Bonilla, X., EL-Habib Dakir, EL-H., Mollinedo, F., and Gajate, C. (2015). Endoplasmic reticulum targeting in Ewing's sarcoma by the alkylphospholipid analog edelfosine. *Oncotarget* 6, 14596-14613.

Ewing's sarcoma (ES) is the second most common bone cancer in children and young people. Edelfosine (1-*O*-octadecyl-2-*O*-methyl-*rac*-glycero-3-phosphocholine) is the prototype of a family of synthetic antitumor compounds, collectively known as alkylphospholipid analogs (APLs). We have found that APLs ranked edelfosine>perifosine>erucylphosphocholine>miltefosine for their capacity to promote apoptosis in ES cells. Edelfosine accumulated in the endoplasmic reticulum (ER) and triggered an ER stress response that eventually led to caspase-dependent apoptosis in ES cells. This apoptotic response involved mitochondrial-mediated processes, with cytochrome *c* release, caspase-9 activation and generation of reactive oxygen species. Edelfosine-induced apoptosis was also dependent on sustained c-Jun NH_2-terminal kinase activation. Oral administration of edelfosine showed a potent *in vivo* antitumor activity in an ES xenograft animal model. Histochemical staining gave evidence for ER stress response and apoptosis in the ES tumors isolated from edelfosine-treated mice. Edelfosine showed a preferential action on ES tumor cells as compared to non-transformed osteoblasts, and appeared to be well suited for combination therapy regimens. These results demonstrate *in vitro* and *in vivo* antitumor activity of edelfosine against ES cells that is mediated by caspase activation and ER stress, and provide the proof of concept for a putative edelfosine- and ER stress-mediated approach forES treatment.