SCI 2024
Chemistry
ELEMENTS OF FUTURE
XXVIII National Congress
MILANO,
26 - 30 August 2024
Società Chimica Italiana

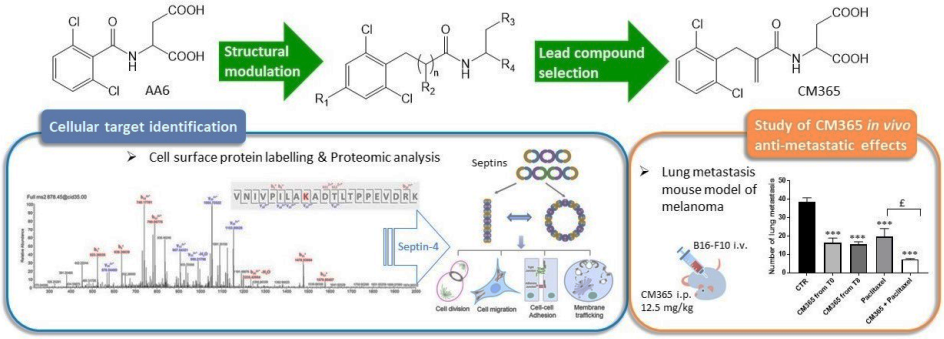
DIV-CC-NNN

Modulation of the aspartic acid scaffold to identify a new septin-4 covalent binder with anti-metastatic activity in a mouse model of melanoma

F. Boccato,[a] F. Blua,[a] A. A. Altomare,[b] S. Vittorio[b], N. Clemente,[c] C. Monge,[a] E. Marini,[a] M. Bertinaria,[a]

[a] *Department of Drug Science and Technology, University of Turin, Via P. Giuria 9, Turin, Italy*
[b] *Department of Pharmaceutical Sciences, University of Milan, Via L. Mangiagalli 25, Milan, Italy*
[c] *Settore Centri di Ricerca e Infrastrutture, University of Piemonte Orientale, Corso Trieste 15/A, Novara, Italy*
francesca.boccato@unito.it

Tumour metastases are still the leading cause of cancer-related death, being often responsible for the failure of current therapies.[1] In our previous work, we have developed a compound, AA6, that proved able to counteract the metastatic spread in a mouse model of breast cancer.[2] To identify the essential structural elements and the cellular target involved in the activity of our lead compound, a new series of AA6-derivatives was designed and synthesised. New compounds were tested for the inhibitory activity on tumour cell invasion, migration and adhesion in B16-F10 melanoma cells. From the *in vitro* results, compound CM365 was selected as the most promising derivative, showing good efficacy and most likely able to interact with the target through covalent binding. To pinpoint the cellular target, a proteomic analysis was carried out and this allowed to select septin-4 as the most likely protein involved. Septins are GTP-binding proteins, able to assemble into large filaments on the plasma membrane, modifying its rigidity in migrating cells and promoting tumour metastasis.[3] To study and compare the binding modes of the two derivatives, AA6 and CM365, with the molecular target, computational analyses were performed. Finally, the anti-metastatic properties of CM365 were evaluated *in vivo* in a murine model of metastatic melanoma. This compound proved capable of reducing metastases dissemination at different times of administration and of enhancing the antitumour effect of a known anticancer drug, paclitaxel, when administered in combination. The discovery of septin-4 as a new molecular target for the prevention of metastatic spread may encourage the future development of more specific inhibitors.



References:
[1] A. Chatterjee, E. J. Roger et all, Semin. Cancer Biol., 2018, 51, 149–159.
[2] S. Atlante, A. Visentin, Cell Death Dis., 2018, 9, 756
[3] C. Poüs, L. Klipfel, Front. Cell Dev. Biol., 2016, 4, 126.