QL415, a tumor targeted IL-15 fusion protein stimulating both lymphoid and myeloid immune cells

Irene Tang[1], Lauren Schwimmer[1], Monica Jin[1], Shenda Gu[1], Wei Wei Prior[1], Arianne Capacio[1], Hieu V Tran[1], Allan Chan[1], Anna McClain[1], Shihao Chen[1], Chuanzeng Cao[2], Xiaoran Wu[2], Yanling Xu[2], Dongmei Guan[2], Xi Chen[3], Xianli Su[2]

1. QLSF Biotherapeutics, Inc., South San Francisco, CA | 2. QILU Pharmaceutical Co., Ltd. Jinan, China | 3. QILU Pharmaceutical Co., Ltd. Shanghai, China

Abstract #3406 AACR 2022

Background

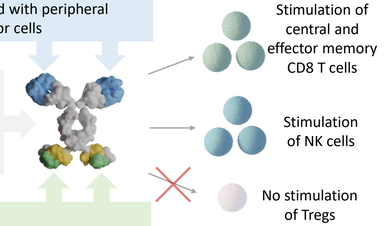
Cytokines are potent stimulators of the immune system and have long been investigated and used as therapeutics to treat cancer. However, free cytokines have a short half-life and the lack of tumor targeting often results in systemic toxicity. IL-15 is a stimulatory cytokine and its receptor shares the beta and gamma common chains with IL-2. In contrast to IL-2, IL-15 is more selective for NK and effector memory T cells, with less proliferative effect on Tregs, making it a more preferred therapeutic candidate. QL415 is a PD-L1 x IL-15 fusion protein that was designed to enhance accumulation in tumors and prolong circulation in blood, thereby widening the therapeutic window.

Design Parameters

PD-L1 Binding
- Promotes tumor targeting and accumulation
- Minimizes toxicity associated with peripheral activation of immune effector cells

Inert Human Fc
- Prolongs blood circulation time
- No ADCC or CDC, no depletion of effector cells

IL-15
- Provides potent stimulation of effector immune cells but not immunosuppressive regulatory cells
- Stabilized with IL-15 receptor alpha sushi domain



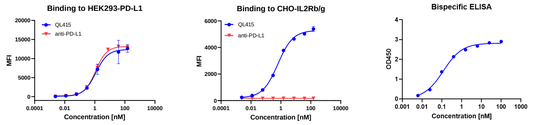
Stimulation of central and effector memory CD8 T cells

Stimulation of NK cells

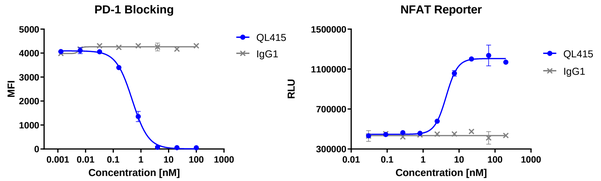
No stimulation of Tregs

Target Validation

QL415 binds to HEK293 cells expressing PD-L1, and to CHO-K1 cells expressing IL-2 receptor βγ by flow cytometry. QL415 simultaneously binds to PD-L1 and IL-2 receptor βγ demonstrated using a sandwich ELISA.

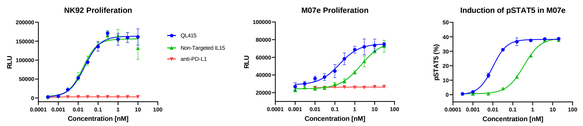


QL415 blocked the binding of PD-1 on cells analyzed by flow cytometry. PD-1 blocking released the inhibitory signal and reactivated TCR signaling in an NFAT reporter assay.

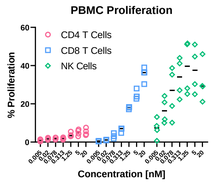


In Vitro Activity

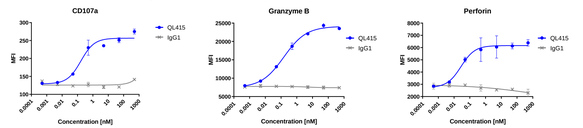
QL415 induced the proliferation of IL-15 responding NK92 and MO7e cells. Phosphorylation of STAT5 downstream of IL-2 receptor was observed in MO7e cells by flow cytometry.



QL415 was incubated with PBMC in the presence of A431 cancer cells expressing PD-L1. QL415 induced the proliferation of primary immune cells, selective for CD8+ T and NK cells. Each data point represents one of 4 donors.

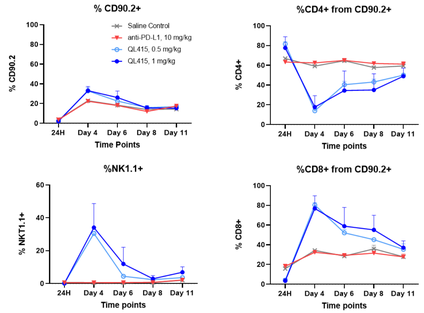


QL415 induced the expression of NK functional markers CD107a, granzyme B and perforin in a dose-dependent manner.

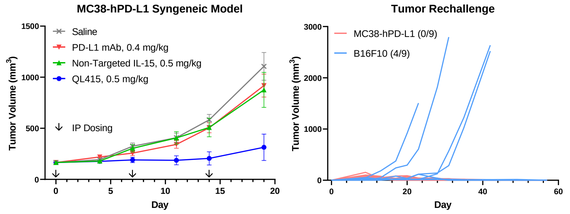


In Vivo Efficacy

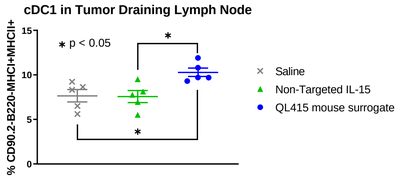
QL415 induced the proliferation of mouse CD8+ and NK1.1+ cells in C57BL/6 mice following a single IV dose.



QL415 inhibited the growth of MC38-hPD-L1 tumors in C57BL/6 mice and instilled protective memory. Tumor-free mice were rechallenged with MC38-hPD-L1 and B16F10 cancer cells, but only B16F10 tumors grew.

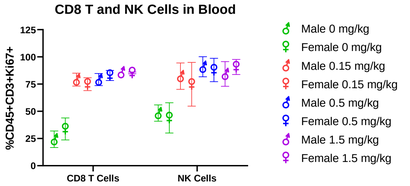


A QL415 mouse surrogate molecule with a cross-reactive PD-L1 induced the expansion of conventional dendritic cells in the tumor draining lymph nodes of C57BL/6 mice bearing MC38 tumors. A single dose of the QL415 surrogate was administered after the tumors were established.



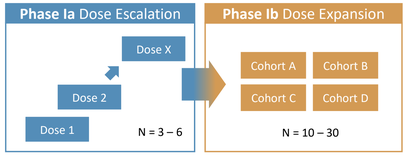
NHP Toxicology

QL415 was safe in cynomolgus monkeys up to 1.5 mg/kg after 5 repeated weekly s.c. dosing, well above the expected efficacious therapeutic dose. Expansion of CD8 T and NK cells was observed after the first dose, supporting the results shown in vitro as well as in vivo mouse model studies.



Phase 1 Clinical Study

- Ongoing, first patient dosed in November of 2021. NCT05108779.
- Objectives: safety, tolerability, and early efficacy as monotherapy or combo
- Format: i3 + 3, QWx4 IV infusion, DLT period = 28 days
- Indications: locally advanced, recurrent or metastatic solid tumors



Summary

- QL415 is a potent PD-L1 targeted IL-15 cytokine fusion protein that is selective for effector T cells and NK cells.
- QL415 had robust activity in vitro and anti-tumor efficacy in vivo.
- QL415 was well tolerated in cynomolgus monkeys.
- QL415 is currently being evaluated in a phase 1 dose escalation study.

Disclosures

I Tang, L Schwimmer, M Jin , S Gu, WW Prior, A Capacio, HV Tran, A Chan, A McClain, and S Chen are current or former employees of QLSF Biotherapeutics, Inc. receiving salaried compensation and stock options.

C Cao, X Wu, Y Xu, D Guang, X Chen, and X Su are current or former employees of QILU Pharmaceutical Co., Ltd. receiving salaried compensation.