Learning from evolution to target cancer with combinatorial strategies

Chemotherapy is the most prominently used therapy for many cancers yet it effects multiple and, in many cases, unknown targets. Of the most modern advancements in cancer treatment is the targeting of single key gene products, for example, by deploying monoclonal antibodies, and thereby reducing side effects and increasing patient survival. Recently, combinatory approaches of multiple drugs, each with a specific therapeutic target, have been very actively pursued, leading to exciting results. Among the main advantages of this multitargeting therapy are the ability to circumvent the regulation of parallel pathways, which can lead to the appearance of resistance mechanisms, while taking advantage of any synergistic effect between targets. New developments in the design of multitargeting therapies are required in order to overcome the current dominance of chemotherapy in the clinic.

A future set of guidelines for the use of these combinations of targets will presumably require multiple rounds of bioinformatic analysis and empirical validation. Ideally, a combination of therapeutic targets would be available for each different genetic background leading to the disease, i.e., therapy would be patient specific. This study aims to facilitate the design of a single molecule which is capable of specifically targeting multiple genes or proteins within key therapeutic pathways to treat complex diseases. A script to search for DNA and protein sequences with the potential for multitarget regulation was utilized to build a library of tools to target more than one gene product.

This study describes and encourages the adoption of the same strategies that have evolved in organisms to modify complex traits. For example, complex organisms display a high interactivity in their nucleotide and protein sequences in that mutational biases facilitate the search for advantageous interactions. This feature of the human genome has facilitated the recruitment of an ever increasing sophistication in the simultaneous regulation of multiple gene products. In this context, we are in a unique moment in which we are now developing the next layer of regulation, but this time, the tools will be assembled in laboratories and stored online.

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Identification of sequences common to more than one therapeutic target to treat complex diseases: simulating the high variance in sequence interactivity evolved to modulate robust phenotypes.
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