AETIONOMY - Data, Disease Modeling and Reasoning

Martin Hofmann-Apitius

Academic Co-Coordinator of AETIONOMY

PRISME Forum Spring 2017 Meeting

Berlin, May 18, 2017

innovative medicines initiative

Mission

To increase knowledge of the causes of Alzheimer´s and Parkinson´s Disease by generating a mechanism-based taxonomy; to validate the taxonomy in a prospective clinical study that demonstrates its suitability for identifying patient subgroups (based on discrete disease mechanisms); to support future drug development and lay the foundation for improved identification and treatment of patient subgroups currently classified as having AD or PD.

Inspired by patients. Driven by science.

Fraunhofer SCAI

efpia

AETIONOMY

A Non-Trivial Challenge: Development of a "mechanism-based taxonomy for neurodegenerative diseases"

In 2011, Kola and Bell published a remarkable paper in Nature Reviews Drug Discovery. With their **"Call to reform the taxonomy of human disease"** they proposed a new, **mechanism-based classification of human disease.**

A call to reform the taxonomy of human disease

Ismail Kola and John Bell

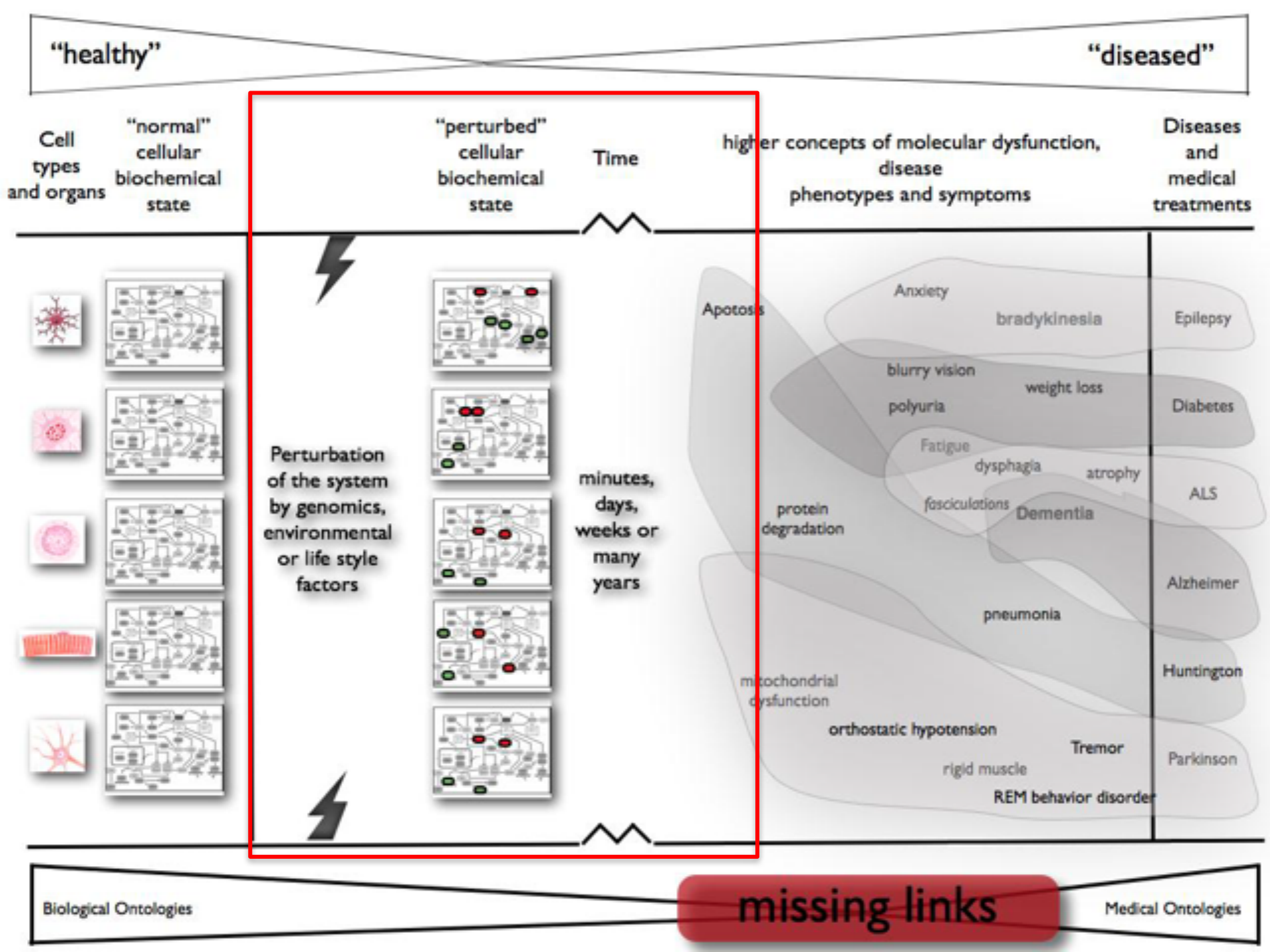
A coordinated effort to incorporate advances in the understanding of the molecular and genomic variations in common diseases, such as hypertension, into their diagnosis and treatment could transform drug development and medicine.

Many common human diseases are still diagnosed as if they were homogenous entities, using criteria that have hardly changed for more than a century. For example, a person with a systolic blood pressure of 140 mm Hg or greater and a diastolic blood pressure of 90 mm Hg or greater is diagnosed with hypertension, irrespective of the heterogeneous underlying molecular mechanisms in different individuals. Furthermore, the treatment approach for diseases that are diagnosed in this way is generic, with empiricism as its cornerstone. Continuing

based on the presence of a shared mutation and/or a deregulated pathway, rather than on tumour location, has not yet been initiated to our knowledge, but is an approach that regulatory agencies may be comfortable with in the future.

The lack of recognition of disease heterogeneity in clinical development and medical practice has a number of well-known consequences. First, it will probably reduce the likelihood of success of clinical trials, perhaps more so for targeted therapies that have been pursued in

Kola, I., & Bell, J. (2011). A call to reform the taxonomy of human disease. *Nature Reviews Drug Discovery*, *10*(9), 641-642.

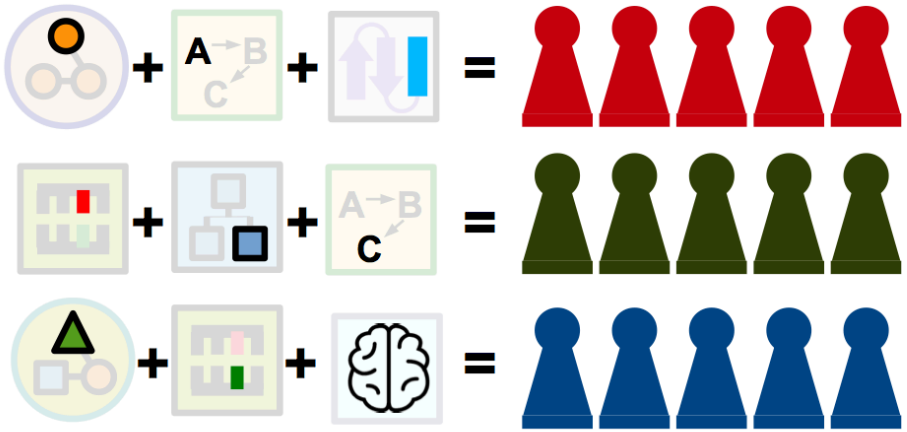

"healthy"
"diseased"
Cell types and organs
"normal" cellular biochemical state
"perturbed" cellular biochemical state
Time
higher concepts of molecular dysfunction, disease phenotypes and symptoms
Diseases and medical treatments
Perturbation of the system by genomics, environmental or life style factors
minutes, days, weeks or many years
Apotosis
Anxiety
bradykinesia
Epilepsy
blurry vision
weight loss
polyuria
Diabetes
Fatigue
dysphagia
atrophy
fasciculations
ALS
protein degradation
Dementia
Alzheimer
pneumonia
Huntington
mitochondrial dysfunction
orthostatic hypotension
Tremor
Parkinson
rigid muscle
REM behavior disorder
Biological Ontologies
missing links
Medical Ontologies

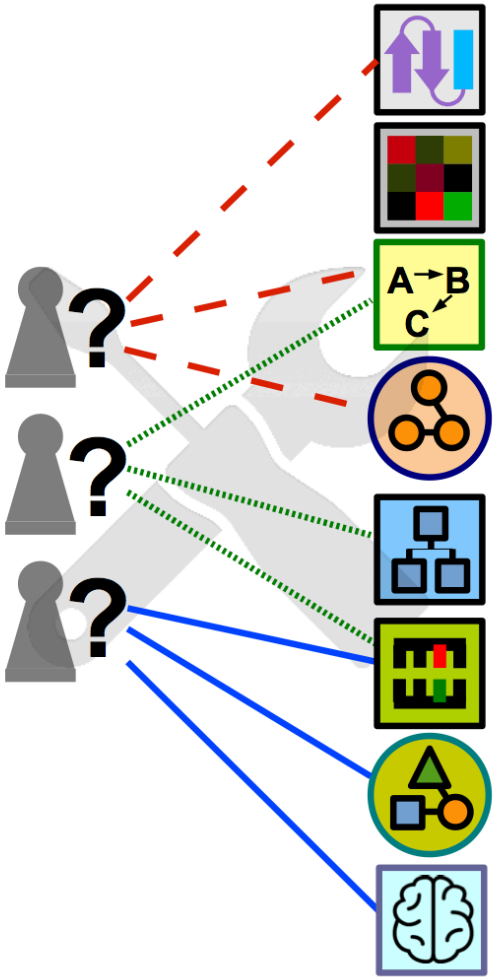
Data and Knowledge in Neurodegenerative Disease Research: incomplete, scattered, mono-modal

Data resources

- Ontologies
- Imaging indices
- PPI networks
- Pathways
- BEL&SBML models
- Gene Expression
- SNP
- Protein domains & families

Addtional: UniProt, PubMed, OMIM, Reactome, HGNC, ENSEMBL, ChEMBL, ...


A
B
C
A
B
C


A
B
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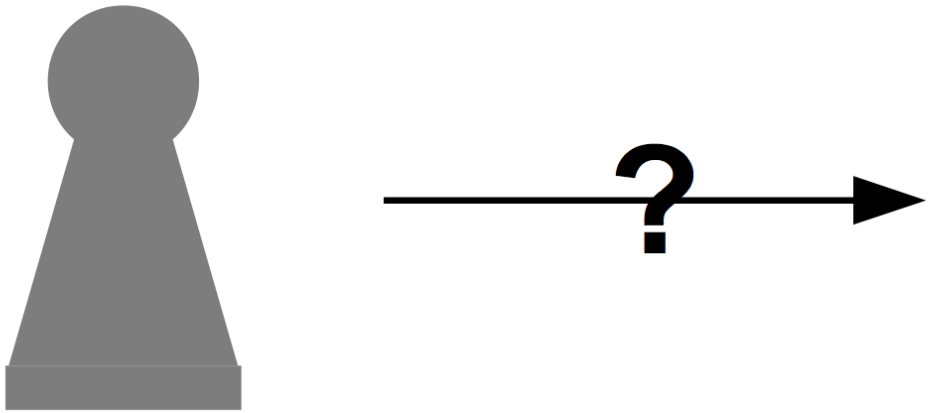
classifying system / patient cohort covering all tests?

correlations between different parameters?



We therefore need to integrate heterogeneous data and knowledge and glue them together in *models* ....

Excursion:

Making Data Findable, Accessible, Interoperable, and Re-Usable: FAIR data principles

Making Data and Knowledge FAIR

FAIR data principles:

- **F**indable
- **A**ccessible
- **I**nteroperable
- **R**e-usable

This is about (clinical) data and their role in translational biomedicine

This is also about the way we do science:

Iqbal, S. A., Wallach, J. D., Khoury, M. J., Schully, S. D., & Ioannidis, J. P. (2016). *Reproducible research practices and transparency across the biomedical literature*. *PLoS Biol*, *14*(1), e1002333.

Making Data and Knowledge FAIR

To be Findable:

F1. (meta)data are assigned a globally unique and eternally persistent identifier.

F2. data are described with rich metadata.

F3. (meta)data are registered or indexed in a searchable resource.

F4. metadata specify the data identifier.

Making Data and Knowledge FAIR

To be Accessible:

A1 (meta)data are retrievable by their identifier using a standardized communications protocol.

A1.1 the protocol is open, free, and universally implementable.

A1.2 the protocol allows for an authentication and authorization procedure, where necessary.

A2 metadata are accessible, even when the data are no longer available.

Making Data and Knowledge FAIR

To be Interoperable:

I1. (meta)data use a formal, accessible, shared, and broadly applicable language for knowledge representation.

I2. (meta)data use vocabularies that follow FAIR principles.

I3. (meta)data include qualified references to other (meta)data.

Making Data and Knowledge FAIR

To be Re-usable:

R1. meta(data) have a plurality of accurate and relevant attributes.

R1.1. (meta)data are released with a clear and accessible data usage license.

R1.2. (meta)data are associated with their provenance.

R1.3. (meta)data meet domain-relevant community standards.

Step 1:
Building Resources

Taking care of interoperability of data and knowledge: Shared Semantics

Ashutosh Malhotra

Erfan Younesi

ADO: Alzheimer Disease Ontology

ADO: A disease ontology representing the domain knowledge specific to Alzheimer's disease

Ashutosh Malhotra[a,b], Erfan Younesi[a,b], Michaela Gündel[a], Bernd Müller[a], Michael T. Heneka[c], Martin Hofmann-Apitius[a,b,*]

[a]*Department of Bioinformatics, Fraunhofer Institute for Algorithms and Scientific Computing, Sankt Augustin, Germany*
[b]*Rheinische Friedrich-Wilhelms-Universität Bonn, Bonn-Aachen International Center for IT, Bonn, Germany*
[c]*Department of Neurology, Clinical Neurosciences Unit, University of Bonn, Bonn, Germany*

Abstract

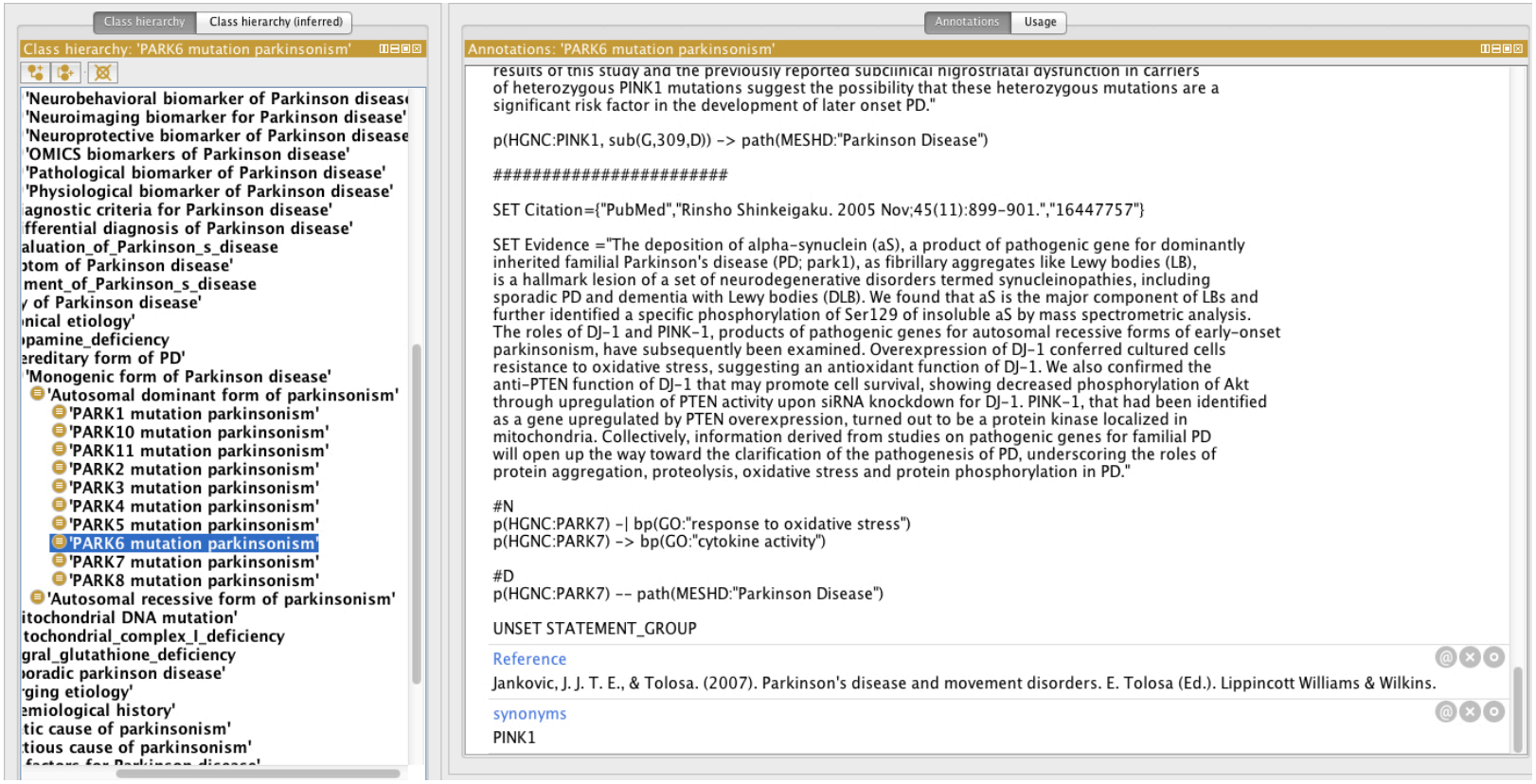
Background: Biomedical ontologies offer the capability to structure and represent domain-specific knowledge semantically. Disease-specific ontologies can facilitate knowledge exchange across multiple disciplines, and ontology-driven mining approaches can generate great value for modeling disease mechanisms. However, in the case of neurodegenerative diseases such as Alzheimer's disease, there is a lack of formal representation of the relevant knowledge domain.

Methods: Alzheimer's disease ontology (ADO) is constructed in accordance to the ontology building life cycle. The Protégé OWL editor was used as a tool for building ADO in Ontology Web Language format.

Results: ADO was developed with the purpose of containing information relevant to four main biological views—preclinical, clinical, etiological, and molecular/cellular mechanisms—and was

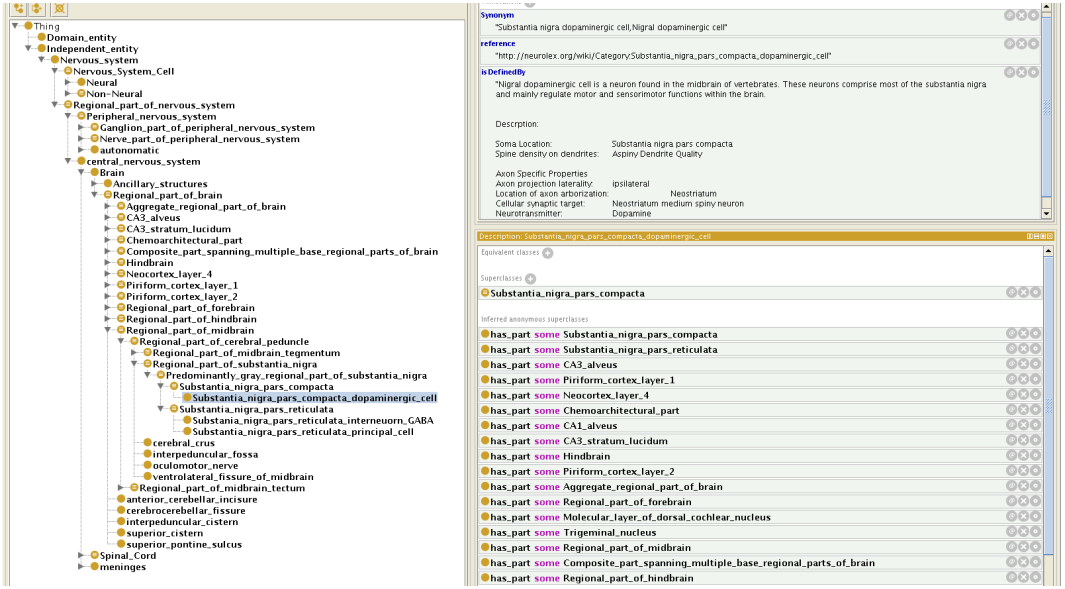
Malhotra, A., Younesi, E., Gündel, M., Müller, B., Heneka, M. T., & Hofmann-Apitius, M. (2014).
ADO: A disease ontology representing the domain knowledge specific to Alzheimer's disease.
Alzheimer's & dementia, *10*(2), 238-246.

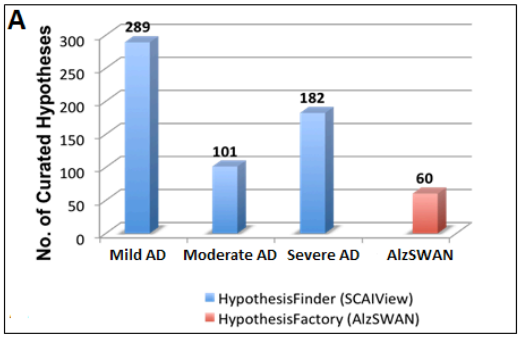
PDON: Parkinson Disease Ontology integrating Mechanisms

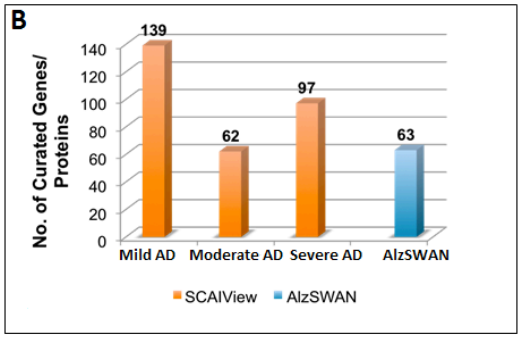


Younesi, E., Malhotra, A., Gündel, M., Scordis, P., Page, M., Müller, B., ... & Hofmann-Apitius, M. (2015). **PDON: Parkinson's disease ontology for representation and modeling of the Parkinson's disease knowledge domain**. *Theoretical Biology and Medical Modelling*, *12*(1), 1.

Shared semantics for Neurodegeneration Research







- Human Physiology Simulation Ontology (HUPSON) (Gündel et al., 2013)
- Brain Region and Cell- Type Terminology (BRCT) (unpublished)
- Clinical Trial Ontology (NDD-CTO) (unpublished)
- Alzheimer Disease Ontology (ADO) (Malhotra et al., 2013)
- Parkinson Disease Ontology (PDON) (Younesi et al., 2015)
- Multiple Sclerosis Ontology (MSO) (Malhotra et al., 2015)
- Biomarker Terminology (Younesi et al., 2012)
- Hypothesis Finder (Malhotra et al., 2013)
- Pathway Terminology System (Iyappan et al., 2016)
- PTSD Terminology (Kodamullil et al., in preparation)

ucb Fraunhofer SCAI efpia

Usage of Ontologies / Terminologies in Text Mining Services

NDD-CTO terminology markup

8 . Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: final analysis of a US multicentre open-label study.

PubMed PubMedCentral 10793322 **Authors:** Rogers, S L; Doody, R S; Pratt, R D; Ieni, J R **Date:** 2000-05 **Journal:** European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology **SciMago: Affiliation:** Eisai Co. Ltd., 6-10 Koishikawa 4 chrome, Bunkyo-ku, Tokyo, Japan.

☐ Statistics

This multicentre, open-label study evaluated the long-term efficacy and safety of donepezil in the treatment of patients with mild to moderately severe Alzheimer's disease (AD). The 133 patients who entered the study had previously completed a 14-week randomized, double-blind, placebo-controlled study with donepezil. In this open-label study, patients were treated initially with 3 mg per day donepezil, which could be increased to 5, 7 and 10 mg per day in a step-wise fashion. Patients attended the clinic for assessments at 3-week intervals for the first 12 weeks, then subsequently at 12-week intervals for up to 240 weeks (254 cumulative weeks). Efficacy was assessed using the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and the Clinical Dementia Rating-Sum of the Boxes scale (CDR-SB), and data were compared with those predicted for historical untreated AD patients. During the first 6-9 months of the study, mean ADAS-cog and CDR-SB scores showed evidence of clinical improvement from baseline. After this time scores gradually deteriorated. Overall the decline was less than that estimated if this cohort of patients had not been treated. The most common adverse events were related to the nervous and digestive systems, and were generally mild and transient, resolving without the need for dose modifications. There was no evidence of hepatotoxicity. In conclusion, these data demonstrate that donepezil is a well-tolerated, realistic symptomatic treatment for AD over a period of up to 4.9 years. An interim report of the first 98 weeks of the study has been published previously.

MeSH: Aged; Aged, 80 and over; Aged; Neuropsychological Tests;

Title and Me

1 . Altered expression of zinc transporters-4 and -6 in mild cognitive impairment, early and late Alzheimer's disease brain.

PubMed 16580781 **Authors:** Smith, J L; Xiong, S; Markesbery, W R; Lovell, M A **Date:** 2006-07- **Journal:** Neuroscience **Affiliation:** Department of Chemistry, University of Kentucky, Lexington, KY 40536, USA.

☐ Statistics ☐ Select ID with comment:

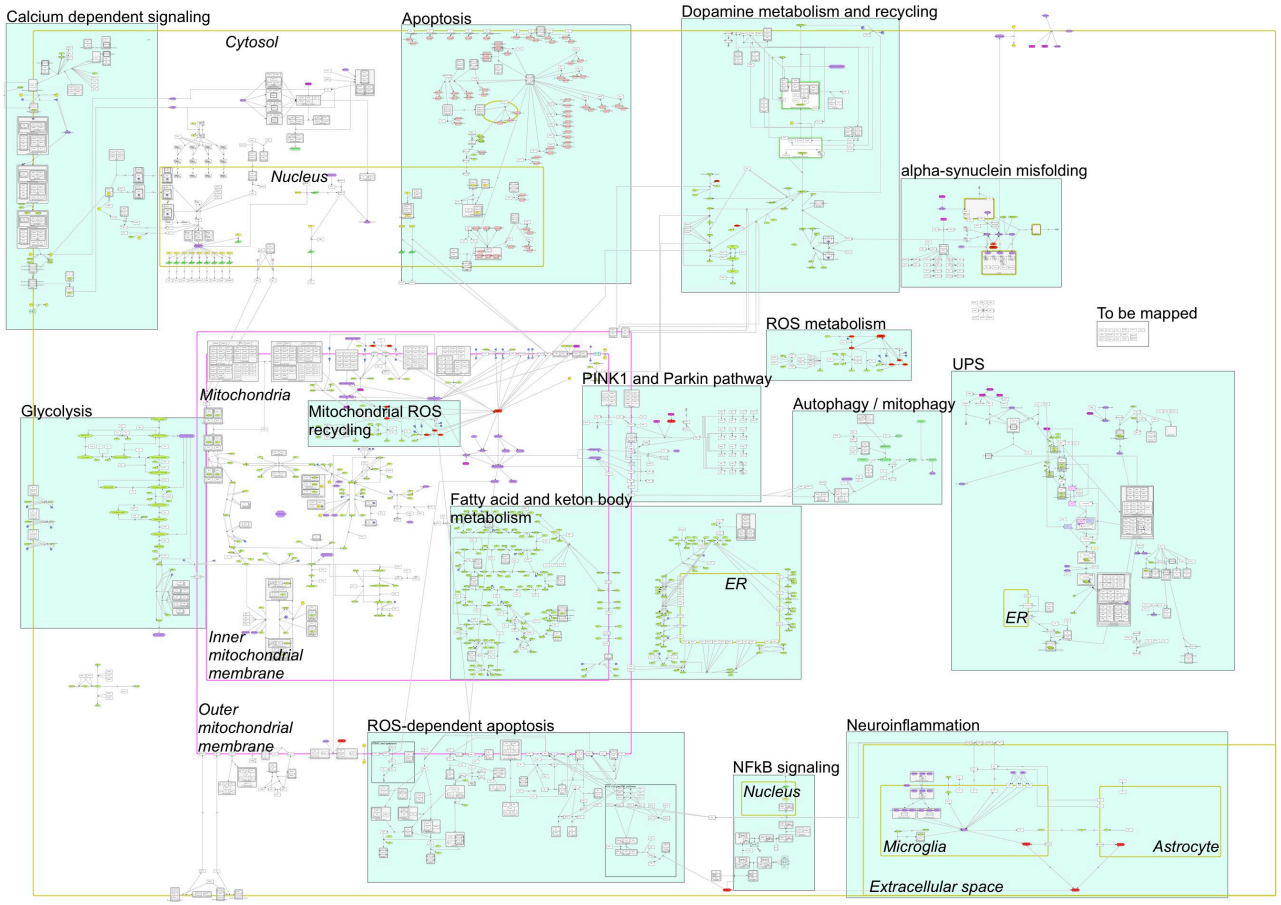
BRCO + ADO terminology markup

Accumulating evidence suggests that a disruption of zinc (Zn) homeostasis may play a role in the pathogenesis of Alzheimer's disease. Although several Zn transporter proteins responsible for the regulation of Zn balance are present in the brain, there has been little study of these proteins in Alzheimer's disease. To determine if alterations of Zn transporter proteins exist, levels of Zn transporter-4, which functions to remove Zn from the cytoplasm to endosomal/lysosomal compartments, and Zn transporter-6, which allocates cytoplasmic Zn to the trans-Golgi network, were measured in the hippocampus/parahippocampal gyrus, superior and middle temporal gyrus, and cerebellum of subjects with mild cognitive impairment, early Alzheimer's disease, late stage Alzheimer's disease, and age-matched controls using Western blot analysis and protein specific antibodies. Our results show that Zn transporter-4 and Zn transporter-6 are significantly ($P<0.05$) increased in hippocampus/parahippocampal gyrus of early Alzheimer's disease and Alzheimer's disease subjects. Zn transporter-6 is also increased ($P<0.1$) in the superior and middle temporal gyrus of Alzheimer's disease brain.

Generating Models of Disease: A Plurality of Modeling Approaches

Alpha Tom Kodamullil

Stephan Gebel



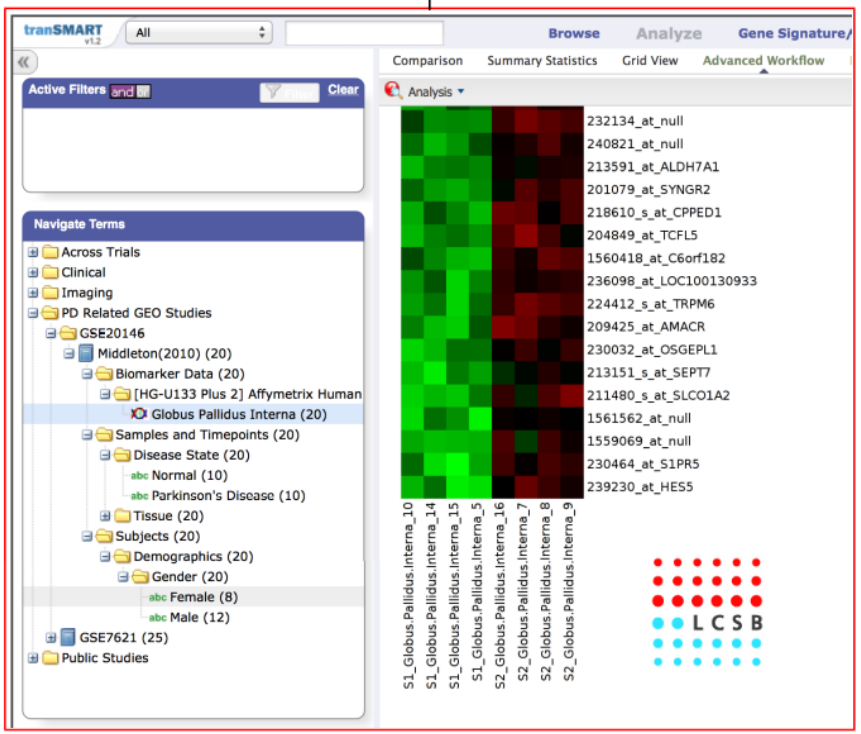
"PD map"
SBML model representing essential processes and pathways in Parkinson´s Disease (generated by partner LCSB)

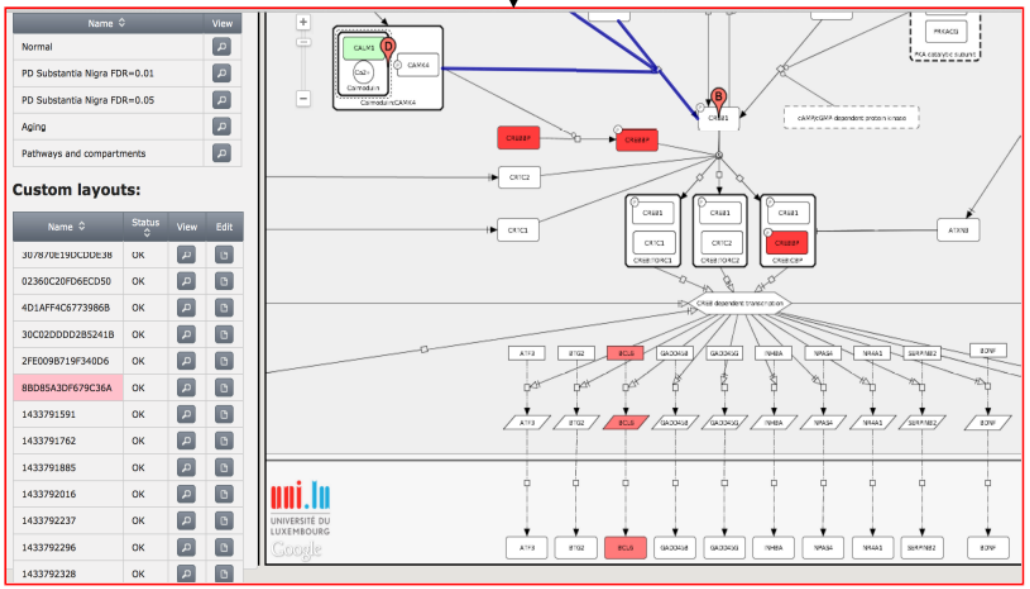
http://pdmap.uni.lu/pd_map/

Fujita, Kazuhiro A., et al. "Integrating pathways of Parkinson's disease in a molecular interaction map." *Molecular neurobiology* 49.1 (2014): 88-102.

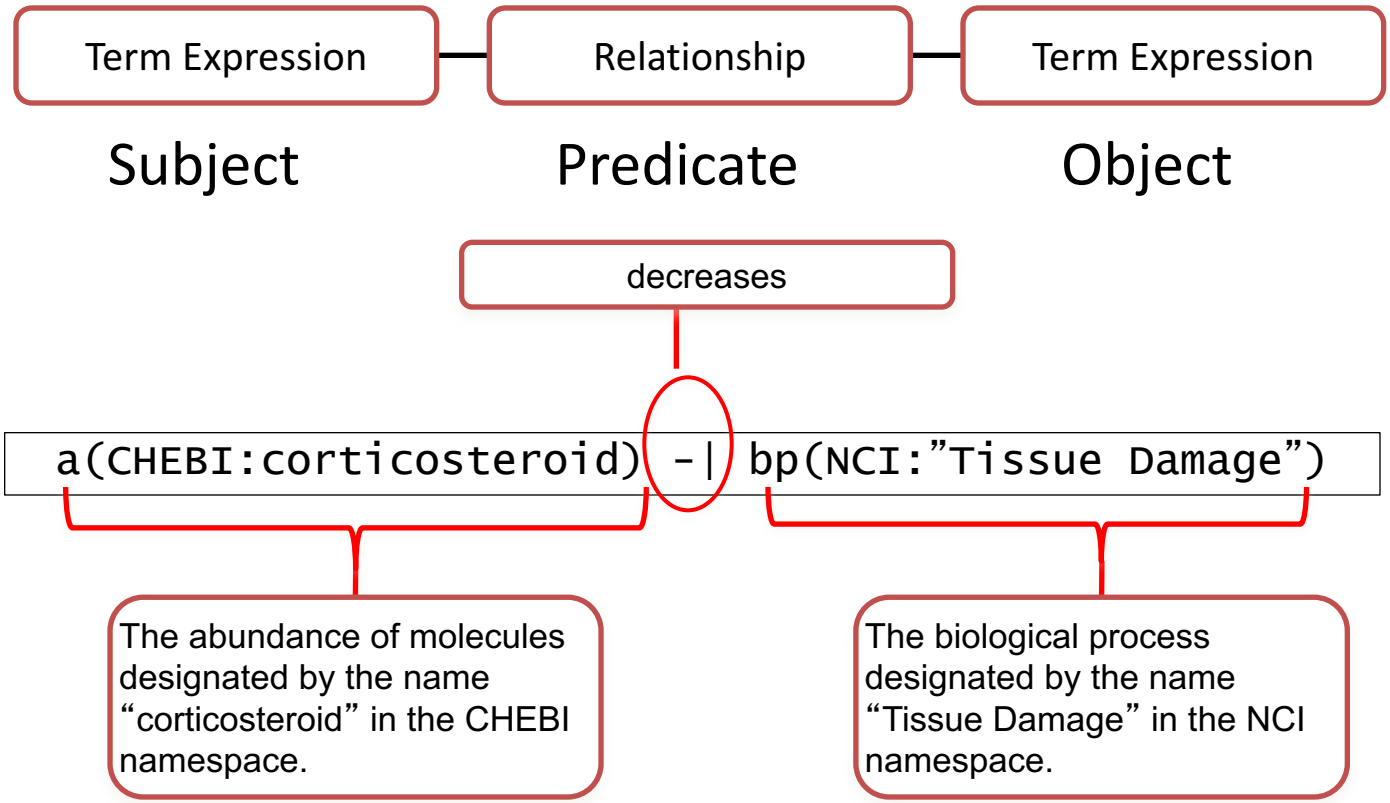
Overlay Marker Selection Results to PD Map

Marker selection from
GSE20146



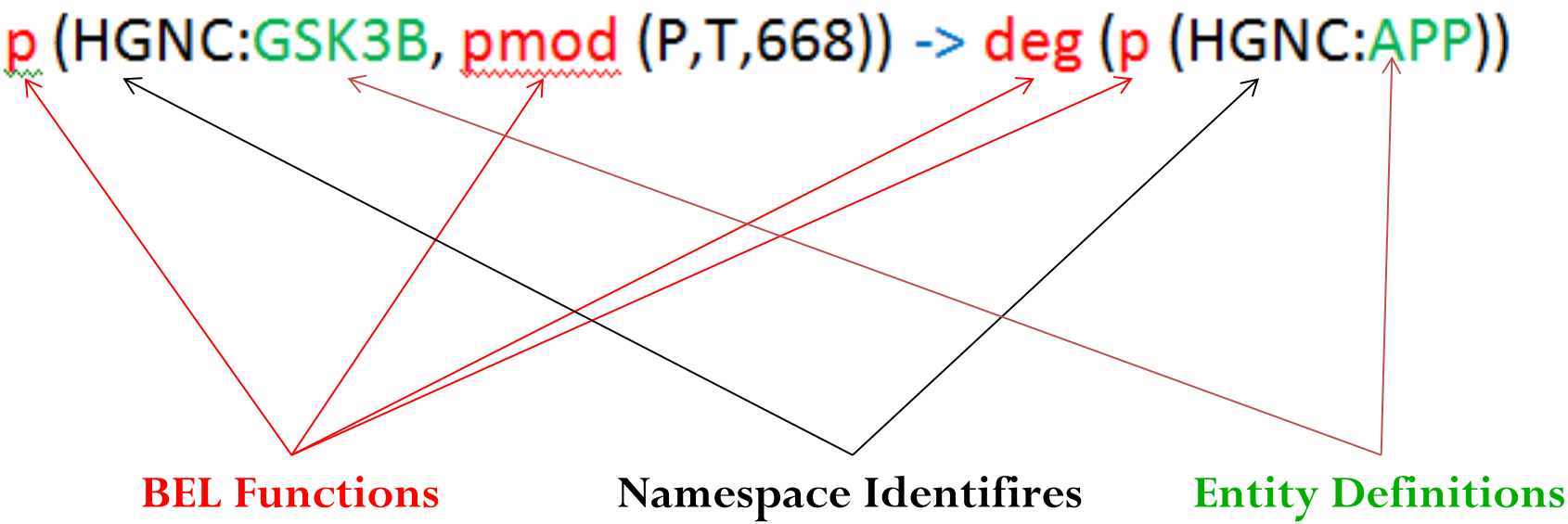


Capturing Knowledge on Causes and Effects: OpenBEL

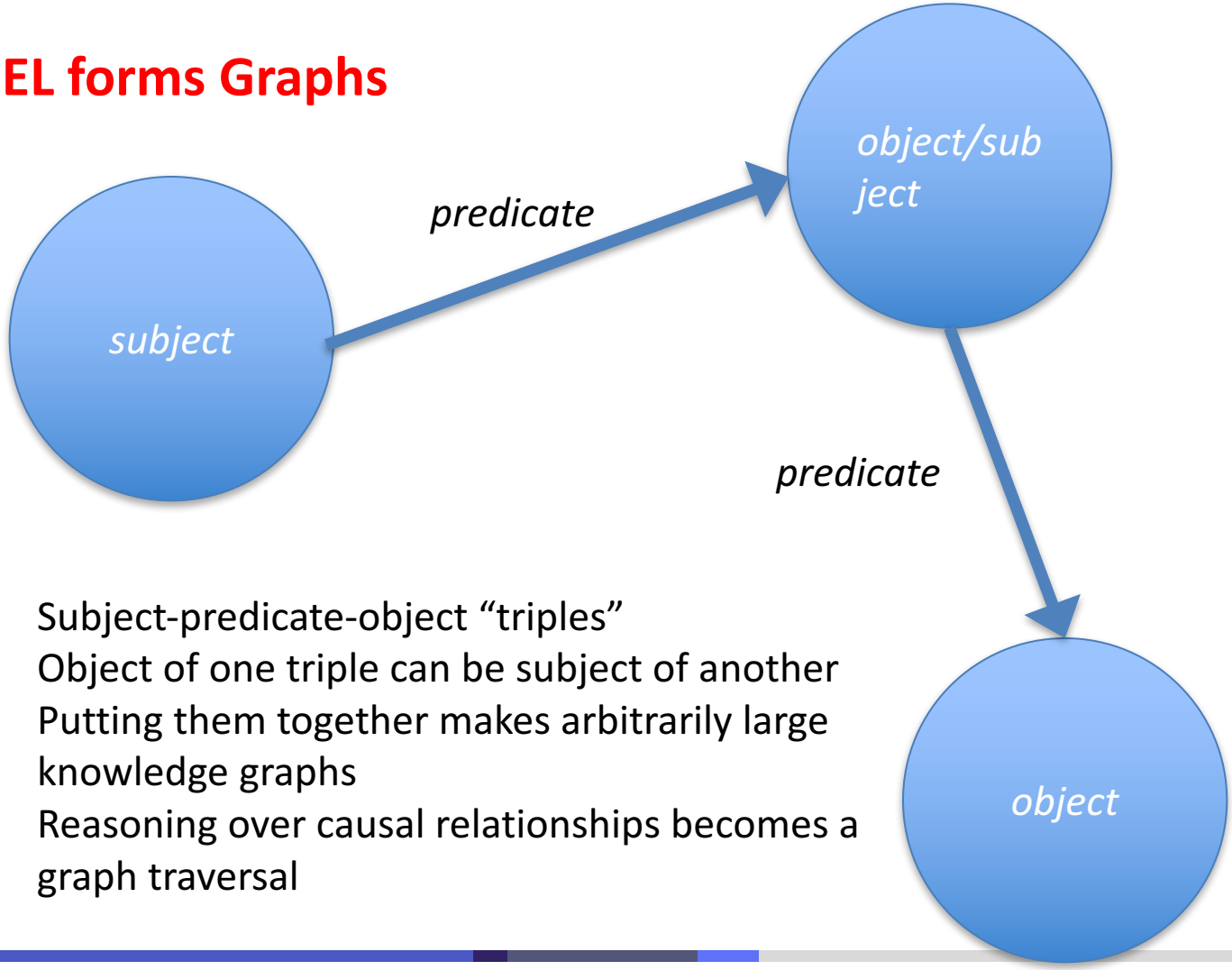


OpenBEL: Capturing of Knowledge and "encoding" of data

Phosphorylation of **glycogen synthase kinase 3beta** at **Threonine, 668** **increases** the **degradation** of **Amyloid precursor protein**.

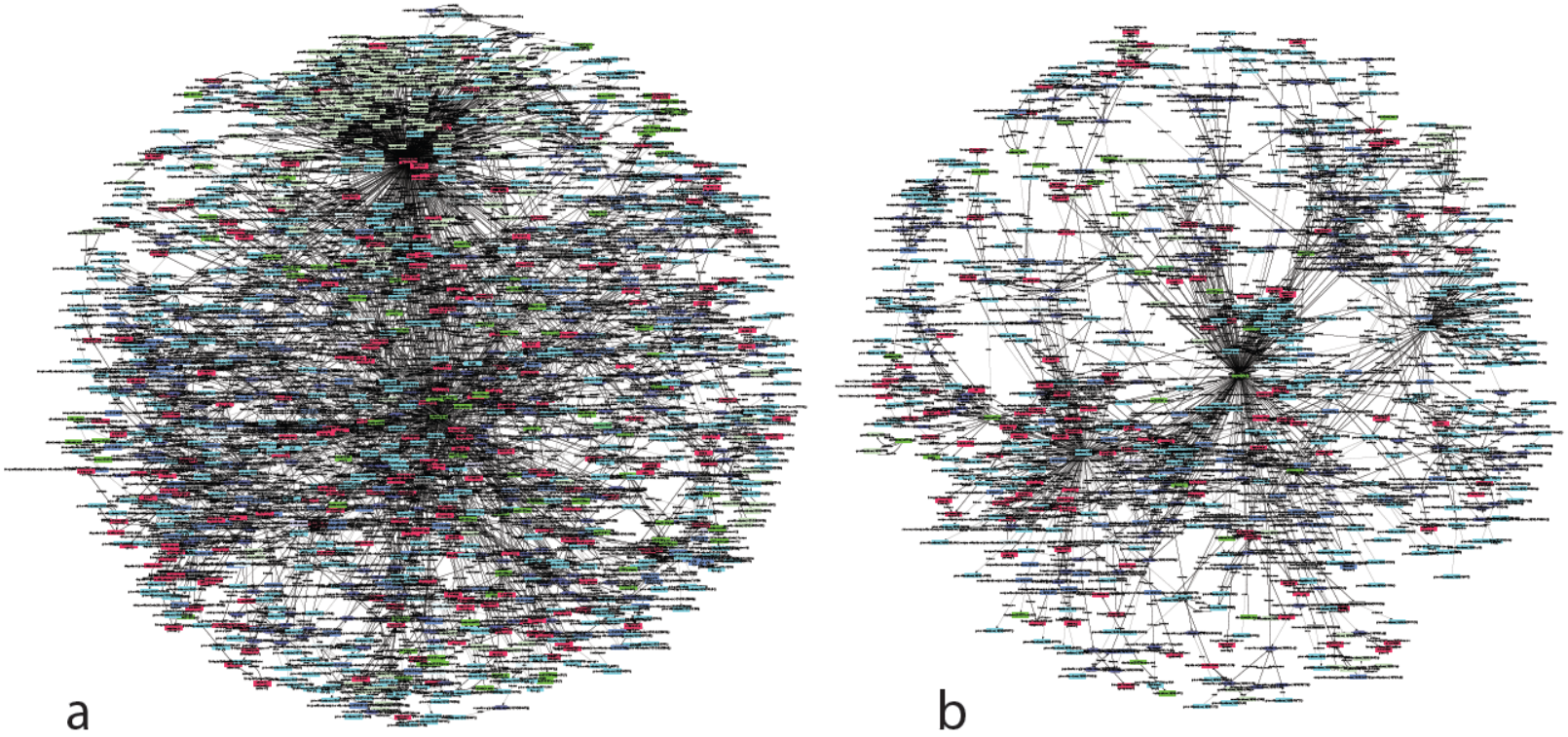


BEL forms Graphs



- Subject-predicate-object “triples”
- Object of one triple can be subject of another
- Putting them together makes arbitrarily large knowledge graphs
- Reasoning over causal relationships becomes a graph traversal

Model-driven Integration of Data- and Knowledge in AD



diseased

normal

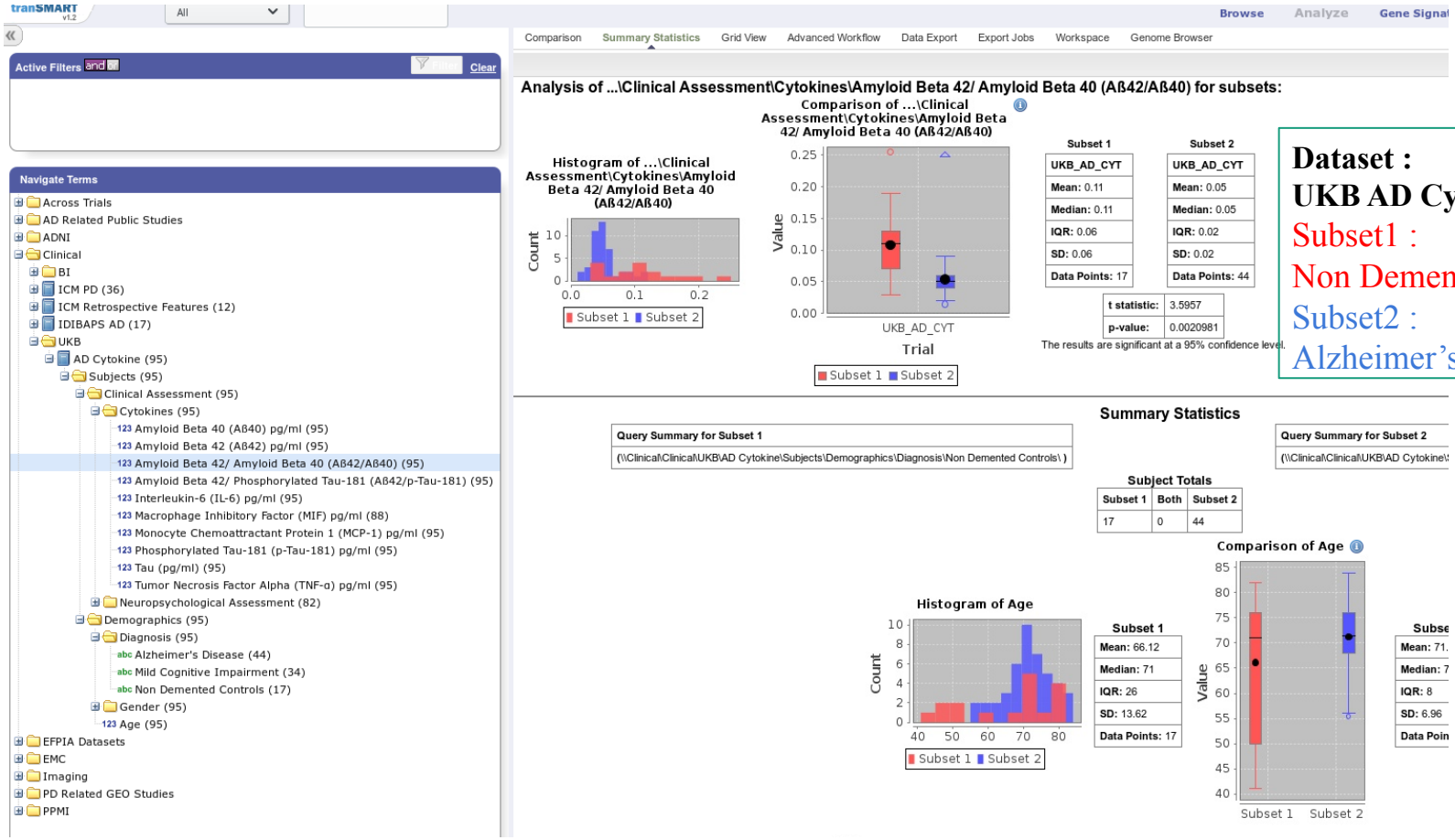
Kodamullil, A. T., Younesi, E., Naz, M., Bagewadi, S., & Hofmann-Apitius, M. (2015). **Computable cause-and-effect models of healthy and Alzheimer's disease states and their mechanistic differential analysis**. *Alzheimer's & Dementia*, *11*(11), 1329-1339.

The AETIONOMY Knowledge Base

Christian Ebeling

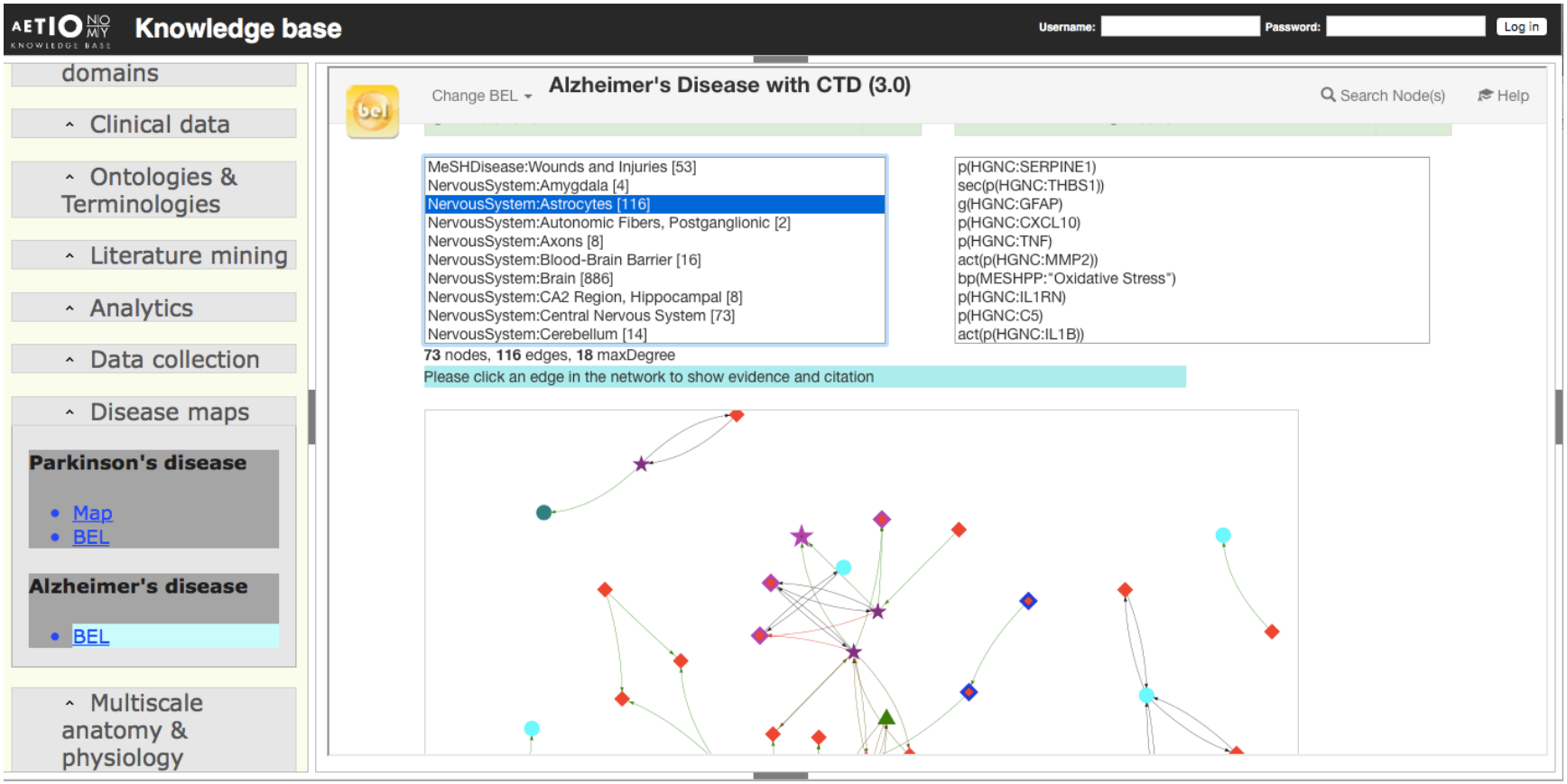
Aishwarya Alex

tranSMART : Summary Statistics for Selected Cohorts



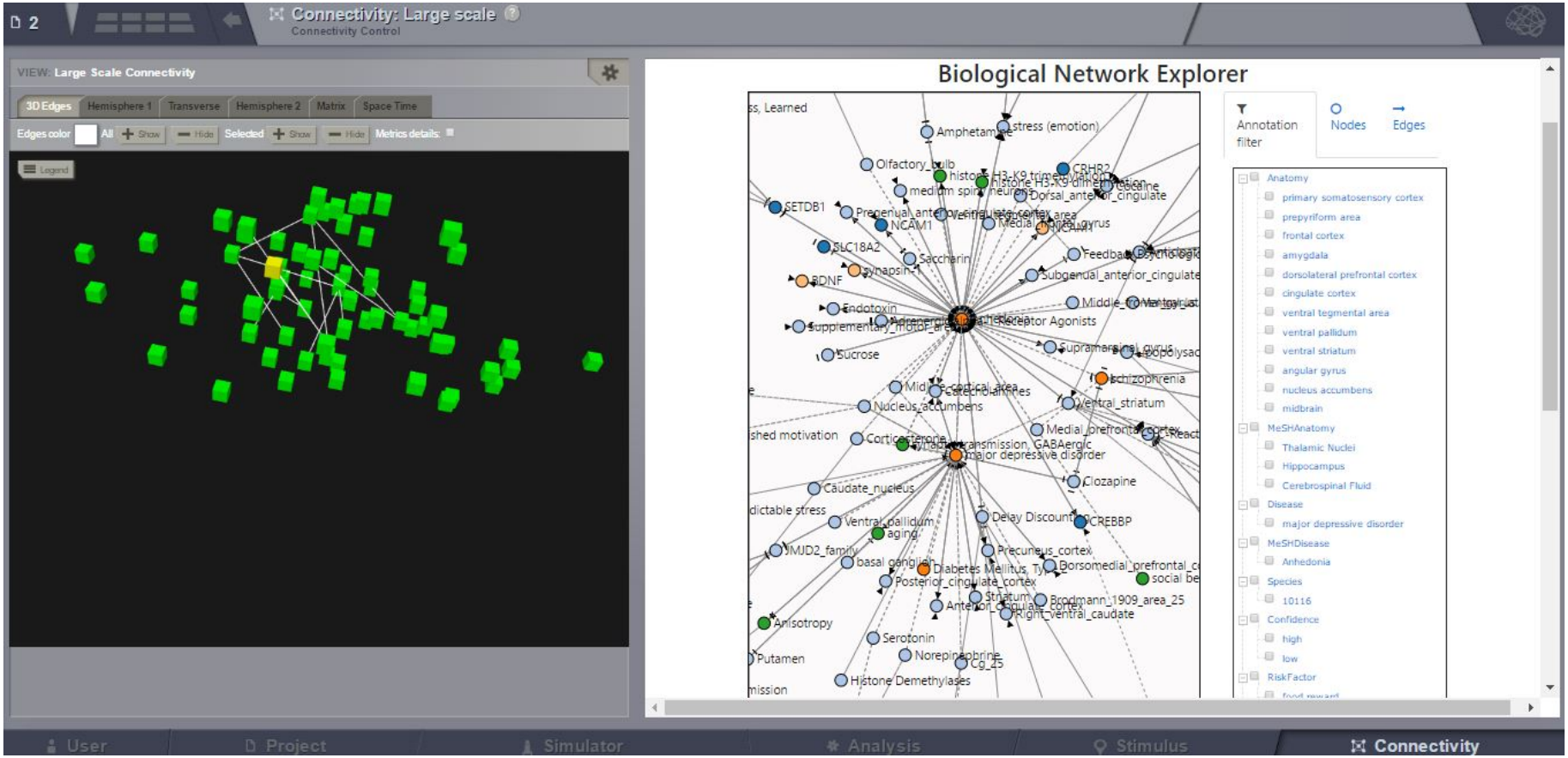
Dataset :
UKB AD Cytokine (95)
Subset1 :
Non Demented Controls (17)
Subset2 :
Alzheimer's Disease (44)

AETIONOMY KB (non-tranSMART portion): Model Explorer



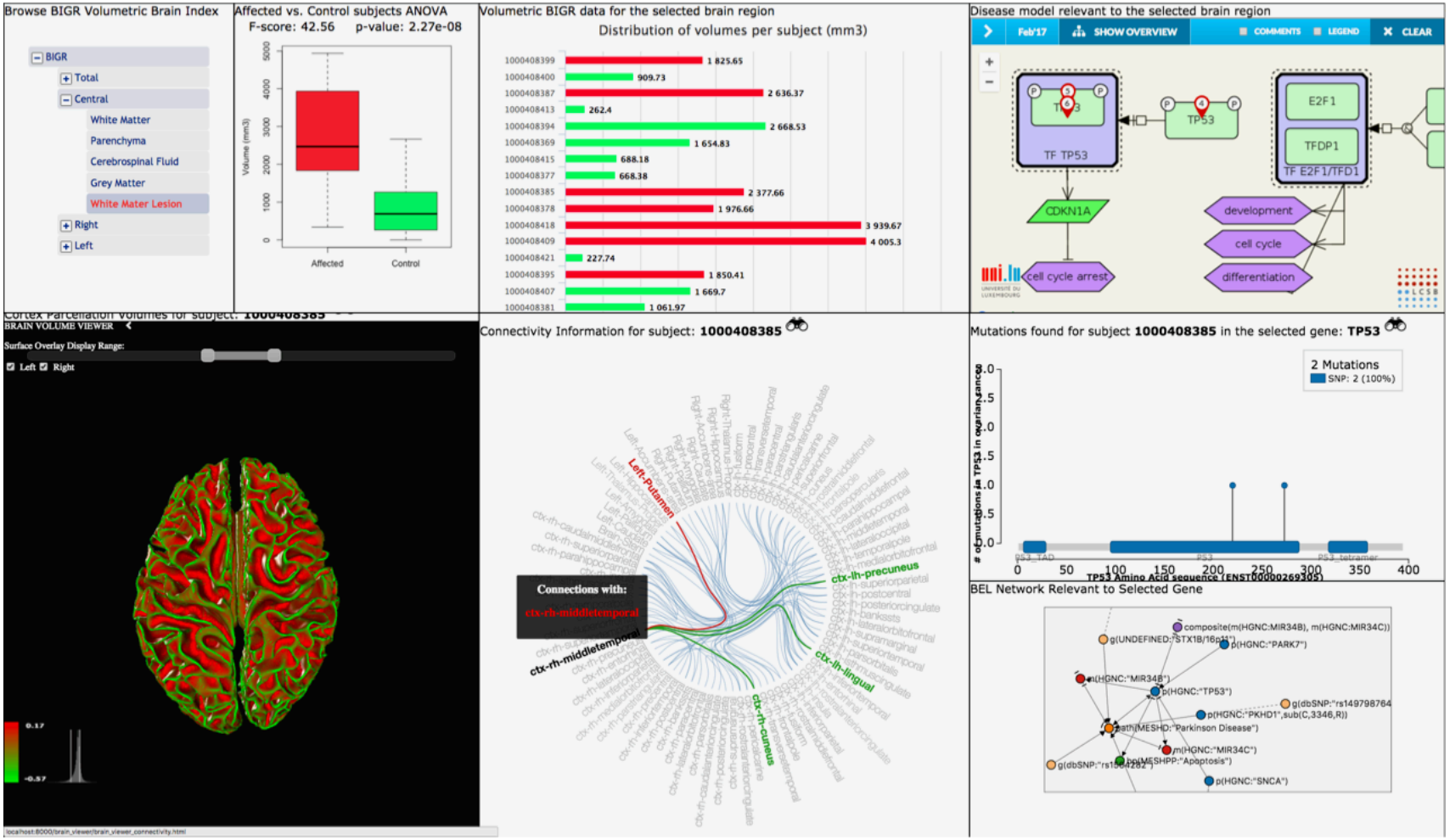
http://aetionomy.scai.fhg.de

Mapping Models into the “The Virtual Brain” (TVB)



Work of Aliaksandr Masny, Asif Emon and Daniel Domingo-Fernandez

Integrated Information System for Translational Neuroscience



Step 2:
Making Use of the Resources

Identification of Candidate Mechanisms: The Mining Strategies

Anandhi Iyappan

Shweta Bagewadi

Alpha Kodamullil

Erfan Younesi

Reverse Causal Reasoning (RCR; Catlett et al., 2013)

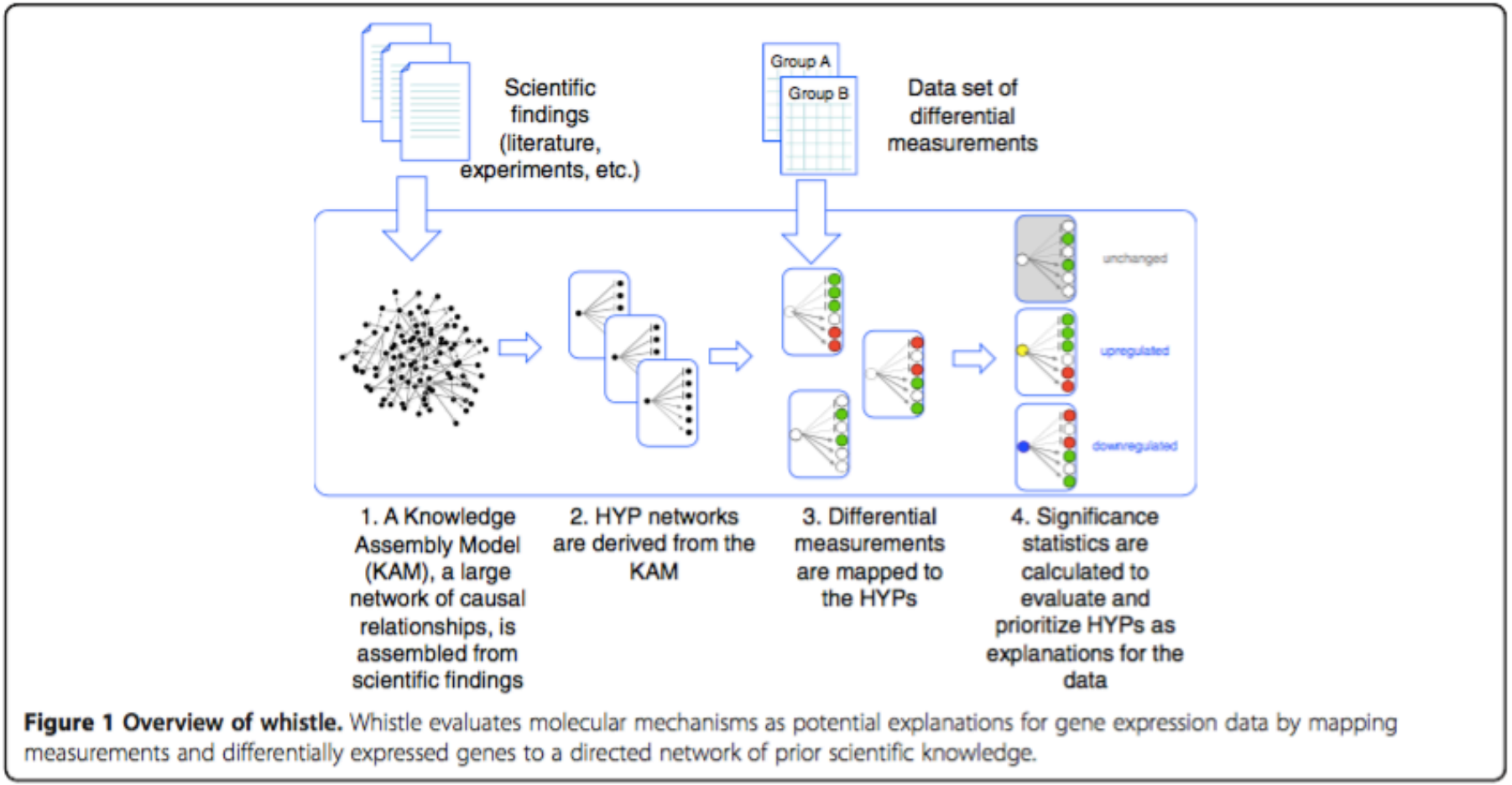
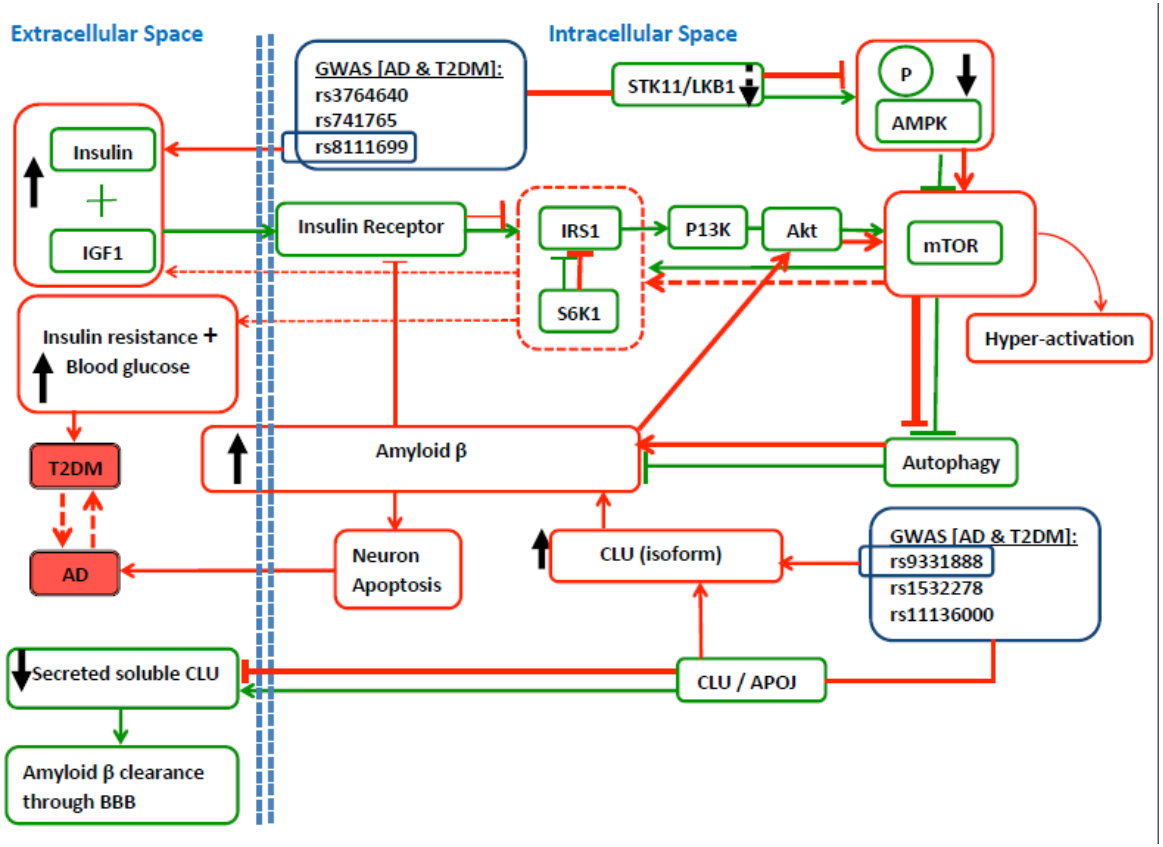


Figure 1 Overview of whistle. Whistle evaluates molecular mechanisms as potential explanations for gene expression data by mapping measurements and differentially expressed genes to a directed network of prior scientific knowledge.

A Mechanistic Link between AD and T2DM

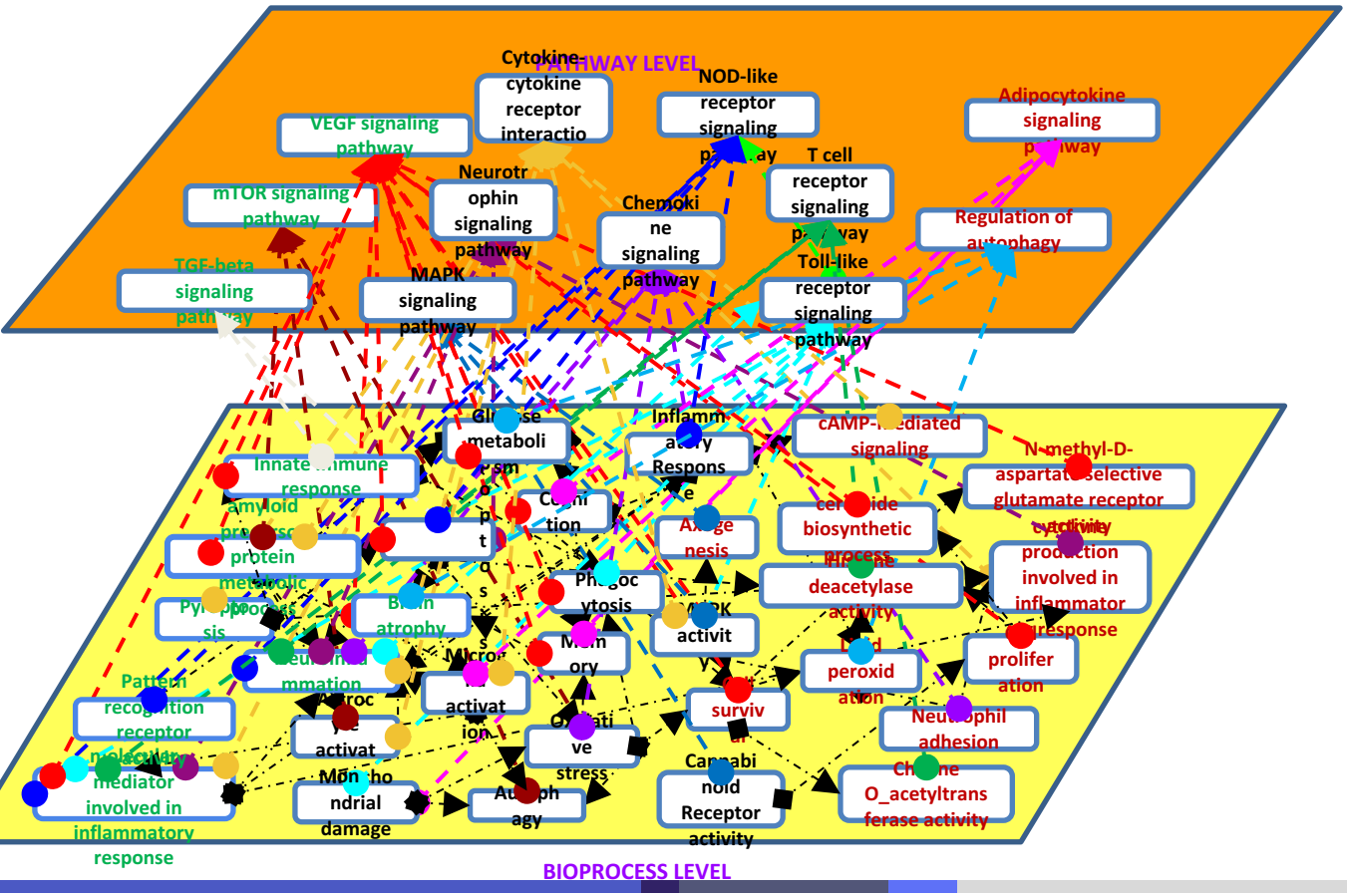


Mining of co-morbidity information results in the second mechanism-hypothesis generated in AETIONOMY: a possible link between insulin receptor pathway, mTOR-induced autophagy and APP peptide clearance

Supportive evidence from SNPs that are shared by AD and T2DM

Comparative Modeling of Neuroinflammation in Mice and Men

Kodamullil, A. T., et al., submitted

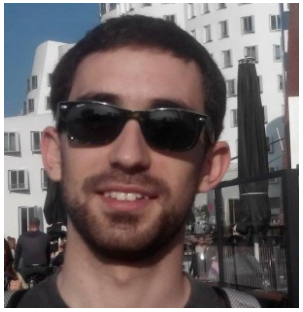


Separate modeling of causes-and-effects in neuroinflammation in mice and men reveals insight into the functional repertoire and the functional equivalence of rodent models. Our findings put a question mark behind the extensive usage of mouse models for neuroinflammation studies.

NeuroMMSigDB – a server for mechanism-enrichment

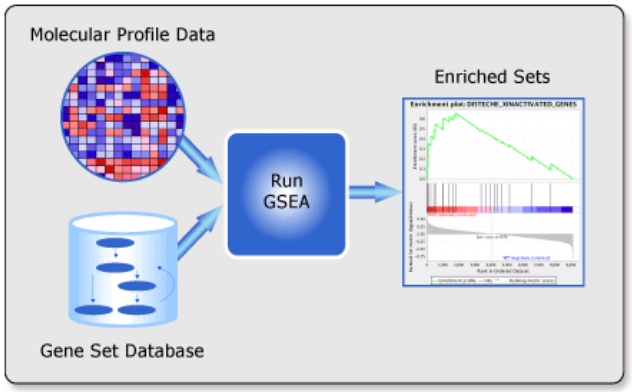
Christian Ebeling

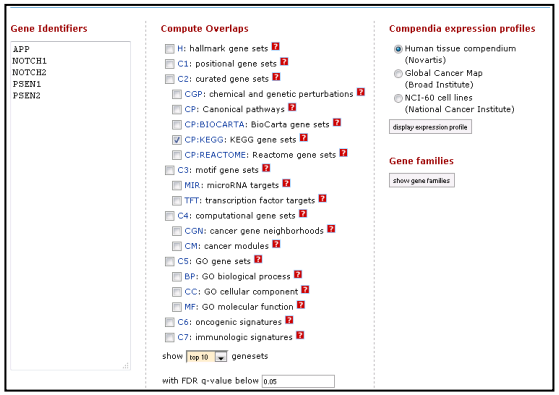
Alpha T. Kodamullil



Daniel Domingo-Fernandez

An Adaptation of GSEA / MSigDB: Mechanism Enrichment Server





We have adapted the strategy underlying **GSEA / MSigDB**

(developed by the Broad Institute http://www.broadinstitute.org/gsea/msigdb/index.jsp)

for the area of dementia research.

Compute Overlaps for Selected Genes

Collections	# Overlaps Shown	# Gene Sets in Collections	# Genes in Comparison (n)	# Genes in Universe (N)
CP:KEGG	3	186	5	45956

Click the gene set name to see the gene set page. Click the number of genes [in brackets] to download the list of genes.

Color bar shading from light green to black, where lighter colors indicate more significant FDR q-values (< 0.05) and black indicates less significant FDR q-values (>= 0.05).

Save to: Excel | GenomeSpace

Gene Set Name [# Genes (K)]	Description	# Genes in Overlap (k)	k/K	p-value	FDR q-value
KEGG_NOTCH_SIGNALING_PATHWAY [47]	Notch signaling pathway	4		$4.8\ e^{-12}$	$8.92\ e^{-10}$
KEGG_ALZHEIMERS_DISEASE [169]	Alzheimer's disease	3		$4.86\ e^{-7}$	$4.52\ e^{-5}$
KEGG_DORSO_VENTRAL_AXIS_FORMATION [25]	Dorso-ventral axis formation	2		$2.84\ e^{-6}$	$1.76\ e^{-4}$

NeuroMMSig DB Server is different from GSEA / MSigDB

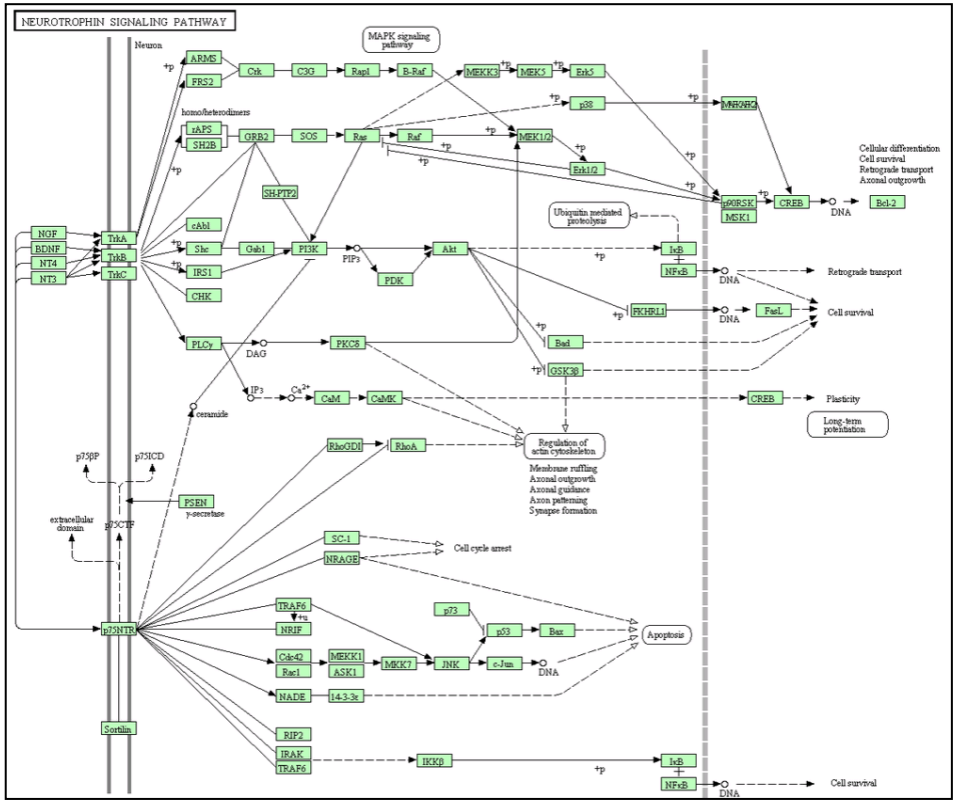
Molecular Profiles are highly specific for Neurodegenerative Diseases: the “profiles“ or “signatures” in NeuroMMSigDB are graph models representing pathophysiology context

NeuroMMSigDB entries are Multimodal: Multiple entity types constitute knowledge based mechanistic models. They contain genes, proteins, chemicals, ions, drugs, SNPs, epigenetics, imaging features, cognitive tests, clinical data, etc.

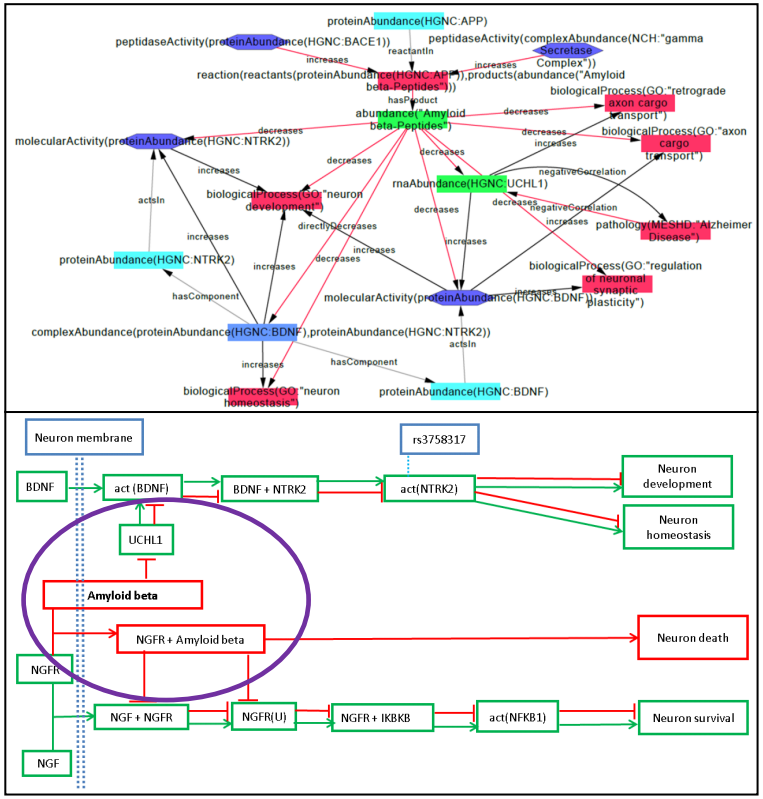
Mechanisms are not pathways: canonical pathways (KEGG, REACTOME etc) are usually not disease specific. Pathways representing “how stuff works“ in a a general way, pathways are **not disease mechanisms**. Dysregulation of pathways may be a disease mechanism. Examples:

- According to KEGG, there are only 10 pathways under NervousSystem
- Not all genes and relationships described in one canonical pathway ***may or may not be involving as same as*** in a disease specific mechanism or ***some genes are irrelevant*** to disease context.

Canonical Pathways are NOT Disease Mechanisms



Canonical Pathway



Cause and effects of an entity from BEL mechanistic model

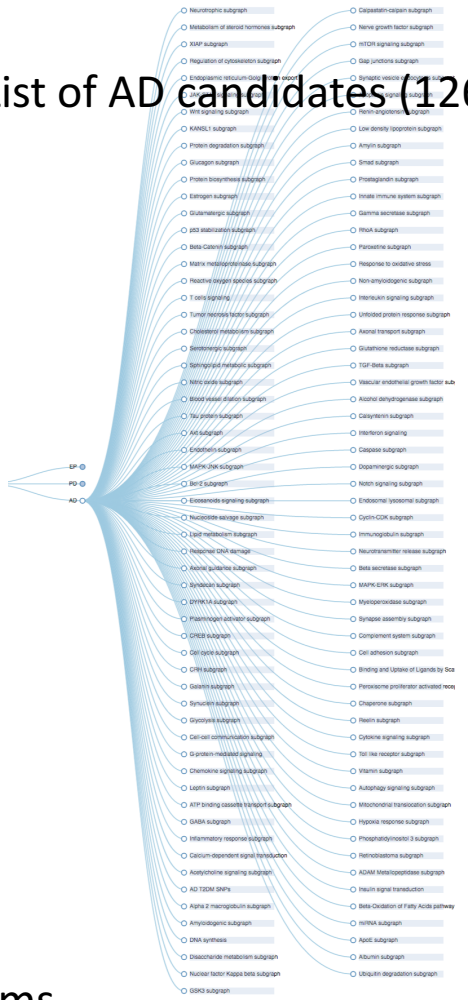
NeuroMMSigDB – the mechanism-inventory

CHI3L1 (YKL-40) subgraph

Inflammatory response subgraph

List of PD candidates (76)

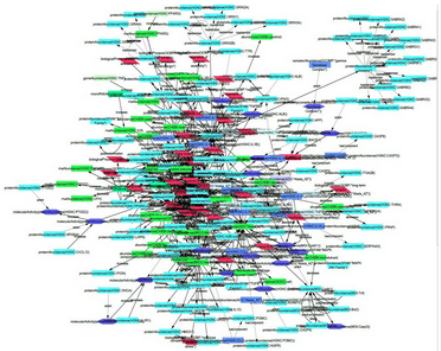
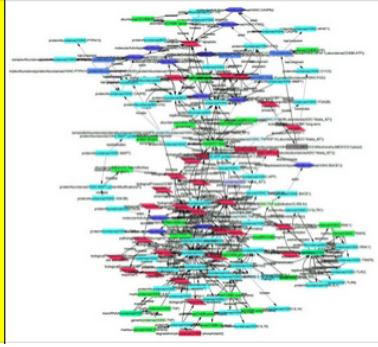
List of AD candidates (126)



Domingo-Fernandez et al., submitted

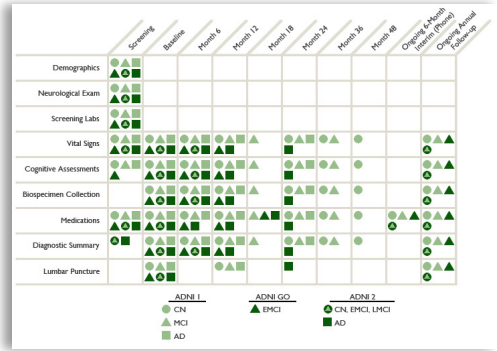
Subgraph example and tree representations of candidate mechanisms

Current Design of the NeuroMMSigDB Mechanism Inventory

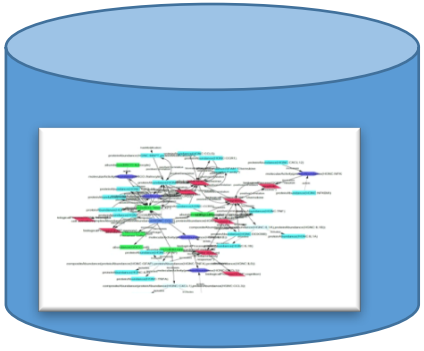
Root Pathways	Sons of Root Pathways	BEL Sub-Networks	BRCO Terms associated from BEL models	Genetic Variants from literature	Genes associated with SNPs	PMIDs for Genetic variants	Imaging Features	Brain Region	PMIDs for imaging	Genes from GE data
Innate immune system pathway	Cytokines pathway		astrocytes, microglia, neuron	rs1800587, rs1800896 (protective),	IL1-A, IL10	24103372, 23838435	neuronal damage, axonal degeneration, Serotonin	striatum, hippocampus,	15465624, 17189680, 25069615,	IL13, TNFRSF25, ACVR1,TNFRSF21,TNFRSF11B, GH1, BMPR1B, IL17RA, CCL22, CXCL2, KIT, FLT1, LIFR, AMHR2, IFNL2, TNFSF8, CTF1 IL1B, CLCF1, CX3CR1, NGFR,, EPOR, CCL3L3, LEP, IFNAR1, IFNGR1, PDGFRB
	Tumor necrosis factor pathway		astrocytes, hippocampus, brain, neuron	rs1799724	TNF-a	21509504	hippocampal volume, neuronal damage,	hippocampus, cortex, amygdala	24938671, 22666474, 19320056, 15626822	-

NeuroMMSigDB: Multimodal, Multiscale Mechanism Enrichment

NeuroMMSigDB Server

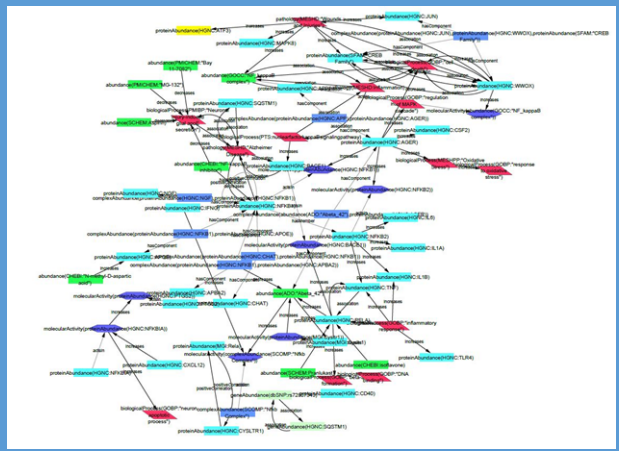


Clinical data & variables

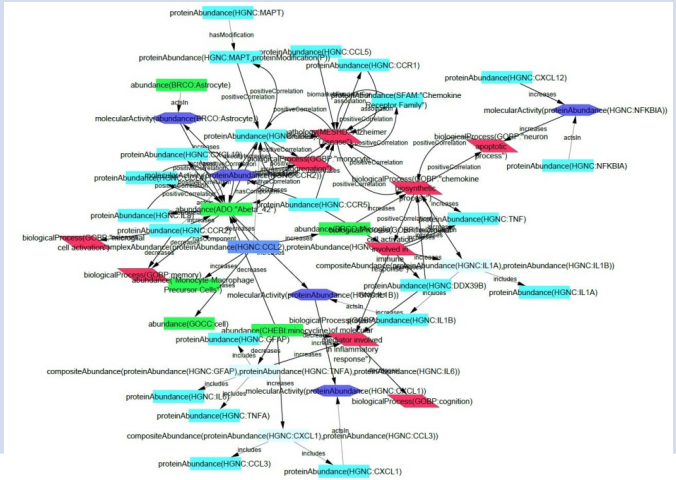


List of mechanisms that fit to the patterns in the clinical data

Use Case Scenarios for Mechanism-Enrichment: Genes

INPUT	OUTPUT	
List of differential expressed genes	**Enriched Mechanisms from disease specific model**	
✓ APP ✓ PSEN ✓ NOTCH1 ✓ NOTCH2	Amyloid beta signaling Notch signaling	

Use Case Scenarios for Mechanism-Enrichment: Genetics

INPUT	OUTPUT		
List of SNPs from a disease subgroup	**Associated genes**	**Enriched Mechanisms**	
rs12769316, rs1056890, rs11160707, rs1799724	NFKB2, TNF	Nuclear factor kappa signaling, Tumour Necrosis Factor signaling	

Ranking of Candidate Mechanisms

1. Map gene expression values (different stages of the disease) to BEL networks

2. Devise a scoring function
   - Apply Network Perturbation Amplitude (NPA) algorithm (*see the work of Florian Martin, Julia Hoeng, and Manuel Peitsch on that method*)
   - Calculate score for dysfunctional mechanism(s) for different stages
     - $\text{Score} = \frac{1}{N} \sum_{i=1}^{N} S_i \cdot ß_i$

       where
       ß is $\log_2$ fold change
       S is the sign (+1 for increase, -1 for decrease)
       N is the no. of downstream nodes
   - Rank mechanisms based on the score

Ranking of Candidate Mechanisms part II

Represent clinical data in Bayesian dependency graphs

Devise a scoring function

Systematically test subgraphs in the conditional dependency graph for their concordance with BEL-encoded cause-and-effect graphs

Score each individual triple match

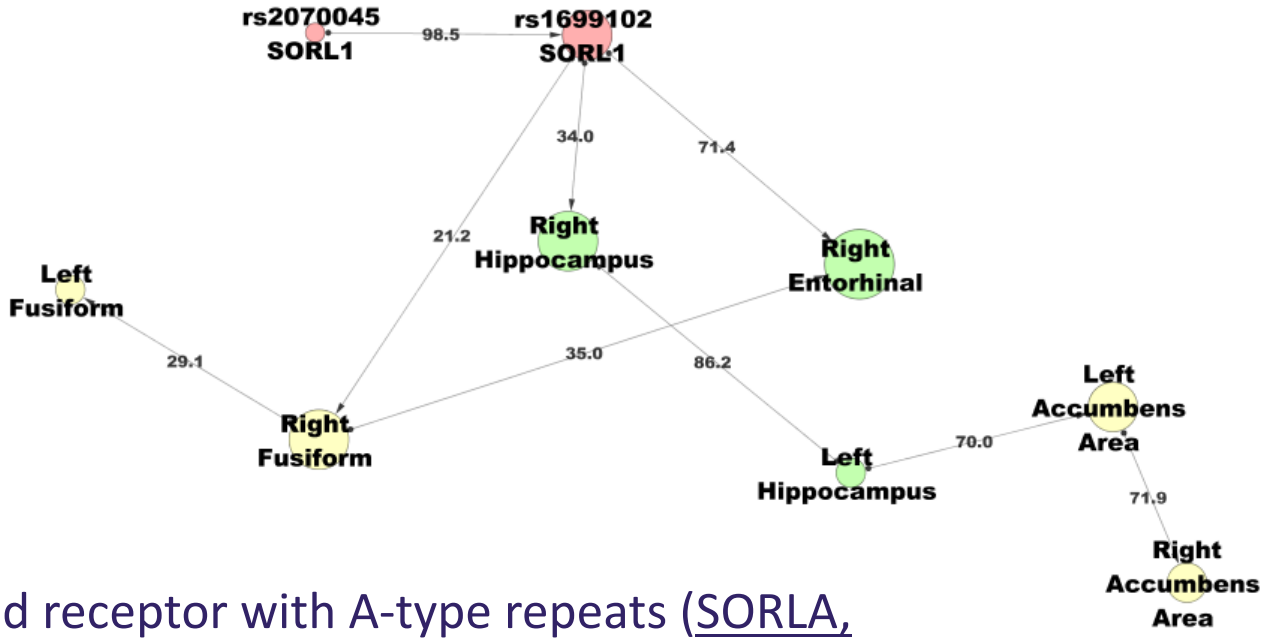
Score each individual directionality match

Flag concordance / discordance areas

Conditional Dependency Graph representing Patient Level data: Bayesian Network learned from ADNI

Work of Shashank Khanna (Fraunhofer)
Supported by Prof. Holger Fröhlich (UCB)

Bayesian Network links SNPs to Brain Regions

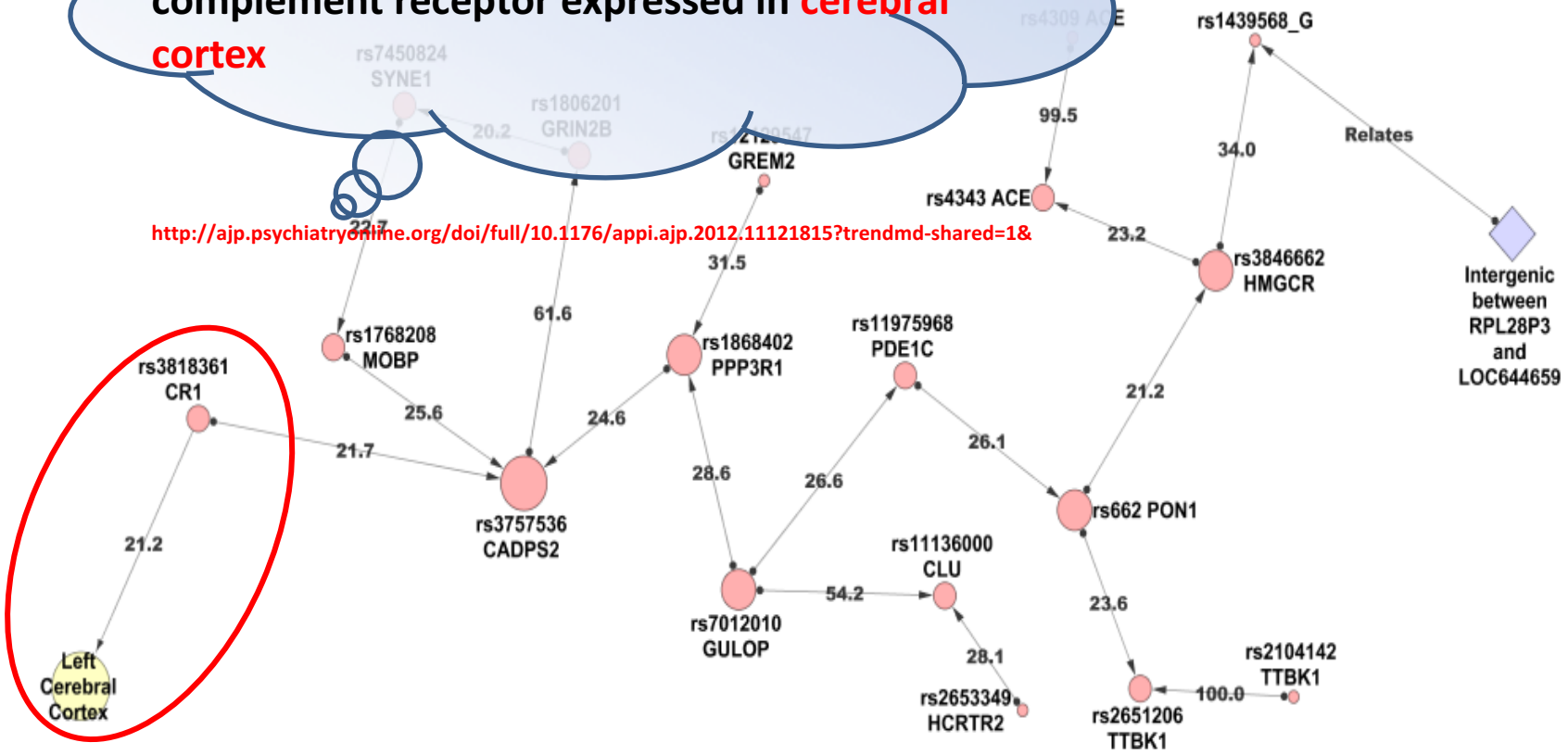


Sorting protein-related receptor with A-type repeats (SORLA, also known as LR11) is a type 1 membrane protein highly expressed in neurons of the cortex, hippocampus, and cerebellum.[1,2]

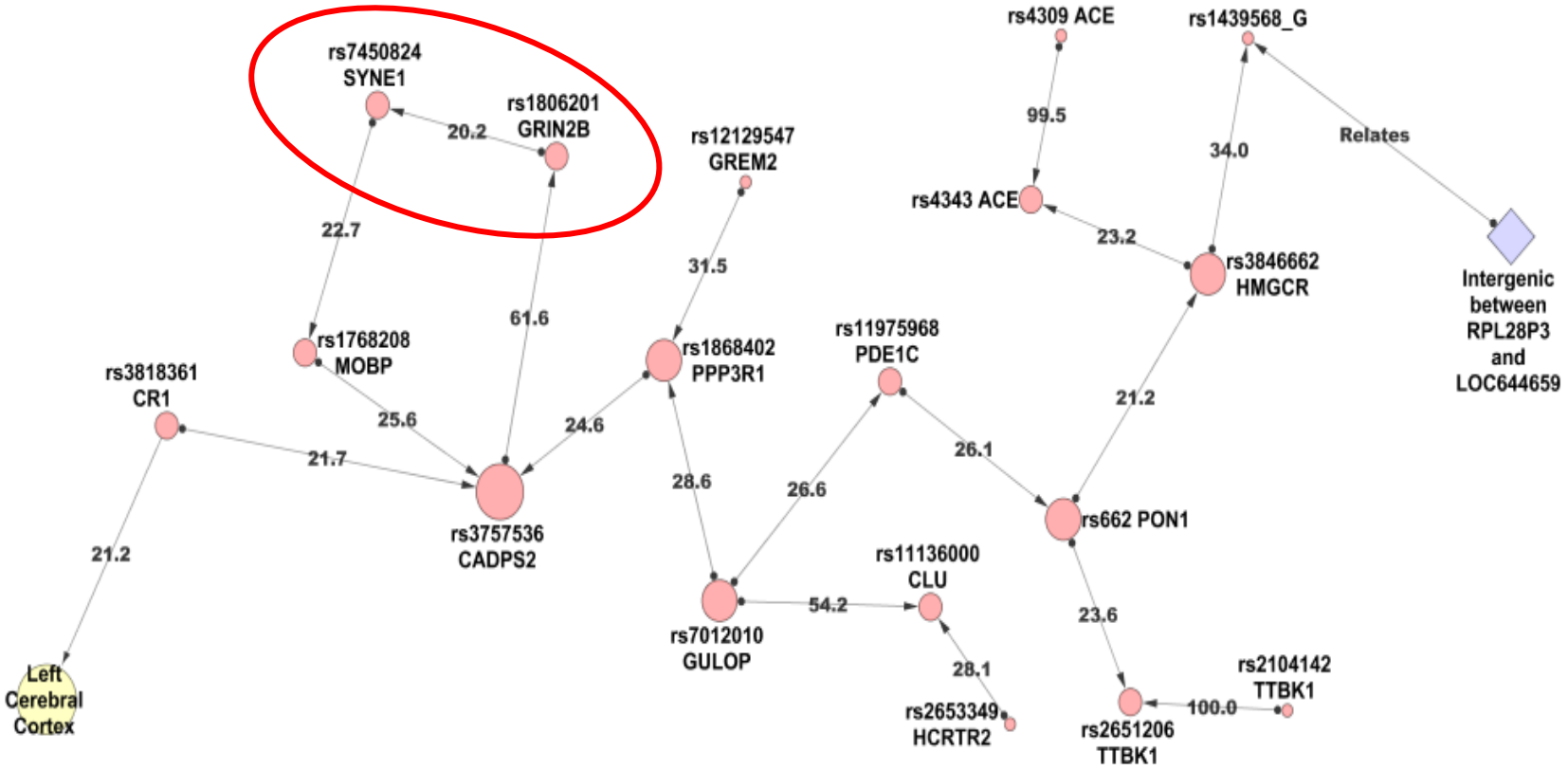
Genetic data and protein levels revealed that two SNPs in SORL1, rs2070045 and rs1699102, are associated with reduced SORLA expression levels in the brain

[*http://jamanetwork.com/journals/jamaneurology/fullarticle/1108012*]

We found that rs3818361 in *CR1* was associated with more rapid cognitive decline. *CR1* is a complement receptor expressed in cerebral cortex



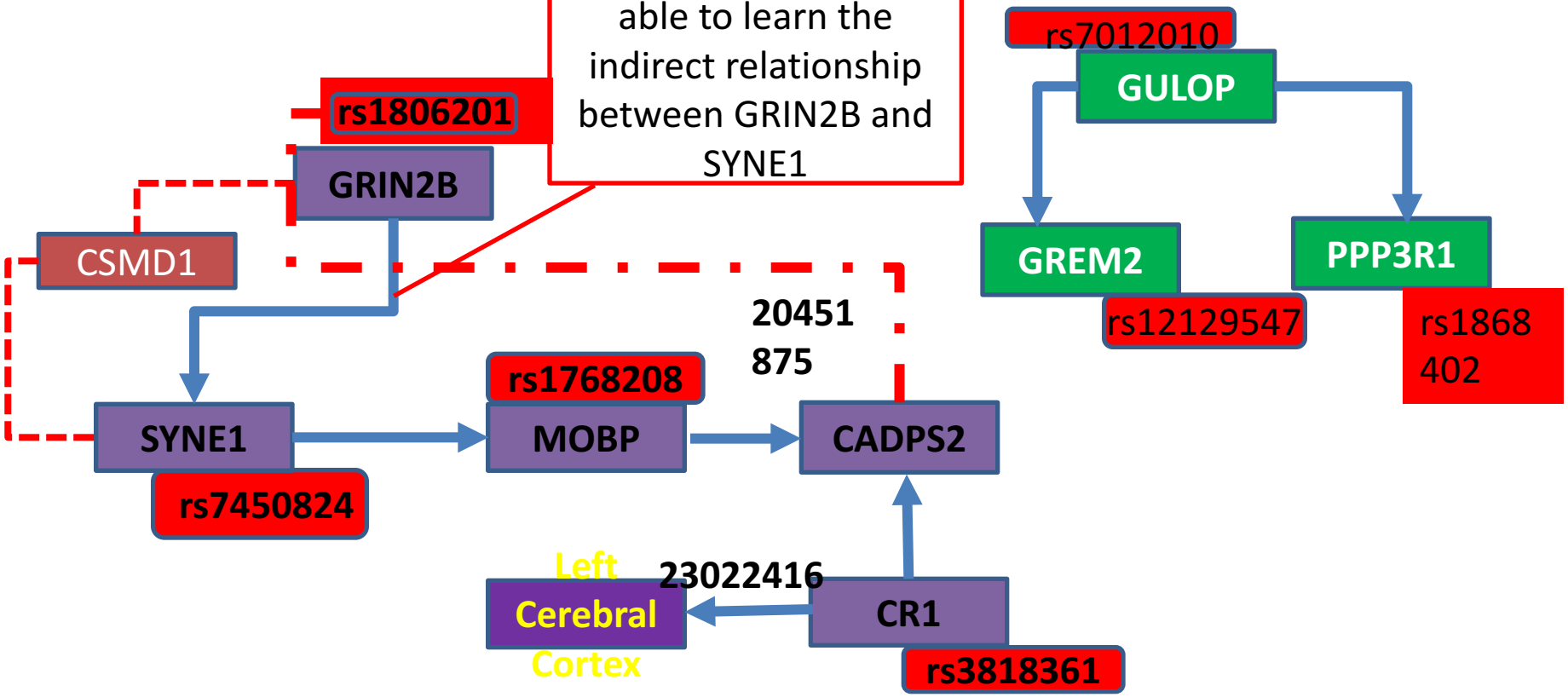
A big SNP-SNP interaction network is seen. CR1 gene related to SNP rs3818361 has some literature talking about cognitive decline.



A link between GRIN2B and SYNE1 is shown by the BN.

"Learning" indirect relationships from data

Bayesian network was able to learn the indirect relationship between GRIN2B and SYNE1



From literature we get to know that GRIN2B is connected to CSMD1; CSMD1 is regulating the expression of gene SYNE1 btw: This would be represented in a BEL model. Since we did not have any SNP related to CSMD1 in our data, therefore this link was generated by the BN but the indirect link between GRIN2B and SYNE1 was created.

Temporal and Spatial Representation of Simulated Patients: Virtual Dementia Cohort

Marc Jacobs
Sven Hodapp
Meemansa Sood

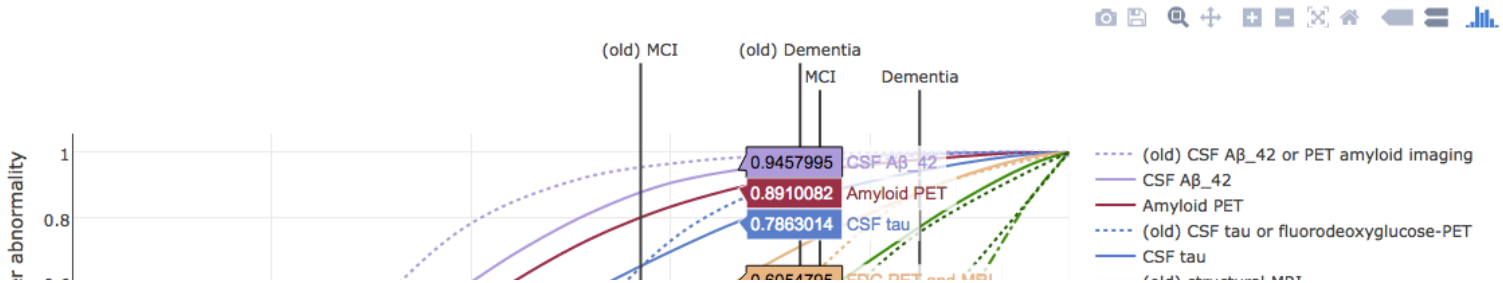
for the EPAD consortium

EPAD Longitudinal Study Viewer

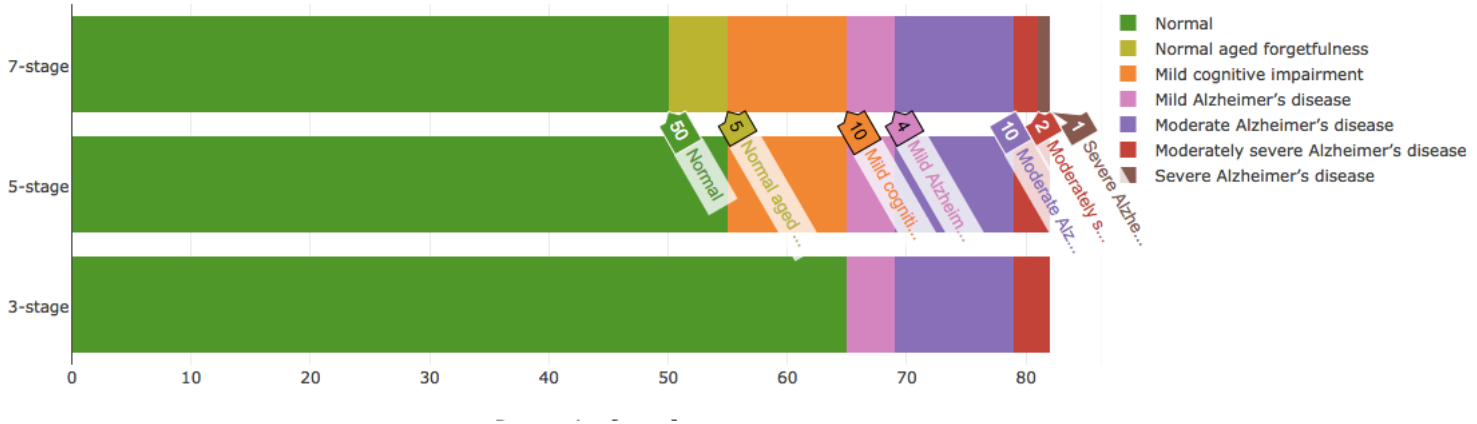
Fraunhofer SCAI

app/alzheimer-model

Hypothetical longitudinal standard model for Alzheimer's disease



Clinical stages of Alzheimer's disease



Referen

1. Jac
2. Jac
3. Wir
4. Hyr

Caption: Clinical stages of Alzheimer's disease

http://epad.scai.fraunhofer.de/app/alzheimer-model

EPAD
European Prevention of Alzheimer's Dementia Consortium

www.ep-ad.org

Extraction from Tables

Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study

	Healthy controls (n=145)	Mild cognitive impairment (n=36)	p value*	Alzheimer's disease (n=19)	p value*
Age, years	71·3 (7·1)	74·6 (6·5)	0·012	69·8 (9·4)	0·49
Male sex	74 (51%)	20 (56%)	0·71	10 (53%)	1·00
MMSE	28·9 (1·1)	27·3 (2·1)	<0·0001	22·0 (2·9)	<0·0001
CDR-SOB	0·06 (0·3)	1·03 (0·7)	<0·0001	3·84 (1·1)	<0·0001
Positive for APOE ε4	58 (40%)	20 (58%)	0·037	12 (63%)	0·047
Years of education	13·6 (3·7)	13·0 (3·8)	0·36	12·6 (3·8)	0·28
Episodic memory composite score	−0·23 (0·88)	−2·10 (0·91)	<0·0001	−3·21 (0·6)	<0·0001
Non-memory composite score	−0·15 (0·65)	−0·77 (0·80)	<0·0001	−2·46 (1·19)	<0·0001
Grey matter volume (cm^3)†	349 (15)	339 (16)	0·0012	326 (23)	0·0008
Hippocampal volume (cm^3)†	4·18 (0·30)	3·76 (0·60)	0·005	3·92 (0·37)	0·014
Amyloid β burden (SUVR)	1·38 (0·39)	1·94 (0·64)	<0·0001	2·27 (0·43)	<0·0001
High ^{11}C-PiB retention	38 (26)%	24 (67%)	<0·0001	18 (95%)	<0·0001

Data are mean (SD) or number (%) unless otherwise stated. MMSE=mini-mental state examination. CDR-SOB=clinical dementia rating scale sum of boxes. APOE=apolipoprotein E. SUVR=standard uptake value ratio. ^{11}C-PiB=Carbon-11-labelled Pittsburgh compound B. *Compared with healthy controls. †Grey matter and hippocampal volumes normalised to intracranial volume.

Table 1: **Characteristics of the study cohort**

Fraunhofer SCAI

https://www.ncbi.nlm.nih.gov/pubmed/23477989

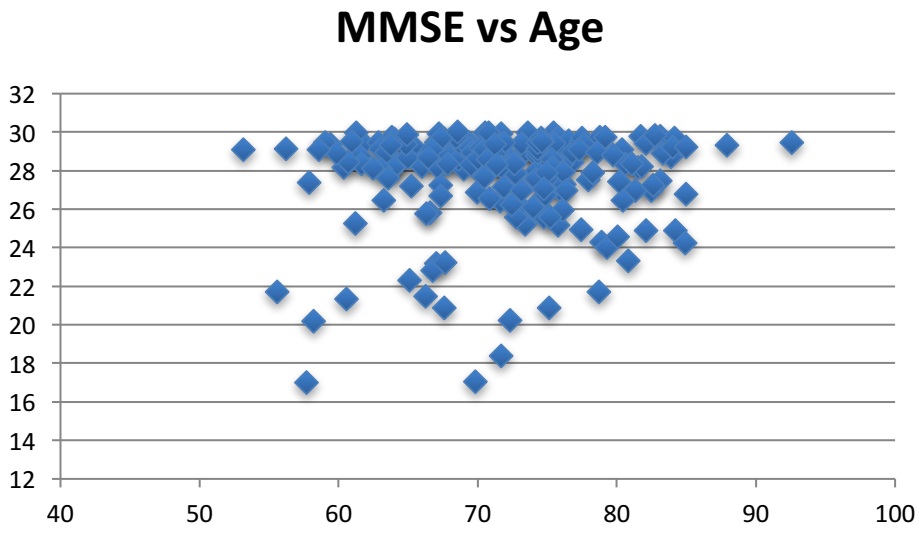
Generation of a Virtual Cohort

EPAD European Prevention of Alzheimer's Dementia Consortium

www.ep-ad.org

	Age	Male sex	MMSE	CDR-SOB	Positive for APOE ε4	Years of education	Episodic memory composite score	Non-memory composite score	Grey matter volume (cm3)†	Hippocampal volume (cm3)†	Amyloid β burden (SUVR)	High 11C-PiB retention	DX
1	75	M	26	0,009	1	9	0,532	-0,275	354,847	3,947	1,315	1	NL
2	72	M	29	-0,031	1	16	-0,111	-1,934	348,312	3,803	1,585	1	NL
3	82	M	27	0,246	1	8	-1,020	0,364	335,034	4,225	1,706	1	NL
4	64	M	30	-0,221	1	9	0,403	-0,212	351,737	4,381	1,112	1	NL
5	59	M	29	-0,825	1	9	-0,480	-0,517	355,043	4,123	1,888	1	NL
6	74	M	28	-0,104	1	20	-0,176	0,056	318,458	4,247	1,577	1	NL
7	64	M	28	-0,027	1	12	1,750	-0,506	358				
8	65	M	27	-0,239	1	12	0,207	-0,794	346				
9	74	M	29	-0,109	1	19	0,570	0,684	375				
10	73	M	29	0,171	1	14	0,431	-0,352	358				
11	82	M	30	0,373	1	13	0,985	-0,159	337				
12	67	M	29	0,600	1	14	0,167	0,855	345				
13	74	M	29	0,356	1	13	-0,520	-0,049	324				
14	70	M	27	0,043	1	17	-0,830	-0,645	339				
15	62	M	29	-0,039	1	5	1,828	-1,137	344				
16	75	M	29	-0,386	1	18	1,376	0,292	356				
17	72	M	30	0,194	1	18	0,394	-0,387	346				
18	61	M	30	0,183	1	11	-0,769	0,622	357				
19	69	M	29	0,087	1	12	-0,346	0,611	320				
20	67	M	30	0,332	1	11	-0,373	-0,603	384				
21	71	M	28	0,093	1	17	-0,650	-0,134	354				
22	75	M	30	0,419	1	19	1,035	0,440	342				
23	68	M	28	0,092	1	14	-1,389	-1,551	372				
24	69	M	29	0,033	1	13	-0,013	0,522	354				
25	71	M	30	-0,097	1	13	1,732	-0,092	344				

Sampling of distributions taken from the literature



Fraunhofer SCAI

Task: Correlating Biomarkers to Disease Stages

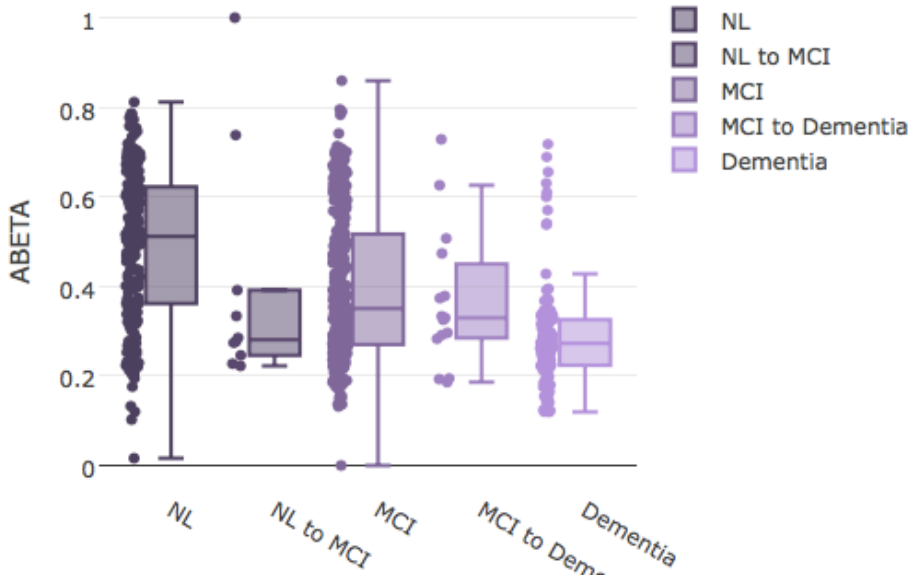
- **ADNI data**

Document Header (ISO 690 style)

Meemansa, Sven, Marc. *Fraunhofer SCAI: ADNI Plot Experiment 1* 2016 n/a.

https://api.scaiview.com/§§:header/adni.experiment1

Distributions taken from patient data



The Virtual Dementia Cohort

As never seen before:

- Here should have been the Virtual Dementia Cohort video -

The People and the Institutions behind the Project

AETIONOMY Partners

Fraunhofer SCAI

EBC European Brain Council

uni.lu UNIVERSITÄT LUXEMBURG

NEURORAD CENTRU DE RADIOLOGIE

Leibniz Universität Hannover

ICM Institut du Cerveau et de la Moelle épinière

UCL

PHARMACOIDEA

Erasmus MC

ucb

universitätsklinikumbonn

IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

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Boehringer Ingelheim