PhD Thesis proposal[1]

General Information	
PhD Thesis Title	**Global approach for Leptospiral risk analysis and management in livestock and wildlife**
USEK Doctoral Degree	PhD in Agriculture and Food Sciences
Research Unit	USC 1233, INRAe VetAgro Sup, Rongeurs Sauvages, risque Sanitaire et gestion des populations
Laboratory	NA
Axis	Public Health and Molecular Pathology

Co-Supervisor	Name & Title : Afif Abdel Nour (PhD) Email : afifabdelnour@usek.edu.lb	University Address: Holy Spirit University of Kaslik - USEK
Co-Supervisor	Name & Title : Christo Hilan (PhD, HDR) Email : christohilan@gmail.com	University Address : Holy Spirit University of Kaslik - USEK
Co-supervisor	Name & Title : Zoree Djelouadji (PhD, HDR) Email :zoree.djelouadji@vetagro-sup.fr	University Address : VetAgro Sup Lyon France
Co-supervisor	Name & Title : Florence Ayral (PhD) Email : florence.ayral@vetagro-sup.fr	University Address : VetAgro Sup Lyon France
Location (s)	Location 1: USEK	Work shift calendar /per year (40%):
	Location 2: VetAgro Sup	Work shift calendar /per year (60%):
Potential funding and scholarship	Bourses Doctorales CNRS-L/USEK	

Applicant Profile and/or Special Requirements	Agricultural Engineer, fluent in molecular biology techniques (qPCR and NGS), fluent in handling blood samples, fluent in English and French.

Subject's national or worldwide Context, Objectives & Research lines

[1] Thesis proposal should not exceed two pages

Leptospira sp. are endemic in many domestic and wild mammals, which may shed the bacteria in their urine. Humans may acquire potentially fatal leptospirosis through direct contact with the urine of infected animals or indirectly through interaction with a urine-contaminated environment. In mainland France, an increasing incidence of 1 per 100 000 inhabitants since 2014, has been observed without clear explanations. Hypothesis included the climate change and the modification of the reservoir population dynamics. Data are not available in Lebanon nonetheless a greater incidence is expected according to the warmer climate. In ruminants, *Leptospira*, mainly non-maintenance serovars, infection is responsible for abortion and infertility that lead to product losses and raise a public health issue with number of leptospirosis occurrences reported in farmers and abattoir employees.

Rodents and more specifically commensal rodents such as *Rattus sp* and *Mus sp* are the predominant culprits however many mammals can be maintenance hosts of pathogenic *Leptospira* including cattle. The multiple sources of *Leptospira* lead to a complex disease epidemiology and many basic components of the epidemiology remain unknown so far. In this context, appropriate management measures are required to reduce the threat for human health and economic losses in cattle herds. They relies on (1) a clear understanding of basic epidemiological knowledge such as animal species that are maintenance hosts, their characteristics as maintenance hosts (infection's length, specificity of *Leptospira* carriage) and environmental features leading to indirect *Leptospira* transmissions; (2) a surveillance strategy that is reliable, affordable and easily implemented and (3) available tools to assess the relevance of management measures such as the chemical control of farm rodents.

The objectives are:

1. To implement animal models of chronic *Leptospira* infection and co infections and generate epidemiological knowledge.
2. To characterize the risk of *Leptospira* infection or exposure in herds through environmental and wildlife indices considering various contexts in France and Lebanon.
3. To implement a new Leptospira surveillance strategy in commensal rodents based on the intestinal microbiota analysis.
4. To recommend the best management approach to mitigate the risk depending on the context.

	Outcomes (OCs): What do we wish to achieve?
OC1:	Through the implementation of rat models of chronic *Leptospira* infection and co infections we will be able to define (1) the potential for specific carriage depending on *Leptospira* strains, (2) the length of bacteria carriage, (3) the variations in immunity markers
OC2:	Using a cross sectional study in various breeding administrative regions in France and Lebanon through blood samples in cattle and commensal rodent sampling, we will characterize *Leptospira* genetic profiles (qPCR and typing) or serological profiles (Micro agglutination test) and determine through a case-control approach, the environmental, animal and zootechnic variables associated with a greater risk of infection or exposure.

OC3:	Considering the variation in immunity markers in infected and non-infected individuals, a variation of the intestinal microbiota in the two sub-populations is expected. Applying the microbiota analysis on rat feces obtained through the experimental (OC1) and cross sectional (OC2) studies could reveal variation between infected and non-infected rodents and suggest the use of such an approach for infected population surveillance on the field.
OC4 :	Characterization of Vkorc1 mutations in commensal rodents obtained from OC2 concurrently with the presence of anticoagulant residues (AR) in the liver will oriented future strategies of pest control. Characterization of the resistance phenotype induced by mutation will be done by protein engineering and enzymology studies. AR will be detected and quantified by Liquid chromatography and mass spectrometry.

	References (R)
R1:	**Ayral F**, Kodjo A, Guédon G, Boué F, Richomme C (2020) Muskrats are greater carriers pathogenic Leptospira than coypus in ecosystems with temperate climates. PLoS ONE e0228577. https://doi.org/10.1371/journal.pone.0228577
R2:	Guillois Y, Bourhy P, **Ayral F** *et al.* An outbreak of leptospirosis among kayakers in Britt North-West France, 2016. Euro Surveill. 2018;23(48):pii=1700848. https://doi.org/10.2807/1560-7917.ES.2018.23.48.1700848
R3:	Goulois J, Lambert V, Legros L, Benoit E, **Lattard V** (2017) Adaptive evolution of the Vk gene in Mus musculus domesticus is influenced by the selective pressure of anticoagul rodenticides. Ecol Evol, 7(8), 2767-2776. doi: 10.1002/ece3.2829.
R4:	Goulois J, Hascoët C, Dorani K, Besse S, Legros L, Benoit E, **Lattard V** (2017) Study of th efficiency of anticoagulant rodenticides to control Mus musculus domesticus introgres with Mus spretus Vkorc1. Pest Manag Sci 73(2), 325-331. doi: 10.1002/ps.4319.
R5:	Lefebvre S, Rannou B, Besse S, Benoit E, **Lattard V** (2016) Origin of the gender differen the natural resistance to antivitamin K anticoagulants in rats. Toxicology 344-346, 34-4 doi: 10.1016/j.tox.2016.02.002.
R6:	Zilber AL, Belli P, Artois M, Kodjo A, **Djelouadji Z**. First Observation of Leptospira interr in the Lungs of Rattus norvegicus. Biomed Res Int.2016:9656274.
R7:	**Ayral F**, Djelouadji Z, Raton V, Zilber A-L, Gasqui P, Faure E, et al. (2016) Hedgehogs an Mustelid Species: Major Carriers of Pathogenic Leptospira, a Survey in 28 Animal Speci France (2012-15). PLoS ONE
R8:	Zilber AL, Belli P, Grezel D, Artois M, Kodjo A, **Djelouadji Z.** Comparison of Mucosal, Subcutaneous and Intraperitoneal Routes of Rat Leptospira Infection. PLoS Negl Trop D 2016 Mar 31;10(3):e0004569. doi: 10.1371
R9:	**Ayral F**, Zilber A-L, Bicout DJ, Kodjo A, Artois M, **Djelouadji Z** (2015) Distribution of Leptospira interrogans by Multispacer Sequence Typing in Urban Norway Rats (Rattus norvegicus): A Survey in France in 2011-2013. PLoS ONE 10(10)

R10:	**Ayral F,** Artois J, Zilber AL, Widén F, Pounder KC, Aubert D, Bicout DJ, Artois M.The relationship between socioeconomic indices and potentially zoonotic pathogens carrie wild Norway rats: a survey in Rhône, France (2010-2012). Epidemiol Infect. 2015 Feb;143(3):586-99. doi: 10.1017/S0950268814001137
R11:	**Ayral F**, Bicout D, Pereira H, Artois M, Kodjo A (2014). Distribution of Leptospira Serogroups in Cattle Herds and Dogs in France. The American Journal of Tropical Medicine and Hygiene, 91(4), 756–759.
R12:	Zilber AL, Picardeau M, Ayral F, Artois M, Demont P, Kodjo A, **Djelouadji Z**. High-resolu typing of Leptospira interrogans strains by multispacer sequence typing. J Clin Microbi 2014 Feb;52(2):564-71. doi: 10.1128/JCM.02482-13.