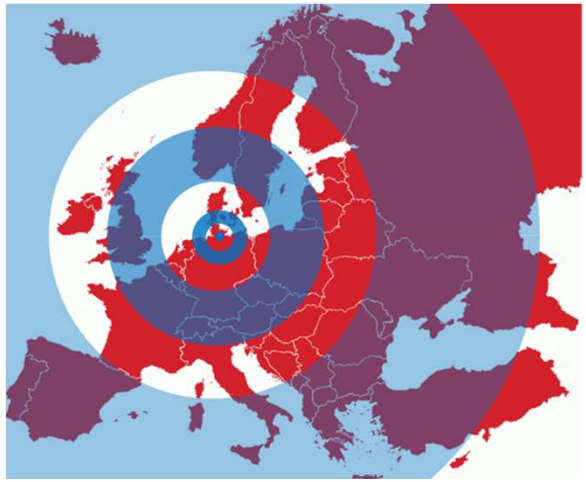
Academic drug discovery in Europe

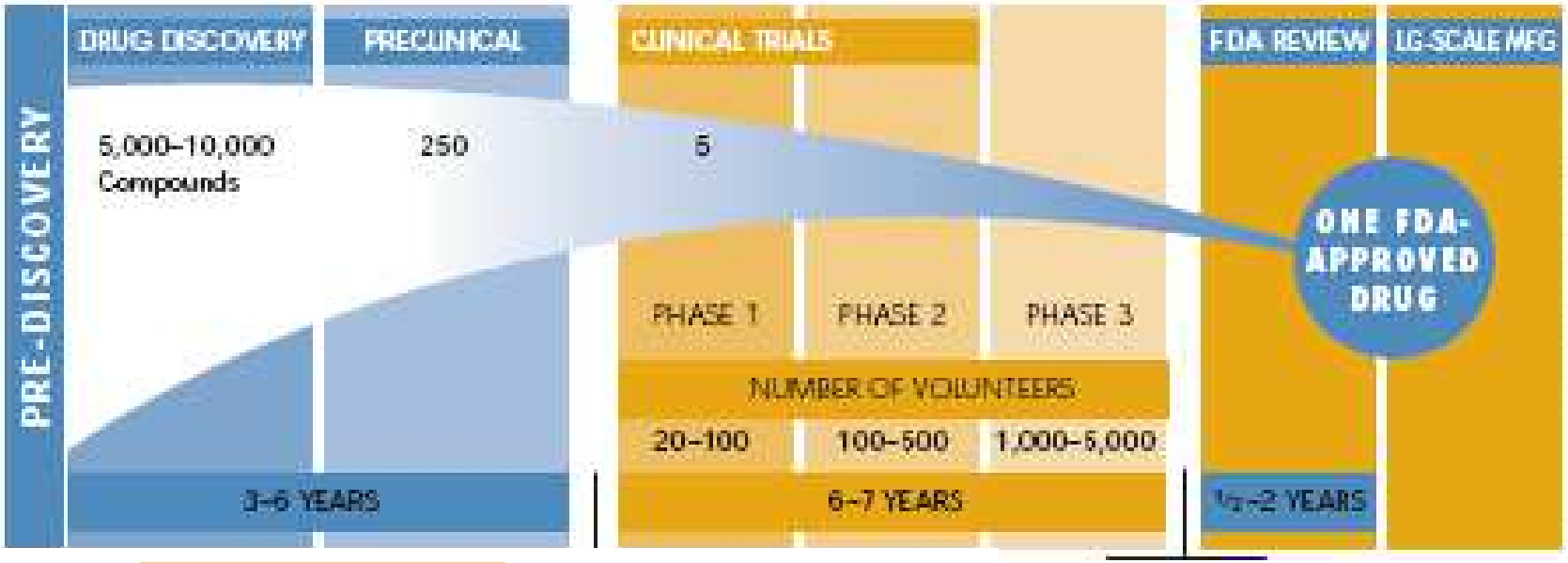
European ScreeningPort

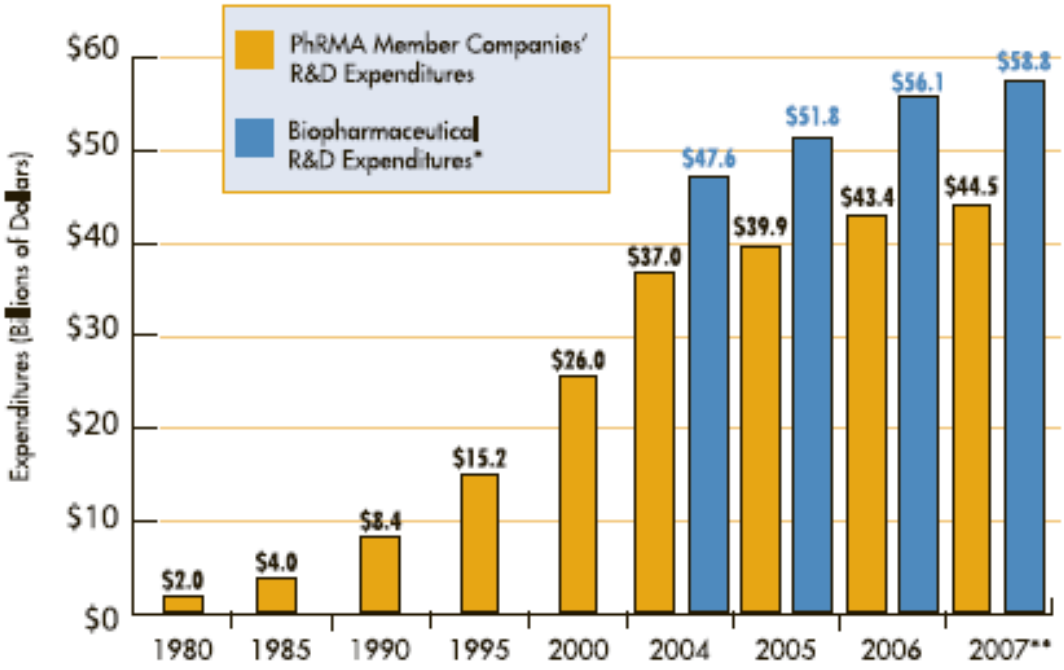


Kiel 28th June 2012

contact@screeningport.com
www.screeningport.com

Drug Discovery Living with Failure



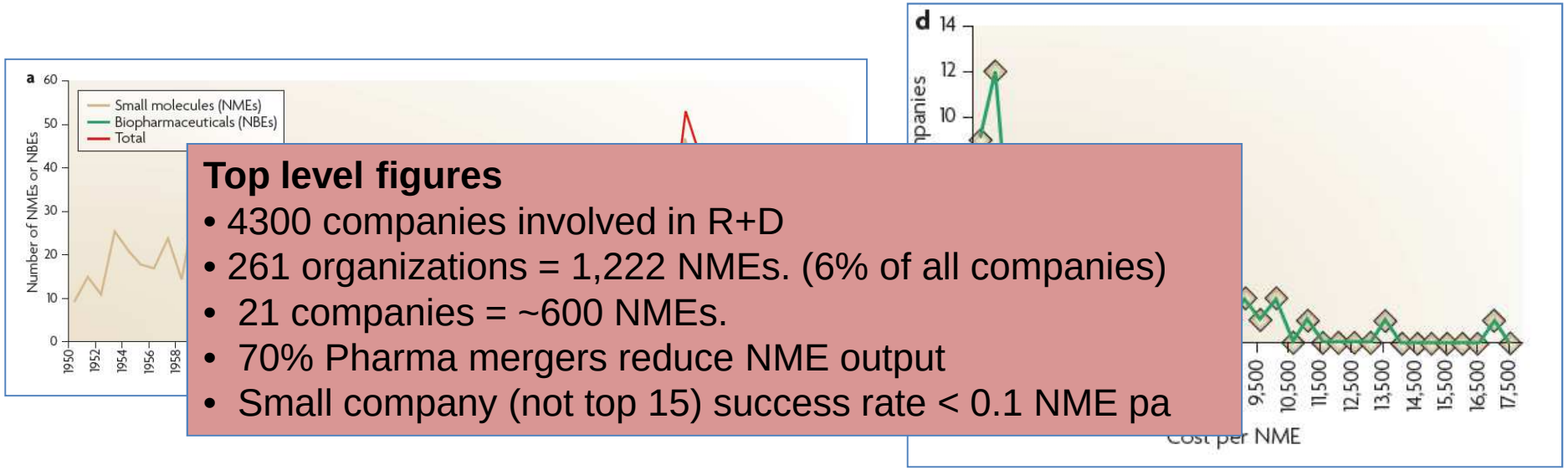


Approvals

- Drugs approved in 2007 = 23[12]
- Only 2 of 10 marketed drugs ever produce revenues that match or exceed R&D costs.
- In the 25 years since the *Orphan Drug Act* was established, more than 300 orphan drugs have been approved.[14]
- Average effective patent life for major pharmaceuticals in 2005 = 11 years[15]

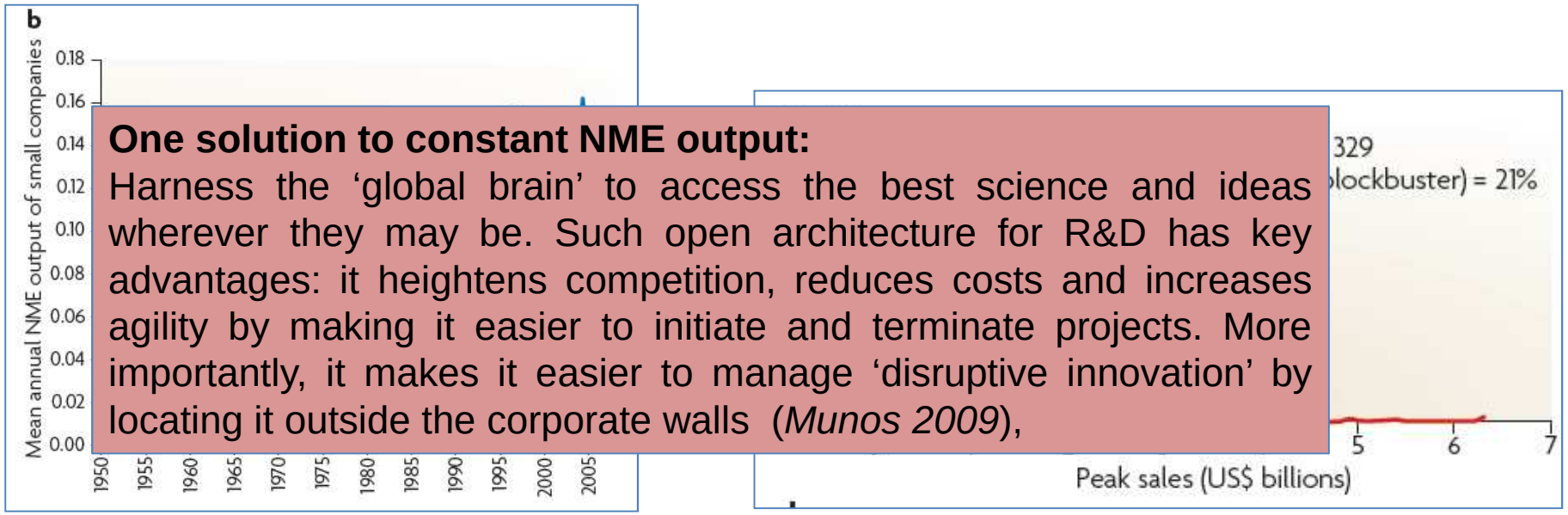
The innovation gap updated

European ScreeningPort



Top level figures

- 4300 companies involved in R+D
- 261 organizations = 1,222 NMEs. (6% of all companies)
- 21 companies = ~600 NMEs.
- 70% Pharma mergers reduce NME output
- Small company (not top 15) success rate < 0.1 NME pa



One solution to constant NME output:

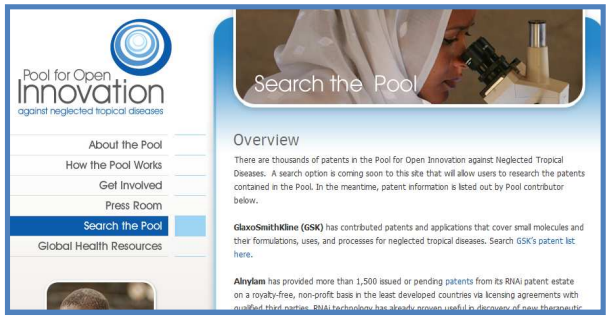
Harness the 'global brain' to access the best science and ideas wherever they may be. Such open architecture for R&D has key advantages: it heightens competition, reduces costs and increases agility by making it easier to initiate and terminate projects. More importantly, it makes it easier to manage 'disruptive innovation' by locating it outside the corporate walls (*Munos 2009*),

All figs from Munos 2009 Nature Drug Discovery

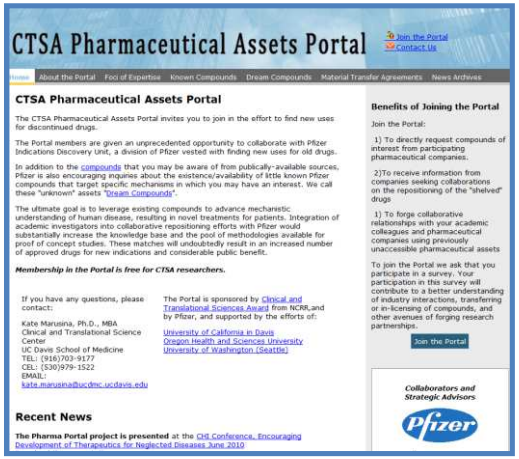
European ScreeningPort

Industry response to the innovation gap

Data and IP pooling



New collaboration models

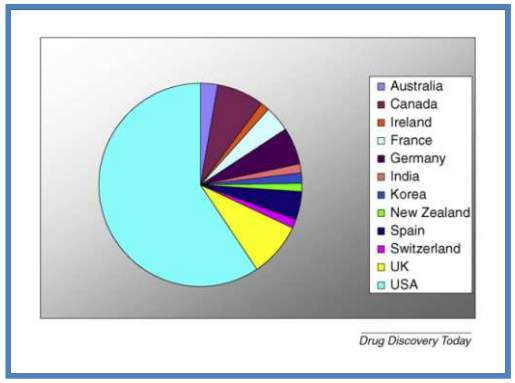


Talking the talk

European ScreeningPort

Academic Initiatives in Drug Discovery

> 70 Screening Centres



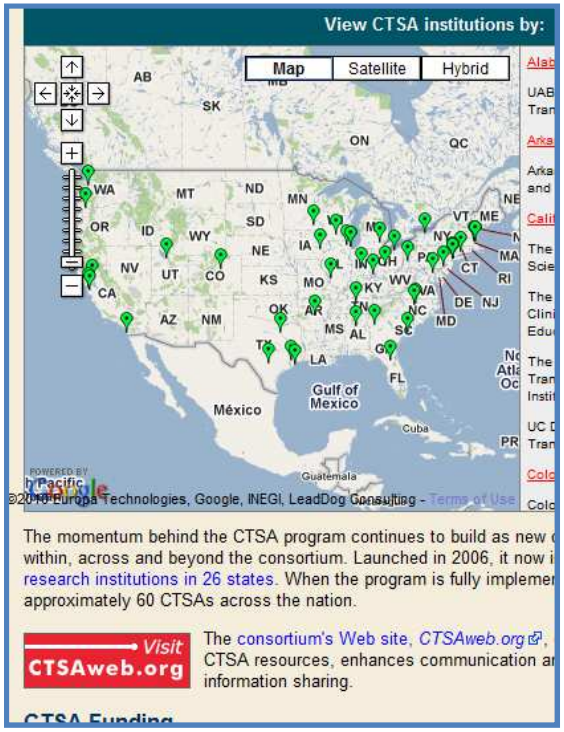
Frearson and Collie 2009


The Drug Discovery Portal: A Computational Platform for Identifying Drug Leads from Academia

Authors: L. Clark, Rachel; F. Johnston, Blair; P. Mackay, Simon; J. Breslin, Catherine; N. Robertson, Murray; B. Sutcliffe, Oliver; J. Dufton, Mark; L. Harvey, Alan

CURRENT PHARMACEUTICAL DESIGN

Clinical and Translational Science Centres USA



Planned 60 centres
> $500 million
of NIH funds

http://www.ncrr.nih.gov/

Initiatives in Europe

http://imi.europa.eu
http://www.eatris.eu/
http://www.eu-openscreen.eu/

Lead Finding in Big Pharma

OPINION

Impact of high-throughput screening in biomedical research

Ricardo Macarron, Martyn N. Banks, Dejan Bojanic, David J. Burns, Dragan A. Cirovic, Tina Garyantes, Darren V. S. Green, Robert P. Hertzberg, William P. Janzen, Jeff W. Paslay, Ulrich Schopfer and G. Sitta Sittampalam

NATURE REVIEWS | DRUG DISCOVERY

188 | MARCH 2011 | VOLUME 10

Table 1 | **Contributions of HTS in 2009 in four pharmaceutical companies***

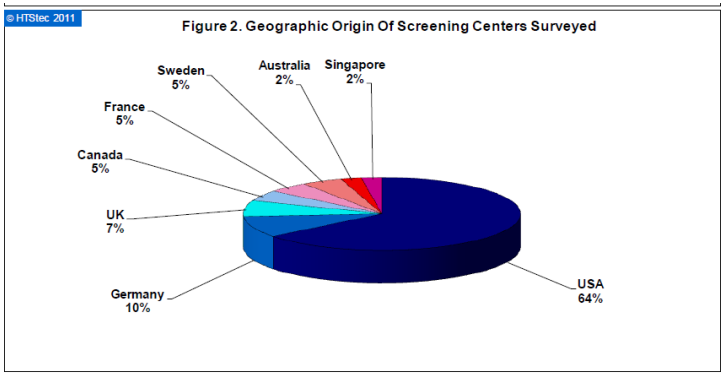
Company	Percentage of current portfolio derived from in-house HTS		
	Chemical optimization	Candidate selected	Clinical development
A	84%	30%	32%
B	60%	N/A	N/A
C	76%	N/A	N/A
D	48%	18%	19%

HTS, high-throughput screening; N/A, not available. *Data taken from GlaxoSmithKline, Novartis, Sanofi-Aventis and Wyeth (now part of Pfizer).

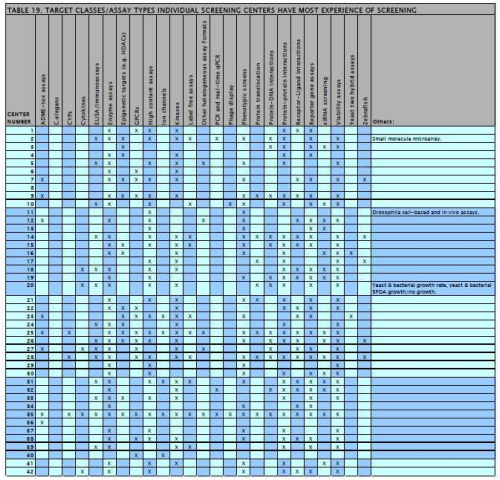
Table 2 | **Examples of recently approved drugs with origins in HTS hits**

Drug (US trade name; company)	Indication	Target class	Year HTS was run	Year of FDA approval
Gefitinib (Iressa; AstraZeneca)	Cancer	Tyrosine kinase	c. 1993	2003
Erlotinib (Tarceva; Roche)	Cancer	Tyrosine kinase	c. 1993	2004
Sorafenib (Nexavar; Bayer/Onyx Pharmaceuticals)	Cancer	Tyrosine kinase	1994	2005
Tipranavir (Aptivus; Boehringer Ingelheim)	HIV	Protease	c. 1993	2005
Sitagliptin (Januvia; Merck & Co)	Diabetes	Protease	c. 2000	2006
Dasatinib (Sprycel; Bristol-Myers Squibb)	Cancer	Tyrosine kinase	1997	2006
Maraviroc (Selzentry; Pfizer)	HIV	GPCR	1997	2007
Lapatinib (Tykerb; GlaxoSmithKline)	Cancer	Tyrosine kinase	c. 1993	2007
Ambrisentan (Letairis; Gilead)	Pulmonary hypertension	GPCR	c. 1995	2007
Etravirine (Intelence; Tibotec Pharmaceuticals)	HIV	Reverse transcriptase	c. 1992	2008
Tolvaptan (Samsca; Otsuka Pharmaceutical)	Hyponatraemia	GPCR	c. 1990	2009
Eltrombopag (Promacta; GlaxoSmithKline)	Thrombocytopaenia	Cytokine receptor	1997	2008

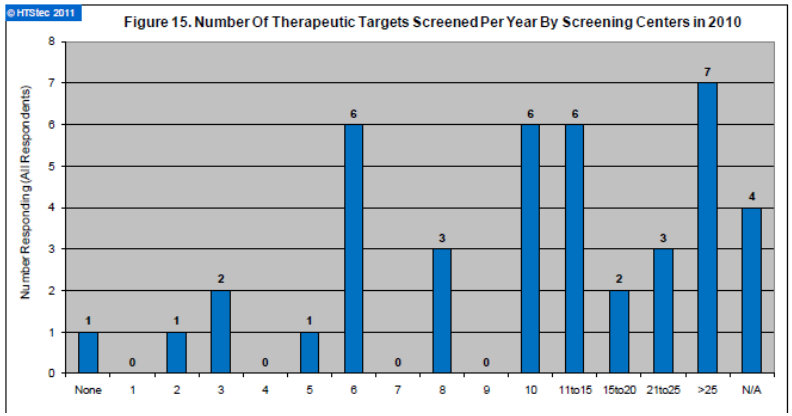
European Academic Screening Centres – 2011 figures



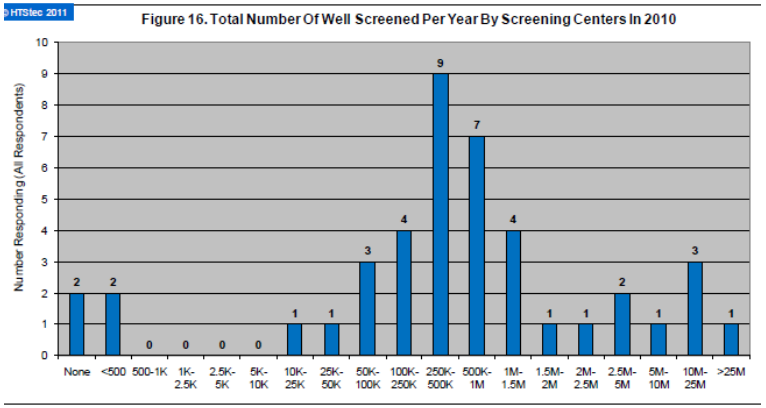
European, approx 27% of the total (64% USA)



Typically cover all main target classes



For all centres, average of 13 targets p/a



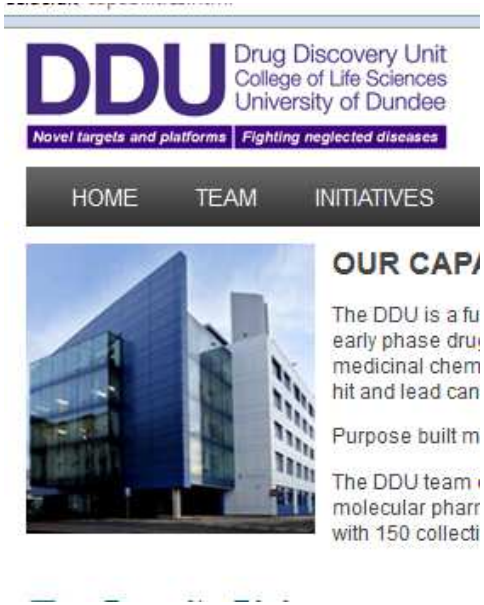
Most centres screen < 1 million wells per year

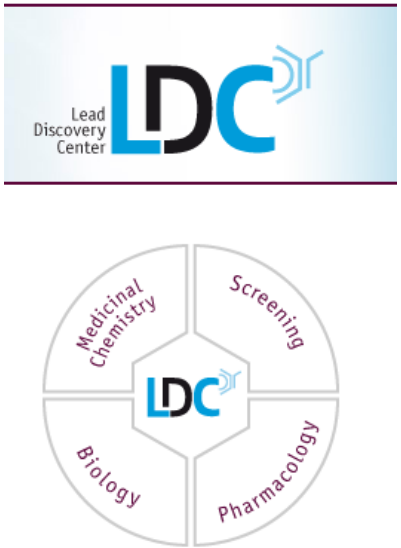
All figures courtesy of John Comley - HTStec ‘**Academic Outreach and Screening Trends 2011**’ Report

European ScreeningPort

Regional and centralised drug discovery facilities

- Assay development, compound logistics and Screening facilities on par with what might be found in small and medium Biotechnology organisation
- Assay biology and targets originate from Institutional or regional networks (eg Max Planck), Scottish Universities etc) but also free to bring in external targets from other institutions
- Large libraries > 200k and facilities to profile (ADME, tox, Med-chem, Computational)
- Diverse, fragment and focussed sets with emphasis on small molecules
- Integrated robotics and workstation based infrastructures
- Emphasis on drug discovery (eg tropical diseases) as well as Chemical Biology
- Staff led typically by experienced ex-Pharma scientists





European ScreeningPort

Pan European Initiatives on horizon

Scale will be less than MLP, but still order of magnitude > than previous efforts (ChemBioNet etc)

EATRIS
European Advanced Translational Research Infrastructure in Medicine

Scope of EATRIS Consortia

EATRIS has built its consortia around five technology areas (called prod

- Vaccines
- Imaging and Tracers
- Biomarkers
- Advanced Therapy Medicinal Products (ATMP) and Biologics
- Small Molecules

Implementation Phase Oct 2011

EU-OPENSCREEN
ESFRI ROADMAP 2008

IMPLEMENTATION PLAN

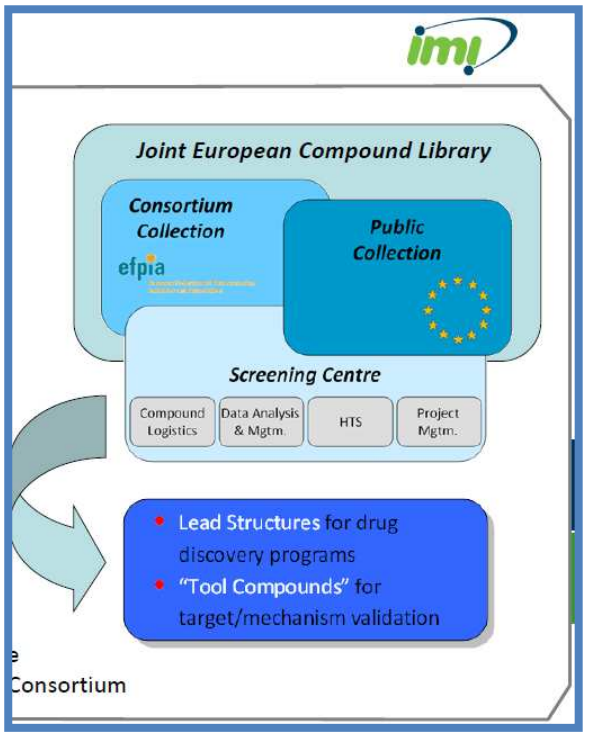
2011-2013 | 2014 | After 2015

Preparation | Construction | Operation

- **Preparatory Phase** (3 years): Preparation of a master plan describing in detail the mode of construction and operation. EU funding 3.7 M€.
- **Construction Phase** (1 year): Construction of infrastructure (existing and new sites). National funding.
- **Operation Phase:** Run the infrastructure and provide access to researchers. Diverse funding sources.

Implementation 2013/2014

European Lead factory



Implementation 2013

http://imi.europa.eu
http://www.eatris.eu/
http://www.eu-openscreen.eu/

ESP Centralized Screening Hub

European ScreeningPort

Research | Screening | Discovery | Development | Marketing

Academia

European ScreeningPort

Compound Management

Target + Biol. IP

HTS System

Validated Hit:
- xC_{50}
- Cytotox
- Cyp P450
- Apoptosis
- Biol. IP + Chem. IP

Project Funding

Basic Funding by BMBF and Shareholders

ESP infrastructure

European ScreeningPort

Research | Screening | Discovery | Development | Marketing

Academia | European ScreeningPort | Pharma | Patients

Chemistry

Evotec Library
- 250.000 cpds
- Proven track record

ESP Library
- proof of concept / known drug library
- Joint academic ChemBioNet

ViSoR
- Virtual system for molecular docking

Infrastructure

Services

Project development:
- Funding support
- Grant applications
- Build up consortia

Project prosecution:
- Assay Development
- Screening (prim., sec., HC, fragment based)
- Hit Validation

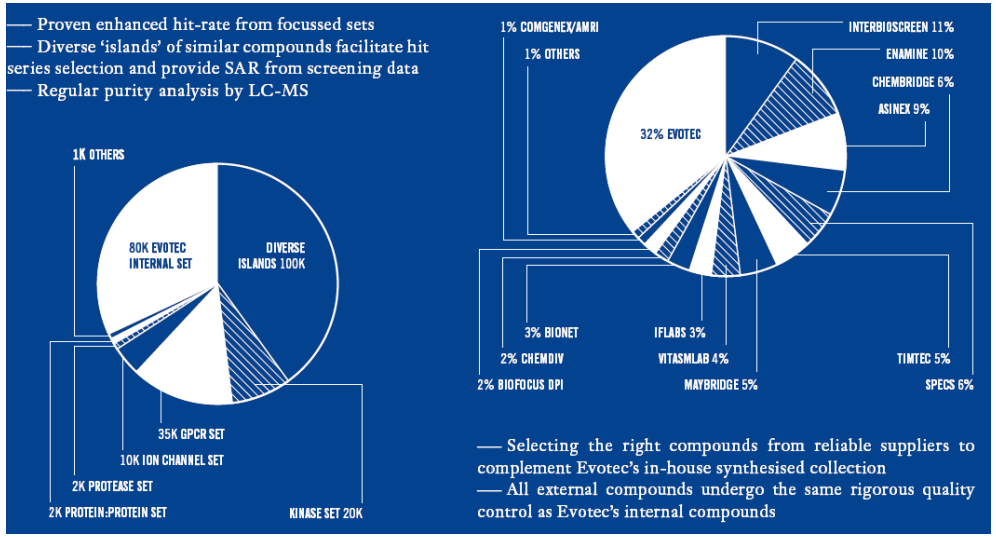
Chemical Libraries at ESP

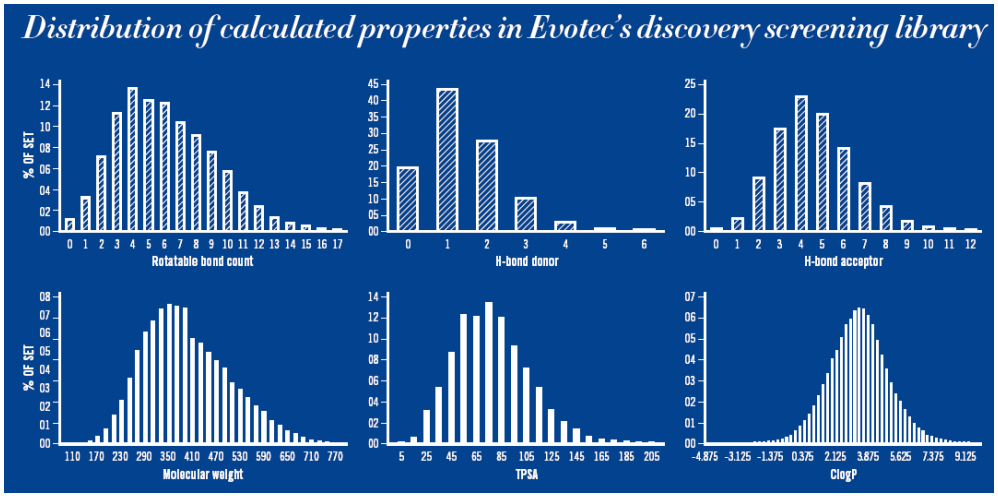
- Access to Evotec Library
  - Σ = 250,000 compounds (cpds)
- Enamine Library hosted
  - Σ = 200,000 compounds (cpds) (70% diverse, gene and target family including PPI's)
- ESP Library
  - Σ = 35,000 compounds (NP's, lead-like synthetic, 10% blinded)
- Access to Hypha Discovery
  - Σ = 10,000 compounds

Evotec small molecule library

Access to Evotec Library

- Σ = 250,000 compounds (cpds)
- 20k Additional fragment based library
- All cpds QC-checked (LC/MS)
- Optimized cpd storage for long term stability
- Proven enhanced hit-rate from focussed sets
- Cpd design guided by Lipinski's Rule-of-Five and knowledge-based filters to enhance drug likeness
- Privileged scaffolds and drug-like functionality complimented with extensive use of proprietary building blocks
- More than 40 different structural cpd classes
- Cpd preparation via validated, synthetic routes ensuring rapid access to analogues



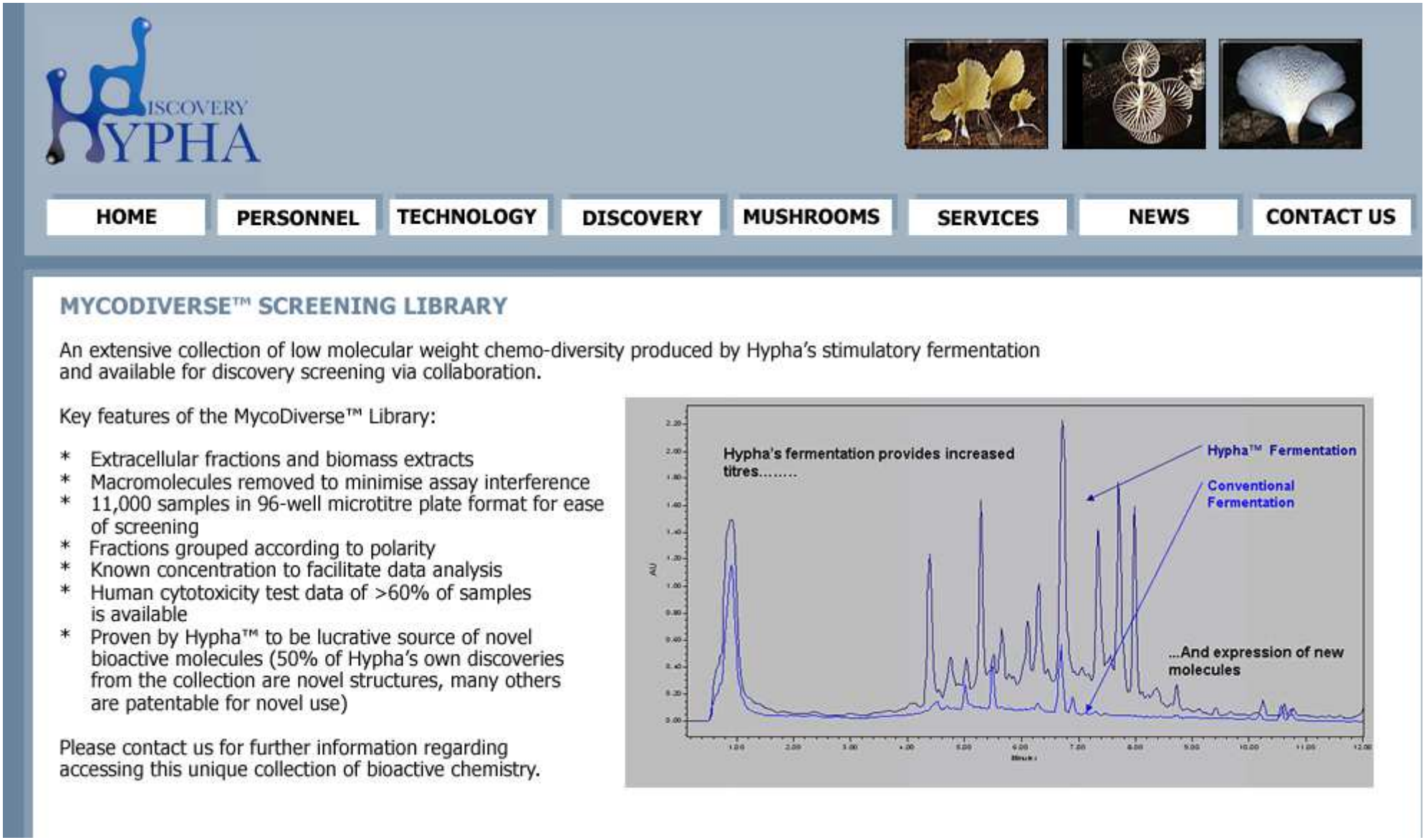


ESP Library - Blinded

- 2000 compounds Natural products and synthetic molecules from a German research Institute
- 300 compounds - anti infectives from a German research Institute
- Future – an additional 1000 marine derived Natural products from a German research Institutes

These compounds have a less straightforward IP position but are available for screening in all projects

Hypha Discovery Library



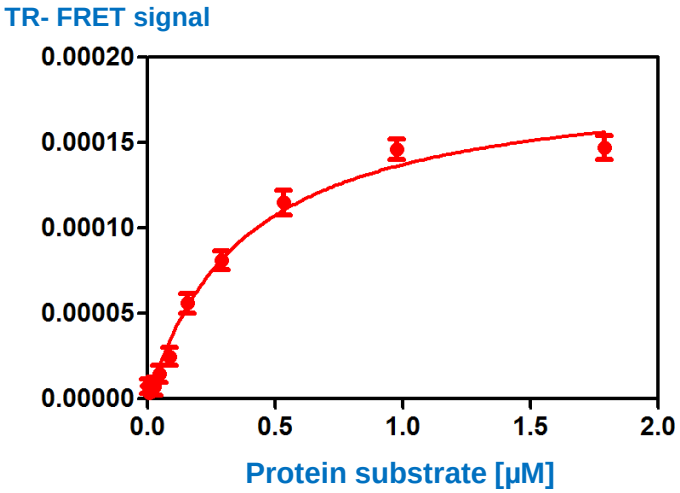
Case Study 1 North American University
Indication Neurodegenerative disease
Target Protease

European ScreeningPort

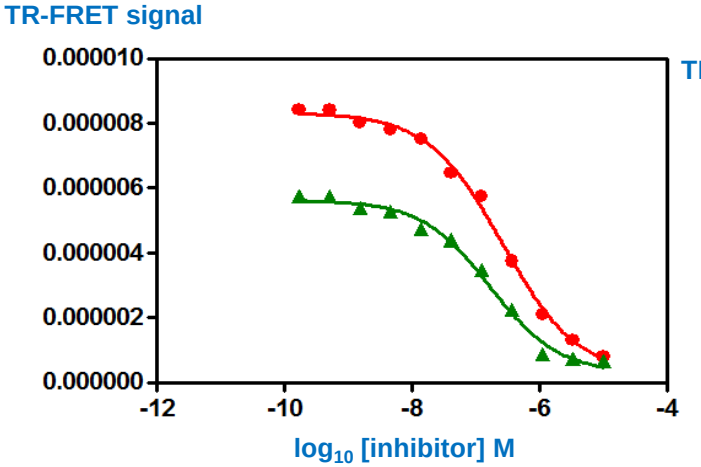
- Assay development
  - Using full length protein substrate
  - TRF readout with antibody detection of cleavage site
  - enzyme titration, kinetics of substrate turnover, standard compound profiling
  - DMSO tolerance, day-to-day and plate-to-plate variability

- HTS campaign
  - Primary screen 23k compounds
  - Hit Confirmation in Primary 11pt dose response
  - Hit characterization 2 additional orthogonal assay formats
    - Secondary assay 1 – Luminescence
    - Secondary assay 2 - Fluorescence

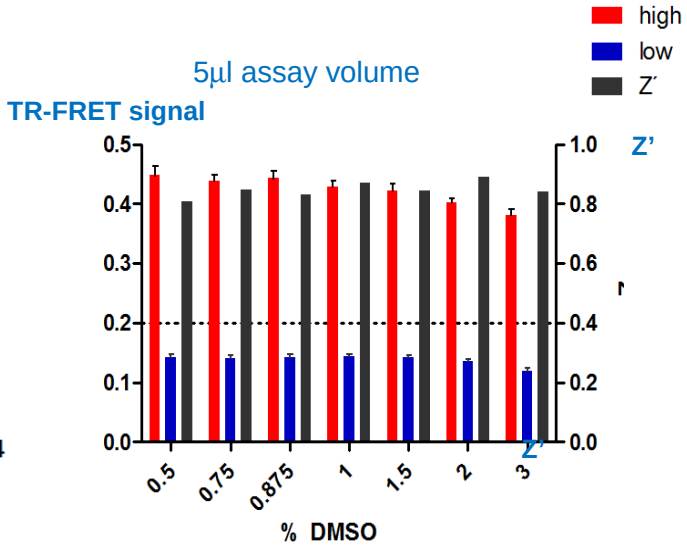
Screening and Profiling 23k cpds



Substrate Km

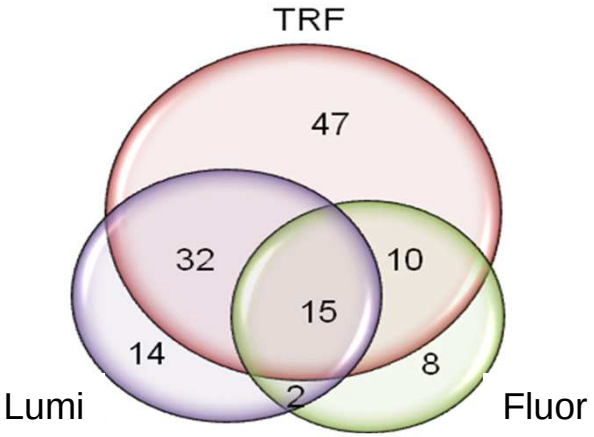


Pharmacology

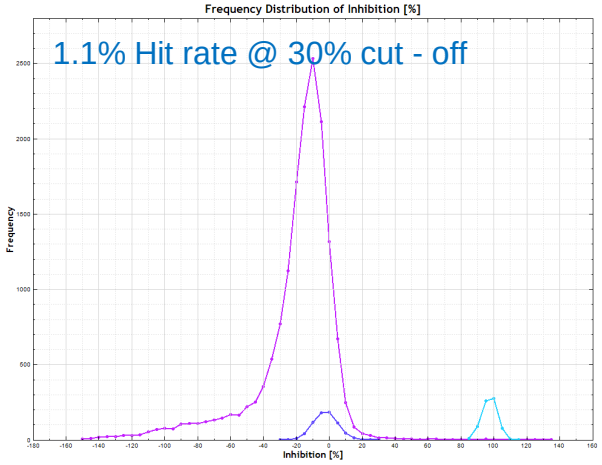


DMSO tolerance

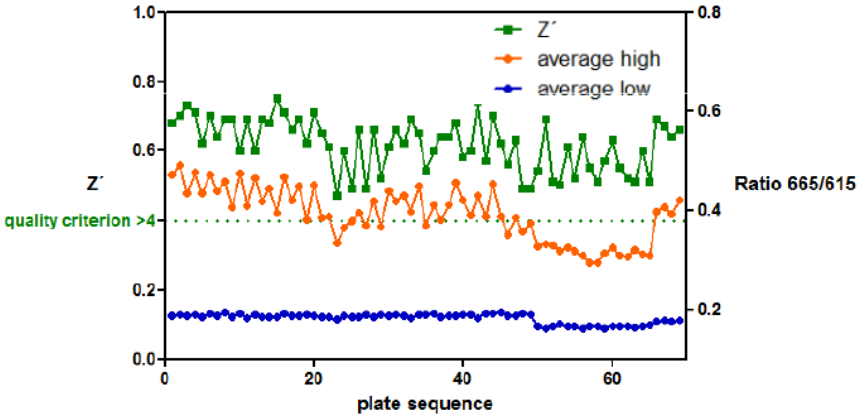
Secondary screens



Primary screen



Screen Stats



Case Study 2 German Research Institute

Indication Malaria

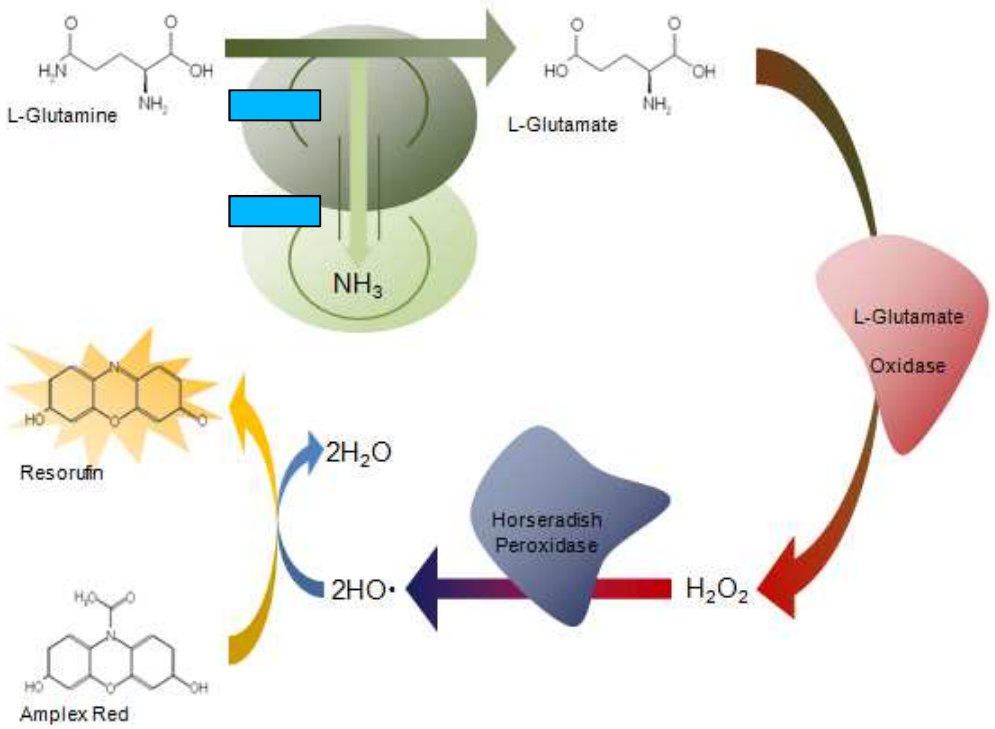
Target Synthesis of an essential co-factor

Assay development

- Hetro-dimer complex
- Coupled detection of synthase product
- Enzyme titration and kinetics, (no standard compounds)
- DMSO tolerance, day-to-day and plate-to-plate variability

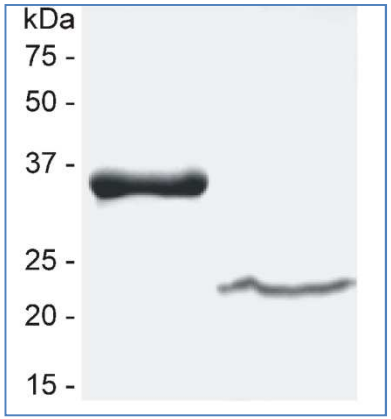
HTS campaign

- Primary screen 250k compounds
- Hit Confirmation 2500 compounds
- Hit Profiling 512 compounds
- Secondary assay parasite proliferation assay in human rbc's (Safety Level 3)

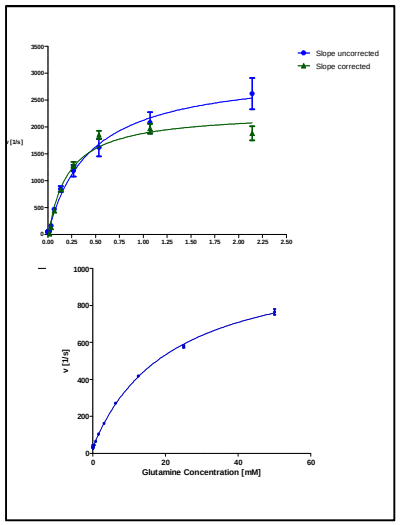


Assay Development (3 months)

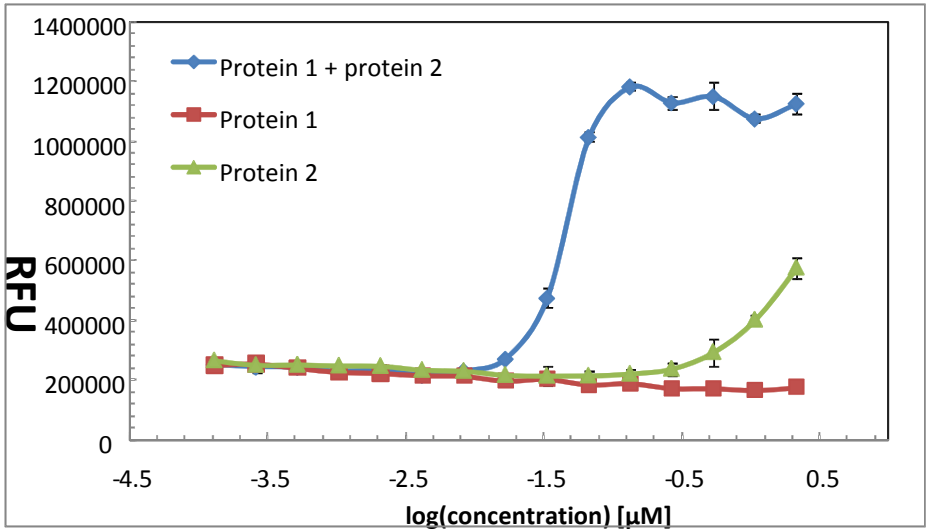
Reagent production



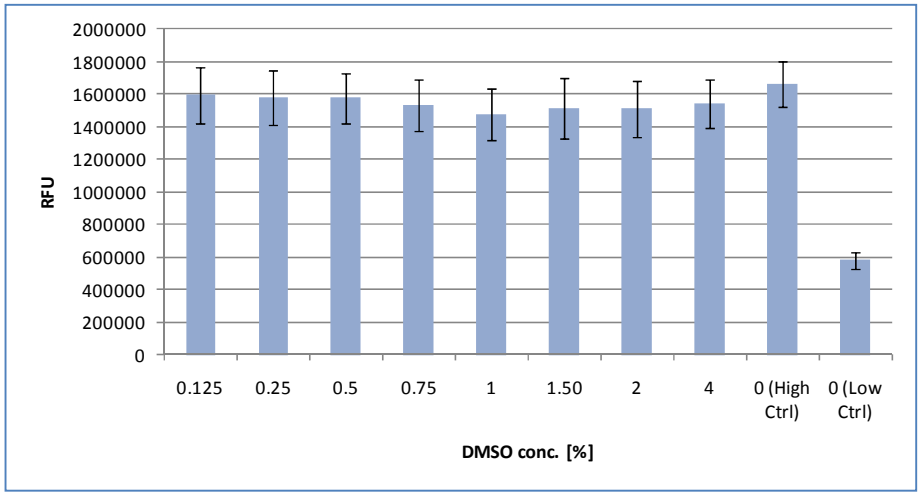
Enzyme titrations



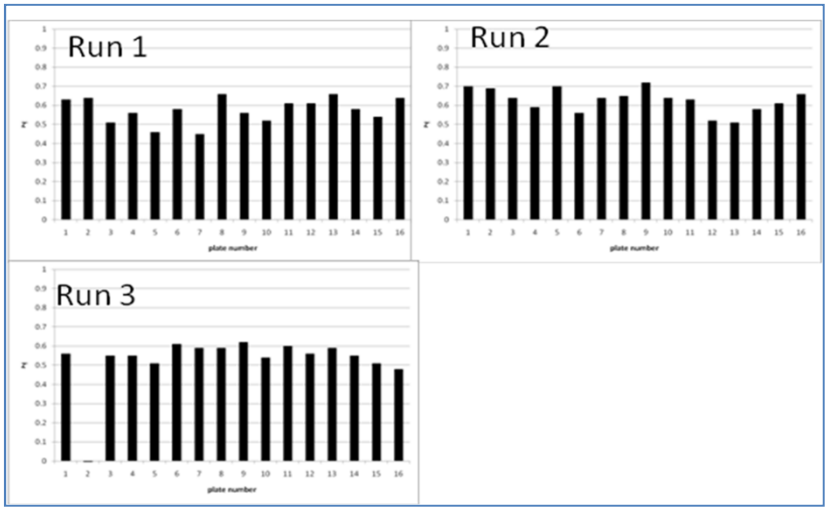
Heterodimer functional testing



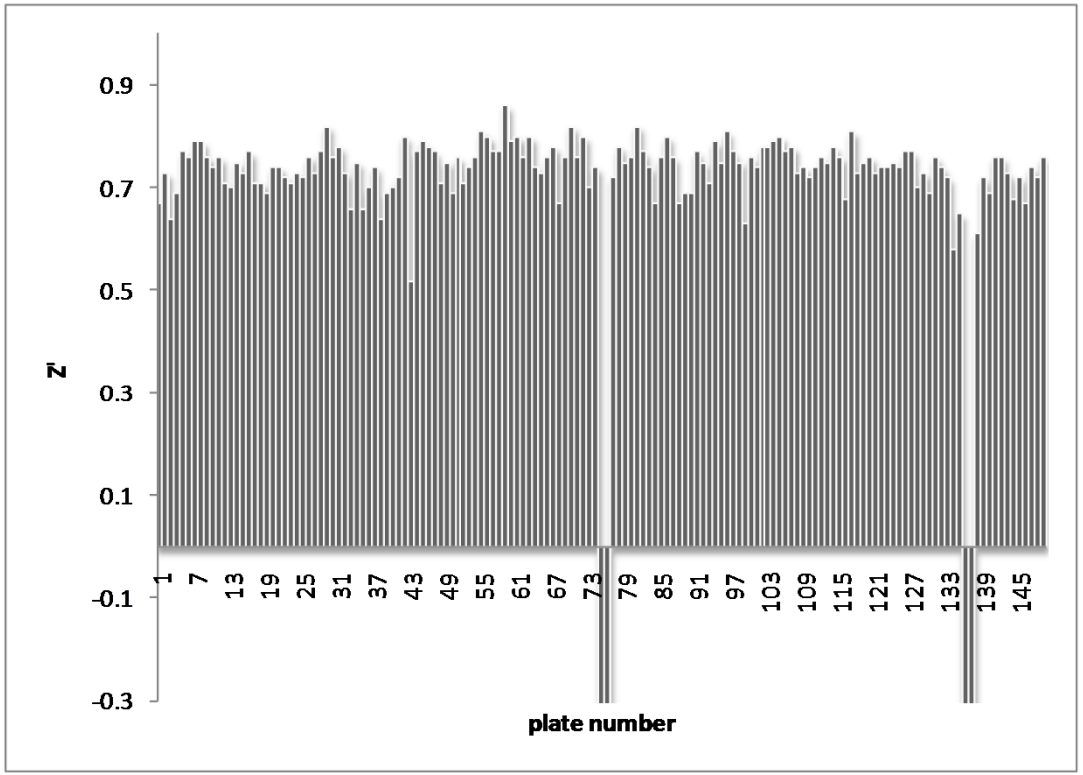
DMSO Tolerance



Marker Mini-screen



Primary Screening Statistics



384 well Plates screened	945 (plus DMSO sacrificial plates)
Plate QC failures	104
Median Z'	0.72
Screened cpds	251,000
Hit Rate	1.4% (3607)
Confirmation Pick size	2500

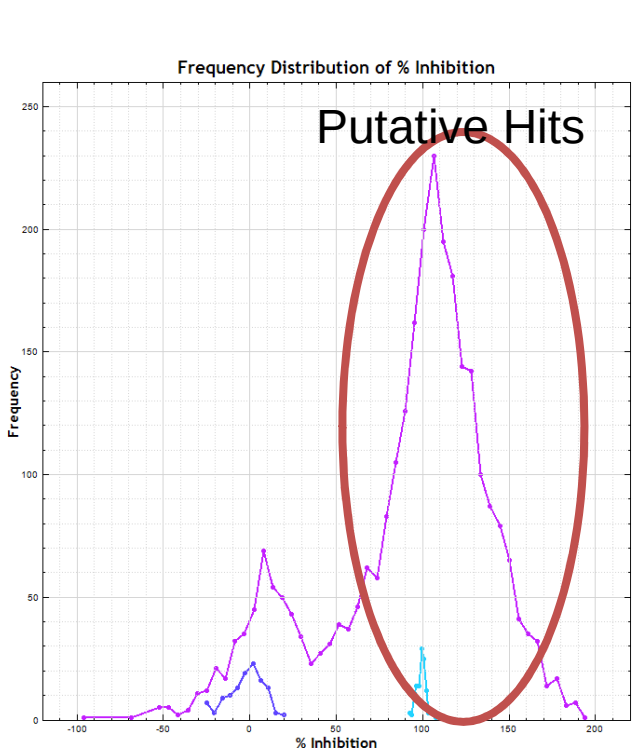
- Compound Triage by expert Medicinal Chemist
  - Structural classification and selection based on potency and attractiveness as starting points
  - Prioritized hits from known drug library to facilitate re-purposing

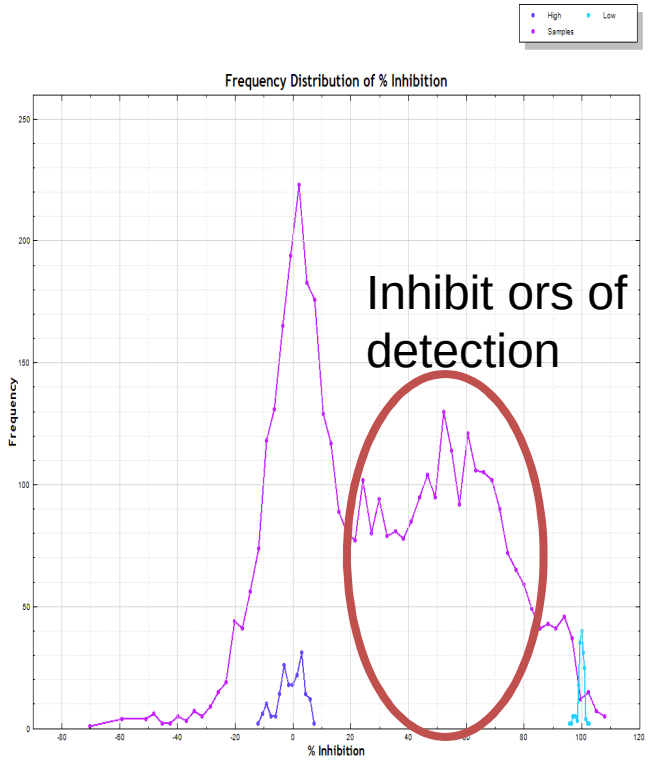
Confirmation and Counter Assay

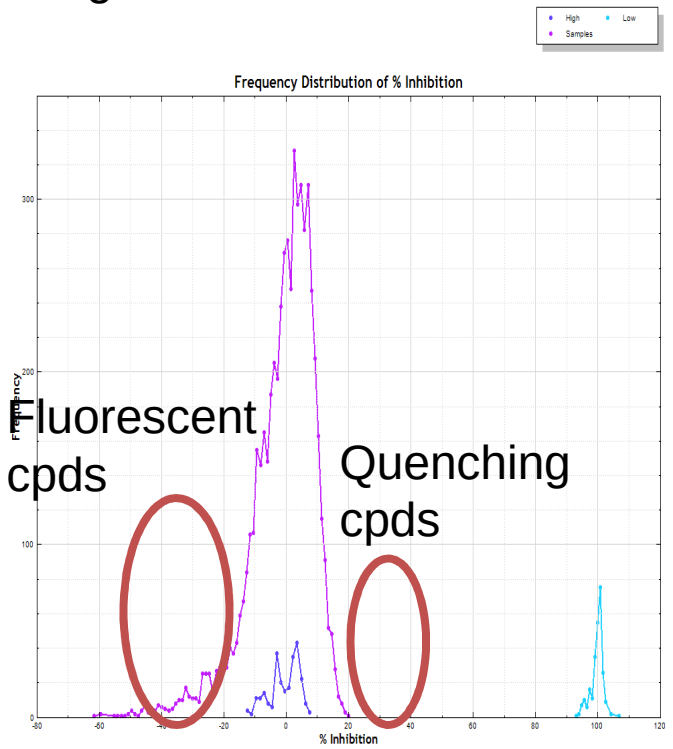
Confirmation assay
- Primary in triplicate
- 80% Hit recovery
- Significant # "super" inhibitors – artefacts?

Counter Assay 1
- Detection system only
- 1uM Glutamate
- >50% Compounds inhibit detection system
- Crucial readout

Counter Assay 2
- Run reaction as primary
- Add compound then read
- Quenchers false +ve
- Fluorescent false -ve
- Resorufin produces robust signal!

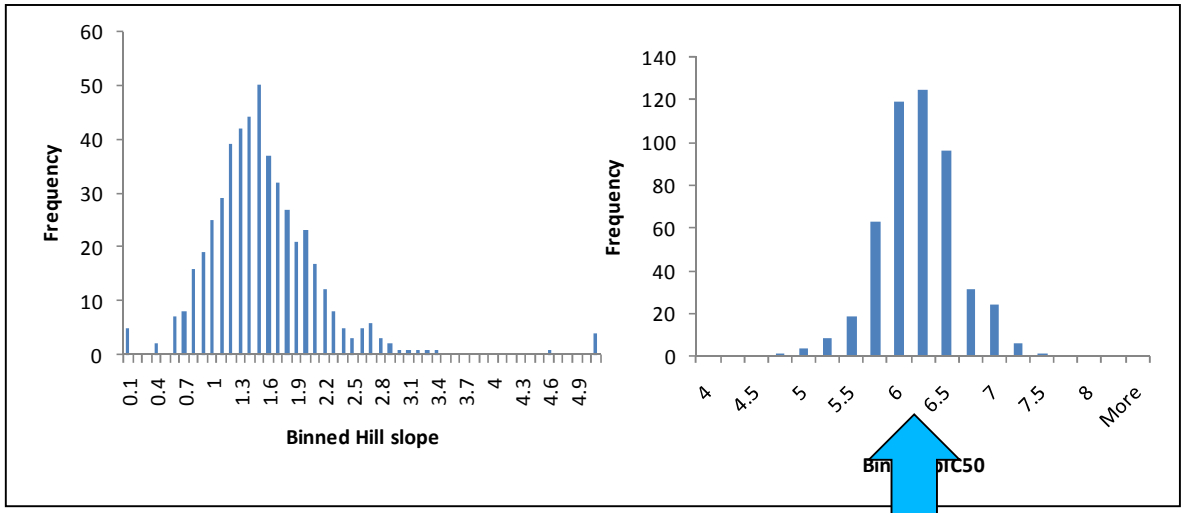


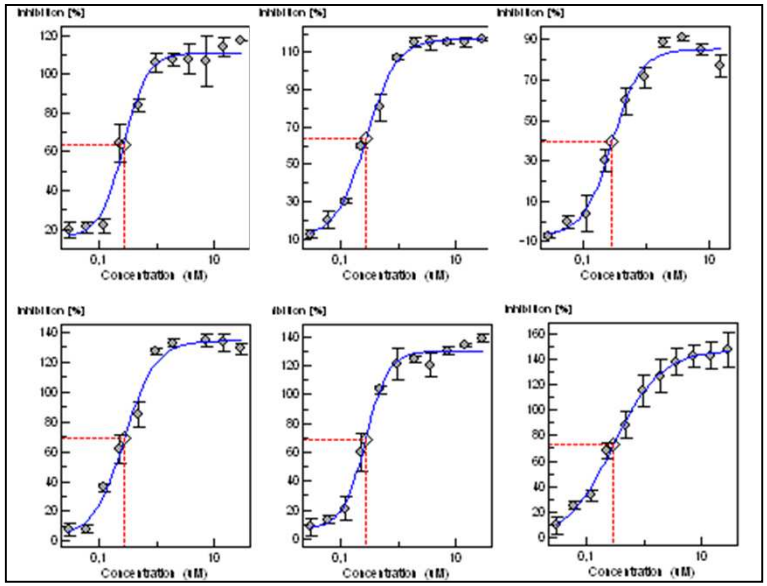


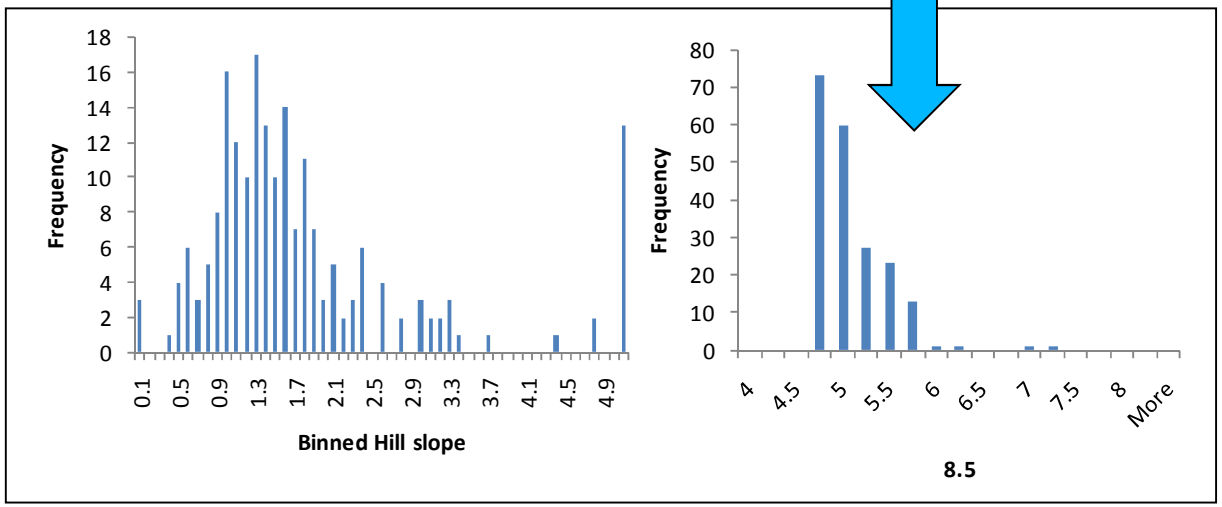


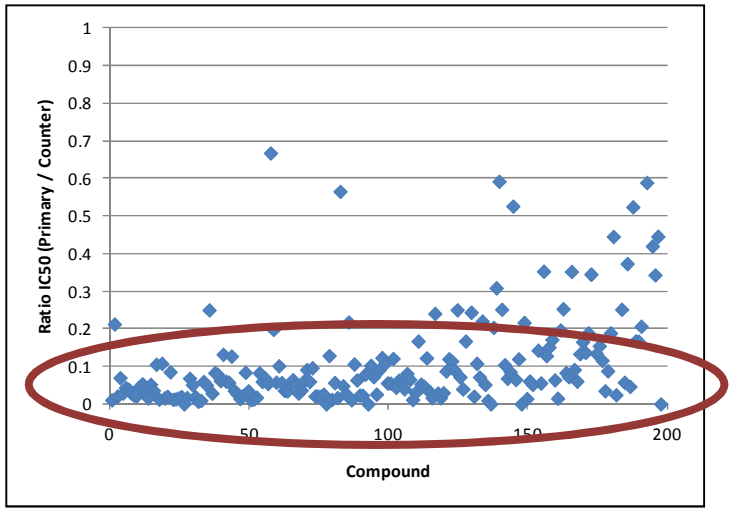
Dose Response + Hit profiling

Primary Assay - 497 compounds (of 512) with curve fits







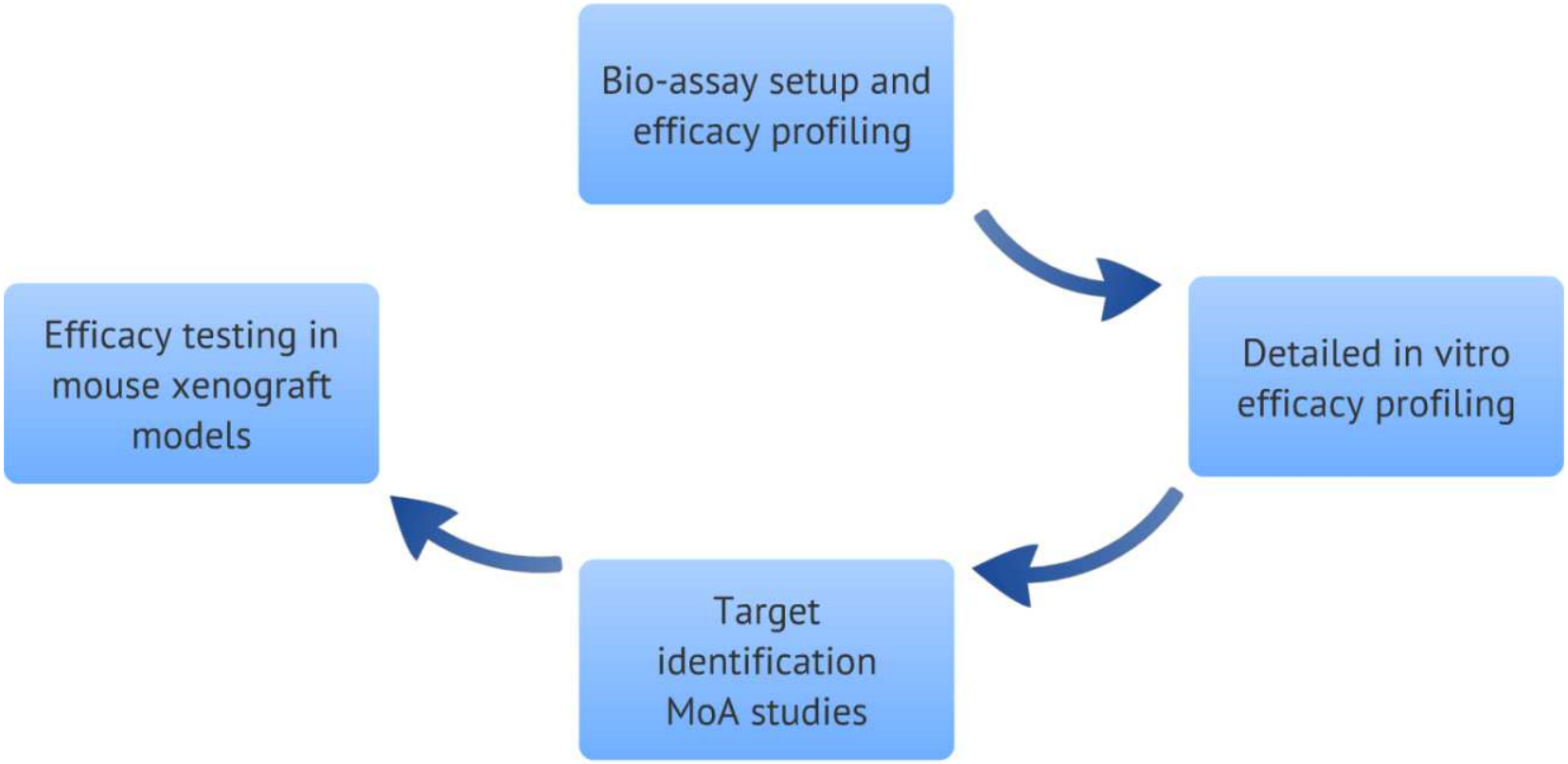


Counter Assay - 200 compounds (of 512) with curve fits

(IC-50 Primary) / (IC-50 Counter)

Marine Fungi Project – Drug discovery

The aim is to identify specific marine fungi derived compounds which are suitable starting points for drug discovery. Parties in Drug Discovert Worrking groups: ESP, GEOMAR, UIO (Oslo), DTI (Denmark), Hypha discovery (UK)



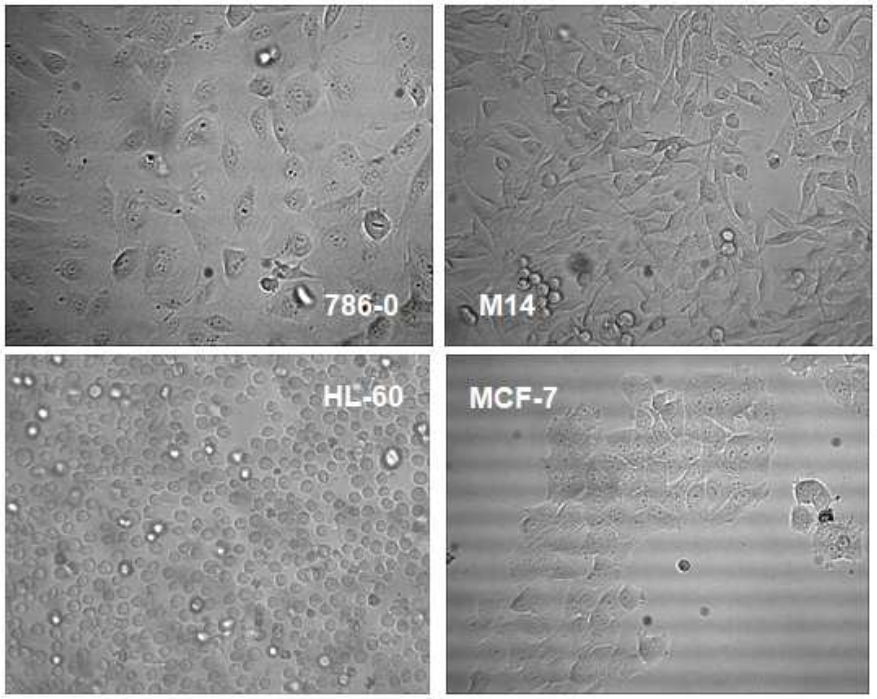
Cell line panel

- NCI cell line panel

sourced all 60 cell lines

Preliminary panel consisting of M14, 786-0, MCF-7 and HL-60

→ cell culture protocols set up for 20 cell lines

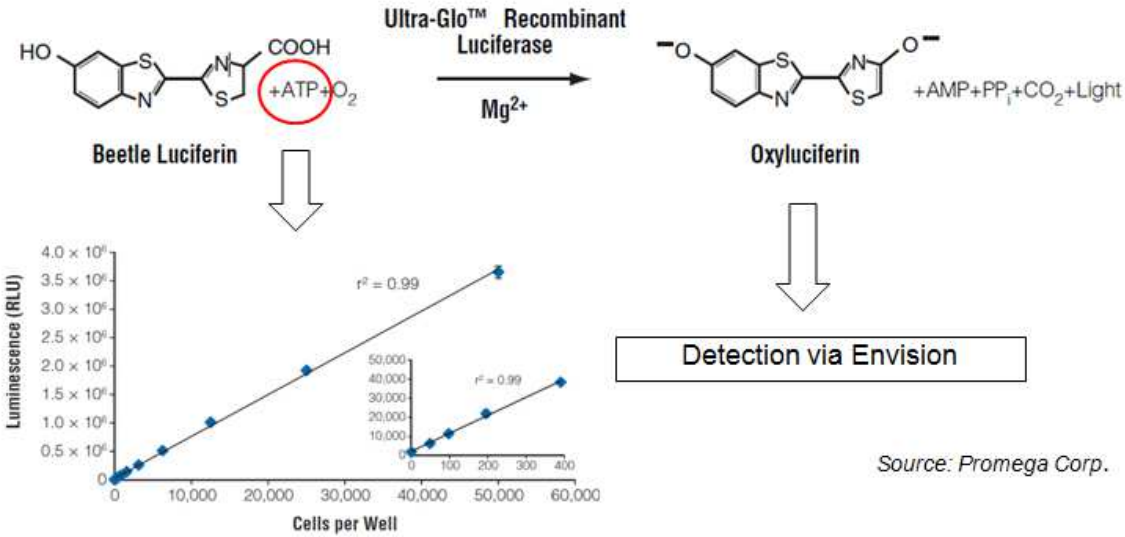


Efficacy assessment assays at 3 sites

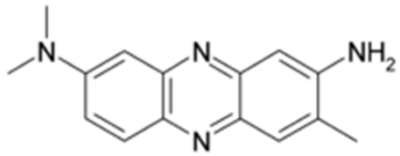
- Profile compounds effects on growth and viability of NCI panel

ESP	UIO	HD

Cell Titer Glo Luminescence Viability Assay (Promega Corp., US)



Neutral Red Assay

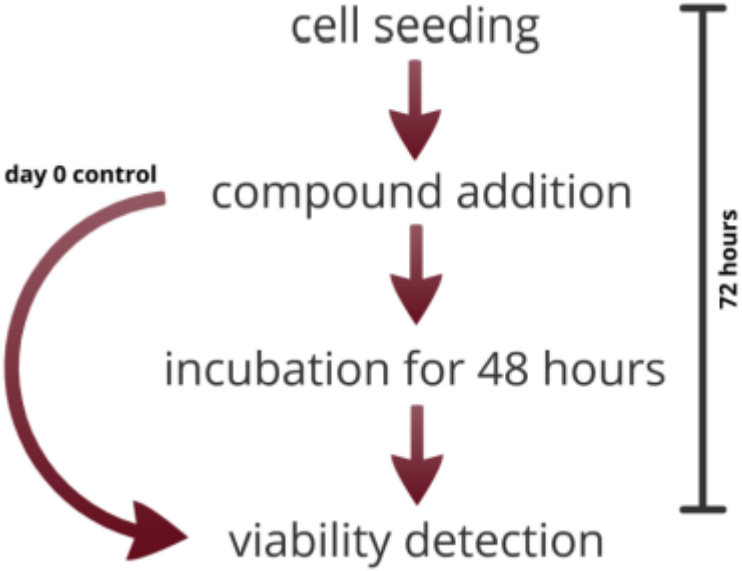


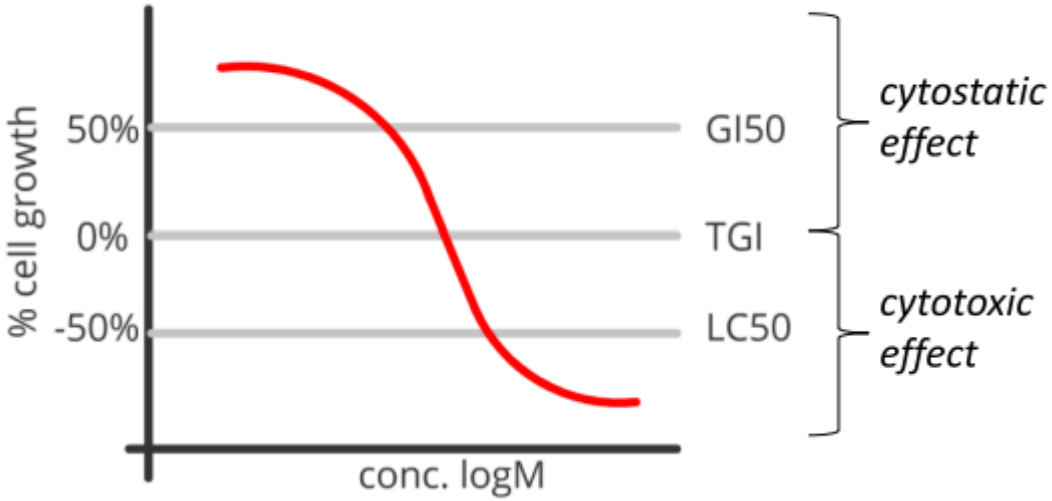
toluylene red

stains lysosomes in living cells

Methods

- NCI cancer cell line screen



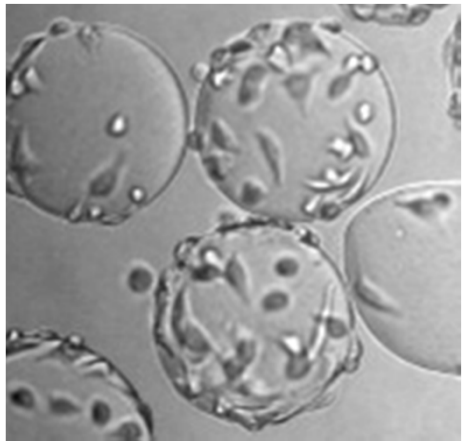


Concentrations at 50% cell growth (GI50), 0% cell growth (TGI) and -50% cell growth (LC50) were collected for each cell line per compound.

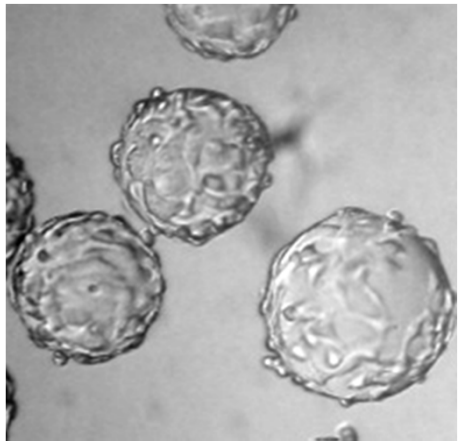
Aim: Screening of interesting compounds in the whole panel to obtain GI50, TGI and LC50 in each cell line

Optimisation of protocols

- 3D cell culture (BioLevitator)

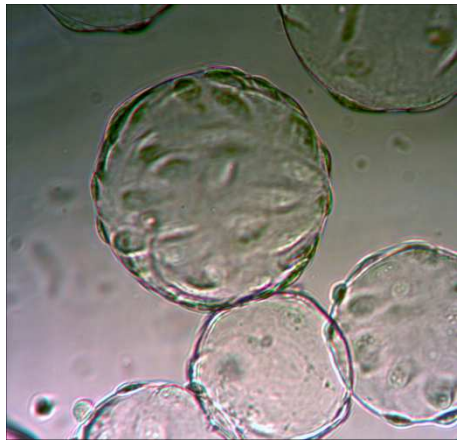


SF-593



A549-ATCC

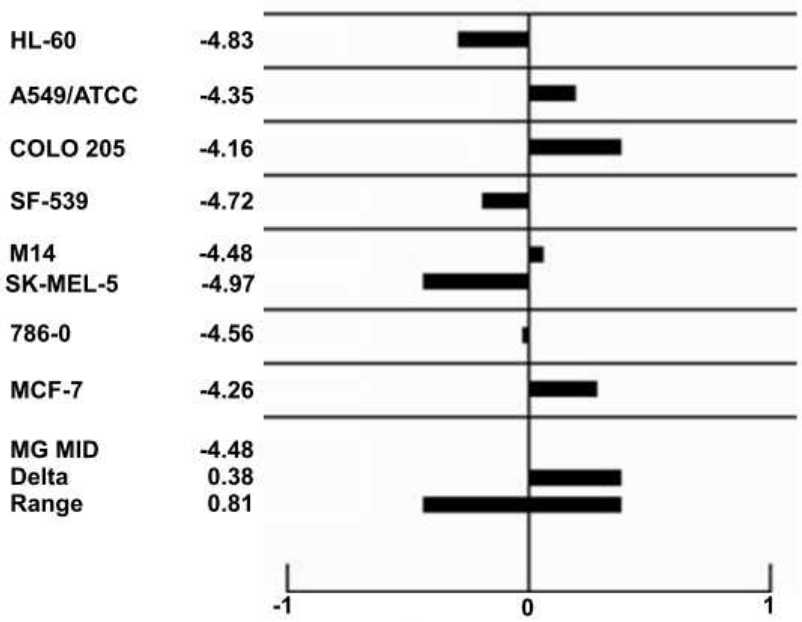
M14



786-0

Bioinformatics tools for Cpd analysis

data	**COMPARE online tool**	**Output**	**MoA studies**
GI50 TGI LC50	NCI Mean graph	Correlation of test compounds to known compounds	Target directed studies



NCI Mean Graph TGIs of compound 954 in 8 cell lines displayed relative to the mean (MG MID) of -4.48 log molar . Unit: log molar

Assay Validation

Bio-assay setup and efficacy profiling

- NCI cancer cell lines

Cell growth inhibition and Cytotoxicity assay validated for 17 cell lines

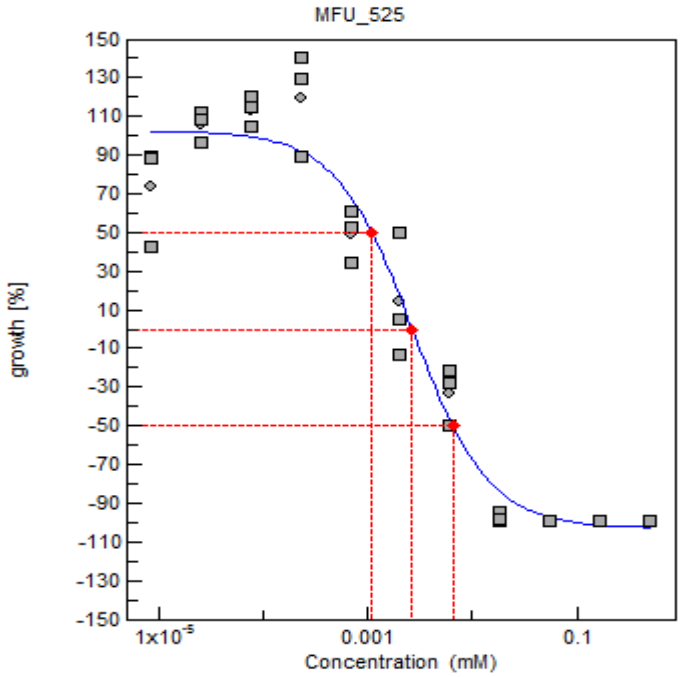
→ Validation includes:

- DMSO tolerance
- Titration/Linearity experiments
- Signal stability experiments
- Cell growth evaluation
- Standard compound dose-response experiments (cisplatin, paclitaxel, staurosporine, 6-mercaptopurine)

→ Selected fractions and pure compounds screened in preliminary panel and all other validated cell lines

Purified compound – Example results

- Compound A



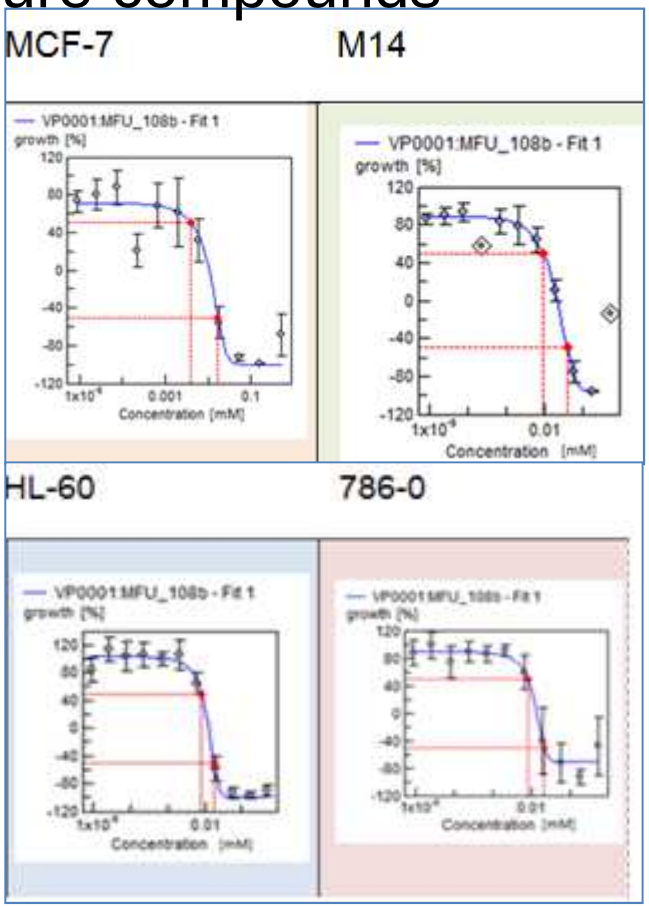
Dose-response curve compound 525n in SF-539

About 300 compounds screened in the preliminary panel

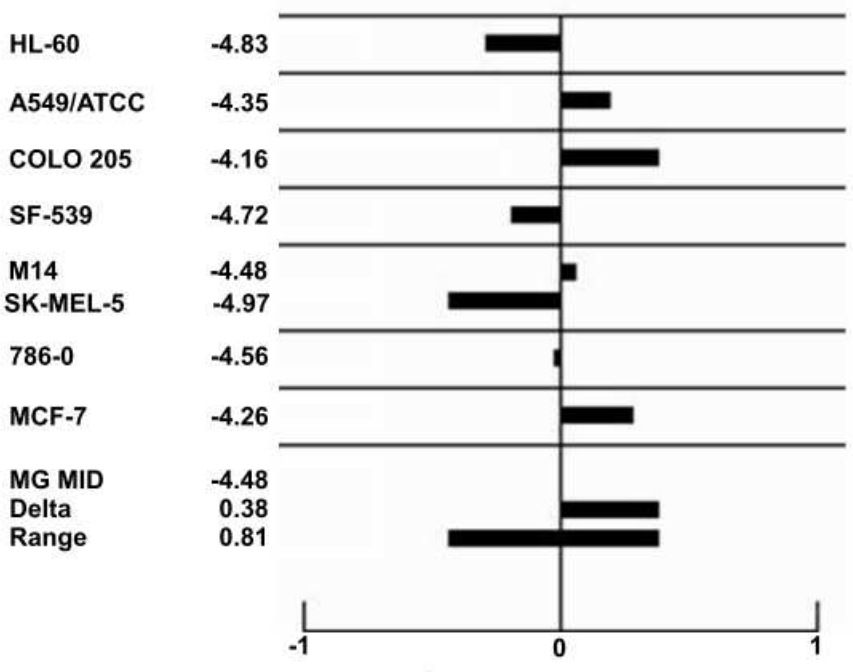
Hits identified and profiled in 17 cell lines (ESP&UIO)

Purified compound studies

Profiling results (DRC) pure compounds



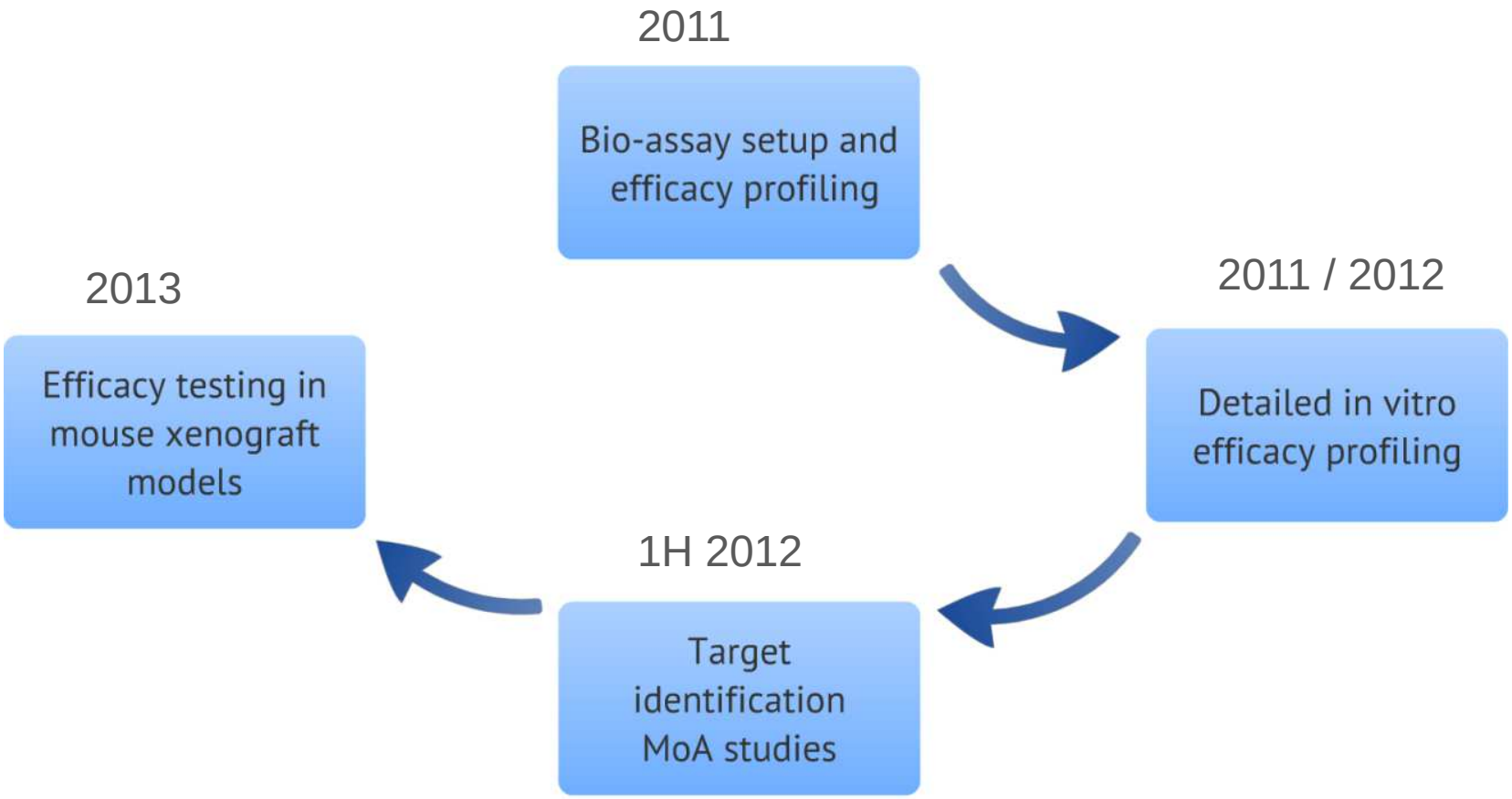
mean graphs in all screened cell lines for COMPARE algorithm



Mean graph of compound B in 8 cell lines

Marine Fungi Project

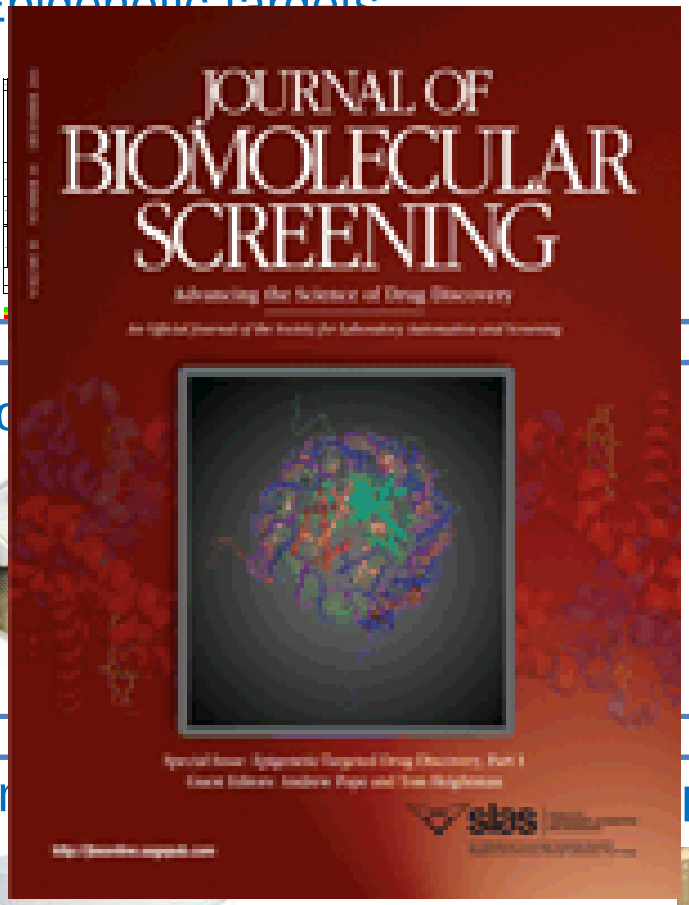
Project on track to deliver in-vitro Proof of Concept (2013)



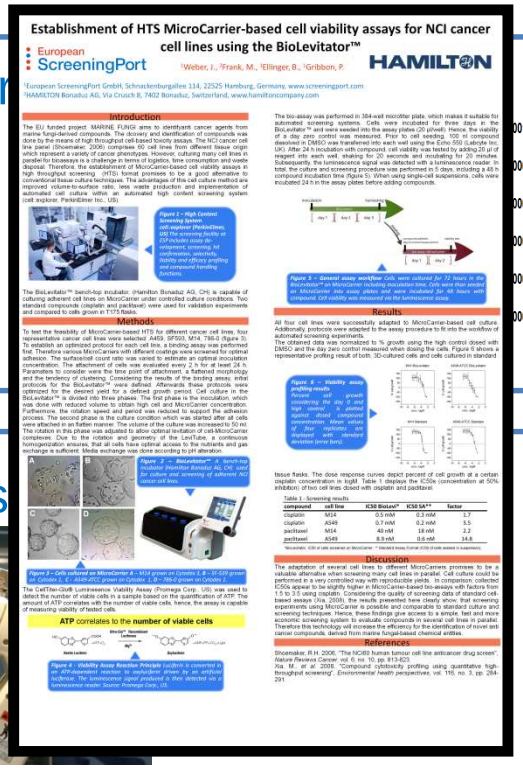
ESP Enabling Technologies group
Partner with Bioassay Discovery Tools Company (USA)
Validation of new reagent portfolio for epigenetic targets

European ScreeningPort

Epigenetic targets



ESP Experi


Establishment of HTS MicroCarrier-based cell viability assays for NCI cancer cell lines using the BioLevitator™

European ScreeningPort

HAMILTON

Introduction

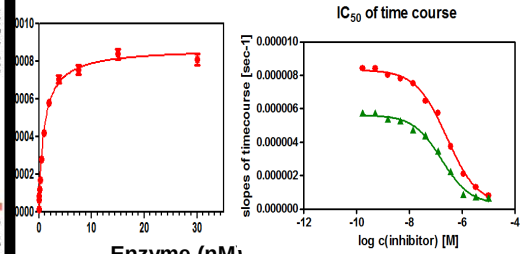
Methods

Results

Discussion

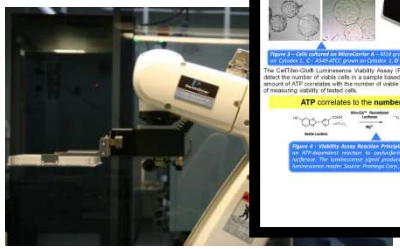
References

Industrialised format

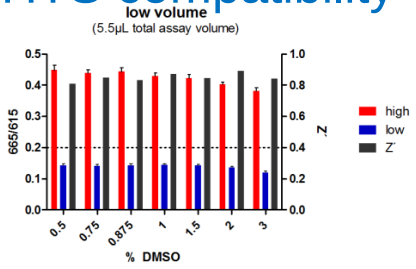


No

ESP Infras

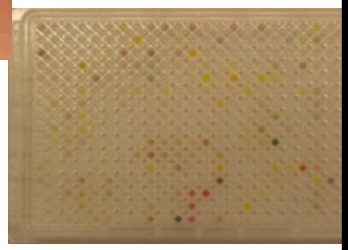


HTS compatibility

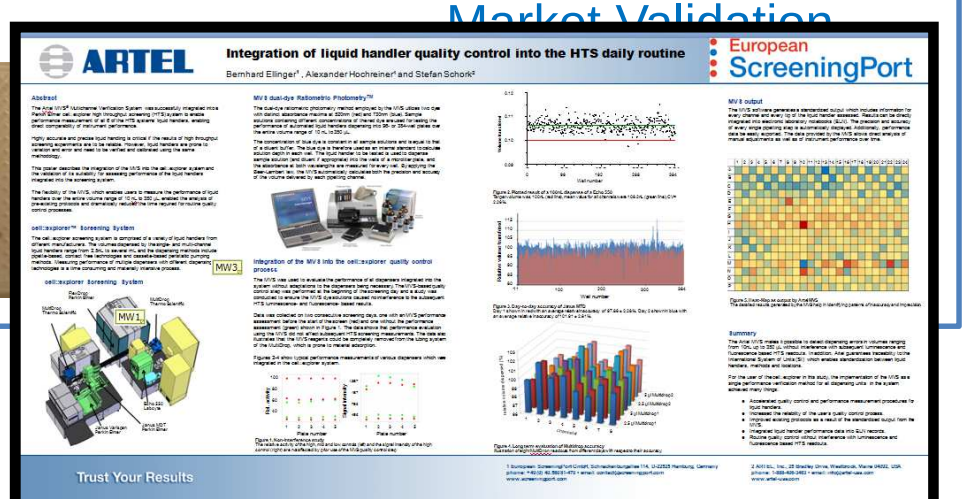


Li

ESP Library



Market Validation


ARTEL

Integration of liquid handler quality control into the HTS daily routine

Bernhard Ellinger[1], Alexander Hochreiner[1] and Stefan Schork[2]

European ScreeningPort

Abstract

MW 8 dual-dye Ratiometric Photometry™

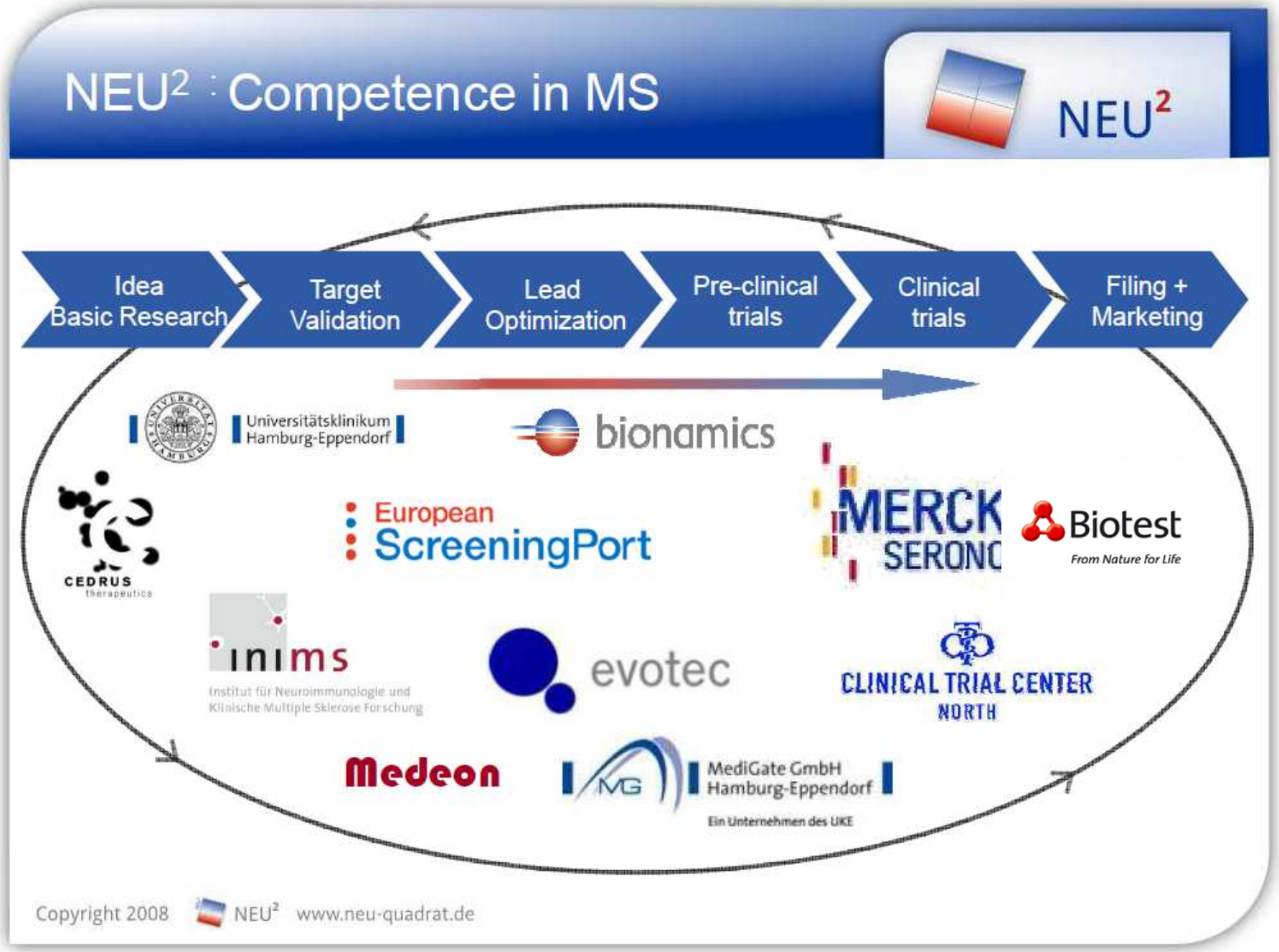
cell::explorer™ Screening System

Integration of the MW 8 into the cell::explorer quality control process

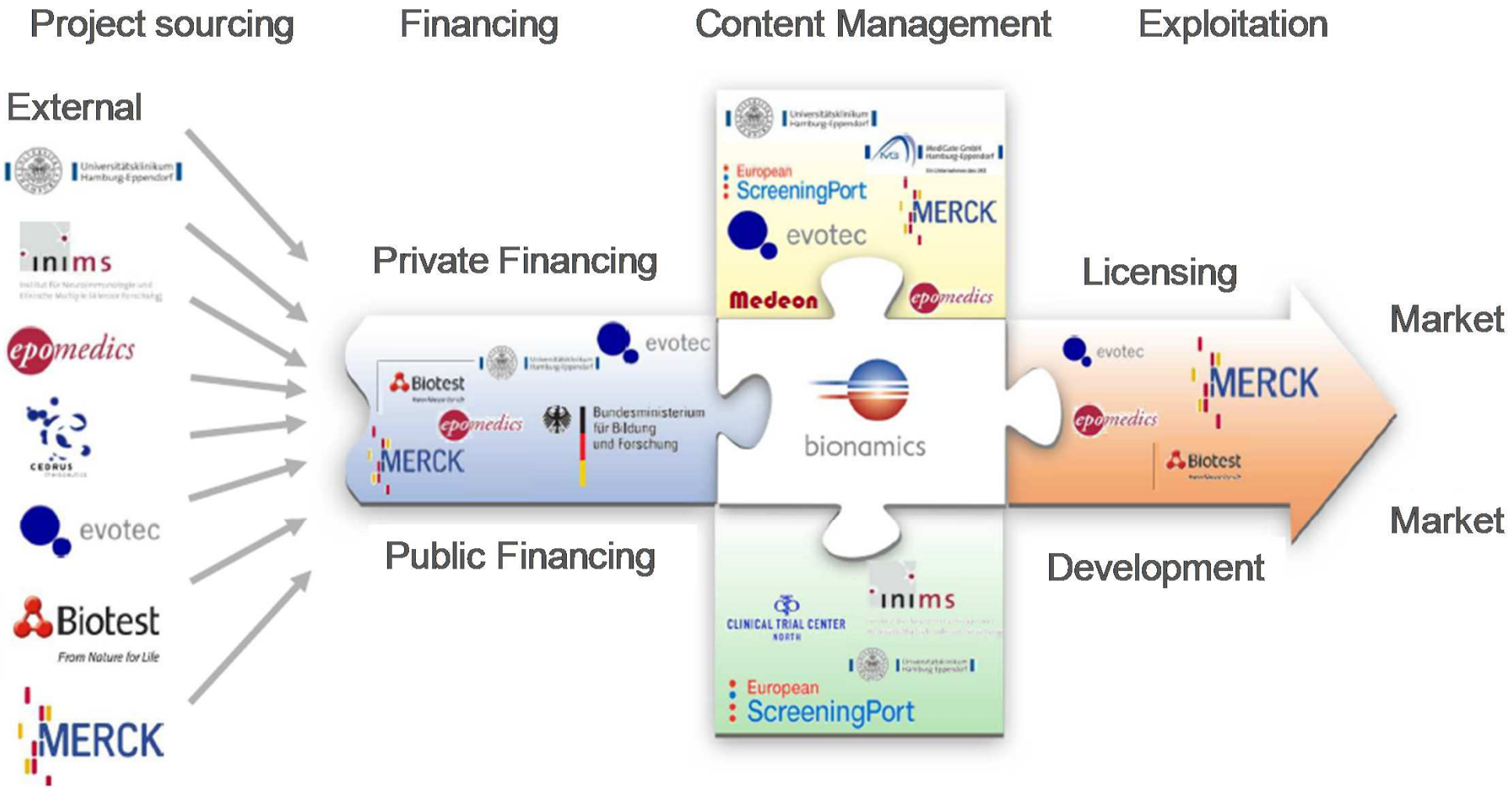
Trust Your Results

Open Innovation in Practice:
Neu2 - A Competence Consortium in MS

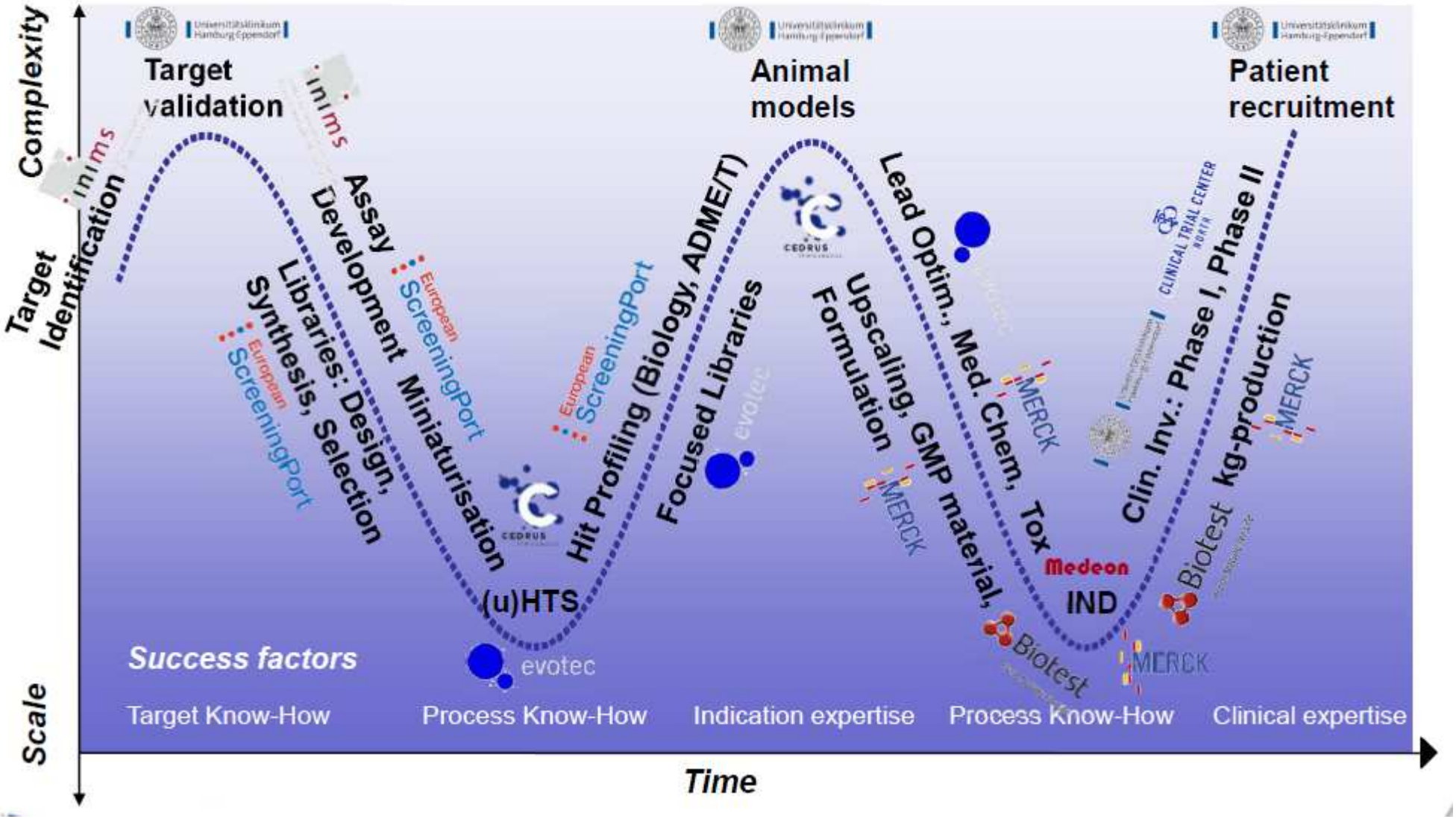
European ScreeningPort



Neu2 Project flow

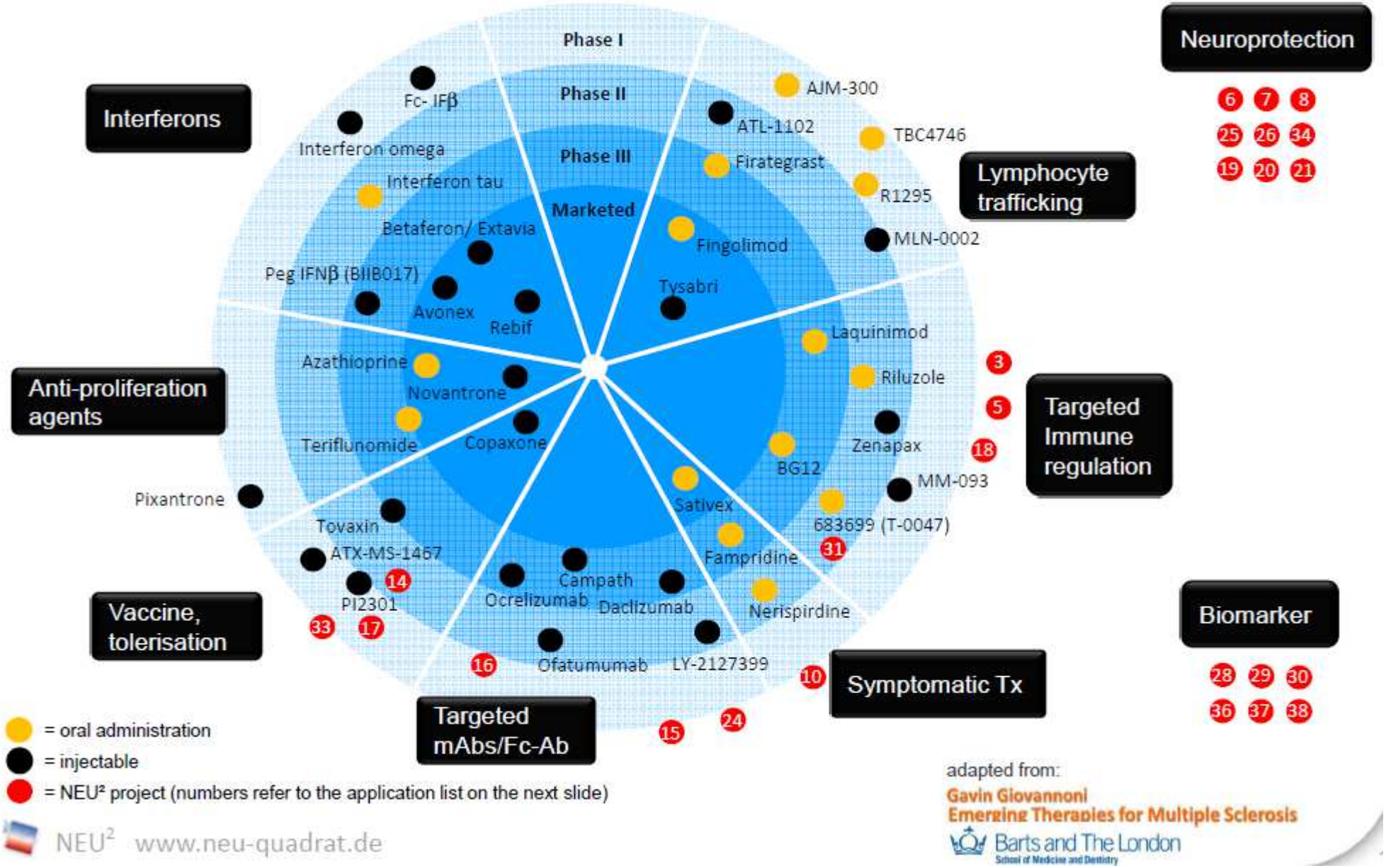


Neu2 - Competence Cascade

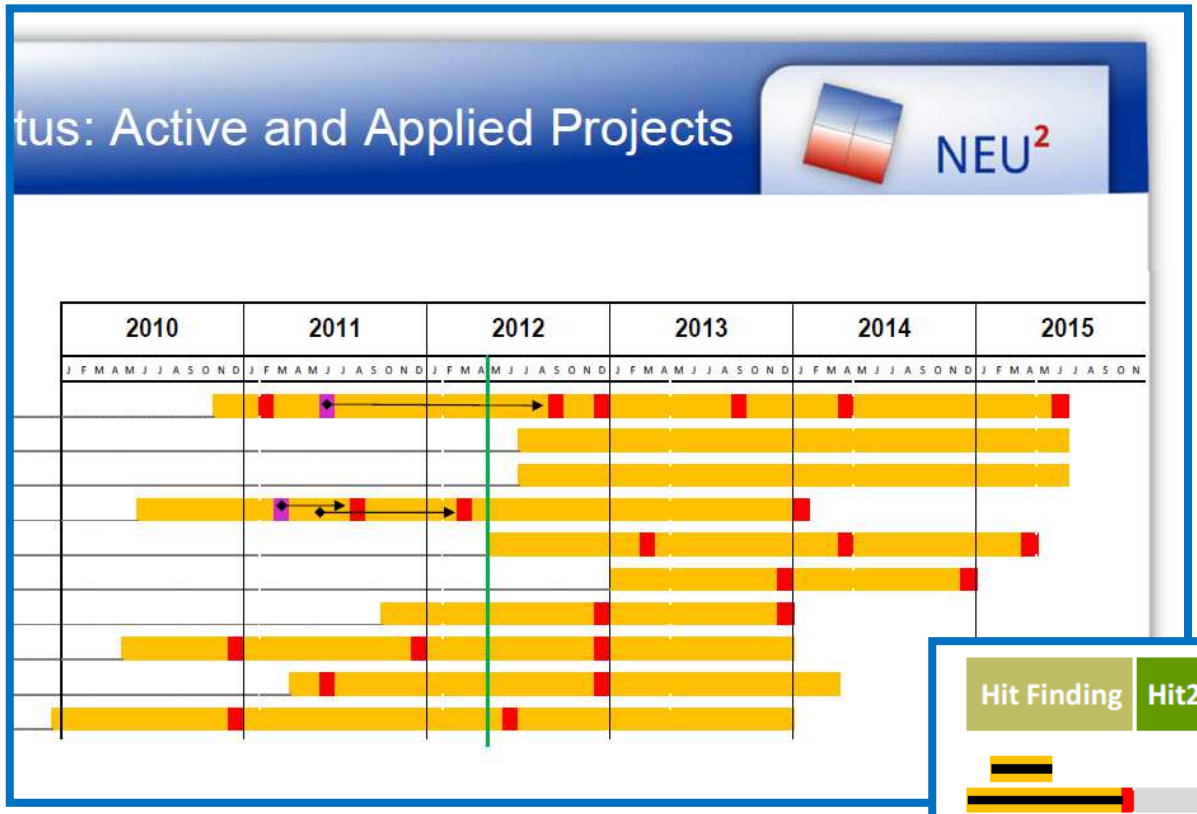


European ScreeningPort

Positioning of Neu2 portfolio

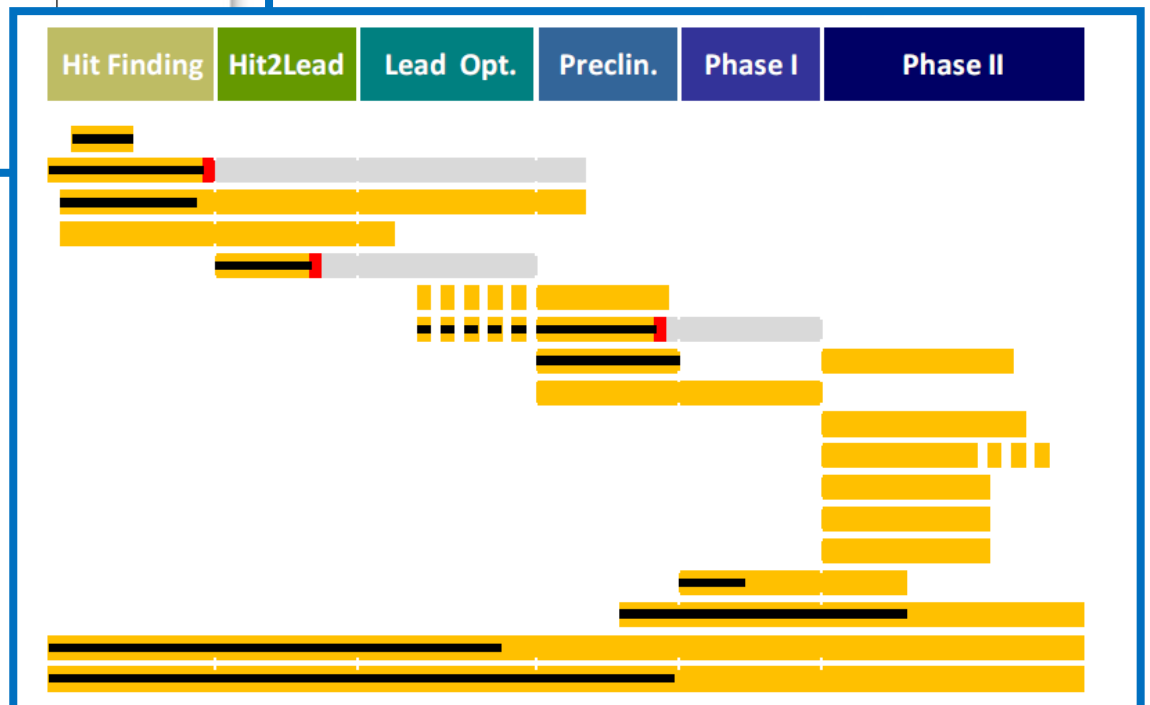


Neu2 Project portfolio April 2012



Scope and project finances

- Acute focus on Multiple Sclerosis
  - Novel mechanisms favoured
  - Higher risk than typical portfolio
- BMBF 25Mio first 3 years
  - all projects need counter-financing
  - No “double funding” allowed
- Renewal process mid 2012, goal is to secure additional 3 – 5 years funding



Activities

- Hit Finding – Phase II trial
- ScreeningPort involved in 3 running projects
- 2 new MS Biomarker related projects accepted for next round
- 1 new target for comprehensive Hit finding

Summary

- Pharma companies are increasingly moving out of early Discovery being replaced by Universities and Biotech
- Academic drug discovery is a vibrant activity, but the impact in terms of addressing unmet patient needs has yet to be fully realised
- Sources of compounds for Hi finding and Lead identification is increasingly varied and natural products still have a significant role to play
- Academia should not try to replicate Industry activities, rather to complement and be prepared to take on greater risks