

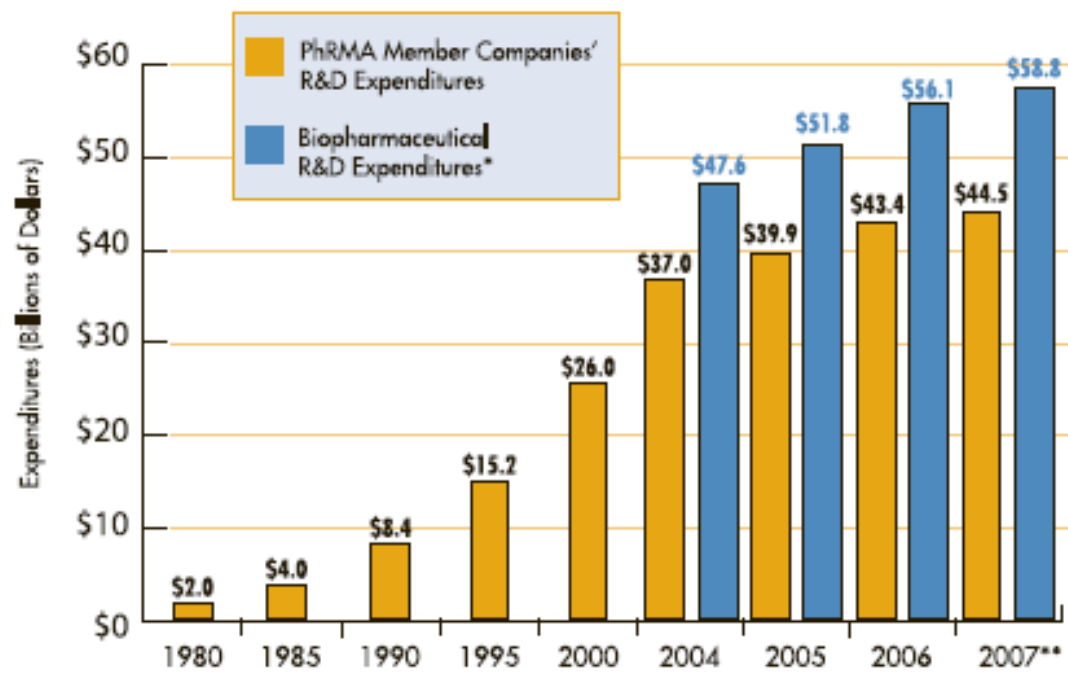
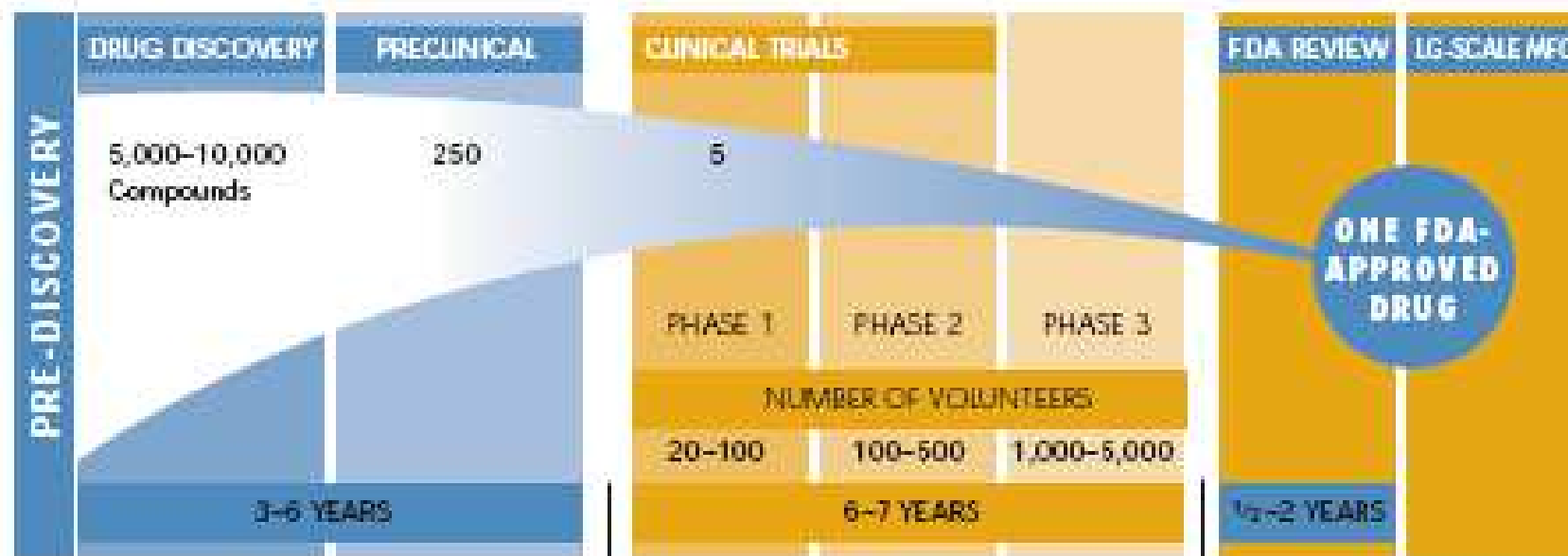
Academic drug discovery in Europe



Kiel 28th June 2012

contact@screeningport.com
www.screeningport.com

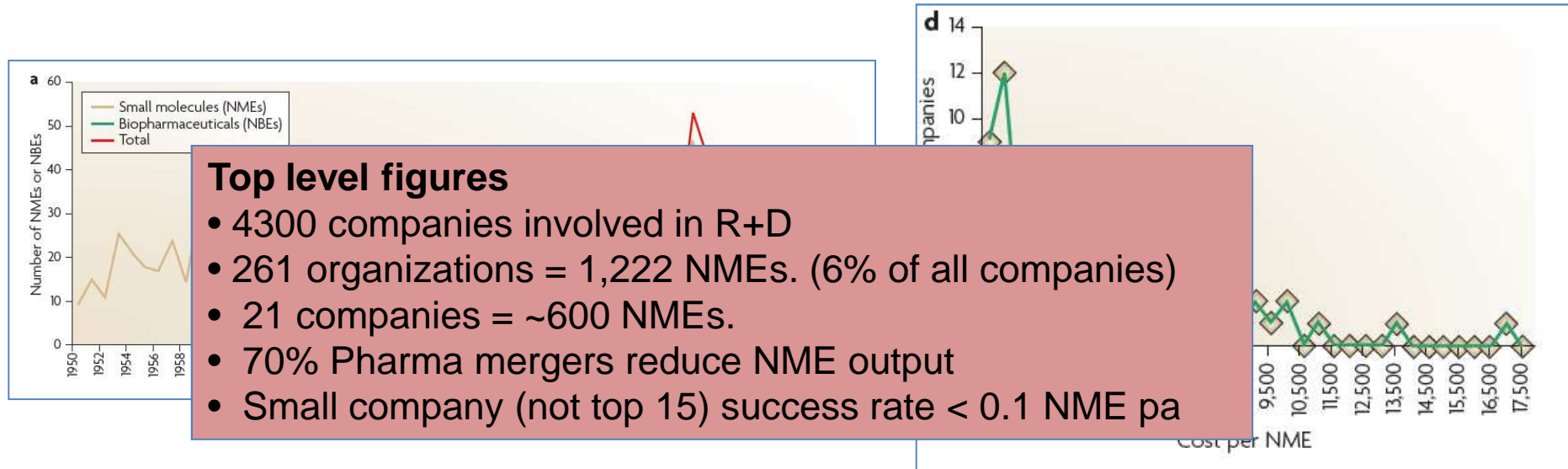
Drug Discovery Living with Failure



Approvals

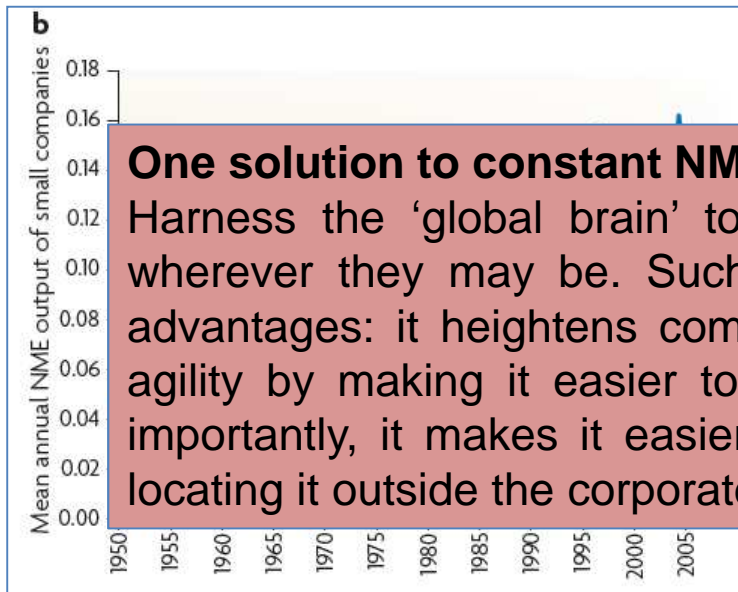
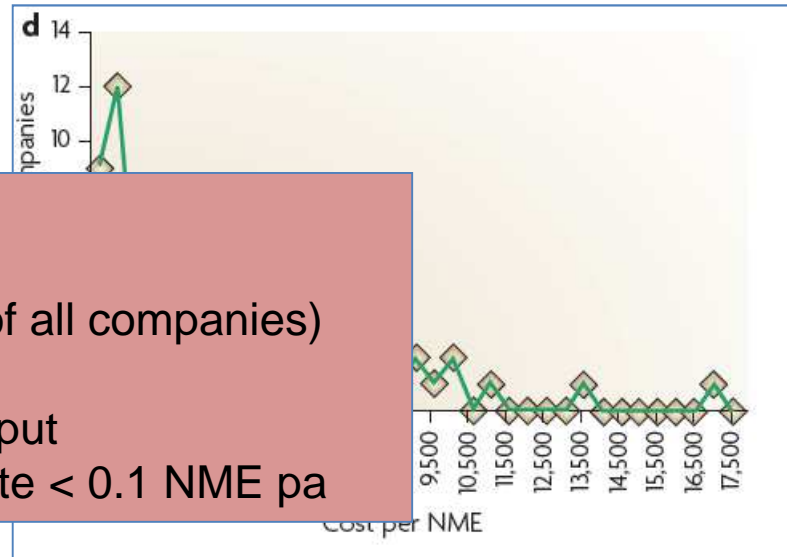
- Drugs approved in 2007 = 23¹²
- Only 2 of 10 marketed drugs ever produce revenues that match or exceed R&D costs.
- In the 25 years since the *Orphan Drug Act* was established, more than 300 orphan drugs have been approved.¹⁴
- Average effective patent life for major pharmaceuticals in 2005 = 11 years¹⁵

The innovation gap updated

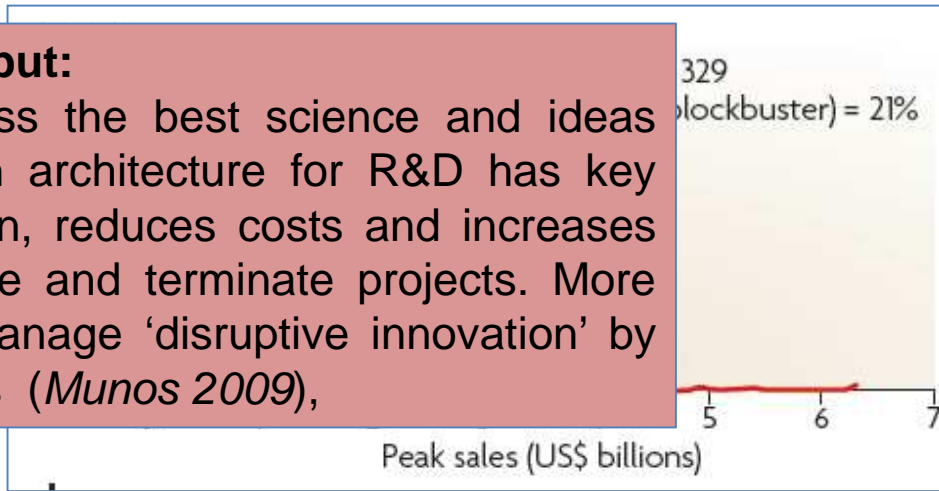


Top level figures

- 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*),



Industry response to the innovation gap

Data and IP pooling

Pool for Open Innovation
against neglected tropical diseases

Search the Pool

Overview
There are thousands of patents in the Pool for Open Innovation against Neglected Tropical Diseases. A search option is coming soon to this site that will allow users to research the patents contained in the Pool. In the meantime, patent information is listed out by Pool contributor below.

GlaxoSmithKline (GSK) has contributed patents and applications that cover small molecules and their formulations, uses, and processes for neglected tropical diseases. Search GSK's patent list here.

Athyrium has provided more than 1,500 issued or pending patents from its RNAi patent estate on a royalty-free, non-profit basis in the least developed countries via licensing agreements with qualified third parties. RNAi Technology has already proven useful in discovery of new therapeutic

New collaboration models



Talking the talk

PHARMA OPEN INNOVATION SYMPOSIUM 2011

10th June 2010, La Balme-sur-Py, Montreux, Switzerland

The event will be analysing the critical importance of Open Innovation within the Pharmaceutical Industry. This event takes place before our 11th Annual Drug Discovery Leaders Summit (http://www.drugdiscovery-summit.com) which will take place on the 26-28th June 2010. By sponsoring the Open Innovation symposium also means that you can attend the 2nd and 3rd day and take advantage of meeting the senior R&D leaders of the pharma industry.

Over the day, the open innovation event and the Drug Discovery Summit attracts over 200 senior attendees working in international business development, external collaboration, open innovation, research & development and knowledge management from leading pharmaceutical, biotechnology, companies as well as academic institutions in UK, Europe and the US. The programme covers insights from leading influential thinkers on the benefits of Open Innovation (OI) including their views on topics such as IP & collaboration issues whilst discussing the value Open Innovation can bring to Pharmaceutical R&D.

Key topic areas that will be explored include - Business Models, IP and Collaboration Issues, Academia Open Innovation, Biopharma Open Innovation, Current Open Innovation Initiative and Case Studies, Lessons learned from outside Pharma.

Key speakers on the first day include:
 Thomas Senderowitz, Senior Vice President Global Development, Genentech
 Philip Owen, Associate Director for Global External R&D Strategy, Eli Lilly
 Giuseppe Ciaramatta, Executive Director, Head of Biopharmaceutics, Sanofi-Synthelabo
 Chris Bourne, Chief Scientist, University of Oxford, Structural Genomics Consortium
 Peter Lake, Senior Director, Worldwide Business Development (Strategic Alliances) Pfizer
 Patricia Talsaga, Director, Chemistry Outsourcing, UCB
 Jason Sandford, Professor of Quantitative Cell Biology, Wellcome Trust Centre for Gene Regulation & Expression, College of Life Sciences, University of Dundee
 Rob Cooke, Director, Science Environment Development, GSK



Lilly Phenotypic Drug Discovery Initiative

Answers That Matter.

Connecting Compounds to Patients

Open Innovation

Blog Researchers Teachers Contact Us

Open Innovation

"Open Innovation is the use of purposive inflows and outflows of knowledge to accelerate internal innovation, and expand the markets for external use of innovation, respectively. [This paradigm] assumes that firms can and should use external ideas as well as internal ideas, and internal and external paths to market, as they look to advance their technology."

Henry Chesbrough, *Open Innovation: Researching a New Paradigm*

Deposited Sat 1: 20th May 2010: GSK TCMAS Dataset (Data from P. Rajkumar whole cell screening)

Access to the TCMAS experimental 'Open' dataset: Screening of approximately 2 million compounds in approximately 1000 cell lines identifying 1000s of potential PPIs. The dataset contains the structures and screening data for over 1,500 compounds from the TCMAS experimental 'Open' dataset. The dataset is available for download and use. The dataset is available for download and use. The dataset is available for download and use.

Deposited Sat 2: 20th May 2010: Novartis GMI Molecular Box Dataset (Data from P. Rajkumar whole cell screening)

Access to the GMI Molecular Box dataset: Screening of approximately 2 million compounds in approximately 1000 cell lines identifying 1000s of potential PPIs. The dataset contains the structures and screening data for over 1,500 compounds from the GMI Molecular Box dataset. The dataset is available for download and use. The dataset is available for download and use. The dataset is available for download and use.

CTSA Pharmaceutical Assets Portal

The CTSA Pharmaceutical Assets Portal invites you to join in the effort to find new uses for discontinued drugs.

The Portal members are given an unprecedented opportunity to collaborate with Pfizer Indications Discovery Unit, a division of Pfizer, vested with finding new uses for old drugs. In addition to the compounds that you may be aware of from publically-available sources, Pfizer is also encouraging inquiries about the existence/availability of little known Pfizer compounds that target specific mechanisms in which you may have an interest. We call these "unknown" assets "Orphan Compounds".

The ultimate goal is to leverage existing compounds to advance mechanistic understanding of human disease, resulting in novel treatments for patients. Integration of academic investigators into collaborative repurposing efforts with Pfizer would substantially increase the knowledge base and the pool of methodologies available for proof of concept studies. These matches will undoubtedly result in an increased number of approved drugs for new indications and considerable public benefit.

Membership in the Portal is free for CTSA researchers.

If you have any questions, please contact:
 Kate Marasina, Ph.D., MBA
 Clinical and Translational Science Center
 UC Davis School of Medicine
 TSL: (530)703-9127
 Cell: (530)979-1522
 Email: kate.marasina@ucdmc.ucdavis.edu

The Portal is sponsored by **Clinical and Translational Science Award** from NCI, and by Pfizer, and supported by the efforts of:
 University of California - Davis
 Oregon Health and Sciences University
 University of Washington (Seattle)

Recent News

The Pharma Portal project is presented at the **CHI Conference, Encouraging Development of Therapeutics for Neglected Diseases June 2010**

How open innovation could reinvigorate the pharmaceutical industry with fresh R&D opportunities

Expert Rev. Clin. Pharmacol. 2(6), 585-587 (2009)

"... healthcare solutions can best be innovated, developed and probably even marketed through the collaboration of many different companies from different industries sharing their expertise and intellectual property."

Thomas Senderowitz, MD, FCF
 Vice President Global Exploratory Development, UCB NewMed/medines, Chemin du Forest, B-1420 Braine-l'Alleud

The pharmaceutical industry is struggling... high costs of drug discovery/research tools. It has reached a critical point in time, as chronic and complex indications, clinical

Academic Initiatives in Drug Discovery

> 70 Screening Centres

BOX 1
A selection of some representative 'academic' screening facilities:

Imperial College London - Drug Discovery Centre, London, UK
http://www.imperial.ac.uk/med/medresearch/strategicdrugdiscovery/centre/

Medical Research Council Technology - Centre for Therapeutic Discovery, London, UK
http://www.mrc-technology.org/CTD.htm

University of Dundee - Drug Discovery IMU, Dundee, UK
http://www.drugdiscovery.dundee.ac.uk/

University of Leuven - Centres for Drug Design and Discovery (CD3), Leuven, Belgium
http://cd3.uva.be/en/centres/leuven/uk/infrastructure/vdi/about.htm

Broad Institute, Cambridge, MA, USA
http://www.broadinstitute.org/

NIH Chemical Genomics Center, Rockville, MD, USA
http://www.nhgri.nih.gov/

Johns Hopkins University - ChemCORE Facility, Baltimore, MD, USA
http://www.jhu.edu/chemcore/

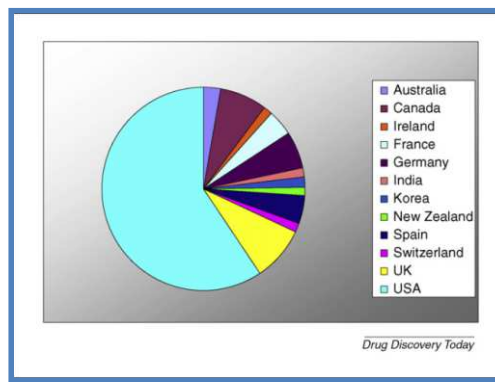
The Scripps Research Institute - Translational Research Institute, Florida, USA
http://www.scripps.edu/facilities/

Harvard Medical School Screening Facility (HSCS), Boston, MA, USA
http://www.hms.harvard.edu/

St Jude Children's Research Hospital - Chemical Biology and Therapeutics Department HTS Core Facility, Memphis, TN, USA
http://www.stjude.org/hts-core/

Southern Research Institute, Birmingham, AL, USA
http://www.southernresearch.org/

University of British Columbia - Centre for Drug Research and Development, Vancouver, Canada
http://www.cdrd.ubc.ca/



Frearson and Collie 2009

Clinical and Translational Science Centres USA

View CTSA institutions by:

Map Satellite Hybrid

Mexico Gulf of Mexico Cuba

POWERED BY
h Pacific
i Pacific
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The momentum behind the CTSA program continues to build as new centres within, across and beyond the consortium. Launched in 2006, it now includes research institutions in 26 states. When the program is fully implemented, approximately 60 CTSA centres will be operational across the nation.

Visit CTSAweb.org for CTSA resources, enhances communication and information sharing.

CTSA Funding

Planned 60 centres
> \$500 million
of NIH funds

Initiatives in Europe



EATRIS

European
Advanced Translational
Research Infrastructure in Medicine

EU-OPENSREEN

ESFRI ROADMAP 2008

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

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. Dutton, Mark; L. Harvey, Alan



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

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*

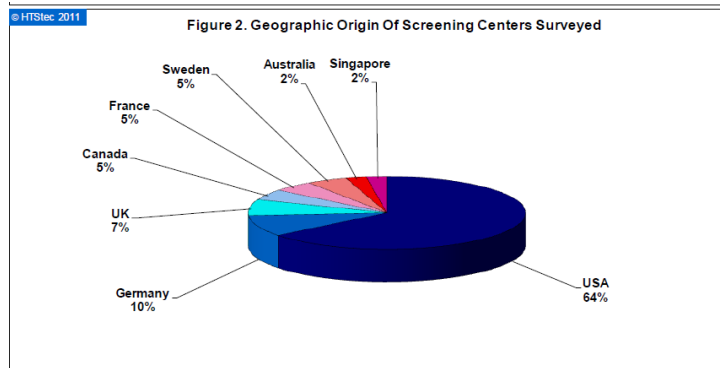
Company	Percentage of current portfolio derived from in-house HTS		
	Chemical optimization	Candidate selected	Clinical development
A	84%	30%	32%
B	60%	N/A	N/A
C	76%	N/A	N/A
D	48%	18%	19%

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

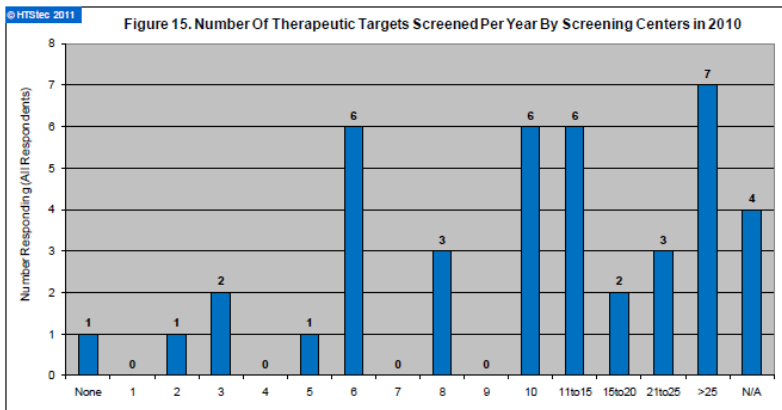


European, approx 27% of the total (64% USA)

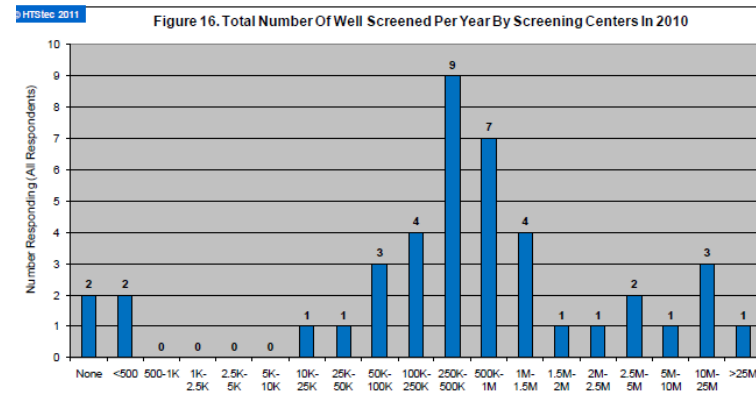
TABLE 19. TARGET CLASSES/ASSAY TYPES INDIVIDUAL SCREENING CENTERS HAVE MOST EXPERIENCE OF SCREENING

CENTER NUMBER	ADME/Tox assays	Cell-based	ELISA (immunoassays)	Flow cytometry	High content assays	High resolution microscopy	Label free assays	Other non-optical assay formats	PCR and real-time qPCR	Phage display	Protein-DNA interactions	Protein-protein interactions	Receptor ligand interactions	Reporter gene assays	Small molecule assays	Targeted cell-based assays	Other(s)
1			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
2			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
3			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
4			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
6			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
7			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
8			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
9			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
10			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
11			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
13			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
14			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
15			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
16			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
17			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
18			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
19			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
20			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
21			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
22			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
23			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
24			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
25			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
26			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
27			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
28			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
29			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
30			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
31			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
32			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
33			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
34			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
35			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
36			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
37			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
38			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
39			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
40			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
41			X	X	X	X	X	X	X	X	X	X	X	X	X	X	
42			X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Typically cover all main target classes



For all centres, average of 13 targets p/a



Most centres screen < 1 million wells per year

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




Pan European Initiatives on horizon

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



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



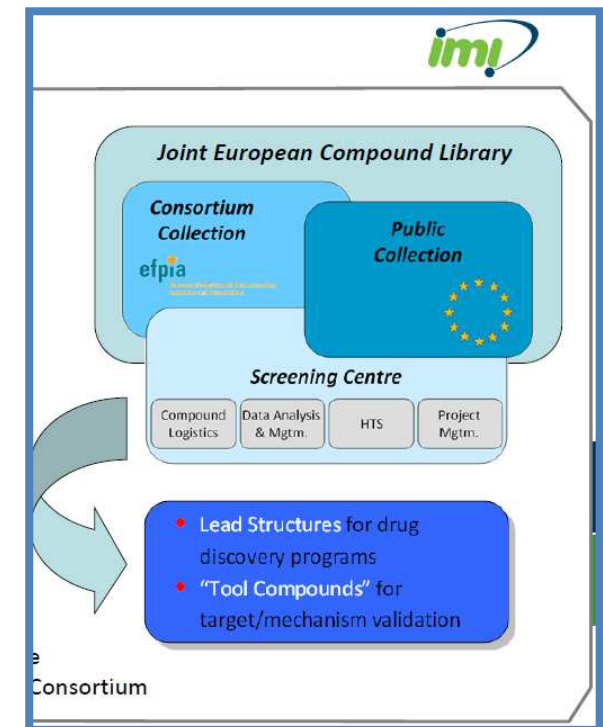
IMPLEMENTATION PLAN



- **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



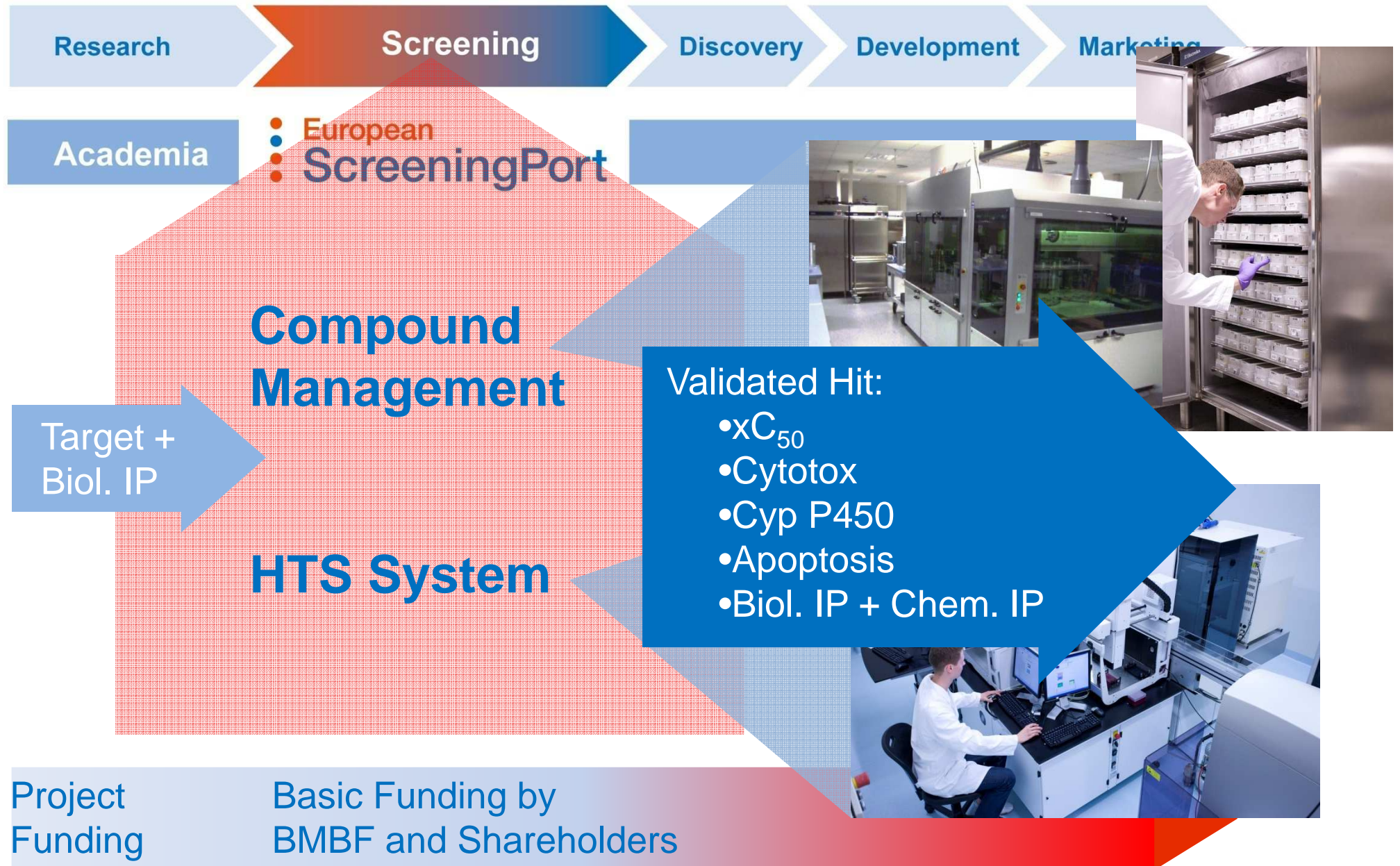
Implementation 2013

<http://imi.europa.eu>

<http://www.eatris.eu/>

<http://www.eu-openscreen.eu/>

ESP Centralized Screening Hub



ESP infrastructure



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

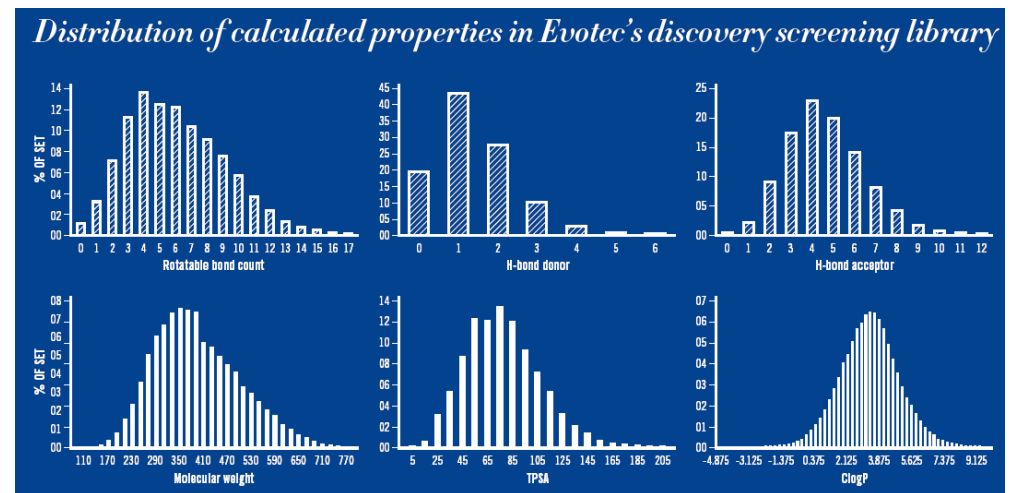
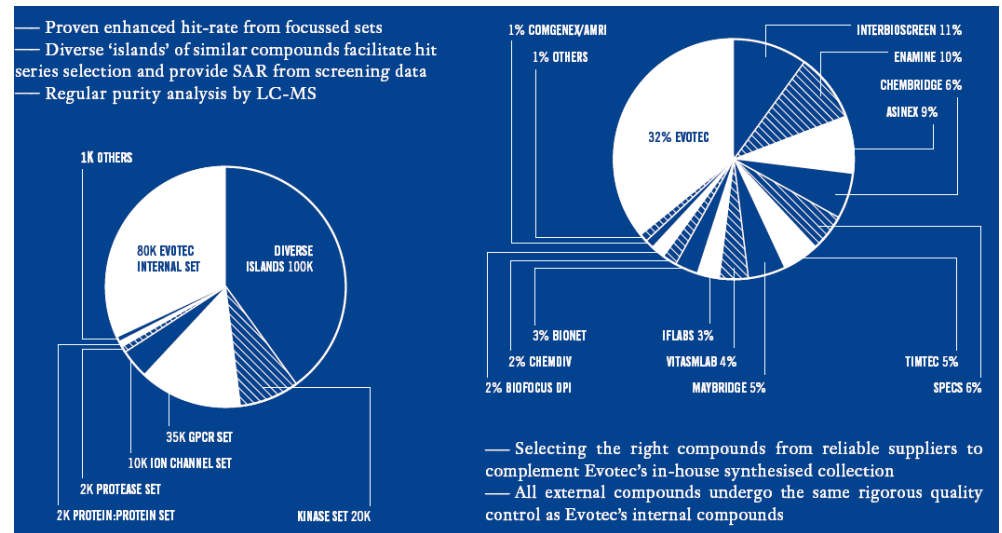
- **Access to Evotec Library**
 - $\Sigma = 250,000$ compounds (cpds)
- **Enamine Library hosted**
 - $\Sigma = 200,000$ compounds (cpds)
(70% diverse, gene and target family including PPI's)
- **ESP Library**
 - $\Sigma = 35,000$ compounds (NP's, lead-like synthetic, 10% blinded)
- **Access to Hypha Discovery**
 - $\Sigma = 10,000$ 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
 - Proven enhanced hit-rate from focussed sets
 - Diverse 'islands' of similar compounds facilitate hit series selection and provide SAR from screening data
 - Regular purity analysis by LC-MS
- 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



HOME

PERSONNEL

TECHNOLOGY

DISCOVERY

MUSHROOMS

SERVICES

NEWS

CONTACT US

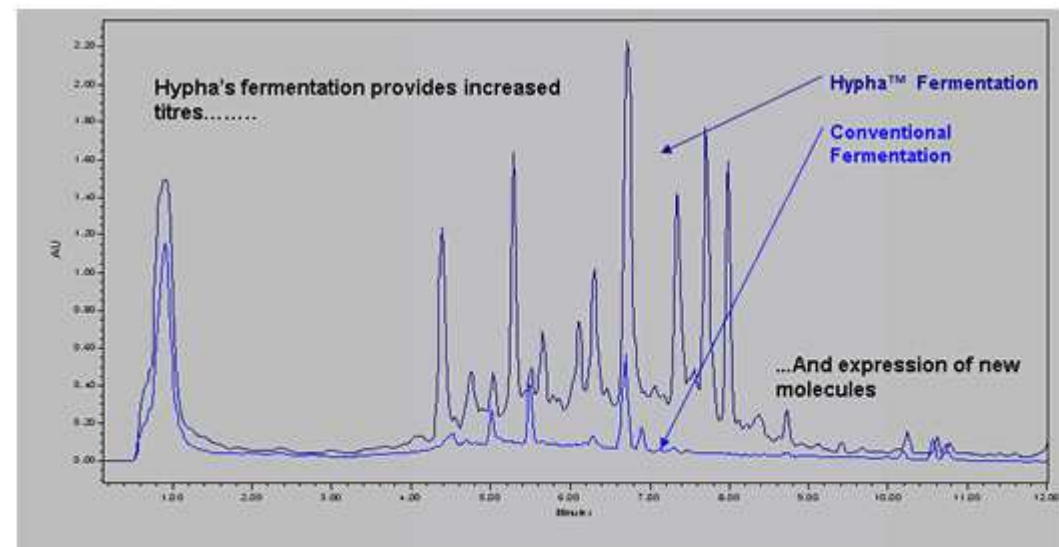
MYCODIVERSE™ SCREENING LIBRARY

An extensive collection of low molecular weight chemo-diversity produced by Hypha's stimulatory fermentation and available for discovery screening via collaboration.

Key features of the MycoDiverse™ Library:

- * Extracellular fractions and biomass extracts
- * Macromolecules removed to minimise assay interference
- * 11,000 samples in 96-well microtitre plate format for ease of screening
- * Fractions grouped according to polarity
- * Known concentration to facilitate data analysis
- * Human cytotoxicity test data of >60% of samples is available
- * Proven by Hypha™ to be lucrative source of novel bioactive molecules (50% of Hypha's own discoveries from the collection are novel structures, many others are patentable for novel use)

Please contact us for further information regarding accessing this unique collection of bioactive chemistry.



Case Study 1

North American University

Indication

Neurodegenerative disease

Target

Protease

- **Assay development**

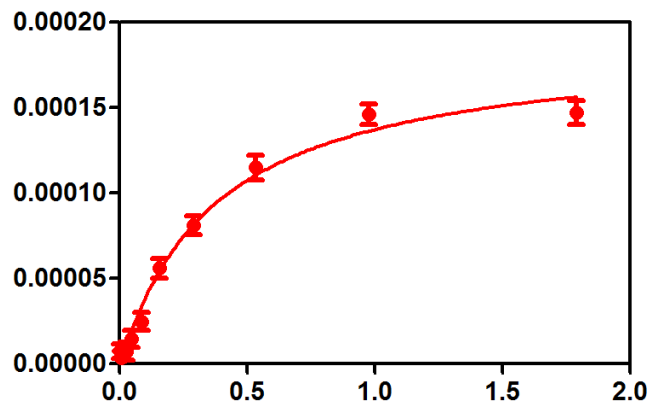
- Using full length protein substrate
- TRF readout with antibody detection of cleavage site
- enzyme titration, kinetics of substrate turnover, standard compound profiling
- DMSO tolerance, day-to-day and plate-to-plate variability

- **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

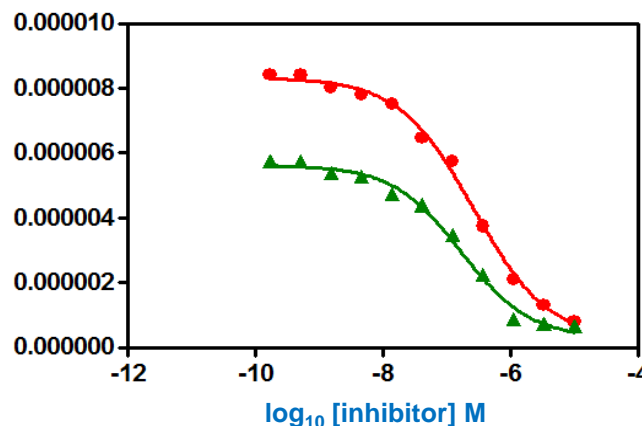
Screening and Profiling 23k cpds

TR- FRET signal



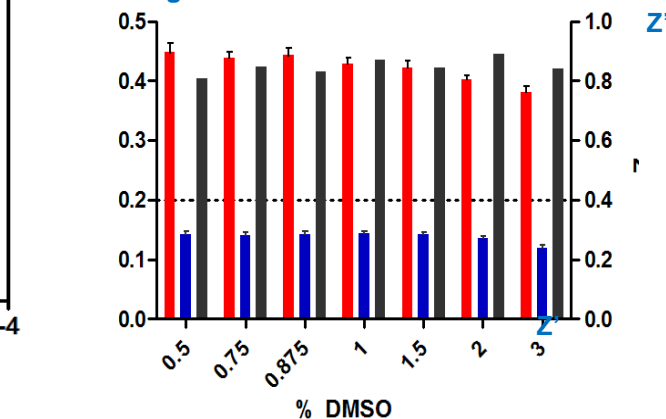
Substrate Km

TR-FRET signal



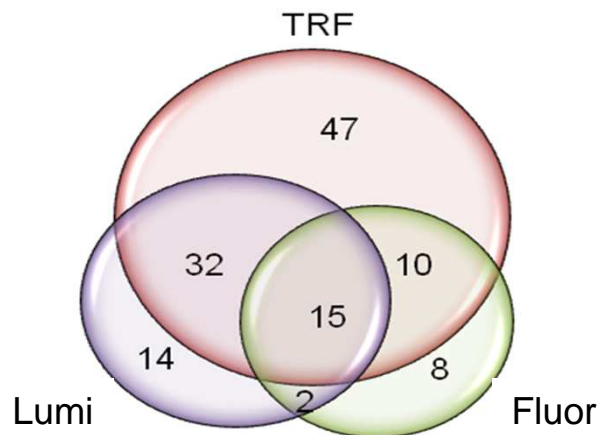
Pharmacology

5µl assay volume
TR-FRET signal
Legend: high (red), low (blue), Z' (black)

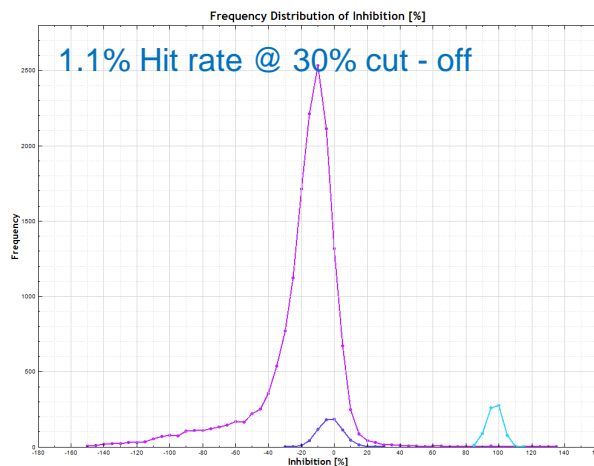


DMSO tolerance

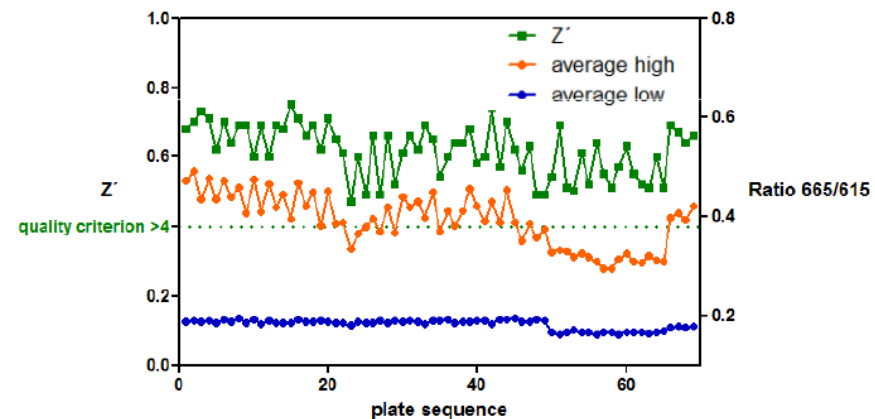
Secondary screens



Primary screen



Screen Stats

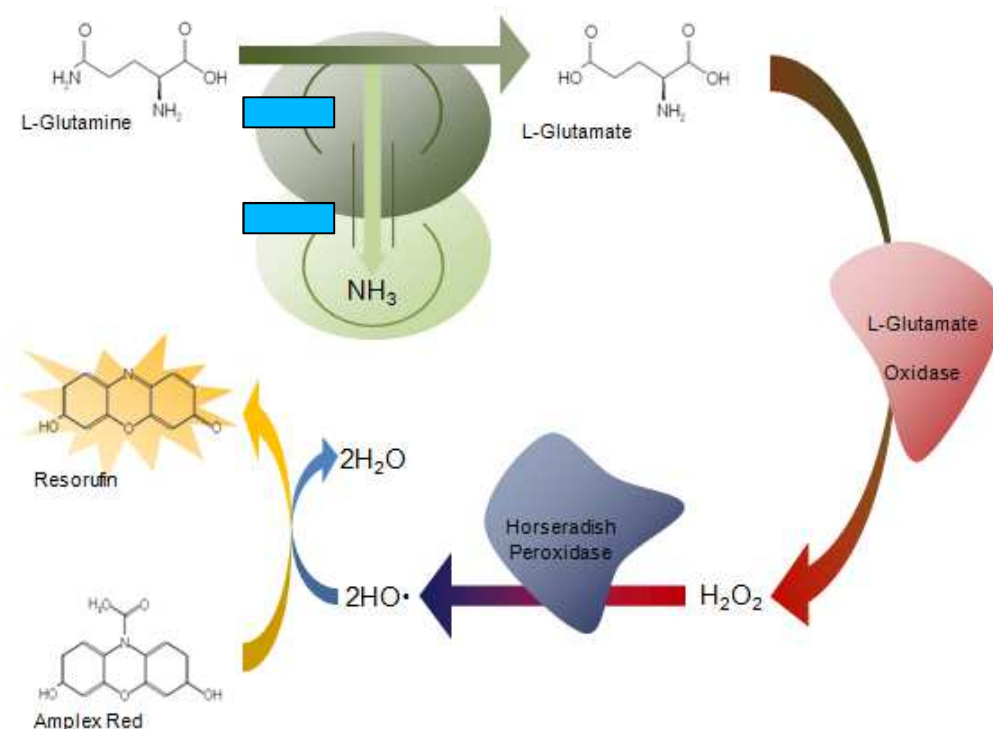


Assay development

- 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

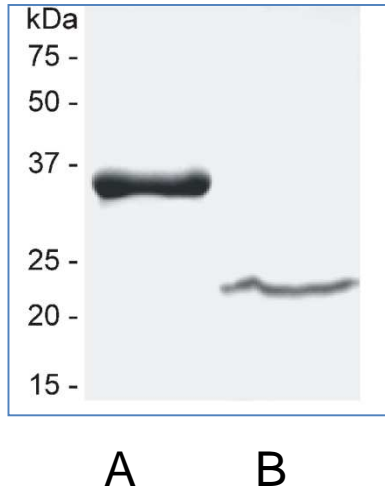
HTS campaign

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

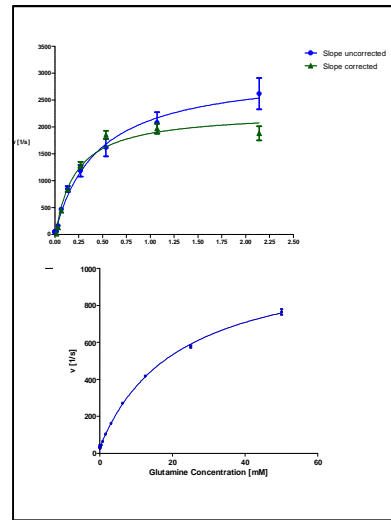


Assay Development (3 months)

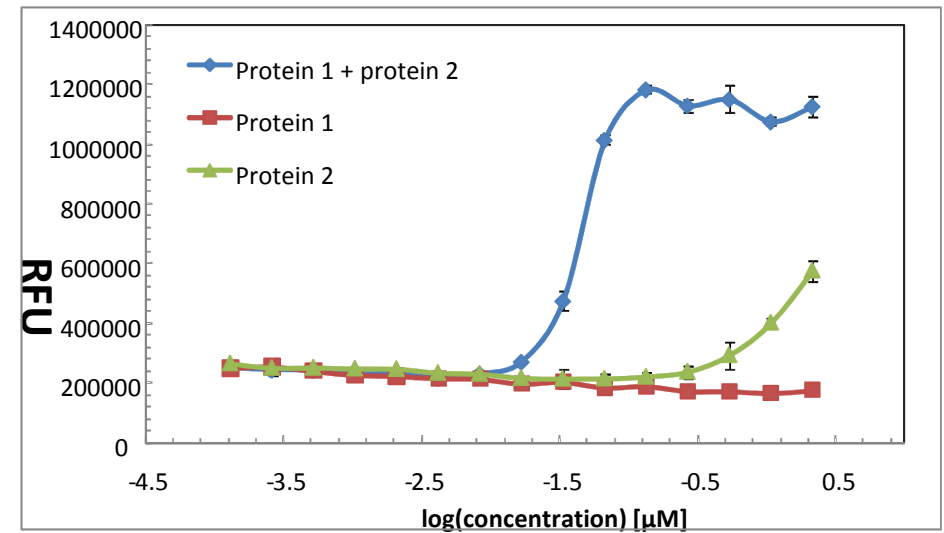
Reagent production



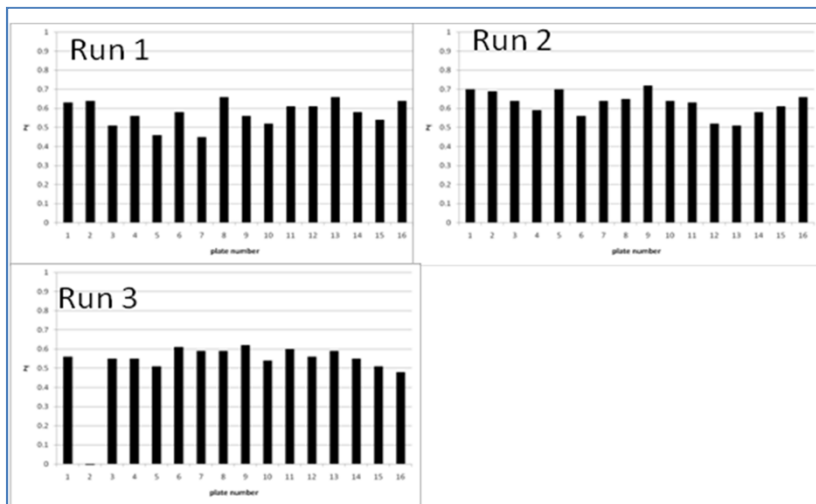
Enzyme titrations



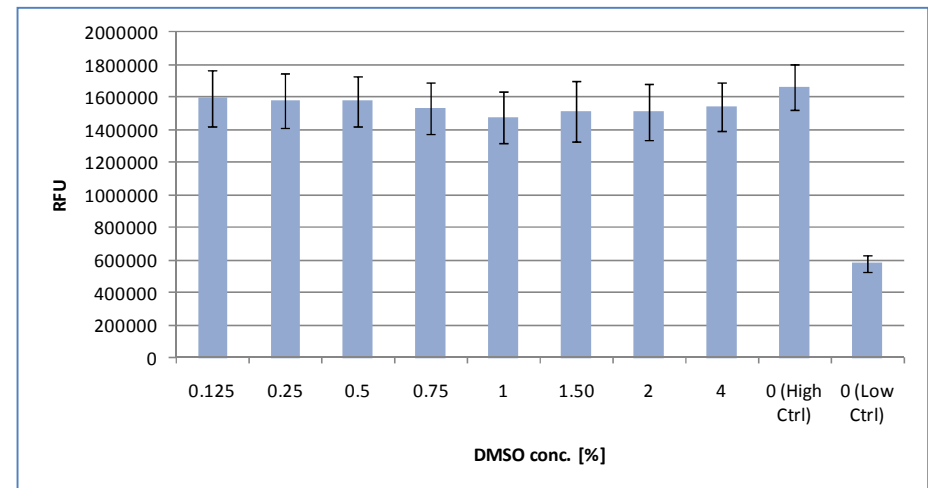
Heterodimer functional testing



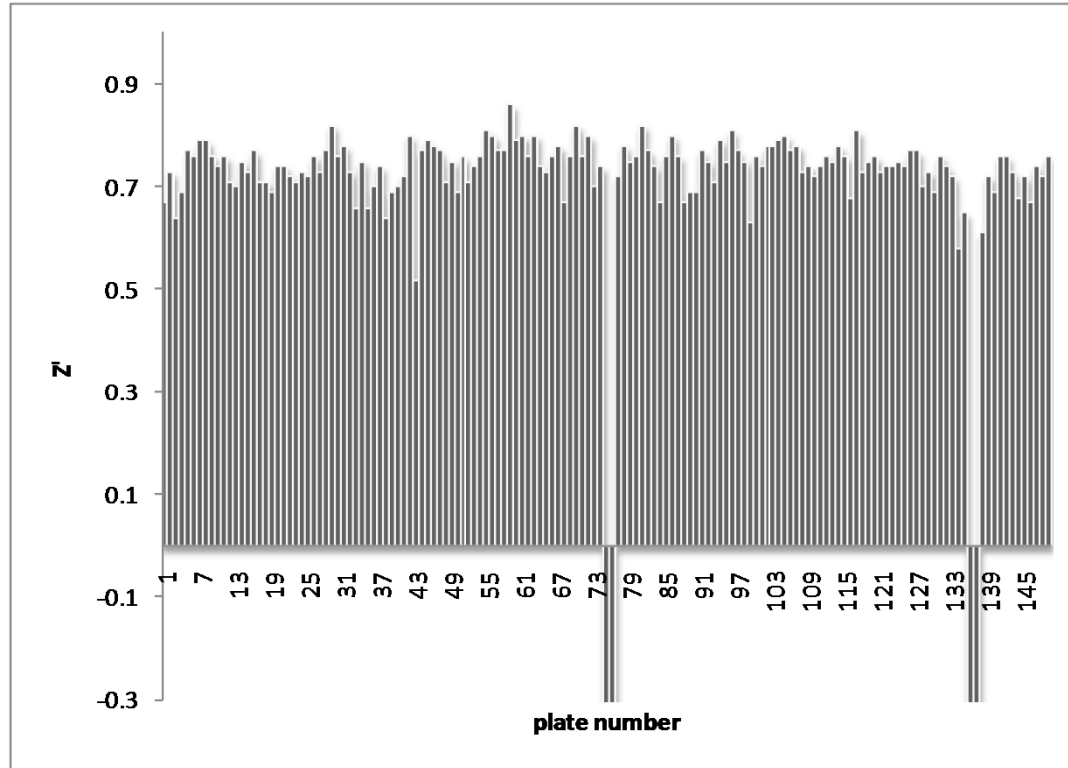
Marker Mini-screen



DMSO Tolerance



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

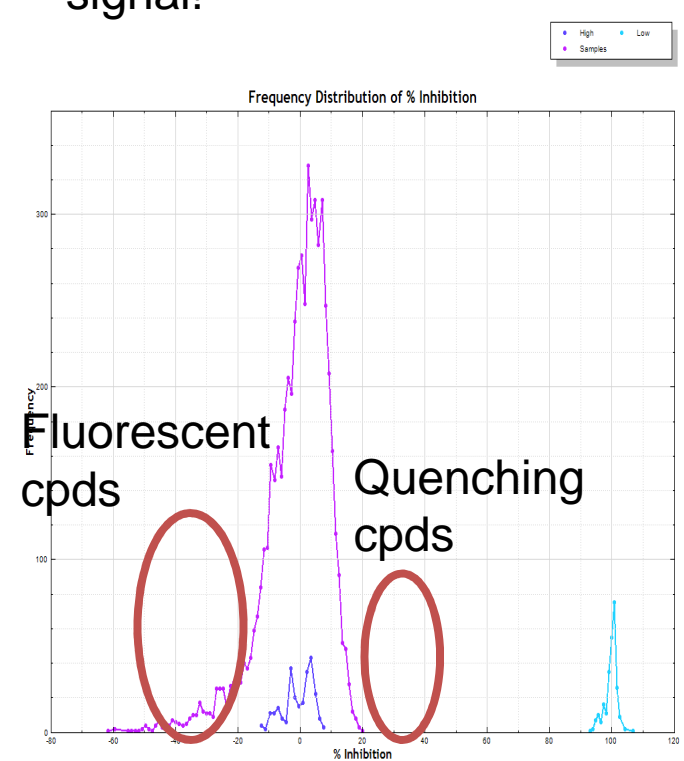
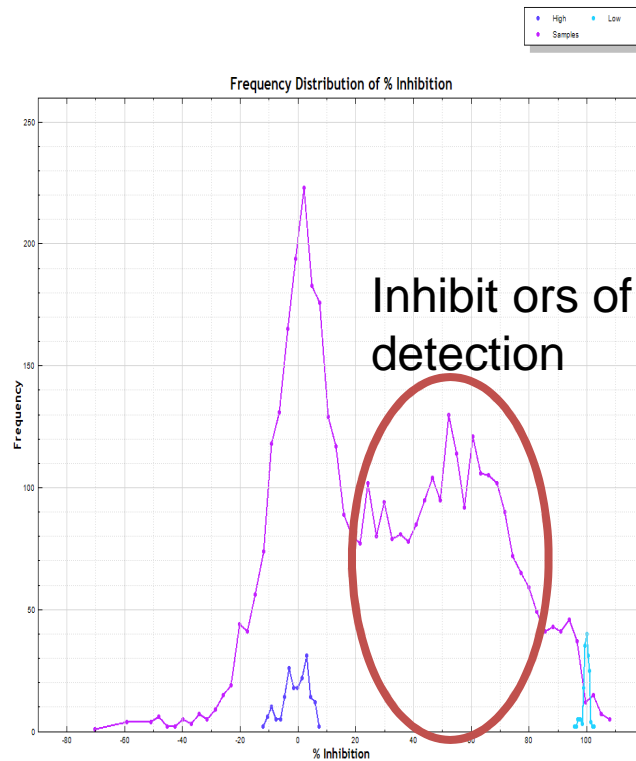
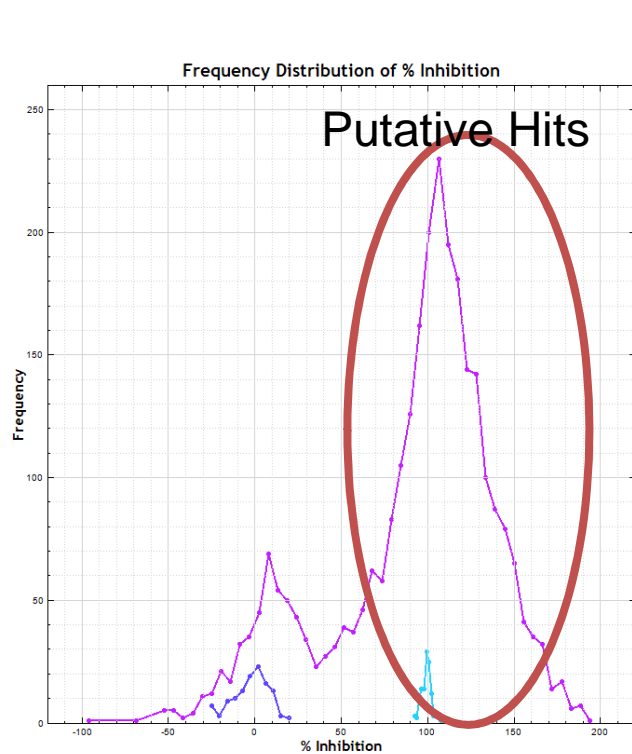
- Primary in triplicate
- 80% Hit recovery
- Significant # “super” inhibitors – artefacts?

Counter Assay 1

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

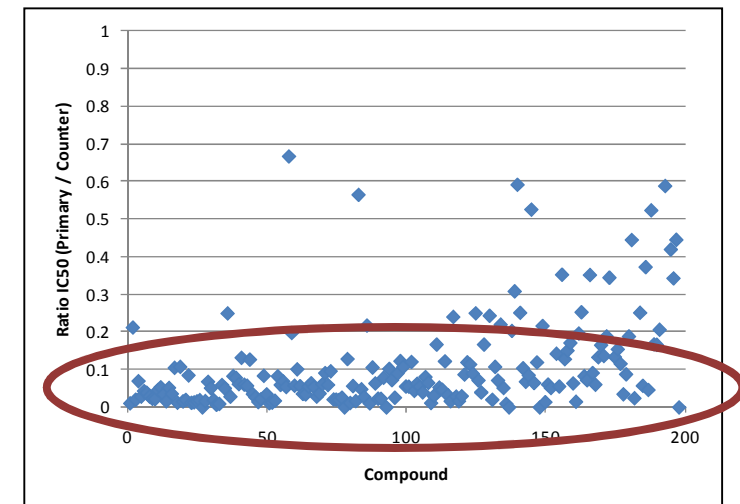
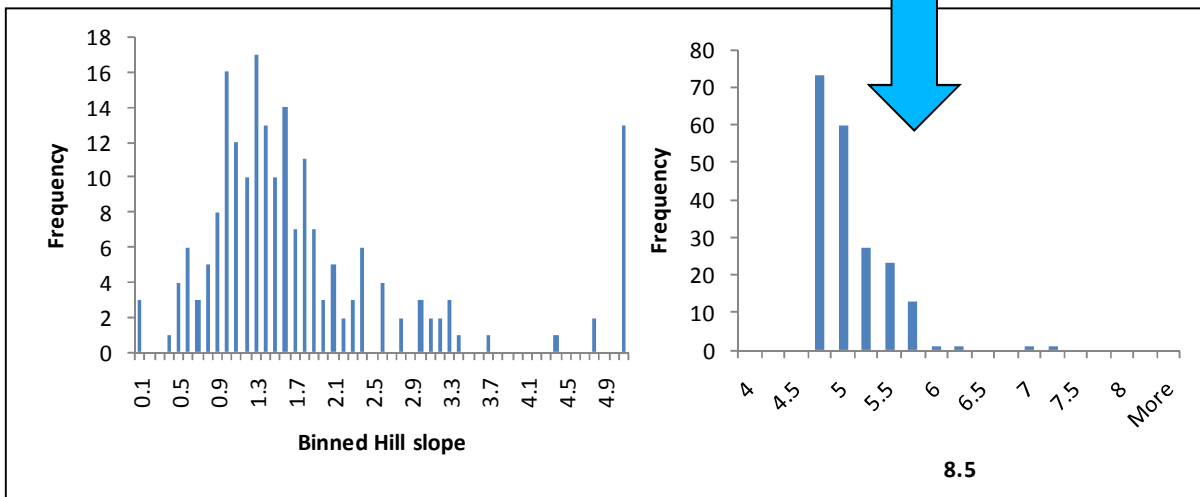
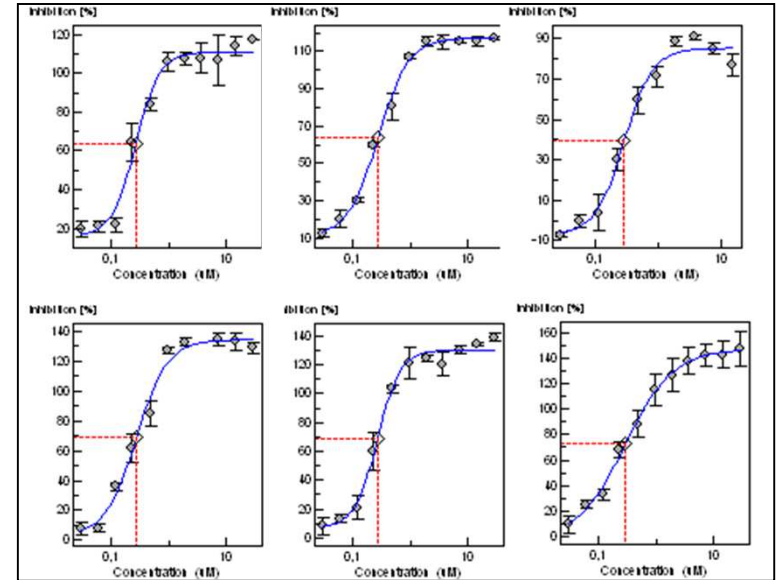
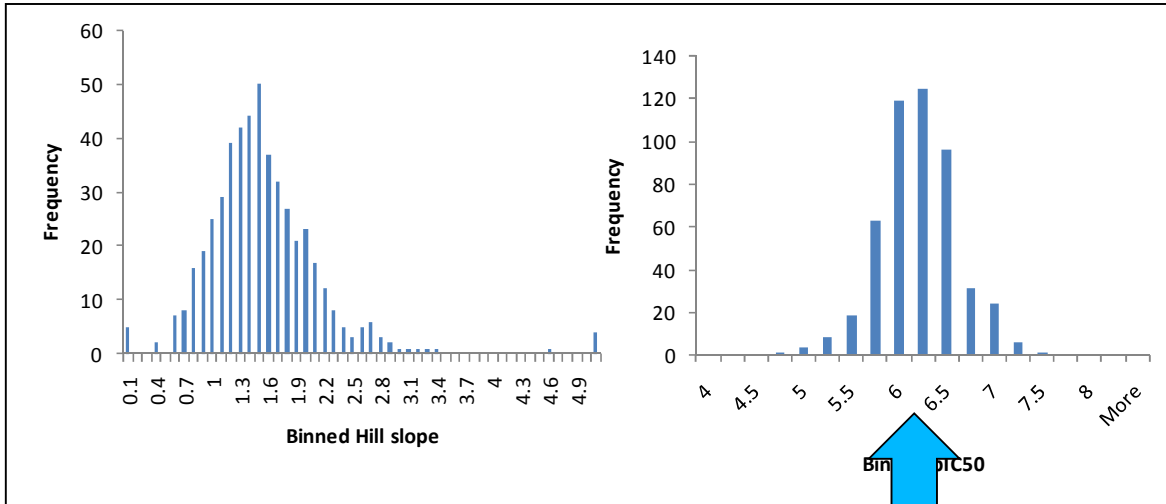
Counter Assay 2

- 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

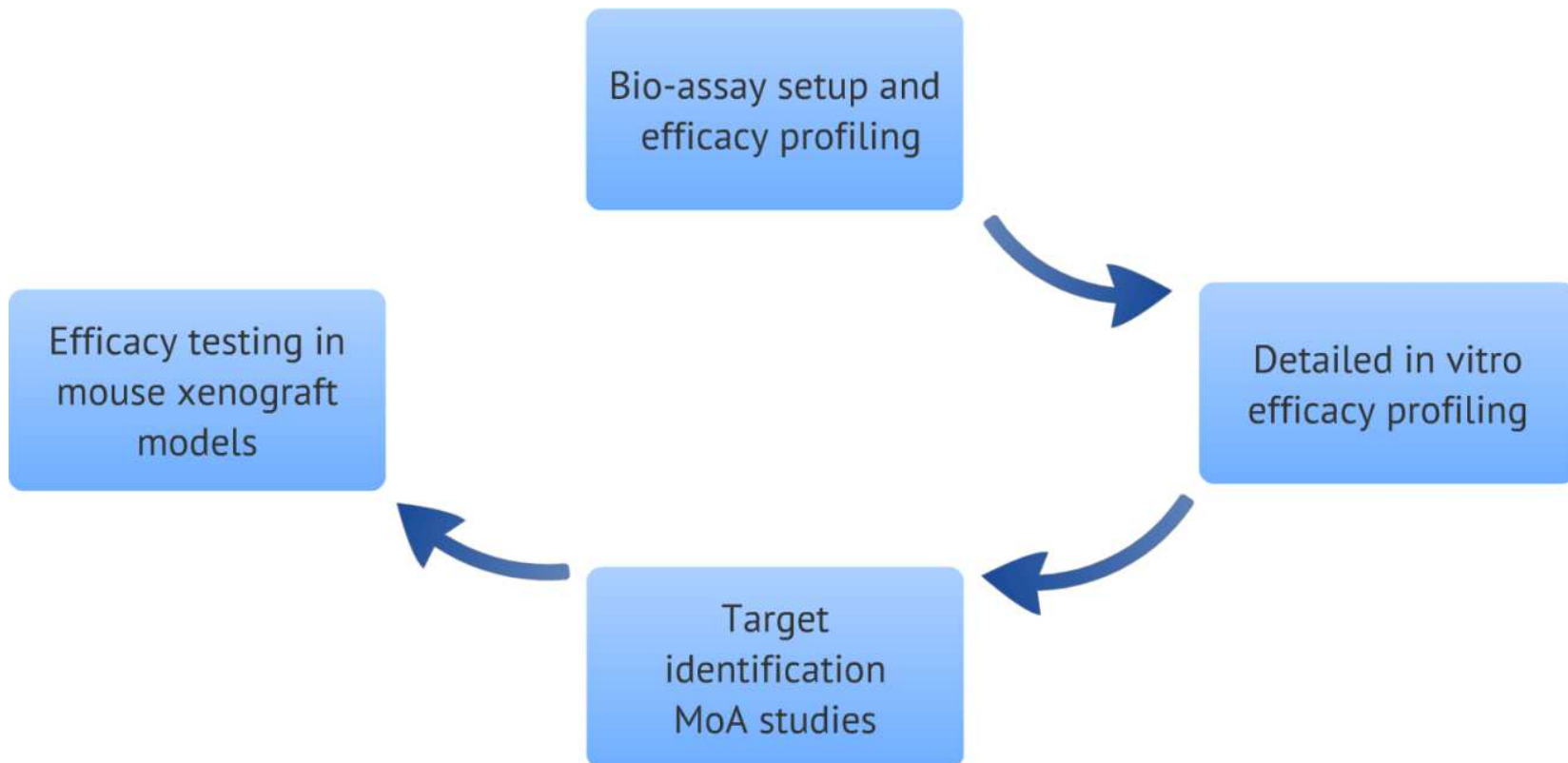


Counter Assay - 200 compounds (of 512) with curve fits

(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 Discover Working groups: ESP, GEOMAR, UIO (Oslo), DTI (Denmark), Hypha discovery (UK)



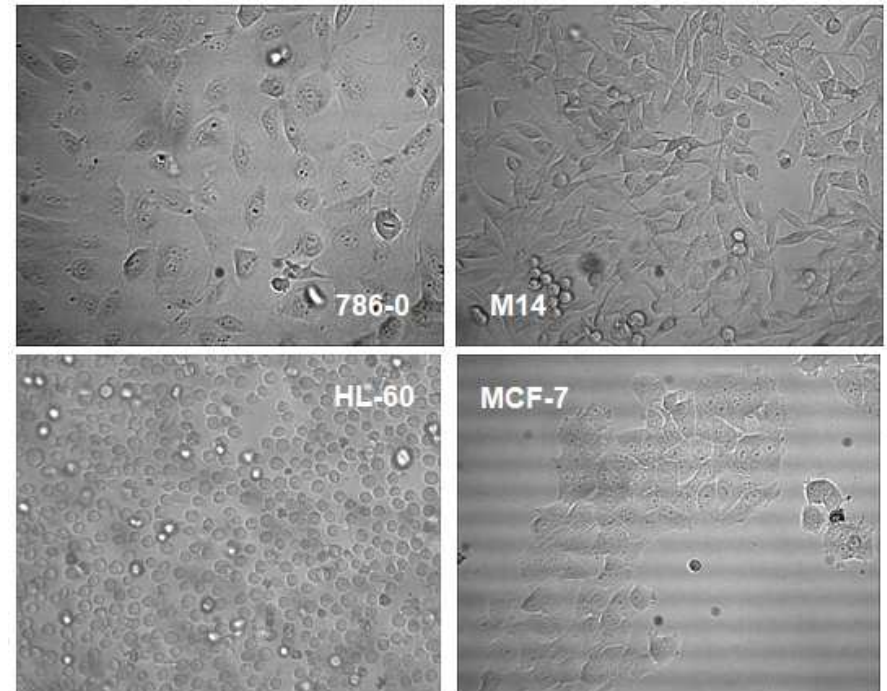
Cell line panel

- 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

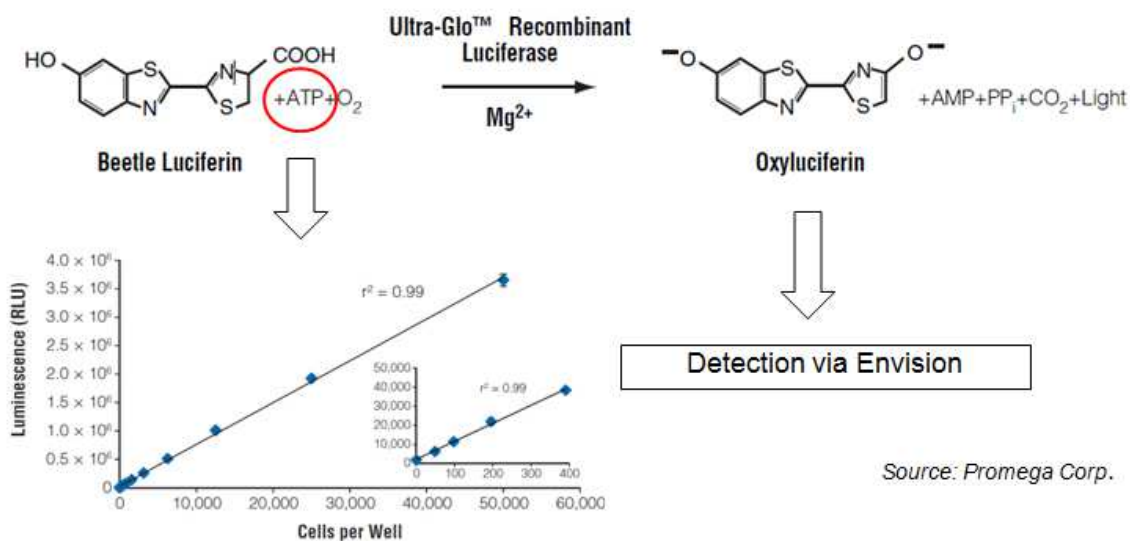
- Profile compounds effects on growth and viability of NCI panel

ESP

UIO

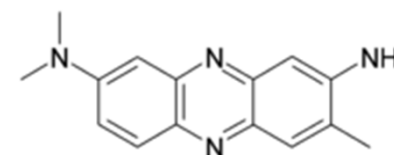
HD

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



Source: Promega Corp.

Neutral Red Assay

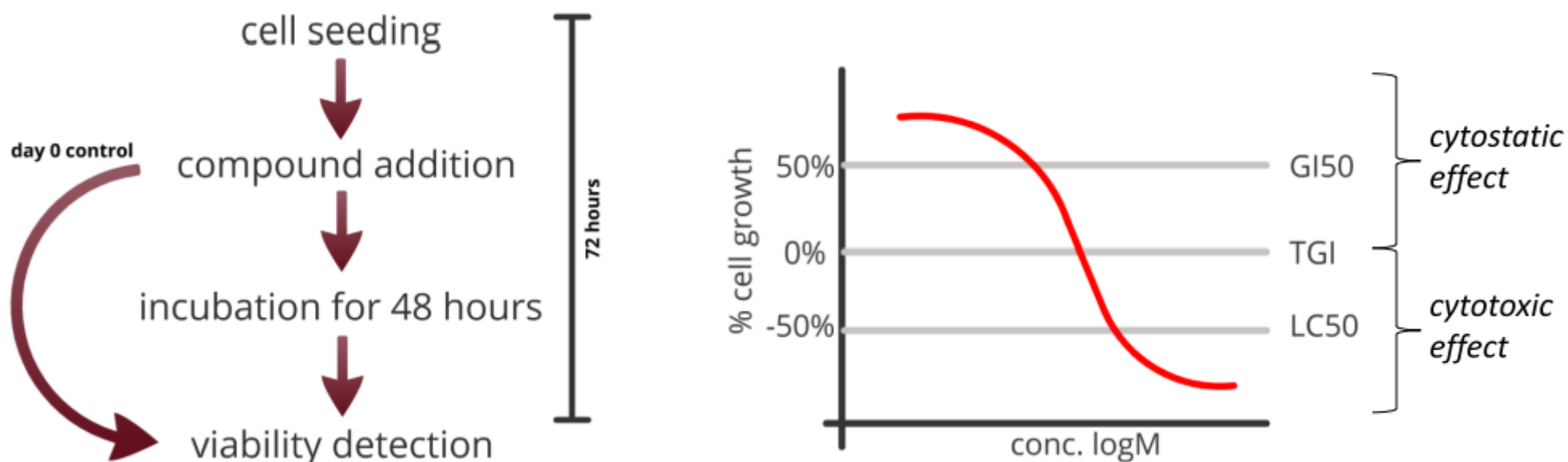


toluylene red

stains lysosomes in living cells

Methods

- NCI cancer cell line screen

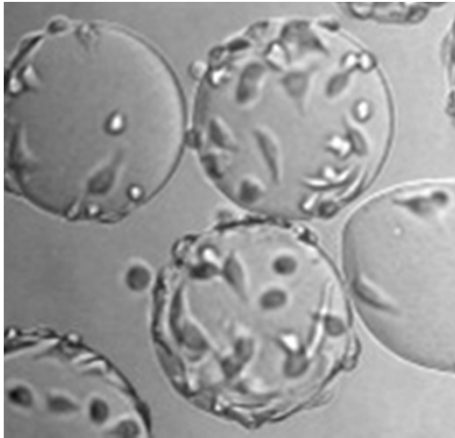


Concentrations at 50% cell growth (GI50), 0% cell growth (TGI) and -50% cell growth (LC50) were collected for each cell line per compound.

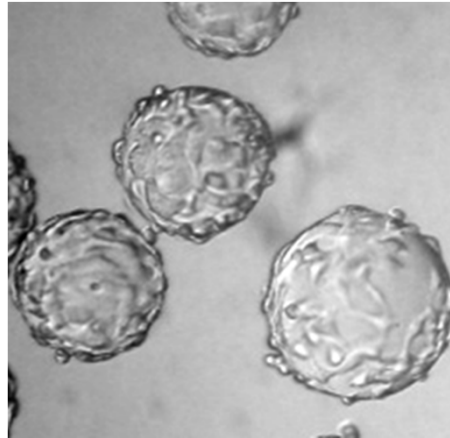
Aim: Screening of interesting compounds in the whole panel to obtain GI50, TGI and LC50 in each cell line

Optimisation of protocols

- 3D cell culture (BioLevigator)



SF-593



A549-ATCC



M14



786-0



Bioinformatics tools for Cpd analysis

data

COMPARE
online tool

Output

MoA
studies

GI50
TGI
LC50



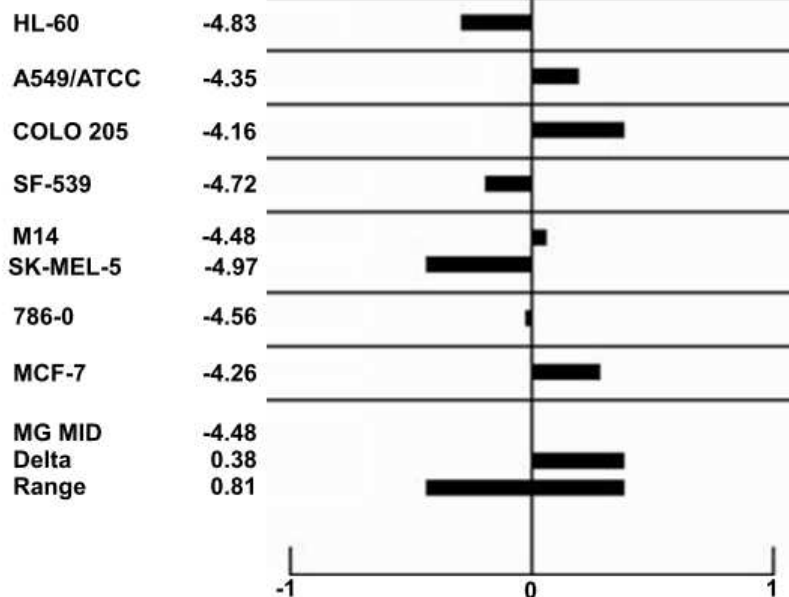
NCI
Mean
Graph



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

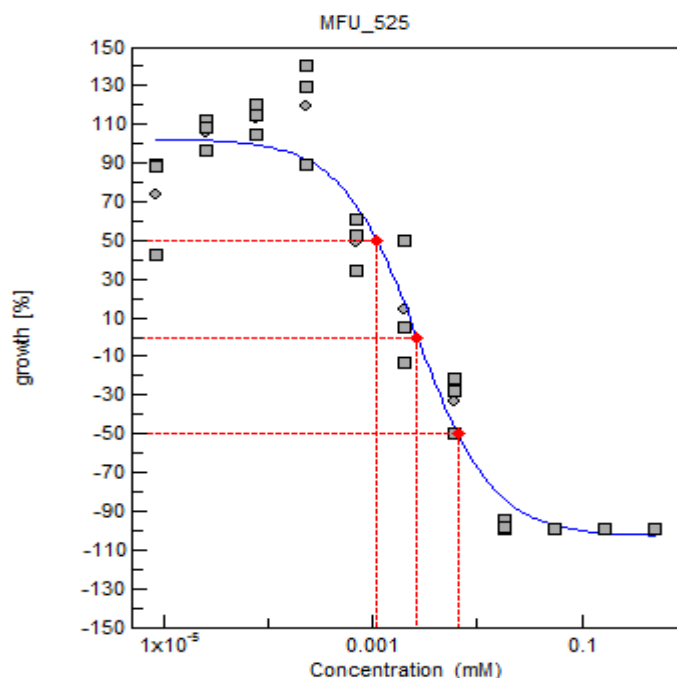
→ Validation includes:

- 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



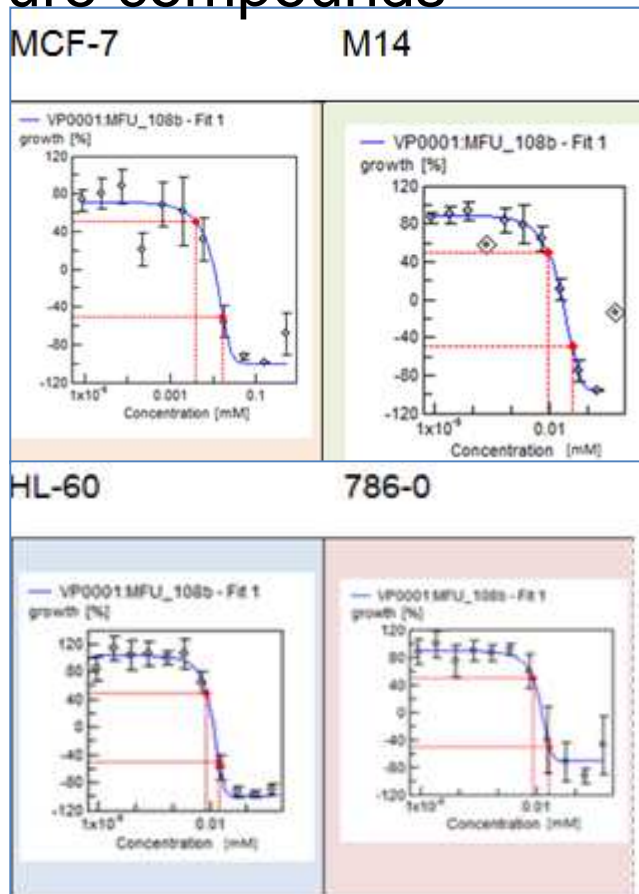
About 300 compounds screened in the preliminary panel

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

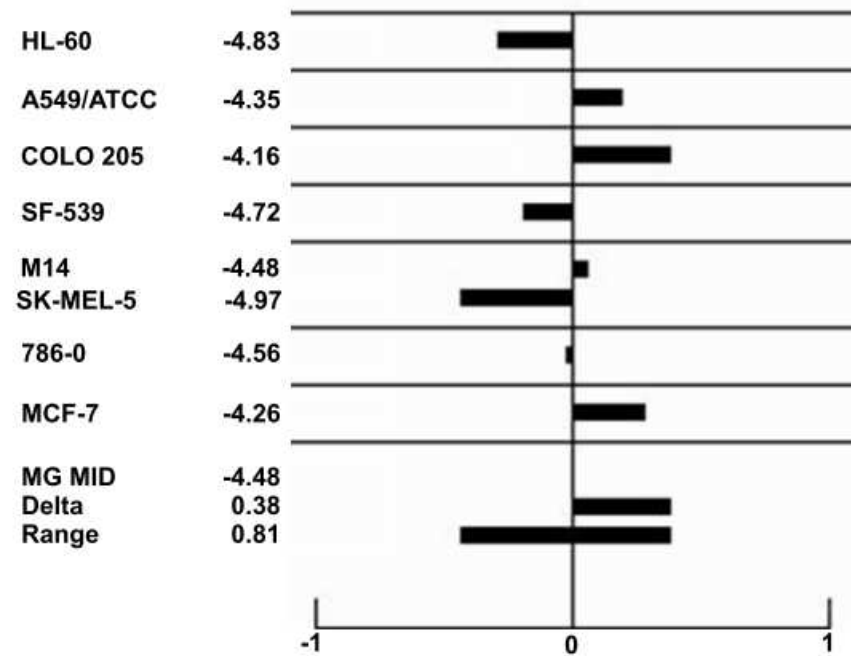
**Dose-response curve
compound 525n in SF-539**

Purified compound studies

Profiling results (DRC)
pure compounds



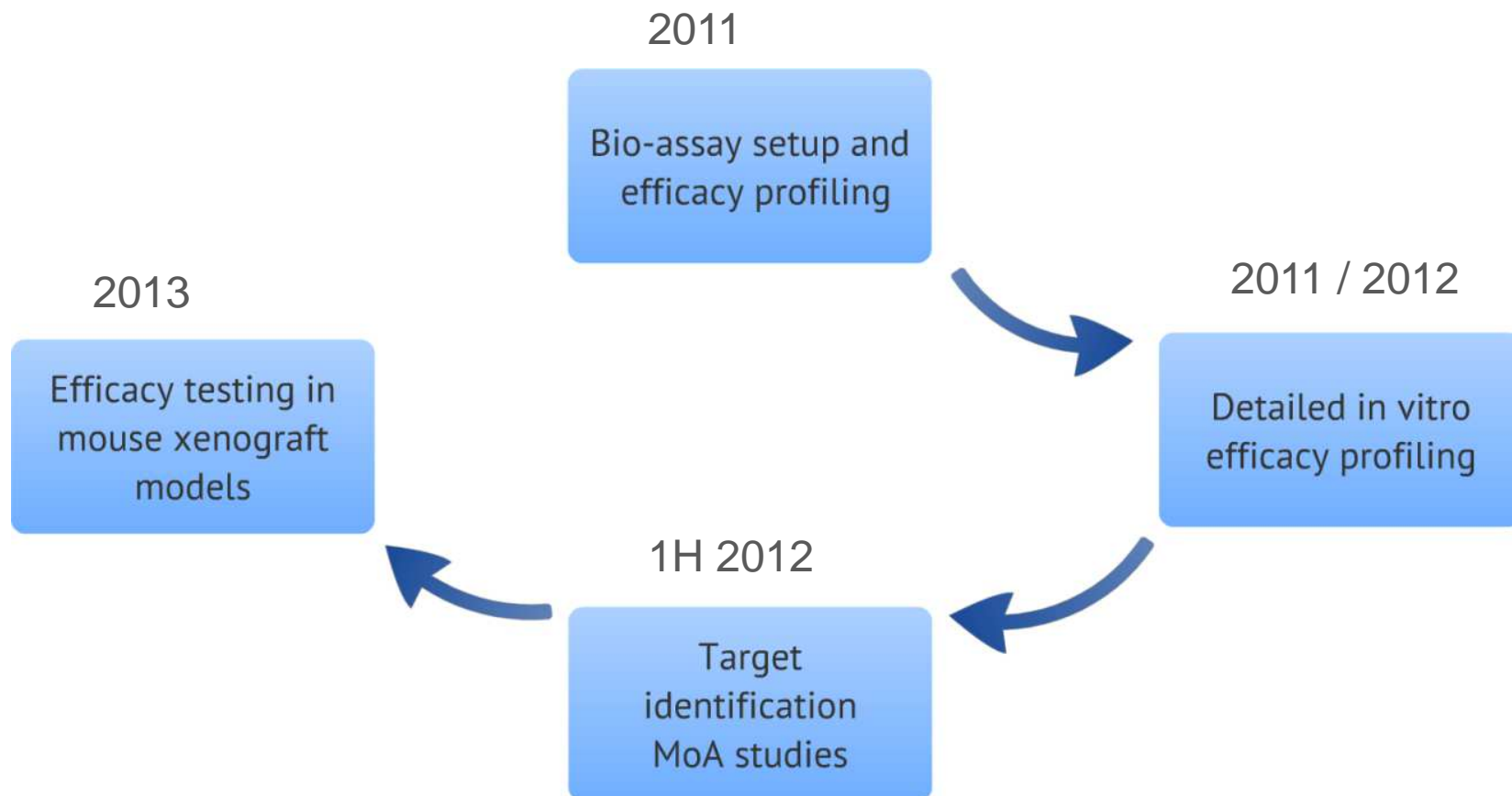
mean graphs in all screened cell
lines for COMPARE algorithm



Mean graph of compound B in 8 cell lines

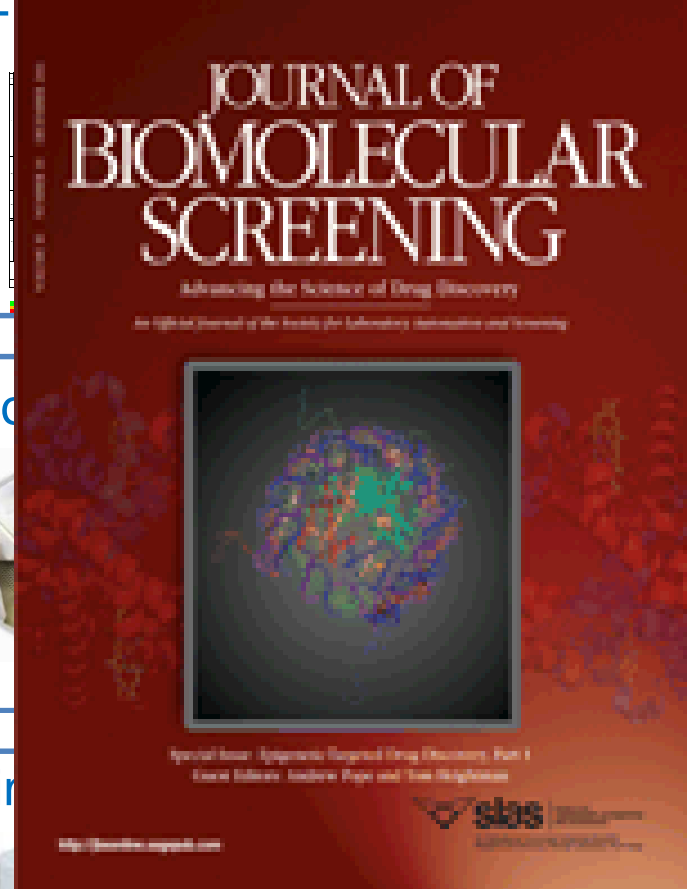
Marine Fungi Project

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

Epigenetic targets



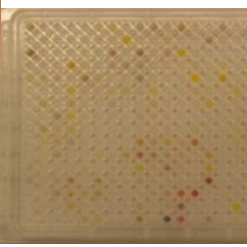
ESP Exper



ESP Infras



ESP Library



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

European ScreeningPort | HAMILTON

Webster, J., Frank, M., Ellinger, B., Gribben, P.

European ScreeningPort GmbH, Schmalzbergstraße 114, 22225 Hamburg, Germany, www.screeningport.com

bioassaydiscovery.com

Introduction

The EU funded project MARINE FLUID aims to establish cancer agents from marine natural compounds. The isolation and identification of compounds was done by the means of high throughput cell based screening. The NCI Cancer cell lines represent a variety of cancer phenotypes. However, culturing many cell lines is required to be done in a 96-well format. This is a challenge in terms of space and waste disposal. Therefore, the establishment of MicroCarrier-based cell viability assays in high throughput screening (HTS) format promises to be a good alternative to conventional 96-well plate based assays. The aim of this project is to establish and improve volume to surface ratio, less waste production and simplification of compound cell culture volume on microcarrier high content screening system (cell explorer, Pharmacia LKB, US).

Figure 1: High Content Screening format

High content screening (HCS) is a high throughput screening (HTS) format that allows the simultaneous measurement of multiple parameters in a single assay. This is achieved by the use of multi-well plates (e.g. 96-well) and the use of multi-channel detection systems (e.g. fluorescence, absorbance, luminescence, etc.).

Figure 2: Cell based assay on MicroCarrier™

The cell based assay on MicroCarrier™ involves the attachment of cells to a microcarrier bead. The cells are then grown in a 96-well format. The assay is performed by measuring the cell viability using a colorimetric assay (e.g. MTT, WST-1, etc.).

Figure 3: Dose response curves

The dose response curves show the effect of increasing concentrations of a compound on cell viability. The curves are sigmoidal and show a decrease in cell viability as the concentration of the compound increases.

Figure 4: Viability assay

The viability assay shows the effect of increasing concentrations of a compound on cell viability. The curves are sigmoidal and show a decrease in cell viability as the concentration of the compound increases.

Table 1: Dose response results

Compound	IC50 (nM)	IC20 (nM)	IC80 (nM)	Factor
Compound 1	0.5	0.1	1.0	1.0
Compound 2	0.7	0.15	1.1	1.5
Compound 3	0.9	0.2	1.2	2.7
Compound 4	1.1	0.25	1.3	3.8

Conclusions

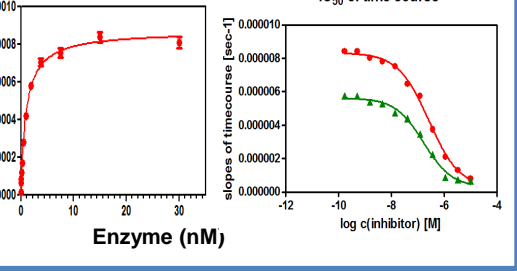
The establishment of several cell lines in different MicroCarrier systems to be a viable alternative when screening many cell lines in parallel. Cell culture can be performed in a very controlled way with reproducible results. In comparison, collected IC50s appear to be slightly higher in MicroCarrier based systems than in 96-well plates. This is likely due to the fact that the cells are grown in a 96-well format. The results presented here clearly show that screening using MicroCarrier™ is possible and can be used in a high throughput screening system. These results indicate that the use of a simple, fast and more economic screening system is possible compared to several 96-well plates. Therefore, the technology will increase the efficiency for the identification of novel anti-cancer compounds, derived from marine natural products.

References

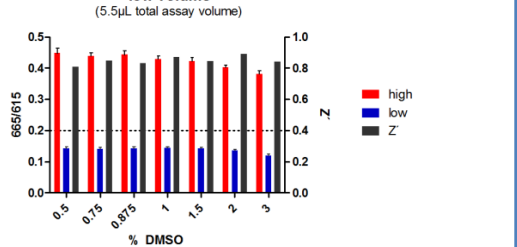
Ellinger, B. H. (2008). "The NCI60 human tumor cell cell anticancer drug screen." *Nature Reviews Cancer*, 8(10), 611-620.

Frank, M. et al. (2008). "Combinatorial screening of natural products for anticancer activity." *Environmental Health Perspectives*, vol. 116, no. 3, pp. 284-291.

Industrialised format



HTS compatibility



Market Validation

Integration of liquid handler quality control into the HTS daily routine

European ScreeningPort

Bernhard Ellinger¹, Alexander Hochreiner¹ and Stefan Schork²

Abstract

The high throughput screening (HTS) process is a complex task that requires a high degree of automation and precision. The integration of liquid handler quality control into the HTS daily routine is essential to ensure the reliability and accuracy of the results. This paper describes the implementation of a quality control system into the HTS workflow, which allows for the detection and correction of errors in real-time. The system is based on a combination of hardware and software components, and it is designed to be easy to use and maintain. The results of the implementation show that the system is effective in detecting and correcting errors, and it significantly improves the overall quality and efficiency of the HTS process.

Introduction

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Materials and Methods

The quality control system is based on a combination of hardware and software components. The hardware components include a liquid handler, a microscope, and a camera. The software components include a data acquisition system, a data analysis system, and a quality control system. The quality control system is designed to detect and correct errors in real-time, and it is integrated into the HTS workflow. The results of the implementation show that the system is effective in detecting and correcting errors, and it significantly improves the overall quality and efficiency of the HTS process.

Results

The results of the implementation show that the quality control system is effective in detecting and correcting errors in real-time. The system is able to detect errors in the liquid handler, the microscope, and the camera, and it is able to correct these errors automatically. The results show that the system is able to detect and correct errors with a high degree of accuracy, and it significantly improves the overall quality and efficiency of the HTS process.

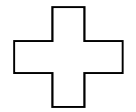
Conclusions

The implementation of a quality control system into the HTS workflow is essential to ensure the reliability and accuracy of the results. The system is based on a combination of hardware and software components, and it is designed to be easy to use and maintain. The results of the implementation show that the system is effective in detecting and correcting errors in real-time, and it significantly improves the overall quality and efficiency of the HTS process.

References

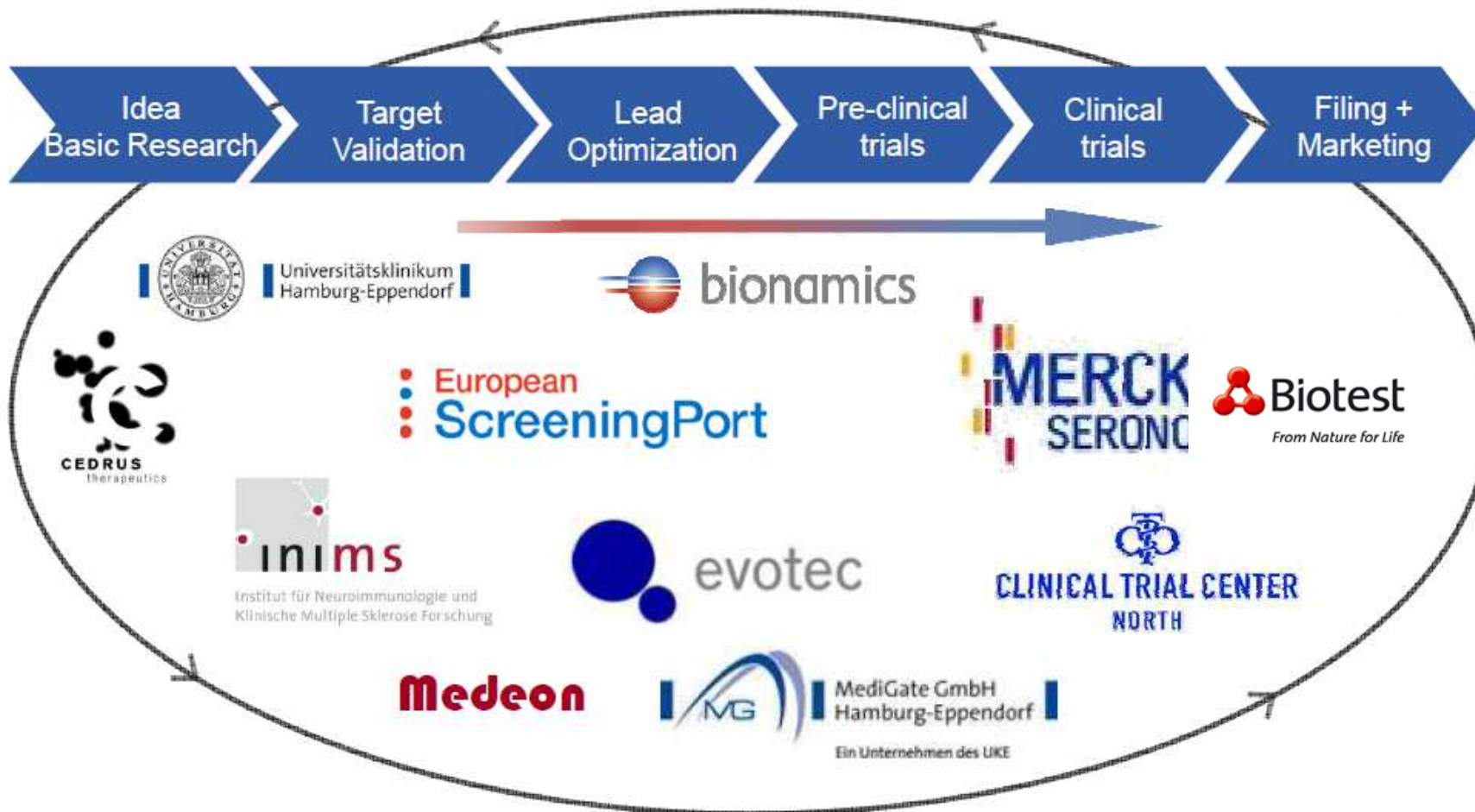
Ellinger, B. H. (2008). "The NCI60 human tumor cell cell anticancer drug screen." *Nature Reviews Cancer*, 8(10), 611-620.

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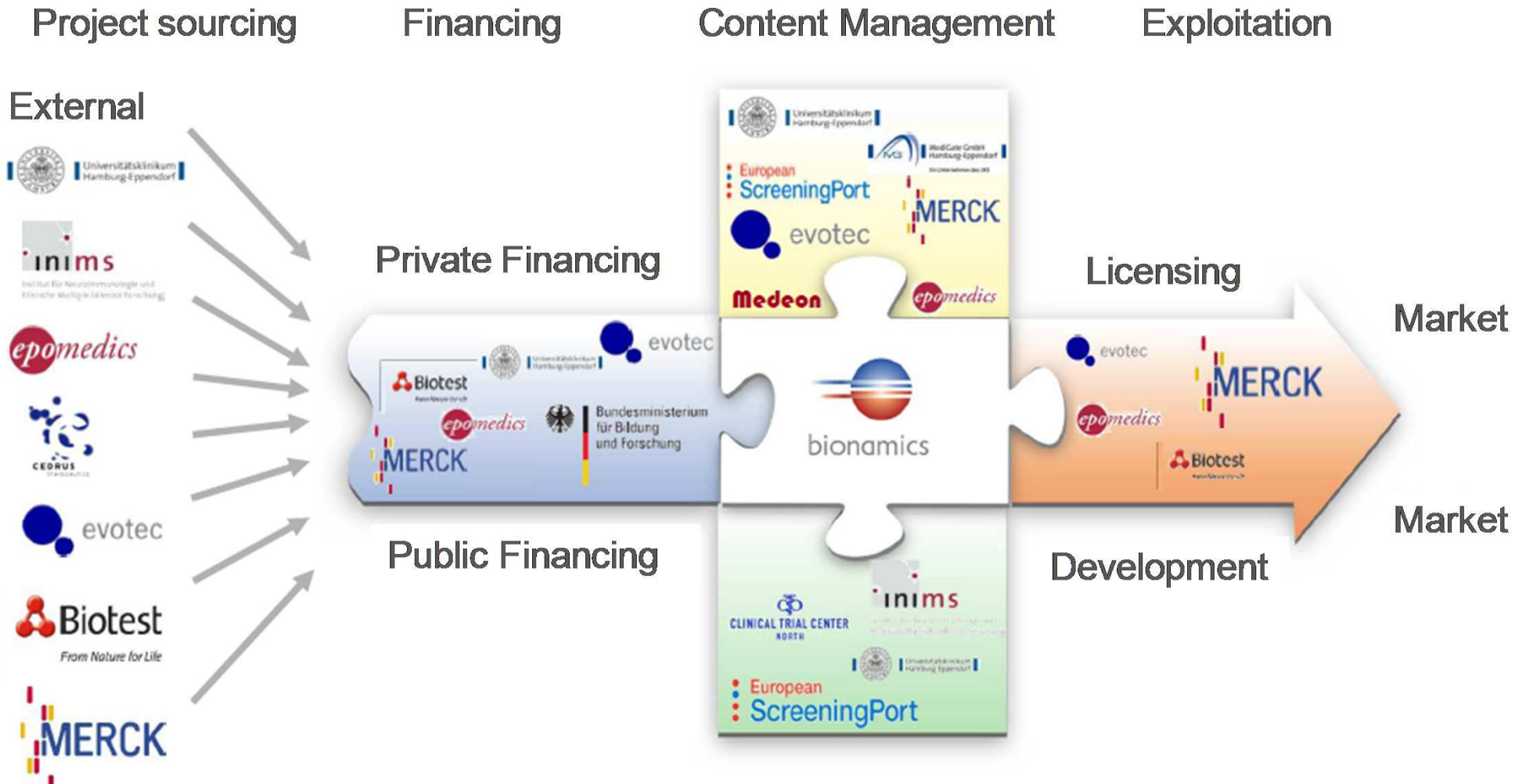


Open Innovation in Practice: Neu2 - A Competence Consortium in MS

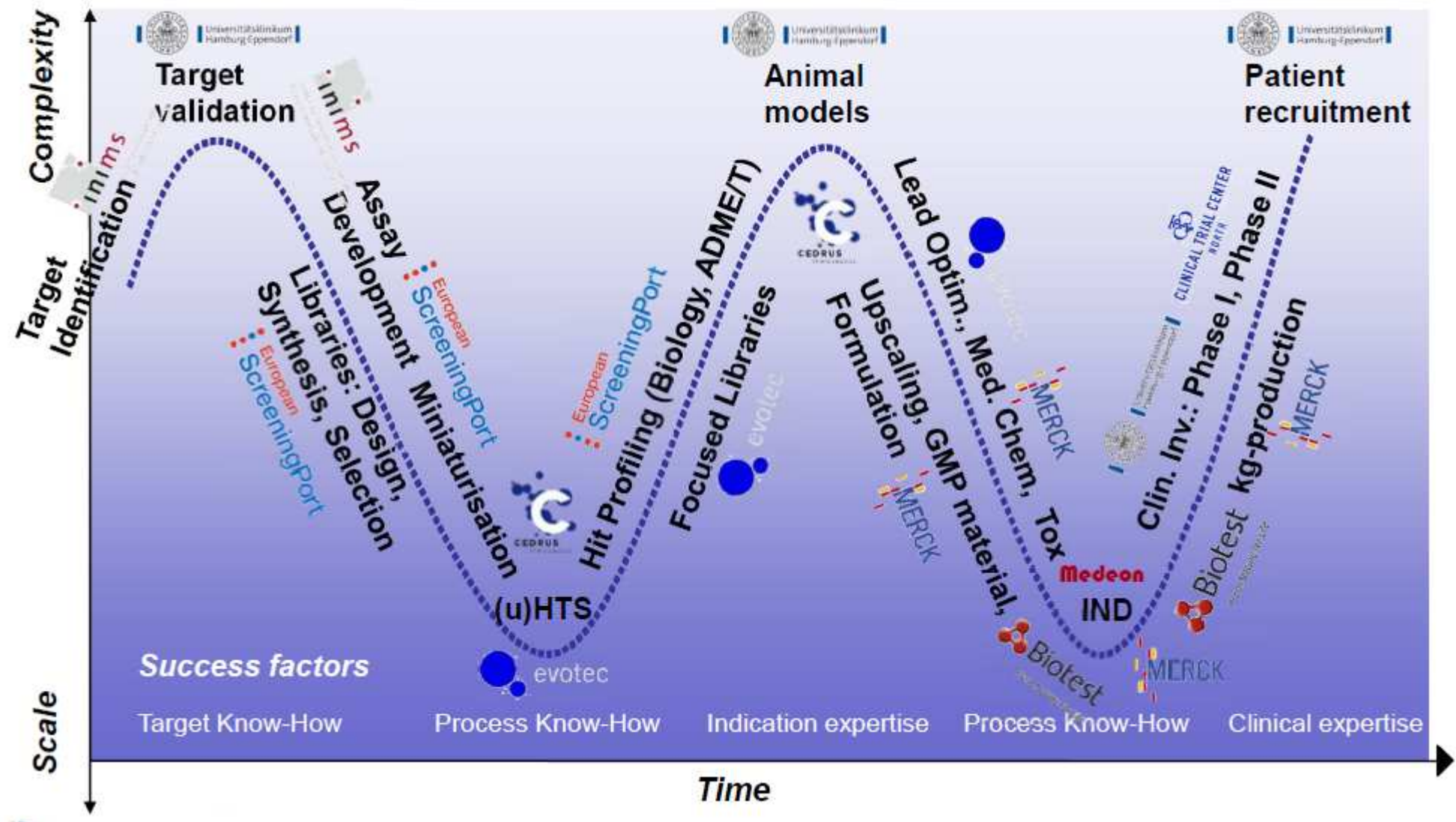
NEU² : Competence in MS



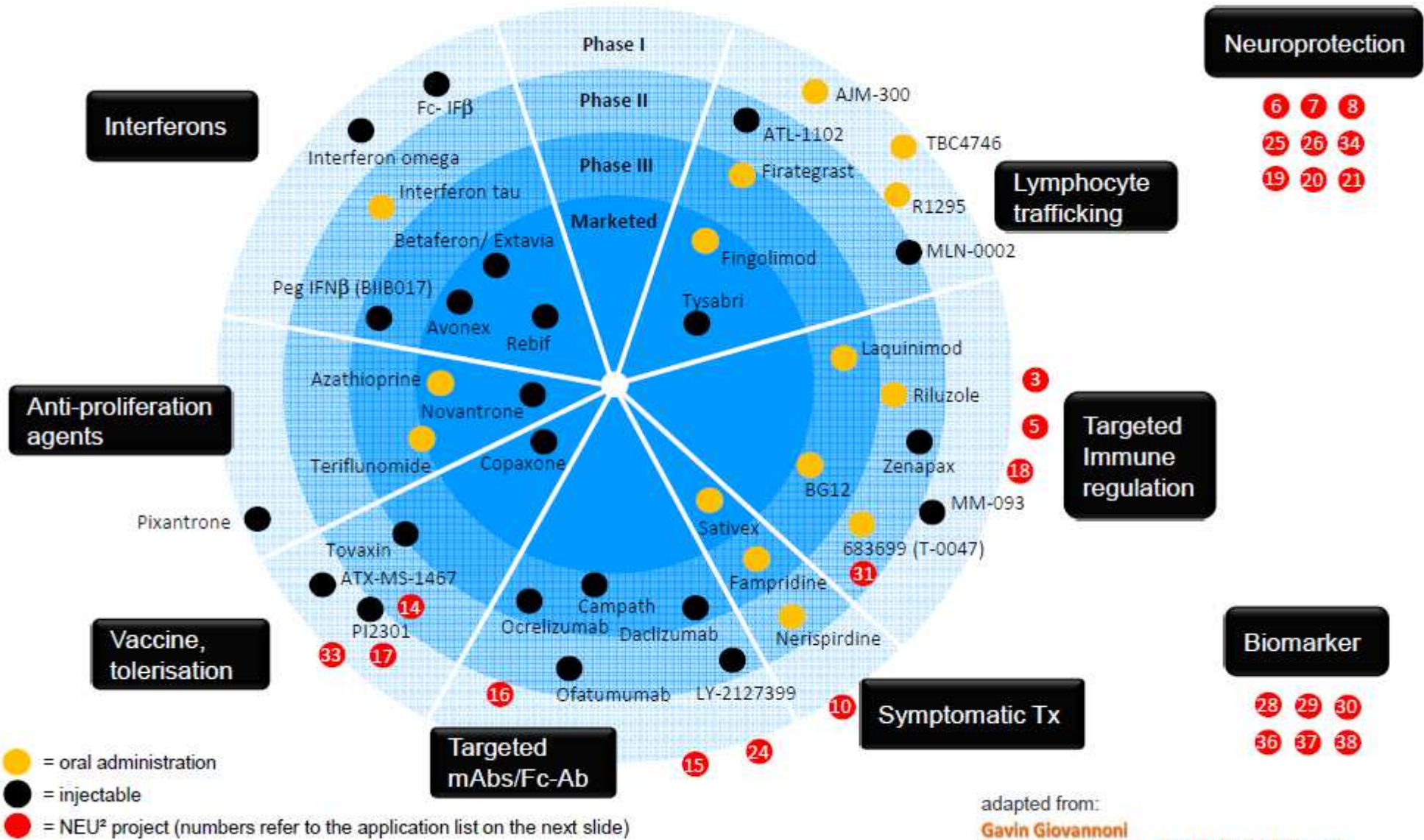
Neu2 Project flow

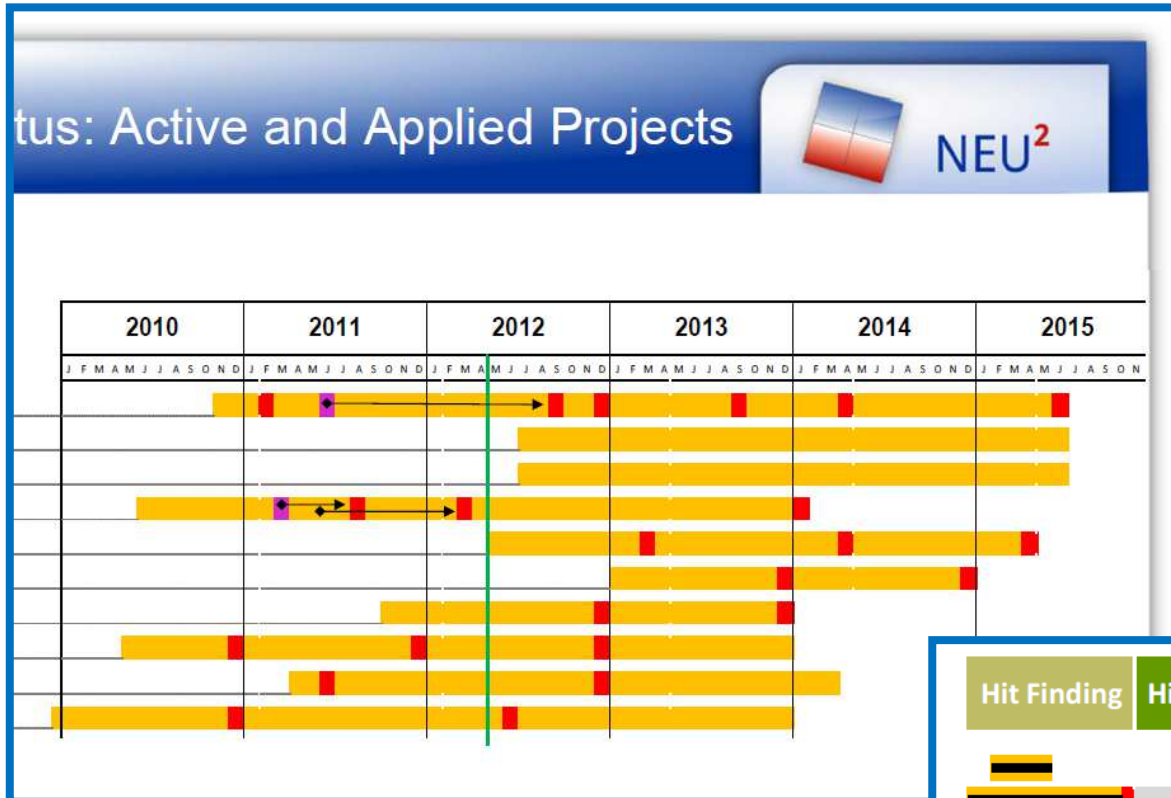


Neu2 - Competence Cascade



Positioning of Neu2 portfolio



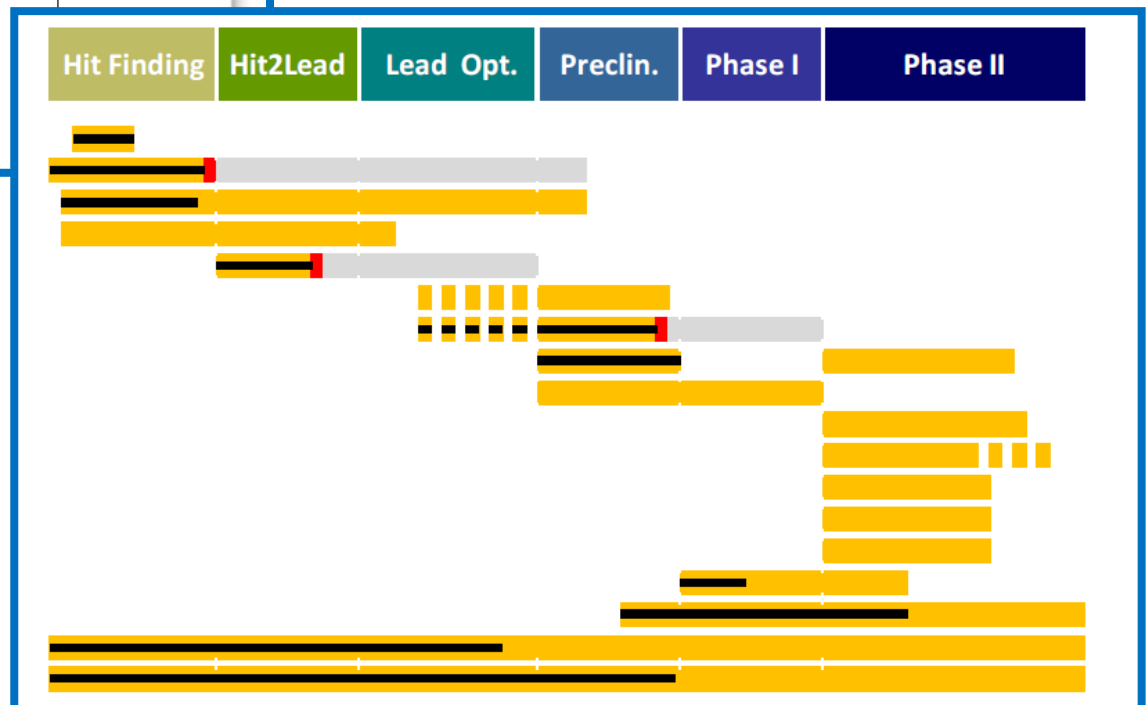


Scope and project finances

- 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 Hit 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