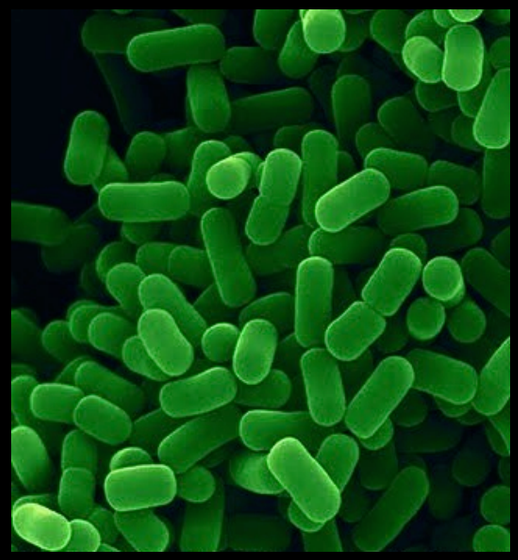
« Nutrition, Microbiote et Probiotiques: apport du modèle Drosophile"

François Leulier
DR2 CNRS

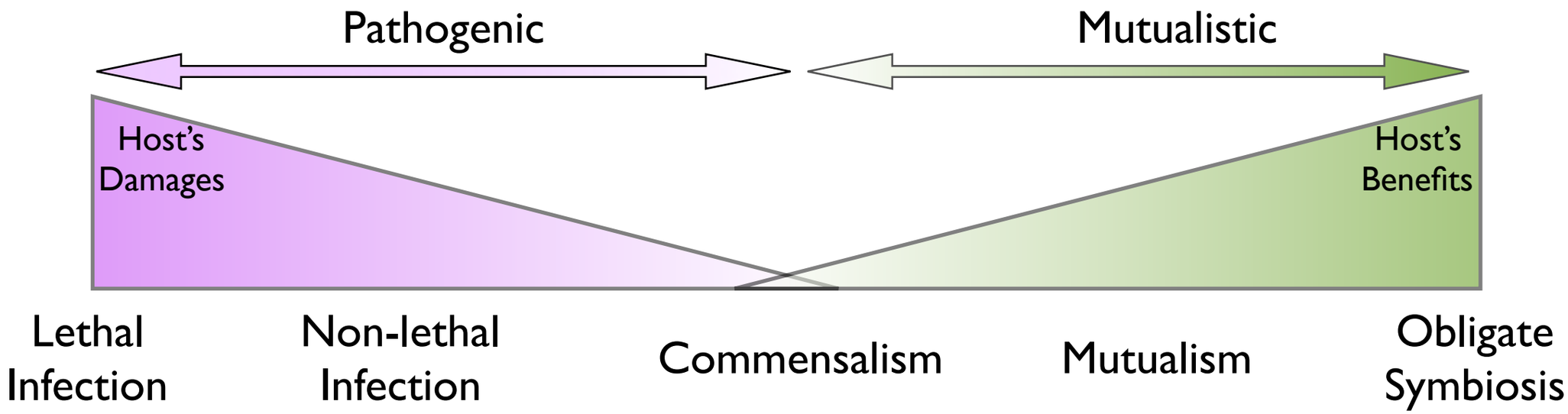


Institut de Génomique Fonctionnelle de Lyon

Ecole Normale Supérieure de Lyon

France

Symbiosis : Host-microbe interactions



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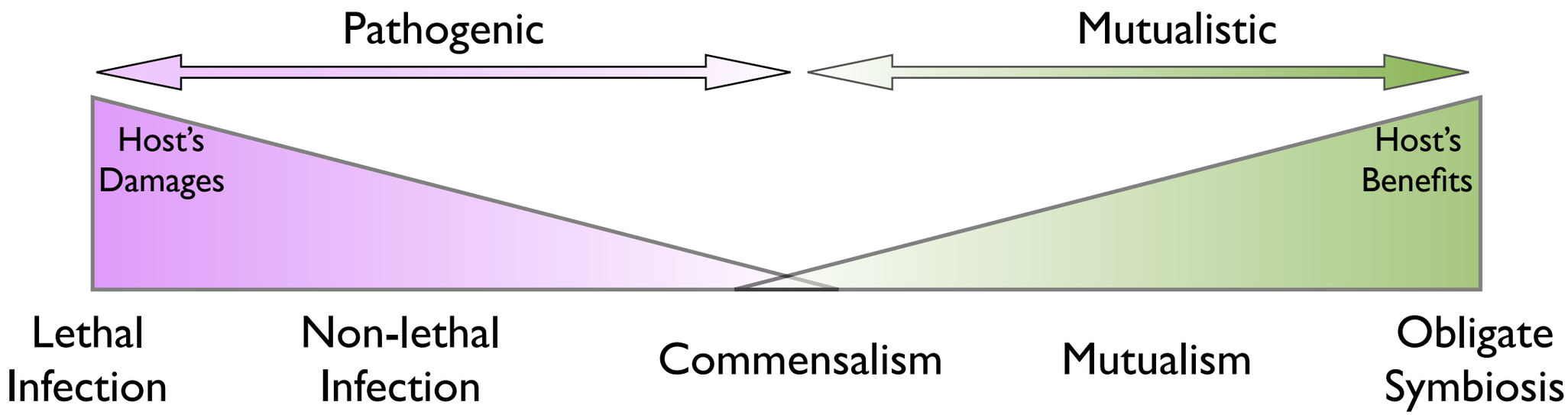
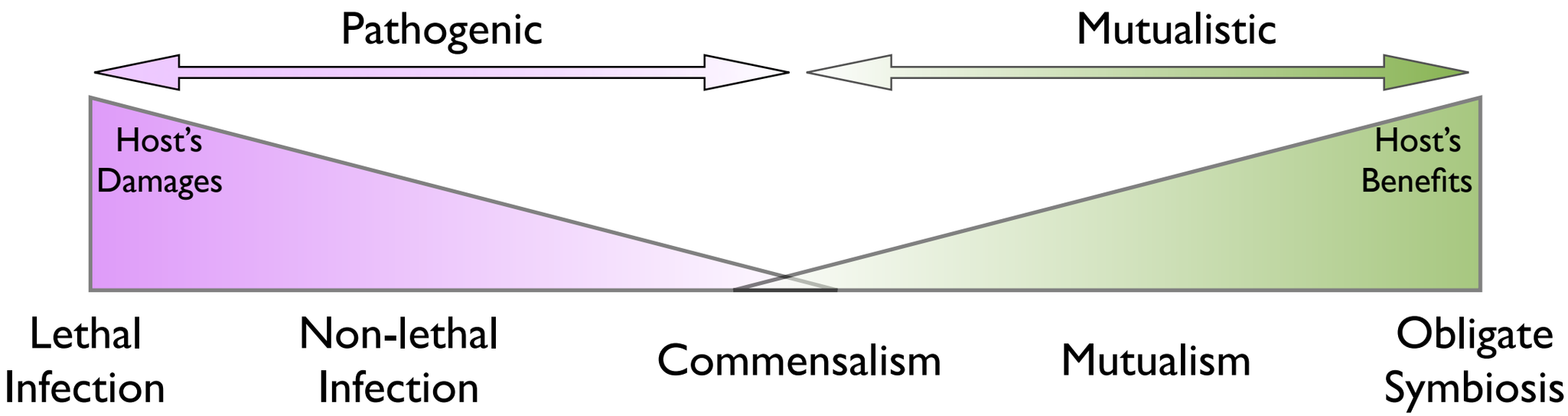


Intestinal Microbiota

Complex microbial ecosystem

A vast genetic and metabolic potential

Symbiosis : Host-microbe interactions



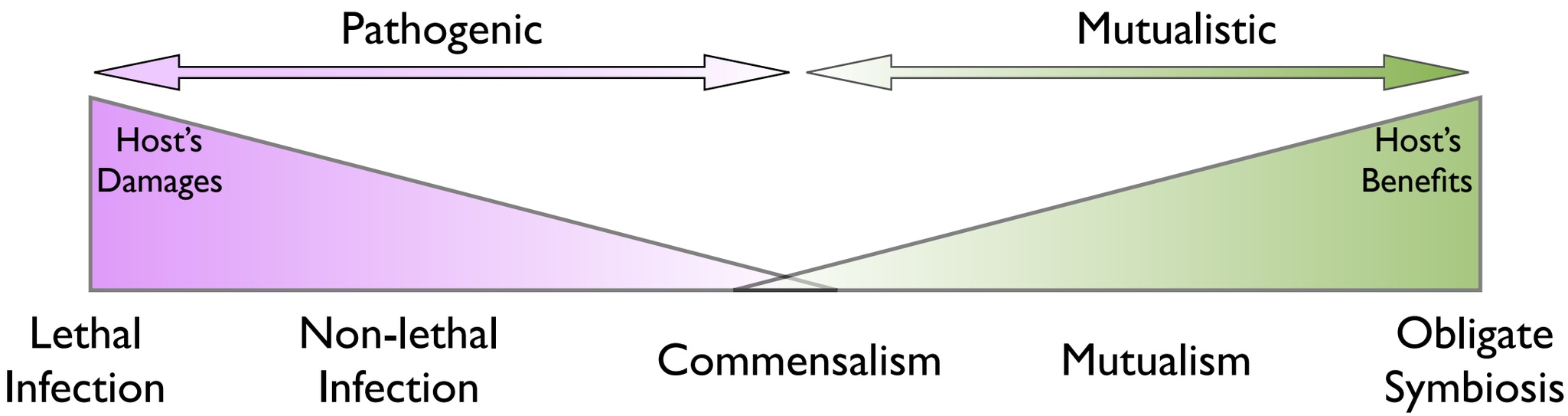
Intestinal Microbiota

Complex microbial ecosystem

A vast genetic and metabolic potential

Clear view of physiological benefits / Molecular mechanisms engaged?

Symbiosis : Host-microbe interactions



Intestinal Microbiota

Complex microbial ecosystem

A vast genetic and metabolic potential

Clear view of physiological benefits / Molecular mechanisms engaged?

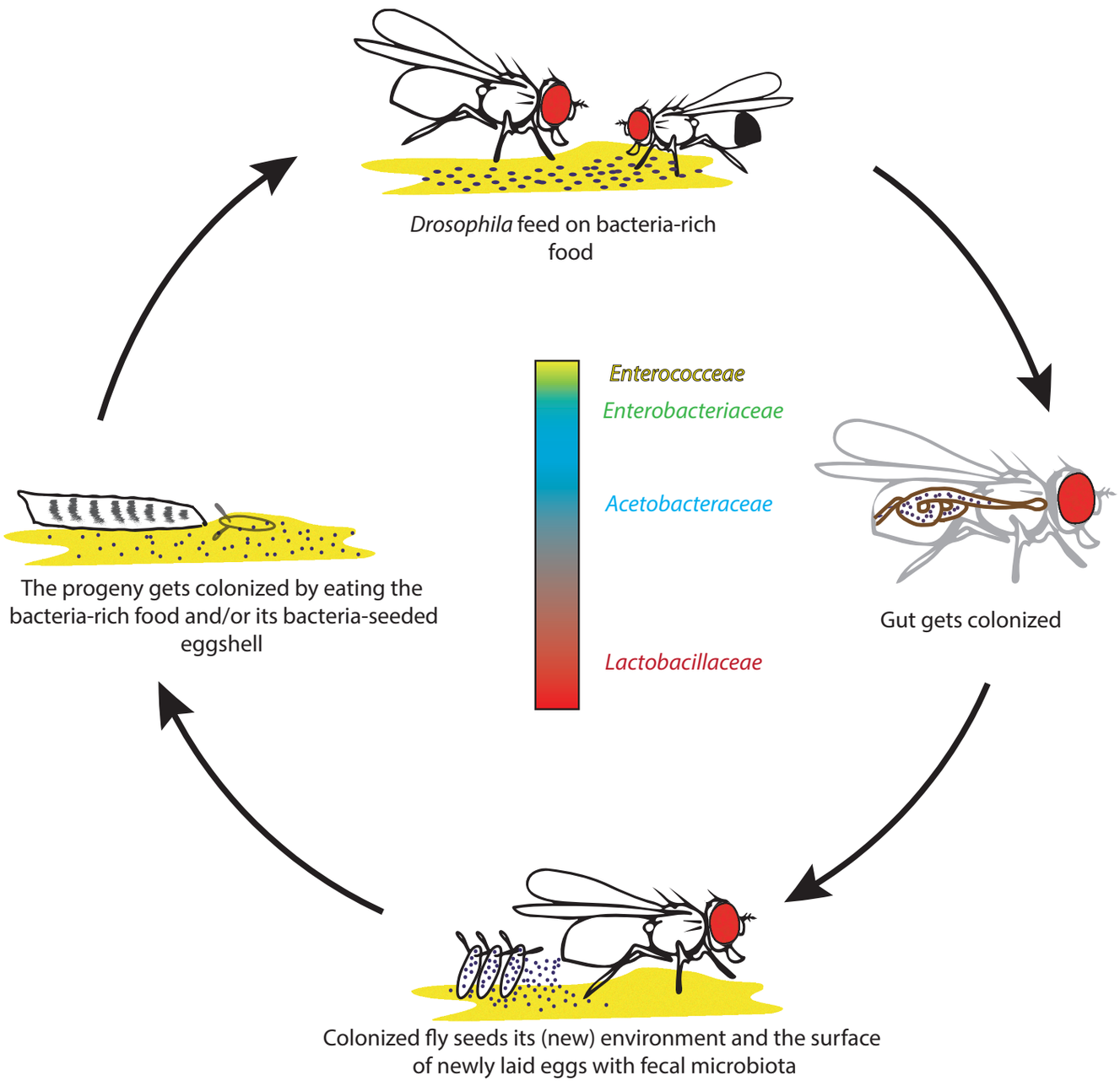
Accumulate basic knowledge using simple animal models

Drosophila melanogaster a host model to study host-commensals interactions

Live and feed on fermenting fruits:
microbe rich environments

Drosophila melanogaster a host model to study host-commensals interactions

Live and feed on fermenting fruits:
microbe rich environments



Simple commensal bacterial communities:

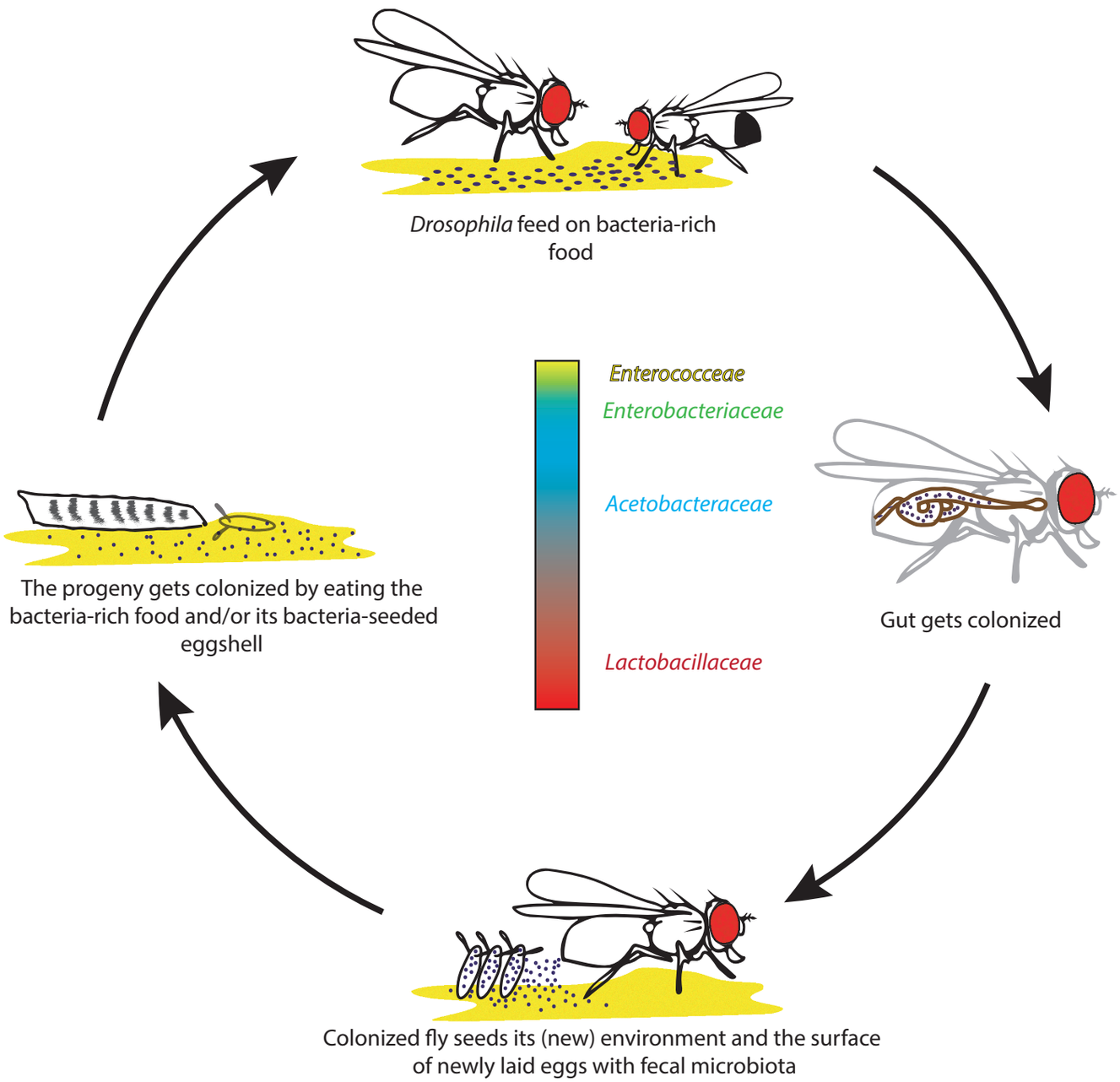
Lactobacillales

Acetobacteraceae

3-5 dominant species

Drosophila melanogaster a host model to study host-commensals interactions

Live and feed on fermenting fruits:
microbe rich environments



Simple commensal bacterial communities:

Lactobacillales

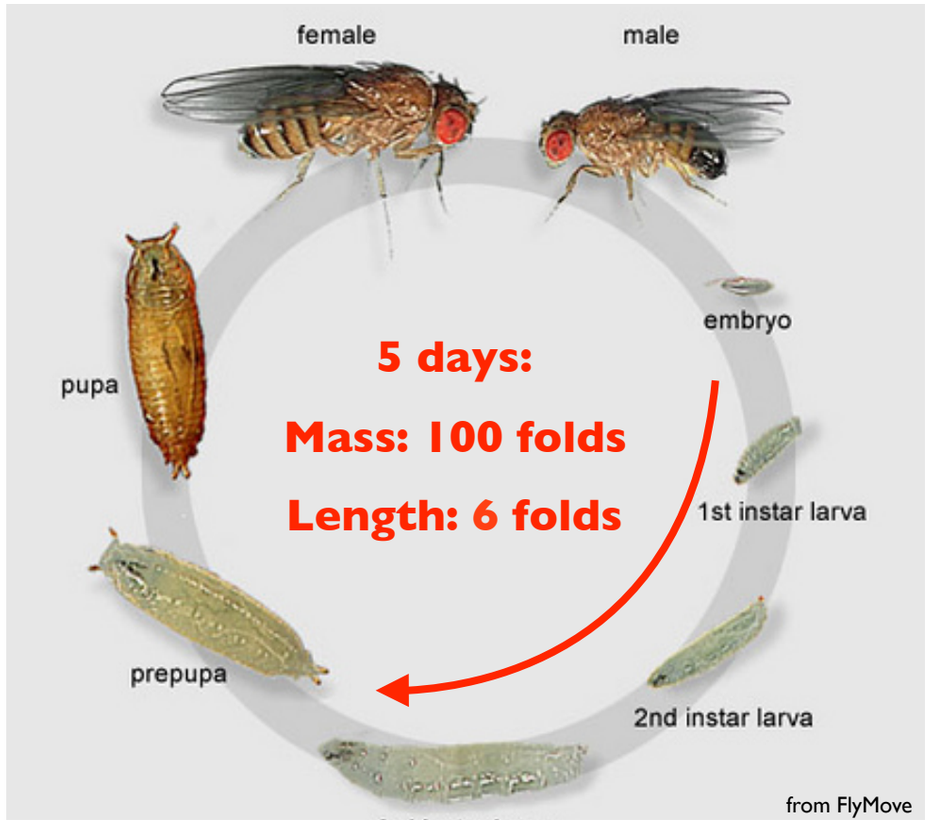
Acetobacteraceae

3-5 dominant species

Are there mutualists among commensals?

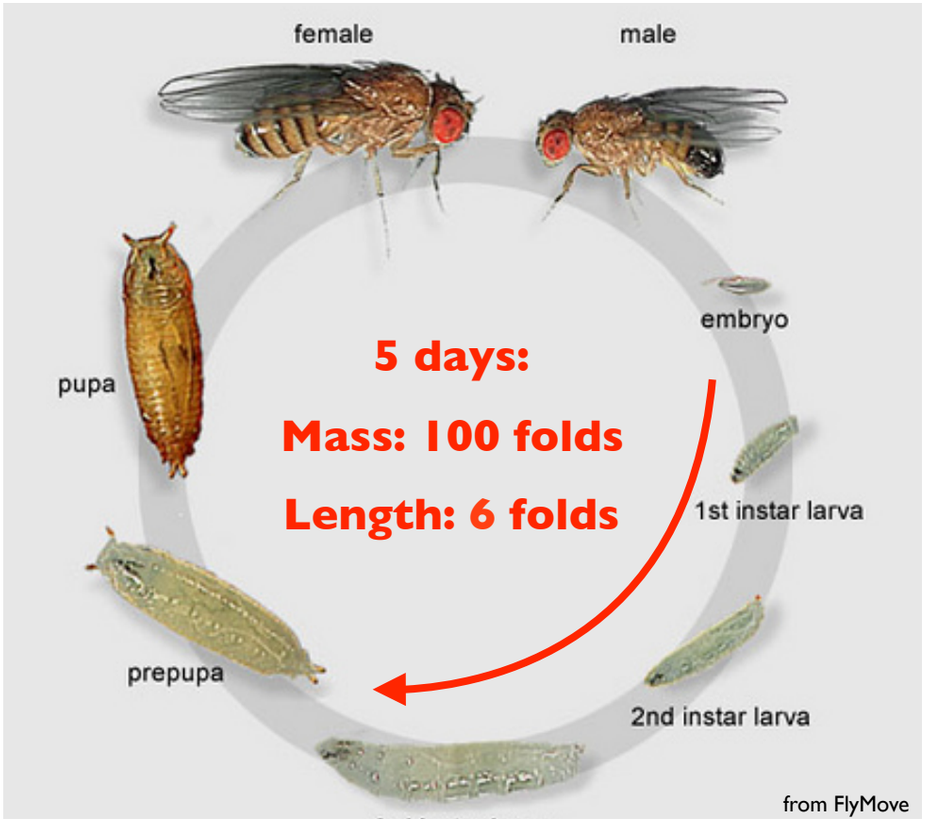
Does microbiota influence *Drosophila* juvenile growth?

Laboratory breeding diet
=
Optimized nutrition

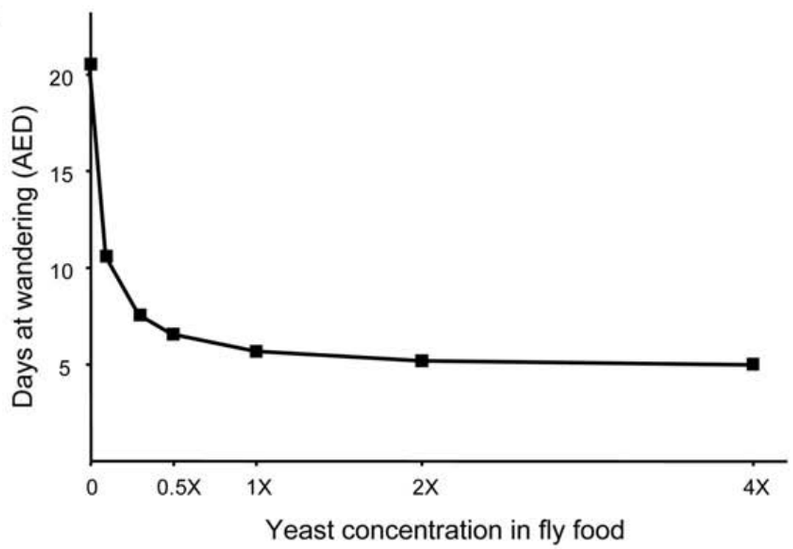


Does microbiota influence *Drosophila* juvenile growth?

Laboratory breeding diet = Optimized nutrition



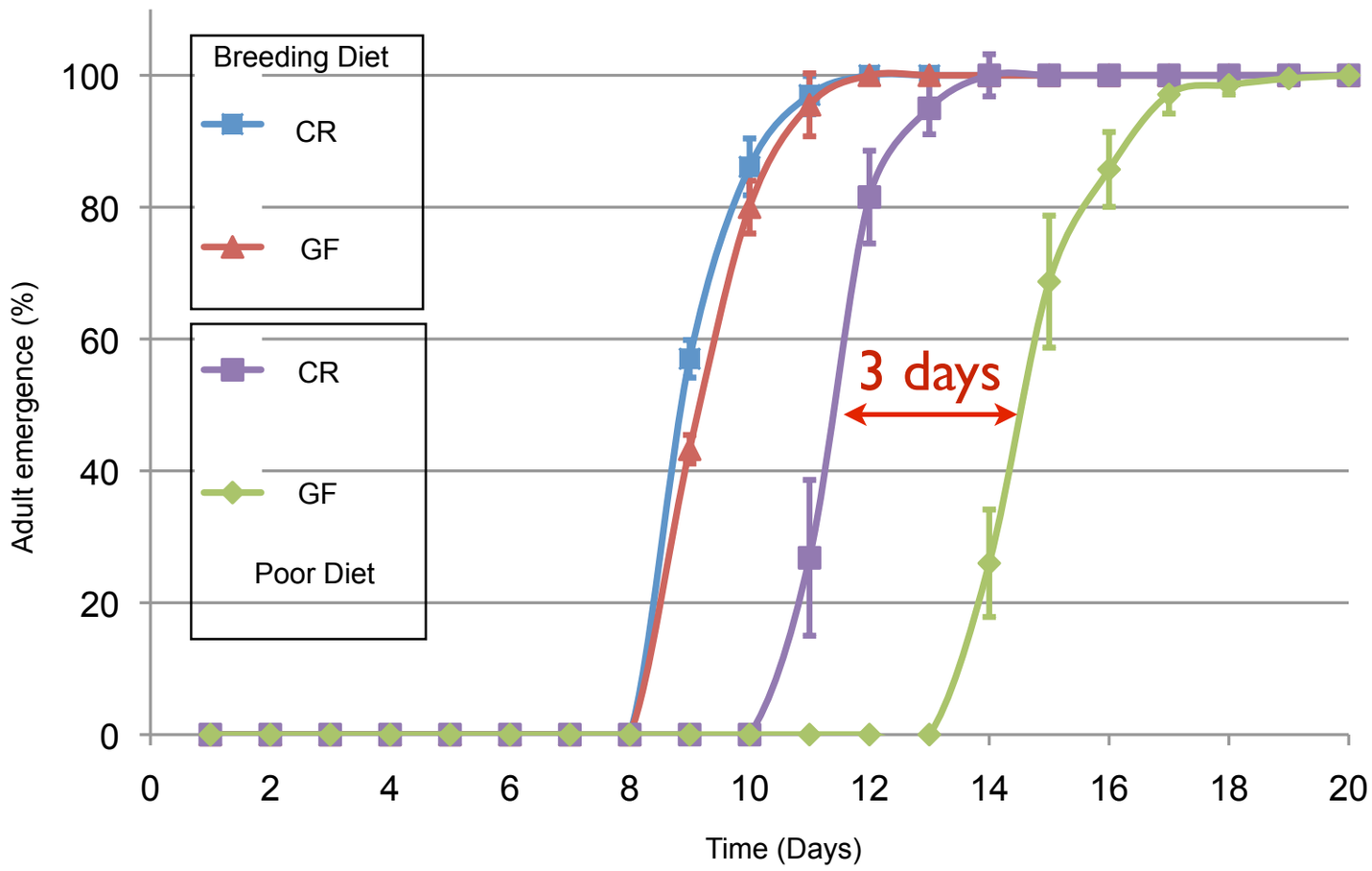
Undernutrition (reduced nutrient intake) impacts systemic growth and developmental timing



Undernutrition

Normal nutrition

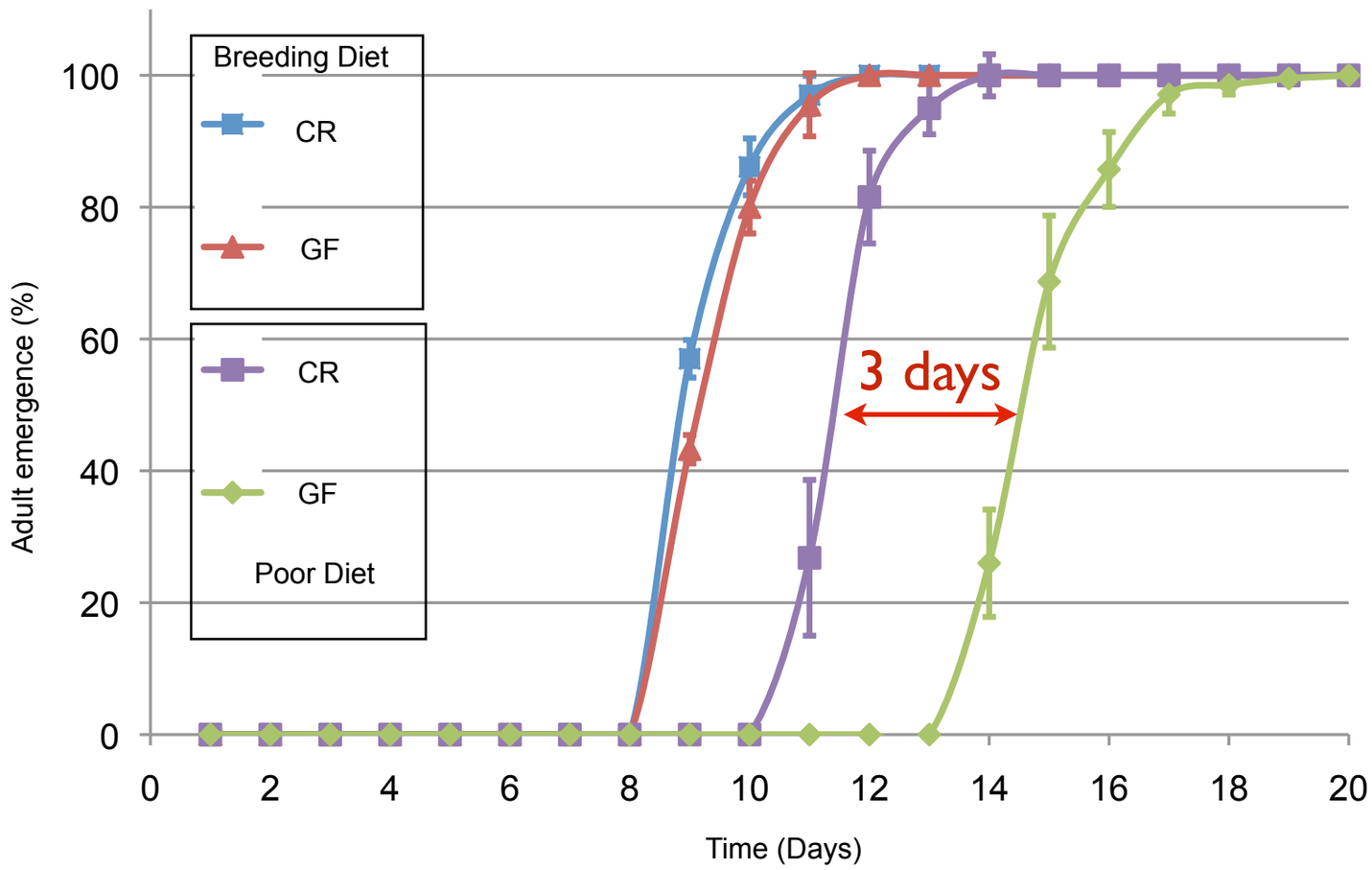
Drosophila microbiota promotes juvenile growth upon undernutrition



CR: Conventionally reared (+commensals)

GF: Germ-Free

Drosophila microbiota promotes juvenile growth upon undernutrition



16S rDNA gene profiling

CR *yw* whole body library

Phylotype	Closest strain	% identity
Enterococcus faecalis	*Enterococcus faecalis* V583	99%
Lactobacillus plantarum	*Lactobacillus plantarum* WCFS1	99%
Aerococcus spp.	*Aerococcus viridans* ATCC11563	97%

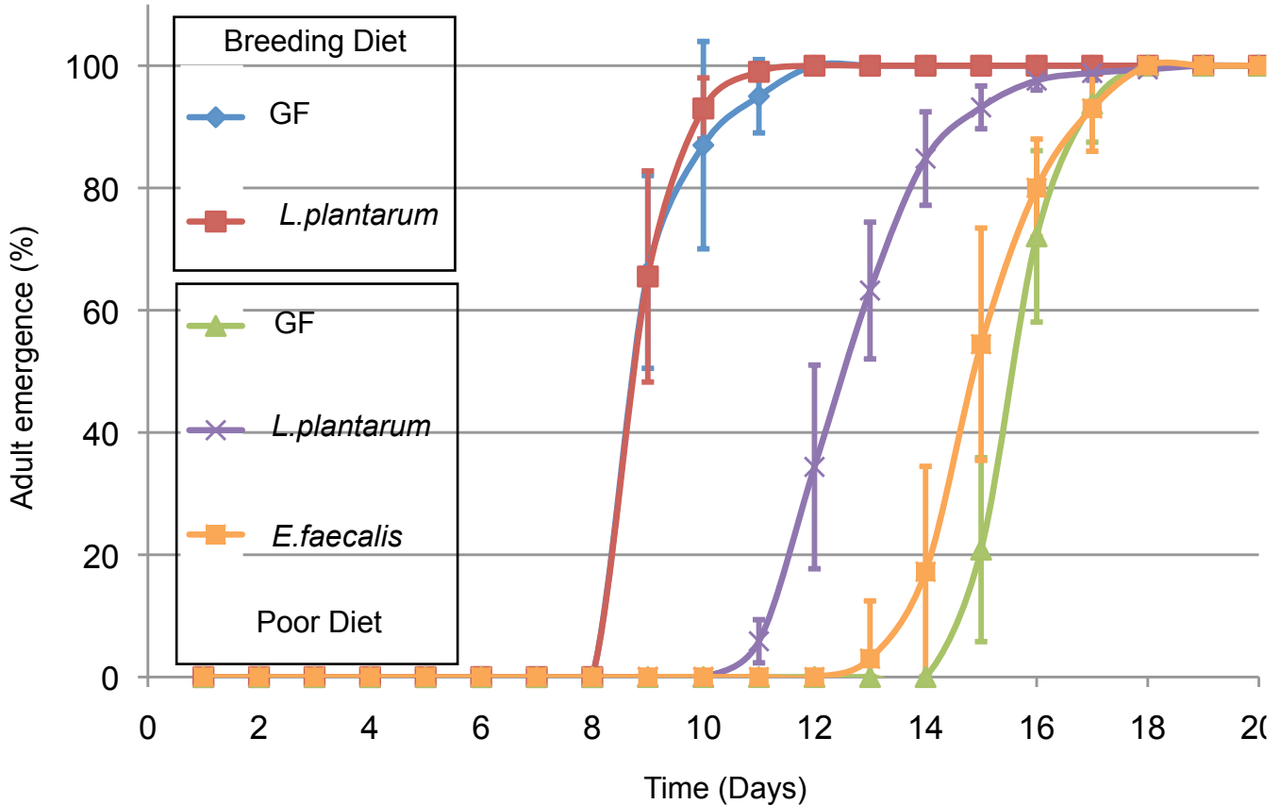
CR *yw* adult midgut library

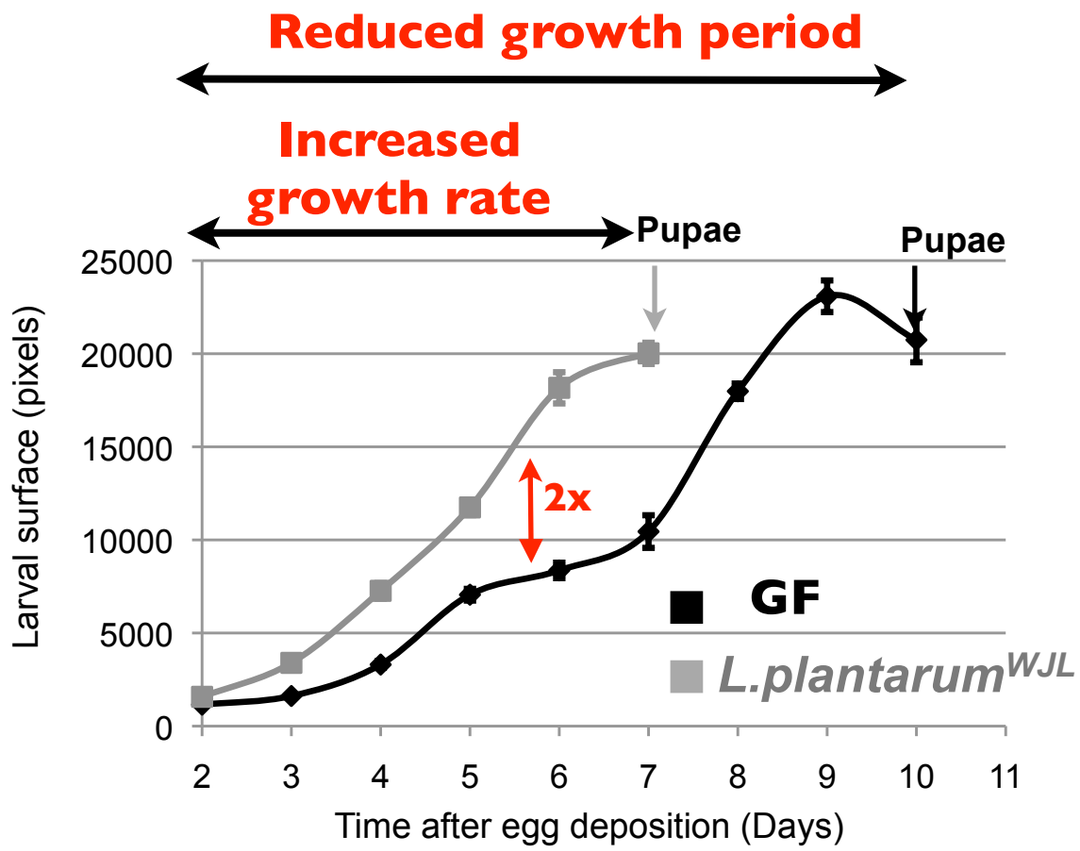
Phylotype	Closest strain	% identity
Enterococcus faecalis	*Enterococcus faecalis* V583	99%
Lactobacillus plantarum	*Lactobacillus plantarum* WCFS1	99%
Corynebacterium variabile	*Corynebacterium variabile* DSM20132	98%

CR: Conventionally reared (+commensals)

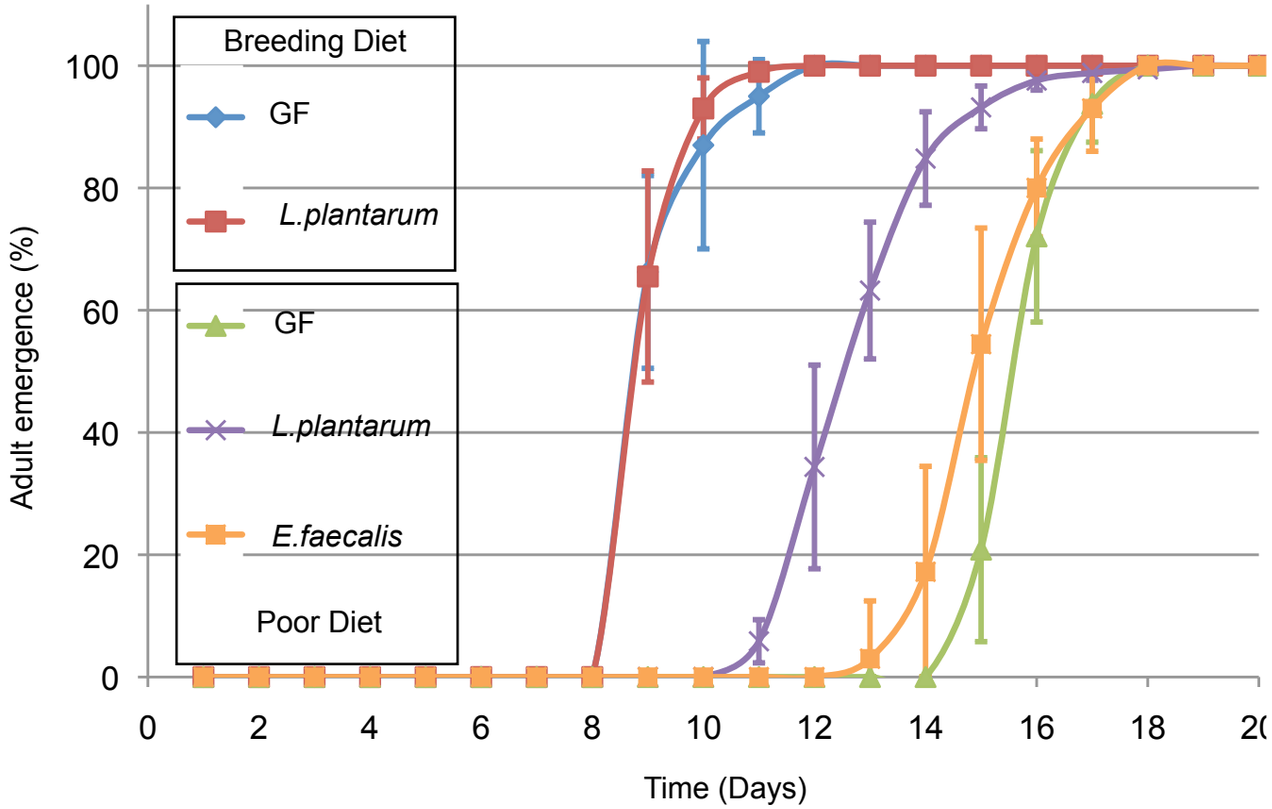
GF: Germ-Free

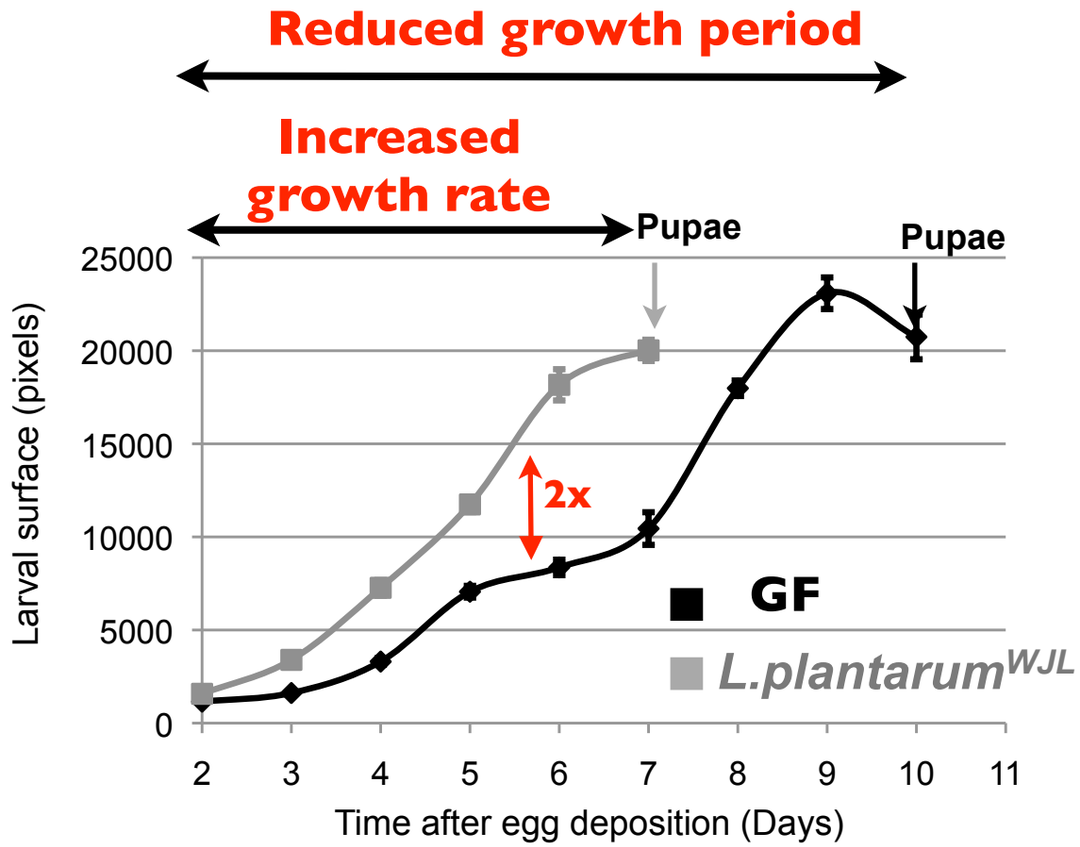
Mono-association of GF animals with one commensal: *Lactobacillus plantarum* promotes *Drosophila* juvenile growth





Mono-association of GF animals with one commensal: *Lactobacillus plantarum* promotes *Drosophila* juvenile growth



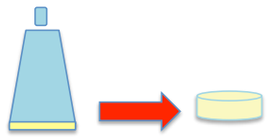


Lactobacillus plantarum^{WJL} = *Drosophila* mutualist

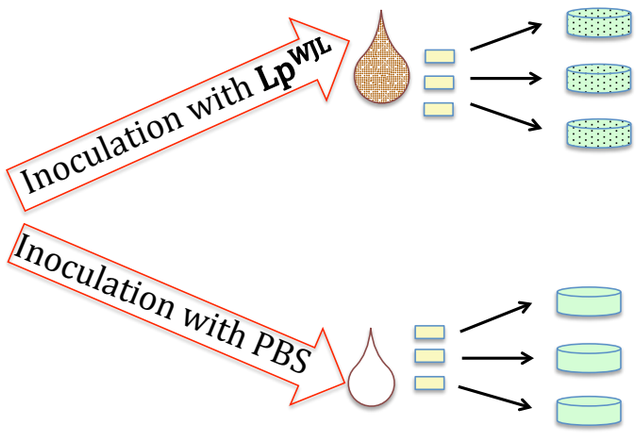
(some strains of *Acetobacter* too)

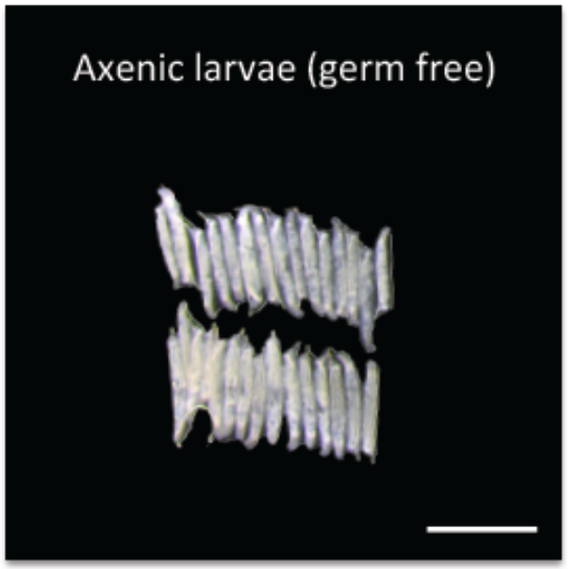
Selection of growth-promoting Lactobacilli strains (size gain)

Make germ-free flies



Collect axenic embryos





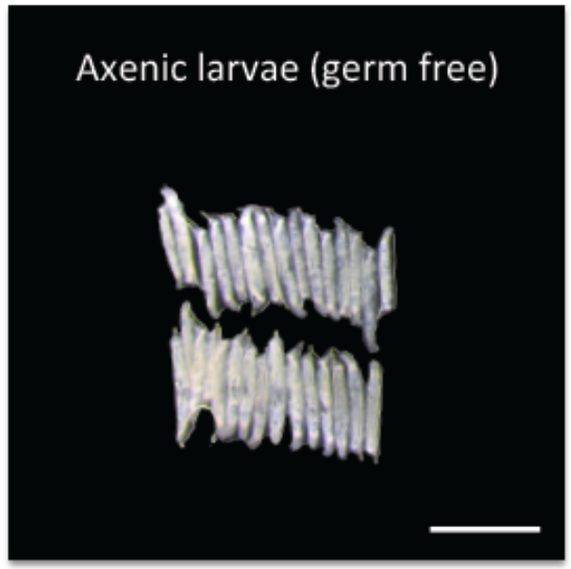
Selection of growth-promoting Lactobacilli strains (size gain)

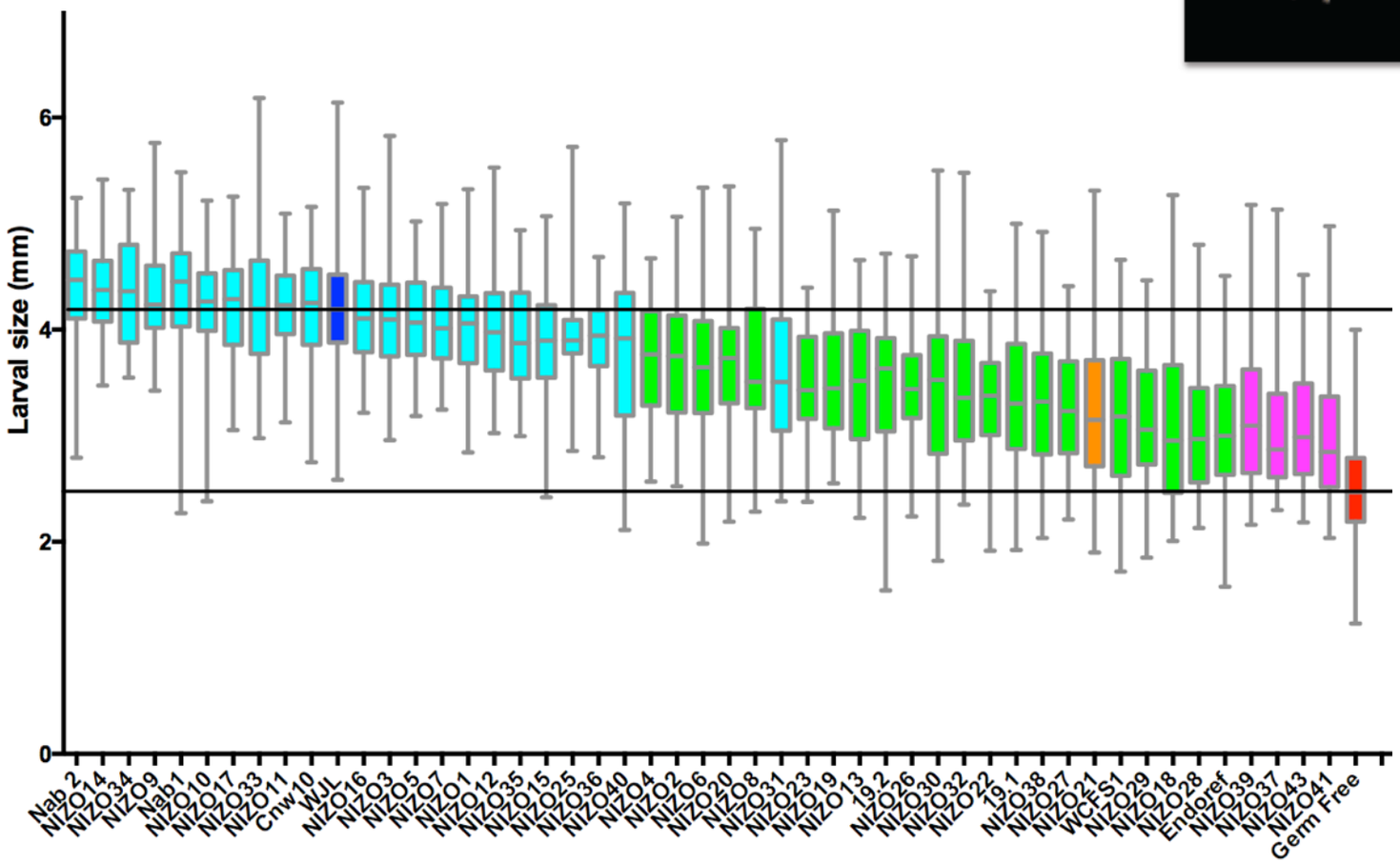
Make germ-free flies

Collect axenic embryos

Inoculation with Lp^{WJL}

Inoculation with PBS





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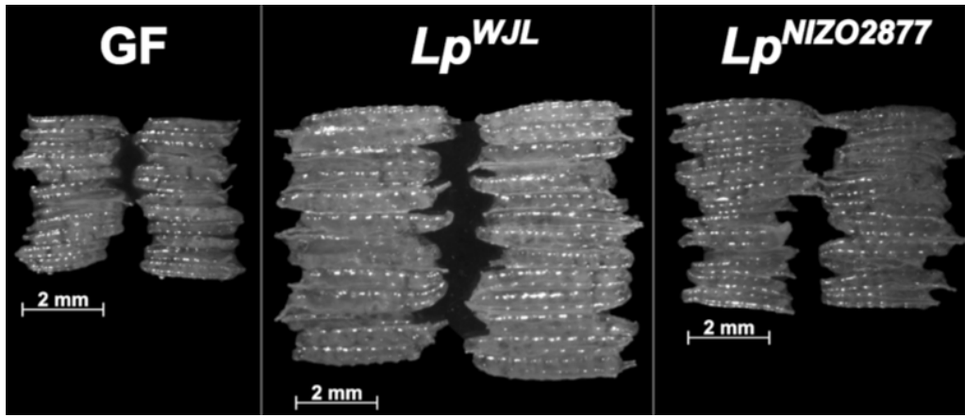
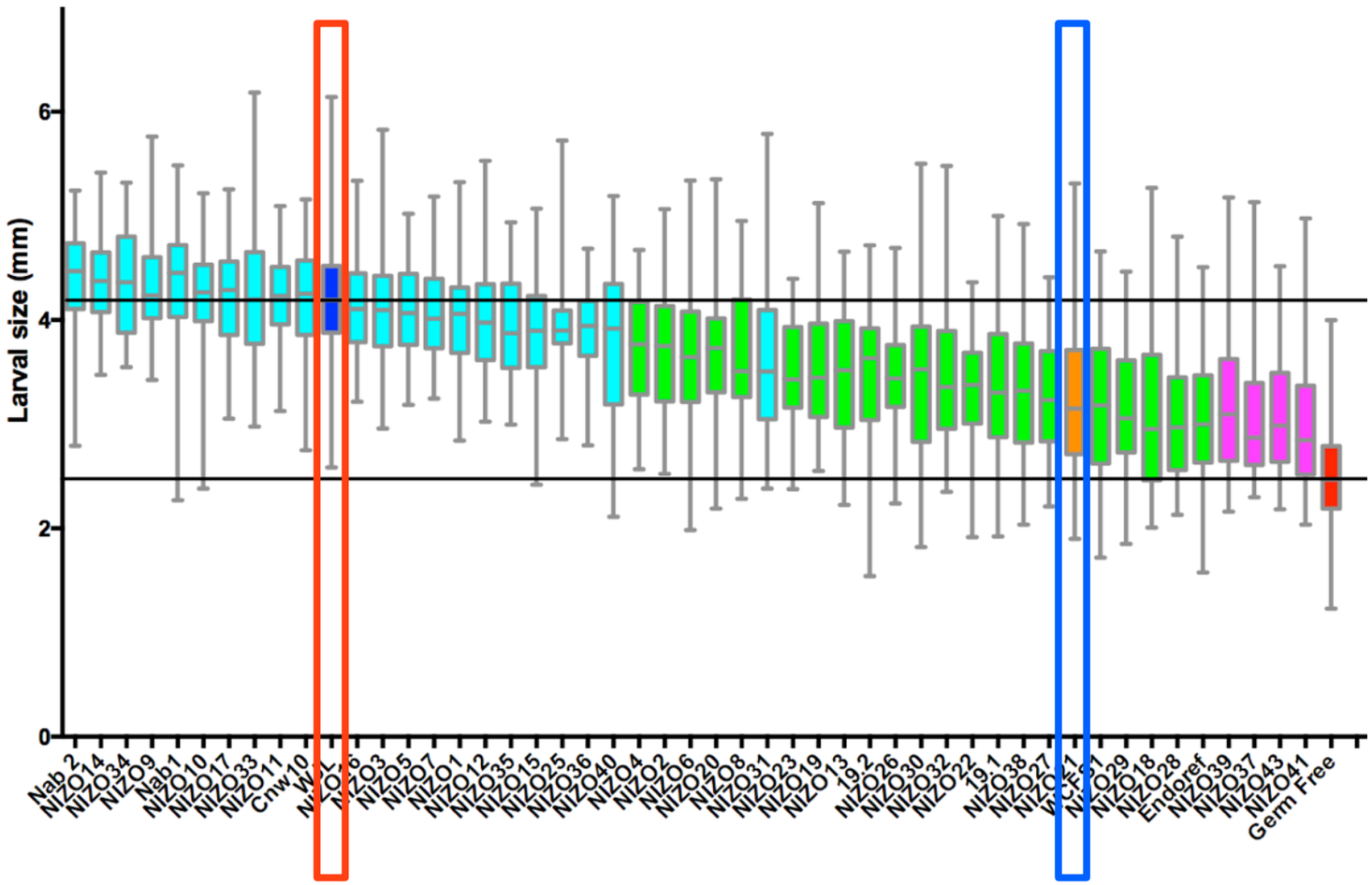
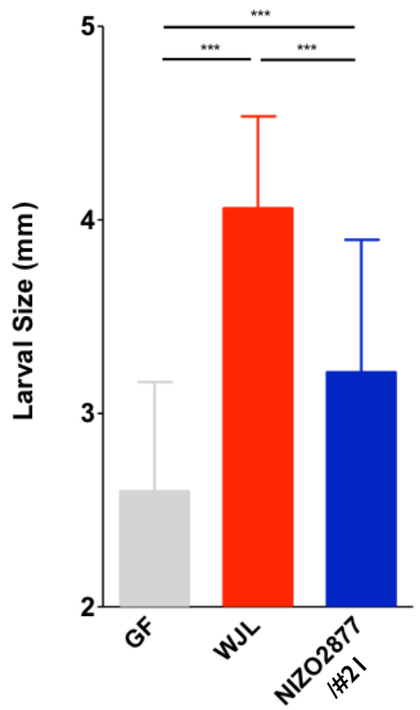






Qualified Lactobacilli
growth promoting strains

Ideal experimental model to probe the molecular underpinnings of Lactobacilli-mediated juvenile growth performance

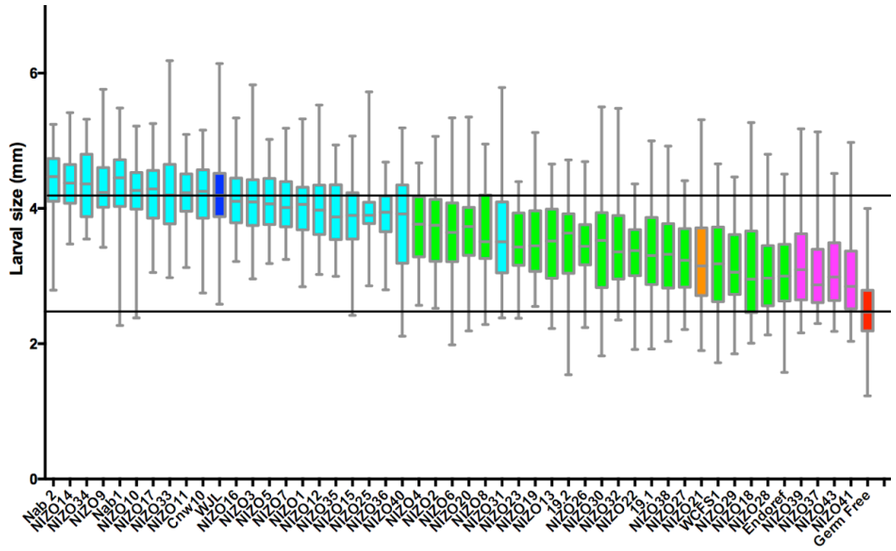
Bacterial side:

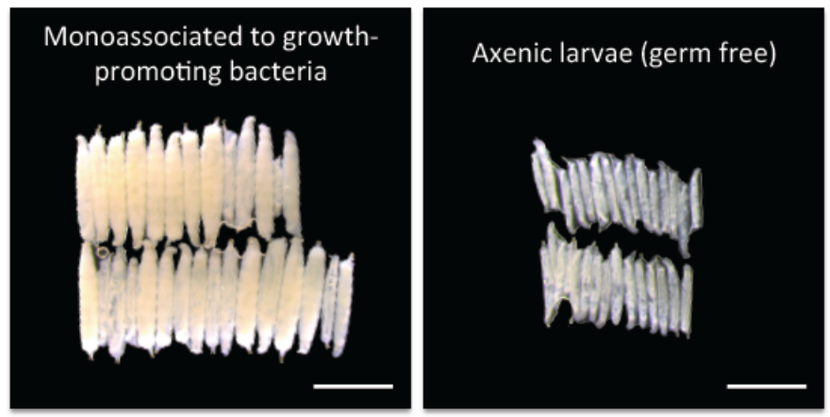
-Comparative genomics

-Gene-Trait matching approaches

-Functional genetic screens

-Experimental evolution of bacterial isolates



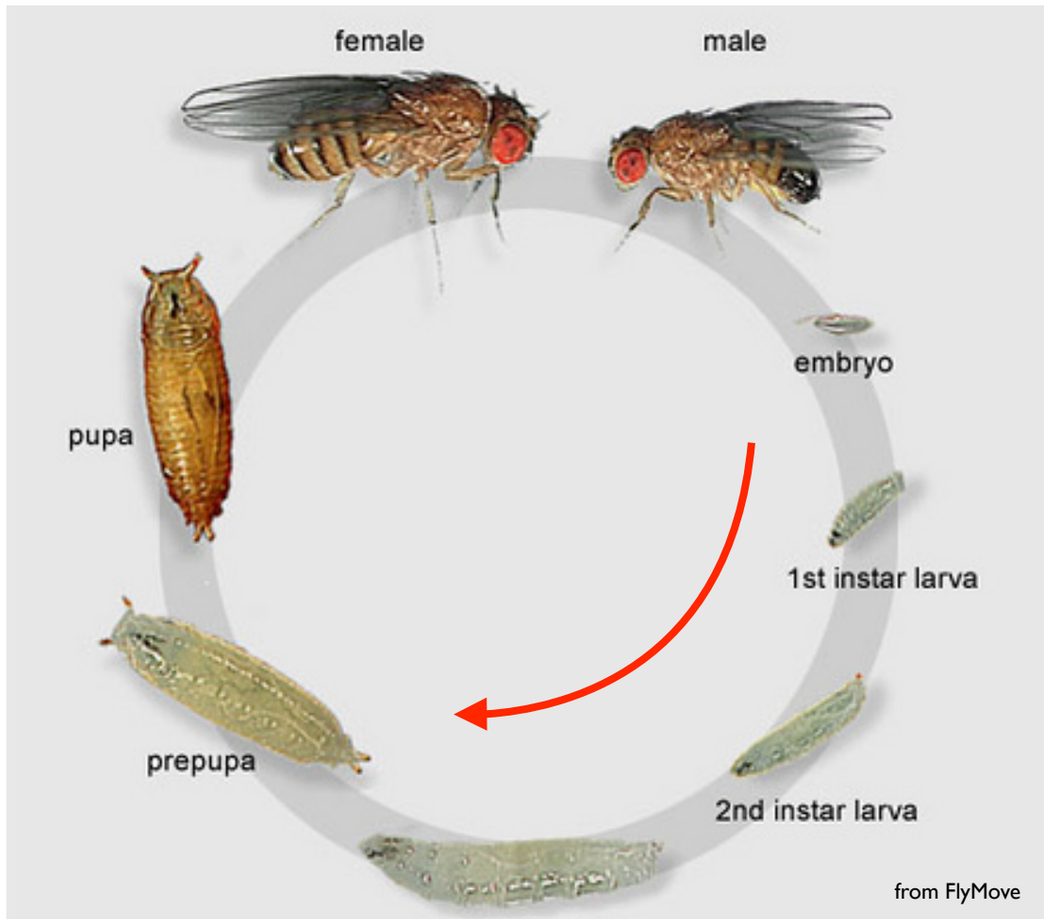


Unpublished

Host side:

Upon undernutrition, microbiota in general and *L.plantarum* in particular promote juvenile growth...

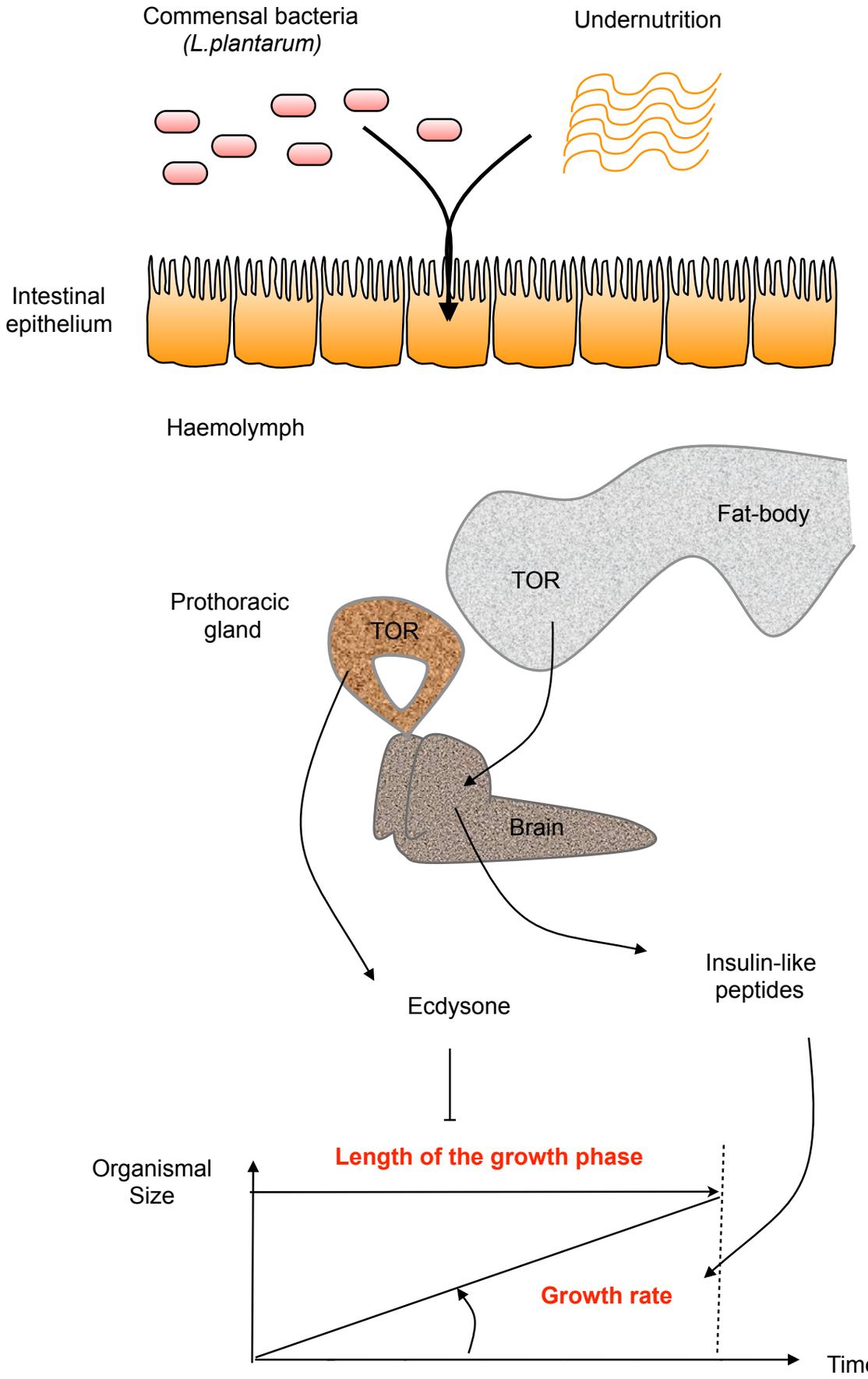
...in a strain dependent manner



Storelli et al. (2011) Cell Metabolism 14, 403-414

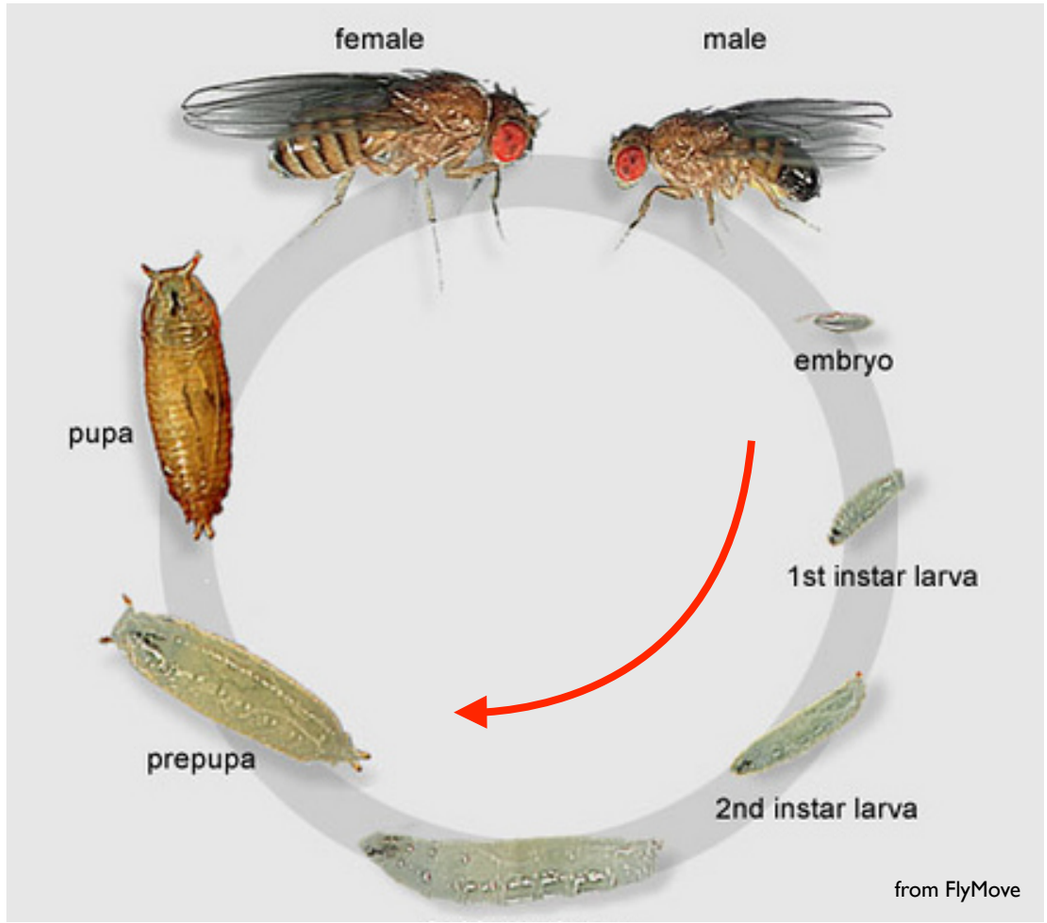
Host side:

Upon undernutrition, microbiota in general and *L.plantarum* in particular promote juvenile growth...



...via enhanced maturation hormone and growth factors activity...

...in a strain dependent manner



Storelli et al. (2011) Cell Metabolism 14, 403-414

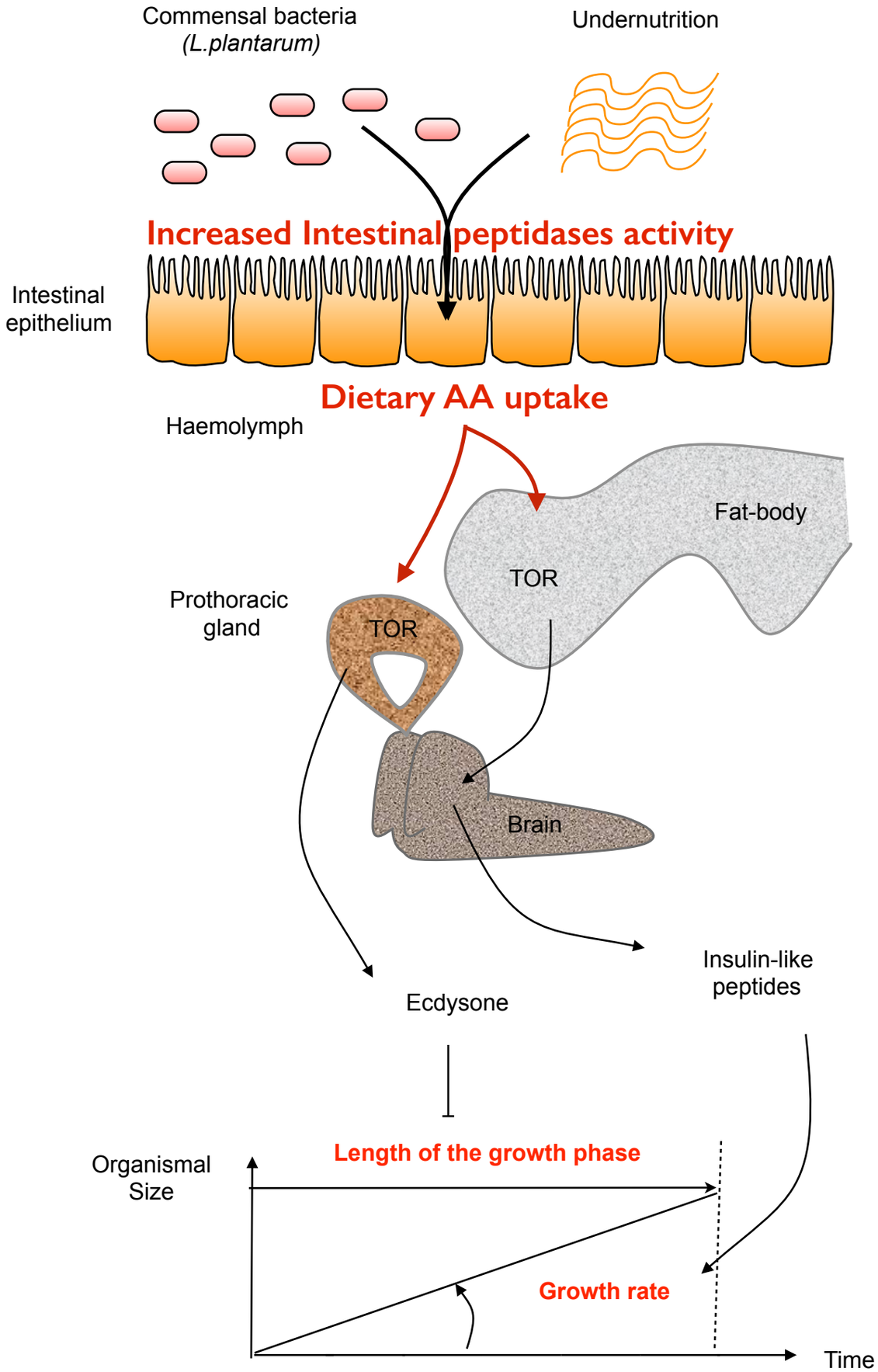
Host side:

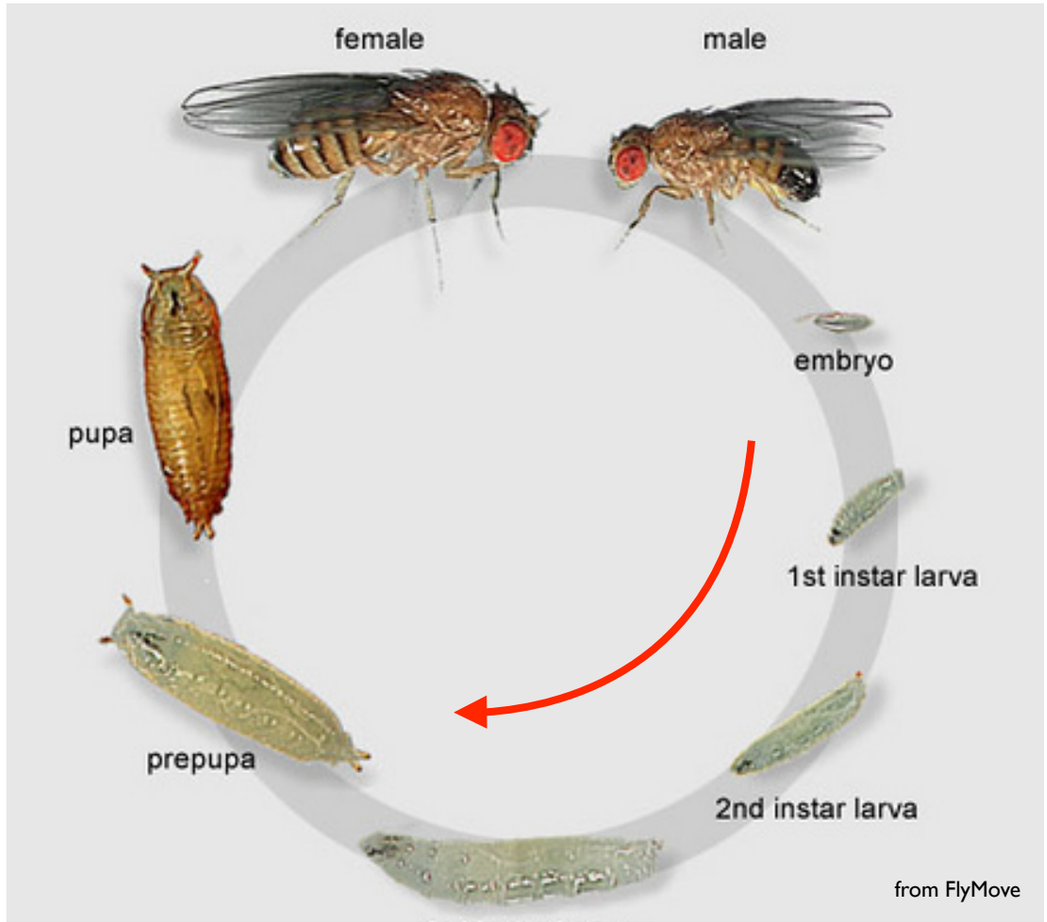
Upon undernutrition, microbiota in general and *L.plantarum* in particular promote juvenile growth...

...via enhanced dietary AA uptake...

...via enhanced maturation hormone and growth factors activity...

...in a strain dependent manner





Storelli et al. (2011) Cell Metabolism 14, 403-414

Erkosar et al. (2014) PLoS ONE 9, e94729

Erkosar et al. (2015) Cell Host and Microbe 18, 445-55

Role of microbial environment on mammalian juvenile growth upon undernutrition?

Undernutrition in mammals

Acute undernutrition or Protein-energy undernutrition

Chronic undernutrition or prolonged nutritional deficit

Undernutrition in mammals

Acute undernutrition or Protein-energy undernutrition

Wasting: weigth loss diagnosed by a reduction in weight-for-height index

Chronic undernutrition or prolonged nutritional deficit

Stunting: growth failure leading to short stature

Undernutrition in mammals

Acute undernutrition or Protein-energy undernutrition

Wasting: weigth loss diagnosed by a reduction in weight-for-height index

Gut Microbiomes of Malawian Twin Pairs Discordant for Kwashiorkor

Michelle I. Smith,[1]* Tanya Yatsunenko,[1]* Mark J. Manary,[2,3,4] Indi Trehan,[2,3] Rajhab Mkakosya,[5] Jiye Cheng,[1] Andrew L. Kau,[1] Stephen S. Rich,[6] Patrick Concannon,[6] Josyf C. Mychaleckyj,[6] Jie Liu,[7] Eric Houpt,[7] Jia V. Li,[8] Elaine Holmes,[8] Jeremy Nicholson,[8] Dan Knights,[9,10]† Luke K. Ursell,[11] Rob Knight,[9,10,11,12] Jeffrey I. Gordon[1]‡

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Persistent gut microbiota immaturity in malnourished Bangladeshi children

Sathish Subramanian[1], Sayeeda Huq[2], Tanya Yatsunenko[1], Rashidul Haque[2], Mustafa Mahfuz[2], Mohammed A. Alam[2], Amber Benezra[1,3], Joseph DeStefano[1], Martin F. Meier[1], Brian D. Muegge[1], Michael J. Barratt[1], Laura G. VanArendonk[1], Qunyuan Zhang[4], Michael A. Province[4], William A. Petri Jr[5], Tahmeed Ahmed[2] & Jeffrey I. Gordon[1]

19 JUNE 2014 | VOL 510 | NATURE | 417

Immature dysbiotic microbiota triggers weight loss

Chronic undernutrition or prolonged nutritional deficit

Stunting: growth failure leading to short stature

?

Do the intestinal microbiota and/or selected Lactobacilli strains influence mouse juvenile growth upon chronic undernutrition

Collab:
Dr M.Schwarzer & Dr H.Kozakova
Laboratory of Gnotobiology
Institut of Microbiology
Science Academy of Czech Republic

Dr H.Vidal & Dr J.Rieusset
CarMeN Laboratory
INSERM/Univ. Claude Bernard Lyon

Gnotobiotic
Balb/c line

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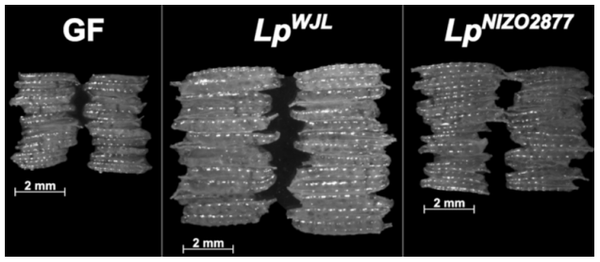
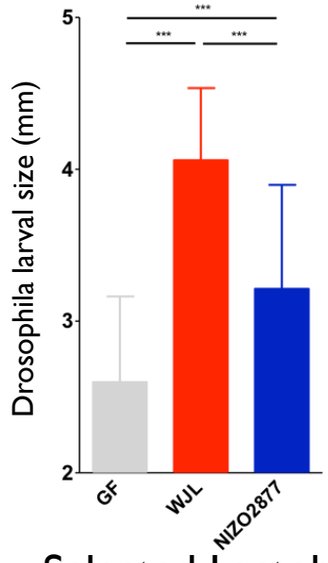
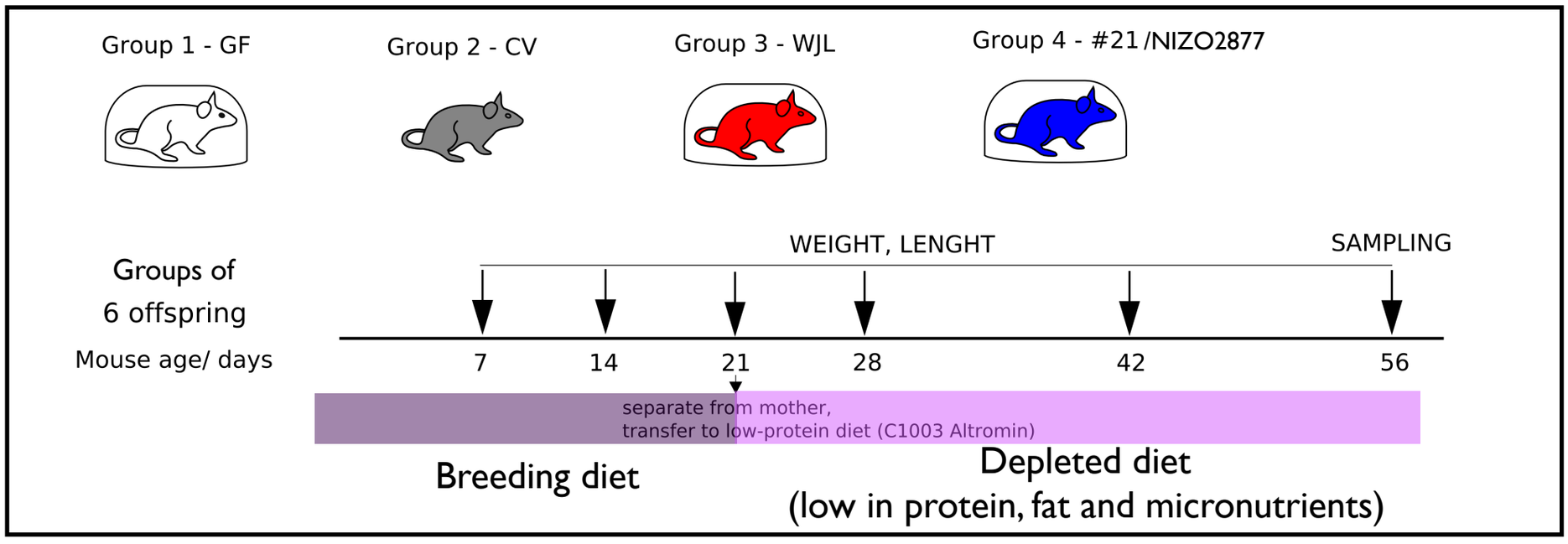
Gnotobiotic
Balb/c line

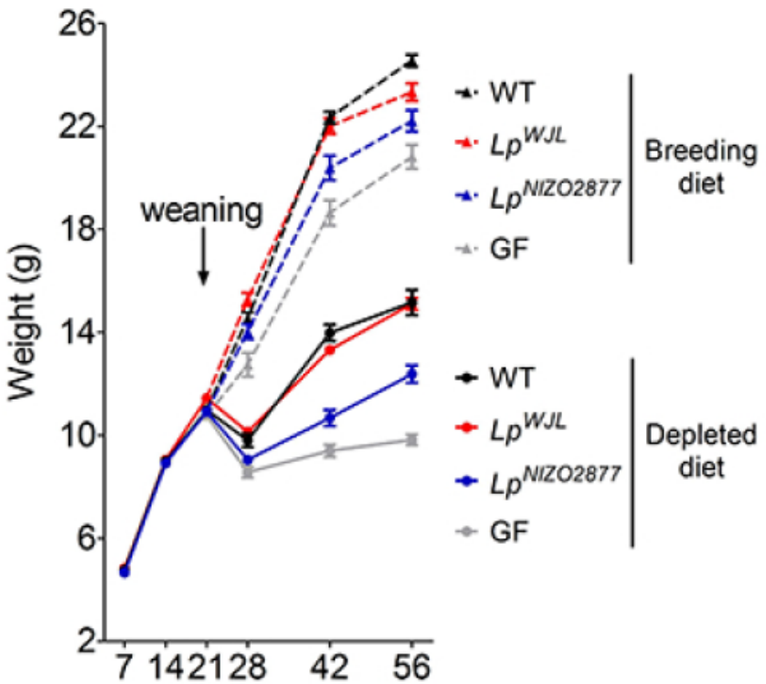


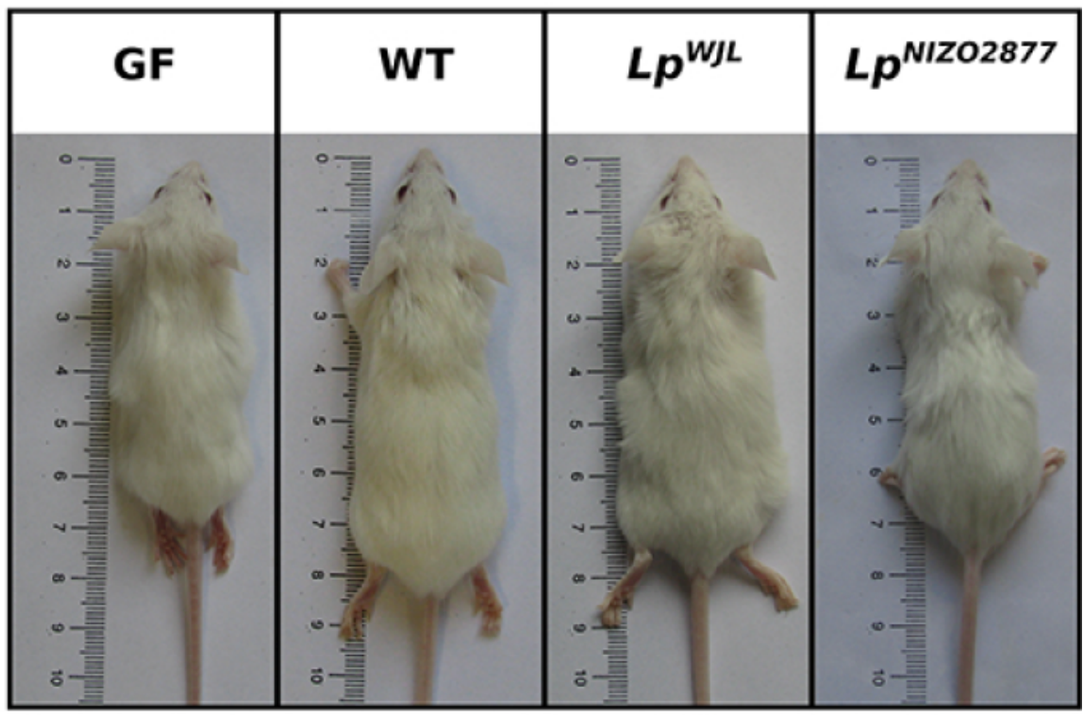


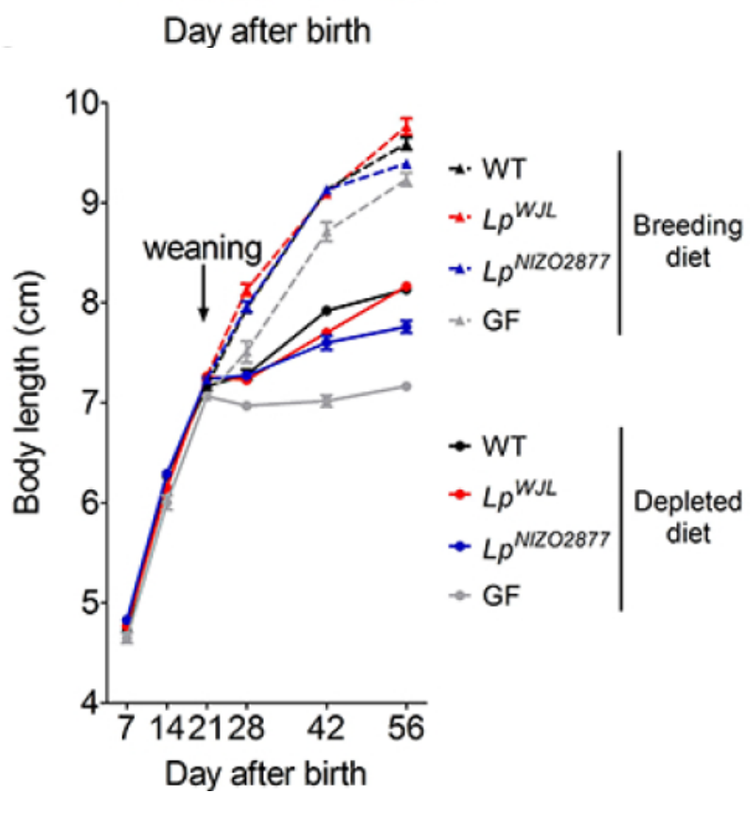
Selected Lactobacilli
growth promoting strains



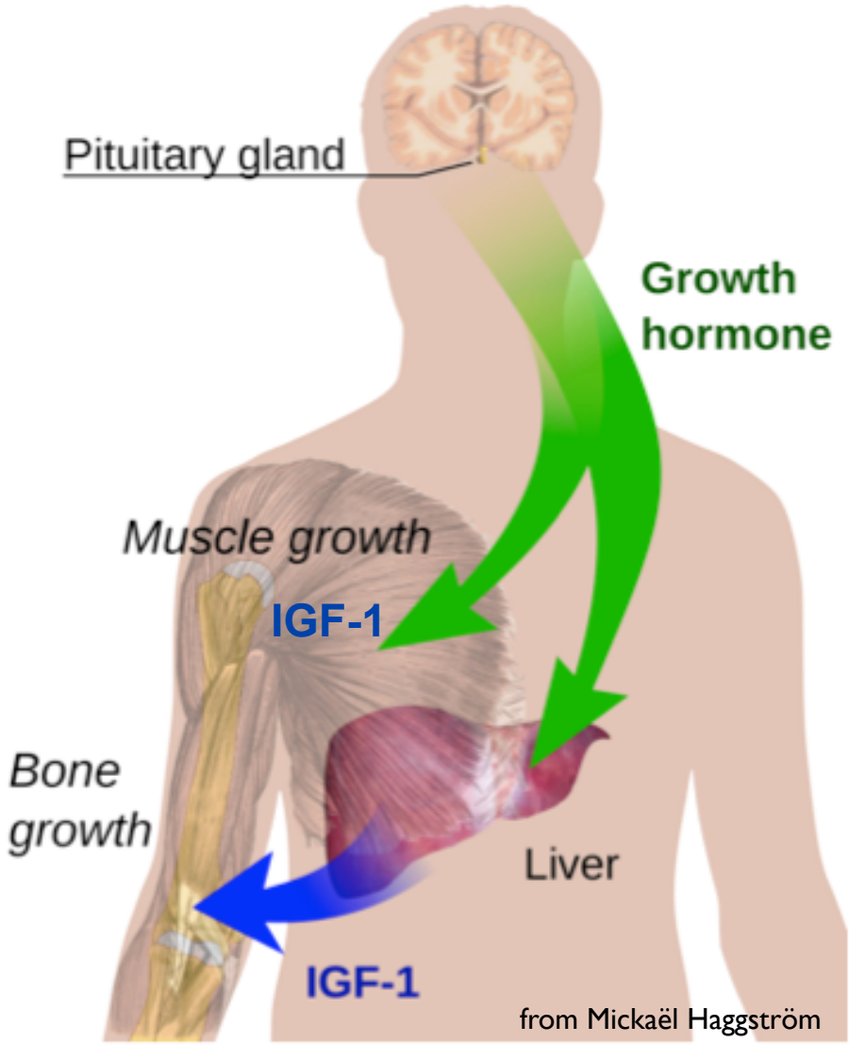
Microbiota and selected Lactobacilli strains maintain mouse juvenile growth upon chronic undernutrition







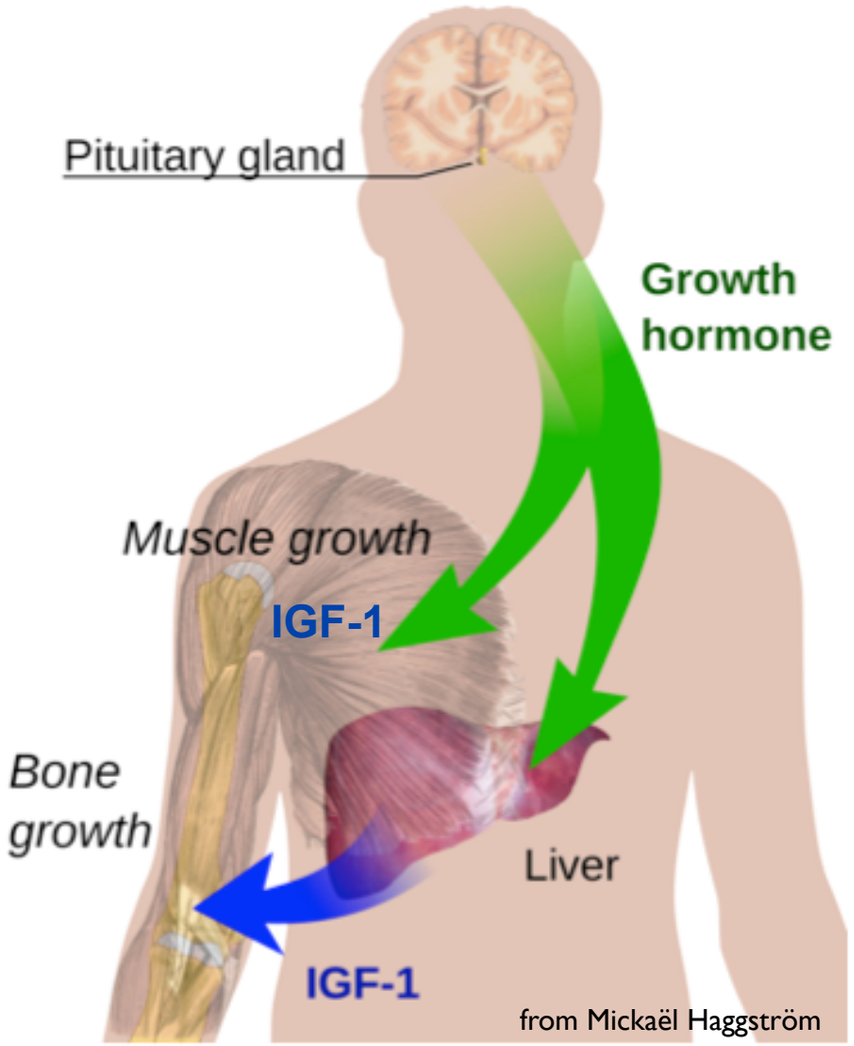
Somatotropic axis regulates post-natal growth...



from Mickaël Haggström

Somatotropic axis regulates post-natal growth...

...its activity is altered upon undernutrition (state of GH-resistance)



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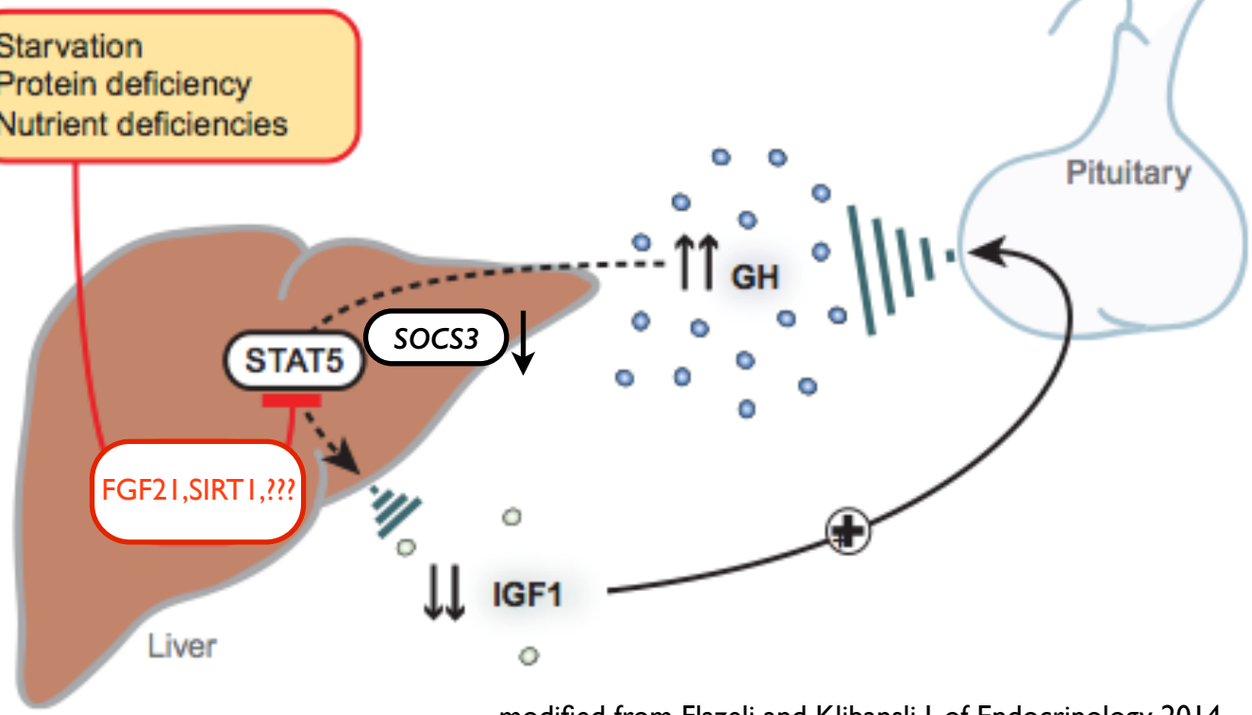
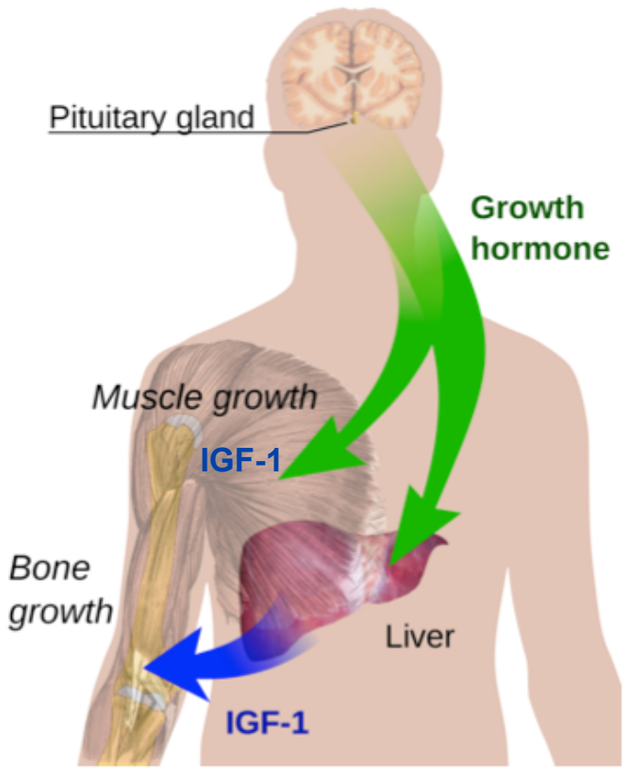
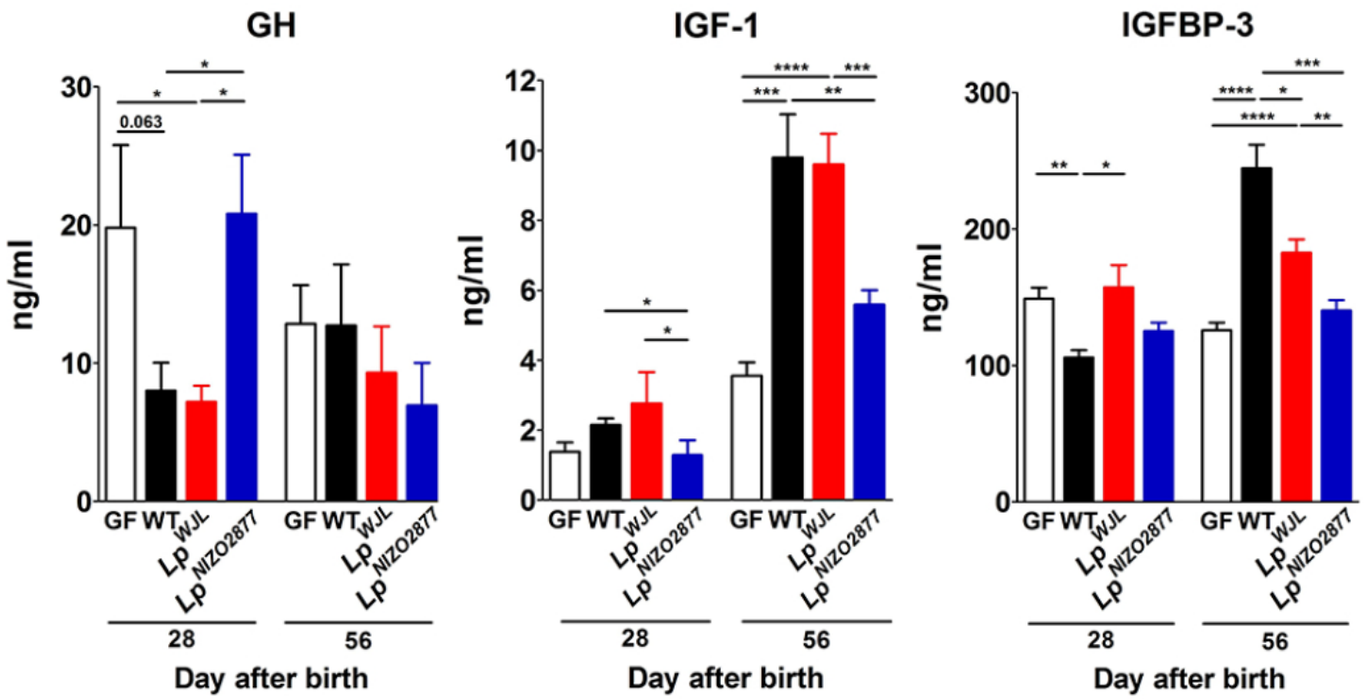


modified from Flazeli and Klibansli J. of Endocrinology 2014

Microbiota and selected Lactobacilli maintain tissue sensitivity to GH upon chronic undernutrition





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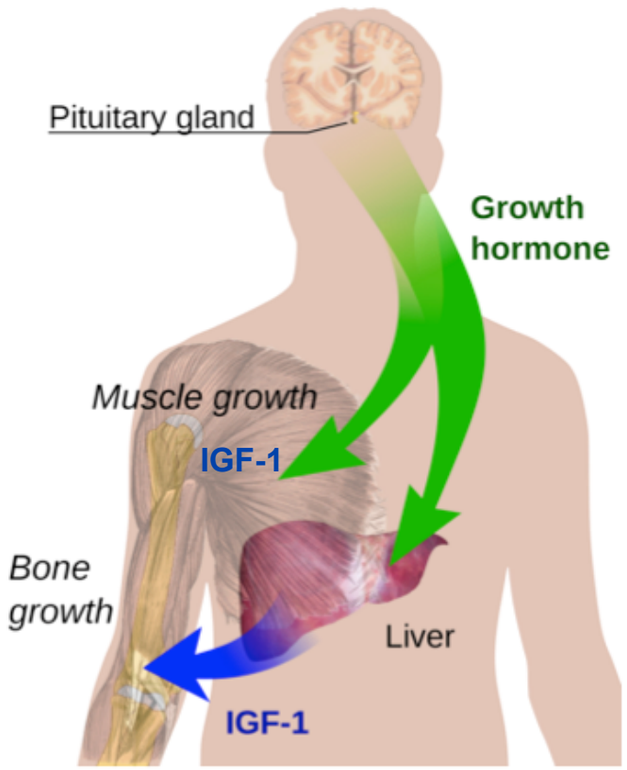
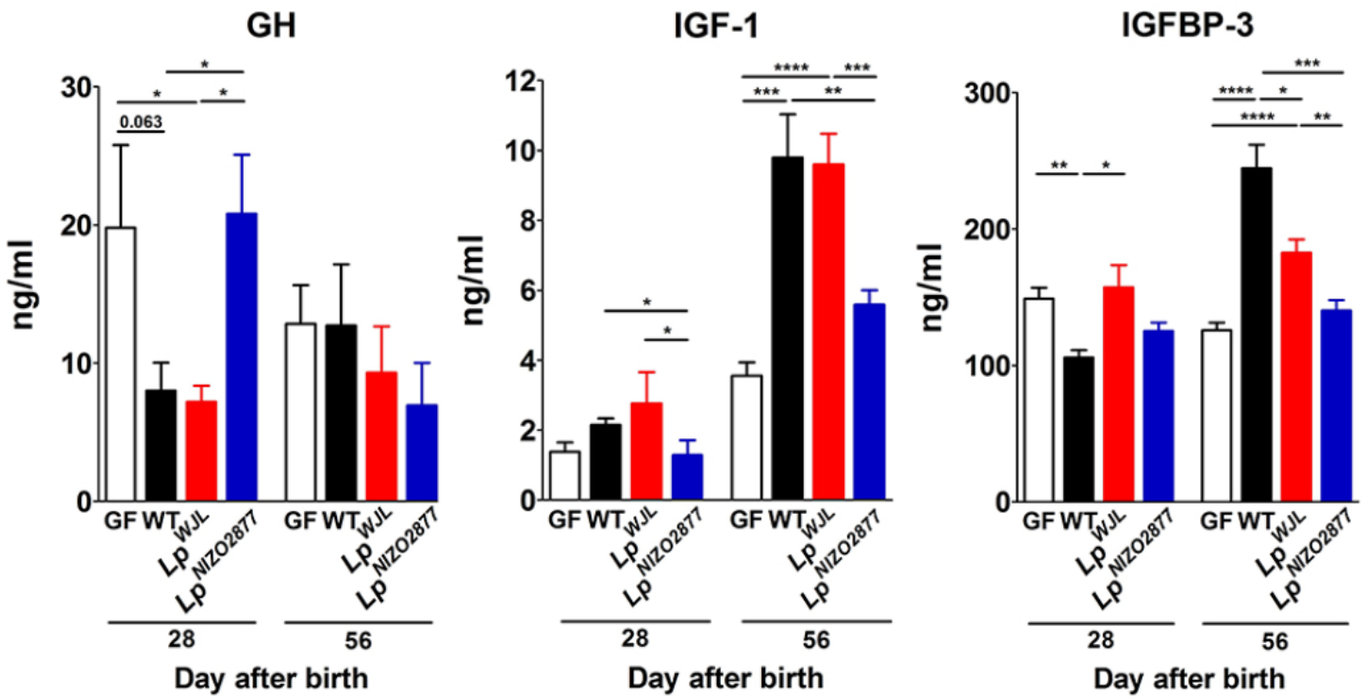
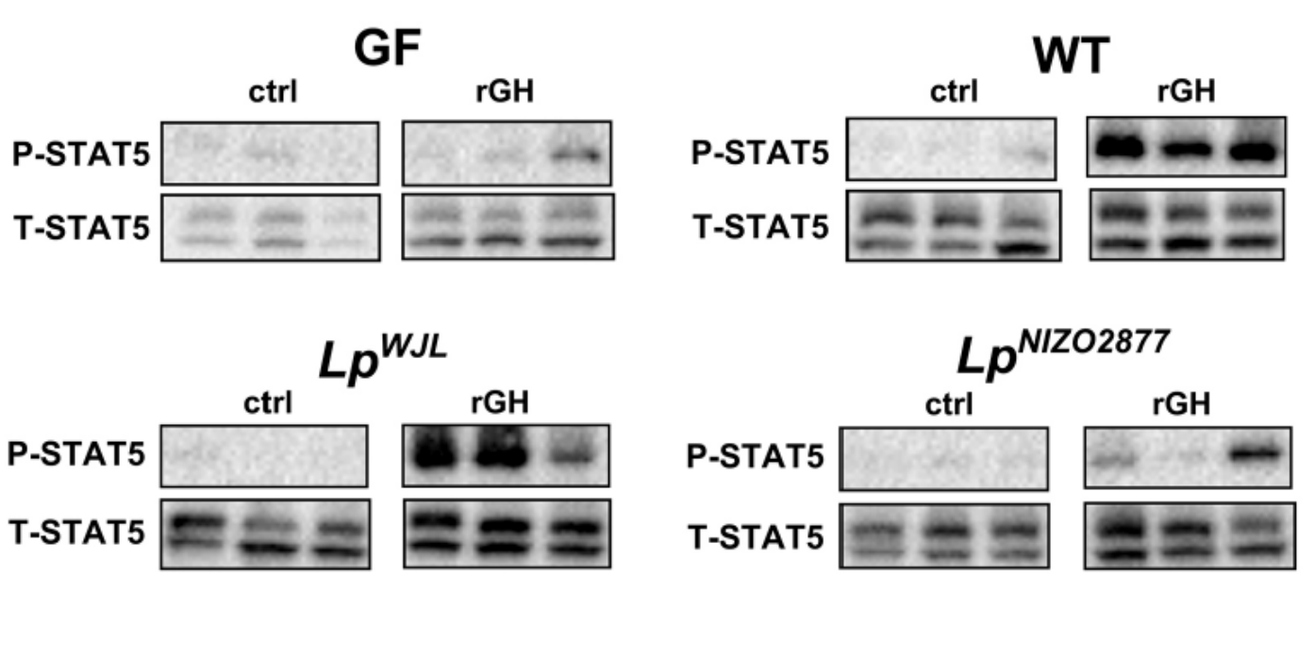
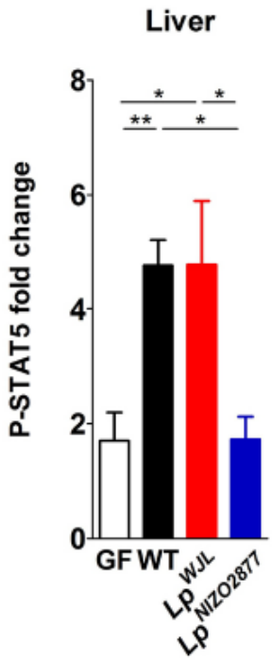






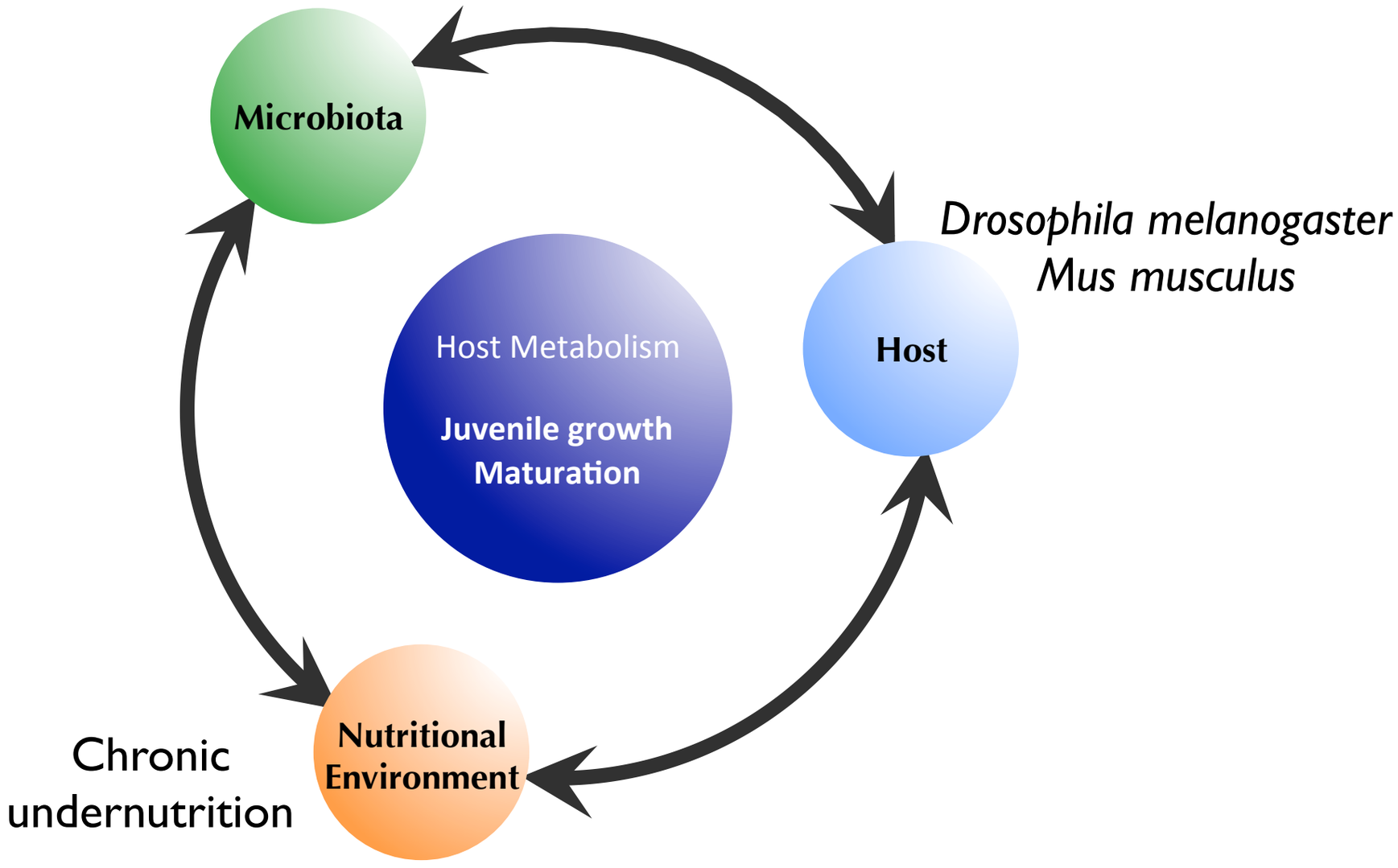


Schwarzer et al. (2016) Science, *in press*

« Génomique Fonctionnelle des Interactions Hôte/Bactéries Intestinales »

PI: François Leulier @LeulierLab

Lactobacillus plantarum



Drosophila melanogaster
Mus musculus

Chronic
undernutrition

« Génomique Fonctionnelle des Interactions Hôte/Bactéries Intestinales »

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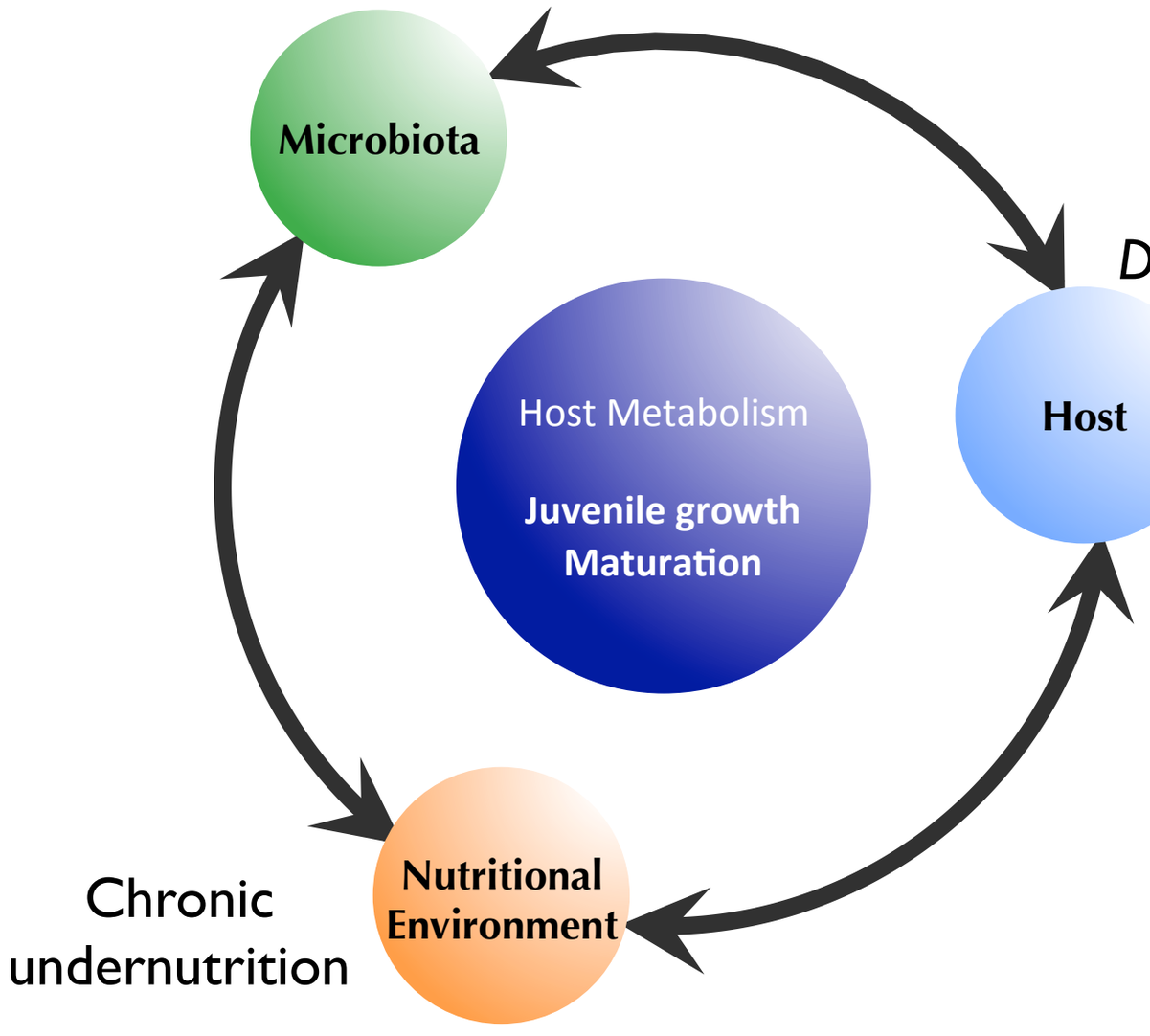
Lactobacillus plantarum



Drosophila melanogaster
Mus musculus

Lacto side
Renata Matos (post-doc)
Maria-Elena Martino (post-doc)
Mélanie Mitchell (IE CDD)
Hugo Gervais (AI CDD)

Fly side
Maura Strigini (post-doc)
Dali Ma (IR CDD)
Mélisandre Téfit (Ph'D)
Claire-Emmanuelle Indelicato (Ph'D)
Loan Bozonnet (AI CDD)

Mouse side
Martin Schwarzer (post-doc)
Kassem Makki (post-doc)
Anne Lambert (AI UCBL1)

Past members
Berra Erkosar (post-doc)
Gilles Storelli (Ph'D)
Noémie Bozonnet (IE CDD)

Host-Lactobacilli mutualism: «*Learning on the Fly*»