**Triple reuptake inhibitor antidepressant candidates: Variations on the
PRC200 scaffold**

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Approximately 15% of the U.S. population is subject to depression; of those receiving pharmacotherapy, roughly 30-50% are resistant to treatment with serotonin-selective reuptake inhbitors (SSRIs) or serotonin/norepinephrine reuptake inhibitors (SNRIs).1 Combination therapy with SSRIs and bupropion (a norepinephrine/dopamine reuptake inhibitor) in the STAR\*D trial suggested improved antidepressant response and reduced side effects relative to monotherapy.2,3 Addition of a dopamine reuptake component to antidepressant therapy may also address anhedonia, and lead to a faster onset of action.1 PRC200 potently inhibits reuptake of all three neurotransmitters4 and like DOV21,9471 is considered a triple reuptake inhibitor. PRC200 was thus explored for its antidepressant-like activity, and was found to dose-dependently decrease immobility in the forced-swim test in rats and in the tail-suspension test in mice.4 Importantly PRC200 did not affect locomotion in mice or rats, and was not self-administered by rats.4 Based on these favorable results an extensive campaign was undertaken to improve the drug-like properties of PRC200 while retaining triple reuptake inhibition. Several compounds with promising pharmacological profiles were identified5 and will be disclosed in this poster.

**References**

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**Acknowledgement**

The compounds disclosed in this poster were developed with funding and collaboration from AstraZeneca; all rights to them reverted to Virginia Tech and the Mayo Foundation in 2012. We gratefully acknowledge partnership with Michael Wood and Thomas R. Simpson (AstraZeneca).