The cells of animals, plants and fungi, together called Eukaryotes, with their labyrinthine system of internal compartments are a product of an extraordinary evolutionary event that happened about two billion years ago. Two (or maybe more) simple cells resembling today's bacteria were joined in symbiosis, giving rise to the nucleus – the modern eukaryotic cell's information storage and mitochondria – its powerplants. In a similar fashion plants acquired their chloroplasts. Subsequent evolution led to the concentration of the bulk of hereditary information in the nucleus, but mitochondria retained as the legacy of their bacterial ancestors a small rudimentary genome, encoding only a handful of proteins. It is, however, essential for the functioning of mitochondria, as it encodes key subunits of the respiratory complexes that turn nutrients into electrochemical energy for the whole cell. Mutations in the mitochondrial DNA (mtDNA) cause a variety of rare metabolic disorders in humans. Remarkably, the nuclear genome provides almost all of the factors that the mitochondrial genome needs to multiply and function. Nuclear genes are also regulated by the state of mitochondria, so that the entire cell can adapt to the functioning of its powerhouse. These complex interdependencies are known as nucleo-mitochondrial interactions. These interactions show great variability in evolution. The mitochondrial genome changes quickly, and the nuclear genome has to evolve to keep up. In some cases this so-called nucleo-mitochondrial compatibility is responsible for the splitting of evolutionary lineages into separate species.

For many years yeasts were a favorite model system to study nucleo-mitochondrial interactions. Many yeast species can survive without a functioning mitochondrial respiratory chain by switching to fermentative metabolism. When they hear about "yeasts" most people, including molecular geneticists, think about the baker's yeast *Saccharomyces cerevisiae*. Indeed it (as well as its very distant relative *Schizosaccharomyces pombe*) is one of the best known model organisms that made immense contributions to modern biology, including mitochondrial genetics. Yet yeasts are an old and diverse group, and their evolutionary history spans hundreds of millions of years (as much as that of, for example, animals). They seem to be the perfect group to study the way the mitochondrial and nuclear genome evolved together for millions of years, adapting to each other and to the environment. Until recently, however, not much was known about the genetics of yeast species other than the baker's yeast. We have therefore decided to look into the nucleo-mitochondrial interactions in another yeast species – *Candida albicans*. Most people associate *Candida* with fungal infections (and indeed it is a significant problem, particularly in people with a compromised immune system). But it is also a fascinating organism in its own right, as a member of a distinct evolutionary lineage that is as distant form the baker's yeast as humans are from fish. Its mitochondrial genome is in many aspects different from the well known baker's yeast mtDNA, for example it contains seven genes encoding subunits of complex I of the respiratory chain, that are absent from *S. cerevisiae* mtDNA, but can be found in animal mitochondria. We expect that the genes in the nucleus that encode proteins necessary for the functioning of the mitochondrial DNA evolved to accommodate these differences and will show some unexpected roles and features. They have not, however, been subject to experimental studies previously. The essence of our project is thus to study the nucleo-mitochondrial interactions in *Candida albicans* for the first time.

To achieve this goal we plan to use the typical strategy of molecular genetics. We'll make a series of mutant *C. albicans* strains, where genes that should be responsible for the functioning of the mitochondrial genes (identified using comparative DNA sequence analysis on a computer) get inactivated. Then we'll observe, how these mutations affect the functioning of mitochondria, concentrating on the expression of the mitochondrial genes. Finally, we'll use powerful Next Generation Sequencing (NGS) methods to see how the nuclear genome adjusts the expression of its genes in response to the mitochondrial dysfunction. Finally, we'll compare the results of our observation with what is already known in the baker's yeast, and try to deduce how evolution adjusts the nuclear genes to the changes in the mitochondrial genome.

This is a basic research project aimed at gaining more understanding of the ways cells function and evolve. It does not mean, however, that its results will not be important for more practical applications. We know that interfering with the mitochondrial function affects the capability of *Candida* to infect human hosts and cause disease. A better understanding of *C. albicans* mitochondria may therefore provide hints about new possible ways of controlling its pathogenicity.