# NEW CXCR4 INHIBITORS COUPLED WITH LIPOSOMES INHIBIT LUNG METASTASES DEVELOPMENT

S. Lusa[1], G. Salzano[1], L. Portella[2], A. Barbieri[3], P. Amodeo[4], RM. Vitale[4], S. De Luca[5], C. Arra[3], S. Scala[2], G. De Rosa[1]

[1]Department of Pharmacy, University of Naples Federico II. [2]Oncological Immunology, Institute for the Study and Treatment of Cancer, Fondazione "Pascale". [3]Animal Facility, Institute for the Study and Treatment of Cancer, Fondazione "Pascale". [4]Institute of Biomulecular Chemistry, CNR, [5]Institute of Biostrutture e Bioimagini, CNR.

E-mail: gderosa@unina.it

**Purpose.** Development of liposomes functionalized with peptides antagonist of CXCR4 receptor, such as a potential therapeutic systems in the prevention of lung metastases.

**Methods.** Two different anti CXCR4 peptides were synthesized, respectively pepR and pepS, with a sequence of three amminoacidis common to the amminoterminal chain of CXCL12, the CXCR4 ligand, and the viral secreted chemokine vMIP-II. Liposomes composed of DPPC/Chol/DSPE-PEG or DPPC/Chol/DSPE-PEG-Mal were prepared. Then, the peptides were conjugated with liposomes containing DSPE-PEG-Mal. The mean diameter, the size distribution and the zeta potential (ζ) of liposomes, with and without CXCR4 antagonists, were determined by photon correlation spectroscopy and by means of a Zetasizer Nano Z, respectively. Selected formulations were tested on several cancer cell lines and *in vivo* in an experimental model of lung metastases (C57/BL).

**Results.** The mean diameter of conjugated and non-conjugated liposomes was found to be between 130 nm and 140 nm, with a narrow size distribution (P.I.≤ 0.1). Moreover, after conjugation of anti-CXCR4 peptides with liposomes, compared with the unconjugated liposomes, showed a significant charge shielding, as demonstrated by the reduction of the ζ from -23 to -6 mV. In the human renal cancer cell (RXF393), anti-CXCR4 peptides, naked or conjugated with liposomes, significantly inhibit cell migration. In *vivo,* mice treated with pepR-conjugated liposomes showed greater reduction of pulmonary metastases, if compared to mice treated with the same dose of naked pepR.

**Conclusion.** Liposomes conjugation to an CXCR4 antagonist could represent a new strategy to prevent or reduce the onset of lung metastases.