The DNA in our cells is not ‘naked’, rather it is packaged by histone proteins into an assembly called chromatin. Differences in the structure and chemical composition of chromatin at specific locations, known as epigenetic features, are the key to gene regulation. By epigenetically ‘turning on’ certain genes while ‘switching off’ others, this is how the exact same DNA sequence can give rise to many distinct types of cells in the body, and it is also a major part of what makes cancer cells, and even aged cells, different from healthy cells.

Epigenetic drugs are a family of anticancer agents that target a variety of different proteins, referred to as chromatin-associated proteins, which modify the chemistry or structure of chromatin in specific ways. However, in spite of their initial promise, these drugs are limited in effectiveness and by side effects, leaving a demand for the discovery of novel types of cancer therapeutics. Indeed, the current epigenetic drugs target specific chromatin-modifying proteins that act on chromatin, as opposed to targeting the most relevant chromatin sites directly. The efficacy of these therapeutic agents is attributed to a greater reliance of the cancer cells, compared to healthy tissue, on the chromatin pathways that are affected by the drugs. This translates to a vulnerability of the cancer cells that makes them more susceptible to drug treatment relative to healthy cells. Such vulnerabilities of cancer cells have been referred to as ‘epigenetic addictions’, but they can in principle be more specifically undermined to kill cancer cells by targeting the actual chromatin sites that are involved in the dependency.

Considering the spectrum of chromatin-associated dependencies and vulnerabilities displayed by cancer cells, the fact that the histone proteins themselves have barely been explored as possible therapeutic targets is noteworthy. Indeed, we believe that the histone proteins should be considered neglected therapeutic targets. In fact, it has recently come to light that particular changes to the histone proteins are common drivers of carcinogenesis, indicating that these histone alterations are genuine cancer drug targets. Beyond cancer, histone dysregulation is also a signature of the aging process, which shares multiple chromatin hallmarks with cancer, thus rationalizing the fact that cancer is an aging-promoted disease. As such, there is a distinct need and precedence to discover histone-targeting compounds, which can be explored for the development of anti-cancer and anti-aging drugs, as well as biotechnological tools. We plan to address this by establishing a unique methodological platform, and we propose here to develop novel technologies for the discovery of site-selective histone-binding and chromatin-modifying agents.

Having already had success in discovering chromatin-targeting antitumour and antimetastasis agents that are more site-selective than and have a distinct impact compared to existing drugs, we are in a unique position to develop useful drug discovery methods and improved therapeutic agents. Towards this end, we will combine our cutting-edge in vitro chromatin methods with state-of-the-art techniques for biochemical and biophysical characterization of small molecule binding and impact on chromatin structure/dynamics. The overall objective is to develop a methodology that can be used to rapidly screen through 1000s or even millions of compounds to find ones that bind to histone/chromatin sites. We hypothesize that the proposed platform would permit the discovery of a variety of compounds, some of which could be translated into pharmaceutical agents. As such, the ultimate (long-term) goal is to develop precision histone-targeting/chromatin-modulating therapeutic agents— a new class of epigenetic drug. In addition to holding promise for yielding life-extending anti-cancer/anti-aging therapies, this initiative would facilitate the discovery of biotechnological tools, like molecular labels and probes, for use in research and diagnostics.