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Host Laboratory

Name of the laboratory: Institut de Biologie Structurale/ Viral Infection & Cancer Group
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Master Thesis Title:
Identification & validation of inhibitors of the hNTH1-YB1 interface: a new therapeutic strategy for the treatment of drug-resistant tumours

Research problem:
DNA repair enzymes play an important role in the mechanisms of resistance to anti-cancer treatments. Human endonuclease III, or hNTH1, is responsible for the repair of oxidized pyrimidine bases and is involved in the development of cisplatin resistance used in the treatment of solid tumors. In these cells, hNTH1 interacts with YB1, a transcription factor involved in the genotoxic stress response, which stimulates hNTH1 repair activity. Downregulating either of these two proteins has been shown to resensitize cells to cisplatin. Developing drugs that target the hNTH1-YB1 interface could thus constitute a new therapeutic strategy for the treatment of drug-resistant tumours.

Objectives:
The objective of this project is to validate *in vitro* and *in vivo* a set of potential inhibitors of the hNTH1/YB1 complex identified recently during the robotic screen of a large chemical library (>10,000 compounds) using a FRET-based biosensor. The aim is to further characterize these hits and identify the most promising inhibitors for subsequent optimization.

Work program:
We recently developed a FRET-based biosensor composed of two FRET-compatible fluorescent proteins and our target proteins in a single polypeptide chain that allows us to reliably detect the interaction between hNTH1 and YB1 *in vitro*. With this tool we have screened a large chemical library in collaboration with the CMBA platform at the CEA/IRIG in Grenoble in order to identify potential inhibitors of the hNTH1-YB1 complex. Several compounds of interest have been identified and will be further tested in a secondary screen. The project will consist in further characterizing a set of 10-20 hits. This will involve several tests: (i) dose-response curves using FRET-based biosensor and alternative assay (AlphaScreen), (ii) identification of molecular targets of hits on hNTH1 or YB1 using thermal shift assay or differential scanning fluorimetry, and (iii) *in vivo* measurements of the capacity of these compounds to restore the sensitivity of MCF7 cells to cisplatin. The latter will be performed on the CMBA platform at the CEA.

Keywords: Cancer; Inhibitors; Protein-protein interactions; Drug-resistance; FRET