e-therapeutics

Network-driven Drug Discovery

ENHANCEMENT OF ANTI-TUMOUR IMMUNE RESPONSES THROUGH ELEVATION OF STING

BACKGROUND

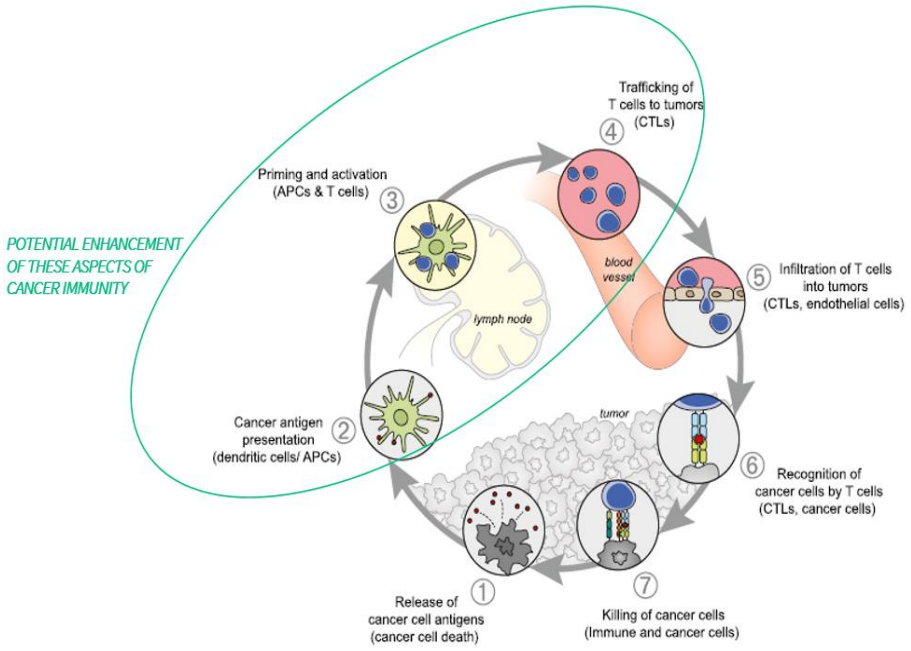
Only 20-40% of patients respond to immune checkpoint blockade (ICB) therapy. The reason for this is believed to be related to the immuno-phenotype of the tumour microenvironment (TME). In many cancer types, the presence of activated CD8+ T cells in solid tumours correlates with better clinical outcomes. A T cell-inflamed TME may be predictive of response to immunotherapies, as a high percentage of non-responders to ICB therapies have non-inflamed tumours. It may therefore be beneficial to covert non-inflamed tumours to an inflamed phenotype. This may be achieved by interventions directed at promoting T cell priming, and T cell recruitment into tumour sites.

THE OPPORTUNITY

e-therapeutics' platform can be used in diverse therapeutic areas to identify novel and differentiated hits for subsequent hit-to-lead and lead optimisation.

e-therapeutics can apply its **Network-driven Drug Discovery** platform to identify small-molecules that could potentially convert a non-inflamed tumour microenvironment to an inflamed phenotype by elevating STING.

One approach to achieving this may be via the activation of STING (Stimulator of interferon genes) protein which may enhance treatment with immune checkpoint blocker therapy by stimulating T cell priming and migration to the tumour. STING has recently garnered attention in the immune-oncology space, as it has been found that it can be activated by self-DNA fragments of tumour cells, and agonists of STING have been shown to exert potent anti-tumour activity. Notably, STING activation has been shown to enhance tumour regression where treatment with immune checkpoint inhibitors alone has not worked.



Priming of $CD8^+$ T cells

Induction of chemokines that increase migration of T cells to the tumour

Repolarization of macrophages from M2 to M1

Conversion of immune-suppressive MDSCs to immune-stimulating MDSCs

Picture from Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013; 39: 1–10.

THE APPROACH

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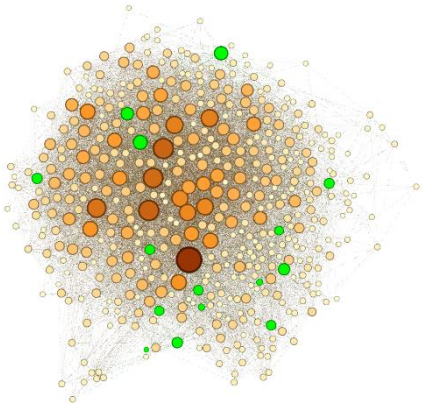
Most STING-targeting therapies currently in development are synthetic cyclic dinucleotides, aimed at direct activation of STING. However, these molecules have short half-lives and must be injected directly into tumours. A small molecule STING agonist would allow a longer half-life, as well as oral administration, offering systemic exposure and access to tumours inaccessible through direct injection.

A number of approaches can be utilized that combine biological expertise with *in silico* analyses and network-driven drug discovery.

We have built networks based around STING activation and its negative regulators, as well as networks based upon gene knockdowns and mutations that result in elevation of STING. These can be combined with data derived from chemoproteomic footprints of compounds that are known to elevate STING, as well as proteins derived from relevant functional Gene Ontology (GO) annotations. Interrogation of these networks using our NDD platform can output high impact compounds that can be put into phenotypic screens.



Example network based on regulation of STING activity (Green dots = Negative regulators of STING)

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