# Site-Specific Immunomodulators exploit the potent immune response to infection to effectively mobilize innate anti-tumour immunity

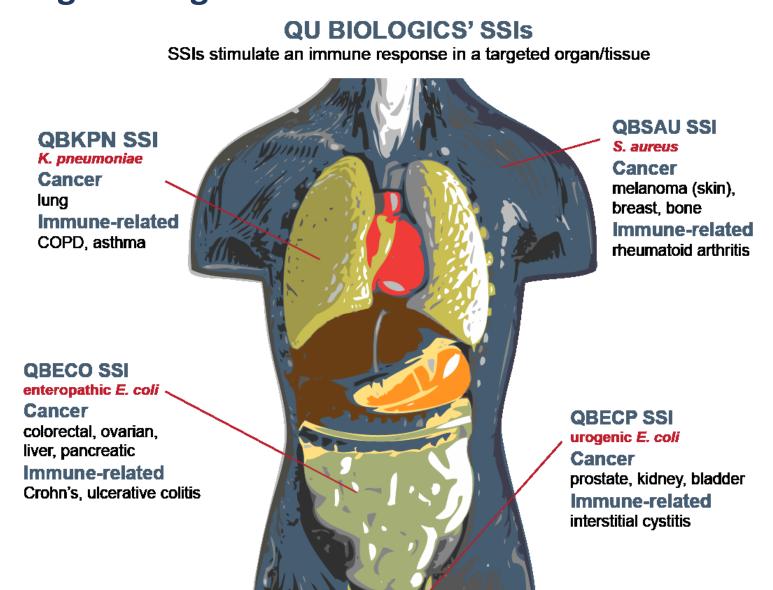
Shirin Kalyan<sup>1,2</sup>, Mark Bazett<sup>1</sup>, Momir Bosiljcic<sup>1</sup>, Jim Pankovich<sup>1</sup>, Simon Sutcliffe<sup>1</sup>, David W. Mullins<sup>3</sup>, Hal Gunn<sup>1</sup>

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

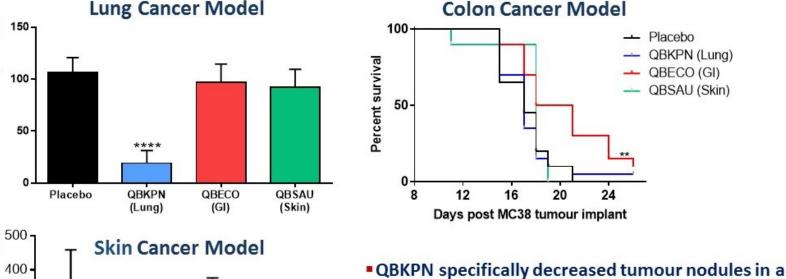
#### INTRODUCTION

Clinical application of the relationship between infection and cancer inhibition was documented on papyrus from Iberia dating back to 1550 BC. Dr. William Coley brought this insight to Western Medicine in the late 1800's when he noted spontaneous tumor remission in some patients experiencing acute infections. Optimal use of microbial immunotherapeutic strategies has been hampered by poor understanding of their bases. Qu Biologics, a clinical stage biotechnology company, has discovered a means to target the immunological mechanisms that underlie this phenomenon. Repeated subcutaneous injections of Site-Specific Immunomodulators (SSIs), made from pathogens known to commonly cause infection in a particular organ or tissue, show efficacy in treating cancers growing in the targeted organ (Figure 1).

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



## RESULTS Figure 2. SSIs show site specificity for the treatment of cancer

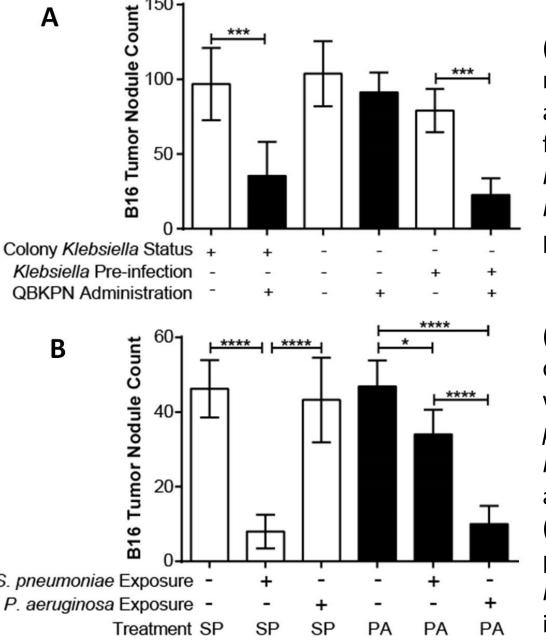


- QBECO specifically increased survival in a mouse colon cancer model
- QBSAU specifically decreased tumour volume in a mouse skin cancer model

Mean +/- SD, n = 10-20 mice / group. \*P < 0.05; \*\*P < 0.01; \*\*\*\*P < 0.0001 by 1-way ANOVA followed by Tukey's multiple comparison test.

QBKPN in the context of lung cancer was subsequently used to dissect the mechanism of SSI-mediated efficacy

### Figure 3: QBKPN anti-tumour efficacy requires host exposure to lung microbe, *Klebsiella*

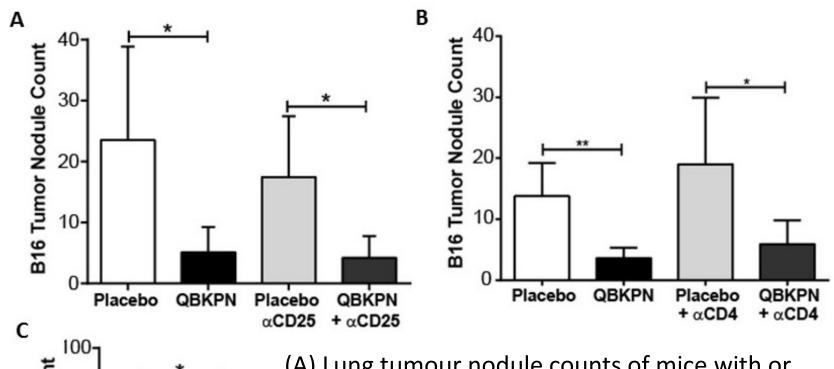


(A) Lung surface tumour nodule counts at day 18 in animals obtained from facilities positive for *Klebsiella* or negative for *Klebsiella* administered placebo or QBKPN.

(B) Lung tumour nodule counts in mice pre-infected with *Streptococcus pneumoniae* or *Pseudomonas aeruginosa* and administered SP (derived from S pneumoniae) or a *Pseudomonas*-derived immunotherapy (PA).

Mean +/- SD, n = 4-8 mice / group. \*P < 0.05; \*\*P < 0.01; \*\*\*\*P < 0.0001 by 1-way ANOVA followed by Tukey's multiple comparison test.

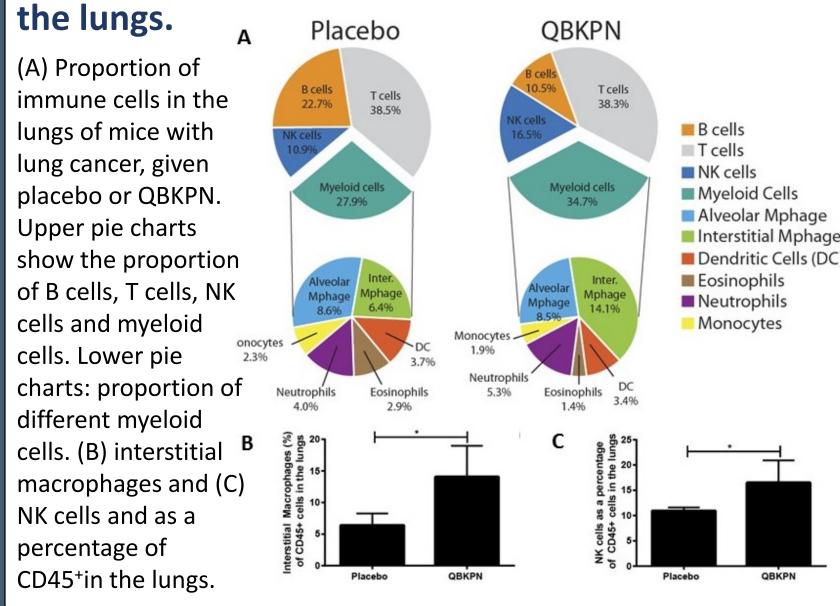
## RESULTS Figure 4. Adaptive Immunity is dispensable for QBKPN anti-tumour efficacy



(A) Lung tumour nodule counts of mice with or without CD25+ cell depletion, after administration of placebo or QBKPN. (B) Lung tumour nodule counts of mice with or without CD4+ cell depletion, after administration of placebo or QBKPN. (C) Lung tumour nodule counts in Rag2 knockout mice administered with placebo or QBKPN.

Mean +/- SD, n =4-5 mice / group. \*P < 0.05; \*\*P < 0.01 by Student's t-test.

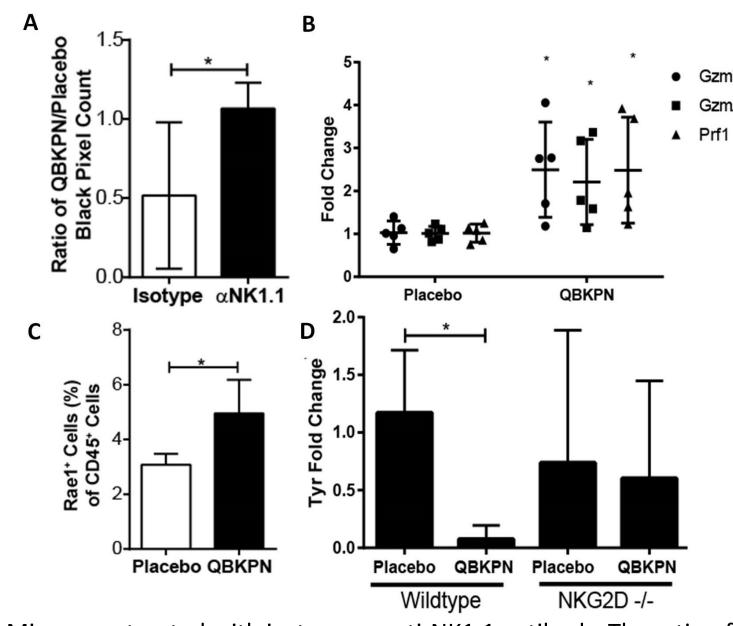
## Figure 5. QBKPN stimulates an acute-like immune response, leading to innate cell recruitment into



Mean +/- SD, n = 5-10 mice / group. \*P < 0.05; \*\*\*P< 0.005 by Student's t-test.

### RESULTS

Figure 6. QBKPN anti-tumour efficacy dependent on NK cell effector functions



(A) Mice were treated with isotype or anti-NK1.1 antibody. The ratio of tumour cells of mice administered with QBKPN/placebo. (B) Quantitative RT-PCR of Granzyme B (*GzmB*), Granzyme A (*GzmA*) and Perforin 1 (*Pfr1*) in the lungs of mice administered placebo or QBKPN. (C) Rae1+ (stress-associated ligand for NKG2D) cells as a percentage of CD45+ cells in the lungs of mice given QBKPN or placebo. (D) Lung tumour levels, measured by qualitative RT-PCR of *Tyr*, of wildtype and NKG2D -/- mice given QBKPN or placebo.

#### DISCUSSION AND CONCLUSIONS

Treatment with a lung directed SSI, QBKPN, provided a safe and effective method to mimic an acute infection leading to significantly reduced lung tumour burden and increased survival. QBKPN efficacy was driven largely by innate immune mechanisms including a marked increase in the number of phagocytic leukocytes in circulation, shift in monocyte polarization to M1 dominance in the organ, up-regulation of NKG2D ligands on tumour cells, and enhanced cytotoxic lymphocyte activity. Blocking adaptive immune function, using depleting antibodies against T cell subsets or Rag2 knockout mice, did not alter QBKPN efficacy. SSIs' targeted antitumour effects were replicated in colon and skin cancer models. In collaboration with the BC Cancer Agency, a Phase I clinical trial in patients with non-small cell lung cancer confirmed the safety and tolerability of this innovative cancer immunotherapy strategy.