

A network pharmacology approach to novel therapeutic strategies



INSTITUTE
FOR RESEARCH
IN BIOMEDICINE



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Framàcia UB, May 2014



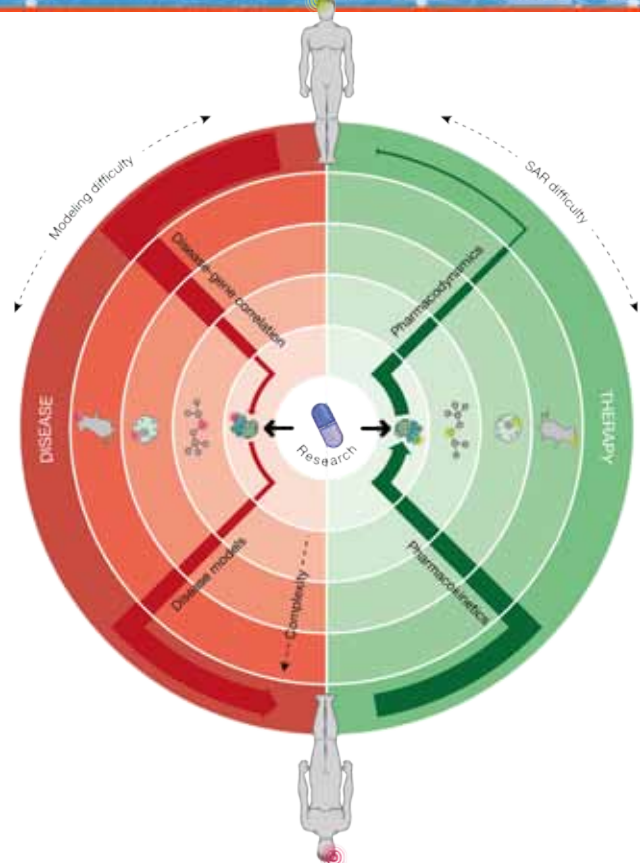
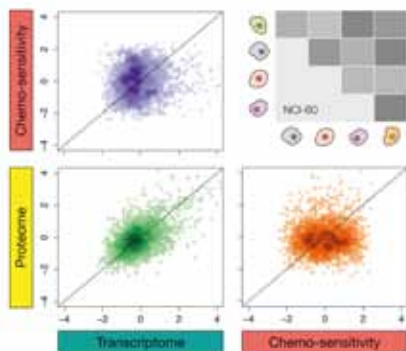
Human biology is a complex system



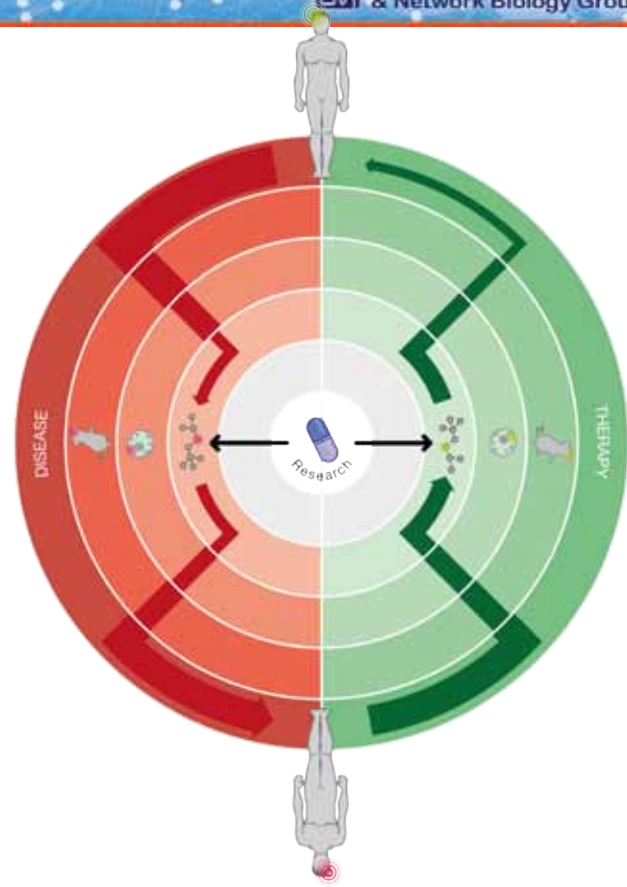
For every complex problem there is a solution that is simple, neat and wrong (HL Mencken).

The problem

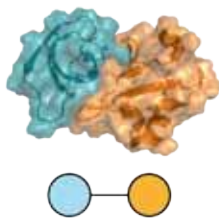
- High attrition rates in drug discovery.
- Complex diseases are difficult to address.
- Challenging drug side effect anticipation.
- Public and private research work separately.



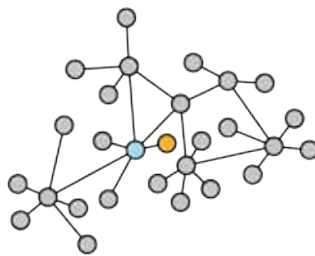
Targeting networks



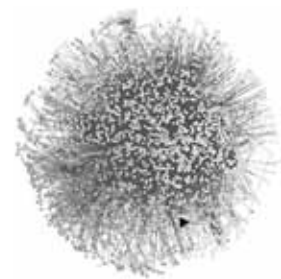
Protein networks



Protein—Protein Interaction



Pathways / Functional Modules



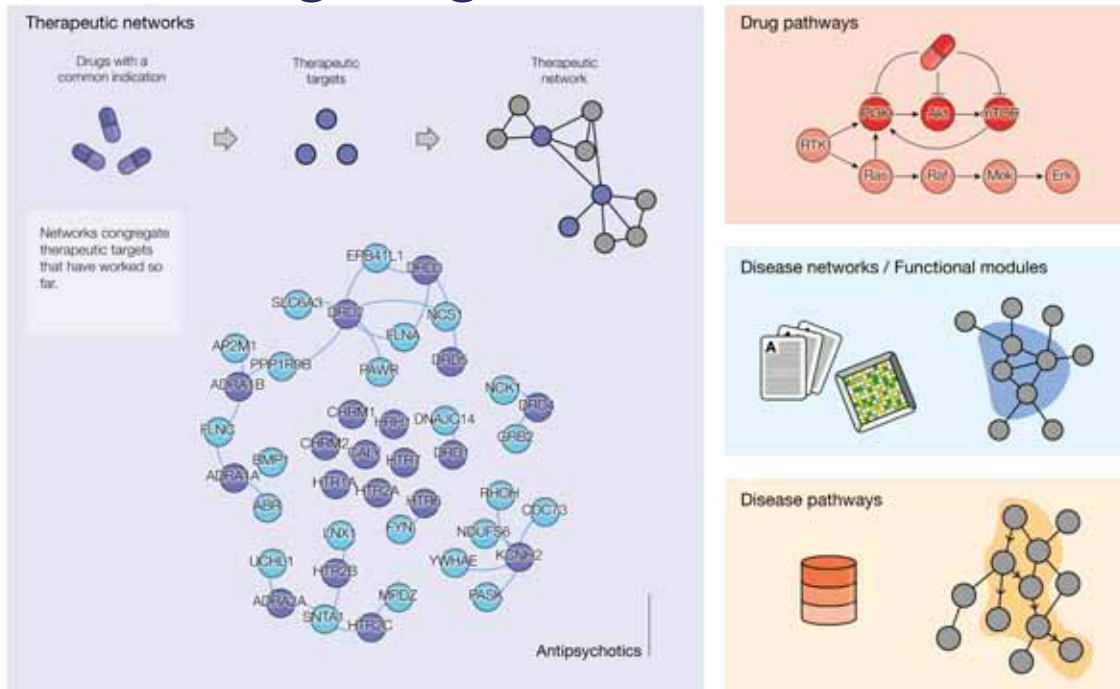
Human Interactome

Interpretability

Comprehensiveness

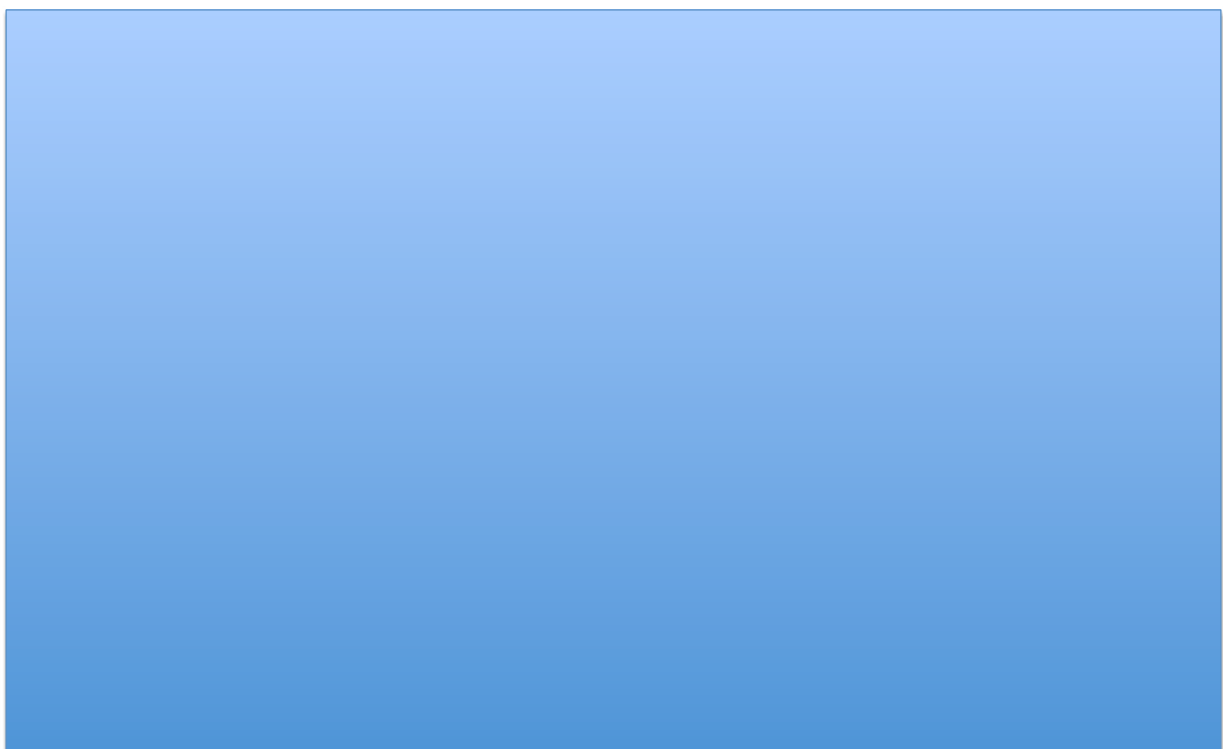
Usefulness

Promising target combinations



Knight et al, Nat Rev Cancer (2010)

Systems pharmacology in BC

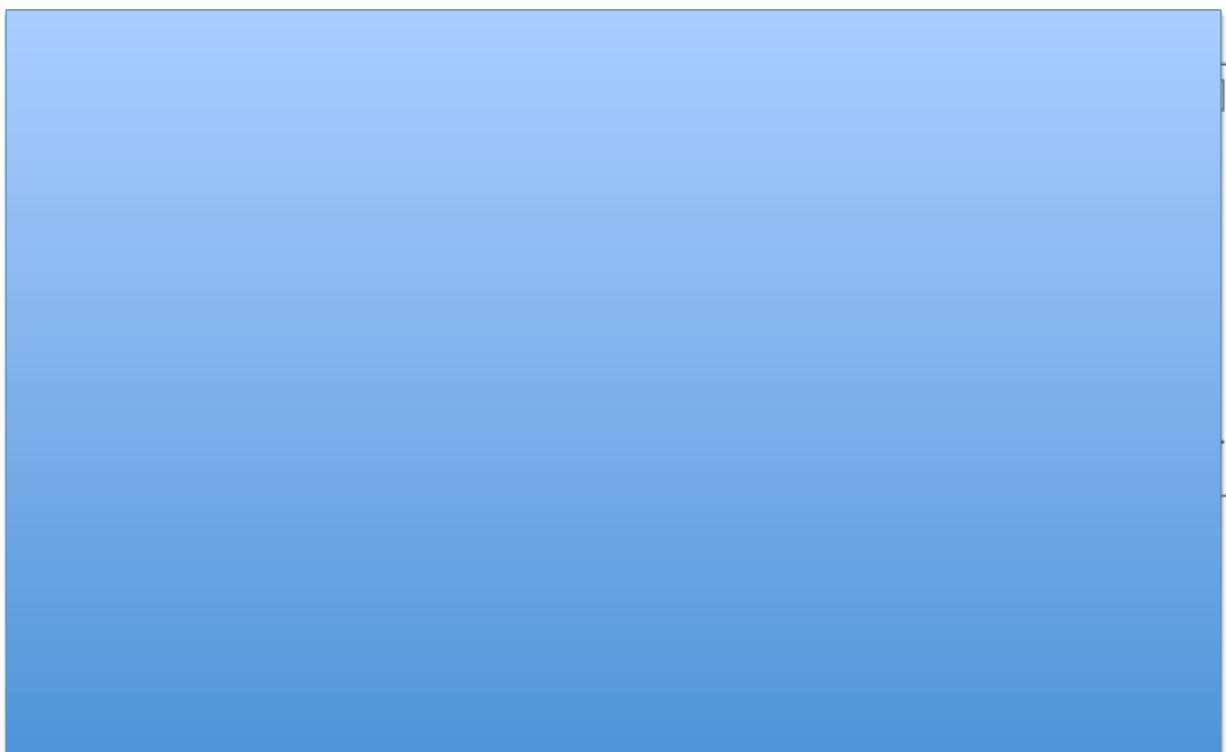


in silico and experimental strategy validation



in silico and experimental strategy validation

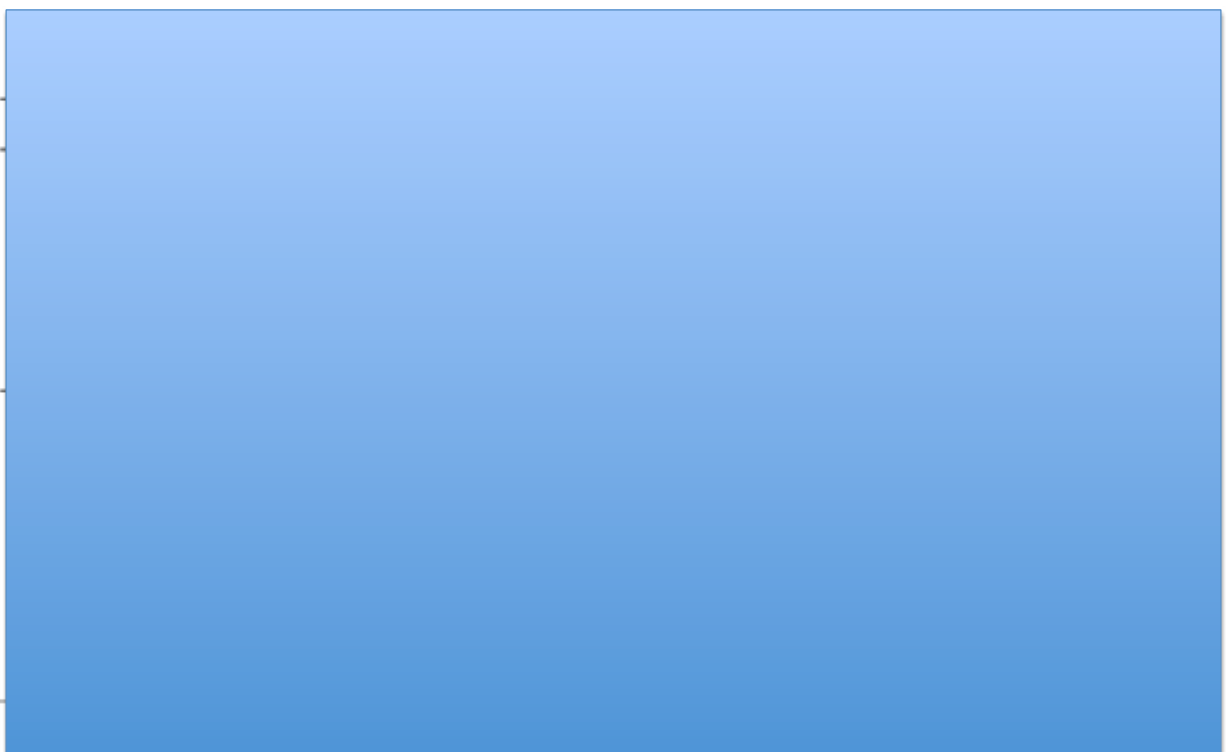
Effect over 5 breast cancer cell lines



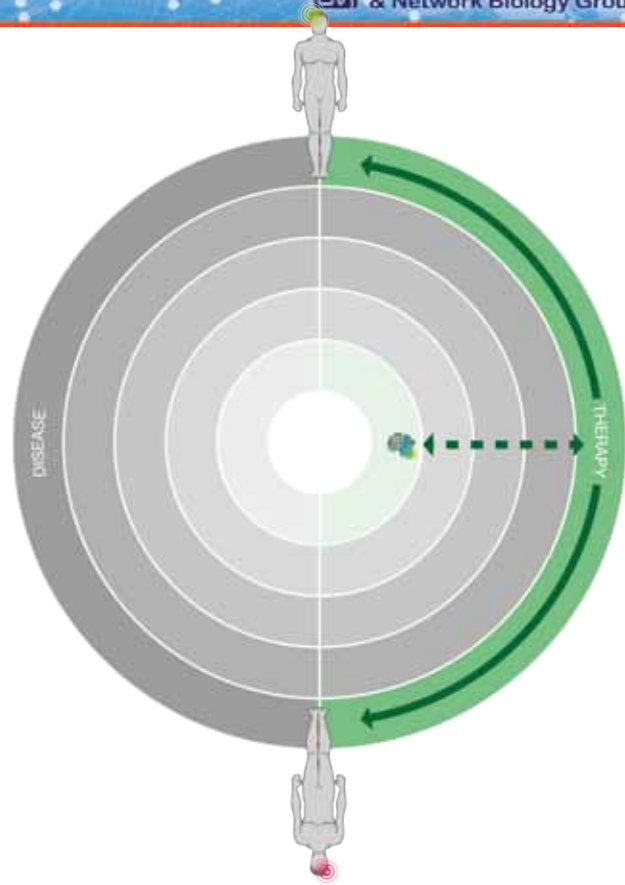
Is there a synergistic effect ?



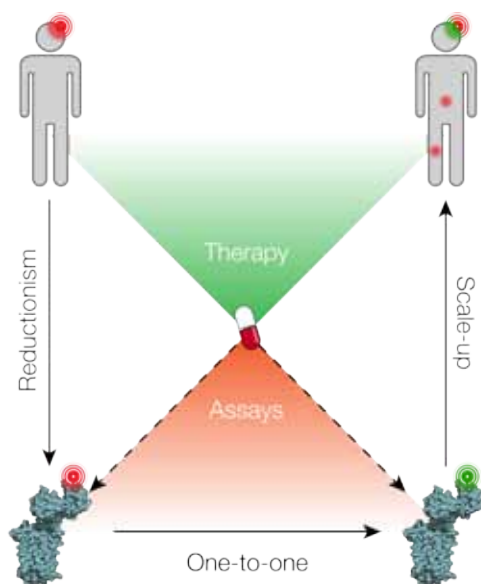
Is there a synergistic effect ?



Drug reprofiling



Magic bullets

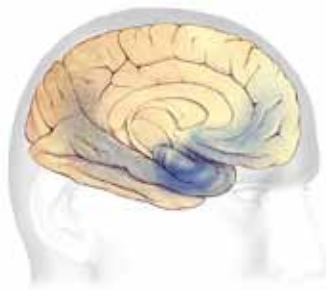


Alzheimer's disease (AD)



Preclinical AD

>20 years before diagnosis
Short-term memory loss



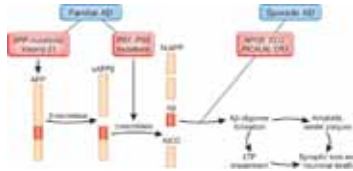
Mild and moderate AD

2 - 10 years
Reading problems
Poor object recognition
Poor direction sense

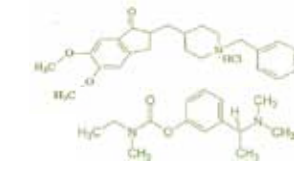


Severe AD

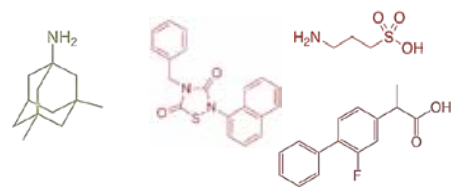
1 - 5 years
Poor judgment
Short attention
Visual problems



Pre-symptomatic diagnose



Disease modifying treatments



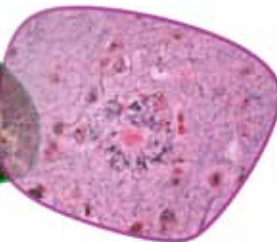
Effective biomarkers to monitor progress and response to treatment

AD is a complex and heterogenic disease

Neuronal dysfunction



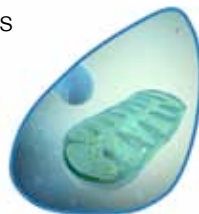
Amyloid plaques



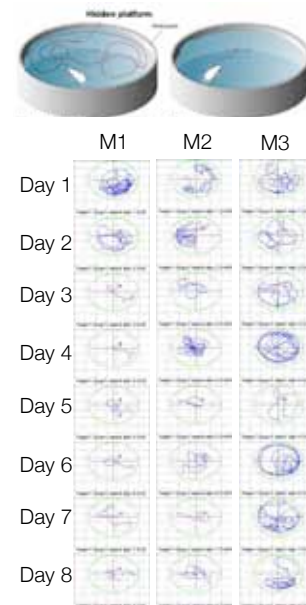
Environmental factors



Neurofibrillary tangles



Oxidative stress



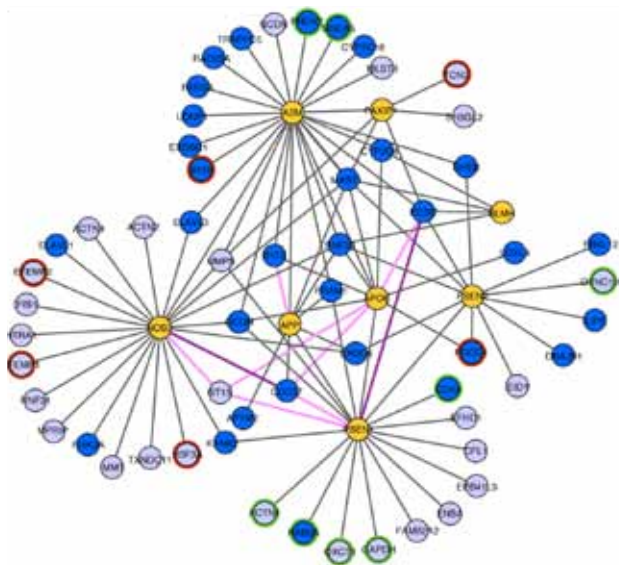
We need disease-modifying therapeutic treatments that also alleviate the clinical symptoms

Network biology and systems pharmacology



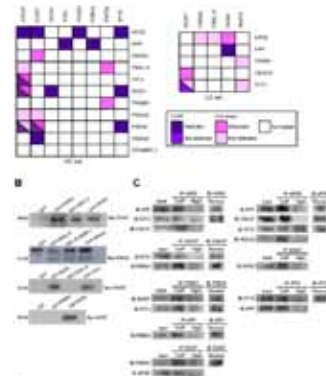
Interaction discovery applied to AD

HC AD-related network

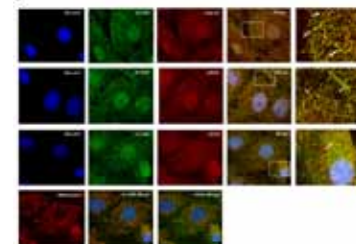


200 PPI involving 8 AD causative/susceptibility genes and 66 candidates, 17 of which appear up- or down-regulated in AD patients ($p < 3 \cdot 10^{-4}$)

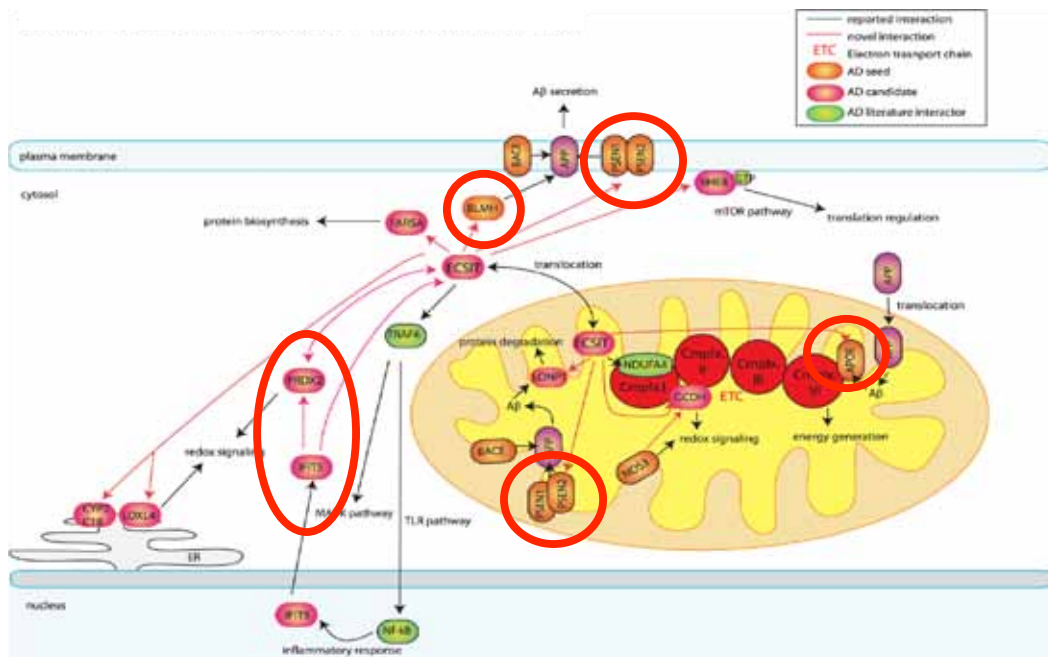
GST pull-downs and Co-IPs



Co-localization

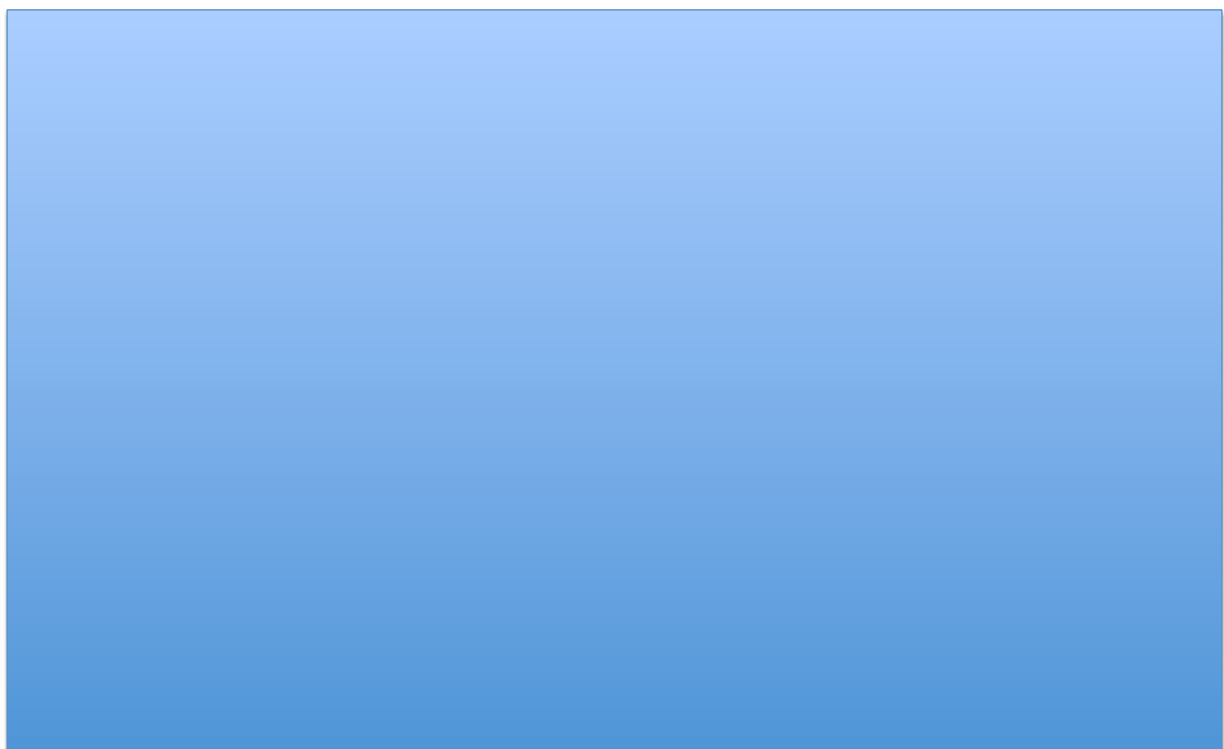


ECSIT might act as a molecular link between oxidative stress, inflammation and mitochondrial dysfunction in AD



Soler-López*, Zanzoni*, et al. 2011. Genome Res
Soler-López et al. 2012. BioEssays

ECSIT-amyloid Ab40/Ab42 levels



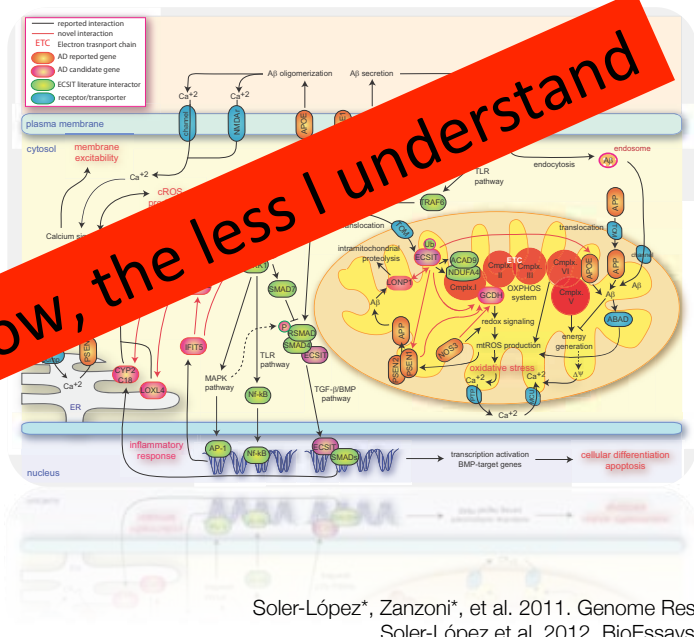
ECSIT-subcellular localization



Building networks is (ahem) easy, but how about therapeutics ?

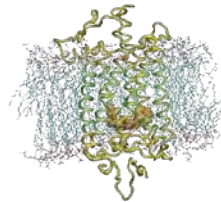


The more we know, the less I understand

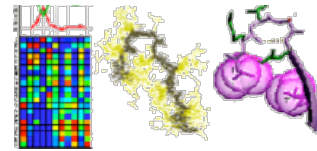


How can we USE the information hidden in the complex maps?

Structural bioinformatics



Newton equation

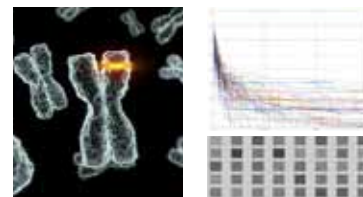


Empirical potentials

Systems biology

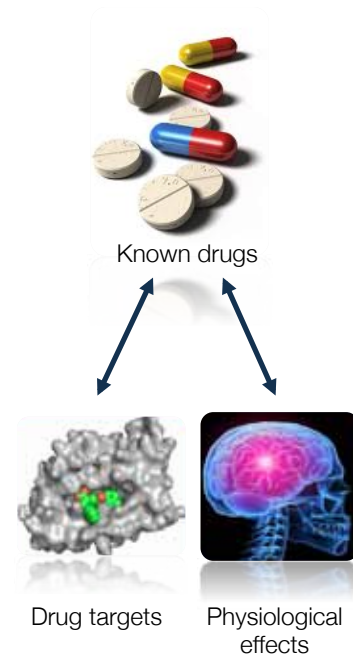
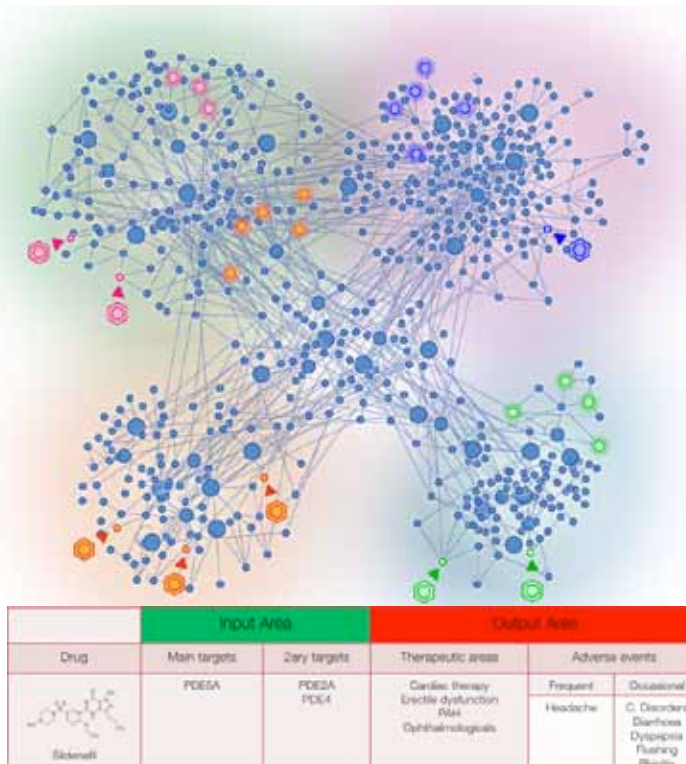


ODEs

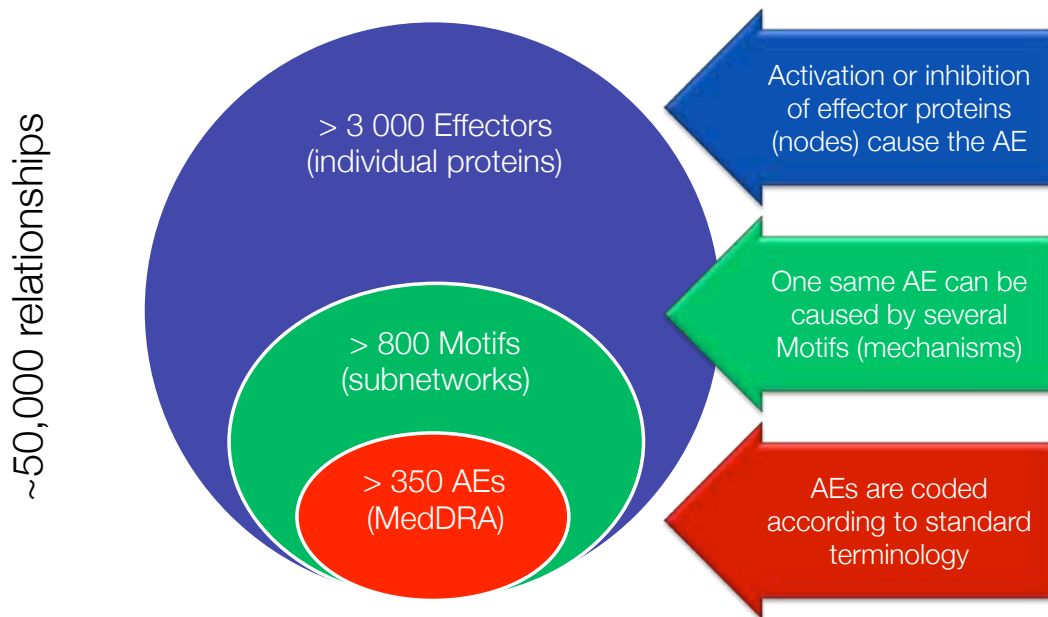


KDD

A top-down approach to systems biology



Our own Rosetta stone



Comprehensive, hand-curated database (more than 15 000 articles reviewed)

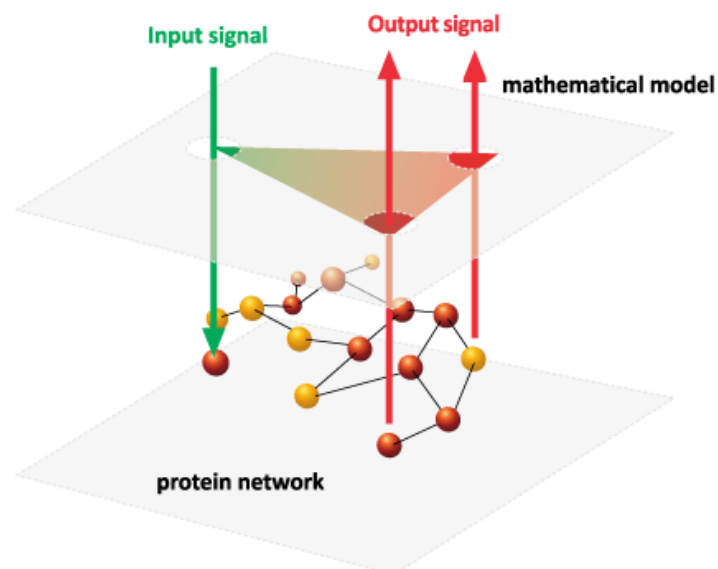
How does the actual data look like ?

MOTIVE ID	MOTIVE NAME	MOTIVE DESCRIPTION	Organ or System affected	Tissue affected	Cell type affected	Seed Proteins
1	Amyloid pathology	Amyloid plaques_Abnormal clusters of protein fragments build up between nerve cells.	CNS	Brain	Neurons , Endothelial cells, VSMCs, Microglia	26
2	Tau pathology	Neurofibrillary tangles_insoluble twister fibers inside neurons	CNS	Brain	Neurons	14
3	Oxidative Stress	Oxidative stress plays a role in the etiology and also in the pathophysiology of the disease .	CNS	Brain	Microglia, Astroglia	77
4	Neuronal dysfunction and death	Neuronal loss and brain conductance disturbances associated to memory loss	CNS	Brain	Neurons	13

How does the actual data look like ?

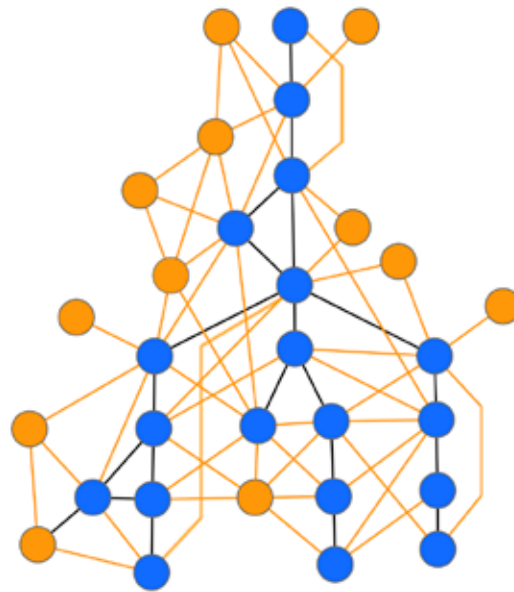
MOTIVE Level	MOTIVE ID	Effector Protein	Name	Uniprot	Causative Effect	Relevance	Reference	Evidence
M	1	Amyloid-precursor protein	APP	P05067	1	100	20232515	A β comes from the proteolytic processing of amyloid precursor protein
M	1	Low-density lipoprotein receptor-related protein 1 85 kDa subunit	LRP1	Q86SWO	-1	90	20854368	Protein involved on A β clearance from the brain
M	2	Microtubule-associated protein tau	MAPT, TAU	P10636	1	90	20510151	Tau is the component of Neurofibrillary tangles, the insoluble twister fibers inside neurons
M	2	glycogen synthase kinase	GSK3 β	P49841	1	90	20510151	The main kinase that phosphorylates TAU protein
M	3	Interleukin-1 beta	IL1 β	P01584	1	80	20149872	Neuroinflammatory changes (activated glial cells and elevated levels of proinflammatory IL-1 β and TNF- α) are present in AD brains
M	3	Superoxide dismutase [Cu-Zn]	SOD1	P00441	-1	90	10880853	proinflammatory IL-1 β and TNF- α
M	4	Acetylcholinesterase	AChE	P22303	-1	90	20525543	Patients with AD has a decline of cholinergic pathways

Building predictive disease models

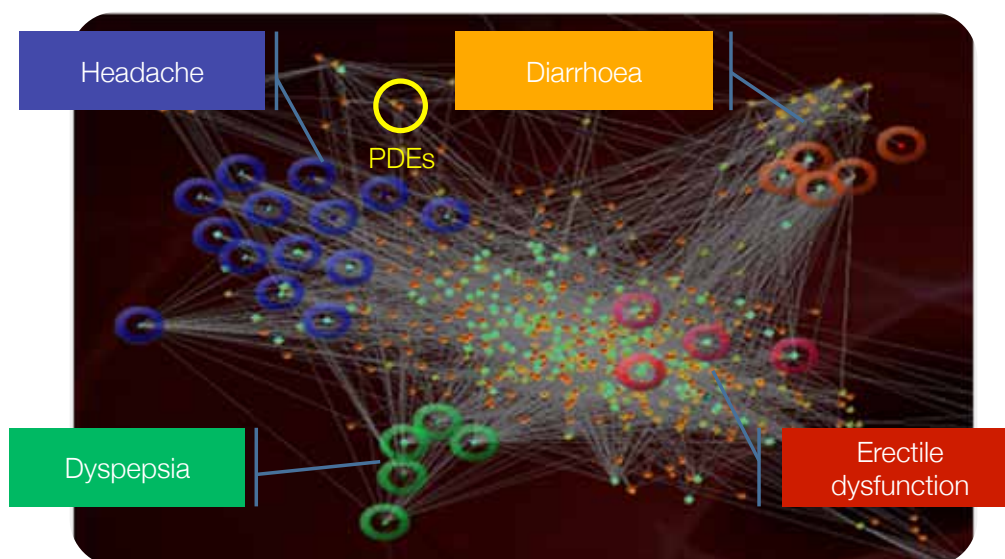


~50,000 relationships

Soft (molecular) data, soft models



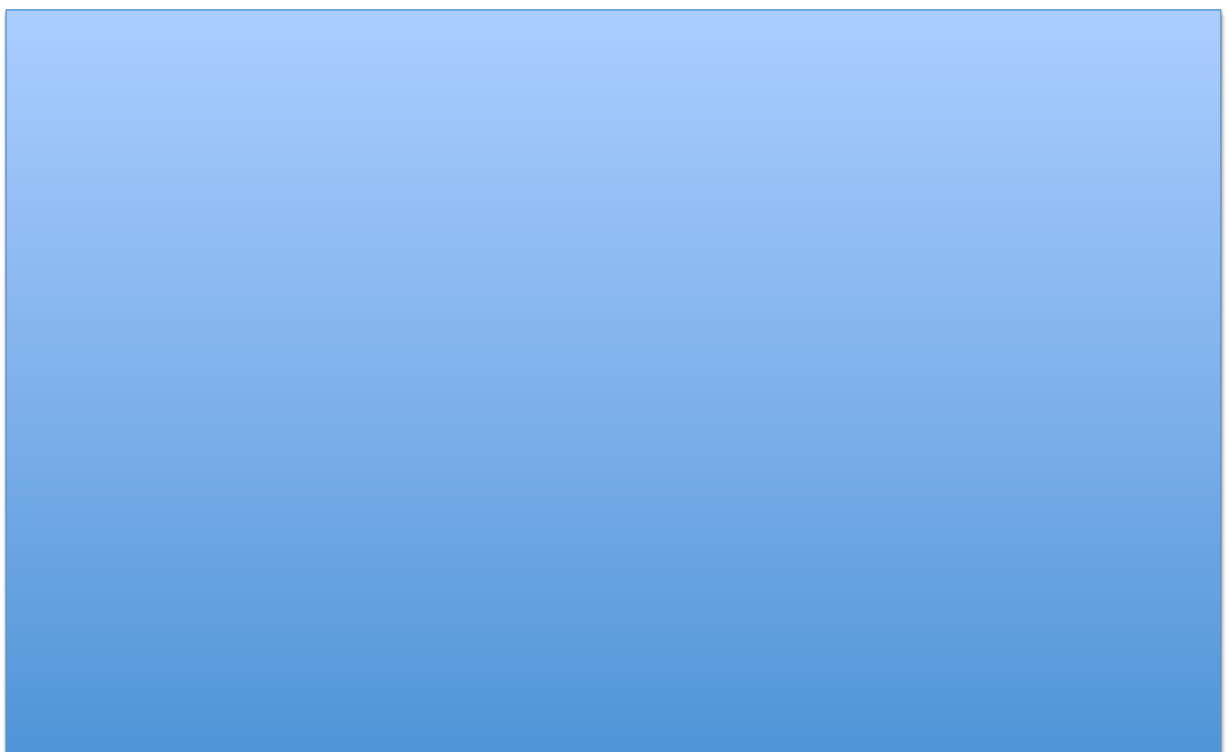
Soft (physiological) data, soft models



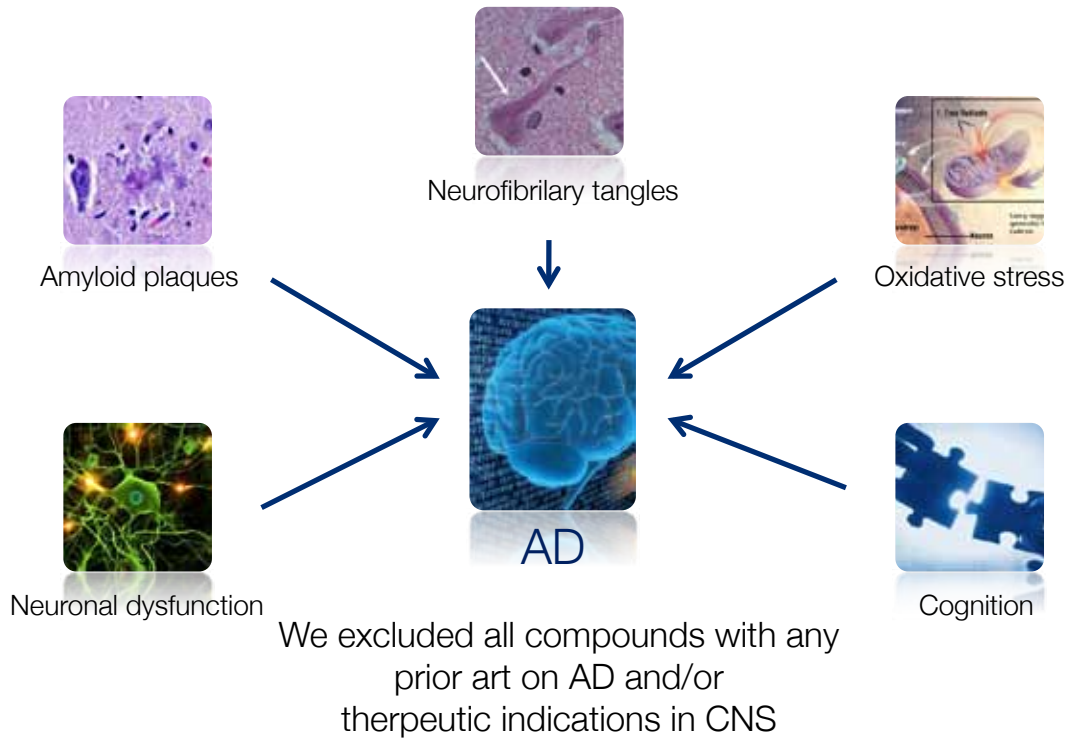
Building predictive disease models



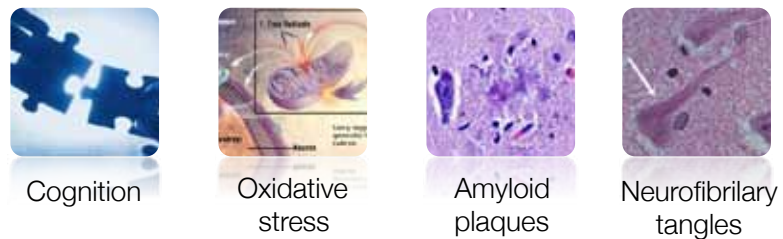
in silico results - Benchmark



The real test: reprofiling experiment in AD



Cell-based assays and animal models

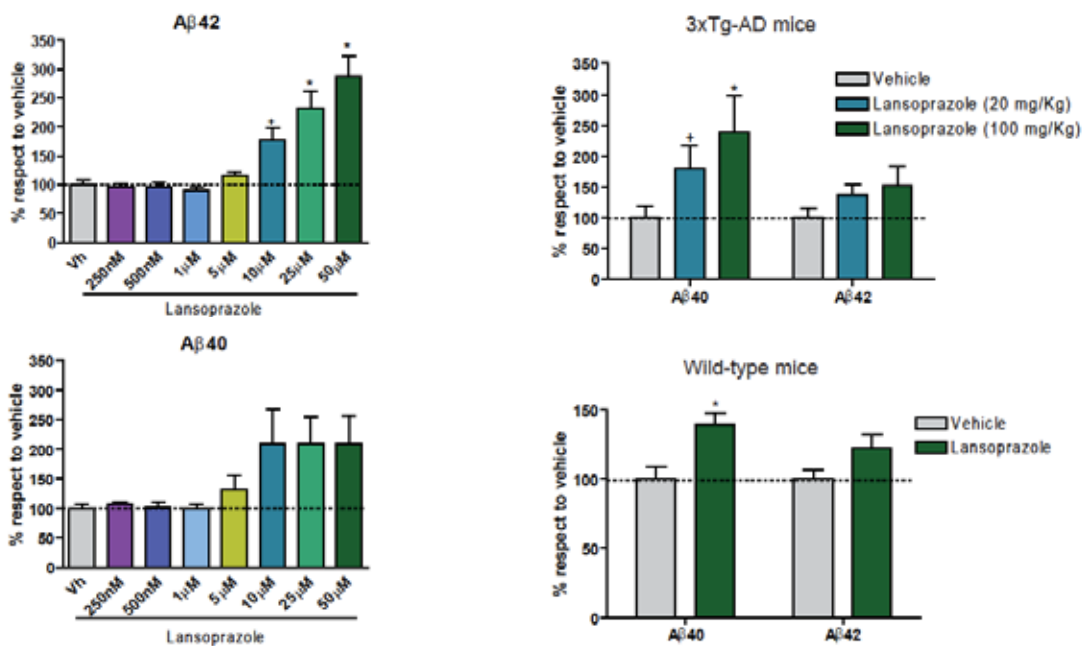


AX_ALZ_002				
AX_ALZ_003				
AX_ALZ_004				
AX_ALZ_005				
AX_ALZ_006				
AX_ALZ_007				

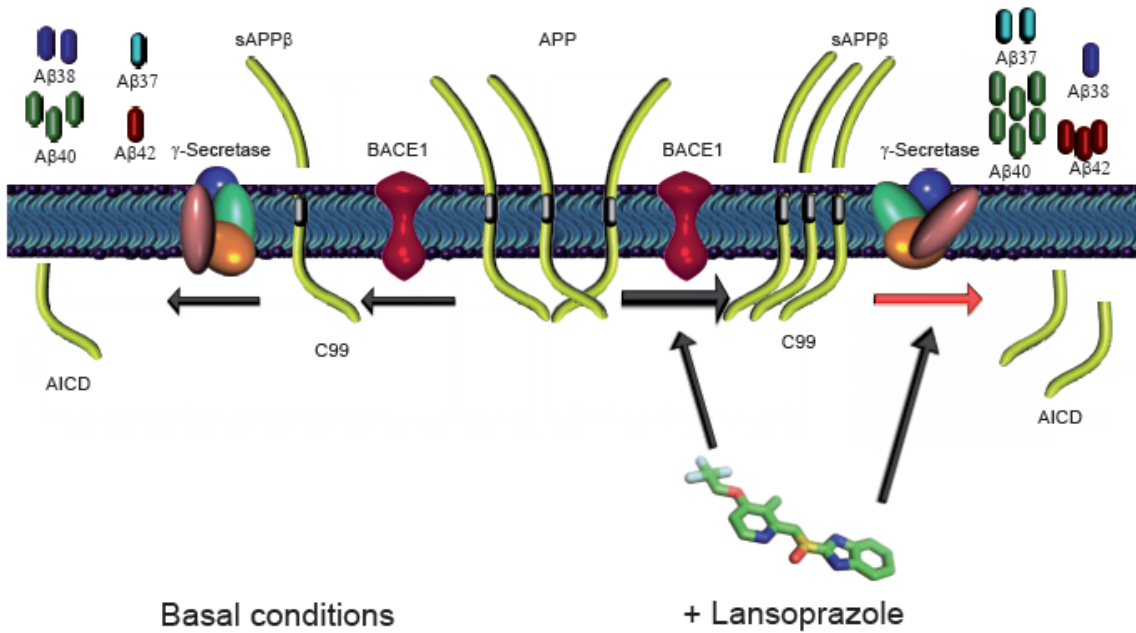
Cell-based assays and animal models



Proton-pump inhibitors increase A β production by modulating β - and γ -secretase activities



Proton-pump inhibitors increase A β production by modulating β - and γ -secretase activities



Badiola et al. *PLoS ONE* 2013



Neuronal dysfunction (Ax_Alz_011+013)

Mice Groups:



AD mice (3xTg AD)
APP^{Swe}, PS1^{M146V}, tau^{P301L}



Healthy mice

Group 1: Vehicle

Group 2: Treatment

Group 3: Vehicle

Experiment:



10 weeks treatment
daily dose by gavage

4 mo 6'5 mo

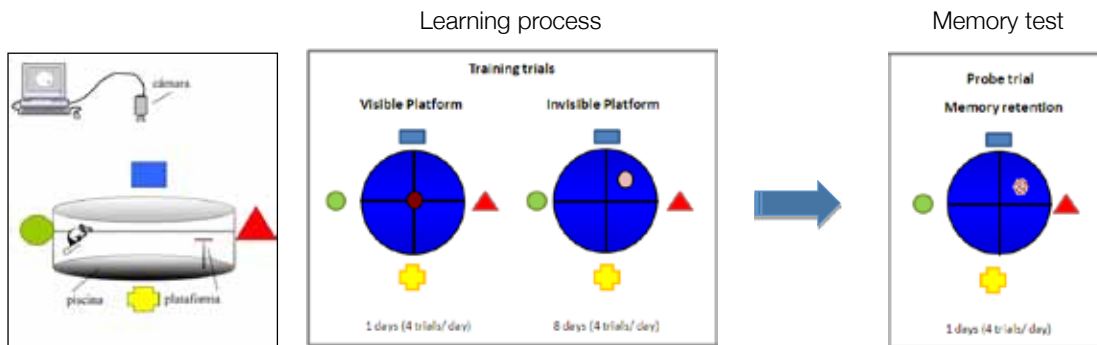
Low Mild

Pathology level



Morris water-maze test
to check
Memory impairment at
early-stage

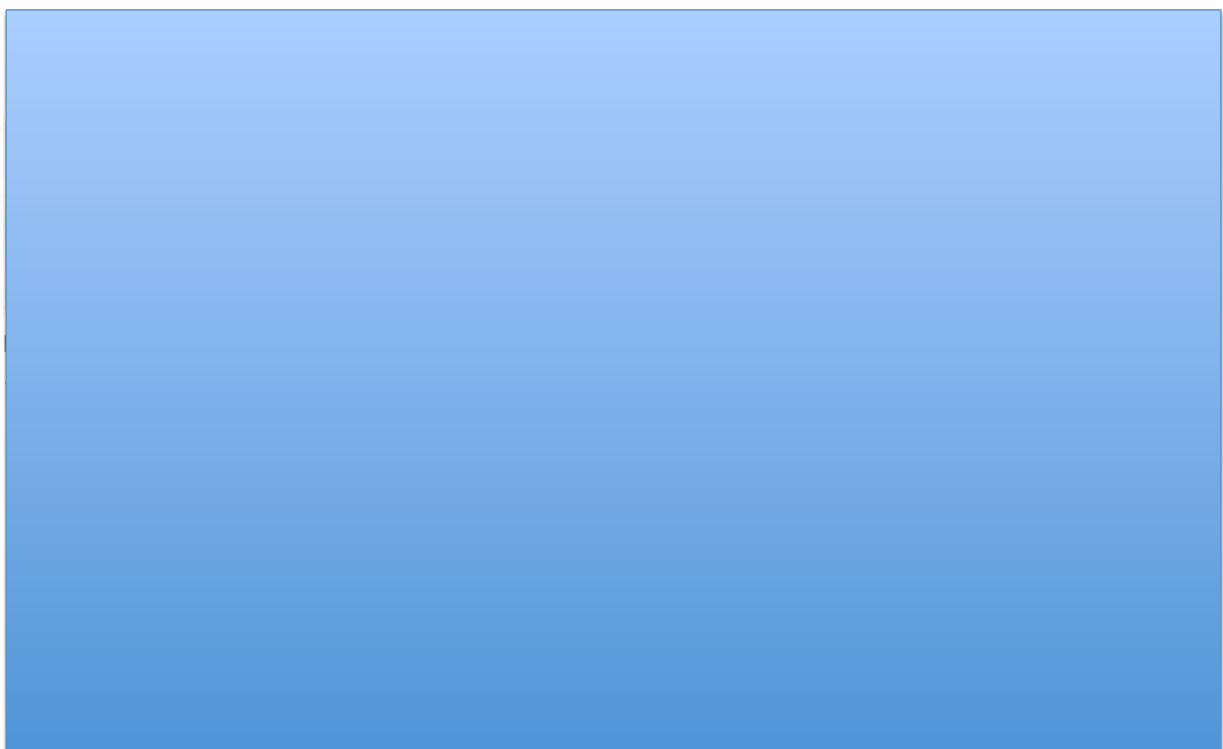
Morris water-maze test



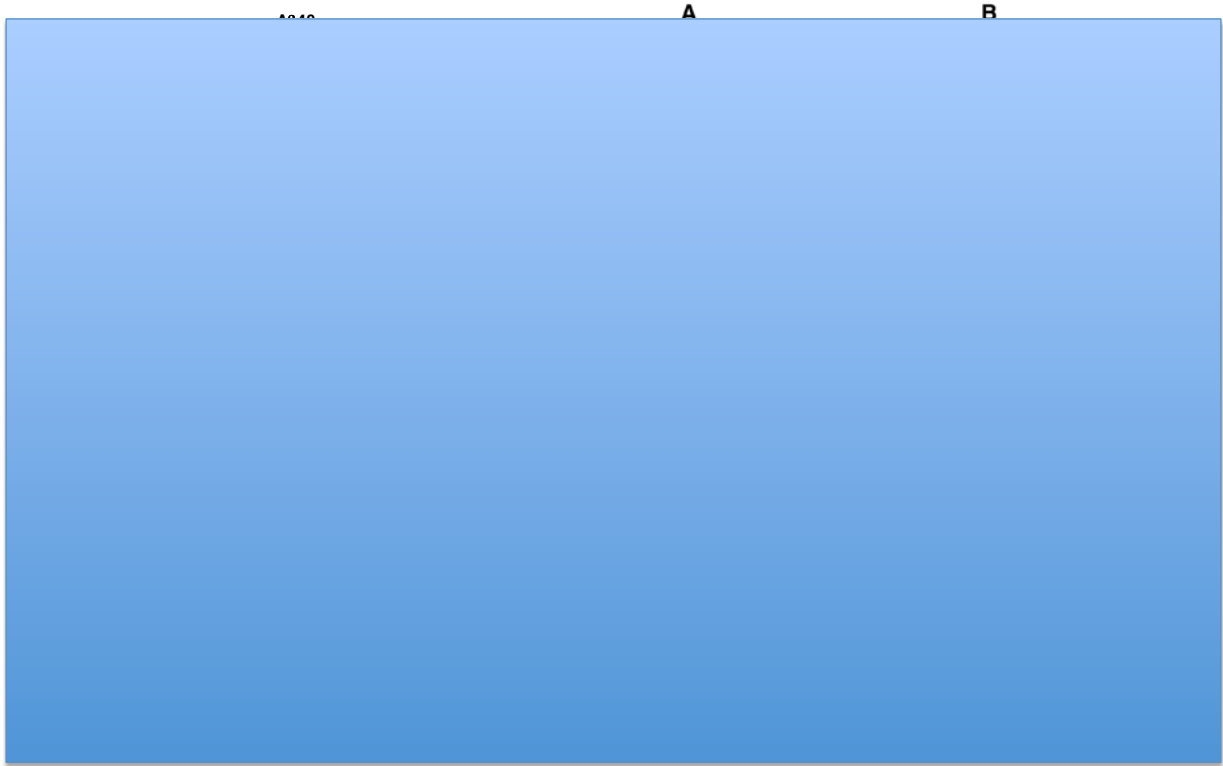
Spatial memory measurements

- Ratio of time spent in the target quadrant vs opposite quadrant
- Area of influence around the platform
- Platform crossings

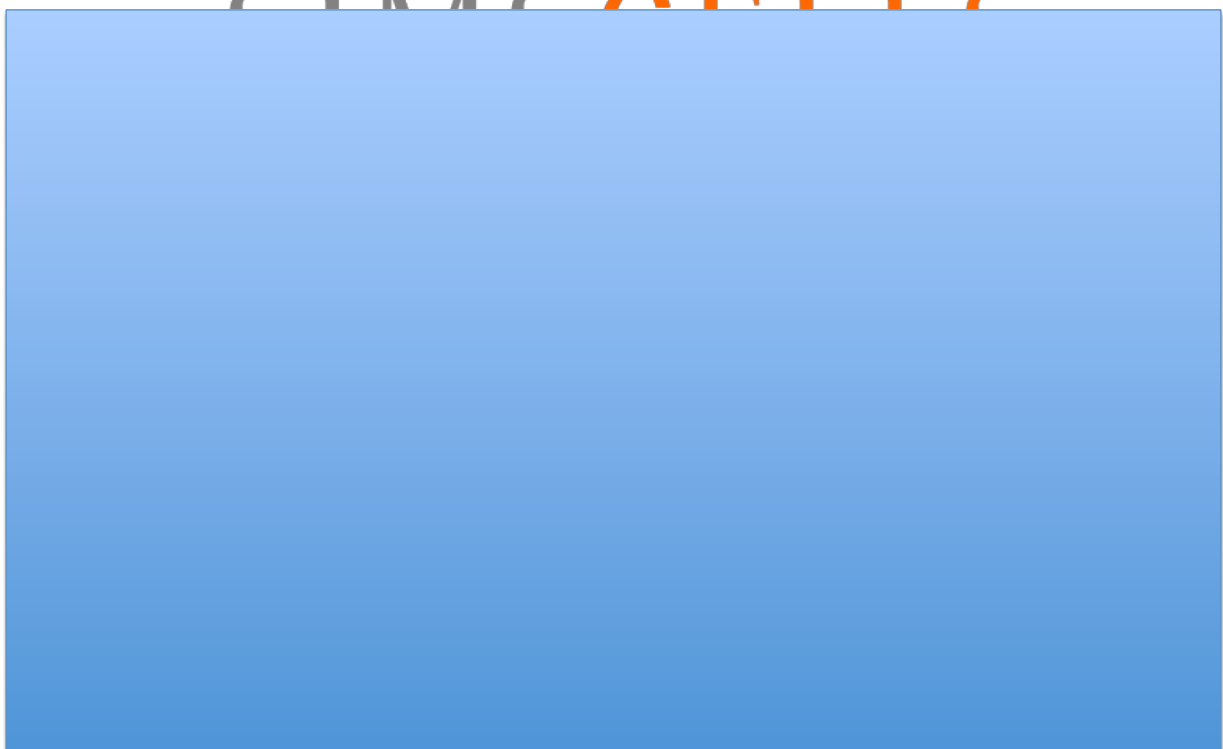
Spatial memory test on 7m old 3xTg-AD



Is it disease-modifying ?



Potential mechanism of action



Concluding remarks

- Have set up a network biology approach to generate global blockades in breast cancer
- Have set up a top-down systems biology approach that uses clinical data to suggest therapeutically relevant biology in protein networks
- Have applied our strategy to AD (+ ALS and glaucoma), and found a few compounds that show very interesting activities in cell and animal models (positive and negative). Need to investigate them further
- Our approach is based on protein networks, and thus won't work on complex diseases that mainly involve other type of macromolecules
- Just our 5 cents towards network medicine approaches that should take us beyond "cherry-picking" examples, and fully exploit the information contained in the cell networks that we're charting

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Teresa Juan
Jofre Tenorio
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Eva Capdevila
Victor Alcalde

Your Name Here !!



Collaborators:



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Alberto Lleó

José M Mas, Mireia Coma
& Teresa Sardón

Funding agencies:



!! New !!

Interactome3d and 3did websites and databases updated



Mosca et al. *Nat Methods* 2013



Mosca et al. *Nucleic Acids Res* 2014