Project Title	Environmental maternal effects and intergenerational inheritance
University (where student will register)	University of Warwick
Which institution will the student be based at?	As above
Theme (Max. 2 selections)	Climate & Environmental Sustainability ☐ Organisms & Ecosystems ☒ Dynamic Earth ☐
Supervisory team (including institution & email address	**PI:** Andre Pires da Silva (University of Warwick; andre.pires@warwick.ac.uk) **Co-I:** Robin Allaby (University of Warwick; r.g.allaby@warwick.ac.uk)

Project Highlights:

- Mechanisms by which organisms rapidly respond to sudden environmental changes
- Mother senses environmental stress signals to produce stress-resistant progeny
- Use of the most recent genome-editing tools, as well as biochemistry, and next-gen sequencing

Overview (including 1 high quality image or figure): *Maximum 350 words*

Sudden environmental changes are challenging for the survival of many organisms. Some organisms evolved mechanisms to cope with uncertainty, by sensing the environment and transmitting selected adaptive traits to the next generation.

We use the nematode *Auanema freiburgensis* as model to study the mechanisms by which environmental signals sensed by the mother results in the modification of the germline to produce stress-resistant progeny. In this nematode, chemicals produced by nematodes of the same species are used as signals for overcrowding. Thus, by sensing these chemicals, the mother 'prepares' the progeny to withstand the lack of food that occurs in overcrowded conditions. The progeny arrests development in the form of larvae, and can survive in the absence of food for several months. Once in a benign environment, the larvae resume development to become self-fertilizing adults. The main objectives of the project are to identify the chemical nature sensed by the mothers, how the sensory neurons convey the information to the gonad, and how the germline changes result in different kinds of progeny.

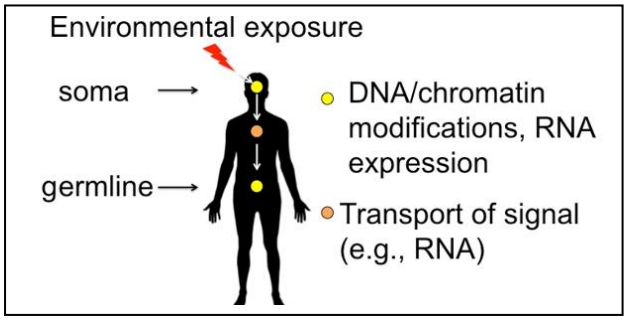

Figure 1: *Conceptual framework. An environmental trigger changes the state of the soma, which sends a signal to modify the germline.*

Methodology: *Maximum 150 words*

Chemicals will be isolated from nematode cultures and tested for their influence on the sex determination and stress-resistance in the F1 generation. To identify the neuron sensing the chemicals, single cells will be tested by killing them with the use of a laser microbeam. The nature of the communication signal between the neuron and the germline will be tested by performing gene knockouts using the genome editing technology. Changes in the germline upon neuronal signal will be tested using immunoprecipitation with antibodies recognizing histone modification markers.

Training and skills: *Maximum 100 words – excluding CENTA training information*

Students will be awarded CENTA2 Training Credits (CTCs) for participation in CENTA2-provided and 'free choice' external training. One CTC equates to 1⁄2 day session and students must accrue 100 CTCs across the three years of their PhD.

Students will learn to use the latest genome editing technologies (CRISPR-Cas9) to inactivate gene function and to tag genes to visualize their time and site of expression. Furthermore, students will acquire skills in bioinformatics (learn how to code in Unix and R), how to ablate single cells and immunocytochemistry. In addition, students will learn how to organize and execute their experiments in a timely fashion, how to document experiments, prepare presentations, write professional articles and work in a team. Many of those skills are transferable to other disciplines and professions.

Partners and collaboration (including CASE): *Maximum 100 words*

The chemical characterization of the signals produced by nematodes will be in collaboration with the chemist Frank C. Schroeder at Cornel University (USA). The characterization of gene expression changes will be performed with the collaboration with the laboratory of Oded Rechavi at Tel-Aviv University (Israel).

COVID-19 Resilience of the Project: *Maximum 100 words:*

Please give concise information about how the COVID-19 pandemic might potentially affect project delivery and how far mitigation efforts can be made available. Give a clear overview of those mitigation efforts, if the project or parts of it might be affected. If a shift of topic would be possible, please indicate in which direction any adjustment could be made. Please note: Project proposals without COVID-19 resilience information will not be advertised.

The project has RNAseq analysis component that would entail analysis of different strains and species that respond to environmental stimuli. Since RNAseq can be done from home, it would this would be able to mitigate for experiments that cannot be performed in the laboratory.

Possible timeline:

Year 1: Fraction and test chemicals produced by the nematode. Make laser ablations of single neurons.

Year 2: Generate mutants for neuroamines and neuropeptides using CRISPR/Cas9. Characterize mutants. Start immunocoprecipitation experiments.
Year 3: Transcriptome analysis of animals exposed to defined chemicals. Characterise candidate genes involved in cross-generational inheritance using genome editing technologies

Further reading: (*in Harvard Reference Style*)

1. Pembrey, M.E., Bygren, L.O., Kaati, G., Edvinsson, S., Northstone, K., Sjostrom, M., Golding, J., and Team, A.S. (2006). Sex-specific, male-line transgenerational responses in humans. Eur J Hum Genet *14*, 159-166.
2. Grossniklaus, U., Kelly, W.G., Ferguson-Smith, A.C., Pembrey, M., and Lindquist, S. (2013). Transgenerational epigenetic inheritance: how important is it? Nat Rev Genet *14*, 228-235.
3. Cossetti, C., Lugini, L., Astrologo, L., Saggio, I., Fais, S., and Spadafora, C. (2014). Soma-to-germline transmission of RNA in mice xenografted with human tumour cells: possible transport by exosomes. PLoS One *9*, e101629.
4. Dias, B.G., and Ressler, K.J. (2014). Parental olfactory experience influences behavior and neural structure in subsequent generations. Nat Neurosci *17*, 89-96.
5. Kaati, G., Bygren, L.O., and Edvinsson, S. (2002). Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. Eur J Hum Genet *10*, 682-688.
6. Sharma, A. (2015). Transgenerational epigenetic inheritance: resolving uncertainty and evolving biology. Biomol Concepts *6*, 87-103.
7. Devanapally, S., Ravikumar, S., and Jose, A.M. (2015). Double-stranded RNA made in C. elegans neurons can enter the germline and cause transgenerational gene silencing. PNAS *112*, 2133-2138.
8. Heard, E., and Martienssen, R.A. (2014). Transgenerational epigenetic inheritance: myths and mechanisms. Cell *157*, 95-109.
9. Rechavi, O., Houri-Ze'evi, L., Anava, S., Goh, W.S., Kerk, S.Y., Hannon, G.J., and Hobert, O. (2014). Starvation-induced transgenerational inheritance of small RNAs in C. elegans. Cell *158*, 277-287.
10. Rechavi, O., Minevich, G., and Hobert, O. (2011). Transgenerational inheritance of an acquired small RNA-based antiviral response in C. elegans. Cell *147*, 1248-1256.
11. Greer, E.L., Beese-Sims, S.E., Brookes, E., Spadafora, R., Zhu, Y., Rothbart, S.B., Aristizabal-Corrales, D., Chen, S., Badeaux, A.I., Jin, Q., et al. (2014). A histone methylation network regulates transgenerational epigenetic memory in C. elegans. Cell Rep *7*, 113-126.
12. Edison, A.S. (2009). *Caenorhabditis elegans* pheromones regulate multiple complex behaviors. Curr Opin Neurobiol *19*, 378-388.
13. Schroeder, F.C. (2015). Modular assembly of primary metabolic building blocks: a chemical language in *C. elegans*. Chem Biol *22*, 7-16.
14. Kanzaki, N., Kiontke, K., Tanaka, R., Hirooka, Y., Schwarz, A., Muller-Reichert, T., Chaudhuri, J., and Pires-daSilva, A. (2017). Description of two three-gendered nematode species in the new genus *Auanema* (Rhabditina) that are models for reproductive mode evolution. Sci Rep *7*, 11135.

Further details:

Andre Pires da Silva
University of Warwick

Email: andre.pires@warwick.ac.uk