SAFAN-ISP: SMALL MOLECULE IN-SILICO PROFILING. FINDING NEW USES for OLD COMPOUNDS by CHEMOGENOMICS and MACHINE LEARNING approches

ABSTRACT:

It has been estimated that bringing a new drug to the market requires in average 15 years and 800 million US dollars. The cost can be dramatically reduced by reoptimizing approved drugs that lately might have been discontinued, based on old molecules with established pharmacokinetic and pharmacodynamic profiles, whose safety in human subjects is extensively tested.

Chemogenomics

Using powerful concepts in modern chemistry and biology and linking combinatorial chemistry with genomics and proteomics, chemogenomics includes systematic relationships between targets and ligands. By applying a Support Vector Machine algorithm to known small molecule-bioactivity relationships, SAFAN-ISP searches for and predicts new interactions.

In the U.S. the Food and Drug Administration (FDA) and in Europe the European Medicines Agency (EMEA) must approve any drug - whether it is prescription or over-the-counter - before it can be sold. They evaluate the safety of a drug by looking at side effects and its efficacy by evaluating clinical trial results.

How to prevent side effects?

Early in the drug discovery process SAFAN-ISP can help you to uncover and evaluate possible interactions between the compound and undesired targets allowing you to modify its specificity and avoid side effects.

What if the clinical trial fails?

One reason for clinical trial failure is that multiple receptors are involved in driving the pathophysiology of the disease and your molecule targets only one of them.

If this is the case SAFAN-ISP can help you find other targets involved in the same disease, showing how to modify your lead and how to create a pool of molecules for all the interesting targets.

What if some of your patented molecules could hit an unexpected drug target or if you need help in interpreting phenotypic screen results?

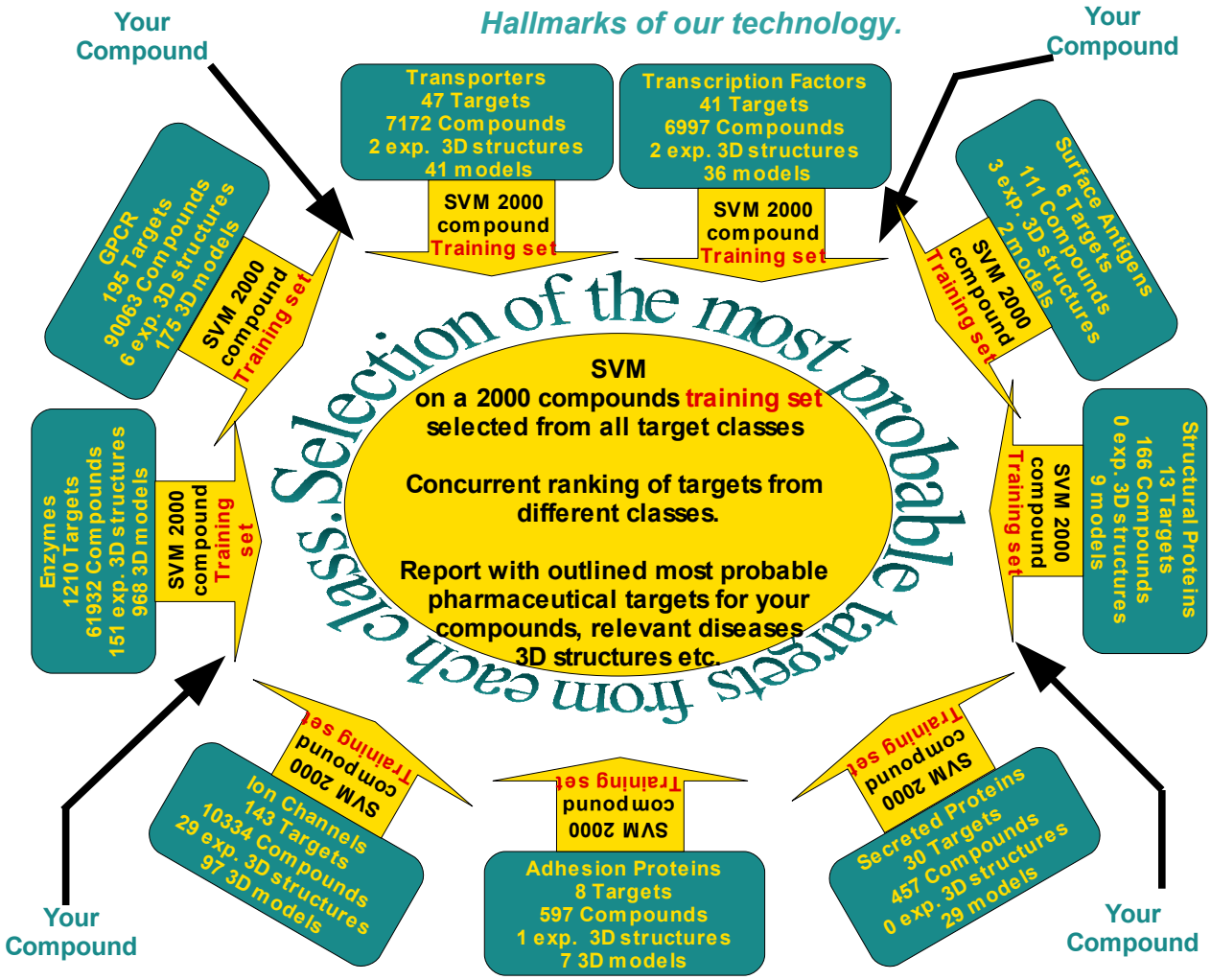
SAFAN-ISP will tell you which other targets bind to your molecules, for which diseases they have already been exploited and if the Structure Based Drug Design approach is suitable.

Using SAFAN-ISP you will save time and money!

Don't miss the opportunity to:

- ***Find the best target related to phenotypic screens.***
- ***Prevent side effects.***
- ***Prevent clinical trial failure.***
- ***Discover if some left behind molecule might become a new blockbuster.***

Hallmarks of our technology.



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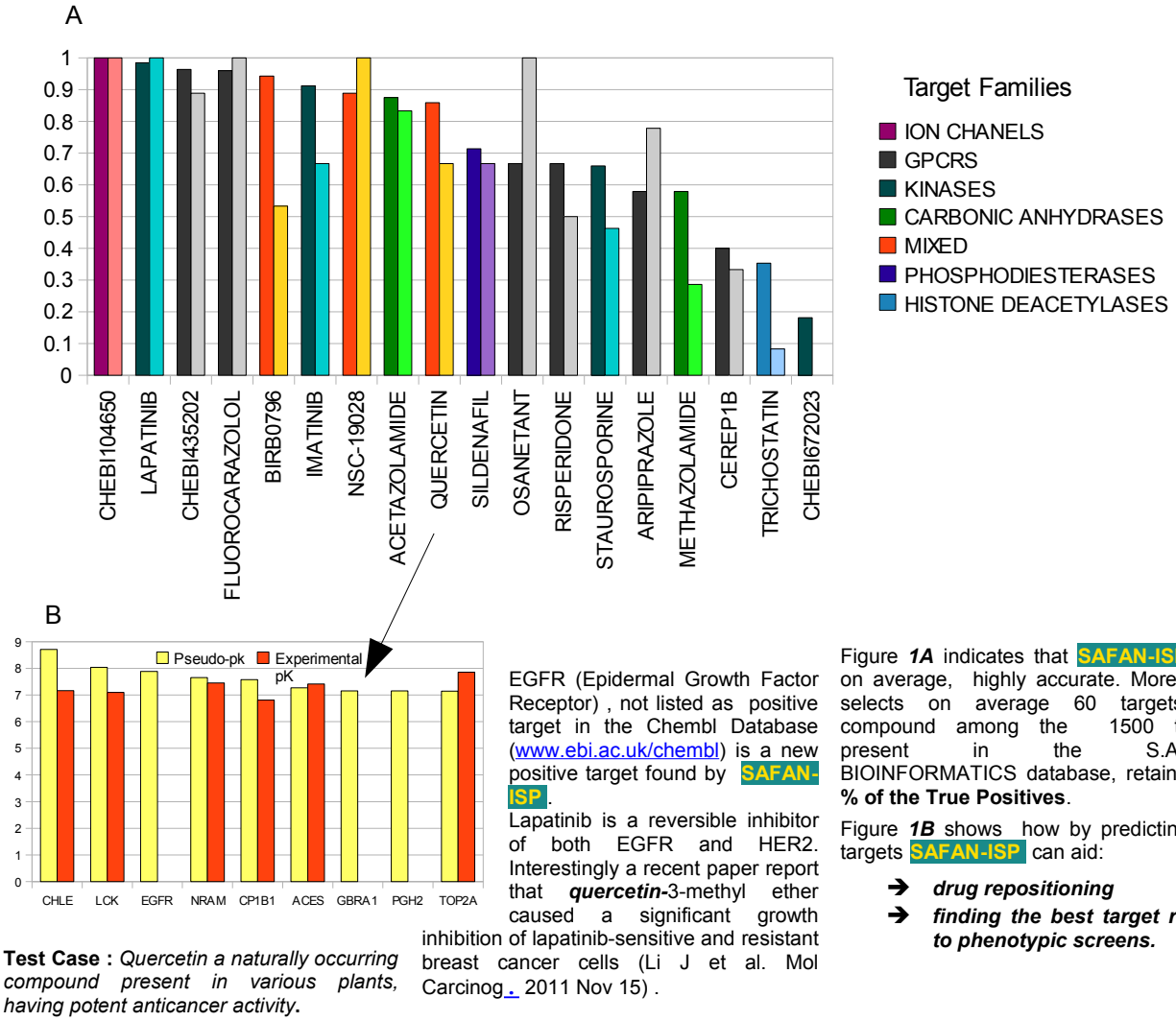
Validation of the technology

Figure 1: ***A.*** *Accuracy and Recall of the predictions: The accuracy (dark bars), computed as (True Positives + True Negatives)/ Total number of experimental data, measures the fraction of the correct predictions. The Recall (pale bars), computed as True Positives / (True Positives + False Negatives), is a measure of how many targets are not included in the prediction.*

B. *Application example: Outline of the most probable target predicted for quercetin-3-methyl ether, a naturally occurring compound present in various plants, having potent anticancer activity.*



Test Case : *Quercetin a naturally occurring compound present in various plants, having potent anticancer activity***.**

EGFR (Epidermal Growth Factor Receptor) , not listed as positive target in the Chembl Database (www.ebi.ac.uk/chembl) is a new positive target found by **SAFAN-ISP**.

Lapatinib is a reversible inhibitor of both EGFR and HER2. Interestingly a recent paper report that ***quercetin***-3-methyl ether caused a significant growth inhibition of lapatinib-sensitive and resistant breast cancer cells (Li J et al. Mol Carcinog . 2011 Nov 15) .

Figure ***1A*** indicates that **SAFAN-ISP** is, on average, highly accurate. Moreover it selects on average 60 targets per compound among the 1500 targets present in the S.A.F.AN. BIOINFORMATICS database, retaining **71 % of the True Positives**.

Figure ***1B*** shows how by predicting new targets **SAFAN-ISP** can aid:

- ➔ ***drug repositioning***
- ➔ ***finding the best target related to phenotypic screens.***

S.A.F.AN. BIOINFORMATICS offers:

- **SAFAN-SET**: **Derives** training and test sets for your compound based on S.A.F.AN. BIOINFORMATICS target library.
- **SAFAN-ISP**: **Ranks** the binding of your compound to S.A.F.AN. BIOINFORMATICS target library.
- **ISP-Docking**: **Performs** the molecular docking of your compound to the highest probable targets for which 3D structure is available or homology models can be built: i.e. 92% of S.A.F.AN. BIOINFORMATICS target library.
- **Docking-Refinement**: **Refines** the complexes that result from docking by Molecular Dynamic Simulation.

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