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THE HORSE HOLOBIONT IN A STRESSFUL WORLD: FROM MICROBES TO ECOSYSTEMS

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**THE HORSE HOLOBIONT IN A STRESSFUL WORLD
FROM MICROBES TO ECOSYSTEMS**

NURIA MACH



HABILITATION A DIRIGER DES RECHERCHES

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From microbes to ecosystems

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The horse holobiont in a stressful world: From microbes to ecosystems

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HABILITATION A DIRIGER DES RECHERCHES



To Marco, Marina and Sofia

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T A B L E O F C O N T E N T S

	Pre-text	11
	Aknowledgements	15
	Overview	17
Horse athletes: emotional and physical stress impacts the holobiont		21
	The horse winning gut	35
The gut is big enough for both of us: helminth-microbiota interactions in horse		51
	Outlook of a 8-year path	63
	Perspectives	65
	<i>Curriculum Vitae</i>	73
	Selected articles	97
	Bibliography	105

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P R E - T E X T : W H A T I S T H I S
J O U R N E Y A B O U T ?

This is the parable of a scientific-humanistic trip that tries to determine where an organism ends and where the outside world begins.

After five years of studies at the faculty of Veterinary Medicine at the Autonomous University of Barcelona (UAB), in 2005, I obtained a predoctoral fellowship to perform a European joint doctorate on animal welfare and nutrition (2008). This doctorate was defined by three international institutions, namely the UAB (Spain), the Royal Veterinary and Agricultural University of Copenhagen (Denmark), and the Wageningen UR Livestock Research (WUR, The Netherlands). The main thrust of my doctoral research was the characterisation of the relationship between nutrition, management practices, behaviour and performance in beef cattle (Mach et al., 2006, 2008, 2009) ¹⁻⁵. Under the primary supervision of Dr Maria Devant and Dr Àlex Bach from the Ruminant department of the Institute for Food and Agricultural Research and Technology (IRTA, Spain), I reached the qualification of outstanding *cum laude* with the special mention of the Extraordinary PhD Award. This joint PhD program research allowed me to feed my curiosity and enhance the adaptability,

problem-solving, and open-mindedness necessary to work and live abroad (Figure 1).

Beyond the scientific goals, this research program sensitised me to know the influence intensive livestock upstream and downstream activities have in developing countries. Next to the never-ending demands of thesis research, I collaborated with veterinarians without borders, did a Master's in International Development held by the Polytechnic University of Catalonia (2006) and travelled around South America to understand how local farmers work, pastoralists, and others involved in livestock rearing. Concomitantly, I satisfied my intellectual curiosity by studying for a five-years humanities degree at the Open University of Catalonia (2007-2012). Interestingly, this humanities degree bolstered my science career by enhancing my multicultural and global understanding, cultivating an appreciation for history, languages (I speak five languages currently), aesthetics, the human experience, and team networking.

In the same period, I also got passionate about Iyengar yoga, the standardised and rigorous type of yoga that emphasises

detail, precision and alignment in the performance of *asanas*. Still, now, I practice every day. Yoga helps me, for example, to balance the negative feelings of failed experiments, vetoed grant applications and rejected manuscripts. In other words, practising yoga helps me to unwind and recalibrate.

Evidence suggests that this scientific-humanistic trip nourished more than just the belly. Following my PhD defence (2008), I decided not to adopt a play-it-safe research and publication strategy that allowed me to accelerate my career advancement but move into a wholly new and unexplored area. I moved to Wageningen University (*Postdoc 1*: 2009-2011, WUR, The Netherlands), considered one of the best agricultural universities in the world, under the scientific supervision of Prof Mari Smits. I jumped into the nutrigenomics world. That was at the beginning of 2009. Nutrigenomics puts together a broad range of disciplines such as nutrition, genomics, biochemistry and several different ‘omic’ technologies. The main objective of my first post-doc was to study the molecular relationships between the transcriptome in the mammary gland tissue of dairy cows and specific nutrients (Mach et al., 2011, 2013)^{6,7} or genetic backgrounds (Mach et al., 2012)⁸. My analysis showed that the supplementation of unsaturated fatty acids produced extensive transcriptional adaptations in the mammary gland of grazing dairy and enhanced milk quality composition.

The solid bioinformatics and biostatistics formation and training received in the Academic Medical Center University of Amsterdam, together with the close interaction with researchers specialised in biochemistry, nutrition, molecular biology and statistics, helped me to increase my

understanding of systems as a whole throughout data integration and prediction. My research gradually evolved from experimental to computational systems biology. Step by step, I discovered the incredible creativity and excitement about how code gives new ways to look at the data and come to well-grounded conclusions and drive science.

Next to my research program, I followed teaching and academic leadership. In 2009, I became a lecturer in Nutrigenomics and Nutrigenetics at the Master of Food and Health Science organised by the Open University of Catalonia. Concomitantly, I started devoting hours of my working week to mentoring some of these Master's students. Since 2009 I have trained over 40 Master's students, providing them with constructive feedback, research project guidance and professional contacts. Moreover, I have been invited to give regular talks at foundations and public statements, telling people about nutrition and the new microbiota therapeutic avenues. Together with my students, we have regularly written reviews for peer-reviewed national⁹⁻¹⁵ and international journals¹⁶⁻²⁰. My humanistic background strengthened the need to address and share scientific results with the general public to arouse interest and educate the reader about new developments.

After concluding my post-doc in nutrigenomics at Wageningen University, I joined INRAE, the world's top institute for research on agriculture, food, and the environment. I enrolled on the Animal Genetics and Integrative Biology (GABI) unit at the Animal Genetics Department (Jouy en Josas, France) to start a second post-doc (July 1st 2011/September 30th 2012). Dr Claire Rogel-Gaillard scientifically supervised this second post-

doc. When I began my second post-doc, I wanted to deepen and consolidate the skills I had already developed in The Netherlands. Still, I also wanted to broaden my knowledge in genetics and immunology. Immunogenomics is a burgeoning research field that addresses the interface between the host, and the immune system, bridging bioinformatics and biostatistics technology, “omics” data, immune parameters, and a large set of clinical phenotypes.

Interestingly, with Claire’s team, we showed that the genetic architecture of transcriptome variation of immune cells is very complex. We found five transcriptional biomarkers which were good predictors for animal immunocompetence (*e.g.*, CD4-/CD8+ and phagocytosis activity (Mach et al., 2013) ²¹. These results provided a first overview from which new genetic selection strategies can be launched to elucidate the underlying molecular mechanisms of pig immunocompetence. Additionally, I published the first transcriptome atlas across different small intestine tissues in pigs (Mach et al., 2014) ²². Little by little, I learnt how to combine omics readouts into a systems biology approach.

Up to here, all my studies focused on hosts. From October 2012 to August 2013, I enrolled on my last post-doc in the Functionality of the Intestinal Ecosystem (FInE) group, which makes part of the MICALIS unit at the MICA department (INRAE, Jouy en Josas, France). Here started my great fun combining eukaryotic hosts and their microbes, the functional unit termed holobionts ²³. Under the supervision of Dr Patricia Lepage, Dr Joël Doré, and Dr Hervé Blottière, specialists in human microbiota and metagenomics, I got fascinated and passionned by the

subject. I learnt that microbiota is not as important as its relationship with the host: how it interacts with the organism. They taught me to use metagenomics tools to take a “molecular photograph” of intestinal microbiota quickly and with unprecedented detail. Using that, I significantly contributed to a global overview of the correlations between gut microbiota, performance and immune system response in animals (Mach et al., 2015; Ramayo-Caldas et al., 2016; Jaucouton et al., 2015) ^{24,25,26}. I learnt state-of-the-art biostatistics and bioinformatics approaches to dissect holobiont components. From here on, it was increasingly clear to me that animals' development, growth, welfare and health (in one word, all functions) were influenced by the complex microbial communities they host.

Though there is much still to learn about microbiomes, it was clear that health, performance and well-being in species of veterinary interest rely on more than those cells described by host DNA. When I got a permanent researcher position at the Genetics Department in the INRAE (GABI unit, Jouy en Josas, September 2013), I was asked to analyse data from existing projects designed and carried out to understand endurance horses vary in their ability to achieve success in sports (Mach et al., 2016, 2017) ^{27,28}. By looking at the data from various perspectives and trying different ways of representing them visually and mathematically, I hypothesised that microorganisms scaffolded around my charismatic eukaryote (the horse) were pivotal in understanding the athlete's performance and the functioning of the holobionts. Here began my eighth years-journey towards these questions at the INRAE: Does the holobiont add crucial context to athletic performance or irrelevant

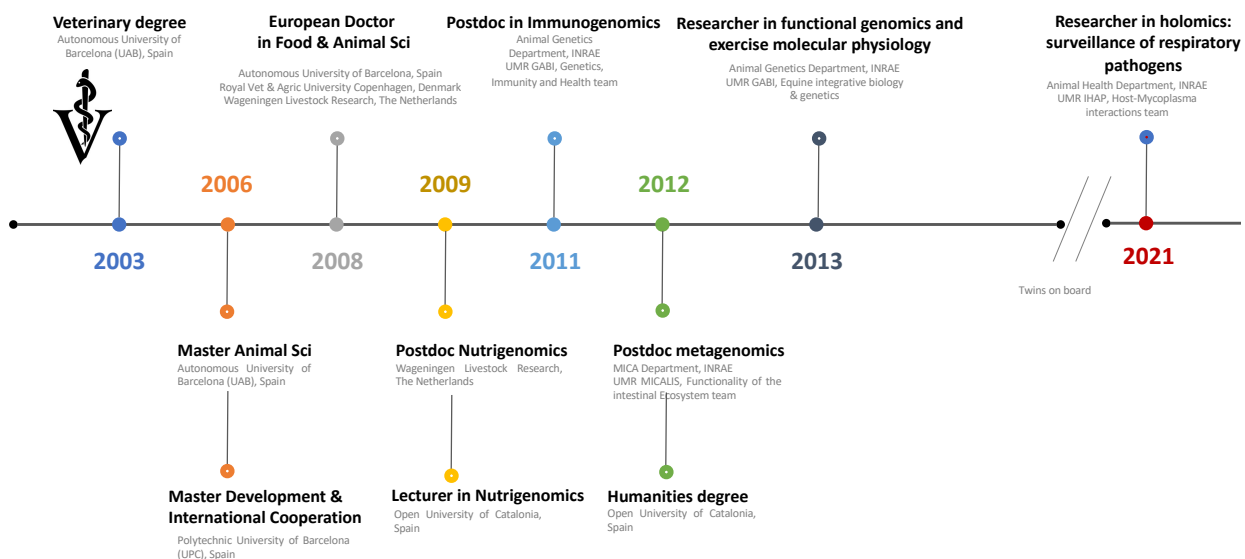
complexity? Who is doing what, and how do they contribute to the whole?

Such questions spanned my knowledge of many of the most critical domains of natural science, bringing together subjects such as animal science, nutrition, functional genomics, immunology, metagenomics, biostatistics, bioinformatics, and systems biology. The travel has been an odyssey involving degrees in odd fields, interdisciplinary research projects, success in pursuing research outside the comfort zone, and studying different biological systems. This multi-disciplinary approach has been the catalyst that enhanced the originality of my research, the scientific rigour, and my capacities to communicate, mentor, evaluate and transfer bits of knowledge to my peers and the general public. Nevertheless, none of these skills crucial for my research success could have been possible without my students' patience, perseverance, and help. Concomitantly to the Michel Boisseau PhD mentoring (2019-2022), I have begun to work more toward a collective good. I started to help colleagues to run seminar series, take the lead of other PhD students and postdoc mentoring, connect students with careers outside academia, interface between

industry/animal care facilities and researchers, work as an associated editor in several journals and research topics, and manage works that required specialisation (*e.g.*, basic software coding and big data on cloud-based platforms). To summarise all this professional growth, I met many eager scientists worldwide who helped me in such grand adventures.

These eight years of science at INRAE have brought beautiful results about the holobiont (*e.g.* Mach et al., 2017, 2020, 2021)²⁹⁻³⁴ that have ultimately resumed into a charming bottom-up type of work (Mach et al., 2022)³⁵. Some of them have been yet translated into action in the horse industry. I could have continued on such a wonderful and delightful well-rooted trip. Nevertheless, it urged the need to do something to cope with the problems of the modern world, the issues of whether and which, as well as how.

Figure 1 - Inflexion points in my road to science



A K N O W L E D G E M E N T S

First, I would like to thank Christelle Koechlin-Ramonatxo, Eric Oswald, and Diego Morgavi, who kindly agreed to review this manuscript. I would also like to thank the other committee members, Christine Citti, Rafael Muñoz-Tamayo, and Claire Rogel-Gaillard, for their time and availability. Claire guided my first steps at INRAE and generously provided knowledge, expertise, and continued support in my independent research line at GABI. I am delighted to have her on my habilitation committee.

I sincerely thank the Equine Integrative Biology and Genetics (BIGE) team at INRAE. My special thanks go to my colleagues on this team for the warm and friendly atmosphere, the many scientific and non-scientific meetings and conversations, and their collaborative effort during data collection. I could not have undertaken this journey without the invaluable feedback and expertise of Eric Barrey and Sophie Pollet. My research has been conducted closely with Guillaume Sallé, Léa Lansade, Marie-Pierre Moisan, and Sandra Plancade. I warmly thank them for countless hours of scientific discussions over the years and for providing guidance and a sounding board when required. I would especially like to

thank all the young researchers with whom I have had the pleasure to work during the last few years: Allison Clark, Alice Ruet, David Bars, Francesca Massaci, Vitoria Bisutti, Alizé Nevot, Jesús M^a López, and Michel Boisseau. I am also grateful to the Animal Genetics and Integrative Biology (GABI) unit at the INRAE Animal Genetics Department for supporting this multidisciplinary research and providing an excellent peer environment. I have had a joyful and productive time in this unit and Department.

The research presented in this manuscript results from a broad collaborative effort. A special thank you to all my collaborators for their support, guidance and comprehensive insights in this field. You have made this an exciting adventure for me. I want to thank, in particular, Mari Smits, André Bannink, Yulixaxis Ramayo-Caldas, Jordi Estellé, Joël Doré, Patricia Lepage, Alessio Cecchinato, Sara Pegolo, Vincent Gerber, Han van Der Kolk, Maria Ballester, Marine Beinat, Edin Hamzic, Marcio Costa, among others. For the conciseness of the manuscript, I have had to omit some of the papers we have worked on together. Our discussions were vital in inspiring me to think outside the box.

I also want to express my warm and sincere gratitude to the IHAP unit, mainly to Christine Citti, Eric Baranowski, Xavier Nouvel, and Jean-Luc Guérin. They have hosted me since 2021 and bet on my future as a researcher. I appreciate your faith in my soft and hard skills, and I hope to get my hands dirty and dig into these new scientific issues from now on.



I am incredibly grateful to my parents and my two brothers for their love and for supporting me during my scientific path.

From the bottom of my heart, my deepest gratitude goes to Marco, Marina, and Sofia, who fulfil my life.

1



O V E R V I E W

“The time has come to replace the purely reductionist ‘eyes-down’ molecular perspective with a new and genuinely holistic, eyes-up, view of the living world, one whose primary focus is on evolution, emergence, and biology’s innate complexity.”—Carl Woese³⁶

This manuscript traces a selection of outputs and outcomes over the last eight years in the sea of science within the Equine Integrative Biology and Genetics (BIGE) team (INRAE, Jouy en Josas). The helm of this thesis is the horse holobiont, the functional unity encompassing the host and the associated microorganisms³⁷. My last eight years of research have been mainly devoted to constructing knowledge around the horse holobiont concept through different data integration approaches and multidisciplinary. Horses contain many microorganisms, including archaea, bacteria, fungi, microalgae, protozoa, and viruses, but differ markedly from the assemblages³⁵. Host-associated microorganisms influence nutrient exchange, defence mechanisms, physiology, behaviour, reproduction, and host fitness^{38–40}. Their collective genomes (including elements for the nuclear genome, organelles and microbiome) forge a hologenome, and models of animals that do not account for these intergenomic associations are regarded as incomplete³⁷. This single ecological unit is a complex entity with highly specialised symbiotic interactions that are important in holobiont³⁷ (Figure 1).

To afford a holistic, eyes-up view through the horse holobiont concept, I will first highlight how environmental stressors, especially human-induced ones, alter the gut microbial communities and disturb the symbiotic relationship, resulting in a holobiont break-up (Chapter II). With the cascading effects of a holobiont break-up, the results of these changing conditions may be more severe and resilient than predicted. Then, using Arabian horses as a model, in Chapter III, we will show how the gut microbiome communicates with the host under extreme physical and physiological stressors. Gut microbiota sends chemical signals to mitochondria, which has the effect of helping to extend their energy output, control oxidative stress and reduce fatigue during long-distance races. In chapter IV, I will show how interactions between microbial species may evolve during increasing amounts of stressors (parasite infection + drug administration). Thus, growing mutualisms, facilitative interactions, and cooperative behaviour between microbial species may provide holobionts with additional resistance to changing conditions and tolerance to infection. All these pioneering studies in the horse domain indicate how biotic and abiotic stressors affect the entire holobiont (both the microbial communities and the host) and pave the way for dietary supplements and management practices that could enhance equine athletic health, welfare and performance. Then, I will resume my last 8-years of science with some concluding remarks in Chapter V. Finally, I will highlight a way forward for my future research in Chapter VI. The annexe includes a *curriculum vitae* and a list of the critical articles highlighted in the manuscript.

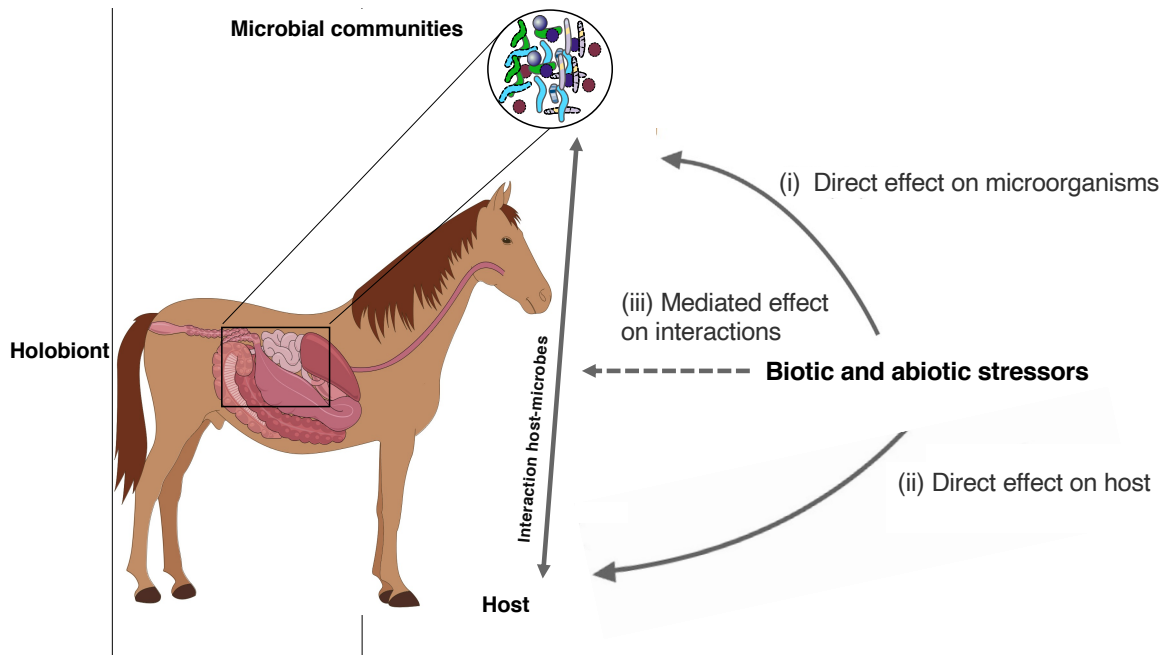


Figure 1 - Overview of the interactions between the host, the microbial community and stressors. Biotic and abiotic stressors or changes in environmental conditions will separately affect (i) the microbes associated with the host and (ii) the host itself, causing changes in host physiology and microbial community traits. This will affect the interactions between the host and the microbial communities (iii) and, thus, the outcome of the symbiotic relationship.

2



H O R S E A T H L E T E S : E M O T I O N A L A N D
P H Y S I C A L S T R E S S I M P A C T S T H E
H O L O B I O N T

This chapter synthesis the research work on the microbiota-gut-brain axis in athletes. This work was performed as part of the Alice Ruet PhD program, supervised by Dr Lansade and Dr Arnauld, under the title: “*Altération de l’état de bien-être du cheval domestique. Effets de pratiques d’hébergement liées au box individuel et relations avec l’équitation*”(2017-2020). I hosted Alice in my lab for three months. Because it was a long and rich scientific adventure, I enrolled on board David Bars and Francesca Massacci, two international PhD students, and Allison Clark, an M2 from the Open University of Catalonia.

The mentoring trajectory with the abovementioned students is reflected as follows:

- 1.[Research article] **Núria Mach** (Corresponding author), Léa Lansade, **David Bars-Cortina**, Sophie Dhorne-Pollet, Aline Foury, Marie-Pierre Moisan, **Alice Ruet** (2021). Gut microbiota resilience in horse athletes following holidays out to pasture. *Scientific Reports*, 11, <https://dx.doi.org/10.1038/s41598-021-84497-y>, <https://hal.inrae.fr/hal-03197215>, OA
- 2.[Research article] **Núria Mach** (Corresponding author), **Alice Ruet, Allison Clark, David Bars-Cortina**, Yulixaxis Ramayo-Caldas, Elisa Crisci, Samuel Pennarun, Sophie Dhorne-Pollet, Aline Foury, Marie-Pierre Moisan, Léa Lansade (2020). Priming for welfare: gut microbiota is associated with equitation conditions and behaviour in horse athletes. *Scientific Reports*, 10, <https://dx.doi.org/10.1038/s41598-020-65444-9>, <https://hal.inrae.fr/hal-03197220>, OA
- 3.[Research article] **Francesca Massacci**, Allison Clark, Alice Ruet, Léa Lansade, Márcio Costa, **Núria Mach** (Corresponding author)(2020). Inter-breed diversity and temporal dynamics of the faecal microbiota in healthy horses. *Journal of Animal Breeding and Genetics*, 137 (1), 103-120, <https://dx.doi.org/10.1111/jbg.12441>, <https://hal.inrae.fr/hal-02624117>

Stress is an essential adaptation necessary for homeostasis, performance and survival⁴¹. The stress response occurs whenever an individual faces an endogenous or exogenous challenge perceived as unpleasant, adverse or threatening. It can be induced by physical, physiological or psychological stimuli⁴¹. Intense exercise implies adaptive processes involving affective, physiological, biochemical, and cognitive-behavioural responses to regain homeostasis (reviewed by Morgan et al.⁴²). Additionally, it associates with high-demand training plans⁴³, special dietary programs, attending competitions, long-distance travelling, and exposition to the unfamiliar. Therefore, the physical and psychological demands during intense exercise are stressful. Although there is no consensus as to which symptoms or biomarkers define stress, some common signs include clinical and hormonal indicators and other symptoms associated with fatigue, performance decline, insomnia, change in appetite, weight loss and mood disturbances such as irritability, anxiousness, loss of motivation, poor concentration and depression, as well as inflammation and immunosuppression (reviewed by Clark and Mach¹⁹).

The two central, interrelated systems that affect the stress response during exercise are the sympatho-adrenomedullary (SAM) and hypothalamus-pituitary-adrenal (HPA) axes. The activation of these axes results in the release of catecholamines (norepinephrine and epinephrine) and glucocorticoids into the circulatory system (reviewed by Ulrich-Lai et al.⁴⁴; Figure 1). During exercise, stress also activates the autonomic nervous system (ANS), which provides the most immediate response to stressor stimuli through its sympathetic and parasympathetic arms. It increases the neuronal release of norepinephrine and other neurotransmitters in peripheral tissues such as the gastrointestinal tract or cardiovascular system⁴⁴. The bidirectional communication between the ANS and the enteric nervous system (ENS) in the gut, the gut-brain axis, mainly occurs by way of the vagus nerve, which runs from the brain stem through the digestive tract and regulates almost every aspect of the passage of digested material through the intestines. Other ways of communication between the gut-brain axis are (i) gut hormones (*e.g.*, gamma-aminobutyric acid, neuropeptide Y, dopamine) and (ii) gut microbiota molecules (*e.g.*, short chain fatty acids (SCFA), tryptophan)^{45,46}. To describe these ways of relationships: the “microbiota-gut-brain axis” was coined⁴⁵.

Horses have been domesticated for thousands of years and have foraged in herds as fight-or-flight animals. Like humans, elite sports horses expected to perform at the top of their game are subjected to high levels of physical and mental engagement⁴⁷. They follow high-intensity training with different trainers, riders and devices from the age of two years. They also go to national and international shows and are thus often required to live in other stables and cope with various environments, including extended distances and air travel. Moreover, they predominantly live in individual loose boxes rather than open paddocks, a safe environment that indeed deteriorates their welfare⁴⁸. Up to 90 % of domesticated horses live at least 12 hours daily in individual boxes with artificial bedding and without *ad libitum* feeding, moving, and social interactions with conspecifics⁴⁹⁻⁵². Indeed, this housing system prevents animals from performing natural behaviours, one of the welfare concerns stated by the five freedoms framework⁵³. Individual box housing induces aberrant, chronic, and repetitive behaviours (the so-called stereotypies), including cribbing and weaving, hypervigilance, or more aggressive behaviours such as kicking and

biting⁵⁴⁻⁵⁶. Horses like to be free to move and interact with other horses as part of a complex social group and to have nearly constant access to grass or hay to eat. Additionally, most of these potential athletes are weaned through abrupt physical separation early in age, affecting their overall well-being with likely long-term effects^{48,57}.

The horse gut harbours more than 100 trillion microorganisms in the gastrointestinal tract, representing roughly 25 million genes³⁵. The gut microbiota comprises seven phyla^{33,58-62}, approximately 200 species in the large intestine^{31-33,63-66}, and a myriad of protozoa, archaea and anaerobic fungi^{30,34,35,67}. As for humans, the horse gut microbiota promotes digestion and food absorption for host energy production⁶⁸, provides folate⁶⁸, vitamin K, and metabolites important for host health⁶⁹ (*e.g.*, SCFA, dimethyl sulfone, trimethylamine oxide, indoles, tryptamine, oligosaccharides, peptidoglycans, and secondary bile acids^{70,71}). The gut microbiota also neutralises drugs and carcinogens, modulates intestinal motility, protects the host from pathogens, and stimulates and matures the immune system and epithelial cells^{34,72}. As mentioned above, gut microbiota also modulates excitatory and inhibitory neurotransmitters in response to physical and emotional stress (reviewed by Clark and Mach¹⁹; Mach and Fuster¹⁶ and others^{73,74}; Figure 1).

In horses, the imbalance in the microbiota-gut-brain axis has been posited by Destrez et al.⁷⁵, who observed that the concentration of amyolytic bacteria and the abundance of *Succinivibrionaceae* positively correlated to bowing (considered an alert or alarm type of behaviour) following a low-fibre but high-starch diet. In ponies fed high-starch diets, increased behavioural reactivity was related to gut microbiota changes, suggesting that gut microbiota composition and behaviour are strictly intertwined and influence each other⁷⁶. Perry et al.⁷⁷ did not measure gut-brain interactions but reported reductions in Proteobacteria in the equine cecal microbiota following travel stress and disruption in the sequence of the regular daily routine. However, beyond those studies, the relationship between the long-term exposition of physical and mental stress, the gut microbiota composition, the aberrant behaviour, and the possible pathophysiological mechanisms remains scant. To render this hypothesis testable, I contacted Léa Lansade (UMR 85 PRC, IFCE, INRAE, University of Tours, Nouzilly, France), an internationally recognised ethologist in the horse domain. She works on personality, cognition and welfare in horses. At that time, she was already working with Dr Marie-Pierre Moisan (University of Bordeaux, INRAE, INP, NutriNeuro, UMR 1286, 33076 Bordeaux, France), a primarily known expert on the physiological mechanisms of stress and their consequences. Given my fascination, passion, and acquired metagenomic skills (Mach et al., 2015²⁴; Ramayo et al., 2016²⁵), I proposed to them an integrative biology perspective to help understand the complex host-gut microbiota interactions and their association with behaviour and welfare. The fact that I learned how to combine omics readouts into a systems biology approach helped in such a proposition (Mach et al., 2010⁷⁸; Mach et al., 2011⁶; Mach et al., 2013ab^{7,21}, Mach et al., 2016²⁸ and 2017²⁷).

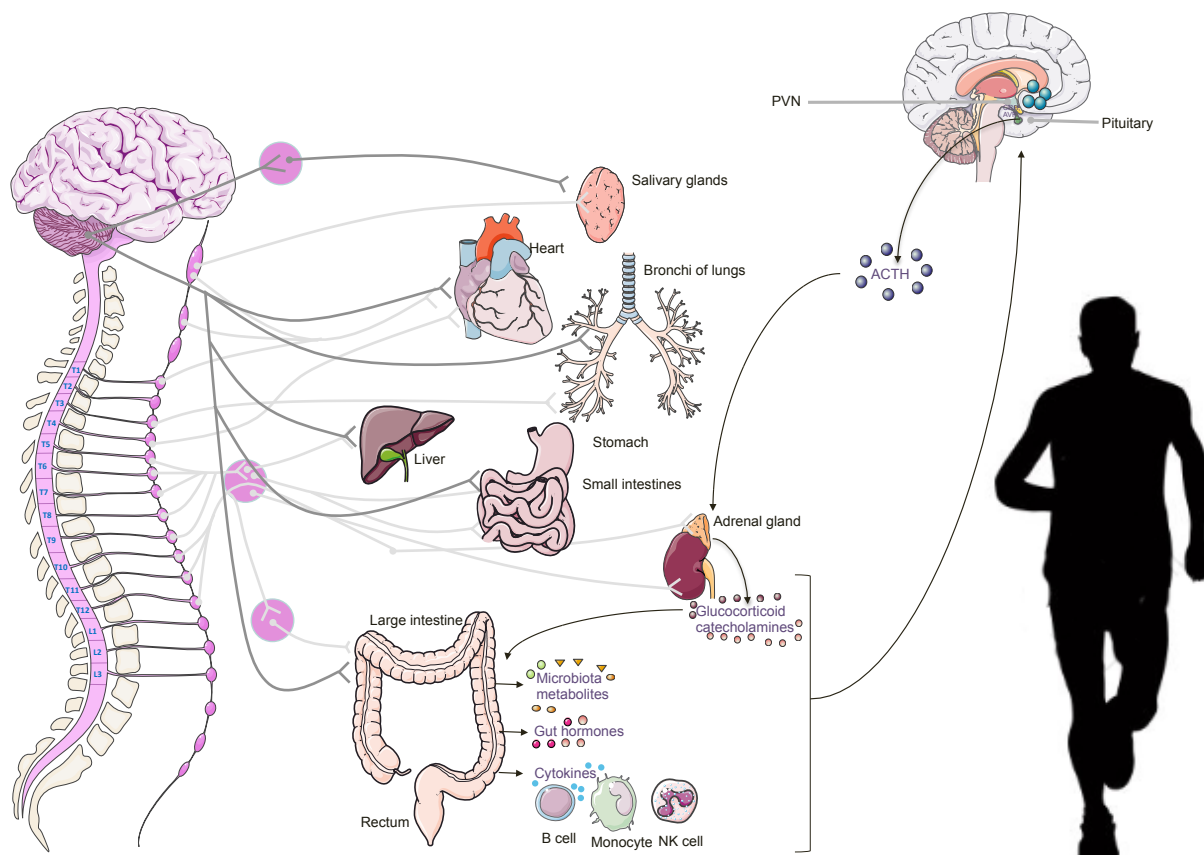


Figure 1 - Stress hormones are released during highly intense exercise.

Stress responses to intense exercise are mediated by largely overlapping circuits in the limbic forebrain, the hypothalamus and the brainstem so that the stressor and intensity tune the respective contributions on the neuroendocrine and autonomic systems ⁴⁴. Exercise-induced stress results in the activation of preganglionic sympathetic neurons in the intermediolateral cell column of the thoracolumbar spinal cord (shown in purple and clear grey). This sympathetic activation represents the classic fight or flight response, generally increasing catecholamines' circulating levels. Parasympathetic tone can also be modulated during stress (shown in dark grey). Within the HPA axis, stress activates hypophysiotropic neurons in the paraventricular nucleus of the hypothalamus (PVN) that secrete releasing hormones, such as corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP), into the portal circulation of the median eminence. These releasing hormones act on the anterior pituitary to promote the secretion of adrenocorticotrophic hormone (ACTH), which in turn acts on the inner adrenal cortex to initiate the synthesis and release of glucocorticoid hormones. Moreover, the sympathetic nervous system directly innervates the adrenal cortex, which can regulate corticosteroid release. Additionally, the gastrointestinal tract responds to stress in an endocrine manner by releasing hormones such as Gamma-aminobutyric acid (GABA), neuropeptide Y and dopamine that have been purported to be involved in gastrointestinal disturbances, anxiety, depression, reduced food intake and less stress coping. Microorganisms that colonise the digestive tract can regulate the HPA axis through the code or production of short-chain fatty acids and neurotransmitters such as GABA, dopamine and serotonin, as well as cytokines. The neuroendocrine stress response to exercise is determined by emotional stress and the volume of physical exposure. As exercise intensity is increased, there are approximately proportional increases in circulating concentrations of ACTH and cortisol. More details are found in Clark and Mach (2017) ¹⁹; <https://dx.doi.org/10.1186/s12970-016-0155-6>, <https://hal.inrae.fr/hal-01606853>, OA.

This project was funded by the “Institut français du cheval et de l'équitation” (IFCE), a government agency set up to encourage equine breeding and horse-related activities, and Fonds Éperon (“Encouragement aux Projets Equestres Regionaux ou Nationaux”), an incentive fund for regional or national equestrian projects, managed by industry professionals. Alice Ruet was enrolled in the project as a PhD student, and I hosted her in my lab for three months. Alice's PhD program directors were Dr Lansade and Dr Arnould (both at the UMR 7247, Physiologie de la reproduction et des comportements, Tours, France). I had an unofficial role of co-supervisor which can be detailed as follows: (i) development of the experimental design (20%), verification of the experiment development (20%), data analysis and interpretation (30%), and writing of articles (30%). For this first project, Alice Ruet moved to the Cadre Noir de Saumur for more than 1.5 years. She measured the behaviour and collected blood and faecal samples in a cohort of 185 healthy elite athletes housed in individual boxes for eight months. In “le Cadre noir de Saumur”, all animals were reared in similar conditions. In between, Alice Ruet spent three months in my lab to help with faecal DNA extraction, PCR analysis and microbiota results interpretation.

Strickling enough, behaviour assessment of those horse athletes showed that the expression of both oral and locomotion-related stereotypies was observed in 17% of the individuals, whilst 99% of the individuals were experiencing unresponsiveness to the environment (the so-called withdrawn posture or depression) at least once within the eight months. Hypervigilance, a stress-related response, was observed in 75% of our individuals, and aggressiveness was observed in 43% of our horses. Results confirmed that using individual boxes as housing systems for sport horses induces the expression of behaviours reflecting a welfare alteration. We proved that separate confinement triggered the face of both oral and locomotion-related stereotypies and aggressiveness toward humans in both young horses and adults, while almost all horses individually stabled experienced unresponsiveness to the environment expressed through the “withdrawn posture” with an increase in stress-related behaviours expressed through the alert posture (further details are depicted by Ruet et al., 2019; <https://hal.inrae.fr/hal-02623360>, OA)⁷⁹.

Expectedly, the gut microbiota composition was influenced by environmental and host variables (Figure 2 a,b), including equine discipline (eventing, dressage, show-jumping or vaulting). Beyond the variables outlined here, we also observed that the compromised welfare state (*e.g.*, stereotypies, hypervigilance and aggressiveness) was associated with particular gut microbiota profiles, reinforcing the notion of the existence of the microbiota-gut-brain axis (Figure 2c-d; [article 1 Mach et al., 2020](https://doi.org/10.1038/s41598-020-65444-9)³¹; <https://dx.doi.org/10.1038/s41598-020-65444-9>, <https://hal.inrae.fr/hal-03197220>, OA). The most substantial effect was observed in animals experiencing oral stereotypies. Levels of *Roseburia*, a butyrate-producing genus, positively correlated to oral stereotypies prevalence. Stereotypies also correlated to amylolytic (*e.g.*, *Ruminobacter*) and fibrinolytic proteobacteria (*e.g.*, *Acinetobacter*) or hydrogen sulphide (H₂S)-producers (*e.g.*, *Desulfurispora* and *Helicobacter*). Evidence shows that *Roseburia* exerts beneficial effects on host behaviour through its anti-inflammatory activity within the gut⁸⁰.

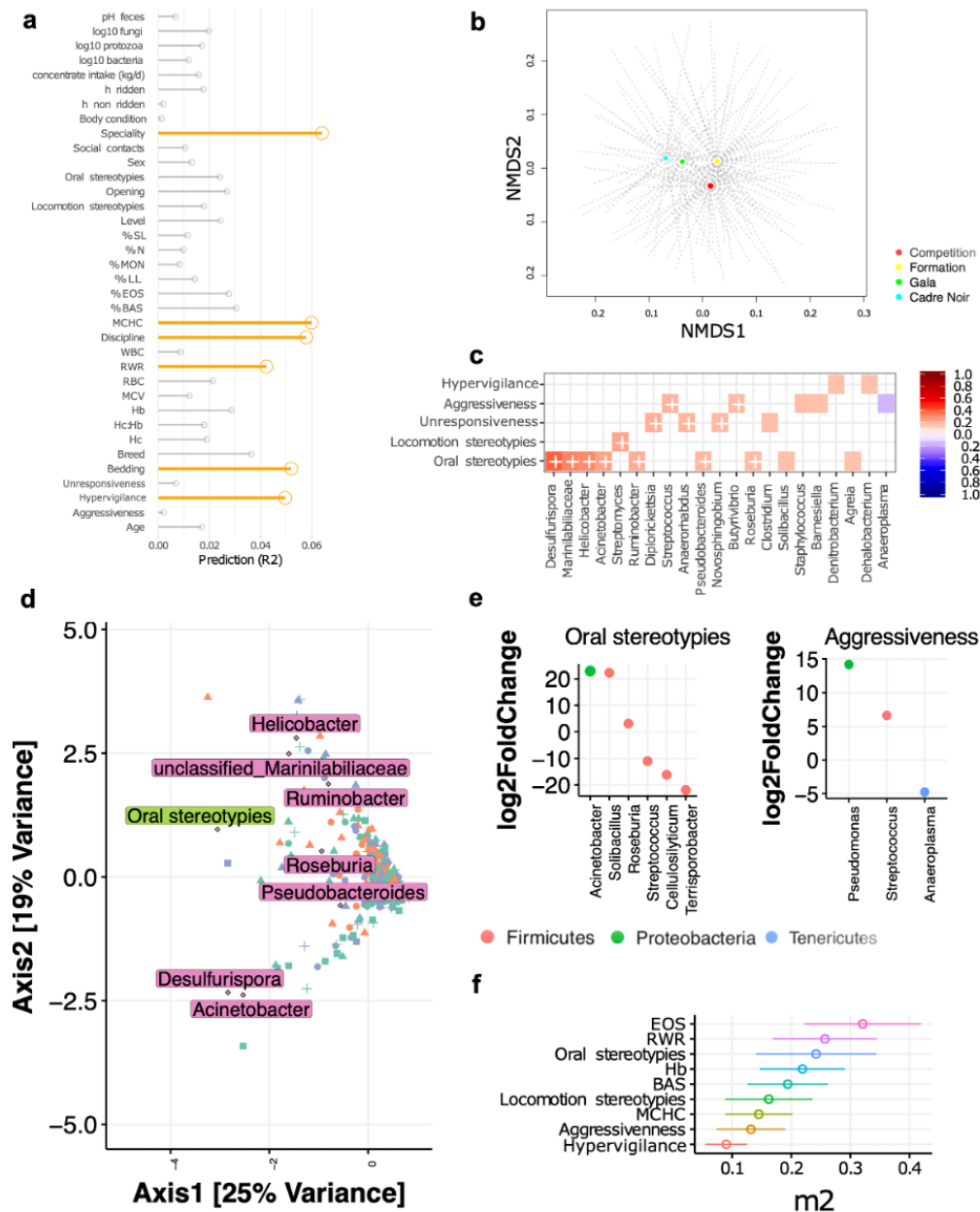


Figure 2 - Associations between gut microbiota, host and environmental covariables

(a) Effect size of covariates of faecal microbiota composition. Each bar shows the fraction of microbial variation explained in the model; (b) Dissimilarities in faecal microbiota composition represented by the non-metric multidimensional scaling (NMDS) ordination plot, with Bray–Curtis dissimilarity index calculated on un-scaled OTU abundances. Samples centroids are coloured by speciality; (c) Cross-correlation matrix between behaviour indicators and genera. Each entry in the heatmap is the correlation coefficient of a particular genus and a behaviour indicator. In the heatmap, red = positive correlation values, and blue = negative correlation values. Colour intensity is proportional to the correlation coefficients. On the right side of the correlogram, the legend colour shows the correlation coefficients and the corresponding colours. Correlations with adjusted $p < 0.05$ are considered significant. In these cases, white crosses are added in the corresponding cell. The correlations with $p > 0.10$ are left blank in the matrix; (d) Canonical Correspondence Analysis (CCA) ordination plot of genus table, and results of the analysis of host factors affecting bacterial divergence. Significant host variables are indicated as rectangles, and genera associated with the corresponding significant variable are depicted in diamonds with text labels. Points, triangles, squares and crosses represent the speciality, whereas the features' colour represents the discipline; (e) Dot plot representations of the log-transformed fold change of genera that were significantly different between horses expressing oral stereotypies or aggressiveness. In both graphs, the logs of fold changes superior to 0 indicate that genera were more abundant in individuals expressing the behaviour indicator than individuals not showing the

behaviour at any time of the experiment. By contrast, the logs of fold changes inferior to 0 indicate that the genera abundances were lower in individuals expressing the behaviour indicator. Dots are coloured by phyla; (f) Microbiability estimates. Each microbiability estimate is defined as a percentage of the phenotypic variance followed by its standard error (Mach et al., 2020³¹; <https://hal.inrae.fr/hal-03197220>, OA).

Additionally, H₂S, a gasotransmitter that protects the central nervous system⁸¹, has been shown to mitigate chronic restraint stress-induced depression in rats. A synergistic effect could exist between butyrate- and H₂S-producing bacteria, conferring to the host adaptive responses to reverse or counteract the potentially negative impact of oral stereotypies. This could include the bloom of potential pathobionts such as *Helicobacter* (which is known to be directly affected by norepinephrine secretion⁸²) and modifications in the environmental characteristics of the intestinal milieu through the autonomic nervous system (*e.g.*, gut motility, intestinal transit and secretion, gut permeability and hormone secretion; Figure 2cd). In addition, the oral stereotypies indicator was moderately predictable from gut microbiota composition, with a microbiability (m^2) of $\sim 25\%$ (Figure 2f). The m^2 , by analogy with genetic heritability, quantifies the overall proportion of host phenotypic variance explained by the microbial community after accounting for breed, discipline and host genetics. Thus, results suggest that intestinal microbiota could be considered an essential metabolic organ with significant relevance to horse behaviour.

Interestingly, two lactate-producing bacteria correlated to aggressiveness, specifically, *Streptococcus* and *Butyrivibrio* genera (Figure 2c). Impairment of the lactic acid metabolic pathway has been associated with the overgrowth of lactic acid-tolerant bacteria and aggressive behaviour in rats⁸³ and acidosis in ruminants⁸⁴. All these associations were more prevalent in horses trained for dressage and jumping (Gala events and Cadre Noir shows), likely because of the degree of the physical and mental stress during training and show events, as well as the focus of being transported to more international competitions, trained many hours per day, five days per week, without taking time off from intense training.

At that point, however, we asked ourselves whether the association between microbiota and horse disciplines was a genetic effect. Europe has a long history of breeding horses for various fields, such as dressage, eventing and show jumping. Even if the influence of genetics on gut microbiota composition is likely low (2-8% heritability⁸⁵) compared to lifestyle factors such as diet⁸⁶ or stochastic factors, it may participate in building diverse profiles of gut microbiota⁸⁷. Breed-specific abundances of specific taxa have been reported in chickens⁸⁸, ruminants⁸⁹, and horses⁹⁰⁻⁹². Those horse-reported studies suggested the weak influence of breed on the intestinal microbiota, but, in all cases, the effect of the horse breed on the gut microbiota composition was confounded by environmental factors such as nutrition, management, breeding selection proposes, housing and geography. Therefore, the extent to which the host breed modulates the equine microbial composition remained unknown, especially among European horse breeds. We, hence, assessed in our cohort of horses reared in equal environments if breed could affect the faecal microbiota. To do so, I trained Francesca Massacci, a PhD student (2017-2020) supervised by Dr Trevisi (University of Bologna, Italy) and Dr Claire Rogel-Gaillard (GABI, INRAE, Université Paris-Saclay). Despite a notable variation in the

diversity and composition of the gut microbiota, breed exerted limited effects on the equine gut microbiota (article 2 Massacci et al., 2020⁹³; <https://dx.doi.org/10.1111/jbg.12441>, <https://hal.inrae.fr/hal-02624117>).

While the breed was not influencing the microbiota composition, so did the type of bedding (Figure 2a). Horses housed in stalls on straw bedding were clustered apart from those housed in stalls on shavings and wood pellets. The interaction between gut microbiota and bedding material could be due to the higher fibre intake of animals housed on straw bedding. In line with this, a recent study in pigs suggested that chopped straw bedding enriches the diet with non-soluble polysaccharides and seemingly positively selects for the members of Bacteroidetes and Fibrobacteres⁹⁴. Straw bedding has been proposed to reduce aggressiveness in horses as it facilitates lying down, exploration, and increased time during which the horse is occupied with feeding compared to those housed in boxes on shavings or wood pellets⁴⁸.

Our results suggest that brain function and behaviour are influenced by gut microbiota. However, future studies must determine how gut microbiota interact with the host, that is, through immune, neuroendocrine or neural pathways. We caution against the need to precisely evaluate how the gut microbiota or even their metabolites interact directly with stress hormones in peripheral tissues, such as the mucosal layer of the gastrointestinal tract of equine athletes. Metabolite profile coupled with shotgun metagenomics or metatranscriptomics could be an increasingly practical way to survey microbial community gene function and regulation at scale. A first step should determine whether microbiota SCFAs travel via the bloodstream to the brain and affect behaviour.

This exciting new data urge the application of drastic changes in horse athletes' living and management conditions. Modifications of the gut microbiota using antimicrobials, probiotics and prebiotics, or other dietary interventions, could be a means to improve welfare. However, we urge the need to give space to the horses and social contact with conspecifics to preserve the welfare and health of horse athletes. We recommend keeping horses in straw bedding instead of shavings or wood pellets. Boxes remain the primary housing system for sports horses in the field, and the horse industry is reluctant to change it. We know this is against practicality, safety, and comfort issues for caretakers and animals. However, our data indicate that elite athletes present behaviour troubles with alterations in gut-microbial composition substantially affecting central physiology (Figure 3).

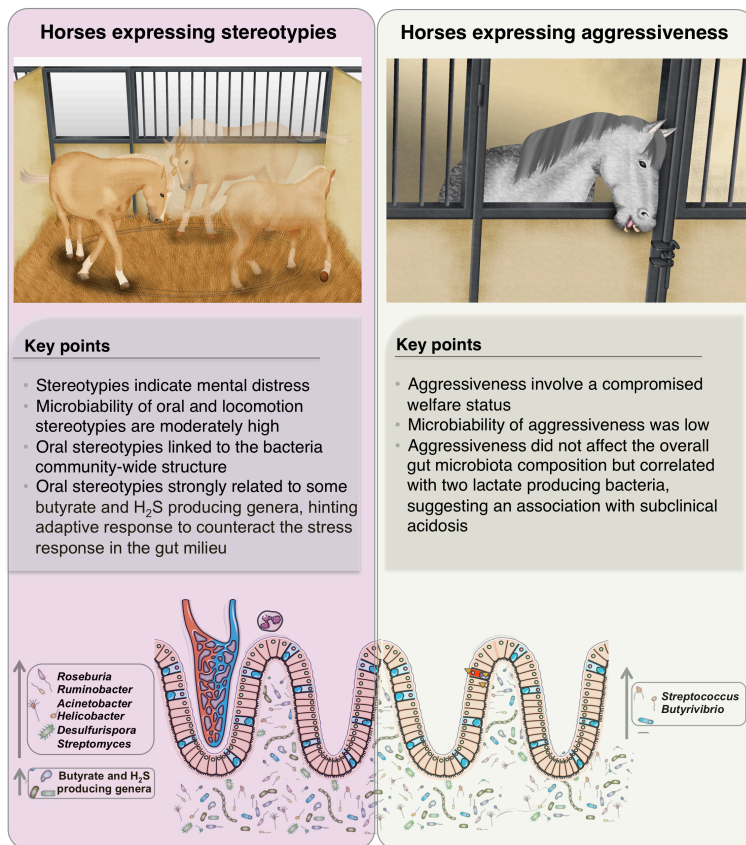


Figure 3 - Behaviour indicators are related to gut microbiota composition

We show that behaviours reflecting welfare deterioration, such as stereotypes and aggressiveness, are associated with the gut microbiota composition.

On the one hand, oral stereotypes were significantly linked to the overall gut microbiota structure and single taxa. Oral stereotypes might presumably alter the central nervous system, stress hormone release and feed intake behaviour, modifying the gut milieu and the microbiota composition. Butyrate and H₂S-producing bacteria might give the host an adaptive response to reverse the potential adverse effects of oral stereotypes. Reinforcing this idea, the microbiability of stereotypes was moderately high, suggesting that gut microbiota might be considered an essential metabolic organ relevant to horse behaviour (Mach et al., 2020³¹; <https://hal.inrae.fr/hal-03197220>, OA).

Based on these gut microbiota-behaviour results (detailed in [article 1](https://hal.inrae.fr/hal-03197220); Mach et al. 2020³¹; <https://hal.inrae.fr/hal-03197220>), with Léa Lansade and Marie-Pierre Moisan, we decided to design a follow-up approach to understand the gut-brain axis further. In 2019, we developed a second project funded by the IFCE and Fond Éperon. Based on the same cohort of individuals in the Cadre Noir, we assessed if a temporary period out to pasture with conspecifics could theoretically satisfy these species' needs and thus restore an optimal welfare state and a “healthier” intestinal microbiota. Alice Ruet, our PhD student, monitored 27 athletes before and after 1.5 months out to pasture. Their faecal microbiota and behaviour profiles were compared to those of 18 horses kept in individual boxes.

Within this project, David Bars, a PhD student co-supervised by Dr Motilva and Dr Piñol from the University of Lleida (Spain), obtained a Spanish national grant to join me for three months and learn about metagenomic data analysis. After his thesis defence, he was contracted in my team as a postdoc for almost one year (2020). The experience in my lab provided the skills needed to obtain another post-doc in metagenomics at the Bellvitge Biomedical Research Institute -IDIBELL (Barcelona, Spain). Unexpectedly, we observed that the overall diversity and microbiota composition were temporally similar (Figure 4a). Holidays in the pasture did not modify them, suggesting resilience to environmental challenges. Pasture exposure only increased the Clostridiales Ruminococcus and Coprococcus, but they only lasted 1-month after returning to individual boxes (Figure 4b-f). Unfortunately, these results evoke the dark side of microbiota resilience. Chronic stress induces the establishment of gut microbiota with a high resilience potential and,

therefore, resistance to changes. This can be a significant obstacle to effective dietary and management interventions. Furthermore, pasture not only did not improve the microbiota composition, but individuals expressed a substantial occurrence of stereotypies, periods of withdrawn posture, and spells of hypervigilance during the first five days after the return to the box compared to the control horses ([article 3; Mach et al., 2021](#)³²; <https://hal.inrae.fr/hal-03197215>, [OA](#))

Furthermore, the pasture horses tended to express more alert postures than the control group up to three months after the return to the individual boxes. Thus, short exposure to pasture in chronically stressed individuals is not associated with a fitness improvement of the gut microbiota and does not contribute to host health and welfare. Therefore, our findings suggested that repeated management practices maintained over an extended period (more than 1.5 months) are required to moderate the gut ecosystem beyond its resilience potential (Figure 4; Results are further detailed in [article 3; Mach et al., 2021](#)³²; <https://dx.doi.org/10.1038/s41598-021-84497-y>, <https://hal.inrae.fr/hal-03197215>, [OA](#)). As stated above, to preserve the welfare and health of horses, we strongly recommend that the owners and riders allow for free exercise, interactions with conspecifics, and fibre consumption as often as possible to ensure the satisfaction of the species' behavioural and physiological needs. We insist that repeated exposures to pasture with other horses may be required to provide a welfare improvement and a bloom of butyrate-producing Clostridiales such as *Ruminococcus* and *Coproccoccus*, which in turn, may drive long-lasting positive immune, metabolic and psychological changes in sport horses. Additionally, the number of events should be limited and introduce a certain number of rest days (Results are detailed in [article 3; Mach et al., 2021](#)³²; <https://dx.doi.org/10.1038/s41598-021-84497-y>, <https://hal.inrae.fr/hal-03197215>, [OA](#)).

That said, the potential role of the microbiome in mediating the capacity for holobionts to acclimate and adapt to long-term environmental challenges (e.g., stressors) remains to be further elucidated. More studies are warranted to elucidate different specific mechanisms through which these behaviour troubles and gut microbiota composition contribute to the risk for health disorders from early to late in life. Our first study already delineated early life stress and their ties might affect the horse's psychological and behavioural development and gut microbiota ([article 4; Mach et al., 2017](#)³³; <https://dx.doi.org/10.3389/fphys.2017.00535>, <https://hal.inrae.fr/hal-01578843>, [OA](#)). Early life stress can persistently and permanently impact the gut-brain axis. In 2017, together with Léa Lansade and Marie-Pierre Moisan, we demonstrated that weaning is a stressful event in the life of horses, regardless of the weaning method (progressive or abrupt). Maternal separation shaped gut microbiota during the first days in a manner that correlated with alterations in host phenotypes (e.g., salivary cortisol, telomere lengths, parasite egg counts and body weight). We showed that the less stressed individuals after maternal separation (lower cortisol levels in saliva) presented higher telomere length and n-butyrate producers in the gut and more significant average daily gain. Therefore, bacterial communities enriched with n-butyrate producers likely confer better stress response adaptation following weaning. Butyrate might influence several physiological processes, such as cell signalling, neurotransmitter synthesis and release, mitochondrial function and oxidative stress (reviewed by Clark and Mach, 2017¹⁸). Although other

factors undoubtedly contribute to telomere length, it might be suggested that butyrate-producing bacteria protect from telomere damage. This later protection may be attributable to the influence of n-butyrate on the cyclooxygenase 2 (*COX-2*) activity, which detoxifies and reduces H_2O_2 and reactive oxygen species levels⁹⁵.

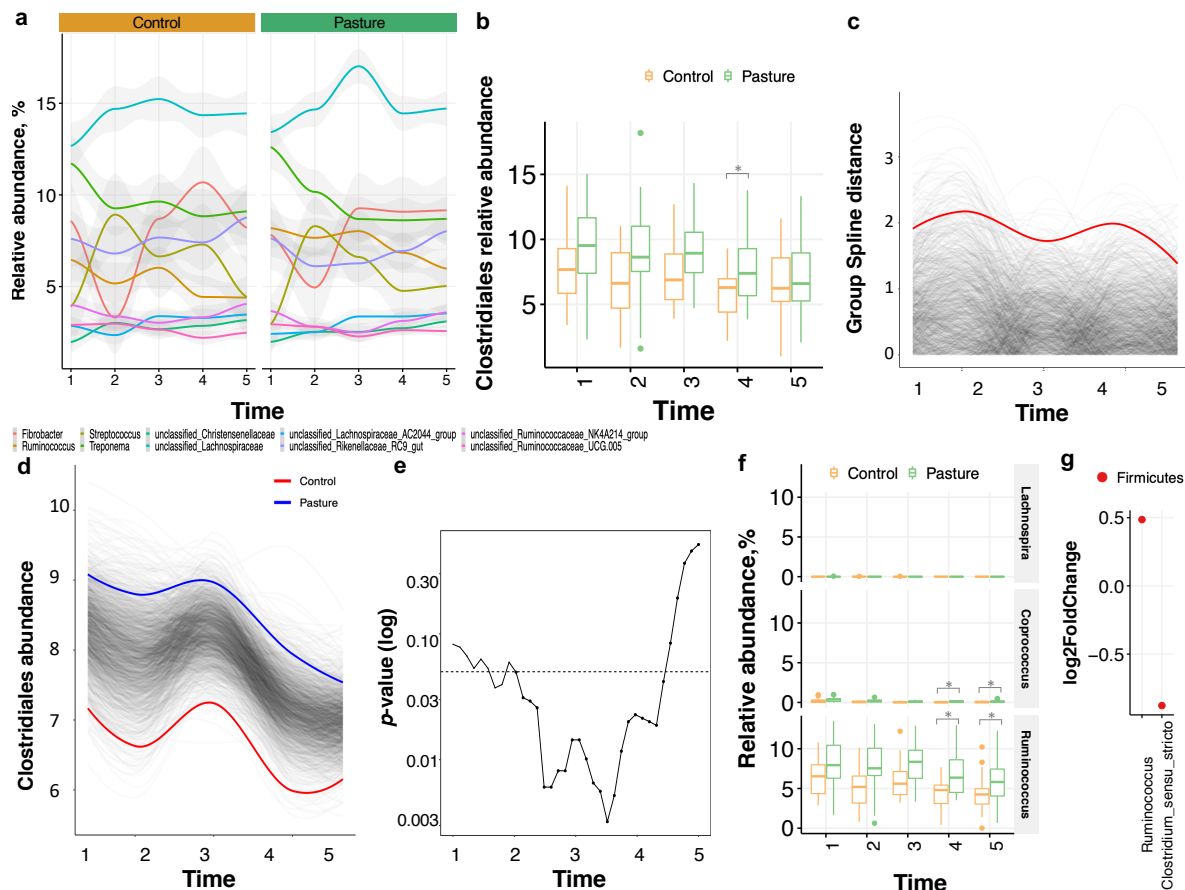


Figure 4 - Longitudinal faecal microbiota composition differences between groups

(a) The longitudinal variation of the ten most abundant genera in the horse faecal microbiota between groups. The graph shows the relative abundance (y-axis) of the most common bacterial genera over time (x-axis), averaged across control and pasture groups; (b) Box plot representation of the relative abundance of Clostridiales between groups and across time. The box plots feature the median (centre line) and interquartile range, and whiskers indicate the 5th to 95th percentile; (c) Permuted spline tests for statistical significance using the entire 21-month time series. Group distance plot for the Clostridiales comparison. The graph shows that permuted splines support a trend toward a more significant actual statistical difference after T3. The observed difference between the groups exceeded the random permuted distribution, which supports the statistically significant finding ($p < 0.05$); (d) Clostridiales abundance was different between pasture group (group spline in red) and control horses (group spline in blue; 9999 permutations, < 0.05); (e) The plot output of the sliding spline function shows a window of significance between the T3 and T4 time points. The p-value at each specified interval is derived from the distribution of points from individuals' smoothed splines. The dotted line indicates $p = 0.05$; (f) Box plot represents the relative abundance of the single taxa included within Clostridiales between groups and across time. The box plots feature the median (centre line) and interquartile range, and whiskers indicate the 5th to 95th percentile. Asterisk indicates $p < 0.05$; (g) Dot plot representation of log-transformed fold change of genera that significantly differed between pasture and control across time using DESeq2. The log of fold changes superior to 0 indicates that genera were more abundant in pasture individuals than control individuals at any time of the experiment. By contrast, the log of fold changes inferior to 0 indicates that the genera abundances were lower in pasture relative to control individuals.

Altogether, our translational research on the microbiota-gut-brain axis has produced meaningful and applicable results that directly benefit horse health and welfare. Horse

sport is essential to society in terms of spectator enjoyment, human mental and physical health benefits, and economic impact. However, our studies demonstrate that elite sports inevitably expose horses to psychological and physical harm that has consequences for the holobiont. Future studies should aim to identify the mechanisms underlying holobiont dynamics under multiple stressors and their long-term, lasting effects and develop management strategies to preserve the critical functions provided by microbiota in the gastrointestinal tract of horses. Nevertheless, I finish this chapter knowing that these pieces of work help to settle up an ethical framework for using animals across equestrian sports while reducing the welfare detriment and refining their riding, training techniques, management, and relationship with the horse.

3



T H E H O R S E W I N N I N G G U T

The work described in this chapter represents the core of my research topic at the Equine Integrative Biology and Genetics team (BIGE) at INRAE. During this exciting episode, I mentored Allison Clark, a brilliant Master's student from the Open University of Catalonia with whom I have published lovely pieces of work ^{17-19,28,30,31,34,93,96}. By owing, not doing, she made a great transition from a Master's to a PhD student at the University Hospital Vall d'Hebron (Barcelona, Spain), one of the leading research centres in gut microbiota in human health and disease. I also enrolled Jesus M^a López and Dolors Fuster-Botella, two other Master's students from the Open University of Catalonia. Alizée Nevot came on board to perform her veterinarian medicine thesis, under the title: “*Prédiction des status métabolique et de Santé de chevaux d’endurance via l’intégration de données “omiques”: vers l’identification de biomarqueurs*” (2016).

This mentoring adventure with my students is reflected as follows:

1. **Núria Mach** (Corresponding author), **Dolors Fuster-Botella** (2017). Endurance exercise and gut microbiota: a systematic review. *Journal of Sport and Health Science*, 6 (2), 179-197, <https://dx.doi.org/10.1016/j.jshs.2016.05.001>, <https://hal.inrae.fr/hal-02620229>, OA
2. [Review] **Allison Clark, Núria Mach** (Corresponding author) (2017). The Crosstalk between the Gut Microbiota and Mitochondria during Exercise. *Frontiers in Physiology*, 8, 1-17, <https://dx.doi.org/10.3389/fphys.2017.00319>, <https://hal.inrae.fr/hal-01604194>, OA
3. [Research article] **Núria Mach** (Corresponding author), Yulixaxis Ramayo Caldas, Allison Clark, Marco Moroldo, Céline Robert, Eric Barrey, **Jesús Maria López**, Laurence Le Moyec (2017). Understanding the response to endurance exercise using a systems biology approach: combining blood metabolomics, transcriptomics, and miRNomics in horses. *BMC Genomics*, 18 (1), 1-17, <https://dx.doi.org/10.1186/s12864-017-3571-3>, <https://hal.inrae.fr/hal-01602618>, OA
4. [Research article] **Núria Mach**, (Corresponding author) Sandra Plancade, Alicja Pacholewska, Jérôme J. Lecardonnell, Julie Riviere, Marco Moroldo, Anne Vaiman, Caroline Morgenthaler, Marine Beinat, **Alizée Nevot**, Céline Robert, Eric Barrey (2016). Integrated mRNA and miRNA expression profiling in blood reveal candidate biomarkers associated with endurance exercise in the horse. *Scientific Reports*, 6, 22932, <https://dx.doi.org/10.1038/srep22932>, <https://hal.inrae.fr/hal-02489989>, OA
5. [Review] **Allison Clark, Núria Mach** (Corresponding author) (2016). Exercise-induced stress behaviour, gut-microbiota-brain axis and diet: a systematic review for athletes. *Journal of the International Society of Sports Nutrition*, 13, 1-21, <https://dx.doi.org/10.1186/s12970-016-0155-6>, <https://hal.inrae.fr/hal-01606853>, OA

Endurance exercise can be defined as cardiovascular exercise —such as running, cross-country skiing, cycling, aerobic exercise or swimming— performed for an extended period ¹⁶. The physiological and biochemical demands of endurance exercise elicit muscle-based and systemic responses. Endurance athletes expose their bodies to extreme physiological circumstances that disrupt the inner body's homeostasis, overwhelming organs and the system's normal function ¹⁶. Physical exertion at a very high level for a prolonged time means that the whole body initiates a defence response through synthesising acute phase proteins, hormone release and shifts in fluid and metabolic balance ¹⁶. The central adaptations to endurance exercise include improving mechanical, metabolic, neuromuscular and contractile functions in muscle, a rebalance of electrolytes, a decrease in glycogen storage and an increase in mitochondrial biogenesis in muscle tissue ¹⁶. Furthermore, endurance exercise profoundly impacts oxidative stress, intestinal permeability, muscle damage, systemic inflammation and immune responses (see review by Mach and Fuster-Botella, 2017 ¹⁶).

Through years of selective breeding for athletic performance and tailored training practices, Arabian horses have gained built-in biological mechanisms to compete in endurance races (distances of up to 160 km in a single day), an effort comparable to a human marathon or ultra-marathon ²⁹. Endurance racing is a test of stamina, discipline, fitness and patience and has been traditionally known as the ultimate challenge in equestrian sports. The ability to run for such long distances at high speed is an uncommon feat for land mammals. Undoubtedly, endurance exercise performance entails complex multifactorial processes that are still not fully understood, including prolonged cardiovascular capacity, optimised energetic ability and withstanding physiological fatigue and stress that disrupts the body's homeostasis.

The cost of breeding and training endurance horses is very high, requiring a lot of time and effort. In this discipline, competitions start late (at around six years) and often finish early (withdrawal from competition at about 12 years of age, even though some individuals can race until 16). Arising from these concerns, Dr Eric Barrey, the leader of my team (Jouy en Josas, INRAE) and Prof. Céline Robert from the National Veterinary School – Maison-Alfort (ENVA) created the GenEndurance project (2011-2016; endowed with more than 700 K) to predict the capacity of a young endurance horse to win a race, combining phenotypic and genotypic data. The final goal was to find the physical and genetic characteristics early in the age that could give them an edge over other participants in the race. In other words, is the horse athlete's fate in his genome? Could we apply genetic tests early in age to predict athletic potential? To achieve this objective, they collected a vast amount of omic data to estimate the nuclear and mitochondria genetic variability, the metabolomic, transcriptomic and microtranscriptomic profiles, and parameters related to race performance.

At the end of 2013, when I got a permanent researcher position and landed within Eric Barrey's team, he asked me to analyse these different types of omics data and come out with translating results. I started by looking at transcriptomic, microtranscriptomic and metabolomic data from various perspectives and trying different ways of integrating them. I stumbled upon connections that others were unaware of when the project started, and beyond their genetic allotment, I showed how their metabolism work to adapt to intensive exercise. To begin with, I could provide a comprehensive overview of

the microRNA-mRNA co-regulation networks that may have a crucial role in controlling post-transcriptomic regulation during endurance exercise in horses. I found miR-21-5p, miR-181b-5p and miR-505-5p to be candidate regulatory molecules for the adaptation to endurance exercise in the horse (Mach et al., 2016; <https://dx.doi.org/10.1038/srep22932>, <https://hal.inrae.fr/hal-02489989>, OA). This work was performed as part of the veterinarian thesis of Alizée Nevot (2016), whom I supervised.

Then, I integrated the blood metabolome profiles on top of the mRNA-miRNA networks. Jesús M^a López, an M2 at the Open University of Catalonia, was enrolled in this topic. Remarkably, the “omic” integration of molecular data in our study predicted some functional links between metabolites and the transcriptome that could not be characterised by analysing separately any of the three individual data sets, namely: (i) a reduction of glucose concentration and inhibition of FoxO signalling, which up-regulate genes involved in gluconeogenesis, lipid metabolism and ketone body production and utilisation, and activation of miR-21-5p expression; (ii) increased oxidative phosphorylation in the mitochondria to compensate for ATP production; and (iii) increased concentration of acetate, which subsequently induced AMPK. Additionally, we found several associations within our regulatory network, which have not been fully described to the best of our knowledge. For example, the results suggested that an elevated respiration rate during endurance exercise may have led to more ROS than the antioxidant systems can scavenge (Mach et al., 2017; <https://hal.inrae.fr/hal-01602618>, OA).

Athletic performance was too complex to narrow down to genetic determinism. Beyond host genetics and genomics, there were likely some other attributes that make horses better for running than others. So tightly intertwined was the microbiome with the molecular choreography of endurance exercise that I started hypothesising that the symbiosis between the host and gut microbiome could impact horse physiology and athletic performance. More than 100 trillion bacteria inhabit a horse's intestinal tract. The gut microbiota provides the host with nutrients, induces host immune development and metabolism, and protects the host against invading pathogens, including parasites^{31,34}. These microorganisms are their life companions, and their arrangements and functions are essential for their health and welfare. With that in mind, at the end of 2014, I got the opportunity to begin my independent research program to entangle the effects of intestinal ecosystems under biotic and abiotic stressors on horse health, welfare and athletic performance. I started with an “EcaOmic” project funded by the Animal Genetic department at INRAE, with an initial endowment of 20,000 €.

Although the gut microbiome has been implicated in numerous aspects of health and disease, links with athletic performance were less evident. However, interest was growing, helped by advances over the past decade that enabled us to identify which microorganisms the gut harbours and what they do. I wanted to establish the enormous diversity of organisms that make up an athlete's gut microbiota – each as unique as a fingerprint – and how they converge on essential functions for the host athletic performance. In other words, I sought to glimpse a relationship between exercise and the gut microbiome and potential mechanisms. Covered by my passion for science, perseverance, hard work and lifelong learning, this project has given high achievements to the horse community.

Notably, the Equine Integrative Biology and Genetics team and the Animal Genetics and Integrative Biology (GABI) unit at INRAE integrated this emerging topic with great interest. However, I then faced one of the most challenging parts of the project: obtaining samples from elite athletes in actual endurance races. Getting this kind of field-based research to work effectively takes time and effort. In the field, the logistics of convincing the riders and owners to participate in scientific studies and the complexity of sampling and metadata compilation are not accessible. Why? First, many potential volunteers decline to participate because they are worried about mechanical phlebitis or chemical phlebitis after blood sampling. Second, some other potential volunteers are afraid about the type of analysis performed on blood. The risk of doping in horse sports has been recognised for almost 15 years. To solve this, in September 2014, I created a team of more than ten technicians and scientists who travelled with me in the field. Managing this kind of collaboration was complex and required cooperation amongst different work cultures and disciplines. It was a success!

A total of 52 endurance horses were recruited in a volunteer base that competed in long-distance races (90km, 120km or 160km). Faecal samples were collected with time-matched blood and questionnaire data (with emphasis on estimated nutrient consumption and athletic performance). Faecal samples were obtained before the race to profile the gut microbiome, the SCFA concentration and pH. Faecal samples were also used to describe other gut microbial populations (*e.g.*, anaerobic fungi and ciliate protozoa). Blood samples obtained before and after the endurance race were used to profile the metabolome, the nucleus and mitochondrial transcriptome, biochemical parameters, and telomere length. We investigated metabolomics using the untargeted broad-window nuclear magnetic resonance (NMR). Encompassing an equilibrated range of age, sex, genetic background and environmental factors, our cohort was expected to represent the average endurance horse population. Today, this cohort is considered a precious data set to be exploited from different perspectives. For that reason, we made samples and all produced data publicly available. Samples are stocked at the biological facility at INRAE (@BRIDGE, Jouy en Josas: <http://abridge.inra.fr/index.php?lang=en>), while raw data and codes are available at NCBI and the INRAE data repository.

In the face of this amount of phenomics data and its heterogeneity, I decided to apply a bottom-up approach, piecing together a single type of data to give rise to a more complex holistic view. Thus, we first detailed the gut microbiota composition of our 52 athletes through the 16S rRNA marker-gene sequencing. This technique enables us to characterise microbiome composition at a low cost rapidly. The variation in the gut microbiota composition in equine endurance athletes still needed to be determined. Indeed, it still needed to be determined whether inter-individual variation results from a continuum of different bacterial compositions or whether individual gut microbiota gathers around stable communities that could be associated with athletic performance. These descriptive analyses revealed the existence of two gut microbial communities, mainly driven by diet, as host properties showed little effect (Figure 1 a,b; [article 5; Plancade et al., 2019; https://hal.inrae.fr/hal-02489982, OA](#)).

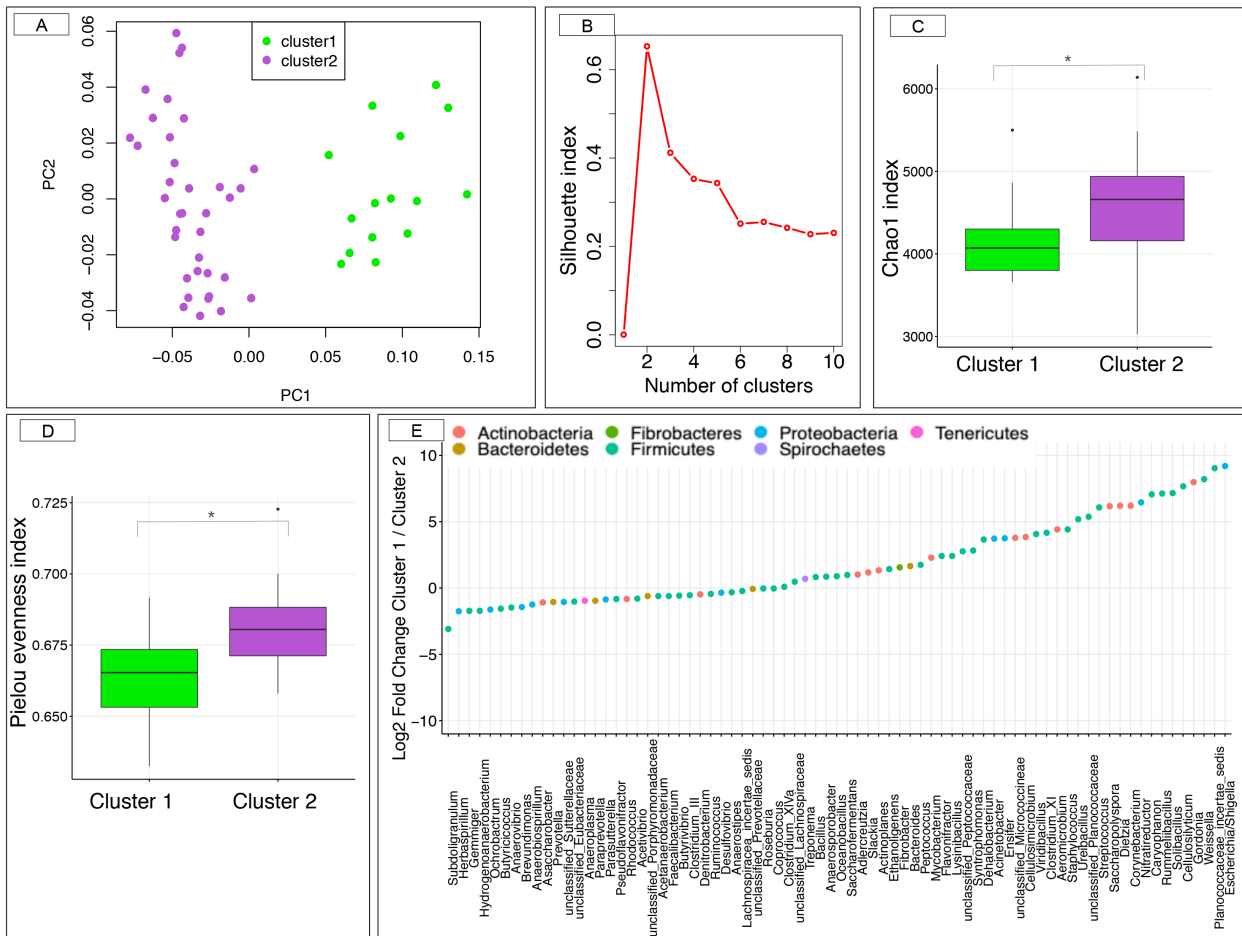


Figure 1 - Estimating the α - and β -diversity within the study cohort.

(a) Principal coordinate analysis (PCoA) with weighted UniFrac distance based on the OTUs table. Colour corresponds to the gut microbiota community types based on the medoids (PAM) algorithm. The first community contained 15 individuals, whereas the second included 36 individuals. (b) The number and quality of clusters were validated by maximising the silhouette index; (c) Box plot graph representation of the α -diversity indexes (Chao1) using the rarefied OTU table for each community type; (d) Box plot graph representation of Pielou's evenness index using the rarefied OTU table for each community type; (e) Dot plot representation of log-transformed fold change of genera that were significantly different between the community type 1 and type 2. Dot colours represent the different phyla.

Microbiota community one was observed in horses with lower forage and energy intakes but a higher proportion of faecal acetate, plasmatic choline-containing phospholipids, the most abundant lipids within the cell membrane, and pathways involved in lipid metabolism. The modulation of the host energy metabolism was also reflected by the relationship between the type one community and blood alanine concentration, whose metabolism is involved in the glycolysis pathway. Moreover, community type-1 was lined to a higher abundance of branched-chain amino acids in the blood, which can be converted into a complex mixture of metabolic end products, including ammonia and SCFA. Conversely, community two was related to higher richness and microbial diversity (Figure 1c-e), higher loads of anaerobic fungi, higher proportions of propionate and butyrate and enrichment of predicted carbohydrate metabolism and inflammation pathways. The higher *n*-butyrate concentration could have ameliorated mucosal inflammation and oxidative status⁹⁷, common occurrences among athletes as body

temperature increases and blood pools away from the gastrointestinal tract to periphery muscles and organs such as the heart and lungs during intense physical activity (reviewed by Clark and Mach, 2016¹⁹). However, this higher butyrate proportion in community two was not associated with protective effects on telomere lengths (Results are detailed in article 5; Plancade et al., 2019; <https://hal.inrae.fr/hal-02489982>, OA).

We then sought to explore the metabolomic profile of our athletes better. Prof. Laurence Le Moyec, a metabolomic expert from the "Muséum National Histoire Naturelle" in Paris, assessed the adaptive metabolism response to endurance exercise in detail. Given that energy metabolism is closely related to the intensity and duration of training (and therefore the race distance), the primary objective of the investigation was to determine the plasma metabolic profile shift after three different racing distances (90, 120, and 160 km). The model revealed that in the highest race category (160 km), there appeared to be a metabolic switch from carbohydrate consumption to lipid consumption to maintain glycaemia (Le Moyec et al., 2019; <https://hal.inrae.fr/hal-02409471>, OA).

Arising from these interesting metabolomic results, I contacted Prof. Vinzenz Gerber from the Swiss Institute of Equine Medicine in Switzerland. He is an expert in contextualising mitochondrial β -oxidation during exercise. Mitochondrial β -oxidation is essential in fat metabolism and can be monitored with acylcarnitine profiling in blood as partly degraded fatty acids accumulate as carnitine esters. Electrospray tandem mass spectrometry was used to determine the serum acylcarnitine profiles of the ten horses in our cohort before and after finishing a 160 km endurance race. Confirming our metabolomic profile results, endurance exercise significantly increased mitochondrial β -oxidation by eight times, associated with 17 times increased lipolysis (Van der Kolk et al., 2020; <https://hal.inrae.fr/hal-03356899>).

Putting these pieces of work together with Allison Clark, my M2 student, we postulated that gut microbial metabolites could enhance performance by regulating mitochondrial biogenesis and function. Gut microbiota and their byproducts (*e.g.*, acetate, valerate, dimethyl sulfone, trimethylamine oxide, formate) could influence energy production in the mitochondria, mitochondrial biogenesis, but also redox balance, inflammation and intestinal barrier function in different types of cells (Figure 2; article 6; Clark & Mach, 2017; <https://hal.inrae.fr/hal-01604194>, OA). This review showed recent evidence of bidirectional interaction between mitochondria and gut microbiota. The gut microbiota has been shown to regulate critical transcriptional co-activators, transcription factors and enzymes involved in mitochondrial biogenesis, such as *PGC-1 α* , *SIRT1*, and *AMPK* genes. Furthermore, the gut microbiota and its metabolites also contribute to host energy production, reactive oxygen species (ROS) modulation and inflammation in the gut by attenuating TNF α -mediated immune responses and inflammasomes such as *NLRP3* (Figure 2).

On the other hand, mitochondria ROS production has a crucial role in regulating the gut microbiota via modulating intestinal barrier function and mucosal immune responses. Recently, it has also been shown that genetic variants within the mitochondrial genome could also affect mitochondrial function and intestinal microbiota composition and activity (Figure 2).

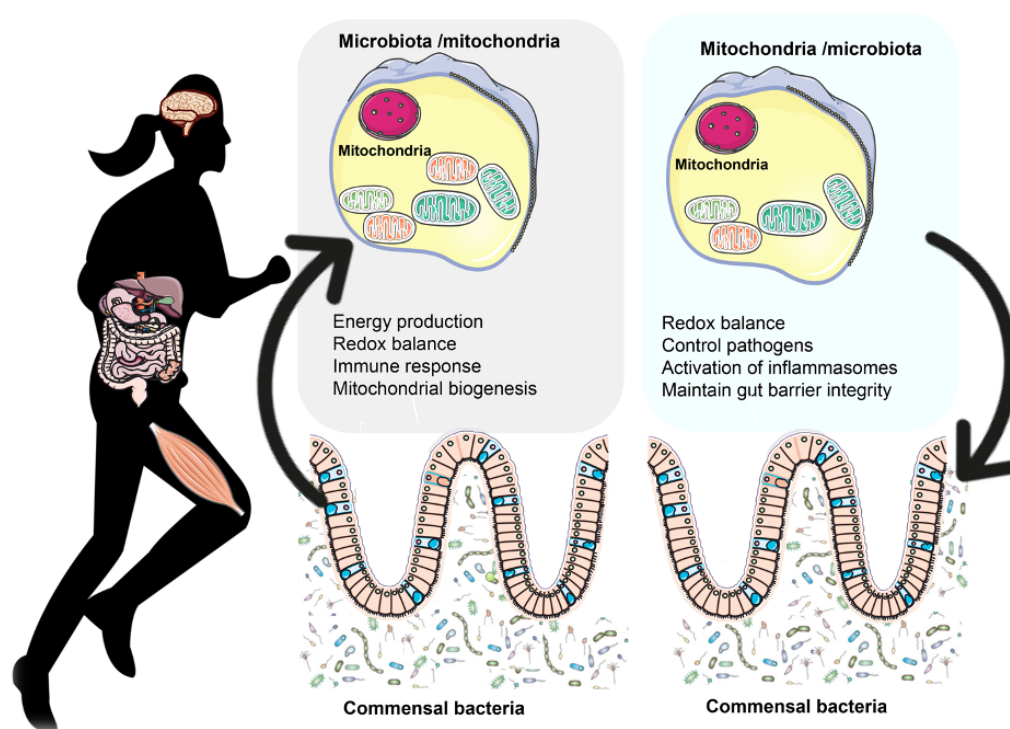


Figure 2 - The bidirectional crosstalk between the gut microbiota and mitochondria.

In the mitochondria of colonocytes, butyrate undergoes fatty acid β -oxidation, producing acetyl-CoA that enters the TCA cycle, resulting in ATP and CO_2 . Among the SCFA, butyrate is a crucial regulator of energy production and mitochondrial function by inducing PGC-1 α gene expression in skeletal muscles and brown adipose tissue and improving respiratory capacity and fatty acid β -oxidation via AMPK-ACC pathway activation. On the other hand, *SIRT1* supports intestinal barrier function through various mechanisms such as enhancing crypt proliferation and suppressing villous apoptosis, stimulating intestinal stem cell expansion in the gut and regulating tight junction expression of zonulin occludin-1, occludin and claudin-1 during hypoxia (article 6; Clark & Mach, 2017; <https://hal.inrae.fr/hal-01604194>, OA).

To understand the crosstalk between mitochondria and gut microbiota in our athlete's cohort, I performed a three-pronged association study, connecting horse gut microbiota with untargeted serum metabolome and transcriptome data in the context of endurance (article 7; Mach et al., 2021; <https://hal.inrae.fr/hal-03197210>, OA). In doing so, we sought to identify how nuclear and mitochondrial transcriptomes coordinate and how gut microbiota and circulating metabolites can dynamically modulate this process. By characterising the whole blood transcriptome, metabolome, faecal microbiota and SCFAs of 20 elite horses of our cohort, we aimed to provide a functional readout of microbial activity and improve our understanding of the gut microbiota-mitochondria axis during prolonged exercise. Intriguingly, a subset of mitochondria-related differentially expressed genes involved in pathways such as energy metabolism, oxidative stress and inflammation was discovered and then shown to be associated with butyrate-producing bacteria of the *Lachnospiraceae* family, especially *Eubacterium*. The mechanisms involved were not fully understood, but the action of their metabolites likely acted on *PPARc*, the *FRX-CREB* axis and their downstream targets to delay the onset of hypoglycemia and inflammation and extend the running time. In agreement, the DIABLO framework from mixOmics⁹⁸ highlighted that the mitochondrial-related genes showed high levels of covariation with

the faecal microbiota ($r^2 > 0.91$, Fig 3a). A more fine-grained view of this biological system was then obtained by focusing on pairwise correlations between variables. The first component of the DIABLO analysis highlighted a significant link between a subset of 45 mitochondrial-related genes (all encoded by the nuclear genome) and four gut taxa (*e.g.*, the genus *Mogibacterium*, the species *Eubacterium coprostanoligenes* and the groups *Rikenellaceae* RC9 and *Ruminococcaceae* NK4A214). A link to blood metabolites related to energy supply (*e.g.*, methyl groups of fatty acids and choline-containing compounds) and metabolites related to the TCA cycle, such as glutamine, glutamate, and α -glucose was also unveiled (Fig 3b,c). Moreover, mitochondrial-related genes co-occurred with pronounced variations of microbiota-derived metabolites, including faecal acetate and valerate, and plasmatic concentrations of TMAO, dimethyl sulfone, and formate. Our results also suggested that circulating free fatty acids may act as fuel and drive mitochondrial inflammatory responses triggered by the translocation of gut bacterial polysaccharides following endurance ([article 7; Mach et al., 2021; https://hal.inrae.fr/hal-03197210, OA](https://hal.inrae.fr/hal-03197210)).

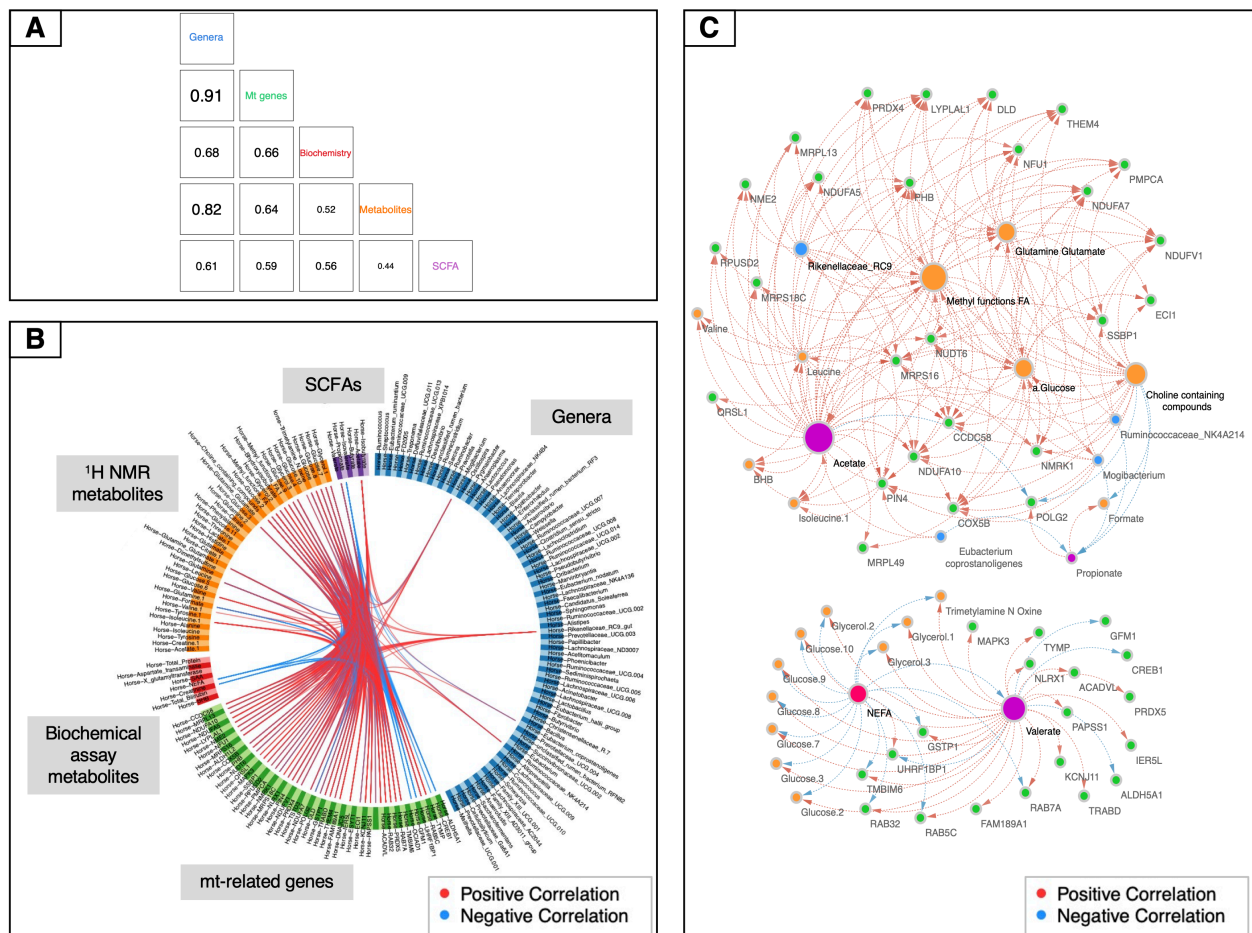


Figure 3 - Data integration using mitochondrial-related genes, ¹H NMR metabolites, biochemical assay metabolites, faecal SCFAs and gut bacteria

(a) Matrix scatterplot showing the correlation between the first components related to each dataset in DIABLO according to the input design; (b) CIRCOS plot of the final multi-omics final signature. Each dataset is given a different colour: green mitochondrial-related genes, ¹H NMR metabolites in orange, biochemical assay metabolites in red, faecal SCFAs in violet and gut bacteria in dark blue. Red and blue lines indicate positive and negative correlations between the two variables, respectively ($r \geq |0.70|$); (c) Visualization of the network obtained with

Cytoscape using the final DIABLO multi-omics signature as an input. Only features with more than 15 connections are shown. The size of the nodes indicates the number of interacting partners within the network (Mach et al., 2021; <https://hal.inrae.fr/hal-03197210>, OA).

Although these recent findings suggest that gut microbial metabolites in endurance horses regulate mitochondrial function by preventing hypoglycemia, which is the limiting factor for fatigue onset and, thus, athletic performance, if and how gut microbiome functions are responsible for better adaptations to resist fatigue and succeed in athletic performances were unresolved, hence, I was fronting up the challenge of sequencing everything in the gut to address this knowledge gap (article 8, Mach et al., 2022; <https://hal.inrae.fr/hal-03794437>, OA). Known as shotgun sequencing, this technique provides more detailed insights than 16S rRNA gene sequencing – microorganisms can be distinguished beyond even their species right down to the strain, and we can more easily characterise their potential functions on the bases of known genes. Whole metagenome shotgun sequencing assures non-amplification bias and unbiased estimation of taxonomic profiles⁹⁸. Based on this metagenomic data, we built an extensive gene catalogue of the gut microbiome in endurance horses of the EcaOmic cohort. This expands the current representation of the equine gut microbiome with more than 25 million non-redundant genes! This microbial gene catalogue has widened 20-fold the number of genera known to reside in the gastrointestinal tract of horses^{31,65,100–103}, uncovering a substantial number of bacteria ($n = 2,927$), archaea ($n = 174$), and Eukaryota ($n = 1,081$). This catalogue also captured a wide array of functions related to complex carbohydrate fermentation and functional capacities that enabled more energy extraction from dietary, microbial, and host resources, which likely provided a performance advantage for athletes (Figure 4a). For example, genes encoding enzymes for glycosidic-bond cleavage (GHs and PLs) represented the majority (67%) of the CAZyme genes, highlighting the indispensable role of gut microorganisms in glycan metabolism (Figure 4b).

Intriguingly, 6.38% of GHs and PLs were involved selectively in cleaving endogenous host-related glycosylated proteins and glycans¹⁰⁴. It is yet unclear whether these CAZymes correspond simply to the peptidoglycan-processing machinery required for bacterial cell growth and division or whether peptidoglycan and highly glycosylated proteins represent a significant carbon source for some bacteria or the host after being transformed to acetate¹⁰⁵. Additionally, we have identified 57 clusters of antimicrobial resistance (AMR) genes representing the major antibiotic classes, including tetracycline ($n = 20$), aminoglycosides ($n = 20$) and macrolides, lincosamides, and streptogramins (MLS, $n = 9$; Figure 4c). The strong representation of Firmicutes and Bacteroidetes-associated tetracyclines resistance genes (*tet(W)*, *tet(Q)*, *tet(O)*, *tet(40)*) and MLS resistance genes (*lnu(C)* and *mef(A)*) mirrored past observations in horses¹⁰⁶ and matched that found in humans¹⁰⁷, and livestock species such as cattle, pig, and chicken^{108–110}. Lastly, we reported a set of 372 MAGs (figure 4d-f). The number of microbial genes and MAGs will likely increase as more samples are analysed, as seen in equids^{101,103} and other livestock gut metagenomes^{111–114}. Nonetheless, the present metagenomic genes and MAGs repertoire are a step forward in explaining the composition and function of the horse gut microbiome, especially in the context of endurance exercise.

Then, each data type was linked to tie together the gut phylotypes with the horse performances until a complete top-level method was formed. The ordination analysis of the dominant microbial phylotypes (Figure 5a) yielded two distinct clusters of samples that recapitulated variation along the first axis (non-metric multidimensional scaling (NMDS), Bray–Curtis distances; Figure 5b). Cluster1 individuals ($n = 3$ horses) exhibited higher α -diversity despite the small sample size (Shannon and inverse Simpson indices; $p = 0.0134$ for both, two-sided Wilcoxon rank-sum test, Figure 5c-d). We then investigated which microbial taxa underpinned each cluster. Cluster 1 mainly included the enrichment of many poorly-characterized taxa ($n = 318$; IQR: $2.90e^{-04}$ - $1.16e^{-04}$; Figure 5e-f) that encompassed Proteobacteria ($n = 132$), Actinobacteria ($n = 49$), Verrucomicrobia ($n = 17$), Planctomycetes ($n = 17$), and Cyanobacteria ($n = 7$). Methanogens previously described in the bovine rumen ^{115,116} - including those belonging to the Methanomicrobiales (*Methanotherix*), Methanobacteriales (*Methanosphaera*, *Methanobacterium*, *Methanothermobacter*), and Thermococcales (*Thermococcus*) orders – were also more abundant in that cluster. In contrast to the overwhelming diversity observed in cluster 1, a dwarfed biodiversity defined cluster 2 that assembled around highly efficient fibre degraders (members from the *Lachnospiraceae* taxa: *Anaerostipes*, *Butyrivibrio*, *Blautia*, *Coproccoccus*, *Dorea*, *Eubacterium*, *Hespellia*, *Lachnospira*, *Oribacterium*, *Roseburia*, and *L-Ruminococcus*) and downstream users of degradation products (*Prevotella*, and *Treponema*) ¹¹⁶. Remarkably, the holo-omics data integration from the host and microbiome domains showed that gut microbiome composition, functions, and mitochondria activity were critical determinants for cardiovascular fitness (Figure 5). Cardiovascular fitness - a composite variable of post-exercise heart rate, cardiac recovery time, and average speed during the race - was the primary driver of the overall structural variation of the gut metagenome (*envfit*, $R^2 = 0.9192$, adjusted $p = 0.005$). This cardiovascular composite parameter aggregated 39.64% of faecal microbiome community variation (Figure 5g-h). Horses from cluster 1 had significantly higher cardiovascular fitness than cluster 2 members ($p = 0.048$, two-sided Wilcoxon rank-sum test, Figure 5i). That did not increase blood lactate concentration ($p = 0.921$, two-sided Wilcoxon rank-sum test), a proxy for glycolytic stress and disturbance in cellular homeostasis ¹¹⁷.

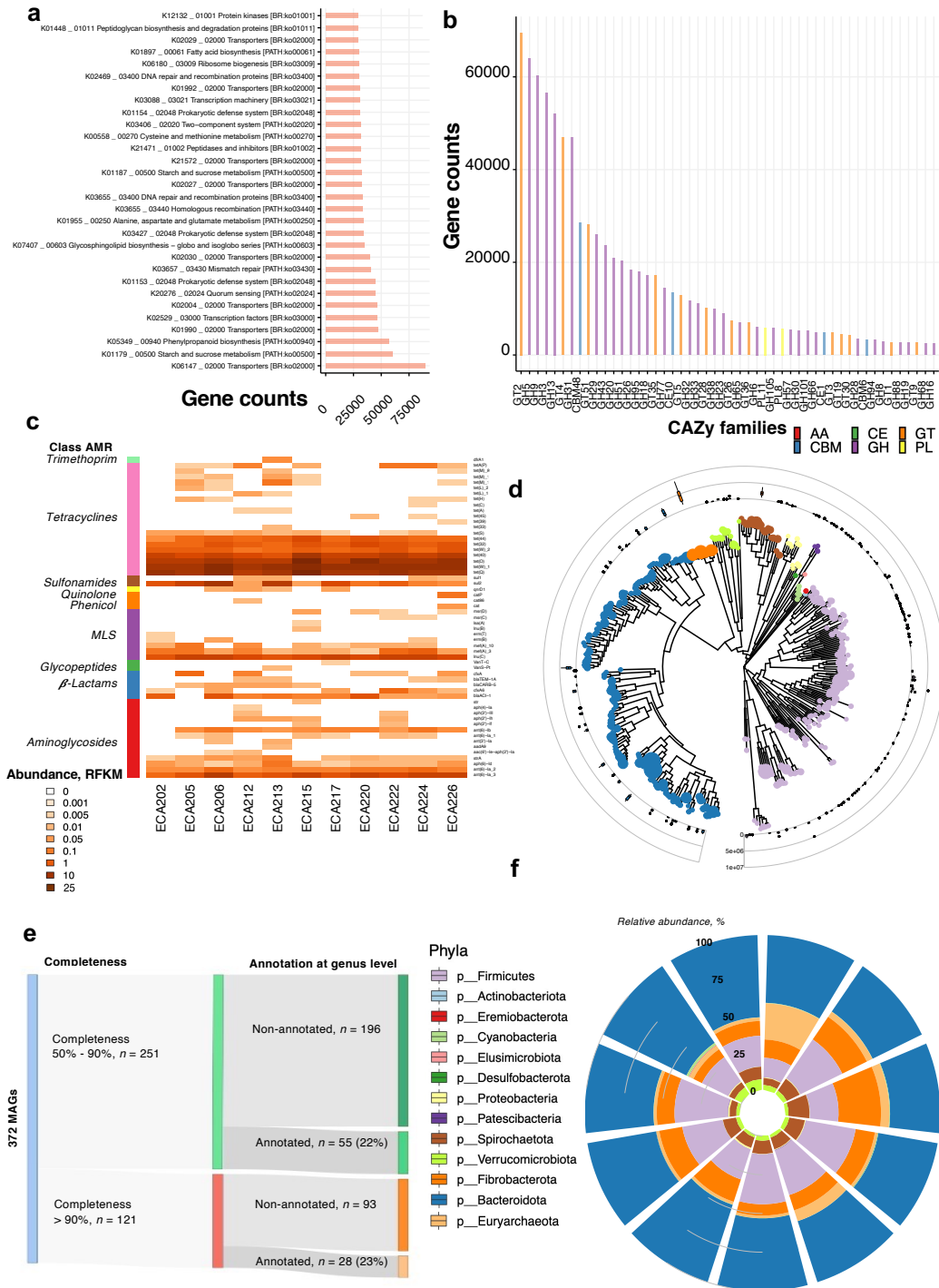


Figure 4 - Functional diversity of the equine microbial genes catalogue, antimicrobial genes, and MAGs landscape

(a) Frequency of KEGGs pathways in the gut microbial gene catalogue estimated from the orthologous groups (KOs). The horizontal bars represent the absolute number of genes found in each KEGG pathway; (b) the Frequency of total carbohydrate-active enzyme (CAZymes) families estimated in the gut microbial gene catalogue. CAZymes are coloured according to their class; (c) Heatmap shows each individual's ($n = 11$) normalised counts of antimicrobial resistance (AMR) genes based on the ResFinder database. The left column depicts the AMR class; (d) the Phylogenetic tree of the $n = 372$ MAGs detected. The outer cycle boxplots represent the abundance of each MAG. Boxplots are coloured according to phyla; (e) Sankey diagram showing the numbers of MAGS with completeness between 50-90% or > 90%. Only a relatively small fraction of the MAGs (73 out of 372) was annotated at the genus level; (f) Circular stacked bar plot of the MAGs phyla abundance detected for each individual in the cohort ($n = 11$).

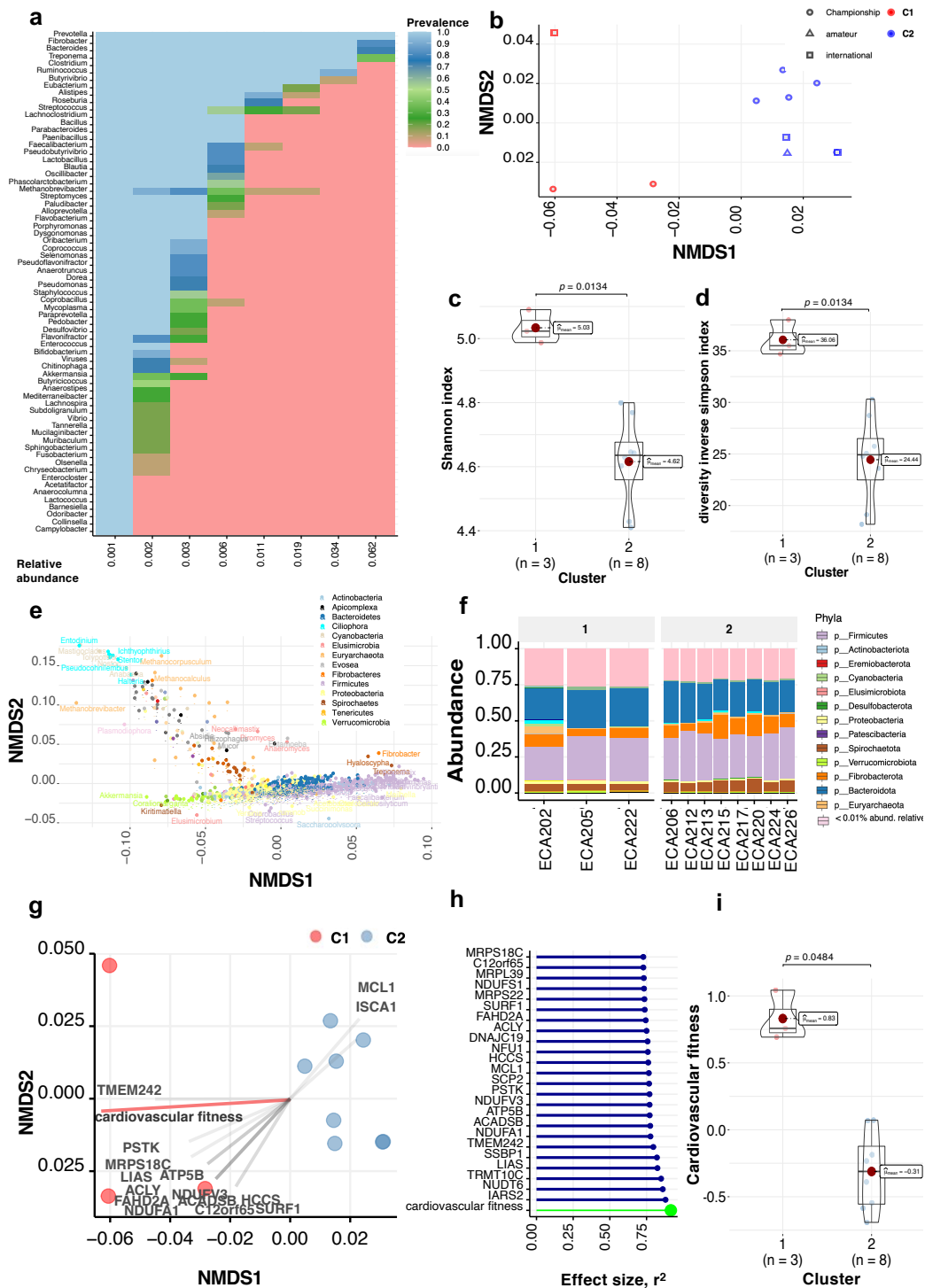


Figure 5 - Basal dominant gut phylotypes composition is associated with cardiovascular fitness

(a) Dominant phylome and its prevalence at different detection thresholds (relative abundance); (b) NMDS ordination analysis (Bray-Curtis distance) of dominant phylotype composition. Points denote individual samples ($n = 11$); (c-d) Violin plot representing the Shannon Diversity Index and inverse Simpson index of dominant phylotypes according to the clustering groups, respectively; (e) Biplot values of the discriminant phylotypes driving the NMDS ordination. The phylotypes contributing to the distinction between groups on at least one axis are depicted. Points are coloured by phylum; (f) Taxonomic distribution of the dominant phylotypes grouped by phyla in each individual ($n = 11$). Individuals are split by cluster: cluster 1 ($n = 3$) and cluster 2 ($n = 8$); (g) NMDS ordination plot shows the covariates contributing significantly to the variation of dominant phylotypes determined by the “*envfit*” function. The arrows for each variable indicate the direction of the effect and are scaled by the unconditioned r^2 value. Dots represent samples ($n = 11$), which are coloured according to the type of community: cluster 1 (red colour, $n = 3$) and

cluster 2 (blue colour, $n = 8$); (h) Effect sizes of the main variables affecting the NMDS ordination. The length of the horizontal bars shows the amount of variance (r^2) explained by each covariate in the model. Covariates are coloured according to the type of dataset: athletic performance are in green and mitochondrial-related genes in blue; (i) Violin plot representing the cardiovascular fitness of each cluster, which was calculated as a composite of post-exercise heart rate, cardiac recovery time, and average speed during the race. Colours indicate community classification, cluster 1 (red colour, $n = 3$) and cluster 2 (blue colour, $n = 8$). The boxplots show the median, 25th, and 75th percentile, and the whiskers indicate the minima and maxima. The points lying outside the whiskers of boxplots represent the outliers. Adjusted p values from the two-sided Wilcoxon rank-sum test.

Therefore, fitness was associated with greater microbial diversity! We found a clear separation between fit and non-fit athletes regarding gene function, including differences in carbohydrate metabolism, glycan catabolism and amino-acid synthesis. Highly diverse microbiomes, enriched in relatively poorly-described genera and their pool of genetic resources, likely regulate metabolic pathways to fine-tune mitochondrial function and enhance cardiovascular capacity. On the contrary, microbial communities with reduced diversity but a higher abundance of core taxa from the *Lachnospiraceae* family were associated with poorer performance (Figure 6). With just 11 runners, the sample size was limited, but we also replicated the finding in an independent cohort of elite runners using 16S rRNA sequencing. Notably, combining all available data from the host, the microbiome and the gut environment, we found an interesting association between the athlete's cardiovascular capacity and the microbiome composition and function—the greater the microbiome diversity in the gut, the greater the ability to win the race.

This holistic study illustrates the power of shotgun sequencing for assembling the puzzle of microbiome function and paves the way to confirm the role mitochondrial function and cardiovascular capacity have on reducing muscle fatigue and running time. A big issue now is drawing causation from this observational study. We need some longitudinal and, importantly, experimental work. Nevertheless, this work encourages translating the information of the “fittest” athletes into nutritional modalities that could benefit the masses. In light of these findings, dietary interventions to reduce *Lachnospiraceae* taxa like *Dorea* and *L-Ruminococcus* while creating more space for non-core species will likely be required to increase microbiome diversity, functional plasticity, and athletic performance. Dietary changes can promote swift changes in *Lachnospiraceae* abundance⁶⁵. Consumption of nutritional pectins could strongly reduce the faecal abundance of *Ruminococcus*, *Blautia*, and *Roseburia* (all in the *Lachnospiraceae* family)¹¹⁸. Conceptually, the partial replacement of diet-derived polysaccharides needed to expand *Lachnospiraceae* taxa (e.g., starch, inulin, xylans, and arabinoxylan) by other structurally diverse dietary fibres (e.g., soluble pectins such galactan, arabinan, and arabinogalactan) could be the front-line for nutritional interventions. Due to the minor involvement of the *Lachnospiraceae* phylotypes in proteolytic metabolism¹¹⁹, increasing protein consumption could be another way to optimise the microbiome function in horse athletes⁹⁹ (see [article 8](#); [Mach et al., 2022](#); <https://hal.inrae.fr/hal-03794437>, [OA](#)).

This project has traced the path of my travel across disciplines. It has been an integration odyssey in which I have studied different biological systems, including horses, bacteria, fungi, archaea, protozoa and omic host layers. This work illustrates how much working in the field was helpful for prediction and a powerful tool to formalise knowledge and generate and test hypotheses that are difficult to evaluate experimentally—recruiting elite athletes in the area provided high-quality data to facilitate the quantitative and qualitative description of the hologenome dynamics. However, the complexity underlying the

exercise response in such athletes would have been impossible to decipher alone. It is here where interdisciplinary science has metamorphosed from words into action, and I have collaborated with brilliant people worldwide and motivated peers.

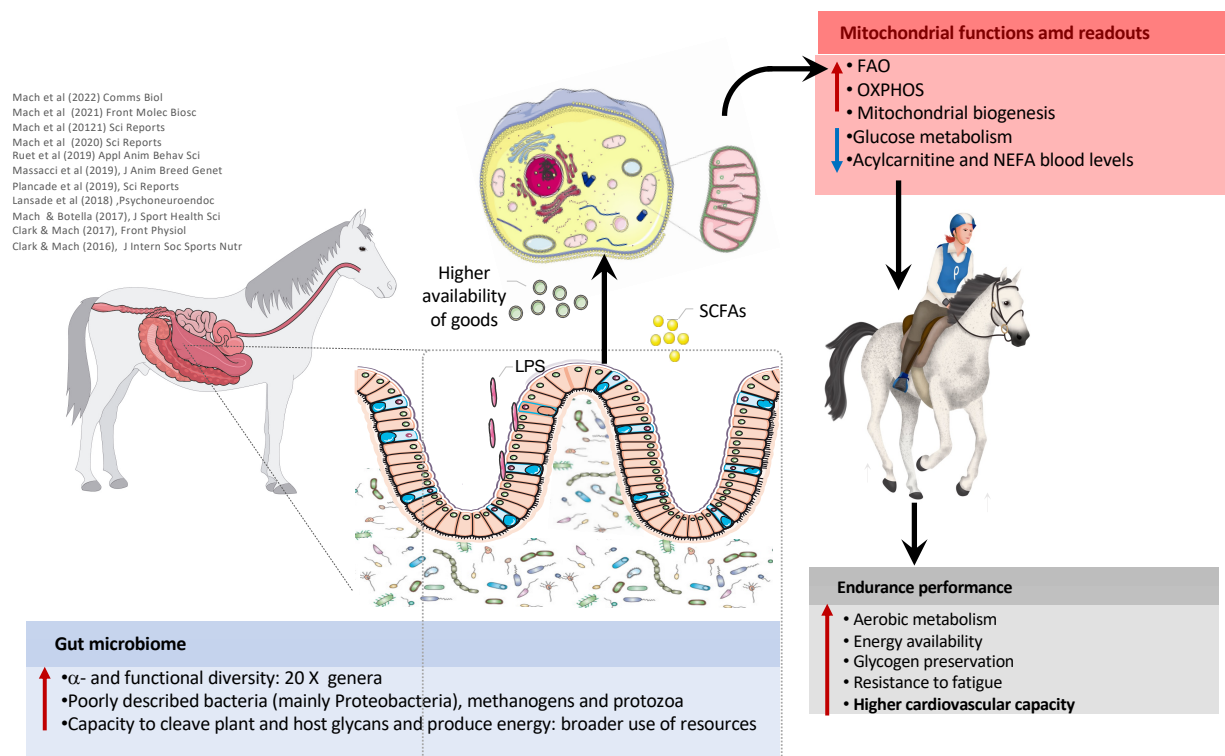


Figure 6 - The bidirectional crosstalk between the gut microbiota and mitochondria in endurance horses.

Microbiota-derived byproducts likely mediated the intertwined communication between mitochondria and gut microbiota. Among the SCFA, butyrate appeared as a critical regulator of mitochondrial energy production and oxidative stress. Increased lactate and urea concentrations upon prolonged exercise likely entered the gut lumen and were transformed into SCFA. It is also suggested that circulating free fatty acids participated in the mitochondrial regulation of the inflammatory processes elicited by oxidative stress, microbial dissemination and microbial lipopolysaccharides translocation outside the gastrointestinal tract, as often occurs in endurance athletes. Whether these mechanisms confer an advantage for endurance performance remains still speculative. Still, results suggest that gut-microbiota crosstalk is pivotal for greater energy availability, aerobic metabolism, glycogen preservation, fatigue resistance, and maintaining speed during the race.

Given that this exciting discovery paves the way for dietary supplements that could enhance equine athletic performance, results must have attracted much interest from the media. Results of this chapter were followed by two press releases at INRAE (<https://www.inrae.fr/actualites/secrets-metaboliques-lendurance-du-cheval-athlete>; <https://www.inrae.fr/actualites/endurance-microbiote-du-cheval-entre-course>), and we were interviewed at RadioFrance (<https://www.radiofrance.fr/franceinter/et-si-on-pouvait-augmenter-les-performances-sportives-grace-au-microbiote-6137604>). Furthermore, several non-specialized journals contacted me to explain the link between gut microorganisms and athletic performance (*e.g.*, https://www.sciencesetavenir.fr/animaux/chevaux/les-chevaux-aussi-ont-besoin-d-un-bon-microbiote_167263; <https://www.vet-alfort.fr/actualites-de-l-ecole/publication-les-secrets-metaboliques-de-l-endurance-du-cheval-athlete>; <https://www.technologynetworks.com/immunology/news/gut-bacterias-pep-talk-enhances-horses-athletic-performance-347505>; <https://www.vetofficine.com/fiches/fiche-pharmacie-microbiote-et-mitochondries-une-cle-de-lendurance-cheval>; <https://www.eurekalert.org/news-releases/837598>; <https://studyfinds.org/horse-gut-bacteria-winning-edge/>; <https://scitechdaily.com/gut-bacteria-talk-to-horses-cells-to-extend-energy-output-improve-their-athletic-performance/>; <https://www.earth.com/news/horses-gut-bacteria-talk-to-their-cells-to-regulate-energy/>; <https://scientificinquirer.com/2021/04/09/horses-microbiome-plays-a-role-in-its-athletic-performance/>; <https://www.horsetalk.co.nz/2021/04/10/gut-bacteria-horses-cells-athletic-performance/>; <https://croixdusudlaboratoire.com/2020/12/02/lien-entre-hypervigilance-et-qualite-du-microbiote-intestinal/>; <https://www.vetitude.fr/microbiote-intestinal-les-bienfaits-du-pre-pour-les-chevaux-de-competition/>).

By interacting with journalists, I tried to make our results public without contributing to sensationalism and exaggeration of research findings.

4



T H E G U T I S B I G E N O U G H F O R B O T H
O F U S : H E L M I N T H - M I C R O B I O T A
I N T E R A C T I O N S I N H O R S E

This axis is the core of the Michel Boisseau PhD program (2019-2022), which I co-supervised with Guillaume Sallé under the title: “*Résilience des communautés de cyathostomes et du microbiote digestif du cheval au traitement anthelminthique*”. This axis of study has been a long and rich scientific adventure that started with the help of Allison Clark, my master's student at the Open University of Catalonia (Spain). David Bars, a Postdoc, was also enrolled in this topic on 2020 to help with the metagenomic analysis. This research topic continues nowadays through a new line of study on our team agenda and the Joshua Malsa PhD thesis supervised by Guillaume Sallé and Geraldine Fleurance, dedicated to analysing nutraceuticals with anthelmintic properties on the gut ecosystem.

The mentoring trajectory with my students is reflected as follows:

1. [Research article] **Michel Boisseau**, Sophie Dhorne-Pollet, **David Bars-Cortina**, Elise Courtot, Delphine Serreau, Gwenolah Annonay, Jérôme Lluch, Amandine Gesbert, Fabrice Reigner, Guillaume Sallé, **Núria Mach** (Corresponding author) (2022). Species interactions, stability, and resilience of the gut microbiota - helminth assemblage in horses. <https://dx.doi.org/10.21203/rs.3.rs-1955749/v1>, <https://hal.inrae.fr/hal-03767875>, OA [Under revision in the iScience journal]
2. [Research article] Elise Courtot, **Michel Boisseau**, Sophie Dhorne-Pollet, Delphine Serreau, Amandine Gesbert, Fabrice Reigner, Marta Basiaga, Tetiana Kuzmina, Jerome Lluch, Gwenolah Annonay, Claire Kuchly, Irina Diekmann, Jürgen Krücken, Georg von Samson-Himmelstjerna, **Núria Mach**, Guillaume Sallé (2022). Evaluation of the nemabiome approach for the study of equine strongylid communities. <https://dx.doi.org/10.1101/2022.07.22.501098>, <https://hal.inrae.fr/hal-03767915>, OA [In revision in the PeerJ journal]
3. [Research article] **Michel Boisseau**, **Núria Mach**, Marta Basiaga, Sławomir Kornaś, Tetiana Kuzmina, Claire Laugier, Guillaume Sallé (2022). Patterns of variation in equine strongyle community structure across age groups and gut. <https://dx.doi.org/10.1101/2021.05.17.441725>, n° biorxiv: 2021.05.17.441725, <https://hal.inrae.fr/hal-03794670>, OA [In revision, Parasites and Vectors]
4. [Review] **Michel Boisseau**, **Núria Mach**, Marta Basiaga, Slawomir Kornas, Tetiana Kuzmina, Claire Laugier, Guillaume Sallé (2022). Acta Parasitologica Meta-analysis of equine strongyle community structure. <https://hal.inrae.fr/hal-03792762>, OA [In revision, Acta parasitologica]
5. [Research article] **Allison Clark**, Guillaume Salle, Valentine Ballan, Fabrice Reigner, Annabelle Meynadier, Jacques Cortet, Christine Koch, Mickaël Riou, Alexandra Blanchard, **Núria Mach** (Corresponding author)(2018). Strongyle infection and gut microbiota: profiling resistant and susceptible horses over a grazing season. *Frontiers in Physiology*, (9), 1-18, <https://dx.doi.org/10.3389/fphys.2018.00272>, <https://hal.inrae.fr/hal-02625557>, OA

Strongylosis is one of the most critical internal parasitic diseases of equines caused by gastrointestinal nematodes that constitute one of the main threats to horses' health and welfare ¹²⁰. They affect more than 80% of equids worldwide and are responsible for morbidity and up to 50% of mortality ¹²¹. Equid strongyles encompass a diverse fauna of 14 *Strongylinae* and 50 *Cyathostominae* described species ¹²². Contrary to the large strongyles, cyathostomins cause mild disease symptoms, which make them challenging to diagnose ^{123,124}.

Consequently, they are considered the most important parasite of horses in economic losses and pathology ¹²⁵. If up to 26 species have been identified sharing the same host ¹²⁶, usually up to 5-10 species can colonise the same host at ¹²⁴. The release of modern anthelmintics has drastically reduced the prevalence of *Strongylus* ¹²⁷. However, treatment failure against cyathostomins has been found on many occasions across every continent for all drug classes currently available ¹²⁷.

Factors contributing most to the selection of drug-resistant cyathostomin populations in equids remain uncertain. However, significant and heritable between-horse variation in strongylid egg excretion has been reported in domestic horses ^{124,128}. These observations hence suggest that some horses can limit parasite egg production, the mechanisms of which remain to be uncovered but likely apply to two broad categories, e.g., reduction of overall worm burden, reduction of worm fertility, or changes in the gut environment (e.g., immune system or microbiome composition and function).

New approaches need to be considered and developed to improve strongyles management taking into account the tryptic system involved in the parasite's success, e.g., hosts, parasite and gut environment ^{120,129}. Identifying gut microbiota perturbations associated with strongyle infection could suggest novel mitigation strategies based on tuning bacterial communities.

Gastrointestinal parasites and their host gut microbiota form a complex ecological system ¹³⁰, harbouring direct ¹³¹ and indirect interactions mediated by modulation of the host immune system ¹³². Observations to date have shown diverse degrees of gut microbiota perturbations to helminth infection in humans ¹³³, wild animal populations ^{134,135}, species of veterinary interest like pigs ^{136,136,137}, ruminants ^{138,139-141}, cats ¹⁴², horses ¹¹⁸⁻¹²⁰, and laboratory animals ^{146,147-150}. Across studies, gastrointestinal parasites are generally responsible for mild effects on bacterial composition and diversity, with little evidence of dysbiosis. Nevertheless, the dynamic interactions between equine strongyle infection, the gut microbiota and host physiology across the parasite life cycle inside the horse's guts remain unknown in horses.

To that end, I collaborated with Guillaume Sallé at INRAE Tours (UMR1282 ISP, Université de Tours). By pooling techniques, skills and resources, we have constructed a rich and long history of collaboration. Moreover, we decided to co-direct Michel Boisseau, our first PhD student, to decipher the genomic and metagenomic approaches for the sustainable management of cyathostomins in horses. Before Michel's thesis, however, I mentored Allison Clark, a master's student from the Open University of Catalonia. With Allison and Guillaume, we selected two groups of 10 Welsh ponies with increased resistance/susceptibility to strongylosis based on their faecal egg counts (FEC)

history to guide the development of new microbiota-based control strategies. As such, horse resistance to strongylid disease is defined as the ability to control the strongyle life cycle. This divergence was sustained across a 10-year time window. We first monitored gut microbiota profiles, FEC, blood cell populations and biochemical parameters over a grazing season (article 9, Clark, Sallé et al., 2018; <https://dx.doi.org/10.3389/fphys.2018.00272>, <https://hal.inrae.fr/hal-02625557>, OA) ³⁴.

Our selection procedure effectively selected individuals with divergent susceptibility toward strongylid infection (twice as many eggs susceptible as in resistant ponies by the end of the trial). Analysis of blood parameters revealed limited modifications associated with strongyle infection. Nonetheless, we found that resistant ponies exhibited a reduced lymphocyte-to-monocyte ratio throughout the study period and higher eosinophil counts by the end of the trial. After exposure to natural infection, the resistant ponies showed lower FEC after 92 and 132 grazing days and maintained higher levels of circulating monocytes and eosinophils, while lymphocytosis persisted in susceptible ponies. Although the overall gut microbiota diversity and structure remained similar in all individuals, parasite-susceptible ponies exhibited a reduction in butyrate-producing bacteria such as *Ruminococcus*, *Clostridium* XIVa and members of the *Lachnospiraceae* family, which could have contributed to intestinal inflammation. In line with this hypothesis, an increase in pathobionts such as *Pseudomonas* and *Campylobacter* together with changes in several predicted immunological pathways, including pathogen sensing, lipid metabolism, and activation of signal transduction that are critical for the regulation of the immune system and energy homeostasis were observed in susceptible relative to resistant counterparts.

Moreover, susceptible individuals displayed increased ciliate protozoan concentrations at day 92, suggesting that strongyles and protozoa may contribute to each other's success in the equine intestines. It could also be that susceptible individuals favour the increase of these carbohydrate-degrading microorganisms to enhance the supply of nutrients needed to fight strongyle infection. On the other hand, butyrate-producing bacteria such as members of *Ruminococcus*, *Clostridium* XIVa and *Lachnospiraceae* family were depleted in susceptible ponies but enriched in resistant animals, suggesting a possible effect of *n*-butyrate on the protection of inflammation in resistant animals. Because butyrate is a potent inflammation inhibitor, it is suggested that susceptible ponies are prone to gut inflammation because of the altered abundance of butyrate-producing bacteria (Figure 1).

To better understand the mechanisms underpinning the relationship between equines and natural strongyle infection, we combined metabolomic profiles with faecal microbiota in parasitised horses (article 10; Sallé et al., 2021; <https://dx.doi.org/10.1038/s41598-021-93468-2>, <https://hal.inrae.fr/hal-03284457>, OA; ¹⁵¹). Notably, our analyses identified the concomitant rise in plasma phenylalanine level and faecal *Prevotella* abundance and the reduction in circulating monocyte counts as biomarkers of the need for drug treatment (egg excretion above 200 eggs/g). This biological signal was replicated in other independent populations. We also unravelled an immunometabolic network encompassing plasma beta-hydroxybutyrate level, short-chain fatty acid-producing bacteria and circulating neutrophils that form the discriminant baseline between susceptible and resistant individuals. Altogether our observations opened new

perspectives on the susceptibility of equids to strongylid infection and left scope for both new biomarkers of disease and nutritional intervention.

Still, these patterns of microbial shifts under parasite infection did not reflect the dynamics and the qualitative nature of the interactions between species^{152–154}. The characterisation of the interactions between microbial and parasite species in helminth-infected hosts is largely unknown. Evidence for direct interactions between helminth and gut microbial species mainly bear on the reciprocal feedback between *Lactobacillaceae* and *Heligmosomoides polygyrus*¹⁵⁵ *Lactobacillaceae* or *Trichuris muris* in mice or the need for gut microbiota attachment to *Trichuris muris* egg caps for triggering worm hatching¹³¹. Additionally, the longitudinal monitoring of the nemabiome-gut microbiota ecosystem combined with methodological developments to account for non-linear trajectories and isolate direct species interactions remain scant.

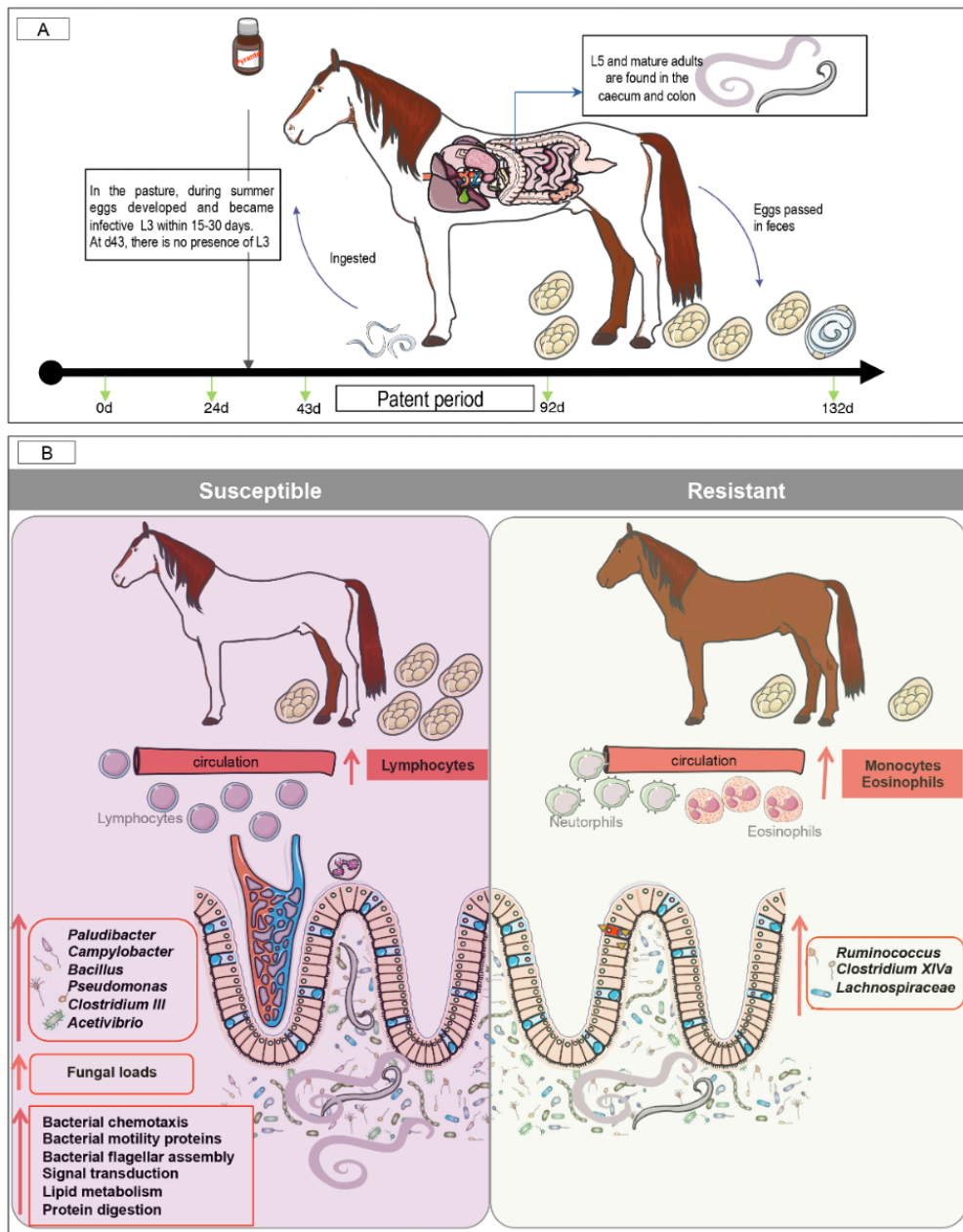


Figure 1 - A model for gut microbiota modifications and their effects on host physiology after natural strongyle infection.

(a) A set of 20 female ponies [10 susceptible (S) and ten resistant (R) to strongylosis] were selected based on their faecal egg counts history during previous pasture seasons. Longitudinal monitoring of the parasitism level in each animal was performed through five-time points from June to October. Faecal samples were collected from all ponies 0, 24, 43, 92, and 132 days after the beginning of the grazing season to carry out faecal egg counts, pH measurements, and microbiota profiling. Blood samples were taken at the same time points to analyse biochemical and haematological parameters. Body weight (BW) was also recorded at the same time points; (b) Parasite infection induced alterations in bacterial-anaerobic fungal-protozoal inter-kingdom, increasing the abundance of *Paludibacter*, *Campylobacter*, *Bacillus*, *Pseudomonas*, *Clostridium III*, *Acetivibrio* and the overall concentrations of anaerobic fungi, protozoa and parasite egg counts in the faeces. On the other hand, butyrate-producing bacteria such as members of *Ruminococcus*, *Clostridium XIVa* and *Lachnospiraceae* family were depleted in susceptible ponies but enriched in resistant animals, suggesting a possible effect of *n*-butyrate on the protection of inflammation in resistant animals. Because butyrate is a potent inflammation inhibitor, it is suggested that susceptible ponies are prone to gut inflammation because of the altered abundance of butyrate-producing bacteria.

In addition to longitudinal observations, system disturbance, *e.g.* following drug treatment targeting the parasite, offers a complementary strategy to unravel species interactions in the gut ecosystem^{145,156}.

Altogether, the nature of the interactions between the gut microbiota and helminth species remains largely unresolved. Understanding the source and consequences of dynamic variation in the host-parasite-microbiota ecosystem and how this complex system's stability is of particular interest to guiding and evolving control strategies in the medical and veterinary settings. This hypothesis was tested during Michel's Boisseau doctoral program. Together, we aimed to bridge this knowledge gap with longitudinal monitoring of the equine gut microbiota and parasite communities after parasite removal and reappearance. To start with, we developed a nemabiome metabarcoding approach, a convenient tool to quantify and identify species in bulk samples that could overcome cyathostomin morphological identification's hurdle. This approach relied on the internal transcribed spacer 2 (*ITS-2*) rDNA barcode and a newly developed *COX1* gene barcode (Courtot, Boisseau et al., 2022; <https://dx.doi.org/10.1101/2022.07.22.501098>, <https://hal.inrae.fr/hal-03767915>, OA). Then, using 40 naturally infected Welsh ponies maintained under controlled facilities during a 42-day trial, we explored the ecological resilience of both communities to parasite removal and re-appearance (Figure 2).

Contrasting records from before and after anthelmintic treatment, we quantified compositional and interaction strength variations in the gut microbiota and nemabiome community while accounting for the host response using whole blood transcriptomic data. Infected ponies harboured 14 species of cyathostomins, overwhelmed by the abundance of *Cylicocyclus nassatus*. Parasite carriers exhibited gut environment modifications, higher Shannon entropy and orderly rearrangements of prokaryotic assemblages, with protective *Clostridia* species contributing to the successional nemabiome-microbiota crosstalk. Nevertheless, the gut ecosystem was remarkably stable, and the host systemic response defined enrichment for B-cell activation and IgA production without corresponding changes in parasite burdens. Therefore, *Clostridia* likely reduced temporal instability between the microbiota-parasite-host triad and favoured parasite tolerance (Article 11; Boisseau et al., 2022; <https://dx.doi.org/10.21203/rs.3.rs-1955749/v1>, <https://hal.inrae.fr/hal-03767875>, OA).

However, this ecosystem stability was disrupted by the anthelmintic treatment (pyrantel) and parasite removal, with dire early consequences on the gut environment, microbiota diversity, and cytokine networks. Moreover, there was a detrimental effect of cyathostomin burdens on *Enterococcus* spp (Figure 3). Precisely, parasite removal in the high shedders furthered the sharpest reduction in faecal pH 24h post-treatment (pH difference = -0.28; $P = 0.0538$, Figure 3a). This was coupled with acute disbalance of the gut microbiota β -diversity in HIGH-TRT individuals and significant changes from the original state from 18 to 24 h post-treatment when the host expelled the worms (Dunn test of mean Bray Curtis distance within time points, adj $P = 3.14 \times 10^{-5}$; Figure 3b). Accordingly, a skewed decrease in nestedness ($\beta_{\text{NEST}} = 0.027 \pm 0.03$; GLM; $P = 0.00154$) and microbial richness (GLM; $P = 0.0012$) was observed at 18h post-treatment. Additionally, parasite removal had slight but noticeable effects on the host blood transcriptomic response. The top 5% of most treatment-affected genes in high-shedders defined significant enrichment for interferon-related pathways, IL-27 signalling pathways,

and nucleotide-binding oligomerisation domain (NOD) ligand-associated signalling, resulting in highly selective recognition and reactivity pattern in response to invasion. Altogether, these observations suggest that pyrantel treatment *per se* had little effect on the gut microbiota or the host response. Still, parasite removal significantly disturbed the gut ecosystem, with slight but noticeable changes in the host blood transcriptome.

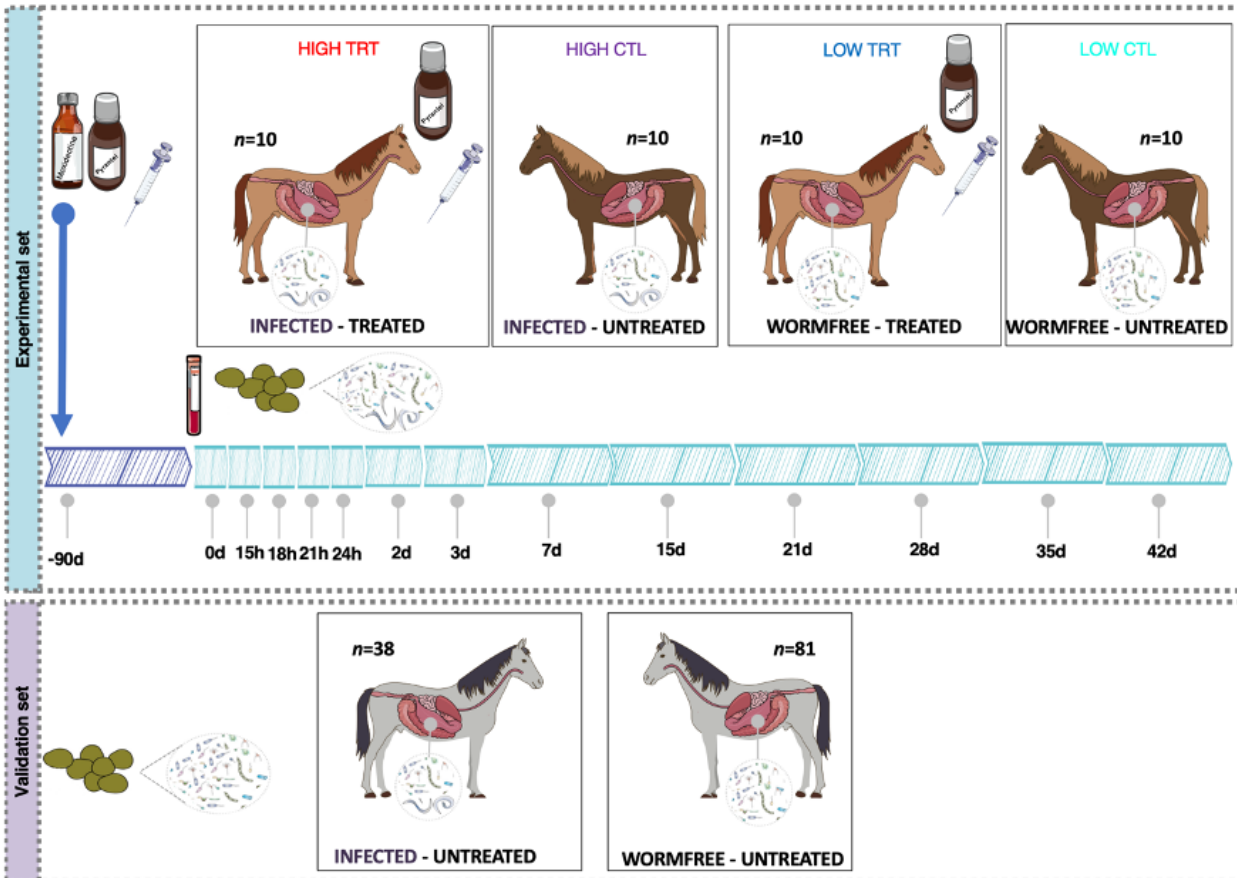


Figure 2 - Experimental design

The experimental cohort comprised 40 female Welsh ponies divided into four subgroups. The "HIGH-CTL" group corresponds to the high shedders and untreated ponies, while the "HIGH-TRT" group corresponds to the high shedders treated with pyrantel. The "LOW-CTL" group corresponds to the worm-free and untreated ponies, while the "LOW-TRT" group corresponds to the non-high shedders treated group. Sampling started on day 0 (before treatment with pyrantel) and ended on day 42 post-treatment. The validation cohort included faecal microbiota profiles from four independently published studies. The four studies were Clark ³⁴, Peachey ¹⁴³, Kunz ¹⁴⁵, and Daniels ¹⁵⁶ (Boisseau et al., 2022; <https://dx.doi.org/10.21203/rs.3.rs-1955749/v1>, <https://hal.inrae.fr/hal-03767875>, OA).

Following the antihelmintic treatment, the gut microbiota composition rebounded to baseline level 48h after pyrantel treatment (Figure 3c). As specific examples, *Treponema*, *Cellulosilyticum*, and *Eubacterium ruminantium* genera sharply decreased by day one but recovered by day three, showing a solid resilience along the timeline (MaAsLin, adj $P = 0.04584$). On the parasite side, the first available nemabiome data were produced for two individuals at 28- and 35-days post-treatment. On both occasions, *C. nassatus*, *C. minutus* and *C. coronatus* represented more than 95% of total abundance, although a more diverse combination (*C. nassatus*, 68.9%; *C. longibursatus*, 8.3%; *C. minutus*, 6.5%; *C. coronatus*, 3.8%,

and *C. pateratum*, 3.2%) was found in one pony at day 35. After 42 days, pyrantel treatment reduced cyathostomin Simpson's index (Wilcoxon's test = 30, $P = 0.048$) but not Shannon's index (Wilcoxon's test = 29, $P = 0.07$), suggestive of an effect bearing on the most dominant taxa. In line with this, differential species count modelling found a significant reduction in *C. longibursatus* abundance (4th most abundant species) upon treatment (Wald test = -3.01, adj $P = 0.038$). This latter observation underscored the cyathostomin community resilience to the therapy (despite short-term pyrantel efficacy), as suggested by its non-significant effects on the β -diversity ($F_{1,20} = 2.92$, adj $P = 0.11$, $R^2 = 0.21$ for Jaccard distance; $F_{1,20} = 1.64$, adj $P = 0.43$ and $R^2 = 0.07$ for Bray Curtis dissimilarity).

We then sought to identify the bacterial members most affected by parasite re-emergence. The abundance of *Enterococcus* spp - represented by members of the *E. asini* (54.37%), *E. mediterraneensis* (38.23%) and *E. casseliflavus* (7.36%) - was lower in the high-shedders before treatment (Figure 3d); $\beta_{\text{HIGH}} = -0.99 \pm 0.3$, $P = 0.001$; MaAsLin, adj $P = 0.0458$; AUROC = 0.6230 and recall of 73.84%). Following worm re-emergence, this rare genus was significantly disfavoured in the treated high-shedders ($\beta_{\text{After treatment} \times \text{Treated} \times \text{HIGH}} = -2.62 \pm 0.69$, $P = 9.80 \times 10^{-6}$; Fig 3d). Inspection of pairwise relationships with a multi-spatial convergent cross-mapping approach found evidence of *C. pateratum* directly forcing this genus in the treated ponies ($P = 0.07$; Figure 3e).

In sum, both ecological communities were highly resilient to disturbance and recovered their pre-treatment compositions, except for *Cylicostephanus longibursatus* in the parasite community. However, gut microbiotas failed to restore their original stability. They shifted towards an interacting unstable state, with transient coexistence between Clostridia and core bacterial taxa, e.g. *Fibrobacter* and *Prevotella*, evoking their crucial role as stabilising forces for this new equilibrium.

Overall, this study highlighted the detrimental effect of cyathostomin infection on *Enterococcus* spp. Moreover, it delineated the putative protective role of Clostridia and core taxa (e.g. gatekeepers) to cascade the community stability and host immune tolerance towards cyathostomins. This does raise the controversial question of whether it is necessarily beneficial to eradicate all helminths. While it is true that parasitic infections can have negative impacts on horse health, with subsequent detrimental effects on performance, low-level infections can be relatively benign. Indeed, helminth infections can positively influence host health and microbiota and protect against autoimmune disease (hygiene hypothesis¹⁵⁷). It also revealed a microbial community that bent with global rearrangements after pyrantel treatment yet exhibited resilience but shifted towards another interacting and unstable state through which the abundance of co-infecting parasite strains influenced the assemblage. Therefore, to retain the benefits to microbiota associated with low levels of helminth infection, antihelmintic treatment should target just those individuals showing morbidity associated with the disease (although this would require ethical considerations). A more comprehensive field study and more profound functional resolution of the host-gut microbiota-parasite system will be essential to anticipate how this drug-defined equilibrium may affect functional redundancy in the bacterial community and the assembly of the parasite community on

pasture. Future studies should also consider the long-term impacts and the effects of higher dosages of anthelmintics.

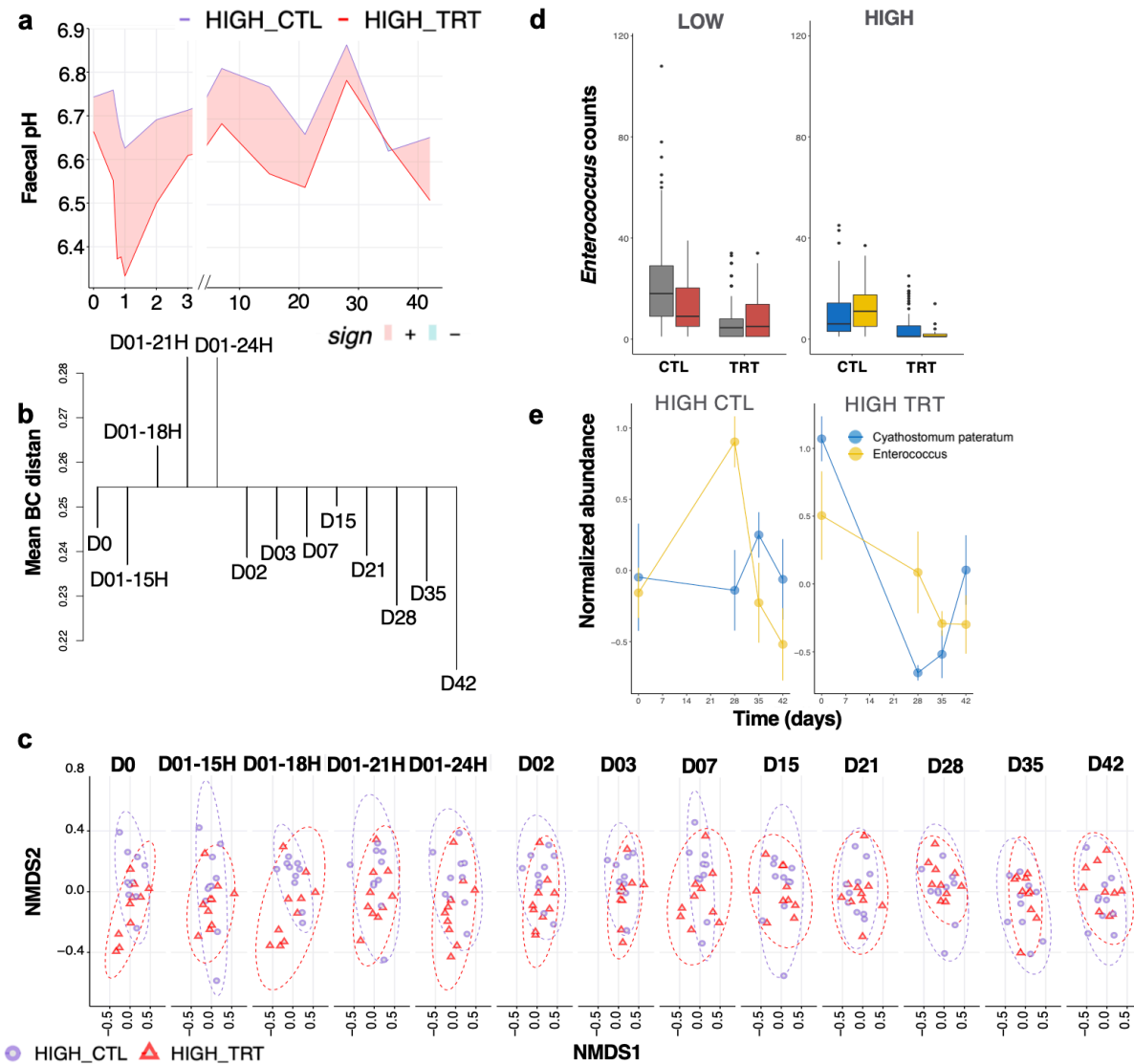


Figure 3 - Parasite removal has a drastic effect on the gut environment and microbiota composition, but limited response in the host blood

(a) Evolution of faecal pH across time in high shedders. To display differences between group series, the ribbon was filled with red colour when the max in HIGH-CTL was higher than the min in HIGH-TRT, and in cyan colour when the maximum in HIGH-TRT was higher than the min in HIGH-CTL; (b) Dendrogram plot based on the within-time and between time dissimilarities in the HIGH-TRT group. The leaf segment is reversed if some time points are more heterogeneous than the combined time class. The horizontal line is drawn at the level of mean between-time dissimilarity, and vertical lines connect within-time dissimilarities to this line; (c) NMDS ordination analysis (Bray-Curtis distance) of the ASV composition in HIGH_CTL (violet), and HIGH_TRT (red) samples across the time points; (d) *Enterococcus* count distribution in the untreated (CTL) and treated (TRT) low- and high-shedders. Boxplots are coloured according to whether counts were measured before (grey or blue) or after (red or yellow) significant parasite reappearance period (28 days after pyrantel treatment); (e) Trajectory of *Enterococcus* and *Cyathostomum pateratum* in the infected untreated and treated ponies. Boisseau et al., 2022; <https://dx.doi.org/10.21203/rs.3.rs-1955749/v1>, <https://hal.inrae.fr/hal-03767875>, OA).

Although studies on gut bacteria have shed light on this community's interactions, other gut biome components, such as the virome and macrobiota, should be given more

attention to truly understand the gut ecosystem dynamics. Research into parasite-gut microbiota associations in veterinary species is in its early stages, and it remains to be established how the host's microbiome and pathogen interact and communicate, how any of such interaction impacts the host immune response, the pathogen resistance and the host performance. The ability of parasites to influence host response and to dictate disease outcomes of co-infections is also an active area of research in veterinary science, and it is more complex than previously thought.

To complement this research topic, we explored how bioactive plant compounds with antihelmintic properties could affect the gut ecosystem. Some dietary compounds, such as tannins, have anthelmintic properties and can decrease nematode abundances and faecal egg counts ¹⁵⁸. The anthelmintic effect of tannins has been attributed to their protein-binding properties. Tannins may limit the protein available for helminth nutrition or bind to the helminth larvae cuticle, both of which can lead to helminth death ¹⁵⁸. Among tannin-rich plants, sainfoin (*Onobrychis viciifolia*) is often used as a model ¹⁵⁹. Very recently, Joshua Malsa, a PhD student that will follow very soon, demonstrated how bioactive forages like sainfoin (*Onobrychis viciifolia*) could contribute to reducing antihelmintic drug use ¹⁶⁰. Precisely, he established a significantly lower increase in larval development rate was observed for the sainfoin group at the end of trial ¹⁶⁰. Whether the consumption of tannins will have a rapid and reproducible effect on the gut microbiome and, in turn, affect the horse resistance to helminths or affect the microbiota-helminths interactions needs to be yet tested. Going further, together with Joshua Malsa and Guillaume Sallé, we will determine if using a tannin-rich diet to treat helminth infection could avoid some negative impacts associated with treating the disease with anthelmintics (*e.g.*, dynamic instability of the gut ecosystem).

Moreover, we will investigate how these plant extracts interact with the horse's immune system. A breakdown of these vast research questions will identify several vital components forming my nearest future research activities. The comprehensive nature of this approach will range from community to the molecular level, considering the parasite and microbiota species life-cycle continuum and environmental stressors.

5



O U T L O O K O F A 8 - Y E A R P A T H

This manuscript has traced my scientific path during the last 8-years. The travel has been a pilgrimage involving degrees in odd fields, interdisciplinary research projects across different topics, success in pursuing research outside the comfort zone, and studying biological systems that largely contribute to science. I have provided an overview of my past research activities at the interface of animal physiology, ethology, nutrition, data integration, bioinformatics, biostatistics, microbiology and parasitology. Building on my multidisciplinary background, I have explored biotic (parasites) and abiotic factors (related to human management practices) underpinning the composition and function of the gut microbiota in horses. I have proposed novel management strategies to improve their health and welfare and a novel antihelmintic approach less reliant on drug administration. I have demonstrated the importance of the holobiome - the host, the symbiotic microbial communities, and their genomes - in regulating host homeostasis and disease onset. The results have been organised into IV chapters around my scientific representative axes. The evolution of the work described here reflects the increased availability of quantitative data characterising host and microorganism phenotypes at multiple levels of the organisation. As discussed in each chapter, the work has been carried out in the context of several research projects in collaboration with peers in France and abroad. Additional research activities not discussed in this manuscript relate to past and current partnerships with Alessio Checcinato from Padova University and Eric Barrey, my team leader at Jouy en Josas.

I always felt the need to use whatever influence I had to help my peers and trust that my peers would do the same. What is this story about? Next to science, I have devoted hours of my working week to mentoring students. I have trained more than 40 Master's students, providing them with constructive feedback, research project guidance and professional contacts. Next to Master's students, since 2020, I have followed 4 PhD students (Alice Ruet, David Bars, Francesca Massacci and Vittoria Bisutti), and I have supervised Michel Boisseau as a PhD student and David Bars as a postdoc. I have put much energy into instilling a sense of responsibility in all of them. I like them to work out how to manage their time and take ownership of the results. I have taught students how to present scientific results using visuals. Images and graphs can be compelling, it effortlessly communicates. I provide means for them to think more critically about things, improve their computation scale, writing skills, or soft skills, and enjoy it along the way. Armed with academic knowledge and enthusiasm, I have always offered professional advice and helped my students to publish their articles in highly recognised and open-source journals and to divulge science into society. Being a mentor of these Master's and PhD students has been one of the most personally satisfying roles I have ever held. Additionally, I have had the opportunity to develop my scientific knowledge through exposure to different disciplines and the expertise and opinions of my peers. The latter has been enhanced by being a member of Scientific Reports and Veterinary Quarterly editorial board journals, where interactions with authors, reviewers and fellow board members raise interdisciplinarity.

Thanks to those research activities and the complementary scientific outputs not described here, the Equine Integrative Biology and Genetics team (INRAE, Jouy en Josas) is today an internationally leading group in horse metagenome research. For a “successful” story like this, many would have made the rational choice not to shift towards

areas outside this core expertise. I spent so much effort trying to find my “own area of expertise” and “international recognition” that it was easy to stick to the past instead of trying new paths and less-fulfilling security of ‘productivity’. However, this was not the case. In hindsight, I wanted new challenges on my scientific road and to do more for livestock, society and the planet. I tried to carry out science dedicated more to life, humans and the Earth. Therefore, I decided to change my research topics and enrich my scientific path with new peers and perspectives by applying for the INRAE mobility program, which offers many opportunities to evolve in missions and take up new challenges. Nonetheless, I close my “horse chapter”, knowing that the work I have carried out is at the forefront of equine microbiota research and will help improve welfare and health while refining training techniques, dietary management, and housing during competition and rest.

During these last eight years, I experienced wonder, awe and beauty in my work, bringing high satisfaction levels.

6



P E R S P E C T I V E S

In April 2021, I joined the host-pathogen interaction (IHAP) unit at the Health Department at INRAE to explore questions that had more significant potential than my original focus and are more relevant to animals, society and the environment. Mainly, IHAP offered me to bring nuance to the hologenomic approach by combining the airway and gut microbiomes, as well as their functions, while expanding the knowledge of the ecological mechanisms underlying the onset of respiratory infections in livestock, a relevant issue for animal health and welfare, as well as public health, and the planet.

The increase in the prevalence of respiratory disorders in farm and companion animals has reached epidemic statistical levels in wealthy countries that generate a greater need to monitor and control their impact on morbidity and mortality. The increasing demands for livestock products coupled with the intensification of marked-oriented systems in many countries, climate change, ecology incursion, and movements of people, animals and products increase the risk of respiratory disease development worldwide ¹⁶¹. The global burden of respiratory infections in species of veterinary interest includes high treatment costs, premature mortality, loss of productivity, and severe consequences for public health and the environment ^{161–163}. Because domestic animals are regularly and increasingly in close contact with humans, one of the most relevant research questions is to understand the contribution of the pathogen, the host and the environment in promoting infectious diseases in animals and, occasionally, in allowing transmission of zoonotic pathogens to humans ¹⁶⁴.

The importance of the holobiome—the host, the symbiotic microbial communities, and their genomes—in preventing pathogens from establishing an infection on the mucosal surface and spreading to the lungs is still poorly understood. The commensal airway microbiota likely inhibits pathogen colonisation through direct elimination or indirect suppression, thereby acting as a gatekeeper that provides resistance to infection and transmission ^{165,166}. Disorders in the respiratory tract are compatible with a “ménage à quatre” situation, as they depend on the intricate interactions between the pathogen(s), multiple symbionts of the respiratory tract, the host response and the environmental conditions.

Research into virus-microbiota associations in these veterinary species is in its early stages, and it remains to be established how the host’s microbiome and pathogen interact and communicate, how any such interaction impacts the host immune response to both natural infections and vaccines, on the pathogen resistance and the production performance. The ability of respiratory viruses to influence host response and to dictate disease outcomes of co-infections is also an active area of research in veterinary sciences, and it is more complex than previously thought ¹⁶⁷. An ever-expanding field is now positing that the gut microbiota-derived metabolites could be vital molecular mediators of the microbiota-gut-lung axis and affect the onset of respiratory diseases.

The diversity of animal physiologies and the complexity of environmental factors likely influencing respiratory bacterial communities remains challenging to uncover the most critical causal interactions. However, there is evidence supporting the existence of an interplay between respiratory pathogens, commensal microbiota, host and environment in the respiratory apparatus of domestic animals ([article 12](#); [Mach et al., 2021](#); <https://>

hal.inrae.fr/hal-03228289, OA). The sterility of the airways has been rejected. The mechanisms behind lung colonisation in the different species have started to be explored, as well as the microbial communities occupying the various niches in the airways. Nevertheless, nothing is known about the role eukaryotes, archaea and phages play in the respiratory tract of domestic animals.

Before starting my new research field, I reviewed whether the airway microbiota act as a gatekeeper that provides resistance to pathogen colonisation, thus ensuring resiliency, health, and improved performance in domestic animals. Moreover, I offered an overview of the covariation between airway microbiota ¹⁶⁸ and host and environmental factors within and between species ^{169,170}. We suggested potential applications of this knowledge in veterinary medicine (Figure 1). The exploration of the relationships between respiratory pathogens, hosts and respiratory microbiota in domestic animals is timely and novel!

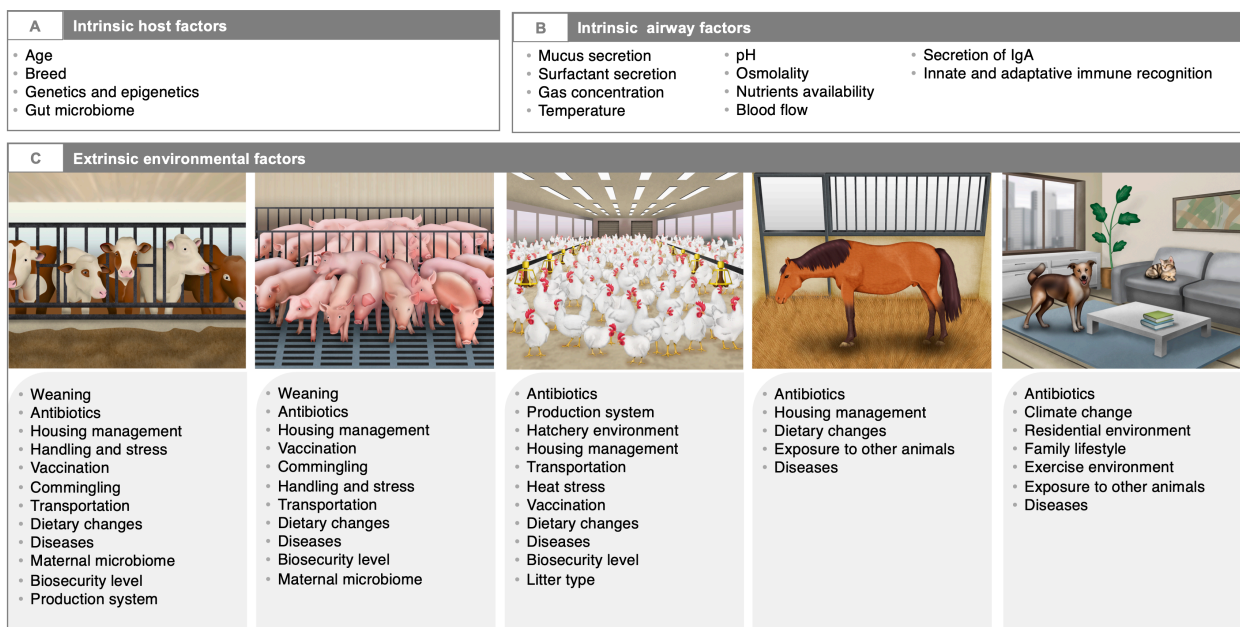


Figure 1 - Intrinsic and extrinsic factors affect domestic animals' airway microbiota composition and development. The respiratory tract microbiota composition and development are dynamic and are shaped by various intrinsic host factors (A), as well as intrinsic airway milieu conditions (B) and environmental variables (C); Mach et al., 2021; <https://hal.inrae.fr/hal-03228289>, OA)

Slowly but steadily, I have started to extend my network in this new area of research. To begin, I will create phylogenomic cartography of *Mycoplasmas* with my new team members (Christine Citti, Eric Baranowski and Xavier Nouvel). There are more than 100 well-described species, many of which are pathogenic for humans and a wide range of domestic and wild animals ¹⁷¹. Nevertheless, the spectrum of *Mycoplasma* species still needs to be understood because they are fastidious in detecting, cultivating and identifying in the laboratory. Several species cause significant health burdens worldwide, including high treatment costs, high morbidity, decreased performance and severe consequences to the medical and veterinary fields. For example, in ruminants, *Mycoplasma agalactiae* induces contagious agalactia and *Mycoplasma mycoides subsp. mycoides* led to severe

infectious pleuropneumonia. Both syndromes are listed in the World Organization for Animal Health (OIE) ¹⁷¹. Cattle are also infected by *Mycoplasma bovis*, one of the more pathogenic strains that manifest in causing mastitis, pneumonia, otitis and arthritis ¹⁷², while *Mycoplasma ovipneumoniae* is now emerging worldwide as a respiratory pathogen in domestic flocks of sheep and goats in addition to wildlife ¹⁷³. In poultry, the OIE has tackled avian mycoplasmosis caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae* and has a worldwide distribution of ¹⁷⁴. Even without overt clinical signs, they impair significant economic losses. *Mycoplasma* species differ markedly concerning pathogenicity, infectivity, tissue tropism and transmissibility, and the pathophysiology of *Mycoplasma*-associated diseases seems more complex than previously assumed. *Mycoplasma* often acts as secondary invaders when other pathogenic viruses and bacteria are present or when normal host defences are impaired by abiotic and biotic stressors ¹⁷⁵. Many examples in ruminants, swine and poultry illustrate the framework in which co-infection occurs. For instance, low pathogenic avian influenza viruses (LPAIV) are often coupled to co-infections by *Mycoplasma gallisepticum* and *Mycoplasma synoviae* ¹⁷⁶. Another case in point is the commensal *Mycoplasma dispar* and *Mycoplasma bovirhinis* in the upper respiratory tract in cattle, which proliferate, reaching exceptionally high abundance and invading the lung via inhalation ¹⁷⁷.

Despite recent advances based on the implementation of culture-independent diagnostic tests and antigen-based assays for *Mycoplasma* diagnosis, our knowledge about *Mycoplasma* species diversity, prevalence, and population dynamics worldwide still needs to be completed ¹⁷¹. *Mycoplasma* ecology is considered incredibly diverse, and most species have not yet been cultured and isolated (e.g., mycoplasmal dark matter). Shotgun sequencing of microbial communities could provide the solution to understanding the *Mycoplasma* association with different environments and hosts by enabling *in situ* and culture-free genomic characterisation. My main objective is to re-visit *Mycoplasma* species ecology by creating a comprehensive catalogue of *Mycoplasma* genomes from public repositories, which interrogates known and unknown genomes without prior knowledge. We will first reveal their ecological patterns across hosts and habitats by mining and organising *Mycoplasma* data from human and animal hosts, protists, ticks and other eukaryotes.

Next, within the IHAP unit, I am participating in an ANR project to understand the impact of respiratory glycome variations on the susceptibility of cattle to viral infections. We hypothesise that shifting the bovine airway microbiome taxonomic and metabolite profiles through selective antibiotic treatments will alter the glycome patterns in the respiratory tract and facilitate specific pathogen replications. By expanding shotgun metagenomic sequencing of the respiratory tract, I will help them to address this critical issue and optimise the methods to mitigate respiratory diseases.

Moreover, IHAP opened the scientific doors to me and offered a responsibility promotion and a bet on the future. In other words, I have accepted to be one of the deputy directors in the IHAP unit led by Prof. Jean-Luc Guerin. Working toward this new role will enhance my skill set and push me to gain organisational, management and leadership of complex experiences. This is important as, in the nearest future, we will be the ones to have ownership and supervision of the objectives decided today. Given that I am still an up-to-date expert on big-data technology and methodologies, I still get my hands on the bench, dive deeply into the literature, come from a different cultural background

(polyglot, $n =$ five languages) and have experienced other European research centres; I believe I will bring fresh perspectives at the unit.

The beauty and wonder of science boost researchers' well-being.

7



C U R R I C U L U M V I T A E

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Catalan (native)

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Research Experience

Date	Role	Stabilishment
2021-04-01-today	Researcher in holomics for surveillance of respiratory pathogens	INRAE, “ <i>Interactions hôtes-agents pathogènes</i> ”, École Nationale Vétérinaire de Toulouse, France
2013-09-01 > 2021-04-01	Researcher in functional genomics and exercise physiology	INRAE, Génétique Animale et Biologie Intégrative, Jouy-en-Josas
2012-10-01 > 2013-08-31	PostDoc in metagenomics- host genetics and gut microbiota interplay	INRAE, “ <i>Microbiologie de l’Alimentation au service de la Santé</i> ”, Jouy-en-Josas, France
2011-07-01 > 2012-09-30	PostDoc in n immunogenetics - multi-omics analysis of the immune response	INRAE, “ <i>Génétique Animale et Biologie Intégrative</i> ”, Jouy-en-Josas, France
2009-02-01 > 2011-05-31	PostDoc in livestock nutrigenomics - recent advances in milk quality	Wageningen UR Livestock Research, Wageningen, The Netherlands
2004/01/01 > 2008/12/31	PreDocPhD fellow in animal science - nutrition and welfare, who cares? European Joint Doctorate directed by Dr Devant and Dr Bach and issued by UAB, the Royal Veterinary and Agricultural University of Copenhagen, and Wageningen UR Livestock Research (The Netherlands)	Institute of Agrifood Research and Technology (IRTA), Barcelona, Spain
2003-07-01 > 2003-12-31	Veterinarian assistant	Girona, Spain

Academic Education

Date	Degree	Stablishment
2012	Bachelor’s Degree in Humanities	Open University of Catalonia, Barcelona, Spain
2008	European doctor in Food and Animal Science <i>Cum laude</i> qualification and outstanding doctorate award	Autonomous University of Barcelona, Barcelona, Spain
2006	D.E.A. in Animal Science	Autonomous University of Barcelona, Barcelona, Spain
2006	M2 in Development and International Cooperation	Polytechnic University of Barcelona, Barcelona, Spain
2003	Bachelor’s Degree in Veterinary Science	Autonomous University of Barcelona, Barcelona, Spain

Teaching

Bachelor Level (2010):

Thirty-six hours supervising the study of automatic sequencing of transposable elements in the genome.

Field of study (UNESCO codes): 24

Institution: Open University of Catalonia

Department: Informatics, Multimedia, and Telecommunications

visitors' address: Rambla Poblenou, 156, 08018 Barcelona, Spain

e-mail: nmach@uoc.edu

Internet: http://www.uoc.edu/portal/castellano/estudis_arees/informatica_multimedia_telecomunicacio/presentacio/missio/index.html

Master Degree (2009- 2017):

600 h of lecturer in Nutrigenomics and Nutrigenetics for the Master of Nutrition and Health

Field of study (UNESCO codes): 32

Institution: Open University of Catalonia

Department: Food and Health Science

visitors' address: Rambla Poblenou, 156, Barcelona, 08018 Barcelona, Spain

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Internet: http://www.uoc.edu/portal/castellano/institut_internacional_postgrau/index.html,

I launched this master's course in 2009 at the Open University of Catalonia (UOC; <https://www.uoc.edu/portal/en/metodologia-online-qualitat/index.html>). The UOC was created in 1995 as the world's first university with a virtual campus, which allowed its students to study at any time from any location. The University continually uses cutting-edge e-learning research and innovation to refine the UOC methodology. My teaching in the UOC's online master's degree in Nutrition and Health incorporated nutrigenomics, nutrigenetics, metagenomics, and epigenetics to offer a broad education to future professionals willing to work in personalised human nutrition. Most of the lessons strengthened the potential of these disciplines to provide strategies for developing safe and effective dietary interventions against the obesity epidemic and metabolic diseases. In 2009, I designed, prepared, and created teaching materials. Since then, I have been responsible for updating the materials, assessing the student's coursework, and setting and marking examinations for each edition. Because it is an online master's, there is some degree of flexibility, allowing me to plan the timings of tutorials during weekends and evenings. It has to be highlighted that from 2009 to 2017, the number of students who attended my course increased by 400%, going from an initial number of 40 to the final one of 160. Furthermore, international students accounted for over one-third of the growth in first-time enrolment.

I have taught over 600 students with diverse backgrounds and trained more than 40 Master's students, providing them with constructive feedback, research project guidance, and professional contacts. The supervision of Master's students undertaking research projects helped expand my organisation skills, my capacity to mentor people, create new connections at the national level and learn how to get the most out of students through delegating responsibilities. Additionally, working on length, selectivity, writing style, interpretation of data, and quality of the contents, I have been able to publish these Master theses into 11 peer-reviewed international articles (see list of publications) and 16 extension articles. Being a mentor of these Master's students has been one of the most personally satisfying roles I have ever held. I have experienced the joy of launching students in their professional careers and helping them publish their master's theses either in peer-reviewed international reviews or in Spanish peer-reviewed journals for general public diffusion.

Peer-reviewed articles

1. [Research article] **Núria Mach** (Corresponding author), Cédric Midoux, Sébastien Leclercq, Samuel Pennarun, Laurence Le Moyec, Olivier Rué, Céline Robert, Guillaume Sallé, Eric Barrey (2022). Mining the equine gut metagenome: poorly-characterized taxa associated with cardiovascular fitness in endurance athletes. *Communications Biology*, 5, <https://dx.doi.org/10.1038/s42003-022-03977-7>, <https://hal.inrae.fr/hal-03794437>, OA
2. [Research article] Alice Ruet, Cécile Arnould, Julie Lemarchand, Celine Parias, **Núria Mach**, et al. (2022) Horse welfare: A joint assessment of four categories of behavioural indicators using the AWIN protocol, scan sampling, and surveys. *Animal Welfare Journal*, Universities Federation for Animal Welfare, 2022, <10.7120/09627286.31.3.008>.
3. [Research article] Joshua Malsa, Elise Courtot, Michel Boisseau, Bertrand Dumont, Pascale Gombault, Tetiana A. Kuzmina, Marta Basiaga, Jérôme Lluch, Gwenolah Annonay, Sophie Dhorne-Pollet, **Núria Mach**, Jean-François Sutra, Laurence Wimel, Cédric Dubois, Fabrice Guégnard, Delphine Serreau, Anne Lespine, Guillaume Sallé, Géraldine Fleurance (2022). Effect of sainfoin (*Onobrychis vicifolia*) on cyathostomin egg excretion, larval development, larval community structure and efficacy of ivermectin treatment in horses. *Parasitology*, <https://dx.doi.org/10.1017/S0031182022000853>, <https://hal.inrae.fr/hal-03753744>, OA
4. [Review] **Núria Mach** (Corresponding author), Núria Mach, Eric Baranowski, Laurent Xavier Nouvel, Christine Citti (2021-05-14). The Airway Pathobiome in Complex Respiratory Diseases: A Perspective in Domestic Animals. *Frontiers in Cellular and Infection Microbiology*, 11, 583600, <https://dx.doi.org/10.3389/fcimb.2021.583600>, <https://hal.inrae.fr/hal-03228289>, OA
5. [Research article] **Núria Mach** (Corresponding author), Léa Lansade, David Bars-Cortina, Sophie Dhorne-Pollet, Aline Foury, Marie-Pierre Moisan, Alice Ruet (2021-03-03). Gut microbiota resilience in horse athletes following holidays out to pasture. *Scientific Reports*, 11, <https://dx.doi.org/10.1038/s41598-021-84497-y>, <https://hal.inrae.fr/hal-03197215>, OA
6. [Research article] **Núria Mach** (Corresponding author), Marco Moroldo, Andrea Rau, Jérôme Lecardonnel, Laurence Le Moyec, Céline Robert, Eric Barrey (2021). Understanding the Holobiont: Crosstalk Between Gut Microbiota and Mitochondria During Long Exercise in Horse. *Frontiers in Molecular Biosciences*, 8, <https://dx.doi.org/10.3389/fmolb.2021.656204>, <https://hal.inrae.fr/hal-03197210>, OA
7. [Research article] Guillaume Salle, Cécile Canlet, Jacques Cortet, Christine Koch, Joshua Malsa, Fabrice Reigner, Mickaël Riou, Noémie Perrot, Alexandra Blanchard, **Núria Mach** (2021). Integrative biology defines novel biomarkers of resistance to strongylid infection in horses. *Scientific Reports*, 11 (1), 15 p., <https://dx.doi.org/10.1038/s41598-021-93468-2>, <https://hal.inrae.fr/hal-03284457>, OA
8. [Research article] Yulíaxis Ramayo-caldas, Laura Zingaretti, Milka Popova, Jordi Estellé, Aurelien Bernard, Nicolas Pons, Pau Bellot, **Núria Mach**, Andrea Rau, Hugo Roume, Miguel Perez-enciso, Philippe Faverdin, Nadège Edouard, Dusko Ehrlich, Diego Morgavi, Gilles G. Renand (2020). Identification of rumen microbial biomarkers linked to methane emission in Holstein dairy cows. *Journal of Animal Breeding and Genetics*, 137 (1), 49-59, <https://dx.doi.org/10.1111/jbg.12427>, <https://hal.inrae.fr/hal-02495627>, OA
9. [Research article] Francesca Massacci, Allison Clark, Alice Ruet, Léa Lansade, Márcio Costa, **Núria Mach** (Corresponding author)(2020). Inter-breed diversity and temporal dynamics of the faecal microbiota in healthy horses. *Journal of Animal Breeding and Genetics*, 137 (1), 103-120, <https://dx.doi.org/10.1111/jbg.12441>, <https://hal.inrae.fr/hal-02624117>
10. [Research article] J.H. van Der Kolk, S. Thomas, **Núria Mach**, A. Ramseyer, D. Burger, V. Gerber, J-M. Nuoffer (2020). Serum acylcarnitine profile in endurance horses with and without metabolic dysfunction. *Veterinary Journal*, 255, 105419, <https://dx.doi.org/10.1016/j.tvjl.2019.105419>, <https://hal.inrae.fr/hal-03356899>
11. [Research article] **Núria Mach** (Corresponding author), Alice Ruet, Allison Clark, David Bars-Cortina, Yulíaxis Ramayo-Caldas, Elisa Crisci, Samuel Pennarun, Sophie Dhorne-Pollet, Aline Foury, Marie-Pierre Moisan, Léa Lansade (2020). Priming for welfare: gut microbiota is associated with equitation conditions and behaviour in horse athletes. *Scientific Reports*, 10, <https://dx.doi.org/10.1038/s41598-020-65444-9>, <https://hal.inrae.fr/hal-03197220>, OA
12. [Research article] Alice Ruet, Cécile Arnould, Justine Levray, Julie Lemarchand, **Núria Mach**, Marie-Pierre Moisan, Aline Foury, Christine Briant, Léa Lansade (2020). Effects of a temporary period on pasture on the welfare state of horses housed in individual boxes. *Applied Animal Behaviour Science*, 228, 1-8, <https://dx.doi.org/10.1016/j.applanim.2020.105027>, <https://hal.inrae.fr/hal-03536907>, OA
13. [Research article] Alice Ruet, Julie Lemarchand, Céline Parias, **Núria Mach**, Marie-Pierre Moisan, Aline Foury, Christine Briant, Léa Lansade (2019). Housing horses in individual boxes is a challenge with regard to welfare. *Animals*, 9 (9), 1-19, <https://dx.doi.org/10.3390/ani9090621>, <https://hal.inrae.fr/hal-02623360>, OA
14. [Research article] Sophie Dhorne-Pollet, Elisa Crisci, **Núria Mach** (Co-first author), Patricia Renson, Florence Jaffrezic, Guillemette Marot, Tatiana Maroilley, Marco Moroldo, Jerome Lecardonnel, Fany Blanc, Nicolas Bertho, Olivier Bourry, Elisabetta Giuffra (2019). The miRNA-targeted transcriptome of porcine alveolar macrophages upon infection with porcine reproductive and respiratory syndrome virus. *Scientific Reports*, 9 (1), 3160, <https://dx.doi.org/10.1038/s41598-019-39220-3>, <https://hal.inrae.fr/hal-02573144>, OA
15. [Research article] Sandra Plancade, Allison Clark, Catherine Philippe, Jean-Christophe Helbling, Marie-Pierre Moisan, Diane Esquerré, Laurence Le Moyec, Céline Robert, Eric Barrey, **Núria Mach** (Corresponding author)(2019). Unraveling the effects of the gut microbiota composition and function on horse endurance physiology. *Scientific Reports*, 9 (1), 9620, <https://dx.doi.org/10.1038/s41598-019-46118-7>, <https://hal.inrae.fr/hal-02489982>, OA

16. [Research article] Laurence Le Moyec, Céline Robert, Mohamed Triba, Nadia Bouchemal, **Núria Mach**, Julie Riviere, Emmanuelle Zalachas-Rebours, Eric Barrey (2019-06-12). A First Step Toward Unraveling the Energy Metabolism in Endurance Horses: Comparison of Plasma Nuclear Magnetic Resonance Metabolomic Profiles Before and After Different Endurance Race Distances. *Frontiers in Molecular Biosciences*, 6, <https://dx.doi.org/10.3389/fmolb.2019.00045>, <https://hal.inrae.fr/hal-02409471>, OA
17. [Research article] Léa Lansade, Aline Foury, Fabrice Reigner, Marianne Vidament, Elodie Guettier, Gwenaëlle Bouvet, Delphine Soulet, Céline Parias, Alice Ruet, **Núria Mach**, Frédéric Lévy, Marie-Pierre Moisan (2018). Progressive habituation to separation alleviates the negative effects of weaning in the mother and foal. *Psychoneuroendocrinology*, 97, 59-68, <https://dx.doi.org/10.1016/j.psyneuen.2018.07.005>, <https://hal.inrae.fr/hal-02623405>
18. [Research article] Sara Pegolo, **Núria Mach**, Yulixias Ramayo Caldas, Stefano Schiavon, Giovanni Bittante, Alessio Cecchinato (2018). Integration of GWAS, pathway, and network analyses reveals novel mechanistic insights into the synthesis of milk proteins in dairy cows. *Scientific Reports*, 12 (8), 566, <https://dx.doi.org/10.1038/s41598-017-18916>, <https://hal.inrae.fr/hal-02627260>, OA
19. [Research article] Allison Clark, Guillaume Salle, Valentine Ballan, Fabrice Reigner, Annabelle Meynadier, Jacques Cortet, Christine Koch, Mickaël Riou, Alexandra Blanchard, **Núria Mach** (Corresponding author)(2018). Strongyle infection and gut microbiota: profiling resistant and susceptible horses over a grazing season. *Frontiers in Physiology*, (9), 1-18, <https://dx.doi.org/10.3389/fphys.2018.00272>, <https://hal.inrae.fr/hal-02625557>, OA
20. [Research article] Carol Lee, Marco Moroldo, Alvaro Perdomo-Sabogal, **Núria Mach**, Sylvain Marthey, Jérôme Lecardonnel, Per Wahlberg, Amanda Y. Chong, Jordi Estellé, Simon Y.W. Ho, Claire Rogel Gaillard, Jaime Gongora (2018). Inferring the evolution of the major histocompatibility complex of wild pigs and peccaries using hybridization DNA capture-based sequencing. *Immunogenetics*, 70 (6), 401-417, <https://dx.doi.org/10.1007/s00251-017-1048-9>, <https://hal.inrae.fr/hal-02629389>, OA
21. [Research article] Anne Ricard, Céline Robert, Christine Blouin, Fanny Baste, Gwendoline Torquet, Caroline Morgenthaler, Julie Riviere, **Núria Mach**, Xavier Mata, Laurent Schibler, Eric Barrey (2017). Endurance exercise ability in the horse: A trait with complex polygenic determinism. *Frontiers in Genetics*, 8, Non paginé, <https://dx.doi.org/10.3389/fgene.2017.00089>, <https://hal.inrae.fr/hal-02623665>, OA
22. [Review] **Núria Mach** (Corresponding author), Dolores Fuster-Botella (2017). Endurance exercise and gut microbiota: a systematic review. *Journal of Sport and Health Science*, 6 (2), 179-197, <https://dx.doi.org/10.1016/j.jshs.2016.05.001>, <https://hal.inrae.fr/hal-02620229>, OA
23. [Review] **Núria Mach** (Corresponding author; INVITED), Allison Clark (2017). Micronutrient Deficiencies and the Human Gut Microbiota. *Trends in Microbiology*, 25 (8), 607-610, <https://dx.doi.org/10.1016/j.tim.2017.06.004>, <https://hal.inrae.fr/hal-01606579>
24. [Review] Allison Clark, **Núria Mach** (Corresponding author) (2017). The Crosstalk between the Gut Microbiota and Mitochondria during Exercise. *Frontiers in Physiology*, 8, 1-17, <https://dx.doi.org/10.3389/fphys.2017.00319>, <https://hal.inrae.fr/hal-01604194>, OA
25. [Research article] Robert J Schaefer, Mikkel K Schubert, Ernest K Bailey, Danika L Bannasch, Eric Barrey, Gila Kahila Bar-Gal, Gottfried J Brem, Samantha A Brooks, Ottmar K Distl, Ruedi K Fries, Carrie J Finno, Vinzenz K Gerber, Bianca K Haase, Vidhya K Jagannathan, Ted K Kalbfleisch, Tosso K Leeb, Gabriella K Lindgren, Maria Susana Lopes, **Núria Mach**, Artur Dacamara Machado, James N Macleod, Annette K Mccoy, Julia K Metzger, Cecilia K Penedo, Sagi K Polani, Stefan K Rieder, Imke K Tammen, Jens K Tetens, Georg P Thaller, Andrea P Verini-Supplizi, Claire M Wade, Barbara T Wallner, Ludovic Orlando, James R Mickelson, Molly E Mccue (2017). Developing a 670k genotyping array to tag similar to 2M SNPs across 24 horse breeds. *BMC Genomics*, 18, <https://dx.doi.org/10.1186/s12864-017-3943-8>, <https://hal.inrae.fr/hal-02626769>, OA
26. [Research article] **Núria Mach** (Corresponding author), Aline Foury, Sandra Kittelmann, Fabrice Reigner, Marco Moroldo, Maria Ballester, Diane Esquerre, Julie Riviere, Guillaume Salle, Philippe Gerard, Marie-Pierre Moisan, Léa Lansade (2017). The effects of weaning methods on gut microbiota composition and horse physiology. *Frontiers in Physiology*, 8, 21 p., <https://dx.doi.org/10.3389/fphys.2017.00535>, <https://hal.inrae.fr/hal-01578843>, OA
27. [Research article] Sara Pegolo, Christos Dadousis, **Núria Mach**, Yulixias Ramaya Caldas, Marcello Mele, Giuseppe Conte, Stefano Schiavon, Giovanni Bittante, Alessio Cecchinato (2017). SNP co-association and network analyses identify E2F3, KDM5A and BACH2 as key regulators of the bovine milk fatty acid profile. *Scientific Reports*, 7, 1-19, <https://dx.doi.org/10.1038/s41598-017-17434-7>, <https://hal.inrae.fr/hal-02629106>, OA
28. [Research article] **Núria Mach** (Corresponding author), Yulixias Ramayo Caldas, Allison Clark, Marco Moroldo, Céline Robert, Eric Barrey, Jesús María López, Laurence Le Moyec (2017). Understanding the response to endurance exercise using a systems biology approach: combining blood metabolomics, transcriptomics, and miRNomics in horses. *BMC Genomics*, 18 (1), 1-17, <https://dx.doi.org/10.1186/s12864-017-3571-3>, <https://hal.inrae.fr/hal-01602618>, OA
29. [Research article] **Núria Mach**, (Corresponding author) Sandra Plancade, Alicja Pacholewska, Jérôme J. Lecardonnel, Julie Riviere, Marco Moroldo, Anne Vaiman, Caroline Morgenthaler, Marine Beinat, Alizée Nevot, Céline Robert, Eric Barrey (2016). Integrated mRNA and miRNA expression profiling in blood reveal candidate biomarkers associated with endurance exercise in the horse. *Scientific Reports*, 6, 22932, <https://dx.doi.org/10.1038/srep22932>, <https://hal.inrae.fr/hal-02489989>, OA
30. [Review] Allison Clark, **Núria Mach** (Corresponding author) (2016). Role of Vitamin D in the hygiene hypothesis: the interplay between vitamin D, vitamin D receptors, gut microbiota, and immune response. *Frontiers in Immunology*, 7, np, <https://dx.doi.org/10.3389/fimmu.2016.00627>, <https://hal.inrae.fr/hal-01604340>, OA
31. [Review] Maria Oliver Bonet, **Núria Mach** (Corresponding author) (2016). Factores nutricionales y no nutricionales pueden afectar la fertilidad masculina mediante mecanismos epigenéticos. *Nutrición Hospitalaria*, 33 (5), 1236-1244, <https://dx.doi.org/10.20960/nh.591>, <https://hal.inrae.fr/hal-01602825>, OA
32. [Review] Allison Clark, **Núria Mach** (Corresponding author) (2016). Exercise-induced stress behaviour, gut-microbiota-brain axis and diet: a systematic review for athletes. *Journal of the International Society of Sports Nutrition*, 13, 1-21, <https://dx.doi.org/10.1186/>

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33. [Research article] Alicja Pacholewska, **Núria Mach**, Xavier Mata, Anne Vaiman, Laurent Schibler, Eric Barrey, Vincent Gerber (2016). Novel equine tissue miRNAs and breed-related miRNAs are expressed in serum. *BMC Genomics*, 17, 1-15, <https://dx.doi.org/10.1186/s12864-016-3168-2>, <https://hal.inrae.fr/hal-01602357>, OA
34. [Research article] Sara Pegolo, Alessio Cecchinato, **Núria Mach**, Massimiliano Babbucci, Marianna Pauletto, Luca Bargelloni, Stefano Schiavon, Giovanni Bittante (2016). Transcriptomic changes in the liver of young bulls caused by diets low in mineral and protein contents and supplemented with n-3 fatty acids and conjugated linoleic acid. *PLoS ONE*, 11 (12), 1-24, <https://dx.doi.org/10.1371/journal.pone.0167747>, <https://hal.inrae.fr/hal-01602348>, OA
35. [Short article] Yulixaxis Ramayo-Caldas, **Núria Mach**, Patricia P. Lepage, Florence F. Levenez, Catherine C. Denis, Gaetan G. Lemonnier, Jean Jacques J. J. Leplat, Yvon Y. Billon, Mustapha M. Berri, Joël Doré, Claire Rogel Gaillard, Jordi Estellé (2016). Phylogenetic network analysis applied to pig gut microbiota identifies an ecosystem structure linked with growth traits. *ISME Journal*, 10 (12), 2973-2977, <https://dx.doi.org/10.1038/ismej.2016.77>, <https://hal.inrae.fr/hal-02637857>, OA
36. [Research article] Edin Hamzic, Rikke Brødsgaard Kjaerup, **Núria Mach**, Guilietta Minozzi, Francesco Strozzi, Valentina Gualdi, John L. Williams, Jun Chen, Eva Watrang, Bart Buitenhuis, Helle Risdahl Juul-Madsen, Tina Sørensen Dalgaard (2016). RNA sequencing-based analysis of the spleen transcriptome following infectious bronchitis virus infection of chickens selected for different mannose-binding lectin serum concentrations. *BMC Genomics*, 17, <https://dx.doi.org/10.1186/s12864-016-2403-1>, <https://hal.inrae.fr/hal-02633637>, OA
37. [Review] Maria Oliver Bonet, **Núria Mach** (Corresponding author) (2016). Factores nutricionales y no nutricionales pueden afectar la fertilidad masculina mediante mecanismos epigenéticos. *Nutrición Hospitalaria*, 33 (5), 1236-1244, <https://dx.doi.org/10.20960/nh.591>, <https://hal.inrae.fr/hal-01602825>, OA
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Conference papers

1. [Oral presentation] Michel Boisseau, Sophie Dhorne-Pollet, David Bars, Elise Courtot, Delphine Serreau, Gwenolah Annonay, Claire Kuchly, Amandine Gesbert, Fabrice Reigner, **Núria Mach**, Guillaume Sallé (2022-07-04). Dynamic stability of the cyathostomin – gut microbiota interactions in horses. Presented at: Journées d'Animation Scientifique de la FéRI 2022 - FéRI Scientific Days 2022, Joué-Lès-Tours, France (2022-07-04 - 2022-07-05), <https://hal.inrae.fr/hal-03735407>
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3. [Oral presentation ; INVITED] **Núria Mach** (2021-11-16). A catalog of gut microbial genes: Compelling new clues as to how the microbiome can influence endurance performance in horses. Presented at: Journées du PEPI IBIS 2021, Toulouse, France (2021-11-16), <https://hal.inrae.fr/hal-03767908>
4. [Oral presentation] Sandra Placade, Allison Clark, Catherine Philippe, Jean-Christophe Helbling, Marie-Pierre Moisan, Diane Esquerré, L. Le Moyec, Céline Robert, Eric Barrey, **Núria Mach** (2019-07-07). Unraveling the effects of the gut microbiota composition and function on horse endurance physiology. Presented at: 37. International Society for Animal Genetics, Lleida, Espagne (2019-07-07 - 2019-07-12), <https://hal.inrae.fr/hal-02734533>
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7. [Oral presentation] Jordi Estellé, **Núria Mach**, Yulixaxis Ramayo Caldas, Florence Levenez, Gaetan Lemonnier, Catherine Denis, El Mostafa Berri, Marie-José Mercat, Yvon Billon, Joel Dore, Catherine Larzul, Patricia Lepage, Claire Rogel Gaillard (2018-08-27). On the influence of host genetics on gut microbiota composition in pigs. Presented at: 69. Annual Meeting of the European Association of Animal Production (EAAP), Dubrovnik, Croatie (2018-08-27 - 2018-08-30), <https://hal.inrae.fr/hal-02733939>
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- 18.[Oral presentation] Eric Barrey, **Núria Mach**, Xavier Mata, Anne Vaiman, Marco Moroldo, Jérôme Lecardonnell, Rachel Legendre, Sylvain Marthey, Denis Laloë, Florence Jaffrezic, Andrea Rau, Alice Ruet, Sean S. Kennedy, Laurent Schibler (2014-02-25). Design a custom equine microRNA expression microarray using RNAseq data analysis of various equine tissues. Presented at: Agilent I. European Animal and Plant Symposium, Amsterdam, Pays-Bas (2014-02-25 - 2014-02-26), <https://hal.inrae.fr/hal-02801791>
- 19.[Oral presentation] **Núria Mach**, El Mostafa Berri, Diane Esquerre, Gaetan Lemonnier, Yvon Billon, Patricia Lepage, Isabelle P. Oswald, Joel Dore, Claire Gaillard, Jordi Estellé (2013-08-28). Extensive comparison of genome-wide transcription along small pig intestine and in Peyer's patches by RNA-seq. Presented at: 10. International Veterinary Immunology Symposium (IVIS), Milano, Italie (2013-08-28 - 2013-09-01), <https://hal.inrae.fr/hal-01193881>
- 20.[Oral presentation] **Núria Mach**, Gaetan Lemonnier, Jérôme Lecardonnell, Jordi Estellé, Claire Gaillard (2013-08-28). The peripheral blood transcriptome reflects variations in swine immunity traits: towards identifying biomarkers. Presented at: 10. International Veterinary Immunology Symposium, Milano, Italie (2013-08-28 - 2013-09-01), <https://hal.inrae.fr/hal-01193882>
- 21.[Oral presentation] Claire Gaillard, **Núria Mach**, Jordi Estellé (2012-07-15). Genome-wide association and transcriptome studies for immunity traits in French Large White pigs. Presented at: 33. Conference of the International Society for Animal Genetics (ISAG), Cairns, Australie (2012-07-15 - 2012-07-20), <https://hal.inrae.fr/hal-01193964>, OA
- 22.[Oral presentation] **Núria Mach**, Yu Gao, Gaetan Lemonnier, Jérôme Lecardonnell, Jordi Estellé, Claire Gaillard (2012-02-16). Blood transcriptome as an emerging molecular phenotype to study immunocompetence in swine. Presented at: COST Action FA0902 Understanding and combating PRRS in Europe, Lodi, Italie (2012-02-16 - 2012-02-17), conférence invitée. <https://hal.inrae.fr/hal-01193961>
- 23.[Oral presentation] Jaime Gongora, **Núria Mach**, Jordi Estellé, Per Wahlberg, Sylvain Marthey, Jérôme Lecardonnell, Marie-Thérèse Bihoreau, Claire Gaillard, Marco Moroldo (2012-01-14). The efficiency of heterologous capture for targeted resequencing of the Major Histocompatibility Complex in Suidae and Tayassuidae. Presented at: 20. Plant and Animal Genome, San Diego, CA, États-Unis (2012-01-14 - 2012-01-18), <https://hal.inrae.fr/hal-01019000>
- 24.[Oral presentation] Claire Gaillard, Yu Gao, **Núria Mach**, Jordi Estellé (2012-09-02). Genetics and genomics of immune traits in swine. Presented at: 4. European Veterinary Immunology Workshop (EVIW), Edimbourg, Royaume-Uni (2012-09-02 - 2012-09-04), <https://hal.inrae.fr/hal-01193962>
- 25.[Oral presentation] **Núria Mach**, Yu Gao, Gaetan Lemonnier, Jérôme Lecardonnell, Jordi Estellé, Claire Gaillard (2011-10-10). Blood transcriptome as an emerging molecular phenotype to refine immune traits in pigs. Presented at: 4. International Symposium on Animal Functional Genomics, Dublin, Irlande (2011-10-10 - 2011-12-10), <https://hal.inrae.fr/hal-01193877>
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- 27.[Oral presentation] **Núria Mach**, Yuna Blum, David Causeur, Sandrine Lagarrigue, M. A. Smits (2011-08-29). Effect of the gene diacylglycerol-O-transferase 1 (DGAT1) polymorphism on the global expression pattern of genes in the mammary gland tissue of dairy cows. Presented at: 62. Annual Meeting of the European Federation of Animal Science (EAAP), Stavanger, Norvège (2011-08-29 - 2011-09-02), <https://hal.inrae.fr/hal-02747109>
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- 29.[Oral presentation] **Núria Mach**, A.A.A. Jacobs, L. Kruijt, J. van Baal, M.A. Smits (2010-07-26). Alteration of gene expression in mammary gland tissue of dairy cows in response to dietary unsaturated fatty acids. Presented at: 32. Conference for the International Society for Animal Genetics (ISAG), Edinburgh, Royaume-Uni (2010-07-26 - 2010-07-30), <https://hal.inrae.fr/hal-02755768>
- 30.[Oral presentation] **Núria Mach**, E. Keuning, L. Kruijt, M. Hortós, J. Arnau, M. F. W. Te Pas (2009-08-24). Comparative proteomic profiling of two muscles from five divergent pig breeds using SELDI-TOF proteomics technology. Presented at: 60. Annual Meeting of the European Federation of Animal Science, Barcelona, Espagne (2009-08-24 - 2009-08-27), <https://hal.inrae.fr/hal-02755683>
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- 32.[Oral presentation] **Núria Mach**, A. Bach, M. Devant (2008-07-07). Glycerin affects the performance and meat quality of young Holstein bulls fed high-concentrate diets. Presented at: ADSA/ASA Joint Meeting Congress, Indianapolis, États-Unis (2008-07-07 - 2008-07-11), <https://hal.inrae.fr/hal-02755688>

- 33.[Oral presentation] **Núria Mach**, M. Devant, A. Bach, A. Velarde (2007-07-08). Effect of animal, transportation, and slaughterhouse variables on beef behaviour at the slaughterhouse. Presented at: ADSA/ASA Joint Meeting Congress, San Antonio, États-Unis (2007-07-08 - 2007-07-12), <https://hal.inrae.fr/hal-02755690>
- 34.[Oral presentation] **Núria Mach**, M. Devant, A. Bach, A. Velarde (2006-07-09). Associations between animal, transportation, slaughterhouse practices and beef's meat pH. Presented at: ADSA/ASA Joint Meeting Congress, Minneapolis, États-Unis (2006-07-09 - 2006-07-13), <https://hal.inrae.fr/hal-02755687>
- 35.[Oral presentation] **Núria Mach**, M. Devant, A. Bach, I. Diaz, M. Font I Furnols, M. Oliver, J.A. Garcia (2005-07-24). Improve the omega-3 fatty acid content of meat from young Holstein bulls receiving a high-concentrate diet. Presented at: ADSA/ASA Joint Meeting Congress, Cincinnati, États-Unis (2005-07-24 - 2005-07-28), <https://hal.inrae.fr/hal-02763195>
- 36.[Poster] Sophie Dhorne-Pollet, Anne Boland-Augé, Robert Olasso, Claire Hoede, Christine Gaspin, **Núria Mach**, Jean-Francois Deleuze, Eric Barrey (2017-10-23). Hippocode: A project to improve the annotation of equine non-coding RNAs involved in regulating mitochondrial functions. Presented at: Targeting Mitochondria world congress, Berlin, Allemagne (2017-10-23 - 2017-10-24), <https://hal.inrae.fr/hal-02786720>
- 37.[Poster] **Núria Mach**, El Mostafa Berri, Diane Esquerre, Claire Chevalyere, Gaetan Lemonnier, Yvon Billon, Patricia Lepage, Isabelle P. Oswald, Joel Dore, Claire Gaillard, Jordi Estellé (2014-01-11). Exhaustive comparison of gene expression along small pig Intestine and in Peyer's patches performed by RNA-Seq. Presented at: Plant and Animal Genome XXII, San Diego, États-Unis (2014-01-11 - 2014-01-15), <https://hal.inrae.fr/hal-01193883>
- 38.[Poster] Jordi Estellé, **Núria Mach**, Yulixais Ramayo Caldas, Florence Levenez, Gaetan Lemonnier, Catherine Denis, Joel Dore, Yvon Billon, Marie-José Mercat, Catherine Larzul, Patricia Lepage, Claire Gaillard (2014-07-28). Gut microbiota composition in swine: genetic parameters and links with immunity traits. Presented at: 34. International Society for Animal Genetics Conference (ISAG), Xi'an, China (2014-07-28 - 2014-08-01), <https://hal.inrae.fr/hal-01193953>
- 39.[Poster] Jordi Estellé, **Núria Mach**, Yulixais Ramayo Caldas, Florence Levenez, Gaetan Lemonnier, Catherine Denis, Joel Dore, Catherine Larzul, Patricia Lepage, Claire Gaillard (2014-08-17). The influence of host genetics on the gut microbiota composition in pigs and its links with immunity traits. Presented at: 10. World Congress of Genetics Applied to Livestock Production, Vancouver, Canada (2014-08-17 - 2014-08-22), <https://hal.inrae.fr/hal-01193952>
- 40.[Poster] Núria Mach, Patricia Lepage, Florence Levenez, Gaetan Lemonnier, Catherine Denis, Jean-Denis Bailly, Jean Jacques Leplat, Joel Dore, Jordi Estellé, Claire Gaillard (2013-01-24). Gut microbiota and immunity interplay at the mucosal interface in swine, a data integration approach. Presented at: Statistical Methods for (Post)-Genomics Data workshop, Amsterdam, Pays-Bas (2013-01-24 - 2013-01-25), <https://hal.inrae.fr/hal-01193880>
- 41.[Poster] **Núria Mach**, Yu Gao, Gaetan Lemonnier, Jérôme Lecardonnel, Jordi Estellé, Claire Gaillard (2012-07-15). The peripheral blood transcriptome dynamically reflects immunocompetence in swine. Presented at: 33. Conference of the International Society for Animal Genetics, Cairns, Australie (2012-07-15 - 2012-07-20), <https://hal.inrae.fr/hal-01193879>
- 42.[Poster] **Núria Mach**, Marco Moroldo, Sylvain Marthey, Asako Ando, Jun-Heon Lee, Chak-Sum Ho, Joan Lunney, Jordi Estellé, Claire Gaillard (2012-07-15). Diversity studies of SLA haplotypes by targeted high-throughput resequencing of the whole locus. Presented at: 33. Conference of the International Society for Animal Genetics, Cairns, Australie (2012-07-15 - 2012-07-20), <https://hal.inrae.fr/hal-01193878>
- 43.[Poster] **Núria Mach**, A. M. van Vuuren, R Zom, M. A. Smits (2011). Effect of linseed supplementation on gene expression in mammary gland tissue of early-lactating dairy cattle. Presented at: Eight International Symposium on the Nutrition of Herbivores, Wales, Royaume-Uni (2011 - 2011), <https://hal.inrae.fr/hal-02807298>
- 44.[Poster] **Núria Mach**, J. van Baal, L. Kruijt, M.A. Smits (2010-08-01). Lipid metabolism gene expression profiles correlated with fatty acids in the milk of dairy cows fed unprotected unsaturated fatty acids. Presented at: 9. World Congress on Genetics Applied to Livestock Production (WCGALP), Leipzig, Allemagne (2010-08-01 - 2010-08-06), <https://hal.inrae.fr/hal-02754643>
- 45.[Poster] **Núria Mach**, M. Font I Furnols, M. Devant (2008-08-10). Effects of pre-pubertal Burdizzo castration on performance, carcass characteristics and meat quality from young Holstein bulls fed high-concentrate diets. Presented at: 54. International Congress of Meat Science and Technology (54th ICoMST), Cape Town, Afrique du Sud (2008-08-10 - 2008-08-15), <https://hal.inrae.fr/hal-02822781>
- 46.[Poster] **Núria Mach**, A. Bach, M Devant (2008-08-10). Effects of glycerin supplementation on meat pH of young Holstein bulls mixed at the slaughterhouse. Presented at: 54. International Congress of Meat Science and Technology (54th ICoMST), Cape Town, Afrique du Sud (2008-08-10 - 2008-08-15), <https://hal.inrae.fr/hal-02821094>
- 47.[Poster] **Núria Mach**, M. Font I Furnols, M. Devant (2008-08-10). Near-infrared transmission spectroscopy for predicting intramuscular fat content from young Holstein bulls fed high-concentrate diets. Presented at: 54. International Congress of Meat Science and Technology (54th ICoMST), Cape Town, Afrique du Sud (2008-08-10 - 2008-08-15), <https://hal.inrae.fr/hal-02820861>
- 48.[Poster] Susanne Knochel, **Núria Mach**, Anders Hans Karlsson (2007-08-05). Microbial and physical changes in high and normal pH marinated beef during storage in different atmospheres. Presented at: 53. International Congress on Meat Science and Technology (ICoMST), Beijing, China (2007-08-05 - 2007-08-09), <https://hal.inrae.fr/hal-02821092>
- 49.[Poster] Núria Mach, S. Knochel, A. Karlsson, M. Devant (2006-11-30). Changes in DFD beef: bacterial diversity, marination meat characteristics, and different MAP conditions. Presented at: 2. European Symposium of Food Safety, Barcelona, Espagne (2006-11-30 - 2006-12-01), <https://hal.inrae.fr/hal-02821090>

- 50.[Poster] **Núria Mach**, M. Devant, A. Bach, I. Diaz, M. Font I Furnols, M. A. Oliver, J. A. García (2005-07-24). Improve the omega-3 fatty acid content of meat from young Holstein bulls receiving a high-concentrate diet. Presented at: ADSA/ASA Joint Meeting Congress, Cincinnati, États-Unis (2005-07-24 - 2005-07-28), <https://hal.inrae.fr/hal-02763197>
- 51.[Oral presentation] Jordi Estellé, Catherine Larzul, **Núria Mach**, Florence Levenez, Yuliaxis Ramayo-Caldas, François Meurens, Marie-José Mercat, Gaëtan Lemonnier, Catherine Denis, Yvon Billon, Isabelle P. Oswald, Joël Doré, El Mostafa Berri, Patricia Lepage, Claire Rogel Gaillard (2016-02-02). *Microbiote intestinal chez le porc : paramètres génétiques de sa composition et liens avec des caractères immunitaires*. Presented at: 48. Journées de la Recherche Porcine, Paris, France (2016-02-02 - 2016-02-03), <https://hal.inrae.fr/hal-02288150>, OA
- 52.[Oral presentation] Jordi Estellé, Catherine Larzul, **Núria Mach**, Florence F. Levenez, Yuliaxis Ramayo Caldas, Francois Meurens, Marie-josé Mercat, Gaetan G. Lemonnier, Catherine C. Denis, Yvon Y. Billon, Isabelle P. Oswald, Joël Doré, Mustapha M. Berri, Patricia P. Lepage, Claire Rogel Gaillard (2016-02-02). *Microbiote intestinal chez le porc : paramètres génétiques de sa composition et liens avec des caractères immunitaires*. Presented at: 48. Journées de la Recherche Porcine, Paris, France (2016-02-02 - 2016-02-03), <https://hal.inrae.fr/hal-02742708>
- 53.[Poster] Guillaume Salle, **Núria Mach**, Jacques Cortet, Christine Koch, Fabrice Reigner, Mickaël Riou, Cécile Canlet, Alexandra Blanchard (2017-03-16). *Identification et caractérisation de marqueurs liés aux infestations par les petits strongles pour l'optimisation des schémas de vermifugation chez les équins*. Presented at: 43. Journée de la Recherche Equine, Paris, France (2017-03-16 - 2017-03-16), <https://hal.inrae.fr/hal-01604763>
- 54.[Poster] Aline Foury, Léa Lansade, Marianne Vidament, Frédéric Lévy, Jean-Marie Yvon, Fabrice Reigner, **Núria Mach**, Marie-Pierre Moisan (2017-03-16). *Effets du stress induit par le sevrage sur les indicateurs biologiques et transcriptomiques su stress chez les équins : Analyse comparative d'un sevrage progressif et d'un sevrage brutal*. Presented at: 43. Journée de la Recherche Equine, Paris, France (2017-03-16 - 2017-03-16), <https://hal.inrae.fr/hal-01607656>
- 55.[Poster] Guillaume Salle, **Núria Mach**, Jacques Cortet, Christine Koch, Fabrice Reigner, Alexandra Blanchard (2016-10-12). *Recherche de marqueurs liés aux infestations par les petits strongles pour l'optimisation des schémas de vermifugation chez les équins : caractérisation du métabolome, des paramètres biochimiques et du microbiote fécal*. Presented at: 42. Colloque annuel de l'AFSTAL, Nantes, France (2016-10-12 - 2016-10-14), <https://hal.inrae.fr/hal-01533912>

Extension articles

- [Review] Carlos Pardos-Sevilla, **Núria Mach** (Corresponding author) (2014). Efectos del té verde sobre el riesgo de cáncer de mama. *Revista Española de Nutrición Humana y Dietética*, 18 (1), 211-220, <https://hal.inrae.fr/hal-03774170>, OA
- [Review] Carol López Moriana, Núria Mach (Corresponding author) (2014). Influencia de la gestación, el parto y el tipo de lactancia sobre la microbiota intestinal del neonato. *Acta Pediátrica Española*, 72 (2), 37-44, <https://hal.inrae.fr/hal-02630600>
- [Review] Carol López Moriana, **Núria Mach** (Corresponding author) (2014). Influencia de la gestación, el parto y el tipo de lactancia sobre la microbiota intestinal del neonato. *Acta Pediátrica Española*, 72 (2), 37-44, <https://hal.inrae.fr/hal-02630600>
- [Review] Ángeles Molina Peralta, **Núria Mach** (Corresponding author) (2014). Alimentos ricos en ácidos grasos ω -3 libres de contaminantes y aptos para vegetarianos, y su importancia en el desarrollo neurológico normal. *Revista Española de Nutrición Humana y Dietética*, 18 (2), 89-99, <https://hal.inrae.fr/hal-02636586>
- [Review] María Aubets-Fuster, **Núria Mach** (Corresponding author) (2013). Mecanismos moleculares implicados en los posibles efectos de los compuestos fenólicos en la disminución del riesgo de enfermedades cardiovasculares. *Revista Española de Nutrición Humana y Dietética*, 17 (3), 110-116, <https://hal.inrae.fr/hal-01193869>, OA
- [Review] Encarna Mata González, **Núria Mach** (Corresponding author) (2013). La ingestión de la L-carnitina puede reducir la infertilidad masculina. *Revista Española de Nutrición Comunitaria*, 19 (3), 70-75, <https://hal.inrae.fr/hal-02647276>
- [Review] Concepción González Isabel, **Núria Mach** (Corresponding author) (2013). Influencia de la dieta sobre las citoquinas antiinflamatorias en la enfermedad de Crohn. *Revista Española de Nutrición Comunitaria*, 19 (1), 44-52, <https://hal.inrae.fr/hal-01193870>
- [Review] Amparo Arias, **Núria Mach** (Corresponding author) (2012). Efecto de los probióticos en el control de la obesidad humana: hipótesis no demostradas. *Revista Española de Nutrición Humana y Dietética*, 16 (3), 100-107, <https://hal.inrae.fr/hal-01193874>
- [Review] Patricia López Roldán, **Núria Mach** (Corresponding author) (2012). Efecto del consumo de astaxantina en la salud. *Revista Española de Nutrición Comunitaria*, 18 (3), 162-175, <https://hal.inrae.fr/hal-01193871>
- [Review] Laura Llacuna, **Núria Mach** (Corresponding author) (2012). Papel de los antioxidantes en la prevención del cáncer. *Revista Española de Nutrición Humana y Dietética*, 16 (1), 16-24, [https://dx.doi.org/10.1016/S2173-1292\(12\)70067-4](https://dx.doi.org/10.1016/S2173-1292(12)70067-4), <https://hal.inrae.fr/hal-03775181>
- [Review] Albert Cabrera, **Núria Mach** (Corresponding author) (2012). Flavonoides como agentes quimiopreventivos y terapéuticos contra el cáncer de pulmón. *Revista Española de Nutrición Humana y Dietética*, 16 (4), 143-153, <https://hal.inrae.fr/hal-01193873>
- [Review] Andrea Pérez Rovira, **Núria Mach** (Corresponding author) (2012). Efecto del consumo de soja en relación con los síntomas de la menopausia. *Revista Española de Nutrición Humana y Dietética*, 16 (2), 69-76, <https://hal.inrae.fr/hal-01193875>
- [Review] Montserrat Belmar López, Secundino López, Silvia Monserrat Vila, **Núria Mach** (2011). Dieta Mediterránea y enfermedad de Alzheimer. *Alimentaria: Revista de tecnología e higiene de los alimentos*, (427), 89-95, <https://hal.inrae.fr/hal-03774160>

- 14.[Review] Josefina Llargués Truyols, **Núria Mach** (Corresponding author) (2011). Hongos medicinales: prevención y apoyo al tratamiento del cáncer. *Alimentación, nutrición y Salud*, 11, 16-23, <https://hal.inrae.fr/hal-03774222>
- 15.[Review] Felix Rueda, J. C. Domingo, **Núria Mach** (2011). Efectos de los ácidos grasos omega 3 y otros suplementos alimenticios en procesos patológicos relacionados con la tercera edad. *Revista Española de Nutrición Humana y Dietética*, 15 (1), 20-29, <https://hal.inrae.fr/hal-03774165>
- 16.[Review] Rosa Álvarez, **Núria Mach** (Corresponding author) (2011). Estrategias para la prevención de la osteoporosis en la tercera edad: ¿alimentos o fármacos?. *Alimentaria: Revista de tecnología e higiene de los alimentos*, (425), 105-111, <https://hal.inrae.fr/hal-03774249>
- 17.[Research article] Rosa Álvarez Álvarez, Núria Mach (2011). Efecto de los ácidos grasos poliinsaturados omega-3 y omega-6 en el riesgo de cáncer de mama. *Revista Española de Nutrición Humana y Dietética*, 15 (2), 187-191, <https://hal.inrae.fr/hal-03774156>
- 18.[Review] Xavier Villanueva, **Núria Mach** (Corresponding author) (2011). Papel de los ácidos grasos omega 3 en la prevención del cáncer de colon. *Revista Española de Nutrición Humana y Dietética*, 15 (1), 30-38, <https://hal.inrae.fr/hal-03774167>
- 19.[Review] **Núria Mach** (Corresponding author) (2009). El marinado con vino orgánico: Una alternativa comercial para las carnes de vacuno DFD. *Eurocarne: La revista internacional del sector cárnico*, (175), 2-12, <https://hal.inrae.fr/hal-03774252>
- 20.[Review] **Núria Mach** (Corresponding author), Alex Bach, Carolina Realini, Maria Font I Furnols, Antonio Velarde, Maria Devant (2009). Efecto de la castración en terneros; rendimientos productivos y calidad de la canal y la carne. *Albétar: publicación veterinaria independiente*, (125), 1-4, <https://hal.inrae.fr/hal-03774226>
- 21.[Review] Isabel Diaz, **Núria Mach**, José-Antonio García-Regueiro (2004). Ácidos grasos trans y cis-trans en carnes y productos cárnicos. *Eurocarne: La revista internacional del sector cárnico*, (130), 1-6, <https://hal.inrae.fr/hal-03774224>
- 22.[Review] **Núria Mach** (Corresponding author) (2009). El marinado con vino orgánico: Una alternativa comercial para las carnes de vacuno DFD. *Eurocarne: La revista internacional del sector cárnico*, (175), 2-12, <https://hal.inrae.fr/hal-03774252>
- 23.[Review] **Núria Mach** (Corresponding author), Alex Bach, Carolina Realini, Maria Font I Furnols, Antonio Velarde, Maria Devant (2009). Efecto de la castración en terneros; rendimientos productivos y calidad de la canal y la carne. *Albétar: publicación veterinaria independiente*, (125), 1-4, <https://hal.inrae.fr/hal-03774226>
- 24.[Review] Isabel Diaz, **Núria Mach**, José-Antonio García-Regueiro (2004). Ácidos grasos trans y cis-trans en carnes y productos cárnicos. *Eurocarne: La revista internacional del sector cárnico*, (130), 1-6, <https://hal.inrae.fr/hal-03774224>

Pre-prints

- [Research article] Michel Boisseau, Sophie Dhorne-Pollet, David Bars-Cortina, Elise Courtot, Delphine Serreau, Gwenolah Annonay, Jérôme Lluch, Amandine Gesbert, Fabrice Reigner, Guillaume Sallé, **Núria Mach** (Corresponding author)(2022-09-02). Species interactions, stability, and resilience of the gut microbiota - helminth assemblage in horses. <https://dx.doi.org/10.21203/rs.3.rs-1955749/v1>, <https://hal.inrae.fr/hal-03767875>, OA [Under revision in the iScience journal]
- [Research article] Elise Courtot, Michel Boisseau, Sophie Dhorne-Pollet, Delphine Serreau, Amandine Gesbert, Fabrice Reigner, Marta Basiaga, Tetiana Kuzmina, Jerome Lluch, Gwenolah Annonay, Claire Kuchly, Irina Diekmann, Jürgen Krücken, Georg von Samson-Himmelstjerna, **Núria Mach**, Guillaume Sallé (2022-09-02). Evaluation of the nemabiome approach for the study of equine strongylid communities. <https://dx.doi.org/10.1101/2022.07.22.501098>, <https://hal.inrae.fr/hal-03767915>, OA [Under revision in the PeerJ journal]
- [Research article] Michel Boisseau, **Núria Mach**, Marta Basiaga, Sławomir Kornaś, Tetiana Kuzmina, Claire Laugier, Guillaume Sallé (2022-10-03). Patterns of variation in equine strongyle community structure across age groups and gut. <https://dx.doi.org/10.1101/2021.05.17.441725>, n° biorxiv: 2021.05.17.441725, <https://hal.inrae.fr/hal-03794670>, OA [Under revision, Parasites and Vectors]
- [Review] Michel Boisseau, **Núria Mach**, Marta Basiaga, Sławomir Kornaś, Tetiana Kuzmina, Claire Laugier, Guillaume Sallé (2022). Acta Parasitologica Meta-analysis of equine strongyle community structure. <https://hal.inrae.fr/hal-03792762>, OA [Under revision, Acta parasitologica]

PhD students supervision

Name	BISUTTI, Vittoria
Subject	Next-generation phenomics and genomic tool to enhance mammary gland in dairy cattle. Tesis supervised by Prof Alessio Cecchinato.
Date of defence	En cours
Supervision rate (%)	20% (PhD internship in my lab)
Published works	[Oral Presentation] V. Bisutti, Núria Mach, D. Giannuzzi, S. Pegolo, E. Capra, R. Negrini, A. Cecchinato, P. Ajmone-Marsan (2022-09-05). <i>Transcriptomic map of mastitis in dairy cows: clues on S. agalactiae and Prototheca infections</i> . Presented at: 73rd Annual Meeting of the European Federation of Animal Science, Porto, Portugal (2022-09-05 - 2022-09-09), https://hal.inrae.fr/hal-03767906 , OA
Student situation	Temporal IR contract at the University of Padova, Department of Agronomy, Food, Natural resources, Animals and Environment (DAFNAE).

Name	BOISSEAU, Michel
Subject	Résilience des communautés de cyathostomes et du microbiote digestif du cheval au traitement anthelminthique. Thesis supervised by Dr Guillaume Sallé and myself
Date of defence	Date of defence: 14/12/2022
Supervision rate (%)	50%
Published works	<p>[Research article] Elise Courtot, Michel Boisseau, Sophie Dhorne-Pollet, Delphine Serreau, Amandine Gesbert, Fabrice Reigner, Marta Basiaga, Tetiana Kuzmina, Jerome Lluch, Gwenolah Annonay, Claire Kuchly, Irina Diekmann, Jürgen Krücken, Georg von Samson-Himmelsjerna, Núria Mach, Guillaume Sallé (2022-09-02). Evaluation of the nemabiome approach for the study of equine strongylid communities. https://dx.doi.org/10.1101/2022.07.22.501098, https://hal.inrae.fr/hal-03767915, OA [In revision in the PeerJ journal]</p> <p>[Research article] Michel Boisseau, Sophie Dhorne-Pollet, David Bars-Cortina, Elise Courtot, Delphine Serreau, Gwenolah Annonay, Jérôme Lluch, Amandine Gesbert, Fabrice Reigner, Guillaume Sallé, Núria Mach (Corresponding author) (2022). Species interactions, stability, and resilience of the gut microbiota - helminth assemblage in horses. https://dx.doi.org/10.21203/rs.3.rs-1955749/v1, https://hal.inrae.fr/hal-03767875, OA [Under revision in the iScience journal]</p> <p>[Research article] Michel Boisseau, Núria Mach, Marta Basiaga, Sławomir Kornaś, Tetiana Kuzmina, Claire Laugier, Guillaume Sallé (2022-10-03). Patterns of variation in equine strongyle community structure across age groups and gut. https://dx.doi.org/10.1101/2021.05.17.441725, n° biorxiv: 2021.05.17.441725, https://hal.inrae.fr/hal-03794670, OA [In revision, Parasites and Vectors]</p> <p>[Review] Michel Boisseau, Núria Mach, Marta Basiaga, Sławomir Kornas, Tetiana Kuzmina, Claire Laugier, Guillaume Sallé (2022). Acta Parasitologica Meta-analysis of equine strongyle community structure. https://hal.inrae.fr/hal-03792762, OA [In revision, Acta parasitologica]</p> <p>[Présentation orale] Michel Boisseau, Sophie Dhorne-Pollet, David Bars, Elise Courtot, Delphine Serreau, Gwenolah Annonay, Claire Kuchly, Amandine Gesbert, Fabrice Reigner, Núria Mach, Guillaume Sallé (2022-07-04). <i>Dynamic stability of the cyathostomin – gut microbiota interactions in horses</i>. Presented at: Journées d'Animation Scientifique de la FéRI 2022 - FéRI Scientific Days 2022, Joué-Lès-Tours, France (2022-07-04 - 2022-07-05), https://hal.inrae.fr/hal-03735407</p>
Student situation	Temporal IR contract at INRAE (ISP, Tours)

Name	BARS, David
Subject	Dietary plant bioactives to prevent pathologies: Olive oil polyphenols and endogenous vitamin E. Red-fleshed apples to control carcinogen induce colon cancer rat model. Thesis supervised by Dr Carme Piñol Felis and dr M ^o José Motilva Casado

Date of defence	5/12/2019
Supervision rate (%)	20% (PhD internship in my lab)
Published works	<p>[Présentation orale] Michel Boisseau, Sophie Dhorne-Pollet, David Bars, Elise Courtot, Delphine Serreau, Gwenolah Annonay, Claire Kuchly, Amandine Gesbert, Fabrice Reigner, Núria Mach, Guillaume Sallé (2022-07-04). <i>Dynamic stability of the cyathostomin – gut microbiota interactions in horses</i>. Presented at: Journées d'Animation Scientifique de la FèRI 2022 - FèRI Scientific Days 2022, Joué-Lès-Tours, France (2022-07-04 - 2022-07-05), https://hal.inrae.fr/hal-03735407</p> <p>[Research article] Michel Boisseau, Sophie Dhorne-Pollet, David Bars-Cortina, Elise Courtot, Delphine Serreau, Gwenolah Annonay, Jérôme Lluch, Amandine Gesbert, Fabrice Reigner, Guillaume Sallé, Núria Mach (Corresponding author) (2022). Species interactions, stability, and resilience of the gut microbiota - helminth assemblage in horses. https://dx.doi.org/10.21203/rs.3.rs-1955749/v1, https://hal.inrae.fr/hal-03767875, OA</p> <p>[Research article] Núria Mach (Corresponding author), Alice Ruet, Allison Clark, David Bars-Cortina, Yulixais Ramayo-Caldas, Elisa Crisci, Samuel Pennarun, Sophie Dhorne-Pollet, Aline Foury, Marie-Pierre Moisan, Léa Lansade (2020-05-20). Priming for welfare: gut microbiota is associated with equitation conditions and behaviour in horse athletes. <i>Scientific Reports</i>, 10, https://dx.doi.org/10.1038/s41598-020-65444-9, https://hal.inrae.fr/hal-03197220, OA</p> <p>[Research article] Núria Mach (Corresponding author), Léa Lansade, David Bars-Cortina, Sophie Dhorne-Pollet, Aline Foury, Marie-Pierre Moisan, Alice Ruet (2021-03-03). Gut microbiota resilience in horse athletes following holidays out to pasture. <i>Scientific Reports</i>, 11, https://dx.doi.org/10.1038/s41598-021-84497-y, https://hal.inrae.fr/hal-03197215, OA</p>
Student situation	Temporal IR contract at University of Lleida (Food Technology Department, Lleida, Spain)

Name	RUET, Alice
Subject	Altération de l'état de bien-être du cheval domestique. Effets de pratiques d'hébergement liées au box individuel et relations avec l'équitation. Thesis supervised by Dr Léa Lansade and Dr Cécile Arnould
Date of defence	16/09/2020
Supervision rate (%)	10% (PhD internship in my lab)
Published works	<p>[Research article] Núria Mach (Corresponding author), Léa Lansade, David Bars-Cortina, Sophie Dhorne-Pollet, Aline Foury, Marie-Pierre Moisan, Alice Ruet (2021). Gut microbiota resilience in horse athletes following holidays out to pasture. <i>Scientific Reports</i>, 11, https://dx.doi.org/10.1038/s41598-021-84497-y, https://hal.inrae.fr/hal-03197215, OA</p> <p>[Research article] Núria Mach (Corresponding author), Alice Ruet, Allison Clark, David Bars-Cortina, Yulixais Ramayo-Caldas, Elisa Crisci, Samuel Pennarun, Sophie Dhorne-Pollet, Aline Foury, Marie-Pierre Moisan, Léa Lansade (2020-05-20). Priming for welfare: gut microbiota is associated with equitation conditions and behaviour in horse athletes. <i>Scientific Reports</i>, 10, https://dx.doi.org/10.1038/s41598-020-65444-9, https://hal.inrae.fr/hal-03197220, OA</p>
Student situation	Temporal IR contract at INRAE (Physiologie de la Reproduction et des Comportements, Tours, France)

Name	ROMANA MASSACI, Francesca
Subject	Enteric disorders at weaning: age, amoxicillin administration, and Enterotoxigenic Escherichia coli infection affecting the gut microbiota of piglets: https://tel.archives-ouvertes.fr/tel-02899340v1 . Thesis supervised by Dr. Claire Rogel-Gaillard, Prof. Paolo Trevisi, Dr Chiara Francesca Magistrali, Prof Giovanni Pezzotti, and Dr Jordi Estellé
Date of defence	17/03/2020
Supervision rate (%)	5%
Published works	[Research article] Francesca Massacci, Allison Clark, Alice Ruet, Léa Lansade, Márcio Costa, Núria Mach (2020) (Corresponding author). Inter-breed diversity and temporal dynamics of the faecal microbiota in healthy horses. <i>Journal of Animal Breeding and Genetics</i> , 137 (1), 103-120, https://dx.doi.org/10.1111/jbg.12441 , https://hal.inrae.fr/hal-02624117
Student situation	Temporal IR contract at INRAE (Université Paris-Saclay, INRAE, AgroParisTech, GABI, 78350, Jouy-en-Josas, France)

PostDoc supervision

Name	Subject / Publications	Period
BARS, David	<p>Omics data analysis of different projects carried in the team. Publications:</p> <p>[Research article] Michel Boisseau, Sophie Dhorne-Pollet, David Bars-Cortina, Elise Courtot, Delphine Serreau, Gwenolah Annonay, Jérôme Lluch, Amandine Gesbert, Fabrice Reigner, Guillaume Sallé, Núria Mach (Corresponding author) (2022). Species interactions, stability, and resilience of the gut microbiota - helminth assemblage in horses. https://dx.doi.org/10.21203/rs.3.rs-1955749/v1, https://hal.inrae.fr/hal-03767875, OA</p> <p>[Présentation orale] Michel Boisseau, Sophie Dhorne-Pollet, David Bars, Elise Courtot, Delphine Serreau, Gwenolah Annonay, Claire Kuchly, Amandine Gesbert, Fabrice Reigner, Núria Mach, Guillaume Sallé (2022-07-04). <i>Dynamic stability of the cyathostomin – gut microbiota interactions in horses</i>. Presented at: Journées d'Animation Scientifique de la FéRI 2022 - FéRI Scientific Days 2022, Joué-Lès-Tours, France (2022-07-04 - 2022-07-05), https://hal.inrae.fr/hal-03735407</p>	01/03/2020-31/12/2020

Master students supervision

Name	Subject/Publication	Year
De Manuel Portero, Anna	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “La importància de la microbiota intestinal en el tractament de la obesitat”	2017
Mesquida Riera, Javier	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Probiòtics i lluita contra els microorganismes multiresistents. Present o futur”	2017
Rodríguez García, Francisco	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Gut microbiota, epigenetic changes, diet and impact on spondyloarthropathies	2017
Vilallonga Serra, Catalina	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Els probiòtics I els seus efectes en la depressió, ansietat i estat anímic”	2017
De la Calle García, Paloma	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Metabolic syndrome: fundamental aspects and genetics. Health benefits of including black garlic in the diet	2017
Marato Caracena, Marta	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Microbiota en la gestación: importancia de la nutrición”	2017
Ramos, Lester	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Influencia de la lactancia materna en la composición de la microbiota intestinal del lactante”	2017
Roza Amengual, Laura	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Untangling the tangle: the underlying epigenetic mechanisms in the microbiota-gut-brain axis and the vulnerability to disease	2017

Clark, Allison	<p>M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Stress and microbiota affect elite athletes' performance and health. Publications associated with her Master's period:</p> <p>[Review] Núria Mach (Corresponding author), Allison Clark (2017). Micronutrient deficiencies and the Human Gut Microbiota. <i>Trends in Microbiology</i>, 25 (8), 607-610, https://dx.doi.org/10.1016/j.tim.2017.06.004, https://hal.inrae.fr/hal-01606579 [</p> <p>Review] Allison Clark, Núria Mach (Corresponding author) (2017). The Crosstalk between the Gut Microbiota and Mitochondria during Exercise. <i>Frontiers in Physiology</i>, 8, 1-17, https://dx.doi.org/10.3389/fphys.2017.00319, https://hal.inrae.fr/hal-01604194, OA</p> <p>[Review] Allison Clark, Núria Mach (Corresponding author) (2016). Exercise-induced stress behaviour, gut-microbiota-brain axis, and diet: a systematic review for athletes. <i>Journal of the International Society of Sports Nutrition</i>, 13, 1-21, https://dx.doi.org/10.1186/s12970-016-0155-6, https://hal.inrae.fr/hal-01606853, OA</p> <p>[Review] Allison Clark, Núria Mach (Corresponding author) (2016). Role of Vitamin D in the hygiene hypothesis: the interplay between vitamin D, vitamin D receptors, gut microbiota, and immune response. <i>Frontiers in Immunology</i>, 7, np, https://dx.doi.org/10.3389/fimmu.2016.00627, https://hal.inrae.fr/hal-01604340, OA</p>	2016-2017
López Serra, Helena	<p>M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Canvis en la microbiota en malalts de Lupus Eritematos Sistèmic (LES) paper beneficiós de la dieta”</p>	2016
Olivella Mayoralgo, Mariona	<p>M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Relación entre microbiota intestinal i hipotiroidisme autoimmune”.</p>	2016
Fuster-Botella, Dolors	<p>M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Deciphering the gut microbiota-exercise relationship. Publication associated with her Master's period:</p> <p>[Review] Núria Mach (Corresponding author), Dolors Fuster-Botella (2017). Endurance exercise and gut microbiota: a systematic review. <i>Journal of Sport and Health Science</i>, 6 (2), 179-197, https://dx.doi.org/10.1016/j.jshs.2016.05.001, https://hal.inrae.fr/hal-02620229, OA (Cited n = 268; Sep 2022)</p>	2016
Oliver Bonet, Maria	<p>M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Los factores nutricionales y no nutricionales pueden afectar la fertilidad masculina mediante mecanismos epigenéticos”. Publication associated with her Master's period:</p> <p>[Review] Maria Oliver Bonet, Núria Mach (Corresponding author) (2016). Factores nutricionales y no nutricionales pueden afectar la fertilidad masculina mediante mecanismos epigenéticos. <i>Nutrición Hospitalaria</i>, 33 (5), 1236-1244, https://dx.doi.org/10.20960/nh.591, https://hal.inrae.fr/hal-01602825, OA</p>	2015
Sancho, Marta	<p>M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Efecto de los polifenoles del vino sobre la prevención del cáncer”. Publication associated with her Master's period:</p> <p>[Review] Marta Sancho, Núria Mach (Corresponding author) (2015). Effects of wine polyphenols on cancer prevention. <i>Nutrición Hospitalaria</i>, 31 (2), 535 - 551, https://dx.doi.org/10.3305/nh.2015.31.2.8091, https://hal.inrae.fr/hal-02634266, OA</p>	2014
Hernando Boigues, Julian	<p>M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: The effect of polyunsaturated fatty acids on obesity through epigenetic modifications. Publication associated with his Master's period:</p> <p>[Review] Julián F Hernando Boigues, Núria Mach (Corresponding author) (2015). The effect of polyunsaturated fatty acids on obesity through epigenetic modifications. <i>Endocrinología y Nutrición</i>, 62 (7), 338-349, https://dx.doi.org/10.1016/j.endonu.2015.03.009, https://hal.inrae.fr/hal-02632001</p>	2014
Pueyo, Blanca	<p>M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Disbiosis intestinal en enfermos de Crohn pediátricos. Publication associated with her Master's period:</p> <p>[Review] Blanca Pueyo, Núria Mach (Corresponding author) (2013). Disbiosis intestinal en enfermos de Crohn pediátricos. <i>Nutrición Hospitalaria</i>, 28 (6), 1820-1828, https://dx.doi.org/10.3305/nh.2013.28.6.6936, https://hal.inrae.fr/hal-02645633, OA</p>	2013
Durand, Marisa	<p>M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “El ácido alfa lipoico y su poder antioxidante frente al cáncer y las patologías desensibilización central”. Publication associated with her Master's period:</p> <p>[Review] Marisa Durand, Núria Mach (Corresponding author). El ácido alfa lipoico y su poder antioxidante frente al cáncer y las patologías de sensibilización central. <i>Nutrición Hospitalaria</i>, 28 (4), 1031-1038, https://dx.doi.org/10.3305/nh.2013.28.4.6589, https://hal.inrae.fr/hal-02647782, OA</p>	2013

López Moriana, Coral	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Influencia de la gestación, parto y tipo de lactancia sobre la microbiota intestinal del neonato”. Publication associated with her Master’s period: [Review] Coral López Moriana, Núria Mach (Corresponding author) (2014). Influencia de la gestación, el parto y el tipo de lactancia sobre la microbiota intestinal del neonato. <i>Acta Pediátrica Española</i> , 72 (2), 37-44, https://hal.inrae.fr/hal-02630600	2013
Agulló, Victoria	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Predisposición genética a la obesidad y enfermedades relacionadas”	2013
Guardiola, Soledad	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: The therapeutic potential of Hibiscus sabdariffa: a review of the scientific evidence. Publication associated with her Master’s period: [Review] Soledad Guardiola, Núria Mach (Corresponding author) (2014). Potencial terapéutico del [i]Hibiscus sabdariffa[/i]: una revisión de las evidencias científicas. <i>Endocrinología y nutrición: órgano de la Sociedad Española de Endocrinología y Nutrición</i> , 61 (5), 274-295, https://dx.doi.org/10.1016/j.endonu.2013.10.012 , https://hal.inrae.fr/hal-01193876	2013
Pardos, Carlos	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Green tea’s effects on the prevention of breast cancer. Publication associated with his Master’s period: [Review] Carlos Pardos-Sevilla, Núria Mach (Corresponding author) (2014). Efectos del té verde sobre el riesgo de cáncer de mama. <i>Revista Española de Nutrición Humana y Dietética</i> , 18 (1), 211-220, https://hal.inrae.fr/hal-03774170 , OA	2012
Avila Castellano, Jose	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Homocisteína como factor emergente de riesgo de enfermedad coronaria y su relación con otros factores de riesgo cardiovascular”	2012
Gonzalez-Isabel, Concepción	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Influencia de la dieta sobre las citoquinas antiinflamatorias en la enfermedad de Crohn”. Publication associated with her Master’s period: Concepción González Isabel, Núria Mach (Corresponding author) (2013). Influencia de la dieta sobre las citoquinas antiinflamatorias en la enfermedad de Crohn. <i>Revista Española de Nutrición Comunitaria</i> , 19 (1), 44-52, https://hal.inrae.fr/hal-01193870	2012
Molina, Angeles	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Vegetarian people and the importance of omega-3 fatty acids consumption on infantile neurological development	2012
Coca, Laura	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Fitoesteroles, una Buena alternativa para prevenir las enfermedades cardiovasculares”	2012
Mata Gonzalez, Encarna	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “La ingestión de la L-carnitina puede reducir la infertilidad masculina”. Publication associated with her Master’s period: [Review] Encarna Mata González, Núria Mach (Corresponding author) (2013). La ingestión de la L-carnitina puede reducir la infertilidad masculina. <i>Revista Española de Nutrición Comunitaria</i> , 19 (3), 70-75, https://hal.inrae.fr/hal-02647276	2012
Aubets Gonzalez, Maria	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Los polifenoles y su papel en las enfermedades cardiovasculares”. Publication associated with her Master’s period: [Review] Maria Aubets-Fuster, Núria Mach (Corresponding author) (2013). Mecanismos moleculares implicados en los posibles efectos de los compuestos fenólicos en la disminución del riesgo de enfermedades cardiovasculares. <i>Revista Española de Nutrición Humana y Dietética</i> , 17 (3), 110-116, https://hal.inrae.fr/hal-01193869 , OA	2012
Belmar, Mon	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Efecto de la Dieta Mediterránea sobre la enfermedad de Alzheimer”. Publication associated with her Master’s period: [Review] Montserrat Belmar López, Secundino López, Sílvia Monserrat Vila, Núria Mach (2011). Dieta Mediterránea y enfermedad de Alzheimer. <i>Alimentaria: Revista de tecnología e higiene de los alimentos</i> , (427), 89-95, https://hal.inrae.fr/hal-03774160	2012
López Roldán, Patricia	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Efecto del Consumo de Astaxantina en la Salud”. Publication associated with her Master’s period: [Review] Patricia López Roldán, Núria Mach (Corresponding author) (2012). Efecto del consumo de astaxantina en la salud. <i>Revista Española de Nutrición Comunitaria</i> , 18 (3), 162-175, https://hal.inrae.fr/hal-01193871	2012

Perez Rovira, Andrea	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Efectos de las isoflavonas de la soja: el tratamiento de los síntomas de la menopausia”. Publication associated with her Master’s period: [Review] Andrea Pérez Rovira, Núria Mach (Corresponding author) (2012). Efecto del consumo de soja en relación con los síntomas de la menopausia. <i>Revista Española de Nutrición Humana y Dietética</i> , 16 (2), 69-76, https://hal.inrae.fr/hal-01193875	2011
Arias, Amparo	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Effect of probiotics on human weight control. Publication associated with her Master’s period: [Review] Amparo Arias, Núria Mach (Corresponding author) (2012). Efecto de los probióticos en el control de la obesidad humana: hipótesis no demostradas. <i>Revista Española de Nutrición Humana y Dietética</i> , 16 (3), 100-107, https://hal.inrae.fr/hal-01193874	2011
Cabrera, Albert	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: The effect of flavonoids on lung cancer. Publication associated with his Master’s period: [Review] Albert Cabrera, Núria Mach (Corresponding author) (2012). Flavonoides como agentes quimiopreventivos y terapéuticos contra el cáncer de pulmón. <i>Revista Española de Nutrición Humana y Dietética</i> , 16 (4), 143-153, https://hal.inrae.fr/hal-01193873	2010
Llacuna, Laura	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: The role of antioxidants on cancer prevention. Publication associated with her Master’s period: [Review] Laura Llacuna, Núria Mach (Corresponding author) (2012). Papel de los antioxidantes en la prevención del cáncer. <i>Revista Española de Nutrición Humana y Dietética</i> , 16 (1), 16-24, https://dx.doi.org/10.1016/S2173-1292(12)70067-4 , https://hal.inrae.fr/hal-03775181	2011
Rueda, Félix	Nutrition and Health Master project, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Effect of n-3 fatty acids and other food supplements on elderly-related pathological processes. Publication associated with his Master’s period: [Review] Felix Rueda, J. C. Domingo, Núria Mach (2011). Efectos de los ácidos grasos omega 3 y otros suplementos alimenticios en procesos patológicos relacionados con la tercera edad. <i>Revista Española de Nutrición Humana y Dietética</i> , 15 (1), 20-29, https://hal.inrae.fr/hal-03774165	2010
Alvarez, Rosa	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Polyunsaturated fatty acids and breast cancer. Publication associated with her Master’s period: [Review] Rosa Álvarez Álvarez, Núria Mach (Corresponding author) (2011). Efecto de los ácidos grasos poliinsaturados omega-3 y omega-6 en el riesgo de cáncer de mama. <i>Revista Española de Nutrición Humana y Dietética</i> , 15 (2), 187-191, https://hal.inrae.fr/hal-03774156	2010
Albiol, Rafael	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: The relationship between the nutritional status and skin ulcers in ATDOM. Publication associated with his Master’s period: [Review] Angela Sancho, Rafael Albiol, Núria Mach (2012). Relación entre el estado nutricional y el riesgo de presentar úlceras por presión en pacientes incluidos en el programa de atención domiciliaria. <i>Atención Primaria</i> , 44 (10), 586-594, https://dx.doi.org/10.1016/j.aprim.2011.09.003 , https://hal.inrae.fr/hal-02646256 , OA	2010
Villanueva, Xavier	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: “Papel de los ácidos grasos omega-3 en la prevención del cáncer de colon”. Publication associated with his Master’s period: [Review] Xavier Villanueva, Núria Mach (Corresponding author) (2011). Papel de los ácidos grasos omega 3 en la prevención del cáncer de colon. <i>Revista Española de Nutrición Humana y Dietética</i> , 15 (1), 30-38, https://hal.inrae.fr/hal-03774167	2010
Llargues, Josefina	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Nutrition and live style related to cancer treatment. Publication associated with her Master’s period: [Review] Josefina Llargués Truyols, Núria Mach (Corresponding author) (2011). Hongos medicinales: prevención y apoyo al tratamiento del cáncer. <i>Alimentación, nutrición y Salud</i> , 11, 16-23, https://hal.inrae.fr/hal-03774222	2010
Valls, Teresa	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Nutrition status of independent older people in Catalonia. Publication associated with her Master’s period: [Research article] Teresa T. Valls, Núria Mach (Corresponding author) (2012). Risk of malnutrition in people older than 75 years. <i>Medicina Clínica</i> , 139 (4), 157 - 160, https://dx.doi.org/10.1016/j.medcli.2012.01.029 , https://hal.inrae.fr/hal-01004176 , OA	2010

Àlvarez, Ma Rosa	M2 Nutrition and Health, Universitat Oberta de Catalunya (Barcelona, Spain). Project title: Strategies to prevent osteoporosis: Food vs Drugs. Publication associated with her Master's period: [Review] Rosa Álvarez, Núria Mach (Corresponding author) (2011). Estrategias para la prevención de la osteoporosis en la tercera edad: ¿alimentos o fármacos?. <i>Alimentaria: Revista de tecnología e higiene de los alimentos</i> , (425), 105-111, https://hal.inrae.fr/hal-03774249	2010
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Committees

PhD committee

CASTO REBOLLO, Cristina (2023), supervised by Dr Ibáez Escriche at Institute for Animal Science and Technology (Universitat Politècnica de València, Valencia, Spain). Title: Unravelling the environmental variance through the genome and the gut microbiome

JOLLET, Maxence Jollet (2020), supervised by Dr Koechlin – Ramonatxo and Dr Goustard at INRAe (UMR 866 Dynamique Musculaire et Métabolisme (DMeM), Montpellier, France). Title: « Compréhension de l'axe microbiote intestinal – muscle squelettique grâce à l'étude de phénotypes musculaires particuliers ».

ELGENDY, Ramy (2017), supervised by Dr Dacasto at Padova University (Italy). Title: “Transcriptomic approaches to study the effects of xenobiotics in ruminants.”

PUIG, Anna Puig (2015), supervised by Dr Folch Albareda and Dr Ballester Devis at the Autonomous University of Barcelona (Spain). Title: “Genetic dissection of growth and meat quality traits in pigs.”

COROMINAS, Jordi (2013), supervised by Dr Folch Albareda and Dr Ballester Devis at the Autonomous University of Barcelona (Spain). Title: “Functional genomics and candidate genes for meat quality traits in pigs.”

PhD progress committee

BENDAHMANE, Iyas (2021-2023), supervised by Dr Mila and Dr Meynadier (ENVT, Toulouse, France). Title: “Prédiction de la santé chez le chien via la mise en place du microbiote digestif lors des premiers jours de vie”.

MASSACCI ROMANA, Francesca (2017-2020), supervised by Dr Trevisi (University of Bologna, Italy) and Dr Claire Rogel-Gaillard (GABI, INRAe, Université Paris-Saclay). Title: “Enteric disorders at weaning: age, amoxicillin administration and enterotoxigenic Escherichia coli infection affecting the gut microbiota of piglets.”

RUET, Alice (2017-2020), supervised by Dr Lansade and Dr Arnauld (UMR 7247, Physiologie de la reproduction et des comportements, Tours). Title: “Altération de l'état de bien-être du cheval domestique. Effets de pratiques d'hébergement liées au box individuel et relations avec l'équitation”.

Reviewing and editorial committees

From 2022- Associated editor in Scientific Reports journal (Q1), an open-access journal publishing original research from across all areas of the natural sciences, psychology, medicine, and engineering. *Scientific Reports* has a 2-year impact factor of 4.9996 (2021), and in 2021, it was the 5th most-cited journal.

From 2022- Associated editor in Veterinary Quarterly (Q1), an open-access journal publishing original research in veterinary science and animal disease. This journal has an impact factor of 8.071 (2021) and a CiteScore of 8.6 (2021), ranking in the 99th percentile in the General Veterinary category on Scopus.

I am running a focused article collection in the *Frontiers in Physiology* journal on **Energy Balance and Gut-Brain-Microbiota Axis**. The excellent editorial team includes Dr Dehua Wang, a Professor from Shandong University, China; Dr Xiaoyun Wang, a Professor from South China Normal University, China; Dr Huan Li, a Professor at Lanzhou University, China; and Dr Xueying Zhang, an Associate Professor from the Institute of Zoology, Chinese Academy of Sciences, China. The topic is online, and the link is <https://www.frontiersin.org/research-topics/39397/energy-balance-and-gut-brain-microbiota>.

I am also currently coordinating the development of another article collection in *Veterinary Quarterly* on **Non-coding RNAs in veterinary diagnostics and therapeutics**. We are still creating the editorial team. The collection should be launched before the end of the year 2022.

I am coordinating another article collection in *Frontiers in Genetics*, within the Evolutionary and Genomic Microbiology section, entitled: “**The host genetics manoeuvre and the microbiome: challenges for stress and disease control**” together with Dr Yulixis Ramayo (IRTA, Spain, Barcelona), Dr Marcio Costa (Montreal University, Montreal, Canada), and Dr Dirkjan Schokker (Wageningen University, Wageningen, The Netherlands).

I am an assiduous reviewer for the following journals: Journals: Microbiome (OA), Frontiers in Microbiology (OA), Frontiers in Physiology (OA), Frontiers in Immunology (OA), Frontiers in Cellular and Infection Microbiology (OA), Molecular Immunology (OA), PloS one (OA), BMC Genomics (OA), Journal of Animal Science, Journal of Dairy Science, Animal Feed Science and Technology, Animal, Veterinary Research, Scientific Reports (OA), among others.

Scientific projects during the last five years

1. **LATSAN: Next-generation omic tools to enhance the sustainability of the dairy chain (2021-2023).** This project was coordinated by Dr Alessio Checchinatto (University of Padova, Italy) and funded by the national government of Italy. This project is part of the PhD thesis of Vittoria Bisutti (2020-2023).
2. **Chiron: Recherche et qualification d'extraits de plantes pour la gestion des cyathostomes (2020-2023).** Co-coordinated by Dr Sallé (Université de Tours, INRAE, UMR1282 ISP, Nouzilly, France) and Dr Fleurance (Clermont Auvergne, INRA, Vetagro Sup, UMR Herbivores, Saint-Genès-Champanelle, France). This project will be part of Joshua Malsa PhD thesis (2020-2023). This project is done in collaboration with the enterprise Pancosma® (Rolle, Switzerland), a world leader and pioneer in using plant extracts for animal feed. Pancosma has developed products based on standardised micro-encapsulated combinations of naturally occurring active substances from aromatic plants and spices.
3. **Chyatomix: Solutions génomiques pour la gestion durable des cythostomes (2019-2022).** Co-coordinated by Dr Núria Mach and Dr Guillaume Sallé (Université de Tours, INRAE, UMR1282 ISP, Nouzilly, France). This project is part of the PhD thesis of Michel Boisseau (2019-2022). IFCE, and Fond Éperon funded the project: https://equipedia.ifce.fr/fileadmin/bibliotheque/3._Guide__pocket_et_autres_pdf/3.7_Projets_recherche/Solutions-genomiques-gestion-durable-cyathostomes-CYATHOMIX.pdf. The funding amount for my lab was 155,000 €.
4. **Marker-OC-Fragmalim: Lésions d'ostéochondrose, fractionnement de la ration, biomarqueurs du métabolome et microtranscriptome sanguin et du microbiote intestinal (2019-2022).** Co-coordinated by Dr Chavatte-Palmer (Université Paris-Saclay, UVSQ, UMR 1198 INRAE, BREED, Jouy-en-Josas, France) and Dr Barrey (UMR 1313 GABI, AgroParisTech, University of Paris-Saclay, Jouy-en-Josas, France). I was in charge of WP2: "Analyse du microbiote intestinal et sanguin". IFCE call. Funding amount: 67,000 €. This project is ongoing, and the results are not published yet.
5. **Mal-Etre du cheval: une résilience est-elle possible? (2019-2021).** Co-coordinated by Dr Núria Mach, Dr Lansade, and Dr Moisan. IFCE and Fond Éperon funds. The funding amount for my lab was 38,000 €. This project is done in collaboration with the Cadre Noir de Saumur: <https://www.ifce.fr/cadre-noir/>.
6. **microFicient: Relations entre microbiote digestif et efficacité alimentaire chez les bovins (2017-2019).** Coordinated by Dr Ramayo-Caldas (UMR 1313 GABI, AgroParisTech, University of Paris-Saclay, Jouy-en-Josas, France). I led the WP4: Integration of omics data into a holistic approach. This work was funded by APIS-GENE and used production data from the Deffilait project cofounded by APIS-GENE and the Agence Nationale de la Recherche (ANR-15-CE20-0014).
7. **Evaluer le bien-être du cheval par une approche multidisciplinaire (2016-2020): comportement, santé, microbiote et transcriptomique et détecter les facteurs de risque.** Co-coordinated by Dr Núria Mach, Dr Lansade (UMR 85 Physiologie de la Reproduction et des Comportements, CNRS, UMR 7247, IFCE, University of Tours, Nouzilly, France) and Dr Moisan (University of Bordeaux, INRAe, Bordeaux INP, NutriNeuro, UMR 1286, Bordeaux, France). It was funded by the IFCE and Fonds Éperon, with an initial allocation of 55,000 € for my lab. The PhD of Alice Ruet was associated with this project (2016-2020). This project is done in collaboration with the Cadre Noir de Saumur: <https://www.ifce.fr/cadre-noir/>
8. **Metafoal: Identifying gut microbiota markers predictive of the weaning-induced stress response (2016-2018).** Co-coordinated by Dr Núria Mach, Dr Léa Lansade (UMR 85 PRC, IFCE, INRAe, University of Tours, Nouzilly, France) and Dr Marie-Pierre Moisan (University of Bordeaux, INRAe, Bordeaux INP, NutriNeuro, UMR 1286, 33076 Bordeaux, France). In 2016, the project was partially funded by the "Institut français du cheval et de l'équitation" (IFCE), with an initial allocation of 10,000 € for the gut microbiota profiling.
9. **StromaEq: Identification de biomarqueurs d'infestation par les cyathostomes chez le cheval pour l'optimisation des schémas de vermifugation (2015-2017).** Co-coordinated by Dr Núria Mach, Dr Guillaume Sallé and Dr Alex Blanchard, both at Université de Tours, INRAE, UMR1282 Infectiologie et Santé Publique, Nouzilly, France. In 2015, the project was funded by the IFCE, with an initial allocation of 33,600 € for my lab.

10. **EcaOmics: Gut Bacteria's Pep Talk" Enhances Horse's Athletic Performance (2014-2018).**
Coordinated by myself ([Dr Núria Mach](#)) and funded by the Animal Genetics department, with an initial endowment of 20,000 €. Then, the project became big and was compiled as a joint effort by funders (IFCE) and input from over ten researchers. Precisely, I engaged in collaborations with statisticians (Dr Plancade), experts in metabolism (Dr le moyec), horse physiology (Dr Barrey and Dr Robert), gut metagenomics (Dr Estellé, Dr Léclercq, Dr Gérard), and bioinformatics (Dr Rué, Dr Midoux).

Scientific and Administrative Duties

In September 2022, I was proposed as deputy director in the IHAP unit led by Prof. Jean-Luc Guerin (ENVT, Toulouse). This role will help me to gain organisational, management and leadership experiences. This is important as, in the nearest future, we will be the ones to have ownership and supervision of the objectives decided today. Given that I am still an up-to-date expert on big-data technology and methodologies, I still get my hands on the bench, dive deeply into the literature, come from a different cultural background (polyglot, $n=5$ languages) and have experienced other European research centres, I believe I will bring fresh perspectives at the unit.

International collaborations

International research collaborations have taught me the benefits of the science of working across borders, cultures, and disciplines. Coauthorship relations are the most formal indicator of international cooperation.

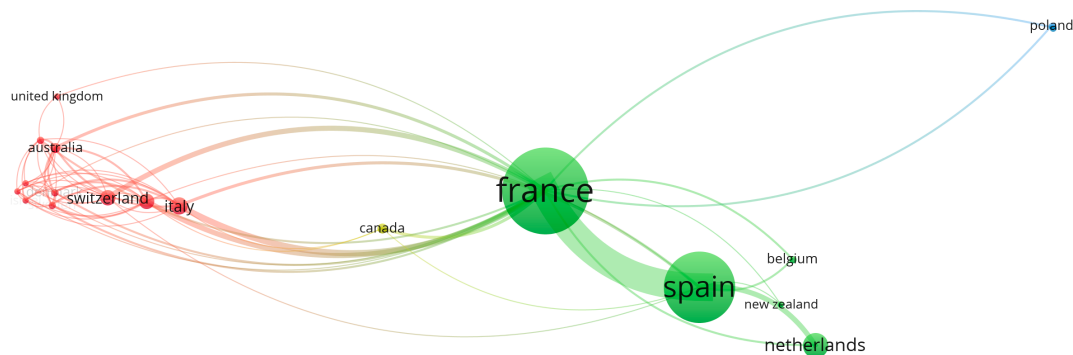


Figure 1. VOSviewer network visualisation map of country co-authorship (international collaboration) for my publications recorded at Scopus: <https://www.scopus.com/authid/detail.uri?authorId=23035606300#>. This map is not exhaustive, as it only includes countries with whom I co-authored publications. I have partnerships that still need to be translated into publications.

8



S E L E C T E D A R T I C L E S

The articles I highlighted in the manuscript and their abstracts are listed in this section.

[Article 1; Mach et al., 2020]

Priming for welfare: gut microbiota is associated with equitation conditions and behaviour in horse athletes

Núria Mach ^{1,*} Alice Ruet ² Allison Clark ³ David Bars-Cortina Yulixias Ramayo-Caldas ⁴ Elisa Crisci ⁵ Samuel Pennarun ⁶ Sophie Dhorne-Pollet ⁵ Aline Foury ⁷ Marie-Pierre Moisan ⁷ Léa Lansade ² Details

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³ [VHIR - Vall Hebron Research Institute](#)

⁴ [IRTA - Institute of Agrifood Research and Technology](#)

⁵ [GABI - Génétique Animale et Biologie Intégrative](#)

⁶ [GeT-PlaGe - Génome et Transcriptome - Plateforme Génomique](#)

⁷ [NutriNeuro - Nutrition et Neurobiologie intégrée](#)

Abstract: We simultaneously measured the faecal microbiota and multiple environmental and host-related variables in a cohort of 185 healthy horses reared in similar conditions for eight months. The pattern of rare bacteria varied from host to host and was vastly different between the two-time points. Among a suite of variables examined, equitation factors were highly associated with gut microbiota variability, evoking a relationship between gut microbiota and high levels of physical and mental stressors. Behavioural indicators that pointed toward a compromised welfare state (e.g., stereotypies, hypervigilance and aggressiveness) were also associated with the gut microbiota, reinforcing the notion of the existence of the microbiota-gut-brain axis. These observations were consistent with the microbiability of behaviour traits (> 15%), illustrating the importance of gut microbial composition to animal behaviour. As more elite athletes suffer stress, targeting the microbiota offers a new opportunity to investigate the bidirectional interactions within the brain-gut microbiota axis.

Scientific Reports, 10, <https://dx.doi.org/10.1038/s41598-020-65444-9>, <https://hal.inrae.fr/hal-03197220>, OA

[Article 2; Massacci et al., 2020]

Inter-breed diversity and temporal dynamics of the faecal microbiota in healthy horses

Francesca Massacci ^{1,2,3} Allison Clark ⁴ Alice Ruet ⁵ Léa Lansade ⁵ Márcio Costa ⁶ Núria Mach ^{1,*} * Corresponding author

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² [Istituto Zooprofilattico Sperimentale dell'Umbria e delle Marche 'Togo Rosati'](#)

³ [UNIBO - Alma Mater Studiorum University of Bologna](#)

⁴ [VHIR - Vall Hebron Research Institute](#)

⁵ [PRC - Physiologie de la reproduction et des comportements \[Nouzilly\]](#)

⁶ [UdeM - Université de Montréal](#)

Abstract: Understanding gut microbiota similarities and differences across breeds in horses has the potential to advance approaches aimed at personalised microbial modifications, particularly those involved in improving sport athletic performance. Here, we explore whether faecal microbiota composition based on faecal 16S ribosomal RNA gene sequencing varies across six sports breeds at two-time points eight months apart within a cohort of 189 healthy horses cared for under similar conditions. Lusitano horses presented the slightest, and Hanoverians the most extraordinary bacterial diversity. We found subtle but significant differences in beta diversity between Lusitano, Anglo-Arabian and the central European breeds, and we reproduced these results across the two-time points. Repeat sampling of subjects showed the community to be temporally more stable in Lusitano and Anglo-Arabian breeds.

Additionally, we found that 27 genera significantly varied in abundance across breeds. Overall, 33% of these taxa overlapped with previously identified ones associated with genetic variation in humans or other species. However, a non-significant correlation was observed between microbial composition and the host pedigree-based kinship. Despite a notable variation in the diversity and composition of the faecal microbiota, breed exerted limited effects on the equine faecal microbiota.

Journal of Animal Breeding and Genetics, 137 (1), 103-120, <https://dx.doi.org/10.1111/jbg.12441>, <https://hal.inrae.fr/hal-02624117>

[Article 3; Mach et al., 2021]**Gut microbiota resilience in horse athletes following holidays out to pasture**

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⁴ PRC - Physiologie de la reproduction et des comportements [Nouzilly]

Elite horse athletes that live in individual boxes and train and compete for hours experience long-term physical and mental stress that compromises animal welfare and alters the gut microbiota. We, therefore, assessed if a temporary period out to pasture with conspecifics could improve animal welfare and, in turn, favourably affect intestinal microbiota composition. A total of 27 athletes were monitored before and after 1.5 months out to pasture, and their faecal microbiota and behaviour profiles were compared to those of 18 horses kept in individual boxes. The overall diversity and microbiota composition of pasture and control individuals were temporally similar, suggesting resilience to environmental challenges. However, pasture exposure induced an increase in *Ruminococcus* and *Coprococcus* that lasted 1-month after the return to individual boxes, which may have promoted beneficial effects on health and welfare. Associations between the gut microbiota composition and behaviour indicating poor welfare were established.

Furthermore, withdrawn behaviour was associated with the relative abundances of the *Lachnospiraceae* AC2044 group and Clostridiales family XIII. Both accommodate a large part of butyrate-producing bacterial genera. While we cannot infer causality within this study, arguably, these findings suggest that management practices maintained over a longer period may moderate the behaviour link to the gut ecosystem beyond its resilience potential.

Scientific Reports, 11, <https://dx.doi.org/10.1038/s41598-021-84497-y>, <https://hal.inrae.fr/hal-03197215>, OA

[Article 4; Mach et al., 2017]**The effects of weaning methods on gut microbiota composition and horse physiology**

Núria Mach ^{1,2,*} Aline Foury ³ Sandra Kittelmann ⁴ Fabrice Reigner ⁵ Marco Moroldo ^{1,2} Maria Ballester ⁶ Diane Esquerre ⁷ Julie Riviere ^{1,2} Guillaume Salle ⁵ Philippe Gerard ^{8,6} Marie-Pierre Moisan ³ Léa Lansade ⁹ Details

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⁴ Grasslands Research Centre

⁵ UMR ISP - Infectiologie et Santé Publique

⁶ Departament de Genètica i Millora Animal - Institut de Recerca

⁷ LGC - Laboratoire de Génétique Cellulaire

⁸ MICALIS - MICrobiologie de l'ALImentation au Service de la Santé

⁹ PRC - Physiologie de la reproduction et des comportements [Nouzilly]

Abstract: Weaning has been described as one of the most stressful events in the life of horses. Given the importance of the interaction between the gut-brain axis and gut microbiota under stress, we evaluated (i) the effect of two different weaning methods on the composition of gut microbiota across time and (ii) how the shifts of gut microbiota composition after weaning affect the host. Thirty-four foals were randomly subjected to a progressive (P) or an abrupt (A) weaning method. In the P method, mares were separated from foals at progressively increasing intervals every day, starting from five min during the fourth week before weaning and ending with six h during the last week before weaning. In the A method, mares and foals were never separated before weaning (0 d). Different host phenotypes and gut microbiota composition across six age strata (days -30, 0, 3, 5, 7, and 30 after weaning) by 16S rRNA gene sequencing. Results revealed that the beneficial species belonging to *Prevotella*, *Paraprevotella*, and *Ruminococcus* were more abundant in the A group prior to weaning than the P group, suggesting that the gut microbiota in the A cohort was better adapted to weaning. *Streptococcus*, on the other hand, showed the opposite pattern after weaning. Fungal loads, which are thought to increase the capacity for fermenting the complex polysaccharides from the diet, were higher in P relative to A. Beyond the effects of weaning methods, maternal separation at weaning markedly shifted the composition of the gut microbiota in all foals, which fell into three distinct community types at three days post-weaning. Most genera in community type 2 (e.g., *Eubacterium*, *Coprococcus*, *Clostridium* XI, and *Blautia* spp.) were negatively correlated with salivary cortisol levels but positively correlated with telomere length and n-butyrate production. The average daily gain was also more significant in the foals harbouring a community type 2 microbiota. Therefore, community type 2 is likely to confer better stress response adaptation following weaning. This study identified potential microbial biomarkers that could predict the likelihood of physiological adaptations to weaning in horses, although causality remains to be addressed.

Frontiers in Physiology, 8, 21 p., <https://dx.doi.org/10.3389/fphys.2017.00535>, <https://hal.inrae.fr/hal-01578843>, OA

[Article 5; Plancade et al., 2019]**Unraveling the effects of the gut microbiota composition and function on horse endurance physiology**

Sandra Plancade ^{1, 2} Allison Clark ³ Catherine Philippe ⁴ Jean-Christophe Helbling ⁵ Marie-Pierre Moisan ⁵ Diane Esquerré ⁶ Laurence Le Moyec ⁷ Celine Robert ^{8, 9} Eric Barrey ⁹ Núria Mach ^{9,*} Details * *Corresponding author*

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³ [Vall d'Hebron Institut de Reserca \[Barcelona\]](#)

⁴ [MICALIS - MICrobiologie de l'ALimentation au Service de la Santé](#)

⁵ [NutriNeuro - Nutrition et Neurobiologie intégrée](#)

⁶ [LGC - Laboratoire de Génétique Cellulaire](#)

⁷ [UBIAE - Unité de biologie intégrative des adaptations à l'exercice](#)

⁸ [ENVA - École nationale vétérinaire - Alfort](#)

⁹ [GABI - Génétique Animale et Biologie Intégrative](#)

Abstract: An integrated analysis of gut microbiota, blood biochemical and metabolome in 52 endurance horses was performed. Clustering by gut microbiota revealed the existence of two communities mainly driven by diet, as host properties showed little effect. Community 1 presented lower richness and diversity but higher dominance and rarity of species, including some pathobionts. Moreover, its microbiota composition was tightly linked to host blood metabolites related to lipid metabolism and glycolysis at basal time. Despite the lower fibre intake, community type 1 appeared more specialised in producing acetate to maintain the energy supply as glucose concentrations fell during the race.

On the other hand, community type 2 showed enrichment of fibrinolytic and cellulolytic bacteria and anaerobic fungi, coupled with a higher production of propionate and butyrate. The higher butyrate proportion in community two was not associated with protective effects on telomere lengths but could have ameliorated mucosal inflammation and oxidative status. The gut microbiota was neither associated with the blood biochemical markers nor metabolome during the endurance race. It did not provide a biomarker for race ranking or risk of failure to finish the race.

Scientific Reports, 9 (1), 9620, <https://dx.doi.org/10.1038/s41598-019-46118-7>, <https://hal.inrae.fr/hal-02489982>, OA

[Article 6; Clark and Mach, 2017]**The Crosstalk between the Gut Microbiota and Mitochondria during Exercise**

Allison Clark ^{1,*} Núria Mach ^{2, 1,*} Details

* *Corresponding author*

¹ [Health Science Department](#)

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Abstract: Many physiological changes occur in response to endurance exercise to adapt to the increasing energy needs, mitochondria biogenesis, increased reactive oxygen species (ROS) production and acute inflammatory responses. Mitochondria are organelles within each cell that are crucial for ATP production and are also significant producers of ROS and reactive nitrogen species during intense exercise. Recent evidence shows there is a bidirectional interaction between mitochondria and microbiota. The gut microbiota has been shown to regulate critical transcriptional co-activators, transcription factors and enzymes involved in mitochondrial biogenesis, such as PGC-1 alpha, SIRT1, and AMPK genes. Furthermore, the gut microbiota and its metabolites, such as short-chain fatty acids and secondary bile acids, contribute to host energy production, ROS modulation and inflammation in the gut by attenuating TNF alpha-mediated immune responses and inflammasomes such as NLRP3.

On the other hand, mitochondria, particularly mitochondrial ROS production, have a crucial role in regulating the gut microbiota via modulating intestinal barrier function and mucosal immune responses. Recently, it has also been shown that genetic variants within the mitochondrial genome could affect mitochondrial function and, therefore, the intestinal microbiota composition and activity. Diet is also known to modulate the composition of the gut microbiota dramatically. Therefore, studies targeting the gut microbiota can help manage mitochondrial-related ROS production, pro-inflammatory signals and metabolic limits in endurance athletes.

Frontiers in Physiology, 8, 1-17, <https://dx.doi.org/10.3389/fphys.2017.00319>, <https://hal.inrae.fr/hal-01604194>, OA

[Article article 7; Mach et al., 2021]**Understanding the Holobiont: Crosstalk Between Gut Microbiota and Mitochondria During Long Exercise in Horse**Núria Mach ^{1,*} Marco Moroldo ¹ Andrea Rau ¹ Jérôme Lecardonnell ¹ Laurence Le Moyec ¹ Céline Robert ² Eric Barrey ¹ Details* *Corresponding author*¹ [GABI - Génétique Animale et Biologie Intégrative](#)² [ENVA - École nationale vétérinaire - Alfort](#)

Abstract: Endurance exercise dramatically impacts the functionality of mitochondria and the composition of the intestinal microbiome, but the mechanisms regulating the crosstalk between these two components are still largely unknown. Here, we sampled 20 elite horses before and after an endurance race and used blood transcriptome, blood metabolome and faecal microbiome to describe the gut-mitochondria crosstalk. A subset of mitochondria-related differentially expressed genes involved in pathways such as energy metabolism, oxidative stress and inflammation was discovered and then shown to be associated with butyrate-producing bacteria of the *Lachnospiraceae* family, especially *Eubacterium*. The mechanisms involved were not fully understood, but the action of their metabolites likely acted on PPARc, the FRX-CREB axis and their downstream targets to delay the onset of hypoglycemia and inflammation and extend the running time. Our results also suggested that circulating free fatty acids may act not merely as fuel but drive mitochondrial inflammatory responses triggered by the translocation of gut bacterial polysaccharides following endurance. Targeting the gut-mitochondria axis, therefore, appears to be a potential strategy to enhance athletic performance.

Frontiers in Molecular Biosciences, 8, <https://dx.doi.org/10.3389/fmolb.2021.656204>, <https://hal.inrae.fr/hal-03197210>, OA

[Article 8; Mach et al., 2022]**Mining the equine gut metagenome: poorly-characterized taxa associated with cardiovascular fitness in endurance athletes**Núria Mach ^{1,2,*} Cédric Midoux ^{3,4,5} Sébastien Leclercq ⁶ Samuel Pennarun ⁷ Laurence Le Moyec ⁸ Olivier Rué ^{4,5} Céline Robert ⁹ Guillaume Sallé ⁶ Eric Barrey ¹ Details* *Corresponding author*¹ [GABI - Génétique Animale et Biologie Intégrative](#)² [ENVT - Ecole Nationale Vétérinaire de Toulouse](#)³ [UR PROSE - Procédés biotechnologiques au service de l'environnement](#)⁴ [MaIAGE - Mathématiques et Informatique Appliquées du Génome à l'Environnement \[Jouy-En-Josas\]](#)⁵ [MIGALE - Université Paris-Saclay, INRAE, BioinfOmics, MIGALE bioinformatics facility](#)⁶ [UMR ISP - Infectiologie et Santé Publique](#)⁷ [CNRGV - Centre National de Ressources Génomiques Végétales](#)⁸ [UBIAE - Unité de biologie intégrative des adaptations à l'exercice](#)⁹ [ENVA - École nationale vétérinaire - Alfort](#)

Abstract: Emerging evidence indicates that the gut microbiome contributes to endurance exercise performance. Still, its functional and metabolic potential remains unknown. Using elite endurance horses as a model system for exercise responsiveness, we built an integrated horse gut gene catalogue comprising ~25 million unique genes and 372 metagenome-assembled genomes. This catalogue represents 4179 genera spanning 95 phyla and functional capacities primed to exploit energy from dietary, microbial, and host resources. The holo-omics approach shows that gut microbiomes enriched in *Lachnospiraceae* taxa are negatively associated with cardiovascular capacity. Conversely, more complex and functionally diverse microbiomes are associated with higher glucose concentrations and reduced accumulation of long-chain acylcarnitines and non-esterified fatty acids in plasma, suggesting increased β -oxidation capacity in the mitochondria. In line with this hypothesis, more fit athletes show upregulation of mitochondrial-related genes involved in energy metabolism, biogenesis, and Ca²⁺ cytosolic transport, all of which are necessary to improve aerobic work power, spare glycogen usage, and enhance cardiovascular capacity. The results identify an associative link between endurance performance and gut microbiome composition and gene function, laying the basis for nutritional interventions that could benefit horse athletes.

Communications Biology, 5, <https://dx.doi.org/10.1038/s42003-022-03977-7>, <https://hal.inrae.fr/hal-03794437>, OA

[Article 9; Clark, Sallé et al., 2018]**Strongyle infection and gut microbiota: profiling of resistant and susceptible horses over a grazing season**

Allison Clark ¹ Guillaume Salle ² Valentine Ballan ³ Fabrice Reigner ⁴ Annabelle Meynadier ⁵ Jacques Cortet ² Christine Koch ² Mickaël Riou ⁶ Alexandra Blanchard ² Núria Mach ^{3,*} Details

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⁴ [UE PAO - Unité Expérimentale de Physiologie Animale de l'Orfrasière](#)

⁵ [GenPhySE - Génétique Physiologie et Systèmes d'Élevage](#)

⁶ [PFIE - Plateforme d'Infectiologie Expérimentale](#)

Abstract: Gastrointestinal strongyles are a major threat to horses' health and welfare. Given that strongyles inhabit the same niche as the gut microbiota, they may interact with each other. These beneficial or detrimental interactions are unknown in horses and could partly explain contrasted susceptibility to infection between individuals. To address these questions, an experimental pasture trial with 20 worm-free female Welsh ponies (10 susceptible (S) and 10 resistant (R) to parasite infection) was implemented for five months. Faecal egg counts (FEC), haematological and biochemical data, body weight and gut microbiological composition, were studied in each individual after 0, 24, 43, 92 and 132 grazing days. R and S ponies displayed divergent immunological profiles and slight differences in microbiological composition under worm-free conditions. After exposure to natural infection, the predicted R ponies exhibited lower FEC after 92 and 132 grazing days and maintained higher levels of circulating monocytes and eosinophils, while lymphocytosis persisted in S ponies. Although the overall gut microbiota diversity and structure remained similar during the parasite infection between the two groups, S ponies exhibited a reduction of bacteria such as *Ruminococcus*, *Clostridium* XIVa and members of the *Lachnospiraceae* family, which may have promoted disruption of mucosal homeostasis at day 92. In line with this hypothesis, an increase in pathobionts such as *Pseudomonas* and *Campylobacter* together with changes in several predicted immunological pathways, including pathogen sensing, lipid metabolism, and activation of signal transduction that are critical for the regulation of the immune system and energy homeostasis, was observed in S relative to R ponies.

Moreover, S ponies displayed an increase in protozoan concentrations at day 92, suggesting that strongyles and protozoa may contribute to each other's success in the equine intestines. It could also be that S individuals favour the increase of these carbohydrate-degrading microorganisms to enhance the supply of nutrients needed to fight strongyle infection. Overall, this study provides a foundation to understand better the mechanisms that underpin the relationship between equines and natural strongyle infection. The profiling of horse immune response and gut microbiota should contribute to developing novel biomarkers for strongyle infection.

Frontiers in Physiology, (9), 1-18, <https://dx.doi.org/10.3389/fphys.2018.00272>, <https://hal.inrae.fr/hal-02625557>, OA

[Article 10; Sallé et al., 2021]

Integrative biology defines novel biomarkers of resistance to strongylid infection in horses

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MetaToul-MetaboHUB, ToxAlim - ToxAlim

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⁵ [PFIE - Plateforme d'Infectiologie Expérimentale](#)

⁶ [Pancosma](#)

⁷ [GABI - Génétique Animale et Biologie Intégrative](#)

Abstract: The widespread failure of anthelmintic drugs against nematodes of veterinary interest requires novel control strategies. Selective treatment of the most susceptible individuals could reduce drug selection pressure but requires appropriate biomarkers of the intrinsic susceptibility potential. To date, this has been missing in livestock species. Here, we selected Welsh ponies with divergent intrinsic susceptibility (measured by their egg excretion levels) to cyathostomin infection and found that their divergence was sustained across a 10-year time window. Using this unique set of individuals, we monitored variations in their blood cell populations, plasma metabolites and faecal microbiota over a grazing season to isolate core differences between their responses under worm-free or natural infection conditions. Our analyses identified the concomitant rise in plasma phenylalanine level and faecal *Prevotella* abundance and the reduction in circulating monocyte counts as biomarkers of the need for drug treatment (egg excretion above 200 eggs/g). This biological signal was replicated in other independent populations. We also unravelled an immunometabolic network encompassing plasma beta-hydroxybutyrate level, short-chain fatty acid-producing bacteria and circulating neutrophils that form the discriminant baseline between susceptible and resistant individuals. Altogether our observations open new perspectives on the susceptibility of equids to strongylid infection and leave scope for both new biomarkers of infection and nutritional intervention.

Scientific Reports, 11 (1), 15 p., <https://dx.doi.org/10.1038/s41598-021-93468-2>, <https://hal.inrae.fr/hal-03284457>, OA

[Article 11; Boisseau et al., 2022]**Species interactions, stability, and resilience of the gut microbiota - helminth assemblage in horses**

Michel Boisseau ^{1,2} Sophie Dhorne-Pollet ³ David Bars-Cortina ⁴ Elise Courtot ¹ Delphine Serreau ¹ Gwenolah Annonay ⁵ Jérôme Lluch ⁵ Amandine Gesbert ⁶ Fabrice Reigner ⁶ Guillaume Sallé ¹ Núria Mach ^{2,3,*} Details

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⁴ Universitat de Lleida

⁵ GeT-PlaGe - Génome et Transcriptome - Plateforme Génomique

GET - Plateforme Génome & Transcriptome, INRAE - Institut National de Recherche pour l'Agriculture, l'Alimentation et l'Environnement : US 1426

⁶ UE PAO - Unité Expérimentale de Physiologie Animale de l'Orfrasière

Abstract: The nature and strength of interactions entertained among helminths and their host gut microbiota remain largely unexplored. Using 40 naturally infected Welsh ponies, we tracked the gut microbiota-cyathostomin temporal dynamics during parasite community removal and reassembly and the associated host immune response. Infected ponies harboured 14 species of cyathostomins, overwhelmed by the abundance of *Cylicocyclus nassatus*. Parasite carriers exhibited gut environment modifications, higher Shannon entropy and orderly rearrangements of prokaryotic assemblages, with protective *Clostridia* species contributing to the successional nemabiome-microbiota crosstalk. Yet, the gut ecosystem was remarkably stable, and the host systemic response defined enrichment for B-cell activation and IgA production without corresponding changes in parasite burdens. Therefore, *Clostridia* microbial protection likely reduced fluctuating dynamics between the microbiota-parasite-host triad and favoured parasite tolerance. The system stability was disrupted by pyrantel treatment and parasite removal, with dire early consequences on the gut environment, microbiota diversity, and cytokine networks while highlighting the detrimental effect of cyathostomin burdens on *Enterococcus* spp. Both ecological communities were highly resilient to disturbance and recovered their pre-treatment compositions, but *Cylicostephanus longibursatus* in the parasite community. However, gut microbiotas failed to restore their original stability and shifted towards an interacting unstable state, with transient coexistence between *Clostridia* and core bacterial taxa, e.g. *Fibrobacter* and *Prevotella*, evoking their crucial role as stabilising forces for this new equilibrium. These observations highlight how anthelmintic treatment alters gut microbiota stability and opens new perspectives for adding nutritional intervention to current parasite management strategies in the field.

<https://dx.doi.org/10.21203/rs.3.rs-1955749/v1>, <https://hal.inrae.fr/hal-03767875>, OA [Under revision in the iScience journal]

[Article 12; Mach et al., 2021]**The Airway Pathobiome in Complex Respiratory Diseases: A Perspective in Domestic Animals**

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² IHAP - Interactions hôtes-agents pathogènes [Toulouse]

Abstract: Respiratory infections in domestic animals are a major issue for the veterinary and livestock industry. Pathogens in the respiratory tract share their habitat with a myriad of commensal microorganisms. Increasing evidence points towards a respiratory pathobiome concept, integrating the dysbiotic bacterial communities, the host and the environment in a new understanding of respiratory disease aetiology. During the infection, the airway microbiota likely regulates and is regulated by pathogens through diverse mechanisms, thereby acting either as a gatekeeper that provides resistance to pathogen colonisation or enhancing their prevalence and bacterial co-infectivity, which often results in disease exacerbation. Insight into the complex interplay taking place in the respiratory tract between the pathogens, microbiota, the host and its environment during infection in domestic animals is a research field in its infancy in which most studies are focused on infections from enteric pathogens and gut microbiota. However, its understanding may improve pathogen control and reduce the severity of microbial-related diseases, including those with zoonotic potential.

Frontiers in Cellular and Infection Microbiology, 11, 583600, <https://dx.doi.org/10.3389/fcimb.2021.583600>, <https://hal.inrae.fr/hal-03228289>, OA

9



B I B L I O G R A P H Y

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About the Author



Initially trained as a veterinarian (2003, Barcelona, Spain), I specialised in animal nutrition and welfare through my internship and the European Joint Doctorate (2004-2008). Afterwards, I enrolled in the emerging field of nutrigenomics (2009-2011, Wageningen, The Netherlands). Concomitantly, I was recruited as a lecturer in the Master of Nutrition and Health at the Open University of Catalonia (2009-2017, Barcelona, Spain), where I transferred my passion for research to younger people, and I invested time and effort in mentoring Master students. Alongside scientific goals, I started my studies in humanities science, which acted as a critical bridge between disciplines (2007-2012) and my regular practice of Iyengar yoga. Together, they taught me to concentrate, reflect on myself, develop a broad

scientific vision, build communication skills (polyglot, five languages), and learn about the crucial attributes of multidisciplinary. Then, in 2011, I joined INRAE as a postdoc (Jouy en Josas, France), where I trained in livestock systems biology approaches and metagenomics.

In June 2013, I got a permanent research position within the animal genetics and integrative biology unit at the INRAE Animals Genetics Department (Jouy en Josas, France). By mining omics data and interdisciplinary projects in horses, I have characterised the holobiont response to abiotic and biotic stressors, including psychosocial and physical demands during exercise and disease. Recognised as an international leader in horse metagenomics, my results have led to rethinking horse management.

As of 2022, Google Scholar reports 85 peer-reviewed papers and over 3,900 citations to my work. My publications record reflects interdisciplinary, student mentoring, international collaboration and intellectual creation (in 71% of the cases, I am the first or last author). Stepping forward, I joined the IHAP unit (ENVT, Toulouse, April 2021) at the INRAE Animal Health Department. Alongside my tasks as associate editor in *Veterinary Quarterly* and *Scientific Reports*, I bring nuance to the hologenomic approach by delving into the respiratory microbiome and its consequences on health, welfare, and the onset of livestock diseases.