DiscoveRx

Simple Solutions for Complex Biology

Drug Discovery Assays for Cancer Research

Cancer: from Cause to Cure

25th September 2013

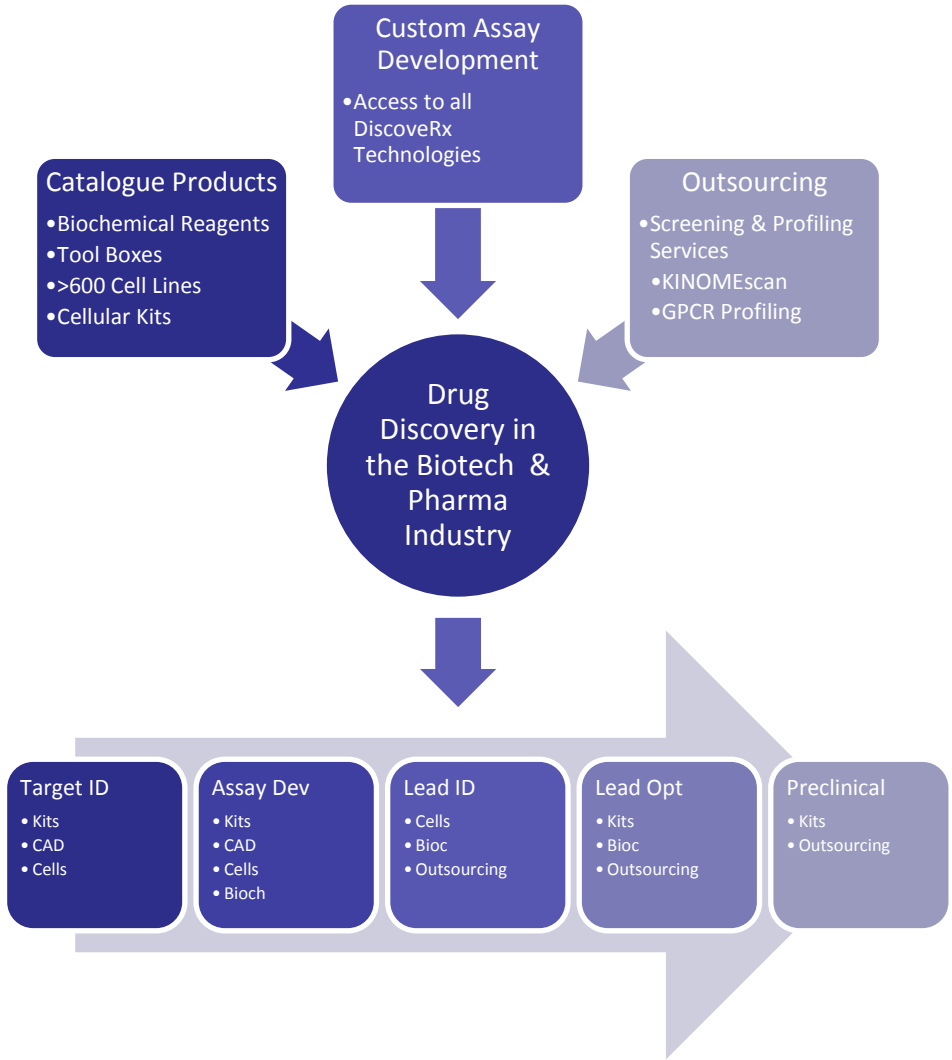
Agenda

- DiscoveRx the Biotechnology Company
  - A biotech success story
- DiscoveRx's Drug Discovery Assays for Cancer Research
  - Polypharmacology
  - Profiling oncology compounds with primary cell lines

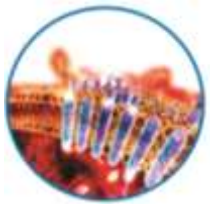
DiscoveRx

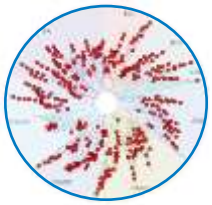
Focus on Innovation to the Drug Discovery Industry

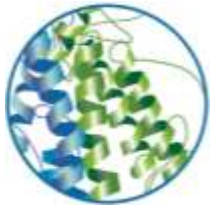
- Founded in 2000
- Privately held, venture-backed company
- Headquarters in Fremont, California
  - GPCR Centre of excellence in Fremont
  - Kinase Centre of excellence in San Diego
  - Primary Cell Line Centre of excellence in South San Francisco
  - European Headquarters in Birmingham, UK
- Commercialize cell-based and biochemical assays for the drug discovery and life science markets
- Extensive profiling services, enhanced by the acquisition of KINOME*scan* in 2010 & Bioseek in 2012



Integrated Platforms to Support All Stages of Discovery

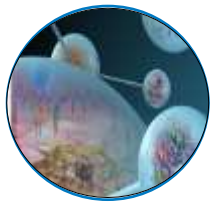

GPCRs


Kinases


NHRs


Pathways


Epigenetics


Primary Cells

LEAD DISCOVERY | HIT ID

- HTS
- Library Profiling
- Phenotypic Screens
- Fragment Screens
- Pathway Screens
- De-orphanisation

LEAD OPTIMIZATION

- Potency
- Selectivity
- Target Panel Profiling
- Custom Panels
- Mechanism of Action

PRECLINICAL | CLINICAL

- Efficacy
- Therapeutic Panels
- Safety Panels
- Primary Cell Assays
- Biomarker Discovery
- Drug Re-positioning

Complete Solution Provider

DiscoveRx

History and Evolution

2000:
Spun off from Microgenics

2002:
Launch HitHunter product line (GPCRs)

2004:
Launch PathHunter product line (GPCRs and kinases)

Begin partnerships with Pfizer and Merck

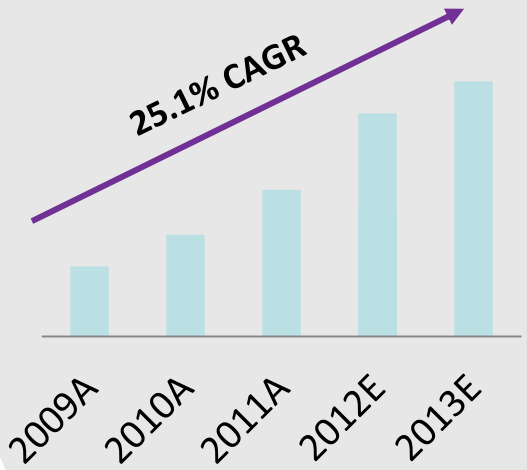
2009:
Launched service business using our proprietary reagents

2010:
Acquired KINOME*scan* from Ambit Biosciences

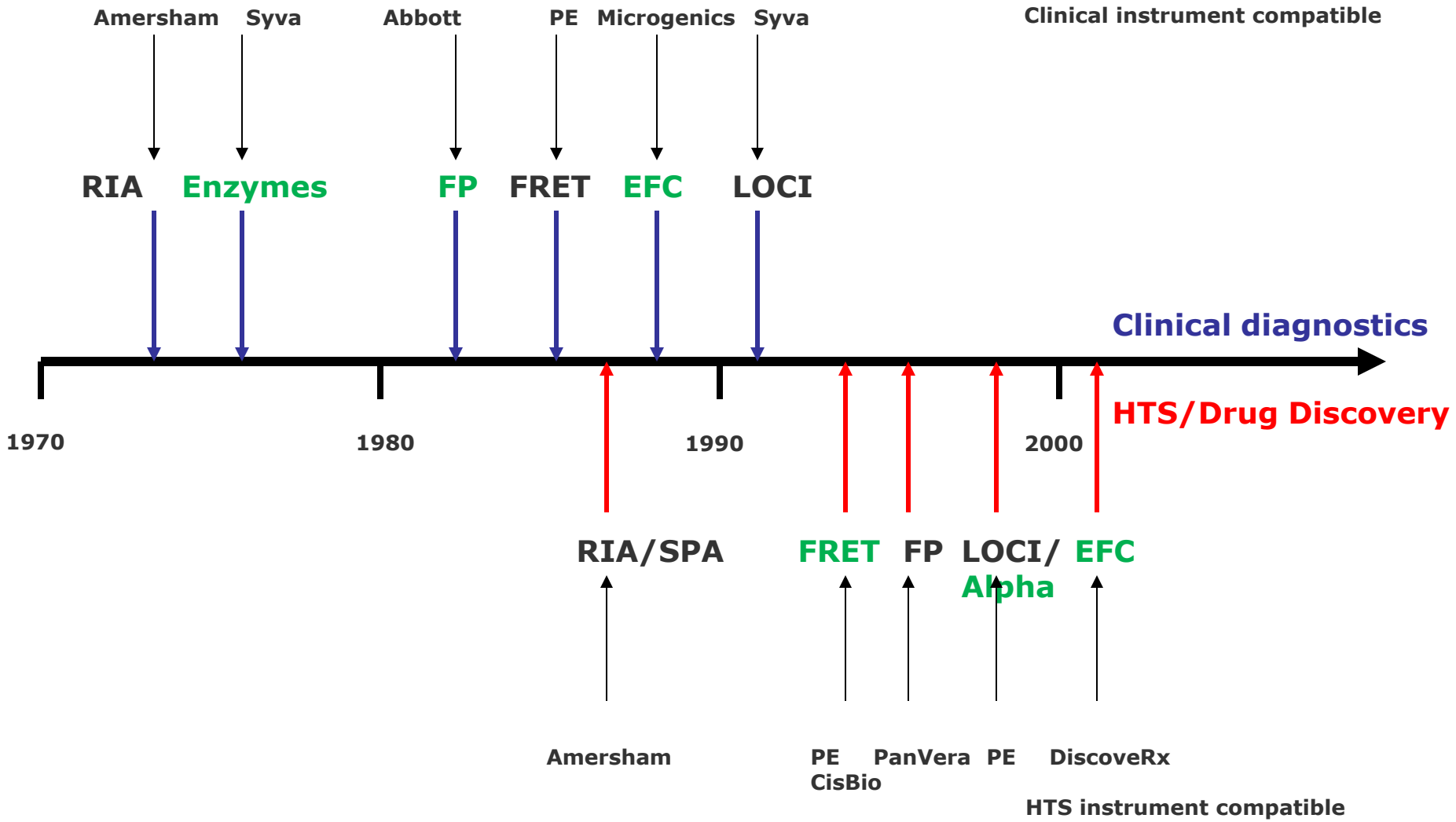
2012:
Acquired BioSeek

DISCOVERX TODAY

- **137 employees**
- **Over 1000 products**
- **3 technology platforms and 5 recognized brands:**
- **Extremely proprietary :**
  - **17 US,12 EU, 3 Japanese patents (11 pending)**
- **Sales in 25 countries**

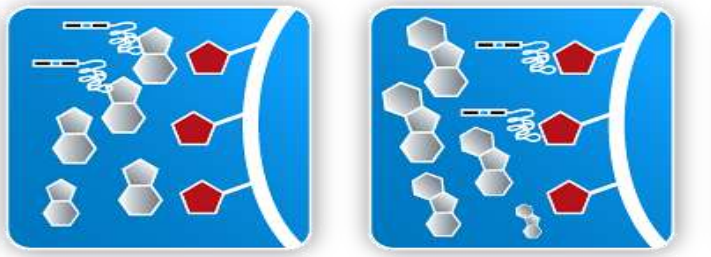


Diagnostics and HTS technology history



Three Core Technology Platforms

Biochemical Assays (Binding)



KINOMEscan

bromoSCAN

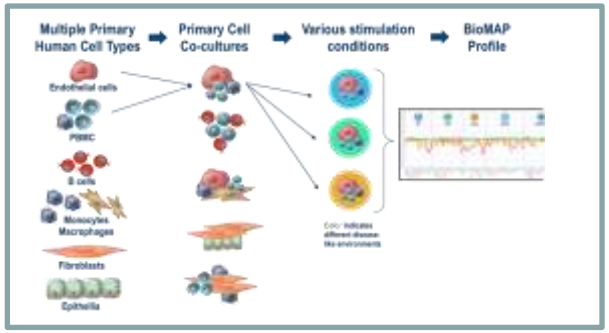
Cellular Assays (EFC)

PathHunter®

HitHunter®

InCELLHunter™

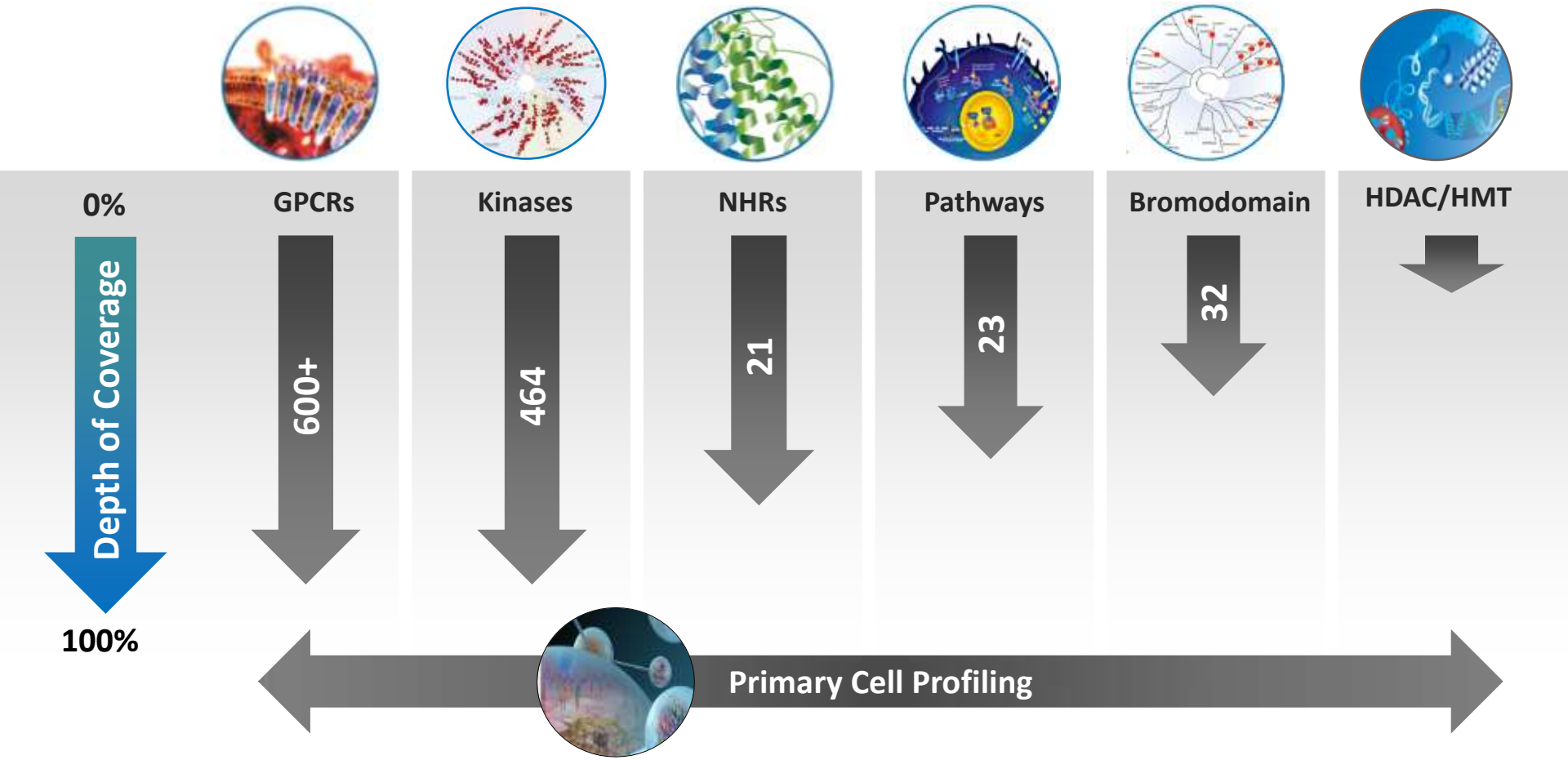
Human Primary Cell Assays



BioMAP

Proven and Robust Platforms with Multi-year Investments

>75% Coverage of Druggable Targets + Primary Cell Phenotypic Assays



1,118 assays covering 741 druggable targets

- All major drug target classes covered
- Multiple assays for single target

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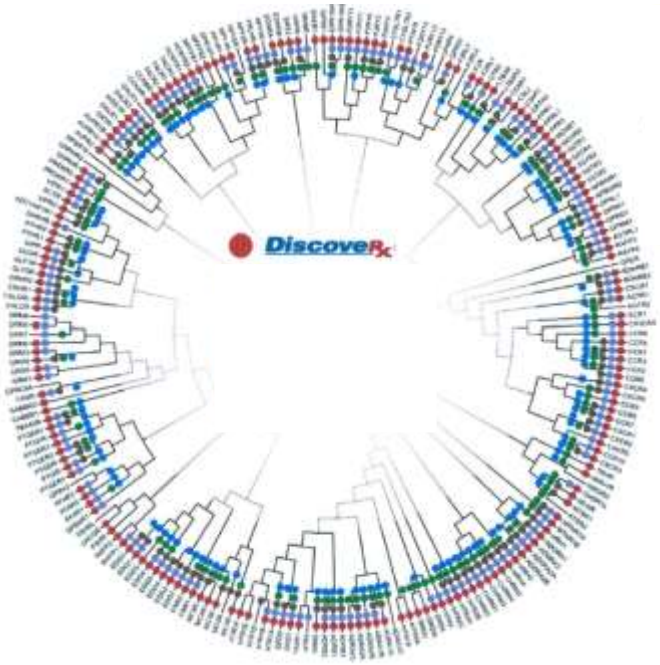
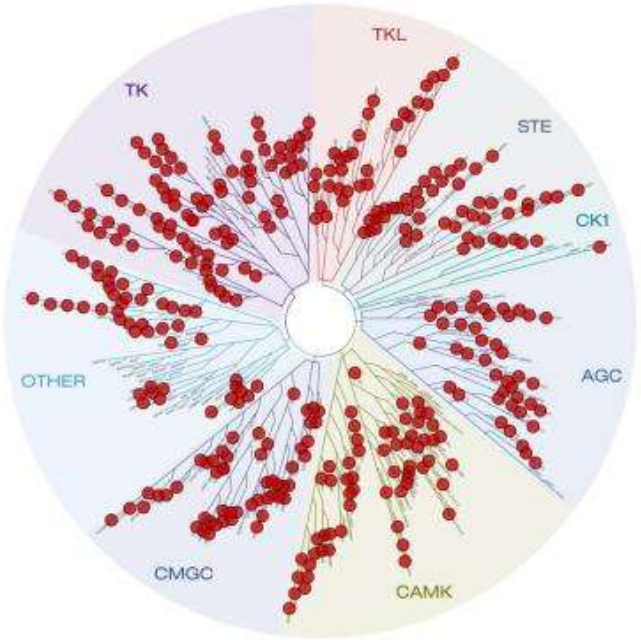
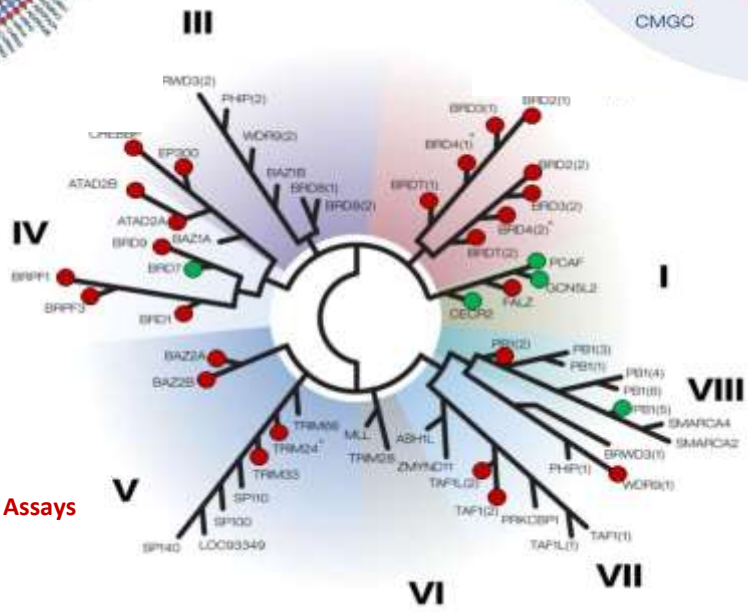
Industry Leading Assay Panels



Nearly 600 GPCR Assays



Nearly 464 Kinase Assays



Nearly 32 Bromodomain Assays

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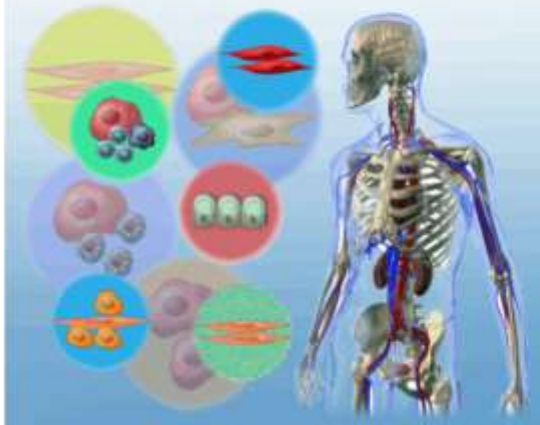
BioMAP® : Primary Cell Compound Profiling Platform

BioMAP® Assay Systems

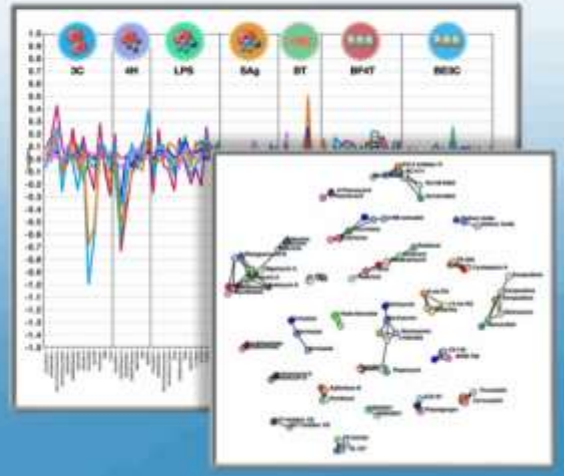


Human primary cells
Disease-models
30+ systems

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

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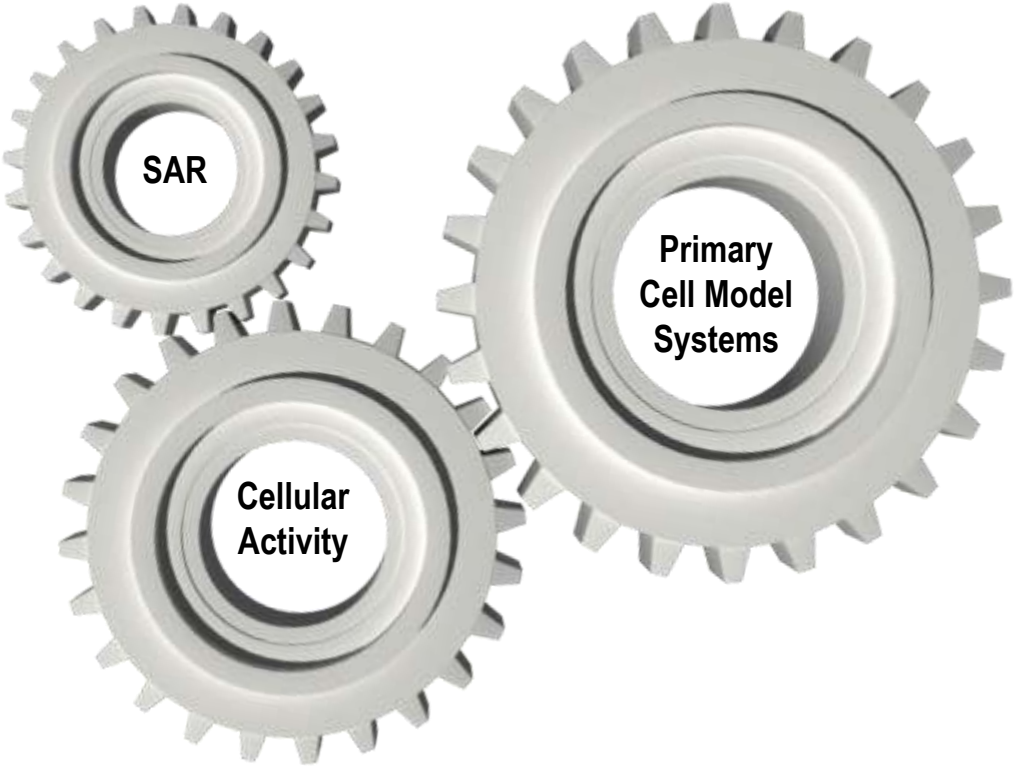
DiscoveRx Integrated Solution Portfolio

- Is my compound potent and selective?

KINOMEscan
bromoSCAN



- What is the phenotypic impact of my compound in the context of disease?
- What efficacy and safety biomarkers are detected?

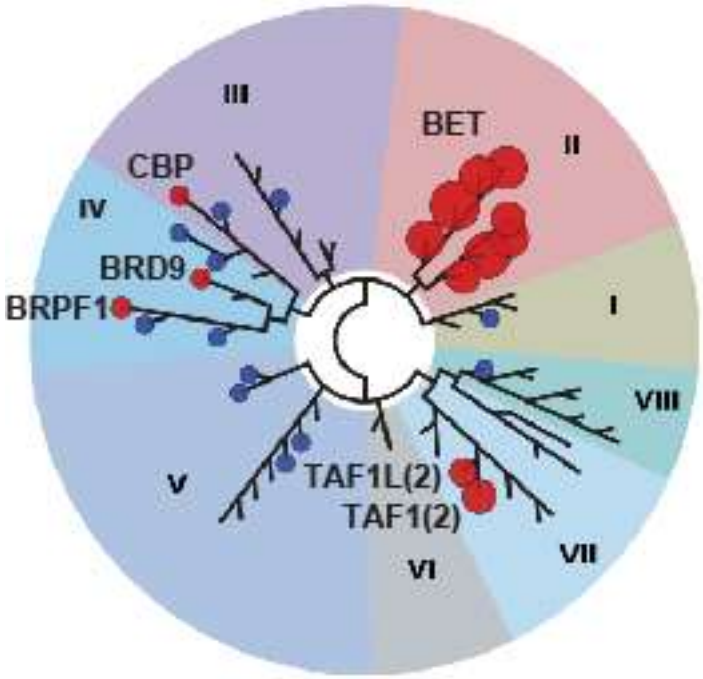
BioMAP

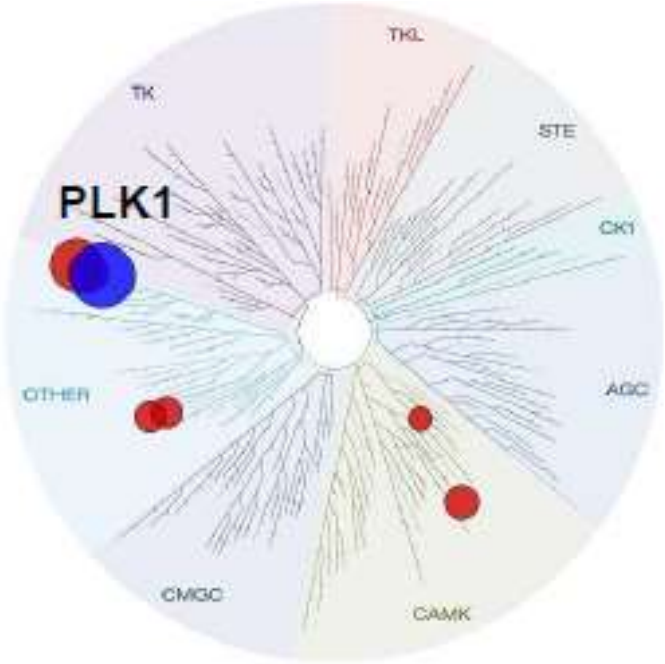
- Does my compound bind the target in a cellular environment?

PathHunter®

Panels Reveal Polypharmacology

Clinical PLK inhibitor; dual PLK/BRD4 activity attractive for certain tumor types (e.g. multiple myeloma)





BRD4 K_d = 12 nM

(S. Knapp, in collaboration with DiscoveRx; manuscript in preparation)

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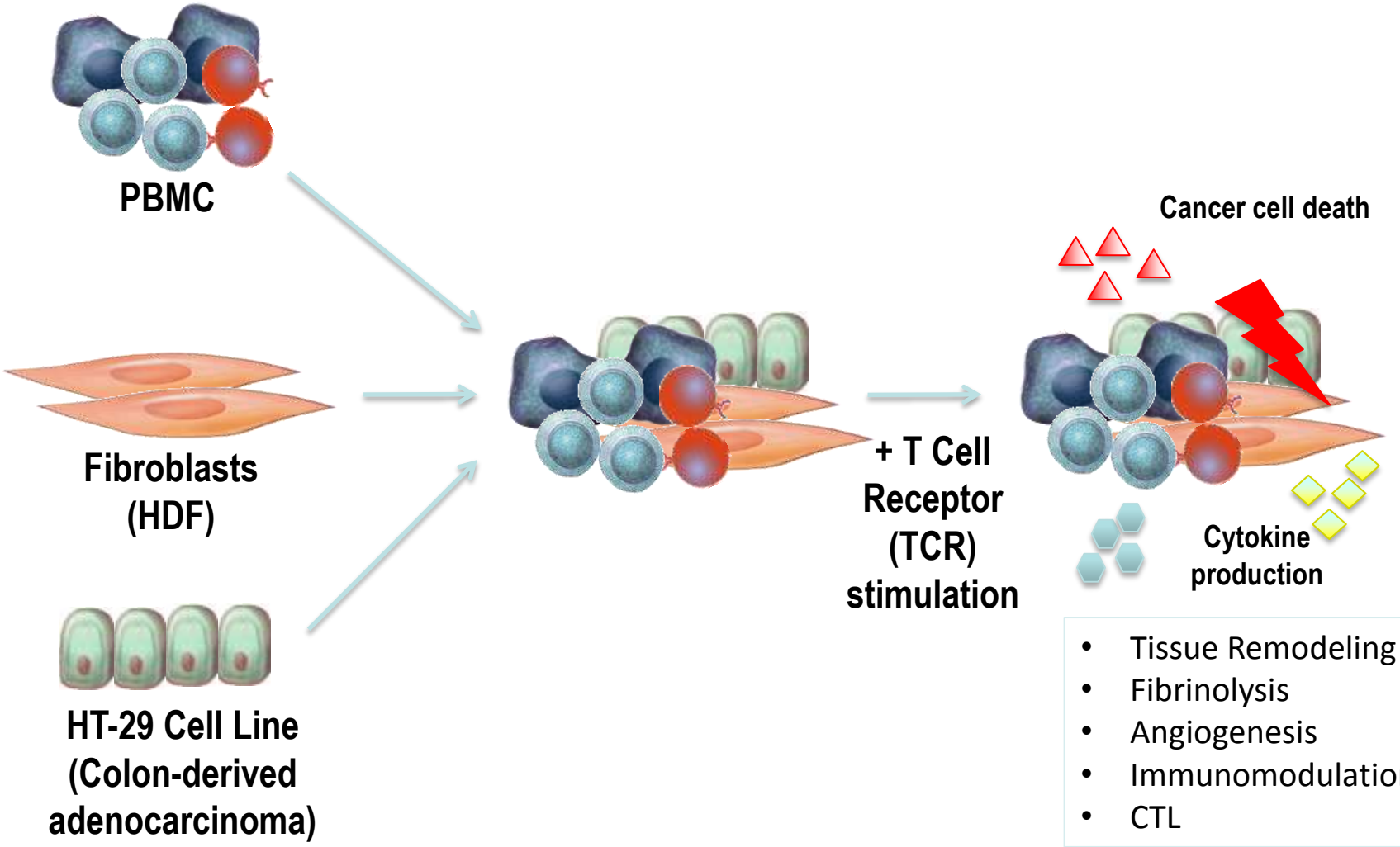
BioMAP® for Oncology Drug Discovery

- Challenges:
  - Tumor-host interactions are important in cancer
  - Currently these are captured only in vivo in animals such as xenograft models or in clinical trials
- Opportunities:
  - BioMAP Oncology Systems model the complex tumor-host environment with human primary cells + tumor cells
  - These systems include human stromal, vascular and immune components → for a more complete coverage of host biology

Construction of BioMAP® StroHT29 System



- Tissue Remodeling
- Fibrinolysis
- Angiogenesis
- Immunomodulation
- CTL

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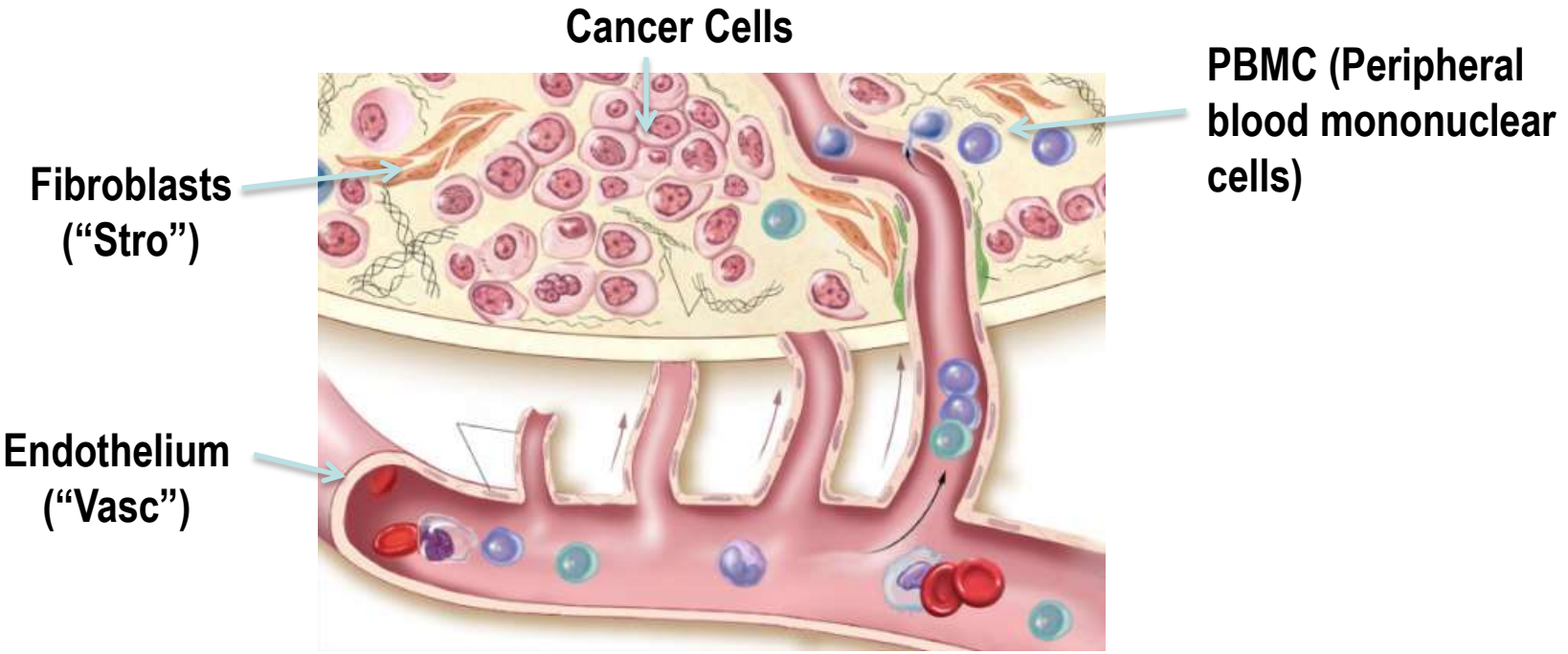
BioMAP® Oncology Systems



Adapted From Burton ER et al., J. Biol. (2009)

System	Primary Human Cell Types	Stimuli	Disease / Tissue Relevance	Readout Parameters
StroHT29 	HT-29 colon Adenocarcinoma cell line + Primary Human Fibroblasts + PBMC	T Cell Receptor (TCR)	Oncology: Host Tumor-Stromal Microenvironment	VCAM-1, uPAR, Collagen I, Collagen III, IP-10, MMP-9, PAI-1, PBMC Cytotoxicity, sGranzyme B, sIFNγ, sIL-10, sIL-17A, sIL-17F, sIL-2, sIL-4, sIL-6, SRB, sTNFα, sVEGF, TIMP2, tPA, uPA
VascHT29 	HT-29 colon Adenocarcinoma cell line + Primary Human Endothelial cells + PBMC	T Cell Receptor (TCR)	Oncology: Host Tumor-Vascular Microenvironment	MCP-1, VCAM-1, CD40, CD69, uPAR, Collagen IV, IP-10, MIG, PBMC Cytotoxicity, sGranzyme B, sIFNγ, sIL-10, sIL-17A, sIL-2, sIL-4, sIL-6, SRB, sTNFα

Benchmark Compounds for Oncology Systems

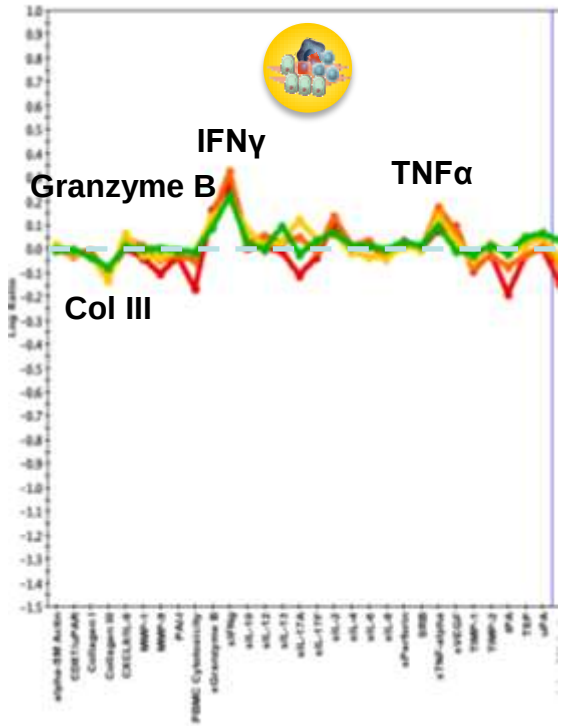
Profiles in StroHT29 and VascHT29 are available for compound comparison

Agent	Mechanism of Action (MOA)
17-AAG	Hsp 90 inhibitor
Vorinostat	HDAC inhibitor
SB431542	TGF-beta1 inhibitor
Oligomycin	ATPase inhibitor
Paclitaxel	microtubule stabilizer
IC87114	PI-3K delta inhibitor
Colchicine	microtubule destabilizer
GSK-1120212	MEK inhibitor
LY294002	Pan PI-3K inhibitor
Daunorubicin	Intercalates DNA
Topotecan	DNA topoisomerase I inhibitor
Erlotinib	EGFR inhibitor
Nutlin-3	MDM2/p53 interaction inhibitor
Vemurafenib	PLX-4032, B-Raf V600E inhibitor
GDC-0879	B-Raf, ERK inhibitor
AZD2281	PARP-1, -2 inhibitor
AZD6244	MEK inhibitor
BIRB-796	p38 MAPK inhibitor
Rapamycin	mTor inhibitor
Everolimus	mTor inhibitor
Dasatinib	RTK inhibitor
5-Fluorouracil	Pyrimidine Analog
Oxaliplatin	DNA Synthesis Inhibitor

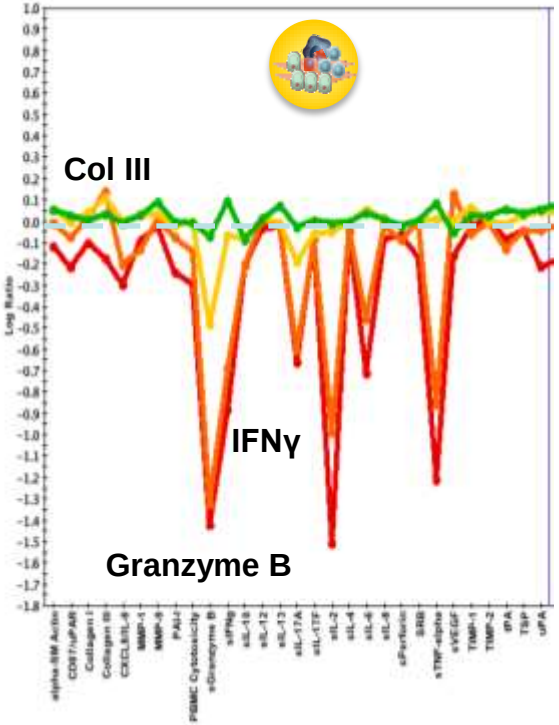
Validation

Drug Activity Profiles in StroHT29

Erlotinib (EGFR)



PLX-4032 (B-Raf)



- **Cancer drugs induce unique activity profiles**
  - Capture tumor/host responses
  - Can be used for testing drug combinations

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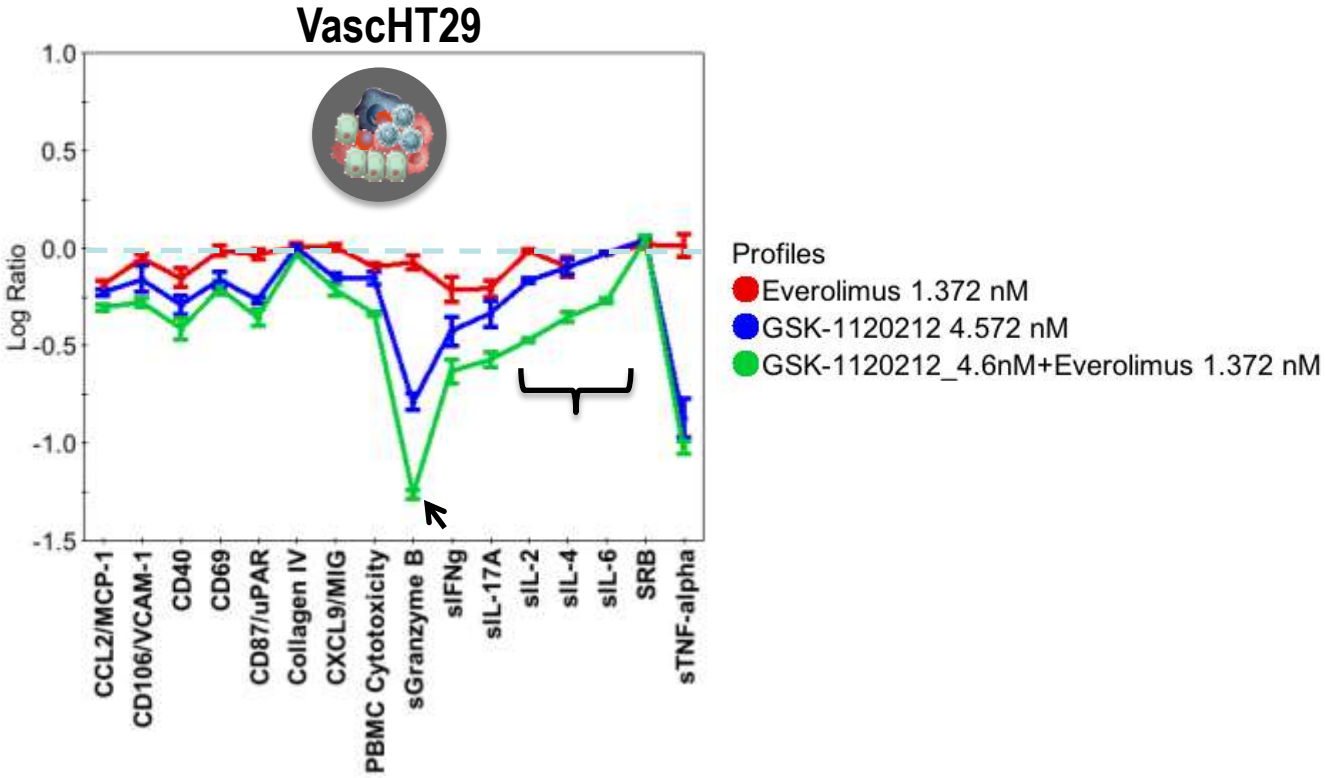
Drug Combinations

Simultaneous treatment with MEK and mTOR compounds



- Arrow and bracket show a synergistic reduction in sGranzyme B, sIL-2, sIL-4 and sIL-6 upon combination treatment with MEK (GSK-1120212) and mTOR (Everolimus) inhibitors

DiscoveRx

DiscoveRx 2015: A Look into the Future

- Our *compelling* product and service offering is a ***must-have*** in every drug discovery program
  - FDA Mandate: Every compound must have a *scan*MAX and BioMAP profile
- Target based and Phenotypic screening products and services
- Largest Portfolio of products based on proprietary and innovative technology platforms
- Key Relationships with Top 20 pharma and Biotech
- Key Strategic acquisitions to service customers in preclinical toxicology and / or Target Validation platform
- Continue to thrive, innovate and collaborate!