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PEARLS

Getting under your skin: The hidden dermal niche of trypanosomatid parasites

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Overview

The TriTryps—*Trypanosoma brucei*, *Leishmania* spp., and *Trypanosoma cruzi*—cause three major neglected diseases: Human African Trypanosomiasis (HAT), Leishmaniasis, and Chagas disease, respectively. A central challenge in the diagnosis and treatment of these diseases is their silent, often lifelong chronic phase. While our understanding of *T. brucei* and *Leishmania* has surged in recent years, knowledge gaps in *T. cruzi* research directly hinder our ability to reliably diagnose, treat, and monitor Chagas disease—which is endemic across the Americas and spreading globally.

Most patients with Chagas disease show no symptoms for decades while the number of parasites in the blood **(parasitaemia)** drops to undetectable levels. While we know the parasite can sequester in heart and digestive tissues—leading to life-threatening complications in roughly one third of infected individuals—the full map of *T. cruzi's* distribution in the host remains unclear, hampering diagnosis and treatment monitoring. If the parasite is not in the blood, how does its **haematophagous**

(blood-feeding) insect vector continue to acquire and transmit infection? What other tissues might *T. cruzi* persist in during these silent decades?

Recent breakthroughs in *T. brucei* and *Leishmania* suggest the answer is hiding in plain sight: the skin. Here, we evaluate the skin's role as a critical parasite reservoir and hidden transmission interface, and propose a dermal-centric roadmap for future *T. cruzi* research. Shifting the paradigm from blood to skin could guide new avenues for the improved diagnosis, treatment and control of Chagas disease.

More than just a bite site: Lessons from *Leishmania* and *Trypanosoma brucei*

Historically, the skin was viewed as merely the entry point for trypanosomatid parasites. Once an insect vector takes a blood meal, parasites were thought to transit the skin briefly before migrating to 'target' tissues: the blood and central nervous system (CNS) for *T. brucei* [1]; the bone marrow, liver, and spleen for visceral *Leishmania* spp. [2]; and the heart and digestive system for *T. cruzi* [3]. While cutaneous Leishmaniasis is a clear exception, the skin was generally dismissed in systemic TriTryp infections, deemed relevant only during bite-site lesions in early-stage disease.

However, far from being a passive barrier, our skin represents the first arena of host-parasite conflict—a sophisticated, three-layered, immunological landscape (Fig 1). The outermost **epidermis** forms a protective barrier of keratinocytes and immune-sensing Langerhans cells; below, the thicker **dermis** is a collagen-rich matrix containing blood and lymph vessels, fibroblasts, and teeming with dermal dendritic cells, macrophages and lymphocytes; and the **hypodermis** provides a vast layer of subcutaneous fat where adipocytes interact with resident immune cells [4]. This environment is uniquely adapted to tolerate diverse antigens—a feature which many parasites exploit to establish and maintain infection within the skin; *Leishmania* spp. dampen protective immunity to persist inside dermal macrophages (reviewed in [2]) and *T. brucei* exploits specific skin-resident T cells and adipocytes to dampen cutaneous inflammation during chronic infection [5]. Given that the skin is a vast, immunologically distinct niche capable of harbouring parasites, could similar mechanisms underpin chronic *T. cruzi* persistence?

Trypanosoma brucei's silent skin reservoir

The most striking evidence for the skin's role as a parasite reservoir comes from *T. brucei.* HAT was long defined by the presence of trypanosomes in the blood and CNS, until landmark studies in 2016 demonstrated that *T. brucei* colonises both the skin [6] and subcutaneous adipose tissue [7], persisting between collagen bundles and adipocytes [8]. Crucially, **xenodiagnosis**—a method where uninfected, lab-reared insect vectors are fed directly on a host's skin—demonstrated that tsetse flies can acquire parasites directly from these skin reservoirs, even in mice with undetectable parasitaemia [6],[8]. More recent findings suggest the skin could be a key, silent reservoir facilitating transmission in humans [9], and that skin biopsies may represent a feasible HAT diagnostic strategy where blood-based methods fail [10].

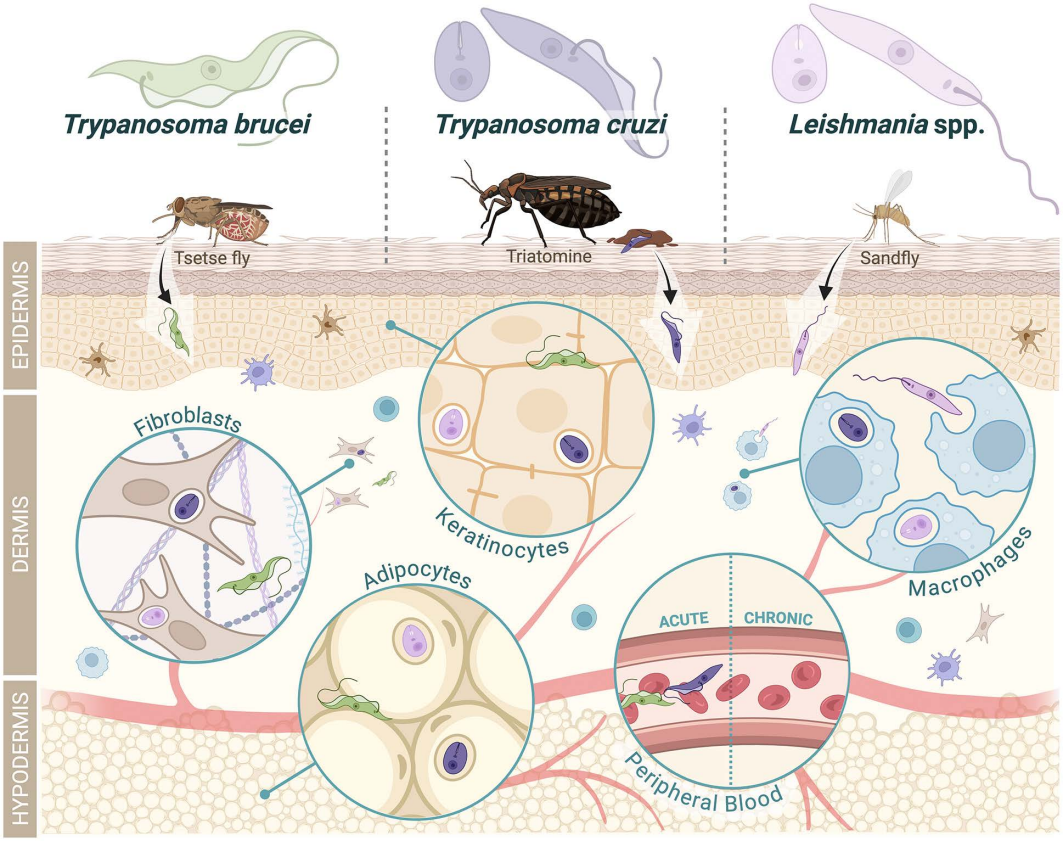


Fig 1. TriTryps in the skin. (Top Panel): Vector-mediated introduction of *Trypanosoma brucei* (tsetse fly), *Trypanosoma cruzi* (triatomine bug) and *Leishmania* spp. (sandfly) into the skin. While *T. brucei* and *Leishmania* spp. are directly inoculated through salivary transmission, vector transmission of *T. cruzi* is stercorarian, meaning the parasite is excreted in the bug's faeces and introduced into the host through the bite wound. *T. brucei* remains an obligate extracellular parasite throughout its lifecycle, whereas both *T. cruzi* and *Leishmania* spp. have a rounded, intracellular life stage called an amastigote. **(Main panel):** Anatomical distribution of the TriTryps across the three layers of human skin: the outermost epidermis, dermis, and hypodermis. Zoom-ins highlight distinct parasite lifestyles and dermal cell tropisms: intracellular *Leishmania* and *T. cruzi* amastigotes can reside within dermal macrophages, fibroblasts, keratinocytes and adipocytes, and *T. brucei* resides extracellularly across these three skin layers. These cutaneous niches may represent critical parasite reservoirs that persist even when parasitaemia falls below detectable levels during chronic infection. *Created with BioRender* (https://BioRender.com/oc05oqn).

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This dermal population is not simply a spillover from the blood; skin-residing *T. brucei* trypanosomes represent an independent, replicative reservoir with uniquely adapted gene expression and metabolic profiles, including the upregulation of lipid metabolism genes in mouse models [7]. Skin-dwelling parasites may even employ distinct immune evasion strategies to survive in this niche. As most antigenic variation occurs not in the blood, but in the mouse tissues—including the subcutaneous adipose layer [11]—the dermis could provide an ideal niche for African trypanosomes to diversify their population while sheltered from the systemic immune response. Further, sub-populations of slow-growing parasites within visceral adipose tissue are able to survive drug treatment [12]. These findings prompt a critical question: could dermal reservoirs contribute to treatment failure in TriTryp pathology?

Dermal persistence of *Leishmania*

Unlike the other TriTryps, some *Leishmania* spp. have a defined skin pathology known as Cutaneous Leishmaniasis (CL), where skin lesions arise from parasites replicating inside dermal macrophages [2]. However, even in Visceral

Leishmaniasis (VL)—a systemic infection of the spleen, liver, and bone marrow—the skin remains a crucial, often overlooked reservoir. This is most evident in Post-Kala-Azar Dermal Leishmaniasis (PKDL), where patients 'cured' of systemic infection develop skin lesions laden with parasites [13].

As with *T. brucei,* xenodiagnostic studies demonstrate that skin-dwelling *Leishmania* parasites in both VL and PKDL patients are highly infectious to sandflies [14]. Strikingly, sandflies fed directly on the skin of PKDL patients—rather than indirectly from the blood—were significantly more likely to become infected, suggesting the skin acts as a potent reservoir for vector transmission [14]. Moreover, murine model xenodiagnosis and modelling directly links skin parasite burden to host infectiousness [15]. High rates of positive xenodiagnosis reflect the density of skin-resident parasites; despite containing 10 times less blood than traditional blood samples, skin biopsies yielded higher rates of *Leishmania* DNA, suggesting the skin could be a more reliable diagnostic source of parasites than the blood [16]. These findings challenge the assumption that only symptomatic, systemic cases drive outbreaks. Instead, the skin is positioned as a hidden reservoir that maintains the transmission cycle even after clinical 'cure'.

Trypanosoma cruzi: Hiding in plain sight?

This paradigm shift in HAT and Leishmaniasis research forces us to reconsider blind spots in Chagas disease research. If both *T. brucei* and visceral *Leishmania* spp. maintain a silent reservoir in the skin, could *T. cruzi* be doing the same?

Perhaps the parasite's affinity for fat facilitates a dermal reservoir; *T. cruzi* is known to sequester in the fat surrounding the heart and colon—so why not also in the hypodermis, the vast layer of fat underlying the skin? Indeed, *T. cruzi* persists within the subcutaneous adipose tissue of both humans [17] and mice [18], whilst bioluminescent imaging demonstrates that parasites persist in the dermal tissues of over 80% of chronically infected mice and hamsters [19],[20].

Further, *T. cruzi's* ability to infect human keratinocytes [21] and fibroblasts [22] suggests the parasite is not simply passing through the skin, but has the potential to actively integrate into the dermal environment. Clinical observations support this: in immunocompromised patients, Chagas reactivation often manifests as "reactivation chagomas"—parasite-laden skin nodules (reviewed in [23]). The sudden emergence of these lesions could suggest that parasites were not recruited from the blood, but were rather 'lying in wait' within local dermal or subcutaneous tissues—supported by the higher sensitivity of xenodiagnosis than traditional PCR [24]. Moreover, host cells infected with *T. cruzi* exhibit an upregulation of lipid synthesis pathways, suggesting that *T. cruzi* may be able to manipulate the host dermal environment to favour its own integration and survival [18],[25].

A dermal niche may resolve a long-standing transmission paradox in Chagas epidemiology: how do triatomines become infected when parasitaemia is almost non-existent? Perhaps the vector can ingest skin-dwelling parasites during the probing phase of feeding, before even reaching a host's capillary. A dermal reservoir could therefore provide a transmission advantage, facilitating vector uptake of amastigotes or locally emerging trypomastigotes simply through proximity—and bypassing the need for high circulating concentrations of parasites that could otherwise trigger an attenuating host immune response. The skin could represent the essential bridge to maintain transmission of *T. cruzi* when the peripheral blood is void of parasites.

A roadmap for the dermal frontier

Emerging clinical and experimental evidence—and a growing list of unanswered questions—highlights the urgent need to formally integrate the skin into the Chagas disease paradigm. To address these knowledge gaps, we propose a conceptual roadmap to guide future skin-centric research (Fig 2).

First, the prevalence and topography of skin-dwelling *T. cruzi* parasites must be mapped in endemic populations. If the dermis acts as a reliable, long-term reservoir, validating dermal-targeted diagnostic and biomarker platforms could revolutionise how we detect active infections and monitor cure—challenges that current blood-based serology and

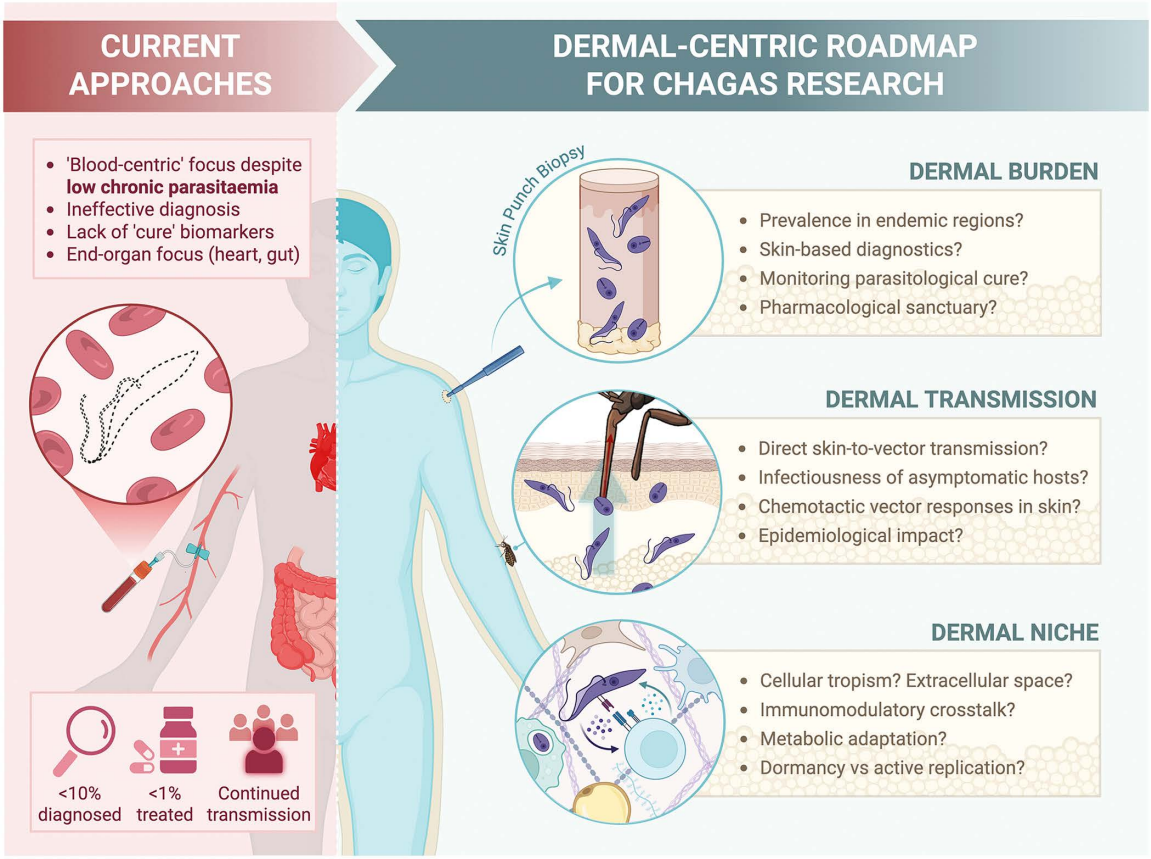


Fig 2. A dermal-centric roadmap for Chagas disease research. (Left) The Blood-Centric Paradigm: Current approaches in Chagas disease diagnosis, treatment and control rely heavily on monitoring blood circulation, despite the clinical reality that chronically infected individuals typically exhibit low or undetectable parasitaemia. This blood-centric focus leaves critical blind spots regarding parasite persistence and treatment failure, contributing to a stark public health gap where less than 10% of Chagas disease cases are diagnosed and less than 1% receive treatment. **(Right)** The Dermal Frontier: A proposed roadmap to bridge these gaps by focusing on three main investigative pillars to explore the role of the skin in Chagas disease pathology, persistence and transmission. Transitioning toward this skin-inclusive model is essential for developing effective biomarkers, refining epidemiological models, and ultimately improving Chagas disease control strategies. *Created with BioRender* (https://BioRender.com/oc05oqn).

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PCR cannot fully resolve. Further, investigating whether the hypodermis acts as a pharmacological sanctuary—with restricted drug penetration or altered parasite metabolic states—is vital to understanding chronic treatment failure. Addressing this requires integrating skin pharmacokinetics into drug discovery pipelines and optimising compounds for dermal delivery.

Second, the contribution of skin-resident parasites to the triatomine transmission cycle requires urgent clarification. We must determine whether vectors can efficiently acquire infection from hosts with low systemic parasitaemia but high dermal burdens. If skin-to-vector transmission is efficient, current epidemiological models significantly underestimate the infectiousness of asymptomatic hosts, necessitating a revision of control strategies.

Finally, the cellular tropism, spatial distribution, lifecycle stages and metabolic states of *T. cruzi* within the complex landscape of the skin remain largely unknown. Characterising the immunomodulatory crosstalk between the parasite and host dermal architecture may shed light on the mechanisms of long-term persistence and tissue reactivation.

Conclusion

Compelling evidence positions the skin as a unifying dimension of TriTryp infection dynamics. However, this niche is critically overlooked in *T. cruzi* research. Reconceptualising the skin—not merely as a transient entry point, but as a persistent parasite reservoir—could transform how we diagnose, treat and ultimately control Chagas disease.

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