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DISSERTATION TITLE: *NEW insights in OLD biology*

My first scientific work is about a short RNA molecule (micro RNA= miRNA) with regulatory function, called let-7, and its role in the metabolic processes of cancer cells. We discovered that let-7 reprogram cancer metabolism towards the metabolism typical of healthy terminally differentiated cells. Cancer cells use a special metabolism that helps them to proliferate fast and to move across the body, invading other tissues. Let-7 is a tumor suppressor miRNA, because it counteracts signaling pathways that support cancer cells growth and aggressiveness. Often, like for many other tumor suppressors, let-7 level is too low in cancer cells to function properly. We wanted to see if, re-introducing let-7 back to cancer cells, would help to change their cancer metabolism. We found that, indeed, after the addition of let-7, the aggressive cancer cells slow down cell cycle, do not form colonies (which is feature of aggressiveness) and become very sensitive to the chemotherapeutic drug doxorubicin. Specifically, this sensitivity derives from the higher level of reactive oxygen species caused by let-7. In conclusion, let-7 can be used in combination with chemotherapy to obtain more efficient treatment. However, the whole-body effect of the exogenous let-7, introduced intravenously, needs to be deeply evaluated.

In my second work, I found a novel role of one specific protein phosphatase in the differentiation of osteoblasts. Protein phosphatases are enzymes that remove phosphate groups from proteins. The addition or removal of phosphate groups from proteins, represent a general regulatory mechanism in a cell. There are several families of phosphatases, each having its own characteristics. The protein phosphatase PP2A is made by three pieces assembled together: catalytic subunit, scaffold and regulatory subunit. There are many types of regulatory subunits, because they make PP2A work in a very specific way in different biological processes. We found that in one of such processes, the differentiation of bone cells, osteoblasts, the regulatory subunit B55 gamma plays a pivotal role. If this protein is lost from the cells, they are unable to differentiate to osteoblasts and instead, start to accumulate fat, like adipocytes. This discovery may be very important for such a disease like osteoporosis, which consists in the loss of bone-forming cells, namely osteoblast. The pathogenic mechanisms at the molecular level are poorly understood. Our discovery opens a new direction of the research for the understand of the osteoporosis.