

Leroy B. Townsend Seminar Series

Hosted by the
Department of Medicinal Chemistry

Non-Traditional Modulation of Polypeptide Messages: Novel Agonists of Hormone-Activated GPCRs

Presented by Samuel Gellman, Ph.D.

December 3, 2026 | 11:00 AM

Kahn Auditorium, BSRB
Biomedical Science Research Building



Samuel Gellman, Ph.D.
University of Wisconsin-Madison

Biology encodes important messages in polypeptides. These messages are often received and transmitted by cell-surface receptors. We seek to expand the peptide language via unnatural modifications at the backbone level. These studies focus on hormones that activate class B1 GPCRs, which are the targets of many human drugs (e.g., semaglutide). One non-traditional modification strategy involves replacement of α -amino acid residues with β -amino acid residues. The β residue may display the natural side chain, or this residue may be preorganized via a ring. A second modification strategy involves replacing natural L- α -amino acid residues with D- α -amino acid residues. A third modification strategy involves the use of appendages to engage receptor surfaces outside the orthosteric site. Such modifications can result in signal bias, i.e., changes in relative potencies for inducing downstream events such as cAMP production, β -arrestin recruitment or receptor internalization in comparison to the native hormone. In addition, these modifications can alter the duration of cellular response or the pattern of receptor trafficking after activation. Novel agonists generated in this way provide tools for elucidating how information is conveyed from the external environment to the cytoplasm via class B1 GPCRs. Incorporation of D residues, for example, alters agonist conformational dynamics, and heterochiral hormone analogues may therefore offer insight on the role of conformational dynamics in GPCR-mediated signal transduction.