

Advancing Alzheimer Research through Collaboration: The AETIONOMY Project

Martin Hofmann-Apitius

European Parliament

November, 2016



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.





Treating Patients
According to the
Disease Mechanism –
a revolutionary concept!

“healthy”

“diseased”

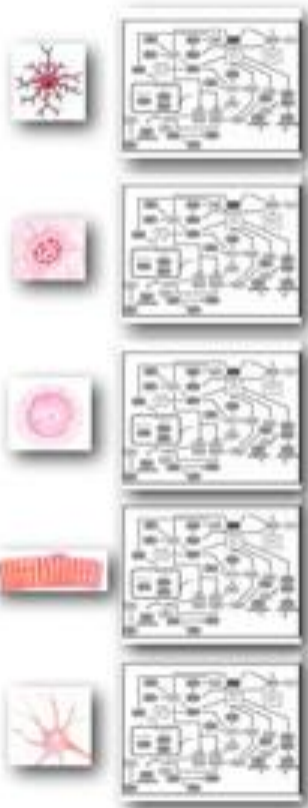
Cell types and organs
“normal” cellular biochemical state

“perturbed” cellular biochemical state

Time

higher concepts of molecular dysfunction, disease phenotypes and symptoms

Diseases and medical treatments



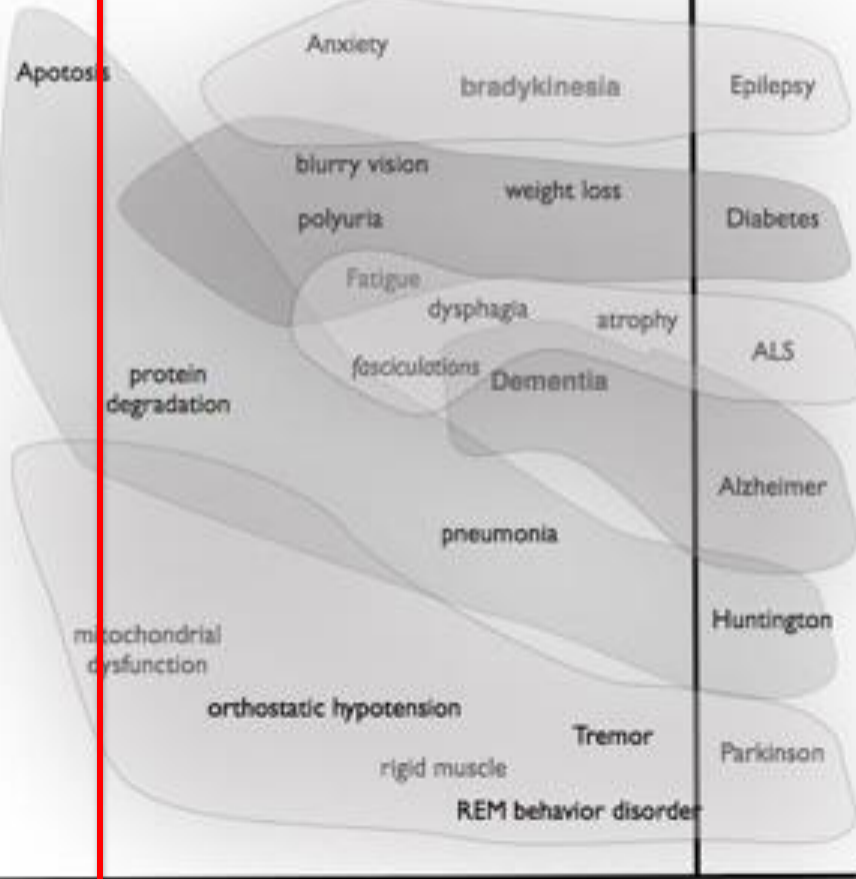
⚡

Perturbation of the system by genomics, environmental or life style factors

⚡



minutes, days, weeks or many years



Biological Ontologies

missing links

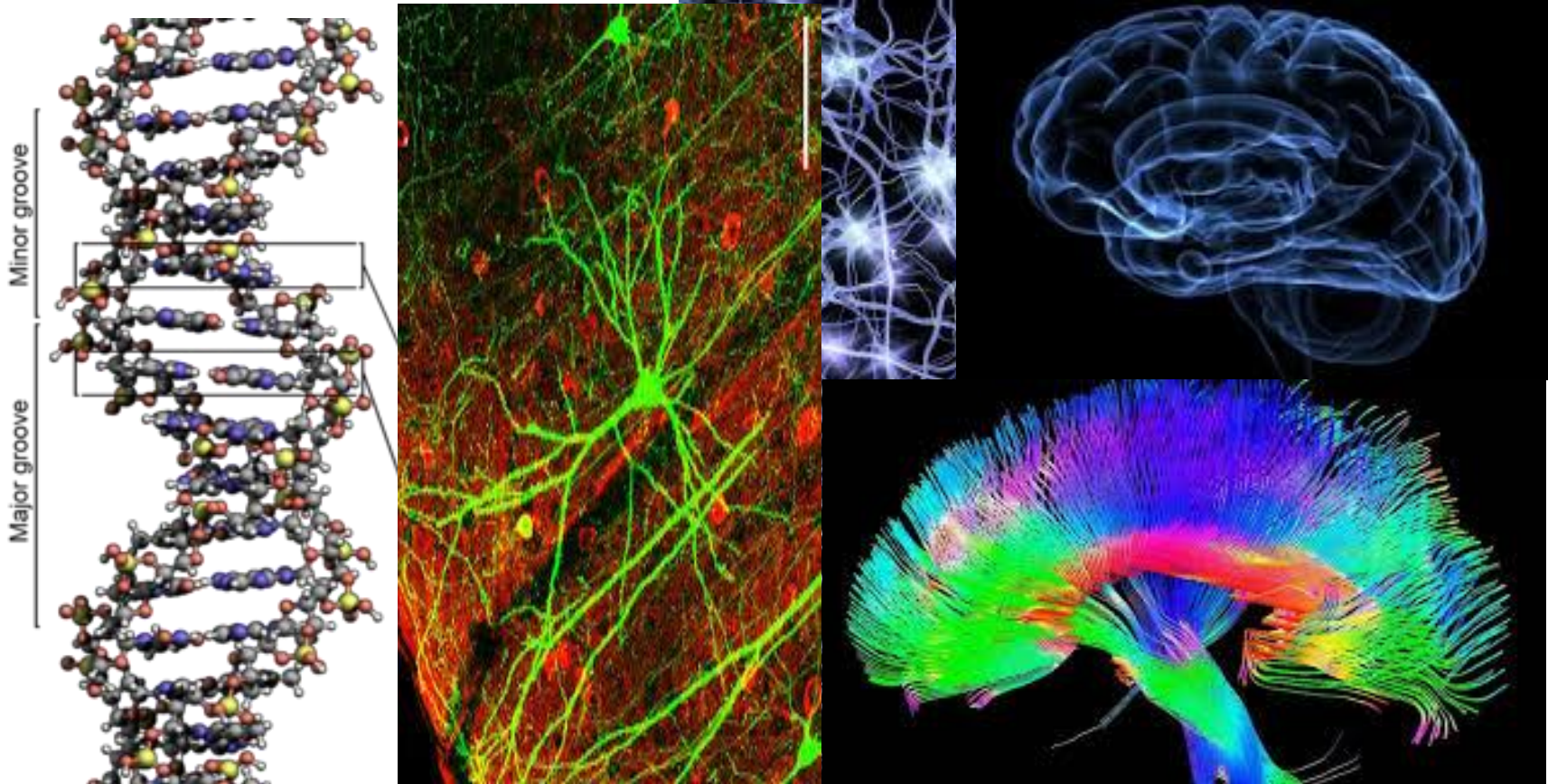
Medical Ontologies



Human Beings are Multi-Dimensional

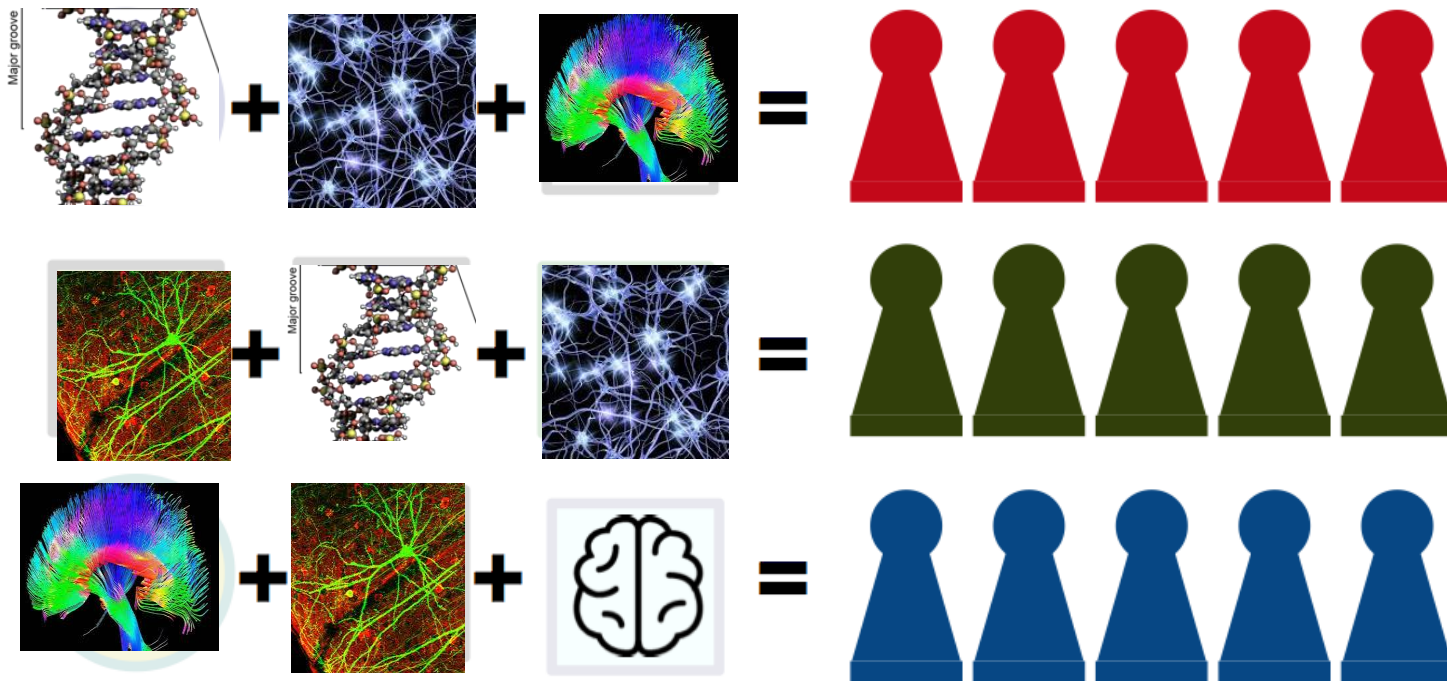


Genes, Brain Cells, Neuro-Imaging, Brain Connectivity ...



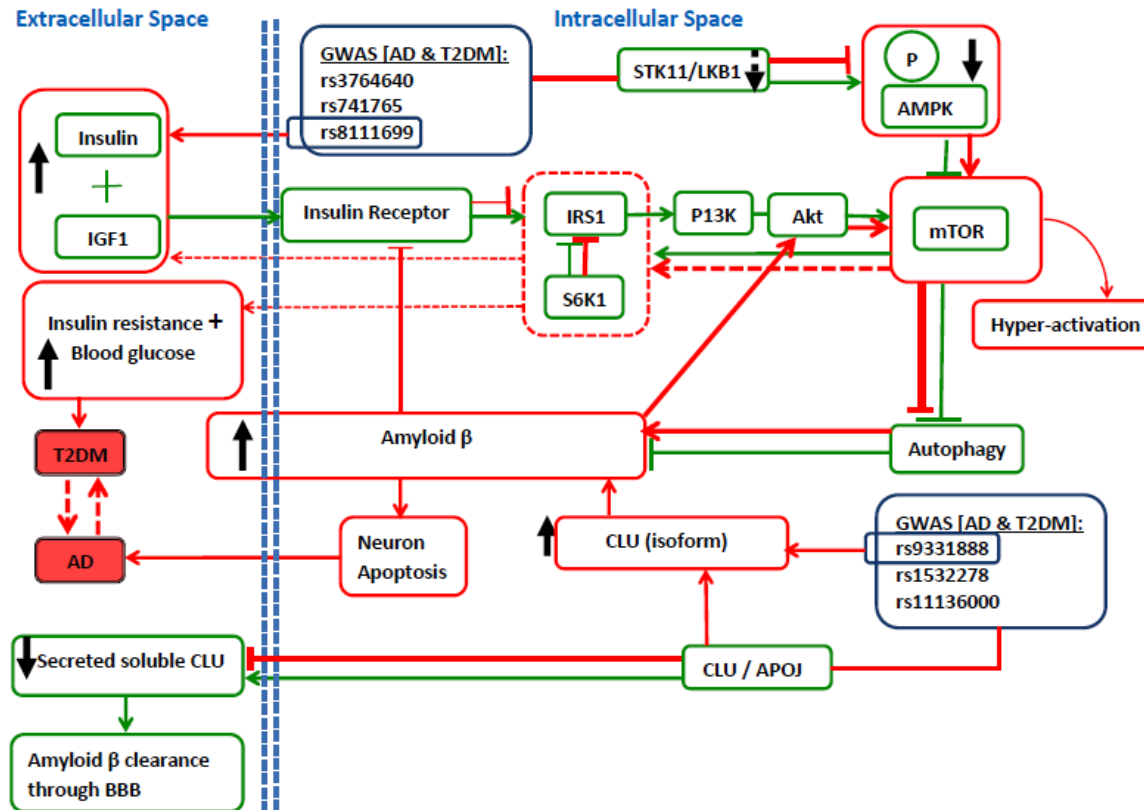


Mechanisms, measurable features and stratification





Mechanism linking Insulin-Signalling and Amyloid Clearance



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



Mapping Pharma R&D Investment to Alzheimer Mechanisms

Target Type	Computable Mechanism	Cartoon Representation	Compounds	Cost in TCU
Amyloid Cascade			RG7129, LY2886721, BI 1181181, AN-1792, Bapineuzumab, PF-04360365, Vanutide cridifigar, Semagacestat, Avagacestat	~8 TCU
Tauopathy			Rember TM, Epothilone D, AN-1792, Bapineuzumab, PF-04360365, Vanutide cridifigar, Tideglusib	~2 TCU
Cholinergic Mechanism			Physostigmine Salicylate, Mefenolate, Linopirdine, Eptastigmine, AF 102B, MEM 1003, Varenicline, ABT-089, Nefiracetam, AZD1446, ABT 418, Estrogen, Acetyl-L-carnitine HCl, SB 202026, LU25-109, Milameline, LU25-109, AF 102B	~11 TCU
Neuroinflammation			Ibuprofen, Lornoxicam, Naproxen, Celecoxib, Rofecoxib, Rosiglitazone, Rofecoxib	~10 TCU

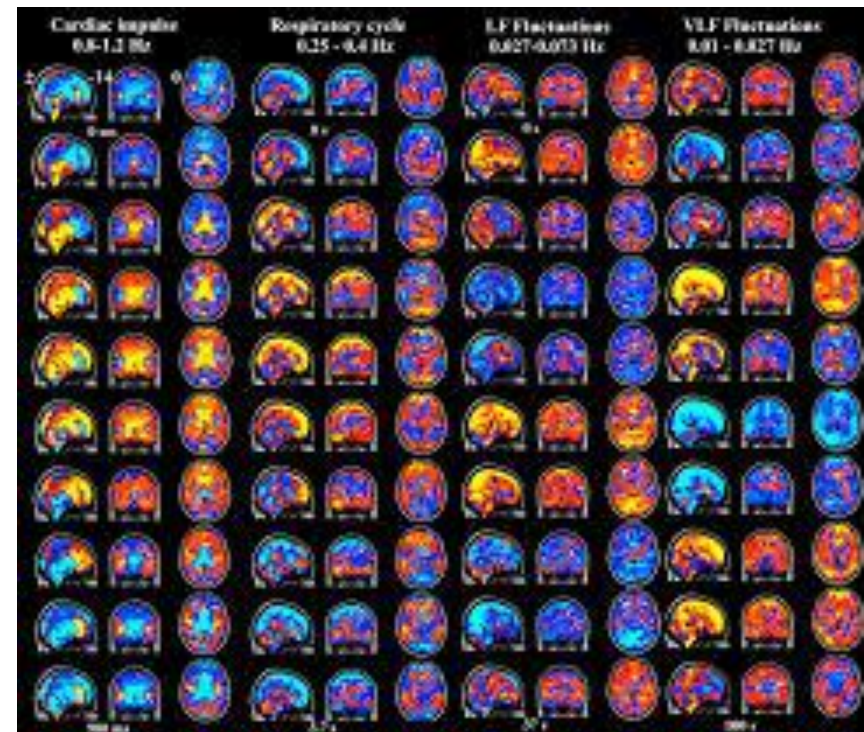
Pharmaceutical industry targets only 4 out of 121 mechanisms underlying Alzheimer's Disease

Need for Collaboration across Disciplines

- **Computer Scientists to collaborate with Clinicians**
- **Molecular Biologists to collaborate with Imaging Specialists**
- **Experts in Artificial Intelligence to collaborate with Experts in Cognition Testing**
- **All listening to patients advocates**
- **All collaborating with Legal and Ethical Experts**

The Virtual Dementia Cohort

- **Simulated Dementia Patients**
 - **No Patient Data Privacy compromised**
 - **Freedom of experimentation**
 - **Approximation to reality**
 - **No problem with statistical power**
-





AETIONOMY Partners



Institut D'Investigacions Biomèdiques August Pi I Sunyer

