ASSESSING DRUG TARGET ASSOCIATION FROM BIOLOGICAL EVIDENCES

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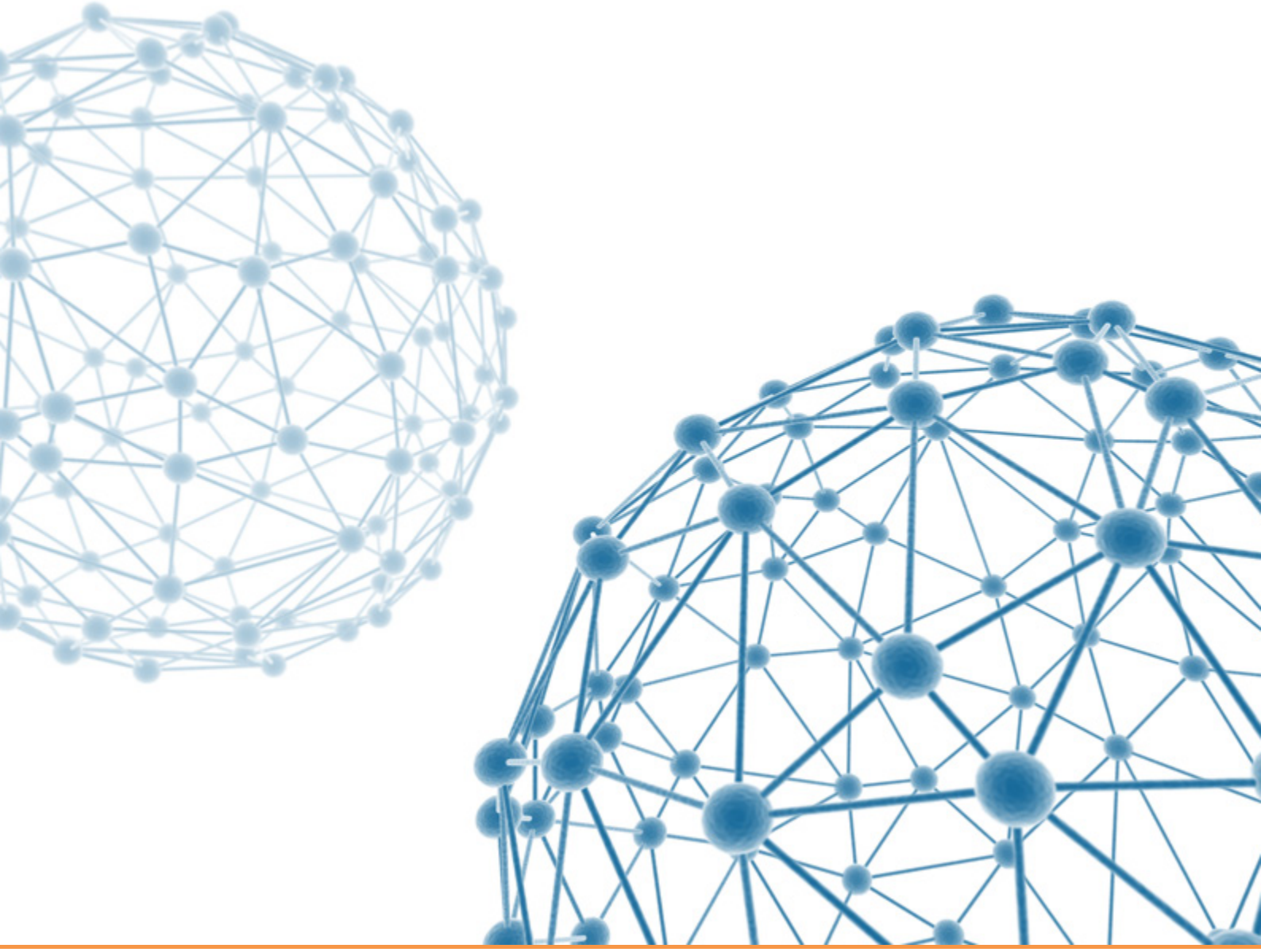

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ANAXOMICS
the pathway to discovery

The full drug target profile identification is many times a necessary step in drug development process. Recently, the move to a more holistic approach in drug discovery has resulted in the increasing use of cell-based assays to discover new biologically active small molecules. The subsequent identification of the molecular targets that underlie an observed phenotypic response--termed target deconvolution--is an essential step.

This paper describes a method developed by Anaxomics for the prioritization of potential drug targets based on general biological knowledge, Systems Biology and drug-related biological and physiological data.

DRUG TARGET IDENTIFICATION

Identifying the molecular targets of a drug candidate it is often a critical step in the drug development process.

- The identification of molecular targets is essential to further development of a lead or a drug candidate that is discovered from a cell-based or a phenotype-based assay or via an in vitro high throughput screening assay. The molecular targets allow identifying or confirming and validating the mechanism of drug action. It also provides information about "off-targets", which may be used to infer side effect or even toxicity. With known drug targets, scientists can use molecular assay or structure based drug design to optimize the lead and further improve their efficacy and toxicity profiles.

- In the case of drug candidates arising from a target-based screening it is also important to identify any potential off-targets in order to be able to address safety issues earlier in the drug discovery process.

- For a marketed drug, the identification of its full target profile may provide important clues about other novel therapeutic applications of the drug (repurposing), which is an important and effective technique in drug lifecycle management.

Several strategies are being applied to identify the full target profile of a drug candidate, including among others: direct biochemical methods [1], metabolomics methods [2], chemoproteomics approaches [3] and computational methods [4], like Anaxomics' drug target profile identification by structural similarity. Most of the strategies for full target profile characterization of a drug result in a long list of potential drug targets with no clear identification of the right target candidate(s).

The identified targets have to be validated by independent biological experiments.

ANAXOMICS TMPS technology can be used to refine the initial full target profile results to be able to prioritize targets and reduce the expenses of validation by validating only rightful target candidates and avoiding validation of false positives.

ANAXOMICS DRUG TARGET PROFILE IDENTIFICATION BY STRUCTURAL SIMILARITY: CHEMOCENTRIC AND TARGET-CENTRIC APPROACHES

Anaxomics combines existing state of the art computational approaches for an initial full drug target profiling.

Two different strategies can be applied depending on the initial starting information. A chemocentric based approach is applied when the structure of the candidate drug is available.

A target-centric approach can be undertaken when the target molecule is known. In case both are known, the two strategies are executed (Figure 1).

- ✓ **Chemocentric approach.**
  Exploits chemical similarity among ligands (drugs, chemical compounds). Relates proteins through the ligands that interact with them. The major drawback is that it depends on prior knowledge of what sorts of ligands might bind to particular targets. For targets for which there is no ligand information the approach is silent. But on the other site it can identify target proteins that are unrelated by biological criteria (such sequence or structure)

- ✓ **Target-centric approach.**
  Identifies proteins that have similar structure as the target protein. Depending on the structural knowledge of the target protein, the similarity search can be done at different levels: sequence similarity, 3D similarity or binding site similarity.

All identified potential drug targets are screened by docking in order to refine the predictions and discard unlikely candidates. For instance when a drug inhibits an enzyme belonging to a big protein family the target-centric approach will identify most of the enzymes belonging to that family. However only those predicted through docking to match the drug with a low binding energy will be accepted. A more extensive review of Anaxomics' drug target profile identification by structural similarity is provided elsewhere.

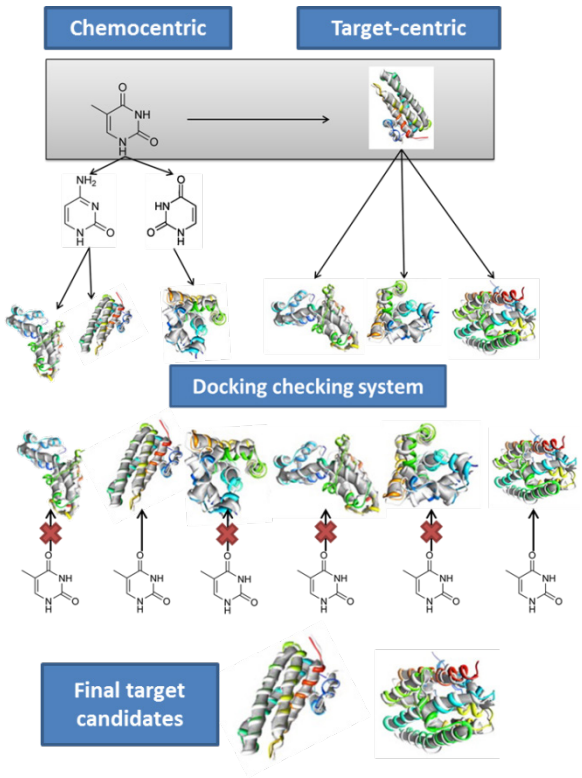

FIGURE 1 SIMPLIFIED VIEW OF ANAXOMICS' TARGET IDENTIFICATION STRUCTURAL METHOD

ANAXOMICS' TPMS TECHNOLOGY APPLIED TO SELECT THE MOST PLAUSIBLE TARGETS OUT OF A DRUG TARGET PROFILING EXPERIMENT

Anaxomics' therapeutic performance mapping system (TPMS) proprietary technology [5,6], hereby briefly described, is intended to be applied in many steps of the drug development process from the mechanism of action (MoA) identification to the early profiling of future potential clinical safety issues, but also for drug target identification or prioritization purposes.

This innovative technology allows the modelling of biological processes, incorporating all the available biological and medical information (Truth Table) stored in Anaxomics databases to the topological information that provides the protein interaction data (Step 1, Figure 2). Anaxomics databases are hand-curated and periodically checked, in order to be updated. Artificial intelligence

techniques like Artificial Neuronal Networks are used to generate a mathematical model that fulfils all the data provided. However, the mathematical model does not give a unique solution; it provides a universe of possible solutions that satisfy the restrictions set in the Truth Table.

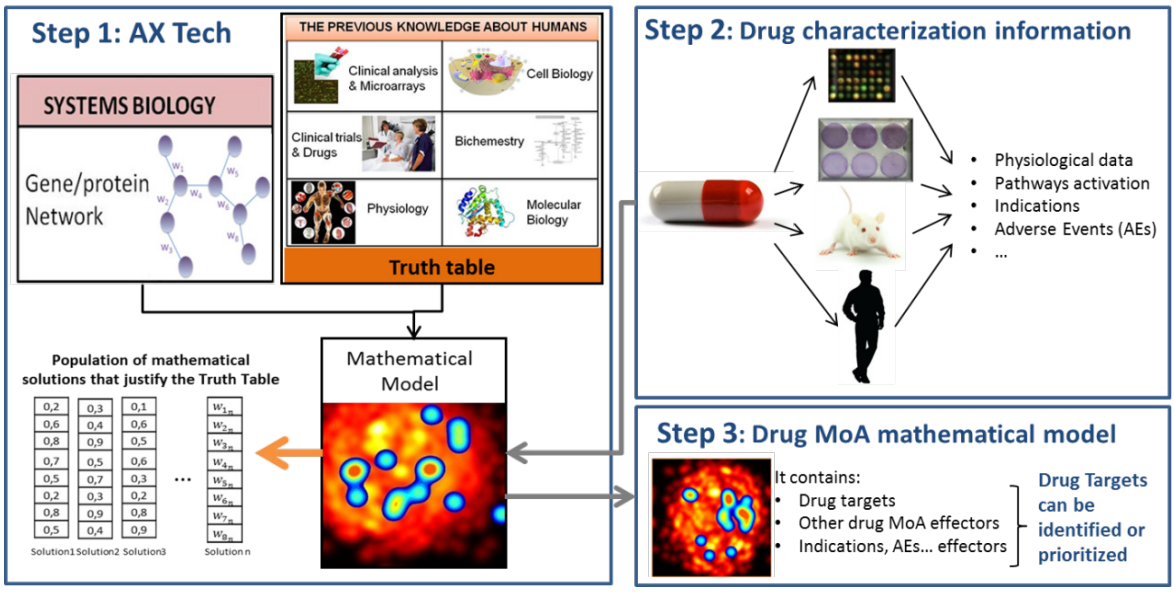

FIGURE 2 ANAXOMICS' TPMS TECHNOLOGY APPLIED TO DRUG TARGET IDENTIFICATION OR PRIORITIZATION USING BIOLOGICAL EVIDENCE AS STARTING POINT.

It is possible to further constrain the number of possible solutions by adding novel information to the model (Step 2, Figure 2). In the case of target identification, any data generated during the drug characterization could be used: microarray data and physiological effects from cell culture or in animal models, known indications or adverse events (AEs),… By adding this information, a mathematical model outlining the potential drug MoA can be build (Step 3, Figure2). The new model, in addition to satisfying the restrictions applied in Step 1 for current biological knowledge, also fulfils all the restrictions derived from the biological evidence generated during drug development (Step 2). The outline of the potential MoA of the drug is used for measuring the likeliness of a protein for being a potential drug target for the drug of interest based on their biological effects and human biology restrictions. This methodology can be used to prioritize lists of potential drug targets derived from any king of computational or experimental target profiling experiment. The system provides with a list of targets or target combinations ranked by biological criteria, i.e. being the first the most probable target to cause the experimental evidences observed. In addition, the system can provide a list of biomarkers for *in vitro* or *in vivo* checking of the potential targets and MoA.

Anaxomics TPMS technology provides a rapid and cost-effective method of identifying or prioritizing drug molecular targets based on any previous biological evidence of the drug and taking into account the human biology restrictions.

ACKNOWLEDGEMENTS

The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement number HEALTH-F3-2009-223101 (AntiPathoGN).

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