PHAR 5091-018
G protein-coupled receptor heteromers: pharmacological and physiological relevance

Class day and time: **TBD**

Location: **2.532U**

Course Director: Kelly A. Berg, Ph.D.
Email: berg@uthscsa.edu

Course Description

G protein coupled receptor (GPCR) heteromers (i.e., complexes formed between different receptor subtypes) display unique signaling characteristics and pharmacological properties that differ from those of the individual receptors. In this course, we will examine in detail the primary literature that describes receptor heteromer formation, signaling, regulation and pharmacology. A list of papers from the primary literature to be evaluated as well as companion review articles (provide background) are listed below. Upon completion of the course, students will have a thorough understanding of the unique pharmacological and physiological characteristics of receptor heteromers. The potential for exploitation of receptor heteromers as drug targets will also be discussed.

Prerequisites: Principles of Pharmacology (PHAR 5013)

Grading: Students will read, critically evaluate, and discuss with the Course Director, each of the assigned primary literature papers (listed under each "discussion topic"). For each paper discussed, a brief (one page) report describing important findings and contributions to the field of receptor heteromers will be required. *Note: One page synopsis of discussion paper due on day of class.* Grades will be based on the one-page reports and the quality of the discussions of each paper with the Course Director.

Semester Credit hours: 1

Tentative Class Schedule- Fall 2017

Date	Topic and Paper
Week 1 Aug 21-25	**Overview** *Ferre et al., (2009) Building a new conceptual framework for receptor heteromers. *Nat Chem Biol.* 5(3): 131–134. *Ferre et al., (2014) G protein-coupled receptor oligomerization revisited: functional and pharmacological perspectives. *Pharm Rev* 66: 413-434 *<u>*Reviews for background and terminology*</u> **Discussion Topic: Early demonstration of GPCR heteromerization**

	Maggio et al., (1993) Coexpression studies with mutant muscarinic/adrenergic receptors provide evidence for intermolecular "cross-talk" between G-protein-linked receptors. *Proc Natl Acad Sci U S A*. 90(7): 3103-3107.
Week 2 Aug 28-Sept 1	**Topic: Methods for Studying GPCR Heteromers** Cottet et al., (2012) BRET and time-resolved FRET strategy to study GPCR oligomerization: from cell lines toward native tissues. *Frontiers in Endocrinology* 3: 1-14. Albizu et al., (2010) Time resolved FRET between GPCR ligands reveals oligomers in native tissues. *Nature Chemical Biology* 6: 587-571. Ambrosio and Lohse (2010) GPCR dimers moving closer. *Nature Chemical Biology* vol 6: 570-571. (*This is a companion review for discussion of Albizu et al 2010)*
Week 3 Sept 4-8	**Topic: Heteromer Receptor Formation: Stable vs Transient Formation** Dorsch et al., (2009) Analysis of receptor oligomerization by FRAP microscopy. *Nature Methods*. 6(3): 225-230. Lambert, N. (2010) GPCR dimers fall apart. *Science Signaling*. 3 (115) 1-3. *(This is a companion review for discussion of Dorsch et al 2009)*
Week 4 Sept 11-15	**Topic: Dimerization Interfaces/ Heteromer Disruption** Hebert et al., (1996) A peptide derived from a □2-adrenergic receptor transmembrane domain inhibits both receptor dimerization and activation. *J Biol Chem*. 271 (27): 16384-16392. Hasbi et al., (2016) A peptide targeting an interaction interface disrupts the dopamine D1-D2 receptor heteromer to block signaling and function in vitro and in vivo: effective selective antagonism. FASEB Journal 28: 4806-4820
Week 5 Sept 18- 22	**Topic: Unique Pharmacology and Signaling** Ward et al., (2011) Heteromultimerization of cannabinoid CB1 receptor and orexin OX1 receptor generates a unique complex in which both protomers are regulated by orexin A. *J Biol Chem* 286 (43) 37414-37428.
Sept 25-29	

	NO CLASS
Week 6 Oct 2-6	**Topic: Unique Pharmacology and Signaling** Guitart et al., (2014) Functional selectivity of allosteric interactions within G protein-coupled receptor oligomers: the dopamine D1-D3 receptor heteromer. *Mol Pharmacol* 86: 417-429
Week 7 Oct 9-13	**Topic: Heteromer Receptors and Drug Discovery** Harvey et al., (2012) Tuned-affinity bivalent ligands for the characterization of opioid receptor heteromers. *ACS Med Chem Lett.* 3:640-644. Hubner et al., (2016) Structure-guided development of heterodimer-selective GPCR ligands. *Nature communications* 7: 12298
Week 8 Oct 16-20	**Topic: Unique Pharmacology and Signaling** Guitart et al., (2014) Functional selectivity of allosteric interactions within G protein-coupled receptor oligomers: the dopamine D1-D3 receptor heteromer. *Mol Pharmacol* 86: 417-429
Week 9 Oct 23 - 27	**Topic: GPCR Heteromers: Still Controversial?** Michel Bouvier and Terence Hebert (2014) Crosstalk proposal: Weighing the evidence for Class A GPCR dimers, the evidence favours dimers. *Journal of Physiology* vol 592.12 pgs 2439-2441 Nevin Lambert and Jonathan Javitch (2014) Crosstalk opposing view: Weighing the evidence for Class A GPCR dimers, the jury is still out. *Journal of Physiology* vol 592.12 pgs 2443-2445 Rebuttal from Bouvier and Hebert *Journal of Physiology* vol 592.12 pg 2447 Rebuttal from Lambert and Javitch *Journal of Physiology* vol 592.12 pg 2449
Oct 30- Nov 3	**NO CLASS**
Week 10 Nov 6-10	Late-breaking publication
Nov 13-	

Nov 24	**No Class- SfN meeting / Thanksgiving break**
Week 11 Nov 27-Dec 1	Student's choice
Dec 4-8	**NO CLASS- ACNP meeting**
Week 12 Dec 11-15	Last class