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Monoclonal Gammopathies & Multiple Myeloma

A NOVEL ANTI-CD138 ANTOBODY AT801 TO EFFECTIVELY DELIVER CHITOSAN NBS FOR TARGETING OF MULTIPLE MYELOMA AND REVERTING TUMOR MICROENVIRONMENTAL INVASIVENESS

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Introduction:CD138, also known as Syndecan-1, may be a useful immunotherapeutic target for multiple myeloma (MM) treatment being highly expressed on MM cell surfaces, whereas it is express at low levels in benign cells. Given its structure, CD138 undergoes a shedding process by metalloproteinase-9 (MMP-9) secreted by different cells, such as M2 macrophages. That leads to interaction between shed-CD138 and different microenvironmental components by which CD138 plays a significant role in tumor growth, adhesion, and invasion (Riccardi et al, Front Oncol 2024). We recently developed a mouse monoclonal antibody of the IgG class directed against a CD138 epitope in close proximity to the cell membrane(AT801, submitted patent n 102025000010005, Ministero delle Imprese e del Made in Italy). Anti-CD138 antibodies such as AT801 can be conjugated with chitosan nanobubbles (CS-NBs) loaded with chemotherapeutics, to enhance their action by increasing the payload amount reaching the tumor site. Here, we proposed the use of CS-NBs conjugated with AT801 and loaded with chemotherapeutic agents for MM and investigate their cytotoxic effects and capability to modify TME interactions.

Methods: AT801 was developed by in-vivo electroporation protocol and hybridoma production. CS-NBs were conjugated with AT801 or left unconjugated as control.

Results: The ability of AT801 to bind CD138 was demonstrated by flow cytometry (95% CD138+ cells) and immunofluorescence (IF) in both CD138-expressing MM-like RPMI 8226 cell line and in human MM samples. A siRNA-mediated knockdown was used to investigate AT801 specificity for CD138. Flow cytometry showed more than 97-98% of positive cells upon transfection with control siRNA; this fluorescent signal drops by 60- 70% upon transfection with the pull siRNA against CD138. When crossreactivity was evaluated by flow cytometry on both mouse bone marrow and human blood sample, AT801 showed high specificity for the human samples whereas it did not bind murine samples. Synthesized CS-NBs had a positive charge and a diameter of about 360nm by DLS analysis. In in vitro experiment using RPMI 8226 cells, CS-NBs showed a cytotoxic effect of more than 50% once loaded with Doxorubicin (1mM). In vivo biodistribution in RPMI 8226 tumor bearing xenograft mice demonstrated that can CS-NBs accumulate in the tumor mass. This effect was enhanced by AT801 conjugation (p=0.0015) on CS-NB surface. The effects of CS-NBs on the TME were also evaluated ex-vivo on extracted tumor masses from biodistribution studies. The M2:M1 ratio of macrophages was investigated in PBS, CS-NBs and AT801-CS-NBs treated groups. IF analysis performed using specific markers such as CD206 (M2) and iNOS (M1) showed no differences in the recruitment of M2 macrophages but revealed an increase of M1 population in the tumor masses of CS-NBs treated mice.

Conclusions: AT801 is an useful targeting agent for the development of drug delivery nanoplatforms for MM treatment.