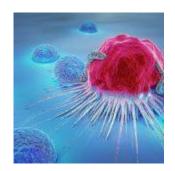
Reprogramming the Tumour Microenvironment — Improving Cancer Survival



Cancer, a disease effecting every population in the world, consistently challenges researchers and clinicians into creating innovative treatments and therapeutic approaches. Claiming the lives of approximately 600,000 people in the United States' of America alone, new therapeutics are needed to combat this destructive disease.

Immunotherapy targeting of immune checkpoints, a relatively new field of cancer treatment, has shown to achieve consistent and favourable responses across several tumour types. However, this benefit does not always clinically translate to most patients with cancer, resulting in low response rates and insufficient responses. New immune-mediating agents and strategies need to be designed and evaluated to improve the current state of immunotherapeutics. A sufficient amount of highly functional immune effector cells within the tumour microenvironment (TME) are required for immune-mediated attack of established poorly immunogenic carcinomas leading to sustained tumour eradication. Clinically there is a need for new and effective therapeutic strategies to convert the TME to a functionally inflamed immune landscape. Researchers from the National Cancer Institute in Bethesda, USA have unlocked the potential of combination therapy to improve cancer survival through the manipulation of the TME.

Playing a significant role in cancer immunotherapy, the cytokine Interleukin-12 (IL-12) provides the link between innate and adaptive immunity. Produced in majority by activated antigen-presenting cells which include: dendritic (DCs), monocytes, and macrophages, IL-12 induces proliferation and lytic function of natural killer (NK), NKT, and T cells. In addition, differentiation of T cells into a type 1 (Th1) effector phenotype, induced by IL-12, further induces cytokine secretion, notably IFNy, favouring cellmediated immunity. NHS-IL12 is a recombinant immunocytokine composed by the human antibody NHS76 fused to two IL12 heterodimers. NHS76 targets exposed DNA in necrotic areas, thus directing IL-12 to the TME, and reducing systemic exposure. There is ever increasing preclinical evidence suggesting that the anti-tumour potential of NHS-IL12 may uncovered when used in combination with other treatments.

Preclinical and clinical evidence suggest that immunotherapy combined with epigenetic modulators, such as histone deacetylase inhibitors (HDACi), can attain significant antitumour efficacy. Entinostat, a class I HDACi, inhibits regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), and promotes tumour infiltration of lytic CD8+T cells. Hicks, et al., hypothesized that the immune-complementary effects of NHS-rmIL12 and Entinostat synergize to promote significant antitumour efficacy in well-established tumours.

In the presented study, Hicks, et al., showed that combination therapy with Entinostat plus NHS-rmIL12 leads to increased and significant survival in murine models i.e. poorly immunogenic EMT6 breast tumours, and MC38 and CT26 colon carcinoma models. They successfully demonstrated an alternative approach to convert the TME to a functionally immune inflamed congregation by stimulating cross-talk between innate and adaptive immunity. Reprogramming and manipulation of the TME efficiently sustained tumour eradication, destroying

established murine breast and colorectal tumours. Through the use of Entinostat with the recombinant immunocytokine NHS-rmIL12 achieved significant tumour resolution in three distinct models with a range of immunogenicity and sensitivity to anti-PD-L1 monotherapy, conferring longlasting protective immunity in all three models. In addition, they were able to confirm protective memory to be tumour specific, also highlighting that the specific combination may be a viable option to treat patients harbouring innate or acquired resistance to immunotherapeutic checkpoint inhibition. However, they did illustrate that NHS-rmIL12 in combination with Entinostat induced only minor, transient toxicity.

To summarise, through the use of TME single-cell transcriptome, proteome, and immune cell analysis, they were able to show that that combination therapy elicits significant and sustained anti-tumour efficacy and complete responses by shifting the TME to a functionally inflamed landscape, where the concerted actions of highly active CD8+ T cells, neutrophils, and M1-like anti-tumour macrophages leads to complete tumour eradication. In addition, they provided further evidence to justify the combination of NHS-IL12 with Entinostat for use in the clinical setting.

Journal Article: Hicks, et al., 2021. <u>Tumour-targeted</u> <u>interleukin-12 and entinostat combination therapy improves</u> <u>cancer survival by reprogramming the tumour immune cell landscape</u>. Nature Communications.

Summary by Stefan Botha