



# Editorial: Sand Flies and Their Interactions With *Leishmania* and Other Pathogens

Yara Maria Traub-Csekö<sup>1\*</sup>, Marcelo Ramalho-Ortigão<sup>2</sup> and Erich Loza Telleria<sup>3</sup>

<sup>1</sup> Instituto Oswaldo Cruz, Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil, <sup>2</sup> Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, IL, United States, <sup>3</sup> Department of Parasitology, Faculty of Science, Charles University, Prague, Czechia

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## Editorial on the Research Topic

### Sand Flies and their Interactions with *Leishmania* and Other Pathogens

Phlebotomine sand flies are best known as vectors of *Leishmania* parasites that cause leishmaniasis but can transmit bacteria and viruses. Leishmaniasis, a multi-spectrum disease, is a serious health threat to millions of people throughout the world, with 700,000 to 1 million cases occurring yearly (1). Among the different clinical manifestations, visceral leishmaniasis is deadly if left untreated. On the other hand, cutaneous and mucocutaneous manifestations, which generally are not fatal, can lead to lifelong scars, disability, and stigma.

Worldwide, many laboratories are actively working on leishmaniasis. Searching PubMed using “leishmaniasis” as keyword brings out approximately 30,000 papers, whereas if one uses “sand fly” approximately 6,000 publications are found. Most of these studies have focused on areas such as taxonomy, epidemiology, and biology. Significantly fewer hits are generated if using combinations such as “vector interaction with *Leishmania*” (300 hits), “sand fly-pathogen” (122 hits), or even “sand fly-virus” (23 hits). The reduced number of publications covering the sand fly interaction with pathogens led us to propose this Research Topic. We were fortunate to have contributions covering a variety of subjects within the Topic proposed.

As indicated above, in addition to *Leishmania* spp., sand flies also vector other pathogens, such as *Bartonella* spp., the bacteria that cause bartonellosis. *Bartonella* is transmitted by different hematophagous arthropods in different locations of the world. In the Andean valleys of Peru, Colombia, and Ecuador, *Bartonella bacilliformis* is the agent of the so-called Carrion’s Disease and is mostly transmitted by *Lutzomyia verrucarum* sand flies. In Mexico, *Bartonella* species have been found associated with lice and fleas, but few studies have investigated their presence in sand flies. Lozano-Sardaneta et al., 2021 detected *Bartonella* DNA in sand fly species from northeastern Mexico. More importantly, they reported the presence of *Bartonella* sp. in *Lutzomyia cruciata* and *Psathyromyia shannoni*, with evidence suggesting a new bacterium lineage. The report of *Bartonella*-infected sand flies outside the endemic area of Carrion’s Disease highlights the diversity of sand fly-*Bartonella* associations and suggests the need for further studies on their cycle in the vector and possible transmission to hosts.

The effect of the natural microbiota on the physiology of their hosts gains more evidence every day. Many studies have explored the diversity of microorganisms harbored by sand flies, and its importance to *Leishmania* survival within the vector. Details of mechanisms potentially involved in these interplays remain to be elucidated. Vivero-Gomez et al., 2021 used chromatography and mass

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David P. Tchouassi,  
International Centre of Insect  
Physiology and Ecology  
(ICIPE), Kenya

### \*Correspondence:

Yara Maria Traub-Csekö  
ytraub@ioc.fiocruz.br

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spectrometry techniques to identify molecules produced by 12 different Gram-negative bacteria isolated from the guts of *Pintomyia evansi*, among which were quorum sensing molecules (QSMs). Quorum sensing (QS) is a complex system mostly regulated by the density of the bacterial population. It involves signaling molecules that act upon regulatory mechanisms and can modify behavior through chemical communication. Moreover, these regulatory mechanisms might be involved in the complex pathogen–microbiota–host interactions found in insect vectors, with specific molecular signals affecting the population composition of the three players. It was previously shown that in *Aedes aegypti*, QSMs from host microbiota can be used by the female mosquito to detect, locate, and select vertebrate hosts (2). In the present study, QSMs from bacteria within sand flies were identified. Establishing the role played by QSMs in the sand fly and their presumed ability to modulate pathogen transmission will provide further details about the intricate relationships of these vectors and the pathogens they transmit.

In *Leishmania*-infected sand flies, the parasites coexist with a complex bacteria community present in the insect gut. From the sand fly point of view, this diverse gut community is likely balanced to control opportunistic pathogens. Similar to other insects, the sand flies' innate immune response comprises pathways that regulate pathogen-killing molecules. Nevertheless, it is not yet clear whether the sand flies' immune responses are activated to target the *Leishmania* development or the gut microbiome with a consequent effect on the parasite. Telleria et al., 2021 investigated the expression of genes associated with the Jak-STAT immunity pathway in *Lutzomyia longipalpis*. Co-culturing of LL5 embryonic cells with *Leishmania* parasites caused the upregulation of pathway repressors, suggesting a parasite-induced suppression of the pathway. Gene silencing of a STAT-like transcription factor in the female sand flies downregulated an inducible nitric oxide synthase gene and increased parasite detection, indicating that oxidative stress can affect the parasite survival. The unveiling of the complex vector–parasite interaction opens new perspectives for molecular-based control strategies tackling the cycle in the insect.

When *Leishmania* parasites are transmitted to a vertebrate host by the bite of an infected female sand fly, the insect ejects its

saliva at the bite site. The sand fly saliva is composed of molecules such as vasodilators and anticoagulants that facilitate the blood-feeding. In cutaneous leishmaniasis caused by *Leishmania major*, the development of skin wounds depends on the parasite load and the vertebrate immune response. However, the effect of repeated sand fly bites on lesions of a previously infected host has been scarcely studied. Vojtkova et al., 2021 investigated the development of skin lesions on BALB/c mice experimentally infected with *L. major* and subsequently exposed to multiple *Phlebotomus duboscqi* sand fly bites. The authors showed that the repeated sand fly bites resulted in increased lesions and parasite loads assessed by quantitative PCR. This finding is important for defining adequate protective measures for infected patients, thus reducing the disease lesions' burden and optimizing preventive transmission measures for endemic areas.

In this regard, Aronson et al., 2022 investigated human IgG antibody levels against *Phlebotomus papatasi* saliva antigens using ELISA and Western blot techniques in a cohort study of American soldiers (generally considered a naïve population with regards to sand fly exposure) deployed to Iraq. Using sera from the US Department of Defense Sera Depository (DoDSR), the largest sera bank in the world, the authors identified biomarkers for vector exposure and cutaneous leishmaniasis infection with a relatively short duration of the antibody response. Molecular markers of sand fly exposure and their association to *Leishmania* infection can improve accurate public health preventive and control measures. Matched to race, sex and other parameters, the results allowed for a comprehensive analysis linking clinical outcomes and risk to the individual's immune response.

This Research Topic reveals new aspects of the sand fly associations with bacteria, *Leishmania* and vertebrate hosts. We expect this will inspire scientists to embark in the investigation of neglected aspects of this very important vector and thus help to optimize strategies for the control of diseases transmitted by sand flies.

## AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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