Chromosomal double-strand breaks (DSBs) are the most detrimental type of DNA damage. DSBs can originate from external sources such as ionizing radiation and chemotherapeutic treatment or from free radicals generated by the organism itself. Efficient DSB repair is essential for the survival of a cell. However, deregulated or error-prone repair causes genomic instabilities that accelerate the multistep process of tumorigenesis. The purpose of our research is to understand the molecular details of genome stabilizing and DNA damage response mechanisms and their deregulation in chromosome instability syndromes, cancer and during aging. We have developed assay systems for the quantitative and qualitative analysis of DSB repair in immortalized and primary cells from different organs including hematopoietic stem cells. Our fluorescence-based assay system comprises a series of different substrates, designed for the qualitative and quantitative analysis of all DSB repair pathways (non-homologous end-joining: NHEJ, single-strand annealing: SSA, homologous recombination: HR). The power of pathway-specific testing to detect even subtle and genetically determined DSB repair deficiencies was documented by testing lymphoblastoid cells derived from a series of Ataxia telangiectasia, Nijmegen breakage syndrome and Fanconi anemia patients with various mutations as well as from a collection of breast cancer patients with heterozygous mutations in BRCA1, BRCA2 or CHEK2. Together with our clinical partners, we now focus on investigations of primary cells from blood samples, skin and tumor material to detect DSB repair defects based on the newly discovered repair patterns associated with predisposing mutations. Additionally, we utilized fluorescence-based DSB repair testing in combination with genomic PCR and quantitative analysis of nuclear structures indicative for DNA lesions, repair intermediates and/or repair enzyme complexes to elucidate the particular mechanisms underlying
genetic destabilization in hematopoietic malignancies involving deregulation of tyrosine kinase signaling, such as upon mutation of Janus kinase 2 or expression of BCR-ABL, or of constitutive NF-κB activation. Our goal is to solve questions related to the specific mechanisms underlying tumorigenic genome rearrangements and to develop novel biomarkers for the identification of cancer risk and therapeutic responsiveness.

Evidence from genetic, mouse model, cell biological, and biochemical studies in existing literature revealed striking links between replicative senescence, telomere maintenance, aging, and DSB repair. There are large differences between DNA repair in rodents and humans and this is why we purposefully focus on man. Interestingly, it has also been demonstrated that the DNA break sensor Poly[ADP-ribose] polymerase 1 (PARP1), which has become an extremely promising target for therapies selectively eliminating HR-defective tumor cells, mediates regulation of telomere length. We have characterized the role of and functional interactions between different aging-related proteins in DSB repair such as SIRT1, WRN and PARP1. The challenge will now be to understand the details of how DSB is regulated during the aging process in differentiated versus stem cells and to identify candidate genes, which underlie these changes.