



# Comprehensive representation of disease mechanisms on multiple levels of granularity in SBGN PD and AF

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**efpia**

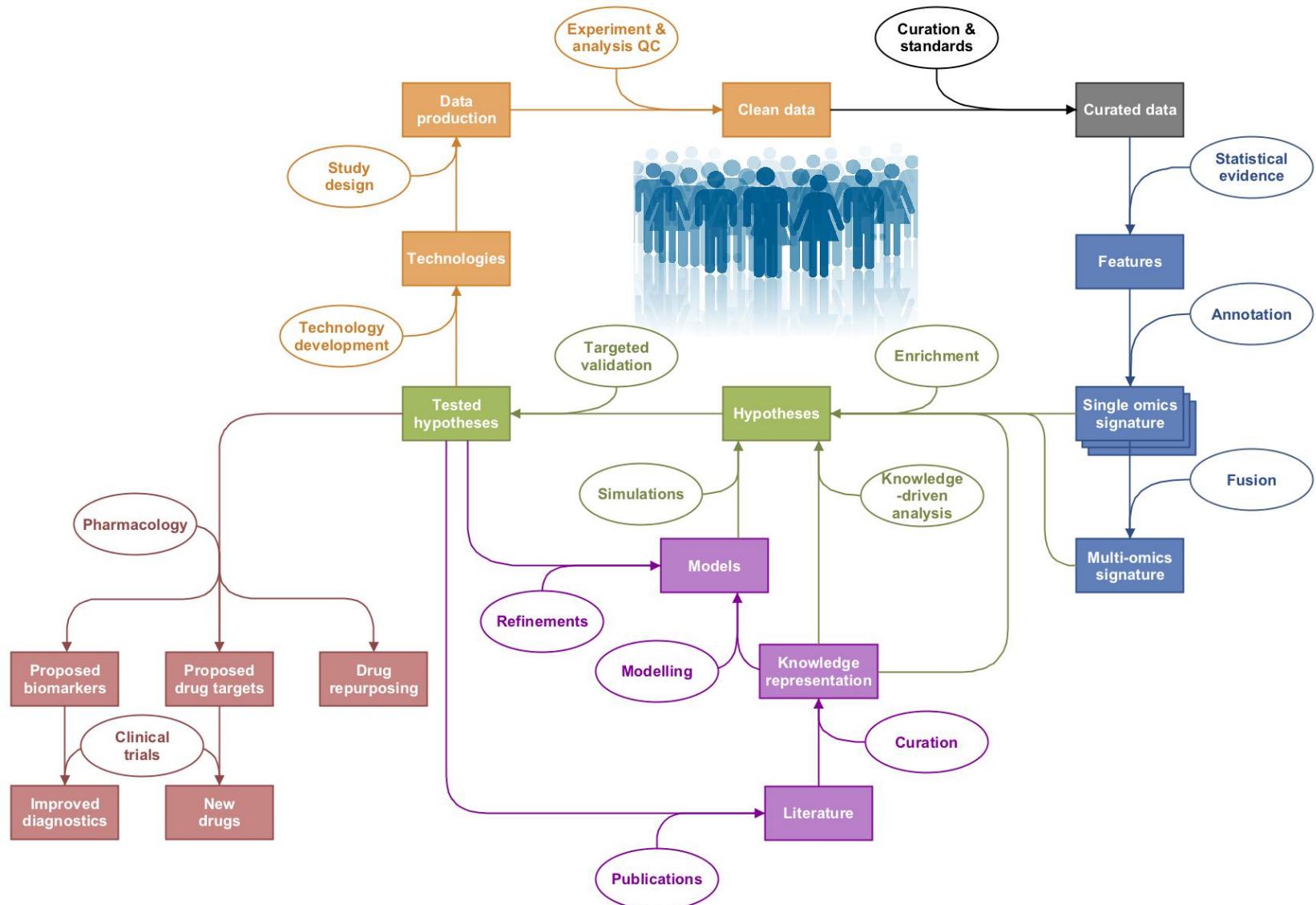


innovative  
medicines  
initiative



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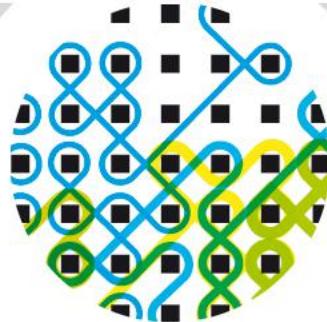
# Systems Medicine Workflow



# diseasemaps

comprehensive representation  
of disease mechanisms

a collection of interconnected signalling,  
metabolic and gene regulatory pathways  
relevant to a disease



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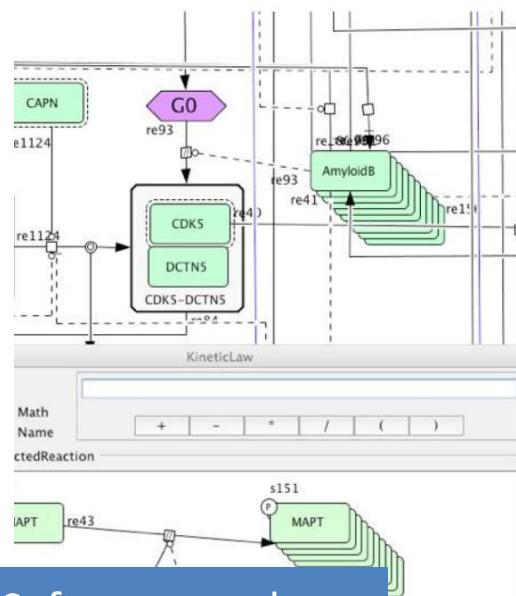
# Part 1

# Background

# Tools for functional analysis

- **DAVID** – functional annotation, 'omics visualization
- **g:Profiler** – functional interpretation of gene lists
- **Ingenuity Pathway Analysis (IPA)** – pathway analysis
- **MetaCore** – pathway analysis
- **Disease Maps** for interpretation and hypothesis generation:
  - ✓ disease-specific
  - ✓ a single network
  - ✓ standard representation
  - ✓ actively creating new content

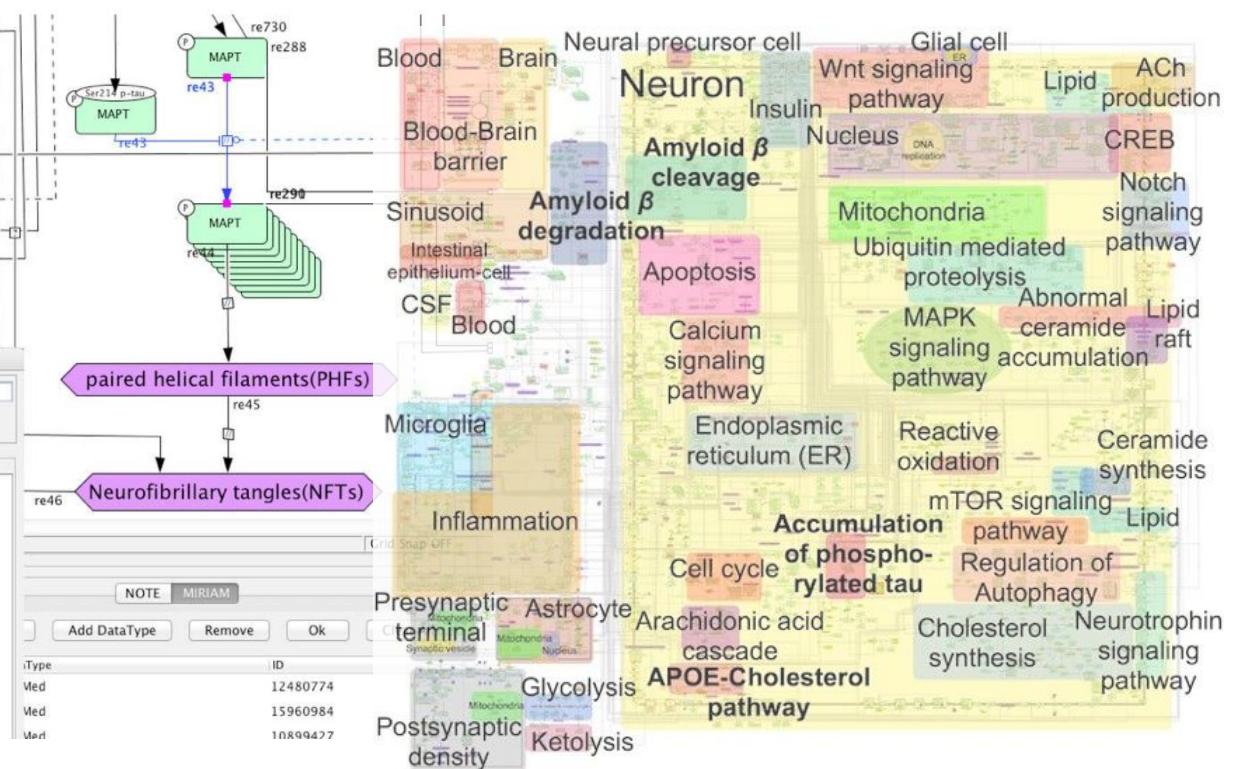
# AlzPathway



Software used:  
CellDesigner

Mizuno et al. AlzPathway: a comprehensive map of signaling pathways of Alzheimer's disease. *BMC Syst Biol.* 2012 May 30;6:52

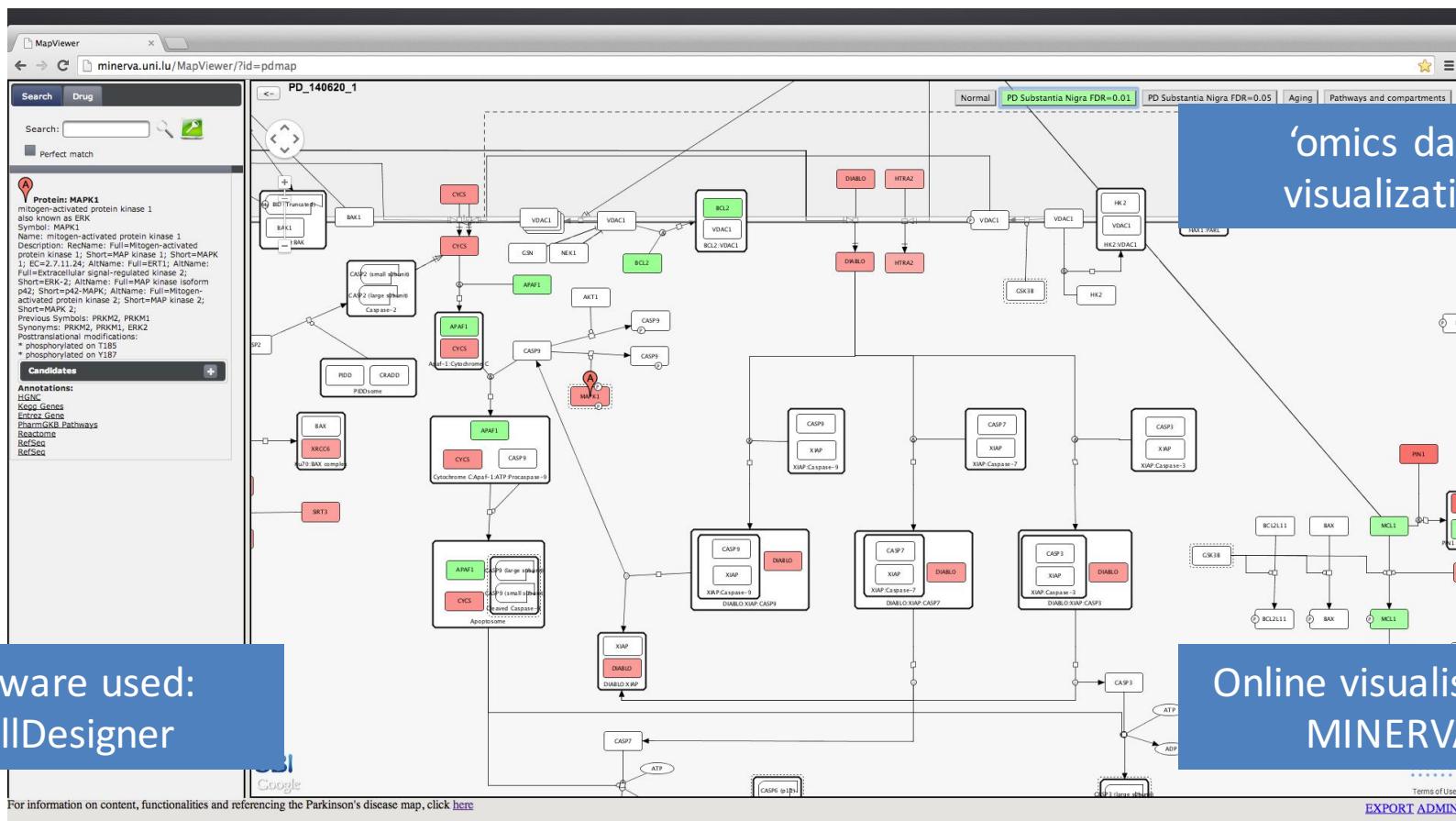
Ogishima et al. AlzPathway, an Updated Map of Curated Signaling Pathways: Towards Deciphering Alzheimer's Disease Pathogenesis. *Methods Mol Biol.* 2016;1303:423-32.



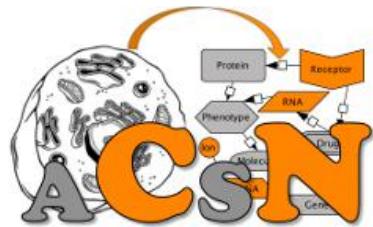
# Parkinson's disease map



Fujita et al. Integrating pathways of Parkinson's disease in a molecular interaction map. *Mol Neurobiol.* 2014



# The Atlas of Cancer Signaling Network



Kuperstein et al. **Atlas of Cancer Signalling Network: a systems biology resource for integrative analysis of cancer data with Google Maps.** Oncogenesis. 2015 Jul 20;4:e160.

**MAP: APOPTOSIS/MODULE: CASPASE-3**

Search (e.g.)

**Protein**  
BCL2

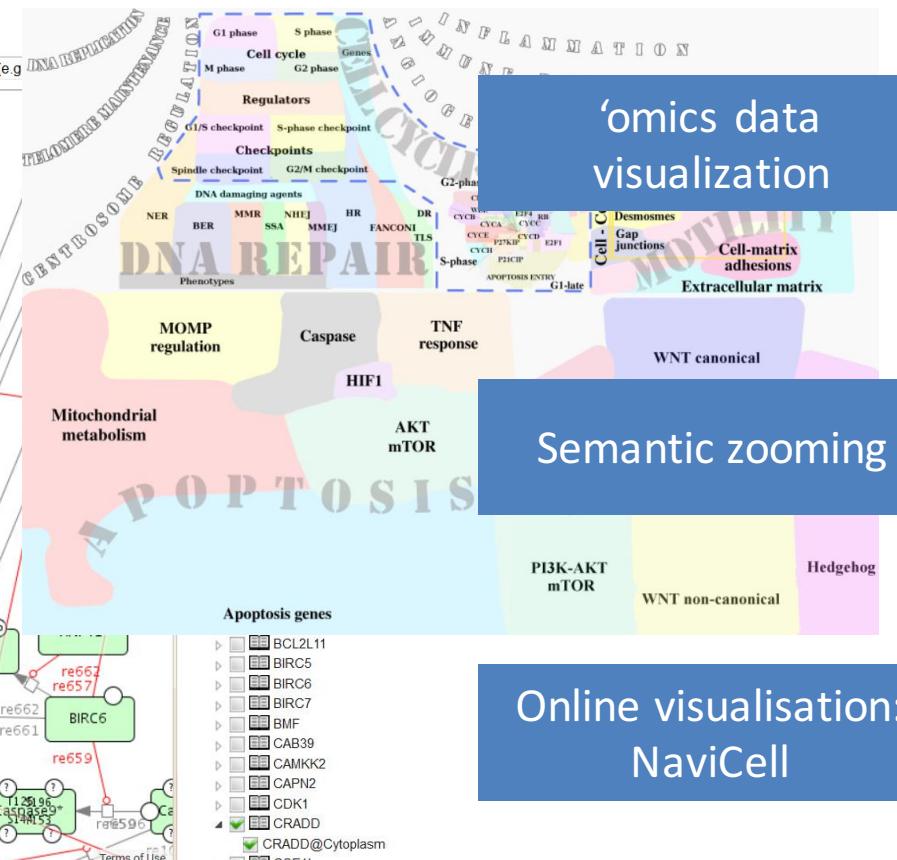
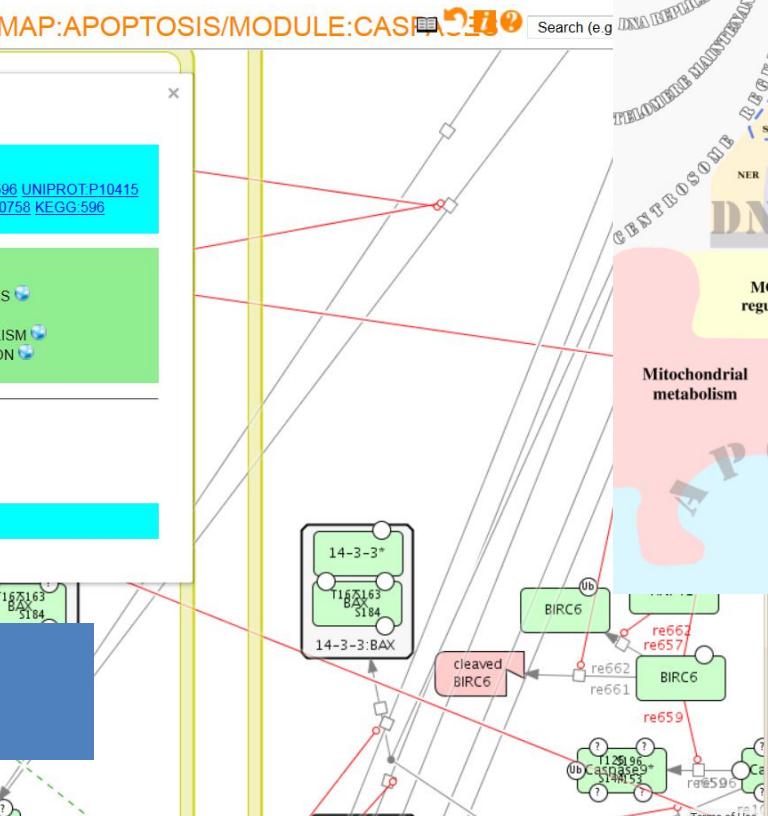
**Identifiers**  
B-cell CLL/lymphoma 2  
HUGO BCL2 HGNC 990 ENTREZ 596 UNIPROT P10415  
GENECARDS BCL2 REACTOME 50758 KEGG 596  
ATLASONC BCL2 ID49 WIKI BCL2

**Maps\_Modules**  
Apoptosis / AKT\_MTOR  
Apoptosis / APOPTOSIS\_GENES  
Apoptosis / CAPSASES  
Apoptosis / MITOCH\_METABOLISM  
Apoptosis / MOMP\_REGULATION  
Survival / MAPK

**Modification:**  
BAX(S163\_unk)T167\_unkBCL2  
in Mitochondrial outer membrane

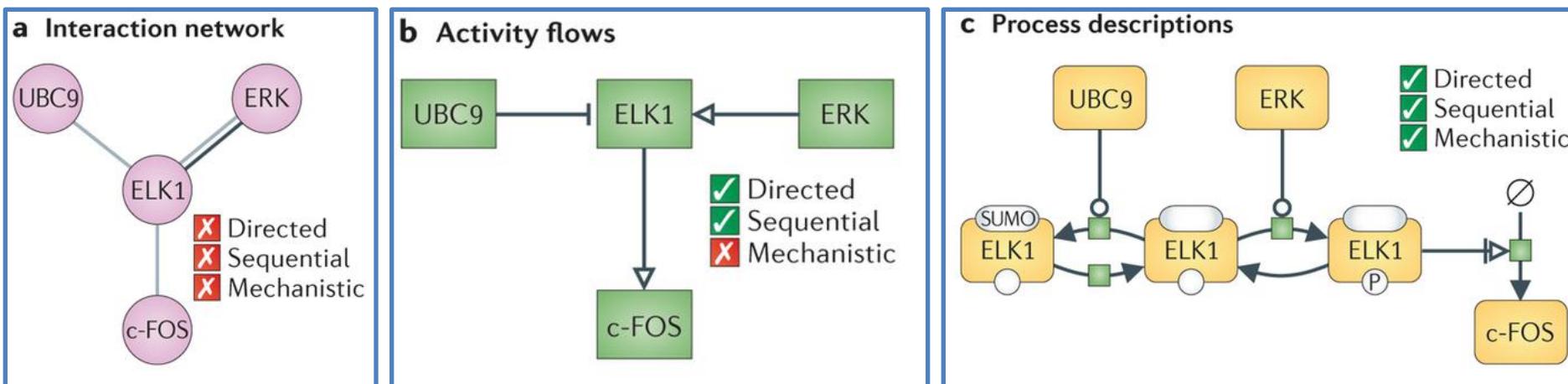
**Identifiers**  
NAME\_BAX-BCL2

Software used:  
CellDesigner



# Different types of networks

Le Novère N. Quantitative and logic modelling of molecular and gene networks. Nature Reviews Genetics, 2015. PMID 25645874



Different types of networks used to represent biological processes and their features are shown.

- An **interaction network** can be used to represent physical interactions (black line) - such as that between extracellular signal-regulated kinase (ERK) and ELK1 - and functional interactions (grey lines), such as those between UBC9 (also known as UBE2I), ERK, ELK1 and c-FOS.
- An **activity flow** can be used to show the stimulation of c-FOS activity by ELK1 activity, the stimulation of ELK1 activity by ERK activity, and its inhibition by UBC9 activity.
- A detailed **process description** can be used to show the catalysis of ELK1 sumoylation (SUMO) and phosphorylation (P), their reversed reactions, and the trigger of c-FOS expression. The graph is simplified by the inexistence of ELK1 with both covalent modifications.

# Standards in Systems Biology



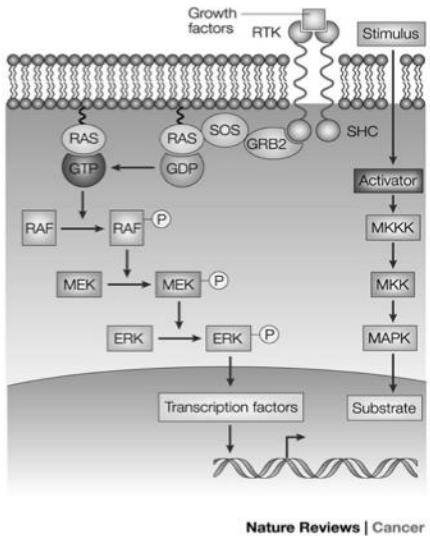
The 'COmputational Modeling in Biology' NEtwork (COMBINE) is an initiative to coordinate the development of the various community **standards and formats** for computational models. By doing so, it is expected that the federated projects will develop a set of interoperable and non-overlapping standards covering all aspects of modeling in biology.



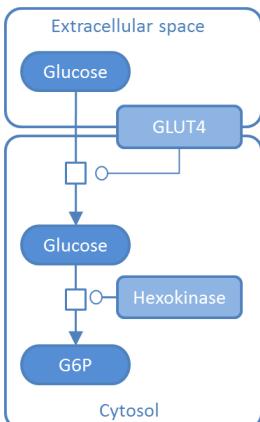
# SBGN standard

Systems Biology Graphical Notation (SBGN) Process Description language ensures unambiguous and consistent knowledge representation.

Human-readable



SBGN can do both



Machine-readable

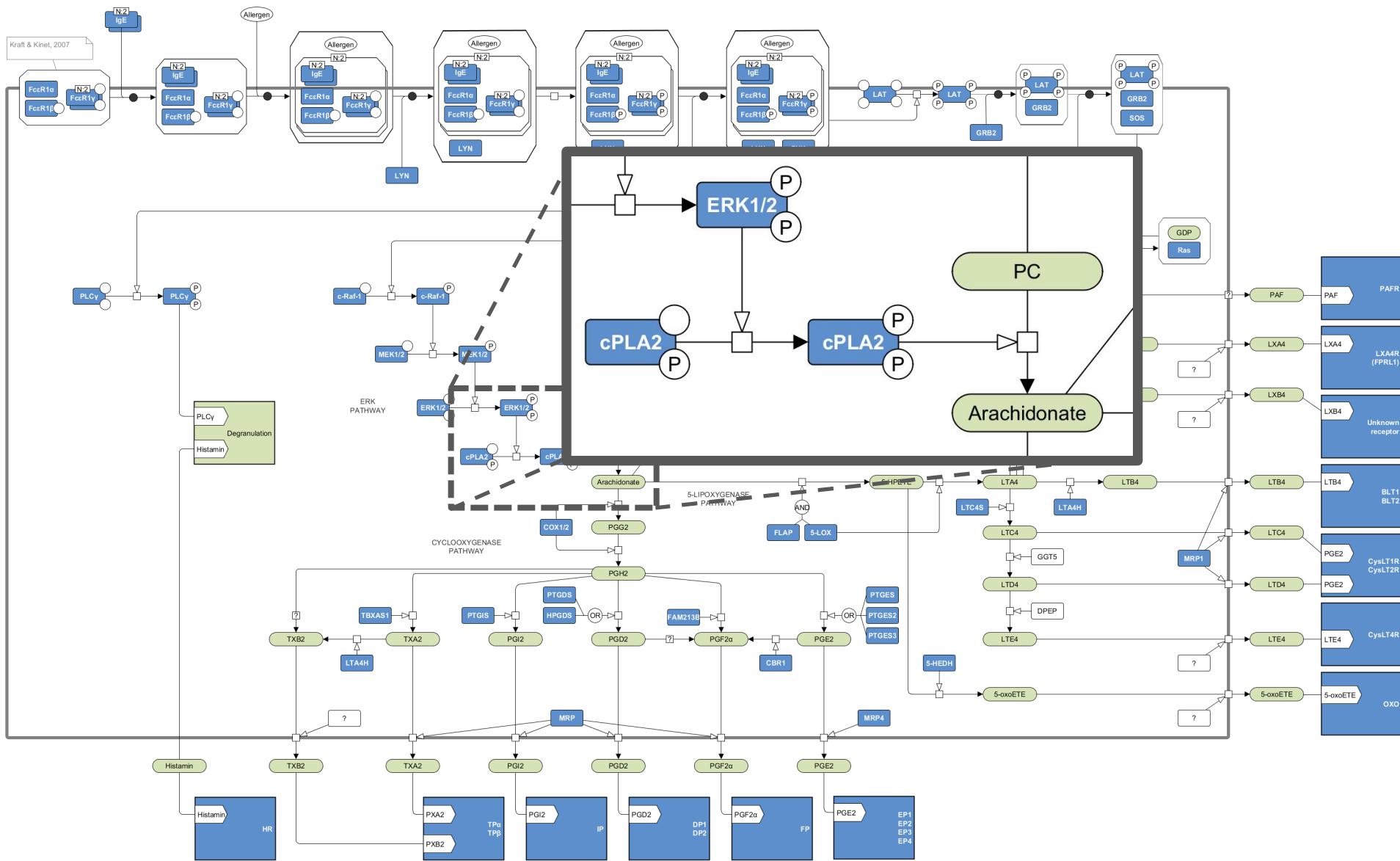
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  initialConcentration="0">
<annotation>
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    <owl:imports xmlns="http://www.w3.org/1999/xhtml">
      Glucose_imparted followed by the first step of glycolysis.
    </owl:imports>
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      <bbox y="25" x="55" h="38" w="38"/>
    </owl:annotationPropertyRef>
    <owl:annotationPropertyRef="c" id="j" class="simple chemical">
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    </owl:annotationPropertyRef>
    <owl:annotationPropertyRef="c" id="k" class="simple chemical">
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</owl:annotation>
</species>
[...]
```

.xml



BioPAX

# An example of SBGN Process Description diagram



# Conversion between formats

Rodriguez *et al.* BMC Bioinformatics (2016) 17:154  
DOI 10.1186/s12859-016-1000-2

BMC Bioinformatics

SOFTWARE

Open Access

## The systems biology format converter

Nicolas Rodriguez<sup>1,2†</sup>, Jean-Baptiste Pettit<sup>1†</sup>, Piero Dalle Pezze<sup>2†</sup>, Lu Li<sup>1,2</sup>, Arnaud Henry<sup>1</sup>, Martijn P. van Iersel<sup>1</sup>, Gael Jalowicki<sup>1</sup>, Martina Kutmon<sup>3</sup>, Kedar N. Natarajan<sup>1</sup>, David Tolnay<sup>4</sup>, Melanie I. Stefan<sup>4</sup>, Chris T. Evelo<sup>3</sup> and Nicolas Le Novère<sup>1,2\*</sup>

### Abstract

**Background:** Interoperability between formats is a recurring problem in systems biology research. Many tools have been developed to convert computational models from one format to another. However, they have been developed independently, resulting in redundancy of efforts and lack of synergy.

**Results:** Here we present the System Biology Format Converter (SBFC), which provide a generic framework to potentially convert any format into another. The framework currently includes several converters translating between the following formats: SBML, BioPAX, SBGN-ML, Matlab, Octave, XPP, GPML, Dot, MDL and APM. This software is written in Java and can be used as a standalone executable or web service.

**Conclusions:** The SBFC framework is an evolving software project. Existing converters can be used and improved, and new converters can be easily added, making SBFC useful to both modellers and developers. The source code and documentation of the framework are freely available from the project web site.

**Keywords:** Converter, Format, Systems biology, SBML



# The MINERVA platform (LCSB)

AA V41 SBGN

asthma.uni.lu/MapViewer/index.xhtml?id=AA\_V41

AA V41SBGN

SEARCH DRUG LAYOUTS LOGIN SUBMAPS

GENERAL LAYOUTS:

Name	View	Data
Pathways and compartments		
Normal		

CUSTOM LAYOUTS:

YOU ARE NOT LOGGED IN. PLEASE, LOG IN TO UPLOAD AND VIEW CUSTOM LAYOUTS

L C S B

ADMIN EXPORT Google Terms of Use

## SEARCH:

enter keyword



PERFECT MATCH

## 1 Protein: ALOX12

Full name: arachidonate 12-lipoxygenase

Symbol: ALOX12

Charge: 0

Synonyms: 12S-LOX,

Description: RecName: Full=Arachidonate

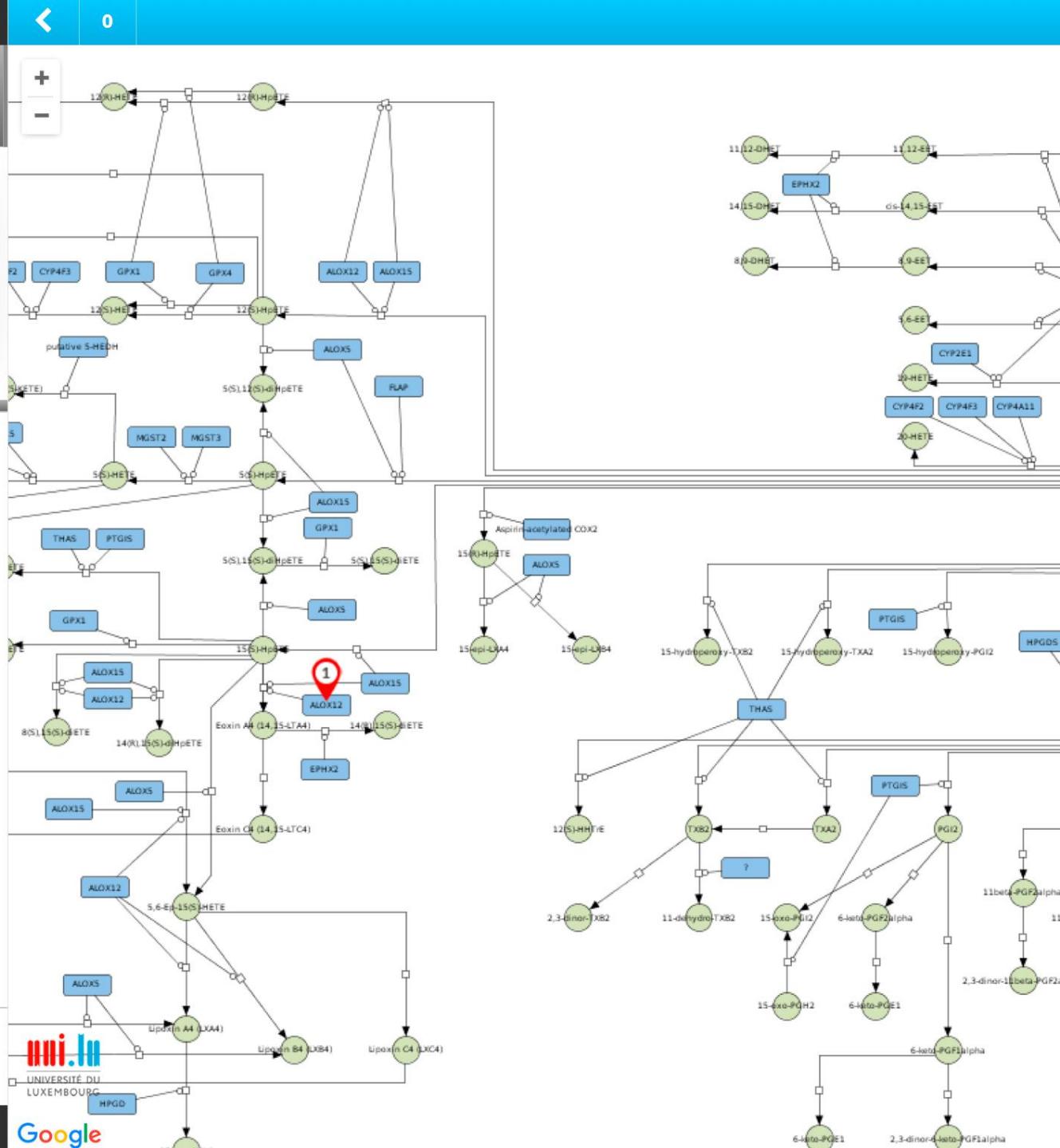
12-lipoxygenase, 12S-type; Short=12S-LOX; Short=12S-lipoxygenase; EC=1.13.11.31; AltName: Full=Platelet-type lipoxygenase 12;

## Annotations:

- [1] Ensembl (ENSG00000108839)
- [2] Entrez Gene (239)
- [3] HGNC (429)
- [4] HGNC Symbol (ALOX12)
- [5] RefSeq (NM\_000697)

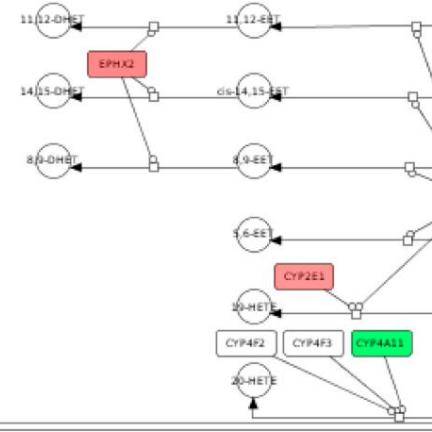
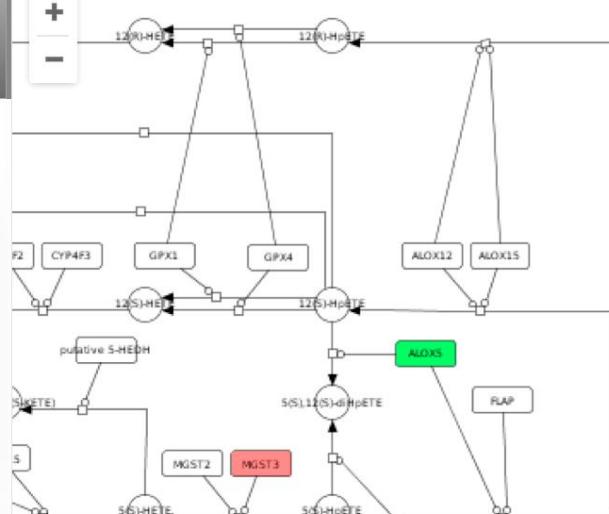
EXPORT

Google



## GENERAL LAYOUTS:

Name	View	Data
Pathways and compartments		
Normal		



## CUSTOM LAYOUTS:

Name	View	Data	Edit
5 vs 2 proper FC (status: OK)			
SomaLogic All (status: OK)			

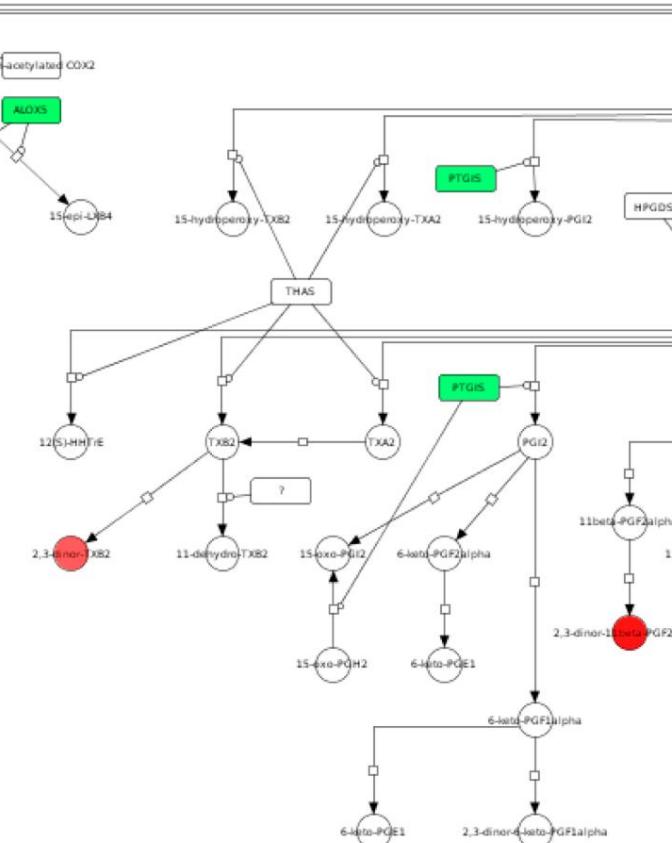
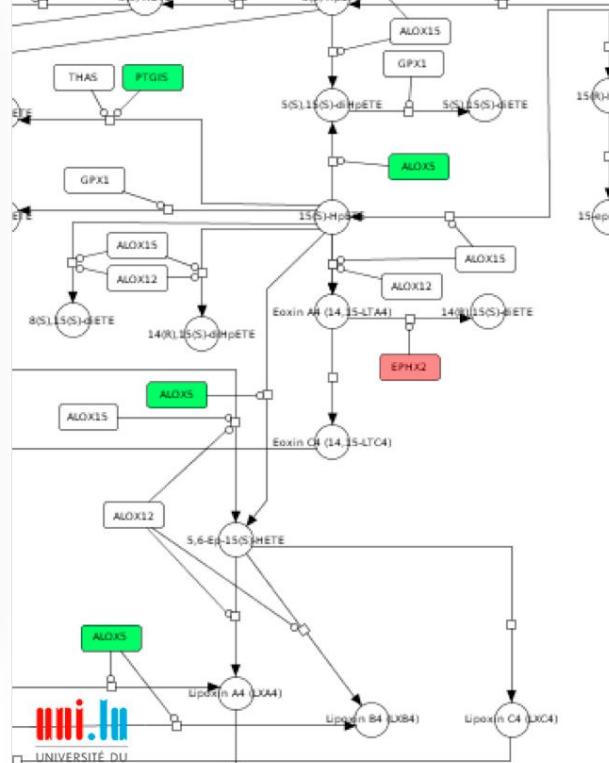


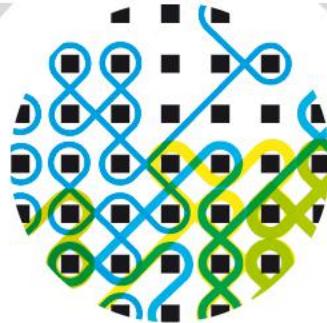
## ADDING

NAME:

FILE:

AVAILABLE LAYOUTS: **93**



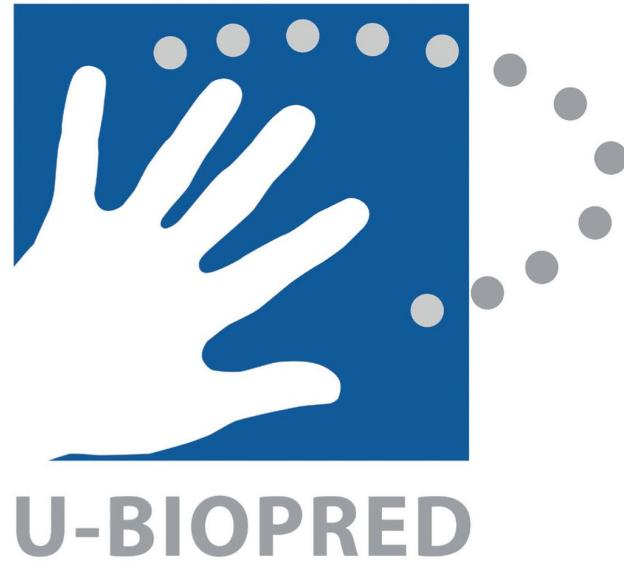


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## Part 2

# Our experience: **U-BIOPRED** **AsthmaMap**



**U-BIOPRED**

# **Unbiased BIOMarkers in Prediction of Respiratory Disease outcomes**

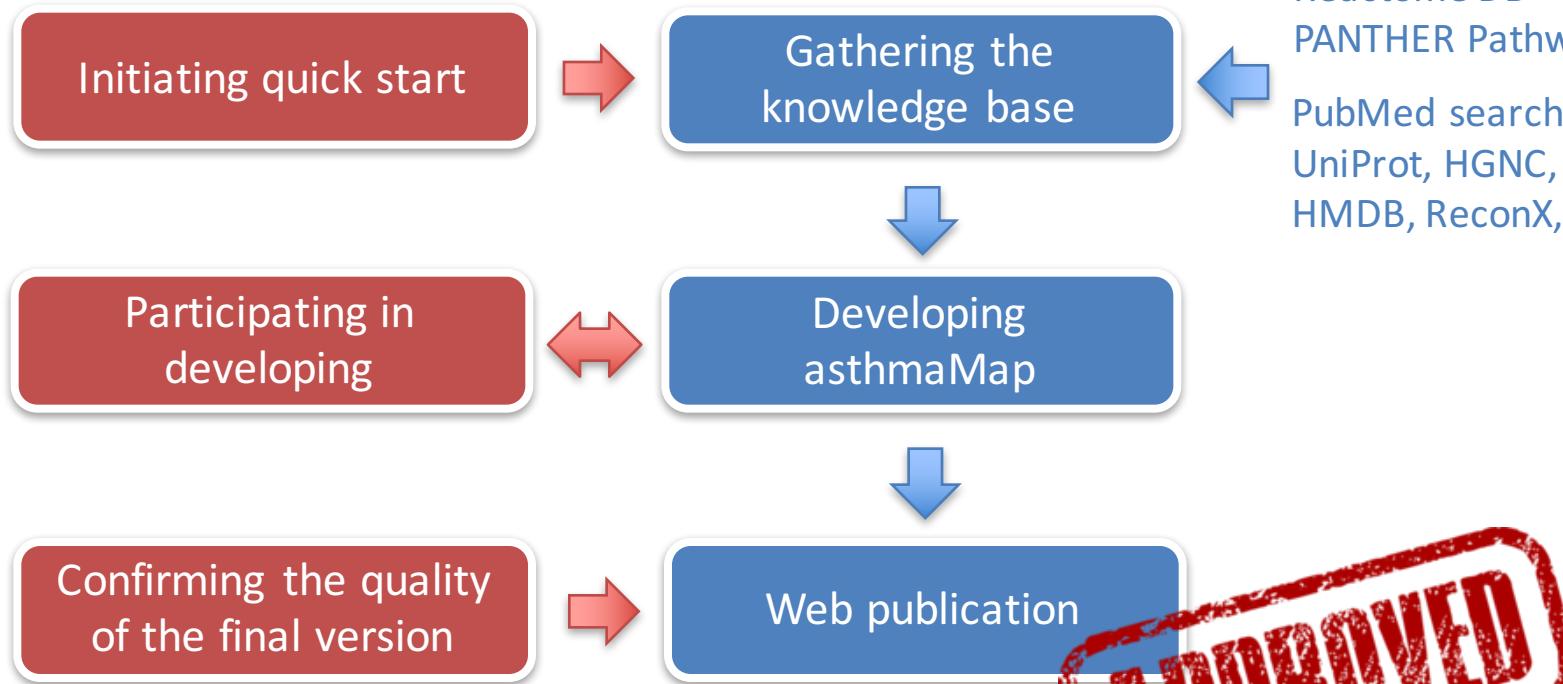
**40 partners including 10 big pharma**

U-BIOPRED is a research project using information and samples from adults and children to learn more about different types of asthma to ensure **better diagnosis and treatment for each person**

# Important: involving domain experts

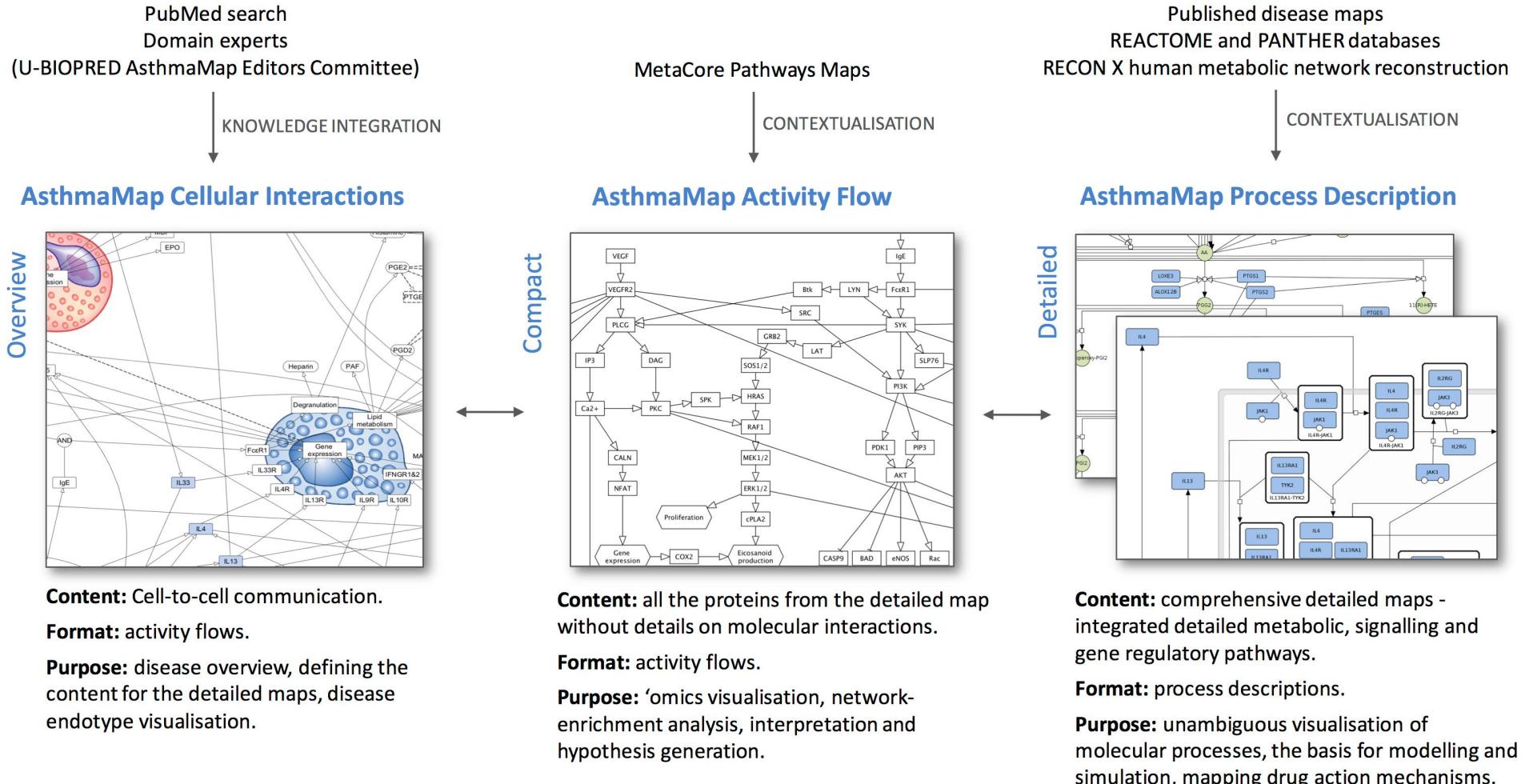
**Editors Committee  
(domain experts)**

**Computational Biology  
working group**



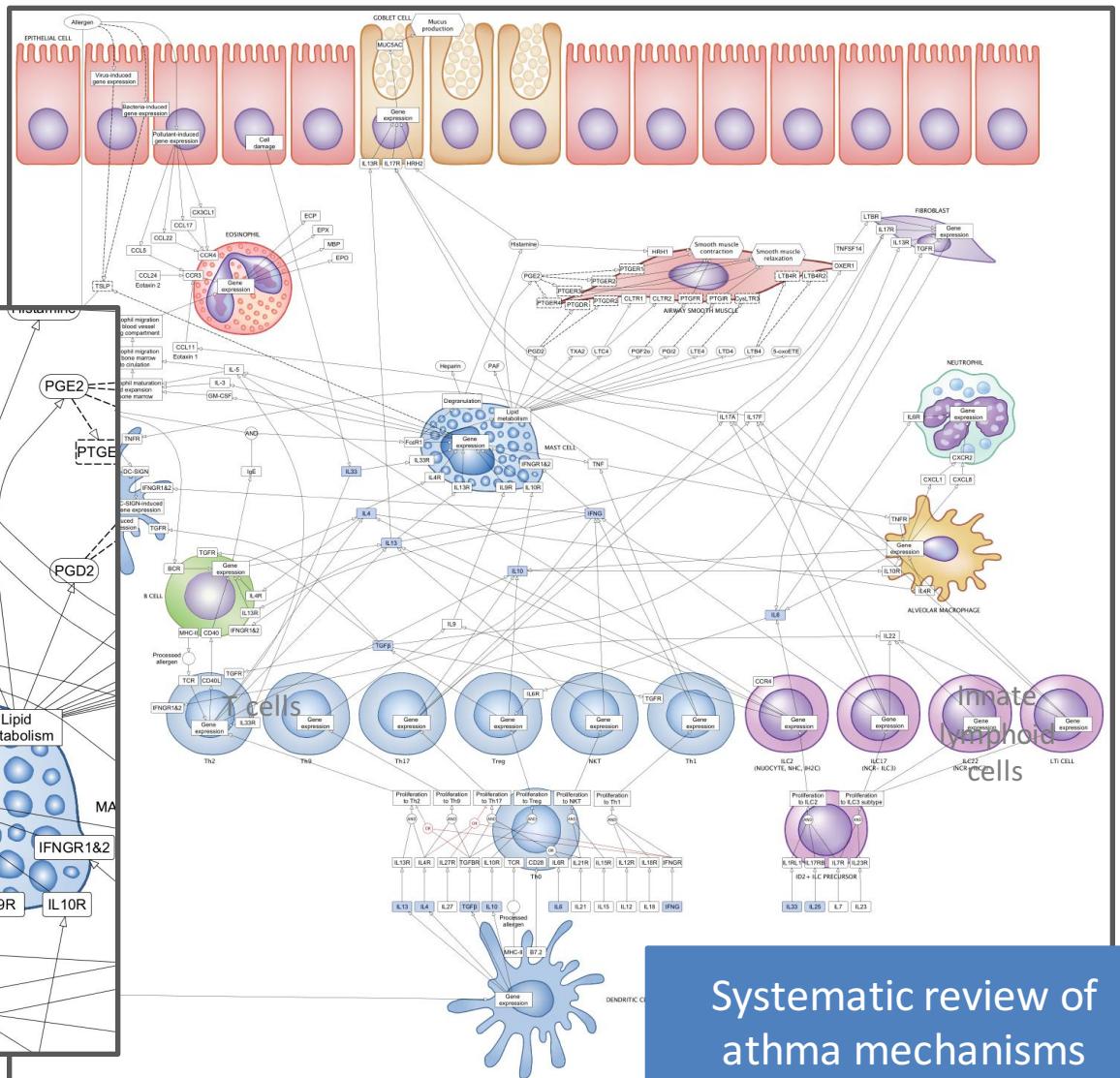
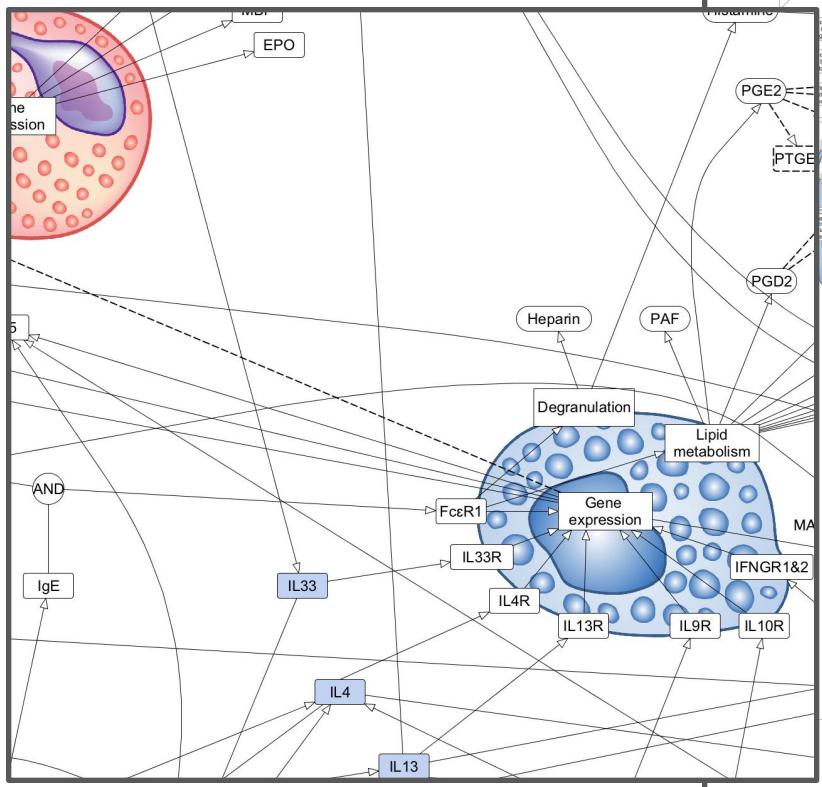
Parkinson's disease map  
Alzheimer disease map  
ACSN  
Reactome DB  
PANTHER Pathway DB  
PubMed search  
UniProt, HGNC, ChEBI  
HMDB, ReconX, LIPID MAPS

# U-BIOPRED AsthmaMap: interconnected layers of granularity



# AsthmaMap Cellular Interactions

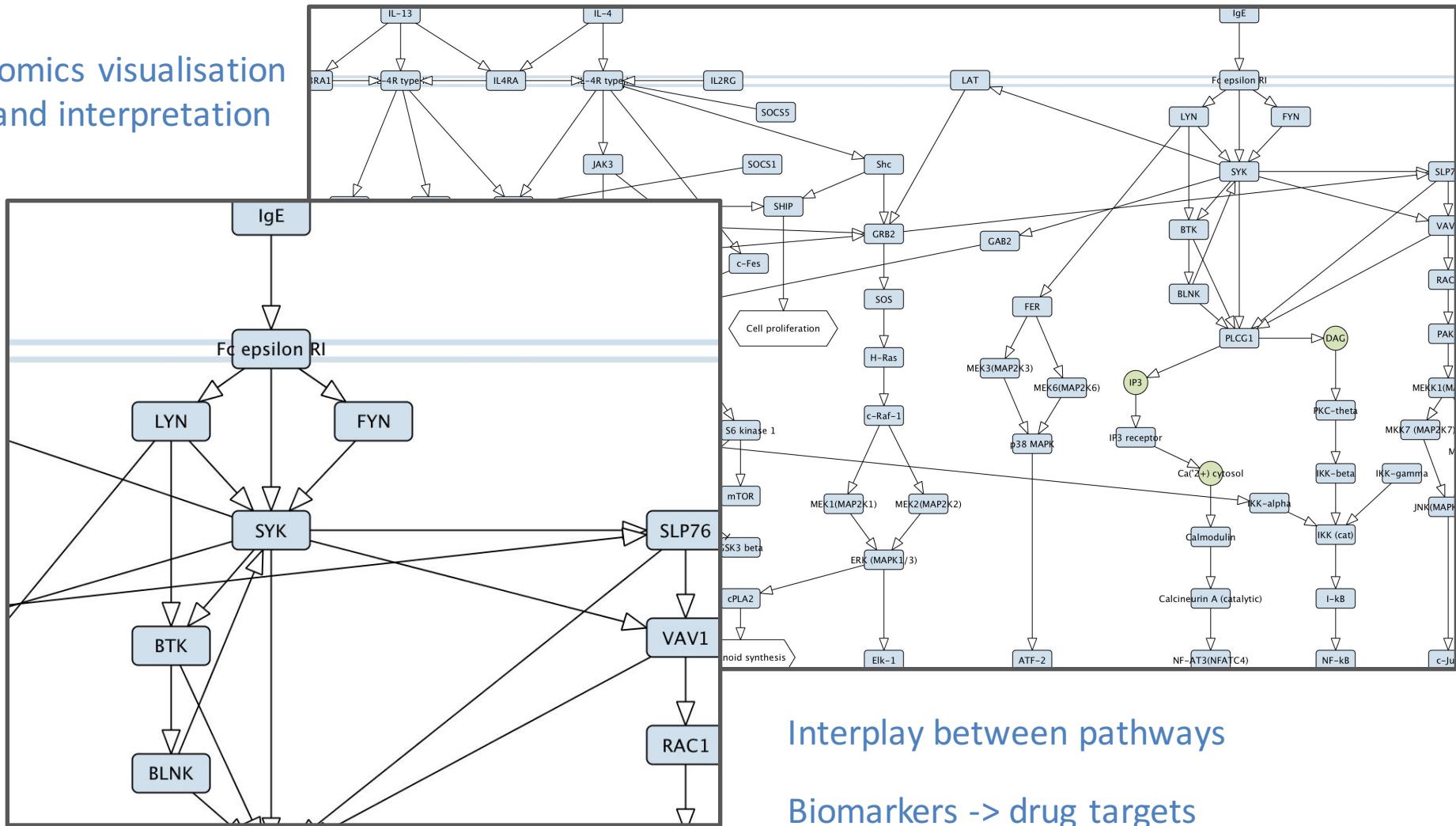
Rule-based reconstruction  
Consensus among the experts  
Fingerprints and handprints  
patterns (endotypes)



Systematic review of  
asthma mechanisms

# AsthmaMap Activity Flow

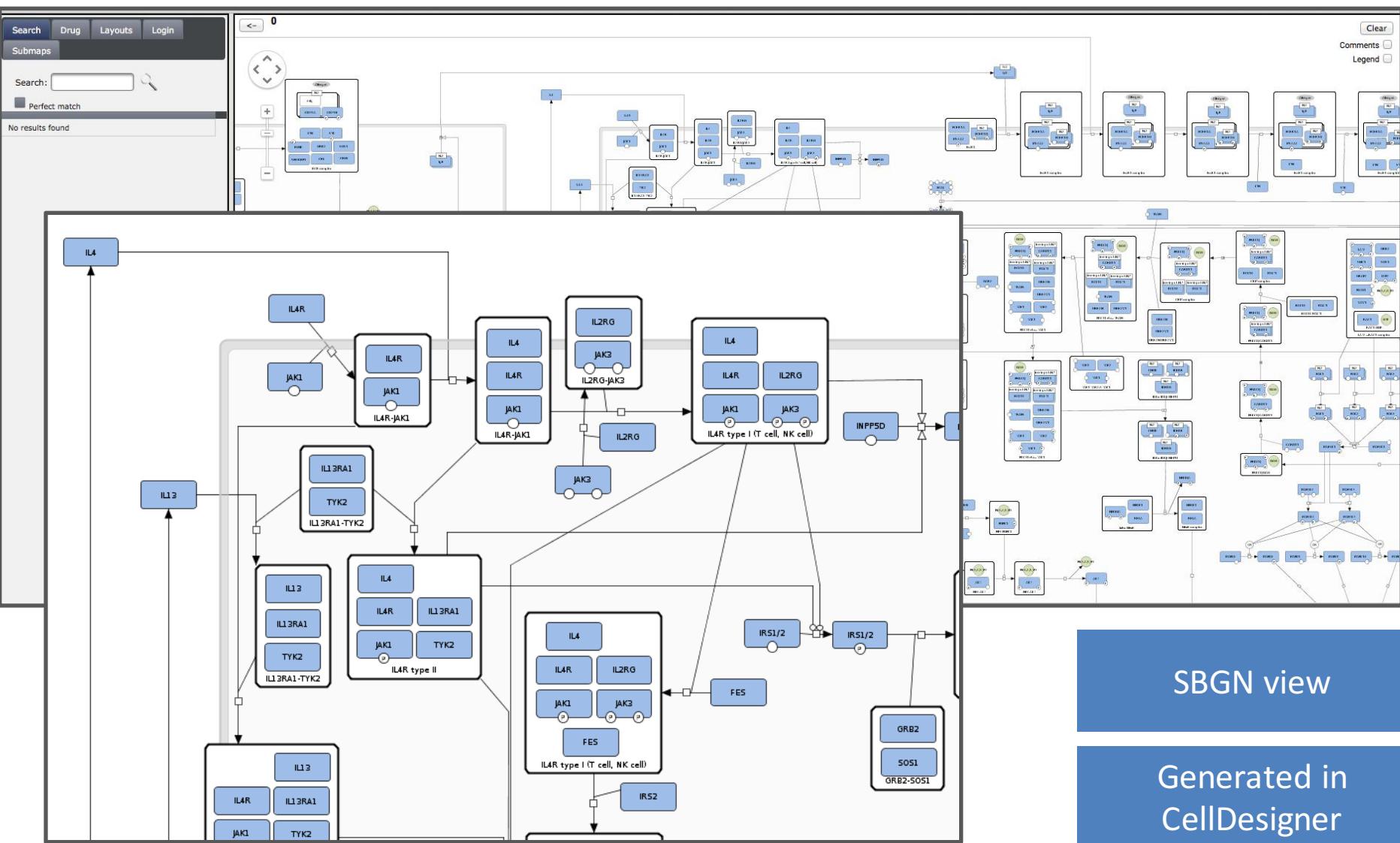
'omics visualisation  
and interpretation

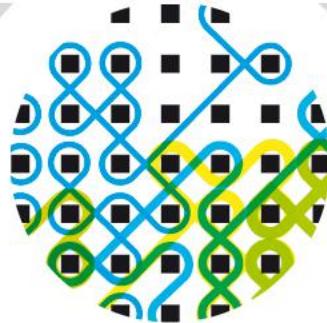


Interplay between pathways

Biomarkers -> drug targets

# AsthmaMap Process Description





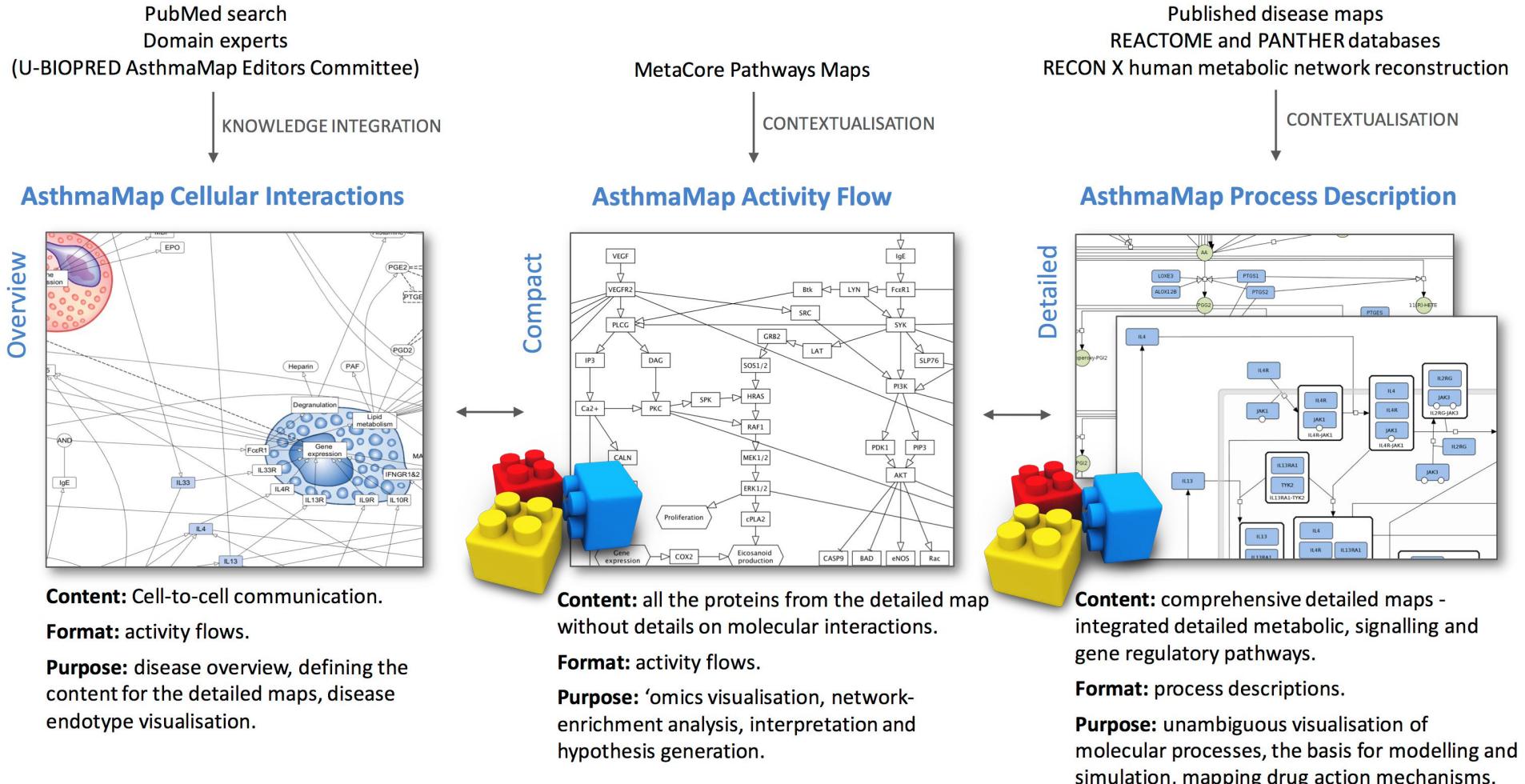
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# Part 3

# Beyond the state of the art

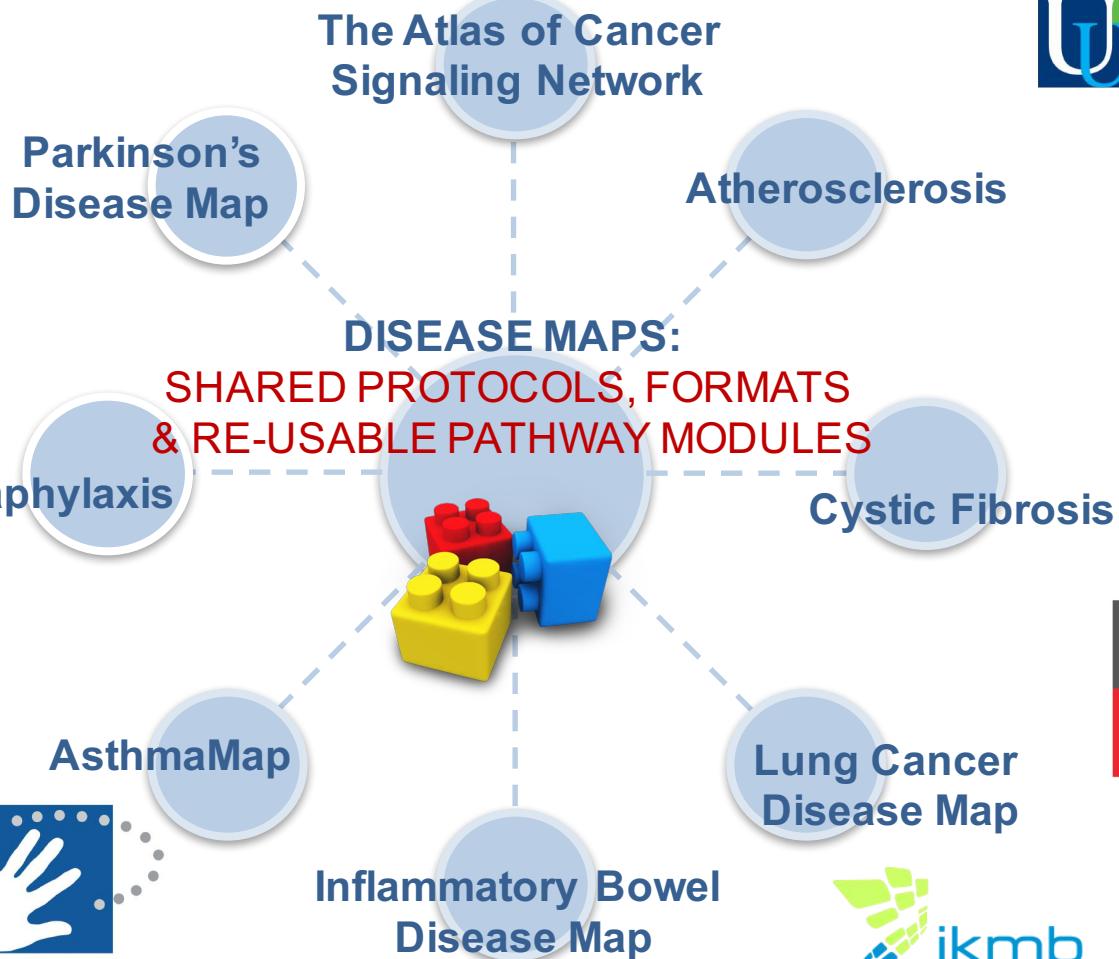
# Interconnected layers of granularity



# The Disease Maps Project



European Institute  
for Systems Biology & Medicine



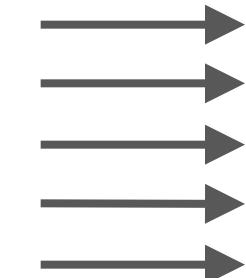
# Automatic assembly of disease maps

MetaCore  
Pathway Maps

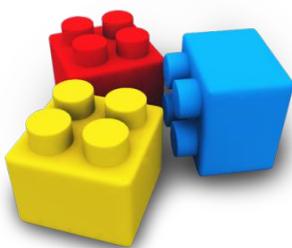
REACTOME

PANTHER

RECON X



3  
**BUILDING BLOCKS**  
(reusable pathways)

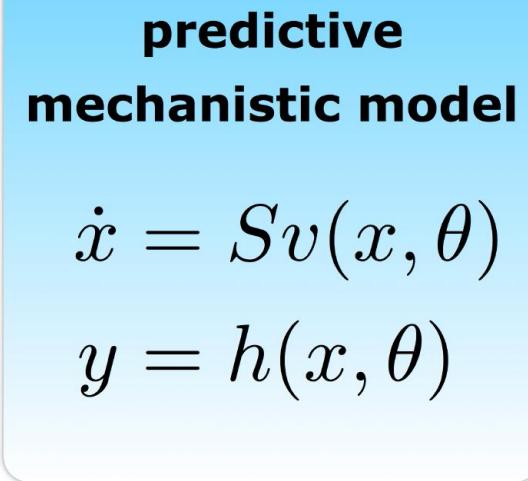
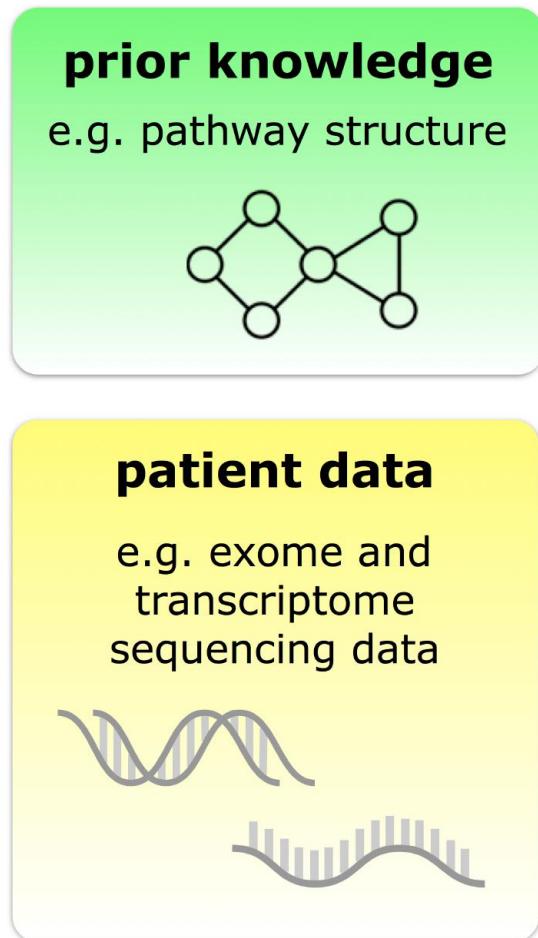


Domain expertise  
PubMed Search

- 1 WHAT PATHWAYS TO INCLUDE?
- 2 HOW TO MERGE PATHWAYS?

disease map  
Automatic generation of maps  
with 'human-like' layout

# Towards dynamic models and predictions



Large-scale mechanistic modelling  
ongoing collaboration with Dr. Jan Hasenauer,  
Institute of Computational Biology, Munich, Germany

**knowledge-based:** literature  
**mechanistic** level of details

**machine-readable:** standard format

**human-readable:** accessible, browsable

**consensus, community-driven:** domain experts

**data interpretation:** hypothesis generation

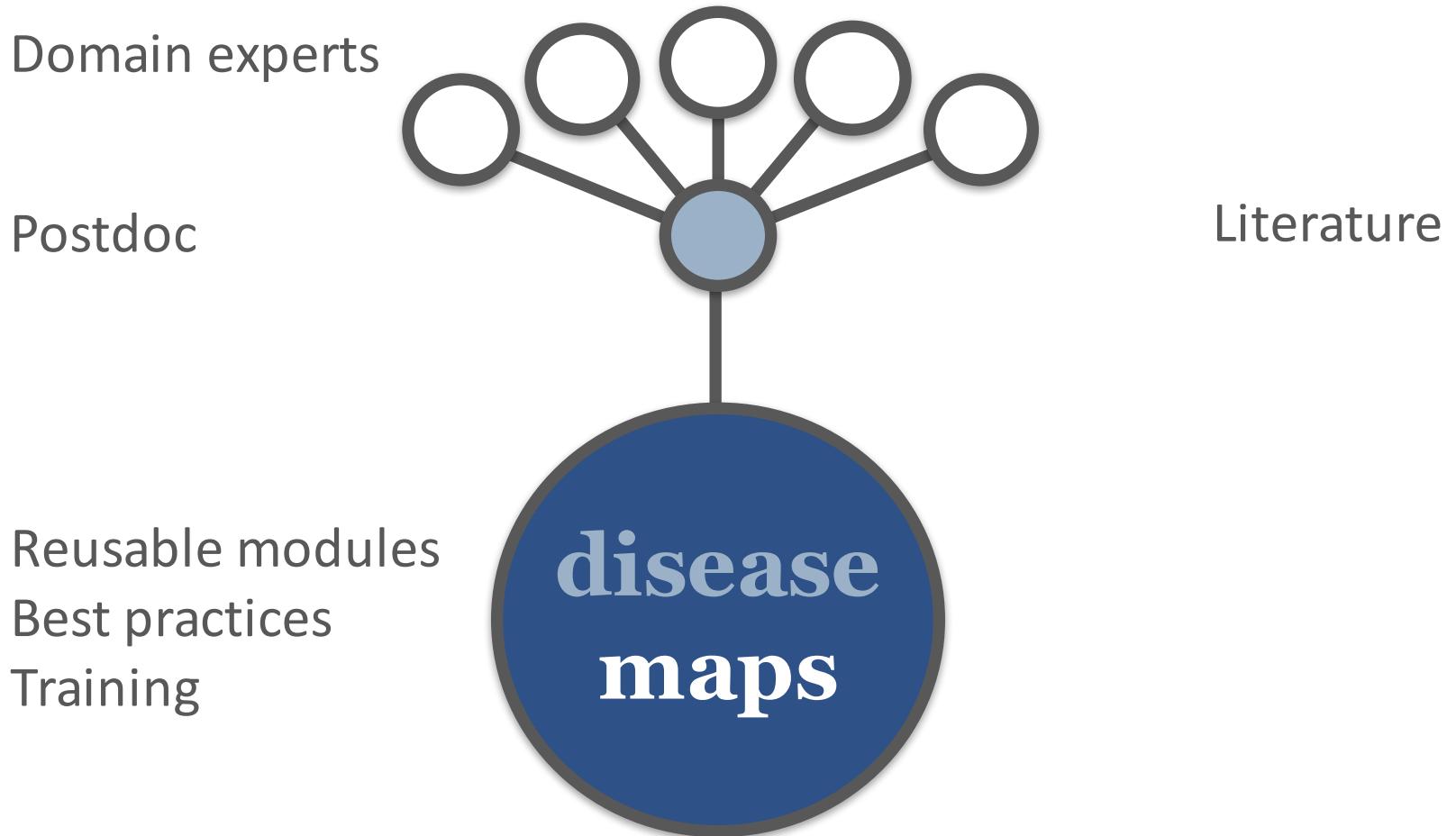
**shareable:** modular approach

**dynamic:** mathematical modelling

# diseasemaps

comprehensive representation  
of disease mechanisms

# Starting a new disease map project



# Join the effort!

- Projects that are focused on a particular disease
- Groups that work on a particular system / pathway
- Large-scale mathematical modelling
- Software development



knowledge-based: literature  
mechanistic level of details  
machine-readable: standard format  
human-readable: accessible, browsable  
consensus, community-driven: domain experts  
data interpretation: hypothesis generation  
shareable: modular approach  
dynamic: mathematical modelling

# diseasemaps

comprehensive representation  
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