e-therapeutics

Network-driven Drug Discovery

PREVENTING MACROPHAGE POLARIZATION IN CANCER

BACKGROUND

Tumour-associated macrophages (TAMs) are the most abundant leukocytes in tumour stroma. TAMs derive from tissue-resident macrophages or from recruited inflammatory monocytes conditioned by the tumour microenvironment.

TAMs show a high level of diversity and plasticity and are critical for tumour initiation, propagation, and dissemination. This is achieved by suppressing anti-tumour cytotoxic T-cells, and promoting tumour growth, angiogenesis and extracellular matrix (ECM) modulation. Macrophages differentiate phenotypically into different populations according to the local environment, with two extreme subsets being M1, or classically activated macrophages (pro-inflammatory phenotype, with increased HLA-DR, IL-12, and IL-6), and M2, or alternative activated macrophages (pro-tumorigenic, driven by tumour environmental factors such as hypoxia, IL-10, IL-4 and TGFβ). TAMs are predominated by the pro-tumoural M2-like phenotype.

In solid tumors, such as those in breast and pancreatic cancer, infiltrating TAMs correlate with poor outcome. TAMs respond to hypoxia *via* expression of HIF factors, thus hypoxia may represent one of the polarization signals favouring the pro-tumoural M2-like TAM subset.

THE OPPORTUNITY

e-therapeutics has successfully applied its **Network-driven Drug Discovery (NDD)** platform to identify active small-molecules across different areas of disease.

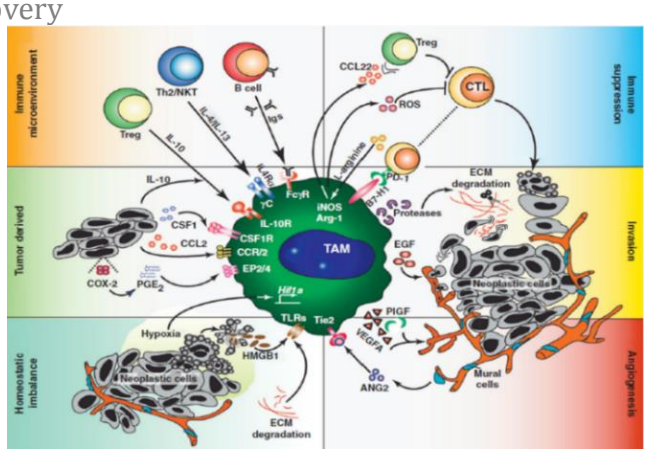
e-therapeutics' platform can be used to discover distinctive chemical matter hits which serve as rational starting points for medicinal chemistry programmes.

In the tumour surroundings, stromal and tumour factors lead to an immunosuppressive microenvironment that disrupts the tumoricidal function of macrophages. The application of omics data, network biology and NDD could help to discover new drugs in an area of biological complexity.

THE APPROACH

Network-driven Drug Discovery

Targeting the biological processes behind TAM polarization (to be anti-tumoural) is a promising approach for cancer immunotherapy. Multiple signals converge in the tumour micro-environment that contribute to the macrophage phenotype. Macrophage plasticity indicates that polarization can be manipulated. By using network biology our approach is to target the network of interactions that underpins polarization to modulate the macrophage pro-tumoural phenotype.



Tumour associated macrophages polarization signals

Figure from Ruffell *et al*. 2012.

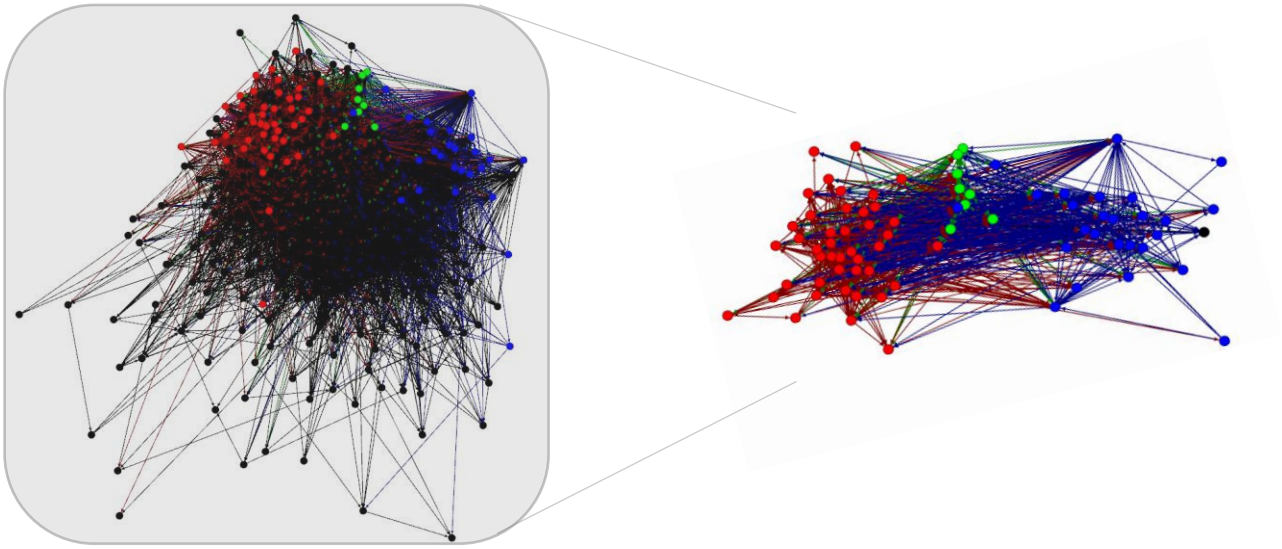
STRATEGIES

Networks can be constructed using a diversity of data and approaches

- Genes that are modulated and rewired by tumour cell activators and homeostasis imbalance
- Expression of macrophages genes induced by immune microenvironment and immune system regulators
- Extraction of networks from TAM-specific gene signature (disease-macrophage signature)
- Using proteins & genes of mechanisms known to drive/prevent macrophage polarization

Example of network derived from genes upregulated in breast cancer associated - macrophages

Hypoxia and IL-4 signature extracted from breast cancer TAMs



An example of a network derived using differentially expressed gene signatures from macrophages isolated from breast cancer patients is shown on the left panel above (data from Chung *et al*. 2016) in which the hypoxia gene signature (red) and IL-4 gene signature (blue) are highlighted. Green nodes represent the up-regulated genes in macrophages that overlap with IL-4 and hypoxia processes.

Analysing the networks using our proprietary *in silico* platform we can identify compounds that are able to prevent macrophage polarization. Those compounds can then be tested *in vitro*. Primary human macrophages are difficult to isolate in sufficient numbers; however, macrophages of the M1 or M2 phenotype can be differentiated, *in vitro,* from human monocytes. Markers of polarization can be analysed *in vitro* to assess phenotype (*e.g*. receptor expression, arginase, IL-10, CCL2, for the M2 immunosuppressive phenotype). Those markers can be followed for compound screening and selection.

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