Discovery of First-in-Class Subtype Selective $GABA_A$ Alpha5 Positive Allosteric Modulators (PAMs) for the treatment of neurological disorders

Valerie Runtz-Schmitt, F. Hoffmann-La Roche AG

Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Grenzacherstrasse 124, 4070 Basel, Switzerland

valerie.runtz-schmitt@roche.com

$GABA_A$ receptors are ligand-gated chloride channels and the main mediators of inhibitory synaptic transmission in the human brain. There are 19 genes encoding for $GABA_A$ receptor subunits that assemble as pentamers, with the most common stoichiometry of two α, two β, and one γ subunit. The α5 subunit-containing $GABA_A$ receptors are of particular interest given their specific expression pattern and physiological properties.[1-3] Multiple lines of evidence suggest that excessive neural activity in selected brain regions with consequent imbalance between excitatory/inhibitory neurotransmission underlie a variety of neurological disorders such as epilepsy, Autism Spectrum Disorder (ASD), Schizophrenia and Alzheimer's disease. The presentation will highlight our effort to discover highly potent, selective $GABA_A$ α5 PAMs from a program that had delivered Basmisanil,[4] a negative allosteric modulator (NAM) in the clinics. Key medicinal chemistry concepts involved in the optimization of the ligands and structural determinants underlining the NAM-to-PAM switch will be discussed. Finally, optimization of a structurally differentiated series, to serve as a back-up of isoxazole-ether Alogabat will be presented.

1. Sur, C.; Fresu, L.; Howell, O.; McKernan, R. M.; Atack, J. R., Autoradiographic localization of α5 subunit-containing GABAA receptors in rat brain. *Brain Res.* **1999,** *822* (1,2), 265-270.
2. Möhler, H., The rise of a new GABA pharmacology. *Neuropharmacology* **2011,** *60* (7), 1042-1049.
3. Donegan, J. J.; Boley, A. M.; Yamaguchi, J.; Toney, G. M.; Lodge, D. J., Modulation of extrasynaptic GABAA alpha 5 receptors in the ventral hippocampus normalizes physiological and behavioral deficits in a circuit specific manner. *Nature Communications* **2019,** *10* (1), 2819.
4. Hipp, J. F.; Knoflach, F.; Comley, R.; Ballard, T. M.; Honer, M.; Trube, G.; Gasser, R.; Prinssen, E.; Wallace, T. L.; Rothfuss, A.; Knust, H.; Lennon-Chrimes, S.; Derks, M.; Bentley, D.; Squassante, L.; Nave, S.; Nöldeke, J.; Wandel, C.; Thomas, A. W.; Hernandez, M.-C., Basmisanil, a highly selective GABAA-α5 negative allosteric modulator: preclinical pharmacology and demonstration of functional target engagement in man. *Scientific Reports* **2021,** *11* (1), 7700.