Network based Drug Repositioning Methodology for Neurodegenerative Diseases

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Drug discovery is a costly and time-consuming process. Although huge amount of sources has been put into drug discovery, only 20 of new drugs are approved by US Food and Drug Administration (FDA) each year. Even so, there is a declining trend in number of new drugs. Proving that drug entities already approved for one disease also works in another indication can be highly beneficial and cost effective. Repositioning refers to this concept or process, taking a drug developed for one indication and applying it to another. Many of today's re-purposed drugs were discovered through surprising observation as well as through rational observations. Although computer-aided techniques have been used in pharmaceutical research, the power of dynamical models has not yet been exploited in drug discovery. The identification of the molecular pathway that is targeted by a compound, combined with the dissection of the following reactions in the cellular environment, i.e. the drug mode of action, is a key challenge in biomedicine and the bottleneck in drug discovery. Drug discovery processes should delineate new drugs targeting the intracellular networks and immune-related pathways. In this paper we propose a computational methodology to address this challenge. For the purposes of this project we focus exclusively on the unique challenges of re-purposing drugs in Drug bank as possible combination to enhance the effect of Statin as treatment in neurodegenerative diseases. Treatment of Coronary Artery Disease (CAD) by statins is one of the top success stories in modern medicine. Statins inhibit the 3-hydroxy-3-methylglutary coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol synthesis pathway, leading to decreased circulating cholesterol level, which provide the original rationale of treating cardiovascular disease. However, accumulating evidence had emerged in the last decade; demonstrate that statins have strong pleiotropic effects such as anti-inflammatory actions in addition to the lowering of LDL both in clinical trials and pre-clinical studies. Naturally, much effort has been directed towards their therapeutic potential in diseases other than cardiovascular disease, such as neurodegenerative disease without treatment in practice. However, the reported outcome from clinical trials hasnt been so promising or even a bit controversial sometimes. Many factors contribute to the inconsistency, like

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sample size in general small in those trials, and enrolled patients have very diverse disease stages, plus pathogenesis of the disease is complex. Investigation on searching for potential synergy with another approved drug would be one attractive strategy. Therefore first we examine the biological networks that control and modulate the immune and neurological pathways using omics-based assays. We analyses the network to find drug targets in the cellular networks or pathways. Then list of connectivity map (CMap) CMap substances (build 02) were obtained from CMap webpage (https://www.broadinstitute.org/CMap/), all drug target/protein information of the CMap substances were extracted from drugbank database, drug-target network were generated from drug-protein interaction in which if a protein is a known target of a drug in drugbank, a drug-drug network were constructed from drug-drug interaction if at least one common target protein is shared. We classified the filtered CMap list (some of CMap substances are not in drugbank) into different groups according to indications information extracted from drugbank. As the next step, we utilize inferred drug-drug and drug-target networks as extra layer into our network then we searched for drugs with possible synergy with Statin. By applying our computational pipeline we could identify two candidates in context of neurodegenerative diseases to combine with Statin. As validation experiment, purified human primary T-cells were activated by plate bounding anti-CD3 antibody and soluble anti-CD28 antibody, then exposure to different conditions, the cells were stained with a fluorescence dye and followed flow cytometry to assess the viability of the cells after 6 days. Compare to control group, statin alone inhibit T cell proliferation, and compound AZ doesnt influence so much of cell viability, while combine with compound AZ could rescue the proliferation inhibition caused by Statin. The results are promising and these finding may shed light on the controversial observations in the reported outcome from recent clinical trials.

Keywords: Biological Network analysis; Drug repositioning; Neurodegenrative disease; Flow cytometry; Statin

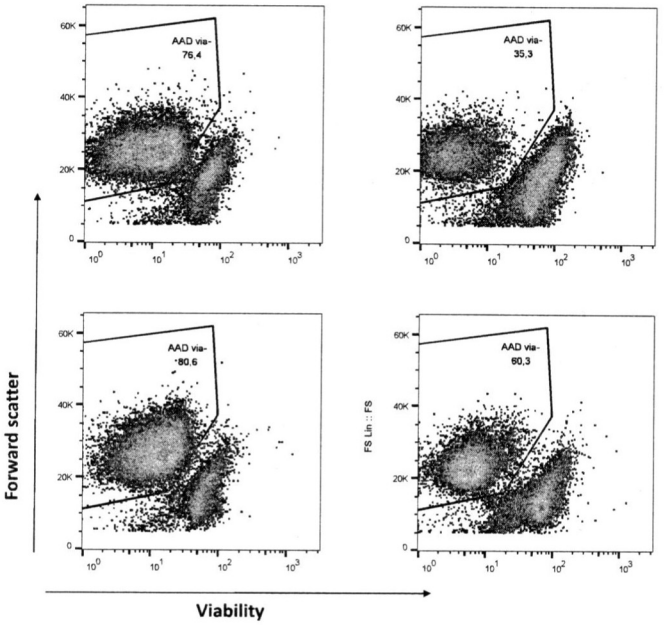

Fig. 1. Shown are the effect of stimulated control (upper left panel), Statin(upper right panel) , Az compound(bottom left panel) and combination of Statin and AZ compound(bottom right panel) on T-cell proliferation. Combination can rescue proliferation