DiscoveRx

Simple Solutions for Complex Biology

Target-Based and Phenotypic Screening Assay Platforms for Novel Compound Discovery

Royle Fernandopulle MD., MPH

Business Development Manager

Asia Pacific Region

DiscoveRX Corporation-2013

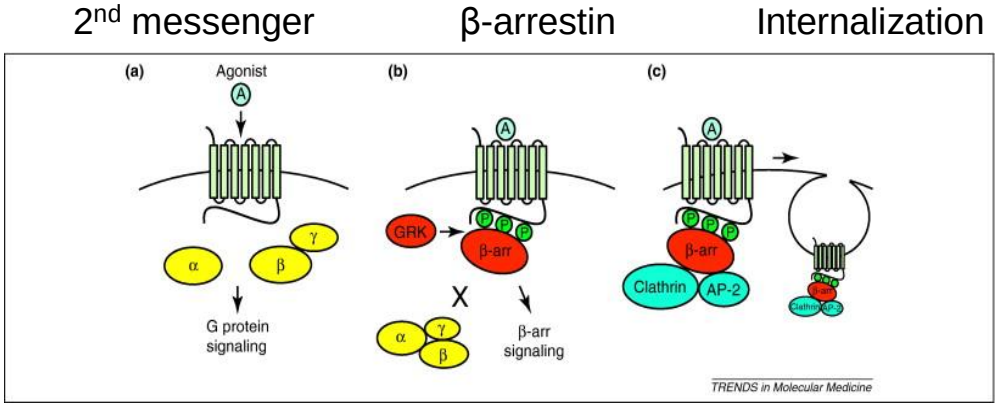
GPCR Nobel Prize Winning Product

2012 Nobel Prize in Chemistry

Robert J. Lefkowitz

Brian K. Kobilka

Functional GPCR signaling in cell surface



E. J. Whalen, S. Rajagopal, and R. J. Lefkowitz, *Trends Mol Med,* Mar 2011.

DiscoveRx

Go with Nobel Laureate

A unique mechanism of beta-blocker action: carvedilol stimulates beta-arrestin signaling.

Authors:	Wisler JW, DeWire SM, Whalen EJ, Violin JD, Drake MT, Ahn S, Shenoy SK, Lefkowitz RJ.
Publisher/Year:	Proc Natl Acad Sci U S A. 2007 Oct 16;104(42):16657-62. Epub 2007 Oct 9.
Pub Med ID/Journal ID:	PMID:17925438

Abstract

For many years, beta-adrenergic receptor antagonists (beta-blockers or betaAR antagonists) have provided significant morbidity and mortality benefits in patients who have sustained ac
antagonists have b
failure, although th
One drug, carvedil
effective in the tre
are controversial. I
carvedilol displays
in beta2 adrenergi
inverse efficacy fo
stimulates (i) phos
documented G pro
the beta2AR; (iii) re
kinase 1/2 (ERK 1/

Beta-arrestin-biased ligands at seven-transmembrane receptors.

Authors:	Violin JD, Lefkowitz RJ.
Publisher/Year:	Trends Pharmacol Sci. 2007 Aug;28(8):416-22. Epub 2007 Jul 20.
Pub Med ID/Journal ID:	PMID:17644195

Abstract

Seven-transmembrane receptors (7TMRs), the most common molecular targets of modern drug therapy, are critically regulated by beta-arrestins, which both inhibit classic G-protein signaling and initiate distinct beta-arrestin signaling. The interplay of G-protein and beta-arrestin signals largely determines the cellular consequences of 7TMR-

Beta-arrestins and cell signaling.

Authors:	DeWire SM, Ahn S, Lefkowitz RJ, Shenoy SK.
Publisher/Year:	Annu Rev Physiol. 2007;69:483-510.
Pub Med ID/Journal ID:	PMID:17305471

Abstract

Upon their discovery, beta-arrestins 1 and 2 were named for their capacity to sterically hinder the G protein co
ultimately resulting in r
beta-arrestins can also
protein activation. By s
of specific signaling pa
demonstrated for an e
mitogen-activated prot

beta-arrestin-biased agonism at the beta2-adrenergic receptor.

Authors:	Drake MT, Violin JD, Whalen EJ, Wisler JW, Shenoy SK, Lefkowitz RJ.
Publisher/Year:	J Biol Chem. 2008 Feb 29;283(9):5669-76. Epub 2007 Dec 17.
Pub Med ID/Journal ID:	PMID:18086673

Abstract

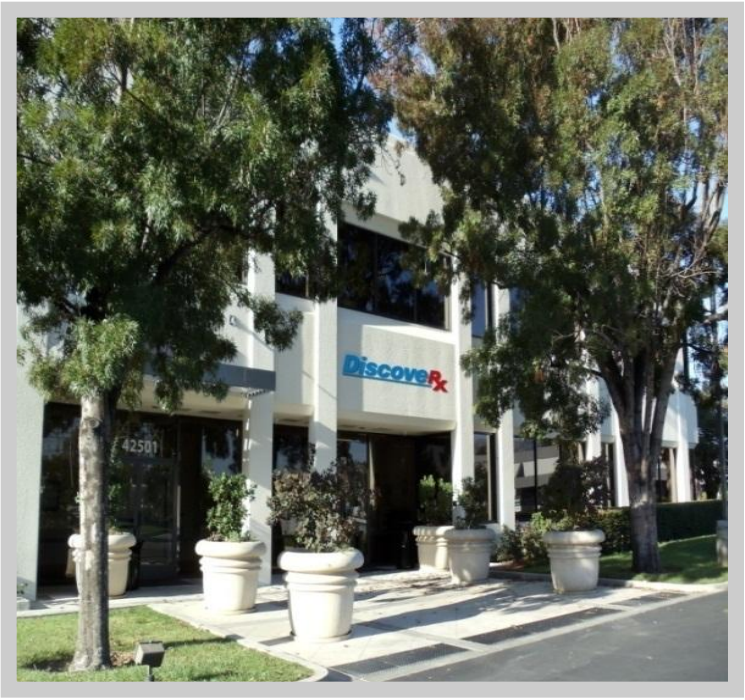
Classically, the beta 2-adrenergic receptor (beta 2AR) and other members of the seven-transmembrane receptor (7TMR) superfamily activate G protein-dependent signaling
y been discovered, however, that
a beta-arrestin-dependent
ently unclear if among beta 2AR
nal via G proteins or beta-
proaches that include highly
ed methodologies, including a

Teaching old receptors new tricks: biasing seven-transmembrane receptors.

Authors:	Rajagopal S, Rajagopal K, Lefkowitz RJ.
Publisher/Year:	Nat Rev Drug Discov. 2010 May;9(5):373-86.

DiscoveRx

DiscoveRx – At a Glance



Founded in 2001

Acquired KINOMEscan and BioSeek

- **Innovative**
  - Premier provider of innovative assays and services for drug discovery researchers
- **Comprehensive**
  - >1,000 proprietary assays
  - Primary cell models for disease biology
  - Product & service offering
- **Proven Expertise**
  - Technology development
  - Drug discovery
  - Screening and profiling

DiscoveRx

DiscoveRx Organization

- **Employees**
  - 137 world-wide
- **R&D**
  - 35 team members
  - 17 US, 12 EU patents issued,
    - 12 pending
- **Technology Platforms**
  - β-gal enzyme fragment complementation (EFC)
  - Competition binding
  - BioMAP ™ Compound Profiling

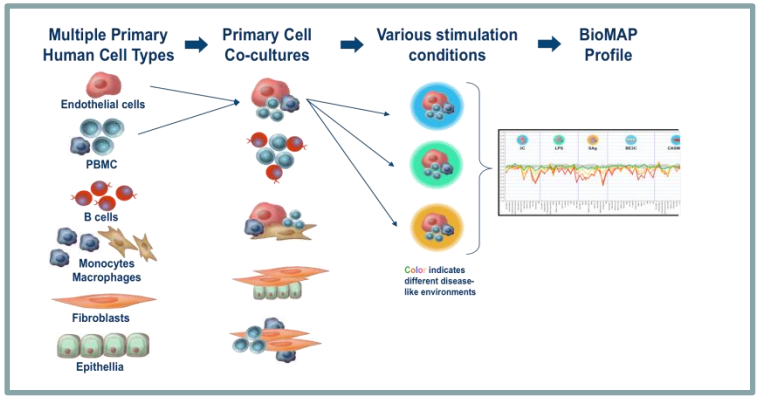
- **Recognized Brands**
  - PathHunter®, HitHunter®, KINOMEscan® , BioMAP™
- **PathHunter, HitHunter and InCELL Hunter Products**
  - GPCR, Kinase, Bromodomain, NHR, Pathway Assays
- **LeadHunter™ Services**
  - Kinase Selectivity profiling
  - GPCR panel profiling
  - Primary cell profiling

Three Core Technology Platforms

Enzyme Fragment Complementation

KINOME*scan* / BROMO*scan*
Competitive Binding

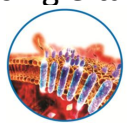
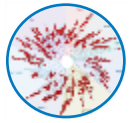
BioMAP
Primary Cell Profiling



Proven and Robust Platforms with Multi-year Investments

Platform Technologies Covering >75% of all Targets

- **DiscoveRx has 1,118 assays covering 736 targets across multiple drug target classes**
  - All major drug target classes covered
  - >75% coverage of targets
  - Multiple assays for single target

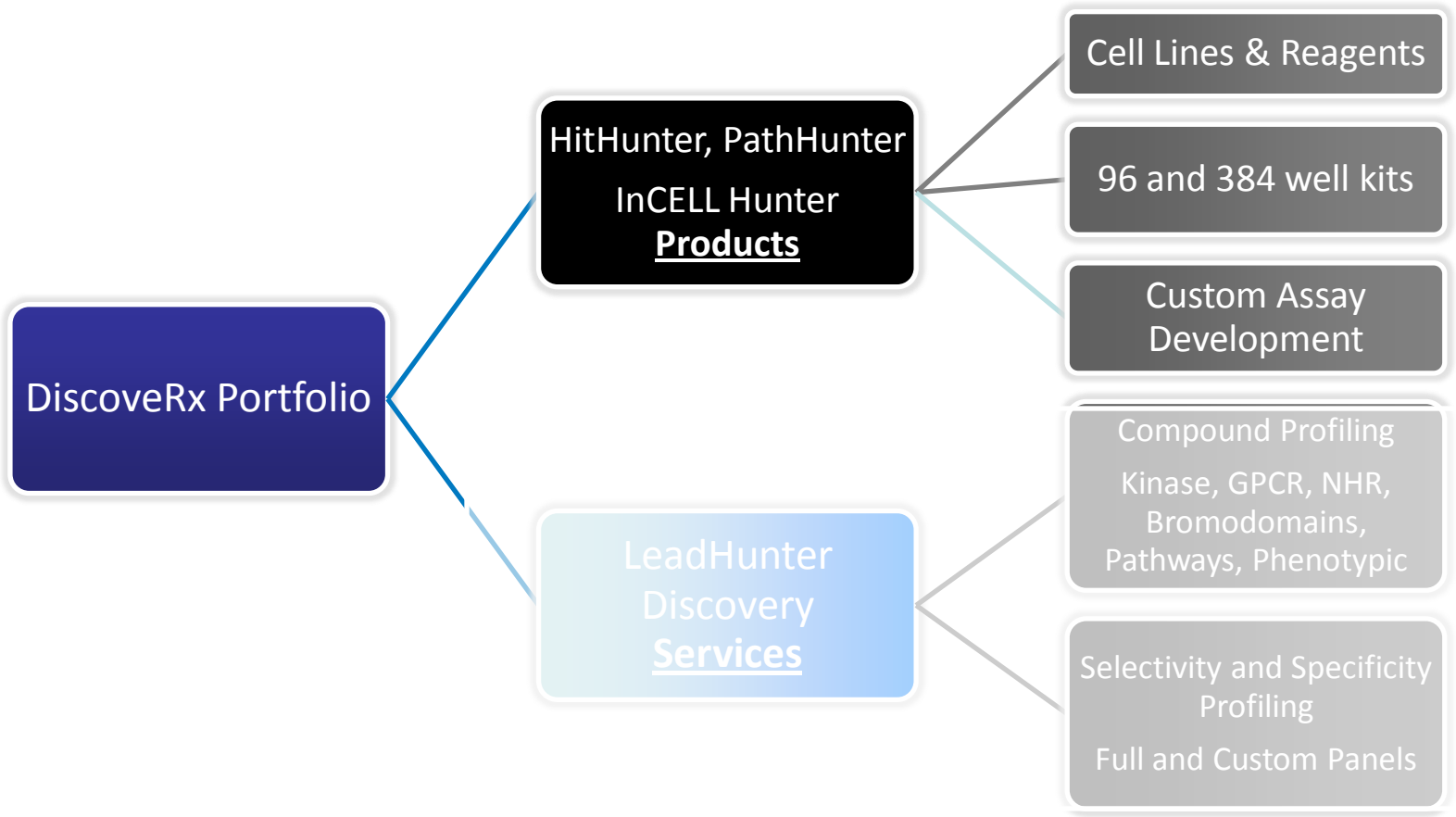




	GPCRs	Kinases	NHRs	Pathways	Bromodomain	
Depth of Coverage						
Targets Covered	284	389	21	23	19	736
Total Druggable Targets	314	518	48	-	57	846

Most comprehensive offering for Discovery Solutions Services

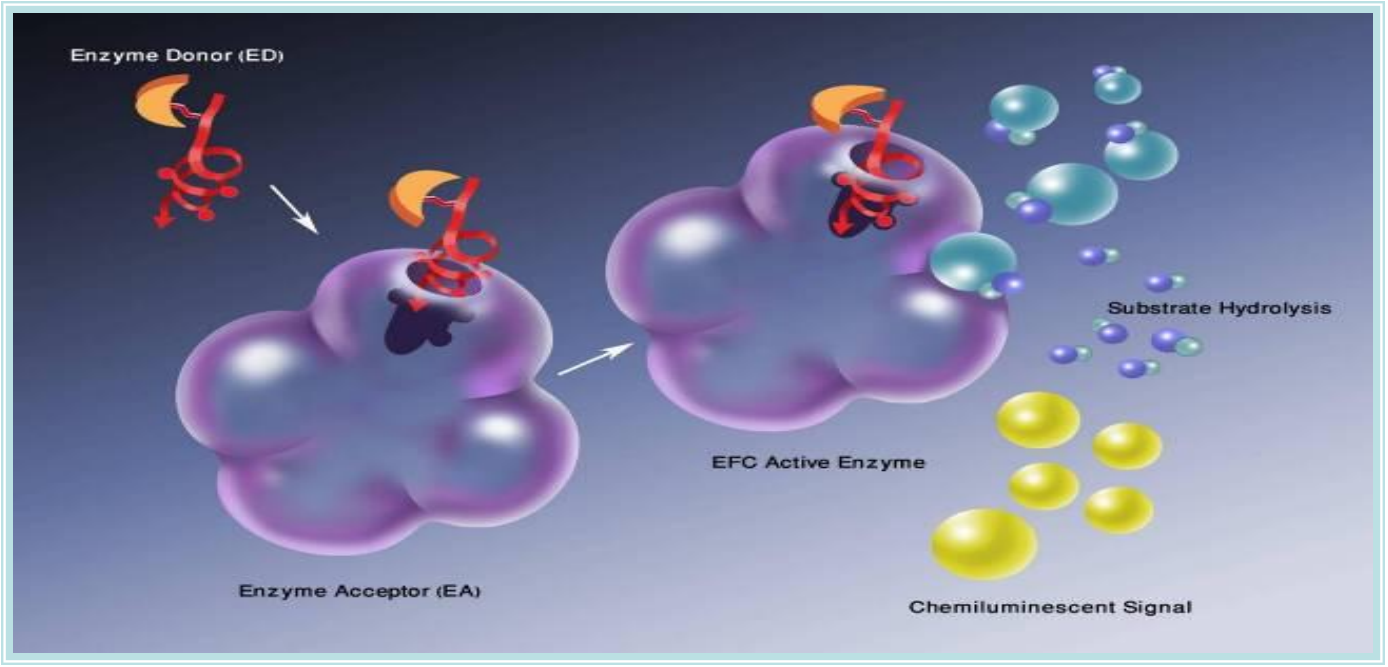
DiscoveRx

DiscoveRx – Your Solution Provider



Complete Solutions for Critical Customer Needs

β-galactosidase based Enzyme Fragment Complementation



- Standard Plate Readers
- 96-384 well protocols
- No Wash , gain of signal assays
- Analyze raw data : no software manipulation
- Compatible with Lysates, Serum, primary cells
- Bioschemical assays or Cell-based Assay configuration

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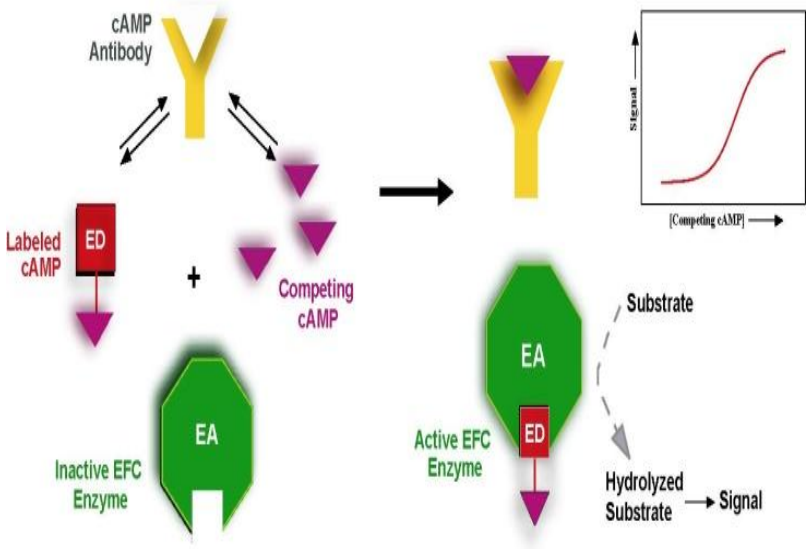
HitHunter ®Platform



- Competitive Immunoassays
- Measure analytes and enzyme products
- Sub-nanomolar sensitivity
- Applications in Biomarker quantitation and preclinical drug studies
  - Excellent serum tolerance
  - Standard plate reader

Available Products
✓cAMP, cGMP and Cortisol Assays
✓Caspase, Secretase, MMP Protease Assays
✓Progestrone and Estrogen Binding Assay

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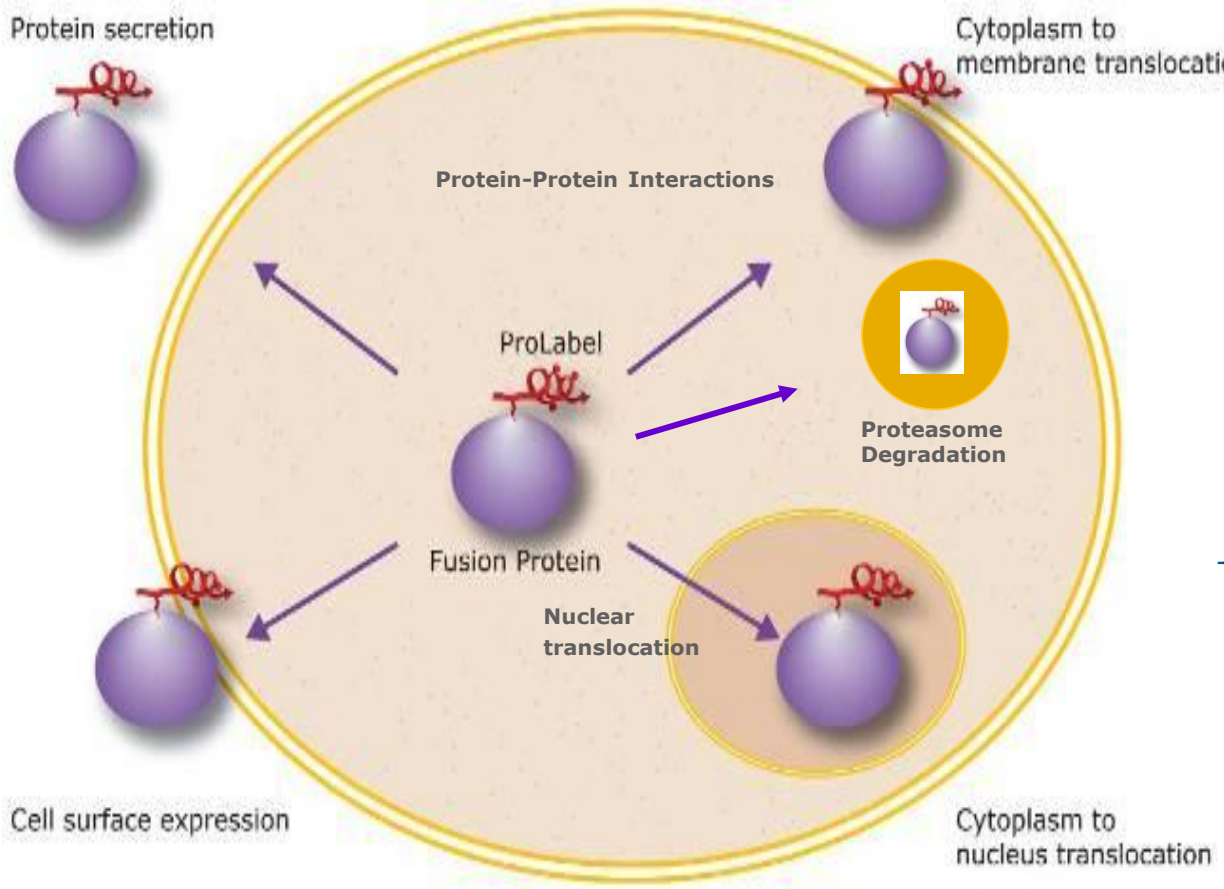
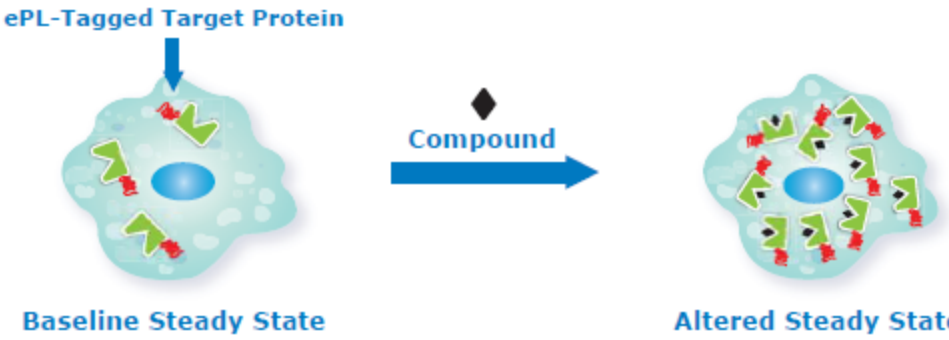
PathHunter ®and InCELL Hunter Cell-Based EFC Platform

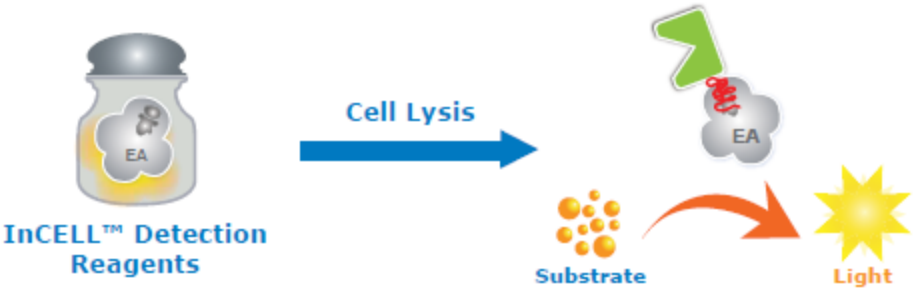


Targets	Biology
GPCRs	Protein Levels Secretion Degradation
Kinases NHRs Pathway Assays	Protein Trafficking Translocation
Bromodomain Assays	Protein Protein Interactions
HMT	Target Engagement Assay InCELL Hunter

InCELL Hunter™ Principle



Assay Principle. The target protein is fused to an enhanced ProLabel (ePL) tag. In the absence of a binding molecule, the target-ePL fusion reaches a steady state inside the cell. When a molecule binds the target, it changes the stability of the target protein and alters the cellular steady-state protein levels.



Detection of Protein Steady State. The protein level is detected with InCELL Hunter detection reagents. The EA fragment in the reagent naturally combines with the ePL epitope on the target protein to create active β-gal enzyme, which converts substrate to a luminescent signal.

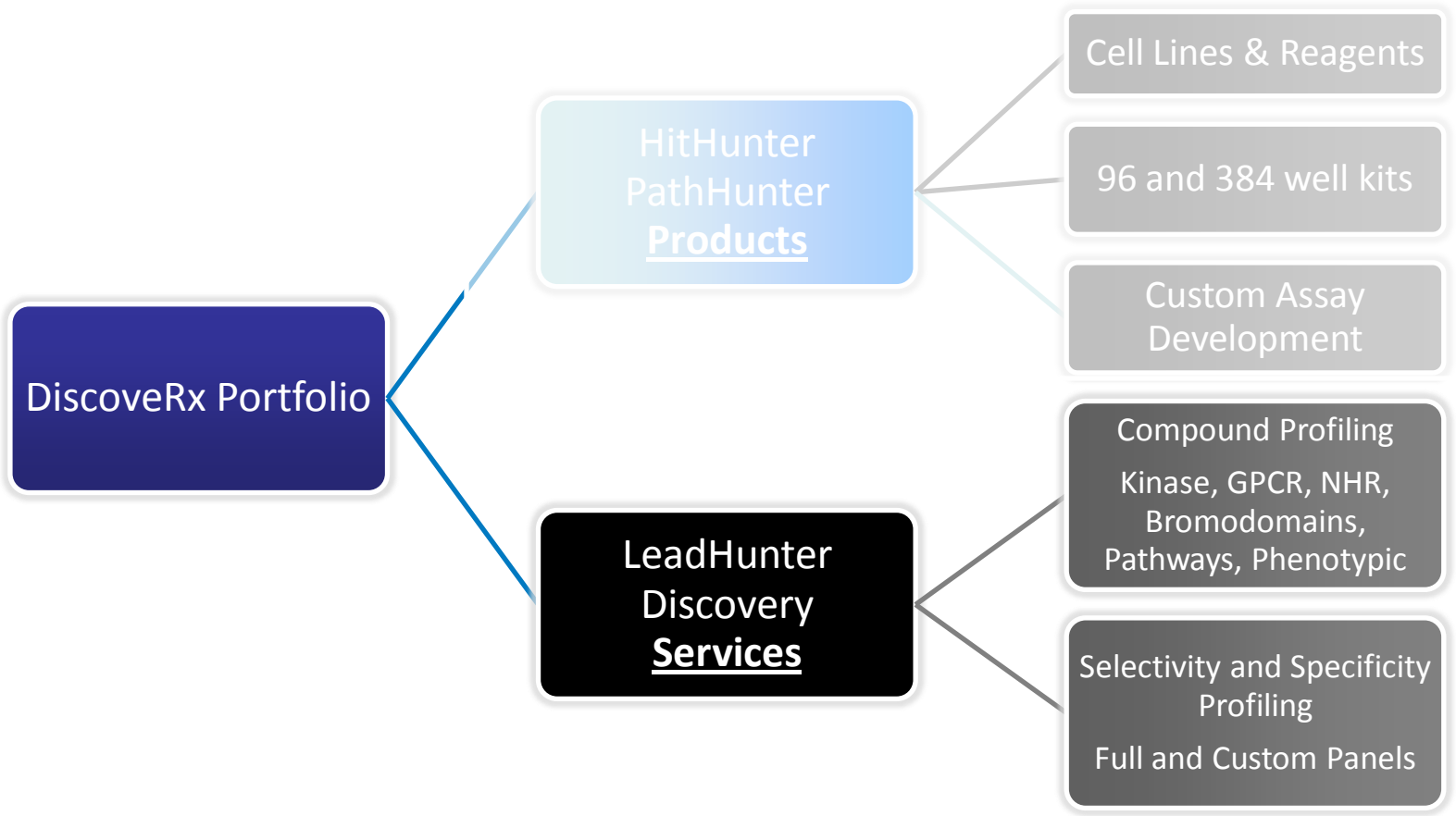
DiscoveRx

PathHunter, HitHunter and InCELL Hunter Assays

- Ready to go cell-based assay kits for over 500 druggable targets
  - Simple, no wash, non-isotopic kits to measure standard analytes
  - Proprietary reagents, buffers, media and substrates
- Single unifying protocol (mix and read) for all products and kits
- >700 stable pharmacologically validated Target Specific cell lines available today
- Over 20 billion datapoints screened with our technology
- >75 publications referencing EFC platform have been published by leading pharma, biotech and academic institutes

DiscoveRx

DiscoveRx – Your Solution Provider



Complete Solutions for Critical Customer Needs

DiscoveRx

LeadHunter Services

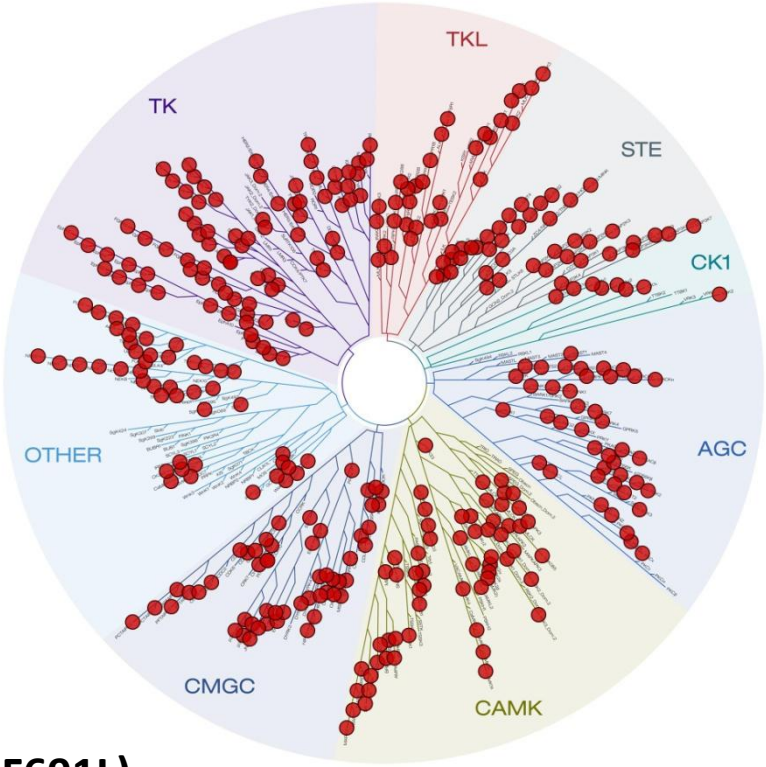
Specialty Service Provider

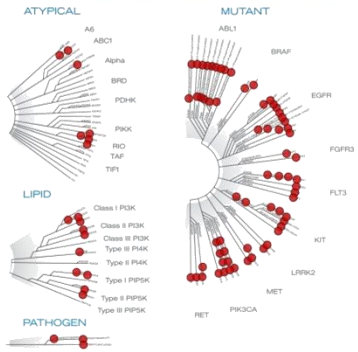
- In-house developed technologies
- Expertise platforms: "*inch wide - mile deep*"
- R&D driven, project focused
- Extension to partner's project teams
- Responsive, dedicated, transparent
- Flexible

KINOMEscan® - World's Largest Kinase Panel

462 Kinase Assays

- 459 human kinases + 3 pathogen
- 392 of the 518 distinct kinases
- 57 clinically relevant mutants
- 133 tyrosine kinase assays
- 20 lipid kinase assays
- >120 unique assays
- ***New Assays (Kd mode)***
  - **FLT3(D835V) FLT3(ITD, D835V) FLT3(ITD, F691L)**
  - **WNK2 WNK4 CDK4**
- Custom assay development





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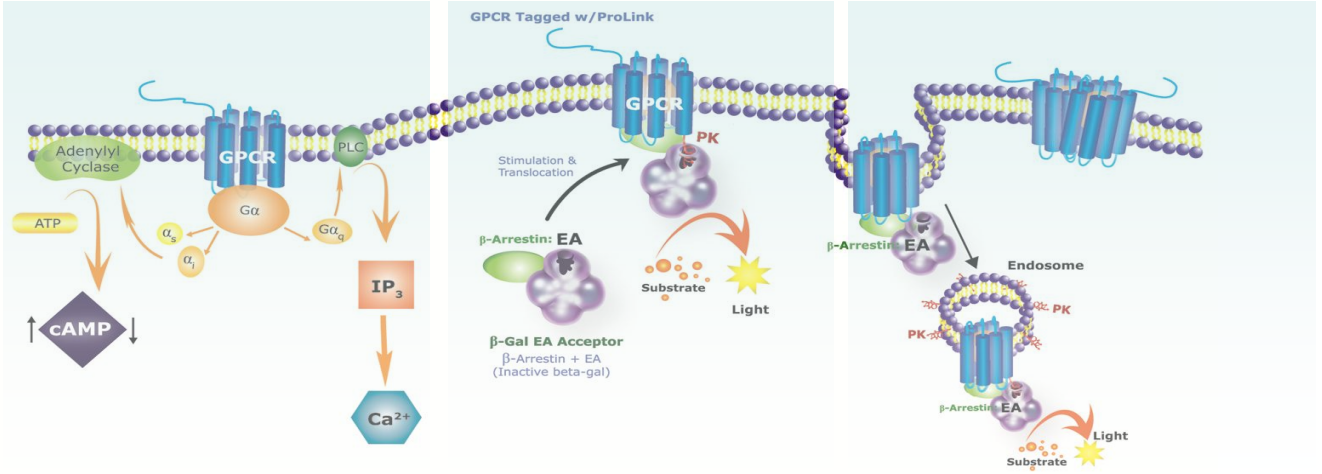
GPCR*scan*™
Industry Leading GPCR Portfolio

Nearly 600 GPCR Assays

- 440 human known GPCR assays
- 78 orphan GPCR assays
- 76 mouse and rat ortholog GPCR
- Custom assay development

- Multiple signaling readouts:
  - Arrestin
  - 2nd Messenger (cAMP/Calcium)
  - Internalization

All naturally coupled assays



DiscoveRx

GPCR*scan*™ – Industry Leading Offering

Over 600 validated, functional GPCR assays

gpcr MAX™	❑ 158 known GPCRs using Arrestin recruitment readout
orphan MAX™	❑ Largest collection of 76 Class A orphan GPCRs
gpcr PANELS™	❑ 11 Therapeutically relevant panels, including the family specific families (chemokine, dopamine, EDG)
gpcr TRIO™	❑ Multiple signaling platforms – full compound activity Arrestin, 2nd messenger, Internalization
gpcr DUO™	❑ Complete menu of non-human orthologs – specificity
gpcr ELECT™	❑ Choose only the GPCR you want, in the readout you want – flexibility
gpcrE/IC_{50}ELECT™	❑ Quantitative affinity measurements for each GPCR/compound combination

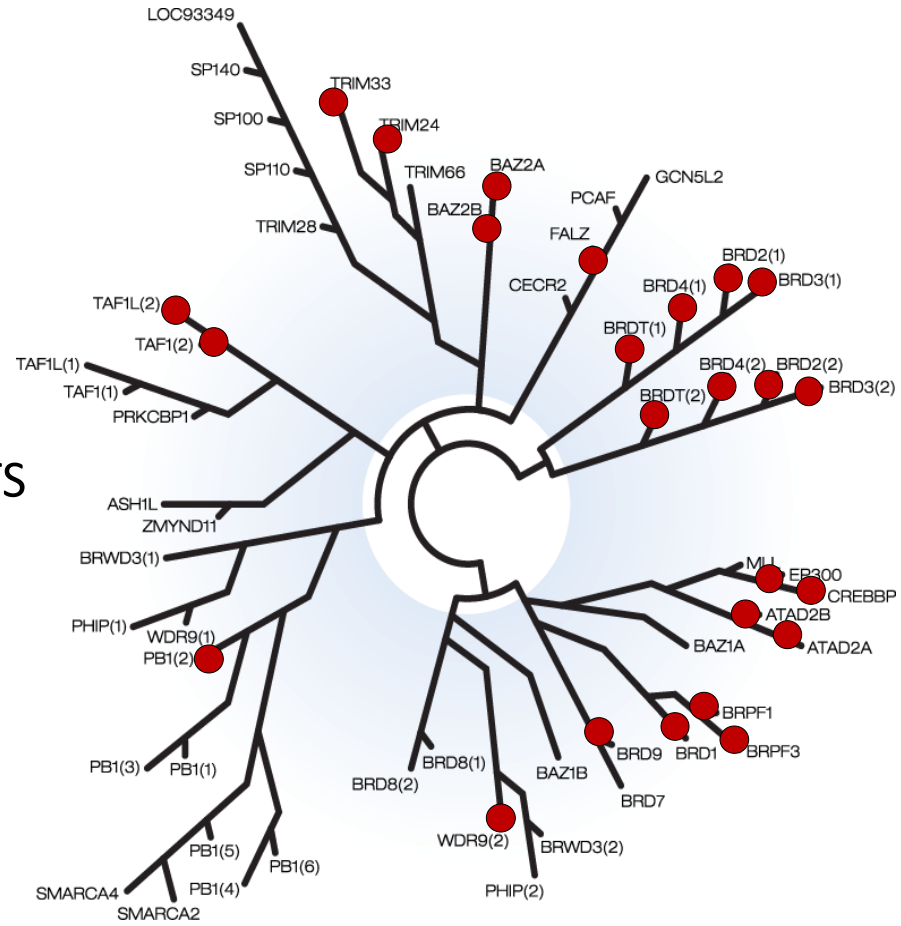
DiscoveRx

BROMO*scan*℠ - First In Class Platform for Screening Epigenetic Drug Targets

25 Human Bromodomain Assays

- 25 of 57 distinct BRDs (44%)
- All 7 families represented
- Many putative therapeutic targets (e.g. BET; ATAD2B)
- All 25 targets in Kd mode
- 12 targets validated in single point HTS

BROMO*scan* Targets			
ATAD2A	BRD3(1)	**BRPF1**	TAF1L(2)
ATAD2B	BRD3(2)	BRPF3	**TRIM24**
BAZ2A	BRD4(1)	CREBBP	**TRIM33**
BAZ2B	BRD4(2)	EP300	WDR9(2)
BRD1	**BRD9**	FALZ	
BRD2(1)	BRDT(1)	**PB1(2)**	
BRD2(2)	BRDT(2)	TAF1(2)	



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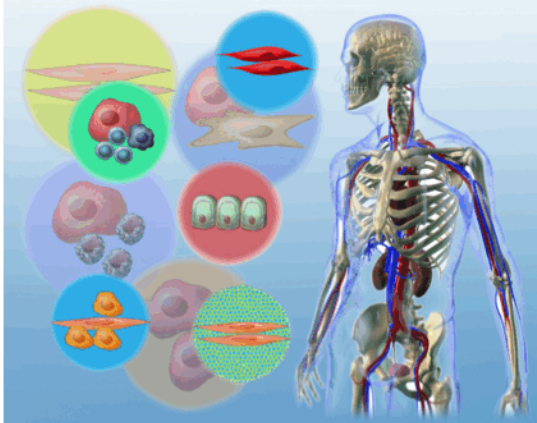
BioMAP® Technology Platform

BioMAP® Assay Systems

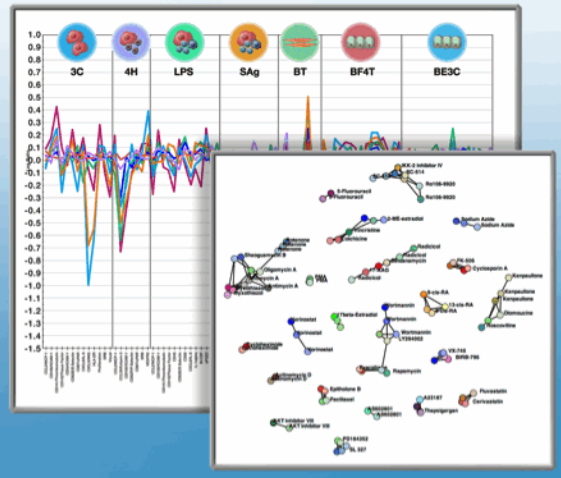


Human primary cells
Disease-models
30+ systems

Reference Profile Database

Biomarker responses to drugs
are stored in the database
>3000 drugs

Predictive Informatics Tools



Custom informatics tools are
used to predict clinical outcomes

Human Biology Integrated into a Robust, Scalable Platform

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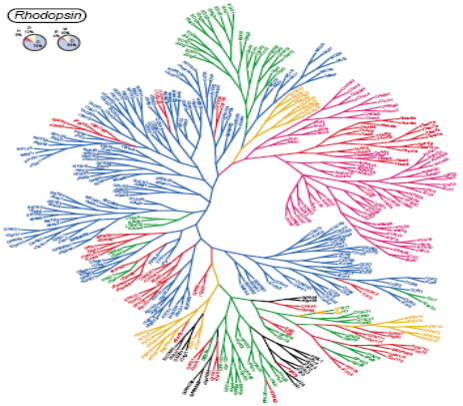
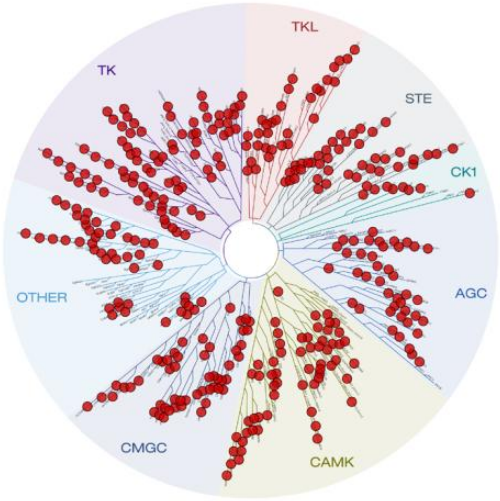
BioMAP® Diversity Plus Panel

- **12 Systems include a variety of immune and tissue cell types**
  - Vascular cells (endothelial and smooth muscle), epithelial cells (skin and lung), fibroblasts, myofibroblasts, T cell, B cell, monocytes, macrophages
  - Good blend of co-culture and single cell type BioMAP Systems
- **144 assay readouts; 4-dose, single well format (576 dpts)**
- **Covers most mechanisms represented in BioMAP Database**
  - Useful for mechanism of action studies
  - Useful for assessment of safety-related compound properties
  - Useful for assessment of efficacy-related properties of compounds targeting autoimmune or inflammatory diseases

Summary

- Innovative, differentiated product and service vendor
- A Product *and* Service Business Model allows the company to provide flexibility and convenience to clients
- Strong product development engine exponentially increases the assay menu
- Small, flexible and a nimble business organization allows us to tailor / customize our services to meet client needs

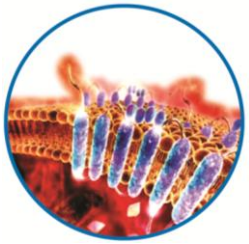


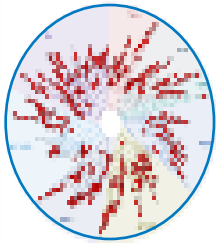


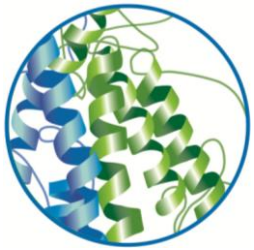
DiscoveRx

Industry Leading Portfolio that Addresses your Needs

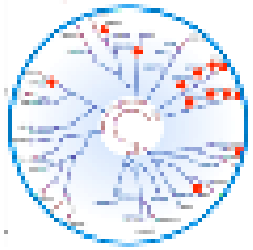
Products for In-House Screening Needs


GPCR


Kinases


NHR


Pathways


Bromodomains

Services for Outsource Screening Needs

LEAD DISCOVERY | HIT ID	LEAD OPTIMIZATION	PRECLINICAL | CLINICAL
• HTS	• Potency / Selectivity	• Selectivity
• Library Profiling	• Full Panel Profiling	• Therapeutic Panels
• Drug Re-positioning	• Custom Panel	• Safety and Liability
• De-orphanisation	• Mechanism of Action	• Disease Models
•Phenotypic Screening		

DiscoveRx