



Application to be sent to Claire Mendoza and Clemence Grosnit:  
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Deadline: March 1<sup>st</sup>, 2024

## EUR CARE PhD program pre-proposal

(2 pages maximum)

**PhD Director:** Kerstin Bystricky, [kerstin.bystricky@univ-tlse3.fr](mailto:kerstin.bystricky@univ-tlse3.fr)  
(Name and email)

**PhD Director affiliation:** Center for Integrative Biology (CBI), University of Toulouse Paul Sabatier - CNRS

**PhD co-Director:** Manon Fallet, [manon.fallet@oru.se](mailto:manon.fallet@oru.se)  
(Name and email)

**PhD co-Director affiliation:** Man-Technology-Environment (MTM) Research Centre, S. Keiter team, Orebro University.

**Research project title:** Response of chromatin structure to climate changes and perfluoroalkyl substances during zebrafish development and ageing

### Research program abstract (max 500 words):

One of the major challenges of our century is environmental sustainability. Indeed, anthropic activities are threatening ecosystems' balance and biodiversity survival. Assessing the effects of human's disturbances is then urgently needed for both human health and biodiversity protection. Aquatic organisms are particularly in danger due to climate changes and chemicals exposure. An increase in temperature is suspected to increase the growth rate of ectothermic animals, like fish, and to induce thermal stress. Thus, leading to accelerate ageing through the increase of the metabolic demand. In addition, chemical exposures are likely to accelerate the ageing process in living organisms by modifying biological pathways. Nevertheless, to what extent environmental alterations could affect living organisms, both during development and ageing, still needs to be quantified and little is known about the molecular mechanisms driving adverse outcomes that can be expected when several environmental stresses arise in the same environment. Epigenetic modifications are very sensitive to hormonal and chemical exposures making them a powerful means to study the impact of anthropogenetic disturbances on cellular phenotypes and ageing.

Therefore, the proposed PhD project aims at:

1. Study the effect of increased water temperature and PFOS chemical exposure on epigenetic marks, nuclear organization and metabolic changes in single cells using fluorescence imaging, chromatin immunoprecipitation and RNAseq using zebrafish eggs and embryos (CBI)
2. Adapt chemical exposure concentration, dilutions using UPLC-MS/MS (MTM)
3. Assess the adverse effect of the exposures on zebrafish development and phenotype at different time points during lifespan (MTM) and decipher if the observed changes are transmitted to the next generations (tools as in 1; CBI)
4. Identify factors limiting and/or enhancing the observed effects using mutants of identified epigenetic writers or readers (Crspr candidate screen).

This project will merge **chemistry**, in vivo tests, and molecular analysis, with both genome-scale and targeted methods, **bioinformatics**, to decipher the impact of climate changes and chemical pollutions (separated and simultaneously), on aquatic species and their descendants. This knowledge is key to predicting long-term

consequences of anthropic effects on cells, in particular in aquatic ecosystems and to improve risk assessment and environmental pollution monitoring in the future. Funding for the project's running costs has been obtained through the FORMAS program for 2023-27 (<https://formas.se/> to MF).

**Describe in 50 words max for each how this project fits the 3 defining criteria of the CARE graduate programme:**

**1) Relation to CARE topics of Cancer, Ageing and/or Rejuvenation**

This project is related to the CARE topics of ageing by investigating the effect of climate change and chemical exposure on zebrafish development and ageing together with deciphering the molecular mechanisms beyond such effects (metabolic changes, epigenetic modifications).

**2) Multidisciplinary aspect**

The project will be at the interface of biology (fish husbandry, molecular biology, physiology, imaging, metabolomics), chemistry (chemical exposure, dilutions, UPLC-MS/MS), and computational sciences (OMICS analysis, statistics, linear models, and network analysis). The successful applicant will gain knowledge and skills in these fields.

**3) International and/or industrial aspect(s)**

This research project has been developed in collaboration between the CBI (France) and researchers from MTM (Sweden). The first part of the project is expected to be performed at the MTM (Fish husbandry, sampling and metabolism analysis)/ Imaging and epigenetic analyses will be done at the CBI.

**5 keywords in line with EUR CARE**

Development, ageing, epigenetics, chemical exposure, adaptation.

**5 references of the teams, highlighting the co-signatory students (underlined):**

**Manon Fallet**, Mélanie Blanc, **Michela Di Criscio** Philipp Antczak, Magnus Engwall, Carlos Guerrero Bosagna, Joëlle Rüegg, **Steffen H. Keiter**. Present and future challenges for the investigation of Transgenerational Epigenetic Inheritance. *Environment International* 172 (2023). DOI: <https://doi.org/10.1016/j.envint.2023.107776>.

**Ludmila Recoules**<sup>1</sup>, Alexandre Heurteau<sup>1</sup>, Flavien Raynal<sup>1</sup>, Fatima Moutahir<sup>1</sup>, Fabienne Bejjani<sup>3</sup>, Isabelle Jariel-Encontre<sup>3</sup>, Olivier Cuvier<sup>1</sup>, Anne-Claire Lavigne<sup>1</sup>¶ and **Kerstin Bystricky**<sup>1,2</sup>¶ « The histone variant macroH2A1.1 activates transcription of paused genes by direct association with their transcription start site. », *J Cell Sci.* 2022 Apr 1;135(7):jcs259456. doi: 10.1242/jcs.259456.

Shaban HA¶, Barth R., **Recoules, L.** and **Bystricky K.**¶ "HiD: Nanoscale mapping of nuclear dynamics in living human cells" *Genome Biology* 21(1):95. doi: 10.1186/s13059-020-02002-6, 2020

**Thomas Germier**\*, Silvia Kocanova\*, Nike Walthers, Aurélien Bancaud, Hafida Sellou, Haitham Shaban, Jan Ellenberg, Franck Gallardo and **Kerstin Bystricky**# "Real-time chromatin dynamics of the single gene level during transcription activation" doi.org/10.1016/j.bpj.2017.08.014, *Biophysical Journal*, 2017

**M Blanc**, A Kärrman, P Kukucka, N Scherbak, **S Keiter** "Mixture-specific gene expression in zebrafish (*Danio rerio*) embryos exposed to perfluorooctane sulfonic acid (PFOS), perfluorohexanoic acid (PFHxA) and 3,3',4,4',5-pentachlorobiphenyl (PCB126)" *Science of the Total Environment*, 2017, 590, 249-257