Postdoctoral researcher in medicinal chemistry: *Rational design and synthesis of enzyme inhibitors for the treatment of neurodegenerative diseases*

Start date: 2nd of January 2023 **Duration:** 12 months (6 months renewal) **Salary:** 2100-2600€ Net

Location: Team 9 of the Institute IBMM at the Pôle Balard (**Montpellier- France**, ibmm.umontpellier.fr)

Project: Microtubules (MT) are dynamically assembled/dis-assembled tubes formed by the association of α and β-tubulin heterodimers. As major constituents of the cellular cytoskeleton, they are involved in a number of essential functions including cell division, intracellular transport and cell morphology. One major way in which MT are adapted to such divers functions is via posttranslational modifications (PTM). This is especially important in the case of neurons where their complex cell transport and morphology are finely regulated by a combination of tubulin PTMs.

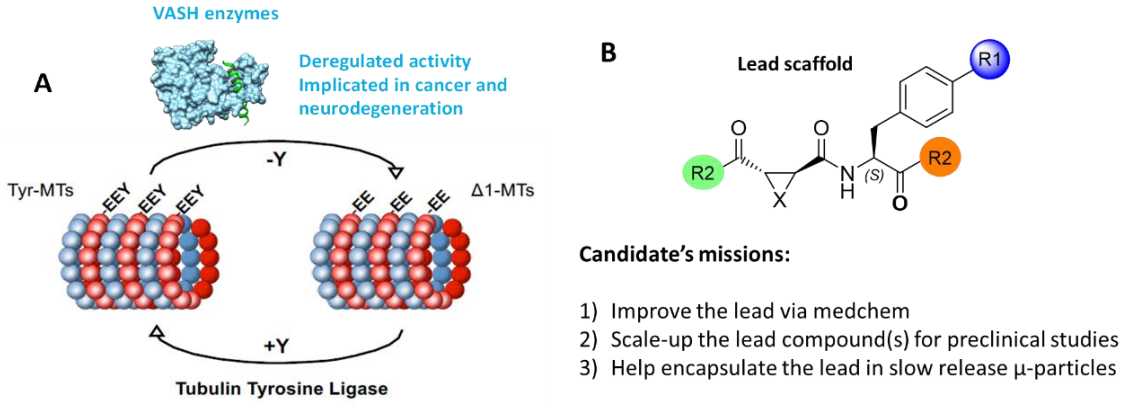

Figure 1 A) *Tubuline tyrosination/detyrosination cycle* ***B)*** *Lead detyrosination inhibitor and its major modification sites*

The first such modification discovered was the removal of the ultimate C-terminal Tyrosine residue from α-tubulin (Fig **1A**). Surprisingly, it took more than 40 years to identify the enzymes involved in this modification and only recently, the group of Dr Rogowski discovered that the long sought enzymes were the VASH proteins (Science 2017, 358 (6369), 1448-1453, Cell Reports 2019, 29 (12), 4159-4171. e6). Upregulated tubulin detyrosination is detrimental for neuronal health and as such represent a potential therapeutic target. **In this context, the project aims at developing potent, selective and bioavailable VASH inhibitors as innovative therapeutics in the field of neurodegenerative diseases (exact drug target is confidential).**

Work context: The study will take place in team 9 of the IBMM institute (https://ibmmpeptide.com) in collaboration with a biomedical startup Mt-Act (https://www.mt-act.com/) and the materials' chemistry institute ICGM. Our group (around 40 members) is extremely well equipped (NMR, HPLC, LC-MS, combiflash, automated synthesizers…) for the realization of *medchem* and *chembio* projects. The study will be supervised by Dr Lubomir Vezenkov (associate professor at ENSCM, https://ibmmpeptide.com/lubomir-vezenkov) and Dr Muriel Amblard (Director of Researcher at CNRS, https://ibmmpeptide.com/muriel-amblard).

Missions: **The candidate will fist work on improving the affinity and the bioavailability of our lead VASH inhibitors by medicinal chemistry techniques (Fig1 B). Rational design in combination with molecular modelling and artificial intelligence will be privileged**. Then she (he) will perform a scale up synthesis of the best available compound(s) that will allow testing them *ex vivo* and *in vivo*. As last objective, she (he) will work in a tight collaboration with the ICGM team in order to incorporate our lead compound(s) into microparticles. Such particles will allow a progressive release of our drug candidate, thus lowering the number of injections and improving patients' compliance.

Skills: The candidate should be ready to work in highly transversal collaborative study. He (she) should have good experience in organic and medicinal chemistry. Notions of molecular modelling and artificial intelligence / deep learning are a plus.

Send a CV and cover letter to lubomir.vezenkov@enscm.fr