

The Open Pharmacological Concepts Triple Store

www.openphacts.org

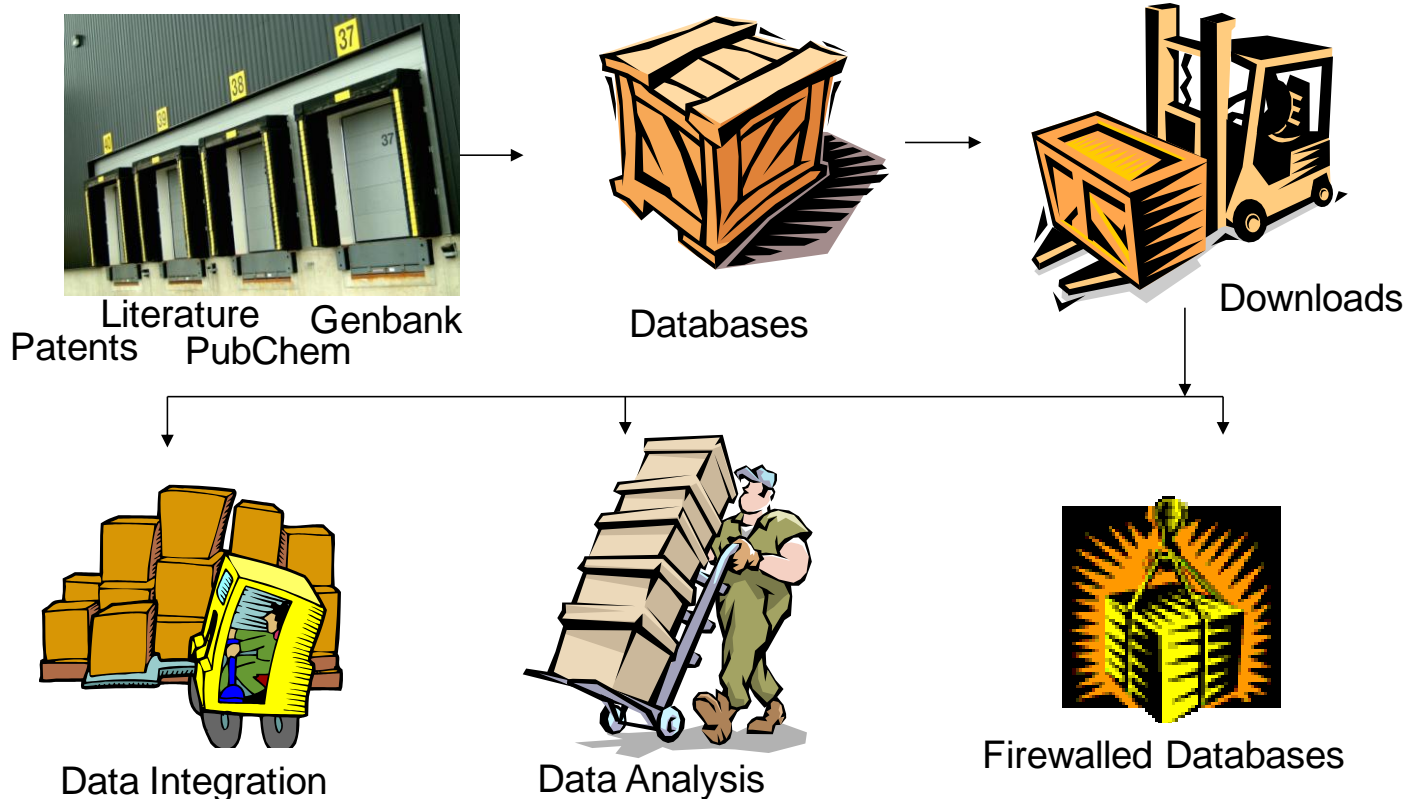


efpia



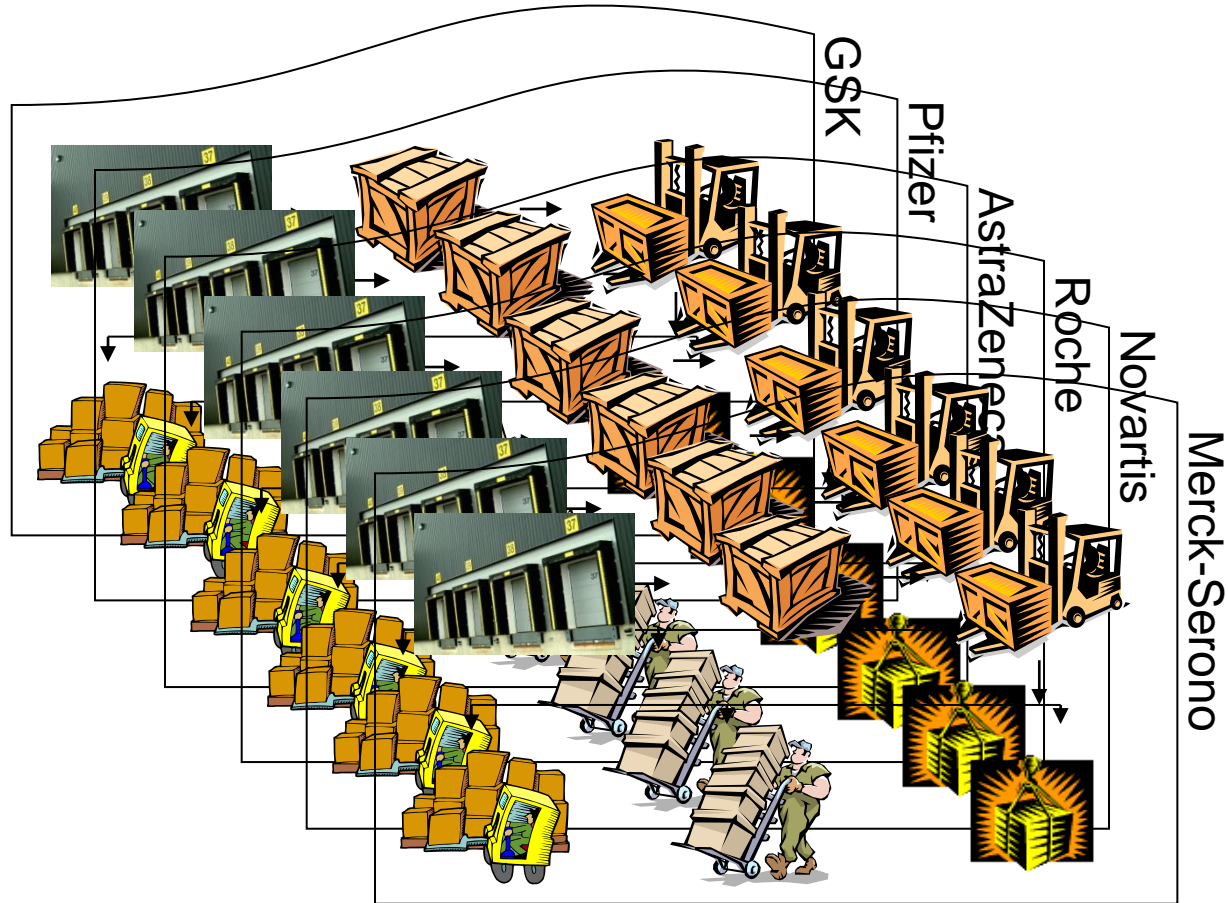
Public Domain Drug Discovery Data:

Pharma are accessing, processing, storing & re-processing





We are all doing this many times.....





A user-friendly, full featured interface that allows scientists to explore and interrogate integrated biological and chemical data

What will users see?



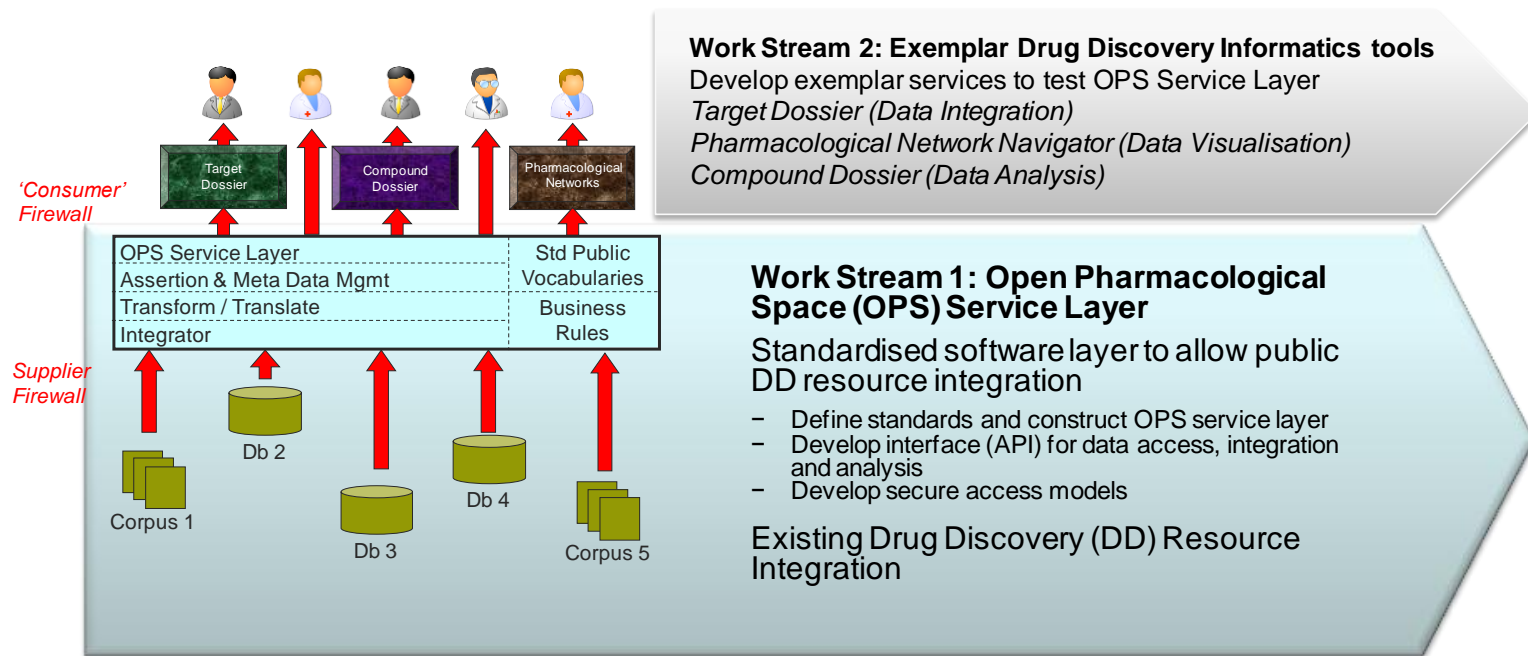
OPS Services should allow to

- ❖ integrate data on target expression, biological pathways and pharmacology to identify the most productive points for therapeutic intervention
- ❖ investigate the *in vitro* pharmacology and mode-of-action of novel targets to help develop screening assays for drug discovery programmes
- ❖ compare molecular interaction profiles to assess potential off-target effects and safety pharmacology
- ❖ analyse chemical motifs against biological effects to deconvolute high content biology assays



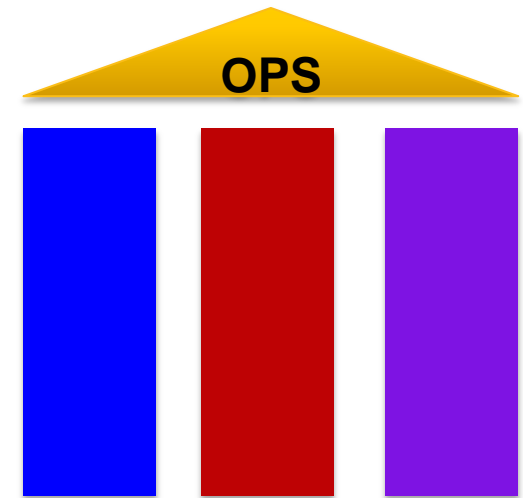
Major Work Streams:

- “Build”: OPS service layer and resource integration
- “Drive”: Development of exemplar work packages & Applications
- ”Sustain”: Community engagement and long-term sustainability





- **A Precompetitive Infrastructure**
 - Begin the task of creating an environment that can also power future collaborative efforts (public & industry)
 - **Expose Industry Experience:** Create drug-discovery focused tools outside of the firewall, influenced by decades of practical experience
- **A Pharmacology Use Case**
 - Showcase one application of this technology: a stable, responsive, user-orientated system for Pharmacology Analysis
- **A Data Publishing Methodology**
 - Develop standards and methodologies to promote good data sharing and interoperability
 - An exemplar project for the use of the Nanopublication concept
 - A technical approach that can be repeated in other areas





Current Status

Prototype released to the consortium for broad testing

Datasets in this release

- ❖ **Enzyme**: Necessary for the enzyme classifications
- ❖ **ChEMBL v2**: Essential SAR database (**soon updated to v13**)
- ❖ **Drugbank v3**: Provides additional information on known drugs
- ❖ These are connected through **ConceptWiki IDs** (which contains **Uniprot mappings**) and **ChemSpider Ids** (chemistry resolution service)

The following queries are possible:

- ❖ Query pharmacology data by target (via target name search)
- ❖ Query pharmacology data by compound (via compound name search)
- ❖ Query pharmacology data by target family (via Enzyme hierarchy)
- ❖ Structure searches to identify compounds in the system (which can then be used in pharmacology searches)
- ❖ Text search to identify targets/proteins

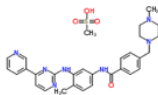


Compound by name ✕

Hint: Type in compound name. E.g. "Aspirin"

Compound name:

Compound by Name search results



Gleevec

Imatinib is a drug used to treat certain types of cancer. It is currently marketed by Novartis as Gleevec (USA) or Glivec (Europe/Australia) as its mesylate salt, imatinib mesilate (INN). It is occasionally referred to as CGP57148B or STI571 (especially in older publications). It is used in treating chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs) and a number of other malignancies. It is the first member of a new class of agents that act by inhibiting particular tyrosine kinase enzymes, instead of non-specifically inhibiting rapidly dividing cells.

Primarily hepatic via CYP3A4. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4.

ChemSpider ID: [5101](#)

Molecular Formula: C29 H31 N7 O

SMILES: Cc1ccc(cc1Nc2nccc(n2)c3cccnc3)NC(=O)c4ccc(cc4)CN5CCN(CC5)C

Standard InChI: InChI=1S/C29H31N7O/c1-21-5-10-25(18-27(21)34-29-31-13-11-26(33-29)24-4-3-12-30-19-24)32-28(37)23-8-6-22(7-9-23)20-36-16-14-35(2)15-17-36/h3-13,18-19H,14-17,20H2,1-2H3,(H,32,37)(H,31,33,34)

Standard InChIKey: KTUFNOKKBVMGRW-UHFFFAOYSA-N

Affected Organism: Humans and other mammals

Indication: For the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (CML). Also indicated for the treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. Also indicated with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

Protein Binding: Very high (95%)

Toxicity: Side effects include nausea, vomiting, diarrhea, loss of appetite, dry skin, hair loss, swelling (especially in the legs or around the eyes) and muscle cramps

Melting Point: 226 oC (mesylate salt)

AlogP:	# H-Bond Receptors:	# H-Bond Donors:	Mol Weight:	MW Freebase:	# Rule of 5 Violations:
2.503	7	2	483.613	483.603	0

Compound Information. As the user types, ConceptWiki uses ChemSpider validated synonyms to map text entry to a Concept. This is then linked to a Chemspider ID which is used to retrieve data from both ChemSpider and the DrugBank database

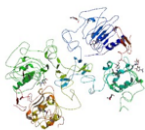


Compound by name Target by name

Hint: Start typing in protein name and species. E.g. "Adenosine receptor A2a (Homo sapiens)"

Protein name:

Target Data



Epidermal growth factor receptor (Homo sapiens)

Target Type: PROTEIN
 Organism: *Homo sapiens*
 Description: Epidermal growth factor receptor
 Synonyms: Epidermal growth factor receptor Receptor tyrosine-protein kinase ErbB-1
 Specific Function: Isoform 2/truncated isoform may act as an antagonist
 Cellular Location: single-passTypeI MembraneProtein.Isoform2:secretedProtein
 Keywords: 3D-structure Alternative splicing ATP-binding Cell membrane Complete proteome Direct protein sequencing Disease mutation Disulfide bond Glycoprotein Isopeptide bond Kinase Membrane Nucleotide-binding Phosphoprotein Polymorphism Receptor Repeat Secreted Signal Transferase Transmembrane Tumor suppressor Tyrosine-protein kinase Ubi conjugation
 PDB Entry: [1IVQ](#)

Molecular Weight: 134279	Number of Residues: 1230	Theoretical Pi: 6.67
-----------------------------	-----------------------------	-------------------------

Target Information. As with compounds, ConceptWiki is used to translate entered text to an OPS Concept, using Uniprot as the main protein information system

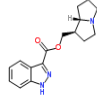
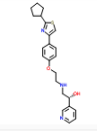




Compound by name Target by name **Pharmacology by Target Name**

Hint: Type in protein name and species. E.g. "ADA protein human"

Protein name:

Pharmacology by Target name search results - Records loaded: 100

Structure	Target name	Compound name	Smiles	Inchi	Inchikey	Molweight	Num ro5 violations	Std type
	Beta-2 adrenergic recepto...	(1R,7aS)-hexahydro-1H-py...	<chem>O=C(OC[C@@H]1CCN2C...</chem>	InChi=1/C16H19N3O2/c2...	DJPQWKJCTULKTC-FZM2J...	285.345	0	IC50
	Beta-2 adrenergic recepto...	(1R)-2-((2-(4-(2-cyclopent...	<chem>O[C@@H](CNCCOC)ccc(c...</chem>	InChi=1/C23H27N3O2S/c...	ISJPANQFRQVZLQ-QFIPX...	409.551	0	Intrinsic activit
	Beta-2 adrenergic recepto...	N-(3-Chloro-4-(2-hydroxy...	<chem>CC(C)(C)NCC(O)Coc1ccc...</chem>	InChi=1/C18H23ClN2O3S...	WBEJBAFFWFWTGI-UHFF...	382.91	0	ID50
	Beta-2 adrenergic recepto...	ethanesulfonamide, N-[3-...	<chem>Oc1ccc(CCNCCNS(=O)(...</chem>	InChi=1/C22H29N3O5S2/...	XLFAIMOWBKQDIE-UHFFF...	479.619	0	Beta2 duration

Pharmacology search for the B2-adrenergic receptor



Associated partners

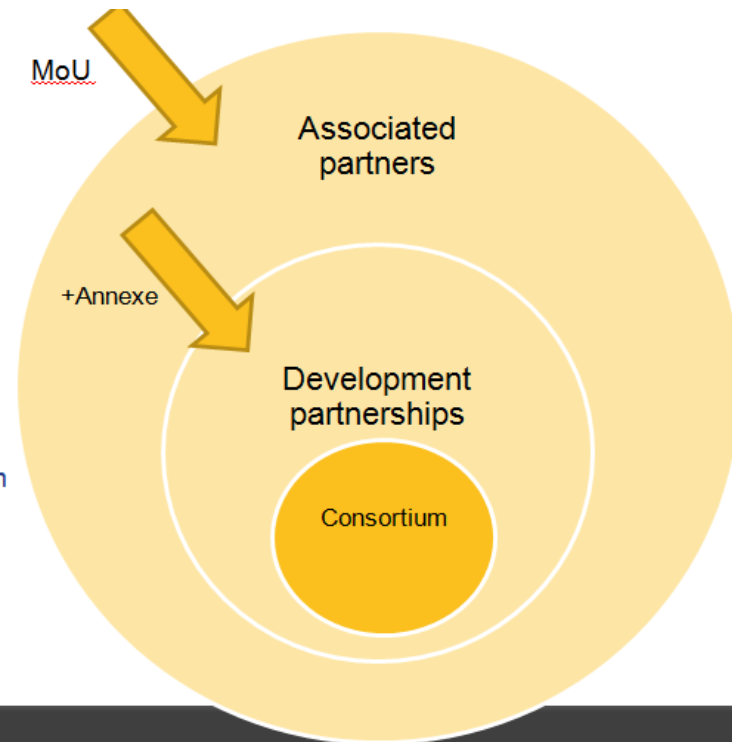
Organisations, most will join here
Support, information
Exchange of ideas, data, technology
Opportunities to demo at community webinars
Need MoU

Development partnerships

Influence on API developments
Opportunities to demo ideas & use cases to core team
Need MoU and annexe

Consortium

22 current members

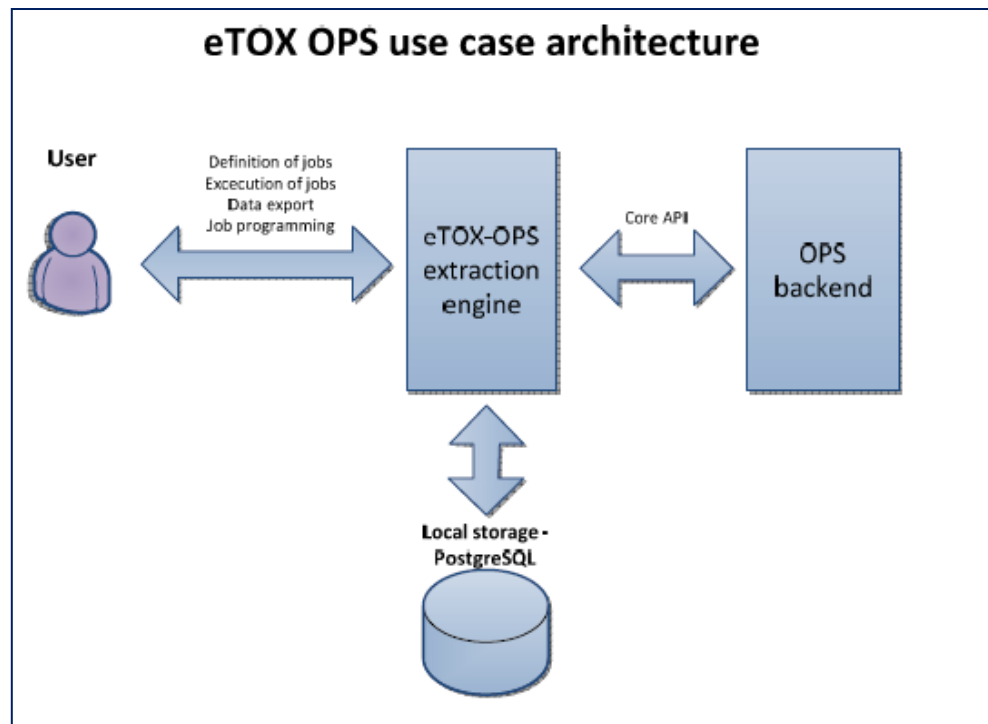


Open PHACTS and the scientific community



Build an automated tool to obtain the data needed to build eTOX predictive models with the following goals:

- ❖ Use the OpenPHACTS platform to extract relevant data to build toxicity models in eTOX.
- ❖ Develop a data crawler to extract the data needed to build toxicity models
- ❖ Develop a data curation platform that will filter the data extracted from OpenPHACTS
- ❖ Develop a web tool to browse the results obtained





Next Steps

- ❖ Get licensing done
- ❖ complete call for professional hosting
- ❖ Go public
- ❖ Start 2nd wave pilots

www.openphacts.org



Open PHACTS Project Partners

www.openphacts.org

Pfizer– Coordinator

(Bryn Williams-Jones)

Universität Wien – Managing entity of IMI JU funding *(Gerhard Ecker)*

Technical University of Denmark
(Sören Brunak)

University of Hamburg, Center for Bioinformatics
(Mattias Rarey)

BioSolveIT GmbH
(Christian Lemmen)

Consorci Mar Parc de Salut de Barcelona
(Ferran Sanz)

Leiden University Medical Centre
(Barend Mons)

Royal Society of Chemistry
(Richard Kidd, Antony Williams)

Vrije Universiteit Amsterdam
(Paul Groth, Frank van Harmelen)

Spanish National Cancer Research Centre
(Alfonso Valencia)

University of Manchester
(Carole Goble, Steve Pettifer)

Maastricht University
(Chris Evelo)

AQnowledge
(Jan Velterop)

University of Santiago de Compostela
(Mabel Loza)

Rheinische Friedrich-Wilhelms-Universität Bonn
(Martin Hofmann-Apitius)

AstraZeneca
(Niklas Blomberg)

GlaxoSmithKline
(Andrew Leach)

Esteve
(Leo Salgado)

Novartis
(Edgar Jacoby)

Merck Serono
(Thomas Grombacher)

H. Lundbeck A/S
(Askjaer Sune)

Eli Lilly
(Hans Constandt)

Stichting Netherlands Bioinformatics Centre
(Barend Mons)

Swiss Institute of Bioinformatics
(Christine Chichester)

Connected Discovery
(Bryn Williams-Jones)

European Bioinformatics Institute
(John Overington)

Janssen Pharmaceutica
(Herman van Vlijmen)

