Cancer is an aggressive and heterogeneous disease that represents one of the main cause of death worldwide. For instance, in lung cancer the five-year average survival rate does not exceed 15%, caused mainly because the lack of early diagnosis and poor prognosis. One of the proteins involved in fightingwith cancer cells is p53, called “the guardian of the genome” since its multiple and key role as a tumour suppressor.

Briefly, p53 make a call to other many proteins that will dirige the tumour cell to the death thanks to binding to DNA and the help of a zinc ion. Unfortunately, the guardian p53 is not always working because of the presence of multiple mutations. Researchers discovered that mutated-p53 proteins exhibits impairment in zinc binding properties that produces weak binding towards DNA. Therefore, we can imagine how zinc ion is highly important to control how strong p53 is bound to DNA. In the cell, the zinc status must be tightly controlled since too much zinc is toxic, but still below some threshold many proteins are not working properly. Zinc ion is extremely important for proper cell functioning. It is estimated that Zinc-binding proteins account for approximately 10% of the human proteome.

In order to maintain zinc ions homeostasis, there is one main family of proteins (highly concentration in cell) with zinc buffering capacities that is able to donate or accept zinc ions from proteins and thus regulate the proper zinc proteome, namely metallothionein. Other important cellular ligand highly concentrated in the cell is glutathione. This low molecular weight ligand is involved in redox chemistry in the cell so, it has abilities to accelerate or decrease release and acceptance of zinc ions from one protein to other by oxidation or reduction processes.

In our project, we will dissect what is the interaction between metallothionein, glutathione and p53.To address this question, we will use a combination of spectroscopic methods, mass spectrometry approaches and molecular dynamics simulations. There is no doubt this research is worth since after many years of research on p53, there is lack of information about the interaction and the role of metallothionein in controlling the zinc status in mutated-p53 proteins. It is still unclear after 30 years of research the link of the p53 mutation status to cancer prognosis and treatment. Metallothioneins are the most important zinc buffering system in the cell, and thus, if zinc ion is related with p53-DNA binding activity, it is of outmost importance to gain new insight into these processes.