



Case #759

PAC1R Inhibitors for Treatment of Stress Related Disorders

The healthcare and loss of productivity costs of pain and stress related disorders now exceed those of cardiovascular disease, cancer and diabetes. More than 65 million adults are affected by anxiety disorders in the United States and Europe alone and healthcare costs in the US exceed \$42 billion a year. There are currently few therapeutic options to address this problem and what is available often fails to offer relief or produces undesirable side effects.

Pituitary adenylate cyclase-activating polypeptide (PACAP) signaling has been identified in multiple intersecting stress and pain associated pathologies, including PTSD, migraine, neuropathic and emotional pain and panic disorders. More specifically, antagonists that preferentially block the internalization and endosomal signaling of the G-protein coupled receptor (GPCR) pituitary adenylate cyclase-activating polypeptide receptor (PAC1R) have been shown to have high efficacy in attenuating these behavioral and pain disorders, but until now, no small molecule antagonists have been developed. GPCR structure-based drug design in Dr. Li's laboratory has identified several lead compounds, which show the necessary efficacy to have therapeutic potential in Dr. May's assays and in vivo stress/anxiety tests. Current work in Dr. Brewer's lab is modifying these leads to increase potency and specificity.

Applications:

- Treatment of stress and pain disorders.
- Inhibitors may treat PACAP mediated endocrine and metabolic disease as well.

Advantages:

- Novel therapeutic target for pain and stress disorders.
- First small molecule therapeutic antagonists of PAC1R.
- Non-opioid based treatment for pain and stress disorders.
- Efficacious in *in-vivo* models of stress, anxiety and pain sensitivity.

Intellectual Property and Development Status:

US Provisional Application 62/804874

Looking for both licensing and industry partners for lead optimization.

References:

Conformational Transitions of the Pituitary Adenylate Cyclase-Activating Polypeptide Receptor, a Human Class B GPCR, Liao C *et al* PMC5511175

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