Module Title: Parasitology
Module Code: BS42012

This is reading list A. Abstracts are provided below and you should use both reading lists to supplement the lecture content of the module.

Pawlowic

Lancet Infect Dis. 2015 Jan;15(1):85-94. doi: 10.1016/S1473-3099(14)70772-8. Epub 2014 Sep 29.
A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium.

Checkley W1, White AC Jr2, Jaganath D3, Arrowood MJ4, Chalmers RM5, Chen XM6, Fayer R7, Griffiths JK8, Guerrant RL9, Hedstrom L10, Huston CD11, Kotloff KL12, Kang G13, Mead JR14, Miller M15, Petri WA Jr9, Priest JW4, Roos DS16, Striepen B17, Thompson RC18, Ward HD19, Van Voorhis WA20, Xiao L4, Zhu G21, Houpt ER9.
Author information
Abstract
Cryptosporidium spp are well recognised as causes of diarrhoeal disease during waterborne epidemics and in immunocompromised hosts. Studies have also drawn attention to an underestimated global burden and suggest major gaps in optimum diagnosis, treatment, and immunisation. Cryptosporidiosis is increasingly identified as an important cause of morbidity and mortality worldwide. Studies in low-resource settings and high-income countries have confirmed the importance of cryptosporidium as a cause of diarrhoea and childhood malnutrition. Diagnostic tests for cryptosporidium infection are suboptimum, necessitating specialised tests that are often insensitive. Antigen-detection and PCR improve sensitivity, and multiplexed antigen detection and molecular assays are underused. Therapy has some effect in healthy hosts and no proven efficacy in patients with AIDS. Use of cryptosporidium genomes has helped to identify promising therapeutic targets, and drugs are in development, but methods to assess the efficacy in vitro and in animals are not well standardised. Partial immunity after exposure suggests the potential for successful vaccines, and several are in development; however, surrogates of protection are not well defined. Improved methods for propagation and genetic manipulation of the organism would be significant advances.

Trends Parasitol. 2019 Dec 10. pii: S1471-4922(19)30275-2. doi: 10.1016/j.pt.2019.11.003. [Epub ahead of print]
Cryptosporidium parvum.

Dumaine JE1, Tandel J1, Striepen B2.
Author information
PMID: 31836286 DOI: 10.1016/j.pt.2019.11.003

Nat Microbiol. 2019 Dec;4(12):2226-2236. doi: 10.1038/s41564-019-0539-x. Epub 2019 Sep 2.
Life cycle progression and sexual development of the apicomplexan parasite Cryptosporidium parvum.

Tandel J1, English ED1, Sateriale A1, Gullicksrud JA1, Beiting DP1, Sullivan MC1, Pinkston B1,2, Striepen B3.
Author information
Abstract
The apicomplexan parasite Cryptosporidium is a leading global cause of severe diarrhoeal disease and an important contributor to early childhood mortality. Currently, there are no fully effective treatments or vaccines available. Parasite transmission occurs through ingestion of oocysts, through either direct contact or consumption of contaminated water or food. Oocysts are meiotic spores and the product of parasite sex. Cryptosporidium has a single-host life cycle in which both asexual and sexual processes occur in the intestine of infected hosts. Here, we genetically engineered strains of Cryptosporidium to make life cycle progression and parasite sex tractable. We derive reporter strains to follow parasite development in culture and in infected mice

and define the genes that orchestrate sex and oocyst formation through mRNA sequencing of sorted cells. After 2d, parasites in cell culture show pronounced sexualization, but productive fertilization does not occur and infection falters. By contrast, in infected mice, male gametes successfully fertilize female parasites, which leads to meiotic division and sporulation. To rigorously test for fertilization, we devised a two-component genetic-crossing assay using a reporter that is activated by Cre recombinase. Our findings suggest obligate developmental progression towards sex in Cryptosporidium, which has important implications for the treatment and prevention of the infection.
PMID: 31477896 PMCID: PMC6877471 DOI: 10.1038/s41564-019-0539-x

Cell Host Microbe. 2019 Jul 10;26(1):135-146.e5. doi: 10.1016/j.chom.2019.05.006. Epub 2019 Jun 20.
A Genetically Tractable, Natural Mouse Model of Cryptosporidiosis Offers Insights into Host Protective Immunity.

Sateriale A1, Šlapeta J2, Baptista R3, Engiles JB1, Gullicksrud JA1, Herbert GT3, Brooks CF3, Kugler EM1, Kissinger JC4, Hunter CA1, Striepen B5.
Author information
Abstract
Cryptosporidium is a leading cause of diarrheal disease and an important contributor to early childhood mortality, malnutrition, and growth faltering. Older children in high endemicity regions appear resistant to infection, while previously unexposed adults remain susceptible. Experimental studies in humans and animals support the development of disease resistance, but we do not understand the mechanisms that underlie protective immunity to Cryptosporidium. Here, we derive an in vivo model of Cryptosporidium infection in immunocompetent C57BL/6 mice by isolating parasites from naturally infected wild mice. Similar to human cryptosporidiosis, this infection causes intestinal pathology, and interferon-γ controls early infection while T cells are critical for clearance. Importantly, mice that controlled a live infection were resistant to secondary challenge and vaccination with attenuated parasites provided protection equal to live infection. Both parasite and host are genetically tractable and this in vivo model will facilitate mechanistic investigation and rational vaccine design.

KEYWORDS:
Apicomplexa; Cryptosporidium; cryptosporidiosis; diarrhea; host-pathogen; immunity; intestine; parasite
PMID: 31231045 PMCID: PMC6617386 DOI: 10.1016/j.chom.2019.05.006

Cell Host Microbe. 2019 Jul 10;26(1):123-134.e8. doi: 10.1016/j.chom.2019.05.007. Epub 2019 Jun 20.
A Stem-Cell-Derived Platform Enables Complete Cryptosporidium Development In Vitro and Genetic Tractability.

Wilke G1, Funkhouser-Jones LJ1, Wang Y2, Ravindran S1, Wang Q1, Beatty WL1, Baldridge MT3, VanDussen KL2, Shen B1, Kuhlenschmidt MS4, Kuhlenschmidt TB4, Witola WH4, Stappenbeck TS2, Sibley LD5.
Author information
Abstract
Despite being a frequent cause of severe diarrheal disease in infants and an opportunistic infection in immunocompromised patients, Cryptosporidium research has lagged due to a lack of facile experimental methods. Here, we describe a platform for complete life cycle development and long-term growth of C. parvum in vitro using "air-liquid interface" (ALI) cultures derived from intestinal epithelial stem cells. Transcriptomic profiling revealed that differentiating epithelial cells grown under ALI conditions undergo profound changes in metabolism and development that enable completion of the parasite life cycle in vitro. ALI cultures support parasite expansion > 100-fold and generate viable oocysts that are transmissible in vitro and to mice, causing infection and animal death. Transgenic parasite lines created using CRISPR/Cas9 were used to complete a genetic cross in vitro, demonstrating Mendelian segregation of chromosomes during meiosis. ALI culture provides an accessible model that will enable innovative studies into Cryptosporidium biology and host interactions.

KEYWORDS:
Mendelian genetics; development; host-pathogen interactions; meiosis; organoids; pathway analysis; stem cells; transcriptomics
Comment in
PMID: 31231046 PMCID: PMC6617391 DOI: 10.1016/j.chom.2019.05.007

Front Public Health. 2019 Dec 11;7:360. doi: 10.3389/fpubh.2019.00360. eCollection 2019.
Direct Sequencing of Cryptosporidium in Stool Samples for Public Health.

Morris A1, Robinson G2,3, Swain MT1, Chalmers RM2,3.
Author information
Abstract
The protozoan parasite Cryptosporidium is an important cause of diarrheal disease (cryptosporidiosis) in humans and animals, with significant morbidity and mortality especially in severely immunocompromised people and in young children in low-resource settings. Due to the sexual life cycle of the parasite, transmission is complex. There are no restrictions on sexual recombination between sub-populations, meaning that large-scale genetic recombination may occur within a host, potentially confounding epidemiological analysis. To clarify the relationships between infections in different hosts, it is first necessary to correctly identify species and genotypes, but these differentiations are not made by standard diagnostic tests and more sophisticated molecular methods have been developed. For instance, multilocus genotyping has been utilized to differentiate isolates within the major human pathogens, Cryptosporidium parvum and Cryptosporidium hominis. This has allowed mixed populations with multiple alleles to be identified: recombination events are considered to be the driving force of increased variation and the emergence of new subtypes. As yet, whole genome sequencing (WGS) is having limited impact on public health investigations, due in part to insufficient numbers of oocysts and purity of DNA derived from clinical samples. Moreover, because public health agencies have not prioritized parasites, validation has not been performed on user-friendly data analysis pipelines suitable for public health practitioners. Nonetheless, since the first whole genome assembly in 2004 there are now numerous genomes of human and animal-derived cryptosporidia publically available, spanning nine species. It has also been demonstrated that WGS from very low numbers of oocysts is possible, through the use of amplification procedures. These data and approaches are providing new insights into host-adapted infectivity, the presence and frequency of multiple sub-populations of Cryptosporidium spp. within single clinical samples, and transmission of infection. Analyses show that although whole genome sequences do indeed contain many alleles, they are invariably dominated by a single highly abundant allele. These insights are helping to better understand population structures within hosts, which will be important to develop novel prevention strategies in the fight against cryptosporidiosis.

KEYWORDS:
cryptosporidium; genome; genotyping; multiplicity of infection; public health; sequencing
PMID: 31921734 PMCID: PMC6917613 DOI: 10.3389/fpubh.2019.00360

De Rycker

1: Wyllie S, Brand S, Thomas M, De Rycker M, Chung CW, Pena I, Bingham RP, Bueren-Calabuig JA, Cantizani J, Cebrian D, Craggs PD, Ferguson L, Goswami P, Hobrath J, Howe J, Jeacock L, Ko EJ, Korczynska J, MacLean L, Manthri S, Martinez MS, Mata-Cantero L, Moniz S, Nühs A, Osuna-Cabello M, Pinto E, Riley J, Robinson S, Rowland P, Simeons FRC, Shishikura Y, Spinks D, Stojanovski L, Thomas J, Thompson S, Viayna Gaza E, Wall RJ, Zuccotto F, Horn D, Ferguson MAJ, Fairlamb AH, Fiandor JM, Martin J, Gray DW, Miles TJ, Gilbert IH, Read KD, Marco M, Wyatt PG. Preclinical candidate for the treatment of visceral leishmaniasis that acts through proteasome inhibition. Proc Natl Acad Sci U S A. 2019 May 7;116(19):9318-9323. doi: 10.1073/pnas.1820175116. Epub 2019 Apr 8. PubMed PMID: 30962368; PubMed Central PMCID: PMC6511062.

2: Wyllie S, Thomas M, Patterson S, Crouch S, De Rycker M, Lowe R, Gresham S, Urbaniak MD, Otto TD, Stojanovski L, Simeons FRC, Manthri S, MacLean LM, Zuccotto F, Homeyer N, Pflaumer H, Boesche M, Sastry L, Connolly P, Albrecht S, Berriman M, Drewes G, Gray DW, Ghidelli-Disse S, Dixon S, Fiandor JM, Wyatt PG, Ferguson MAJ, Fairlamb AH, Miles TJ, Read KD, Gilbert IH. Cyclin-dependent kinase 12 is a drug target for visceral leishmaniasis. Nature. 2018 Aug;560(7717):192-197. doi: 10.1038/s41586-018-0356-z. Epub 2018 Jul 25. PubMed PMID: 30046105; PubMed Central PMCID: PMC6402543.

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Cell. 2017 Jul 13;170(2):260-272.e8. doi: 10.1016/j.cell.2017.06.030.
Functional Profiling of a Plasmodium Genome Reveals an Abundance of Essential Genes.
Bushell E1, Gomes AR1, Sanderson T1, Anar B1, Girling G1, Herd C1, Metcalf T1, Modrzynska K1, Schwach F1, Martin RE2, Mather MW3, McFadden GI4, Parts L1, Rutledge GG1, Vaidya AB3, Wengelnik K5, Rayner JC6, Billker O7.
Author information
Abstract
The genomes of malaria parasites contain many genes of unknown function. To assist drug development through the identification of essential genes and pathways, we have measured competitive growth rates in mice of 2,578 barcoded Plasmodium berghei knockout mutants, representing >50% of the genome, and created a phenotype database. At a single stage of its complex life cycle, P. berghei requires two-thirds of genes for optimal growth, the highest proportion reported from any organism and a probable consequence of functional optimization necessitated by genomic reductions during the evolution of parasitism. In contrast, extreme functional redundancy has evolved among expanded gene families operating at the parasite-host interface. The level of genetic redundancy in a single-celled organism may thus reflect the degree of environmental variation it experiences. In the case of Plasmodium parasites, this helps rationalize both the relative successes of drugs and the greater difficulty of making an effective vaccine.

KEYWORDS:
Plasmodium falciparum; Toxoplasma gondii; genome evolution; gene essentiality; PlasmoGEM; genetic screen; drug target validation; apicoplast; mitochondria; transporters
PMID:
28708996
PMCID:
PMC5509546
DOI:
10.1016/j.cell.2017.06.030

Science. 2018 May 4;360(6388). pii: eaap7847. doi: 10.1126/science.aap7847.
Uncovering the essential genes of the human malaria parasite Plasmodium falciparum by saturation mutagenesis.
Zhang M1, Wang C1, Otto TD2, Oberstaller J1, Liao X1, Adapa SR1, Udenze K1, Bronner IF2, Casandra D1, Mayho M2, Brown J2, Li S1, Swanson J1, Rayner JC3, Jiang RHY4, Adams JH4.
Author information
Abstract
Severe malaria is caused by the apicomplexan parasite Plasmodium falciparum. Despite decades of research, the distinct biology of these parasites has made it challenging to establish high-throughput genetic approaches to identify and prioritize therapeutic targets. Using transposon mutagenesis of P. falciparum in an approach that exploited its AT-rich genome, we generated more than 38,000 mutants, saturating the genome and defining mutability and fitness costs for over 87% of genes. Of 5399 genes, our study defined 2680 genes as essential for optimal growth of asexual blood stages in vitro. These essential genes are associated with drug resistance, represent leading vaccine candidates, and include approximately 1000 Plasmodium-conserved genes of unknown function. We validated this approach by testing proteasome pathways for individual mutants associated with artemisinin sensitivity.

Comment in
• Indispensable malaria genes. [Science. 2018]
PMID:
29724925
PMCID:
PMC6360947
DOI:
10.1126/science.aap7847

Elife. 2018 Mar 26;7. pii: e34039. doi: 10.7554/eLife.34039.
Spontaneous dormancy protects Trypanosoma cruzi during extended drug exposure.
Sánchez-Valdéz FJ#1, Padilla A#1,2, Wang W1, Orr D1, Tarleton RL1,2.
Author information
Abstract
The ability of the Chagas disease agent Trypanosoma cruzi to resist extended in vivo exposure to highly effective trypanocidal compounds prompted us to explore the potential for dormancy and its contribution to failed drug treatments in this infection. We document the development of non-proliferating intracellular amastigotes in vivo and in vitro in the absence of drug treatment. Non-proliferative amastigotes ultimately converted to trypomastigotes and established infections in new host cells. Most significantly, dormant amastigotes were uniquely resistant to extended drug treatment in vivo and in vitro and could re-establish a flourishing infection after as many as 30 days of drug exposure. These results demonstrate a dormancy state in T. cruzi that accounts for the failure of highly cytotoxic compounds to completely resolve the infection. The ability of T. cruzi to establish dormancy throws into question current methods for identifying curative drugs but also suggests alternative therapeutic approaches.

KEYWORDS:
Chagas disease; Trypanosoma cruzi; dormancy; drug resistance; infectious disease; microbiology
PMID:
29578409
PMCID:
PMC5906098
DOI:
10.7554/eLife.34039

Nature. 2018 Aug;560(7717):192-197. doi: 10.1038/s41586-018-0356-z. Epub 2018 Jul 25.
Cyclin-dependent kinase 12 is a drug target for visceral leishmaniasis.
Wyllie S1, Thomas M1, Patterson S1, Crouch S2, De Rycker M1, Lowe R3, Gresham S3, Urbaniak MD1,4, Otto TD5,6, Stojanovski L1, Simeons FRC1, Manthri S1, MacLean LM1, Zuccotto F1, Homeyer N1, Pflaumer H7, Boesche M7, Sastry L1, Connolly P8, Albrecht S1, Berriman M5, Drewes G7, Gray DW1, Ghidelli-Disse S7, Dixon S9, Fiandor JM2, Wyatt PG1, Ferguson MAJ1, Fairlamb AH1, Miles TJ10, Read KD11, Gilbert IH12.
Author information
Abstract
Visceral leishmaniasis causes considerable mortality and morbidity in many parts of the world. There is an urgent need for the development of new, effective treatments for this disease. Here we describe the development of an anti-leishmanial drug-like chemical series based on a pyrazolopyrimidine scaffold. The leading compound from this series (7, DDD853651/GSK3186899) is efficacious in a mouse model of visceral leishmaniasis, has suitable physicochemical, pharmacokinetic and toxicological properties for further development, and has been declared a preclinical candidate. Detailed mode-of-action studies indicate that compounds from this series act principally by inhibiting the parasite cdc-2-related kinase 12 (CRK12), thus defining a druggable target for visceral leishmaniasis.
Comment in
- Drug candidate and target for leishmaniasis. [Nature. 2018]
PMID:
30046105
PMCID:
PMC6402543
DOI:
10.1038/s41586-018-0356-z

Science. 2018 Oct 26;362(6413). pii: eaau7735. doi: 10.1126/science.aau7735. Epub 2018 Sep 13.
Evolutionary shift toward protein-based architecture in trypanosomal mitochondrial ribosomes.

Ramrath DJF1, Niemann M2, Leibundgut M1, Bieri P1, Prange C1, Horn EK2, Leitner A3, Boehringer D1, Schneider A2, Ban N4.
Author information
Abstract
Ribosomal RNA (rRNA) plays key functional and architectural roles in ribosomes. Using electron microscopy, we determined the atomic structure of a highly divergent ribosome found in mitochondria of Trypanosoma brucei, a unicellular parasite that causes sleeping sickness in humans. The trypanosomal mitoribosome features the smallest rRNAs and contains more proteins than all known ribosomes. The structure shows how the proteins have taken over the role of architectural scaffold from the rRNA: They form an autonomous outer shell that surrounds the entire particle and stabilizes and positions the functionally important regions of the rRNA. Our results also reveal the "minimal" set of conserved rRNA and protein components shared by all ribosomes that help us define the most essential functional elements.

PMID:
30213880
DOI:
10.1126/science.aau7735

Cell. 2019 Jan 10;176(1-2):306-317.e16. doi: 10.1016/j.cell.2018.10.041. Epub 2018 Nov 29.
Oligopeptide Signaling through TbGPR89 Drives Trypanosome Quorum Sensing.
Rojas F1, Silvester E1, Young J1, Milne R1, Tettey M1, Houston DR2, Walkinshaw MD2, Pérez-Pi I2, Auer M2, Denton H3, Smith TK3, Thompson J4, Matthews KR5.
Author information
Abstract
Trypanosome parasites control their virulence and spread by using quorum sensing (QS) to generate transmissible "stumpy forms" in their host bloodstream. However, the QS signal "stumpy induction factor" (SIF) and its reception mechanism are unknown. Although trypanosomes lack G protein-coupled receptor signaling, we have identified a surface GPR89-family protein that regulates stumpy formation. TbGPR89 is expressed on bloodstream "slender form" trypanosomes, which receive the SIF signal, and when ectopically expressed, TbGPR89 drives stumpy formation in a SIF-pathway-dependent process. Structural modeling of TbGPR89 predicts unexpected similarity to oligopeptide transporters (POT), and when expressed in bacteria, TbGPR89 transports oligopeptides. Conversely, expression of an E. coli POT in trypanosomes drives parasite differentiation, and oligopeptides promote stumpy formation in vitro. Furthermore, the expression of secreted trypanosome oligopeptidases generates a paracrine signal that accelerates stumpy formation in vivo. Peptidase-generated oligopeptide QS signals being received through TbGPR89 provides a mechanism for both trypanosome SIF production and reception.

KEYWORDS:
GPR89; Trypanosome brucei; differentiation; oligopeptide; parasite; quorum sensing; sleeping sickness; stumpy induction factor
Comment in
- A Major Step towards Defining the Elusive Stumpy Inducing Factor in Trypanosoma brucei. [Trends Parasitol. 2019]

PMID:
30503212
PMCID:
PMC6333907
DOI:
10.1016/j.cell.2018.10.041

PLoS Pathog. 2019 Jun 26;15(6):e1007828. doi: 10.1371/journal.ppat.1007828. eCollection 2019 Jun.
Genetic dissection of a Leishmania flagellar proteome demonstrates requirement for directional motility in sand fly infections.

Beneke T1, Demay F2, Hookway E3, Ashman N1, Jeffery H1, Smith J1, Valli J1, Becvar T4, Myskova J4, Lestinova T4, Shafiq S1,5, Sadlova J4, Volf P4, Wheeler RJ1,6, Gluenz E1.
Author information
Abstract
The protozoan parasite Leishmania possesses a single flagellum, which is remodelled during the parasite's life cycle from a long motile flagellum in promastigote forms in the sand fly to a short immotile flagellum in amastigotes residing in mammalian phagocytes. This study examined the protein composition and in vivo function of the promastigote flagellum. Protein mass spectrometry and label free protein enrichment testing of isolated flagella and deflagellated cell bodies defined a flagellar proteome for L. mexicana promastigote forms (available via ProteomeXchange with identifier PXD011057). This information was used to generate a CRISPR-Cas9 knockout library of 100 mutants to screen for flagellar defects. This first large-scale knockout screen in a Leishmania sp. identified 56 mutants with altered swimming speed (52 reduced and 4 increased) and defined distinct mutant categories (faster swimmers, slower swimmers, slow uncoordinated swimmers and paralysed cells, including aflagellate promastigotes and cells with curled flagella and disruptions of the paraflagellar rod). Each mutant was tagged with a unique 17-nt barcode, providing a simple barcode sequencing (bar-seq) method for measuring the relative fitness of L. mexicana mutants in vivo. In mixed infections of the permissive sand fly vector Lutzomyia longipalpis, paralysed promastigotes and uncoordinated swimmers were severely diminished in the fly after defecation of the bloodmeal. Subsequent examination of flies infected with a single paralysed mutant lacking the central pair protein PF16 or an uncoordinated swimmer lacking the axonemal protein MBO2 showed that these promastigotes did not reach anterior regions of the fly alimentary tract. These data show that L. mexicana need directional motility for successful colonisation of sand flies.
PMID:
31242261
PMCID:
PMC6615630
DOI:
10.1371/journal.ppat.1007828

Nat Commun. 2019 Jul 9;10(1):3023. doi: 10.1038/s41467-019-10823-8.
Monoallelic expression and epigenetic inheritance sustained by a Trypanosoma brucei variant surface glycoprotein exclusion complex.
Faria J1, Glover L1,2, Hutchinson S1,3, Boehm C1, Field MC1, Horn D4.
Author information
Abstract
The largest gene families in eukaryotes are subject to allelic exclusion, but mechanisms underpinning single allele selection and inheritance remain unclear. Here, we describe a protein complex sustaining variant surface glycoprotein (VSG) allelic exclusion and antigenic variation in Trypanosoma brucei parasites. The VSG-exclusion-1 (VEX1) protein binds both telomeric VSG-associated chromatin and VEX2, an ortholog of nonsense-mediated-decay helicase, UPF1. VEX1 and VEX2 assemble in an RNA polymerase-I transcription-dependent manner and sustain the active, subtelomeric VSG-associated transcription compartment. VSG transcripts and VSG coats become highly heterogeneous when VEX proteins are depleted. Further, the DNA replication-associated chromatin assembly factor, CAF-1, binds to and specifically maintains VEX1 compartmentalisation following DNA replication. Thus, the VEX-complex controls VSG-exclusion, while CAF-1 sustains VEX-complex inheritance in association with the active-VSG. Notably, the VEX2-orthologue and CAF-1 in mammals are also implicated in exclusion and inheritance functions. In trypanosomes, these factors sustain a highly effective and paradigmatic immune evasion strategy.
PMID:
31289266
PMCID:
PMC6617441
DOI:
10.1038/s41467-019-10823-8

Field

Proc Natl Acad Sci U S A. 2020 Jan 21. pii: 201914423. doi: 10.1073/pnas.1914423117. [Epub ahead of print]
Single-cell RNA sequencing of Trypanosoma brucei from tsetse salivary glands unveils metacyclogenesis and identifies potential transmission blocking antigens.

Vigneron A1, O'Neill MB2, Weiss BL2, Savage AF2, Campbell OC2, Kamhawi S3, Valenzuela JG3, Aksoy S1.
Author information
Abstract
Tsetse-transmitted African trypanosomes must develop into mammalian-infectious metacyclic cells in the fly's salivary glands (SGs) before transmission to a new host. The molecular mechanisms that underlie this developmental process, known as metacyclogenesis, are poorly understood. Blocking the few metacyclic parasites deposited in saliva from further development in the mammal could prevent disease. To obtain an in-depth perspective of metacyclogenesis, we performed single-cell RNA sequencing (scRNA-seq) from a pool of 2,045 parasites collected from infected tsetse SGs. Our data revealed three major cell clusters that represent the epimastigote, and pre- and mature metacyclic trypanosome developmental stages. Individual cell level data also confirm that the metacyclic pool is diverse, and that each parasite expresses only one of the unique metacyclic variant surface glycoprotein (mVSG) coat protein transcripts identified. Further clustering of cells revealed a dynamic transcriptomic and metabolic landscape reflective of a developmental program leading to infectious metacyclic forms preadapted to survive in the mammalian host environment. We describe the expression profile of proteins that regulate gene expression and that potentially play a role in metacyclogenesis. We also report on a family of nonvariant surface proteins (Fam10) and demonstrate surface localization of one member (named SGM1.7) on mature metacyclic parasites. Vaccination of mice with recombinant SGM1.7 reduced parasitemia early in the infection. Future studies are warranted to investigate Fam10 family proteins as potential trypanosome transmission blocking vaccine antigens. Our experimental approach is translationally relevant for developing strategies to prevent other insect saliva-transmitted parasites from infecting and causing disease in mammalian hosts.

KEYWORDS:
African trypanosome; metacyclic; single-cell RNA-seq; tsetse; vaccine
PMID: 31964820 DOI: 10.1073/pnas.1914423117

Trop Med Infect Dis. 2020 Jan 19;5(1). pii: E14. doi: 10.3390/tropicalmed5010014.
The Drugs of Sleeping Sickness: Their Mechanisms of Action and Resistance, and a Brief History.

P De Koning H1.
Author information
Abstract
With the incidence of sleeping sickness in decline and genuine progress being made towards the WHO goal of eliminating sleeping sickness as a major public health concern, this is a good moment to evaluate the drugs that 'got the job done': their development, their limitations and the resistance that the parasites developed against them. This retrospective looks back on the remarkable story of chemotherapy against trypanosomiasis, a story that goes back to the very origins and conception of chemotherapy in the first years of the 20 century and is still not finished today.
KEYWORDS:
drug resistance; drugs; history; human African trypanosomiasis; sleeping sickness; trypanosoma brucei
PMID: 31963784 DOI: 10.3390/tropicalmed5010014