Master project in Biophysics / Systems Biology: “Dynamic chromatin interaction networks of multivalent epigenetic effectors”

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**Aim:** In this project, we aim to **develop a kinetic model** to analyze and predict the interaction dynamics of multivalent epigenetic effector proteins with chromatin carrying histone post-translational modifications.

**Background:** Chromatin is highly chemically modified. Combinations of these post-translational modifications form a molecular language, interpreted by protein ‘readers’ or effectors, which results in a defined biological output. Due to the critical role of chromatin in cell function, differentiation and disease a deeper insight into these processes is of critical importance for the development of advanced treatments.

We recently developed a single-molecule assay based on total internal reflection microscopy (see Figure) that allows to directly monitor effector protein interaction dynamics with modified chromatin fibers. We investigated the dynamic interactions of one such effector, heterochromatin protein 1 (HP1), with its cognate histone mark, H3 trimethylated at lysine 9 (H3K9me3) in chromatin fibers.

These studies revealed that the HP1 residence time on chromatin depends on the density of H3K9me3 marks, as dissociated factors can rapidly rebind at neighboring sites. Moreover, by chemically controlling HP1 dimerization we found that effector multivalency prolongs chromatin retention and, importantly, accelerates the association rate. This might be a key feature of effector multivalency, allowing for fast and efficient competition for binding sites in the crowded nuclear compartment.

**Project:** Having the possibility to directly measure single-molecule interaction dynamics enables us to interrogate complex chromatin binding processes on the molecular level. **However, a solid theoretical framework to analyze and integrate the kinetic data is lacking.** Such a framework would possibly also enable the integration of *in vitro* kinetic data with dynamic measurements in living cells to obtain a quantitative picture of HP1 – chromatin interaction mechanisms.

The proposed project thus aims at developing such a theoretical framework and integrate the available single-molecule dynamic data to determine fundamental parameters of the HP1 - chromatin interaction.

**If you are interested, please contact us at beat.fierz@epfl.ch**