

Cheryl Frye
Department of Psychology

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**EAGER: The Role of Membrane Progesterin Receptors in
Progesterin-Facilitated Lordosis**

Background: Steroid signaling is typically considered to be mediated through nuclear steroid receptors, which act as transcriptional factors, regulating gene transcription and translation. The genomic signaling of steroids at nuclear steroid receptors has been well-characterized. In contrast, studies on rapid and “non-genomic” actions of steroids are more controversial, mainly due to well-established genomic signaling of steroids and lack of well-recognized non-genomic-steroid receptors. One potential target of interest is the membrane progesterin receptor (mPR). mPRs alter progesterin binding and rapid non-genomic signaling in various *in vitro* expression systems, such as *E. coli*, yeast, and mammalian cell lines. However, localization and non-genomic signaling of mPRs can be challenging due to difficulties in expressing recombinant mPR proteins and/or rapid degradation of mPR proteins in mammalian cell lines. Indeed, a rate-limiting step in the field of non-genomic steroid actions is the challenge of conducting elegant, reproducible biochemical and molecular analyses in systems that involve complex responses. Non-genomic signaling pathways initiated through mPRs have yet to be examined systematically *in vivo*. Rapid change in sexual receptivity of rodents is one of the best-studied *in vivo* models for non-genomic actions of progestins. Progesterone’s (P₄) rapid facilitation of sexual responses (lordosis) in rodents can be readily evaluated and replicated through its actions in the ventral tegmental area (VTA), a midbrain area in which few nuclear PRs have been observed.

Objectives: *Our objective is to determine whether mPRs in the VTA are targets for progestins to rapidly facilitate mating in rodents. Aim 1: What is the expression/localization and functional effects of mPRs in rats?* Expression and localization of mPRs in different brain regions (prefrontal cortex, hippocampus, amygdala, hypothalamus, and midbrain) and peripheral tissues (spleen, heart, lungs, kidney, liver, intestines) of sexually-receptive rats will be determined. The functional effects of mPRs will be determined by assessing whether knocking down mPRs in the midbrain VTA of rats, with antisense oligonucleotides (ODNs), alters progesterin-facilitated lordosis.

Aim 2: What is the expression/localization and functional effects of mPRs in mice? The expression and localization of mPRs in the brain and peripheral tissues of sexually-receptive mice will be determined. By knocking down mPRs in the VTA with antisense ODNs, or activating mPRs with mPR ligands, the functional effects of mPRs will be elucidated by assessing whether these manipulations alter progesterin-facilitated lordosis of mice.

Expertise of Investigators: In-depth characterization of the functional effects of mPRs in rodents will require unique expertise in behavioral neuroscience and molecular biology. The PI, Dr. Cheryl Frye, has established rodent models for non-genomic steroid action at UAlbany, a research-intensive university. The co-PI, Dr. Yong Zhu (East Carolina Univ.), has experience in molecular biology and characterization of mPRs. Funding of this proposal would provide a rare opportunity for initiating a breakthrough in characterizing mPRs’ functional effects.

Rationale for EAGER: Support of this proposal will provide for training of faculty, and their students, to develop their skills in behavioral neuroscience and molecular biology, in the context of investigating the role of mPRs as targets for non-genomic actions of progestins to facilitate mating behavior of rodents. This is a high-risk, but potentially high impact proposal.

Broader impact: Dr. Frye's skills in molecular biology in general, and to target mPRs, will be enhanced by working with Dr. Zhu. Dr. Zhu will develop skills in working with rodents. Trainees will be involved in this project and will have the opportunity to work with two excellent scientists who are committed to research and education. Funding of this research will support an exciting new area of investigation that is only possible through collaboration, and can lead to breakthroughs in non-genomic actions of steroids.