CPPC 2021

sciforum

Abstract

Application of Urea-Based Foldamers to the Design of Ligands Targeting the Histone Chaperone ASF1

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† Presented at the First Canadian Peptide and Protein Community Virtual Symposium, 27–28 May 2021; Available online: https://cppc2021.sciforum.net/

Published: 27 May 2021

Abstract: Histone chaperones are key actors in genome integrity maintenance; they escort histones and assist their deposition on DNA, thus contributing to chromatin dynamics. Among them, the histone chaperone ASF1 (Anti-Silencing Function 1), which handles the histone H3-H4 dimer, was shown to constitute a new target in cancers. Consistently, ASF1 plays an important role in cell growth and proliferation. Its depletion sensitizes cells to doxorubicin, a drug currently used in chemotherapies. Our team initiated the design of ASF1 inhibitors competing with its association with the H3-H4 dimer. Taking advantage of the high-resolution structure of the human ASF1A-H3-H4 complex, a first generation of inhibitory peptides was designed on a rational based strategy, combining epitope tethering and optimization of interface contacts. The designed peptides reached binding affinities in the nanomolar range for ASF1 and showed anti-tumoral properties on cancer cell lines and in mouse allograft models. However, their biological activity was largely impaired by their poor bioavailability and significant sensitivity to protease degradation. The objective of my thesis project is to generate new generations of inhibitors based on urea-based foldamers that showed improved resistance to proteolysis. The last generations of ASF1 inhibitors, integrating full-length peptidomimetics as well as full-urea helixes, will be presented.