Melo-Lima, S., Lopes, M.C., and Mollinedo, F. (2014). Necroptosis is associated with low procaspase-8 and active RIPK1 and -3 in human glioma cells. *Oncoscience* 1, 649-664. *The cover of the journal was given to this manuscript.*

Necroptosis is a regulated necrotic cell death that involves receptor-interacting protein kinases RIPK1 and RIPK3. Here, we report that edelfosine triggers a rapid and massive cell death in human glioblastoma cells with characteristics of necrosis. Only a minor proportion of edelfosine-treated cells underwent caspase-dependent apoptosis. Autophagy and a rapid influx of extracellular calcium into the cells had little impact on cell death. Levels of procaspase-8 were very low in necroptosis-prone glioma cells compared with the levels in other cancer cell types that underwent apoptosis upon edelfosine treatment. The RIPK1-dependent necroptosis inhibitors necrostatin-1 (Nec-1) and Nec-1s as well as siRNA-mediated silencing of RIPK3 inhibited edelfosine-induced necroptosis, resulting in increased caspase-dependent apoptosis in edelfosine-treated glioblastoma U118 cells. Inhibition of the RIPK3 substrate MLKL with necrosulfonamide also increased apoptosis in edelfosine-treated cells. These data support a major role for RIPK1 and RIPK3 in the induction of necrotic cell death and in the switch from necrosis to apoptosis following edelfosine treatment. These results indicate that the ether lipid edelfosine exerts a rapid necroptotic cell death in apoptosis-reluctant glioblastoma cells, suggesting that induction of necroptosis could constitute a new approach for glioblastoma therapy.