Novel microbial-based immunotherapy approach enables application of adoptive cell therapy for solid tumors by enhancing both immune access to tumor microenvironment and cancer cell immunogenecity

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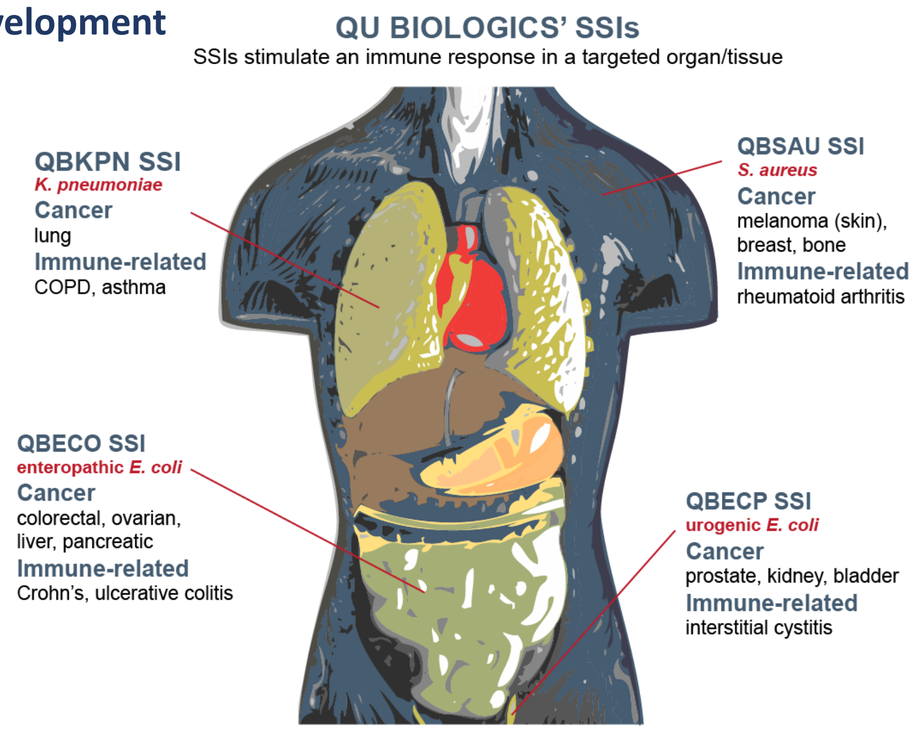
Background

Clinical application of the relationship between acute infection and cancer inhibition has been well documented historically. Dr. William Coley has been credited with bringing this insight to the attention of Western Medicine in the late 1800's when he noted spontaneous tumor remission in some patients experiencing acute microbial infections. The mechanisms driving this phenomenon have lacked sufficient characterization, and the ability to harness it *safely* and *reliably* has been elusive. As a consequence, the greater potential of microbial-based immunotherapeutic strategies have yet to be fully realized in clinical application to fight malignancy. The primary exception is the use of Bacillus Galmette-Guerin (BCG) for the treatment of high-risk non-muscle invasive bladder cancer, which is the only microbe-based therapy that is currently part of the approved standard of care.

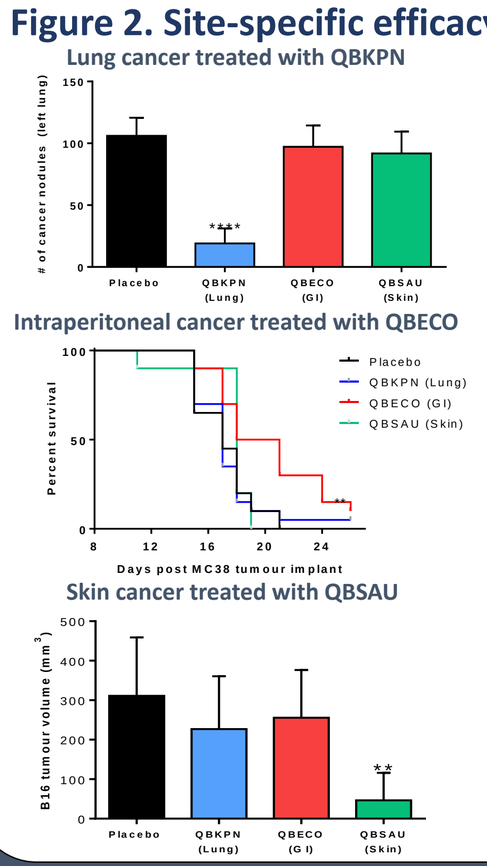
Figure 1. Site-Specific Immunomodulators (SSIs) in clinical development



Changing the tumor microenvironment to allow the immune system to clear cancer

This work describes the development of a novel platform of microbial-based immunotherapies, called Site-Specific Immunomodulators (SSIs) (**Figure 1**), that function to consistently recruit activated anti-cancer immune effector cells into solid tumors in specific organ sites while simultaneously overcoming immune suppression in the tumor microenvironment (**Figure 2**). SSIs are *inactivated* (i.e. non-infectious) microbial-based immune modulators that are formulated from a bacterial species that is an endogenous cause of infection in the specific organ where the pathology exists, and they are easily self-administered subcutaneously (s.c.) by the patient.

Figure 2. Site-specific efficacy in clearing cancer



SSI treatment leads to immune cell recruitment and activation of anti-cancer immune effector functions in the targeted organ where the bacterial species from which the SSI is derived is endogenous and a common cause of infection. Site specificity has been demonstrated using lung, gastrointestinal (GI)/intraperitoneal (IP) and skin cancer models.

Top graph: QBKPN (*Klebsiella,* lung pathogen), but not QBECO or QBSAU, is effective in **lung cancer**

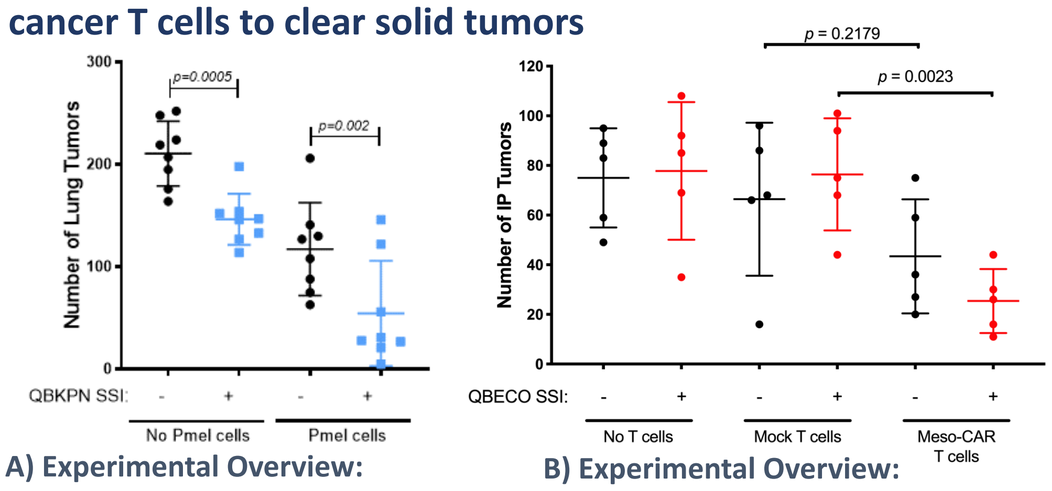
Middle graph: QBECO (*E. coli,* gut pathogen), but not QBKPN or QBSAU, is effective in **GI / IP cancer**

Bottom graph: QBSAU (*S. aureus,* skin pathogen), but not QBKPN or QBECO, is effective in **skin cancer**

Overcoming the limitations of adoptive cell therapies for solid tumors

The development of SSIs has overcome many of the issues that have plagued microbe-based cancer treatments to date. We have shown treatment with SSIs markedly increases the number of phagocytic leukocytes in circulation, shifts myeloid cell polarization to anti-cancer in function, up-regulates NKG2D ligands on tumor cells, and heightens cytotoxic lymphocyte recruitment and activity in the tumor microenvironment [1]. We now show these same processes can significantly enhance efficacy of adoptive T cell therapies for solid cancers, which to date has been problematic due to 1) poor infiltration of cells into the tumor, and 2) the immunosuppressive tumor microenvironment.

Figure 3. SSIs synergize with adoptively transferred anti-cancer T cells to clear solid tumors



A) Experimental Overview:

- Lung cancer metastasis mouse model in which B16 melanoma is seeded to the lungs via i.v. injection
- QBKPN is a lung-targeted SSI delivered s.c. every 2nd day
- Pmel cells are TCR-tg T cells specific for a B16 melanoma antigen
- Vehicle administered for (-) SSI

B) Experimental Overview:

- Intraperitoneal (IP) ovarian cancer (human SK-OV-3) model in which cells are seeded by IP injection in NSG (immune deficient) hosts
- QBECO SSI is a GI/IP-targeted SSI delivered s.c. every 2nd day
- Human scFv-CD28-4-1BB-CD3ζ CAR T cells target mesothelin SK-OV-3

Results

Using different solid tumor models, representing lung and ovarian cancers, combination treatment with SSIs is shown to enhance the infiltration and efficacy of adoptively transferred tumor-specific transgenic T cells (**Figure 3**). In these models, the increased anti-cancer efficacy is in large part due to SSI-induced secretion of chemokines from both the tissues surrounding the tumor as well as the tumor cells themselves (**Figure 4**).

Figure 4. SSIs induce chemokine release from both the tumor microenvironment and the tumor

A) The secretion of CXCL9 and CXCL10 chemokines from cancer-bearing lungs is induced by QBKPN in an adoptive T cell model (Figure 3A has model details).

B) CXCL9 (and CXCL10, not shown) secretion by human ovarian cancer cells seeded in the peritoneum is induced by QBECO in an NSG (immune deficient) CAR T cell model.

Conclusions

These results indicate SSIs can successfully overcome the major hurdles adoptive cell therapies have faced in treating solid tumors, specifically in relation to inadequate infiltration of effector cells into the tumor and the immune suppression that is inherent in the tumor micro-environment. This unique immunotherapeutic approach may prove to be a transformative tool for the treatment of solid tumors, especially when used synergistically in combination with adoptive cell therapies.

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