

## **ABSTRACT (EN)**

Humans and cells in their bodies are exposed to various mutagens in their lifetime that cause DNA damage and mutations, which affect the biology and physiology of the target cell, and can lead to the expansion of an immortalized cell clone. Genome-wide massively parallel sequencing allows the identification of DNA mutations in the coding sequences (whole exome sequencing, WES), or even the entire genome of a tumour. Mutational signatures of individual mutagenic processes can be extracted from these data, as well as mutations in genes potentially important for cancer development ('cancer drivers', as opposed to 'passengers', which do not confer a comparative growth advantage to a cell clone). Many known mutational signatures do not yet have an attributed cause; and many known mutagens do not have an attributed signature. Similarly, it is estimated that many cancer driver genes remain to be identified. This Thesis proposes a system based on immortalization of mouse embryonic fibroblasts (MEF) upon mutagen treatment for modelling of mutational signatures and identification and testing of cancer driver genes and mutations. The signatures extracted from WES data of 25 immortalized MEF cell lines, which arose upon treatment with a variety of mutagens, showed that the assay recapitulates the signatures of these compounds found in human tumours. The cell lines also harboured numerous mutations in genes known to act as cancer drivers in certain contexts, as well as mutations in a list of genes implicated in regulation of the epigenome. A scoring system devised for this study identified multiple putative drivers of the cancer-like phenotype of the cell lines, both well-known drivers (Tp53, Hras) as well as yet unrecognized putative ones (Smarcc1, Smarcd2 subunits of the BAF chromatin remodeling complex). Experiments using a small molecule inhibitor showed that the Smarcd2 mutation is likely to create a dependency of the affected cells on the PRC2 complex, as was previously demonstrated for other mutations in the BAF complex subunits in human cancer cell lines. In summary, the data presented in this Thesis show that the MEF cell lines are an invaluable resource for studies of certain aspects of human cancer development.

**Keywords:** mutations, mutational signature, mutagen, cancer driver, Ras, BAF