State the objective of the project, reasons for choosing the research topic

The subject of this project is to study interaction between the HSPA2 chaperone protein and the products of wild type and mutated *TP53* gene. The HSPA2 protein is a poorly characterized member of the human HSPA (HSP70) family, which function for years has been linked exclusively to spermatogenesis. Currently, mostly due to our research, it is known that HSPA2 is synthesized in some populations of somatic cells and in many types of cancer. Limited literature data, and our initial results allow to assume, that HSPA2 acts as a chaperone protein for mutant p53 proteins in cancer cells. Mutated variants of p53 not only loose its tumour suppressive activity but can also gain new, cancer promoting functions.

Our working hypothesis assumes that structurally unstable mutants of p53 are substrates ("clients") of the HSPA2 chaperone. Moreover we believe, that cancer cells developed a regulatory mechanism dependent on the mutant p53 protein, which maintains an adequate level of HSPA2. In turn the HSPA2 chaperone supports stability and pro-cancerogenic activity of p53 mutants. Our hypothesis has been formulated on the basis of results of our preliminary experiments and results of literature search. We have observed that HSPA2 affected the level of mutant p53 in cancer cells. In addition, we have noticed that the wild type p53 may inhibit the transcription of the *HSPA2* gene, while p53 mutants can operate oppositely. I*n silico* analysis of the *HSPA2* gene DNA sequence revealed several interesting features of its promoter: the presence of p53 binding site and several other regulatory sequences that potentially bind transcription factors whose activity can be modulated differently by p53 and p53 mutants.

The proposed project has two related objectives. The first goal is to determine the role of HSPA2 in regulation of the stability of oncogenic p53 variants. The second aim is examination of regulatory mechanisms by which normal p53 and mutant p53 protein exert opposite effects on the activity of the *HSPA2* gene promoter.

The results that will be obtained during the implementation of the project extend knowledge on cancer cell biology and also have clinical implications. They will help to better understand the role of molecular chaperones in acquirement of pro-oncogenic activity by p53 mutants. Our results will extend knowledge on the mechanisms by which mut-p53 can modulate networks of transcription factors to promote cancer phenotype. The completion of this project can also provide a theoretical basis for design of new anti-cancer treatment strategies (in particular, aimed at establishing a personalized therapy based on molecular signature of the patient).