Characterising the role of in vivo cell-to-cell communication in the stress system

Supervisory team:
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Project description:
Stress is a dynamic phenomenon. Within seconds of experiencing a stressful situation, the brain hypothalamic neuronal circuits flood the pituitary gland with a cocktail of "stress neurohormones", leading to a wave of adrenocorticotrophin hormone (ACTH) release from the pituitary, which in turn drives the secretion of adrenal glucocorticoid hormones such as cortisol. Why doesn't the brain signal directly to the adrenal rather than communicating via the pituitary? Scientists have proposed that there is some "intelligence" in the pituitary: pituitary cells can function as networks and these networks can change their behaviour according to environmental conditions.

In this project we will explore whether such intelligence exists within the pituitary ACTH network. To do so, we will use zebrafish larvae, which are transparent and will enable us to observe the activity of the entire ACTH cell network in vivo for the first time. Using this approach we will address key questions, such as:

- What is the role of inter-cellular communication in coordinating the output of the network?
- How are significant stressful experiences, such as early life stress or chronic stress, encoded in the network of ACTH cells?

To answer these questions, we will use zebrafish that have been genetically modified so their ACTH cells express a fluorescent marker of activity. This will enable us to image the activity of the network in real time. We will image this activity when the animal is not stressed and when it is subject to a mild stressor. Using mathematical analysis of whole network activity, we will determine which cells are connected to which, and how strongly. Then, we will manipulate the network, either by removing parts of the network, or by interfering with cell-to-cell communications. These manipulations will be important to understand the network mechanisms that enable the pituitary to release the right amount of ACTH at the right time.

We will repeat these experiments in animals that have experienced significant stress. This will enable us to see if stressful experiences can reprogram the ACTH network, and how. Anxiety, which affects a large part of the population, has been linked to early life events. Understanding how the ACTH network encodes these early life events will help us better understand anxiety. This understanding in turn may lead to new treatments for anxiety that target pituitary cell communications rather than brain circuits.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.