RespireRx Pharmaceuticals Inc. Announces Publication of Review Article Describing Advances in the Discovery, Development and Commercialization of GABAkines, Including KRM-II-81

Glen Rock, N.J., December 6, 2021 /Globe Newswire – RespireRx Pharmaceuticals Inc. (OTCQB: RSPI) ("RespireRx" or the "Company"), a leader in the discovery and development of innovative and revolutionary treatments to combat diseases caused by disruption of neuronal signaling, is pleased to announce that scientists associated with the Company have published a review article entitled "GABAkines – Advances in the discovery, development, and commercialization of positive allosteric modulators of $GABA_A$ receptors" in the peer reviewed journal *Pharmacology and Therapeutics* (Elsevier, https://doi.org/10.1016/j.pharmthera.2021.108035). The multidisciplinary team of authors was led by Drs. James M. Cook and Jeffrey M. Witkin, both of whom are RespireRx Research Fellows and Dr. Rok Cerne, RespireRx Senior Research Scientist, in addition to their academic affiliations at University of Wisconsin-Milwaukee, Ascension St. Vincent and Indiana University/Purdue University, respectively. Authors also include Arnold Lippa, RespireRx Executive Chairman and Chief Scientific Officer, Michael M. Poe, Jodi L. Smith, Xiaoming Jin, Xingjie Ping and Lalit K. Golani.

This article discusses the history, evolution and present day development of GABAkines, a term which refers to a broad class of drugs that produce their pharmacological properties by enhancing the actions of the neurotransmitter GABA, the major inhibitory neurotransmitter in the brain, at $GABA_A$ receptors. Traditional GABAkines such as the benzodiazepines (BDZ) Valium® (diazepam), Librium® (chlordiazepoxide) and Xanax® (alprazolam) have been widely used medicines for over 70 years for the treatment of anxiety, epilepsy, sleep, and other disorders. Unfortunately, because GABA is found throughout the brain and BDZ indiscriminately act upon all $GABA_A$ receptors, they also produce undesirable side effects such as sedation, motor-impairment, tolerance, dependence and abuse, which have raised concerns regarding their safety and tolerability.

As a result of the prior research of Dr. Lippa identifying specific subtypes of $GABA_A$ receptors, hopes were raised regarding the possibility that different subtypes might be responsible for the different pharmacological properties produced by $GABA_A$ receptor activation. Shortly thereafter, Dr. Lippa identified novel compounds that, unlike like the broadly acting BDZ, acted upon a specific $GABA_A$ subtype and produced anti-anxiety effects in animals and humans without the attendant sedation and motor impairment common to BDZ. While clinical development of these compounds was halted due to potential liver enzyme concerns, they nevertheless encouraged considerable research and development into $GABA_A$ receptor subtype specific drugs. This article describes the current state of GABAkines undergoing development, including KRM-II-81, the Company's lead GABAkine.

KRM-II-81, originally synthesized by Dr. Cook, is being developed by the Company's EndeavourRx business unit because of its ability to selectively amplify inhibitory neurotransmission at a highly specific, subset of $GABA_A$ receptors, thus producing a unique efficacy profile with reduced side effects. Preclinical studies have documented its efficacy in a broad array of animal models of interrelated neurological and psychiatric disorders including epilepsy, pain, anxiety, and depression in the absence of or with greatly reduced propensity to produce sedation, motor-impairment, tolerance, dependence and abuse. The Company currently is focusing on developing KRM-II-81 for the treatment of epilepsy and pain.

As described in the article, KRM-II-81 has displayed a high degree of anti-convulsant activity in a broad range of preclinical studies, including in treatment resistant and pharmaco-resistant models. Treatment resistant models are used to predict efficacy in difficult to treat forms of epilepsy. Pharmaco-resistance occurs when medications that once controlled seizures lose efficacy as a result of chronic use and it is a principle reason some epileptic patients require brain surgery to control their seizures. Not only was KRM-II-81 highly effective in treatment resistant and pharmaco-resistant models, but pharmaco-resistance did not develop to its anti-convulsant properties. These latter results are particularly important because, while BDZ are front-line treatment for seizures, their chronic use for epilepsy is limited due to the rapid development of tolerance. In support of its potential clinical efficacy, translational studies have demonstrated the ability of KRM-II-81 to dramatically reduce epileptiform electrical activity when administered *in situ* to brain slices excised from treatment resistant epileptic patients undergoing surgery.

In addition, KRM-II-81 has displayed a high degree of analgesic activity in a broad range of preclinical studies. In cellular studies, KRM-II-81 preferentially bound to specific subtypes of $GABA_A$ receptors and boosted the ability of GABA to inhibit pain sensory neurons in the spinal dorsal root ganglia. In intact animal models of acute and chronic pain, the analgesic efficacy of KRM-II-81 was comparable to or greater than commonly used analgesics. At the same time, KRM-II-81 did not display side effects such as sedation and motor impairment, but even more importantly, it did not produce tolerance, dependence, respiratory depression or behavioral changes indicative of abuse liability, which are produced by opioid narcotics and are at the heart of the opioid epidemic.

Dr. Witkin commented, "We believe that the expansion of our knowledge regarding how GABA functions through its various receptors has created a new surge in the discovery and development of GABAkines targeted at specific $GABA_A$ receptors, and with it comes the promise of improved medicines for neurological and psychiatric disorders."

Dr. Lippa added, "We are very excited about developing KRM-II-81 and going forward into IND enabling studies. Pending clinical validation, we believe that KRM-II-81 has the potential to represent a breakthrough treatment for epilepsy as well as the long sought after alternative to narcotic analgesics for chronic pain."

About RespireRx Pharmaceuticals Inc.

RespireRx Pharmaceuticals Inc. is a leader in the discovery and development of medicines for the treatment of psychiatric and neurological disorders, with a focus on treatment options that address conditions affecting millions of people, but for which there are few or poor treatment options, including obstructive sleep apnea ("OSA"), attention deficit hyperactivity disorder ("ADHD"), epilepsy, chronic pain and recovery from spinal cord injury ("SCI"), as well as certain neurological orphan diseases. RespireRx is developing a pipeline of new and re-purposed drug products based on our broad patent portfolios for two drug platforms: (i) pharmaceutical cannabinoids, which include dronabinol, a synthetic form of Δ9-tetrahydrocannabinol ("Δ9-THC") that acts upon the nervous system's endogenous cannabinoid receptors and (ii) neuromodulators, which include AMPAkines and GABAkines, new, proprietary chemical entities that positively modulate (positive allosteric modulators or "PAMs") AMPA-type glutamate receptors and $GABA_A$ receptors, respectively.

The Company holds exclusive licenses and owns patents and patent applications or rights thereto for certain families of chemical compounds that claim the chemical structures and their uses in the treatment of a variety of disorders, as well as claims for novel uses of known drugs.

***ResolutionRx: Pharmaceutical Cannabinoids*.**

Dronabinol. RespireRx is developing dronabinol, Δ-9-THC, a synthetic version of the naturally occurring substance in the cannabis plant, for the treatment of OSA, a serious respiratory disorder that impacts an estimated 29.4 million people in the United States according to the American Academy of Sleep Medicine ("AASM"), published in August 2016. OSA has been linked to increased risk for hypertension, heart failure, depression, and diabetes, and has an annual economic cost in the United States of $162 billion according to the AASM. There are no approved drug treatments for OSA.

Two Phase 2 clinical trials have been completed demonstrating the ability of dronabinol to significantly reduce the symptoms of OSA and, subject to raising sufficient financing (of which no assurance can be provided) and pending the outcome of an intended meeting with the FDA, RespireRx believes that it will be able to commence a pharmacokinetic study for a recently discovered and to-be-developed formulation followed by a Phase 3 clinical study for the treatment of OSA with the new formulation. Because dronabinol is already FDA approved for the treatment of AIDS related anorexia and chemotherapy induced nausea and vomiting, the Company further believes that its re-purposing strategy would only require approval by the FDA of a 505(b)(2) new drug application ("NDA"), an efficient regulatory pathway that allows the use of publicly available data.

EndeavourRx: Neuromodulators

GABAkines. Under a License Agreement with the University of Wisconsin-Milwaukee Research Foundation, Inc. ("UWMRF"), an affiliate of the University of Wisconsin-Milwaukee, RespireRx has licensed rights to certain selectively acting GABAkines that have shown impressive activity in a broad range of animal models of pain, refractory/drug resistant epilepsy and other convulsant disorders, as well as in brain tissue samples obtained from epileptic patients. Epilepsy is a chronic and highly prevalent neurological disorder that affects millions of people world-wide. While many

anticonvulsant drugs have been approved to decrease seizure probability, seizures are not well controlled and, in as many as 60-70% of patients, existing drugs are not efficacious at some point in the disease progression. We believe that the medical and patient community are in clear agreement that there is desperate need for improved antiepileptic drugs. In addition, these GABAkines have shown positive activity in animal models of migraine, inflammatory and neuropathic pain, as well as other areas of interest. Because of their GABA receptor subunit specificity, the compounds have a greatly reduced liability to produce sedation, motor incoordination, memory impairments and tolerance, side effects commonly associated with non-specific GABAkines, such as Valium® and Xanax®.

AMPAkines. Through an extensive translational research effort from the cellular level through Phase 2 clinical trials, the Company has developed a family of novel, low impact AMPAkines, including CX717, CX1739 and CX1942 that may have clinical application in the treatment of CNS-driven neurobehavioral and cognitive disorders, spinal cord injury, neurological diseases, and certain orphan indications. From our AMPAkine platform, our lead clinical compounds, CX717 and CX1739, have successfully completed multiple Phase 1 safety trials. Both compounds have also completed Phase 2 proof of concept trials demonstrating target engagement, by antagonizing the ability of opioids to induce respiratory depression.

AMPAkines have demonstrated positive activity in animal models of ADHD, results that have been extended translationally into statistically significant improvement of symptoms observed in a Phase 2 human clinical trial of CX717 in adults with ADHD. At present, the major pharmacotherapies available for ADHD are made up of two types of drugs. Stimulants, such as amphetamine, rapidly produce robust effects, but suffer from side effects typical of stimulants, including tolerance, dependence, withdrawal and abuse. For these reasons, stimulants are scheduled by the FDA. Non-stimulants, such as Straterra® (atomoxetine) tend to be less effective than stimulants, with a much longer (approximately 4 – 8 week) latency to onset of action. In a number of animal and human studies, CX717 and other AMPAkines did not display any stimulant properties typically associated with drugs like amphetamine. In the Phase 2 ADHD clinical trial, statistically significant therapeutic effects were observed within one week. Therefore, we believe AMPAkines may represent a novel, non-stimulant treatment for ADHD with a more rapid onset of action than alternative non-stimulant treatment options.

Additional information about RespireRx and the matters discussed herein can be obtained on the Company's web-site at www.RespireRx.com or in the Company's filings with the Securities and Exchange Commission at www.sec.gov.

Not a Securities Offering or Solicitation

This communication shall not constitute an offer to sell or the solicitation of an offer to buy any securities, nor shall there be any sales of securities in any jurisdiction in which such offer, solicitation or sale of securities would be unlawful before registration or qualification under the laws of such jurisdiction.

Cautionary Note Regarding Forward-Looking Statements

This press release contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act") and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and the Company intends that such forward-looking statements be subject to the safe harbor created thereby. These might include statements regarding the Company's future plans, targets, estimates, assumptions, financial position, business strategy and other plans and objectives for future operations, and assumptions and predictions about research and development efforts, including, but not limited to, preclinical and clinical research design, execution, timing, costs and results, future product demand, supply, manufacturing, costs, marketing and pricing factors.

In some cases, forward-looking statements may be identified by words including "assumes," "could," "ongoing," "potential," "predicts," "projects," "should," "will," "would," "anticipates," "believes," "intends," "estimates," "expects," "plans," "contemplates," "targets," "continues," "budgets," "may," 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 products candidates, (iv) reorganization plans, and (v) the need for, and availability of, additional financing. 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 in this press release.

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, and other risk factors disclosed in "Item 1A. Risk Factors" in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2020, as filed with the SEC on April 15, 2021 (the "2020 Form 10-K").

You should read these risk factors and the other cautionary statements made in the Company's filings as being applicable to all related forward-looking statements wherever they appear in this press release. We cannot assure you that the forward-looking statements in this press release will prove to be accurate and therefore prospective investors, as well as potential collaborators and other potential stakeholders, are encouraged not to place undue reliance on forward-looking statements. You should read this press release completely. Other than as required by law, we undertake no obligation to update or revise these forward-looking statements, even though our situation may change in the future.

We caution investors, as well as potential collaborators and other potential stakeholders, not to place undue reliance on any forward-looking statement that speaks only as of the date made and 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, due to the risks and uncertainties described in the 2020 Form 10-K and in this press release, as well as others that we may consider immaterial or do not

anticipate at this time. 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, including those described in the 2020 Form 10-K and in this press release. These risks and uncertainties are not exclusive and further information concerning us and our business, including factors that potentially could materially affect our financial results or condition, may emerge from time to time.

For more information about the risks and uncertainties the Company faces, see "Item 1A. Risk Factors" in our 2020 Form 10-K. Forward-looking statements speak only as of the date they are made. The Company does not undertake and specifically declines any obligation to update any forward-looking statements or to publicly announce the results of any revisions to any statements to reflect new information or future events or developments. We advise investors, as well as potential collaborators and other potential stakeholders, to consult any further disclosures we may make on related subjects in our annual reports on Form 10-K and other reports that we file with or furnish to the SEC.

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