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Maladies tropicales négligées

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DENGUE, CHIKUNGUNYA ET MALADIE A VIRUS ZIKA

Identification of acridinedione scaffolds as potential inhibitor of DENV-2 C protein: An in silico strategy to combat dengue.

Kumar, S., Bhardwaj, V., Singh, R., Das, P., Purohit, R.
21-03-2022
J Cell Biochem
https://doi.org/10.1002/jcb.30237

Dengue is a prominent viral disease transmitted by mosquitoes to humans that affects mainly tropical and subtropical countries worldwide. The global spread of dengue virus (DENV) is mainly occurred by Aedes aegypti and Aedes albopictus mosquitoes. The dengue virus serotypes-2 (DENV-2) is a widely prevalent serotype of DENV, that causes the hemorrhagic fever and bleeding in the mucosa, which can be fatal. In the life cycle of DENV-2, a structural capsid (DENV-2 C) protein forms the nucleocapsid assembly and bind to the viral progeny RNA. For DENV-2 maturation, the nucleocapsid is a vital component. We used virtual ligand screening to filter out the best in-house synthesized acridinedione analogs (DSPD molecules) that could efficiently bind to DENV-2 C protein. The molecular docking and dynamics simulations studies were performed to analyze the effect of DSPD molecules on DENV-2 C protein after binding. Our findings showed that DSPD molecules strongly interacted with DENV-2 C protein, as evident from molecular interactions and several time-dependent molecular dynamics-driven analyses. Moreover, this study was also supported by the thermodynamic binding free energy and steered molecular dynamics simulations. Therefore, we intend to suggest that the DSPD3 molecule could be used as a potential therapeutic molecule against dengue complications as compared to the cocrystallized inhibitor ST-148. However, further studies are required to demonstrate the ability of DSPD3 to induce DENV-2 C tetramer formation.

Symbionts and gene drive: two strategies to combat vector-borne disease.

Revue de littérature

Wang, G., Du, J., Chu, C., Madhav, M., Hughes, G., Champer, J.
18-03-2022
Trends Genet
https://pubmed.ncbi.nlm.nih.gov/35314082

Mosquitoes bring global health problems by transmitting parasites and viruses such as malaria and dengue. Unfortunately, current insecticide-based control strategies are only moderately effective because of high cost and resistance. Thus, scalable, sustainable, and cost-effective strategies are needed for mosquito-borne disease control. Symbiont-based and genome engineering-based approaches provide new tools that show promise for meeting these criteria, enabling modification or suppression approaches. Symbiotic bacteria like Wolbachia are maternally inherited and manipulate mosquito host reproduction to enhance their vertical transmission. Genome engineering-based gene drive methods, in which mosquitoes are genetically altered to spread drive alleles throughout wild populations, are also proving to be a potentially powerful approach in the laboratory. Here, we review the latest developments in both symbionts and gene drive-based methods. We describe some notable similarities, as well as distinctions and obstacles, relating to these promising technologies.

The epidemiology and outcomes of central nervous system infections in Far North Queensland, tropical Australia; 2000-2019.

Gora, H., Smith, S., Wilson, I., Preston-Thomas, A., Ramsamy, N., Hanson, J.
21-03-2022
PLoS One
https://doi.org/10.1371/journal.pone.0265410

The epidemiology of central nervous system (CNS) infections in tropical Australia is incompletely defined. A retrospective study of all individuals in Far North Queensland, tropical Australia, who were diagnosed with a CNS infection between January 1, 2000, and December 31, 2019. The microbiological aetiology of the infection was correlated with patients' demographic characteristics and their clinical course. There were 725 cases of CNS infection during the study period, meningitis (77.4%) was the most common, followed by brain abscess (11.6%), encephalitis (9.9%) and spinal infection (1.1%). Infants (24.3%, p<0.0001) and Aboriginal and Torres Strait Islander Australians (175/666 local residents, 26.3%, p<0.0001) were over-represented in the cohort. A pathogen was identified in 513 cases (70.8%); this was viral in 299 (41.2%), bacterial in 175 (24.1%) and fungal in 35 (4.8%). Cryptococcal meningitis (24 cases) was diagnosed as frequently as pneumococcal meningitis (24 cases). There were only 2 CNS infections with a S. pneumoniae serotype in the 13-valent pneumococcal vaccine after its addition to the National Immunisation schedule in 2011. Tropical pathogens-including Cryptococcus species (9/84, 11%), Mycobacterium tuberculosis (7/84, 8%) and Burkholderia pseudomallei (5/84, 6%)-were among the most common causes of brain abscess. However, arboviral CNS infections were rare, with only one locally acquired case-a dengue infection in 2009-diagnosed in the entire study period. Intensive Care Unit admission was necessary in 14.3%; the overall case fatality rate was 4.4%. Tropical pathogens cause CNS infections as commonly as traditional bacterial pathogens in this region of tropical Australia. However, despite being highlighted in the national consensus guidelines, arboviruses were identified very rarely. Prompt access to sophisticated diagnostic and supportive care in Australia's well-resourced public health system is likely to have contributed to the cohort's low case-fatality rate.

Luciferase Immunosorbent Assay Based on Multiple E Antigens for the Detection of Chikungunya Virus-Specific IgG Antibodies.

Li, X., Wan, X., Liu, J., Wang, H., Li, A., Ke, C., Tang, S., Zhao, W., Cai, S., Wan, C.
21-03-2022
Microbiol Spectr
https://doi.org/10.1128/spectrum.01496-21

In recent years, the chikungunya virus (CHIKV) has continued to spread from local epidemics to nonnative habitats until eventually reaching pandemic status. Nonendemic areas such as China have also emerged as potential epidemic areas of CHIKV. Serological detection of CHIKV is the key to diagnosing and controlling the prevalence of this virus. In this study, we review the progress of the serological detection of the envelope (E) protein in CHIKV, and we provide a novel research assay and ideas for the serological detection of CHIKV. The luciferase immunosorbent assay (LISA) does not require species-specific labeled secondary antibodies for detection, making it universally suitable for tracking samples from various animals or carriers. At present, most research on CHIKV antigen detection technology tends to combine two or more proteins to avoid the decrease in detection ability caused by antigen mutation. Our results indicate that two or more kinds of CHIKV E antigens combined with LISA detection can improve the detection rate of anti-CHIKV immunoglobulin G (IgG) antibodies in CHIKV-infected patient sera and detect antibodies in the early stage of infection accurately and sensitively. After 235 days of infection, the anti-CHIKV IgG antibodies could still be detected in CHIKV-infected patients. All serum samples were tested with a detection rate of 100% after combining various recombinant CHIKV E antigens. Our proposed CHIKV-specific LISA could be a useful tool for serum diagnosis of CHIKV infection and serum epidemic research in areas where CHIKV is endemic, which would help to manage potential epidemics in the future. IMPORTANCE At present, chikungunya virus (CHIKV) is still circulating in some parts of the world, and mutated strains have emerged, making it easier for the virus to spread among humans. With the continuous variation of CHIKV, its antigen variation leads to the decline of detection ability. In addition, the risk of transmission of CHIKV in areas where CHIKV is not endemic, such as China, has increased dramatically, which compels us to enhance the detection capacity of CHIKV and continuously monitor CHIKV antibody levels in the population. Real-time quantitative PCR (RT-PCR) detection technology will not be reliable when the infection time is chronic or in subclinical infection due to decreases in virus concentration, and an antibody detection technology must be adopted. In this study, multiple CHIKV envelope (E) antigens were used to detect anti-CHIKV IgG antibodies in serum for the first time. The new assay is characterized by convenient operation, high detection rate, and high sensitivity and has significance for early warning and monitoring. Moreover, it contributes to the prevention and control of CHIKV.

Synthesis of new series of quinoline derivatives with insecticidal effects on larval vectors of malaria and dengue diseases.

Murugan, K., Panneerselvam, C., Subramaniam, J., Paulpandi, M., Rajaganesh, R., Vasanthakumaran, M., Madhavan, J., Shafi, S., Roni, M., Portilla-Pulido, J., Mendez, S., Duque, J., Wang, L., Aziz, A., Chandramohan, B., Dinesh, D., Piramanayagam, S., Hwang, J.
19-03-2022
Sci Rep
https://doi.org/10.1038/s41598-022-08397-5

Mosquito borne diseases are on the rise because of their fast spread worldwide and the lack of effective treatments. Here we are focusing on the development of a novel anti-malarial and virucidal agent with biocidal effects also on its vectors. We have synthesized a new quinoline (4,7-dichloroquinoline) derivative which showed significant larvicidal and pupicidal properties against a malarial and a dengue vector and a lethal toxicity ranging from 4.408 µM/mL (first instar larvae) to 7.958 µM/mL (pupal populations) for Anopheles stephensi and 5.016 µM/mL (larva 1) to 10.669 µM/mL (pupae) for Aedes aegypti. In-vitro antiplasmodial efficacy of 4,7-dichloroquinoline revealed a significant growth inhibition of both sensitive strains of Plasmodium falciparum with IC_{50} values of 6.7 nM (CQ-s) and 8.5 nM (CQ-r). Chloroquine IC_{50} values, as control, were 23 nM (CQ-s), and 27.5 nM (CQ-r). In vivo antiplasmodial studies with P. falciparum infected mice showed an effect of 4,7-dichloroquinoline compared to chloroquine. The quinoline compound showed significant activity against the viral pathogen serotype 2 (DENV-2). In vitro conditions and the purified quinoline exhibited insignificant toxicity on the host system up to 100 µM/mL. Overall, 4,7-dichloroquinoline could provide a good anti-vectorial and anti-malarial agent.

Global prevalence of dengue and chikungunya coinfection: A systematic review and meta-analysis of 43,341 participants.

Irekeola, A., Engku Nur Syafirah, E., Islam, M., Shueb, R.
16-03-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35305942

Dengue and chikungunya virus are important arboviruses of public health concern. In the past decades, they have accounted for numerous outbreaks of dengue and chikungunya in different parts of the world. Several cases of concurrent infection of dengue and chikungunya have been documented. However, the true burden of this concurrent infection is unknown. Here, a systematic review and meta-analysis of published data on the prevalence of dengue and chikungunya coinfection in the human population was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Six electronic databases (Web of science, Embase, PubMed, ScienceDirect, Scopus, and Google Scholar) were searched without year or language restrictions for relevant studies. The study protocol

was registered with PROSPERO (CRD42020175344). Eighty-three studies involving a total of 43,341 participants were included. The random-effects model was employed to calculate the summary estimates. A pooled global prevalence of 2.5% (95% CI: 1.8-3.4) was obtained for dengue and chikungunya coinfection. Males and females appear to be coinfected at a fairly similar rate. Among the regions, Asia accounted for the highest prevalence (3.3%, 95% CI: 2.3-4.6) while North America was the least (0.8%, 95% CI: 0.3-2.4). The prevalence estimates varied across different countries. A much higher prevalence rates were obtained for Colombia (37.4%, 95% CI: 9.1-78.1), Madagascar (18.2%, 95% CI: 10.1-30.6), Laos (12.5%, 95% CI: 5.3-26.7), Maldives (4.5%, 95% CI: 1.5-13.0) and Thailand (3.7%, 95% CI: 0.4-26.3). This first extensive systematic review and meta-analysis reveals dengue and chikungunya coinfection as a global problem worthy of consideration. It is therefore pertinent that both infections be assessed during diagnosis, mosquito vector control practices be implemented, and vaccine development strides be supported globally.

Temporal Correlation Between Urban Microclimate, Vector Mosquito Abundance, and Dengue Cases.

Faridah, L., Fauziah, N., Agustian, D., Mindra Jaya, I., Eka Putra, R., Ekawardhani, S., Hidayath, N., Damar Djati, I., Carvajal, T., Mayasari, W., Ruluwedrata Rinawan, F., Watanabe, K.
19-03-2022
J Med Entomol
https://pubmed.ncbi.nlm.nih.gov/35305089

Dengue Hemorrhagic Fever (DHF) is a major mosquito-borne viral disease. Studies have reported a strong correlation between weather, the abundance of Aedes aegypti, the vector of DHF virus, and dengue incidence. However, this conclusion has been based on the general climate pattern of wide regions. In general, however, the human population, level of infrastructure, and land-use change in rural and urban areas often produce localized climate patterns that may influence the interaction between climate, vector abundance, and dengue incidence. Thoroughly understanding this correlation will allow the development of a customized and precise local early warning system. To achieve this purpose, we conducted a cohort study, during January-December 2017, in 16 districts in Bandung, West Java, Indonesia. In the selected areas, local weather stations and modified light mosquito traps were set up to obtain data regarding daily weather and the abundance of adult female Ae. aegypti. A generalized linear model was applied to analyze the effect of local weather and female adult Ae. aegypti on the number of dengue cases. The result showed a significant non-linear correlation among mosquito abundance, maximum temperature, and dengue cases. Using our model, the data showed that the addition of a single adult Ae. aegypti mosquito increased the risk of dengue infection by 1.8%, while increasing the maximum temperature by one degree decreased the risk by 17%. This finding suggests specific actionable insights needed to supplement existing mosquito eradication programs.

ZIKV can infect human term placentas in the absence of maternal factors.

Villazana-Kretzer, D., Wuertz, K., Newhouse, D., Damicis, J., Dornisch, E., Voss, K., Muruato, A., Paymaster, J., Schmiedecke, S., Edwards, S., Napolitano, P., Tisoncik-Go, J., Ieronimakis, N., Gale, M.
18-03-2022
Commun Biol
https://doi.org/10.1038/s42003-022-03158-6

Zika virus infection can result in devastating pregnancy outcomes when it crosses the placental barrier. For human pregnancies, the mechanisms of vertical transmission remain enigmatic. Utilizing a human placenta-cotyledon perfusion model, we examined Zika virus exposure in the absence of maternal factors. To distinguish responses related to viral infection vs. recognition, we evaluated cotyledons perfused with either active or inactivated Zika virus. Active Zika virus exposure resulted in infection, cell death and syncytium injury. Pathology corresponded with transcriptional changes related to inflammation and innate immunity. Inactive Zika virus exposure also led to syncytium injury and related changes in gene expression but not cell death. Our observations reveal pathologies and innate immune responses that are dependent on infection or virus placenta interactions independent of productive infection. Importantly, our findings indicate that Zika virus can infect and compromise placentas in the absence of maternal humoral factors that may be protective.

Circulation of genotypes of dengue virus serotype 2 in Guangzhou over a period of 20 years.

Jiang, L., Liu, Y., Su, W., Cao, Y., Jing, Q., Wu, X., Yang, Z.
18-03-2022
Virol J
https://doi.org/10.1186/s12985-022-01773-7

The dengue epidemic in Guangzhou has imposed a rising burden on society and health infrastructure. Here, we present the genotype data for dengue virus serotype 2 (DENV-2) to improve understanding of this dengue epidemic. We sequenced the envelope gene of DENV-2 obtained from patient serum samples and subsequently performed maximum-likelihood phylogenetic analysis using PhyMLv3.1, maximum clade credibility analysis using BEAST v.1.10.4, and selection pressure analysis using Datamonkey 2.0. The prevalent DENV-2 strains identified in Guangzhou region are related to those in Southeast Asian countries. In particular, the Malaysia/Indian subcontinent genotype is prevailing in Guangzhou with no apparent genotype shift having occurred over the past 20 years. However, episodic positive selection was detected at one site. Local control of the DENV-2 epidemic in Guangzhou requires effective measures to prevent and monitor imported cases. Moreover, the shift between the Malaysia/Indian subcontinent genotype lineages, which originated at different time points, may account for the rise in DENV-2 cases in Guangzhou. Meanwhile, the low rate of dengue haemorrhagic fever in Guangzhou may be explained by the dominance of the less virulent

Malaysia/Indian subcontinent genotype.

Periodic synchronisation of dengue epidemics in Thailand over the last 5 decades driven by temperature and immunity.

García-Carreras, B., Yang, B., Grabowski, M., Sheppard, L., Huang, A., Salje, H., Clapham, H., Iamsirithaworn, S., Doung-Ngern, P., Lessler, J., Cummings, D.
18-03-2022
PLoS Biol
https://doi.org/10.1371/journal.pbio.3001160

The spatial distribution of dengue and its vectors (spp. Aedes) may be the widest it has ever been, and projections suggest that climate change may allow the expansion to continue. However, less work has been done to understand how climate variability and change affects dengue in regions where the pathogen is already endemic. In these areas, the waxing and waning of immunity has a large impact on temporal dynamics of cases of dengue haemorrhagic fever. Here, we use 51 years of data across 72 provinces and characterise spatiotemporal patterns of dengue in Thailand, where dengue has caused almost 1.5 million cases over the last 30 years, and examine the roles played by temperature and dynamics of immunity in giving rise to those patterns. We find that timescales of multiannual oscillations in dengue vary in space and time and uncover an interesting spatial phenomenon: Thailand has experienced multiple, periodic synchronisation events. We show that although patterns in synchrony of dengue are similar to those observed in temperature, the relationship between the two is most consistent during synchronous periods, while during asynchronous periods, temperature plays a less prominent role. With simulations from temperature-driven models, we explore how dynamics of immunity interact with temperature to produce the observed patterns in synchrony. The simulations produced patterns in synchrony that were similar to observations, supporting an important role of immunity. We demonstrate that multiannual oscillations produced by immunity can lead to asynchronous dynamics and that synchrony in temperature can then synchronise these dengue dynamics. At higher mean temperatures, immune dynamics can be more predominant, and dengue dynamics more insensitive to multiannual fluctuations in temperature, suggesting that with rising mean temperatures, dengue dynamics may become increasingly asynchronous. These findings can help underpin predictions of disease patterns as global temperatures rise.

Baseline mapping of Oropouche virology, epidemiology, therapeutics, and vaccine research and development.

Revue de littérature

Files, M., Hansen, C., Herrera, V., Schindewolf, C., Barrett, A., Beasley, D., Bourne, N., Milligan, G.
17-03-2022
NPJ Vaccines
https://doi.org/10.1038/s41541-022-00456-2

Oropouche virus (OROV) is an arthropod-borne orthobunyavirus found in South America and causes Oropouche fever, a febrile infection similar to dengue. It is the second most prevalent arthropod-borne viral disease in South America after dengue. Over 500,000 cases have been diagnosed since the virus was first discovered in 1955; however, this is likely a significant underestimate given the limited availability of diagnostics. No fatalities have been reported to date, however, up to 60% of cases have a recurrent phase of disease within one month of recovery from the primary disease course. The main arthropod vector is the biting midge Culicoides paraensis, which has a geographic range as far north as the United States and demonstrates the potential for OROV to geographically expand. The transmission cycle is incompletely understood and vertebrate hosts include both non-human primates and birds further supporting the potential ability of the virus to spread. A number of candidate antivirals have been evaluated against OROV in vitro but none showed antiviral activity. Surprisingly, there is only one report in the literature on candidate vaccines. We suggest that OROV is an undervalued pathogen much like chikungunya, Schmallenberg, and Zika viruses were before they emerged. Overall, OROV is an important emerging disease that has been under-investigated and has the potential to cause large epidemics in the future. Further research, in particular candidate vaccines, is needed for this important pathogen.

Could species-focused suppression of Aedes aegypti, the yellow fever mosquito, and Aedes albopictus, the tiger mosquito, affect interacting predators? An evidence synthesis from the literature.

Revue de littérature

Bonds, J., Collins, C., Gouagna, L.
16-03-2022
Pest Manag Sci
https://doi.org/10.1002/ps.6870

The risks of Aedes aegypti and Aedes albopictus nuisance and vector-borne diseases are rising and the adverse effects of broad-spectrum insecticide application has promoted species-specific techniques, such as sterile insect technique (SIT) and other genetic strategies, as contenders in their control operations. When specific vector suppression is proposed, potential effects on predators and wider ecosystem are some of the first stakeholder questions. These are not the only Aedes vectors of human diseases, but are those for which SIT and genetic strategies are of most interest. They vary ecologically and in habitat origin, but both have behaviourally human-adapted forms with expanding ranges. The aquatic life stages are where predation is strongest due to greater resource predictability and limited escape opportunity. These vectors' anthropic forms usually use ephemeral water bodies and man-made containers as larval habitats; predators that occur in these are mobile, opportunistic and generalist. No literature indicates that any predator depends on larvae of

either species. As adults, foraging theory predicts these mosquitoes are of low profitability to predators. Energy expended hunting and consuming will mostly outweigh their energetic benefit. Moreover, as adult biomass is mobile and largely disaggregated, any predator is likely to be a generalist and opportunist. This work, which summarises much of the literature currently available on the predators of Ae. aegypti and Ae. albopictus, indicates it is highly unlikely that any predator species depends on them. Species-specific vector control to reduce nuisance and disease is thus likely to be of negligible or limited impact on non-target predators. This article is protected by copyright. All rights reserved.

Oil palm expansion increases the vectorial capacity of dengue vectors in Malaysian Borneo.

Gregory, N., Ewers, R., Chung, A., Cator, L.
16-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0009525

Changes in land-use and the associated shifts in environmental conditions can have large effects on the transmission and emergence of mosquito-borne disease. Mosquito-borne disease are particularly sensitive to these changes because mosquito growth, reproduction, survival and susceptibility to infection are all thermally sensitive traits, and land use change dramatically alters local microclimate. Predicting disease transmission under environmental change is increasingly critical for targeting mosquito-borne disease control and for identifying hotspots of disease emergence. Mechanistic models offer a powerful tool for improving these predictions. However, these approaches are limited by the quality and scale of temperature data and the thermal response curves that underlie predictions. Here, we used fine-scale temperature monitoring and a combination of empirical, laboratory and temperature-dependent estimates to estimate the vectorial capacity of Aedes albopictus mosquitoes across a tropical forest-oil palm plantation conversion gradient in Malaysian Borneo. We found that fine-scale differences in temperature between logged forest and oil palm plantation sites were not sufficient to produce differences in temperature-dependent demographic trait estimates using published thermal performance curves. However, when measured under field conditions a key parameter, adult abundance, differed significantly between land-use types, resulting in estimates of vectorial capacity that were 1.5 times higher in plantations than in forests. The prediction that oil palm plantations would support mosquito populations with higher vectorial capacity was robust to uncertainties in our adult survival estimates. These results provide a mechanistic basis for understanding the effects of forest conversion to agriculture on mosquito-borne disease risk, and a framework for interpreting emergent relationships between land-use and disease transmission. As the burden of Ae. albopictus-vectored diseases, such as dengue virus, increases globally and rising demand for palm oil products drives continued expansion of plantations, these findings have important implications for conservation, land management and public health policy at the global scale.

Replication is the key barrier during the dual-host adaptation of mosquito-borne flaviviruses.

Zhang, Y., Liang, D., Yuan, F., Yan, Y., Wang, Z., Liu, P., Yu, Q., Zhang, X., Wang, X., Zheng, A.
16-03-2022
Proc Natl Acad Sci U S A
https://doi.org/10.1073/pnas.2110491119

SignificanceMost viruses have a relatively narrow host range. In contrast, vector-borne flaviviruses, such as dengue virus and Zika virus, maintain their transmission cycle between arthropods and vertebrates, belonging to different phyla. How do these viruses adapt to the distinct cellular environments of two phyla? By comparing the single-host insect--specific flavivirus and dual-host Zika virus, we identified three key molecular factors that determine MBF host tropism. This study will greatly increase the understanding of entry, replication, and cross-species evolution of mosquito-borne flaviviruses.

Targeting the Annexin A1-FPR2/ALX pathway for host-directed therapy in dengue disease.

Costa, V., Sugimoto, M., Hubner, J., Bonilha, C., Queiroz-Junior, C., Gonçalves-Pereira, M., Chen, J., Gobbetti, T., Libanio Rodrigues, G., Bambirra, J., Passos, I., Machado Lopes, C., Moreira, T., Bonjour, K., Melo, R., Oliveira, M., Andrade, M., Sousa, L., Souza, D., Santiago, H., Perretti, M., Teixeira, M.
16-03-2022
Elife
https://doi.org/10.7554/eLife.73853

Host immune responses contribute to dengue's pathogenesis and severity, yet the possibility that failure in endogenous inflammation resolution pathways could characterise the disease has not been contemplated. The pro-resolving protein Annexin A1 (AnxA1) is known to counterbalance overexuberant inflammation and mast cell (MC) activation. We hypothesised that inadequate AnxA1 engagement underlies the cytokine storm and vascular pathologies associated with dengue disease. Levels of AnxA1 were examined in the plasma of dengue patients and infected mice. Immunocompetent, interferon (alpha and beta) receptor 1 knockout (KO), AnxA1 KO and FPR2 KO mice were infected with *Dengue virus* (DENV) and treated with the AnxA1 mimetic peptide Ac_{2-26} for analysis. Additionally, the effect of Ac_{2-26} on DENV-induced MC degranulation was assessed *in vitro* and *in vivo*. We observed that circulating levels of AnxA1 were reduced in dengue patients and DENV-infected mice. While the absence of AnxA1 or its receptor FPR2 aggravated illness in infected mice, treatment with AnxA1 agonistic peptide attenuated disease manifestations. Both clinical outcomes were attributed to modulation of DENV-mediated viral load-independent MC degranulation. We have thereby identified that altered levels of the pro-resolving mediator AnxA1 are of pathological relevance in DENV infection, suggesting FPR2/ALX agonists as a therapeutic target for dengue disease.

Cluster Analysis of Dengue Morbidity and Mortality in Mexico from 2007 to 2020: Implications for the Probable Case Definition.

Baak-Baak, C., Cigarroa-Toledo, N., Pinto-Castillo, J., Cetina-Trejo, R., Torres-Chable, O., Blitvich, B., Garcia-Rejon, J.
14-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-0409

Dengue cases and deaths occur frequently in Mexico, although the trend is not uniform across the country. We performed a Spatio-temporal analysis of dengue cases and deaths in Mexico from 2007 to 2020, and clustered states according to whether there was a low, moderate, or high risk of dengue. A total of 501,600 confirmed dengue cases were registered from 2007 to 2020, with 378,122 cases classified as dengue fever (DF) and 123,478 cases classified as dengue hemorrhagic fever (DHF). For each confirmed case, there were 4.68 probable cases. There were 1,230 dengue deaths, with highest numbers reported in 2009, 2012, 2013, and 2019. The number of deaths had a significant correlation ($P \leq 0.01$) with DF ($r = 0.82$), DHF ($r = 0.94$), and probable dengue cases ($r = 0.84$). States were clustered using Machine Learning technique according to select indices associated with dengue. Cluster 1 (low risk) primarily contained states in the northwest, northcentral, and east. Cluster 2 (moderate risk) includes states in the northeast. Cluster 3 (high risk) mostly contained coastal states in the southeast, southwest, and west. The generation of the clusters was supported by the Kruskal-Wallis test. A significant difference was found in the incidence, mortality rates, and case-fatality rates of dengue among the clusters ($P \leq 0.01$). Notably, cluster 3 contributed 71.4% of the confirmed cases and 89.2% of the deaths. Public health and vector control strategies designed to mitigate the burden of dengue in Mexico should consider the states in cluster 3 as high priority areas.

The Asian tiger mosquito Aedes albopictus (Skuse) in Kosovo: First record.

Muja-Bajraktari, N., Kadriaj, P., Zhushi-Etemi, F., Sherifi, K., Alten, B., Petrić, D., Velo, E., Schaffner, F.
15-03-2022
PLoS One
https://doi.org/10.1371/journal.pone.0264300

The Asian tiger mosquito, Aedes albopictus, is an invasive mosquito species that is considered a potential vector of about 22 arboviruses, among which dengue, chikungunya and Zika. Here we report the first record of Aedes albopictus in the territory of the Republic of Kosovo. The first finding, in July 2020, was driven by a photo of an adult mosquito published by a citizen in social media. The subsequent field investigation in July 2020 confirmed the presence of adult mosquitoes by human landing catch and collection of eggs in ovitraps at the village Zhur. Monitoring was performed for 7 weeks with ovitraps and BG-Sentinel adult traps at 36 sampling stations from 7 localities, in the Southern part of Kosovo, on the border with Albania. Fifty-two out of 81 ovitrap samples resulted positive for the presence of Ae. albopictus. A total of 2,711 eggs are collected in 22 out 36 stations and a total of 78 adults from 4 out 4 stations with BG Sentinel trap and 15 adults with handled electric aspirator. Our finding shows that the tiger mosquito is expanding its geographical range in the Balkans, southeastern Europe.

A phase I randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and immunogenicity of a live-attenuated quadrivalent dengue vaccine in flavivirus-naïve and flavivirus-experienced healthy adults.

Russell, K., Rupp, R., Morales-Ramirez, J., Diaz-Perez, C., Andrews, C., Lee, A., Finn, T., Cox, K., Falk Russell, A., Schaller, M., Martin, J., Hyatt, D., Gozlan-Kelner, S., Bili, A., Coller, B.
15-03-2022
Hum Vaccin Immunother
https://doi.org/10.1080/21645515.2022.2046960

Dengue (DENV) is a mosquito-borne virus with four serotypes causing substantial morbidity in tropical and subtropical areas worldwide. V181 is an investigational, live, attenuated, quadrivalent dengue vaccine. In this phase 1 double-blind, placebo-controlled study, the safety, tolerability, and immunogenicity of V181 in baseline flavivirus-naïve (BFN) and flavivirus-experienced (BFE) healthy adults were evaluated in two formulations: TV003 and TV005. TV005 contains a 10-fold higher DENV2 level than TV003. Two-hundred adults were randomized 2:2:1 to receive TV003, TV005, or placebo on Days 1 and 180. Immunogenicity against the 4 DENV serotypes was measured using a Virus Reduction Neutralization Test ($VRNT_{60}$) after each vaccination and out to 1year after the second dose. There were no discontinuations due to adverse events (AE) or serious vaccine-related AEs in the study. Most common AEs after TV003 or TV005 were headache, rash, fatigue, and myalgia. Tri- or tetravalent vaccine-viremia was detected in 63.9% and 25.6% of BFN TV003 and TV005 participants, respectively, post-dose 1 (PD1). Tri- or tetravalent dengue $VRNT_{60}$ seropositivity was demonstrated in 92.6% of BFN TV003, 74.2% of BFN TV005, and 100% of BFE TV003 and TV005 participants PD1. Increases in $VRNT_{60}$ GMTs were observed after the first vaccination with TV003 and TV005 in both flavivirus subgroups for all dengue serotypes, and minimal increases were measured PD2. GMTs in the TV003 and TV005 BFE and BFN groups remained above the respective baselines and placebo through 1-year PD2. These data support further development of V181 as a single-dose vaccine for the prevention of dengue disease.

Tracking the Replication-Competent Zika Virus with Tetracysteine-Tagged Capsid Protein in Living Cells.

Li, S., Wang, D., Ghulam, A., Li, X., Li, M., Li, Q., Ma, Y., Wang, L., Wu, H., Cui, Z., Zhang, X.
14-03-2022
J Virol
https://doi.org/10.1128/jvi.01846-21

Real-time imaging of viruses in living cells considerably facilitates the study of virus-host interactions. However, generating a fluorescently labeled recombinant virus is challenging, especially for Zika virus (ZIKV), which causes microcephaly in neonates. The monocistronic nature of the ZIKV genome represents a major challenge for generating a replication-competent genetically engineered ZIKV suitable for real-time imaging. Here, we generated a fluorescent ZIKV by introducing the biarsenical tetracysteine (TC) tag system. After separately inserting the TC tag at six sites in the capsid protein, we found that only when we inserted the TC tag at the site of amino acids 27/28 (AA27/28, or TC27) could the genetically engineered ZIKV be rescued. Importantly, the TC27 ZIKV is characterized as replication and infection competent. After labeling the TC tag with the fluorescent biarsenical reagents, we visualized the dynamic nuclear import behavior of the capsid protein. In addition, using the single-particle tracking technology, we acquired real-time imaging evidence that ZIKV moved along the cellular filopodia and entered into the cytoplasm via endocytosis. Thus, we provide a feasible strategy to generate a replication-competent TC-tagged ZIKV for real-time imaging, which should greatly facilitate the study of ZIKV-host interactions in living cells. IMPORTANCE Zika virus (ZIKV) is the mosquito-borne enveloped flavivirus that causes microcephaly in neonates. While real-time imaging plays a critical role in dissecting viral biology, no fluorescent, genetically engineered ZIKV for single-particle tracking is currently available. Here, we generated a replication-competent genetically engineered ZIKV by introducing the tetracysteine (TC) tag into its capsid protein. After labeling the TC tag with the fluorescent biarsenical reagents, we visualized the nuclear import behavior of the capsid protein and the endocytosis process of single ZIKV particle. Taken together, these results demonstrate a fluorescent labeling strategy to track the ZIKV-host interactions at both the protein level and the viral particle level. Our replication-competent TC27 ZIKV should open an avenue to study the ZIKV-host interactions and may provide applications for antiviral screening.

Reprogramming of red blood cell metabolism in Zika virus-infected donors.

Catala, A., Stone, M., Busch, M., D'Alessandro, A.
14-03-2022
Transfusion
https://doi.org/10.1111/trf.16851

Diseases caused by arthropod-borne viruses remain a burden to global health; in particular, Zika virus (ZIKV) has been reported in 87 countries and territories. In healthy blood donors, ZIKV RNA can be detected in red blood cells (RBCs) months after infection, clearance of detectable nucleic acid in plasma, and seroconversion. However, little information is available on the impact of ZIKV infection to metabolism. We applied mass spectrometry-based metabolomics and lipidomics approaches to investigate the impact of ZIKV infection on RBCs over the course of infection. ZIKV-infected blood donors (n = 25) were identified through molecular and serologic methods, which included nucleic acid amplification testing and real-time polymerase chain reaction (PCR) for detection of ZIKV RNA and enzyme-linked immunosorbent assay (ELISA) for detection of flavivirus-specific IgM and IgG. In ZIKV RNA-positive donors, we observed lower glucose and lactate levels, and higher levels of ribose phosphate, suggestive of the activation of the pentose phosphate pathway. The top pathways altered in RBCs from ZIKV-IgM-positive donors include amino acid metabolism and biosynthesis, fatty acid metabolism and biosynthesis, linoleic acid and arachidonate metabolism and glutathione metabolism. RBCs from ZIKV-infected donors had increased levels of early glycolytic metabolites, and higher levels of metabolites of the pentose phosphate pathway. Alterations in acyl-carnitine and fatty acid metabolism are consistent with impaired membrane lipid homeostasis in RBCs from ZIKV IgM positive donors. RBC from healthy blood donors who had been infected by ZIKV are characterized by long-lasting metabolic alterations even months after infection has resolved.

Drug repurposing in silico screening platforms.

Mullins, J.
14-03-2022
Biochem Soc Trans
https://pubmed.ncbi.nlm.nih.gov/35285479

Over the last decade, for the first time, substantial efforts have been directed at the development of dedicated in silico platforms for drug repurposing, including initiatives targeting cancers and conditions as diverse as cryptosporidiosis, dengue, dental caries, diabetes, herpes, lupus, malaria, tuberculosis and Covid-19 related respiratory disease. This review outlines some of the exciting advances in the specific applications of in silico approaches to the challenge of drug repurposing and focuses particularly on where these efforts have resulted in the development of generic platform technologies of broad value to researchers involved in programmatic drug repurposing work. Recent advances in molecular docking methodologies and validation approaches, and their combination with machine learning or deep learning approaches are continually enhancing the precision of repurposing efforts. The meaningful integration of better understanding of molecular mechanisms with molecular pathway data and knowledge of disease networks is widening the scope for discovery of repurposing opportunities. The power of Artificial Intelligence is being gainfully exploited to advance progress in an integrated science that extends from the sub-atomic to the whole system level. There are many promising emerging developments but there are remaining challenges to be overcome in the successful integration of the new advances in useful platforms. In conclusion, the essential component requirements for development of powerful and well optimised drug repurposing screening platforms are discussed.

Anti-inflammatory, anti-angiogenetic and antiviral activities of dammarane-type triterpenoid saponins from the roots of *Panax notoginseng*.

Zheng, Y., Fan, C., Chen, Y., Quan, J., Shi, L., Tian, C., Shang, X., Xu, N., Ye, W., Yu, L., Liu, J.
21-03-2022
Food Funct
https://doi.org/10.1039/d1fo04089h

Panax notoginseng has been used both as a traditional medicine and as a functional food for hundreds of years in Asia. However, the active constituents from *P. notoginseng* and their pharmacologic properties still need to be further explored. In this study, one new dammarane-type triterpenoid saponin (1), along with fourteen known analogs (2-15) were isolated and identified from the roots of *P. notoginseng*. The anti-inflammatory, anti-angiogenetic and anti-dengue virus effects of these isolated compounds were further evaluated. Compounds 1, 3, 5-7 and 10-12 exerted anti-inflammatory effects in two different zebrafish inflammatory models. Among them, 11, with the most significant activities, alleviated the inflammatory response by blocking the MyD88/NF-κB and STAT3 pathways. Moreover, compound 15 showed anti-angiogenetic activities in Tg(*fli1:EGFP*) and Tg(*flk1:GFP*) zebrafish, while 3 and 5 only inhibited angiogenesis in Tg(*fli1:EGFP*) zebrafish. Additionally, compounds 1, 3, 6, 8, 9 and 12 suppressed the replication of dengue virus either at the viral adsorption and entry stages or at the intracellular replication step. In conclusion, these findings enrich knowledge of the diversity of saponins in *P. notoginseng* and suggest that the dammarane-type triterpenoid saponins from *P. notoginseng* may be developed as potential functional foods to treat inflammation, angiogenesis or dengue-related diseases.

Recent Progress in Graphene- and Related Carbon-Nanomaterial-based Electrochemical Biosensors for Early Disease Detection.

Revue de littérature

Fahmy, H., Abu Serea, E., Salah-Eldin, R., Al-Hafiry, S., Ali, M., Shalan, A., Lanceros-Méndez, S.
01-03-2022
ACS Biomater Sci Eng
https://doi.org/10.1021/acsbiomaterials.1c00710

Graphene- and carbon-based nanomaterials are key materials to develop advanced biosensors for the sensitive detection of many biomarkers owing to their unique properties. Biosensors have attracted increasing interest because they allow efficacious, sensitive, selective, rapid, and low-cost diagnosis. Biosensors are analytical devices based on receptors for the process of detection and transducers for response measuring. Biosensors can be based on electrochemical, piezoelectric, thermal, and optical transduction mechanisms. Early virus identification provides critical information about potentially effective and selective therapies, extends the therapeutic window, and thereby reduces morbidity. The sensitivity and selectivity of graphene can be amended via functionalizing it or conjoining it with further materials. Amendment of the optical and electrical features of the hybrid structure by introducing appropriate functional groups or counterparts is especially appealing for quick and easy-to-use virus detection. Various techniques for the electrochemical detection of viruses depending on antigen-antibody interactions or DNA hybridization are discussed in this work, and the reasons behind using graphene and related carbon nanomaterials for the fabrication are presented and discussed. We review the existing state-of-the-art directions of graphene-based classifications for detecting DNA, protein, and hormone biomarkers and summarize the use of the different biosensors to detect several diseases, like cancer, Alzheimer's disease, and diabetes, to sense numerous viruses, including SARS-CoV-2, human immunodeficiency virus, rotavirus, Zika virus, and hepatitis B virus, and to detect the recent pandemic virus COVID-19. The general concepts, mechanisms of action, benefits, and disadvantages of advanced virus biosensors are discussed to afford beneficial evidence of the creation and manufacture of innovative virus biosensors. We emphasize that graphene-based nanomaterials are ideal candidates for electrochemical biosensor engineering due to their special and tunable physicochemical properties.

Oncolytic Zika virus promotes intratumoral T cell infiltration and improves immunotherapy efficacy in glioblastoma.

Chen, L., Zhou, C., Chen, Q., Shang, J., Liu, Z., Guo, Y., Li, C., Wang, H., Ye, Q., Li, X., Zu, S., Li, F., Xia, Q., Zhou, T., Li, A., Wang, C., Chen, Y., Wu, A., Qin, C., Man, J.
01-02-2022
Mol Ther Oncolytics
https://doi.org/10.1016/j.omto.2022.01.011

Glioblastoma (GBM) is the deadliest primary brain tumor and is generally resistant to immunotherapy because of severe dysfunction of T cells. Novel treatment options are critically needed to overcome the immunotherapy resistance of GBM. Here we demonstrate that Zika virus (ZIKV) treatment improves the efficacy of anti-PD ligand 1 (PD-L1) immunotherapy in GBM. We found that ZIKV induces a strong pro-inflammatory response and increases $CD4^+$ and $CD8^+$ T cell intratumoral infiltration and activation in GBM mouse models. ZIKV treatment of mice bearing GBM tumors inhibits tumor growth and prolongs survival. These therapeutic effects of ZIKV on GBM tumors are negated in mice depleted of T cells. Moreover, ZIKV dramatically promotes activation of the type I interferon signaling pathway in GBM cells. ZIKV treatment potently sensitizes GBM to PD-L1 blockade and provides significant and durable survival benefits. Our findings reveal that ZIKV overcomes the resistance of GBM to immune checkpoint blockade, which may lead to therapeutic applications of ZIKV in individuals with GBM receiving immunotherapy.

Synthesis and antiviral activities of quinazolinamine-coumarin conjugates toward chikungunya and hepatitis C viruses.

Hwu, J., Kapoor, M., Gupta, N., Tsay, S., Huang, W., Tan, K., Hu, Y., Lyssen, P., Neyts, J.
01-02-2022
Eur J Med Chem
https://pubmed.ncbi.nlm.nih.gov/35176562

Development of new drugs with broad-spectrum to combat RNA viruses would be beneficial to mankind but faces a great challenge. We designed and efficiently synthesized a series of quinazolin-4-amine-SCH_2-coumarin conjugated compounds. Our data of the virus-cell-based assay show five new conjugates inhibit chikungunya virus with EC_{50} values as potent as 1.96 μM and two conjugates inhibit hepatitis C virus with EC_{50} values as low as 16.6 μM. These conjugates possess a xylene substituent at the C-4 amino group of quinazoline and a t-butyl substituent at the C-6' position of coumarin.

Cellulose Hydrogels Containing Geraniol and Icaridin Encapsulated in Zein Nanoparticles for Arbovirus Control.

Rogerio, C., Carvalho Abrantes, D., de Oliveira, J., Ribeiro de Araújo, D., Germano da Costa, T., de Lima, R., Fernandes Fraceto, L.
15-02-2022
ACS Appl Bio Mater
https://doi.org/10.1021/acsabm.1c01286

The most important arboviruses are those that cause dengue, yellow fever, chikungunya, and Zika, for which the main vector is the *Aedes aegypti* mosquito. The use of repellents is an important way to combat mosquito-borne pathogens. In this work, a safe method of protection employing a repellent was developed based on a slow release system composed of zein nanoparticles containing the active agents icaridin and geraniol incorporated in a cellulose gel matrix. Analyses were performed to characterize the nanoparticles and the gel formulation. The nanoparticles containing the repellents presented a hydrodynamic diameter of 229 ± 9 nm, polydispersity index of 0.38 ± 0.10, and zeta potential of +29.4 ± 0.8 mV. The efficiencies of encapsulation in the zein nanoparticles exceeded 85% for icaridin and 98% for geraniol. Rheological characterization of the gels containing nanoparticles and repellents showed that the viscoelastic characteristic of hydroxypropylmethylcellulose gel was preserved. Release tests demonstrated that the use of nanoparticles in combination with the gel matrix led to improved performance of the formulations. Atomic force microscopy analyses enabled visualization of the gel network containing the nanoparticles. Cytotoxicity assays using 3T3 and HaCaT cell cultures showed low toxicity profiles for the active agents and the nanoparticles. The results demonstrated the potential of these repellent systems to provide prolonged protection while decreasing toxicity.

Novel and Broadly Applicable Microsatellite Markers in Identified Chromosomes of the Philippine Dengue Mosquitoes, Aedes aegypti (Diptera: Culicidae).

Labiros, D., Catalig, A., Ymbong, R., Sakuntabhai, A., Lluisma, A., Edillo, F.
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J Med Entomol
https://doi.org/10.1093/jme/tjab194

Dengue is the leading arboviral infection in the Philippines. Its endemicity in the country is due to the presence of its primary mosquito vector, Aedes aegypti (L.). This species has limited microsatellite markers. This study characterized microsatellite markers screened in silico from intergenic regions of the updated reference genome of Ae. aegypti from Liverpool, U.K. Criteria for good markers are: polymorphic, inherited in a Mendelian codominant manner, no null alleles, selectively neutral, randomly associated, and broadly applicable across different regions. Genotypes were scored using ABI Peak Scanner and were screened for the presence of null alleles. Hardy-Weinberg equilibrium, linkage disequilibrium, and robustness of the markers were determined by GENEPOP using Ae. aegypti samples from selected highland and lowland sites (n = 30 each) in the Philippines and outgroups (Thailand and Vietnam). Mendelian codominant inheritance was examined using F1 offspring of Ae. aegypti family (n = 30 each) derived from samples collected from Cebu city highlands and Maramag, Bukidnon. From the 63 randomly selected markers, nine were polymorphic. Two markers (Aaeg1-3D of chromosome 1 and Aaeg3-4C of chromosome 3) satisfied all criteria, hence, are good broadly useful microsatellite markers. Two other markers (Aaeg2-2E of chromosome 2 and Aaeg3-2A of chromosome 3) met all criteria but deviated from Mendelian codominant inheritance. These new markers of the Philippine Ae. aegypti with their chromosomal locations relative to the other published markers are presented, and will ultimately be useful in a variety of population genetic studies of Ae. aegypti to protect the public health.

Biology and Transmission Dynamics of Aedes flavivirus.

Peinado, S., Aliota, M., Blitvich, B., Bartholomay, L.
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J Med Entomol
https://doi.org/10.1093/jme/tjab197

Aedes albopictus (Skuse) and Aedes aegypti (Linnaeus) (Diptera: Culicidae) mosquitoes transmit pathogenic arthropod-borne viruses, including dengue, chikungunya, and Zika viruses, with significant global health consequences. Both Ae. albopictus and Ae. aegypti also are susceptible to Aedes flavivirus (AEFV), an insect-specific flavivirus (ISF) first isolated in Japan from Ae. albopictus and Ae. flavopictus. ISFs infect only insect hosts and evidence suggests that they are maintained by vertical transmission. In some cases, ISFs interfere with pathogenic flavivirus infection, and may have potential use in disease control. We explored the host range

of AEFV in 4 genera of mosquitoes after intrathoracic injection and observed greater than 95% prevalence in the species of Aedes and Toxorhynchites tested. Anopheles and Culex species were less permissive to infection. Vertical transmission studies revealed 100% transovarial transmission and a filial infection rate of 100% for AEFV in a persistently-infected colony of Ae. albopictus. Horizontal transmission potential was assessed for adult and larval mosquitoes following per os exposures and in venereal transmission experiments. No mosquitoes tested positive for AEFV infection after blood feeding, and infection with AEFV after sucrose feeding was rare. Similarly, 2% of adult mosquitoes tested positive for AEFV after feeding on infected cells in culture as larvae. Venereal transmission of AEFV was most frequently observed from infected males to uninfected females as compared with transmission from infected females to uninfected males. These results reveal new information on the infection potential of AEFV in mosquitoes and expand our understanding of both vertical and horizontal transmission of ISFs.

Selective Estrogen Receptor Modulators Limit Alphavirus Infection by Targeting the Viral Capping Enzyme nsP1.

Mudgal, R., Bharadwaj, C., Dubey, A., Choudhary, S., Nagarajan, P., Aggarwal, M., Ratra, Y., Basak, S., Tomar, S.
18-01-2022
Antimicrob Agents Chemother
https://doi.org/10.1128/AAC.01943-21

Alphaviruses cause animal or human diseases that are characterized by febrile illness, debilitating arthralgia, or encephalitis. Selective estrogen receptor modulators (SERMs), a class of FDA-approved drugs, have been shown to possess antiviral activities against multiple viruses, including hepatitis C virus, Ebola virus, dengue virus, and vesicular stomatitis virus. Here, we evaluated three SERM compounds, namely, 4-hydroxytamoxifen, tamoxifen, and clomifene, for plausible antiviral properties against two medically important alphaviruses, chikungunya virus (CHIKV) and Sindbis virus (SINV). In cell culture settings, these SERMs displayed potent activity against CHIKV and SINV at nontoxic concentrations with 50% effective concentration (EC_{50}) values ranging between 400 nM and 3.9 μM. Further studies indicated that these compounds inhibit a postentry step of the alphavirus life cycle, while enzymatic assays involving purified recombinant proteins confirmed that these SERMs target the enzymatic activity of nonstructural protein 1 (nsP1), the capping enzyme of alphaviruses. Finally, tamoxifen treatment restrained CHIKV growth in the infected mice and diminished musculoskeletal pathologies. Combining biochemical analyses, cell culture-based studies, and *in vivo* analyses, we strongly argue that SERM compounds, or their derivatives, may provide for attractive therapeutic options against alphaviruses.

Protocol for *in utero* injection to investigate Zika virus-related fetal microcephaly in mice.

Dong, S., Xie, X., Chen, Y., Long, G., Liang, Q., Zhao, Z., Zeng, J.
22-12-2021
STAR Protoc
https://doi.org/10.1016/j.xpro.2021.101057

Zika virus (ZIKV) is linked to congenital defects including microcephaly. An infection model that can recapitulate most microcephaly-related phenotypes is crucial for understanding ZIKV pathogenesis. Here, we present a protocol to generate ZIKV from an infectious clone through a reverse genetic system and subsequently perform embryonic brain infection with the rescued ZIKV in pregnant mice. We optimized several aspects of the procedures including virus rescue and *in utero* injection. This protocol facilitates reproducible investigation of virus-induced cortical development defects. For complete details on the use and execution of this protocol, please refer to Zeng et al. (2020).

Ecological Characterization of Mosquitoes (Diptera: Culicidae) at the Southern Coast of Mar Chiquita Lake, Argentina.

Visintin, A., Laurito, M., Grech, M., Estallo, E., Grillet, M., Almeida, F., Almirón, W.
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J Med Entomol
https://doi.org/10.1093/jme/tjab186

In the southern coast of Mar Chiquita Lake, central Argentina, mosquitoes affect public health and community livelihood, since they transmit pathogens to human beings causing diseases such as malaria, filariasis, encephalitis, yellow fever, and dengue, among others, and have a negative effect on cattle farming as well. To characterize the structure of the mosquito assemblage of the region, we determined the species composition and diversity, the temporal distribution of different species, and the patterns of species richness, abundance, and diversity across seasons. We collected adult mosquitoes over a two-year period (October 2004-September 2006) by means of CDC light traps baited with CO2 from 18:00 to 08:00 h during the warm season (October-April) and from 12:00 h to 18:00 h in the cold season (May-September). A total of 71,501 individuals from 30 species were collected, with Culex Linnaeus and Aedes Meigen genera representing more than 98% of collected specimens (61.5% and 37.3%, respectively). The higher values of richness and abundance of Culicidae were registered in warm seasons compared to cold seasons. Chao1 estimates suggested that more than 90% of the species were detected in all seasons. Mosquito abundance distribution fit the logarithmic series and log-normal models. Aedes albifasciatus (Macquart), Ae. scapularis (Rondani), Culex interfor Dyar, Cx. saltanensis Dyar, and Cx. dolosus (Lynch Arribálzaga), vectors incriminated in arbovirus transmission, were abundant year-round, with Cx. saltanensis and Cx. dolosus most prevalent in cold seasons. Further studies are needed to assess the role of these species in arbovirus transmission in this region of central Argentina.

RAGE

Rabies anterograde monosynaptic tracing allows identification of postsynaptic circuits receiving distinct somatosensory input.

Pimpinella, S., Sauve, I., Dietrich, S., Zampieri, N.
16-03-2022
Neuroscience
https://pubmed.ncbi.nlm.nih.gov/35306143

Somatosensory neurons detect vital information about the environment and internal status of the body, such as temperature, touch, itch, and proprioception. The circuit mechanisms controlling the coding of somatosensory information and the generation of appropriate behavioral responses are not clear yet. In order to address this issue, it is important to define the precise connectivity patterns between primary sensory afferents dedicated to the detection of different stimuli and recipient neurons in the central nervous system. In this study we describe and validate a rabies tracing approach for mapping mouse spinal circuits receiving sensory input from distinct, genetically defined, modalities. We analyzed the anatomical organization of spinal circuits involved in coding of thermal and mechanical stimuli and showed that somatosensory information from distinct modalities is relayed to partially overlapping ensembles of interneurons displaying stereotyped laminar organization, thus highlighting the importance of positional features and population coding for the processing and integration of somatosensory information.

Risk factors for death and illness in dogs imported into the United States, 2010-2018.

Pieracci, E., Maskery, B., Stauffer, K., Gertz, A., Brown, C.
15-03-2022
Transbound Emerg Dis
https://doi.org/10.1111/tbed.14510

CDC estimates 1 million dogs are imported into the United States annually. With the movement of large numbers of animals into the United States the risk of disease importation, especially emerging diseases, and animal welfare issues are of concern. Dogs that arrive to the United States ill or dead are investigated by public health authorities to ensure dogs are not infected with diseases of concern (such as rabies). We identified factors associated with illness and death in imported dogs and estimated the initial investigation cost to public health authorities. Dog importation data from the CDC's Quarantine Activity Reporting System were reviewed from 2010-2018. The date of entry, country of origin, port of entry, transportation method, and breed were extracted to examine factors associated with illness and death in dogs during international travel. Costs for public health investigations were estimated from data collected by the Bureau of Labor Statistics and Office of Personal Management. Death or illness was more likely to occur in brachycephalic breeds (aOR = 3.88, 95%CI 2.74-5.51). Transportation of dogs via cargo (aOR = 2.41, 95%CI 1.57-3.70) or as checked baggage (aOR = 5.74, 95%CI 3.65-9.03) were also associated with death or illness. On average, 19 dog illnesses or deaths were reported annually from 2010-2018. The estimated annual cost to public health authorities to conduct initial public health assessments ranged from $2,071-$104,648. Current regulations do not provide adequate resources or mechanisms to monitor the rates of morbidity and mortality of imported dogs. There are growing attempts to assess animal welfare and communicable disease importation risks. However, because the responsibility for dogs' health and wellbeing is overseen by multiple agencies it is challenging to coordinate implementation and enforcement measures. A joint federal agency approach to identify interventions that reduce dog morbidity and mortality during flights while continuing to protect U.S. borders from public health and foreign animal disease threats could be beneficial. This article is protected by copyright. All rights reserved.

Molecular analyses of human rabies virus associated with encephalitis in two children in Gabon

N'dilimabaka, N., Mavoungou, D. K., Soami, V., Bohou Kombila, L., Mouguiama, R. M., Mondjo, A., Mangombi Pambou J. B., Ngoma, J. F., Ovengue, F. C., Alilangori, T. P., Koko, J., Bitegue Methe, L., Mboumba, H. M., Sima Zue, A., Edjo Nkili, G., Lekana-Douki, S. E., Maganga, G. D.
2022
IJID Regions
https://doi.org/10.1016/j.ijregi.2022.01.006

Rabies is a zoonotic neurological life-threatening neglected tropical disease present worldwide, and Gabon is listed as an endemic country. However, despite strong clinical suspicion in humans and molecular confirmation of rabies virus (RABV) infections in dogs for several decades, no molecularly confirmed human case in Gabon has ever been reported. In this study, we describe two cases of human rabies and provide the first molecular diagnostic report on suspected human rabies cases in Gabon. Our results showed that the RABVs isolated from the patients are closely related to other RABV strains belonging to the African 1A subclade in the Cosmopolitan lineage isolated more than 20 years ago from Gabonese dog brains, suggesting that only this species circulates in the country. Because both patients had a history of dog bites a few weeks before symptom onset and the main causative agent of human rabies worldwide is dog-associated RABV, we conclude that dogs are likely to be the source of human infection in this study.

TRACHOME

Genomics of Ocular Chlamydia trachomatis After 5 Years of SAFE Interventions for Trachoma in Amhara, Ethiopia.

Pickering, H., Chernet, A., Sata, E., Zerihun, M., Williams, C., Breuer, J., Nute, A., Haile, M., Zeru, T., Tadesse, Z., Bailey, R., Callahan, E., Holland, M., Nash, S.

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J Infect Dis

https://doi.org/10.1093/infdis/jiaa615

To eliminate trachoma as a public health problem, the World Health Organization recommends the SAFE (surgery, antibiotics, facial cleanliness, and environmental improvement) strategy. As part of the SAFE strategy in the Amhara Region, Ethiopia, the Trachoma Control Program distributed >124 million doses of antibiotics between 2007 and 2015. Despite this, trachoma remained hyperendemic in many districts and a considerable level of Chlamydia trachomatis (Ct) infection was evident. We utilized residual material from Abbott m2000 Ct diagnostic tests to sequence 99 ocular Ct samples from Amhara and investigated the role of Ct genomic variation in continued transmission of Ct. Sequences were typical of ocular Ct at the whole-genome level and in tissue tropism-associated genes. There was no evidence of macrolide resistance in this population. Polymorphism around the ompA gene was associated with village-level trachomatous inflammation-follicular prevalence. Greater ompA diversity at the district level was associated with increased Ct infection prevalence. We found no evidence for Ct genomic variation contributing to continued transmission of Ct after treatment, adding to evidence that azithromycin does not drive acquisition of macrolide resistance in Ct. Increased Ct infection in areas with more ompA variants requires longitudinal investigation to understand what impact this may have on treatment success and host immunity.

ULCERE DE BURULI

PIAN

Yaws recurrence in children at continued risk of infection.

González-Beiras, C., Marks, M., Quintó, L., Gavilán, S., Kolmau, R., Ubals, M., Vall-Mayans, M., Mitjà, O.

21-03-2022

PLoS Negl Trop Dis

https://doi.org/10.1371/journal.pntd.0010197

In yaws-endemic areas, children with Treponema pallidum subsp. pertenue infection may suffer recurrent episodes due to either reinfection or relapse. However, the possibility of infection with other cutaneous ulcer causative agents and difficulties in interpreting standard laboratory results challenges the estimation of yaws recurrence rates. We estimated the rates of yaws recurrences in the Lihir Island (Papua New Guinea) using two approaches: passive surveillance based on a retrospective screening of electronic medical records of cutaneous ulcers diagnosed using serological testing between 2005 and 2016, and active surveillance conducted during a cross-sectional prevalence study which included PCR analyses of ulcers of all suspected cases of yaws. The risk of recurrent infection was assessed based on data from the passive surveillance analysis and using two Cox regression models (crude and multivariate), stratified by year of index episode. Data gathered from the active surveillance was used to characterize the recurrences and no hypothesis testing was performed. The electronic medical records included 6,125 patients (7,889 ulcer episodes) with documented serological results of cutaneous ulcers of which1,486 were diagnosed with yaws. Overall, 1,246/6,125 patients (20.3%) presented more than once with a cutaneous ulcer, and 103/1,486 (6.7%) patients had multiple episodes of yaws. The risk of yaws recurrence significantly increased with age and was higher in patients with ≥3 recurrent episodes. In the active surveillance, we identified 50 individuals with recurrent cutaneous ulcer that had PCR results available for both the index and recurrent episode. Of 12 individuals with T. pallidum in the index ulcer, 8 (66%) had T. pallidum in subsequent assessments, relapse related to macrolide-resistance was identified in two of these cases. Our results confirm the need for active follow-up of yaws patients after treatment, particularly children and individuals with a history of recurrence.

LEPRE

Facial Tuberculoid Leprosy.

Parajuli, N., Shrestha, S.

21-03-2022

Am J Trop Med Hyg

https://doi.org/10.4269/ajtmh.21-0696

Initiatives to address leprosy as a human rights issue through the mandate of UN Special Rapporteur: Achievements and challenges.

Nanri, T.

17-03-2022

PLoS Negl Trop Dis

https://doi.org/10.1371/journal.pntd.0010201

Leprosy, or Hansen's disease, is one of the oldest infectious diseases in the world. It has long been associated with stigma and discrimination, but only in recent years has this aspect been formally recognized by the international community as a human rights issue. The UN Human Rights Council first adopted a resolution on leprosy in 2008, and this was later followed by a UN General Assembly resolution in 2010. Nonbinding principle and guidelines on elimination of discrimination against persons affected by leprosy and their family members accompanied the 2010 resolution, but these have yet to be fully implemented. In 2017, the Human Rights Council appointed a Special Rapporteur on leprosy to investigate the extent to which the principles and guidelines have been implemented, and her term was extended for a further 3 years in 2020. Considering the proper implementation of the principles and guidelines to be key to eliminating the discrimination that persons affected by leprosy and their families face in various parts of the world, this paper looks at the contribution the Special Rapporteur can make. Based on an assessment of her activities to date, it concludes that the Special Rapporteur has actively worked to build networks with persons affected by leprosy and related organizations and gain their trust, but has faced challenges in organizing official country visits. It goes on to analyze what sort of legacy the Special Rapporteur should aim to leave behind after completing her second term and how she can go about doing so in the time remaining. To this end, it makes 5 suggestions: (1) gather information systematically on the actual situation of discrimination; (2) compile a collection of success stories; (3) ensure that there is consistency between legally binding international covenants and treaties and the principles and guidelines; (4) present proposals for concrete actions that can be taken after the Special Rapporteur's second term ends; and (5) initiate a feasibility study on creating an "index" and "indicators" to measure the current status of stigma and discrimination and the extent to which the principles and guidelines have been implemented.

Dr. Betty Clements: Breaking Gender Barriers in the Air Force and Neurology.

Coon, E., Smith, K., Boes, C.
15-03-2022
Neurology
https://pubmed.ncbi.nlm.nih.gov/35292557

Women currently make up 45.9% of neurology residents and fellows[1] although little is known about the individual women who broke gender barriers to train as neurologists. Grace Elizabeth "Betty" Clements (1918-1965) was the first woman trainee at the Mayo Clinic to practice neurology and later became a founder of the Barrow Neurological Institute. Prior to paving the way for future women trainees in neurology, she served as a Women Airforce Service Pilot (WASP) including flying atomic bomb planning missions during World War II. Following the war, her path to medicine included volunteering in the American Red Cross in the Philippines where she treated patients with Hansen's disease (leprosy). Clements returned to her home state to complete medical school at the University of Nebraska before seeking neurologic training at the Mayo Clinic in 1954. Following additional training at Queen Square, she became a founder of the Barrow Neurological Institute in Phoenix, Arizona. Many early women in neurology have remarkable backgrounds that have equipped them for their career in medicine which Clements exemplifies.

TRYPANOSOMES (TRYPANOSOMIASE ET MALADIE DE CHAGAS)

Trypanosoma brucei: Metabolomics for analysis of cellular metabolism and drug discovery.

Revue de littérature

Fall, F., Mamede, L., Schioppa, L., Ledoux, A., De Tullio, P., Michels, P., Frédérich, M., Quetin-Leclercq, J.
19-03-2022
Metabolomics
https://doi.org/10.1007/s11306-022-01880-0

Trypanosoma brucei is the causative agent of Human African Trypanosomiasis (also known as sleeping sickness), a disease causing serious neurological disorders and fatal if left untreated. Due to its lethal pathogenicity, a variety of treatments have been developed over the years, but which have some important limitations such as acute toxicity and parasite resistance. Metabolomics is an innovative tool used to better understand the parasite's cellular metabolism, and identify new potential targets, modes of action and resistance mechanisms. The metabolomic approach is mainly associated with robust analytical techniques, such as NMR and Mass Spectrometry. Applying these tools to the trypanosome parasite is, thus, useful for providing new insights into the sleeping sickness pathology and guidance towards innovative treatments. The present review aims to comprehensively describe the T. brucei biology and identify targets for new or commercialized antitrypanosomal drugs. Recent metabolomic applications to provide a deeper knowledge about the mechanisms of action of drugs or potential drugs against T. brucei are highlighted. Additionally, the advantages of metabolomics, alone or combined with other methods, are discussed. Compared to other parasites, only few studies employing metabolomics have to date been reported on Trypanosoma brucei. Published metabolic studies, treatments and modes of action are discussed. The main interest is to evaluate the metabolomics contribution to the understanding of T. brucei's metabolism.

Identifying regions for enhanced control of gambiense sleeping sickness in the Democratic Republic of Congo.

Huang, C., Crump, R., Brown, P., Spencer, S., Miaka, E., Shampa,

C., Keeling, M., Rock, K.
18-03-2022
Nat Commun
https://doi.org/10.1038/s41467-022-29192-w

Gambiense human African trypanosomiasis (sleeping sickness, gHAT) is a disease targeted for elimination of transmission by 2030. While annual new cases are at a historical minimum, the likelihood of achieving the target is unknown. We utilised modelling to study the impacts of four strategies using currently available interventions, including active and passive screening and vector control, on disease burden and transmission across 168 endemic health zones in the Democratic Republic of the Congo. Median projected years of elimination of transmission show only 98 health zones are on track despite significant reduction in disease burden under medical-only strategies (64 health zones if>90% certainty required). Blanket coverage with vector control is impractical, but is predicted to reach the target in all heath zones. Utilising projected disease burden under the uniform medical-only strategy, we provide a priority list of health zones for consideration for supplementary vector control alongside medical interventions.

Immature instars of three species of Rhodnius Stål, 1859 (Hemiptera, Reduviidae, Triatominae): morphology, morphometry, and taxonomic implications.

Lázari Cacini, G., de Oliveira, J., Belintani, T., Dos Santos Souza, É., Olaia, N., Pinto, M., da Rosa, J.
18-03-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05200-2

Among the 18 genera of the Triatominae subfamily, three stand out for their diversity and epidemiological importance: Triatoma, Panstrongylus, and Rhodnius. Rhodnius includes 21 species that can transmit Trypanosoma cruzi (the etiological agent of Chagas disease, also known as American trypanosomiasis) and Trypanosoma rangeli. The Rhodnius prolixus complex comprises seven species, including Rhodnius marabaensis, Rhodnius prolixus, and Rhodnius robustus, which occur in the northern region of Brazil. Since both adults and immatures can carry T. cruzi, in this study the five nymphal instars of the three species mentioned were dorsally characterized. Using microscopy, morphometrics, and geometric morphometrics, the present work measures and describes the morphological characters of the five nymphal instars of R. marabaensis, R. prolixus, and R. robustus. The study enabled the characterization of all five nymphal instars, as well as the distinction between the three species in each of their instars. The morphological, morphometrics of the head, thorax, and abdomen and geometric morphometrics studies of the head enabled the specific distinction of these three species in all five instars.

Repositioning of a Diaminothiazole Series Confirmed to Target the Cyclin-Dependent Kinase CRK12 for Use in the Treatment of African Animal Trypanosomiasis.

Smith, A., Wall, R., Patterson, S., Rowan, T., Rico Vidal, E., Stojanovski, L., Huggett, M., Hampton, S., Thomas, M., Corpas Lopez, V., Gillingwater, K., Duke, J., Napier, G., Peter, R., Vitouley, H., Harrison, J., Milne, R., Jeacock, L., Baker, N., Davis, S., Simeons, F., Riley, J., Horn, D., Brun, R., Zuccotto, F., Witty, M., Wyllie, S., Read, K., Gilbert, I.
18-03-2022
J Med Chem
https://doi.org/10.1021/acs.jmedchem.1c02104

African animal trypanosomiasis or nagana, caused principally by infection of the protozoan parasites *Trypanosoma congolense* and *Trypanosoma vivax,* is a major problem in cattle and other livestocks in sub-Saharan Africa. Current treatments are threatened by the emergence of drug resistance and there is an urgent need for new, effective drugs. Here, we report the repositioning of a compound series initially developed for the treatment of human African trypanosomiasis. A medicinal chemistry program, focused on deriving more soluble analogues, led to development of a lead compound capable of curing cattle infected with both *T. congolense* and *T. vivax* via intravenous dosing. Further optimization has the potential to yield a single-dose intramuscular treatment for this disease. Comprehensive mode of action studies revealed that the molecular target of this promising compound and related analogues is the cyclin-dependent kinase CRK12.

Correction: Comparative dissection of the peripheral olfactory system of the Chagas disease vectors Rhodnius prolixus and Rhodnius brethesi.

Campetella, F., Ignell, R., Beutel, R., Hansson, B., Sachse, S.
16-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010294

[This corrects the article DOI: 10.1371/journal.pntd.0009098.].

The health-related quality of life in patients with Chagas disease: the state of the art.

Almeida, I., Oliveira, L., Figueiredo, P., Oliveira, R., Damasceno, T., Silva, W., Oliveira, L., Ávila, M., Lima, V., Lages, A., Mediano, M., Rocha, M., Costa, H.
14-03-2022
Rev Soc Bras Med Trop
https://pubmed.ncbi.nlm.nih.gov/35293550

Chagas disease (CD) is a neglected tropical disease associated with poverty in which patients are surrounded by stigma. These factors can contribute to reducing health-related quality of life (HRQoL). Therefore, a broad discussion of HRQoL in the CD population is required. This study aimed to discuss the main findings of HRQoL in patients with CD, focusing on the association between sociodemographic and lifestyle factors,

echocardiographic and functional determinants, and the effect of non-invasive interventions on HRQoL. A literature search of the MEDLINE, Web of Science, CINAHL, Scopus, and LILACS databases was performed with no data or language restrictions. Twenty-two articles were included in this meta-analysis. In general, HRQoL is worse in patients with CD than in healthy individuals, particularly in the presence of cardiovascular and/or gastrointestinal symptoms. Sex, age, functional class, level of physical activity, healthy habits, and medications received could affect HRQoL. Among the echocardiographic and functional determinants, decreased systolic function seems to negatively affect HRQoL. No association with the peak oxygen uptake was observed in the maximal tests. By contrast, well-tolerated field tests with submaximal intensities were associated with HRQoL. Both pharmaceutical care and exercise training have a positive effect on the HRQoL of patients with Chagas cardiomyopathy, and the mental component can be a prognostic marker in this population. In conclusion, assessment of HRQoL can provide important information about the health status of patients with CD, and its use in clinical practice is warranted.

Perspectives for a new drug candidate for Chagas disease therapy.

Soeiro, M.
14-03-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35293439

Chagas disease (CD), a neglected tropical illness caused by the protozoan Trypanosoma cruzi, affects more than 6 million people mostly in poor areas of Latin America. CD has two phases: an acute, short phase mainly oligosymptomatic followed to the chronic phase, a long-lasting stage that may trigger cardiac and/or digestive disorders and death. Only two old drugs are available and both present low efficacy in the chronic stage, display side effects and are inactive against parasite strains naturally resistant to these nitroderivatives. These shortcomings justify the search for novel therapeutic options considering the target product profile for CD that will be presently reviewed besides briefly revisiting the data on phosphodiesterase inhibitors upon T. cruzi.

Repositioning drug strategy against Trypanosoma cruzi: lessons learned from HIV aspartyl peptidase inhibitors.

Sangenito, L., d'Avila-Levy, C., Branquinha, M., Santos, A.
16-03-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35293428

Chagas disease (CD) is an old neglected problem that affects more than 6 million people through 21 endemic countries in Latin America. Despite being responsible for more than 12 thousand deaths per year, the disease disposes basically of two drugs for its treatment, the nitroimidazole benznidazole and the nitrofuran nifurtimox. However, these drugs have innumerous limitations that greatly reduce the chances of cure. In Brazil, for example, only benznidazole is available to treat CD patients. Therefore, some proof-of-concept phase II clinical trials focused on improving the current treatment with benznidazole, also comparing it with repositioned drugs or combining them. Indeed, repositioning already marketed drugs in view of combating neglected tropical diseases is a very interesting approach in the context of decreased time for approval, better treatment options and low cost for development and implementation. After the introduction of human immunodeficiency virus aspartyl peptidase inhibitors (HIV-PIs) in the treatment of acquired immune deficiency syndrome (AIDS), the prevalence and incidence of parasitic, fungal and bacterial co-infections suffered a marked reduction, making these HIV-PIs attractive for drug repositioning. In this line, the present perspective presents the promising and beneficial data concerning the effects of HIV-PIs on the clinically relevant forms of Trypanosoma cruzi (i.e., trypomastigotes and amastigotes) and also highlights the ultrastructural and physiological targets for the HIV-PIs on this parasite. Therefore, we raise the possibility that HIV-PIs could be considered as alternative treatment options in the struggle against CD.

Computational approaches towards the discovery and optimisation of cruzain inhibitors.

Revue de littérature

Santos, V., Ferreira, R.
16-03-2022
Mem Inst Oswaldo Cruz
https://pubmed.ncbi.nlm.nih.gov/35293427

The need to develop safer and more efficacious drugs to treat Chagas disease has motivated the search for cruzain inhibitors. Cruzain is the recombinant, truncated version of cruzipain, a cysteine protease from Trypanosoma cruzi with important roles during the parasite life cycle. Several computational techniques have been applied to discover and optimise cruzain inhibitors, providing a molecular basis to guide this process. Here, we review some of the most recent computational studies that provided important information for the design of cruzain inhibitors. Moreover, we highlight the diversity of applications of in silico techniques and their impact.

Chagas Disease, Up Close and Personal.

Revue de littérature

Dunavan, C.
14-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.22-0003

Development and Introduction of Fexinidazole into the Global Human African Trypanosomiasis Program.

Valverde Mordt, O., Tarral, A., Strub-Wourgaft, N.
15-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-1176

In this article, the authors show the strategy used to streamline the introduction of fexinidazole, the first all oral treatment of human African trypanosomiasis (HAT) caused by Trypanosoma brucei gambiense. The dose range was determined in phase 1 studies and a significant food effect was observed, which was tested with field-adapted meals. The pharmacokinetic profile required definition of a higher loading dosage for the first 4 days and administration of the daily dose together with a typical local meal to optimize product absorption and rapidly achieve drug steady state. This allowed for a combined phase II/III pivotal study directly after phase I trials. Partnerships with highly engaged actors from endemic country control programs and international research institutions started early through the HAT platform, building on an agreed target product profile (TPP), establishing a regulatory plan early and transparently including endemic countries in the research and data flow. A key element that enabled a quick start to access activities was preparing for World Health Organization guidelines early and starting the process prior to registration. Distribution plans were identified and supply was established from the start, by taking advantage of the existing supply agreement between the producers of all HAT drugs (Sanofi and Bayer) and the WHO. Pharmacovigilance and phase 4 studies were nested into wider implementation activities. Targeted sequential introduction into national programs was prioritized, based on medical need and epidemiologically updated information.

Identification, Characterization, and Synthesis of Natural Parasitic Cysteine Protease Inhibitors: Pentacitidins Are More Potent Falcitidin Analogues.

Brinkmann, S., Semmler, S., Kersten, C., Patras, M., Kurz, M., Fuchs, N., Hammerschmidt, S., Legac, J., Hammann, P., Vilcinskas, A., Rosenthal, P., Schirmeister, T., Bauer, A., Schäberle, T.
09-03-2022
ACS Chem Biol
https://doi.org/10.1021/acschembio.1c00861

Protease inhibitors represent a promising therapeutic option for the treatment of parasitic diseases such as malaria and human African trypanosomiasis. Falcitidin was the first member of a new class of inhibitors of falcipain-2, a cysteine protease of the malaria parasite *Plasmodium falciparum*. Using a metabolomics dataset of 25 *Chitinophaga* strains for molecular networking enabled identification of over 30 natural analogues of falcitidin. Based on MS/MS spectra, they vary in their amino acid chain length, sequence, acyl residue, and C-terminal functionalization; therefore, they were grouped into the four falcitidin peptide families A-D. The isolation, characterization, and absolute structure elucidation of two falcitidin-related pentapeptide aldehyde analogues by extensive MS/MS spectrometry and NMR spectroscopy in combination with advanced Marfey's analysis was in agreement with the in silico analysis of the corresponding biosynthetic gene cluster. Total synthesis of chosen pentapeptide analogues followed by in vitro testing against a panel of proteases revealed selective parasitic cysteine protease inhibition and, additionally, low-micromolar inhibition of α-chymotrypsin. The pentapeptides investigated here showed superior inhibitory activity compared to falcitidin.

Examination of multiple Trypanosoma cruzi targets in a new drug discovery approach for Chagas disease.

Revue de littérature

Beltran-Hortelano, I., Alcolea, V., Font, M., Pérez-Silanes, S.
01-02-2022
Bioorg Med Chem
https://pubmed.ncbi.nlm.nih.gov/35189560

Chagas disease (CD) is a centenarian neglected parasitosis caused by the protozoan Trypanosoma cruzi (T. cruzi). Despite the continuous efforts of many organizations and institutions, CD is still an important human health problem worldwide. A lack of a safe and affordable treatment has led drug discovery programmes to focus, for years, on the search for molecules enabling interference with enzymes that are essential for T. cruzi survival. In this work, the authors want to offer a brief overview of the different validated targets that are involved in diverse parasite pathways: glycolysis, sterol synthesis, the de novo biosynthesis of pyrimidine nucleotides, the degradative processing of peptides and proteins, oxidative stress damage and purine salvage and nucleotide synthesis and metabolism. Their structural aspects, function, active sites, etc. were studied and considered with the aim of defining molecular bases in the search for new effective treatments for CD. This review also compiles, as much as possible, all the inhibitors reported to date against these T. cruzi targets, serving as a reference for future research in this field.

Review of the Situation of Human African Trypanosomiasis in the Republic of Congo From the 1950s to 2020.

Bemba, I., Bamou, R., Lenga, A., Okoko, A., Awono-Ambene, P., Antonio-Nkondjio, C.
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J Med Entomol
https://doi.org/10.1093/jme/tjab225

Human African trypanosomiasis (HAT), despite considerable progress in the control, is still occurring in many countries in both west and central African regions. The HAT situation in the Republic of Congo has always been overshadowed by its neighbor the Democratic Republic of Congo where over 60% of all HAT cases occur. In the Republic of Congo, HAT cases have been significantly reduced to about 20 reported cases yearly and the disease is still prevalent in few foci across the country. Although continuous assessment of HAT situation in Congo is been led by the National Control Program for HAT,

research on the vector, parasite, and vector control has received little attention. Because there have not been enough reviews summarizing key findings from studies conducted so far, there is still a poor understanding of the global situation of HAT in Congo. In order to achieve sustainable elimination of HAT in Congo a deep appraisal of HAT situation is required. The present study provides a review of studies conducted on HAT in the republic of Congo since the 1950s to date in order to identify gaps in knowledge and help consolidate the gains and progress towards the elimination of sleeping sickness.

Distribution of Triatoma dimidiata sensu lato (Reduviidae: Triatominae) and Risk Factors Associated with Household Invasion in Northern Belize, Central America.

Caranci, A., Grieco, J., Achee, N., Hoel, D., Bautista, K., King, R., Stewart, V., Murphy, J., Masuoka, P., Olsen, C.

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J Med Entomol

https://doi.org/10.1093/jme/tjab227

To date, Triatoma dimidiata sensu lato [Reduviidae: Triatominae (Latreille 1811)] remains the sole vector species associated with Chagas disease transmission reported from Belize. Human infection data are limited for Belize and the disease transmission dynamics have not been thoroughly investigated, yet the likelihood of autochthonous transmission is supported by the widespread collection of infected vectors from within local households. Here, we report updated infection rates of the vector population and infestation rates for villages in north and central Belize. Overall, 275 households were enrolled in an ongoing vector surveillance program. Of the 41 insects collected, 25 were PCR positive for T. cruzi, indicating an infection rate as high as 60%. To further characterize the epidemiological risk of human-vector contact, determinants of household invasion were modeled. Local households were surveyed and characterized with respect to over 25 key factors that may be associated with household infestation by T. dimidiata s.l. While final models were not strongly predictive with respect to the risk factors that were surveyed, likely due to the low number of collection observations, the presence of domestic/peri-domestic dogs, nearby light sources, and household structure materials could be the focus of continued risk assessments. In northern Belize, this vector survey lends support to T. dimidiata s.l. inhabiting sylvatic settings as opposed to the classical paradigm of domiciliated vector populations. This designation has strong implications for the local level of human exposure risk which can help guide vector surveillance and control resources.

Detection of Trypansoma cruzi in Kissing Bugs (Hemiptera: Reduviidae: Triatominae) Collected Across Oklahoma.

Allen, K., Lineberry, M.

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J Med Entomol

https://doi.org/10.1093/jme/tjab211

Trypanosoma cruzi is the causative agent of Chagas disease in humans and dogs in the Americas. Transmission predominantly occurs via the feces of infected kissing bugs (Hemiptera: family Reduviidae; subfamily Triatominae) contaminating bite site wounds or mucous membranes. To better understand Chagas disease entomologic risk in Oklahoma, kissing bugs collected from within the state were tested for T. cruzi DNA. Data including county of insect collection, species and instar, and specific locations where specimens were found were collated. Triatomines were also tested by PCR to potentially identify DNA of vertebrate species on which specimens had recently fed. In total, 110 kissing bugs from 22 counties were tested. All triatomines were identified as Triatoma sanguisuga nymphs or adults, with the exception of one possible T. lecticularia adult. Trypanosoma cruzi DNA was detected in 22 (20%) triatomines from 12 counties spanning the state. The majority of T. cruzi PCR positive kissing bugs were found inside homes or associated structures (i.e., garages, porches). Vertebrate DNA was identified in 27 (24.5%) triatomines, with human DNA detected in 25 (92.6%) of these specimens, and canine and raccoon DNA detected in one specimen each (3.7%). Two specimens tested positive for both T. cruzi and human DNA and one specimen tested positive for both T. cruzi and raccoon DNA. Results from this study indicate that kissing bugs carrying T. cruzi are widespread in Oklahoma, that positive kissing bugs infest homes and associated structures, and that human-vector, canine-vector, and wildlife-vector contact all occur within the state.

Chemotaxonomy of Five South American Species of the Triatoma genus (Hemiptera: Reduviidae: Triatominae) Based on Their Cuticle Hydrocarbon Pattern.

Moriconi, D., Macedo-Lopes, C., Sartorio, A., Juárez, M., Girotti, J., Calderón-Fernández, G.

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J Med Entomol

https://doi.org/10.1093/jme/tjab199

The Triatoma sordida subcomplex traditionally included four triatomine species, T. sordida, Triatoma garciabesi, Triatoma guasayana, and Triatoma patagonica, distributed in the Southern Cone of South America. These species have a large intraspecific variability together with an overall similarity, making difficult to establish their taxonomic status. Many cytogenetic, morphometric, and molecular markers have been applied to address this. Recent studies have posed concerns on the inclusion of T. guasayana and T. patagonica within the subcomplex. Also, T. sordida from Argentina has been designed as a new species, Triatoma rosai. Using the cuticular hydrocarbon pattern as chemotaxonomic marker, the relationships among several populations of these species were analyzed by capillary gas chromatography and linear discriminant analysis along 25 collection sites in Argentina, Bolivia, Brazil, and Paraguay. T. sordida and T. rosai populations were differentially clustered in two CHC-based

groups: "Group 1" included T. sordida from Eastern Brazil, Eastern Paraguay, and the Bolivian populations from La Paz and Izozog G1; "Group 2" included T. rosai, and T. sordida from Izozog G2 (Bolivia), and Western Paraguay. Whereas T. garciabesi remained closely related to T. sordida and T. rosai, T. guasayana, and T. patagonica were clearly separated from the species of the T. sordida subcomplex. Our results agree with those from other several techniques suggesting that the taxonomy of the T. sordida subcomplex should be revised.

LEISHMANIOSE

emisynthetic triterpenes led to the generation of selective antitrypanosomal lead compounds.

Guilhon-Simplicio, F., Serrão, C., da Silva Pinto, A., Pacheco, P., Faria, R., da Rocha, D., Ferreira, V., Pereira-Junior, R., Matheeussen, A., Baán, A., Kiekens, F., de Meneses Pereira, M., Lima, E., De Winter, H., Cos, P.
21-03-2022
Chem Biol Drug Des
https://doi.org/10.1111/cbdd.14040

Triterpenes α,β-amyrin are naturally occurring molecules that can serve as building blocks for synthesizing new chemical entities. This study synthesized acyl, carboxyesther, NSAID, and nitrogenous derivatives and evaluated their antimicrobial activity. A cyclodextrin complexation method was developed to improve the solubility of the derivatives. Of the 17 derivatives tested, five exhibited activity against Trypanosoma cruzi, T. brucei, Leishmania infantum, Candida albicans, Staphylococcus aureus and Escherichia coli. The 9a/9b mixture showed weak activity against the parasites (IC_{50} 24.45-40.32 µM). However, it showed no activity for the other microorganisms. Derivatives 14a/14b exhibited potent activity against T. cruzi (IC_{50} 2.0 nM), in this tested concentration did not show activity to the other microorganisms and were not cytotoxic. Derivatives 15a/15b and 16a/16b demonstrated relevant activity against the parasites (IC_{50} 2.24-5.44 µM), but were also cytotoxic. Derivatives 17a/17b showed low activity against the tested parasites (IC_{50} 21.70-22.79 µM), but they were selective since they did not show activity against other microorganisms. In docking studies, in general, all derivatives showed complementarity with the CYP51 binding site of the trypanosomatid mainly by hydrophobic interactions; thus it is not conclusive that the molecules act by inhibiting this enzyme. Our results showed that triterpenes derivatives with antitrypanosomal activity could be synthesized by an inexpensive and rapid method.

Effect of hybridization on Lipophosphoglycan expression in Leishmania major.

Silveira, K., Nogueira, P., Soares, R.
21-03-2022
Cell Biol Int
https://doi.org/10.1002/cbin.11798

Leishmania major is the causative agent of cutaneous leishmaniasis (CL). It is one of the most studied Leishmania species not only during vector interaction, but also in the vertebrate host. Lipophosphoglycan (LPG) is the Leishmania multifunctional virulence factor during host-parasite interaction, whose polymorphisms are involved in the immunopathology of leishmaniasis. Although natural hybrids occur in nature, hybridization of L. major strains in the laboratory was successfully demonstrated. However, LPG expression in the hybrids remains unknown. LPGs from parental (Friedlin-Fn and Seidman-Sd) and hybrids (FnSd3, FnSd4A, FnSd4B and FnSd6F) were extracted, purified and their repeat units analyzed by immunoblotting and fluorophore-assisted carbohydrate electrophoresis (FACE). Parental strains have distinct profiles in LPG expression, and a mixed profile was observed for all hybrids. Variable levels of NO production by macrophages were detected after LPG exposure (parental and hybrids) and were strain specific. This article is protected by copyright. All rights reserved.

Histological evaluation of skin lesions induced by Leishmania braziliensis treated by PACT using Laser light and 1.9 dimethyl-methylene blue.

Fagnani, S., de Oliveira, S., Monteiro, J., Sampaio, F., Crugeira, P., Dos Santos, J., Pinheiro, A.
16-03-2022
Photodiagnosis Photodyn Ther
https://pubmed.ncbi.nlm.nih.gov/35306211

This study aimed to perform a histological evaluation in skin lesions caused by Leishmania braziliensis after PACT treatment using Laser associated with 1.9. dimethyl methylene blue BALB/c mouse ear infection model was used. A total of 40 animals were assigned into two groups considering time intervals at 5 and 10 weeks and subdivided into four subgroups: Control, Photosensitizer, Laser and PACT. Two therapeutic interventions were performed after the 5th week of infection at 48-h intervals. 1.9 Dimethyl methylene blue was used as a photosensitizer at the concentration of 7 ng/mL, with a non-invasive topical administration method associated with Laser (λ = 660 nm, 40 mW, 12 J/cm^2). Sample collection occurred 5 or 10 weeks after therapeutic interventions. The main histological findings were observed in the laser and PACT groups at the 10-week evaluation. The Laser group showed reduced lymphoplasmacytic inflammation and histiocytes (p=0.0079). The PACT group showed reductions in lymphoplasmacytic inflammation at 5 and 10 weeks, discrete reduction of histiocytes and a higher percentage of tissue remodeling. PACT with non-invasive topical administration of the photosensitizer was able to reduce lymphoplasmacytic inflammation and increase tissue remodeling in leishmaniosis skin lesions. This protocol may be easily used in humans and clinical trial shall be carried out to confirm the animal's findings.

A recombinant Leishmania amastigote-specific protein, rLiHyG, with adjuvants, protects against infection with Leishmania infantum.

Machado, A., Lage, D., Vale, D., Freitas, C., Linhares, F., Cardoso, J., Pereira, I., Ramos, F., Tavares, G., Ludolf, F., Oliveira-da-Silva, J., Bandeira, R., Simões, A., Duarte, M., Oliveira, J., Christodoulides, M., Chávez-Fumagalli, M., Roatt, B., Martins, V., Coelho, E.
16-03-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35305943

Vaccination against visceral leishmaniasis (VL) should be considered as a control measure to protect against disease, and amastigote-specific proteins could help to develop such vaccines, since this parasite form is in contact with the host immune system during the active disease. In this study, a Leishmania amastigote-specific protein, LiHyG, was evaluated as recombinant protein (rLiHyG) as vaccine candidate against Leishmania infantum infection in BALB/c mice. The protein was associated with saponin (rLiHyG/Sap) or Poloxamer 407-based polymeric micelles (rLiHyG/Mic) as adjuvants, and animals receiving saline, saponin or micelle as controls. Immunological and parasitological analyses were performed before (n=8 per group; as primary endpoint) and after (n=8 per group; as secondary endpoint) infection. Results showed that, in both endpoints, rLiHyG/Sap and rLiHyG/Mic induced higher levels of IFN-γ, IL-12 and GM-CSF in spleen cell cultures from vaccinated animals, besides elevated presence of IgG2a isotype antibodies. Decreased hepatotoxicity and ´positive lymphoproliferative response were also found after challenge. Such findings reflected in significantly lower levels of parasite load found in their spleens, livers, bone marrows and draining lymph nodes. In conclusion, rLiHyG associated with Th1-type adjuvant could be considered for future studies as vaccine candidate to protect against VL.

Leishmania (Viannia) braziliensis replicates in mouse bone marrow.

Floro E Silva, M., Roque, G., Machado, D., Rocha, F., Giorgio, S.
15-03-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35304124

Leishmaniasis is a neglected disease caused by species of the protozoan Leishmania. Leishmania (Viannia) braziliensis causes the cutaneous and mucocutaneous forms of the disease. Experimental cutaneous infection of mice is one of the most important preclinical research models of leishmaniasis. Here, we investigated the course of infection in mice inoculated with two reference strains of L. (V.) braziliensis (MHOM/BR/00/BA788 strain [BA] and MHOM/BR/94/H-3227 strain [CE]). Although both parasite strains induced detectable footpad lesions, BA-infected mice developed small non-ulcerated lesions that self-healed, whereas CE-infected mice developed small non-ulcerated lesions that did not regress. The parasites were detected in the footpad lesions, lymph nodes draining the site of inoculation, spleen, and bone marrow of mice infected with BA or CE parasites at 6 and 25 weeks post-inoculation. These data indicate that L (V.) braziliensis-infected mice harbor parasites that spread, even when these animals do not display overt lesions. In addition, this is the first report of the presence of the parasite in the bone marrow of mice inoculated with L. (V.) braziliensis.

An alphavirus-derived self-amplifying mRNA encoding PpSP15-LmSTI1 fusion protein for the design of a vaccine against leishmaniasis.

Savar, N., Shengjuler, D., Doroudian, F., Vallet, T., Mac Kain, A., Arashkia, A., Khamesipour, A., Lundstrom, K., Vignuzzi, M., Niknam, H.
14-03-2022
Parasitol Int
https://pubmed.ncbi.nlm.nih.gov/35301120

The main aims of the present study were to design a fusion protein of Leishmania major stress-inducible protein 1 (LmSTI1) and Phlebotomus papatasi SP15 (PpSP15), and to express it in the form of alphavirus packaged Self-amplifying mRNA (SAM). Two combinations, PpSP15-LmSTI1 and LmSTI1-PpSP15 fusion forms, were analyzed for folding and minimum free energies of the mRNA. Conformational studies on 3D modeled fusion and native forms were performed, and the Root-Mean-Square-distance (RMSD) of the Cα atomic coordinates were calculated. Antigenicity and stability were predicted using bioinformatics tools. The coding sequences of PpSP15-LmSTI1 fusion, PpSP15, and LmSTI1 were cloned into an alphavirus-based vector and used to produce the SAM constructs. All the subcloned constructs were then subjected to packaging in the form of viral replicon particles (VRPs),and were evaluated for their ability to infect BHK-21 cells and express the recombinant fusion proteins. The in-silico analysis indicated that the PpSP15-LmSTI1 combination could be a promising candidate based on lower folding ΔG of mRNA, higher protein antigenicity and lower instability indexes, and less conformational changes compared to the native proteins and the LmSTI1-PpSP15 fusion form. Packaged SAM encoding fusion and native antigens are used for infection of mammalian cells and for recombinant protein expression. This is the first study on in silico designing and successful packaging of an alphavirus-derived SAM in the form of the VRPs to target leishmaniasis.

Targeting chalcone binding sites in living Leishmania using a reversible fluorogenic benzochalcone probe.

Batista, A., Oliveira, S., Pomel, S., Commere, P., Mazan, V., Lee, M., Loiseau, P., Rossi-Bergmann, B., Prina, E., Duval, R.
14-03-2022
Biomed Pharmacother
https://pubmed.ncbi.nlm.nih.gov/35299122

Chalcones (1,3-diphenyl-2-propen-1-ones) either natural or synthetic have a plethora of biological properties including

antileishmanial activities, but their development as drugs is hampered by their largely unknown mechanisms of action. We demonstrate herein that our previously described benzochalcone fluorogenic probe (HAB) could be imaged by fluorescence microscopy in live Leishmania amazonensis promastigotes where it targeted the parasite acidocalcisomes, lysosomes and the mitochondrion. As in the live zebrafish model, HAB formed yellow-emitting fluorescent complexes when associated with biological targets in Leishmania. Further, we used HAB as a reversible probe to study the binding of a portfolio of diverse chalcones and analogues in live promastigotes, using a combination of competitive flow cytometry analysis and cell microscopy. This pharmacological evaluation suggested that the binding of HAB in promastigotes was representative of chalcone pharmacology in Leishmania, with certain exogenous chalcones exhibiting competitive inhibition (ca. 20-30%) towards HAB whereas non-chalconic inhibitors showed weak capacity (ca. 3-5%) to block the probe intracellular binding. However, this methodology was restricted by the strong toxicity of several competing chalcones at high concentration, in conjunction with the limited sensitivity of the HAB fluorophore. This advocates for further optimization of this undirect target detection strategy using pharmacophore-derived reversible fluorescent probes.

Climate Change Influences on the Potential Distribution of the Sand Fly Phlebotomus sergenti, Vector of Leishmania tropica in Morocco.

Daoudi, M., Outammassine, A., Amane, M., Hafidi, M., Boussaa, S., Boumezzough, A.
16-03-2022
Acta Parasitol
https://doi.org/10.1007/s11686-022-00533-5

Leishmaniases are a vector-borne disease, re-emerging in several regions of the world posing a burden on public health. As other vector-borne diseases, climate change is a crucial factor affecting the evolution of leishmaniasis. In Morocco, anthroponotic cutaneous leishmaniasis (ACL) is widespread geographically as many foci across the country, mainly in central Morocco. The objective of this study is to evaluate the potential impacts of climate change on the distribution of ACL due to Leishmania tropica, and its corresponding vector Phlebotomus sergenti in Morocco. Using Ecological Niche Modeling (ENM) tool, the estimated geographical range shift of L. tropica and P. sergenti by 2050 was projected under two Representative's Concentration's Pathways (RCPs) to be 2.6 and RCP 8.5 respectively. P. sergenti records were obtained from field collections of the laboratory team and previously published entomological observations, while, epidemiological data for L. tropica were obtained from Moroccan Ministry of Health reports. Our models under present-day conditions indicated a probable expansion for L. tropica as well as for its vector in Morocco, P. sergenti. It showed a concentrated distribution in the west-central and northern area of Morocco. Future predictions anticipate expansion into areas not identified as suitable for P. sergenti under present conditions, particularly in northern and southeastern areas of Morocco. L. tropica is also expected to have high expansion in southern areas for the next 30 years in Morocco. This indicates that L. tropica and P. sergenti will continue to find suitable climate conditions in the future. A higher abundance of P. sergenti may indeed result in a higher transmission risk of ACL. This information is essential in developing a control plan for ACL in Morocco. However, future investigations on L. tropica reservoirs are needed to confirm our predictions.

A Convenient and Sensitive kDNA-PCR for Screening of Leishmania infantum Latent Infection Among Blood Donors in a Highly Endemic Focus, Northwestern Iran.

Asfaram, S., Fakhar, M., Mohebali, M., Ziaei Hezarjaribi, H., Mardani, A., Ghezelbash, B., Akhoundi, B., Zarei, Z., Moazeni, M.
16-03-2022
Acta Parasitol
https://doi.org/10.1007/s11686-022-00528-2

Recent global evidences showed that asymptomatic blood donor carriers of Leishmania infection will appear as a threat for blood transfusions recipients in endemic areas. As yet, there is no appropriate diagnostic procedure for detecting infection of blood donors in blood banks. The present study was aimed to apply various current diagnostic tests among blood donors in an endemic area of visceral leishmaniasis (VL), Ardabil Province, northwestern Iran. Blood samples were gathered from 860 blood donors in endemic areas of the province between 2017 and 2018, at eight blood donation centers. These samples was assessed using microculture, serological (DAT and rK39-ICT) and molecular based (conventional kDNA-PCR and HRM-PCR) tests. Of 860 eligible donors, 24 (2.8%) were seropositive for VL by DAT, and 388 (45%) were positive by kDNA-PCR. Moreover, 19 (19/860) were positive for both of them. Out of 19 subjects, 5.3% (1/19) was positive by rK39-ICT, 10.5% (2/19), and 79% (15/19) were detected positive in microculture and HRM-PCR methods, respectively. Nineteen donors were followed up for 2 years, of which 16 (84.2%) had a serological conversion, and 4 (21%) were positive by kDNA-PCR. The sensitivity of kDNA-PCR, and HRM-PCR procedures in detecting Leishmania parasite was found to be 98.7%, and 79%, respectively. Our findings justify the use of kDNA-PCR as a convenient and sensitive tool for screening subjects with leishmanial latent infection in blood banks at least in endemic regions. In these areas, however, a PCR-based test should be used to validate Leishmania infection among seropositive donors.

Experimental evolution links post-transcriptional regulation to Leishmania fitness gain.

Piel, L., Rajan, K., Bussotti, G., Varet, H., Legendre, R., Proux, C., Douché, T., Giai-Gianetto, Q., Chaze, T., Cokelaer, T., Vojtkova, B., Gordon-Bar, N., Doniger, T., Cohen-Chalamish, S., Rengaraj, P., Besse, C., Boland, A., Sadlova, J., Deleuze, J., Matondo, M., Unger, R., Volf, P., Michaeli, S., Pescher, P., Späth, G.
16-03-2022

PLoS Pathog
https://doi.org/10.1371/journal.ppat.1010375

The protozoan parasite Leishmania donovani causes fatal human visceral leishmaniasis in absence of treatment. Genome instability has been recognized as a driver in Leishmania fitness gain in response to environmental change or chemotherapy. How genome instability generates beneficial phenotypes despite potential deleterious gene dosage effects is unknown. Here we address this important open question applying experimental evolution and integrative systems approaches on parasites adapting to in vitro culture. Phenotypic analyses of parasites from early and late stages of culture adaptation revealed an important fitness tradeoff, with selection for accelerated growth in promastigote culture (fitness gain) impairing infectivity (fitness costs). Comparative genomics, transcriptomics and proteomics analyses revealed a complex regulatory network associated with parasite fitness gain, with genome instability causing highly reproducible, gene dosage-independent and -dependent changes. Reduction of flagellar transcripts and increase in coding and non-coding RNAs implicated in ribosomal biogenesis and protein translation were not correlated to dosage changes of the corresponding genes, revealing a gene dosage-independent, post-transcriptional mechanism of regulation. In contrast, abundance of gene products implicated in post-transcriptional regulation itself correlated to corresponding gene dosage changes. Thus, RNA abundance during parasite adaptation is controled by direct and indirect gene dosage changes. We correlated differential expression of small nucleolar RNAs (snoRNAs) with changes in rRNA modification, providing first evidence that Leishmania fitness gain in culture may be controlled by post-transcriptional and epitranscriptomic regulation. Our findings propose a novel model for Leishmania fitness gain in culture, where differential regulation of mRNA stability and the generation of modified ribosomes may potentially filter deleterious from beneficial gene dosage effects and provide proteomic robustness to genetically heterogenous, adapting parasite populations. This model challenges the current, genome-centric approach to Leishmania epidemiology and identifies the Leishmania transcriptome and non-coding small RNome as potential novel sources for the discovery of biomarkers that may be associated with parasite phenotypic adaptation in clinical settings.

Rhamnella gilgitica functionalized green synthesis of ZnONPs and their multiple therapeutic properties.

Abbasi, B., Iqbal, J., Israr, M., Yaseen, T., Zahra, S., Shahbaz, A., Rahdar, A., Raouf, B., Khan, S., Kanwal, S., Mahmood, T.
16-03-2022
Microsc Res Tech
https://doi.org/10.1002/jemt.24090

In the recent years, green synthesis of zinc oxide nanoparticles (ZnONPs) using plant extracts and phytochemicals has gained significant attention. In present research study, facile, green, and tunable ZnONPs were biosynthesized from Rhamnella gilgitica leaf aqueous extract as a strong reducing and stabilizing agents. The prepared ZnONPs@Rhamnella were characterized and validated using common nanotechnology techniques (UV-Vis, XRD, EDX, FT-IR, SEM, TEM, DLS, and Raman) and revealed spherical morphology with particle size ~21nm. The asynthesized ZnONPs were further evaluated for different biological applications. Strong antimicrobial efficacies were reported for ZnONPs using disc-diffusion method and were capable of rendering significant antimicrobial potential. ZnONPs were evaluated against HepG2 (IC_{50} : 18.40µg/ml) and HUH7 (IC_{50} : 20.59µg/ml) cancer cell lines and revealed strong anticancer properties. Dose-dependent MTT cytotoxicity assay was confirmed using Leishmania tropica "KWH23 strain" (promastigote: IC_{50} : 26.78µg/ml and amastigote: IC_{50} : 29.57µg/ml). Antioxidant activities (DPPH: 93.36%, TAC: 72.43%) were performed to evaluate their antioxidant potentials. Further, protein kinase and α-amylase inhibition assays were determined. Biocompatibility assays were done using human RBCs and macrophages thus revealed biosafe and non-toxic nature of ZnONPs@Rhamnella. In current experiment, we concluded that greenly orchestrated ZnONPs is an attractive, non-toxic and ecofriendly candidate and showed potential biological activities. In future, different clinical trials and in vivo studies are necessary for the confirmation of these remedial properties of ZnONPs using different animal models.

The Prospective Effects of Climate Change on Neglected Tropical Diseases in the Eastern Mediterranean Region: a Review.

Revue de littérature

Al-Delaimy, A.
14-03-2022
Curr Environ Health Rep
https://doi.org/10.1007/s40572-022-00339-7

An increase in the annual daily temperature is documented and predicted to occur in the coming decades. Climate change has a direct effect and adverse impact on human health, as well as on multiple ecosystems and their species. The purpose of this paper is to review the effect of climate change on neglected tropical diseases including leishmaniasis, schistosomiasis, and lymphatic filariasis in the Eastern Mediterranean Region (EMR). A list of engine web searches was done; 280 full-text records were assessed for eligibility. Only 48 original records were included within the final selection for the review study. Most research results show an alteration of neglected diseases related to climate change influencing specifically the Eastern Mediterranean Region, in addition to the expectation of more effects at the level of vectors and reservoir whether its vector transmission route or its egg hatching and replication or even the survival of adult worms in the coming years. At the same time, not all articles related to the region interpret the direct or indirect effect of climate variations on these specific diseases. Although few studies were found describing some of climate change effects

on neglected tropical diseases in the region, still, the region lacks research funding, technical, and mathematical model expertise regarding the direct effect of climate change on the ecosystems of these neglected tropical diseases.

Bayesian latent class models for identifying canine visceral leishmaniosis using diagnostic tests in the absence of a gold standard.

Ozanne, M., Brown, G., Scorza, B., Mahachi, K., Toepp, A., Petersen, C.
14-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010236

Like many infectious diseases, there is no practical gold standard for diagnosing clinical visceral leishmaniasis (VL). Latent class modeling has been proposed to estimate a latent gold standard for identifying disease. These proposed models for VL have leveraged information from diagnostic tests with dichotomous serological and PCR assays, but have not employed continuous diagnostic test information. In this paper, we employ Bayesian latent class models to improve the identification of canine visceral leishmaniasis using the dichotomous PCR assay and the Dual Path Platform (DPP) serology test. The DPP test has historically been used as a dichotomous assay, but can also yield numerical information via the DPP reader. Using data collected from a cohort of hunting dogs across the United States, which were identified as having either negative or symptomatic disease, we evaluate the impact of including numerical DPP reader information as a proxy for immune response. We find that inclusion of DPP reader information allows us to illustrate changes in immune response as a function of age. Utilization of continuous DPP reader information can improve the correct discrimination between individuals that are negative for disease and those with clinical VL. These models provide a promising avenue for diagnostic testing in contexts with multiple, imperfect diagnostic tests. Specifically, they can easily be applied to human visceral leishmaniasis when diagnostic test results are available. Also, appropriate diagnosis of canine visceral leishmaniasis has important consequences for curtailing spread of disease to humans.

Leishmania infantum reactivation with secondary IgA nephropathy.

Grewe, I., Brehm, T., Kreuels, B., Steinmetz, O., Dumoulin, B., Asemissen, A., Tappe, D., Ramharter, M., Schmiedel, S.
14-03-2022
J Travel Med
https://pubmed.ncbi.nlm.nih.gov/35285886

We report a Leishmania infantum reactivation in an immunocompetent patient manifesting as visceral leishmaniasis with secondary IgA nephropathy nine years after an initial episode of mucosal leishmaniasis, which had been treated with liposomal amphotericin B.

VAMP3 and VAMP8 Regulate the Development and Functionality of Parasitophorous Vacuoles Housing Leishmania amazonensis.

Séguin, O., Mai, L., Acevedo Ospina, H., Guay-Vincent, M., Whiteheart, S., Stäger, S., Descoteaux, A.
07-02-2022
Infect Immun
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To colonize mammalian phagocytic cells, the parasite *Leishmania* remodels phagosomes into parasitophorous vacuoles that can be either tight-fitting individual or communal. The molecular and cellular bases underlying the biogenesis and functionality of these two types of vacuoles are poorly understood. In this study, we investigated the contribution of host cell soluble *N*-ethylmaleimide-sensitive-factor attachment protein receptor proteins to the expansion and functionality of communal vacuoles as well as the replication of the parasite. The differential patterns of recruitment of soluble *N*-ethylmaleimide-sensitive-factor attachment protein receptor to communal vacuoles harboring Leishmania amazonensis and to individual vacuoles housing L. major led us to further investigate the roles of VAMP3 and VAMP8 in the interaction of *Leishmania* with its host cell. We show that whereas VAMP8 contributes to the optimal expansion of communal vacuoles, VAMP3 negatively regulates L. amazonensis replication, vacuole size, as well as antigen cross-presentation. In contrast, neither protein has an impact on the fate of L. major. Collectively, our data support a role for both VAMP3 and VAMP8 in the development and functionality of L. amazonensis-harboring communal parasitophorous vacuoles.

High-resolution inhibition profiling and ligand fishing for screening of nucleoside hydrolase ligands in Moringa oleifera Lamarck.

de Faria, R., Oliveira, P., de Carvalho, M., Peixoto, B., Severino, V., Tinoco, L., Rodrigues, S., de Moraes, M.
29-01-2022
J Pharm Biomed Anal
https://pubmed.ncbi.nlm.nih.gov/35123329

In Leishmania donovani, the causative protozoan of visceral leishmaniasis, nucleoside hydrolase enzyme (NH) is fundamental for the biosynthesis of its DNA and RNA. Therefore, LdNH is considered a potential target for the development of new leishmaniasis chemotherapy. Moringa oleifera Lamarck is a medicinal plant native to northeastern India with numerous pharmacological properties, including antileishmanial activity. Thus, this study aimed to explore the inhibitory activity of different extracts from M. oleifera leaves and flowers on LdNH. Using LdNH covalently immobilized on magnetic particles (LdNH-MPs), a novel activity assay was developed based on the direct quantification of the formed product by HPLC-DAD. This study screened 12 extracts from leaves and flowers of M. oleifera using different extraction methods. The hydroethanolic (70% ethanol) extract from flowers, obtained by infusion (FIEH) or ultrasound-assisted

extraction (FUEH), exhibited respectively IC_{50} values of 26.2 ± 4.63 µg/mL and 4.96 ± 0.52 µg/mL. The most promising extract (FUEH) was investigated by high-resolution LdNH inhibition profiling, which showed different regions of inhibition in the biochromatogram. A ligand fishing assay was attempted to pinpoint the bioactive compounds. Experimental conditions employed in the elution step of the ligand fishing assay did not result in ligands isolation. However, the analyses of the crude extract solution and the supernatants after the incubation with the active and inactive LdNH-MPs indicated missing peaks referring to compounds selectively retained in the active LdNH-MPs incubation. The missing peaks eluted in the same region that exhibits inhibition in the high-resolution LdNH inhibition profiling. The ligands were identified by UHPLC-MS/MS as palatinose, adenosine, 3-p-coumaroylquinic acid, 4-p-coumaroylquinic acid, hyperoside, quercetin-3-O-malonyl glycoside, and kaempferol-3-O-galactoside.

Covalent Conjugation of Amphotericin B to Hyaluronic Acid: An Injectable Water-Soluble Conjugate with Reduced Toxicity and Anti-Leishmanial Potential.

Silva-Carvalho, R., Leão, T., Gama, F., Tomás, A.
13-01-2022
Biomacromolecules
https://doi.org/10.1021/acs.biomac.1c01451

Amphotericin B (AmB) is a highly hydrophobic drug with significant leishmanicidal activity whose use is limited by its poor water solubility and adverse effects. Polymer-drug conjugates are proposed as a delivery system designed to overcome those limitations while improving drug bioavailability, safety, and activity. Here, AmB was covalently linked to periodate-oxidized hyaluronic acid (HA) (oxidation degree of 30.1 ± 5.6%) via a Schiff base (HA-AmB imine). The conjugate presents high water solubility and self-assembles into particles with a mean size of 88.2 ± 17.6 nm, a negative charge (-28.3 ± 0.9 mV), and a drug content of 17.8 ± 1.4%. Spectroscopic studies revealed the presence of AmB in aggregate and super-aggregated forms in the conjugate, which could explain the significant reduction of the *in vitro* cytotoxicity and hemolytic activity. The formulation showed not only *in vitro* anti-leishmanial activity against *L. infantum*-infected macrophages (IC_{50} = 0.023 µM) but also against an *in vivo* infected mouse model, promoting a 1.32- and a 4.98-log_{10} suppression of the *L. infantum* burden in the spleens and liver, respectively, without toxic effects. In summary, this study describes the safe and effective use of water-soluble HA-AmB imine conjugates for leishmaniasis treatment.

Trypanosomatids in Phlebotomine Sand Flies (Diptera: Phlebotominae) From Anthropic and Sinantropic Landscapes in a Rural Settlement in the Brazilian Amazon.

Guimarães, R., Marialva, E., Feijó, J., Pereira-Silva, J., Martins-Campos, K., Gontijo, C., Pereira, A., Rios-Velasquez, C., Pessoa, F.
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J Med Entomol
https://doi.org/10.1093/jme/tjab208

Trypanosomatids (Kinetoplastida:Trypanosomatidae) protozoa are a diverse group of obligate parasites. The genera Trypanosoma and Leishmania are the most studied because of their medical importance. This work aims to evaluate the effects of anthropization processes on the composition of the phlebotomine sand fly fauna and the natural infection by Trypanosomatids, with emphasis on Leishmania. At all 3,186 sand flies were collected, distributed in 13 genera and 52 species, being Ny. umbratilis the most abundant species. There was no difference in the diversity between canopy and soil environments. The species abundance and richness were higher in the forest environment while species diversity and evenness were highest in the forest edge. The ITS1 region was used by PCR-RFLP to identify the fragment profiles of Leishmania species, followed by genetic sequencing. Here were analyzed 100 pools of female sand flies, being six positive for DNA parasite. PCR-RFLP fragment patterns similar to Endotrypanum sp. were observed in Nyssomyia anduzei, Psychodopygus amazonensis and Lutzomyia gomezi, and those fragments similar to Leishmania (Leishmania) amazonensis were observed in Bichromomyia flaviscutellata. ITS1 sequencing confirmed the presence of Leishmania sp. in Bi. flaviscutellata, and Leishmania (Viannia) naiffi in Ny. anduzei, Psychodopygus amazonensis, and Lu. gomezi. This is the first record of Lu. gomezi and Ps. amazonensis infection by L. naiffi in the State of Amazonas. These results show the trypanosomatid infection in sandflies from different landscapes in a rural settlement, and the finding of species infected with L.(V.) naiffi suggest that they can develop a role in the transmission cycle of leishmaniasis.

Detection of Leishmania donovani in Wild-Caught Phlebotomine Sand Flies in Endemic Focus of Leishmaniasis in Himachal Pradesh, India.

Lata, S., Kumar, G., Ojha, V., Dhiman, R.
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J Med Entomol
https://doi.org/10.1093/jme/tjab202

An endemic focus of cutaneous leishmaniasis (CL) is located in the Sutlej River Valley in Himachal Pradesh (India) in the north-western Himalaya where CL co-exists with visceral leishmaniasis (VL). In areas of the Indian subcontinent such as Rajasthan, cutaneous leishmaniasis is transmitted by Phlebotomus papatasi (Scopoli) and Phlebotomus salehi. In Himachal Pradesh, Phlebotomus longiductus (Parrot) is suspected to be the vector for CL. In the current study, sand flies were collected and tested for Leishmania infection and to confirm the vector species causing CL. Sand flies were collected during April and September of 2017-2019 from CL endemic villages of Rampur (Shimla), Nirmand (Kullu) and Nichar (Kinnaur) districts of Himachal Pradesh. The sand flies were identified as Phlebotomus (adlerius) longiductus (Parrot) and Phlebotomus (larrousisus) major (Annandale). The density

of P. longiductus was found highest. The elevation of villages ranged from 947 m to 2,130 m and were far from the presence of subsoil water. Field collected sand flies tested positive (7.69%) for Leishmania donovani by PCR-RFLP. The L. donovani sequences detected from P. longiductus were 97% similar to L. donovani sequences reported from the cases of CL in Himachal Pradesh.The Leishmania positive sand flies were morphologically identified as Phlebotomus adlerious longiductus providing one step further evidence towards the vector status of CL in Himachal Pradesh. The findings of the study are of epidemiological significance for strategic planning of vector control for leishmaniasis in India.

CYSTICERCOSE

Disseminated cysticercosis: a case report and review of treatment protocols.

Dabas, S., Gupta, V., Narula, A.
18-03-2022
BMJ Case Rep
https://pubmed.ncbi.nlm.nih.gov/35304357

Cysticercosis is caused by the larvae of *Taenia solium* and is a significant health problem. Disseminated cysticercosis is an infrequent manifestation of the same. A woman in her 30s presented to us with a history of seizures, outward protrusion of both eyes and multiple soft-tissue swellings over the face and tongue for 3 years. Imaging studies revealed multiple cystic lesions in the brain parenchyma, extraocular muscles, subcutaneous tissue, muscles of mastication and tongue. A high index of suspicion and a planned therapeutic approach is required in such cases.

Cysticercosis: A case of missed diagnosis.

Goyal, S., Goyal, S.
18-03-2022
Diagn Cytopathol
https://doi.org/10.1002/dc.24957

Human cysticercosis caused by the larval stage of the pork tapeworm-Taenia solium, is a potentially dangerous systemic disease with vague clinical manifestations. Subcutaneous and muscular tissues are most commonly involved followed by, the eye and brain. A variety of clinical presentations, pathology that ranges from simple cysts to calcified lesions, and limited familiarity with the parasitic infection can make it challenging to diagnose. Cysticercosis when present as an isolated lesion. Fine needle aspiration cytology (FNAC) can play an important role in the early and rapid detection of this disease, particularly when the lesion is superficial and /or easily sampled. We report a case of cysticercosis diagnosed on FNAC in a 35-year-old female, who presented with an isolated swelling in the neck.

Development of a dose-response model for porcine cysticercosis.

Andrade-Mogrovejo, D., Gonzales-Gustavson, E., Ho-Palma, A., Prada, J., Bonnet, G., Pizzitutti, F., Gomez-Puerta, L., Arroyo, G., O'Neal, S., Garcia, H., Guitian, J., Gonzalez, A., Cysticercosis Working Group in Peru
14-03-2022
PLoS One
https://doi.org/10.1371/journal.pone.0264898

Taenia solium is an important cause of acquired epilepsy worldwide and remains endemic in Asia, Africa, and Latin America. Transmission of this parasite is still poorly understood despite the design of infection experiments to improve our knowledge of the disease, with estimates for critical epidemiological parameters, such as the probability of human-to-pig infection after exposure to eggs, still lacking. In this paper, a systematic review was carried out and eight pig infection experiments were analyzed to describe the probability of developing cysts. These experiments included different pathways of inoculation: with ingestion of proglottids, eggs, and beetles that ingested eggs, and direct injection of activated oncospheres into the carotid artery. In these experiments, different infective doses were used, and the numbers of viable and degenerated cysts in the body and brain of each pig were registered. Five alternative dose-response models (exponential, logistic, log-logistic, and exact and approximate beta-Poisson) were assessed for their accuracy in describing the observed probabilities of cyst development as a function of the inoculation dose. Dose-response models were developed separately for the presence of three types of cysts (any, viable only, and cysts in the brain) and considered for each of the four inoculation methods ("Proglottids", "Eggs", "Beetles" and "Carotid"). The exact beta-Poisson model best fit the data for the three types of cysts and all relevant exposure pathways. However, observations for some exposure pathways were too scarce to reliably define a dose-response curve with any model. A wide enough range of doses and sufficient sample sizes was only found for the "Eggs" pathway and a merged "Oral" pathway combining the "Proglottids", "Eggs" and "Beetles" pathways. Estimated parameter values from this model suggest that a low infective dose is sufficient to result in a 50% probability for the development of any cyst or for viable cyst infections. Although this is a preliminary model reliant on a limited dataset, the parameters described in this manuscript should contribute to the design of future experimental infections related to T. solium transmission, as well as the parameterization of simulation models of transmission aimed at informing control.

Solitary Neurocysticercosis Presenting with Focal Seizure and Secondary Generalized Tonic-Clonic Seizure.

Yingchoncharoen, P., Thongpiya, J., Chankaew, E., Ongsiriporn, M., Sarasombath, P., Roongruangchai, K.
14-03-2022
Am J Case Rep

https://doi.org/10.12659/AJCR.935483

BACKGROUND Neurocysticercosis is the most common central nervous system infection in developing countries. A wide array of clinical manifestations, ranging from asymptomatic to severe neurological symptoms, is observed in patients diagnosed with neurocysticercosis, depending on the number of lesions, cyst location, cyst stage, parasite genotype, and host immunity. CASE REPORT We report the case of a 25-year-old Burmese man who presented with focal seizure and secondary generalized tonic-clonic seizure. Brain imaging studies revealed a 1-cm cyst, which showed rim enhancement, an eccentric scolex, and surrounding brain edema at the left superior frontal gyrus. His serum cysticercus antibody was positive. Thus, the patient was diagnosed with solitary neurocysticercosis based on clinical manifestations, neuroimaging findings, and positive serology. The patient received anti-parasitic and anti-seizure medications before surgical excision of the cyst via computed tomography (CT) scan navigation. Stereomicroscopic examination of the cyst revealed a parasite larva in a fluid-filled cyst, containing a scolex with hooks and 4 suckers, identical to that of Taenia solium. Molecular characterization of the parasite based on T. solium cytochrome c oxidase subunit 1 (COX-1) gene identified the species as being 99.7% identical to T. solium Asia genotype previously reported from pigs in Thailand. CONCLUSIONS Although the prevalence of neurocysticercosis seems to be declining, sporadic cases have been reported throughout the world and the prevalence may be underestimated. Differential diagnosis of neurocysticercosis in patients presenting with adult-onset epilepsy should be considered in disease-endemic areas.

DRACUNCULOSE

ECHINOCOCCOSE

Proteomic profiling of hydatid fluid from pulmonary cystic echinococcosis.

Dos Santos, G., da Silva, E., Kitano, E., Battistella, M., Monteiro, K., de Lima, J., Ferreira, H., Serrano, S., Zaha, A.
21-03-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05232-8

Most cystic echinococcosis cases in Southern Brazil are caused by Echinococcus granulosus and Echinococcus ortleppi. Proteomic studies of helminths have increased our knowledge about the molecular survival strategies that are used by parasites. Here, we surveyed the protein content of the hydatid fluid compartment in E. granulosus and E. ortleppi pulmonary bovine cysts to better describe and compare their molecular arsenal at the host-parasite interface. Hydatid fluid samples from three isolates of each species were analyzed using mass spectrometry-based proteomics (LC-MS/MS). In silico functional analyses of the identified proteins were performed to examine parasite survival strategies. The identified hydatid fluid protein profiles showed a predominance of parasite proteins compared to host proteins that infiltrate the cysts. We identified 280 parasitic proteins from E. granulosus and 251 from E. ortleppi, including 52 parasitic proteins that were common to all hydatid fluid samples. The in silico functional analysis revealed important molecular functions and processes that are active in pulmonary cystic echinococcosis, such as adhesion, extracellular structures organization, development regulation, signaling transduction, and enzyme activity. The protein profiles described here provide evidence of important mechanisms related to basic cellular processes and functions that act at the host-parasite interface in cystic echinococcosis. The molecular tools used by E. granulosus and E. ortleppi for survival within the host are potential targets for new therapeutic approaches to treat cystic echinococcosis and other larval cestodiases.

Unraveling post-translational modifications in Echinococcus granulosus sensu lato.

Miles, S., Magnone, J., García-Luna, J., Dematteis, S., Mourglia-Ettlin, G.
15-03-2022
Acta Trop
https://pubmed.ncbi.nlm.nih.gov/35300939

Echinococcus granulosus sensu lato (s.l.) is the helminth parasite responsible for cystic echinococcosis, a neglected tropical disease currently affecting millions of people worldwide. Incomplete knowledge on the parasite biochemistry contributes, at least partially, to the limited development of useful biotechnological advances for the infection control. In this sense, little information is available regarding post-translational modifications (PTMs) occurring in E. granulosus s.l. proteins, which ultimately may affect the performance of biotechnological products to be developed. Therefore, we report here a proteomic analysis of the parasite PTMs identified through FindMod software applied to a set of tegumental proteins previously characterized by mass spectrometry (MALDI-TOF/TOF) analysis of protein spots from a 2D electrophoresis gel. Manual searches for already annotated proteins exhibiting such PTMs were also performed within proteome databases of E. granulosus s.l. and other platyhelminthes. In addition, key enzymes involved in PTMs modifications were searched for within E. granulosus s.l. proteome. Finally, the presence of selected PTMs was further confirmed by a high-resolution proteomic approach (nanoLC-MS/MS). A set of 22 different PTMs most likely to be present in the parasite was suggested, 9 of them with high confidence as they were identified in the same m/z fragment by both proteomic techniques (acetylation, deamidation, deamidation followed by methylation, mono- and di-hydroxylation, mono- and di-methylation, S-nitrosylation and phosphorylation).

Interestingly, 5 PTMs were herein identified for the first time in E. granulosus s.l. proteins. Our results expand the scarcely studied topic of PTMs in platyhelminthes.

Evaluation of two heterologous recombinant antigens for the serological diagnosis of human polycystic echinococcosis.

Daipert-Garcia, D., Virginio, V., Oliveira, F., Siqueira, N., Ferreira, H., Rodrigues-Silva, R.
17-03-2022
J Helminthol
https://doi.org/10.1017/S0022149X22000086

Polycystic echinococcosis (PE) is a zoonosis endemic in the Neotropical region of the Americas. It is caused by the larval stage of the cestode Echinococcus vogeli, which develops as harmful cysts that slowly grow in the liver, lungs and other organs of humans and other host species. Human PE diagnosis is usually based on clinical and epidemiological aspects and imaging techniques, often requiring confirmation by immunological assays. The currently available serological tests for detecting antibodies against Echinococcus spp. are mostly based on complex, variable and poorly characterized mixtures of native parasite antigens, which impairs specificity and/or sensitivity. In this scenario, the evaluation of well-characterized alternative antigens is urgently needed for the improvement of PE diagnosis. Here, two subunits (AgB8/1 and AgB8/2) of the major secretory antigen from Echinococcus granulosus (antigen B (AgB)), of diagnostic value for cystic echinococcosis, were validated for PE diagnosis. These antigens, produced as pure recombinant proteins (rAgB8/1 and rAgB8/2) in Escherichia coli, allowed detecting specific immunoglobulin G antibodies in sera from PE patients in an enzyme-linked immunosorbent assay, with sensitivities of 83.72% and 81.40%, respectively, and specificities of 83.12% and 80.09%, respectively. The use of recombinant proteins overcomes difficulties to obtain parasite material and reduced non-specific reactions and costs. Our results demonstrated reproducibility and accuracy high enough to be considered valid according to the acceptance criteria for Food and Drug Administration assay validation. This qualifies rAgB8/1 and rAgB8/2 as potential substitutes for the currently used parasite crude or partially purified antigens.

The Role of Tissue Inhibitor of Metalloproteinase-1 and 2 in Echinococcus granulosus senso lato-Induced Human Hepatic Fibrosis.

Hasanzadeh, A., Rafiei, A., Kazemi, M., Beiromvand, M., Bahreini, A., Khanahmad, H.
16-03-2022
Acta Parasitol
https://doi.org/10.1007/s11686-022-00534-4

The main mechanism underlying hepatic fibrosis is the imbalance between tissue Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinases (TIMPs). This study aimed to investigate the potential role of TIMP-1 and TIMP-2 in the process of hepatic fibrosis caused by Echinococcus granulosus senso lato (E. granulosus s.l.). The expressions levels of TIMP-1 and TIMP-2 mRNAs were evaluated in fibrotic and normal hepatic tissues of 30 patients with Cystic Echinococcus (CE) using qRT-PCR. Moreover, their serum levels of TIMP-1 were assessed before CE cyst removal and 6 months after surgery using ELISA. The qRT-PCR results showed that the expression levels of TIMP-1 and TIMP-2 mRNAs were significantly higher in the fibrotic hepatic tissue compared to the normal liver tissue, in a way that the TIMP-1 and TIMP-2 mRNA expression levels were 19.07 and 6.58 folds higher in the fibrotic tissue compared to the normal liver tissue. Among these TIMPs, TIMP-1 exhibited the higher area under the curve (AUC) value for predicting liver fibrosis. However, we could not find a significant difference in the serum levels of TIMP-1 before and after the cyst removal procedure (p=0.48). For the first time, our study showed that the significant overexpression of both TIMP mRNAs in the fibrotic liver tissue of the CE patients may be due to the increased expression of MMPs in the peri-cystic tissue. However, we could not find a significant difference in the pre- and post-operative TIMP-1 levels, which may be due to recurrence or heterogeneity in the cyst type. Therefore, performing further studies with a larger sample size of the CE patients is recommended.

TREMATODOSES D'ORIGINE ALIMENTAIRE (CLONORCHIASE, OPISTHORCHIASE, FASCIOLASE ET PARAGONIMOSE)

Paragonimiasis diagnosed by CT-guided transthoracic lung biopsy: Literature review and case report.

Cong, C., Anh, T., Ly, T., Duc, N.
14-03-2022
Radiol Case Rep
https://doi.org/10.1016/j.radcr.2022.02.046

More than 40 different species of the parasitic flatworm *Paragonimus* have been identified worldwide, including in Vietnam, but only 10 species are known to cause disease in humans, particularly *Paragonimus westermani*. *Paragonimus* are transmitted through the ingestion of raw foods, especially freshwater shrimp, and crab. Paragonimiasis causes pneumonia, which can present as acute or chronic, with symptoms including prolonged cough, chest pain, shortness of breath, and hemoptysis. Hematologic changes include eosinophilia and the presence of specific antibodies for *Paragonimus* in the blood. Diagnosis is confirmed when *Paragonimus* specimens or eggs are found in the sputum or pleural fluid. The specificity of imaging is not high, but imaging can be used to guide the diagnosis. After the failure of

microbiological diagnostic methods, lung biopsy can be used to confirm a diagnosis of paragonimiasis. We present a paragonimiasis case associated with unique features, including epidemiologic factors, atypical clinical signs, no increases in blood eosinophils, and negative microbiological tests. Although the patient was suspected of tuberculosis or lung cancer, imaging studies were consistent with the presence of lung flukes. Three transthoracic lung biopsies were performed, and pathology revealed a cystic structure containing *Paragonimus* on the third biopsy.

Epidemiological characterization of Clonorchis sinensis infection in humans and freshwater fish in Guangxi, China.

Xie, Y., Kanankege, K., Jiang, Z., Liu, S., Yang, Y., Wan, X., Perez, A.

18-03-2022
BMC Infect Dis
https://doi.org/10.1186/s12879-022-07244-2

Clonorchiasis is a widespread yet neglected foodborne disease with over 85% of all cases found in China. Guangxi province, located in southeastern China, ranks among the highest endemic provinces. We explore the epidemiological status and determinants of Clonorchis sinensis (C. sinensis) infection in humans and freshwater fish in Guangxi, China. Data on C. sinensis infection in humans from January 2008 to December 2017were extracted from the China Information System for Disease Control and Prevention. An active surveillance of C. sinensis infection in fish was conducted in 2016-2017. County level data including potential environmental, social-economical and behavioral determinants was also collected. Univariate and multivariate logistic regression models were used to explore the determinants of C. sinensis infection in humans and fish. Simple and multiple zero-inflated Poisson regression models were fit to assess the associated factors of clonorchiasis in humans at the county level. Totally, 4526 C. sinensis cases were reported between 2008 and 2017, with an annual prevalencerate of 0.96/100,000 persons. Of 101 counties in Guangxi, 97 reported at least 1 case. Among 2,098 fish samples, 203 (9.7%) from 70 counties contained C. sinensis. The rate was higher in small fish including Pseudorasbora parva (45.3%), Misgurnus anguillicaudatus (41.2%), Hemiculter leuciclus (34.5%), unclassified small fishes (30.9%), Cyprinidae (20.0%), Cirrhinus molitorella (16.4%), Carassius auratus (13.6%) and Cyprinus carpio (13.3%), while it was lower in fish species that are usually used in preparing raw fish dishes including Ctenopharyngodon idellus (3.6%), Spinibarbus denticulatus (3.7%), Monopterus albus (6.4%), Cyprinus carpio (4.4%), Oreochromis mossambicus (3.3%) and Spualiobarbus Curriculus (6.6%). The C. sinensis infection in fish was only associated with fish species. The estimated human clonorchiasis prevalence at the county level was positively associated with raw fish consumption habits and certain rivers. Clonorchiasis is highly prevalent in both humans and freshwater fish in Guangxi. Environmental, social-economic and behavioral determinants contribute to the high prevalence as well as the significant differential distribution by county. Regular surveillance should be implemented for clonorchiasis to demonstrate the change in epidemiology and burden, which will benefit the design of interventions.

Cerebral paragonimiasis: Clinicoradiological features and serodiagnosis using recombinant yolk ferritin.

Kim, J., Ahn, C., Kang, I., Shin, J., Jeong, H., Nawa, Y., Kong, Y.

16-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010240

Cerebral paragonimiasis (CP), caused by aberrant migration of Paragonimus worms, frequently invokes serious illness. The causal relationship between the lesion characteristics and patients' symptoms has poorly been understood. CP serodiagnosis has not been properly evaluated to date. A total of 111 CP cases were diagnosed in our laboratory between 1982 and 2003. This study retrospectively assessed the clinical and imaging characteristics of the 105 patients along with the evaluation of diagnostic potentials of recombinant P. westermani yolk ferritin (rPwYF) by enzyme-linked immunosorbent assay (ELISA) employing patients' sera and cerebrospinal fluids (CSFs). We analyzed 60 male and 45 female patients; 50 early-stage patients with non-calcified enhancing nodule(s) (median age, 38 years; interquartile range [IQR], 24.75-52; median symptom duration, 0.75 years; IQR, 0.2-2) and 54 chronic cases having calcified lesion(s) (median age, 33 years; IQR, 25-41; median symptom duration, 10 years; IQR, 5-20). One patient showed a normal neuroimage. The patients were largely diagnosed in their 30s. The parietal lobe was most commonly affected, followed by occipital, frontal, and temporal lobes. Twenty-six patients had lesions encompassing ≥ two lobes. The patients complained mainly of seizures, headaches, hemiparesis, and focal neurologic deficits ($P < 0.001$). Seizures and visual defect were predominant in patients with calcified lesion(s) ($P < 0.001$). The diagnostic sensitivity and specificity of rPwYF against serum/CSF were 100%/97% and 97.2%/92.5%, respectively. The specific IgG antibody levels against rPwYF in sera and CSFs showed a positive correlation ($r = 0.59$). The clinical manifestations of the early-stage patients might be associated with cortical lesions or meningeal irritation, while those in the chronic stage were caused by conglomerated space-occupying lesions. rPwYF would be useful for the serodiagnosis of both early and chronic CP cases.

Lung flukes of the genus *Paragonimus*: ancient and re-emerging pathogens.

Revue de littérature

Blair, D.

16-03-2022
Parasitology
https://doi.org/10.1017/S0031182022000300

FILARIOSE LYMPHATIQUE

Compressing the Timelines for Development and Delivery: Accelerating Access to Triple-Drug Therapy to Eliminate Lymphatic Filariasis.

Jacobson, J.
15-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-1174

The traditional timeline for a new innovation in public health to move from initial proof of concept to introduction into national programs is sequential and can take decades. Here, we discuss the development of a new drug therapy for lymphatic filariasis (LF) to help progress toward elimination as a public health problem and how this process was accelerated by a group of partners working together. This article documents the way that these partners worked together and made decisions that made it possible to accelerate the process of the development and introduction of the triple-drug therapy involving ivermectin, diethylcarbamazine, and albendazole (IDA). The partners were able to condense the development timeline from the first clinical efficacy data to delivery in a country program for the triple-drug therapy from a projected ~28 years to less than 5 years while maintaining all of the safety standards. The approach required understanding stakeholders, their roles, need for data to inform decisions, and then looking at timelines focused on prioritizing activities that inform decision-making. This process relied on a close engagement of all stakeholders and good communication. Through this exercise, additional early data review points were added to study designs, studies were run in parallel not sequentially, and a plan put in place to engage all stakeholders necessary for adoption and uptake throughout the process, so they were prepared to make decisions as data became available. This process could provide some insights into how global health can work together in new ways to accelerate the availability of interventions and strategies to promote health and well-being.

Lessons from Large-Scale Tolerability and Acceptability Studies of Triple Drug Mass Drug Administration Performed to Support Policy Change and Accelerate Elimination of Lymphatic Filariasis.

Weil, G., Fischer, P., Krentel, A.
15-03-2022
Am J Trop Med Hyg
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Early clinical trials clearly demonstrated the superior efficacy of triple drug therapy with ivermectin plus DEC and albendazole (IDA) for clearing microfilaremia (Mf) in individuals with lymphatic filariasis (LF). Although these initial pharmacokinetic and efficacy studies were necessary first steps in the clinical development of IDA, they were not sufficient to justify policy changes necessary for widespread use of this new regimen by national filariasis elimination programs. Processes and procedures that led to the World Health Organization's (WHO) endorsement of IDA as a mass drug administration (MDA) regimen for LF are reviewed elsewhere in this supplement. However, the "guideline review process" depended heavily on preliminary results from multicenter studies that were performed to compare the safety, tolerability, and acceptability of IDA versus DA (the two-drug regimen of DEC plus albendazole that was recommended for use for filariasis elimination in countries without co-endemic onchocerciasis or loiasis). Efficacy and tolerability results from those studies have been recently published. Therefore, this paper will focus on practical aspects of the planning and conduct of the large-scale studies that were so critically important for policy change.

Development and Introduction of the Filariasis Test Strip: A New Diagnostic Test for the Global Program to Eliminate Lymphatic Filariasis.

Pantelias, A., King, J., Lammie, P., Weil, G.
15-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-0990

A key component to achieving the global goal of elimination of lymphatic filariasis (LF) is the availability of appropriate tools for disease mapping, monitoring, and surveillance. However, the development of these tools for a neglected disease such as LF can be a challenge. The lack of a commercial market and low familiarity with these diseases leave little incentive for diagnostic manufacturers to invest in this space. The Filarial Test Strip (FTS) development story provides a case study on how a multi-stakeholder, public-private partnership model facilitated the development, evaluation, and introduction of a new monitoring and surveillance tool for LF. This paper will reflect on the experience with the FTS and document the process from development of the target product profile to adoption and scale-up in country programs. Lessons learned from both the successes and challenges experienced during this process may help inform future efforts to develop and introduce new diagnostic or surveillance tools for neglected diseases.

Country Reports on Practical Aspects of Conducting Large-Scale Community Studies of the Tolerability of Mass Drug Administration with Ivermectin/Diethylcarbamazine/Albendazole for Lymphatic Filariasis.

Jambulingam, P., Subramanian, S., Krishnamoorthy, K., Supali, T., Fischer, P., Dubray, C., Fayette, C., Lemoine, J., Laman, M., King, C., Samuela, J., Hardy, M., Weil, G.
15-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-0898

This article is a compilation of summaries prepared by lead investigators for large-scale safety and efficacy studies on

mass drug administration of IDA (ivermectin, diethylcarbamazine, and albendazole) for lymphatic filariasis. The summaries highlight the experiences of study teams that assessed the safety and efficacy of IDA in five countries: India, Indonesia, Haiti, Papua New Guinea, and Fiji. They also highlight significant challenges encountered during these community studies and responses to those challenges that contributed to success.

Introduction of Triple-Drug Therapy for Accelerating Lymphatic Filariasis Elimination in India: Lessons Learned.

Tripathi, B., Roy, N., Dhingra, N.
15-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-0964

There are 670 million people at risk of contracting lymphatic filariasis (LF) in India, which bears 40% of the global burden of the disease. The National Program to Eliminate LF was launched in 2004 first with a single-drug therapy-diethylcarbamazine (DEC), followed by a two-drug therapy-DEC + albendazole (DA). In 2017, following successful drug trials, World Health Organization endorsed a new triple-drug therapy to fight LF using ivermectin with DEC and albendazole (IDA).1 In June 2018, India made new commitments to accelerate their program to eliminate LF and initiated the new IDA protocol in five districts in the country. This article looks at the experience of India in the roll out of the new drug protocol and shares their preparations, successes, challenges, and lessons learned.

The Importance of Partnership in the Rollout of Triple-Drug Therapy to Eliminate Lymphatic Filariasis in the Pacific.

Rainima-Qaniuci, M., Lepaitai, H., Bhagirov, R., Padmasiri, E., Naseri, T., Thomsen, R., Won, K., Brant, T., Dodd, E., Nua, M., Utu, F., Tufa, A., Chutaro, E., Camacho, J., Suiaunoa-Scanlan, L., Thean, L., Mani, J., Hardy, M., Samuela, J., Romani, L., Kaldor, J., Steer, A., Faktaufon, D., Bechu, V., Naqio, F., Sosene, V., Sekihara, M., Otaki, J., Buhagiar, T., Yajima, A.
15-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-1085

We discuss the experience of some Pacific island countries in introducing the new WHO-recommended treatment protocol for lymphatic filariasis-a triple-drug therapy composed of ivermectin, diethylcarbamazine, and albendazole. The successful rollout of the new treatment protocol was dependent on strong partnerships among these countries' ministries of health, WHO, and other stakeholders. Effective communication among these partners allowed for lessons learned to cross borders and have a positive impact on the experiences of other countries. We also describe various challenges confronted during this process and the ways these countries overcame them.

Accelerating the Uptake of WHO Recommendations for Mass Drug Administration Using Ivermectin, Diethylcarbamazine, and Albendazole.

King, J., Jacobson, J., Krentel, A.
15-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-0972

Triple therapy with ivermectin, diethylcarbamazine, and albendazole (IDA) for the elimination of lymphatic filariasis (LF) represents a compelling example of accelerating the timeline from development to introduction and impact. Previous articles outlined how the clinical development process was able to compress timelines and provide the evidence needed for the WHO to issue guidelines on the use of IDA for mass drug administration for LF. We explored the drivers for the rapid and successful introduction of IDA in the early-adopter countries. Lessons from this experience highlight five key elements for moving from WHO recommendations to program uptake after the publication of the guideline: 1) early engagement with stakeholders to create partnerships to coordinate and plan for implementation; 2) recognition by countries and partners of the potential of IDA to improve efforts to eliminate LF; 3) high-level commitment and coordination at regional levels and, most importantly, at the country level; 4) understanding of the perspectives among people living in LF-endemic communities where mass drug administration is warranted; and 5) affirmation of the feasibility of IDA through sharing lessons learned.

Lessons Learned from the Japanese Encephalitis Vaccine Introduction in India That Supported the Introduction of Ivermectin-Diethylcarbamazine-Albendazole for Lymphatic Filariasis Elimination.

Ghosh, R., Haldar, P., Jacobson, J.
15-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.21-1168

We used the introduction of the Japanese encephalitis (JE) vaccine in India as an example to understand more fully the process of introducing any new clinical product in India. We discuss the key decision-making points as well as the many activities involved in introducing a new clinical product in India's public health program. We write from our experience in supporting the government of India to introduce new products successfully-namely, vaccines-to India's health system. In India, the process begins with identifying the public health problem (e.g., an outbreak of JE), deciding to take action, prioritizing where action is needed, securing a supply and price of the intervention (the vaccine; in this case, the live, attenuated SA 14-14-2 vaccine), and determining how to ensure effective rollout of the intervention (the vaccination program). Reflecting on the experience of the JE vaccination program helped to inform the introduction of the triple-drug therapy of ivermectin, diethylcarbamazine, and albendazole in India as a new treatment protocol for lymphatic filariasis.

The Prospective Effects of Climate Change on Neglected Tropical Diseases in the Eastern Mediterranean Region: a Review.

Revue de littérature

Al-Delaimy, A.
14-03-2022
Curr Environ Health Rep
https://doi.org/10.1007/s40572-022-00339-7

An increase in the annual daily temperature is documented and predicted to occur in the coming decades. Climate change has a direct effect and adverse impact on human health, as well as on multiple ecosystems and their species. The purpose of this paper is to review the effect of climate change on neglected tropical diseases including leishmaniasis, schistosomiasis, and lymphatic filariasis in the Eastern Mediterranean Region (EMR). A list of engine web searches was done; 280 full-text records were assessed for eligibility. Only 48 original records were included within the final selection for the review study. Most research results show an alteration of neglected diseases related to climate change influencing specifically the Eastern Mediterranean Region, in addition to the expectation of more effects at the level of vectors and reservoir whether its vector transmission route or its egg hatching and replication or even the survival of adult worms in the coming years. At the same time, not all articles related to the region interpret the direct or indirect effect of climate variations on these specific diseases. Although few studies were found describing some of climate change effects on neglected tropical diseases in the region, still, the region lacks research funding, technical, and mathematical model expertise regarding the direct effect of climate change on the ecosystems of these neglected tropical diseases.

Emerging Mosquito Resistance to Piperonyl Butoxide-Synergized Pyrethroid Insecticide and Its Mechanism.

Zhou, G., Li, Y., Jeang, B., Wang, X., Cummings, R., Zhong, D., Yan, G.
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J Med Entomol
https://doi.org/10.1093/jme/tjab231

Piperonyl butoxide (PBO)-synergized pyrethroid products are widely available for the control of pyrethroid-resistant mosquitoes. To date, no study has examined mosquito resistance after pre-exposure to PBO and subsequent enzymatic activity when exposed to PBO-synergized insecticides. We used Culex quinquefasciatus Say (Diptera: Culicidae), an important vector of arboviruses and lymphatic filariasis, as a model to examine the insecticide resistance mechanisms of mosquitoes to PBO-synergized pyrethroid using modified World Health Organization tube bioassays and biochemical analysis of metabolic enzyme expressions pre- and post-PBO exposure. Mosquito eggs and larvae were collected from three cities in Orange County in July 2020 and reared in insectary, and F0 adults were used in this study. A JHB susceptible strain was used as a control. Mosquito mortalities and metabolic enzyme expressions were examined in mosquitoes with/without pre-exposure to different PBO concentrations and exposure durations. Except for malathion, wild strain Cx quinquefasciatus mosquitoes were resistant to all insecticides tested, including PBO-synergized pyrethroids (mortality range 3.7 ± 4.7% to 66.7 ± 7.7%). Wild strain mosquitoes had elevated levels of carboxylesterase (COE, 3.8-fold) and monooxygenase (P450, 2.1-fold) but not glutathione S-transferase (GST) compared to susceptible mosquitoes. When wild strain mosquitoes were pre-exposed to 4% PBO, the 50% lethal concentration of deltamethrin was reduced from 0.22% to 0.10%, compared to 0.02% for a susceptible strain. The knockdown resistance gene mutation (L1014F) rate was 62% in wild strain mosquitoes. PBO pre-exposure suppressed P450 enzyme expression levels by 25~34% and GST by 11%, but had no impact on COE enzyme expression. Even with an optimal PBO concentration (7%) and exposure duration (3h), wild strain mosquitoes had significantly higher P450 enzyme expression levels after PBO exposure compared to the susceptible laboratory strain. These results further demonstrate other studies that PBO alone may not be enough to control highly pyrethroid-resistant mosquitoes due to multiple resistance mechanisms. Mosquito resistance to PBO-synergized insecticide should be closely monitored through a routine resistance management program for effective control of mosquitoes and the pathogens they transmit.

MYCETOME

ONCHOCERCOSE

SCHISTOSOMIASE

The identification of alternative oxidase in intermediate host snails of Schistosoma and its potential role in protecting Oncomelania hupensis against niclosamide-induced stress.

Jiang, N., Li, S., Zhang, Y., Habib, M., Xiong, T., Xu, S., Dong, H., Zhao, Q.
21-03-2022
Parasit Vectors
https://doi.org/10.1186/s13071-022-05227-5

Snail intermediate hosts are mandatory for the transmission of schistosomiasis, which has to date infected more than 200 million people worldwide. Our previous studies showed that niclosamide treatment caused the inhibition of aerobic respiration and oxidative phosphorylation, and the disruption

of energy supply, in one of the intermediate hosts of schistosomiasis, Oncomelania hupensis, which eventually led to the death of the snails. Meanwhile, the terminal oxidase in the mitochondrial respiratory chain, alternative oxidase (AOX), was significantly up-regulated, which was thought to counterbalance the oxidative stress and maintain metabolic homeostasis in the snails. The aims of the present study are to identify the AOXs in several species of snails and investigate the potential activation of O. hupensis AOX (OhAOX) under niclosamide-induced stress, leading to enhanced survival of the snail when exposed to this molluscicide. The complete complementary DNA was amplified from the AOXs of O. hupensis and three species of Biomphalaria; the sequence characteristics were analysed and the phylogenetics investigated. The dynamic expression and localisation of the AOX gene and protein in O. hupensis under niclosamide-induced stress were examined. In addition, the expression pattern of genes in the mitochondrial respiratory complex was determined and the production of reactive oxygen species (ROS) calculated. Finally, the molluscicidal effect of niclosamide was compared between snails with and without inhibition of AOX activity. AOXs containing the invertebrate AOX-specific motif NP-[YF]-XPG-[KQE] were identified from four species of snail, which phylogenetically clustered together into Gastropoda AOXs and further into Mollusca AOXs. After niclosamide treatment, the levels of OhAOX messenger RNA (mRNA) and OhAOX protein in the whole snail were 14.8 and 2.6 times those in untreated snails, respectively, but varied widely among tissues. Meanwhile, the level of cytochrome C reductase mRNA showed a significant decrease in the whole snail, and ROS production showed a significant decrease in the liver plus gonad (liver-gonad) of the snails. At 24 h post-treatment, the mortality of snails treated with 0.06-0.1 mg/L niclosamide and AOX inhibitor was 56.31-76.12% higher than that of snails treated with 0.1 mg/L niclosamide alone. AOX was found in all the snail intermediate hosts of Schistosoma examined here. AOX was significantly activated in O. hupensis under niclosamide-induced stress, which led to a reduction in oxidative stress in the snail. The inhibition of AOX activity in snails can dramatically enhance the molluscicidal effect of niclosamide. A potential target for the development of an environmentally safe snail control method, which acts by inhibiting the activity of AOX, was identified in this study.

Comparative structural analysis of the human and Schistosoma glutathione transferase dimer interface using selective binding of bromosulfophthalein.

Valli, A., Achilonu, I.
21-03-2022
Proteins
https://doi.org/10.1002/prot.26338

The binding channel of Schistosoma glutathione transferase (SGST) has been identified to possess a non-substrate site implicated in enzyme inhibition. This binding channel is formed by the interface of the GST dimer. We produced a comparative characterisation of the SGST dimer interface with respect to that of human GST (hGST) analogues using the selective binding of bromosulfophthalein (BSP). First, two SGST and three hGST structures were used as search queries to assemble a dataset of 48 empirical GST structures. Sequence alignment to generate a universal residue indexing scheme was then performed, followed by local superposition of the dimer interface. Principal component analysis revealed appreciable variation of the dimer interface, suggesting the potential for selective inhibition of SGST. BSP was found to dock invariably in the dimer interface core pocket, placing it in proximity to the GST catalytic domains, through which it may exert its inhibitory behaviour. Binding poses across the GST forms were distinguished with ligand interaction profiling, where SGST complexes showed stabilisation of ligand aromatic- and sulfonate moieties, which altogether anchor the ligand and produce a tight association. In comparison, missing aromatic stabilisation in the hGST complexes impart large bonding distances, causing mobile poses likely to dissociate. Altogether, this study illustrates the potential for selective inhibition of SGST, rationalises the selective behaviour of the BSP inhibitor, and produces a reliable metric for construction and validation of pharmacophore models of the SGST binding channel. This article is protected by copyright. All rights reserved.

Recombinant P40 protein of Schistosoma japonicum inhibits TREM-1 expression in RAW264.7 cells via FOXO3a.

Shen, P., Zhang, T., Chen, G., Zhang, B., Huang, A., Duan, L., Zhu, D., Chen, J., Wang, J., Duan, Y.
17-03-2022
Biomed Pharmacother
https://pubmed.ncbi.nlm.nih.gov/35306429

Triggering receptor expressed on myeloid cells 1 (TREM-1) is a transmembrane glycoprotein receptor and TREM-1 expression reached the peak at 6 weeks after infection with Schistosoma japonicum and inhibited subsequently. Since TREM-1 may be involved in the macrophage polarization process, the reason for the inhibition of TREM-1 expression in chronic schistosomiasis engaged us in them. In this study, flow cytometry was used to observe TREM-1 expression in peritoneal macrophages from mice infected with Schistosoma japonicum. Since P40 is one of the main components from schistosoma eggs, western blot and dual-luciferase reporter assays were performed to observe the effect of recombinant Schistosoma japonicum P40 protein (rSjP40) on TREM-1 expression in the mouse leukemic monocyte/macrophage cell line RAW264.7. These methods were also conducted to observe the effect of FOXO3a on the expression of TREM-1 in RAW264.7 cells, and a ChIP assay was performed to confirm the binding site of FOXO3a to the TREM-1 promoter. Our results showed that TREM-1 expression reached the peak in peritoneal macrophages from mice at 6 weeks after infection with Schistosoma japonicum. rSjP40 inhibited TREM-1 promoter activity at the position of - 1924 ~ - 1531 bp. rSjP40 down-regulated TREM-1 and FOXO3a protein expression in

RAW264.7 cells. TREM-1 protein expression may be regulated by binding of FOXO3a to the promoter of TREM-1 in RAW264.7 cells. In conclusion, we found that rSjP40 inhibited TREM-1 expression in macrophages by inhibiting FOXO3a expression. This study will provide the basis for the study to explore the role of TREM-1 in Schistosoma japonicum infection.

Screening for parasites in migrant children.

Bustamante, J., Sainz, T., Montojo, F., Almirón, M., Subirats, M., Vega, D., Mellado, M., López-Hortelano, M.
15-03-2022
Travel Med Infect Dis
https://pubmed.ncbi.nlm.nih.gov/35304329

Globalization has pushed population movements in the last decades, turning imported diseases into the focus. Due to behavioral habits, children are at higher risk of acquiring iparasitosis. This study aims to investigate the prevalence of parasites in migrant children and factors associated with parasitic diseases. Retrospective cross-sectional study (2014-2018) including children diagnosed with parasitosis. The diagnosis was based on serology and/or microscopic stool-sample evaluation. Epidemiological and clinical data were recorded. Out of 813 migrant children screened, 241 (29.6%) presented at least one parasite, and 89 (10.9%) more than one. The median age was 6.6 years (IQR: 3.1-11.9) and 58.9% were males. Most cases were referred for a health exam; only 52.3% of children were symptomatic, but 43.6% had eosinophilia. The most common diagnosis were giardiasis (35.3%), schistosomiasis (19.1%), toxocariasis (15.4%), and strongyloidiasis (9.1%). After the multivariate analysis, African origin and presenting with eosinophilia were the main risk factors for parasitism. parasitosis are frequent among migrant children. Children are often asymptomatic, and thus active screening for parasitosis should be considered among high-risk populations. Eosinophilia can be useful to guide complimentary tests, as well as geographical origin, but normal eosinophil count does not exclude parasitosis.

The effect of schistosomiasis and soil-transmitted helminths on expressive language skills among African preschool children.

Mazibuko, X., Chimbari, M.
18-03-2022
BMC Infect Dis
https://doi.org/10.1186/s12879-022-07260-2

Schistosomiasis and soil transmitted helminths (STH) have been associated with compromised child development. We determined the effect of schistosomiasis and STH on expressive language skills among isiZulu speaking preschool children focusing on the variables: age, gender, school and stunting. We quantitatively compared the performance of a cohort of infected and non-infected children using a 2 phased approach. In phase 1 infected children were treated with praziquantel and matched with non-infected children and both groups were tested for expressive language performance. In phase 2 both groups of children were re-tested for expressive language skills using a similar but modified test. The participants were 106 preschool children between the age of 4 and 6 years, 11 months. The Developmental Language Test was adapted as a linguistically and culturally appropriate tool for assessing isiZulu expressive language skills. The overall performance of the children in phases 1 and 2 were statistically similar. There was significant Pearson's correlation of expressive language skills to age (0.002, P<0.01), schistosomiasis i.e. vocabulary 1 (0.024, P<0.05) and narrative skills (0.001, P<0.01) and soil-transmitted helminths i.e. vocabulary 1 (0.006, P<0.05), colours (0.029, P<0.05) and narrative skills (0.001, P<0.01) in phase 2 with small to high Cohen's d effect size for various language subtests. We concluded that even mild schistosomiasis and STH may compromise the performance of preschool children on expressive language. However poor ability in following instructions may have contributed to general poor performance across the two groups tested. Diet, school effect and stunting did not influence the performance of the children on expressive language.

Prevalence, intensity and endemicity of intestinal schistosomiasis and soil-transmitted helminthiasis and its associated factors among school-aged children in Southern Ethiopia.

Zerdo, Z., Bastiaens, H., Anthierens, S., Massebo, F., Masne, M., Biresaw, G., Shewangizaw, M., Tunje, A., Chisha, Y., Yohannes, T., Van Geertruyden, J.
17-03-2022
Sci Rep
https://doi.org/10.1038/s41598-022-08333-7

Preventive chemotherapy (PC), the main strategy recommended by the World Health Organization to eliminate soil-transmitted helminthiasis (STH) and schistosomiasis (SCH), should be strengthened through identification of the remaining SCH transmission foci and evaluating its impact to get a lesson. This study was aimed to assess the prevalence of STH/SCH infections, the intensity of infections, and factors associated with STH infection among school-aged children (SAC) in Uba Debretsehay and Dara Mallo districts (previously not known to be endemic for SCH) in southern Ethiopia, October to December 2019. Structured interview questionnaire was used to collect household data, anthropometric measurements were taken and stool samples collected from 2079 children were diagnosed using the Kato-Katz technique. Generalize mixed-effects logistic regression models were used to assess the association of STH infections with potential predictors. A P-value less than 0.05 was considered statistically significant. The prevalence of Schistosoma mansoni in the Dara Mallo district was 34.3% (95%CI 30.9-37.9%). Light, moderate, and heavy S. mansoni infections were 15.2%, 10.9%, and 8.2% respectively. The overall prevalence of any STH infection was 33.2% with a 95% confidence interval (CI) of 31.1-35.3%. The intensity of infections was light (20.9%, 11.3% & 5.3%), moderate (1.1%,

0.1% & 0.4%) and heavy (0.3%, 0% & 0%) for hookworm, whipworm and roundworms respectively. The overall moderate-to-heavy intensity of infection among the total diagnosed children was 2% (41/2079). STH infection was higher among male SAC with Adjusted Odds Ratio (AOR) of 1.7 (95%CI 1.4-2.1); occupation of the household head other than farmer or housewife (AOR=0.5; 95%CI 0.3-0.8), middle [AOR=1.1; 95%CI 1.0-1.3] or high [AOR=0.7; 95%CI 0.5-0.9] socioeconomic status. Dara Mallo district was moderate endemic for S. mansoni; and it needs sub-district level mapping and initiating a deworming campaign. Both districts remained moderate endemic for STH. Evidence-based strategies supplementing existing interventions with the main focus of the identified factors is important to realize the set targets.

Insights on the Gut-Mesentery-Lung Axis in Pulmonary Arterial Hypertension: A Poorly Investigated Crossroad.

Revue de littérature

Oliveira, S.
17-03-2022
Arterioscler Thromb Vasc Biol
https://doi.org/10.1161/ATVBAHA.121.316236

Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by the hyperproliferation of vascular cells, including smooth muscle and endothelial cells. Hyperproliferative cells eventually obstruct the lung vasculature, leading to irreversible lesions that collectively drive pulmonary pressure to life-threatening levels. Although the primary cause of PAH is not fully understood, several studies have indicated it results from chronic pulmonary inflammation, such as observed in response to pathogens' infection. Curiously, infection by the intravascular parasite Schistosoma mansoni recapitulates several aspects of the widespread pulmonary inflammation that leads to development of chronic PAH. Globally, >200 million people are currently infected by *Schistosoma spp*., with about 5% developing PAH (Sch-PAH) in response to the parasite egg-induced obliteration and remodeling of the lung vasculature. Before their settling into the lungs, Schistosoma eggs are released inside the mesenteric veins, where they either cross the intestinal wall and disturb the gut microbiome or migrate to other organs, including the lungs and liver, increasing pressure. Spontaneous or surgical liver bypass via collateral circulation alleviates the pressure in the portal system; however, it also allows the translocation of pathogens, toxins, and antigens into the lungs, ultimately causing PAH. This brief review provides an overview of the gut-mesentery-lung axis during PAH, with a particular focus on Sch-PAH, and attempts to delineate the mechanism by which pathogen translocation might contribute to the onset of chronic pulmonary vascular diseases.

The Prospective Effects of Climate Change on Neglected Tropical Diseases in the Eastern Mediterranean Region: a Review.

Revue de littérature

Al-Delaimy, A.
14-03-2022
Curr Environ Health Rep
https://doi.org/10.1007/s40572-022-00339-7

An increase in the annual daily temperature is documented and predicted to occur in the coming decades. Climate change has a direct effect and adverse impact on human health, as well as on multiple ecosystems and their species. The purpose of this paper is to review the effect of climate change on neglected tropical diseases including leishmaniasis, schistosomiasis, and lymphatic filariasis in the Eastern Mediterranean Region (EMR). A list of engine web searches was done; 280 full-text records were assessed for eligibility. Only 48 original records were included within the final selection for the review study. Most research results show an alteration of neglected diseases related to climate change influencing specifically the Eastern Mediterranean Region, in addition to the expectation of more effects at the level of vectors and reservoir whether its vector transmission route or its egg hatching and replication or even the survival of adult worms in the coming years. At the same time, not all articles related to the region interpret the direct or indirect effect of climate variations on these specific diseases. Although few studies were found describing some of climate change effects on neglected tropical diseases in the region, still, the region lacks research funding, technical, and mathematical model expertise regarding the direct effect of climate change on the ecosystems of these neglected tropical diseases.

Validation of the isothermal Schistosoma haematobium Recombinase Polymerase Amplification (RPA) assay, coupled with simplified sample preparation, for diagnosing female genital schistosomiasis using cervicovaginal lavage and vaginal self-swab samples.

Archer, J., Patwary, F., Sturt, A., Webb, E., Phiri, C., Mweene, T., Hayes, R., Ayles, H., Brienen, E., van Lieshout, L., Webster, B., Bustinduy, A.
14-03-2022
PLoS Negl Trop Dis
https://doi.org/10.1371/journal.pntd.0010276

Female genital schistosomiasis (FGS) is a neglected and disabling gynecological disease that can result from infection with the parasitic trematode Schistosoma haematobium. Accurate diagnosis of FGS is crucial for effective case management, surveillance and control. However, current methods for diagnosis and morbidity assessment can be inaccessible to those at need, labour intensive, costly and unreliable. Molecular techniques such as PCR can be used to reliably diagnose FGS via the detection of Schistosoma DNA using cervicovaginal lavage (CVL) samples as well as lesser-invasive vaginal self-swab (VSS) and cervical self-swab

samples. PCR is, however, currently unsuited for use in most endemic settings. As such, in this study, we assessed the use of a rapid and portable S. haematobium recombinase polymerase amplification (Sh-RPA) isothermal molecular diagnostic assay, coupled with simplified sample preparation methodologies, to detect S. haematobium DNA using CVL and VSS samples provided by patients in Zambia. VSS and CVL samples were screened for FGS using a previously developed Sh-RPA assay. DNA was isolated from VSS and CVL samples using the QIAamp Mini kit (n = 603 and 527, respectively). DNA was also isolated from CVL samples using two rapid and portable DNA extraction methods: 1) the SpeedXtract Nucleic Acid Kit (n = 223) and 2) the Extracta DNA Tissue Prep Kit (n = 136). Diagnostic performance of the Sh-RPA using VSS DNA extacts (QIAamp Mini kit) as well as CVL DNA extracts (QIAamp Mini kit, SpeedXtract Nucleic Acid Kit and Extracta DNA Tissue Prep Kit) was then compared to a real-time PCR reference test. Results suggest that optimal performance may be achieved when the Sh-RPA is used with PuVSS samples (sensitivity 93.3%; specificity 96.6%), however no comparisons between different DNA extraction methods using VSS samples could be carried out within this study. When using CVL samples, sensitivity of the Sh-RPA ranged between 71.4 and 85.7 across all three DNA extraction methods when compared to real-time PCR using CVL samples prepared using the QIAamp Mini kit. Interestingly, of these three DNA extraction methods, the rapid and portable SpeedXtract method had the greatest sensitivity and specificity (85.7% and 98.1%, respectively). Specificity of the Sh-RPA was >91% across all comparisons. These results supplement previous findings, highlighting that the use of genital self-swab sampling for diagnosing FGS should be explored further whilst also demonstrating that rapid and portable DNA isolation methods can be used to detect S. haematobium DNA within clinical samples using RPA. Although further development and assessment is needed, it was concluded that the Sh-RPA, coupled with simplified sample preparation, shows excellent promise as a rapid and sensitive diagnostic tool capable of diagnosing FGS at the point-of-care in resource-poor schistosomiasis-endemic settings.

Recent trends in praziquantel nanoformulations for helminthiasis treatment.

Mengarda, A., Iles, B., F Longo, J., de Moraes, J.
14-03-2022
Expert Opin Drug Deliv
https://doi.org/10.1080/17425247.2022.2051477

Infections caused by parasitic flatworms impose a considerable worldwide health burden. Recently, World Health Organization launched its roadmap for neglected diseases for the period 2021 to 2030 and oral treatment with praziquantel (PZQ) in tablet form is the main drug therapy for combating these diseases, but its use is limited by many drawbacks, including the high therapeutic dose due to the drug's low solubility and bioavailability. Among the strategies to improve PZQ performance, the use of drug nanocarriers has been cited as an interesting approach to overcome these pharmacological issues. This review focuses on the various types of nanomaterials (polymeric, lipidic, inorganic nanoparticles, and nanocrystals) which have been recently used to improve PZQ therapy. In addition, recent advances in PZQ nanoformulations, developed to overcome the barriers of the conventional drug are described. Considering the poor rate of discovery in the anthelmintic segment observed in recent decades, the effective management of existing drugs has become essential. The application of new strategies based on nanotechnology can extend the useful life of PZQ in new and more effective formulations. Pharmaceutical nanotechnology can solve the pharmacokinetic challenges characteristic of PZQ and improve its solubility and bioavailability.

G-quadruplexes in helminth parasites.

Cantara, A., Luo, Y., Dobrovolná, M., Bohalova, N., Fojta, M., Verga, D., Guittat, L., Cucchiarini, A., Savrimoutou, S., Häberli, C., Guillon, J., Keiser, J., Brázda, V., Mergny, J.
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Nucleic Acids Res
https://doi.org/10.1093/nar/gkac129

Parasitic helminths infecting humans are highly prevalent infecting ∼2 billion people worldwide, causing inflammatory responses, malnutrition and anemia that are the primary cause of morbidity. In addition, helminth infections of cattle have a significant economic impact on livestock production, milk yield and fertility. The etiological agents of helminth infections are mainly Nematodes (roundworms) and Platyhelminths (flatworms). G-quadruplexes (G4) are unusual nucleic acid structures formed by G-rich sequences that can be recognized by specific G4 ligands. Here we used the G4Hunter Web Tool to identify and compare potential G4 sequences (PQS) in the nuclear and mitochondrial genomes of various helminths to identify G4 ligand targets. PQS are nonrandomly distributed in these genomes and often located in the proximity of genes. Unexpectedly, a Nematode, Ascaris lumbricoides, was found to be highly enriched in stable PQS. This species can tolerate high-stability G4 structures, which are not counter selected at all, in stark contrast to most other species. We experimentally confirmed G4 formation for sequences found in four different parasitic helminths. Small molecules able to selectively recognize G4 were found to bind to Schistosoma mansoni G4 motifs. Two of these ligands demonstrated potent activity both against larval and adult stages of this parasite.

Schistosoma Transmission in a Dynamic Seasonal Environment and its Impact on the Effectiveness of Disease Control.

Huang, Q., Gurarie, D., Ndeffo-Mbah, M., Li, E., King, C.
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J Infect Dis
https://doi.org/10.1093/infdis/jiaa746

A seasonal transmission environment including seasonal

variation of snail population density and human-snail contact patterns can affect the dynamics of Schistosoma infection and the success of control interventions. In projecting control outcomes, conventional modeling approaches have often ignored seasonality by using simplified intermediate-host modeling, or by restricting seasonal effects through use of yearly averaging. We used mathematical analysis and numerical simulation to estimate the impact of seasonality on disease dynamics and control outcomes, and to evaluate whether seasonal averaging or intermediate-host reduction can provide reliable predictions of control outcomes. We also examined whether seasonality could be used as leverage in creation of effective control strategies. We found models that used seasonal averaging could grossly overestimate infection burden and underestimate control outcomes in highly seasonal environments. We showed that proper intraseasonal timing of control measures could make marked improvement on the long-term burden reduction for Schistosoma transmission control, and we identified the optimal timing for each intervention. Seasonal snail control, implemented alone, was less effective than mass drug administration, but could provide additive impact in reaching control and elimination targets. Seasonal variation makes Schistosoma transmission less sustainable and easier to control than predicted by earlier modeling studies.

HELMINTHIASES TRANSMISES PAR LE SOL (ASCARIDIOSE, TRICHURIASE, ANKYLOSTOMIASE)

G-quadruplexes in helminth parasites.

Cantara, A., Luo, Y., Dobrovolná, M., Bohalova, N., Fojta, M., Verga, D., Guittat, L., Cucchiarini, A., Savrimoutou, S., Häberli, C., Guillon, J., Keiser, J., Brázda, V., Mergny, J.

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Nucleic Acids Res
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Parasitic helminths infecting humans are highly prevalent infecting ~2 billion people worldwide, causing inflammatory responses, malnutrition and anemia that are the primary cause of morbidity. In addition, helminth infections of cattle have a significant economic impact on livestock production, milk yield and fertility. The etiological agents of helminth infections are mainly Nematodes (roundworms) and Platyhelminths (flatworms). G-quadruplexes (G4) are unusual nucleic acid structures formed by G-rich sequences that can be recognized by specific G4 ligands. Here we used the G4Hunter Web Tool to identify and compare potential G4 sequences (PQS) in the nuclear and mitochondrial genomes of various helminths to identify G4 ligand targets. PQS are nonrandomly distributed in these genomes and often located in the proximity of genes. Unexpectedly, a Nematode, Ascaris lumbricoides, was found to be highly enriched in stable PQS. This species can tolerate high-stability G4 structures, which are not counter selected at all, in stark contrast to most other species. We experimentally confirmed G4 formation for sequences found in four different parasitic helminths. Small molecules able to selectively recognize G4 were found to bind to Schistosoma mansoni G4 motifs. Two of these ligands demonstrated potent activity both against larval and adult stages of this parasite.

GALE

Severe, Recurrent Crusted Scabies in a Psoriatic on Methotrexate.

Khurana, A., B, S., Muddebihal, A., Ahuja, A.

21-03-2022
Am J Trop Med Hyg
https://doi.org/10.4269/ajtmh.22-0008

MORSURES DE SERPENT