Irene Miguel-Aliaga

The sex of organs

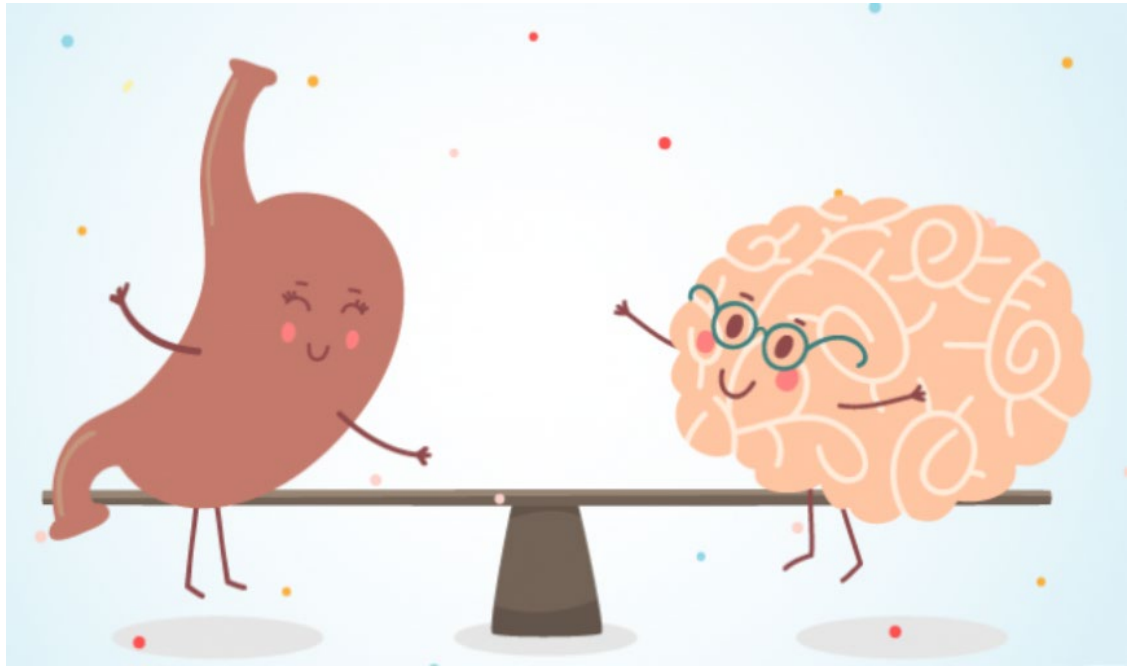
@FlyGutLab

MRC London Institute of Medical Sciences

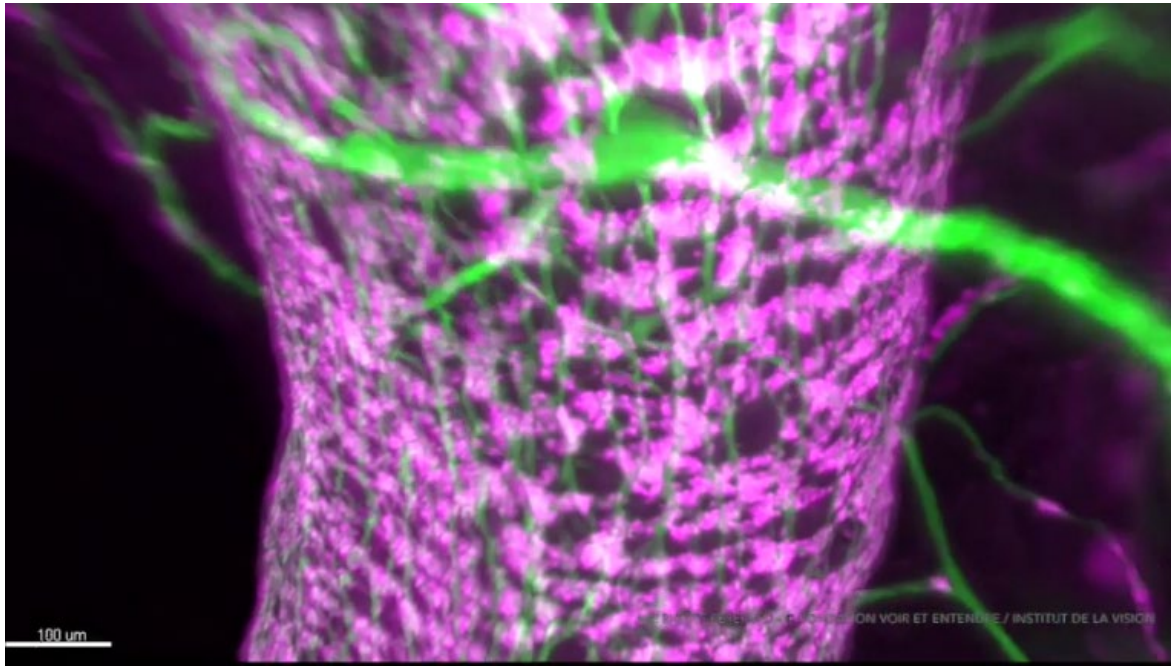
Imperial College London

More to the gut than digestion: the brain-gut axis

- **Bidirectional** communication between our nervous system and GI tract



Broth of Life

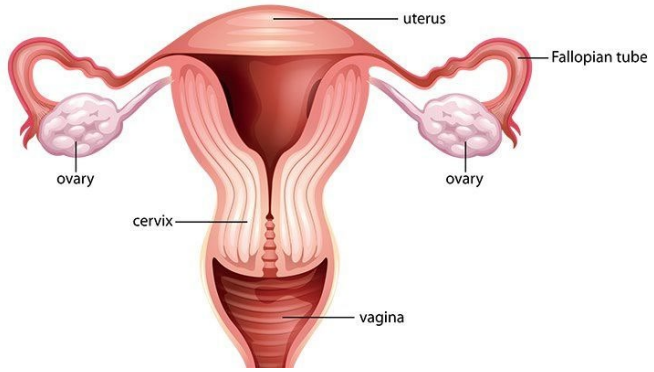


Belle et al (2017) *Cell*, www.transparent-human-embryo.com

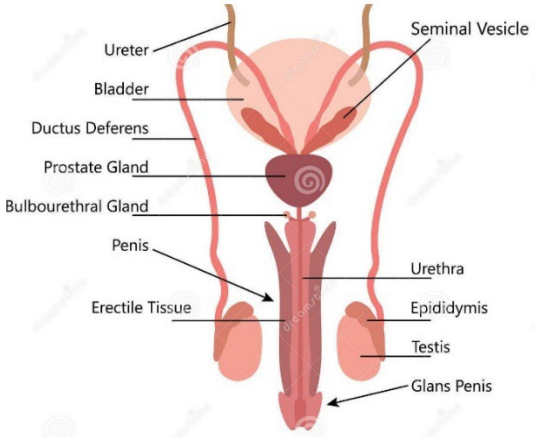
- **Enteric neurons** and **enteroendocrine hormones** as molecular mediators
- But all guts are the same… are they?

Sex differences in our digestive system?

reproductive systems



Depositphotos.com



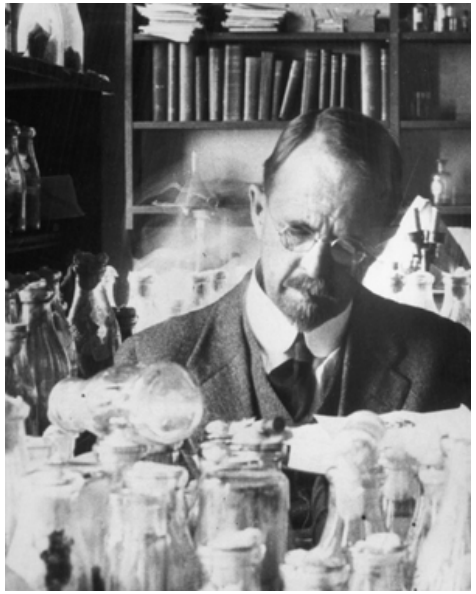
Jilian, Koibana.info

digestive system

anim3D, Microbe Notes

- Historically not considered… but most gastrointestinal disorders are sex-biased, as are many aspects of our physiology

>100 years of *Drosophila* research, 6 Nobel prizes



Thomas Hunt Morgan, 1910

A fly room, >100 years later

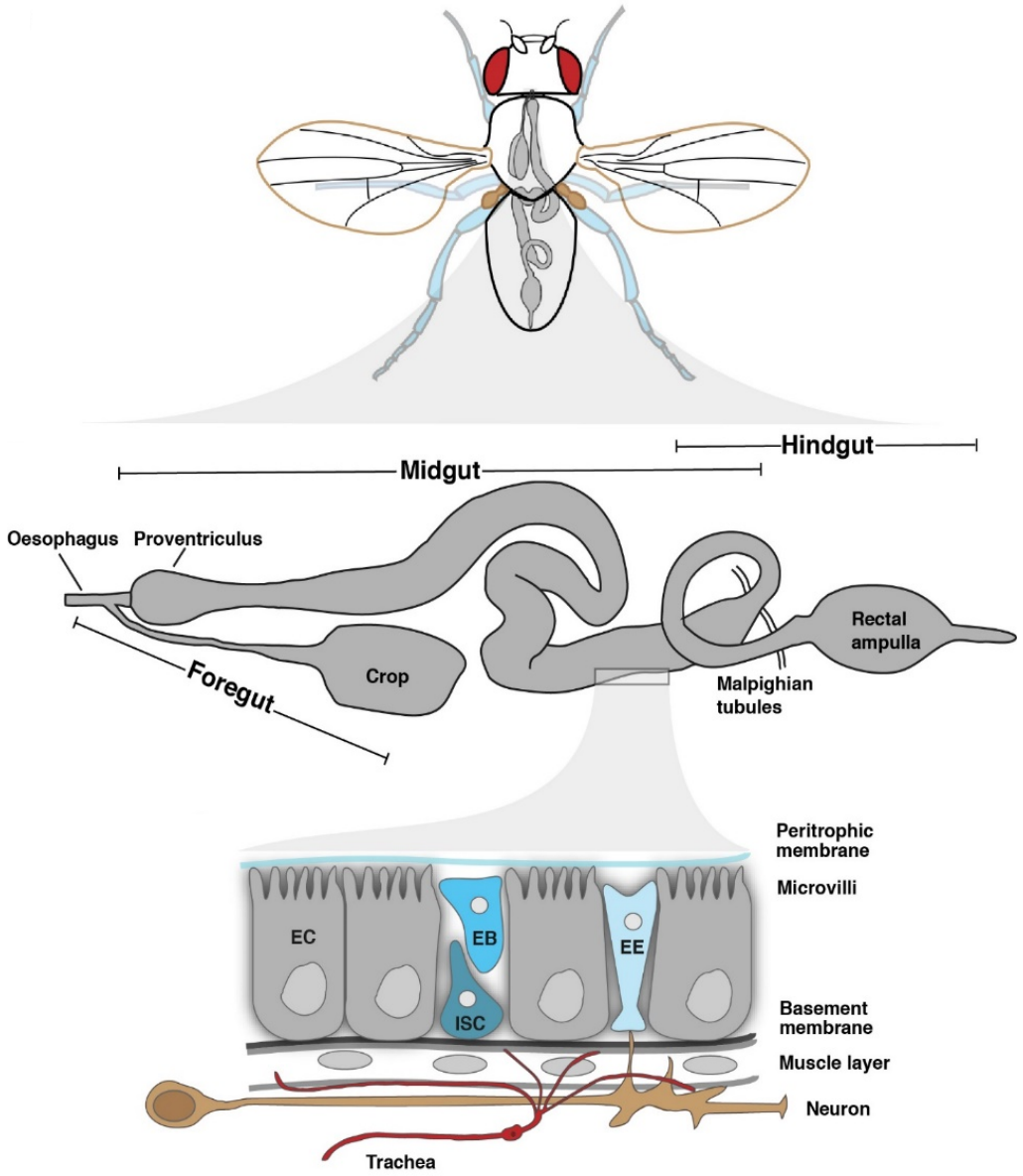
Why flies?

- Genetic similarities: 60-75% genes "shared" between flies and humans
- Inexpensive, short generation time
- Ability to turn genes/nerve cells on/off with temporal/spatial control, many genes at a time

Powerful discovery tool: immunity, neurobiology, developmental biology…

and the **brain-gut axis**?

The *Drosophila* intestine: equally fascinating, genetically tractable

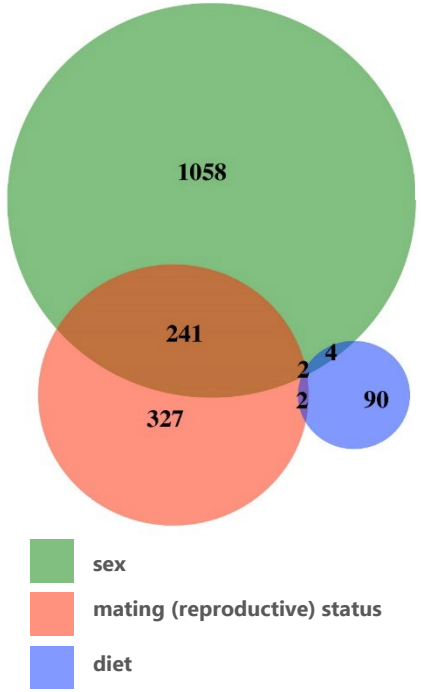


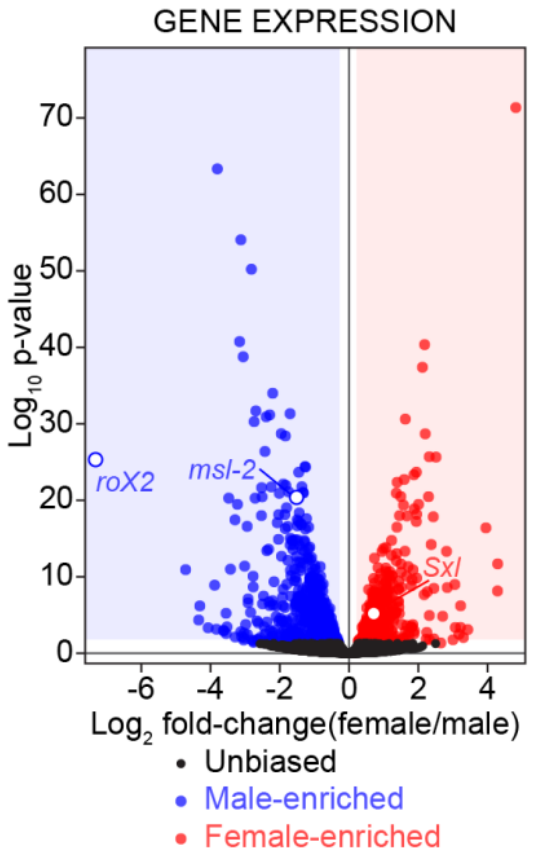
- Complex and plastic **gut**

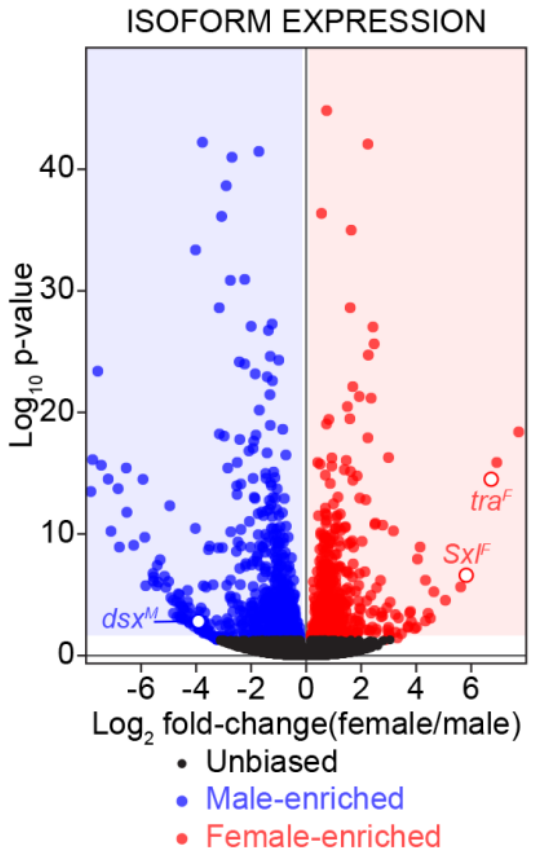
- Complex and plastic **food choices**

Sex differences in gene expression and physiology in fly intestines

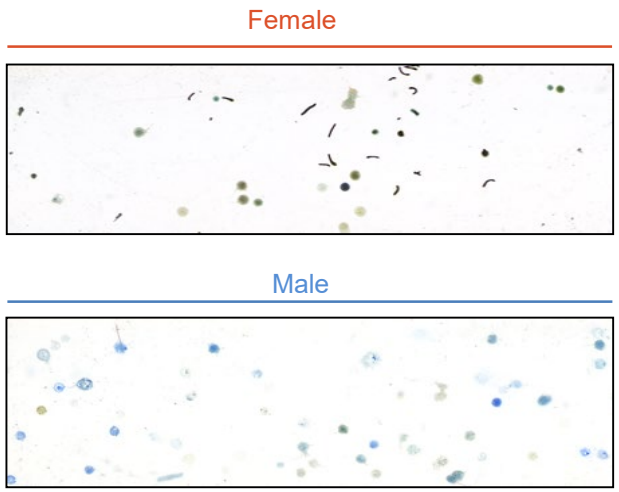
differentially expressed genes







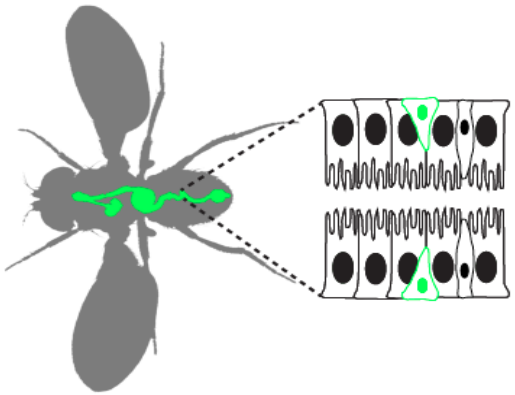
fly excreta



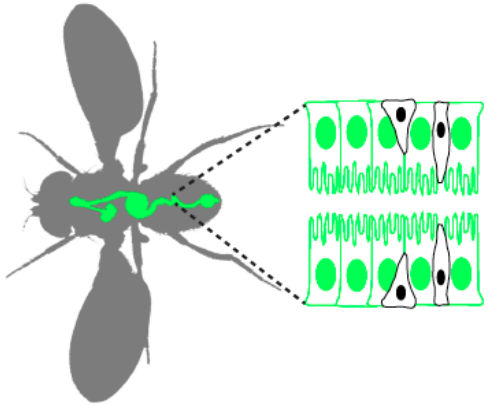
Hudry *et al* (2016) *Nature*
Cognigni *et al* (2011) *Cell Metab*

All gut cells “know their sex”, but through different mechanisms

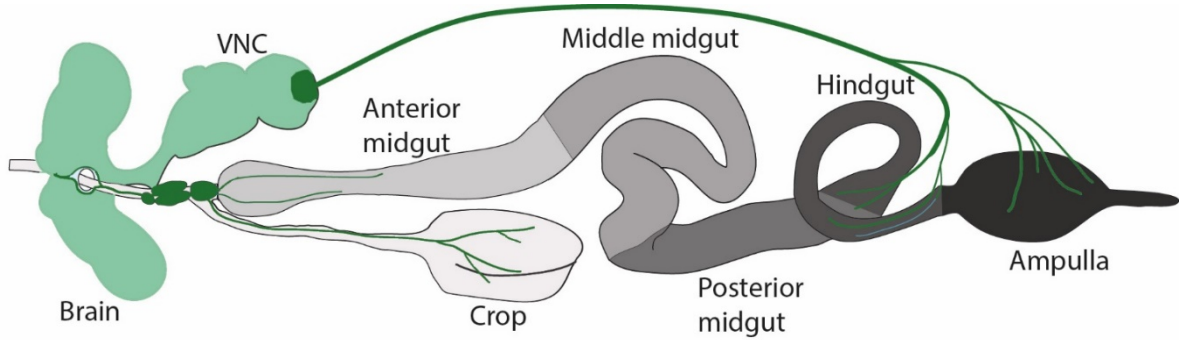
adult intestinal stem cells
(replenish damaged cells)



adult enterocytes
(digestion, absorption)



adult gut neurons
(inter-organ communication, gut transit control)

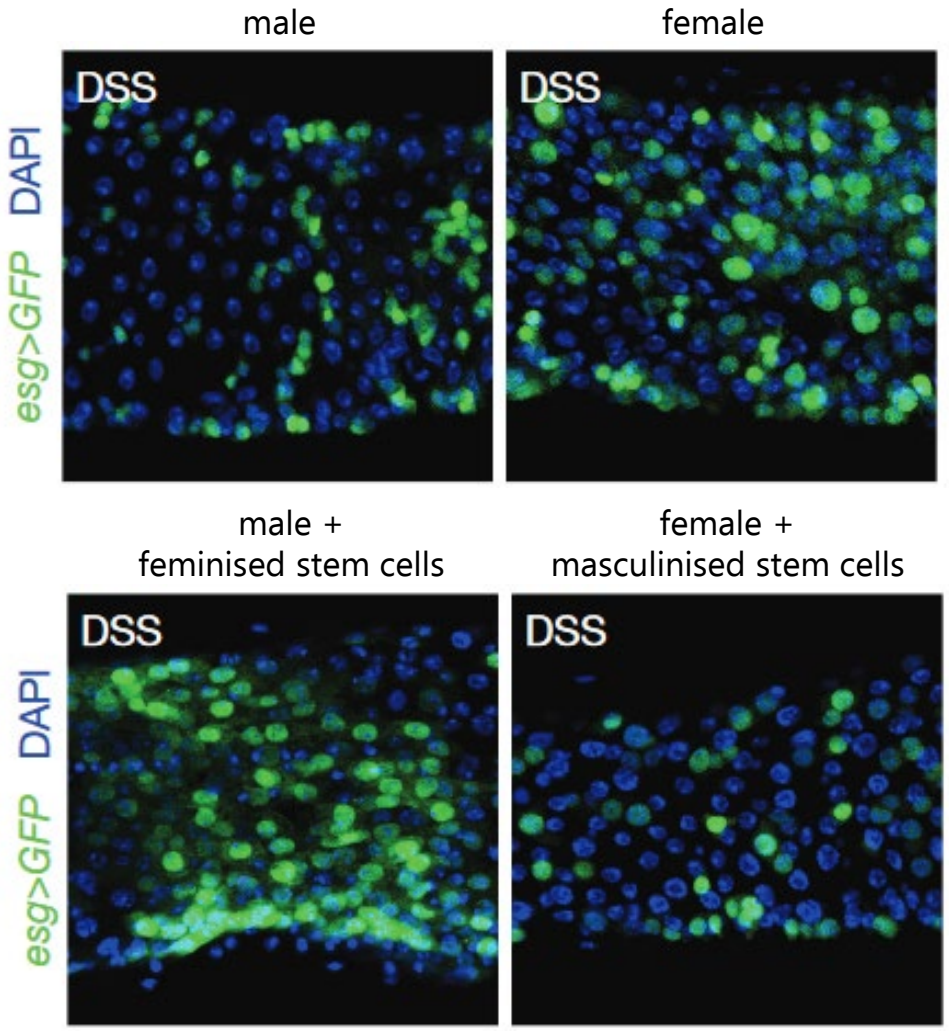


- Three **different ways to specify “sexual fate” within the same organ**: one for each cell type, some intrinsic (sex chromosomes), some extrinsic (sex hormones). **NOT developmental**
- Each mechanism controls **different sexually dimorphic features** of cell/organ biology
- Collectively, they seem to **adjust organ-level properties to optimise female or male reproduction** (but this is not their only role)

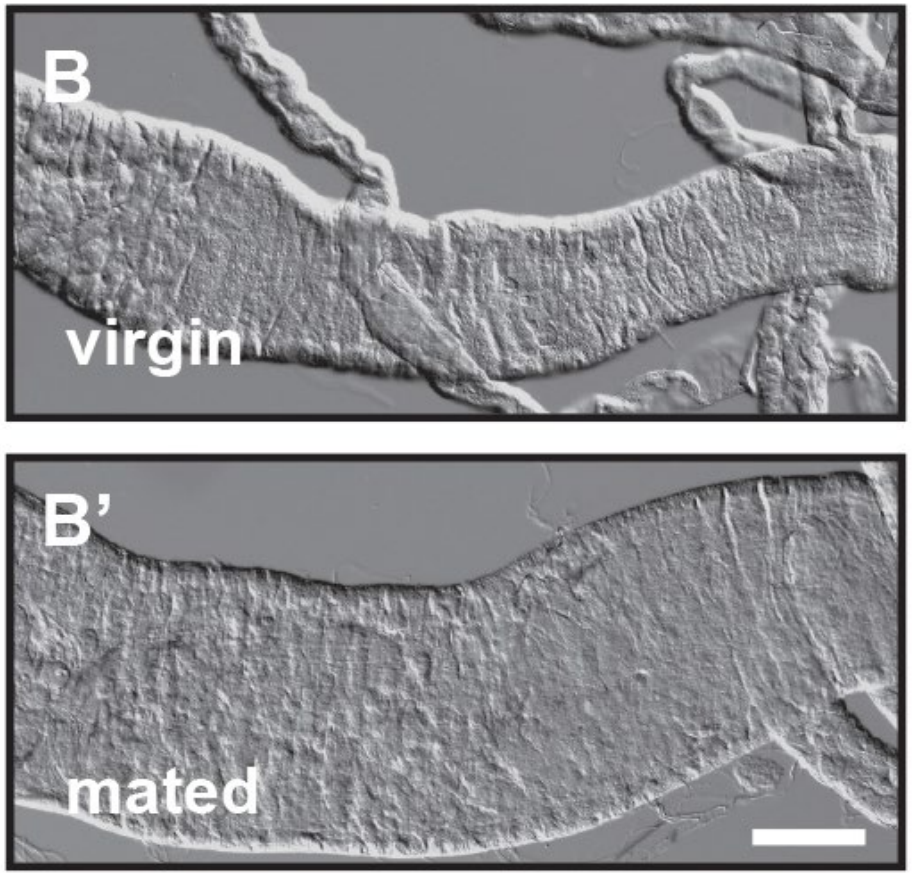
1. The sex of intestinal stem cells

Female stem cells divide more often

- Stem cell sex is **cell-intrinsic** and **adult-reversible**



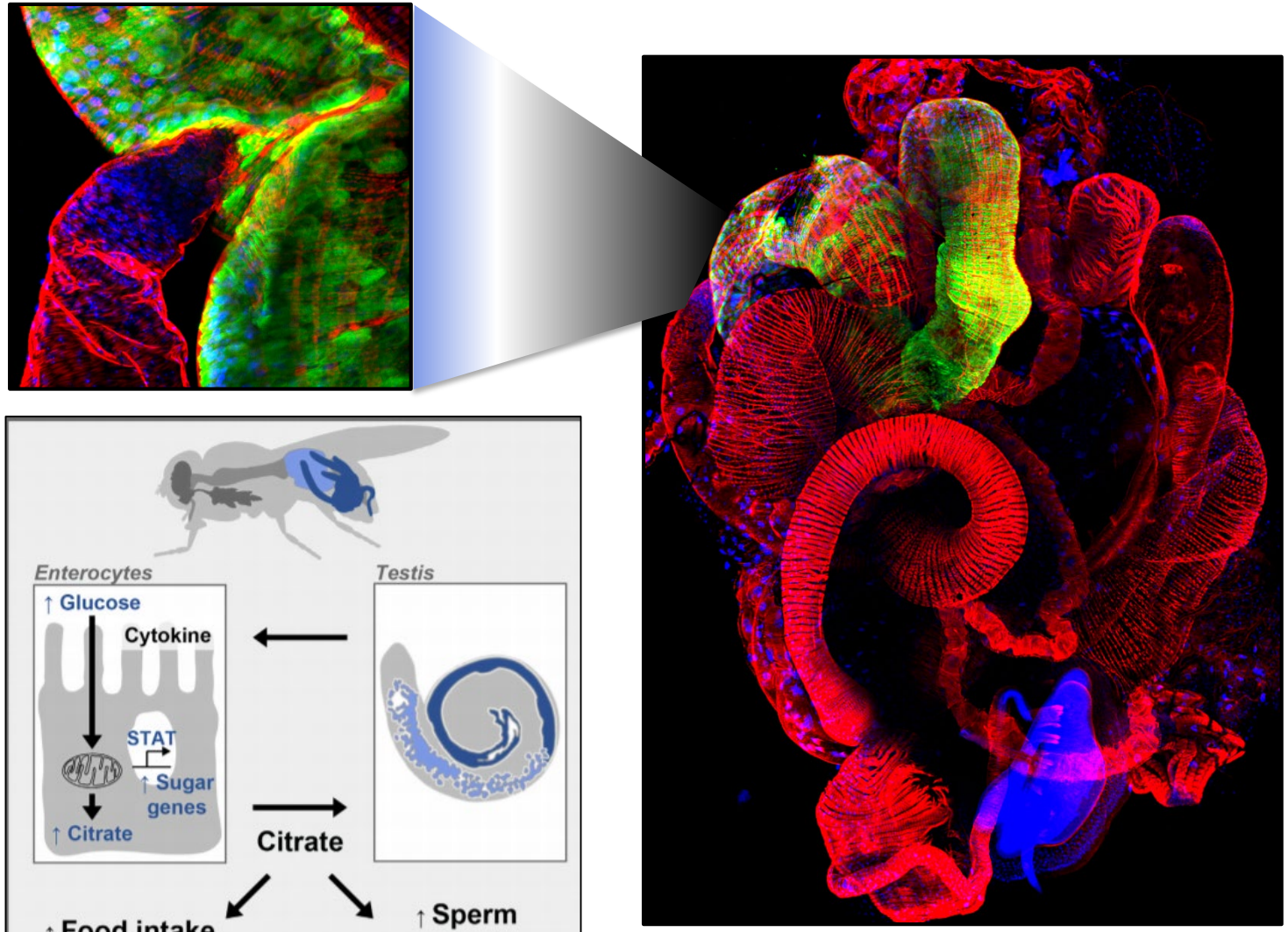
- Female identity required for the maternal gut to **grow during reproduction, sustaining fecundity**



Hudry *et al* (2016) *Nature,* Reiff *et al* (2015) eLife

2. The sex of enterocytes

Male gonad “masculinises” enterocytes to get their citrate

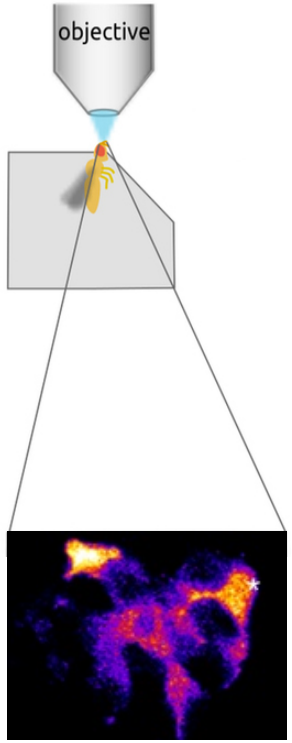


- Male **gonad masculinises adjacent gut region** and changes its handling of carbohydrates
- **Masculinised enterocytes secrete citrate**, which is taken up by male gonad and **used for spermatogenesis**
- Gut-derived **citrate promotes food intake** (in males only)

Hudry *et al* (2019) *Cell*

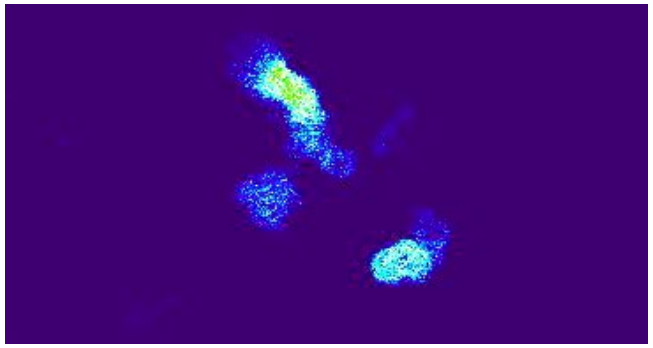
3. The sex (and reproductive status) of enteric neurons

- Female enteric neurons change their activity during reproduction
- They do so in response to reproductive changes in **steroid and enteroendocrine hormones**

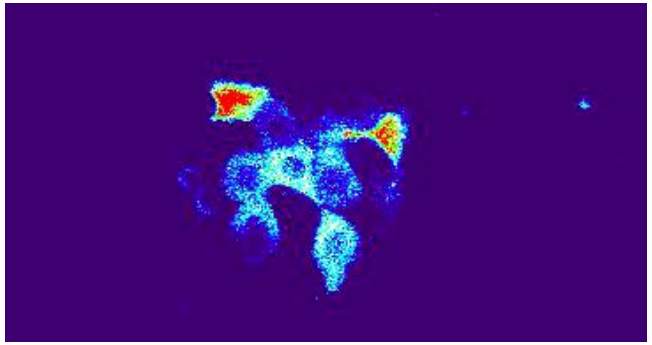


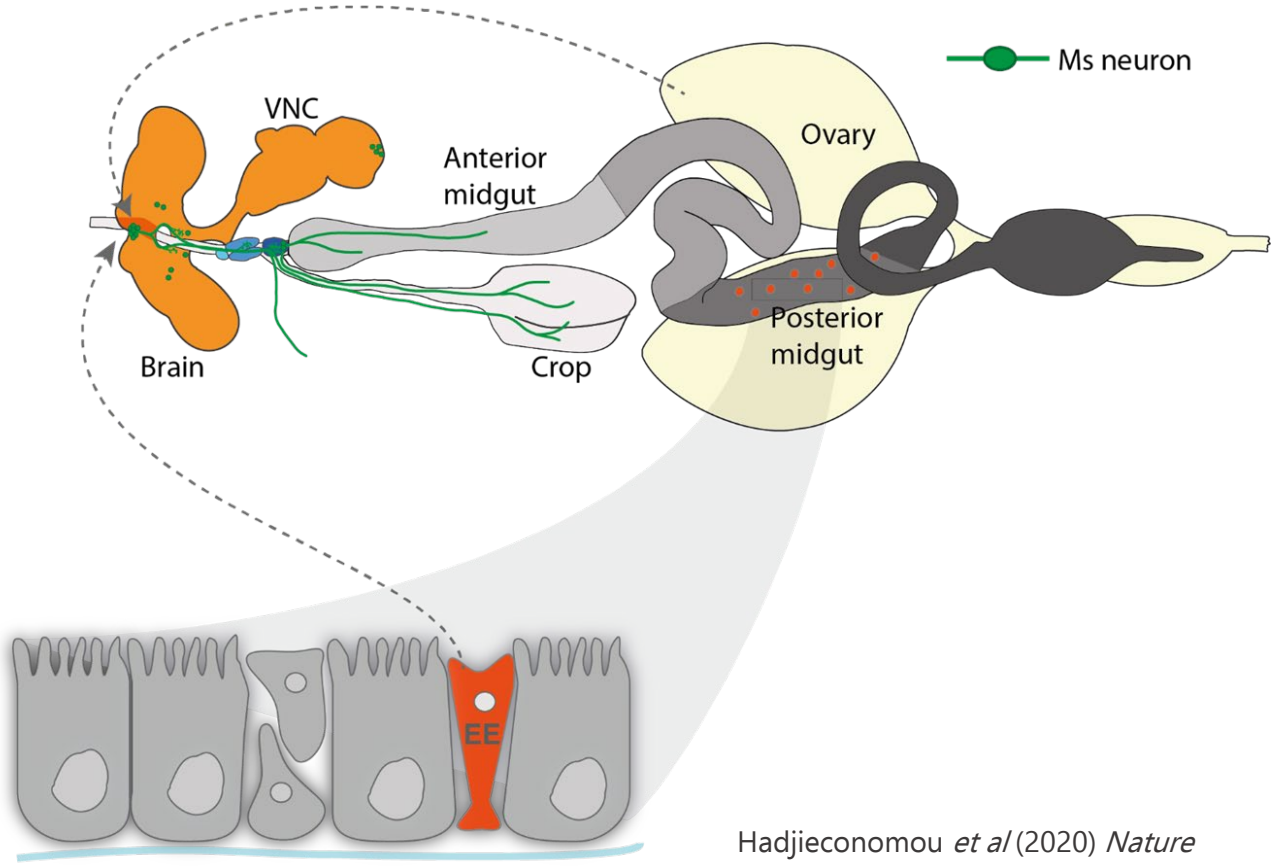
Modified from Strauch (2014) *Sci Reports*

virgin female



mated female





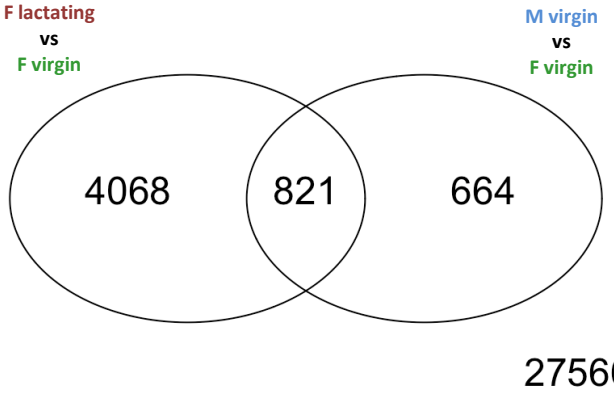
Hadjieconomou *et al* (2020) *Nature*

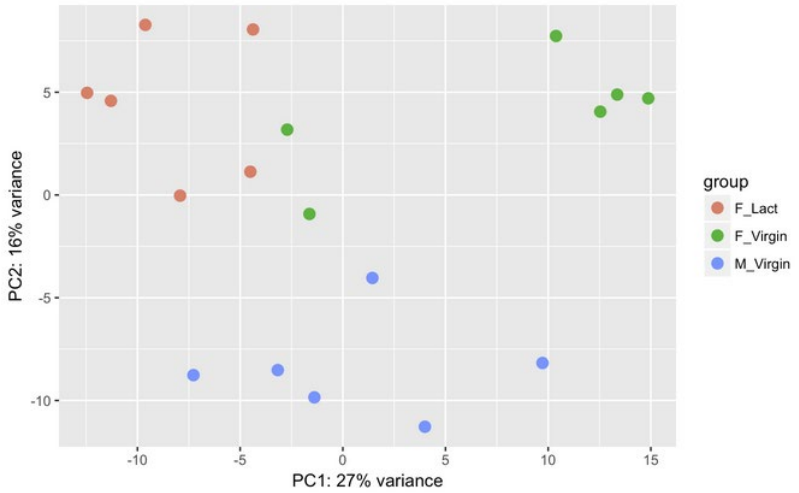
- Reproductive remodelling of **enteric neurons mediates the maternal increase in food intake** during reproduction

Just good for flies?

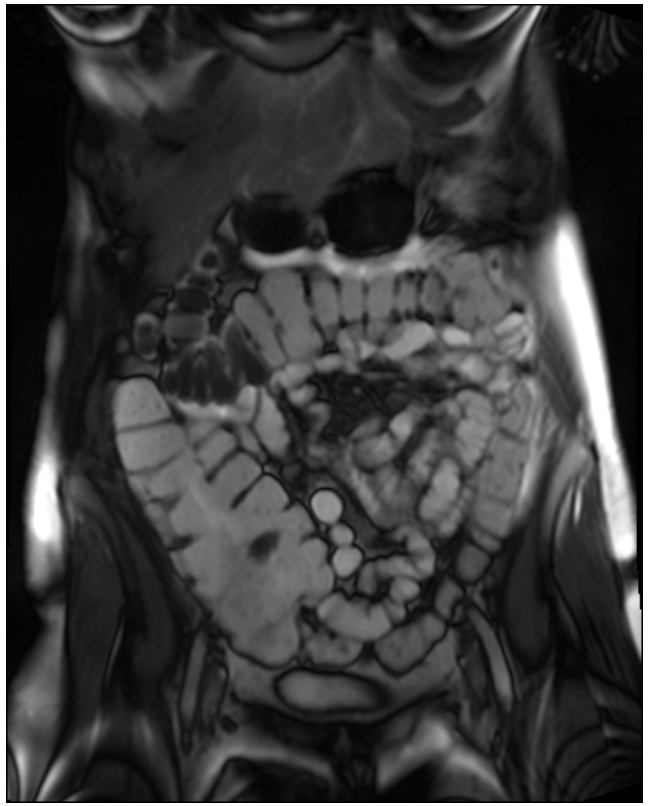
Genetic and anatomical sex differences in mouse and human guts

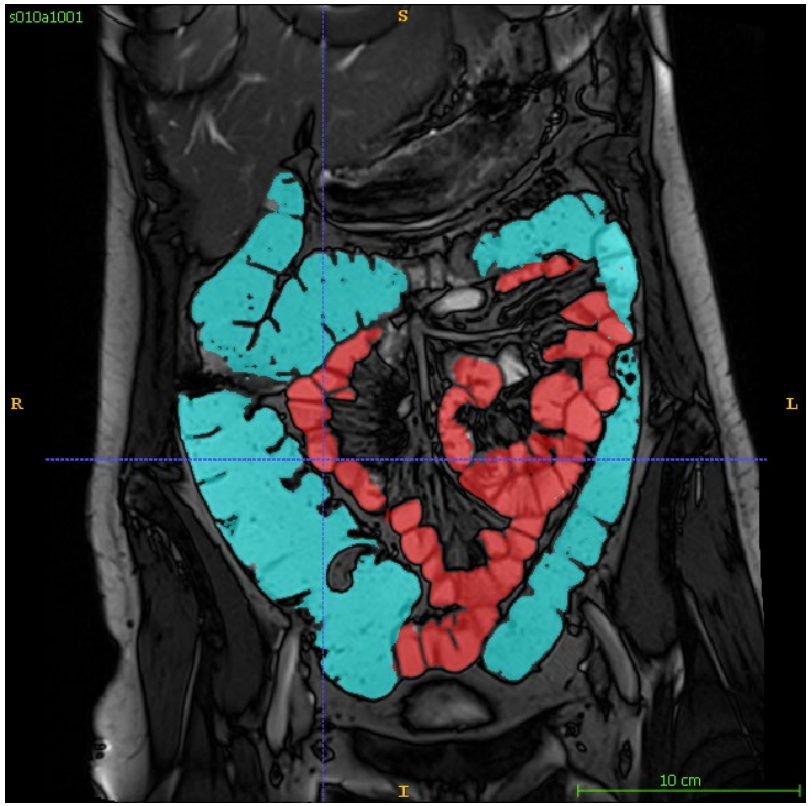
Differential gene expression:
sex and reproductive state





Exploring sex differences in anatomy and function





The bigger picture: trade-offs and “nature vs nurture”

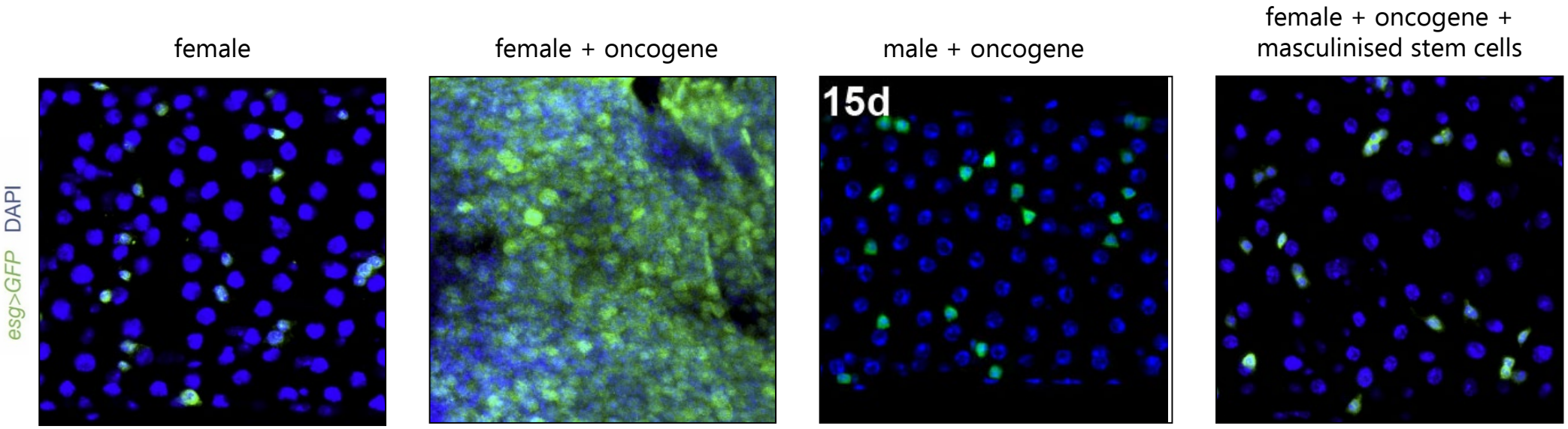
- A “**better**” gut?

  The female gut is more adaptable… is it always more adaptable? PROBABLY NOT

  is it better than the male gut?! NO!

- **Trade-offs**

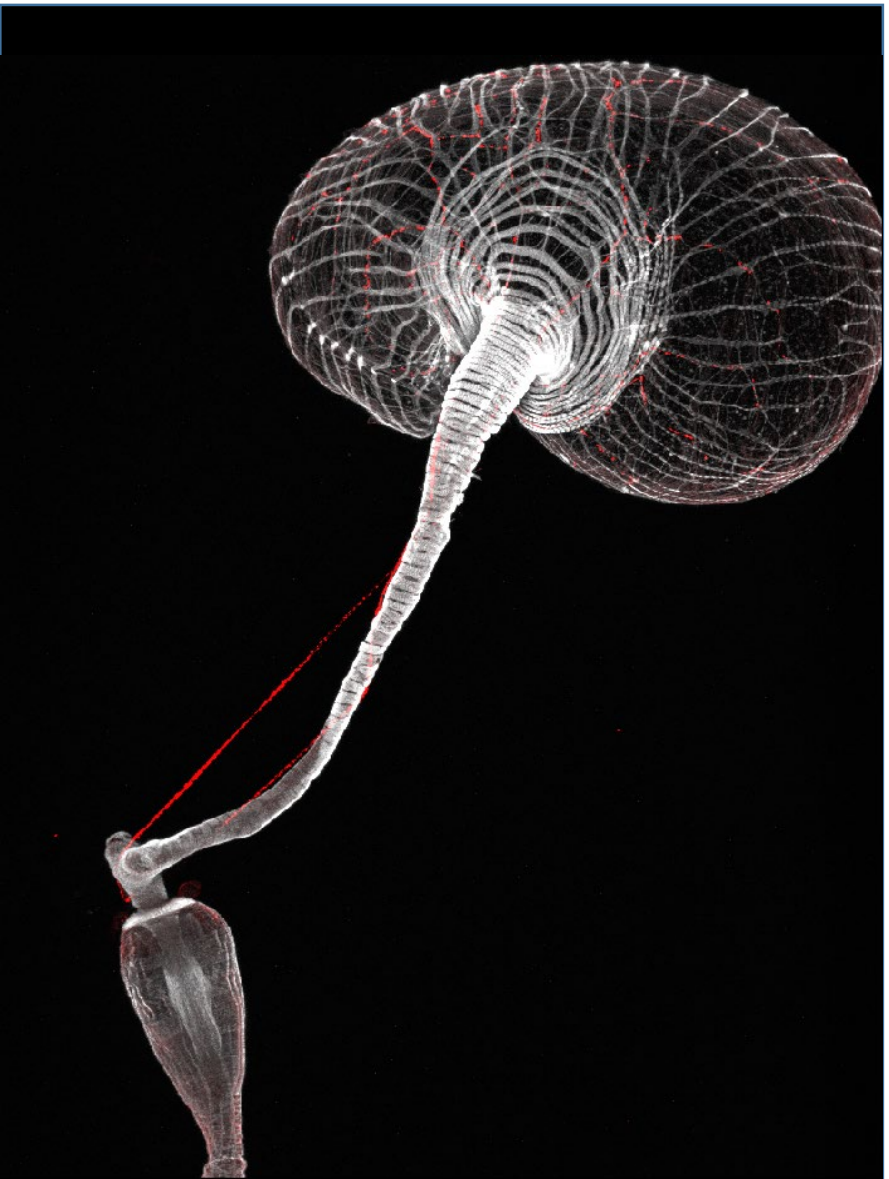
  Higher stem cell proliferation renders female gut more vulnerable to tumorigenic insults



- **Phenotypic plasticity / pleiotropy**

  Nature (biological sex) affects ability to responds to nurture (environment) and vice versa

The sex and gender dimension: a geneticist's perspective



The sex of organs

- Many (most?) features of how our organs work and decline are, at some level, different between the sexes
- Organs "know their sex" in different way (e.g. their sex chromosomes, hormones they listen to)
- It is important to both describe and mechanistically understand these sex differences: they may be predictive of both disease susceptibility and responses to treatment

… and beyond

- "Nature vs nurture" in the context of sex/gender differences can be a false, and ultimately unhelpful, dichotomy
- Biological "equivalence" not a pre-requisite for equal rights/opportunities: whether "biological" or "environmental", diversity leads to resilience
- Other "biological" considerations such as trade-offs and plasticity of traits are relevant from a societal perspective (e.g. value of confidence vs competence)

Acknowledgements

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