For many years, researchers have theorized that canncer cells depend on the activation of certain genes (named oncogenes) or the inactivation of others (tumor suppressors) for their survival — a hypothesis known as ‘oncogene addiction’. Based on the idea that oncogenes and tumor suppressor genes are a critical force in the malignant transformation of cells, pharmaceutical companies have focused on developing drugs that target these genes. However, recent studies have shed light on the vital mechanisms that ensure the survival of cancer cells, including the ability to undergo metabolic adaptations that provide cancer cells with a secure energy supply and form a defense mechanism against various cellular stresses. Thus, **targeting the ‘cart’ (metabolism) rather than the ‘horse’ (oncogenes and tumor suppres¬sor genes) may be a promising strategy for eliminating cancer cells while sparing normal cells.**

The proposed project aims to investigate whether two natural products, neferine (extracted from Lotus) and cucurbitacin B (present in such plants as cucumber or pumpkin) can effectively kill non-small lung cancer cell lines by inhibiting antioxidants and inducing oxidative stress in cancer cells but not in normal lung fibroblasts.

The practical part will start from analyzing the influence of neferine and cucurbitacin B on the viability, migration and induction of programmed cell death of lung cancer cell lines. Then, the inhibition of antioxidant capacity and induction of reactive oxygen species production will be analyzed. Finally, a role of Nrf2, the master regulator of intracellular antioxidants, will be analysed in response to neferine and cucurbitacin B.

It has been estimated that approximately 45–80% of patients with breast cancer use antioxidant supplements after diagnosis or during breast cancer treatment [Greenlee et al., 2009]. **There is still considerable controversy as to whether ROS modulation by either antioxidant supplementation or inhibition is clinically beneficial or detrimental for cancer treatment**. In fact, some investigators have hypothesized that antioxidant supplements can be used both for cancer prevention and to potentiate chemotherapy and radiation therapy by providing protection against toxic side effects. However, none of these theories is supported by solid clinical and experimental data. Numerous recent studies are suggesting an opposite scenario: that is, antioxidants provide crucial survival and proliferation signals to cancer cells; cancer cells depend on an increased antioxidant capacity to counteract elevated ROS levels; and antioxidant inhibitors represent a promising therapeutic strategy in anticancer therapy. Hopefully the result of this project will contribute to the verification of this approach.