Project title: **Investigation of the mode of action of oxfendazole in filariasis**

Background. Infections with nematodes compose the largest part of neglected tropical diseases (NTDs) with an estimated 1.5 billion infections. The NTD roadmap by the WHO aims to eradicate NTDs by 2030. To move towards this goal, new affective, affordable and accessible drugs are needed. In filariasis, to interrupt transmission and eradicate the disease, drugs need to sterilise or kill the long-lived (10-15 years) adult worms. One approach is to repurpose an already available drug for use in humans. One such molecule is Oxfendazole (OXF), currently used in veterinary treatment of helminth infections. This pan-nematode drug candidate, shown in pre-clinical trials to be a potent macrofilaricide, active against at least 3 filariae (*Litomosoides sigmodontis*, *Loa loa* and *Mansonella perstans*) could be a solution without additional investment. OXF belongs to the Benzimidazoles, known tubulin inhibitors. Its specific mode of action on parasite tubulin and the consequences of a disrupture in the tubulin network in the parasites are not known.

Objectives This project aims at investigating the mode of action of OXF in filariae, taking advantage of the availability of the complete life cycle of *L. sigmodontis*, in the host laboratory. We will first determine the selectivity of OXF on mammalian and filarial tubulin (*L. sigmodontis*, *L. loa*, *M. perstans* and *O. volvulus*) and, by purifying tubulins from the different organisms. We will then analyse the respective tubulin polymerization characteristics and determine the concentrations of OXF inhibiting assembly.
The next step is to investigate in detail the effects of OXF on the tubulin network, both in vitro and in vivo. As microtubules can display different properties and functions, we will look at different subpopulations of tubulins, mainly at tubulin post-translational modifications, indicating specific functions for these microtubules. The final aim of the project is to study the impact of OXF on filarial and host metabolism using Nuclear Magnetic Resonance metabolomics.

Expected results. Determining the concentrations of OXF effective on different filarial tubulins, without negative impact on mammalian tubulin, is an essential information for a potential pan-nematode drug, allowing the adaptation of the concentration of drug needed for treatment. Knowing where the different subpopulations of tubulin are expressed in the parasite – considering the complex morphology of these organisms – could give indications for specific functions. It is known that the obligate endosymbiont *Wolbachia* uses microtubules to gain its proper localisation. We will be able to determine if there is a specificity of tubulin populations for the trafficking and what happens to *Wolbachia* if the tubulin network is perturbed by suboptimal concentrations of OXF.
Taken together the different parts of the project will provide a more comprehensive picture of the mode of action of the inhibitor, helping the repurposing of a potential pan-nematode drug.

Host laboratory. The Parasite and Free Living Protist team is located at the Museum National d'Histoire naturelle in Paris town centre, 61 rue Buffon 75005 PARIS, and is affiliated to the doctoral school " Sciences de la nature et de l'Homme : évolution et écologie " (ED227, MNHN-SU). The lab investigates a variety of eukaryotic parasites (filariae, trypanosomes, Plasmodium…).

Candidate profile. The candidate needs to have Master degree with someexpertise in cell biology and parasitology.

To apply:
Applicants should send their CV, a motivation letter and 3 references in a single pdf file to Linda Kohl (PhDsupervisor, Linda.kohl@mnhn.fr) and Coralie Martin (PhD co-supervisor, Coralie.martin@mnhn.fr).