Development of ATF3 inhibitors to restore antitumor immune surveillance*

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6 months internship (M2/Engineering School) at the interface of chemistry and biology - starting january-march 2024.

Urothelial carcinomas of the upper tract (UTUC) are aggressive tumors of the lumbar or pelvic ureter, or of the pyelocal cavities. They are managed in the same way as urothelial cancers of bladder origin, despite a different embryological origin, a specific molecular signature and a low basal level of intratumoral immune infiltrate. In consequence, the risk of relapse is very high (over 50%) justifying the urgent searches for new therapeutic options (Nat Rev Urol 2014; 11: 15–16). To this end, the team of Céline Gongora (IRCM) is investigating drug combinations to stimulate the immune system and increase the immune infiltrate within the tumor through chemotherapy combining gemcitabine with platinum salts: cisplatin (CisGem) and carboplatin (CaboGem). Nevertheless, they identified a mechanism of resistance to the antitumor immunity of cancer cells due to chemotherapy-induced activation of the ATF3 transcription factor (manuscript accepted in Clin Transl Med).

Interestingly, until this year, there was no ATF3 inhibitor available since it lacks binding pockets for small molecules and is predominantly located in the nucleus which impairs its targeting via large biologics such as antibodies. In February, a selective ATF3 peptide inhibitor, called ATF3W_aeg, was described (ACS Chem. Biol. 2024, 19, 753−762). Although, ATF3W_aeg has a rather long sequence with a moderate activity and need to be vectorize, it represents an attractive basis to develop interesting tools for the biology and potent innovative therapeutics to enhance antitumor immunity in the context of many cancer types. Thus**, we propose to develop short peptidomimetics inhibitors and degraders using cutting-edge technologies** to improve both the potency and bioavailability of the parent peptide.

The M2 student will (1) synthesize the ATF3 dimerization domain for the interaction studies and the ATF3W_aeg inhibitor as reference. Then, 5-10 analogs will be synthesized. (2) She/he will determine the helical contents and study the formation and stability of inhibitor/ATF3 complexes using circular dichroism (CD). (3) She/he will assess the effect of the analogs in cell models using UTUC WT cells and ATF3 KO cells as control.

Please do not hesitate to contact us for further information.

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