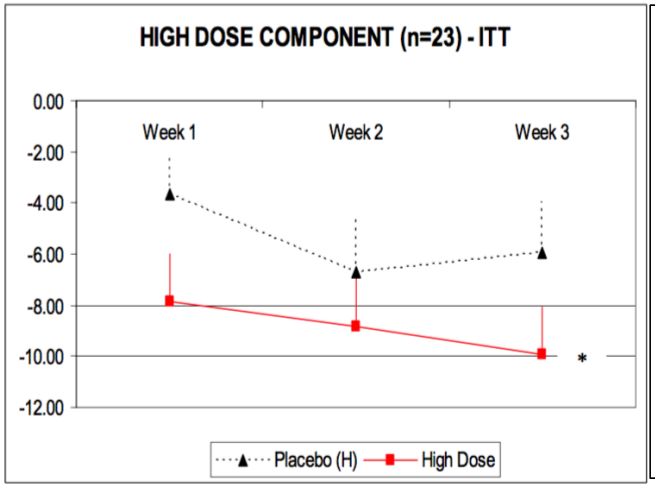
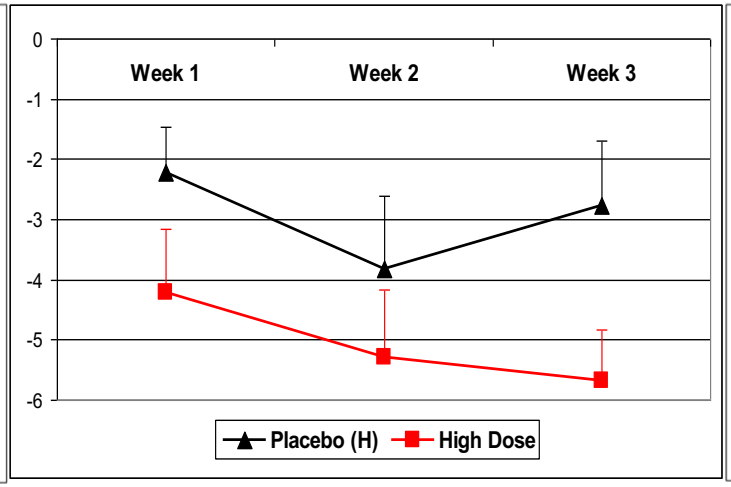
## OVERALL ADHR-RS



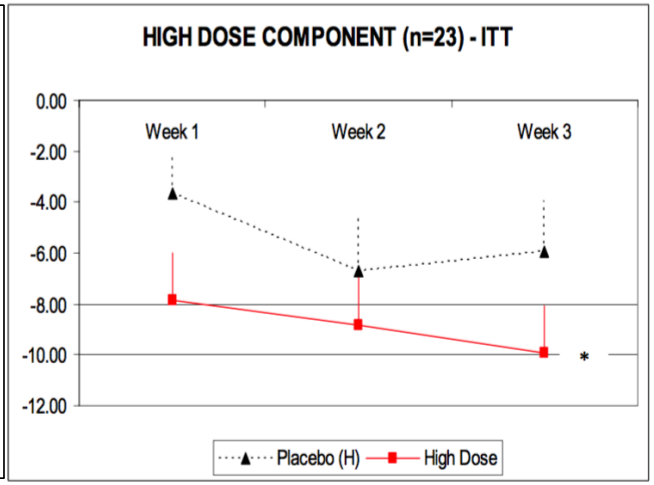

Mean Change from baseline
* Repeated measures analysis , p=0.002

## HYPERACTIVITY




Mean Change from baseline
* Repeated measures analysis , p<0.05

## INATTENTIVENESS




Mean Change from baseline
* Repeated measures analysis , p<0.04

**Phase 2 Study of CX717 in Adult ADHD**: Randomized, double-blind, multi-center, 2-period crossover study that compared 2 doses of CX717 (200 or 800 mg BID) with placebo. Statistically significant effects were observed with 800 mg as early as week 1.

# CX1739 Development Program: Spinal Cord Injury (SCI)[1]

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- **Approximately 288,000 people in US with SCI and 12,500 new cases per year**
- **Treatment costs are prohibitively high and continue for LIFE**
  - **For example, ~$3.4 Million cost for low tetraplegia injury at 25 years old**
- **<1% patients experience complete neurological recovery at time of hospital discharge**
- **Orphan Drug Opportunity**
  - **<200,000 patients with targeted indication of incomplete SCI**

National Spinal Cord Injury Statistical Center, Facts and Figures at a Glance. Birmingham, AL: University of Alabama at Birmingham, 2018.

# Acute doses of CX717 Improve Motor Neuron Firing in Animal Models of Spinal Cord Injury

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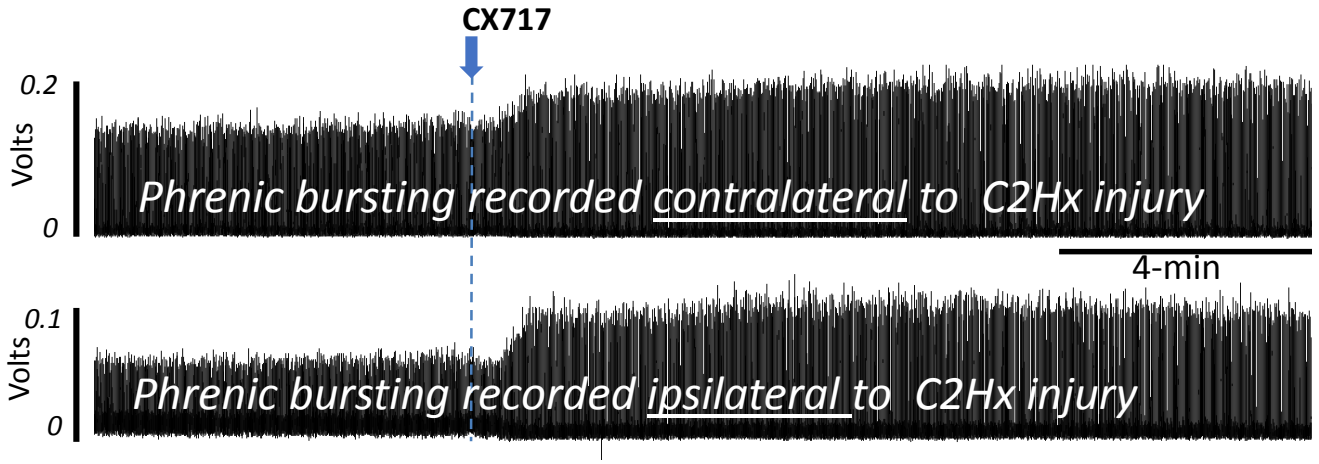
Unilateral hemi-transections at the level of the 2nd cervical vertebra are performed on rats and electrical activity is recorded from phrenic nerves, which innervate the diaphragm and contribute to the regulation of breathing.

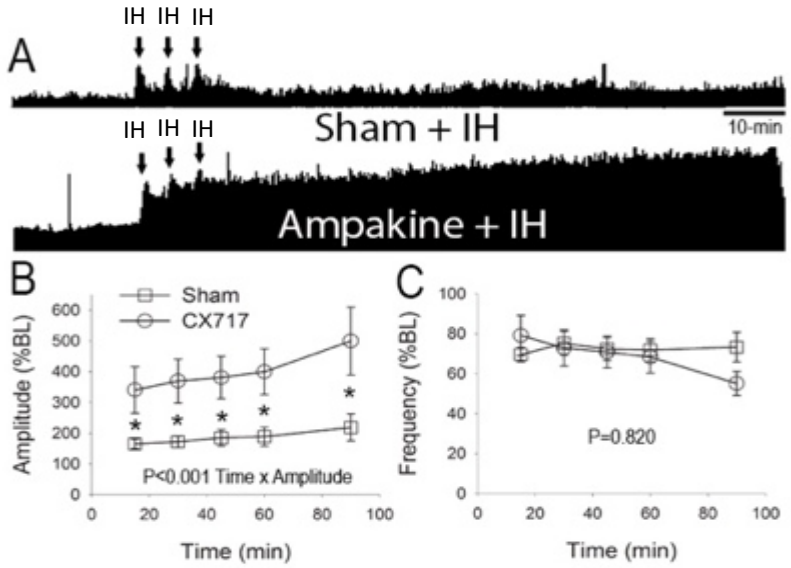



8 weeks following surgery, CX717 (15 mg/kg) increases amplitude in electrical recordings taken from rat phrenic nerves

# CX717 + Acute Intermittent Hypoxia (IH) vastly Improves Motor Neuron Firing

RespireRx Pharmaceuticals Inc

Unilateral hemi-transections at the level of the 2nd cervical vertebra are performed on rats and electrical activity is recorded from phrenic nerves, which innervate the diaphragm and contribute to the regulation of breathing.




8 weeks following surgery, CX717 (15 mg/kg) increases amplitude in electrical recordings taken from rat phrenic nerves

# Next Step: Phase 2 Clinical Trial
# CX1739 +/- AIH in the Treatment of SCI

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***Blinded, Placebo-controlled, Escalating-dose Study of CX1739, With and Without Acute Intermittent Hypoxia (AIH), in Patients with Incomplete Spinal Cord Injury***

**Primary Objectives**

1. Evaluate the safety of acute and multiple daily doses of CX1739 in patients with SCI
2. Evaluate the safety of CX1739 in Combination with AIH in Patients with SCI

**Secondary Objectives**

1. Evaluate the effect of acute and multiple BID doses of CX1739 on motor function and recovery, with and without AIH in patients with SCI
2. Assess the impact of CX1739 on SCI EDGE outcomes measures as appropriate

**RespireRx is working with academic collaborators including the Miami Project at Univ. Miami School of Medicine, University of Florida, The Shirley Ryan Ability Lab and the North American Clinical Trials Network to advance the development of CX1739 for the treatment of spinal cord injury**

# $GABA_A$ Receptor Structure

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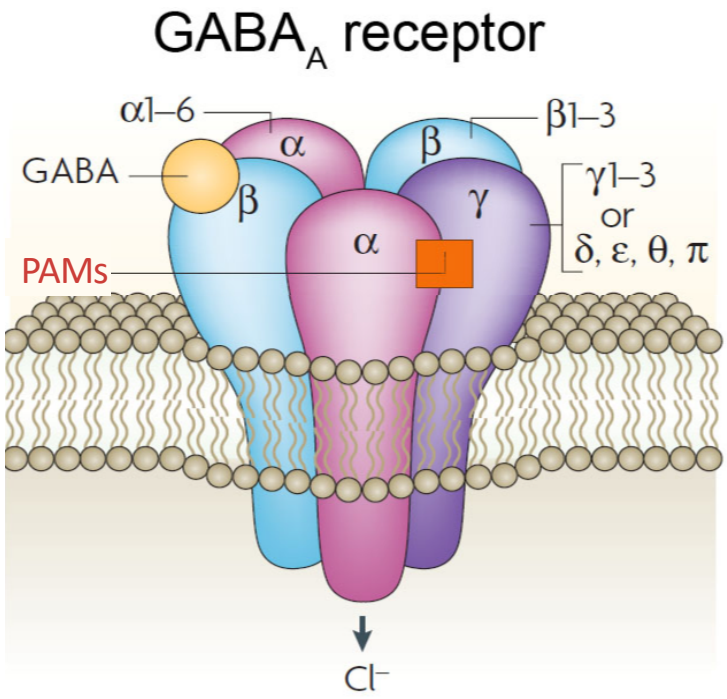
- The $GABA_A$ receptor is composed of five transmembrane proteins that form a pore, which when activated by GABA opens and allows chloride to enter the cell.
- $GABA_A$ Positive Allosteric Modulators (PAM) binding sites are located adjacent to the GABA binding sites and increase the normal inhibitory response to GABA.
- As opposed to direct acting agonists that constantly bombard the GABA binding site in a non-physiological manner, PAMs act by enhancing the natural actions of GABA.
- The GABA receptor proteins are heterogeneous and form various combinations allowing for subtype specificity and neuroanatomical and pharmacological selectivity.



# $GABA_A$ Receptor Heterogeneity

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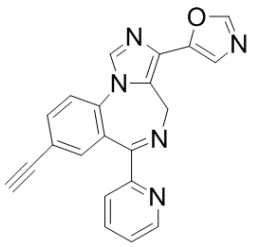
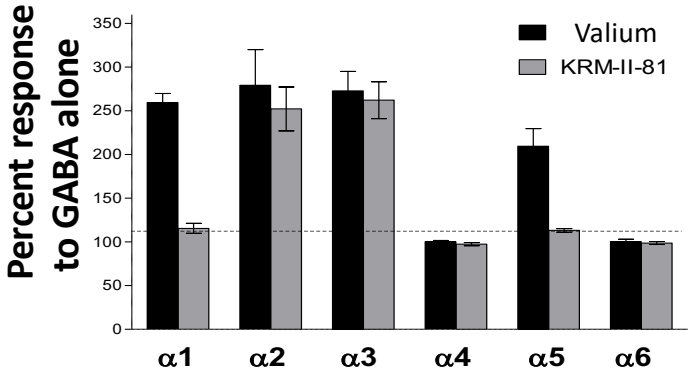
KRM-II-81 is a Selective Potentiator of α2/3-containing $GABA_A$ Receptors Tuned to Treat Pharmaco-resistant Epilepsy




KRM-II-81




**Unlike Valium, KRM-II-81 selectively potentiates GABA at α2/3 receptor subtypes but not at α1 or α5**

# Pharmaco-Resistant Epilepsy

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- Standard of care agents do not fully control epilepsies and have a variety of side-effect and safety issues including sedation, dizziness, cognitive impairment, and weight gain.
- Patients typically take multiple antiepileptic drugs to increase the probability of seizure control and yet many patients continue to have seizures.
- The continued occurrence of seizure activity not only puts the patient at risk, but each new seizure event increases the probability of subsequent epileptic events through sensitization mechanisms called seizure kindling.
- Pharmaco-resistant seizures are life-disrupting and life-threatening
- Pharmaco-resistant epilepsy may require surgical resection of affected brain tissue

# Superior Anti-convulsant Efficacy of KRM-II-81 over Standard of Care

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- **Broad Anticonvulsant Effects in Animal Models**
  - - 9 acute rodent models
  - - 2 chronic rodent models
  - - 3 pharmaco-resistant models
  - - 2 anti-epileptogenic models - unlike many anticonvulsants
  - - Better than standard of care
- **Reduced side-effects enabling higher plasma concentrations for therapeutic effect**
  - - Reduced sedation and motor impairment
  - - Reduced abuse liability
- **Also impacts co-morbid conditions**
  - Anxiety and depression
  - Chronic Pain

# Translational Results Predict Human Efficacy

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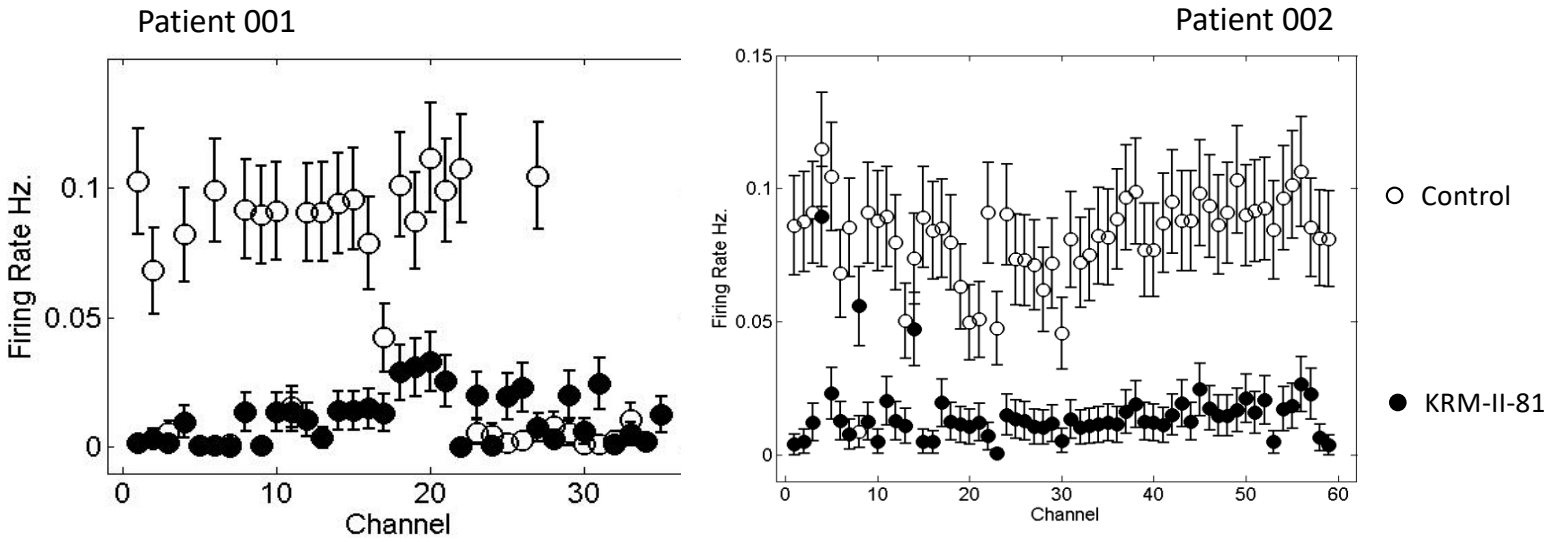
## *KRM-II-81 Reduces Epileptiform Activity in Cortical Slices from Juvenile Epileptic Patients*




Electrical recordings were made from epileptic brain tissues removed from juvenile patients with pharmaco-resistant epilepsy. Data presented with the approval of the parents

*Reference - Witkin et al, Brain Res. 1722 (2019) 146356

# Chronic Pain – Neuropathic and Inflammatory

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- Unmet need
- Opioid limitations – respiratory depression, tolerance, addiction, abuse, side effects such as sedation
- GABAergic drugs such as GABApentin and Neurontin – limited efficacy, side effects, dysphoria, partial tolerance

# Pharmacological Properties of KRM-II-81

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- **Broad anticonvulsant effects in animal models of epilepsy**
- **Broad analgesic effects in animal models of neuropathic and inflammatory pain**
- **Lack of Tolerance**
- **Reduced sedation and motor impairment enabling higher doses to achieve therapeutic effect**

# RespireRx – Summary of Assets

***HMS Discovery***

# A Wealth of Potential Products

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## ***Pharmaceutical Cannabinoids***

### *Dronabinol (Δ9-THC)*

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## ***Neuromodulators - Novel Brain Targeting Drugs***

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- Efficacy in animal models of neuropathic pain
- Lead is druggable and ready for pre-clinical development

# RespireRx – Summary of Assets

- **Highly desirable assets – advancing clinical programs and IP**
- **World Class Management Team and Board of Directors**
- **Expanding portfolio of novel products across multiple therapeutic categories and indications**
- **Broad flexibility in modeling mechanisms of investment**
- **Funding commitments secured through 2021**
- **Exemplary regulatory and financial compliance history with government agencies**
- **Key clinical supply chains established**
- **Strategic Partners afforded the opportunity to share in the financial growth from early clinical to commercialization**

# RespireRx Pharmaceuticals Inc

OTC QB: RSPI


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