Job vacancy (15 months-PostDoctoral Position)

Nanoscale assessment of Toxins-Cells Interactions by Atomic Force Spectroscopy

Type. 15-Months Postdoctoral fellowship.

Start of the position. February-March 2023 (flexible)**.**

Location. Lorraine University, Interdisciplinary Laboratory for Continental Environments (LIEC), Group ''Physical Chemistry and Reactivity of Surfaces And interfaces'' (PhySI). Vandoeuvre-lès-Nancy (direct vicinity of Nancy), FRANCE. Web page: https://liec.univ-lorraine.fr/

Context.

A diverse array of toxin and antitoxin systems widely distributed among organisms has emerged between pathogens and their hosts as strategies for defense or virulence **[1,2]**. These toxins can be found in different organisms, from bacteria to metazoans, and they exhibit highly specific actions over a broad range of cellular pathways, thereby triggering a large spectrum of physiological effects such as neurotoxicity or necrosis **[3-5]**. Selection pressures operating in host-pathogen interactions have generated a repertoire of specific toxins harboring distinct selectivity towards targeted cell types, thus providing promising tools for applications as therapeutic agents in molecular pharmacology **[6-8]**. Among the most common toxins present in all kingdoms of life, Pore-Forming Toxins (PFT) are a large class of biological weapons used by prokaryotes as virulence factors and by eukaryotes in immune responses. Overall, these toxins are secreted as soluble protoxins and undergo a conformational change to form oligomeric pores in membrane subsequent to their interactions with specific receptors located at the membrane surface of the targeted cells **[1,9,10]**. In some cases, proteolytic cleavage is required to form the active toxin **[11]**. Many studies have highlighted the extensive range of receptors recognized by PFTs, which includes lipids, sugars or membrane proteins **[12-14]**.

1. Szczesny et al. 2011. *PLoS ONE* 6: e20349. **2.** Moran et al. 2012. *Mol. Biol. Evol.* **3.** Los et al. 2013. *Microbiol. Molecular Biol. Rev.*: 77: 173-207. **4.** Lubkin et al. 2017. *Curr. Opin. Microbiol.* 35: 58-63. **5.** Rudkin et al. 2017. *PLoS Pathogens* 13: e1006452. **6.** Irena et al. 2012. *Curr. Pharmac. Biotechnol.*13: 1446-73. **7.** Zhang. 2015. *Zoological Research* 36: 183-222. **8.** Akbari al. 2017. *International Reviews of Immunology* 36: 207-19. **9.** Knapp et al. 2010. *The Open Toxicology Journal* 3: 53-68. **10.** Iacovache et al. 2008. *Biochim. Biophys. Acta - Biomemb.* 1778: 1611-23. **11.** Howard and Buckley JT. 1985. In *Activation of the hole-forming toxin aerolysin by extracellular processing*, pp. 336-340. **12.** Rossjohn et al. 1997. *EMBO J.* 16: 3426-34. **13.** Abrami et al. *Trends Microbiol.* 8: 168-72. **14.** Cirauqui et al. 2017. *Sci. Rep.* 7: 13932.

PostDoc position description.

Several PFTs related to the aerolysin toxin have been identified so far from i) *Biomphalaria glabrata,* an intermediate host snail vector of Schistosomiasis, and from ii) its parasite *Schistosoma mansoni*. Among them, Biomphalysin 1 was shown to interact with the surface of the parasite leading to its death. The general scope of this project supported by the ANR grant **AeroSNAIL** led by the IHPE laboratory in Perpignan (http://ihpe.univ-perp.fr/) is to characterize the regulation, the biological activity and the structure of different aerolysin-related toxins in the species *Biomphalaria glabrata* and *Schistosoma mansoni* by combining novel functional, structural and nano-biophysical approaches.

For this PostDoctoral position, the candidate will specifically use Atomic Force Microscopy in both imaging and force spectroscopy modes to quantify, at the molecular scale, the specific interactions operating between selected toxins produced by *Biomphalaria glabrata* and/or *Schistosoma mansoni* and their most relevant cellular targets, *i.e.* synthetic surfaces coated with purified receptors (lipids, polysaccharides, proteins), and living bacteria or blood cells. The candidate will also address the change in the morphology and nanomechanical properties of the targeted cells after their incubation with toxins using nano-indentation Atomic Force Microscopy, possibly complemented by Confocal Microscopy and Holotomography measurements.

The candidate will be located in the Laboratoire Interdisciplinaire des Environnements Continentaux (LIEC, https://liec.univ-lorraine.fr/) in the group 'Physical Chemistry and Reactivity of Surfaces And interfaces'' with renown expertise in Atomic force Spectroscopy and Surface Biophysics. The candidate will have to closely interact with all partners of **AeroSNAIL** consortium, including the group of L. Maveyraud (University Paul Sabatier, Toulouse) in charge of the production of the recombinant toxins and their crystallization, and the group of B. Gourbal (IHPE, University Perpignan) involved in the analysis of toxin biological functions.

Tasks of the successful candidate will thus consist in:

- Monitoring the morphological and nanomechanical properties of targeted cells after incubation with selected recombinant toxins within concentration ranges specified by Perpignan partner.
- Visualization by AFM of prepore and pore formed by oligomerization of toxin monomers on solid substrates, synthetic lipid bilayers and targeted cell surfaces.
- Nanoscale AFM-based single-molecule force spectroscopy measurements of the specific adhesion events using AFM tips functionalized with recombinant toxins.
- Imaging of prepore and pore formation at the surface of *Schistosoma* parasite as a result of recombinant or endogenous toxins from snail plasma.

Selected Publications from AeroSNAIL project partners

1. Pinaud *et al*. New insights into Biomphalysin gene family diversification in the vector snail Biomphalaria glabrata. *Front Immunol.* (2021) 12:635131.
2. Lassalle *et al.* Glabralysins, Potential new β-Pore-Forming Toxin family members from the Schistosomiasis vector snail Biomphalaria glabrata. *Genes* (2020) 11(1) :65.
3. Galinier *et al.* Biomphalysin, a new β pore-forming toxin involved in Biomphalaria glabrata immune defense against Schistosoma mansoni. *PloS Pathog.* (2013) 9(3): e1003216.
4. Pagnout *et al.* Osmotic stress and vesiculation as key mechanisms controlling bacterial sensitivity and resistance to TiO2 nanoparticles. *Communications Biology* (2021) 4:678.
5. Offroy *et al*. Fast automated processing of AFM PeakForce curves to evaluate spatially-resolved Young modulus and stiffness of turgescent cells. *RSC Advances* (2020) 10:19258-19275.
6. Beaussart *et al*. Probing the mechanism of the peroxiredoxin decamer interaction with its reductase sulfiredoxin from the single molecule to the solution scale. *Nanoscale Horizons* (2022) 7:515-525.

To be successful, the candidate should demonstrate the following skills:

- Have a solid experience in AFM (imaging and force spectroscopy measurements applied to biological samples in liquid conditions)

- Knowledge in biochemistry, microbiology, cell culture, and/or supported bilayer formation would be an added value,
- Be results-driven, have a marked sense of autonomy while being eager to work in a dynamic team,
- Able to manage deadlines,
- Have good communication skills (both oral and written) in English (knowledge in French is not required).

Education/Experience:

- PhD in Biophysics or Physical-Chemistry, or related fields with solid background in cellular and molecular biology.

Remuneration

ca. 2200 € (net) /month, depending on the experience of the candidate.

Applications to submit:

Candidates are requested to submit a written application comprising:

1. A letter that addresses one or several of the Selection Criteria set out in the Position Description.
2. An executive summary (no more than approximately 1000 words) that highlights your strengths and reasons why you should be appointed to the position.
3. Your CV.
4. Recommendations letters by at least two referees, including their contact details (emails and phone numbers) and positions.

Supervisors of the Post-Doctoral fellowship:

- Audrey Beaussart, CNRS Researcher
- Jérôme F.L. Duval, CNRS Research Director (https://duvaljfl.webnode.fr/)

Complete applications should be sent to Audrey Beaussart (Audrey.beaussart@univ-lorraine.fr) and Jérôme F.L. Duval (jerome.duval@univ-lorraine.fr) before **December 15th, 2022**. A first round of interviews for pre-selected candidates will take place before the end of January 2023.