Leishmania

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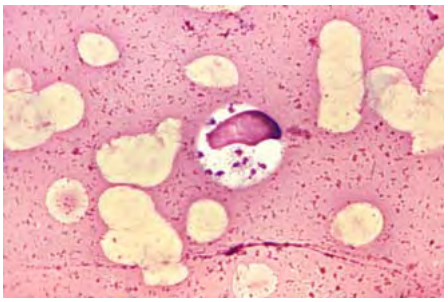
Leishmania /liːˈʃmeɪnɪə/ is a genus of trypanosomes that are responsible for the disease leishmaniasis.[1][2][3] They are spread by sandflies of the genus *Phlebotomus* in the Old World, and of the genus *Lutzomyia* in the New World. At least 93 sandfly species are proven or probable vectors worldwide.[4] Their primary hosts are vertebrates; *Leishmania* commonly infects hyraxes, canids, rodents, and humans.

Contents

Leishmania



L. donovani in bone marrow cell

Scientific classification

Domain:	Eukaryota
(unranked):	Excavata
Phylum:	Euglenozoa
Class:	Kinetoplastida
Order:	Trypanosomatida
Genus:	***Leishmania*** Ross, 1903

Species

L. aethiopica
L. amazonensis
L. arabica
L. archibaldi (disputed species)
L. aristedesi
L. (Viannia) braziliensis
L. chagasi (syn. *L. infantum*)
L. (Viannia) colombiensis
L. deanei
L. donovani
L. enriettii
L. equatorensis
L. forattinii
L. garnhami
L. gerbili
L. (Viannia) guyanensis
L. herreri
L. hertigi
L. infantum

History

The first written reference to the conspicuous symptoms of cutaneous leishmaniasis surfaced in the Paleotropics within oriental texts dating back to the 7th century BC (allegedly transcribed from sources several hundred years older, between 1500 and 2000 BC[5]). Due to its broad and persistent prevalence throughout antiquity as a mysterious disease of diverse symptomatic outcomes, leishmaniasis has been dubbed with various names ranging from “white leprosy” to “black fever”. Some of these names suggest links to negative cultural beliefs or mythology,

which still feed into the social stigmatization of leishmaniasis today.[6] Members of an ancient genus of the *Leishmania* parasite, Paleoleishmania, have been detected in fossilized sand flies dating back to the early Cretaceous period,[7] however, the causative agent for the disease was only discovered in 1901 as a concurrent finding by William Boog Leishman and Charles Donovan. They independently visualised microscopic single-celled parasites (later called Leishman-Donovan bodies) living within the cells of infected human organs. The parasitic genus would later be classed as Trypanosomatid protozoans under the phylogenetic designation, *Leishmania donovani*. Several species have since been classified and grouped under two major subgenera i.e. *Leishmania Viannia* (generally located in the Neotropics) or *Leishmania Leishmania* (generally located in the Paleotropics, with the major exception of the *L. mexicana* subgroup).

L. killicki
L. (Viannia) lainsoni
L. major
L. mexicana
L. (Viannia) naiffi
L. (Viannia) panamensis
L. (Viannia) peruviana
L. (Viannia) pifanoi
L. (Viannia) shawi
L. tarentolae
L. tropica
L. turanica
L. venezuelensis

Epidemiology

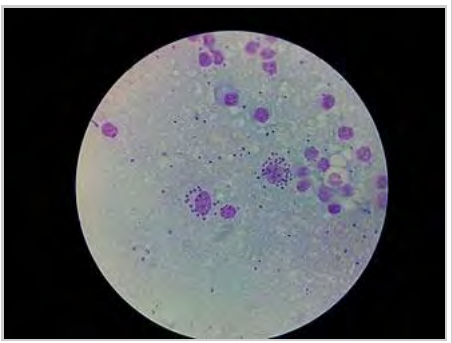
Leishmania currently affects 12 million people in 98 countries. About 2 million new cases occur each year, and 21 species are known to cause disease in humans.

Structure

Leishmania species are unicellular eukaryotes having a well-defined nucleus and other cell organelles including kinetoplasts and flagella. Depending on the stage of their lifecycle, they exist in two structural variants, as:[8][9]

1. The **amastigote** form is found in the mononuclear phagocytes and circulatory systems of humans. It is an intracellular and nonmotile form, being devoid of external flagella. The short flagellum is embedded at the anterior end without projecting out. It is oval in shape, and measures 3–6 µm in length and 1–3 µm in breadth. The kinetoplast and basal body lie towards the anterior end.
2. The **promastigote** form is found in the alimentary tract of sandflies. It is an extracellular and motile form. It is considerably larger and highly elongated, measuring 15-30 µm in length and 5 µm in width. It is spindle-shaped, tapering at both ends. A long flagellum (about the body length) is projected externally at the anterior end. The nucleus lies at the centre, and in front of it are the kinetoplast and the basal body.

Evolution


L. infantum amastigote forms

The details of the evolution of this genus are debated, but *Leishmania* apparently evolved from an ancestral trypanosome lineage. The oldest lineage is that of the Bodonidae, followed by *Trypanosoma brucei*, the latter being confined to the African continent. *Trypanosoma cruzi* groups with trypanosomes from bats, South American mammals, and kangaroos suggest an origin in the Southern Hemisphere. These clades are only distantly related.

The remaining clades in this tree are *Blastocrithidia*, *Herpetomonas*, and *Phytomonas*. The four genera *Leptomonas*, *Crithidia*, *Leishmania*,

and *Endotrypanum* form the terminal branches, suggesting a relatively recent origin. Several of these genera may be polyphyletic and may need further division.[10]

The origins of genus *Leishmania* itself are unclear.[11][12] One theory proposes an African origin, with migration to the Americas. Another proposes migration from the Americas to the Old World via the Bering Strait land bridge around 15 million years ago. A third theory proposes a palearctic origin.[13] Such migrations would entail subsequent migration of vector and reservoir or successive adaptations along the way. A more recent migration is that of *L. infantum* from Mediterranean countries to Latin America (known as *L. chagasi*), since European colonization of the New World, where the parasites picked up their current New World vectors in their respective ecologies.[14] This is the cause of the epidemics now evident. One recent New World epidemic concerns foxhounds in the USA.[15]

Leishmania might have evolved in the Neotropics.[16]

A large data set analysis suggests that *Lesihmania* evolved 90 million years ago-100 million years ago in Gondwana.[17] The reptile infecting species originated in mammalian clades.

Sauroleishmania species were originally defined on the basis that they infected reptiles (lizards) rather than mammals. Molecular studies have cast doubts on this basis for classification and they have been moved to subgenus status within *Leishmania*. This subgenus probably evolved from a group that originally infected mammals.[18]

Taxonomy

53 species are recognised in this genus. The status of several of these is disputed, so the final number may differ. At least 20 species infect humans. To make things more complex, hybrids might be involved, as it has been reported in Brazil with an hybrid between *Leishmania (V.) guyanensis* and *Leishmania (V.) shawi shawi*.[19]

At least three subgenera exist: *Leishmania*, *Sauroleishmania*, and *Viannia*. The division into the two subgenera (*Leishmania* and *Viannia*) was made by Lainson and Shaw in 1987 on the basis of their location within the insect gut. The species in the *Viannia* subgenus develop in the hind gut: *L. (V.) braziliensis* has been proposed as the type species for this subgenus. This division has been confirmed by all subsequent studies.

Endotrypanum is also closely related and may also be moved to subgenus status within *Leishmania*. The subgenus *Endotypanum* is unique in that the parasites of this subgenus infect the erythrocytes of their hosts (sloths). The species in this subgenus are confined to Central and South America.[20]

Sauroleishmania was originally described by Ranquein 1973 as a separate genus, but molecular studies suggest this is actually a subgenus rather than a separate genus.

A proposed division of the *Leishmania* is into *Euleishmania* and *Paraleishmania*.[21] The proposed groups *Paraleishmania* would include all the species in the genus *Endotypanum* and *L. colomubensis*, *L. deanei*, *L. equatorensis*, and *L. hertigi*. The group *Euleishmania* would include those species currently placed in the subgenera *Leishmania* and *Viannia*. These groups may be accorded subgenus (or other) status at some point, but their positions remains undefined at present.

Five subgenera are recognised - *Leishmania*, *Paraleishmania*, *Sauroleishmania*, *Viannia* and the *L. enrittii* complex. The *Endotrypanum* genus is now recognised as a division of *Paraleishmania*.

L. archibaldi may be the same species as *L. dononani*. *L. herreri* may belong to the genus *Endotypanum* rather than to *Leishmania*.

The enzyme *Seltryp* which is involved in selenocysteine synthesis appears to be unique to this order.[22] It has been lost in the subgenus *Viannia*.

Classification

Subgenus **Leishmania**

- *Leishmania aethiopica*
- *Leishmania amazonensis*
- *Leishmania arabica*
- *Leishmania donovani*
- *Leishmania gerbilli*
- *Leishmania hertigi*
- *Leishmania infantum*
- *Leishmania killicki*
- *Leishmania major*
- *Leishmania mexicana*
- *Leishmania siamensis*
- *Leishmania tropica*
- *Leishmania turanica*

Subgenus **Sauroleishmania**

- *Leishmania adleri*
- *Leishmania agamae*
- *Leishmania ceramodactyli*
- *Leishmania deanei*
- *Leishmania garnhami*
- *Leishmania gulikae*
- *Leishmania gymnodactyli*
- *Leishmania hemidactyli*
- *Leishmania hoogstraali*
- *Leishmania nicollei*
- *Leishmania senegalensis*
- *Leishmania tarentolae*

Subgenus **Viannia**

- *Leishmania braziliensis*
- *Leishmania colombiensis*
- *Leishmania equatorensis*
- *Leishmania guyanensis*
- *Leishmania lainsoni*
- *Leishmania naiffi*
- *Leishmania panamensis*
- *Leishmania peruviana*

- *Leishmania pifanoi*
- *Leishmania shawi*
- *Leishmania utingensis*

The genus *Endotrypanum* is also included here as this may be reclassified as Leishmania

Genus **Endotrypanum**

- *Endotrypanum monterogeii*
- *Endotrypanum schaudinni*

L. enrittii complex

- *Leishmania enrittii*
- *Leishmania martiniquensis*[23]

Biochemistry and cell biology

The biochemistry and cell biology of *Leishmania* is similar to that of other kinetoplastids. They share the same main morphological features; a single flagellum which has an invagination, the flagellar pocket, at its base, a kinetoplast which is found in the single mitochondrion and a subpelicular array of microtubules which make up the main part of the cytoskeleton.

Lipophosphoglycan coat

Leishmania possesses a lipophosphoglycan coat over the outside of the cell. Lipophosphoglycan is a trigger for toll-like receptor 2, a signalling receptor involved in triggering an innate immune response in mammals.

Structure

The precise structure of lipophosphoglycan varies depending on the species and lifecycle stage of the parasite. The glycan component is particularly variable and different lipophosphoglycan variants can be used as a molecular marker for different lifecycle stages. Lectins, a group of plant proteins which bind different glycans, are often used to detect these lipophosphoglycan variants. For example, peanut agglutinin binds a particular lipophosphoglycan found on the surface of the infective form of *L. major*.

Function

Lipophosphoglycan is used by the parasite to promote its survival in the host and the mechanisms by which the parasite does this center around modulating the immune response of the host. This is vital, as the *Leishmania* parasites live within macrophages and need to prevent the macrophages from killing them. Lipophosphoglycan has a role in resisting the complement system, inhibiting the oxidative burst response, inducing an inflammation response and preventing natural killer T cells recognising that the macrophage is infected with the *Leishmania* parasite.

Type	Pathogen	Location
Cutaneous leishmaniasis (localised and diffuse) infections appear as obvious skin reactions.	The most common is the *Oriental Sore* (caused by Old World species *L. major*, *L. tropica*, and *L. aethiopica*). In the New World, the most common culprits is *L. mexicana*.	Cutaneous infections are most common in Afghanistan, Brazil, Iran, Peru, Saudi Arabia and Syria.
Mucocutaneous leishmaniasis infections start off as a reaction at the bite, and can go by metastasis into the mucous membrane and become fatal.	*L. braziliensis*	Mucocutaneous infections are most common in Bolivia, Brazil and Peru. Mucocutaneous infections are also found in Karamay, China Xinjiang Uygur Autonomous Region.
Visceral leishmaniasis infections are often recognised by fever, swelling of the liver and spleen, and anemia. They are known by many local names, of which the most common is probably *kala azar*,[24][25]	Caused exclusively by species of the *L. donovani* complex (*L. donovani*, *L. infantum* syn. *L. chagasi*).[1]	Found in tropical and subtropical areas of all continents except Australia, visceral infections are most common in Bangladesh, Brazil, India, Nepal, and Sudan.[1] Visceral leishmaniasis also found in part of China, such as Sichuan Province, Gansu Province, and Xinjiang Uygur Autonomous Region.

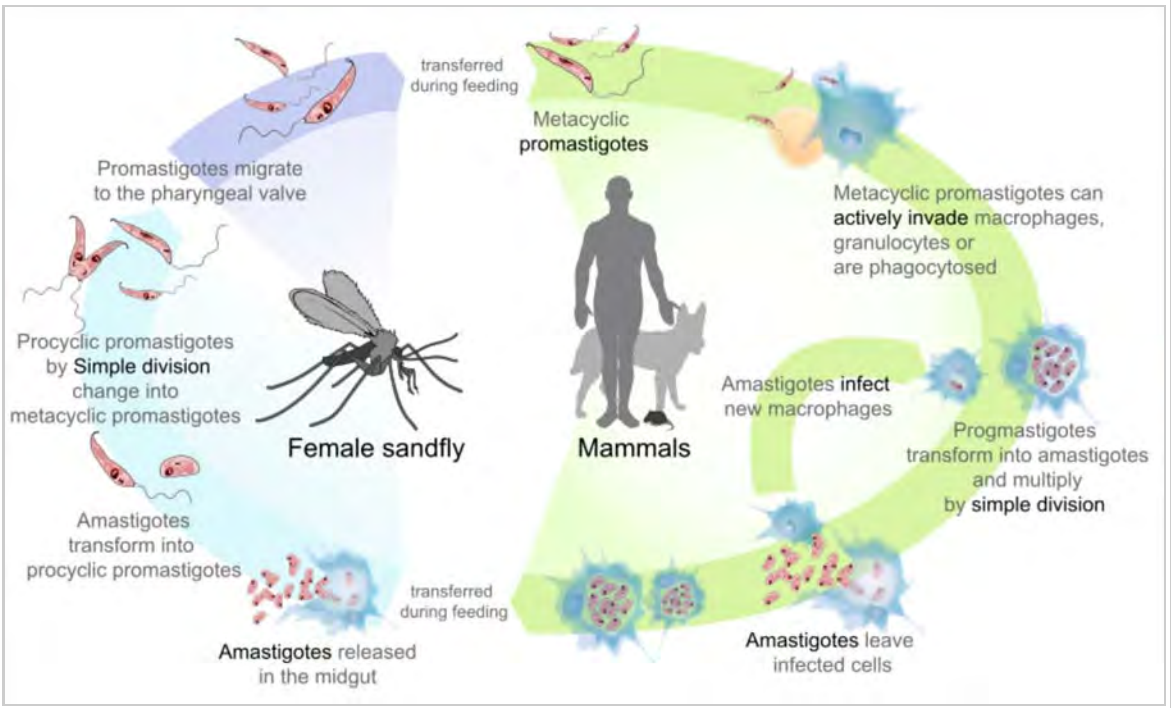
Intracellular mechanism of infection

In order to avoid destruction by the immune system and thrive, the *Leishmania* 'hides' inside its host's cells. This location enables it to avoid the action of the humoral immune response (because the pathogen is safely inside a cell and outside the open bloodstream), and furthermore it may prevent the immune system from destroying its host through nondanger surface signals which discourage apoptosis. The primary cell types *Leishmania* infiltrates are phagocytotic cells such as neutrophils and macrophages.[26]

Usually, a phagocytotic immune cell like a macrophage will ingest a pathogen within an enclosed endosome and then fill this endosome with enzymes which digest the pathogen. However, in the case of *Leishmania*, these enzymes have no effect, allowing the parasite to multiply rapidly. This uninhibited growth of parasites eventually overwhelms the host macrophage or other immune cell, causing it to die.[27]

Transmitted by the sandfly, the protozoan parasites of *L. major* may switch the strategy of the first immune defense from eating/inflammation/killing to eating/no inflammation/no killing of their host phagocyte and corrupt it for their own benefit. They use the willingly phagocytosing polymorphonuclear neutrophil granulocytes (PMNs) rigorously as a tricky hideout, where they proliferate unrecognized from the immune system and enter the long-lived macrophages to establish a “hidden” infection.

Uptake and survival



Lifecycle of *Leishmania*

Upon microbial infection, PMNs move out from the bloodstream through the vessels' endothelial layer, to the site of the infected tissue (dermal tissue after fly bite). They immediately initiate the first immune response and phagocytize the invader by recognition of foreign and activating surfaces on the parasite. Activated PMN secrete chemokines, IL-8 particularly, to attract further granulocytes and stimulate phagocytosis. Further, *L. major* increases the secretion of IL-8 by PMNs. This mechanism is observed during infection with other obligate intracellular parasites, as well. For microbes like these, multiple intracellular survival mechanisms exist. Surprisingly, the coinjection of apoptotic and viable pathogens causes by far a more fulminate course of disease than injection of only viable parasites. When the anti-inflammatory signal phosphatidylserine usually found on apoptotic cells, is exposed on the surface of dead parasites, *L. major* switches off the oxidative burst, thereby preventing killing and degradation of the viable pathogen.

In the case of *Leishmania*, progeny are not generated in PMNs, but in this way they can survive and persist untangled in the primary site of infection. The promastigote forms also release *Leishmania* chemotactic factor (LCF) to actively recruit neutrophils, but not other leukocytes, for instance monocytes or NK cells. In addition to that, the production of interferon gamma (IFNγ)-inducible protein 10 (IP10) by PMNs is blocked in attendance of *Leishmania*, what involves the shut down of inflammatory and protective immune response by NK and Th1 cell recruitment. The pathogens stay viable during phagocytosis since their primary hosts, the PMNs, expose apoptotic cell-associated molecular pattern (ACAMP) signaling "no pathogen".

Persistency and attraction

The lifespan of neutrophil granulocytes is quite short. They circulate in bloodstream for about 6 to 10 hours after leaving bone marrow, whereupon they undergo spontaneous apoptosis. Microbial pathogens have been reported to influence cellular apoptosis by different strategies. Obviously because of the inhibition of caspase3-activation, *L. major* can induce the delay of neutrophils apoptosis and extend their lifespan for at least 2–3 days. The fact of extended lifespan is very beneficial for the development of infection because the final host cells for these parasites are macrophages, which normally migrate to the sites of infection within two or three days. The pathogens are not dronish; instead they take over the command at the primary site of infection. They

induce the production by PMNs of the chemokines MIP-1α and MIP-1β (macrophage inflammatory protein) to recruit macrophages.[28]

Silent phagocytosis theory

To save the integrity of the surrounding tissue from the toxic cell components and proteolytic enzymes contained in neutrophils, the apoptotic PMNs are silently cleared by macrophages. Dying PMNs expose the "eat me"-signal phosphatidylserine which is transferred to the outer leaflet of the plasma membrane during apoptosis. By reason of delayed apoptosis, the parasites that persist in PMNs are taken up into macrophages, employing an absolutely physiological and nonphlogistic process. The strategy of this "silent phagocytosis" has the following advantages for the parasite:

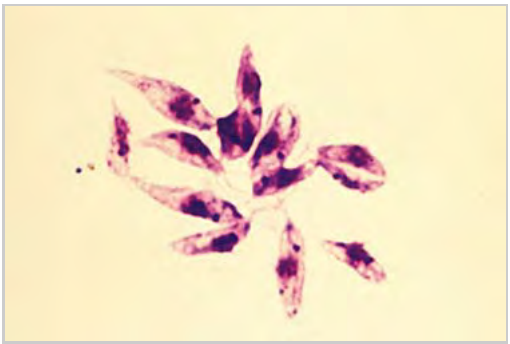
- Taking up apoptotic cells silences macrophage killing activity leading to a survival of the pathogens.
- Pathogens inside of PMNs have no direct contact to the macrophage surface receptors, because they can not see the parasite inside the apoptotic cell. So, the activation of the phagocyte for immune activation does not occur.

However, studies have shown this is unlikely, as the pathogens are seen to leave apoptopic cells and no evidence is known of macrophage uptake by this method.

Molecular biology

An important aspect of the *Leishmania* protozoan is its glycoconjugate layer of lipophosphoglycan (LPG). This is held together with a phosphoinositide membrane anchor, and has a tripartite structure consisting of a lipid domain, a neutral hexasaccharide, and a phosphorylated galactose-mannose, with a termination in a neutral cap. Not only do these parasites develop postphlebotomus digestion, but it is also thought to be essential to oxidative bursts, thus allowing passage for infection. Characteristics of intracellular digestion include an endosome fusing with a lysosome, releasing acid hydrolases which degrade DNA, RNA, proteins and carbohydrates.

Genomics



Leishmania tropica

The genomes of four *Leishmania* species (*L. major*, *L. infantum*, *L. donovani* and *L. braziliensis*) have been sequenced, revealing more than 8300 protein-coding and 900 RNA genes. Almost 40% of protein-coding genes fall into 662 families containing between two and 500 members. Most of the smaller gene families are tandem arrays of one to three genes, while the larger gene families are often dispersed in tandem arrays at different loci throughout the genome. Each of the 35 or 36 chromosomes is organized into a small number of gene clusters of tens-to-hundreds of genes on the same DNA strand. These clusters can be organized in head-to-head (divergent) or tail-to-tail (convergent) fashion, with the latter often separated by tRNA, rRNA and/or snRNA genes. Transcription of protein-coding genes initiates bidirectionally in the divergent strand-switch regions between gene clusters and extends polycistronically through each gene cluster before terminating in the strand-switch region separating convergent clusters. *Leishmania* telomeres are usually relatively small, consisting of a few different types of repeat sequence. Evidence can be found for recombination between several different groups of telomeres. The

L. major and *L. infantum* genomes contain only about 50 copies of inactive degenerated *Ingi*/L1Tc-related elements (DIREs), while *L. braziliensis* also contains several telomere-associated transposable elements and spliced leader-associated retroelements. The *Leishmania* genomes share a conserved core proteome of about 6200 genes with the related trypanosomatids *Trypanosoma brucei* and *Trypanosoma cruzi*, but around 1000 *Leishmania*-specific genes are known, which are mostly randomly distributed throughout the genome. Relatively few (about 200) species-specific differences in gene content exist between the three sequenced *Leishmania* genomes, but about 8% of the genes appear to be evolving at different rates between the three species, indicative of different selective pressures that could be related to disease pathology. About 65% of protein-coding genes currently lack functional assignment.[2]

Leishmania species produce several different heat shock proteins. These incluse Hsp83, a homolog of Hsp90. A regulatory element in the 3' UTR of Hsp83 controls translation of Hsp83 in a temperature-sensitive manner. This region forms a stable RNA structure which melts at higher temperatures.[29]

Sexual reproduction

A microbial pathogen's reproductive system is one of the basic biologic processes that condition the micoroorganism's ecology and disease spread.[30] Akopyants et al.[31] demonstrated that *L. major* has a sexual cycle, including a meiotic process. Hybrid progeny are formed that have full genomic complements from both parents. Mating only occurs in the sand fly vector, and hybrids can be transmitted to the mammalian host by sand fly bite. In *L. braziliensis* matings in nature are predominantly between related individuals resulting in extreme inbreeding.[32] The rate of outcrossing between different strains of *Leishmania* in the sand fly vector depends on the frequency of co-infection. Such outcrossing events appear to be rare in *L. major* [31] and *L. donovani*.[33]

L. infantum produces proteins BRCA1 and RAD51 that interact with each other to promote homologous recombinational repair.[34] These proteins play a key role in meiosis. Thus, meiotic events provide the adaptive advantage of efficient recombinational repair of DNA damages even when they do not lead to outcrossing.[35]

See also

- Canine leishmaniasis
- List of parasites (human)

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External links

Wikimedia Commons has media related to ***Leishmania***.

- The International Leishmania Network (ILN) (http://leishnet.net) has basic information on the disease and links to many aspects of the disease and its vector.
- A discussion list (Leish-L) (http://lineu.icb.usp.br/cgi-bin/mailman/listinfo/leish-l) is also available with over 600 subscribers to the list, ranging from molecular biologists to public health workers, from many countries both inside and outside endemic regions. Comments and questions are welcomed.
- KBD: Kinetoplastid Biology and Disease (http://www.kinetoplastids.com/), is a website devoted to leishmaniasis, sleeping sickness and Chagas disease (American trypanosomiasis). It contains free access to full text peer-reviewed articles on these subjects. The site contains many articles relating to the unique kinetoplastid organelle and genetic material therein.
- Sexual reproduction in leishmania parasites, short review of a "science"-paper (http://www.life-of-science.net/medicine/news/leishmania-parasites-have-sex-in-the-sand-fly.html)
- World Community Grid: Drug Search for Leishmaniasis (http://www.worldcommunitygrid.org/research

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