Our laboratory is interested in how the structure, dynamics and posttranslational modifications of histones and histone-binding proteins orchestrate cellular responses to genotoxic stress. The outstanding questions in this field include why cells need to mobilize large segments of chromatin to safeguard their genomes, how they manage to assemble chromatin-associated genome caretakers in a defined order, and how they prevent excessive spreading of stress-induced chromatin modifications to the healthy parts of the genome. We are trying to address each of these issues by high-content imaging of DNA damage-induced chromatin dynamics and modifications directly in living human cells, with a particular focus on chromatin reprograming induced by errors during DNA replication because of the capacity of such lesions to cause disease-associated genomic fragility.

In my presentation, I will provide evidence that a fraction of genomic loci affected by replications stress escape checkpoint detection and can only be handled by the genome surveillance machinery after conversion to DNA breaks during mitosis. I will show how we use this phenomenon to screen for new factors that orchestrate chromatin reprogramming after DNA damage and present our most recent results including the mechanisms that restrain excessive spreading of break-induced histone ubiquitylations. Throughout the talk, I will highlight the significance of epigenetic responses for guarding against genome instability, and show examples of molecular defects of spatio-temporal epigenetic reprograming in human cancer.