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Review

Control of Neglected Disease Insect Vectors: Future Prospects for the Use of Tools Based on Behavior Manipulation-Interference

Marcelo G. Lorenzo,[a] ***Diogo M. Vidal***[b] ***and Paulo H. G. Zarbin*****[*,b]

[a]*Grupo de Comportamento de Artrópodes Vetores e Interação com Patógenos, Centro de Pesquisas René Rachou (CPqRR)- Fundação Oswaldo Cruz (Fiocruz), Av. Augusto de Lima, 1715, 30190-002 Belo Horizonte-MG, Brazil*

[b]*Laboratório de Semioquímicos, Departamento de Química, Universidade Federal do Paraná (UFPR), CP 19032, 81531-980 Curitiba-PR, Brazil*

A expressão "doenças tropicais negligenciadas" (NTDs) representa uma série de doenças que afetam a população de países de baixa renda, sendo insetos vetores os responsáveis pela transmissão de grande parte dessas doenças. Ferramentas de controle são necessárias para impedir o contato entre humanos e insetos vetores destas doenças. Este controle é comumente realizado pelo uso intensivo de inseticidas, porém, resistência a estes xenobióticos ocorre nos casos mais relevantes de espécies de vetores de doenças. Portanto, metodologias alternativas para o controle de vetores são urgentemente necessárias para evitar a transmissão da maioria das NTDs. Nesta revisão, uma série de compostos químicos que podem auxiliar no desenvolvimento de ferramentas de controle desses vetores, as quais se baseiam na manipulação do comportamento dos insetos associado à estas moléculas, são descritas. Tais relações incluem os odores de hospedeiros usados por artrópodes na busca de fontes de sangue, assim como feromônios utilizados por estes em diversos contextos como, por exemplo, na reprodução. Adicionalmente, são apresentados caminhos recentemente explorados na busca de compostos capazes de modificar comportamentos através de metodologias de alto rendimento. Especificamente, são mostrados exemplos de como estas metodologias mediam a busca por novos repelentes e atrativos.

The expression "neglected tropical diseases" (NTDs) represents a series of illnesses that affect the population of low-income countries, being vector insects responsible for the transmission of a large part of these diseases. Control tools are needed to impede contacts between humans and insects vectoring some of them. This control is currently attained by intensive insecticide use but resistance to such xenobiotics exists in the most relevant disease vector species. Therefore, alternative vector control methodologies are urgently needed to avoid most NTD transmission. The present review describes a series of molecules that could assist on developing vector control tools, which could be based on manipulating insect behaviors associated with them. Such relations include host odors used by arthropods to search for blood sources, as well as pheromones used by them to communicate in diverse contexts, e.g., reproduction. Additionally, avenues recently explored in the search of behavior modifying compounds by means of high throughput methodologies are discussed. Specifically, examples of how such methodologies mediate the search for new repellents and attractants are described.

Keywords: vector insects, pheromones, kairomones, repellents

1. Neglected Tropical Diseases and Control Tools

The expression "neglected tropical diseases" (NTDs) refers to a cluster of maladies endemic to low-income countries.[1-3] The extent of this cluster varies depending on which source analyzes the subject, but there is consensus on the fact that it represents a serious public health burden of high impact almost comparable to most ominous human diseases, such as HIV and tuberculosis.[2,4-6] Many of these illnesses are transmitted by vector organisms, mostly blood-feeding arthropods. Even though several of

*e-mail: pzarbin@ufpr.br

these diseases can be prevented or treated, it is clear that most vector-borne neglected maladies cannot be currently controlled by means other than extensive use of insecticides to eliminate their vector insects.[7] Diseases like dengue fever, leishmaniasis, Chagas disease, lymphatic filariasis, African sleeping sickness and onchocerciasis are considered NTDs and represent the main vector-borne maladies affecting humans around the globe together with malaria.

The virus causing dengue fever, for example, is transmitted by the mosquito *Aedes aegypti* (Figure 1a). Brazil officially reported more than 200,000 cases to the Pan-American Health Organization in 2013.[8] The estimated annual cost with dengue fever in that country amounts to approximately US$ 132 million, including activities of vector control; surveillance; information, education and communication; direct and indirect medical costs.[9] From this global cost, the average investment in control represents 25%, while surveillance requires 4%.[9] The yearly global cost due to dengue fever infections is estimated in 390 million (including symptomatic and asymptomatic cases).[10]

Figure 1. Examples of vectors of neglected tropical diseases: (a) *Aedes aegypti*, the main vector of dengue virus; (b) *Triatoma infestans*, an important vector of the flagellate protozoan *Trypanosoma cruzi*, etiological agent of Chagas disease; and (c) *Lutzomyia longipalpis*, a phlebotome sandfly that can be parasitized by *Leishmania* flagellates, etiological agents of leishmaniasis.

One century after the discovery of Chagas disease, a curative agent is still not available. It is one of the leading causes of mortality/morbidity in Latin America, with approximately 8 million people infected worldwide, more than 25 million people at risk of infection, and approximately 15,000 deaths each year.[11] This debilitating zoonosis is caused by infection with the flagellate protozoan *Trypanosoma cruzi*. The primary vectors in South America are *Triatoma infestans* (Figure 1b) and *Rhodnius prolixus*, however, species such as *Panstrongylus megistus* and *Triatoma brasiliensis*, play an important role in transmission in some regions of Brazil.[12]

Another example of neglected disease caused by a protozoan parasite and transmitted by a vector insect is leishmaniasis, which is caused by parasites of the genus *Leishmania*. Its transmission to humans happens via the bite of phlebotomine sandflies, e.g., *Lutzomyia longipalpis* (Figure 1c) and 70-90% of reported cases come from a list of 12 countries that includes Brazil, Colombia and Peru.[13]

Currently, the intense use of insecticides needed for controlling some of these and other diseases represents an enormous chronic expenditure for the public agencies that combat their transmission, both in terms of cost of active principles and logistics necessary to apply them.[7,14] Nevertheless, in most of the cited cases these xenobiotics currently represent our best tools to avoid disease spread.[15]

2. The Use of Insecticides: Future Limitations

Historic records show that the use of insecticides has allowed effective disease control in many cases.[15] This sustained use and its eventual failures have promoted the appearance of insecticide resistance in many of the vector species transmitting NTDs.[16,17] Resistance to insecticides is widespread for important disease vectors such as mosquitoes,[18,19] triatomines[20-22] and ticks.[23] Populations of other vector arthropods, e.g., sandflies, which have been subjected to intensive selective pressure by insecticide use, will probably develop similar tolerance to current xenobiotics in the future. These processes have promoted increasing control limitations in broad areas, as traditional measures are not as effective anymore.[16,24-27] Due to this, the search for new tools that could act as control alternatives has been an active trend in the field of insect vector biology in the last decade. Diverse strategies have been followed in order to generate innovative alternatives for vector insect control or even detection, but the impact on these objectives is yet to come.[28-33] Paradoxically, the development of similar tools has progressed faster for agricultural pests, probably due to its commercial potential for powerful business branches such as the production of food, biofuels and other plant based commodities such as cotton and tobacco.[34-37] What follows is a series of topics in which we summarize current knowledge on diverse aspects of the chemistry, biology and chemical ecology of vector arthropods, which could lead to the development of tools to assist their control. In connection to this, we suggest several perspectives that could be pursued in the field in order to offer alternatives for control agencies.

3. Host Kairomones and their Potential for Vector Detection/Capture

Host emitted odors have been described as attractants for hematophagous arthropods since long ago.[38-49] This is true for diverse hematophagous arthropod orders and evidence gathered so far indicates that CO_2 is an almost universal cue used by these arthropods to detect and find their hosts.[50] The detection of other substances emitted by hosts is also frequently exploited in order to find emission sources. Examples of female mosquitoes orienting to host odors are diverse[42,51-55] and highlight how much these insects rely on a widespread use of chemical signals to recognize their sources of blood.

L-Lactic acid was identified as the major constituent of acetone extracts from human skin and showed to be attractive to female *Ae. aegypti* when used jointly with CO_2.[42] Later, by employing ammonia in combination with CO_2 and *L*-lactic acid, a strong synergistic effect between those compounds was observed using Y-tube olfactometry.[44] A blend of short carboxylic acids (e.g., propionic, butyric, isovaleric, hexanoic) combined with *L*-lactic acid was shown to be more attractive to *Ae. aegypti* females than *L*-lactic acid alone.[45]

The effect of kairomones in host location by the malaria transmitting mosquito *Anopheles gambiae* was tested by using traps in controlled cages. A synergistic effect was found when ammonia, lactic acid and fatty acids were presented as a blend into trap devices. However, the tripartite synergistic effect observed for *An. gambiae* differed from *Ae. aegypti*, since lactic acid alone attracted *Ae. aegypti* but not *An. gambiae*.[51] *An. gambiae* females preferred human odor over clean air in a Y-tube and avoided cow odor over clean air,[54] a feature that might reinforce the effectiveness of their orientation to human hosts. Analysis of skin rubbings from various vertebrates indicated that human skin levels of *L*-lactic acid are the highest found between studied hosts, suggesting that the lower levels of *L*-lactic acid found on other animals contribute to their lower attractiveness to *An. gambiae*.[55]

The genus *Culex* comprises the vectors of pathogens that cause diverse human diseases, including St. Louis encephalitis, Japanese encephalitis, Venezuelan equine encephalitis, Western equine encephalitis, lymphatic filariasis and West Nile Virus.[56] *Culex quinquefasciatus* are strongly attracted by rabbit chow-baited traps and the bioactive compounds responsible for this were studied. By using solid phase micro-extraction (SPME), gas chromatography-electroantennographic detection (GC-EAD) and gas chromatography-mass spectrometry (GC-MS) techniques three compounds were identified as trimethylamine, nonanal and 3-methylindole.[56] These compounds were tested in the field and were shown to be attractive in binary and ternary combinations.[56]

Odorants from humans from diverse ethnic backgrounds were collected by SPME and the major components identified were 6-methyl-5-hepten-2-one, nonanal, decanal, and geranyl acetone.[57] Volatiles emitted by birds, the principal hosts of *Cx. quinquefasciatus*, were also analysed and nonanal was shown to be their main component.[57] Electroantennography recordings with female *Cx. quinquefasciatus* antennae tested against volatiles from chicken, pigeons and humans showed a consistent response to nonanal.[57] Behavioral experiments showed strong attraction of *Cx. quinquefasciatus* to traps baited with nonanal alone or in combination with CO_2.[57]

Triatomine bugs, another group of relevant vector arthropods that transmit Chagas disease to humans, have also been shown to exploit an array of chemical substances emitted by their hosts.[58-65] For *Rhodnius prolixus*, CO_2 and human odor proved to be attractive, as well as the odor of a hamster, while on the other hand, *L*-lactic acid alone did not seem to play an important role in orientation.[58] A mixture of lactic, propionic, butyric and valeric acid showed a synergistic effect with CO_2 (300 ppm above the ambient level) on the attraction of *Triatoma infestans*, evoking a behavioral response comparable in intensity to that induced by a live mouse.[59] By using electrophysiological single sensillum recordings coupled to gas chromatography, nonanal (from sheep wool and chicken feathers) and isobutyric acid (from rabbit odor) were identified as chemostimulants to receptor neurons from *Triatoma infestans*. Behavioral bioassays showed that nonanal causes the activation of the bugs, while isobutyric acid induces their attraction.[62] 1-Octen-3-ol, which was first isolated from cattle odors and is also present in human sweat, was shown to be attractive to *Triatoma infestans*, even in the absence of CO_2.[64]

A similar perspective can be presented for the relevant vectors of leishmaniasis, the sandflies.[66-71] Male and female *Lu. longipalpis* sandflies showed attraction to human skin extracts[67,69,70] and also to CO_2 emitted at human-equivalent rates.[70] Single sensillum recordings coupled to gas chromatography showed that sixteen compounds from the odor-producing glands of the fox *Vulpes vulpes* stimulate the olfactory organs of sandflies. *Lu. longipalpis* were as attracted to fox extracts as to a synthetic mixture containing all the synthetic compounds (4-methyl-2-pentanone, 2-hexanone, 4-hydroxy-4-methyl-2-pentanone, 3-hydroxy-2-butanone, 4-methylheptanone, 2-butanol, 3-methylbutan-1-ol, 3-methyl-3-buten-1-ol, 1-pentanol, propanoic acid, 2-methyl-propanoic acid, butanoic acid, 3-methyl butanoic acid, pentanoic acid, benzaldehyde and hexanal).[68]

Simulids are a group of small flies that can transmit serious diseases, as onchocerciasis, to humans and seem to rely on host odors in order to find a bloodmeal.[72-75] Biting midges, another group of tiny flies that can affect the production of cattle and represent a nuisance to humans, also use host odors in their orientation.[76-79] Relevant vector flies such as African tripanosomiasis-transmitting tse-tse flies also orient to their hosts by means of olfactory cues.[80,81]

Table 1. Kairomones emitted by hosts used by arthropods to search for blood sources

Kairomone	Source	Vector	Reference
Lactic acid	Human skin	*Ae. aegypti*, *An. gambiae*, *R. prolixus*, *T infestans*	42, 43, 48, 49, 51, 55, 64, 65
Acetone	Human skin	*An. gambiae*, *R. prolixus*, *G. pallidipes*, *G. morsitans*, *C. impunctatus*	52, 65, 77, 78, 80
CO_2	Human breathing	*Ae. aegypti*, *An. gambiae*, *An. stephansi*, *R. prolixus*, *T. infestans*, *Lu. intermedia*, *Lu. whitmani*, *G. palpalis*, *C. impunctatus*	43, 48, 52, 55, 64, 65, 77, 78
NH_3	Human skin	*Ae. aegypti*, *An. gambiae*, *T. infestans*	48, 49, 51, 61
Sweat/skin extract	Human	*Ae. aegypti*, *An. gambiae*, *R. prolixus*, *Lu. longipalpis*, *Lu. intermedia*, *Lu. whitmani*, *G. palpalis*	43, 53-55, 58, 60, 65, 67, 70, 73
Vertebrate odor	Mouse, cow, fox	*Ae. aegypti*, *An. quadriannulatus*, *R. prolixus*, *T. infestans*, *Lu. longipalpis*	38, 54, 58, 60, 65, 68
Fatty acids	Human skin	*Ae. aegypti*, *T. infestans*	49, 59
Carboxylic acids	Limburger cheese	*An. gambiae*	51
1-Octen-3-ol	Human skin, cattle	*An. stephensi*, *R. prolixus*, *T. infestans*, *G. pallidipes*, *G. morsitans*, *C. impunctatus*	52, 64, 65, 76-78, 80
Urine	Rabbit, cow, buffalo	*R. prolixus*, *T. infestans*, *C. impunctatus*	60, 78
Butyric acid	Human skin	*R. prolixus*	65
Nonanal	Sheep, chicken	*T. infestans*, *Cx. quinquefasciatus*	56, 62
Isobutyric acid	Rabbit	*T. infestans*	62
Trimethylamine	Rabbit	*Cx. quinquefasciatus*	56
3-Methylindole	Rabbit	*Cx. quinquefasciatus*	56

This array of examples highlights the potential of chemical substances emitted by hosts and, their associated skin microorganisms, as attractants to manipulate vector behavior, as summarized in Table 1. The search for appropriate formulations of behaviorally active blends is a field that needs attention to allow the development of efficient baits. Particularly, long and sustained emission of a stable blend formulation seems critical for proper bait function under field conditions.

4. Pheromones and their Potential for Vector Detection/Capture

Pheromones, the chemical signals used by animals to communicate with their conspecifics, represent a powerful alternative for the development of behavior-modifying tools. Pheromones have been described for triatomine bugs, flebotomine sandflies, mosquitoes, ticks and other vector arthropods. The appealing potential of pheromones relies in their specificity, powerful behavioral effect and low tendency of target species for developing resistance, if used in control tools. A diverse range of functions can be described for arthropod pheromones and these include the recognition of sexual partners, the promotion of species-specific aggregations, the marking of oviposition sites and shelters, and the rapid communication of the presence of menaces.

Few culicids have been shown to use pheromones to communicate and the most relevant case to date is the discovery of the oviposition pheromone of *Culex quinquefasciatus*.[82] The natural *Cx. quinquefasciatus* pheromone was extracted from the apical droplets found over mosquito eggs and the respective chemical structure was identified by mass spectrometry and microderivatizations as *erythro*-6-acetoxy-5-hexadecanolide (MOP).[82] Enantioselective syntheses for both enantiomers were developed[83,84] and the absotute configuration of the natural pheromone was determined as (–)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide ((5*R*,6*S*)-MOP) (**1**) (Figure 2).[85] From the four possible stereoisomers of 6-acetoxy-5-hexadecanolide, only the natural (5*R*,6*S*)-MOP promotes oviposition by female *Cx. quinquefasciatus* to oviposition.[86] Nowadays, this pheromone is commercially available for trapping systems.[87]

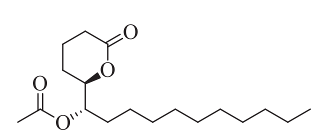

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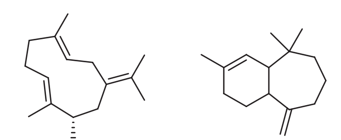
Figure 2. (5*R*,6*S*)-6-Acetoxy-5-hexadecanolide (**1**), the oviposition pheromone of *Cx. quinquefasciatus*.

Whether mosquitoes use chemical signals for sexual communication is not clear to date, but evidence seems to suggest that this is also the case.[88] Vector sandflies have been shown to exploit chemical substances for communication purposes and the two main types of pheromones described to date involve sexual[71,89,90] and oviposition[66] signals.[91-94]

Lutzomya longipalpis is a complex of sibling species and its sexual communication is mediated by blends of terpenes that show large variations in respective composition when populations from different localities are compared.[89] The sex pheromone of *Lu. longipalpis* was first extracted from glands of males of a Brazilian population (Lapinha-MG) and identified as the homoterpene 9-methylgermacrene-B.[95] The absolute configuration of 9-methylgermacrene-B was studied by its respective enantioselective synthesis and analysis through chiral GC, identifying the natural pheromone as (*S*)-9-methylgermacrene-B (**2**) (Figure 3).[96]

Subsequently, another Brazilian *Lu. longipalpis* population (Jacobina-MG) was studied and a mixture of α-himachalene (**3**) (Figure 3) and 3-methyl-α-himachalene (major component) was identified as its sex pheromone by mass spectrometry and microderivatization techniques.[97,98] The stereochemistry of 3-methyl-α-himachalene was identified as (1*S*,3*S*,7*R*)-3-methyl-α-himachalene (**4**) (Figure 3) by behavioral, chromatographic and electrophysiological tests, suggesting that the pheromone has a dual function of promoting male aggregations, as well as attracting females.[99,100]



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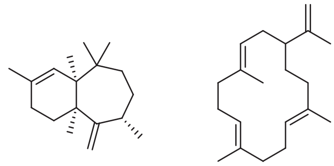

4 **5**

Figure 3. Compounds related to the sexual communication and aggregation behavior of *Lu. longipalpis*: (*S*)-9-methylgermacrene-B (**2**), α-himachalene (**3**), (1*S*,3*S*,7*R*)-3-methyl-α-himachalene (**4**), and cembrene (**5**).

Additional South American populations of this species were studied and showed at least four sex pheromone chemotypes, including one that produces the diterpene cembrene (**5**) (Figure 3).[89,101]

Lu. longipalpis produces dodecanoic acid **(6)** (Figure 4) as an oviposition pheromone, which is secreted onto eggs by accessory glands. This pheromone was shown to be attractive mainly when combined with volatile kairomones found in rabbit feces, e.g., hexanal and 2-methyl-2-butanol.[92]

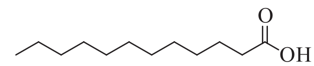

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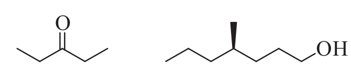
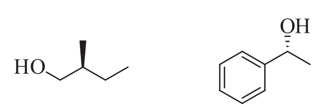
Figure 4. Dodecanoic acid (**6**), the oviposition pheromone of *Lu. longipalpis*.

In recent years, a body of evidence has indicated that triatomine bugs use chemical substances emitted by females in order to promote male orientation to females, mating and male aggregations around mating pairs.[102-107] The metasternal glands (MGs) of these insects are involved in their production at least in *T. infestans*, *T. brasiliensis*, *Triatoma dimidiata* and *R. prolixus*, the main vector species transmitting Chagas disease to humans. The volatile contents of the MGs of these species were extracted by SPME. As a consequence, thirteen compounds were identified in the MGs of *T. brasiliensis* by means of GC-MS and chiral GC-flame ionization detection (FID): 2-butanone, 3-pentanone, (*S*)-2-butanol, 2-methyl-1-propanol, 3-pentanol, (*R*)-2-pentanol, (±)-3-hexanol, (*S*)-3-methyl-2-hexanol, (*R*)-4-methyl-1-hexanol, 1-heptanol, 6-methyl-1-heptanol, (*R*)-4-methyl-1-heptanol and (*R*)-1-phenylethanol.[102] Electrophysiological experiments showed that 3-pentanone (**7**), (*R*)-4-methyl-1-heptanol (**8**), (*S*)-2-methyl-1-butanol (**9**) and (*R*)-1-phenylethanol (**10**) are active on male antennae (Figure 5).[102]



(**7**) (**8**)



(**9**) (**10**)

Figure 5. EAD active compounds from the metasternal gland of female *T. brasiliensis*: 3-pentanone (**7**), (*R*)-4-methyl-1-heptanol (**8**), 2-methyl-1-propanol (**9**) and (*R*)-1-phenylethanol (**10**).

Additionally, twelve compounds produced by the metasternal glands of male and female *R. prolixus* were identified by SPME and GC-MS: 2-butanone (**11**), 2-pentanone (**12**), (*S*)-2-butanol (**13**), 2-methyl-3-buten-2-ol (**14**), 3-methyl-2-butanol (**15**), 3-pentanol (**16**), (*S*)-2-pentanol (**17**), (*E*)-2-methyl-3-penten-2-ol (**18**), (*S*)-4-methyl-2-pentanol (**19**), (*S*)-3-hexanol (**20**), 2-methyl-1-butanol (**21**) and (±)-4-methyl-3-penten-2-ol (**22**) (Figure 6).[103] Behavioral tests suggest that these secretions are involved in the sexual communication of *R. prolixus*.[103-106]

Besides, several triatomine vectors present an aggregation inducing system based on two chemical signals, a volatile one emitted by their feces[108-110] and a contact factor

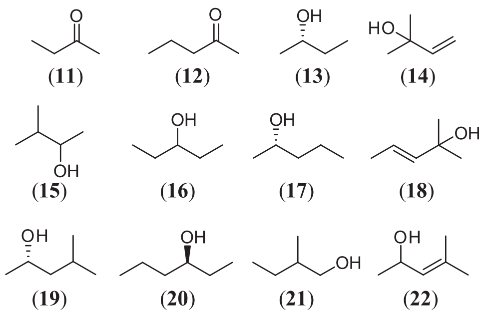


Figure 6. Compounds from metasternal glands probably involved in the sexual communication of the triatomine bug *R. prolixus*: 2-butanone (**11**), 2-pentanone (**12**), (*S*)-2-butanol (**13**), 2-methyl-3-buten-2-ol (**14**), 3-methyl-2-butanol (**15**), 3-pentanol (**16**), (*S*)-2-pentanol (**17**), (*E*)-2-methyl-3-penten-2-ol (**18**), (*S*)-4-methyl-2-pentanol (**19**), (*S*)-3-hexanol (**20**), 2-methyl-1-butanol (**21**) and (±)-4-methyl-3-penten-2-ol (**22**).

deposited on the substrate.[108,111,112] The chemical identities of these pheromones have been reported recently in *T. infestans*. Octadecanoic acid (**23**) and hexacosanoic acid (**24**) were identified as a contact pheromone (Figure 7).[112] Acetic acid (**25**), 3-methylbutanoic acid (**26**), hexanoic acid (**27**) acetamide (**28**) and 2,3-butanediol (**29**) were found in the feces of *T. infestans*, *P. megistus* and *T. brasiliensis* (Figure 8) and would allow the potential development of species-specific baits to detect these relevant disease vectors.[12]

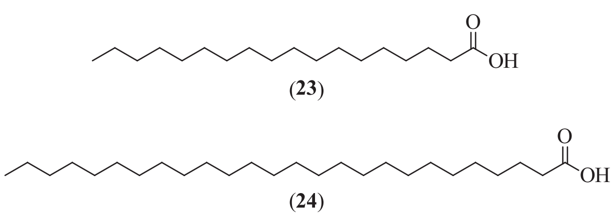


Figure 7. Contact pheromone identified for *T. infestans*, octadecanoic acid (**23**) and hexacosanoic acid (**24**).

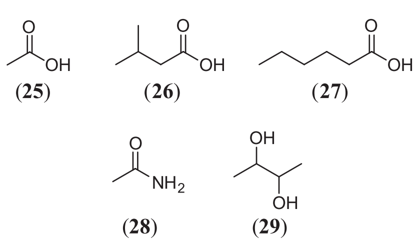


Figure 8. Pheromones found in the feces of *T. infestans*, *P. megistus* and *T. brasiliensis:* acetic acid (**25**), 3-methylbutanoic acid (**26**), hexanoic acid (**27**), acetamide (**28**) and 2,3-butanediol (**29**).

The use of pheromones for developing control tools such as chemical baits and detection devices has been broadly exploited for agricultural pests.[35] This includes their application to diverse methods such as pest detection devices based on their attractivity, the development of trapping systems for attract-and-kill methods and sexual confusion to interrupt mating.[34,36,113-115] Nevertheless, similar approaches are seldom found in relation to disease vector species. Controlling illnesses like dengue fever, Chagas disease and leishmaniasis, among others, relies heavily on monitoring and killing the vector insects transmitting them. This is a critical point that needs to be addressed if knowledge is to be transferred for controlling vector arthropods. Actually, the mere fact that few mosquito pheromones have been characterized indicates the urgent need of intense input into this area to allow a better understanding of reproduction systems (and others) that represent a key target for interfering with the biology of these species, which are otherwise resilient when confronted with traditional insect control methods.

5. Next Generation Sequencing Techniques and Functional Characterization of Molecular Targets to Interfere in Insect Olfaction

The last two decades represent a historical turning point in terms of multidisciplinarity in chemical and biological research. One of the key events driving this phenomenon was the advent of sequencing techniques and, specially, the so-called next generation sequencing techniques (NGS). This allowed accessing the sequence identity of significant genes and even promoting the mass identification of genes actively expressed in target tissues. Likely, insect science benefited from this and the genes and genomes of model insects, e.g., *Drosophila*,[116] have been exhaustively studied through these methodologies. Among diverse outcomes that deserve mentioning, the discovery of several families of sensory receptors was made possible, representing a breakthrough in our understanding of the molecular basis of insect sensory perception. The bases of olfactory, as well as gustatory, detection started to be uncovered at the late 90s when the insect olfactory and gustatory receptor families were discovered.[117-119] The identity of other insect sensory receptors, like thermoreceptors (TRPs),[120,121] water and contact chemoreceptors (ppks)[122,123] and opsins (visual pigments),[124] has also been clarified and their roles are under intense functional evaluation. As receptor proteins are exposed in the membrane of sensory neurons normally housed in insect sensilla, the detection of stimuli depends on their efficiency to bind specific ligands or to react when confronted to specific patterns of energy, e.g., thermal. These functions are considered fundamental for the proper detection of relevant resources and therefore, become natural targets for interfering with the life of pest insects. The development of specific blocking agents or antagonist molecules that impede key sensory detection would allow affecting the recognition of hosts or sexual partners, interfering with fundamental activities such as feeding and reproduction. Recent advances[125,126] suggest that this approach to the development of a new generation of xenobiotics is feasible[127] and deserves attention due to its alternative and specific way of action. Interestingly, the first evidence of the effectiveness of blocking olfactory receptors to interfere with the detection of food sources came from the discovery of a set of substances capable of blocking the CO_2 receptors of *An. gambiae*, *Ae. aegypti* and *C. quinquefasciatus*, the three main mosquitoes vectoring human diseases.[125,126] It is therefore clear that this new perspective should be explored to determine whether other functions such as the detection of pheromones emitted by sexual partners could also be impeded to interfere with the normal development of insect vectors.

6. New Repellents Based on Olfactory Receptor Characterization

Chemical substances considered as repellents have the common feature of avoiding contacts between their users, normally humans, and organisms that could otherwise feed upon them. These can be used to impregnate skin or clothes or, even to fumigate in open areas by means of candles and other emission devices. Technically accepted repellents are very few and vary in their protective power, both in terms of effectiveness to avoid vector-host contacts and duration of protection.[128]

The first synthetic repellent of massive commercial use was *N*,*N*-diethyl-3-methylbenzamide (DEET).[128] Its discovery by the US Department of Agriculture for use by the military dates from 1946 and was first marketed in 1956 and is still considered the most effective substance available to the public, even though it has a certain degree of toxicity and its safe permanent use depends on proper application.[129-131] Nevertheless, it is still considered an adequate personal protection method against dengue and other vector-borne diseases.[128] Aspects related to its mode of action have been a matter of study over the years and it has been claimed that DEET could mask lactic acid detection and it could also do this for other attractive compounds.[132-135] Besides, receptor proteins that react specifically to DEET molecules have been reported and indicated to mediate its repellent effects.[136-140] The recent use of cheminformatic pipelines to predict receptor-odorant interactions and subsequent molecular modeling strategies to uncover shared structural features allowed screening *in silico* for new candidate ligands from libraries including thousands of potential volatiles (i.e., a high throughput search). This approach allowed identifying new compounds potentially tuned to chemosensory receptors that have potential application in avoiding vector-human contacts.[126,127,141] This seems to be a promising area in which molecules could be selected or designed in order to find new effective ligands with high affinity to receptors expressed in neurons known to mediate repellency-related behaviors.

7. Final Remarks

As shown in this revision of our current knowledge on the potential of chemical manipulation of insect behavior vectoring human diseases, there is an arsenal available that needs further evaluation for the purpose of developing control tools. The relevance of this collection of compounds relies in the fact that most of them represent critical signals that have key roles in controlling adaptive vector behaviors. As such, the substances listed, and others still to be uncovered, represent more sustainable alternatives in terms of resistance development probabilities, as insects rely on their use for properly triggering behaviors that are critical for their biology. Apart from chemical approaches, strategies involving genetically modified organisms (GMO) have also been studied. Vector transgenesis and paratransgenesis are new control methods intended to diminish the capacity of vectors to transmit pathogens. Transgenesis is the direct manipulation of a vector to render it incompetent for pathogen transmission.[142] Likewise, paratransgenesis induces genetic alterations on vector symbionts or comensals so that they produce toxic compounds that impede pathogen development, and therefore, transmission.[143] Diverse practical limitations exist in terms of their current application, e.g., governmental agencies, as well as public opinion, are concerned with potential side effects of GMO release. These difficulties must be addressed before any of these promising techniques can allow decreasing vector-borne pathogen transmission.[144] Future years should allow translational research to transform these propositions into tangible realities that help controlling NTDs.

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Marcelo Gustavo Lorenzo *graduated in Biological Sciences at the Buenos Aires University (1991). He holds a PhD in Biological Sciences from the Buenos Aires University (1997). He had posdoctoral trainings at the Buenos Aires University (1998-1999), CPqRR-Fiocruz (1999-2002) and the Swedish Agricultural University (2009-2011). Since 1999, he is a researcher at Oswaldo Cruz Foundation at Belo Horizonte, Brazil. He has experience in physiology with emphasis in behavioral physiology, mainly on the following themes: behavior, pheromones, kairomones, electrophysiology, olfaction functional genomics, triatomines, development of traps and baits for vector control.*

Diogo Montes Vidal *graduated in Chemistry at the Federal University of Paraná (UFPR). He holds a Master's degree in Organic Chemistry from UFPR. Since 2012, he is a PhD student at UFPR (CNPq fellowship holder). He has experience in chemistry with emphasis in organic synthesis, pheromone chemistry and chemical ecology.*

Paulo Henrique G. Zarbin *is associate professor of the Department of Chemistry at UFPR, where he served as chair of the graduate program in Chemistry. He obtained his PhD in 1998 at UFSCar, with part of his thesis developed at the National Institute of Sericultural and Entomological Science, in Tsukuba, Japan. He is former president of the International Society of Chemical Ecology (ISCE), member of the editorial board of the Journal of Chemical Ecology and editor of Chemoecology. His main research interest is focused on the identification, synthesis, biosynthesis and field evaluation of insect pheromones and other semiochemicals.*

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