热带病学术热点追踪报告

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一、国际热带病热点研究

1. 疟疾相关

（1）*Efficacy and safety of artemether + lumefantrine, artesunate + sulphamethoxypyrazine-pyrimethamine and artesunate + amodiaquine and sulphadoxine-pyrimethamine + amodiaquine in the treatment of uncomplicated falciparum malaria in Bangui, Central African Republic: a randomized trial.*

Abstract[*]

The efficacy of artemisinin-based combination therapy (ACT) has been established. The objective of the present study was to compare the efficacy and safety in the Central African Republic (CAR) of three commercially available artemisinin-based combinations, artemether + lumefantrine (AL), artesunate + sulphamethoxypyrazine-pyrimethamine (AS-SMP) and artesunate + amodiaquine (AS-AQ), with those of sulphadoxine-pyrimethamine + amodiaquine (SP-AQ).The conclusion is that the three artemisinin-bsed combinations show similar, satisfactory results, comparable to that with SP-AQ. This evaluation is the first conducted in CAR since the official introduction of ACT. It should guide the National Malaria Control Programme in choosing the appropriate ACT for treatment of uncomplicated P. falciparum malaria in the future [1].

（2）*Influence of deforestation, logging, and fire on malaria in the Brazilian Amazon.*

Abstract

Malaria is a significant public health threat in the Brazilian Amazon. Previous research has shown that deforestation creates breeding sites for the main malaria vector in Brazil, Anopheles darlingi, but the influence of selective

[*] 为了给读者提供更简明扼要的信息，本报告中的英文摘要均经过编辑和精简。

logging, forest fires, and road construction on malaria risk has not been assessed. To understand these impacts, we constructed a negative binomial model of malaria counts at the municipality level controlling for human population and social and environmental risk factors. We show that roads, forest fires, and selective logging are previously unrecognized risk factors for malaria in the Brazilian Amazon and highlight the need for regulation and monitoring of sub-canopy forest disturbance [2].

（3）*The structure of Plasmodium yoelii merozoite surface protein 119, antibody specificity and implications for malariavaccine design.*

Abstract

Merozoite surface protein 1 (MSP1) has been identified as a target antigen for protective immune responses against asexual blood stage malaria, but effective vaccines based on MSP1 have not been developed so far. We have modified the sequence of Plasmodium yoelii MSP119 (the C-terminal region of the molecule) and examined the ability of the variant proteins to bind protective monoclonal antibodies and to induce protection by immunization. In parallel, we examined the structure of the protein and the consequences of the amino acid changes. Naturally occurring sequence polymorphisms reduced the binding of individual protective antibodies, indicating that they contribute to immune evasion, but immunization with these variant proteins still provided protective immunity. One variant that resulted in the localized distortion of a loop close to the N-terminus of MSP119 almost completely ablated protection by immunization, indicating the importance of this region of MSP119 as a target for protective immunity and in vaccine development [3].

（4）*A mathematical model of seropositivity to malaria antigen, allowing seropositivity to be prolonged by exposure.*

Abstract

Malaria transmission intensity is traditionally estimated from entomological studies as the entomological inoculation rate (EIR), but this is labour intensive and also raises sampling issues due to the large variation from house to house. Incidence

of malaria in the control group of a trial or in a cohort study can be used but is difficult to interpret and to compare between different places and between age groups because of differences in levels of acquired immunity. The aim of this paper is to develop superinfection mathematical models that allow for antibody response to be boosted by exposure.This is analogous to Dietz model, which allowed for superinfection and produced more realistic estimates of the duration of infection as compared to the original Ross-MacDonald malaria model, which also ignores superinfection [4].

（5）*Flt3 ligand treatment modulates parasitemia during infection with rodent malaria parasites via MyD88- and IFN-γ-dependent mechanisms.*

Abstract

In this study, we investigated the mechanisms underlying the reduction of parasitemia in Flt3L-treated mice. Studies using gene knockout mice and antibody treatment indicated that the anti-parasitemia effect of Flt3L was mediated by innate immune system and was dependent on MyD88, IFN-γ, IL-12 and natural killer (NK) cells. The number of NK cells and their ability to produce IFN-γ was enhanced in Flt3L-treated mice. Phagocytic activity of splenocytes was increased in Flt3L-treated mice after PbA infection when compared with that in untreated mice, and this activity was mainly mediated by the accumulation of F4/80(mid) CD11b(+) cells in the spleen. In both MyD88(-/-) and IFN-γ(-/-) mice, the proportion of F4/80(mid) CD11b(+) cells was not increased in the spleen of Flt3L-treated mice after infection. These correlations suggest that NK cells produce IFN-γ in Flt3L-treated mice, and accumulation of F4/80(mid) CD11b(+) cells in the spleen is promoted by an IFN-γ -dependent manner, culminating in the inhibition of parasitemia. These findings imply that Flt3L promotes effective innate immunity against malariainfection mediated by interplay among varieties of innate immune cells [5].

2. 血吸虫相关

（1）*Artesunate Effect on Schistosome Thioredoxin Glutathione Reductase and Cytochrome c Peroxidase as New Molecular Targets in Schistosoma mansoni-infected Mice.*

Abstract

The aim of this study is to investigate the possible effect of artesunate (ART) on schistosome thioredoxin glutathione reductase (TGR) and cytochrome c peroxidase (CcP) in Schistosoma mansoni-infected mice. The results showed more reduction in total worm and female worm count in combined ART-PZQ treated group than in monotherapy treated groups by either ART or PZQ. Moreover, complete disappearance (100%) of tissue eggs was recorded in ART-PZQ treated group with a respective reduction rate of 95.9% and 68.4% in ART- and PZQ-treated groups.The current study elucidated for the first time that anti-schistosomal mechanisms of artesunate is mediated via reduction in expression of schistosome TGR and CcP. Linking these findings, addition of artesunate to praziquantel could achieve complete cure outcome in treatment of schistosomiasis [6].

（2）*Differential Expression of microRNAs in the Non-Permissive Schistosome Host Microtus fortis under Schistosome Infection*

Abstract

In the present study, the differences between pathological changes in tissues of M. fortis and of mice (Mus musculus) post-schistosome infection were observed by using hematoxylin-eosin staining. In addition, microarray technique was applied to identify differentially expressed miRNAs in the same tissues before and post-infection to analyze the potential roles of miRNAs in schistosome infection in these two different types of host. Histological analyses showed that S. japonicum infection in M. fortis resulted in a more intensive inflammatory response and pathological change than in mice. The functions of the differentially expressed miRNAs were mainly revolved in nutrient metabolism, immune regulation, etc. Further analysis revealed that important signaling pathways were triggered after infection by S. japonicum in

M. fortis but not in the mice. These results provide new insights into the general mechanisms of regulation in the non-permissive schistosome host M. fortis that exploits potential miRNA regulatory networks. Such information will help improve current understanding of schistosome development and host-parasite interactions[7].

（3）*Two avian schistosome cercariae from Nepal, including a Macrobilharzia-like species from Indoplanorbis exustus.*

Abstract

As part of a global survey of schistosomes, a total of 16,109 freshwater snails representing 14 species were collected from lakes, ponds, rivers, rice fields and swamps mostly in the Terai region of southern Nepal. Only two snails were found to harbor avian schistosome cercariae even though Nepal is well known for its rich avian diversity. One schistosome infection was from an individual of Radix luteola and on the basis of phylogenetic analyses using 28S rDNA and cox1 sequences, grouped as a distinctive and previously unknown lineage within Trichobilharzia. This genus is the most speciose within the family Schistosomatidae. It includes 40 described species worldwide, and its members mostly infect anseriform birds (ducks) and two families of freshwater snails (Lymnaeidae and Physidae). The second schistosome cercaria was recovered from an individual of Indoplanorbis exustus that was also actively emerging a Petasiger-like echinostome cercaria. This study is the first to characterize by sequence data avian schistosomes recovered from Asian freshwater habitats. This approach can help unravel the complex of cryptic species causing cercarial dermatitis here and elsewhere in the world[8].

（4）*Apoptosis in schistosomes: toward novel targets for the treatment of schistosomiasis*

Abstract

Schistosomiasis is one of the world's major neglected tropical diseases. Recent advances in schistosome genomics and transcriptomics have identified components of an intrinsic, B cell lymphoma-2 (Bcl-2)-regulated apoptotic cell death pathway. Molecular characterization of this pathway demonstrates its similarity to that in

mammals. Gene expression and functional data indicate that apoptosis is active throughout the lifecycle. Moreover, drugs that activate apoptosis in human cells kill schistosome cells, raising the prospect of developing new treatments against schistosomiasis of humans. The development of new drugs is increasingly important in the face of the potential for resistance to currently available treatments, and the lack of an effective vaccine[9].

（5）*ABC multidrug transporters in schistosomes and other parasitic flatworm*

Abstract

Treatment and control of schistosomiasis relies almost exclusively on a single drug, praziquantel (PZQ.Though PZQ is highly effective overall, it has drawbacks, and reports of worms showing PZQ resistance, either induced in the laboratory or isolated from the field, are disconcerting. Some of the best studied multidrug transporters are members of the ancient and very large ATP-binding cassette (ABC) superfamily of efflux transporters. ABC multidrug transporters such as P-glycoprotein (Pgp; ABCB1) are also associated with drug resistance in parasites, including helminths such as schistosomes. In addition to their association with drug resistance, however, ABC transporters also function in a wide variety of physiological processes in metazoans. In this review, we postulate that schistosome ABC transporters could be useful targets for compounds that enhance the effectiveness of current therapeutics as well as for agents that act as antischistosomals on their own [10].

3. 其他寄生虫相关

（1）*The Longevity Properties of 1,2,3,4,6-Penta-O-Galloyl-β-D-Glucose from Curcuma longa in Caenorhabditis elegans.*

Abstract

In this study, we isolated 1,2,3,4,6-penta-O-galloyl-β-D-glucose (PGG) from Curcuma longa L. and elucidated the lifespanextending effect of PGG using

Caenorhabditis elegans model system. We determined the protective effects of PGG on the stress conditions such as thermal and oxidative stress. In the case of heat stress, PGG-treated worms exhibited enhanced survival rate, compared to control worms. In addition, PGG-fed worms lived longer than control worms under oxidative stress induced by paraquat. To verify the possible mechanism of PGG-mediated increased lifespan and stress resistance of worms, we investigated whether PGG might alter superoxide dismutase (SOD) activities and intracellular ROS levels. Our results showed that PGG was able to elevate SOD activities of worms and reduce intracellular ROS accumulation in a dose-dependent manner[11].

（2）*Discovery and SAR studies of methionine-proline anilides as dengue virus NS2B-NS3 protease inhibitors*

Abstract

A series of methionine-proline dipeptide derivatives and their analogues were designed, synthesized and assayed against the serotype 2 dengue virus NS2B-NS3 protease, and methionine-proline anilides 1 and 2 were found to be the most active DENV 2 NS2B-NS3 competitive inhibitors with Ki values of 4.9 and 10.5 μM. The structure and activity relationship and the molecular docking revealed that L-proline, L-methionine and p-nitroaniline in 1 and 2 are the important characters in blocking the active site of NS2B-NS3 protease. Our current results suggest that the title dipeptidic scaffold represents a promising structural core to discover a new class of active NS2B-NS3 competitive inhibitors[12].

（3）*The Toxoplasma gondii Cyst Wall Protein CST1 Is Critical for Cyst Wall Integrity and Promotes Bradyzoite Persistence.*

Abstract

We have identified CST1 (TGME49_064660) as a 250 kDa SRS (SAG1 related sequence) domain protein with a large mucin-like domain. CST1 is responsible for the Dolichos biflorus Agglutinin (DBA) lectin binding characteristic of T. gondii cysts. Deletion of CST1 results in reduced cyst number and a fragile brain cyst phenotype characterized by a thinning and disruption of the underlying region of the cyst wall.

These defects are reversed by complementation of CST1. Additional complementation experiments demonstrate that the CST1-mucin domain is necessary for the formation of a normal cyst wall structure, the ability of the cyst to resist mechanical stress, and binding of DBA to the cyst wall. RNA-seq transcriptome analysis demonstrated dysregulation of bradyzoite genes within the various cst1 mutants. These results indicate that CST1 functions as a key structural component that confers essential sturdiness to the T. gondii tissue cyst critical for persistence of bradyzoite forms[13].

（4）*Structure-activity relationships of synthetic cordycepin analogues as experimental therapeutics for african trypanosomiasis*

Abstract

Cordycepin (3'-deoxyadenosine, 1a) is a powerful trypanocidal compound in vitro but is ineffective in vivo because of rapid metabolic degradation by adenosine deaminase (ADA). We elucidated the structural moieties of cordycepin required for trypanocidal activity and designed analogues that retained trypanotoxicity while gaining resistance to ADA-mediated metabolism. 2-Fluorocordycepin (2-fluoro-3'-deoxyadenosine, 1b) was identified as a selective, potent, and ADA-resistant trypanocidal compound that cured T. brucei infection in mice. Compound 1b is transported through the high affinity TbAT1/P2 adenosine transporter and is a substrate of T. b. brucei adenosine kinase. 1b has good preclinical properties suitable for an oral drug, albeit a relatively short plasma half-life. We present a rapid and efficient synthesis of 2-halogenated cordycepins, also useful synthons for the development of additional novel C2-substituted 3'-deoxyadenosine analogues to be evaluated in development of experimental therapeutics[14].

二、国内热带病热点研究

1. 疟疾相关

（1）IL-17和IFN-γ在红内期间日疟原虫感染者外周血T细胞亚群中的表达

【摘要】*

观察分析间日疟原虫感染患者外周血T细胞亚群中分泌IL-17和IFN-γ的细胞的表达水平。采用流式细胞术检测分析患者组(PV)和健康对照组(HD)外周血CD3+、CD3+CD8+、CD3+CD8-和γδT细胞中分泌胞内因子IL-17、IFN-γ的细胞的百分比。结果为在所有检测的细胞亚群中，分泌IFN-γ的CD3+CD8-和γδT细胞在其所属亚群中所占比例明显高于健康对照组，分泌IL-17的γδT细胞的比例明显高于健康对照组。结论本研究对于理解机体抗疟原虫的细胞免疫的功能状态具有一定意义[15]。

（2）回国劳务人员输入性疟疾疫情监测分析

【摘要】

了解回国劳务人员疟疾病例输入情况，为制定防控措施提供科学依据。方法是对回国劳务人员不明原因发热者自愿到新疆国际旅行卫生保健中心进行实验室检查和流行病学调查。结果2009-2011年自愿检查17人中，共检出疟疾13例，恶性疟12例，间日疟1例。结论为出入境检验检疫机构应加强疟疾疫情监测及口岸检疫查验，及时掌握内外疫情信息，一旦发现疫情,及时采取有效的控制措施，防止输入性疟疾的播散[16]。

（3）2004～2012年云南大理州疟疾监测结果分析

【摘要】

对云南省大理州外出疟疾病区务工及本地类似疟疾发热人员进行血涂片法检测，及时发现并治疗疟疾患者，遏制内源性病例的发生。方法是对2004年1月1日~2012年12月31日期间，在云南省大理州疾病预防控制中心做疟疾检验

*为了给读者提供更简明扼要的信息，本报告中的中文摘要均经过编辑和精简。

的寒颤、出汗以及高热等症状的患者取耳垂血，镜检查找疟原虫。结果为共检测227 例发热患者，检出疟疾 71 例，检出率 31.28%；同时检测 49 例本地未外出的发热患者，无阳性病例检出；外出返乡发热居民 166 例，阳性 69 例，占总病例的 97.18%(69/71)；外来流动发热患者 12 例，阳性 2 例，占总病例数的 2.82%(2/71)；检出病例中，以间日疟居多，占 67.6%,其次为恶性疟。结论对从病区返乡、外来及本地的类似疟疾的发热居民进行血涂片镜检，为及时确诊、治疗疟疾患者提供了实验室依据，是控制疟疾传播的关键性环节[17]。

（4）2008-2012 年广州市输入性疟疾病例流行病学分析

【摘要】

对 2008-2012 年广州市 298 例输入性疟疾病例进行流行病学分析。298 例病例中，恶性疟 169 例(56.7%)、间日疟 106 例(35.6%)、未分型疟疾 23 例(7.7%)，恶性疟病例的构成有逐年上升趋势。病例中男女比例为 6.6∶1。感染来源地主要是非洲和东南亚等疟疾流行区。在 298 例中，主要为商业服务者(53.7%，160/298)、外派务工人员(26.2%，78/298)、农民(6.7%，20/398)和自由职业者(6.0%，18/398)等[18]。

2. 血吸虫相关

（1）吡喹酮合成新方法研究

【摘要】

研究了抗血吸虫药物吡喹酮的合成新方法。以甘氨酸乙酯盐酸盐和溴代乙醛缩二乙醇为原料，经 N-烃化、N-酰化和 Pictet-Spengler 缩合三步反应合成出了吡喹酮。探讨了催化剂用量、缚酸剂、反应温度和酸催化剂对反应的影响。三步反应总收率为 32%。产物结构经 IR、1 H NMR、13C NMR、MS 和 HRMS 确证。该方法反应条件温和，成本低，环境污染少，具有一定的工业化前景 [19]。

（2）日本血吸虫重组 Bb(pGEX-Sj26GST-Sj32)疫苗免疫小鼠脾细胞增殖、亚群及凋亡的动态变化

【摘要】

探讨日本血吸虫重组 Bb(pGEX-Sj26GST-Sj32)疫苗免疫 BALB/c 小鼠后脾细胞增殖、亚群及凋亡的动态变化。结论为日本血吸虫重组 Bb(pGEX-Sj26GST-Sj32)疫苗在免疫早期可引起脾细胞增殖，诱导 CD4+和 CD8+T 细胞参与宿主的免疫保护，抑制小鼠脾细胞的凋亡[20]。

（3）日本血吸虫重组两歧双歧杆菌(pGEX-Sj26GST)疫苗的构建及鉴定

【摘要】

构建日本血吸虫重组两歧双歧杆菌(pGEX-Sj26GST)疫苗，并对其进行鉴定。采用 RNeasy Mini 试剂盒提取日本血吸虫成虫总 RNA，采用逆转录聚合酶链反应(RT-PCR)方法获得 Sj26GST 抗原编码基因；将该编码基因与 pGEX-1λT 载体进行连接,得到重组质粒 pGEX-Sj26GST,并对其进行双酶切鉴定；将重组质粒电转化入两歧双歧杆菌中，构建重组两歧双歧杆菌(pGEX-Sj26GST)疫苗，PCR 鉴定疫苗。结果为 RT-PCR 扩增出的日本血吸虫成虫 Sj26GST 基因片段长度为 676bp；双酶切证实 Sj26GST 抗原编码基因成功插入 pGEX-1λT 载体中；PCR 证实从重组两歧双歧杆菌疫苗中扩增出长度为 676bp 的 Sj26GST 基因片段。本研究成功构建了日本血吸虫重组两歧双歧杆菌(pGEX-Sj26GST)疫苗[21]。

（4）安徽省血吸虫病潜在流行区流动人群感染情况调查分析

【摘要】

了解安徽省血吸虫病潜在流行区巢湖地区流动人群血吸虫病感染情况及流行病学特征，为该地区可能发生的突发疫情提供预警信息。方法是采用间接血凝试验法(IHA 法)于 2008-2012 年对巢湖地区流动人群血吸虫病感染情况进行血清学筛查，血检阳性者再用病原学方法 (集卵沉淀法)检查以确诊，并对流动人群血

吸虫病感染特征进行流行病学分析。结论为巢湖地区流动人群中已发现输入性血吸虫病传染源，今后应根据流动人群血吸虫病感染特点，采取有针对性的监测与治理措施，以降低潜在流行区血吸虫病的传播风险[22]。

3. 其他寄生虫相关

（1）登革病毒感染动物模型研究进展

【摘要】

登革病毒感染可以引起登革热、登革出血热和登革休克综合征，是威胁人类生命的重大公共卫生问题。为解决这一问题，迫切需要构建出适宜的动物模型。登革病毒可以在非人灵长类动物体内相关的细胞内复制并引起免疫反应，但无明显症状。具免疫活性的小鼠感染了登革病毒后一般不会出现症状，颅内接种病毒的小鼠可出现麻痹，使用高剂量病毒感染的新小鼠模型可以发生出血的症状。某些改良的免疫缺陷小鼠感染了登革病毒后可以表现出与人类登革出血热相似的症状。人源化小鼠模型支持登革病毒的复制并且可表现出登革热的部分症状。目前的模型各有优缺点，可分别为登革病毒感染的致病机理、免疫机制以及抗病毒药物和疫苗的临床前研究服务[23]。

（2）弓形虫感染间接免疫荧光检测试剂盒的检测效果评价

【摘要】

研制检测弓形虫 IgG 抗体的间接免疫荧光(IFA)检测试剂盒。方法是在成功建立弓形虫感染 IFA 检测方法的基础上，构建人弓形虫感染 IFA 检测试剂盒。对弓形虫阳性血清、羊抗人 FITC-IgG 的最佳稀释浓度进行优化。对试剂盒的敏感性、特异性、稳定性和保存期等进行评价，并与国外同类试剂盒比较。结论是该试剂盒检测弓形虫 IgG 抗体敏感性和特异性较高[24]。

（3）焦磷酸测序技术在确证贾第鞭毛虫和隐孢子虫中的应用

【摘要】

本研究旨在通过对贾第鞭毛虫和隐孢子虫进行序列信息分析的基础上，利用焦磷酸测序技术建立一种快速、简单地确证两虫的方法。方法是通过序列信息比对，对贾第鞭毛虫的磷酸丙糖异构酶(triose phosphate isomerase,tim)基因和隐孢子虫 18SrRNA 基因的保守区段设计扩增引物及测序引物。用 Sheather’s 蔗糖密度离心法从粪便标本中分离纯化贾第鞭毛虫孢囊和隐孢子虫卵囊。酚-氯仿法抽提孢囊、卵囊总 DNA，PCR 扩增目的基因片段，采用焦磷酸测序技术(Pyrosequencing Technology,PSQ)针对两虫基因保守核苷酸区段进行测序分析。同时利用扩增引物与其他原虫进行特异性试验，利用测序引物进行重复性试验。结论为基于序列分析的焦磷酸测序技术可以作为进一步确证两虫的方法使用[25]。

（4）华支睾吸虫感染是胆囊结石患者合并壁间结石的危险因素

【摘要】

探讨华支睾吸虫感染与胆囊结石患者合并壁间结石的关系。方法回顾性分析 2011 年 1~12 月间连续 340 例实施硬镜取石保胆手术的胆囊结石病人合并胆囊壁间结石情况，及其与华支睾吸虫感染、年龄、性别、术前血糖、血脂水平、乙肝病毒感染、胆囊结石的数量和大小的关系。结果①340 例胆囊结石患者中发现合并壁间结石 79 例(23.2%)检出华支睾吸虫感染阳性 153 例(45.0%)。②华支睾吸虫感染阳性患者合并壁间结石 49 例(49/153,32.0%);感染阴性患者合并壁间结石 30 例(30/187,16.0%),感染阳性者合并结石率较高(P=0.01);79 例合并壁间结石的病人中,47 例壁间结石内发现华支睾吸虫卵(59.5%)。③Logistic 回归分析显示,合并壁间结石的发生,与年龄、性别、术前血糖、血脂水平、乙肝病毒感染、胆囊结石的数量和大小等因素关系不大，而与华支睾吸虫感染有关(OR=2.29;95%CI=1.35~3.86,P=0.002)。结论为华支睾吸虫感染是胆囊结石患者合并壁间结石的危险因素[25]。

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