A Novel Small Molecule PABA Derivative C45-NA Enhances Anti-Tumor Activity

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Researchers at NYU Langone Health have identified Para-Amino Benzoic Acid (PABA) as a chemo and radiosensitizer with activity in melanoma and breast carcinoma as well as in ovarian cancers. While PABA had no direct cytotoxic activity, it enhanced the effects of radiation and Taxol. A clinical trial was carried out to assess the effects of PABA on a salvage protocol, which included Taxol and Carboplatin in melanoma subjects that had failed first line therapy with Dacarbazine (DTIC). Based on the results from this trial that showed nearly 35% of the patients exhibited clinical responses, the group identified a more effective PABA-like molecule. After screening several compounds, a molecule termed C45-Na was synthesized and tested in animal models.

C45-Na directly inhibits the growth of histologically distinct tumors while having minimal activity on normal cells. A dramatically enhanced anti-tumor activity was observed in vivo at nanomolar levels of C45-Na. These findings are consistent with the possibility that C45-Na may affect stromal cells within the tumor microenvironment that contribute to malignant tumor growth. While C45-Na exhibited little activity against normal fibroblasts, it potently inhibits the growth of activated CAF-like cells, which were derived from extended culture of dermal fibroblast in the presence of multiple growth factors. C45-Na-treated tumors had fewer CAF-like cells and showed elevated levels of lymphocytic infiltrates. A comprehensive KinomeScanTM screen reveled that C45-Na inhibited a group of kinases including Iκb kinases IKK-α and IKK-βas well as EGFR. Macrophages from tumors treated with C45-Na expressed elevated levels of IL-23 and reduced levels of arginase, a signature profile consistent with an anti-tumorigenic M1 phenotype.

The preliminary studies provide evidence that C45-Na may represent an innovative new therapeutic for the treatment of malignant tumors that functions by reprogramming stromal components of the tumor microenvironment to enhance immune mediated control. C45-Na represents the first of a new class of potentially clinically useful small molecules with the capacity to potently and selectively reprogram stromal cells within the tumor microenvironment to assist in orchestrating enhanced immunological control of malignant tumors such as melanoma growth.

Advantages

- C-45 specifically targets tumor cells
- Potentiates the tumoricidal activity of radiation and ionization therapy
- Potential to develop lead compound resulting in improved tumor-specific treatment for numerous cancers including melanoma

IP Status

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