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NEW YORK STATE OF OPPORTUNITY. New York State Psychiatric Institute

Christine Ann Denny, Ph.D.
Associate Professor
Department of Psychiatry
Columbia University Irving Medical Center (CUIMC)

Research Scientist VI
Division of Systems Neuroscience
New York State Psychiatric Institute (NYSPI)

T32 Program Director
Translational Neuroscience Post-doctoral T32 Program

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RE: Letter of support for the development and certification of FENM for the treatment and prevention of PTSD and other brain disorders

Dear Gilles,

I am writing this letter to offer my strongest and most enthusiastic support for the project being developed by ReST Therapeutics. Since we began a collaboration many years ago, I have come to know you very well and have thoroughly enjoyed working with you. I am delighted to express my support for this project, regarding these innovative therapies for PTSD and other neurodegenerative diseases.

As you know, I am an Associate Professor of Psychiatry at Columbia University Irving Medical Center (CUIMC) and a Research Scientist VI at the New York State Psychiatric Institute (NYSPI). My research interests focus on investigation in learning and memory in diseased states such as in aging, Alzheimer's disease (AD), depression, and post-traumatic stress disorder (PTSD). I have created an activity-dependent tagging system, the ArcCreER^{T2} mice, which allows for the permanent labeling of individual memory traces/engrams (e.g., Denny *et al*., 2014, *Neuron*). This allows us to compare memory formation (e.g., learning) ensembles and memory retrieval neural ensembles. We were the first to demonstrate the *necessity* of these ensembles by inhibiting learning ensembles during memory retrieval and my lab has now validated this model in a number of neurodegenerative settings. Our learning and memory work has been featured in *Neuron*, *Nature*, *Nature Neuroscience*, and *Biological Psychiatry* and has led to funding from numerous agencies to include the NIH, NIA, NINDS, Whitehall Foundation, and a Kavli Award. This work has also been featured on PBS NOVA, and in the Washington Post, The Atlantic, Scientific American, and Business Insider.

In addition to the aforementioned engram work, my laboratory is also developing small molecule compounds to prophylactically protect against stress. In this line of work, we have been elucidating the mechanisms of (*R*,*S*)-ketamine, novel NDMAR antagonists, and more recently, 5-HT$_4$R agonists as both prophylactics against stress and antidepressants. Our work has shown that a single injection of one of these compounds 1 week prior to stress is sufficient to protect against many of the deleterious effects of chronic and/or acute stress.

I know that ReST's lead candidate FENM is completely novel and innovative. FENM is a novel antagonist, which was initially designed as biomarker derived from memantine. At lower concentrations, it binds specifically to the GluN2C/2D subunit of the NMDA receptor. Together, we have shown that it is a novel and proprietary small molecule targeting NMDA receptors in order to decrease the deleterious effects of stress, without triggering adverse side effects like other NMDAR-targeting drugs. As you have discussed with me, FENM will enter first-in-Human studies in 2023 to determine the clinical effectiveness on PTSD.

Columbia University Irving Medical Center (CUIMC) Department of Psychiatry

1051 Riverside Drive, Unit 87, New York, NY 10032
Office: (646) 774-7100 Mobile: (201) 838-2363
E-mail: cad2125@cumc.columbia.edu

Of note, the uniqueness of our technology relies on the specificity of FEMN, which targets specific NMDAR subtypes (2C and 2D), that are beneficial to the pathology while not being active on the others (2A in particular) that may cause off-target effects. Thus, this selective modulation of NMDA subtypes, brings FENM as a first-in-class therapeutic to prevent the pathological consolidation of traumatic memories, while providing a favourable safety and tolerability profile, making FENM an ideal drug candidate as prophylactic solution as well as for treatment of long-term PTSD.

In summary, I believe that ReST's approach is highly innovative, and different from other approaches being developed in this field. It has a high chance of success given its past results in animal models (e.g., Chen *et al*., 2021, *Biological Psychiatry*). I have thoroughly enjoyed our friendship and frequent discussions. I am looking forward to continuing our collaboration on this fascinating project. I am available to provide REST Therapeutics with guidance on protocol parameters that are most suited for your behavioral experiments, and REST Therapeutics will have access to all the unique tools and equipment we have developed to establish this novel and important niche within the neuroscience community. I look forward to continuing working with you and providing you any assistance you may need.

Please don't hesitate to contact me if anything else is needed.

Sincerely,

Christine Ann Denny

Dr. Christine Ann Denny

Columbia University Irving Medical Center (CUIMC) Department of Psychiatry

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Office: (646) 774-7100 Mobile: (201) 838-2363
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