



Speaker:

Jeanette Bertron, PhD



When:

**Friday, October 29th
1:00 pm**

Where:

**GLNN 212
And On Zoom
bit.ly/chicochem**

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Chemistry and Biochemistry

Fall 2021 Seminar

Please join us for the following seminar!

The Power of Basic Science in Therapeutic Development: an mAChR1 Story

Selective activation of the M1 subtype of muscarinic acetylcholine receptor (mAChR1), via positive allosteric modulation (PAM), is an exciting strategy to improve cognition in neurodegenerative disease patients. Unfortunately, highly potent M1 ago-PAMs, such as MK-7622, PF-06764427, and PF-06827443, can engender excessive activation of M1 that impair cognitive function, induce behavioral convulsions, and result in other classic cholinergic adverse effects. Here, we report a fundamentally new and highly selective M1 PAM, VU0486846. VU0486846 possesses weak agonist activity in M1-expressing cell lines with high receptor reserve and is devoid of agonist actions in native prefrontal cortex tissue, unlike previously reported ago-PAMs MK-7622, PF-06764427, and PF-06827443. As opposed to ago-PAMs, VU0486846 produces robust efficacy in the novel object recognition paradigm of cognitive function and we show, for the first time, that an M1 PAM can reverse the cognitive deficits induced by atypical antipsychotics, such as risperidone. These findings further strengthen the argument that compounds with modest in vitro M1 PAM activity and pure-PAM activity in native tissues, display robust procognitive efficacy without AEs mediated by excessive activation of M1.