# "Delayed effect of early-life exposure to 17-α-ethinylestradiol on the DNA methylation landscape, proteome and physiology of the self-fertilizing mangrove rivulus Kryptolebias marmoratus" – Anne-Sophie Voisin

Embryonic development and early-life represent critical plastic windows during which environmental factors can have long-term repercussions on the phenotype later in life. Although this concept is now widely accepted, the molecular mechanisms mediating these delayed effects remain elusive.

Endocrine disrupting chemicals (EDCs) are of particular interest as they can mimic or interfere with endogenous hormone processes that are crucial for the normal development and homeostasis in organisms. Moreover, they are now present in thousands of every-day life products and find their way into the aquatic environment, putting at risk both wildlife and human health. In this thesis, I investigated the delayed effects of an early-life exposure to ethinylestradiol (EE2), a synthetic estrogen used in oral contraceptives, in the mangrove rivulus, *Kryptolebias marmoratus.*

This fish is the world’s only known self-fertilizing hermaphrodite, making it possible to use isogenic lineages and therefore isolate the effects of the environment on the phenotype by excluding genetic variability. After exposing genetically identical hatchlings to EE2 for a month, I monitored their phenotype throughout development until adulthood. While fish growth was impaired during exposure, compensatory growth, changes in fecundity and steroid hormone levels appeared months after the exposure. I then aimed to understand the molecular mechanisms underlying these delayed effects, by measuring the proteome and epigenome (methylome) in brain, liver and gonads of adult fish. I show for the first time that estrogen-responsive pathways, such as lipid metabolism, inflammation, and the innate immune system, that are typically affected after acute exposure to EE2 in several species, were persistently affected months after the exposure ceased.

My results provide further evidence for the role of DNA methylation in mediating long-term changes in cellular processes resulting from early-life exposures.