Three High Profile Publications Support the Potential of Protagenic Therapeutics's Synthetic TCAP to Treat Stress-Related Psychological Disorders

Ancient, central role of brain peptide TCAP in maintenance of brain health elucidated in publications in Cell, Nature Communications, and the Journal of Neuro-endocrinology

NEW YORK, June 11, 2018 (GLOBE NEWSWIRE) -- Protagenic Therapeutics, Inc. (OTCQB: PTIX) announced today that the naturally-occurring brain peptide upon which its lead drug compound, PT00114, is based, known scientifically as teneurin C-terminal associated peptide (TCAP), has been featured in three peer-reviewed publications in major scientific journals.

Li *et al.* (2018) in a paper in *Cell* provide definitive evidence that TCAP (a portion of the brain protein teneurin, expressed on the surface of neurons) signals to adjacent nerve cells through G-protein-couipled receptors termed latrophilins. This signal stabilizes neuronal connections in regions of the brain involved in fear, memory, emotion, and stress responses. The dependence of this signaling on the TCAP portion of teneurin and the role of latrophilin are both demonstrated. This helps solidify the mechanism of action of Protagenics' clinical development candidate PT00114, which is a synthetic form of TCAP, heading toward clinical trials in 2019. PT00114 has been shown to ameliorate a broad range of stress-related behavioral disorders in rodents. This Cell publication supports the view that PT00114 is exerting its anti-stress activities through latrophilins. This paper supports work from the laboratory of Dr. David Lovejoy, Protagenic's scientific founder, implicating latrophilins as the receptors for TCAP and PT00114.

Additionally, a paper in *Nature Communications* (Jackson et al., 2018) has shed light on the possible evolutionary origins of TCAP. TCAP has been present in animals for more than 300 million years, with astonishingly little change in its sequence. This strongly indicates that it carries out some essential functions, since there must be intense selective pressure during evolution to maintain its protein sequence with so little change. Its role in the maintenance of effective cell-to-cell communications, and in particular in stabilizing interactions between nerve cells could be one such essential function. Jackson et al. observe the structural relatedness of TCAP to some bacterial proteins, suggesting that deep in the evolutionary past of multi-cellular animals, TCAP may have originated from a "bacterial hitchhiker", analogous to the evolutionary origin of mitochondria from the incorporation into eukaryotic cells of free-living archaebacteria.

Protagenic Therapeutics is developing PT00114 as a therapeutic for anxiety, depression, post-traumatic stress disorder (PTSD) and addiction. Many of these disorders have been shown to be associated with impaired glucose metabolism in the brain. The third recent TCAP publication, by Hogg et al. (*Journal of Neuroendocrinology,* 2018) demonstrates pharmacologically administered synthetic TCAP increases glucose uptake in brain neurons. Since glucose is the principal energy fuel for brain function, this suggests that administered TCAP has potential to restore disordered nerve function in settings such as depression where it has been found to be deficient.

Previous studies indicate that TCAP and the teneurins, arose very early in animal evolution of animals and play critical roles in intercellular communication. These three recent publications highlight TCAP as a venerable peptide which plays a central role in maintaining healthy function in the brain, counteracting the negative effects of environmental stress, restoring neuronal activity and connectivity. Protagenic's development candidate PT00114, uniquely amongst new drugs, activates this natural system for combatting environmental stress. This series of publications provides insights regarding its ancient origins and its position as one of the earliest neuropeptides, consistent with its perceived function to reduce the impact of environmental stress and the resulting negative behavioral consequences.

The full citations of the three articles are:

Li, J., Shalev-Benami, M., Sando, R., Jiang, X., Kibrom, A., Wang, J. et al. (2018). Structural basis for teneurin function in circuit-wiring: A toxin motif at the synapse. ***Cell*** April 19, 2018, 173(3): 735-748.

Jackson, V.A., Meijer, D.H., Carrasquero, M., van Bezouwen, L.S., Lowe, E.D., Kleanthous, C. et al. (2018). Structure of teneurin adhesion receptors reveal an ancient fold for cell-cell interaction. ***Nature Communications*** Mar 14th, 2018, 9(1): 1079.

Hogg, D.W., Chen, Y., D'Aquila, A.L., Xu, M., Husić, M., Tan, L.A. et al. (2018). A novel role of the corticotrophin-releasign hormone regulating peptide, teneurin C-terminal associated peptide 1, on glucose uptake in the brain. ***J. Neuroendocrinol*** April 2018, 30(4)

About Protagenic Therapeutics, Inc.

Protagenic Therapeutics, Inc. (OTCQB: PTIX) is a pre-clinical biopharmaceutical company endeavoring to develop first-in-class neuro-active peptides into human therapeutics to treat anxiety, treatment-resistant depression, addiction, and other disorders. For more information, visit http://www.protagenic.com.

Forward-Looking Statements

This press release contains forward-looking statements that are made pursuant to the safe harbor provisions of the federal securities laws, including statements regarding Protagenic Therapeutics' product candidates and pre-clinical development and clinical trial plans and activities. Forward-looking statements include words such as "expects," "anticipates," "intends," "plans," "could," "believes," "estimates" and similar expressions. These forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially. These risks and uncertainties include, among others, our ability to obtain additional capital to meet our liquidity needs on acceptable terms, or at all, including the additional capital which will be necessary to complete the pre-clinical testing and eventual clinical trials of our product candidates; our ability to successfully complete research and further development and commercialization of our product candidates; the uncertainties inherent in pre-clinical and clinical testing; the timing, cost and uncertainty of obtaining regulatory approvals; our ability to protect the Company's intellectual property; the loss of any executive officers or key personnel or consultants;

competition; changes in the regulatory landscape or the imposition of regulations that affect the Company's products; and the other factors described under the Risk Factors section of our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission.. Protagenic Therapeutics cautions investors not to place considerable reliance on the forward-looking statements contained in this release. These statements speak only as of the date of this press release, and Protagenic undertakes no obligation to update or revise the statements, other than to the extent required by law. All forward-looking statements are expressly qualified in their entirety by this cautionary statement.

Press Contact:
Protagenic Therapeutics, Inc.
Alexander K. Arrow, MD, CFA
213-260-4342
alex.arrow@protagenic.com