### MCLA-117, A CLEC12AXCD3 BISPECIFIC IGG TARGETING A LEUKEMIC STEM CELL ANTIGEN, INDUCES T CELL MEDIATED AML BLAST LYSIS

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#### Introduction

- Patients with acute myeloid leukemia (AML) have a dismal prognosis despite improvements in chemotherapy and supportive care. Novel, more effective therapies are needed for these patients.
- CLEC12A is a myeloid differentiation antigen that is expressed on 90-95% of newly diagnosed and relapsed AML. Moreover, CLEC12A is selectively expressed on leukemic stem cells (LSCs) but not on normal early hematopoietic progenitors, including hematopoietic stem cells (HSCs) (Van Rheenen et al., 2007). This is in contrast to AML targets like CD33 and CD123, which are more widely expressed on normal CD34+ progenitors.
- Because of its more restricted expression profile, T cell-mediated CLEC12A targeting has the potential to selectively eradicate leukemic stem cells without affecting normal HSCs allowing the subsequent re-establishment of normal hematopoiesis.
- We report the characterization of MCLA-117, a novel T cell redirecting bispecific antibody for the treatment of AML that targets CLEC12A on leukemic cells and CD3 on T cells.

#### MCLA-117 bispecific antibody

- MCLA-117 is a human full length IgG1 bispecific antibody that uses an IgG1κ19/κ1 antibody light chain (scFv) together with anti-CLEC12A-specific VH and an anti-CD3-specific VH.
- The Fc portion of MCLA-117 was engineered to selectively facilitate heavy chain homodimerization and to abrogate Fcγ receptor and C1q-mediated effector function.
- The MCLA-117 affinity for CLEC12A is 60-fold greater than for CD3, 3 nM vs 177 nM respectively, which is predicted to facilitate the preferential opsonization of the AML blasts with MCLA-117.

#### MCLA-117 selectively induces lysis of CLEC12A+ monocytes

- To assess the capacity of MCLA-117 to redirect and activate autologous T cells to induce specific lysis of primary monocytes (expressing CLEC12A) a PBMC-based cytotoxicity assay was performed.
- Primary PBMC samples, at naturally occurring E:T ratios, were incubated for 48 hours with a concentration range of MCLA or MockCD3 control antibody.
- Figure A: MCLA-117 induced a dose-dependent activation of CD4 T cells and CD8 T cells.

#### MCLA-117 induces T cell-mediated target cell lysis

- The capacity of MCLA-117 to induce CLEC12A antigen-dependent cytotoxicity was first investigated using healthy donor-derived resting T effector cells and CLEC12A+ HL-60 target cells.
- Purified T cells were co-cultured for 48 hours with HL-60 cells as an effector to target (E:T) ratio of 5:1 in the presence of MCLA-117 or the MockCD3 control antibody (identical Fc silenced format as MCLA-117).
- These experiments revealed that MCLA-117 efficiently induced CLEC12A antigen dependent T cell activation (EC50 of 44 ng/mL) and tumor target cell lysis (EC50 of 68±37 ng/mL) (n=6 donors).

#### Conclusion

- MCLA-117 binds specifically to CD3 and CLEC12A expressing cells within the normal hematopoietic compartment, but not to early myeloid progenitors or hematopoietic stem cells.
- MCLA-117 efficiently induces CLEC12A-antigen specific T cell activation, T cell proliferation and redirects T cells to lyse CLEC12A+ target cells.
- MCLA-117 efficiently induces AML blast killing by T cells present in bone marrow samples, even at very low E:T ratios, and in parallel results in robust T cell proliferation.
- MCLA-117 is currently being investigated in a Phase I clinical study (MCLA-117-C01) to evaluate the safety, tolerability and preliminary efficacy of MCLA-117 in adult AML patients.

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**Table:** MCLA-117-induced AML blast lysis and T cell expansion in primary AML samples

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>FAB classification</th>
<th>Risk classification</th>
<th>% CLEC12A positive*</th>
<th>E:T ratio</th>
<th>Recovery in control conditions</th>
<th>% Blast killing</th>
<th>Cell T effector expansion</th>
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<tbody>
<tr>
<td>1</td>
<td>M4/M5</td>
<td>Very good</td>
<td>60%</td>
<td>1:2</td>
<td>86%</td>
<td>95%</td>
<td>29%</td>
</tr>
<tr>
<td>2</td>
<td>M4/M5</td>
<td>Good</td>
<td>62%</td>
<td>1:2</td>
<td>83%</td>
<td>98%</td>
<td>23%</td>
</tr>
<tr>
<td>3</td>
<td>M4/M5</td>
<td>Poor</td>
<td>58%</td>
<td>1:2</td>
<td>86%</td>
<td>98%</td>
<td>25%</td>
</tr>
<tr>
<td>4</td>
<td>M4/M5</td>
<td>Very poor</td>
<td>51%</td>
<td>1:2</td>
<td>92%</td>
<td>95%</td>
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<td>97%</td>
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<tr>
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<td>95%</td>
<td>19%</td>
</tr>
<tr>
<td>7</td>
<td>M4/M5</td>
<td>Poor</td>
<td>63%</td>
<td>1:2</td>
<td>95%</td>
<td>97%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*The average CLEC12A positive score (0-100). A score of greater than 50 indicates an AML CLEC12A negative samples. Patient no. = patient number.