Development of Fluorescent Probes of SLMP53-1 for Target Localization

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The development of targeted therapy has made promising progress in cancer treatment. One of the most promising therapeutic targets is the tumor suppressor protein p53, which is inactivated in most human cancers and mutations are found in 50% of malignant tumors. Some strategies have focused on the pharmacology of reactivating p53 by inhibiting its main negative regulator, MDM2 or MDMX, or restoring wild-type-like activity to the mutant p53 form.[1] Therefore, several compounds targeting the p53 pathway have emerged. The (*S*)-tryptophanol-derived oxazoloisoindolinone (SLMP53-1) was developed by our group and has potent *in vitro* and in vivo p53-dependent antitumor activity.[2] This small molecule acts as wt and mut p53 reactivator and its mechanism of action has been intensely studied.[3] Hence, we focused on the development of fluorescent probes to exploit the mechanism of action of SLMP53-1. This approach can give insights into the cellular distribution of SLMP53-1 and, consequently, its target(s) localization (Figure 1). In short, the mechanistic data obtained so far does not conclusively prove that the anti-tumor activity of SLMP53-1 is entirely due to its interaction with wt and mut p53. Therefore, the identification of other possible targets and off-targets, as well as the SLMP53-1 binding site to p53 will bring relevant insights into the development of new effective anticancer agents for tumors with distinct p53 status. The synthesis of the SLMP51-1 fluorescent probes involved attaching different fluorophore tags to the SLMP53-1 scaffold by linker. Photophysical properties studies of these probes are underway and the cellular localization will be imaged using co-staining protocols and confocal microscopy. It is expected that the outcome of this project will ultimately lead to important advances for understanding the mechanism of action of SLMP53-1 on p53-dependent antitumor activity.

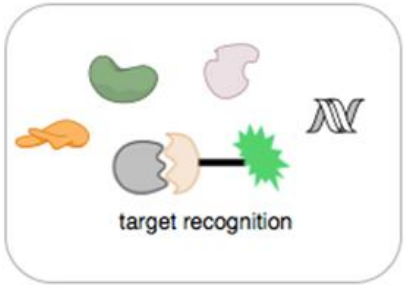

Figure 1.*Cconcept for using fluorescence-tagged bioactive molecules in subcellular localization studies.*

References

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