**Direct Pharmacological Targeting of a Mitochondrial Ion Channel Selectively Kills Tumor Cells In Vivo**

Luigi Leanza[(1)], Andrea Mattarei[(2)], Katrin Anne Becker[(3)], Michele Azzolini[(4,5)], Lucia Biasutto[(4,5)], Roberta Peruzzo[(1)], Livio Trentin[(6)], Mario Zoratti[(4,5)], Erich Gulbins[(3)], Cristina Paradisi[(2)], Ildikò Szabò[(1)]

*(1) Department of Biology, University of Padua, Padua, Italy*

*(2) Department of Chemical Sciences, University of Padua, Italy*

*(3) Department of Molecular Biology, University of Duisburg-Essen, Essen, Germany*

*(4) CNR Institute of Neurosciences, Padua, Italy*

*(5) Department of Biomedical Sciences, University of Padua, Padua, Italy*

*(6) Department of Medicine, University of Padua, Padua, Italy*

Mitochondria are important oncological targets due to their crucial role in apoptosis. Our work identifies a novel therapeutic tool that simultaneously exploits both the high expression of the potassium channel Kv1.3 in the mitochondria of various types of cancer cells and the characteristic altered redox state of malignant cells, thereby leading to the selective elimination of pathological cells by two mitochondria-targeted Kv1.3 inhibitors. Indeed, the inhibition of mitochondrial Kv1.3 by two novel drugs alters mitochondrial function and leads to ROS-mediated cell death. These inhibitors killed 98% of *ex vivo* primary chronic B-lymphocytic leukemia tumor cells while sparing healthy B cells. In orthotopic mouse models of melanoma and pancreatic ductal adenocarcinoma, the compounds reduced tumor size, via ROS-mediated selective apoptosis of cancer cells, by more than 90% and 60%, respectively, without causing significant side effects of healthy tissues, like immune-depression, cardiac toxicity or histological alteration. These findings thus offer the perspective of a major advance in the pharmacological treatment of some high-impact, poor-prognosis cancers.