

PRESENTATION TITLE: *Drug-induced Xenogenization: new frontiers in cancer chemoimmunotherapy*

ABSTRACT: Immune checkpoint inhibitors have provided a huge breakthrough in cancer therapy and renewed interest in immunotherapies. However, not all patients are sensitive to immune checkpoint blockade and different combination strategies are being evaluated in order to increase the number of individuals who can benefit from these therapies. It is well established that non-self-antigens generated by tumour somatic mutations confer immunogenicity and induce powerful specific immune response. Furthermore, it has been demonstrated that anti-PD-1 therapy induces a specific T-cell response directed towards neo-antigens, and shows high efficacy especially when a high mutation load is associated with tumour cells. Therefore, the therapeutic strategies aimed at the induction of neo-antigens must receive careful attention for their potential synergistic effect with immunotherapies.

Much interest has been generated by the possibility of combining chemotherapeutic approaches with immunotherapy. Although cancer chemotherapy has historically been considered immune suppressive, it is now well recognised that specific chemotherapies can enhance anti-tumour immunity. In particular, one hypothesis is that changes induced by chemotherapy within the tumour micro-environment can support a specific T-cell mediated response, further improved by immune-stimulating agents. This has particularly been the case for a widely used class of chemotherapeutics, namely, alkylating agents. Alkylating chemotherapy involves a class of compounds that covalently modify DNA by either bi-functional molecules able to generate inter-strand or intra-strand alkyl crosslinks or mono-functional compounds methylating individual bases (triazenes). The latter in particular [i.e. dacarbazine (DTIC) and temozolomide] can potentially lead to the generation of neo-epitopes immunologically discernible from self antigens.

More than 40 years ago, our group discovered that novel transplantation antigens can be induced in vivo or in vitro by treating murine leukemia with DTIC. This phenomenon, that we called “Chemical Xenogenization” (CX) and more recently named “Drug-Induced Xenogenization” (DIX) suggests that the molecular bases of DIX rely on mutagenesis induced by methyl adducts to oxygen-6 of DNA guanine. These observations suggest that mutation-dependent neo-antigens obtained by appropriate pharmacological intervention can improve the therapeutic efficacy of selected immune checkpoint inhibitors in cancer patients, improving clinical outcomes.

Chemotherapy also improves the response of CD8⁺ T cells to cancer vaccines. In particular, DTIC has confidently been associated with a broadening of the antigenic breadth and clonal diversity of anti-tumour immunity when combined with vaccination, with significant clinical benefit in the prevention of melanoma relapse.

Noteworthy, several antitumour agents including the bi-functional alkylating agent cyclophosphamide, have shown a number of immunoenhancing effects, including modulation of antigen cross presentation, along with an increase in the number of regulatory T cells and the induction of a “cytokine storm”-driven homeostatic lymphoid proliferation.

These observations suggest that alkylating agents can contribute both to the induction of a protective immunity and to immune homeostatic mechanisms, while reveal the valuable opportunity to design specific combined treatments potentially capable of providing a highly efficient suppression of malignant cell growth.