

# Factors of the BRCA2-mediated Homologous Recombination: Uncovering New Players, Their Interplay, and Contribution to Genome Integrity and Stress Response (GENOVA)

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This proposal addresses the maintenance of genome integrity which is one of the most fundamental cellular processes that ensures genome stability by employing molecular factors that are mostly conserved in all domains of life. Therefore, it is not surprising that inherited or newly acquired defects within the mechanisms of genome protection are linked to life-threatening conditions such as cancer, as well as to ageing and other disorders. Namely, DNA is under constant challenge from both endogenous as well as exogenous genotoxins causing its damage so that among the types of lesions, DNA double strand breaks are the most deleterious ones. They are corrected with supreme accuracy via homologous recombination (HR)-mediated repair. Our central contention is that a further breakthrough in understanding of the molecular mechanisms of HR requires identification of new components of the molecular machinery underlying the process.

Thus, focusing on discovery of novel HR-factors and on elucidating their collaboration with known components of the HR machinery we propose here an inter-disciplinary approach using an extremely radiation resistant (yeast-like) fungus *Ustilago maydis* as a model system. As a microbial BRCA2 organism, it offers the advantage of simplicity in experimental design, plus a perspective showing some surprising features in common with the human HR system.

Towards this goal we have already identified 2 novel cellular factors functionally related to HR, supporting the validity of our approach and feasibility of the genetic screen we designed. We will further isolate a collection of factors that regulate/modulate HR and characterize them in considerable details using state-of-the-art molecular tools in experimentation. Given the importance of DNA repair mechanisms for stress-protection in plants the investigations will be extended to *Arabidopsis thaliana*. Collectively, this work promises new insight into the process of HR-mediated DNA repair. The steps defined in the process could be points of intervention not only for guiding new therapeutic strategies but also for crop breeding programs. Indeed, detailed biological knowledge of the fundamental cellular processes, as it is nowadays painfully evident, represents our best hope for efficient medical and other informed interventions.