Site-Specific Immunomodulators (SSIs) are Novel Immunotherapies for Cancer

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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. However, there was a missing link between site of cancer and usual infection site of pathogen. 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 burden and survival, as well as innate immune cell recruitment, in preclinical lung cancer models.

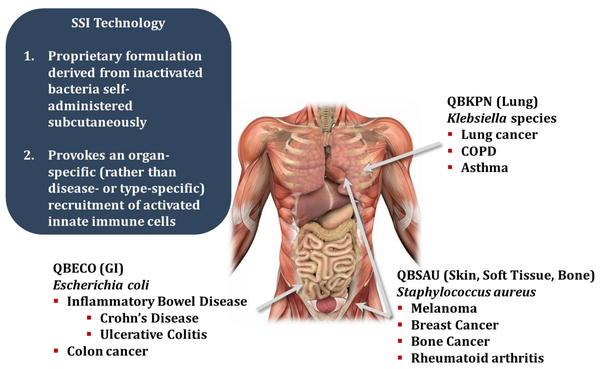

Figure 1. SSIs stimulate immune function in the targeted organ or tissue

Methods

Female C57BL/6 mice aged 8-10 weeks were used in these studies. SSIs **(Figure 2-4)** 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. Lewis Lung Carcinoma (LLC) tumour cells (**Figure 2 and 4**) or 200,000 B16 (**Figure 3**) were injected into the lateral tail vein. For the LLC survival study (**Figure 2A**), animals were euthanized using a humane endpoint scoring scale. For the efficacy studies **(Figure 2B, 3, and 4)**, tumour counts were performed on lungs inflated/flushed with PBS and fixed in Bouin's fixative. Lung tumour nodules were counted manually, and flow cytometry was performed on disaggregated lung tissue. A compassionate use study was conducted in patients with advanced cancer (N=254) (including cancer of the breast, prostate, lung, colon, liver, skin, bone, and ovary) treated with one or more SSIs for up to 3.5 years **(Figure 5)**.

Results

In the LLC model, repeated subcutaneous administration of Qu's lung specific SSI, QBKPN, significantly reduced tumour burden at day 14 post-inoculation ($p<0.001$), improving median survival by 10 days ($p<0.01$) (**Figure 2**). 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 3**), demonstrating that lung-specific anticancer efficacy is independent of cancer type. When compared to mice treated with non-lung specific SSIs (QBECO and QBSAU), only those treated with QBKPN had significantly lowered tumour burden on day 15 **(Figure 4A)**, correlating with increased monocyte recruitment to the lung **(Figure 4B)**. In the compassionate use study, patients treated with SSIs had a 20-month longer median survival than those not treated with SSIs, and a 12-month longer median survival time when case-matched **(Figure 5)**.

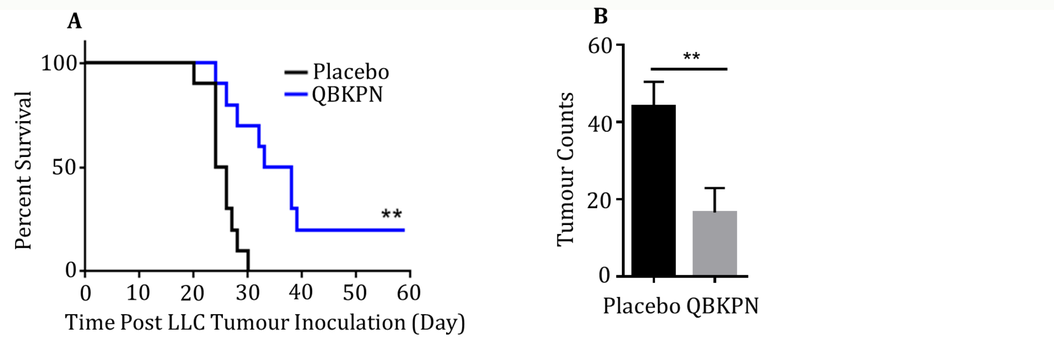

Figure 2. QBKPN SSI treatment improves survival and reduces tumour burden in a LLC lung cancer model
A. QBKPN treatment resulted in significant survival advantage in the LLC model. (N=10 mice/group; ** $p<0.01$ by log-rank test) **B.** Mice treated with QBKPN had significantly fewer tumour nodules in the lungs 14 days after LLC inoculation. (N=5 mice/group; ** $p<0.01$ by two-tailed t-test).

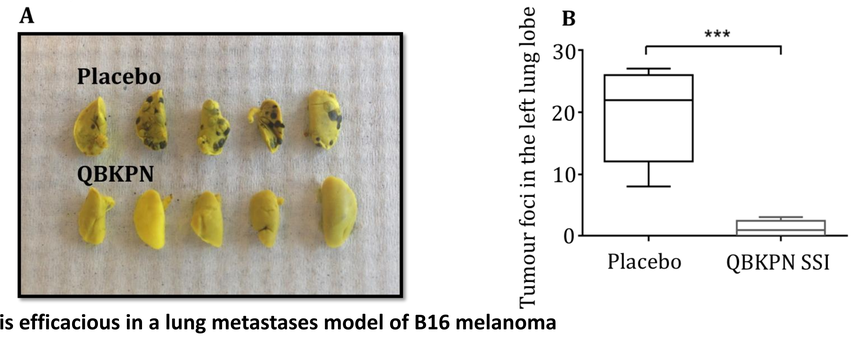

Figure 3. QBKPN is efficacious in a lung metastases model of B16 melanoma
A. Left lung lobes of mice from the B16 lung metastases model. **B.** Lung tumour counts enumerated from **A** were significantly lower in QBKPN-treated mice. (N=5 mice/group; *** $p<0.001$ by two-tailed t-test).

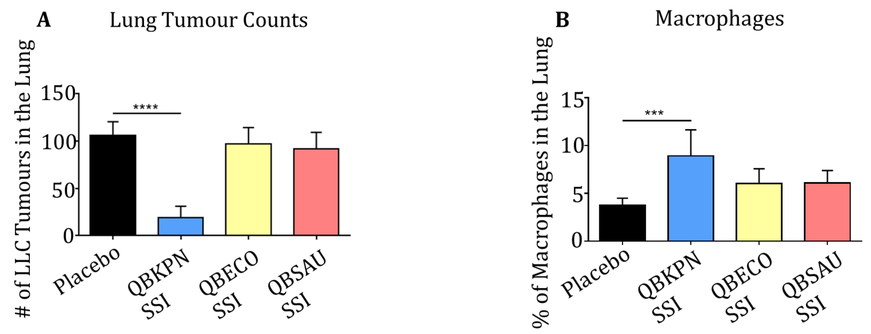

Figure 4. QBKPN SSI shows site specificity in efficacy and immune cell recruitment in a LLC lung cancer model
A. C57BL/6 mice treated with the lung-targeting QBKPN, not other SSIs, had significantly fewer tumour nodules in the lungs 15 days after LLC inoculation. **B.** There was also a significant increase in macrophages ($CD11b^{+}Ly6C^{high}$) in the lungs. (N=5 mice/group; *** $p<0.001$, **** $p<0.0001$ by one-way ANOVA).

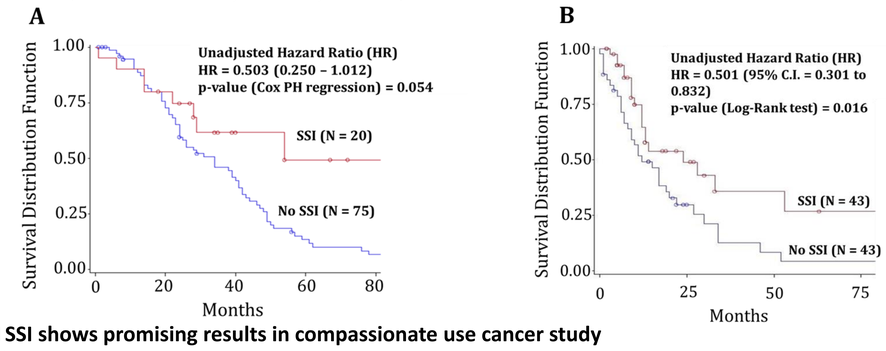

Figure 5. QBKPN SSI shows promising results in compassionate use cancer study
A. Comparison of survival in patients with metastatic breast cancer treated with SSI to those at the same clinic not treated with SSI. **B.** Same comparison in **A** performed in a case-matched study in all cancer patients.

Conclusions

QBKPN SSI is efficacious in two different pre-clinical lung cancer models. It shows site specificity in efficacy and innate cell recruitment when compared side-by-side with other SSIs in the LLC lung cancer model. These data complement our compassionate use clinical experience with SSIs, and provide evidence that Qu's SSI platform may be a novel cancer immunotherapy approach for restoring effective immunosurveillance in the tumour microenvironment and improving therapeutic outcomes for 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).