QL535: A Novel CD2-Costimulating PSMA-Targeted T-Cell Engager with Dose-Responsive Efficacy in PDX Models and a Favorable GLP Toxicology Profile in NHP

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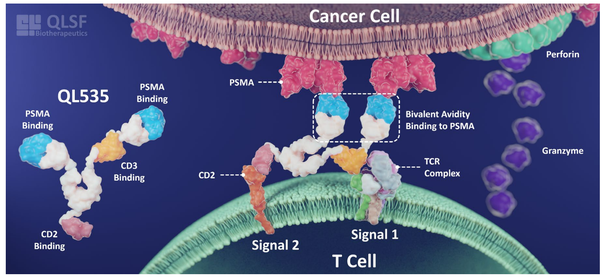
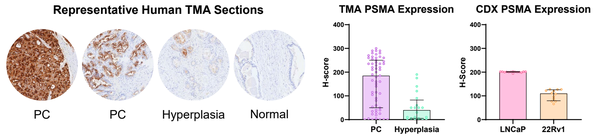
Introduction

Prostate cancer is a leading cause of cancer-related mortality in men, highlighting the need for new therapeutic options due to resistance to current treatments[1,2]. PSMA (Prostate-Specific Membrane Antigen) is overexpressed in prostate cancer tissues compared to normal prostatic tissue rendering it an ideal target for prostate cancer therapies, enabling precise delivery of therapeutic agents to cancer cells[3].

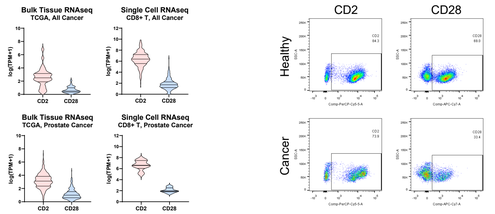
We developed QL535, a novel trispecific antibody in a 2+1+1 format designed to bridge tumor cells via PSMA and activate T cells through CD3 (signal 1) and CD2 (signal 2) via its ligand CD58. This design aims to stabilize the immune synapse and enhance T-cell cytotoxicity. Additionally, it overcomes T-cell exhaustion, with fine-tuned CD3 affinity to improve safety and reduce the risk of cytokine release syndrome (CRS).



Target Discovery and Evaluation

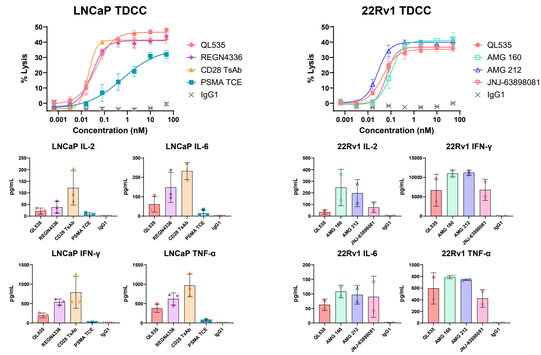


PSMA is a clinically validated prostate cancer target. We confirmed its protein expression level and distribution by IHC staining on tissue microarray (TMA), with a median H-score of 185 for prostate cancer, significantly higher than in hyperplasia and normal tissues. We further determined the expression level in two commonly used cell line derived xenograft (CDX) models of prostate cancer. Staining of ex vivo tumor tissues derived from LNCaP had a median H-score of 201, comparable the median expression level observed in primary tumors. 22Rv1 tumor derived tissues had an H-score of 110, representative of tumors with low PSMA expression.

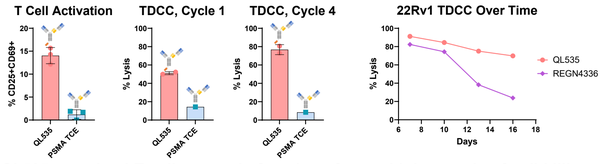


CD2 is a preferred co-stimulatory receptor in the tumor microenvironment. Analysis of TCGA bulk and public single cell RNAseq data shows that CD2 expression is significantly higher than CD28 across all tumor types and in prostate cancer. We further confirmed cell surface expression by flow cytometry analysis. PBMC from cancer patient had significantly more CD2+ T cells and higher expression level than CD28.

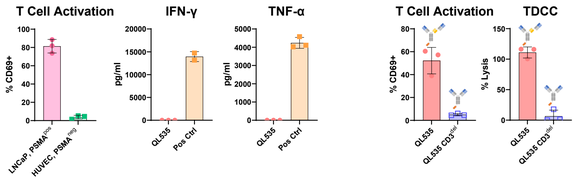
QL535 Has Improved In Vitro Efficacy



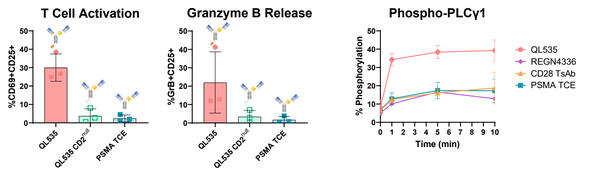
QL535 has improved potency without increase in cytokine release. QL535 was equally potent as the trispecific antibody with CD28 co-stimulation and the clinical benchmarks but with significantly less cytokine release.



QL535 sustained T cell cytotoxic function after multiple rounds of cell killing. QL535 was significantly more potent than the PSMA TCE without CD2 co-stimulation using PBMC from prostate cancer patient as effector cells and maintained TDCC over time. Similar results were obtained when compared to the clinical benchmark REGN4336.



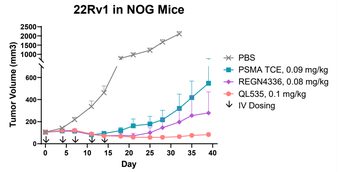
The activity of QL535 is tumor antigen and CD3 dependent. There was no activation of T cells when incubated HUVEC cells lacking PSMA or in PBMC without target cells. A PSMA x CD2 molecule without CD3 did not activate T cells or mediate TDCC of LNCaP cells.



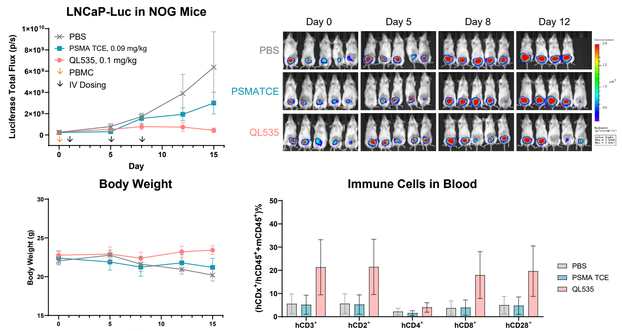
The augmented activity of QL535 is mediated by CD2 co-stimulation. A non-functional CD2 construct did not have better activity compared to the TCE lacking CD2 binding domain. In a PLCγ1 phosphorylation time course experiment, QL535 induced significantly more phosphorylation with faster kinetics compared to bispecific TCE or a CD28 trispecific construct.

QL535 Has Superior In Vivo Efficacy

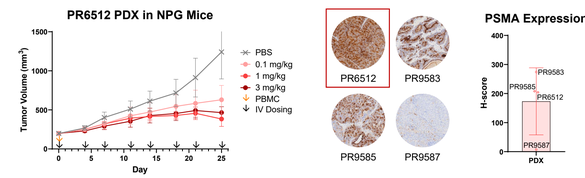
In a 22Rv1 xenograft model with **low PSMA expression**, QL535 demonstrated superior efficacy compared to the bispecific TCE lacking CD2 co-stimulation or the clinical benchmark REGN4336. 22Rv1 cells were mixed with PBMC and co-grafted.



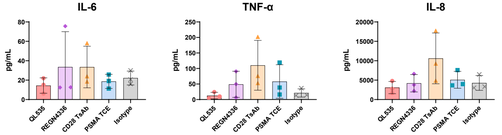
QL535 showed significantly better efficacy compared to the bispecific TCE lacking CD2 co-stimulation in an **orthotopic model** of prostate cancer using LNCaP-Luc cells. There was no significant change in body weight after QL535 treatment. Peripheral blood immunophenotyping at the end of the study shows significantly more human T cells in the QL535 treated group compared to bispecific TCE or PBS.



QL535 demonstrated marked efficacy in a **PDX model** of prostate cancer. The patient had an H-score of 204, which corresponds to the median PSMA expression level observed among prostate cancer patients.



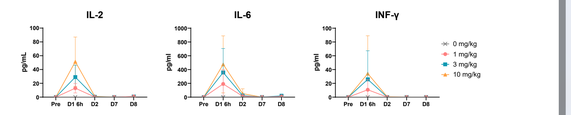
QL535 Showed Low CRS Risk in a Human PBMC Cytokine Release Assay



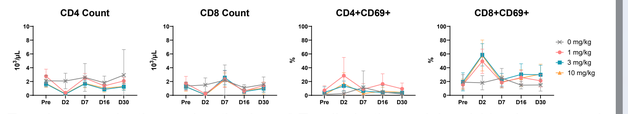
QL535 did not induce the release of IL-6, IL-8, or TNF-α from human PBMC in the absence of PSMA positive target cells, suggesting that the CD2 arm does not introduce a safety risk. Data shown represent the maximum level detected for antibody up to 250 nM across 3 donors over 3 time points: 24h, 48h and 72h.

QL535 Demonstrated a Favorable Safety Profile in a GLP Toxicology Study in NHP

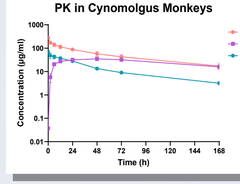
QL535 was well tolerated in cynomolgus monkeys across all tested doses in a repeated-dose toxicology study. HNSTD was 10 mg/kg. All animals received weekly dosing over the course of 4 weeks for a total of 5 doses, followed by a 4-week recovery and observation period. No significant change in clinical observation was noted. There were no remarkable histopathological findings.



A transient increase in IL-2, IL-6 and INF-γ was observed only after the first dose and resolved to baseline after 24 h. There were no further elevation after the subsequent doses. The increase was dose dependent but was well below what is typical for a TCE at this dose range.



Transient margination and activation of T cells in the peripheral blood was noted after the first dose, consistent with the MOA of this molecule.



In a separate PK study, QL535 exhibited a linear PK profile. Exposure was dose proportional. SC dosing was also explored and demonstrated good exposure and bioavailability.

Conclusion

QL535 leverages CD2 co-stimulation to enhance T-cell cytotoxicity while mitigating cytokine release, achieving superior durability under exhaustion conditions and dose-responsive tumor regression in PDX models. Its favorable safety and pharmacodynamic profile in non-human primates further supports CD2 as a clinically viable co-stimulatory axis and validates QL535 as a promising next-generation T-cell engager for prostate cancer.

A phase 1 clinical trial designed to explore safety and early efficacy of QL535 is expected to start at the end of Q2 2026.

References

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3. Scherer, K., Kumar, A., & Lütje, S. (2020). "Prostate-Specific Membrane Antigen: Advancements in Targeted Therapy and Imaging Modalities." *Journal of Nuclear Medicine*, 61(1), 82-89.

Disclosures

- X Liu, S Gu, J Morrissette, G Guo, J Chen, N Ngo, S Chen are current or former employees of QLSF Biotherapeutics, Inc. receiving salaried compensation and stock options.
- K Liu, J Kong, Y Wang, X Zhang, J Cao, M Hu, M Sun, R Ma, H Zhu, L Wang, Y Fang, H Liu, S Zhao are current employees of Qilu Pharmaceutical Co., Ltd. receiving salaried compensation.

Partnering

- QLSF Biotherapeutics is open to co-development, strategic partnerships or out-licensing opportunities to fully leverage our platform and programs.
- For additional information on QLSF programs, please contact **partnering@qlsfbio.com** or visit us at **www.qlsfbio.com**.