4. CONCLUSIONS

Major results of this PhD thesis can be summarized as follows:

1. For full transcriptional activation of ISG (PML, Sp100, IRF1) by interferon α the deacetylation of unknown factor(s) is necessary. IFNα-induced expression of PML at mRNA and protein level and subsequent increase of PML NBs are suppressed by all tested HDACIs independently on cellular origin. Importantly, basal (i.e. IFNα-nonstimulated) expression of PML is not influenced by HDACIs. The classical Jak-STAT pathway mediating transition of IFNα signal remains unaffected by HDACIs and the target of HDACIs lies downstream of ISGF3 binding to PML promoter. Adverse affects of HDACIs used in clinical praxis are predicted.

2. Human mesenchymal stem cells (growing, confluent or terminally differentiated) express PML protein, form PML nuclear bodies and respond to IFNα treatment by dramatic elevation of PML mRNA and protein levels and moderate increase of PML NBs. Number of PML NBs per cell nucleus is dependent on the culture proliferative age. In normal diploid but not in immortal cells PML forms various nucleoli-associated structures. The localization of PML into nucleoli is reestablished in senescent cells. The importance of PML association with nucleoli for its tumor suppressor activities is hypothesized.

3. Drug-induced senescence in several human cell lines leads to increased PML expression and formation of PML NBs. The senescent cells have changed secretory phenotype and exhibited elevated expression of IFNβ and other cytokines. These cytokines probably through auto/paracrine mechanism activate Jak-STAT signaling pathways resulting in up-regulation of ISGs including PML, STAT1, IRF1, IRF7, Mxi1, ISG15, 2',5'-oligoadenylate synthetase 1, and others. Observed activation of IRF1 and IRF7 suggests that senescent phenotype, can be sustained in positive feedback loop.