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Platelets Engineered to Express Interleukin-24 Inhibited Melanoma Tumor Growth in Mice

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Abstract:
Background: Activated platelets secrete agents (e.g., cytokines) that can promote solid tumor growth & cancer metastasis. Previous studies showed that hematopoietic stem cells (HSC) can be genetically modified to induce platelets to express & secrete proteins to establish hemostasis in animal models of bleeding disorders. Interleukin-24 (IL-24) is a cytokine (normally produced by activated monocytes, macrophages & T−helper cells) with cytotoxic & anti-angiogenic activity preferentially towards cancer cells. Thus, we hypothesized it may be feasible use HSC gene transfer to target platelet synthesis, storage & secretion of IL-24 to inhibit tumor growth. **Aims:** To investigate if HSC gene transfer targeting IL-24 synthesis, storage & secretion from platelets can inhibit melanoma in mice. **Methods:** C57BlL/6 mice were transplanted with bone marrow transduced with a lentiviral construct encoding a megakaryocyte−specific *ITGA2B* gene promoter driving synthesis of IL-24 gene. Four weeks after transplant, IL-24 protein was characterized in platelets by flow cytometry. Murine melanoma cells ($1x10^6$) were implanted in mice at 5 weeks after transplant. Tumor size was measured in IL−24 & control groups using a digital caliper periodically for 4 weeks. Then mice were sacrificed to record tumor mass. **Results:** Flow cytometry showed that HSC gene transfer of murine bone marrow led to synthesis & storage of IL-24 in platelets. An elisa assay showed that activated platelets could secrete IL-24 in vitro. At 30 days after implant of melanoma cells, platelet IL−24 mice displayed significantly smaller (≈50%) tumor size (550 ± 101mm^3) & weight (599 ± 120 mg) compared to control mice with larger tumor size (1120 ± 114 mm^3) & weight (1391 ± 134 mg) n≈5 mice/group ($p<0.05$) indicating that platelet IL−24 inhibited tumor growth *in vivo*. **Conclusion:** HSC gene transfer can be utilized to induce synthesis, storage and secretion of anti-oncogenic agent IL−24 in platelets. Melanoma tumor challenge in mice with platelet IL−24 showed a significant decrease in tumor growth suggesting that platelets may serve as an ideal therapeutic vehicle to treat cancer.
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Author Disclosure Information:

D.A. Wilcox: 1; Commercial Interest *i.e. Company X*; Baxter Healthcare Corporation. 1; What was received? *i.e. Honorarium*; Honorarium. 1; For what role? *i.e. Speaker*; Advisory Committee.
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