

Exploring the molecular basis of combination drugs using ToxWiz

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Drug combinations represent intriguing possibilities for new therapies. The basic principle is that two active compounds can lead to effects that are more than the sum of their parts, possibly by simultaneously blocking two parts of the same pathway, or by one compound augmenting the activity of another. Borisy et al (2003), from CombinatoRx systematically screened about 120 000 combinations of reference listed drugs to find combinations that had new activities. We investigated the handful of combinations for which new activities were found, to see if we could, using our database and software, suggest how one drug could complement another.

One of the interesting combination effects they reported was that the antiplatelet drug dipyridamole, when combined with the glucocorticoid dexamethasone, prevented TNF- α production in response to stimulation by phorbol 12-myristate 13-acetate (PMA) or ionomycin. We sought the best possible paths between these two drugs using ToxWiz and also explored additional connections between them by exploring the interaction network around these two compounds (see Figure 1).

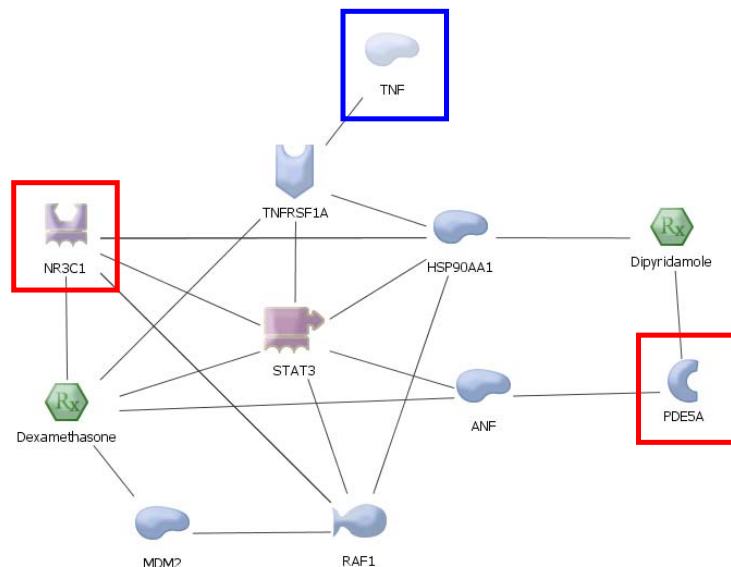


Figure 1 Some of the possible biological links between dexamethasone and dipyridamole suggested by ToxWiz. The targets for the two drugs are boxed in red. TNF-alpha is boxed in blue.

There are several possibilities for how these two drugs can affect each other inside the system. As pointed out by Borisy et al (2003), the effects of steroids, like dexamethasone, on TNF are well documented (Joyce et al, 1997), and anti-TNF effects of dipyridamole are thought to be due to its blockage of adenosine uptake. However, their combined mode of action could not be explained by these prior observations (Borisy et al, 2003).

Interrogation of CCNet's vast database of protein-protein and protein-chemical associations, however, suggested other possibilities (Figure 1). One particularly interesting possibility arises owing to a screening result, where dipyridamole was one of 220 compounds found to inhibit HSP90 in tumor cell lysate (Rodina et al, 2007). The relationship between HSP90 like molecules, such as TRAP-1, and TNF is well understood – complexes involving HSP90 are often critical for TNF mediated signaling (e.g. Chen et al, 2002). It is compelling to suggest that effects of TNF signaling could be due to the inhibition of HSP90, thus operating in a manner similar to the well known HSP90 inhibitor geldanamycin, which itself can decrease TNF secretion in response to inflammatory stimulants (Vega et al, 2003).

There are several other possibilities for interactions between these two drugs suggested by the system. These possible relationships became apparent after just a few minutes of study, thus demonstrating the power of the very fast synthesis of data from diverse sources to arrive at hypotheses very quickly.

References

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The Company was founded in 2002 by eminent scientific figures from the European Bioinformatics Institute in Cambridge, UK, the University of Cambridge and the European Molecular Biology Laboratory in Heidelberg, Germany. CCNet has facilities in three countries and is staffed by a team of expert biochemists, pharmacologists, bioinformaticians, chemists and industrial toxicologists.