Considering a new paradigm for Alzheimer's disease research – a response

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A Human Pathways Approach to Disease Research: the AETIONOMY Project

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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

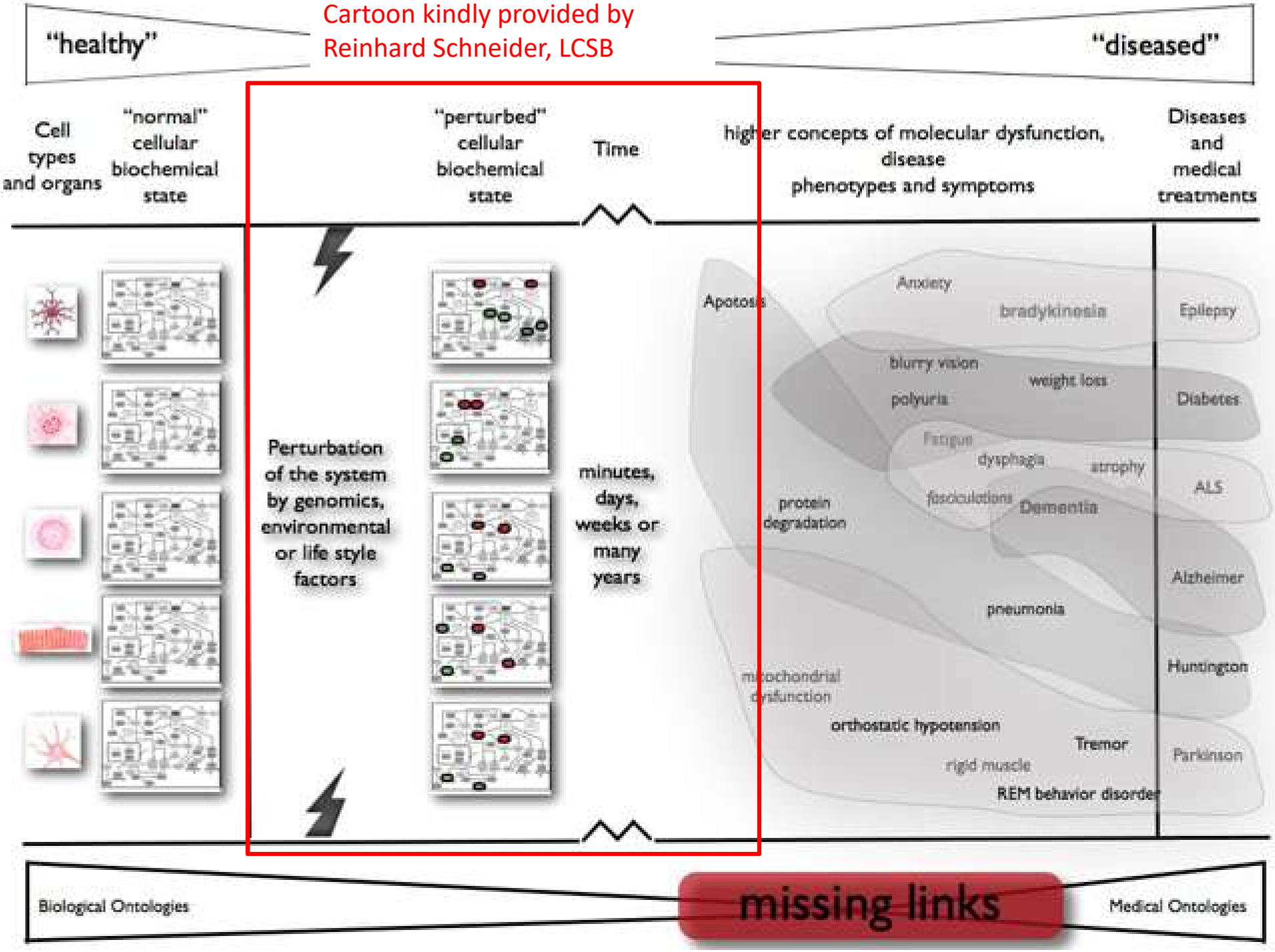
A coordinated effort to incorporate advances in the understanding of the molecular and genomic variations in common diseases, such as hypertension, into their diagnosis and treatment could transform drug development and medicine.

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 with the example of hypertension, the standard initial treatment is dietary changes and exercise, and if these do not lower blood pressure sufficiently, pharmacotherapy will usually be initiated with thiazide diuretics.

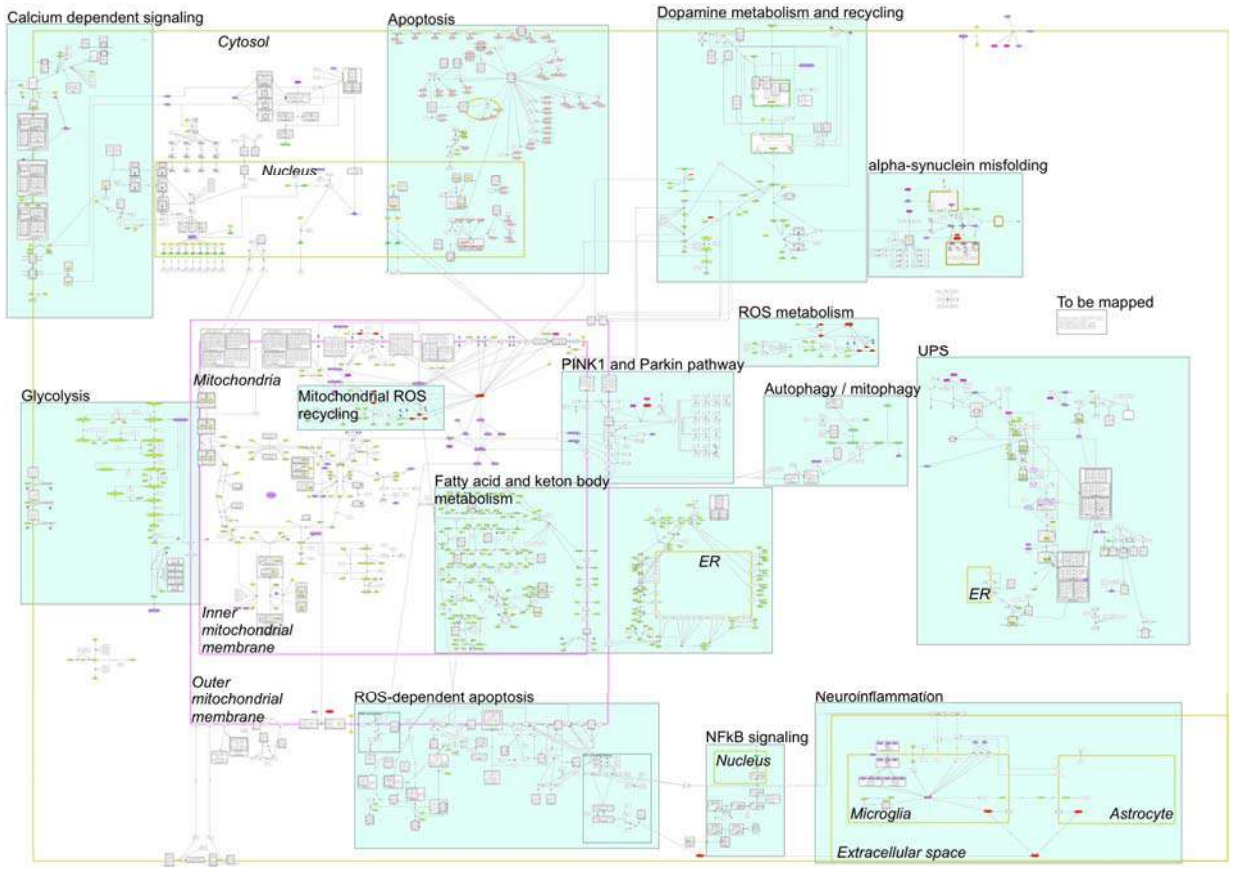
based on the presence of a shared mutation and/or a deregulated pathway, rather than on tumour location, has not yet been initiated to our knowledge, but is an approach that regulatory agencies may be comfortable with in the future.

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 recent years. Indeed, if the pathway that is being targeted is not responsible for disease in an unknown proportion of patients enrolled in the trial of such a therapy, potentially effective drugs may be mistakenly abandoned. In

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


"healthy"
Cartoon kindly provided by
Reinhard Schneider, LCSB
"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
ALS
fasciculations
protein degradation
Dementia
Alzheimer
pneumonia
Huntington
mitochondrial dysfunction
orthostatic hypotension
Tremor
Parkinson
rigid muscle
REM behavior disorder
Biological Ontologies
missing links
Medical Ontologies

Preparatory Work: The Parkinson´s Disease Map

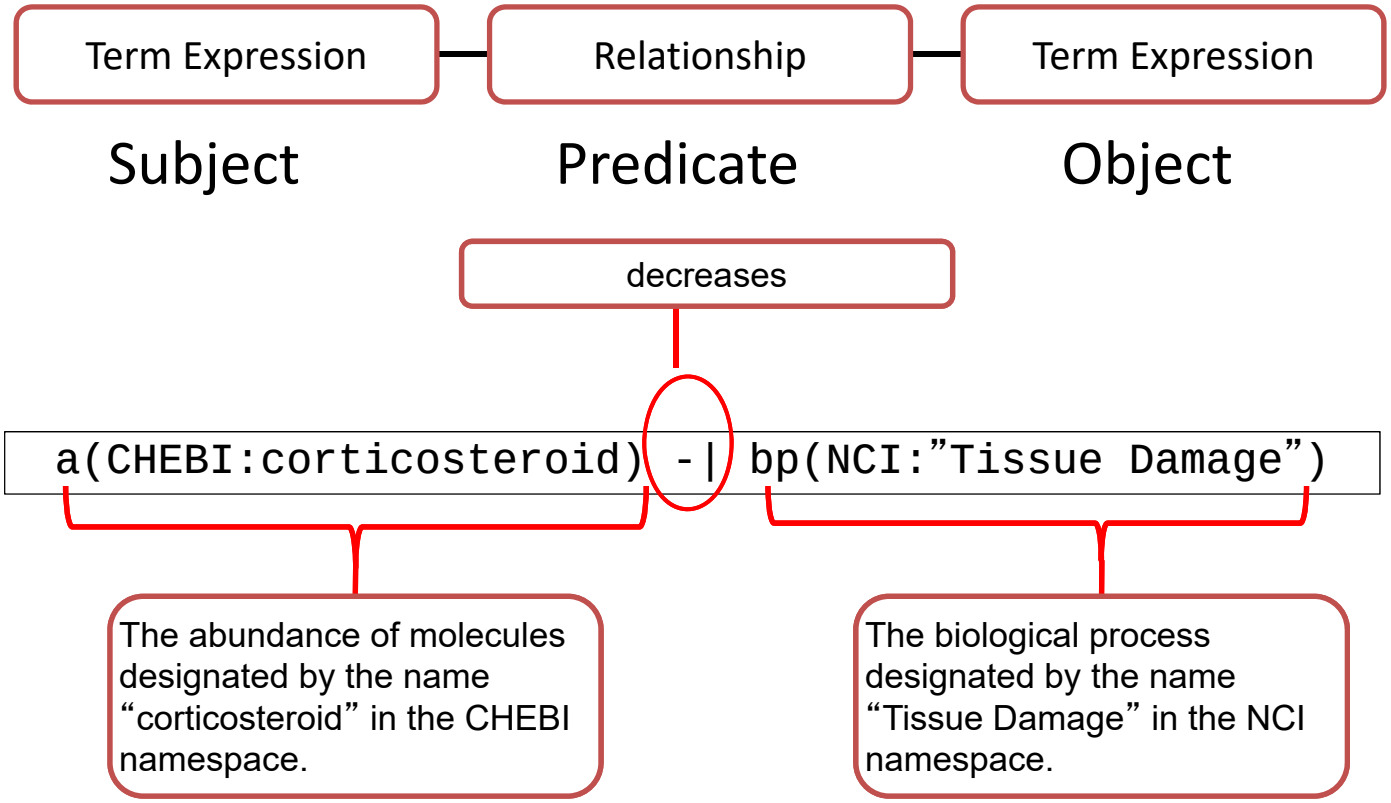


PD Disease Map generated in CellDesigner

Contributed by AETIONOMY partner LCSB (Luxembourg)

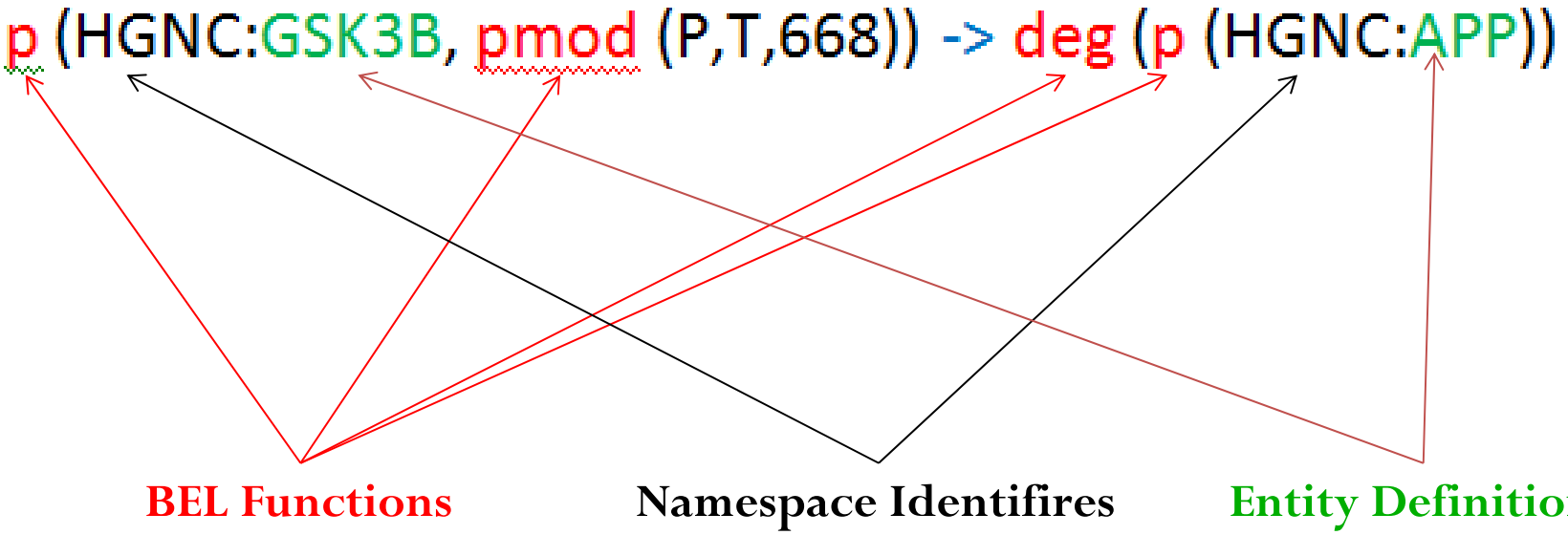
Fujita, et al., (2014). Integrating pathways of Parkinson's disease in a molecular interaction map. *Molecular neurobiology*, *49*(1), 88-102.

Capturing Knowledge on Causes and Effects: OpenBEL

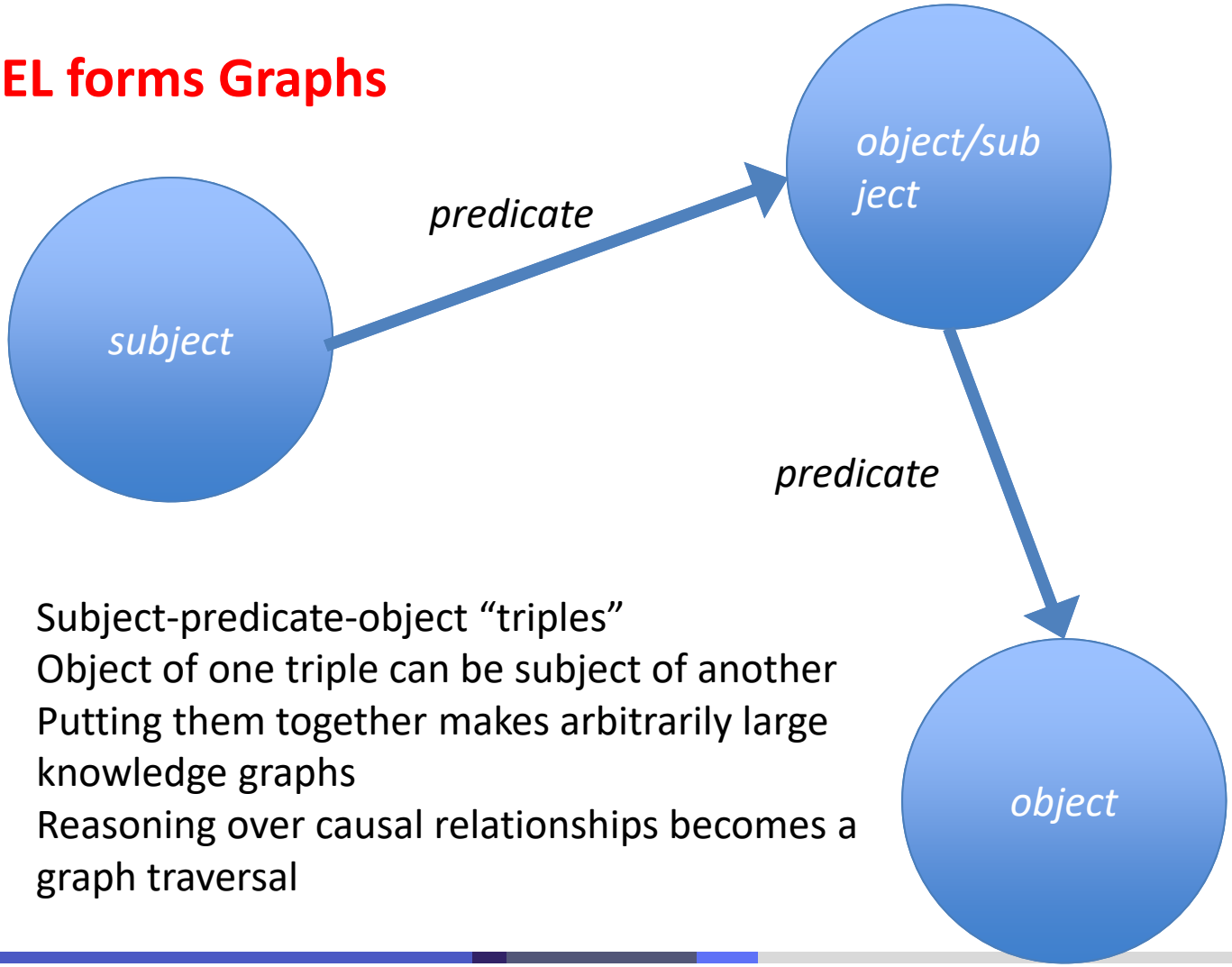


OpenBEL: Capturing of Knowledge and "encoding" of data

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

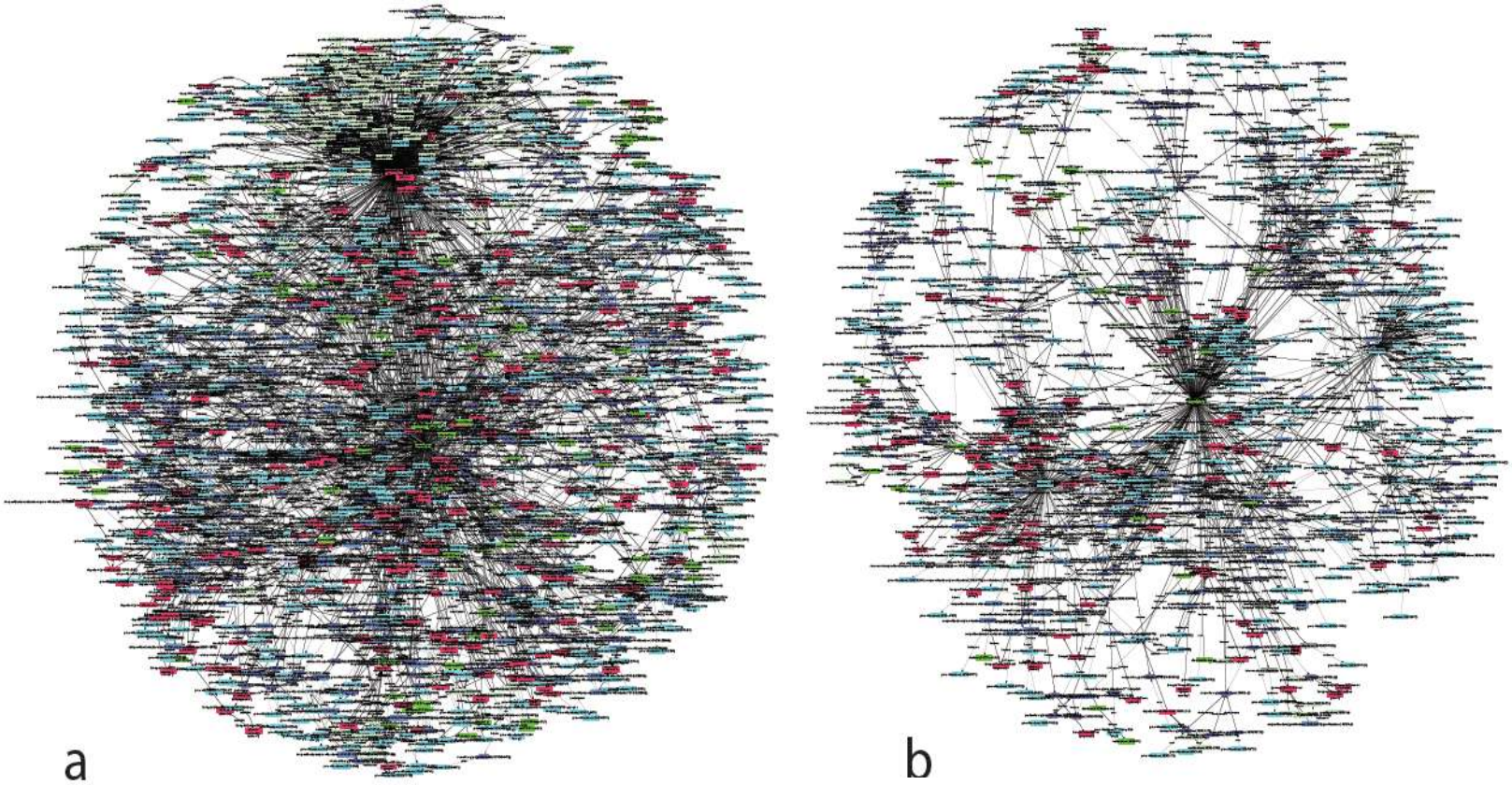


BEL forms Graphs



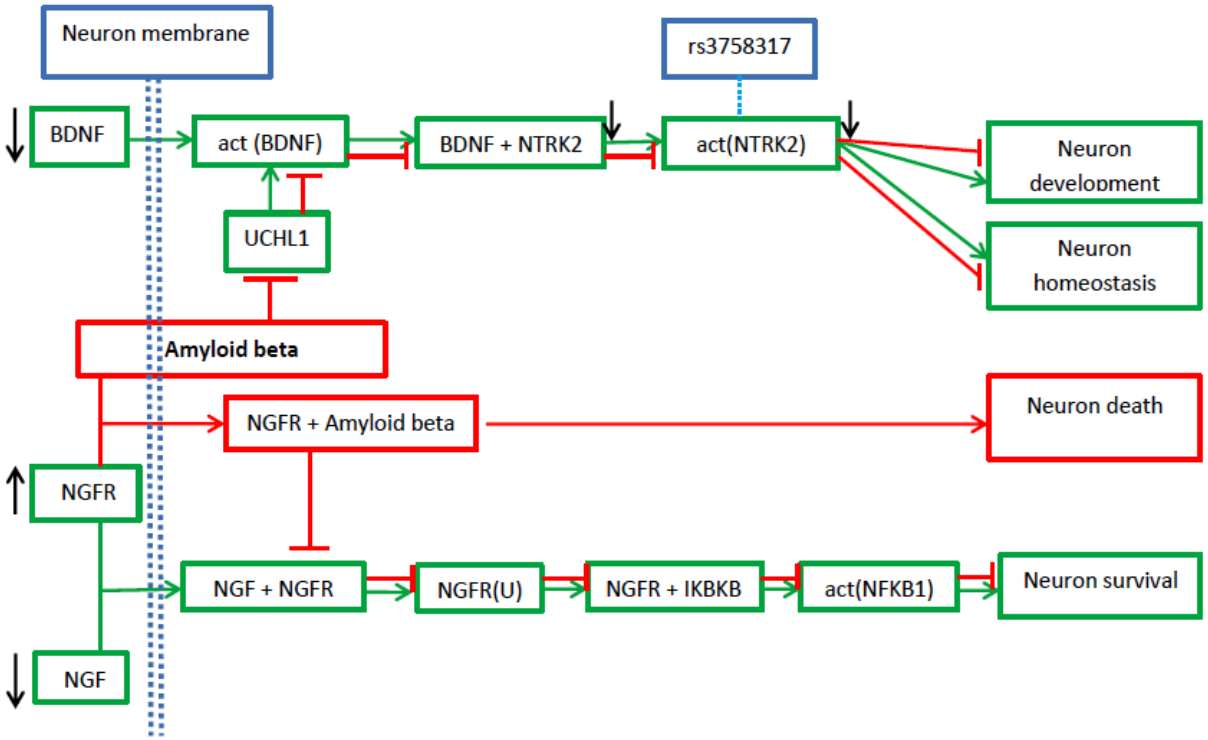
- Subject-predicate-object “triples”
- Object of one triple can be subject of another
- Putting them together makes arbitrarily large knowledge graphs
- Reasoning over causal relationships becomes a graph traversal

Preparatory Work: Causal Relationship Models for Alzheimer´s



Kodamullil, et al. *Alzheimer's & Dementia*, 2015

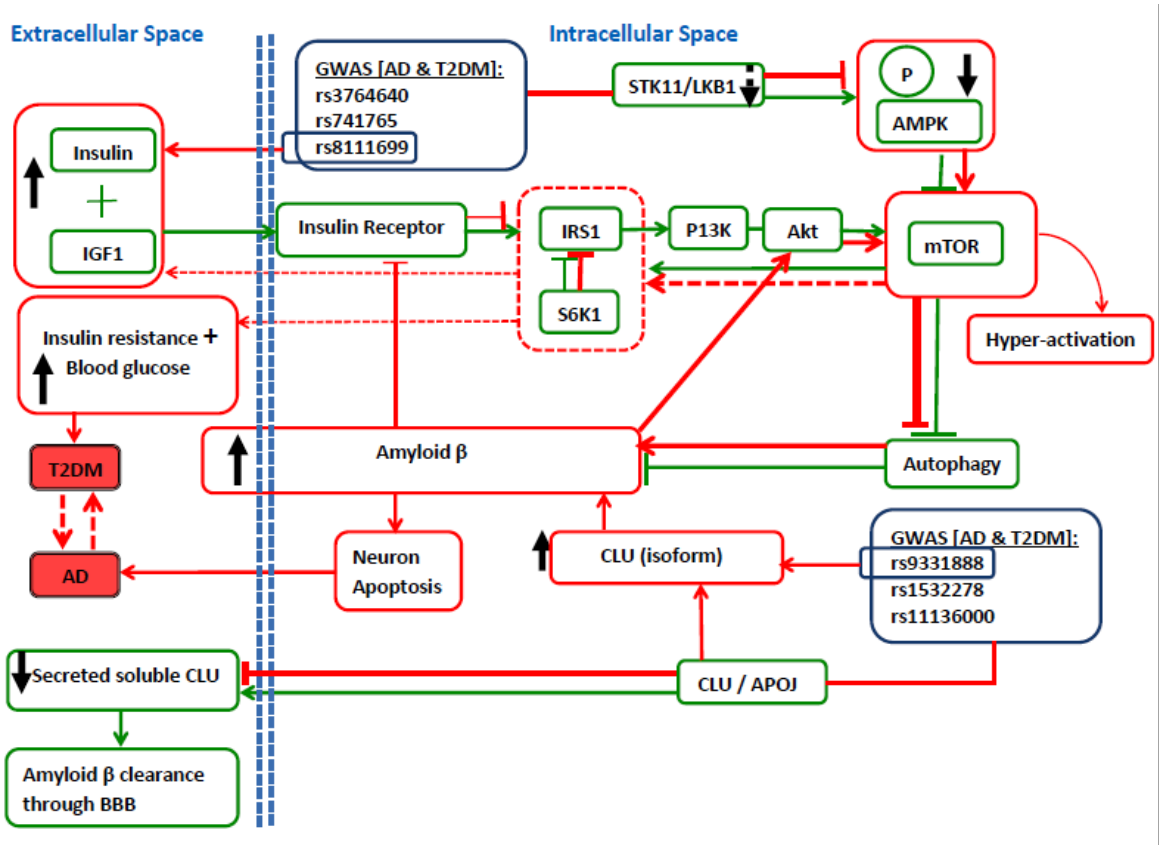
OpenBEL – based Mechanism-Identification



Taken from: Kodamullil et al., Alzheimer´s & Dementia, 2015

OpenBEL model-model comparison results in the first mechanism-hypothesis generated in AETIONOMY: a possible involvement of the NGF-NGFR-BDNF pathway in early decision-making of the neuron on Neuron Survival vs. Apoptosis. **Note the integration of genetic variance information in OpenBEL**

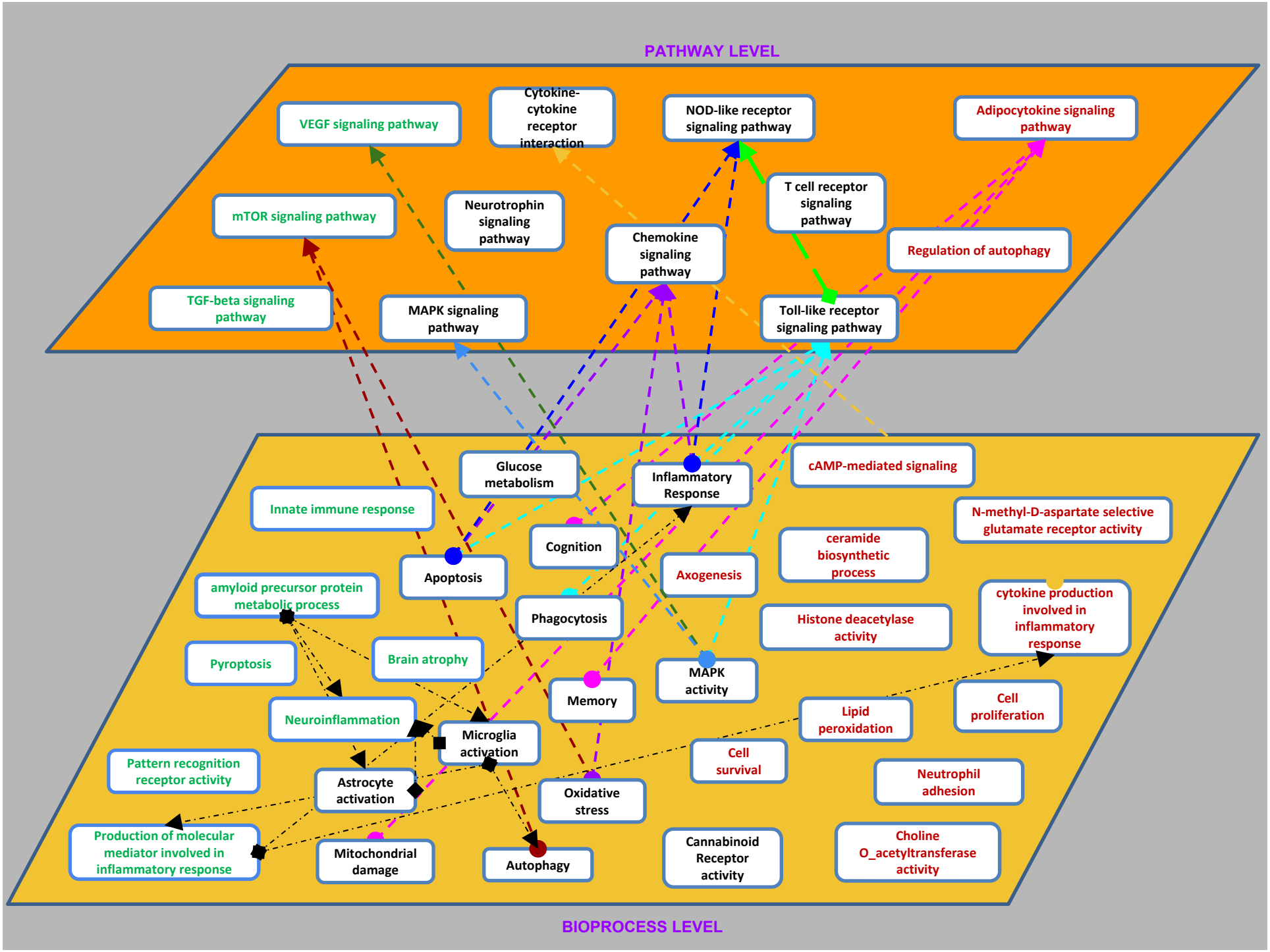
OpenBEL – based Mechanism-Identification

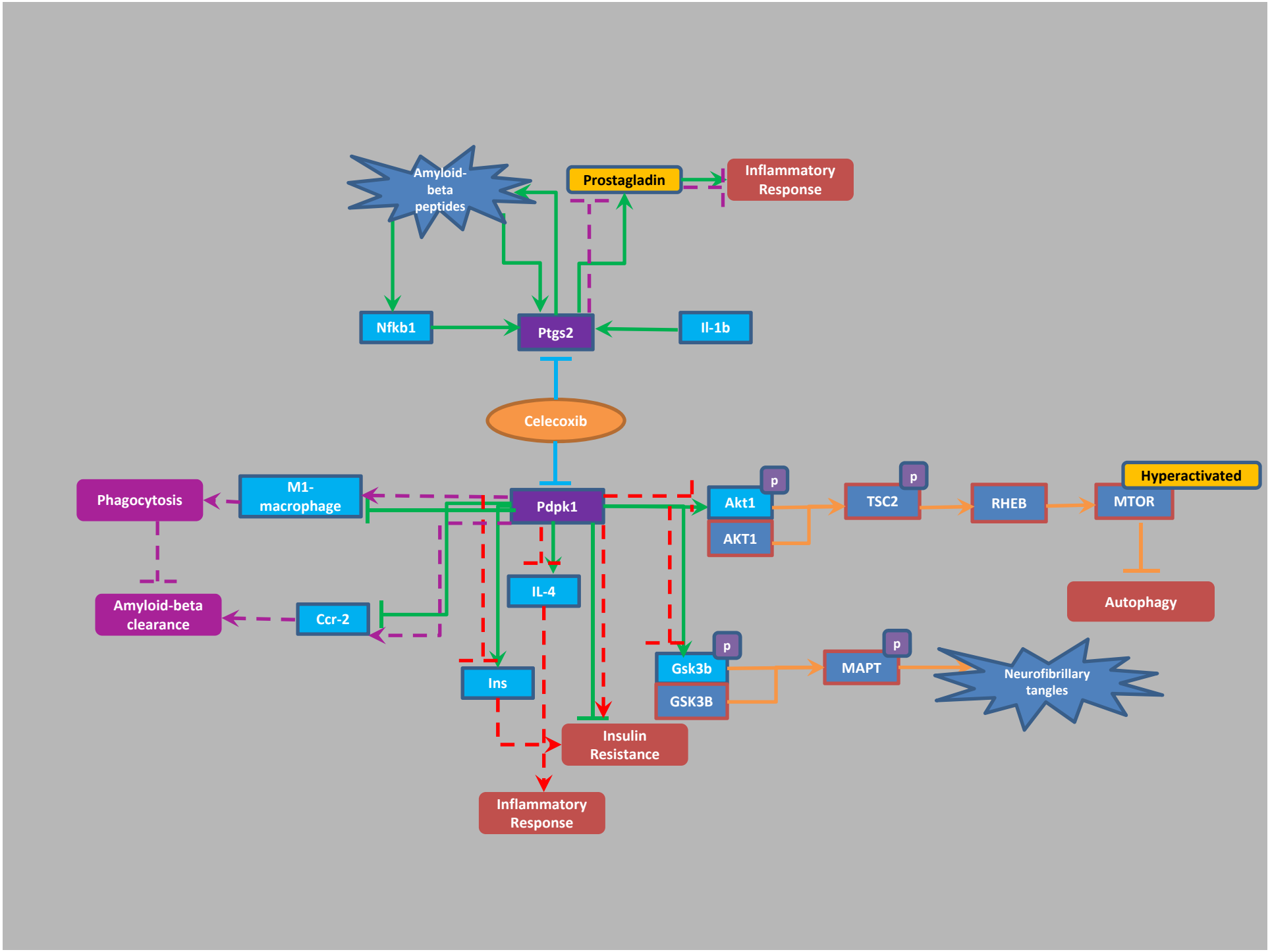


Mining of co-morbidity information results in the second mechanism-hypothesis generated in AETIONOMY: a possible link between insulin receptor pathway, mTOR-induced autophagy and APP peptide clearance

Supportive evidence from SNPs that are shared by AD and T2DM

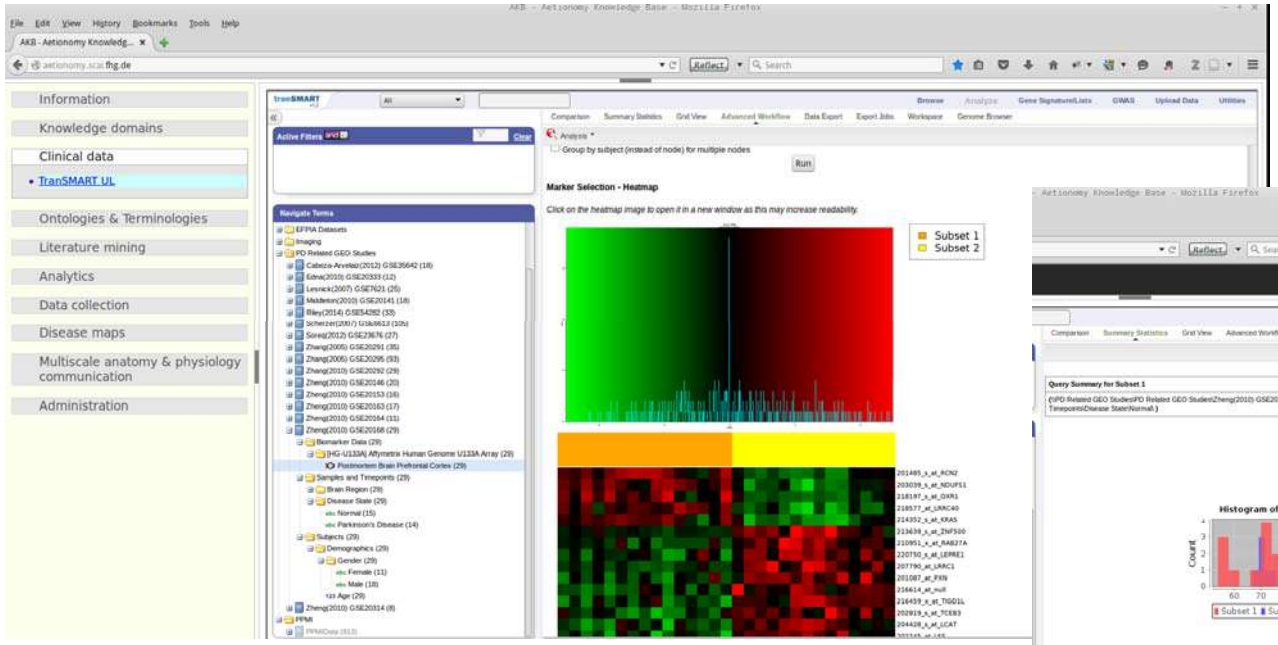
Systematic Comparison of shared mechanisms between mouse and man


PATHWAY LEVEL
VEGF signaling pathway
Cytokine-cytokine receptor interaction
NOD-like receptor signaling pathway
Adipocytokine signaling pathway
mTOR signaling pathway
Neurotrophin signaling pathway
T cell receptor signaling pathway
Chemokine signaling pathway
Regulation of autophagy
TGF-beta signaling pathway
MAPK signaling pathway
Toll-like receptor signaling pathway
Glucose metabolism
Inflammatory Response
cAMP-mediated signaling
Innate immune response
N-methyl-D-aspartate selective glutamate receptor activity
Cognition
ceramide biosynthetic process
Apoptosis
Axogenesis
amyloid precursor protein metabolic process
Phagocytosis
Histone deacetylase activity
cytokine production involved in inflammatory response
Pyroptosis
Brain atrophy
MAPK activity
Memory
Cell proliferation
Neuroinflammation
Lipid peroxidation
Microglia activation
Pattern recognition receptor activity
Cell survival
Astrocyte activation
Neutrophil adhesion
Oxidative stress
Production of molecular mediator involved in inflammatory response
Mitochondrial damage
Autophagy
Cannabinoid Receptor activity
Choline O_acetyltransferase activity
BIOPROCESS LEVEL


Amyloid-beta peptides
Prostagladin
Inflammatory Response
Nfkb1
Ptgs2
Il-1b
Celecoxib
Phagocytosis
M1-macrophage
Pdpk1
Akt1
p
AKT1
TSC2
p
RHEB
Hyperactivated
MTOR
Autophagy
IL-4
Amyloid-beta clearance
Ccr-2
Ins
Gsk3b
p
GSK3B
MAPT
p
Neurofibrillary tangles
Insulin Resistance
Inflammatory Response

Where all this takes place : The AETIONOMY knowledge base

The AETIONOMY Knowledge Base: Organising Data, Models and Knowledge to make them amenable for modelling and mining

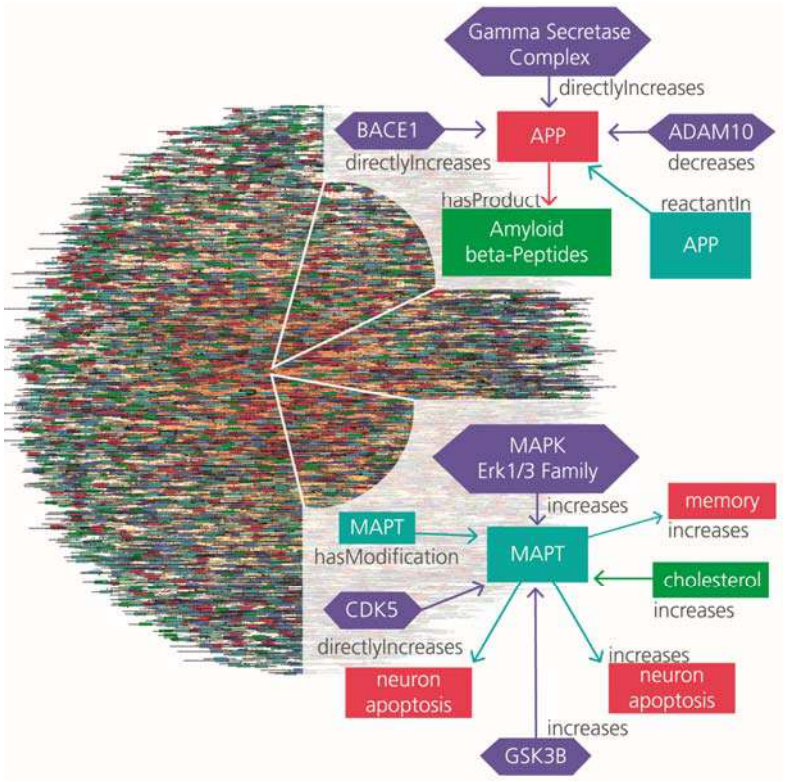


clinical trial data and clinical genomics data

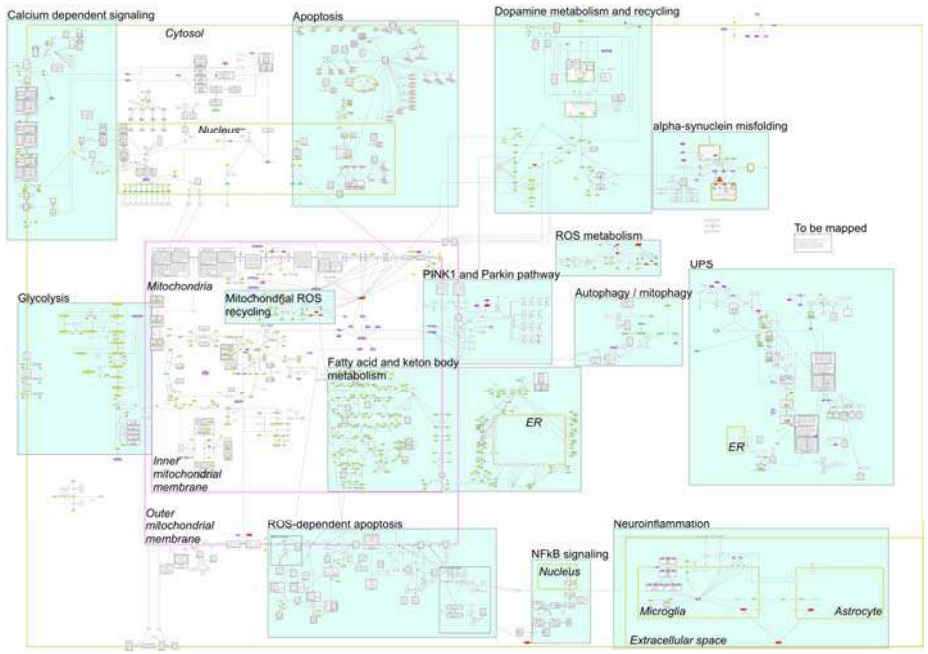
In the tranSMART component

ucb Fraunhofer SCAI efpia imi innovative medicines initiative AETIONOMY

The AETIONOMY Knowledge Base: Model Store supports querying



OpenBEL model for Alzheimer´s Disease



CellDesigner model for Parkinson´s Disease

The AETIONOMY Knowledge Base: Semantic Framework

- Parkinsonism
  - 'Clinical aspects of Parkinson disease'
  - 'Etiology of Parkinson disease'
  - 'Familial neurodegenerative disease'
  - 'Idiopathic Parkinson disease'
  - 'Model of Parkinson disease'
  - 'Neuropathology of Parkinson disease'
  - 'Parkinson-Plus syndrome'
    - Corticobasal_degeneration
    - Dementia_with_pallido-ponto-nigral_degeneration
    - 'Frontotemporal dementia parkinsonism'
    - 'Guamanian parkinsonism-dementia-ALS'
    - 'Lewy body dementia'
    - 'Multiple system atrophy'
    - 'Pick's disease'
    - 'Progressive pallidal atrophy'
    - Progressive_supranuclear_palsy
  - Primary_parkinsonism
    - Early-onset_Parkinson_s_disease_
    - Inherited_Parkinson_s_disease
    - Juvenile_Parkinson_s_disease
    - Late-onset_Parkinson_s_disease
    - Tremor-predominant_Parkinson_s_disease
  - 'Secondary parkinsonism'
    - 'Acquired metabolic parkinsonism'
    - Drug-induced_parkinsonism
    - 'Hemiatrophy-hemiparkinsonism syndrome'
    - Hydrocephalus
    - Machado-Joseph_disease
    - Postencephalic_parkinsonism
    - 'Posttraumatic parkinsonism'
    - Rapid-onset_dystonia-parkinsonism
    - 'Structural lesion-induced parkinsonism'
    - Syphilitic_parkinsonism
    - 'Toxin-induced parkinsonism'
    - Vascular_parkinsonism

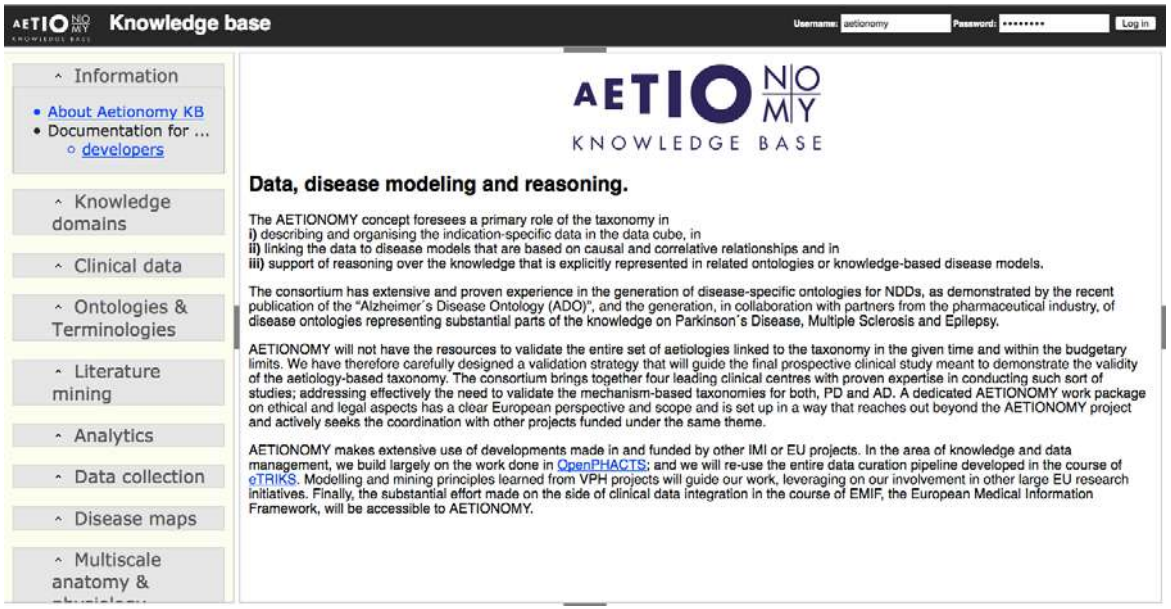
Disease-specific ontologies for PD, AD, and MS

- 'Clinical trial study'
  - 'Study type'
    - 'Analytical study'
    - 'Descriptive study'
    - 'Longitudinal study'
      - 'Hybrid design'
      - 'Prospective study'
        - 'Clinical trial'
          - 'Adverse event'
          - 'Clinical trial methodology'
          - 'Clinical trial outcome'
            - 'Biological outcome'
            - 'Cognitive outcome'
            - 'Disease outcome'
            - 'Molecular outcome'
            - 'Physical outcome'
          - 'Clinical trial type'
            - 'Active control trial'
            - 'Bioavailability trial'
            - 'Bioequivalence trial'
            - 'Combination trial'
            - 'Community trial'
            - 'Dose-response trial'
            - 'Explanatory trial'
            - 'Multicenter trial '
            - 'N-of-1 clinical trial'
            - 'Parallel trial'
            - 'Sequential trial'
            - 'Superiority trial'
            - 'Unicenter trial'
          - 'Conduct of the study'
          - 'Phases of clinical trial'
          - 'Structure of clinical trial'
        - 'Prospective observational cohort'
      - 'Retrospective study'

NDD Clinical Trial Ontology

The AETIONOMY Knowledge Base

- Freely available for everybody
- http://aetionomy.scai.fraunhofer.de/



Why do we need model-driven mining?

Why “model-driven mining”?

- Enhanced data mining and data interpretation capabilities
- Establishing a “computable knowledge layer” representing indications (diseases, syndromes, any sort of pathobiology)
- Reasoning over functional context (e.g. assessment of biological impact of SNPs or mutations in a mechanistic context)
- MSigDB is an example for functional context represented in GO or KEGG or signatures
- Advanced model-validation algorithms such as “reverse causal reasoning” allow to test for concordance between knowledge and data

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