

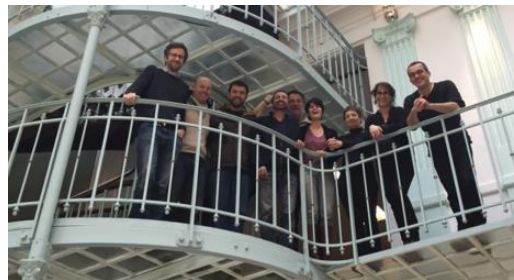
# Shifting from pathogen to pathobiome: the example of tick-borne pathogens



Muriel Vayssier-Taussat  
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*.... And Maria Kazimirova, Zdenek Hubalek, Sandor Hornok, Robert Farkas, Sarah Bonnet, Jean-François Cosson, Gwénaél Vourc'h, Andrei Mihalca, Olivier Plantard, Cornelia Silaghi and Annapaola Rizzoli*



# Common vision of pathogenic agents

- **Old vision of microbe and infectious diseases** : Since the 19th century: link between microbes to infectious diseases (Koch Postulate in 1884): **One microbe – One disease**
  - Today, the predominant vision of infectious disease is still **One Microbe-One Disease**
  - This vision is limited: Ex: association of different microbes may lead to infectious diseases
  - Pathogens are not isolated entities, they live in associations/interactions with other microbes which may influence their transmission, evolution or pathogenicity

# Common vision of pathogenic agents

- **New vision of microbe and infectious diseases :**  
Integrate « pathogens » in their microbial environment (the so called **pathobiome**) to understand infection diseases

## REVIEW ARTICLE

Front. Cell. Infect. Microbiol., 05 March 2014 | <https://doi.org/10.3389/fcimb.2014.00029>

## Shifting the paradigm from pathogens to pathobiome: new concepts in the light of meta-omics

 Muriel Vayssier-Taussat<sup>1\*</sup>,  Emmanuel Albina<sup>2,3,4</sup>,  Christine Citti<sup>5</sup>,  Jean-François Cosson<sup>6</sup>,  Marie-Agnès Jacques<sup>7</sup>,  Marc-Henri Lebrun<sup>8</sup>,  Yves Le Loir<sup>9,10</sup>,  Mylène Ogliastro<sup>11</sup>,  Marie-Agnès Petit<sup>12</sup>,  Philippe Roumagnac<sup>13</sup> and  Thierry Candresse<sup>14</sup>

- **Tick borne Pathogens or Tick Borne Pathobiome?**

- **A lot of tick borne pathogens**
- Till recently, Lab were specialized on **one single pathogen** : few data with the all picture
- In the last few years, development of high throughput molecular techniques allow us to investigate tick borne pathogens as a whole : Beginning of the « **Pathobiome** » story



**The questions the « Tick » community started to address were:**

- 1-** infection/co-infection at the individual tick level?
- 2-** Interactions between pathogens and other microbes?
- 3-** Effect on co-transmission?
- 4-** Co-infection in hosts and effect on symptoms?

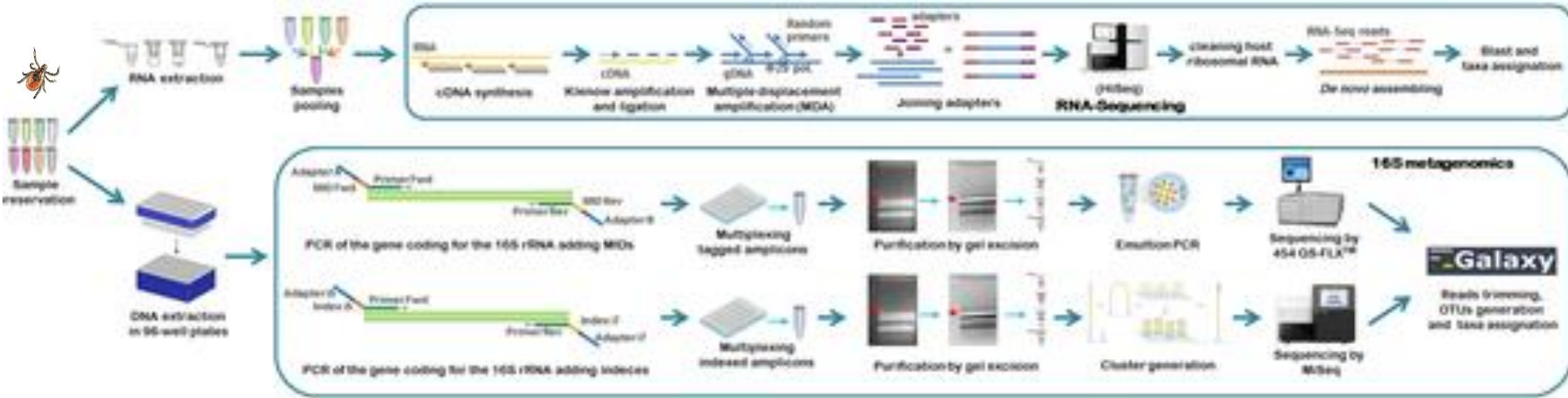
**The first need: an inventory of the tick pathogens and other associated microbes**



- Inventory of tick-borne pathogens

- Identification of microbial sequences in ticks

- Without a priori detection (16S and RNA sequencing)

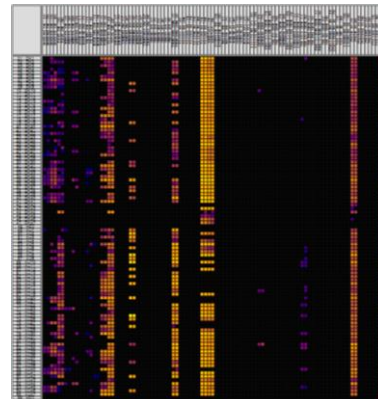
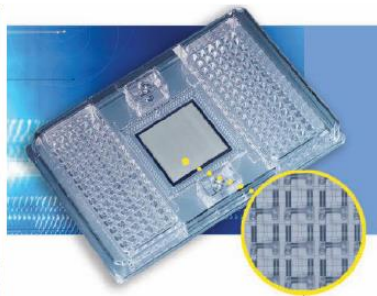


*Razzauti et al. 2017, PNTD*

- With a priori, targeting known tick-borne pathogens



Biomark™ dynamic Assay

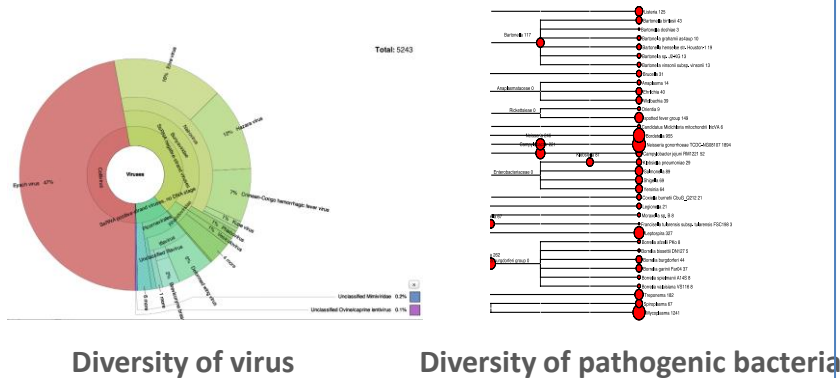


High throughput analysis of simultaneously up to 48 pathogens in the same tick

*Michelet et al. 2014, FCIM*  
*Moutailler et al., 2015 PNTD*

# Inventory of tick-borne pathogens : Main results

- High diversity of bacterial, parasitic and viral sequences



## Main results on european ticks:

- All the **known** Tick Borne Pathogens
- Known but **unexpected** pathogens (i.e., transmitted by other vectors, transmitted by ticks but never detected in France so far, forgotten pathogens)
- Unknwon** micro-organisms

## Ex. of known but unexpected or forgotten pathogens

OPEN ACCESS Freely available online



### Next Generation Sequencing Uncovers Unexpected Bacterial Pathogens in Ticks in Western Europe

Muriel Vayssier-Taussat<sup>1</sup>, Sara Moutailler<sup>1</sup>, Lorraine Michelet<sup>1</sup>, Elodie Devillers<sup>1</sup>, Sarah Bonnet<sup>1</sup>, Justine Cheval<sup>2</sup>, Charles Hébert<sup>2</sup>, Marc Eloit<sup>2,3,4\*</sup>

<sup>1</sup> USC Bipar, INRA, Anses, Maisons-Alfort, France, <sup>2</sup> PathoQuest SAS, Paris, France, <sup>3</sup> Ecole Nationale Vétérinaire d'Alfort, UMR 1161 Virologie ENVA, INRA, ANSES, Maisons-Alfort, France, <sup>4</sup> Institut Pasteur, Laboratory of Pathogen Discovery, Paris, France

- Borrelia miyamotoi*: firstly described in France (same strain as a pathogenic one isolated in The Netherland at the same time)
- Rickettsia felis*: Human pathogen transmitted by fleas. Since other studies demonstrated it might also a TBP

ORIGINAL ARTICLE

### Diversity of viruses in *Ixodes ricinus*, and characterization of a neurotropic strain of Eyach virus

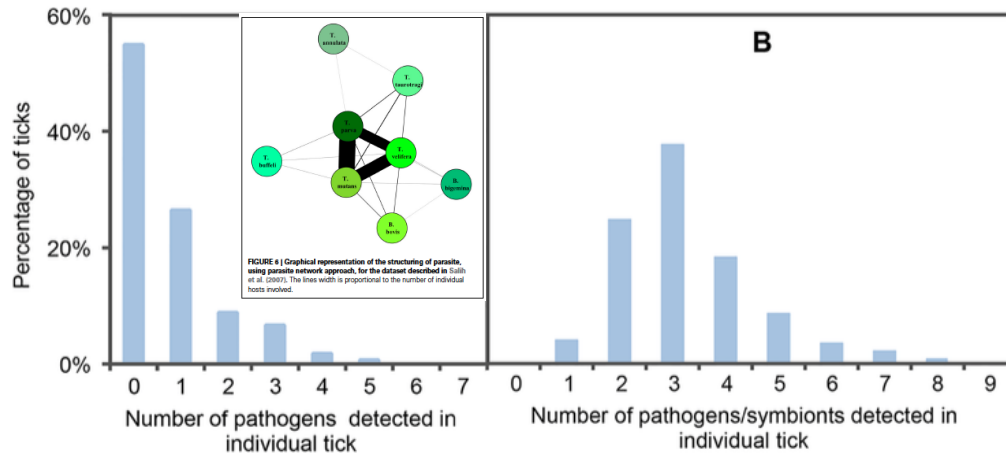
S. Moutailler<sup>1</sup>, I. Popovici<sup>1,2</sup>, E. Devillers<sup>1</sup>, M. Vayssier-Taussat<sup>1</sup> and M. Eloit<sup>1,4</sup>

<sup>1</sup> UMR Bipar, INRA, Anses, ENVA, Maisons-Alfort, France, <sup>2</sup> Faculty of Veterinary Medicine, University of Agricultural Sciences and Veterinary Medicine, Department of Public Health, Iasi, Romania, <sup>3</sup> PathoQuest SAS and <sup>4</sup> Institut Pasteur, Biology of Infection Unit, Inseem U1117, Pathogen Discovery Laboratory, Paris, France

- Eyach virus*: Described in the 70's

# • Inventory of tick-borne pathogens : Main results

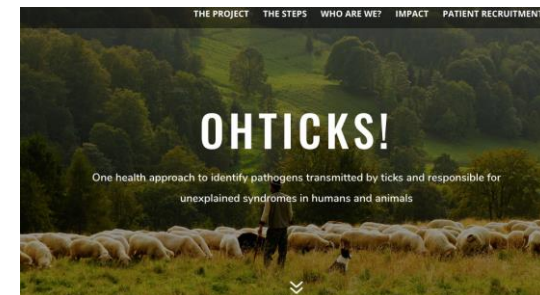
## • What about co-infection in ticks?



- Co-infection within ticks is the rule rather than the exception (*Moutailler et al. 2015*)
- **Positive associations** between some pathogens – different species of *Borrelia* sp. (*Vaumourin et al., 2014*)
- **Negative associations** (*Borrelia* and *Anaplasma*)
- **Possible interactions**

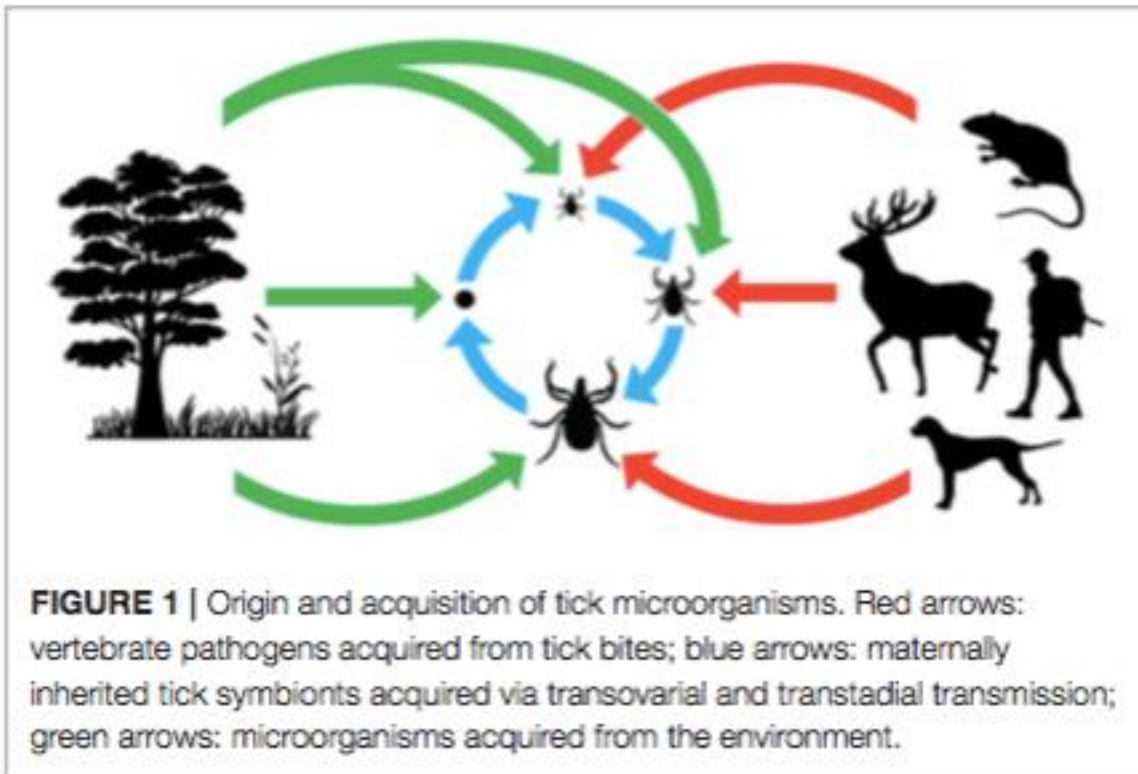
## • What about co-infection in vertebrate hosts?

- From our own preliminary data (OHTicks project) **co-infections in humans and animals are detected** when looked for (probable co-transmission?), impact on symptoms (ECDC Review in preparation – Cutler, Vayssier-Taussat et al., )



# What do we know about other tick associated microbes?

- Where do they come from?

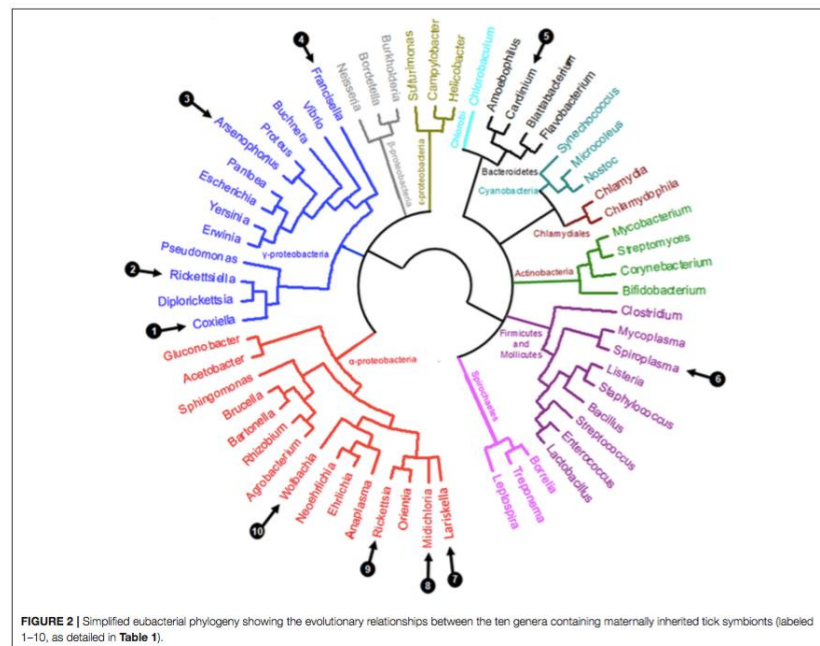
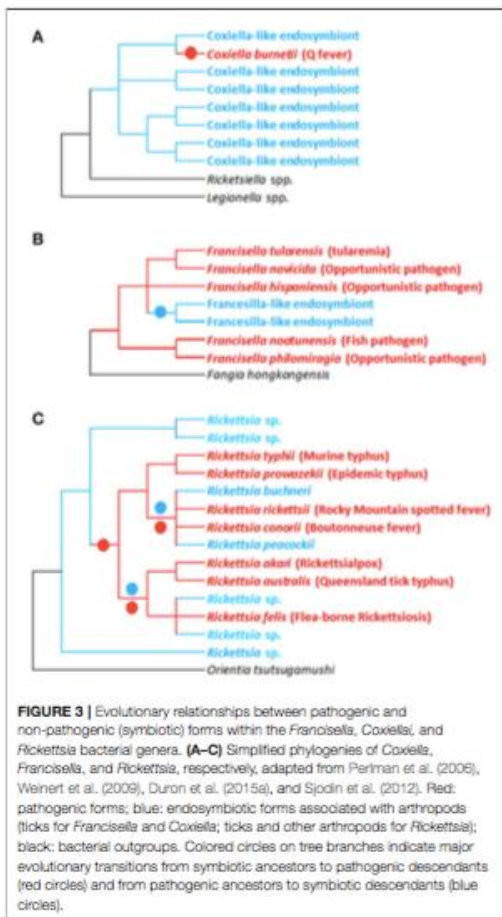


- **Acquired from Environment:** commensals, other?
- **Acquired during blood meals:** commensals, pathogens
- **Inherited:** symbionts (reproduction, nutrition, synthesis of major vitamins, etc...)



# What do we know about other tick associated microbes?

- Inherited bacteria/commensal/ pathogens: no clear frontier



- Symbionts are phylogenetically closed to tick borne pathogens (that might have evolved to infect vertebrates)
- Some tick symbionts are also vertebrate pathogens

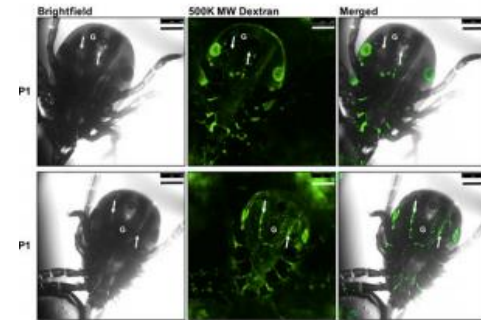
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- Interactions between gut microbiota and pathogens:
- The gut as a barrier pathogens have to disrupt: The ex. of *A. phagocytophilum*

## Pathogen-mediated manipulation of arthropod microbiota to promote infection

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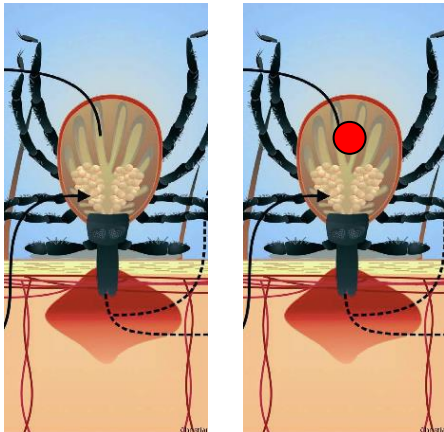
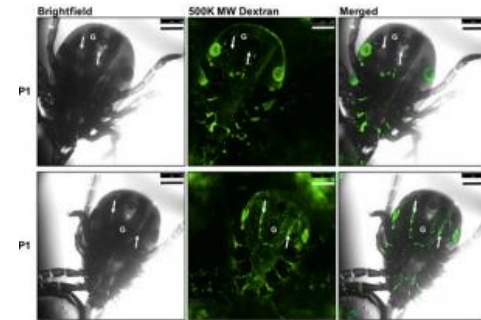
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- *A. phagocytophilum* ingested with infected blood colonize the tick gut

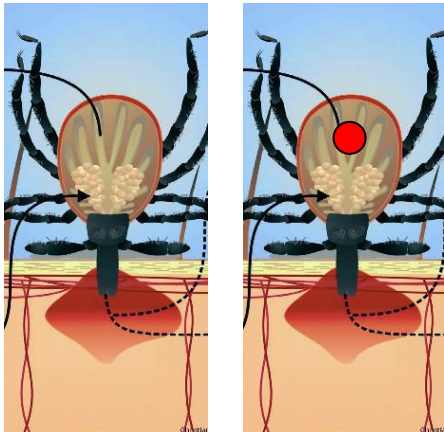
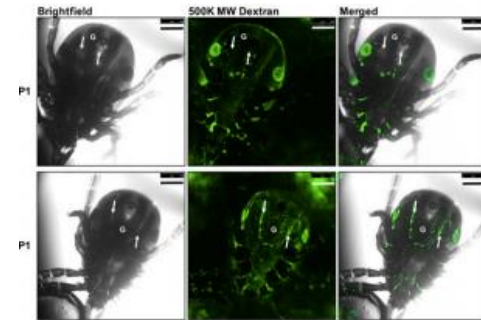
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- *A. phagocytophilum* ingested with infected blood colonize the tick gut

*A. phagocytophilum* induces the production of a tick anti-freeze glycoprotein (iafgp) that alters bacterial biofilm and disrupt the gut barrier

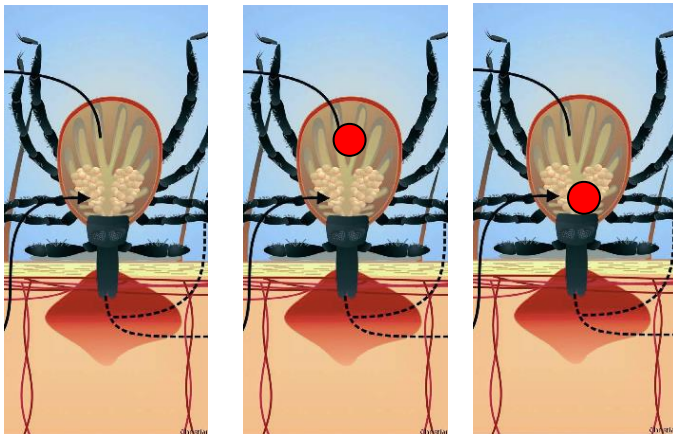
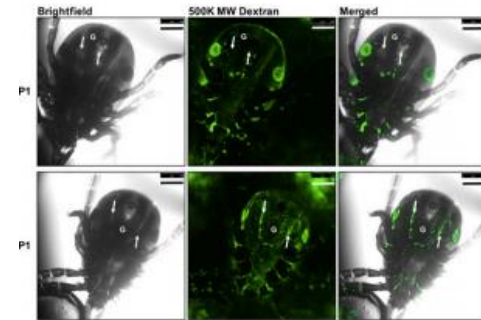
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*A. phagocytophilum* can then cross the gut barrier and colonizes salivary gland from where it will be transmitted.

# How do tick associated microbes interact with pathogenic ones?

- Interactions between gut microbiota and pathogens:
- The gut microbiota as a helper of pathogen colonization: the ex. of *Borrelia burgdorferi*

Published in final edited form as:

*Cell Host Microbe*. 2014 January 15; 15(1): 58–71. doi:10.1016/j.chom.2013.12.001.

## Gut Microbiota of the Tick Vector *Ixodes scapularis* Modulate Colonization of the Lyme Disease Spirochete

Sukanya Narasimhan<sup>1,¶</sup>, Nallakkandi Rajeevan<sup>2,\*</sup>, Lei Liu<sup>1,\*</sup>, Yang O. Zhao<sup>1,\*</sup>, Julia Heisig<sup>1</sup>, Jingyi Pan<sup>1</sup>, Rebecca Eppler-Epstein<sup>1</sup>, Kathleen DePonte<sup>1</sup>, Durland Fish<sup>3</sup>, and Erol Fikrig<sup>1,4,¶</sup>



Normal microbiote

Dysbiosed ticks (Antibiotics)

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- Ticks were fed with *Borrelia* infected blood
- Surprisingly, *Borrelia* did not survive in the gut of dysbiosed ticks

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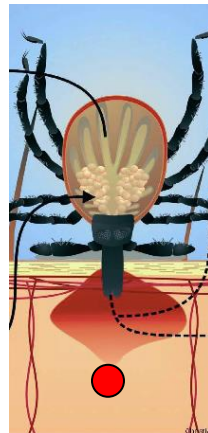
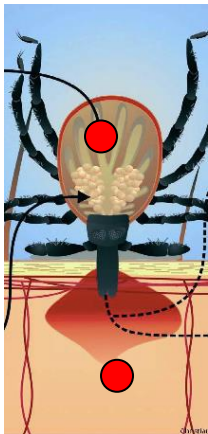
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Normal microbiote

Dysbiosed ticks (Antibiotics)

- Ticks were fed with *Borrelia* infected blood
- Surprisingly, *Borrelia* did not survive in the gut of dysbiosed ticks

In dysbiosed ticks: they observed a decrease of peritrophin that protect *Borrelia* from gut toxic compounds.



# How do tick associated microbes interact with pathogenic ones?

- Summary of interactions between gut microbiota and pathogens:

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PNAS

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Antagonist effects of gut microbiota considering the pathogens: microbiota blocks *A. phagocytophilum* colonization while tick microbiota allows protection of *Borrelia* and its survival in the gut

These results may explain why *A. phagocytophilum* and *Borrelia* are not found associated in ticks.

# How do tick associated microbes interact with pathogenic ones?

- **Interactions between symbionts and pathogens: symbionts seem to block pathogens colonization**
  - First evidence of interaction was done by Burgdorfer in 1981: The presence of Rickettsial symbionts hampered multiplication of the highly pathogenic *R. rickettsii* (Burgdorfer, 1981)
  - *Rickettsia belli* (symbiont) is negatively associated with *A. marginale* in ticks (Gall et al., 2016)
  - Ticks infected with *Rickettsia buchneri* are less infected by *Borrelia burgdorferii*

Rickettsial symbionts might be a key factors to regulate tick borne pathogens abundance and diversity in ticks

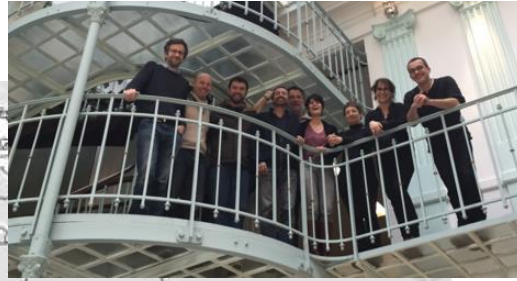
# Summary and conclusion

- ✓ Considering all these data, the tick pathobiome concept is not only a concept but a reality
- ✓ Ticks pathobiome is complex, with many interactions with implications in term of pathogens transmission and diseases
- ✓ For a better understanding of this very complex system , we need to combine our vision of traditionnal infectiology with microbial ecology adapted to pathogens



# Many thanks to the european tick teams

*Les tiques c'est chic!*



**MEM MP**



- Partner 18 – Institut Pasteur (IP), Paris, France.
- Partner 20 – Institute of Vertebrate Biology (IVB), Brno, Czech Republic
- Partner 21 – Sven Istvan University, Faculty of Veterinary Science (SZIE) Budapest, Hungary
- Partner 32 – Institut National de Recherche Agronomique (INRA), Paris, France
- Partner 33 – Slovak Academy of Sciences (SAS), Bratislava, Slovakia
- Partner 34 – Ludwig Maximilians Universitaet Muenchen (LMU), Munchen, Germany
- Partner 35 – Fondazione Edmund Mach (FEM), Trento, Italy
- Partner 36 – Research Centre Borstel (RCB), Borstel, Germany
- Partner 37 – Innovative Diagnostics-VET (ID-VET)
- Partner 38 – Kafkas Universitesi (KAU), Kars, Turkey
- Partner 40 – Friedrich Loeffler Institute (FLI), Riems, Germany

**And to colleagues at INRA (E. Maguin, the first pathobiomer)**