DISEASE-ORIENTED REPOSITIONING
Case studies

What is disease-oriented repositioning?
Disease-oriented repositioning is a strategy that puts the focus on a pathological condition and attempts to identify existing drugs or combinations of drugs to treat the disease of interest.

Why is repositioning useful?
- Ensures the success in drug development process since it offers the advantage that the drug has often already undergone preclinical and clinical testing
- Reduces the risk of adverse events in trial populations
- Reduces development costs and time
- Increases the possibility of rescuing previously failed compounds or out-of-patent compounds

What does Anaxomics offer?
Anaxomics has developed Therapeutic Performance Mapping System (TPMS), a novel proprietary technology that applies the latest advances in systems biology.
TPMS explores the pathophysiological map of a given disease to design the most suitable drug and/or combinations of drugs to treat the disease of interest in a four step process:

1. Disease characterization: Collecting and integrating available scientific knowledge about the disease of interest
2. Creation of the biological map of the disease
3. Mathematical model generation to emulate human disease physiology
4. Data analysis to identify new drugs or combination of drugs

TPMS opens a new horizon for drug repositioning
- Innovative solutions
- Non-obvious results
- Scientific based rationale
- Medical applicability
- Increased success rate

75% of tested drugs show positive results!
A successful example in Amyotrophic Lateral Sclerosis
Drug combinations

The objective:
Designing novel drug combinations to tackle the complexity of amyotrophic lateral sclerosis (ALS) pathophysiology based on drug reprofiling.

The procedure:
We have applied TPMS technology to identify synergistic drug combinations:

1. ALS characterization
2. Creation of ALS biological network
3. Development of mathematical models to emulate ALS pathology
4. Data analysis to identify drug combinations to treat ALS

Chronic glutamate excitotoxicity was induced by the administration of THA to the culture. The neuroprotective effects of drug combinations were assessed by studying their capacity to increase motoneuron survival after chronic excitotoxic insult.

The experimental checking demonstrates the predicted in silico results:
Two drug combinations display an outstanding neuroprotective effect by reducing the effects of THA chronic excitotoxic insult on motoneurons.

Effect of drug combinations on motor neuron survival

A successful example in Alzheimer’s disease

Drug combinations

The objective:

Designing novel drug combinations to treat neuronal dysfunction in Alzheimer’s disease (AD) based on drug repositioning.

The procedure:

We have applied TPMS technology to identify synergistic drug combinations:

1. AD characterization
2. Creation of AD biological network
3. Development of mathematical models to emulate AD pathology
4. Data analysis to identify drug combinations to treat AD.

Experimental checking:

Behavior analysis (Morris water maze test) was conducted in a mouse model of Alzheimer’s disease (3xTg-AD) to study whether the treatments were able to prevent memory impairment.

Wild-type mice and treated-3xTg-AD mice displayed higher occupancy of the target quadrant (NE) compared to the other quadrants, whereas non-treated 3xTg-AD transgenic mice spent less time in the target quadrant.

Efficacy synergy in treating memory impairment was observed with the combined drug administration.

The experimental checking demonstrates the predicted results: The AX_ALZ_011+AX_ALZ_013 are able to improve neuronal dysfunction in a mouse model of AD.

Synergy between AX_ALZ_011 + AX_ALZ_013

TPMS results:

Drug combinations are sorted by their high prediction and synergy scores.

TPMS technology has identified in silico a positive effect of the drug combinations:

AX_ALZ_011 + AX_ALZ_012
AX_ALZ_011 + AX_ALZ_013

Coma et al. US Patent Provisional Nº U.S. 13/660,205 2013

The experimental validation was performed in collaboration with

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The objective:
Identification of existing drugs that could be useful for treating Alzheimer Disease (AD).

The procedure:
We have applied TPMS technology to identify new drugs to treat AD:

1. AD characterization
2. Creation of AD biological network
3. Development of mathematical models to emulate the AD pathology
4. Data analysis to identify new drugs to treat AD.

Experimental checking:
Experimental testing was performed in order to confirm the putative efficacy of the predicted drugs on AD.

Drug efficacy on TAU pathology
The effect of AX_ALZ_002 was evaluated in a mouse hippocampal-derived HT4 cell line transfected with human TAU using a phospho-TAU and TAU ELISA assay. The level of TAU phosphorylation is used as an indicator of the degree of TAU pathology.

AX_ALZ_002 improves Tau pathology by decreasing the levels hyperphosphorylated TAU

Drug efficacy on neuronal dysfunction
The effect of AX_ALZ_006 was studied with an in vitro Acetylcholinesterase (AChE) assay using the Amplex Red Acetylcholine/Assay Kit. AX_ALZ_006 has shown a dose-dependent inhibition of AChE, which highlights its efficacy on memory.

AX_ALZ_006 shows a dose-dependent inhibition of hyperphosphorylation, which highlights its efficacy on memory

Coma et al. US Patent Provisional Nº U.S. 13/660,205 2013

The experimental validation was performed in collaboration with

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A successful example in glaucoma
Drug combinations

The objective:
Designing novel drug combinations to treat glaucoma based on drug repositioning.

The procedure:
We have applied TPMS technology to identify synergistic drug combinations:

1. Glaucoma characterization
2. Creation of glaucoma biological network
3. Development of mathematical models to emulate glaucoma pathology
4. Data analysis to identify drug combinations to treat glaucoma.

Experimental checking:
The efficacy of the drug combination on retinal damage was studied in a rat model of glaucoma. Ocular hypertension (OHT) was induced in the left eye of Albino Sprague Dawley female rats by laser cauterization of limbar and episcleral veins.

The detailed spatial distribution of Retinal Ganglion Cells (RGCs) damage (FG+) or survival (Brn3a+) over the entire retinas was obtained through quadrant analysis, and demonstrated with isodensity maps.

The experimental checking demonstrates the predicted in silico results:
Treated animals display higher percentage of RGCs survival compared to non-treated animals.

TPMS results:
Drug combinations are sorted by their high prediction and synergy scores.
TPMS technology has identified in silico a positive effect of the drug combination:
AX_GLA_001 + AX_GLA_003

Neuroprotective effect of AX_GLA_001 + AX_GLA_003 in an experimental model of glaucoma

(A) Representative image of RGCs distribution in drug combination and vehicle treated retinas. Isodensity maps of the same retina showing the distribution of RGCs FG+ (left) and RGCs Brn3a+ (right). (B) Ratio of survival of RGCs identified by Brn3a+ expression (Brn3a+) respect to FG tracing (FG+) after drug combination or vehicle treatment (p < 0.01; **, p < 0.001; ***, Mann–Whitney U test).
