Triphenylphosphonium bolaamphiphile-liposomes loaded with resveratrol and Trolox: Mitochondriotropic formulations with Therapeutic Potential in Neurodegeneration and Cancer

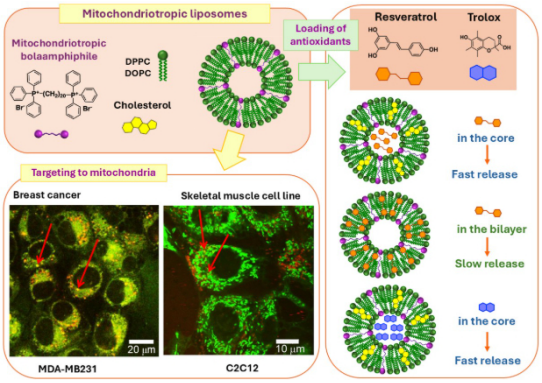
Simona Sennato [a], Francesca Ceccacci [b], Annarica Calcabrini [c], Giuseppina Bozzuto [d], Viviana Moresi[e] Cecilia Bombelli[b]

[a] Institute for Complex Systems (ISC)-CNR and Physics Department Sapienza University, Rome, Italy,
[b] Institute for Biological Systems (ISB)-CNR, c/o Department of Chemistry, Sapienza University, Rome, Italy,
[c] National Centre for Drug Research and Evaluation, National Institute of Health, Rome; Italy,
[d]Institute of Nanotechnology (NANOTEC)-CNR, Rome, Italy.

simona.sennato@cnr.it

Drug delivery to mitochondria represents a promising therapeutic strategy because mitochondrial dysfunctions are associated with many different pathologies, from neurodegenerative diseases to diabetes, obesity, cancer, and physiological disorders related to ageing. Actually, mitocondria targeting is particularly challenging due the inner highly convoluted, densely packed membrane, characterized by a strong negative potential that significantly hinders drug delivery. Cationic amphiphilic structures derived by triphenylphosphonium (TPP) are planar structures with highly delocalized cationic charge which is driven to mitochondria by the strong negative potential of the inner mitochondrial membrane and can cross the membrane barriers due to the "soft" nature of their cationic headgroups. A novel single-chain TPP-bolaamphiphile, with two TPP moieties connected by chains of 20 methylene units [1,2] has been explored to realize novel nanocarriers for mitochondrial delivery [3]. The amount of TPP and liposome composition jointly affect the physicochemical properties of liposomes and the bilayer organization. We explored the ability to reach mitochondria in two different cell lines, the murine skeletal muscle C2C12 and the multi drug-resistant (MDR) human breast cancer MDA-MB231, useful to investigate different pathological situations, namely, the oxidative stress associated with ageing and neurodegenerative muscle diseases and the multidrug resistance in cancer. Liposomes with 2.5% of TPP were non toxic and able to target mitochondria, thus resulting good candidates for encapsulation of the antioxidant *trans* -resveratrol. TPP-liposomes encapsulating *trans* -resveratrol in the bilayer or, for the first time, in the aqueous core, were developed with high entrapment efficiency in both cases. Trolox was encapsulated for the first time in the aqueous core of liposomes by remote loading, with very high entrapment efficiency and enhanced stability following encapsulation. The release rate of resveratrol is dependent on its localization in the bilayer; interestingly, this gives the possibility to modulate release in dependence on the application. Finally, we showed that TPP3-liposomes can deliver resveratrol to the mitochondria in the MDA-MB231 cells, exerting a protective activity on the mitochondrial structure. Our results support its potential therapeutic use as an adjuvant for a protective activity in neurodegenerative diseases or for a sensitizing activity against drug resistant tumor cells [3].

Keywords:
Mitochondriotropic liposomes, Antioxidants, Sensitizing agents, MDR in cancer, Neurodegenerative diseases.



TPP-liposomes loaded with resveratrol or Trolox for delivery to mitochondria

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