

Accelerating GPCR Drug Discovery and Development

Products and Services for Target ID, Functional Screening, Lead Optimization, and QC Lot-Release Testing

What's Inside:

- >650 GPCR Assays
- Functional Readouts
 - cAMP
 - Calcium
 - β -Arrestin
 - Internalization
 - Pharmacotraficking
- Complete Solutions
 - Ready-to-Use Kits
 - Cell Lines
 - Screening Services
 - Toolbox



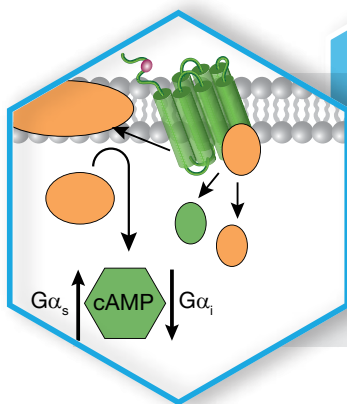
GPCR Pathways and Assays

G-protein coupled receptors (GPCRs) play a crucial role in many physiological functions and in the pathology of multiple diseases including cancer, endocrine, and metabolic disorders. These receptors represent the largest class of validated therapeutic targets. Over 30% of currently marketed drugs target these receptors, and many GPCRs are still active targets for drug discovery.

Largest portfolio of validated products and services to accelerate your GPCR drug discovery.

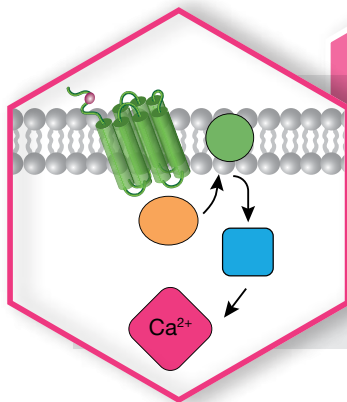
- >400 functional assays measuring β -arrestin recruitment to over 90% of class A and B GPCRs, including assays for over 75 orphan GPCR targets
- >150 naturally-coupled G_i/o , G_s and G_q GPCR cell lines for measurement of cAMP and calcium
- >100 functional cell lines for receptor internalization and trafficking

The assays are available as stable, clonal cell lines or complete ready-to-use kits optimized for small molecules or biologics. With over 700 peer-reviewed customer publications, these assays are the most trusted pharmacologically-relevant functional GPCR assays in the industry.



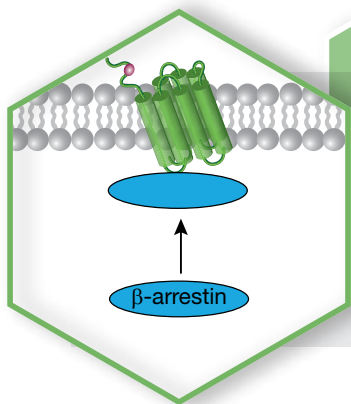
cAMP Assays

- Measure intracellular cAMP with easy-to-use protocols
- Characterize ligand pharmacology with precision
- Reproducible performance with large assay windows and broad sensitivity ranges



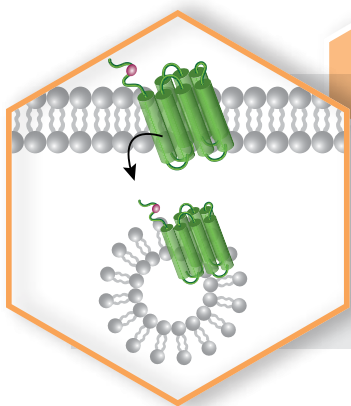
Calcium Assays

- Measure intracellular calcium flux in adherent or suspension cells
- Fast, highly sensitive, and low-cost, HTS-friendly platform
- Homogeneous protocol with large assay windows and broad sensitivity ranges



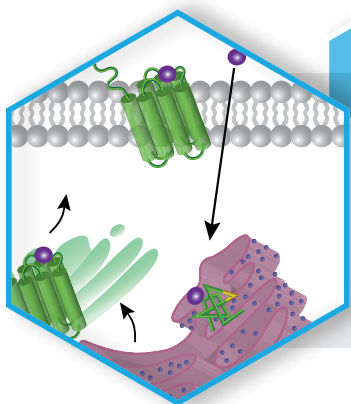
β-Arrestin Assays

- Universal G-protein independent method to quantify GPCR activation
- Easy, add-and-read protocol optimized for screening to QC lot-release testing
- Multiplex with calcium or cAMP readouts for cost-effective screening and ligand bias analysis



Internalization Assays

- Quantitative measurement of GPCR internalization, desensitization, and resensitization
- Simple chemiluminescent readout, without imaging
- Easy protocol enabling rapid lead optimization and ligand bias studies



Pharmacotrafficking Assays

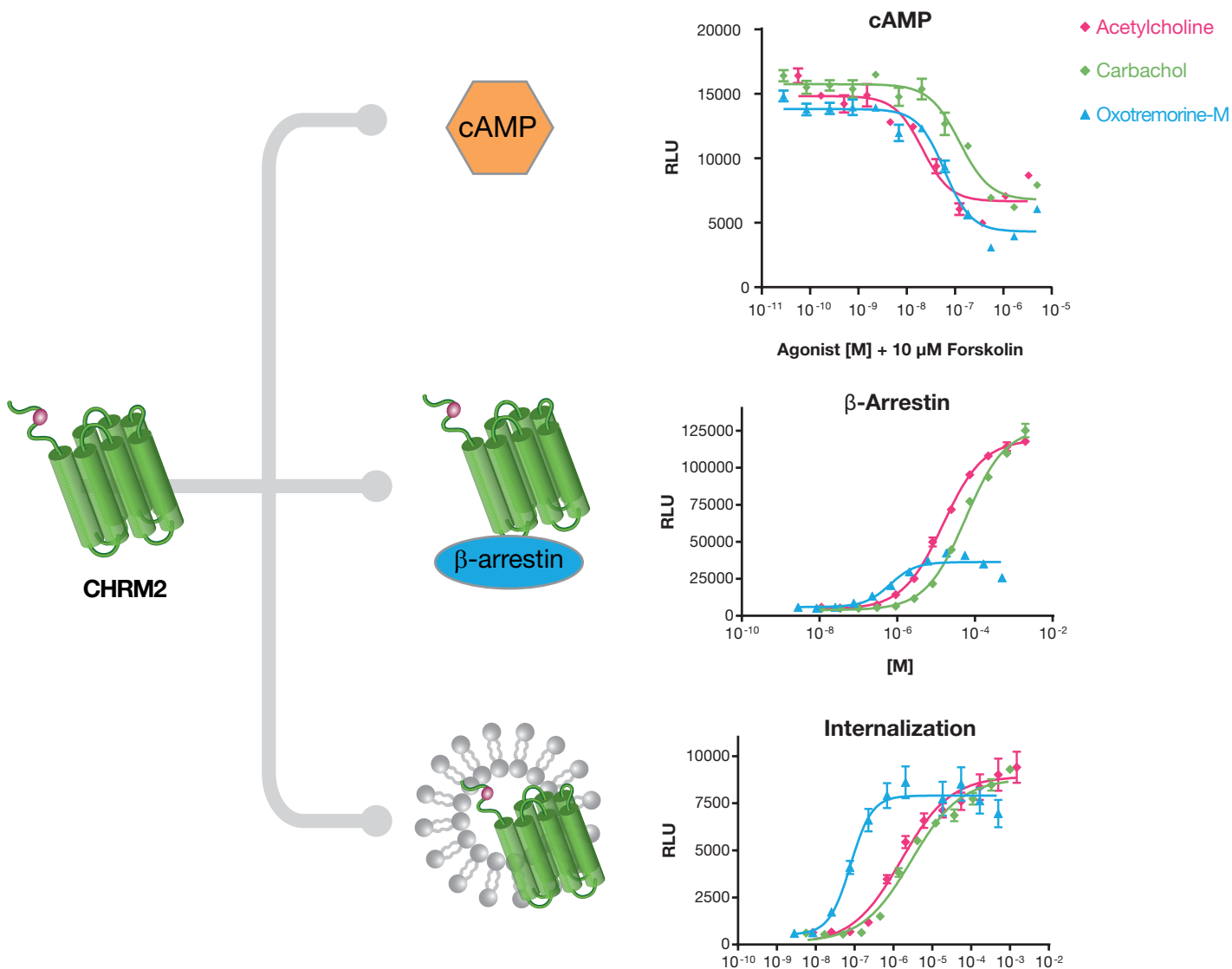
- Detect trafficking in functionally-restored mutant GPCRs
- Identify pharmacochaperones that correct protein misfolding-related diseases
- Quantitative chemiluminescent results without imaging

One GPCR Target, Multiple Functional Readouts

Identify Functionally Selective Ligands

Biased GPCR ligands represent exciting opportunities for developing better and safer drugs, by selectively promoting the desired biological effect relevant for the disease, while simultaneously deselecting the deleterious ones^{1,2}.

DiscoverX provides the largest portfolio of GPCR assays and a unique service, “*gpcrBIAS*” for characterization of ligand bias. These assays offer wide assay windows to allow different functional readouts in single or multiplexed mode for the same GPCR target in a single cell line, to generate a unique efficacy profile of the ligand and capture the full repertoire of possible signaling responses.



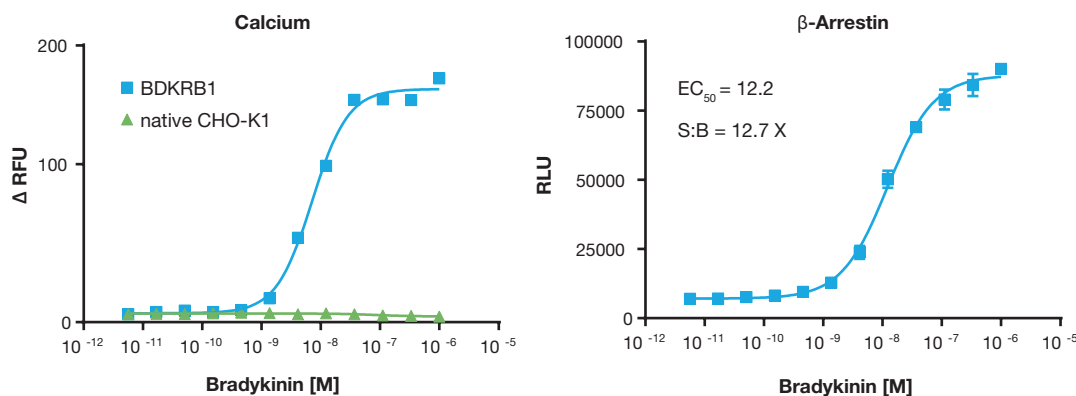
The cholinergic receptor, muscarinic 2 (CHRM2), was expressed in CHO-K1 cells and three assay formats were created for cAMP, β -arrestin, and internalization readouts. Dose-response curves were generated for multiple ligands to determine their functional selectivity. Acetylcholine and Carbachol showed similar agonist responses and potencies in all three readouts. Oxotremorine-M showed similar cAMP response, but as a partial agonist in recruiting β -arrestin and a strong agonist for receptor internalization. Interrogating the three pathways for the same target revealed differences in the mechanism of action of each ligand. These assays provide the ability to quantify “bias” for each potential drug candidate to help determine the overall quality of efficacy possessed by each drug.

“... examples of β -arrestin and G protein biased ligands demonstrate how our new understanding of these two types of signaling pathways, gained initially at a biochemical level, can potentially be harnessed for therapeutic benefit.”— Robert Lefkowitz, Ph.D. 2012 Nobel Prize in Chemistry.

Calcium and β -Arrestin Detection in the Same Well

Several GPCR agonists activate multiple signaling pathways differentially. An increasing awareness of the subtleties of GPCR receptor signaling and the potential for ligand bias requires multiple endpoints to be monitored in any screening campaign.

DiscoverX offers Gq-coupled arrestin targets as clonal cell lines or Ready-to-Use kits, to monitor intracellular calcium flux in real time, followed by the recruitment of β -arrestin in the same cell line or in a single well. This HTS-compatible duplexed assay increases your screening capabilities, removes challenges of running multiple assays, reduces data complexity, and provides significant cost savings and time efficiencies.



Naturally G_q-coupled PathHunter® β -arrestin cell line expressing the Bradykinin B1 Receptor (BDKRB1) was first monitored for calcium mobilization using the Calcium No WashPLUS Kit as a fluorescent readout. β -arrestin recruitment was then analyzed in the same well using the PathHunter Detection Reagents. These duplexed assay provide a simple and efficient approach for measuring different signaling pathways for the same GPCR and define potency ranking of GPCR modulators.

References:

1. Violin JD and Lefkowitz R.J. β -Arrestin-biased ligands at seven-transmembrane receptors. *Trends in Pharmacological Sciences*. 2007, 28 (8), 416–422.
2. Kingwell K. Pioneering biased ligand offers efficacy with reduced on-target toxicity. *Nature Reviews Drug Discovery* 2015, 14 (12), 809–810

Choose the Solution that Best Meets Your Program Needs

Whether you are developing small molecules or biologics, DiscoverX provides you with a choice of different product formats to meet your specific research needs. Learn more at discoverx.com/gpcr.

Human | Orphans | Orthologs

>300 GPCR Targets | >650 Cell Lines

Multiplexed Readouts

- cAMP
- β -Arrestin
- Calcium
- Internalization

Pharmacological Activity

- Agonism
- Ligand Bias
- Antagonism
- Allosteric Modulation

Test Assay Quickly

Ready-to-Use Kits

- Bioassay and eXpress kits include cryopreserved ready-to-use cells and all required reagents
- Save time and money, no cell culture needed
- Ease of assay development and method transfer to global sites

Screen In-House

Cell Lines

- Stable cell lines for continuous cell culture and in-house banking
- Deliver consistent assay performance guaranteed for at least 10 passages
- Obtain reproducible results using optimized culture and detection reagents

Lead Optimization

Screening Services

- Leading provider of GPCR screening and profiling services
- Screen and profile against the broadest menu of cell-based functional assays with the fastest turnaround time
- Select from a pre-defined panel or create a personalized panel with specific assays

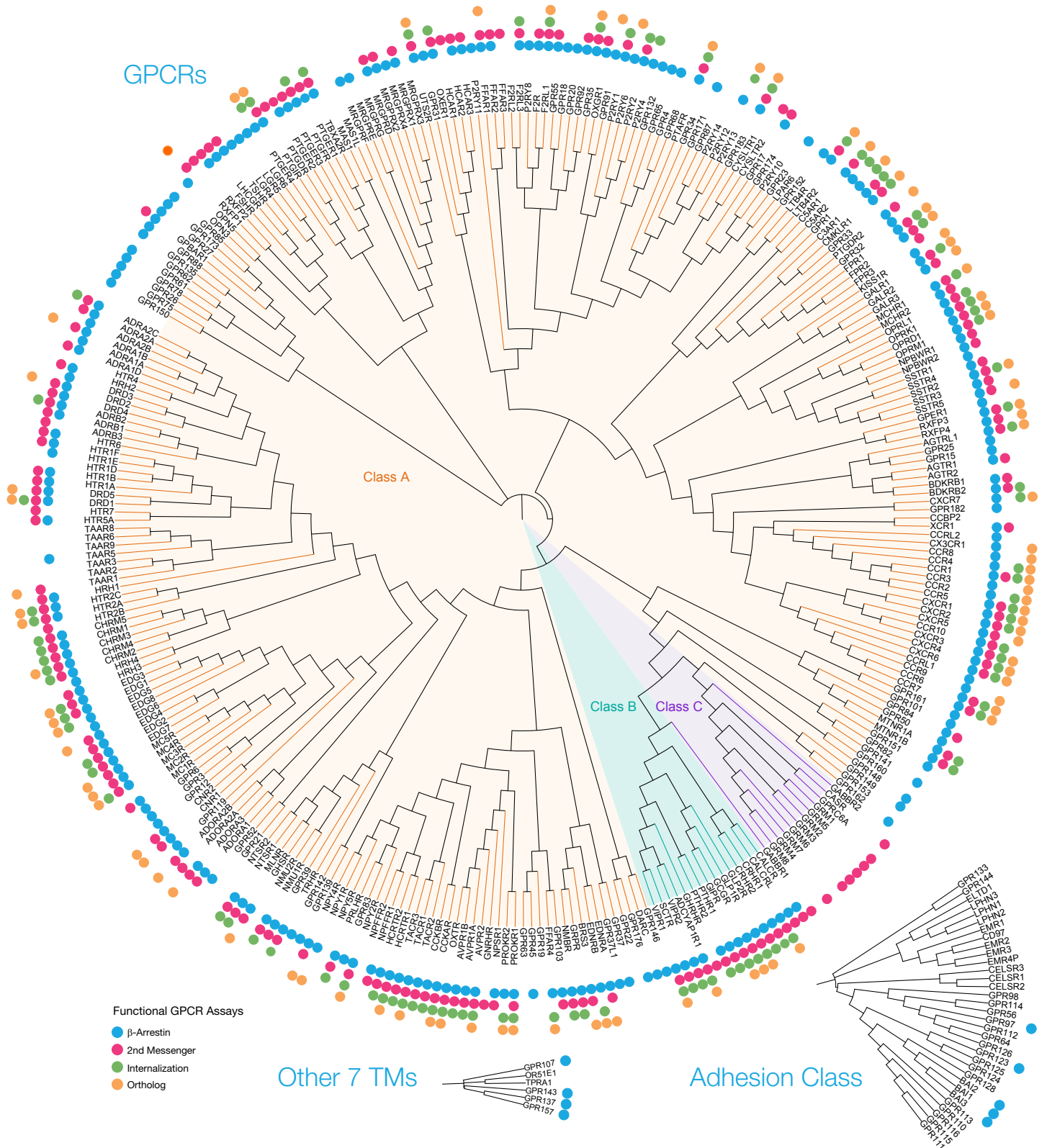
Build Your Own Assay

Toolbox

- Rapidly develop assays for any GPCR with a β -arrestin, trafficking, or internalization readout
- Create your own cell-based assays in any dividing mammalian cell type
- Analyze GPCR mutants, orthologs or novel cell backgrounds

Can't Find Your Assay on Our Menu? Try Our Custom Assay Development Services

For information on requesting a custom assay development, please visit discoverx.com/cad.



Get the latest list of all available GPCR assays at discoverx.com/targets-list

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