ANTICANCER EFFICACY IN A PRECLINICAL MODEL OF LUNG CANCER USING QBKPN SITE-SPECIFIC IMMUNOMODULATION

Momir Bosiljic1, Shirin Kalyan1,2, Rebecca Anderson1, Mark Bazett1, Angela Zhang1, Beryl Luk1, Natalie Wong1, David Mullins1,3, Hal Gunn1

1 Qu Biologics Inc., Vancouver, BC, Canada; 2 University of British Columbia, Vancouver, BC, Canada; 3 Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

Introduction

The immune system is armed with the intrinsic capacity of recognizing and eliminating cells that have undergone malignant transformation. The observation that an intricate relationship exists between immune activation and cancer dates back to the 1700’s, when spontaneous tumour remission was observed in some patients experiencing acute microbial infections. Building upon this history, Qu Biologics has discovered that repeated subcutaneous injection of an immunotherapy derived from a species of killed bacteria known to commonly cause infection in a particular organ or tissue may provide an effective method for the treatment of cancers growing in that organ/body site. We hypothesize that Qu’s proprietary platform of immunotherapies, called Site-Specific Immunomodulators (SSIs) (Figure 1), stimulate the body’s immune system to reverse the immune suppression and dysfunction present in the tumour microenvironment, enabling effective anti-cancer immune responses. To test this hypothesis, we evaluated tumour growth and survival in preclinical lung cancer models.

Methods

Female C57BL/6 mice aged 8-10 weeks were used in these studies. QBKPN (lung targeted SSI) and Placebo (vehicle control) were administered subcutaneously every second day beginning at 10 days prior to tumour inoculation. Injections were continued every second day post tumour injection. 200,000 B16 (Figure 2 and 4) or Lewis Lung Carcinoma (LLC) tumour cells (Figure 3) were injected into the lateral tail vein. For the LLC survival study (Figure 3), animals were euthanized using a humane endpoint scoring scale. Tumour counts were performed on lungs inflated/flushed with PBS and fixed in Bouin’s fixative. Lung tumour nodules were counted independently by 2 researchers and the average was used for statistical analysis. Flow cytometry was performed on disaggregated lung tissue (Figure 2).

Results

Anticancer efficacy was associated with site-specific infiltration of newly recruited neutrophils and monocytes to the lung (Figure 2) and mobilization of antigen presenting cells in the lung-draining lymph node (data not shown) using the B16 i.v. tumour model. In the established LLC model, repeated subcutaneous administration of Qu’s lung specific SSI, QBKPN, significantly reduced tumour burden at day 16 post-inoculation (p<0.0001), improving median survival by 10 days (p<0.005) (Figure 3). Similar results were obtained using the B16 model, an aggressive and poorly-immunogenic melanoma cell line growing as metastatic-like lesions in the lungs (Figure 4), demonstrating that site-specific anticancer efficacy is independent of cancer type.

Conclusions

We demonstrate that QBKPN SSI provides animals with a significant survival advantage in an LLC model by reducing tumour nodules in the lungs. In addition, QBKPN SSI was effective in a B16 melanoma model demonstrating that QBKPN stimulates an anticancer immune response in the lungs regardless of cancer type. These data complement our compassionate use clinical experience with SSI (please see Sutcliffe et al., CCIC poster #28) and provide evidence that Qu’s SSI platform may be an innovative cancer immunotherapy approach for reconstituting effective immunosurveillance in the tumour microenvironment and improving therapeutic outcomes for cancer patients. QBKPN is currently being studied in a Phase 2a clinical trial in patients with non-small cell lung cancer, in collaboration with the BC Cancer Agency (Trial NCT02256852).

Figure 1. SSIs stimulate immune function in the targeted organ or tissue
Through experience, the immune system has learned the tissue specificity of common bacterial pathogens. Qu’s SSIs are designed to recruit activated immune cells to the targeted organ/tissue in which the bacterial species commonly causes infection to restore normal immune function in the context of disease.

Figure 2. QBKPN (lung targeted) SSI recruits immune cells to the lungs
A. Neutrophils (CD11b+Ly6G+) significantly increase in the lungs and circulation (data not shown) following QBKPN SSI treatment in mice challenged with B16 melanoma tumour cells intravenously. B. Inflammatory monocytes (CD11b+Ly6C+) significantly increase in the lungs and circulation (data not shown) with QBKPN SSI treatment compared to Placebo treated animals. (N=5 mice/group; two-tailed t-test used to determine statistical significance; * p<0.05, ** p<0.01).

Figure 3. QBKPN SSI treatment improves survival and reduces tumour burden in a LLC lung cancer model
A. C57BL/6 mice were inoculated intravenously with LLC cells as a way to directly seed tumour cells into the lungs. QBKPN and Placebo treatments were used to assess QBKPN efficacy on animal survival. QBKPN treatment resulted in significant survival advantage compared to the Placebo group. (N=10 mice/group; Mantel-Cox (log rank) test used to determine statistical significance; ** p<0.01) B. Mice treated with QBKPN had a markedly lower number of tumour foci/nodules in the lungs 14 days after LLC inoculation compared to the Placebo group. (N=5 mice/group; two-tailed t-test used to determine statistical significance; * p<0.05).

Figure 4. QBKPN is efficacious in a lung metastases model of B16 melanoma
A. C57BL/6 mice were injected intravenously with B16 melanoma cells in order to seed the lungs with tumour cells. Lungs were excised 18 days post B16 tumour injection. The left lung lobe was fixed in Bouin’s fixative for easier visualization of nodules. B. Tumour counts from panel A are highly significant (box and whiskers plot). (N=5 mice/group; two-tailed t-test used to determine statistical significance; *** p<0.001).