Drug repurposing platform for new targets/new indications search

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Drug repositioning (or drug repurposing) is the process of identification of new indications for existing drugs [1]. The final goal of our repositioning approach is the finding of new targets and new indications for selected marketed compounds whose patents are going to expire within the next 10 years.
For this purpose, a 'drug based' computational strategy was followed and 22 compounds were analyzed by two different *in silico* methodologies, target fishing and 2D-search.
In silico target fishing is a computational method which can be used to predict the biological activity profile of a query molecule. The structure-based version consists in serially docking the query molecule against a collection of protein 3D structures, with the aim of predicting the most likely binding targets which deserve subsequent *in vitro* screening [2-4].
2D-search approach is based on the similarity property principle (SPP) [5], which states that similar compounds should have similar properties. It follows that is possible to predict target interactions *in silico* in order to assess new primary target for known drugs, looking at known target binding profiles of similar compounds using chemical similarity searching. Due to its speed, the similarity search with two-dimensional (2D) fingerprints is a common method for querying databases for structures similar to a given query molecule [6], to identify new molecular targets for existing drugs.
Based on these approaches 225 molecular targets were identified. The molecular targets were filtered by some restriction criteria: target novelty for the specified compound, target related to a therapeutic indication included in our therapeutic core areas (CNS, pain/inflammation, anti-infectives).
About 30% of targets were selected out of total identified targets by target fishing and 2D-search.
The main reasons were:

- compound activity on the target was already known;
- same mechanism of action for which it was approved;
- target was not related to CNS, pain/inflammation, anti-infectives therapeutic areas;
- target was not a therapeutic target;
- therapeutic indication for compounds identified by 2D-search was not correlated to a specific molecular target

Then 14 existing approved drugs were tested on 68 molecular targets by *in vitro* assays (binding, enzyme or cellular assays). Positive results for 2 compounds on 2 innovative targets were evaluated comparing literature and patent data in order to search new potential indications for these molecules. Further characterization activities are in progress.

References

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