QL335, a novel T cell engager with enhanced safety profile targeting MSS colorectal cancer

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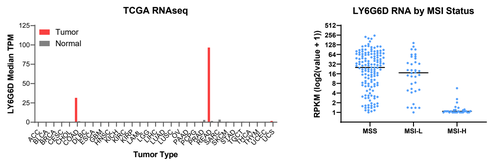
Introduction

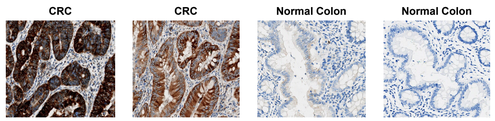
Colorectal cancer (CRC) is the fourth leading cause of death in the world with a global mortality rate of over 700,000 annually. While recent advancement in diagnosis and prevention has reduced the overall number of deaths, the lack of effective and durable treatment has not significantly improved survival rate. Emerging modalities in immunotherapy such as T cell engagers have paved new ways for disease management. However, a common challenge to advancing T cell engagers in the clinic is poor target specificity and high toxicity associated with non-specific T cell activation and cytokine release. To overcome these shortcomings, we have developed QL335, a bispecific antibody bridging LY6G6D antigen on tumor cells and CD3 on T cells.

Target Discovery

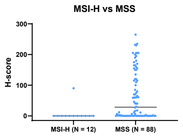
LY6G6D is a GPI-anchored cell surface protein[1] that is highly specific to colorectal cancer based on TCGA RNAseq data. LY6G6D expression is associated with the microsatellite stable (MSS) and low microsatellite instability (MSI-L) subtypes of colon and rectal cancers[2], which represent up to 85% of all CRC cases and are less immunogenic and non-responsive to checkpoint blockers[3].

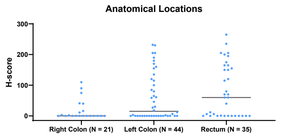


LY6G6D protein expression is CRC specific by IHC staining

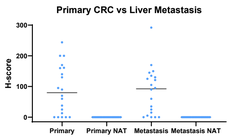


LY6G6D protein expression is associated with the MSS subtype and is more highly expressed in rectal cancer.



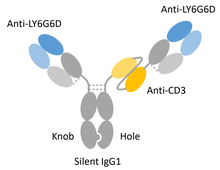


LY6G6D protein is expressed on primary tumor and liver metastasis, but not normal adjacent tissue (NAT).



Antibody Engineering

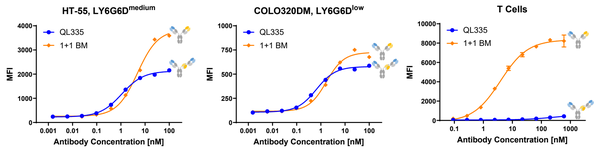
QL335 is a 2+1 molecule, with avidity-driven tumor binding and lowered CD3 affinity to reduced CRS risk. QL335 cross-reacts with cynomolgus LY6G6D and CD3.



Protein Binding by SPR

	ka (1/Ms)	kd (1/s)	K_D (M)
Human LY6G6D	1.47E+05	1.27E-04	8.68E-10
Cyno LY6G6D	1.63E+05	1.99E-04	1.22E-09
Human CD3	1.16E+06	5.89E-03	5.08E-09
Cyno CD3	1.37E+06	3.78E-03	2.75E-09

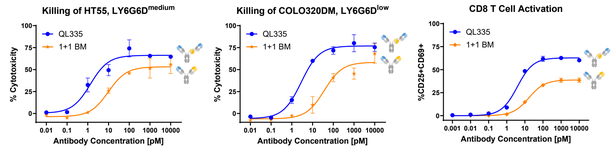
QL335 binds to colon cancer cells with nanomolar affinity while a 1+1 benchmark bispecific antibody showed higher EC_{50} and monovalent binding saturation. QL335 has significantly weaker binding on T cells compared to the benchmark antibody.



In Vitro Efficacy

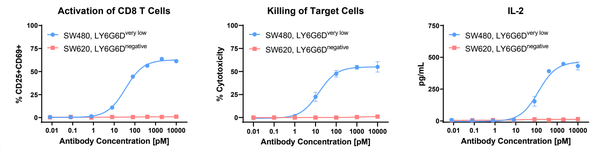
Anti-tumor efficacy at low E:T ratio

At an effector to target ratio of 1:1, QL335 was more potent than the 1+1 benchmark antibody in activating T cells and mediating lysis of colorectal cancer cells.



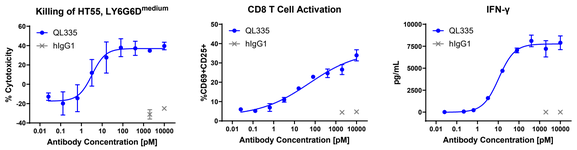
Discriminating between LY6G6D$^{very\ low}$ and LY6G6D^{negative} cells

QL335 was able to discriminate between SW480 colon cancer cells expressing very low level of LY6G6D (< 500 copies per cell) and SW620, which does not express LY6G6D. Both cell lines originated from the same patient.



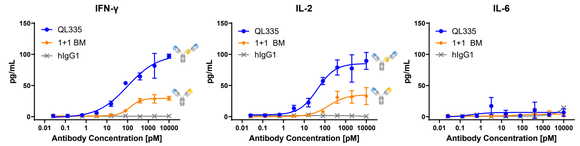
Anti-tumor activity using PBMC of CRC patients as effector cells

QL335 remained potent using PBMC of heavy treated CRC patients as effector cells .



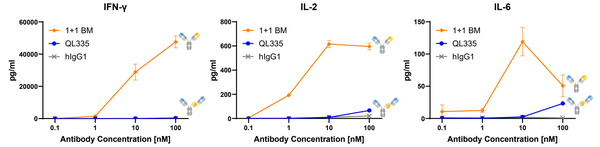
LY6G6D-dependent cytokine release from PBMC

QL335 induced higher level of cytokine release in the presence of LY6G6D^{positive} HT-55 cells.



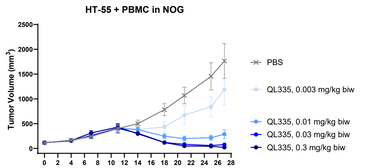
LY6G6D-independent cytokine release from whole blood

QL335 did not induce significant level of cytokine release at high concentration in the absence of LY6G6D in contrast to the benchmark antibody.

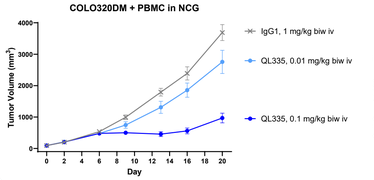


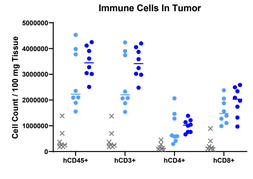
In Vivo Efficacy

Growth inhibition of cell line-derived tumor xenografts



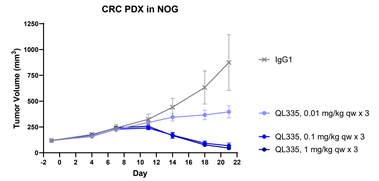
QL335 retained strong anti-tumor efficacy at low dose and was also effective against COLO320DM with low expression of LY6G6D. Higher infiltration and expansion of human immune cells in tumor was observed after QL335 treatment.

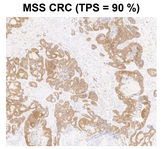




Growth inhibition of patient-derived tumor xenografts

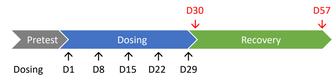
QL335 suppressed the growth of LY6G6D^{positive} MSS CRC patient-derived tumor xenografts.



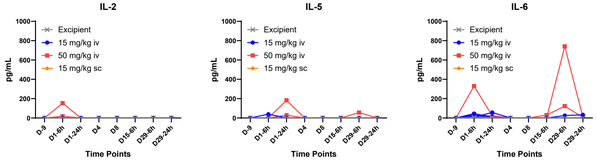


Safety and PK/PD in NHP

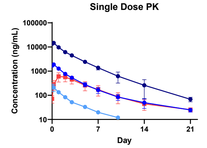
QL335 was well tolerated in cynomolgus monkeys up to 50 mg/kg iv after repeated-dosing.



Only mild and transient increase in IL-2, IL-6 and IL-5 levels were observed in certain animals, which resolved to baseline shortly after dosing.



QL335 had a favorable pharmacokinetics profile with linear clearance across a wide range of doses via either iv or sc dosing.



Conclusion

- **LY6G6D is a highly selective target for MSS CRC**
- **QL335 showed robust in vitro and in vivo anti-tumor activity**
- **QL335 demonstrated excellent safety in vitro and in non-human primates**
- **A phase 1 dose escalation trial is ongoing. Early clinical readouts are expected by late H1 of 2024.**

Disclosures

S Gu, G Guo, H Yee, HV Tran, and S Chen are current employees of QLSF Biotherapeutics, Inc. receiving salaried compensation and stock options. C Cao, K Liu, C Jin, W Lun, R Ma, and L Ren are current employees of Qilu Pharmaceutical Co., Ltd. receiving salaried compensation.

References

1. Mallya, M., Campbell, R. D. & Aguado, B. Characterization of the five novel Ly-6 superfamily members encoded in the MHC, and detection of cells expressing their potential ligands. Protein Science 15, 2244–2256 (2006).
2. Giordano, G. et al. JAK/Stat5-mediated subtype-specific lymphocyte antigen 6 complex, locus G6D (LY6G6D) expression drives mismatch repair proficient colorectal cancer. J Exp Clin Cancer Res 38, 28 (2019).
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