e-therapeutics

Network-driven Drug Discovery

REGULATORY T CELLS (T_{REG}) IN THE TUMOUR MICROENVIRONMENT

BACKGROUND

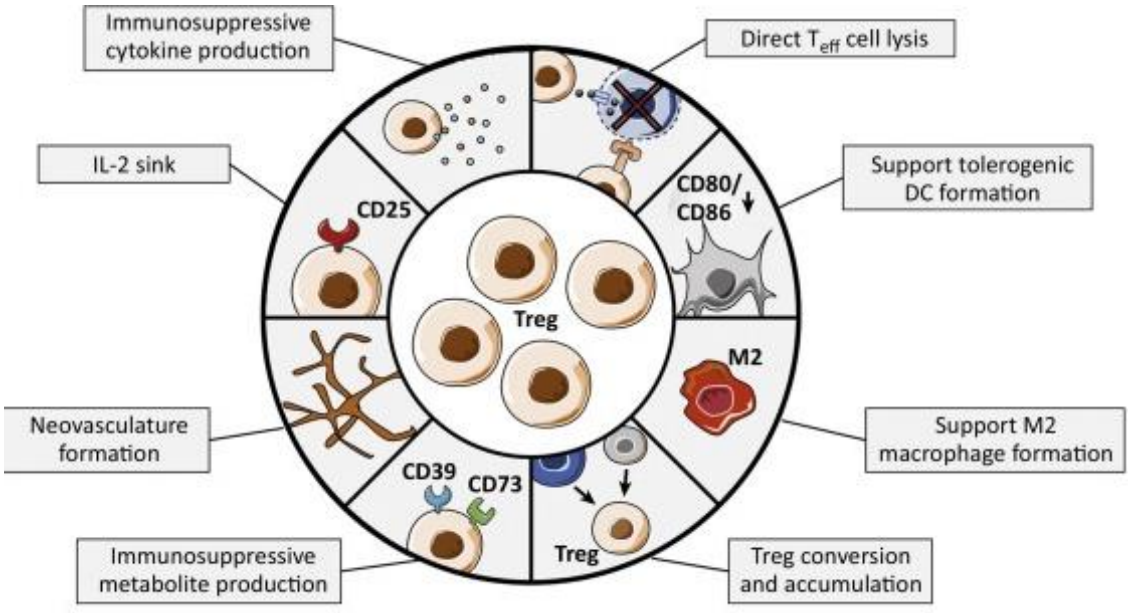
Regulatory T cells (Tregs), present throughout the body, are essential for the prevention of autoimmunity and for the maintenance of immune homeostasis. Tregs also play a pivotal role in inducing tumour-specific immune tolerance. Infiltration of tumours with high numbers of Tregs is often associated with poor clinical prognosis.

The role of Tregs in immune escape is supported by clinical studies and numerous *in vitro* studies where Treg depletion has been reported to increase anti-tumour immune responses and to reduce tumour burden. Tumour immune tolerance brought about by Tregs constitutes a major barrier to therapeutic efforts to mobilize the immune system to induce tumour regression. Breaking down tumour-specific tolerance is a key step in the development of effective and durable cancer immunotherapy, with Treg cells a key target.

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.

Tregs are key cells involved in bringing about tumour-specific immune tolerance. e-therapeutics' **Network-driven Drug Discovery** platform may be used to identify small-molecules that can attenuate intra-tumoral Treg functions and stability.

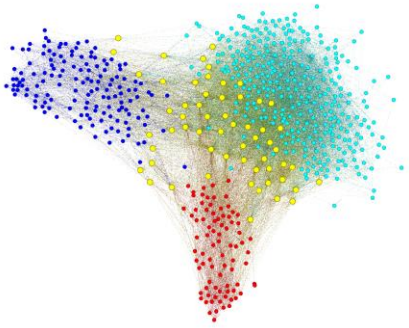


Consequences of intra-tumoral Treg accumulation (Wang *et al*. 2017)

THE APPROACH

Network-driven Drug Discovery

Intra-tumoral Tregs could be targeted via a number of different system level processes, such as Treg depletion, inhibition of Treg trafficking, modulation of plasticity, suppression of Treg functions, or suppression of Treg stability. This is illustrated in the network below.



Blue = Treg Migration
Red = Treg Stability
Cyan = Treg Function
Yellow = Proteins overlapping between functions

It has been shown that intra-tumoral Tregs exhibit some unique requirements that are not shared with Tregs elsewhere in the body... Hence, as well as targeting the general Treg processes above, it may be possible to specifically target intra-tumoral Tregs and thereby avoiding unwanted autoimmunity.

- Rather than targeting processes that are required for general immune maintenance and self-tolerance, identify mechanisms that are selectively used by Tregs in tumours – potential to avoid unwanted autoimmunity

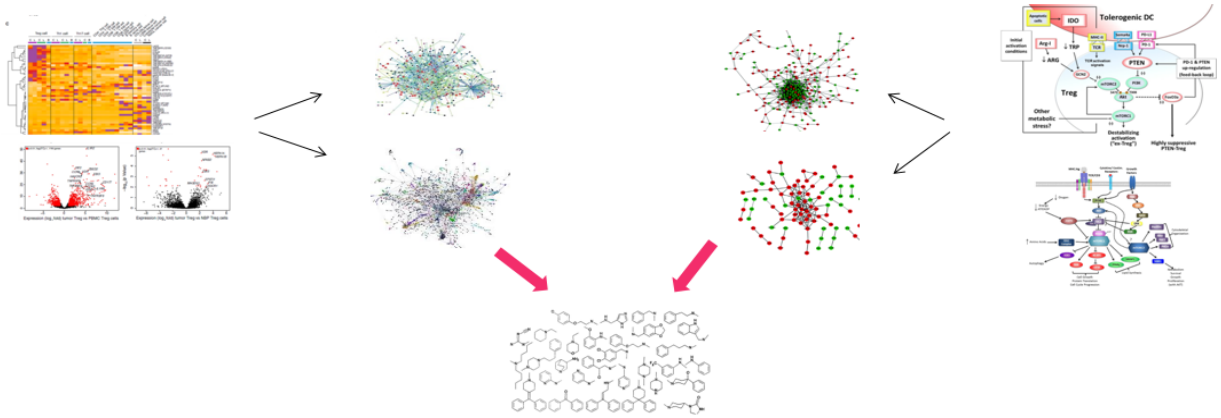
(1) Tumour-infiltrating Treg cells display specific gene signatures

Use these data to construct data-driven networks

Potential to specifically modulate tumour-infiltrating Treg cells without impacting Treg cells elsewhere in the body?

(2) Target signalling mechanisms that maintain Treg functionality and stability within tumours

Build biological networks based around these mechanisms, find compounds which impact the networks



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