7. SUMMARY

The aim of our work was to contribute to evaluation of effects of valproic acid in three different leukaemia cells lines (MOLT-4, HL-60 and U-937) at molecular level. Using various methods of molecular biology we proved that valproic acid causes in all the three mentioned cell lines:

- inhibition of proliferation
- arrest of cell cycle in G1 phase linked to p21 induction and followed by decrease of number of cells in the S phase of cell cycle
- induction of differentiation in HL-60 cells
- induction of apoptosis

Although valproic acid as a histonedeacetylases inhibitor primarily causes acetylation of nuclear histones, this modification is preceeded by activation of non-histone proteins, which play a key role in cell cycle regulation and are crucial for reparation of DNA damage, cell cycle interference and apoptosis induction. Valproic acid seems to be a convenient agens for combination therapy. We proved its synergistic effect with ionizing radiation in MOLT-4 and HL-60 cells in term of increased and prolonged apoptosis induction comparing to noxes acting alone. In U-937 cells, we observed combined effect of valproic acid and a differentiation agens *all-trans*-retinoic acid, which is linked to increased histone H2AX phosphorylation.

Epigenetic changes currently present one of the most exciting fields in the clinical and preclinical investigation of myeloid malignancies. In contrast to genetic alteration, the epigenetic one are amenable to pharmacological reversal. Valproic acid has an immense advantage as it is an established drug in epilepsy treatment, can be applied orally, has good tolerance and mild side effects. Those are reasons why valproic acid with its properties of inhibitor of histondeacetylases presents a promising compound in therapy of leukaemias as well as solid tumours.