ACS Chemical Neuroscience

EDITORIAL

pubs.acs.org/acschemicalneuroscience

Special Issue on the Pharmacology and Medicinal Chemistry of Allosteric Modulators of Metabotropic Glutamate Receptors (mGluRs)

All of us at *ACS Chemical Neuroscience* are very excited about this special issue focusing on the pharmacology and medicinal chemistry of allosteric modulators of the metabotropic glutamate receptors (mGluRs), an area of basic and translational research that is simply exploding![1−3] From a dearth of mGlur ligands just 5 years ago, the reviews in this special issue will attest to the "ligand boom" the field is experiencing. *ACS Chemical Neuroscience* has published a number of basic science papers on allosteric modulators of mGluRs already,[4−7] and this special issue features six review articles and one new basic science paper. For those new to this field of research, this issue will be a valuable and all-encompassing overview of the status of mGluR research directed at novel therapeutics. For those familiar with the mGluR field, this issue will serve as an invaluable up-to-date reference guide. I would like to thank all of the authors for their hard work in preparing what will surely become the seminal reviews on the pharmacology and medicinal chemistry of $mGlu_{1,2,4,5}$ and Managing Editor, Corey Hopkins, for assembling such an impressive issue.

Since the discovery and cloning in the late 1980s, eight mGlu receptor subtypes have been identified and divided into three groups: group I includes $mGlu_1$ and $mGlu_5$, group II includes $mGlu_2$ and $mGlu_3$, and group III consists of $mGlu_4$, $mGlu_6$, $mGlu_7$, and $mGlu_8$.[1] Targeting the orthosteric (glutamate binding site) has proven challenging to impossible for most mGluR subtypes, as ligands lack subtype selectivity and possess unfavorable physiochemical and DMPK properties.[1−3] Due to these limitations, efforts have shifted to functional assays and the discovery of allosteric ligands (positive allosteric modualtors (PAMs), negative allosteric modualtors (NAMs), and silent allosteric modualtors (SAMs)), that afford high levels of subtype selectivity and druggable chemotypes. The most advanced allosteric liagnds in the mGlu receptor field are for $mGlu_1$, $mGlu_2$, $mGlu_4$, and $mGlu_5$.

Dafydd Owen (Pfizer) has contributed a review that summarizes the medicinal chemistry of both orthosteric and allosteric modulators of the metabotropic glutamate receptor 1 ($mGlu_1$) from 2005 to the present. Cosford, Sheffler, and coworkers (Sandford-Burnham, Vanderbilt) provide a review describing recent progress on the synthesis and characterization of $mGlu_2$ allosteric modulators, while colleagues from both Lundbeck and Vanderbilt review orthosteric and allosteric ligands for $mGlu_4$. Both PAMs and NAMs of $mGlu_5$ have garnered a great deal of attention from both industry and academia for multiple CNS indications, with several NAMS in clinical trials affording robust efficacy; therefore, one review focuses on $mGlu_5$ NAMs (Emmitte, Vanderbilt) while a second focuses on $mGlu_5$ PAMs (Stauffer, Vanderbilt). Researchers at Seaside Therapeutics have contributed a timely review on treatment modalities for Fragile X Syndrome (FXS), where $mGlu_5$ NAMs are a promising therapeutic approach. Finally, the issue contains one new basic science research paper, describing a new $mGlu_5$ NAM chemotype and in vivo efficacy in an OSS model of addiction. Again, this special issue should be an informative source of the latest developments in the pharmacology, medicinal chemistry, and therapeutic potential of mGlu receptor allosteric modualtors.

Craig W. Lindsley
Editor-in-Chief

REFERENCES

(1) Nicoletti, F., Bockaert, J., Collingridge, G. L., Conn, P. J., Ferraguti, F., Schoepp, D. D., Wroblewski, J. T., and Pin, J. P. (2011) Metabotropic glutamate receptors: From the workbench to the bedside. *Neuropharmacology 60*, 1017–1041.

(2) Conn, P. J., Lindsley, C. W., and Jones, C. (2009) Allosteric modulation of metabotropic glutamate receptors as a novel approach for the treatment of schizophrenia. *Trends Pharm. Sci. 30*, 25–31.

(3) Conn, P. J., Christopolous, A., and Lindsley, C. W. (2009) Allosteric Modulators of GPCRs as a Novel Approach to Treatment of CNS Disorders. *Nat. Rev. Drug Discovery 8*, 41–54.

(4) Hammond, A. S., Rodriguez, A. L., Niswender, C. M., Lindsley, C. W., and Conn, P. J. (2010) Discovery of a novel chemical class of allosteric ligands of metaboropic glutamate receptor subtype 5 indicates distinct modes of efficacy as well as a unique interaction with the receptor. *ACS Chem. Neurosci. 1*, 702–716.

(5) Williams, R., Zhou, Y., Niswender, C. M., Luo, Q., Conn, P. J., Lindsley, C. W., and Hopkins, C. R. (2010) Re-exploration of the PHCCC scaffold: Discovery of improved positive allosteric modulators of mGluR4'. *ACS Chem. Neurosci. 1*, 411–419.

(6) Mueller, R., Rodriguez, A., Dawson, E. S., Butkiewicz, M., Oleskiewicz, S., Bleckmann, A., Weaver, C. D., Lindsley, C. W., Conn, P. J., and Meiler, J. (2010) Identification of metabotropic glutamate receptor subtype 5 potentiators using virtual high-throughput screening'. *ACS Chem. Neurosci. 1*, 288–305.

(7) Cid, J. M., Duvey, G., Cluzeau, P., Nhem, V., Macary, K., Raux, A., Poirier, N., Muller, J., Bolea, C, Finn, T., Urios, I., Epping-Jordan, M., Chamelot, E., Derouet, F., Girard, F., MacDonald, G. J., Vega, J. A., De Lucas, A. I., Matesanz, E., Lavreysen, H., Linares, M. L., Oehlrich, D., Oyarzabal, H., Tresadern, G., Trabanco, A. A., Andres, J. I., Le Poul, E., Imogai, H., Lutjens, R., and Rocher, J.-P. (2010) Discovery of 1,5-disubstituted pyridines: A new class of positive allosteric modulatorsof the metabotropic glutamate 2 receptor. *ACS Chem. Neurosci. 1*, 788–795.

Published: August 17, 2011