

Abstract:**Case Study: High Throughput Screening for Modulators of the G Protein-Coupled Receptor GPR54 with IP-One Assay**

Marcie A. Glicksman, Sr. Dir. Leads Discovery, Laboratory for Drug Discovery, Harvard Neuroscience Center, Brigham and Women's Hospital, Cambridge, MA.

GPR54 and its ligand kisspeptin have been shown to inhibit tumor invasion and metastasis and to regulate gonadotropin releasing hormone physiology and reproduction. The discovery of drugs that modify GPR54 activation may hence be clinically useful, agonists for infertility or delayed puberty and antagonists for hormone-dependent cancers. Our high throughput screening (HTS) campaigns aims to identify small molecule agonists that activate GPR54 and antagonists that block GPR54 activation by kisspeptin. We have developed and characterized a stably transfected cell line overexpressing human GPR54 for use in HTS. A fluorescence resonance energy transfer (FRET)-based assay measuring intracellular inositol monophosphate production (IP-One HTRF, Cisbio) was optimized for HTS in 384-well format and a 120,000 small molecule library was screened for agonists. A single agonist hit was verified on the primary IP-One HTRF assay and other secondary assays including ERK phosphorylation, a radioactive IP3 assay and the IP-One ELISA (Cisbio) in a 96-well plate format. An antagonist assay was developed using a pentapeptide as ligand. The performance of the IP-One assay format for both screens will be discussed and verification with other secondary assays will be demonstrated.

Resume

Marcie Glicksman, Ph.D. is currently Senior Director of the Leads Discovery Group at the Laboratory for Drug Discovery at the Harvard Neuroscience Center. Dr. Glicksman has extensive experience in assay development, high throughput screening, and chemical databases, as well as animal pharmacology and preclinical development. She has an A.B. from Brown University and a Ph.D. in Neuroscience from Washington University in St. Louis and has been in drug discovery in industry for thirteen years before coming to Brigham and Women's Hospital and Harvard Medical School three years ago. She also consults for the biotech industry recently helping to file an IND and also advising early stage companies in commercial and scientific matters. She currently serves as Chairman of the Board for the Society for Biomolecular Sciences.

Previously, she was at the start-up company, Descartes Therapeutics focused on developing pain therapeutics using imaging techniques. Before this, she was Director of Leads Discovery at Cubist leading a group in the development of antibiotics with a structure-based drug design approach using x-ray crystallography and chemical modeling and resulting in lead molecules suitable for testing in animal models. Before this, she was in Leads Discovery at DuPont-Merck (later DuPont Pharmaceuticals) and Cell Biology at Cephalon. She led the assay development and screening program for a cell-based protease project, and numerous G-protein coupled receptors, many of which were continued when Bristol Myers Squibb bought DuPont Pharmaceuticals. She also has led a small molecule neuroprotection program for Alzheimer's and Parkinson's disease that has resulted in a drug candidate, CEP-1347, directed at a kinase, currently in Phase III clinical trials.