Balancing the CD38 expression in effector and target cells in the multiple myeloma context

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Objective
Multiple myeloma (MM) is an incurable cancer characterized by the proliferation and accumulation of monoclonal plasma cells in the bone marrow. The relapse of the disease often ends with a refractory disease to treatments emphasizing the need to develop new therapeutic approaches.

We wanted to study the cytotoxic effects of daratumumab (anti-CD38 mAb) depending on CD38 expression levels observed on MM cells and NK-92 CD16 effector cells via ADCC as well as the effect of modulating CD38 expression with ATRA and IFNα. In addition, after adding a CD38-blocking nanobody, we follow its impact on fratricide and ADCC.

Methods
The target cells (MM cell lines), labeled with calcein, were incubated in the presence of the effector cells (NK-92 CD16) with or without Daratumumab. The percentage of cytotoxicity was then evaluated by measuring the percentage of release of calcein in the supernatant (calcein release assay).

Results
ADCC works well for LP-1 cells, but not for RPMI-8226 cells. This is explained by different levels of expression of CD38 on target and effector cells. Indeed, CD38 is more expressed on LP-1 cells compared to NK-92 CD16 cells and thus promotes ADCC. Conversely, CD38 is more expressed on NK-92 CD16 cells compared to RPMI-8226 cells and thus promotes fratricide. However, adding adjuvants to the target cells increases their expression of CD38. This increase makes it possible to achieve a sufficient level of CD38 expression on the RPMI-8226 cells to allow the ADCC. In addition, inhibition of fratricide through the use of a CD38-blocking nanobody also increases ADCC. Finally, the combination of adjuvants and anti-CD38 nanobody results in further higher levels of ADCC.

Conclusion
In conclusion, the mechanism of ADCC is inefficient because of fratricide when the CD38 expression is higher on effector cells than target cells. However, the addition of adjuvants to target cells or the inhibition of fratricide using a CD38-blocking nanobody on effector cells can reverse the balance of expression of CD38 and thus promote lysis of target cells by ADCC.