THE HUMAN BRAIN PHARMACOME

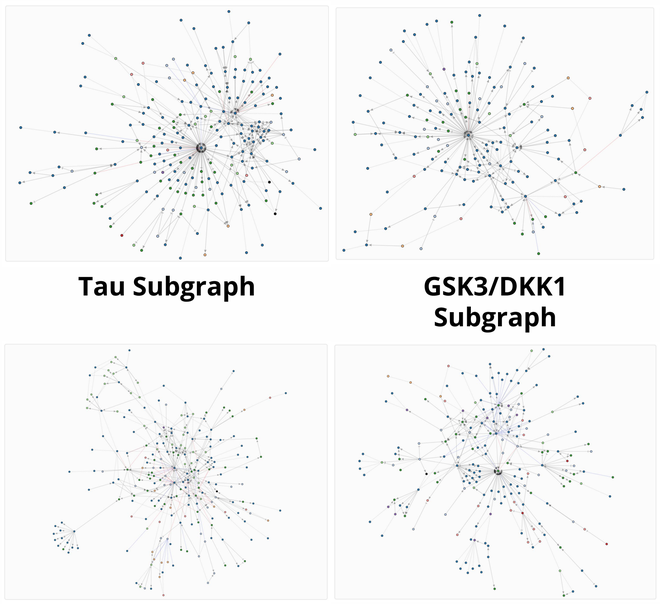
AN OVERVIEW

Charles Tapley Hoyt[1,2,*], Mohammed Asif Emon[1,2], Daniel Domingo Fernández[1,2], Marc Jacobs[1], and Martin Hofmann-Apitius[1,2]

[1]*Department of Bioinformatics, Fraunhofer Institute for Algorithms and Scientific Computing, Sankt Augustin 53754, Germany*

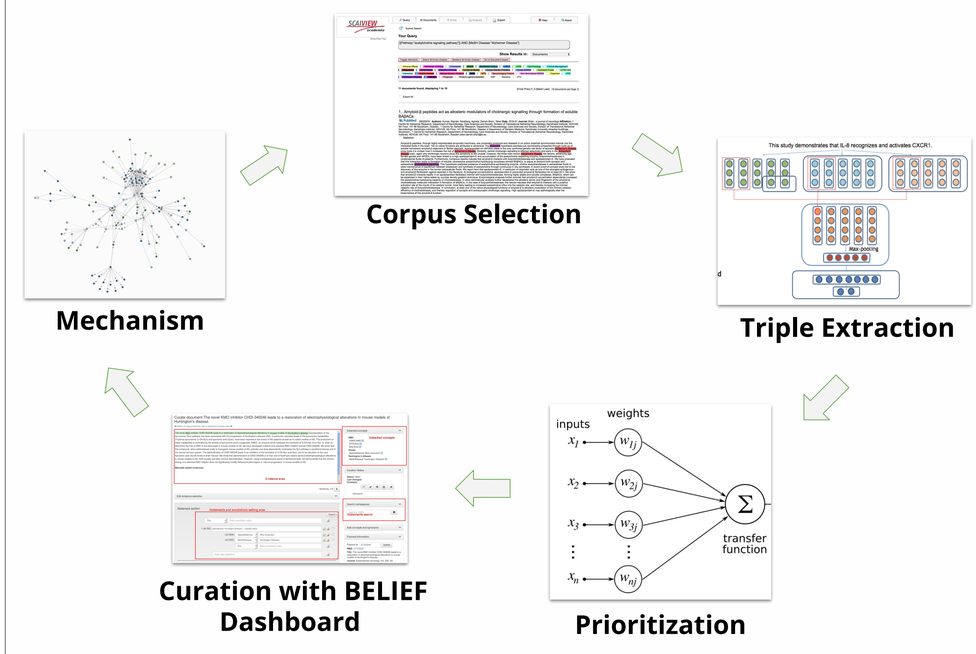
[2]*Rheinische Friedrich-Wilhelms-Universität Bonn, Bonn-Aachen International Center for IT, Bonn 53115, Germany*

Candidate Mechanisms



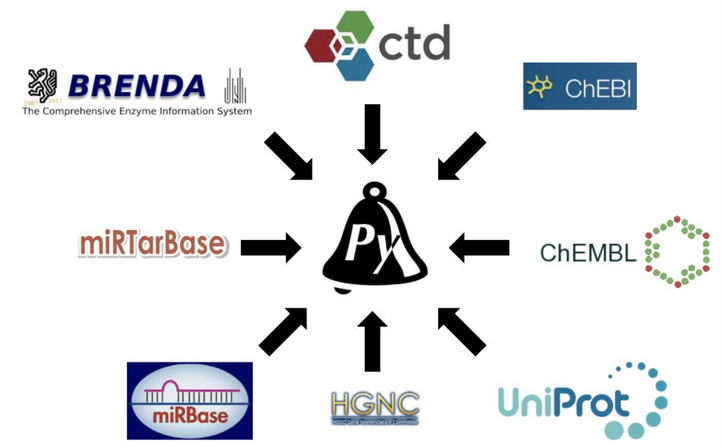
NeuroMMSig uses the Biological Expression Language (BEL) assemble knowledge related to Alzheimer's disease (AD) and identify underlying mechanistic signatures that are more representative of the pathophysiology of the complex disease than individual targets.

Automated Relation Update



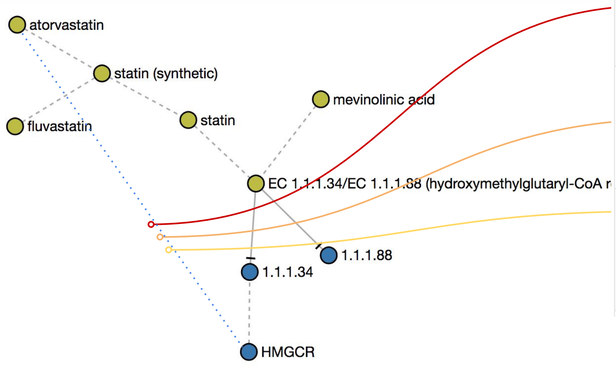
Because knowledge-driven approaches to model the relevant biology and chemistry are inherently limited by the completeness and correctness of their associated knowledge assemblies, natural language processing and relation extraction will be used to continuously extract biomedical relations from the recent biomedical literature and prioritize for semi-automated curation and update.

Semantic BEL



BEL has the potential to serve as a semantic integration platform through which knowledge and data across scales can be integrated and analyzed. Several repositories of chemogenomic have already been integrated using PyBEL and Bio2BEL (https://github.com/bio2bel).

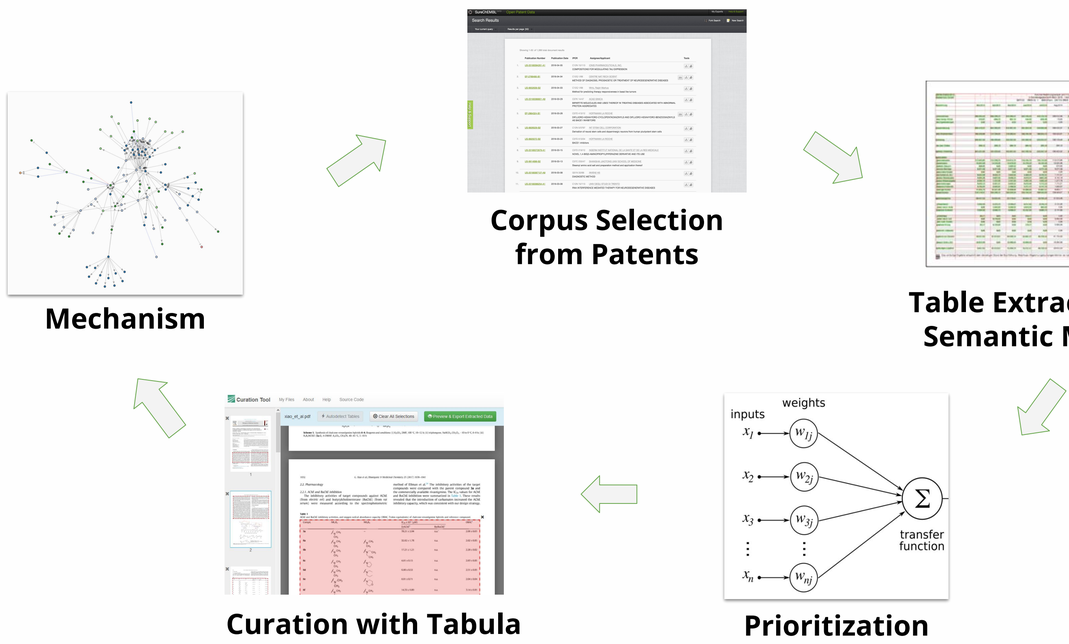
Quantitative BEL



Ingredient	Molweight	Standard Type	Relation	Standard Value	Standard Units	pChEMBL Value	Assay Type	Description
CHEMBL393220	558.64	IC50	>	30000	nM		F	Cytotoxicity against human MCF7 cells after 72 hrs by MTT assay
CHEMBL393220	558.64	IC50		10000	nM		F	PubChem BioAssay, VEGF stimulated ADSC/ECFC co-culture CD31-stained tube area decrease-IC50. (Class of assay: confirmatory)
CHEMBL393220	558.64	IC50		10000	nM		F	PubChem BioAssay, Decreased HeLa cell count-IC50. (Class of assay: confirmatory)

The introduction of quantitative information to previously qualitative mechanistic knowledge assemblies is the first step towards enabling mechanistically-driven chemoinformatics. This will not only involve using chemometrics to identify molecules with the appropriate physical properties, but also generalizing the paradigm of one-drug-one-target used in classic structure-activity-relationship exploration to be applicable for multiple drugs (or drugs with polypharmacology) to either constellations of targets or to entire mechanisms.

Automated Quantitative Information Extraction

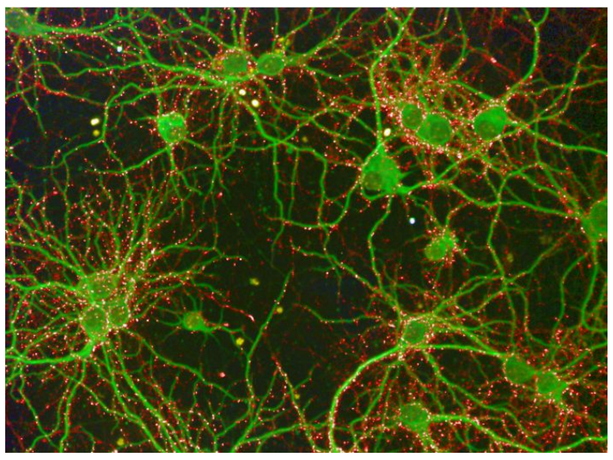


Computer vision and deep-learning techniques from **Fraunhofer IAIS** that will be used to extract quantitative pharmacokinetic and pharmacodynamic information directly from tables embedded in the biomedical literature and patents to complement and extend publicly available resources.

Assays and Drug Repurposing

The HBP will be used to develop several orthologous *in-silico* techniques for proposing repurposing candidates based on classifiers for blood-brain-barrier penetration, chemical space novelty detection, competitive intelligence, and novel network traversal techniques at **Fraunhofer SCAI**.

Assays will be developed concurrently at **Fraunhofer IME** to test the inputs and outputs of the prioritized mechanisms and validate chemicals proposed for repurposing experimentally *in-situ* and *in-vitro*.



Human iPSC cell lines are differentiated to neuron-like cells in which further mechanism-based assays will be developed. Photo credit to Bernhard Ellinger, Fraunhofer IME.

References

Domingo-Fernández, D., *et al*. (2017). Multimodal Mechanistic Signatures for Neurodegenerative Diseases (NeuroMMSig): a web server for mechanism enrichment. *Bioinformatics*, 33(22), 3679-3681.

Emon, M. A. E., *et al*. (2017). Using Drugs as Molecular Probes: A Computational Chemical Biology Approach in Neurodegenerative Diseases. Journal of Alzheimer's Disease, 56(2), 677–686.

Madan, S., *et al.* (2016). The BEL information extraction workflow (BELIEF): Evaluation in the BioCreative V BEL and IAT track. Database, 2016(September 2017), 1–17.

Fraunhofer IME | Fraunhofer IAIS | Fraunhofer SCAI

The Human Brain Pharmacome is a MAVO project jointly between the three Fraunhofer Institutes IAIS, IME, and SCAI. More information can be found at https://pharmacome.scai.fraunhofer.de. Special thanks to Freepik for making part of this icon (Brain Cenit View) available through www.flaticon.com.