Preclinical development of QL325, a novel T cell engager targeting CLEC12A-positive AML

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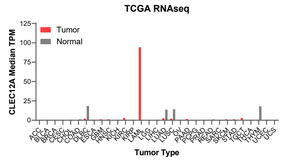
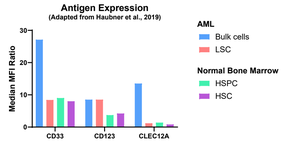
Introduction

Despite advancement in targeted therapies, treatment options for patients with acute myeloid leukemia (AML) that provide a tolerable and durable response remain elusive. We have developed a CD3 bispecific antibody, QL325, targeting CLEC12A, a c-type lectin receptor[1] that is highly expressed on AML blasts[2]. Normally, CLEC12A expression is mostly confined to the CD34+CD38- progenitor population and largely absent on normal and regenerating bone marrow stem cells[2,3].



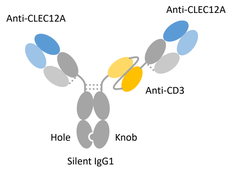
TCGA RNAseq data showing highly specific expression of CLEC12A expression in AML but not on other types of cancer or normal tissues.



CLEC12A surface expression determined by flow cytometry in AML samples and healthy donor bone marrow[3]. In contrast to CD33 and CD123, CLEC12A is not widely expressed on hematopoietic progenitor and stem cells.

Antibody Engineering

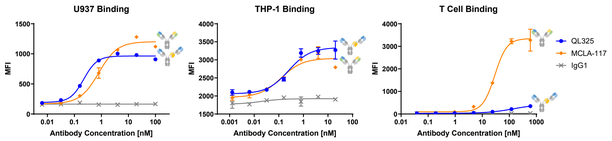
QL325 is a 2+1 molecule, with avidity-driven tumor binding and lowered CD3 affinity for reduced CRS risk. QL325 cross-reacts with cynomolgus CLEC12A and CD3. The binding affinity is comparable to that of human CLEC12A and CD3, and therefore is suitable for toxicology study in cynomolgus monkeys.



Protein Binding by SPR

	K_D (M)	Ka (1/Ms)	Kd (1/s)
Human CLEC12A	4.16E-10	9.66E+05	4.01E-04
Cyno CLEC12A	4.50E-10	4.02E+05	1.81E-04
Human CD3	5.97E-09	1.57E+06	9.32E-03
Cyno CD3	7.97E-09	8.88E+05	7.07E-03

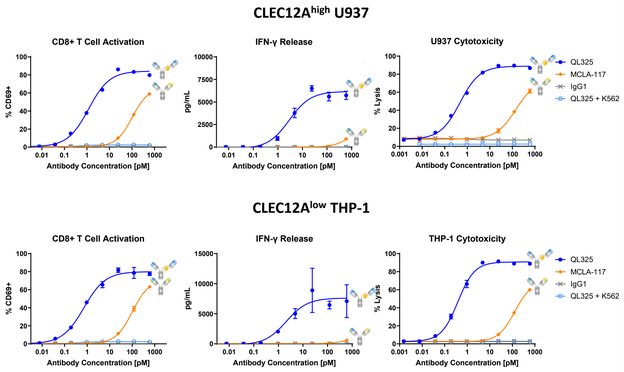
QL325 has strong binding to AML cancer cells but much weaker binding on T cells compared to the 1+1 format clinical benchmark antibody MCLA-117.



In Vitro Efficacy

Potent in vitro activity against CLEC12A^{positive} AML cell lines

QL325 was more potent than the 1+1 format clinical benchmark MCLA-117 in inducing T cell functions in the presence of U937 cells expressing high level of CLEC12A and THP-1 cells expressing low level of CLEC12A. No induction when incubated with CLEC12A^{negative} K562 cells.

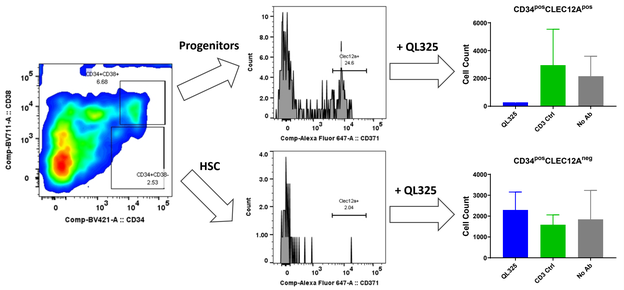


EC_{50} Range (pM)

	QL325	MCLA-117
CD4 T Cell Activation	1.7 - 1.9	171 - 233
CD8 T Cell Activation	1.2 - 1.4	81 - 279
IFN-γ Release	3.2 - 4.8	NA
IL-2 Release	4.9 - 11.8	NA
Cytotoxicity	0.5 - 1.4	132 - 273

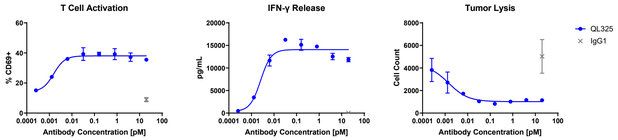
QL325 does not eliminate CLEC12A^{negative} HSC

QL325 eliminates CLEC12A^{positive} progenitors while sparing most CD34^{positive}CLEC12A^{negative} hematopoietic stem cells.



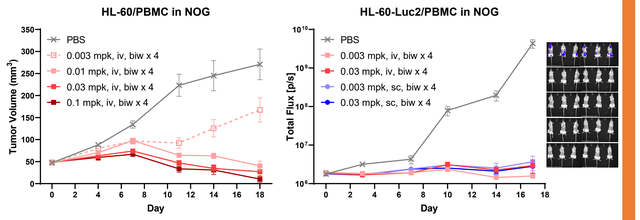
QL325 remains potent using autologous effector cells to target AML blasts from patient samples

QL325 remains highly active using PBMC of AML patient to induce lysis of autologous AML blasts where the effector to target ratio is low.



In Vivo Efficacy

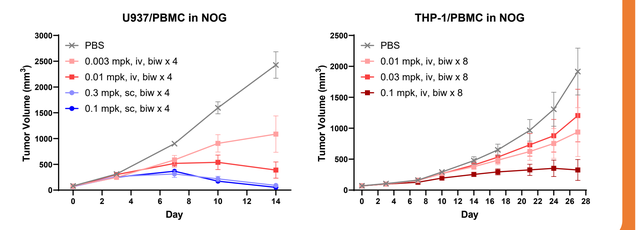
QL325 was effective in suppressing tumor growth in both ectopic and orthotopic models using HL-60 cells.



The efficacy of QL325 is not affected by resistance to venetoclax

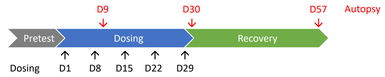
The TDCC MOA of QL325 makes it equally potent in mediating killing of venetoclax sensitive or resistant AML cells[4].

	CLEC12A Expression	In Vitro TDCC EC_{50} (pM)
U937	High	0.8 – 1.9
HL-60	Medium	0.9 – 3.2
THP-1	Low	0.3 – 1.6
MV-4-11	Low	1.3 – 1.6



Safety and PK/PD in NHP

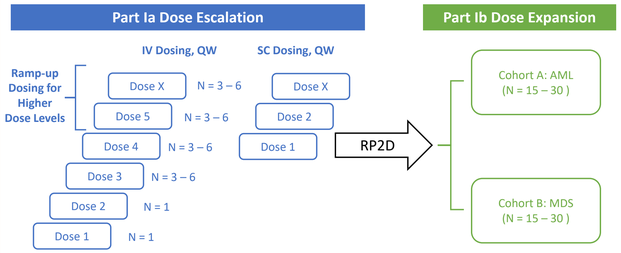
Animals were dosed weekly iv or sc for 5 consecutive weeks followed by a 4-week recovery period. HNSTD was 0.03 mg/kg for IV dosing and 0.01 mg/kg for SC dosing.



Pharmacokinetics: Rapid clearance consistent with TMDD. Subcutaneous dosing showed slower exposure and biodistribution.
Blood routine and histopathology: Decrease in red blood cells and granulocytes were observed. Histopathology showed lymphopenia in immune organs and inflammation in multiple organs.
Phenotyping: Margination of lymphocytes and activation of T cells were observed.
Cytokine Release: TNF-α, IFN-γ, IL-17A, IL-2, and IL-6 levels were elevated 4 hours after dosing, most of which recovered to baseline after 24 h.

Clinical Development

- **Objectives:** safety, tolerability, and early efficacy as monotherapy
- **Format:** i3 + 3, QW IV infusion, DLT period = 28 days
- **Indications:** AML and medium-high risk MDS patients confirmed by histology and cytology
- **Exclusion criteria:** Previously received hematopoietic stem cell transplantation, exposure to any anti-CLEC12A monoclonal antibody or CAR-T cell therapy



Conclusion

- **CLEC12A is an AML target preferentially expressed on CD34+ blasts.**
- **QL325 showed robust in vitro and in vivo anti-tumor activity.**
- **QL325 was tolerated above the predicted effective dose in non-human primates.**
- **A phase 1 dose escalation trial is ongoing with the first patient dosed in March of 2023. Early clinical readouts are expected by H1 of 2024.**

Disclosures

S Gu, M Jin, HV Tran, and S Chen are current or former employees of QLSF Biotherapeutics, Inc. receiving salaried compensation and stock options. K Liu, X Zhang, L Jia, R Ma, J Fu are current employees of Qilu Pharmaceutical Co., Ltd. receiving salaried compensation.

References

1. Marshall, A. S. J. et al. Identification and Characterization of a Novel Human Myeloid Inhibitory C-type Lectin-like Receptor (MICL) That Is Predominantly Expressed on Granulocytes and Monocytes. Journal of Biological Chemistry 279, 14792–14802 (2004).
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