

A systems biology approach for discovering improved immunotherapy drug combinations to alleviate cancer.

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Immunotherapy has recently shown great breakthroughs in the treatment of cancer, with a proportion of patients experiencing long-term survival. However, most patients do not show this positive reactivity after treatment. It is not known what molecular events differentiate a response from a lack thereof, nor what treatments might improve response rates.

In this proposal, I aimed to characterize the events that occur in a cancer that is cured by immunotherapy, while it regresses. By subsequently reinforcing those processes, using already available drugs, I aimed to tip the balance towards a response thereby increasing the cure rate.

To do this, I used animal models in which some mice respond to immunotherapy while some do not, and I used techniques developed in network science that allowed me to pinpoint the key molecules that govern the treatment response. This approach resulted in the identification of several genes that appear to play an important role in the response to immunotherapy: if we stimulated the function of these genes, the response to immunotherapy improved. I subsequently identified already existing drugs that modify these molecules in the desired manner, using online databases of drug-treated cells. Lastly, I tested whether indeed the identified drugs increase the response rate to immunotherapy. These drugs, which are commonly used in heart and skin diseases, indeed dramatically improved the cure rate when they were combined with immunotherapy.

These results show that an entirely new way of discovering drugs may be very effective: by focusing on the mechanisms that occur in a cancer when a therapy works, we can identify new combinations of drugs to improve the response to this therapy.

The approach and the drug combinations have been patented, and we are currently in negotiation with pharmaceutical companies to try and bring these therapies truly to patients with cancer, and start a clinical trial in Australia, based on these results.

In addition, based on these studies the fellow has successfully obtained subsequent nationally competitive funding to continue this work, as well as a personal research fellowship from the NHMRC.