Investigating the mechanisms of epigenetic memory at the example of the responsiveness of human immune cells to vitamin D

In each of the trillions of cells forming our body we have same genome, but our 400 tissues and cell types differ in how this DNA is complexed with histone proteins, in order to form active or inactive chromatin. Chromatin serves as the physical expression of the epigenome, which is a layer of information above the genome (epi (Greek) = above). This study aims to answer the question, whether things that we do or experience during our lifetime can be stored in form of the epigenome of our cells. Thus, has the epigenome a memory function about our lifestyle?

The most dominant daily exposure of our body is diet. It is known that many nutritional molecules have a direct effect on regulatory proteins, such as transcription factors and chromatin modifying enzymes, in the nucleus of our cells. These proteins communicate with our genome and affect the epigenome. In this way, our daily breakfast, lunch and dinner talk with the (epi)genome. This is the basis of the discipline nutrigenomics.

One of the nutritional molecules that has a direct effect on the epigenome is the micronutrient vitamin D. In this study, we will take vitamin D as a master example for study the epigenome programming effect of food. We plan to perform a vitamin D intervention study over 2 years, where participants will be asked to take during the first winter a monthly bolus of vitamin D_3 and during the second winter a daily supplementation. This is a safe *in vivo* vitamin D experiment. At 12 time points during the 2 years we will ask the participants for blood samples, of which we will isolate immune cells. Most of the cells will be immediately analyzed, while others will be treated *in vitro* with the biologically most active form of vitamin D, 1,25-dihydroxyvitamin D_3. The effects of vitamin D on the epigenome of immune cells and their functional response in terms of gene activity (transcriptome) will be measured by a series of so-called next generation sequencing methods. The data will be analyzed by bioinformatic methods and used to build mechanistic *in silico* models of vitamin D's function in immune cells.

We expect to observe responses of the epigenome and transcriptome of immune cells to vitamin D that are found in all study participants as well as individual-specific responses. This will allow us to understand the molecular basis of individual differences in the response to vitamin D, referred to as the vitamin D response index. As a consequence, we will be able to provide more personalized advices for vitamin D supplementation, in order to obtain optimized health benefits in terms of a well-functioning immune system.