Melo-Lima, S., Lopes, M.C., and Mollinedo, F. (2015) ERK1/2 acts as a switch between necrotic and apoptotic cell death in ether phospholipid edelfosine-treated glioblastoma cells. *Pharmacological Research* 95-96, 2-11.

Glioblastoma is characterized by constitutive apoptosis resistance and survival signaling expression, but paradoxically is a necrosis-prone neoplasm. Incubation of human U118 glioblastoma cells with the antitumor alkylphospholipid analog edelfosine induced a potent necrotic cell death, whereas apoptosis was scarce. Preincubation of U118 cells with the selective MEK1/2 inhibitor U0126, which inhibits MEK1/2-mediated activation of ERK1/2, led to a switch from necrosis to caspase-dependent apoptosis following edelfosine treatment. Combined treatment of U0126 and edelfosine totally inhibited ERK1/2 phosphorylation, and led to RIPK1 and RelA/NF-κB degradation, together with a strong activation of caspase-3 and -8. This apoptotic response was accompanied by the activation of the intrinsic apoptotic pathway with mitochondrial transmembrane potential loss, Bcl-xL degradation and caspase-9 activation. Inhibition of ERK phosphorylation also led to a dramatic increase in edelfosine-induced apoptosis when the alkylphospholipid analog was used at a low micromolar range, suggesting that ERK phosphorylation acts as a potent regulator of apoptotic cell death in edelfosine-treated U118 cells. These data show that inhibition of MEK1/2-ERK1/2 signaling pathway highly potentiates edelfosine-induced apoptosis in glioblastoma U118 cells and switches the type of edelfosine-induced cell death from necrosis to apoptosis.