e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
Volume:02/Issue:07/July -2020 Impact Factor- 5.354 www.irjmets.com

ARTEMISININ RESISTANCE AND K 13-A SYSTEMIC REVIEW

Sultan Ahmad[*1], Nishat Anjum[*2], Gulistan Anjum[*3], Fakiha Khan[*4], Alkama Aziz[*5]

[*1,2]Senior Research Fellow, Department of Microbiology, Shri Guru Ram Rai University, Dehradun, UK, India

[*1,2]Junior Research Fellow, Department of Microbiology, Shri Guru Ram Rai University, Dehradun, UK, India

[*3,5]Junior Research Fellow, Department Of Botany, Ch. Charan Singh University, Meerut, UP, India

[*4]Senior Research Fellow, Department Of Biotechnology, Jamia MilliaIslamia, New Delhi, India

[*3,5]Junior Research Fellow, Department Of Botany, Ch. Charan Singh University, Meerut, UP, India

ABSTRACT

Malaria is caused by Plasmodium species of which P. falciparum is the most lethal. All the clinical symptoms of malaria are attributed to the blood stage of the parasite's life cycle. The propagation of the blood-stage requires repeated cycles of erythrocyte invasion and multiplication. All pathogenesis and death associated with Plasmodium falciparum malaria are due to parasite-infected erythrocytes. Invasion of erythrocytes by P. falciparum merozoites requires specific interactions between host receptors and parasite ligands that are localized in apical organelles called micronemes. The blood stage of malaria parasites is responsible for all the morbidity and mortality associated with malaria. During the blood stage, malaria parasites invade and multiply within host erythrocytes. The process of erythrocyte invasion requires specific interactions between host receptors and parasite ligands.

Keywords: Malaria Vaccine, drug discovery, K13, Artimisnine, ASO1.

I. INTRODUCTION

As per the WHO world malaria report 2018, there were an expected 219 million cases and 435 000 intestinal sickness related passings in 2017 around the world. Without an effective immunization that would offer security against malaria, we have to depend on antimalarial prescription to treat just as diminish the odds of getting the disease. Artemisinin in blend with other moderate acting medications is suggested for the treatment of P. falciparum malaria yet to our consternation first reports of Artemisinin opposition began surfacing around 2008. Subsequently it is the need of great importance to distinguish and describe the markers of medication obstruction just as track the safe genotypes to follow the way and spread of these safe parasites. Presentation the main endorsed immunization for malaria starting at 2015 is RTS,S, that has a moderately low adequacy.

Since intestinal sickness causes high mortality around the world, it is fundamental to recognize and approve new contender for antibody just as discover novel systems that would help in building up a superior immunization. Toward this path the recognized a thrombospondin related protein (PfTRAMP) that is associated with attack of the red platelets by the intestinal sickness parasite and antibodies against this protein hinder this intrusion procedure.But blood-stage malaria immunizations that target single antigens engaged with erythrocyte intrusion have not instigated ideal insurance in field preliminaries because of antigenic polymorphisms and sub-atomic repetition. Antibodies that focus on different attack related parasite proteins may hinder erythrocyte intrusion all the more effectively. Along these lines the significance of building up a receptor-blocking blood-stage immunization approach against P. falciparum that objectives the erythrocyte restricting areas of different parasite proteins, hindering their association with their receptors and in this manner repressing erythrocyte invasion.Malaria has been the broad and destructive parasitic contamination brought about by anopheline mosquitoes. It has become a worldwide issue with 214 million late cases and 438,000 passings in 2015, primarily in the sub-Saharan African regions[1].Over the most recent decade, intestinal sickness endemic locales have decided the dropping pace of malaria and moving the concentration from lessening to killing this dangerous infection.

It has been appeared in the past that the diminishing in malarial spread is feasible however extremely difficult to support. The overall battle to destroy malaria has truly bombed because of the improvement of parasitic protection from productive antimalarial medications and opposition of mosquito to bug sprays. Presently the worldwide concern stays to present proficient medications as a substitution of old and bombed drugs [2, 3].People are influenced by mostly four kinds of parasitic Plasmodium, yet the falciparum species is eminent for

most of fatalities around the world. The greater part of the examinations are centered around the falciparum intestinal sickness, yet more endeavors ought to be coordinated towards the understanding of other malaria species that would assist us with getting a handle on the seriousness of malaria diseases and configuration better intercession techniques [4, 5].At a similar time, it is need of great importance to search for new immunization up-and-comers and plan antibodies utilizing novel procedures for intestinal sickness elimination[6-8].

It has been noted as the species, delivering frightful malarial conditions, has created protection from each antimalarial compound accessible. The utilization of antimalarial drugs like chloroquine, sulfadioxine and pyrimethamine has been widely actualized before, and hence, been abused. The parasites have created obstruction under specific tension because of the planning of antimalarial drugs on a wide scale[9, 10].At the point when the parasites created protection from these antimalarial drugs in Southeast Asia, the P. falciparum endemic districts, mefloquine supplanted different medications, however soon obstruction created for this compound [11].

II. ARTEMISININ-BASED COMBINATION THERAPY (ACT)

Artemisinin-based Blend Treatment (ACT) With the exception of one prominent medication - artemisinin (Craftsmanship), obstruction has been created to all realized antimalarial drugs.

For a considerable length of time, Artemisinins have been utilized as conventional Chinese natural medication, got from the plant, Artemisia annua and demonstrated its adequacy against the hazardous sickness [12, 13]. To forestall the development of opposition, artemisinins in blend with accomplice drugs, where other antimalarial drugs like chloroquine, sulfadioxine-pyrimethamine and so on are utilized as accomplices, are broadly utilized. because of the high power of Workmanship with moderate acting and less intense accomplice drugs, ACTs are known for higher parasite murdering rate, absence of symptoms and nonappearance of resistance[14-16]. Expressions of the human experience being exceptionally dynamic against the abiogenetic pattern of P. falciparum are equipped for decreasing the biomass of the malarial parasite alongside short half-life (<1h) of Expressions in plasma, which requires the utilization of durable accomplice drugs [17]. Be that as it may, despite the huge use, clinical Craftsmanship obstruction has not yet been illustrated. Strikingly, the method of activity and restraint of parasite development with respect to Artemisinin stays an inquisitive case and a secret to-date [18, 19]. Subordinates of artemisinin that incorporate dihydroartemisinin, artemether, arteether and artesunate and numerous others are known as the original subsidiaries of Craftsmanship and accordingly combined and utilized in treating intestinal sickness [20].

These subsidiaries are sesquiterpene lactones known for their high action and quick disposal of malarial parasites nearly at all phases of development[16]. The proposed component for Craftsmanship enactment is a Fe-heam intervened process dividing the endoperoxide moiety of Expressions of the human experience and framing the receptive oxygen species (ROS), which focuses on the nucleophilic bunches in parasitic proteins and lipids. The artemisinin is known to covalently tie to 124 parasitic proteins, the majority of which are engaged with natural digestion basic for endurance. As suggested by WHO in 2001, artemisinin-based blend treatments (ACTs) are broadly utilized as first-line multidrug-treatment impervious to P. falciparum[21, 22]. In Southeastern Asia, artesunate-mefloquine has been adequately utilized for straightforward intestinal sickness brought about by P. falciparum. The Demonstration being broadly utilized and suggested is the dihydroartemisininpiperquine in the Southeastern nations because of its promising adequacy [15]. White and others recommended that Workmanship subsidiaries utilized alongside antimalarial accomplice medications could quickly diminish the parasite thickness to a base, though keeping the ideal degrees of the by longer actuation of the medication components[23].

High adequacy of ACTs has been appeared in the past in treating straightforward malaria in Asia and Africa; nearby information isn't accessible despite the away from of antimalarial wastefulness during ongoing years[24-28]. The adequacy of ACTs was exhibited in Afghanistan by one of the ongoing investigations while directing clinical preliminaries using a mix treatment of a Workmanship subordinate - artesunate (AS) and sulfadoxine-pyrimethamine (SP).

This examination showed the nearness of medication safe alleles which didn't create opposition against ACT

treatment and consequently, demonstrated effective for the intercession of malaria brought about by P. falciparum[29].

III. ART RESISTANCE PHENOTYPES

Craftsmanship Obstruction Phenotypes Since a couple of years, Workmanship opposition has risen as a rising concern. The principal report of Workmanship opposition goes back to mid 2000s close to the Thai-Cambodian outskirt for which the outcomes are still ambiguous.The indications of inefficacy of ACTs and artesunate monotherapy were plainly shown in western Cambodian artesunate-safe parasitic confines [30].

As indicated by WHO, the development of piperaquine obstruction in relationship to Craftsmanship opposition and its guide in the determination of piperaquine-safe parasites are contemporarily hazy. It is, notwithstanding, recommended that the piperaquine obstruction may have autonomously risen because of the long existence of piperaquine and its earlier use as monotherapy[31]. Different late clinical, in vitro, transcriptomics and genomic concentrates in Southeast Asia have sketched out the in vivo and in vitro Craftsmanship safe phenotypes, decided its hereditary premise, and have contemplated its clinical effect.

Fractional opposition is offered by the moderate parasite leeway rates communicated distinctly in the early-ring phases of the parasite[16].A gainful knowledge was given by Duru and others in exhibiting the disappointment of ACTs, especially dihydroartemisinin-piperquine in Cambodian separates. The entirety of the parasites in this investigation showed the choice of parasite that were at that point impervious to artemisinin [32].

IV. CLINICAL ART RESISTANCE

Clinical Workmanship Opposition Clinical Craftsmanship obstruction can be characterized as increased half-life freedom of the parasite or the nearness of perceivable parasites on the third day of ACT intercession. The parasitic half-life is profoundly connected with the in vitro and ex vivo ring-stage examines (RSAs), which assess the perseverance of the underlying ring-stage parasites presented to the 700nM measurement for 6 hours of the dynamic metabolite of Craftsmanship - the DHA (dihydroartemisinin) [17, 33].

In any case, the meaning of clinical opposition is influenced by different components like host invulnerability, tranquilize focus in blood or movement of accomplice sedate in the artemisinin-based blend treatment (ACT) [34]. Regardless of how amazing the additions of Expressions of the human experience and ACTs, the rise of Workmanship opposition has been noted in More prominent Mekong Subregion (GMS)(Laos, Cambodia, Thailand, Vietnam, and Mayanmar), which can prompt terrible impacts of malariaand a possible spread to the African sub-continent.On the other hand, the danger of Craftsmanship obstruction in the malarial separates is a more noteworthy issue when contrasted with the disappointment of the chloroquine and sulphadioxinepyremethamine obstruction in different pieces of the worlddue to its developing protection from falciparum malaria where different medications have failed[17, 22, 35, 36].

V. PARASITE CLEARANCE RATES

Parasite Leeway Rates So as to expound the parasite freedom rates in Upper Mayanmar in spite of the nearness of Workmanship obstruction, another examination uncovered the restorative impact of another Craftsmanship subordinate - dihydroartemisinin-piperquine (DP). Tunet al. assessed the middle half-existence of the parasite and decided it to be under 5 h (4.7 h) because of the successive assessment of parasitaemia showing a transitional opposition when contrasted with different sorts of changes in the significant district. Likewise, the significance of connection of site with the deferred parasite leeway rate[33, 37]. In an examination by Amaratunga et al., the leeway of parasites took longer time than expected with a half-existence of 11.28 h, demonstrating the across the board nearness of Workmanship safe phenotype outside Palin, Cambodia.

It was likewise noticed that some host factors represented the more prominent half-life while 40% half-life variety was because of parasite hereditary qualities. The ID of parasitic hereditary clusterwas discovered validated with the hereditary reason for the Workmanship opposition phenotype [38]. The postponed parasite leeway rate and obstruction has likewise been noted because of the nearness of safe parasitic hypnozoite stores as saw in P. falciparum and P. vivax[39]. Different examinations relate that the parasitic freedom half-life relies on the vulnerability of the parasite to Workmanship just as on the formative stage during Craftsmanship

treatment[17, 36]. Be that as it may, Craftsmanship obstruction stays undetected because of the inefficacy of opposition phenotypes in tranquilize weakness tests in vitro.

Some achievement has been accomplished utilizing progressed in vitro examines giving a knowledge into the parasitic weakness at formative ring stages in the erythrocytes. Besides, artemisinin-safe phenotypes have been accounted for with decreased defenselessness to Craftsmanship in a T0 [3H] hypoxanthine examine during the improvement of ring stage, delayed safe (ring) stage and diminished trophozoite stage during advancement. The all-encompassing safe stages and transitory pressure of the most vulnerable formative stage are seen to be exceptionally connected with Craftsmanship opposition. The modified example of advancement in the parasitic cell cycle is because of the expanding common sense of the Craftsmanship safe parasites during Workmanship introduction at ring stages. Such phenotype in the measured examples demonstrates abbreviated abiogenetic life pattern of the parasite.These epic phenotypes give a chance to distinguish the capacity of changes connected to Craftsmanship obstruction and deciding sub-atomic markers connected to Workmanship clinical resistance[17].

VI. IDENTIFICATION OF K13 MUTATIONS AS A MOLECULAR MARKER OF ART RESISTANCE

Recognizable proof of K13 Transformations as an Atomic Marker of Craftsmanship Opposition So as to find the quality answerable for artemisinin obstruction, genome-wide affiliation contemplates (GWAS) were done. The relationship of deferred leeway parasite rates with P. falciparum in Southeast Asia was shown.

After a solitary nucleotide polymorphism (SNP) examine, Takala-Harrison et al.,via linkage-disequilibrium windows utilized as a marker of the decelerated freedom rate, perceived that four SNPs on chromosomes 10, 13, and 14 were connected near the postponed parasite leeway. The SNPs on chromosome 10 and 13 demonstrated relationship with the qualities engaged with a DNA harm resilience pathway. These SNPs were later connected to the qualities PF3D7_1343700 (Kelch 13) and PF3D7_1459600 (ENTH area containing protein engaged with clathrin intervened endocytosis) through a methodology dependent on populace genetics. The GWAS examination has been used to feature the heritable characteristics of clinical Craftsmanship opposition and positive determination in geological districts of Workmanship resistance[40].

In ongoing investigations, the K13-propeller changes have been related with artemisinin obstruction in vivo and in vitro in Southeast Asia[36].In importance with the past examination, clinical protection from Expressions have demonstrated postponed parasite freedom rate, parasite leeway half-existence of >5h, nearness of heritable Kelch propeller transformations in the Pf3D7_1343700 area, and its quick spread, as noted in Southeast Asia [22, 41].It has now been demonstrated through screening of the Workmanship safe P. falciparum with K13 changes that the nearness of transformed P.falciparum has gone past the traditional western Thai-Cambodia border[42]. As straightforward as it appears, the hereditary reason for Workmanship opposition is tested by the presentation of sub-atomic markers, which uncovered an intricate puzzle that remaining parts unsolved. With the goal to recognize the hereditary premise of ACT attributes for adjustment, Cheeseman et al. used a two-phase procedure to decide the hereditary reason for hidden quality choice by looking at three geological locales (Cambodia, Thailand and Laos).

Screening and genotyping of 91 parasite clones decided single-nucleotide polymorphisms (SNPs) and duplicate number varieties (CNVs). Therefore, geological separation and haplotype structure at 6969 SNPs decided a locale of solid determination on chromosome 13 which compares to the decelerated parasite leeway rates[43]. Airey et al.led a quick examination to dissect changes in lab adjusted parasite clones chose for endurance while accepting high Craftsmanship measurements in vitro. The data yielded by such examination can manage polymorphism investigation in Workmanship safe parasitic examples from Cambodia. Sequencing a Workmanship delicate F-32 Tanzania parasite line showed artemisinin safe K13 propeller changes during DHA treatment in the RSA.

The nearness of connected disequilibrium around qualities showed four K13 propeller changes (Y493H, R539T, I543T, and C580Y) in the normally happening parasites in Cambodia. These changes were found related with long parasite freedom half-life and higher recurrence of endurance rates in the RSA 0-3h. It was likewise discovered that various degrees of K13 transformations present differing levels of Craftsmanship obstruction,

which show the hereditary foundation of the parasite affecting these levels. The requirement for an atomic marker perseveres to recognize and control the across the board Workmanship opposition.

Along these lines, it was inferred that the common changes can be used as markers to decide the decelerated parasite leeway rates in malarial patients accepting Craftsmanship treatment[36]. Comparative examinations were led by Ye et al., who recognized the K13-propeller locale of the P. falciparum quality as a sub-atomic marker to distinguish artemisinin-safe parasites in vitro.

K13-propeller transformations are likewise ready to distinguish parasitic leeway half-life (>5h) with 98.1% Workmanship affectability and 88.4% host particularity [14]. Late examinations expand that the recurrence of K13 transformations increment with Craftsmanship utilization, alongside the decontaminated choice taking a shot at the propeller locale of the K-13 quality. The number of inhabitants in parasites unexposed to ACTs give the essential data about K13-propeller quality acting as a sub-atomic marker of the Workmanship obstruction and expound an instance of positive choice in the untreated propeller area. In addition, many differentiated K13-propeller changes happen under Workmanship pressure[44]. In vitro tests have decided decrease in the P. falciparum vulnerability to Craftsmanship, however no proof has yet been found.

Feng and others got to five transformations with three being later. F446I transformation was transcendent among the examples gathered from China-Mayanmar outskirt demonstrating the dangers for developing obstruction in the More noteworthy Mekong Subregion (GMS)[45]. Another sub-atomic marker A578S was controlled by Hawkes and partners so as to expound the hereditary reason for the spread of malaria in the Ugandan Youngsters. Being the extreme instance of intestinal sickness in Uganda, the nonsynonymous SNP A578S in the K13 quality might be another recognized marker, in spite of the fact that not being straightforwardly connected with Craftsmanship obstruction, deciding a deferred reaction and parasitic leeway rate to Workmanship subsidiary [46].

Utilizing the PCR technique, DNA layouts were gotten from solidified examples for assessment and estimation of the Plasmodium parasite by Tripura et al. The creators related the diminished Craftsmanship part sedate affectability with the K13 propeller freak quality (C580Y) trying to forestall, treat and dispense with contaminations brought about by P. falciparum and P. vivax[39].

Another advancement with respect to the K13-propeller change (C580Y) has raised a worry among different investigations giving to its broad protection from artemisinin[39, 47-51]. The C580Y is more pervasive than other Workmanship safe molecularmarkers, in spite of the fact that it has not been seen as a predictable marker for Craftsmanship resistance[33, 36, 37].

It is in any case an affirmed sub-atomic marker of the K13 quality prevailing along the Thailand-Mayanmar and Cambodia-Thailand fringe, while the F446I prevails along the Mayanmar-India and China-Mayanmar outskirt [16]. Sequencing and genotyping of the PfK13 of 98 P. falciparum separates in Guyana by Chenetet al. decided the nearness of K13 transformation (C580Y) in solid relationship with sedate resistance[49]. As of late, an effective report communicated K13mutation (C580Y) in the hereditarily built clones of P. falciparum utilizing the CRISPR-Cas9 framework and exhibited moderate parasitic leeway rate. Through this examination, direct connection was set up between K13 change and Craftsmanship resistance[52]. Thusly, in an examination led by Straimeret al., P.falciparum K13 locus were hereditarily changed utilizing zinc-finger nuclease and the ring-endurance rates were assessed after medication presentation in vitro. These investigations recommended the abatement in the parasitic endurance rates after expulsion of K13 changes from Craftsmanship safe Cambodian disengages. Rather than applicable perceptions, Straimer and others distinguished higher opposition in some K13 changes (M4761,R493H, I543T) than other K13 transformations (Y493H and C580Y), showing the unobtrusive obstruction of C580Y being transcendent freak allele in Cambodia. Likewise, it proposed that extra factors were engaged with increasing K13-intervened opposition in the Cambodian isolates[17].

VII. K13 POLYMORPHISM ACROSS THE GLOBE

K13 Polymorphism over the globe Since the distinct Craftsmanship opposition phenotype is remarkable, the relationship of polymorphisms in marker qualities is difficult to relate with proficient results[53]. As per Mitaet al., 60 non-equivalent transformations have been distinguished in the K13 quality [44], while Fairhurst and Dondrop show that solitary 20 of 124 nonsynonymous K13 changes can be related with Craftsmanship

opposition (P441L, F446I, G449A, N458Y, C469Y, A481V, Y493H, S522C, G538V, R539T, I543T, P553L, R561H, V568G, P574L, C580Y, D584V, F673I, A675V, and H719N). Be that as it may, just four of these have been approved in vivo and in vitro: Y493H, R539T, I543T, and C580Y[16]. As of late, Arieyet al. uncovered the relationship of K13-propeller polymorphisms with Workmanship opposition. They demonstrated the solid connection between Craftsmanship obstruction and four K13-propeller polymorphisms, i.eC580Y, Y493H, R539T, and M476L[36]. So also, numerous SNPs have been accounted for in K13-propeller quality alongside various causes of the K13-propeller polymorphisms over the world, including Africa just as Southeast Asia[53, 54]. As showed by Tanabe et al., various SNPs alongside haplotype (3D7 succession) exist in the four landmasses being topographically particular and mainland explicit [55]. The crucial data about K13-propeller quality carrying on as an atomic marker of the Craftsmanship opposition gave an instance of positive choice in the untreated propeller domain[44]. The K13 propeller polymorphisms are known to exist broadly around the globe. As indicated by a report by Edwards et al.,the scattering of malarial contamination gets far reaching because of the moving populaces of higher transmission territories to bring down transmission zones, which thus hinder the control and disposal of the unpleasant sickness by bringing in the disease and spreading drug opposition. Such has been shown in the cross Cambodian fringe, the French Island of Mayaotte, and China, where the malarial diseases are for the most part imported from different areas or sent locally[45, 56, 57].

Reports of autonomous worldwide development of K13 transformation in an assortment of areas like Mayotte(N490H, F495L, N554H/K, and E596G) and Guyana(C580Y) have been gotten as of late, albeit no data on the clinical or phenotypic opposition has been noted in these disengages [49, 57].To imprint a norm for the spread of K13 polymorphisms, a novel report sequenced and genotyped 581 P.falciparum K13-propeller disconnects from Asia, Africa, Maleneia and South America gathered when ACT mediation. The number of inhabitants in disengages presented to drugs demonstrated higher frequencies of changes, nucleotide and haplotype assorted variety when contrasted with the unexposed parasite populace. Further signs incorporated the pervasiveness of C580Y transformations sooner than that of the principal report of Craftsmanship obstruction in 2007[2, 21, 44]. A worldwide examination was led by Menard et al to plan the K13-propeller polymorphisms. The creators used 14,037 examples from 59 nations and sequenced K13-propeller polymorphisms to assess the development and dispersal of transformations by haplotyping neighboring loci. Segregates having a comparable K13 transformation were connected hereditarily by assessing two adjoining loci.Such wonder uncovered the rise of occasions adjacent to the spread of changes for Workmanship opposition. Additionally, the distinction of transformations and haplotypes in the two obstruction locales in Asia recommended determination pressure in the relative regions because of the use of ACTsmainly. The proportion of heterogenous nonsynonymous K13 transformations in Asia extended from fixed to high in western Cambodia, middle of the road in Mayanmar and Vietnam, moderate in eastern Cambodia, Thailand, China and Laos, and low wherever else. K13 changes were accounted for extraordinary in South America, Oceania and Africa aside from a couple of African nations[58].

It is anyway fascinating to discover that the K13 polymorphisms related with Craftsmanship opposition in Southeast Asia (Y493H, R539T, I543Tand C580Y)have been missing in the sub-Saharan locales and as opposed to it, the other non-equal SNPs distinguished in sub-Saharan districts have not been seen in the Southeast Asian P. falciparum disengages. Along these lines, it is recommended that the K13 polymorphisms can fluctuate geologically and assurance of K13 propeller hereditary examinations can uncover and screen the worldwide development of protection from Workmanship [34, 59, 60]. In importance to the past examinations, other K13 polymorphisms were concentrated by Tacoli et al. Two K13 polymorphisms (P574L and A675V) are universally present in Southeast Asia and related with decelerated leeway rate. The significant request likewise reports that the K13 polymorphism P574L was watched without precedent for Rwanda, proposing their one of a kind nearness with the consideration of strains connected to Craftsmanship opposition [61]. In any case, the low predominance of K13 propeller in Africa was affirmed by Torrentino-Madamet et al while distinguishing K13 propeller polymorphisms in the P.falciparum separates gathered from 29 patients getting AL treatment on the French Island of Mayotte in 2013-2014[57]. An investigation by Duru and partners demonstrated the constrained hereditary decent variety of the parasites indicating the nearness of K13 polymorphisms in pretty much every parasite separate from Cambodia [32]. In any case, the Workmanship obstruction was noted to be kept to Southeast Asia and China. Since Workmanship safe K13 transformation has not been predominant in

Africa, the plentiful nearness of K13-propeller polymorphism A578S and others have been accounted for by different investigations which present genuine danger to K13 propeller functioning[58, 62, 63]. In spite of the fact that it is essential to direly create and actualize focused on intercessions to contain and dispose of Workmanship protection from its current locations[42], what is all the more disturbing is the free rise of K13 transformations in numerous geographic areas proposing that endeavors to take out artemisinin-safe malarial parasites in a single district may limitedly affect the rise of obstruction in neighboring regions.It further features the need to plan K13 changes all through the malaria endemic world.

This report is reliable in the examinations deciding polymorphisms in Haiti [59], Uganda[46, 64, 65], Angola and Mozambique[34], Rwanda[61], Kenya [66, 67], Ethiopia [68, 69], Senegal[70], Mayotte [57], Southeast Asia [40], Cambodia [36], Vietnam [71], Bangladesh[72], China [51][73].

VIII. MECHANISM OF ART RESISTANCE AND K13 POLYMORPHISM

Instrument of Craftsmanship opposition and K13 Polymorphism Since K13-propeller changes are exceptionally prognostic of obstruction, the information on fundamental systems that yields Workmanship resistantP.falciparum stays obscure [74]. It has been accounted for that the scope of K13 transformations and advancement of Workmanship opposition by single changes point towards the declining usefulness of the K13 protein. Past exploration has shown the capacity of human kelch-containing proteins as connectors bringing substrates into ubiquitination buildings [75]. In any case, when contrasted with human kelch proteins (Keap 1), K13 has a place with the kelch super group of proteins, comprising of a specific Plasmodium area and a N-terminal space, a BTB/POZ area and a six-sharp edge C-terminal propeller area comprised of essential kelch themes [76, 77]. The propeller space engages numerous protein-protein destinations and intervenes cell capacities like ubiquitin-controlled protein corruption and oxidative pressure reactions. It is recommended that the Fe-subordinate age of responsive oxygen species (ROS) intervenes the potential antimalarial impact of the Craftsmanship and its subsidiaries, initiating modification in the redox balance, and henceforth harms the cell targets.

It appears to be fascinating that the poisonousness of Craftsmanship subordinates relies on their star oxidant action, as opposed to their inclusion in the guideline of cytoprotective and protein corruption reactions to outside stress[36]. Notwithstanding, this theory further backings the proof that K13 is exceptionally homologous to the human Kelch protein (Keap 1), which is required in cell adjustment to oxidative pressure [78].The human kelch protein (Keap 1) is a negative controller of the inducible cytoprotective reaction reliant on the atomic erythroid 2-related factor 2 (Nrf2)[79]. The Nrf2 ties to the cell reinforcement reaction component (ARE) available in the quality advertisers engaged with stage II detoxification and oxidative pressure reactions. The Nrf2 is corrupted by the Keap 1, which targets it through the cullin 3 ligase complex for ubiquilination[80].

Along these lines, it is assumed that the K13 propeller performs comparable capacities in the Plasmodium, i.e coordinating the record factors joined in hostile to oxidant reactions through ligase complex. No orthologues of Nrf2 have been resolved in the parasitic genome [36]. In actuality, many recommended theories have explained the K13 polymorphism job in managing artemisinin obstruction in P. falciparum separates. The medication reactions of Cambodian wild-type K13 and transformed examples of P. falciparum, Dogovski et al showed the affectation of medication hindrance and gathering of ubiquinated proteins by the Craftsmanship.

This activity adds to cell stress reaction. The decelerated protein ubiquitination and postponed early apoptosis after medication presentation is shown by the safe parasite strains, which demonstrates more elevated levels of cell stress reaction.

Because of its similitude to substrate connectors for cullin3 ubiquitin ligases, the job of K13 is resolved in lessening the degree of ubiquitinated proteins[80, 81]. Moreover, Mbengueet al., as of late announced that artemisinins are powerful inhibitors of P. falciparum phosphatidylinositol-3-kinase (PfPI3K). PfPI3K phosphorylates phosphatidylinositol (PI) to create phosphatidylinositol 3-phosphate (PI3P) which advances cell motioning for parasite endurance, for example, hindrance of apoptosis.Hence, restraint of PfPI3K movement by DHA causes a decrease in PI3P level and in this manner prompts parasite demise.

They further indicated that PfPI3K interfaces with K13 and the K13 mutationshinder this collaboration

bringing about diminished polyubiquitination of PfPI3K, prompting the gathering of PfPI3K, just as its lipid item phosphatidylinositol-3-phosphate (PI3P). In this way the creators reasoned that degrees of PI3P can be utilized as an extra marker for forecast of artemisinin resistance.Buthow the raised PI3P prompts obstruction should be additionally assessed [50, 65]. To expound the component of Workmanship further, Mok et al accentuated the far reaching changes of the parasite transcriptional program modifying its physiology as an explanation behind Craftsmanship opposition. Afterward, the creators completed the transcriptome examinations of 1043 P. falciparum confines to reveal the fundamental instrument of artemisinin opposition. They found that Craftsmanship obstruction was exceptionally associated with up-controlled qualities joined in protein process, and since these pathways take an interest in unfurled protein reaction (UPR) including the significant Plasmodium responsive oxidative pressure complex (PROSC) and TCP-1 ring complex (TRiC) chaperone buildings, they may fill in as the significant middle of the road for Workmanship opposition brought about by K13 transformation in P. falciparumand relieve protein harm brought about by artemisinin [82]. It has been suggested that the K13 changes intervene Workmanship opposition by constraining their impacts on specific focuses at ring stage. Late investigations have given proof that the phosphatidylinositol-3-kinase (PfPI3K) of the P. falciparum is focused on explicitly by the artemisinins and its levels are expanded with K13 transformations in parasites[50].

Accordingly screening of K13 and PI3K proteins in Plasmodium vivax may assist us with extrapolating our present information on sedate protection from Vivax parasites [83-85].Another report by Wang and others recommends that the parasites with K13-propeller changes can conquer protein harm because of the medication adjustments by initiating the pressure reaction; in this manner, they are chosen as they have a higher capacity to endure the medication treatment at the early ring stage, so, all things considered medication enactment and medication pressure are moderately low; subsequently enhancing these transformations in the parasitepopulation[33].Different proteins have been presented in interceding the Craftsmanship obstruction without K13 changes. TRAC examines have uncovered that nonsynonymous polymorphisms in multidrug-opposition protein 2, apicoplast ribosomal protein S10 , chloroquine-obstruction carrier (pfcrt), and ferredoxin decide the hereditary foundation for the K13 changes to emerge [86].

It would likewise be essential to interpret the K13-autonomous components of Workmanship obstruction [87][88, 89, 98] The job of these proteins and pathways in artemisinin opposition is conceivable, however needs further assessment. It would be intriguing to portray the ordinary capacity of K13 and the impact of different changes found in the propeller area of K13.

Moreover, it would likewise be fascinating to unravel the character of putative K13 targets and their relationship with ubiquitin ligase movement. K13-atomic targets would give the basic knowledge for interrogatingits job in the hidden component of Workmanship resistance. Currently K13-propeller polymer.

IX. CONCLUSION AND FUTURE IMPLICATIONS

The spread of malaria and the danger to the viability of anti malarial drugs have raised a worldwide concern. Artemisinin has been utilized as a potential enemy of malarial in mix with less powerful medications, yet it has faced obstruction in the malaria species. The alleged Craftsmanship obstruction is probably going to be characterized as the expanded pace of decelerated parasite freedom phenotype or the K13-propeller changes, while the affirmed Workmanship opposition conveys the moderate clearing parasite phenotype alongside K13 transformations related with Workmanship resistance[16].

K13 polymorphism has end up being the main pivotal sub-atomic marker accessible for following the Workmanship obstruction. It might be conjectured that changes in K13 may likewise accompany an expense to parasite wellness, and may be lost quickly in populaces without artemisinin choice. Generally basic toward this path is decide the specific physiological jobs of K13 in the parasite and the impact of these polymorphisms on its function.Very strangely, there have been a few reports of moderate parasite leeway rates even without K13 freak alleles recommending the job of extra atoms being developed of Craftsmanship opposition in P. falciparum. It is significant to distinguish extra hereditary loci engaged with Craftsmanship resistance[14, 21, 86].Novel philosophies like GWAS[40, 43], click science [33], hereditary apparatuses [17, 52], transcriptomics[82] and chemogenic profiling [90]can end up being imperative for illuminating this puzzle of parasite sharp getaway from the as of now used antimalarial drugs. Apart from understanding the present

status and instruments of antimalarial sedate obstruction, it is additionally very basic to widen comprehension of this wise parasite [91-93]and simultaneously to extend the current weapons store utilized against the parasite[94-100].

All things considered, the artemisinin obstruction despite everything stays an ill defined situation, about which very little is known. Methodologies for ordinary checking and broad reconnaissance of K13 commonness ought to be executed. The national medication strategies ought to be seen cautiously and adjusted in an opportune manner as indicated by the recurrence of spreading opposition. The disclosure and distinguishing proof of disease phenotypes ought to be checked in the malaria endemic districts and the exploration for the instrument and intercession for the common obstruction should be desperately researched.

X. REFERENCES

[1] WHO, World Malaria Report 2014. 2014, WHO: Geneva.

[2] Fairhurst, R.M., et al., Artemisinin-resistant malaria: research challenges, opportunities, and public health implications. The American journal of tropical medicine and hygiene, 2012. **87**(2): p. 231-241.

[3] Siddiqui FA. Malaria Control and Elimination: How Far we are: An Opinion Article. Journal of Biometrics & Biostatistics 2016. DOI: 10.4172/2155-6180.1000321

[4] Wangdahl, A., et al., Severity of Plasmodium falciparum and Non-falciparum Malaria in Travelers and Migrants: A Nationwide Observational Study Over 2 Decades in Sweden. J Infect Dis, 2019. **220**(8): p. 1335-1345.

[5] Draper, S.J., et al., Malaria Vaccines: Recent Advances and New Horizons. Cell Host Microbe, 2018. **24**(1): p. 43-56.

[6] Pandey AK, Reddy KS, Sahar T, Gupta S, Singh H, Reddy EJ, Asad M,Siddiqui FA,Gupta P, Singh B, More KR, Mohmmed A, Chitnis CE, Chauhan VS, Gaur D. 2013.Identification of a potent combination of key Plasmodium falciparum merozoite antigens that elicit straintranscending parasite-neutralizing antibodies. Infect. Immun. 81:441–451.doi:10.1128/IAI.01107-12

[7] Siddiqui FA, Dhawan S, Singh S, Singh B, Gupta P, Pandey A, Mohmmed A, Gaur D,Chitnis CE. 2013. A thrombospondin structural repeat containing rhoptry protein from Plasmodium falciparum mediates erythrocyte invasion. Cell Microbiol 15:1341–1356.https://doi.org/10.1111/cmi.12118

[8] White, N.J., Antimalarial drug resistance. The Journal of clinical investigation, 2004. **113**(8): p. 1084-1092.

[9] WHO, Global Report on Antimalarial Efficacy and Drug Resistance: 2000-2010. 2010, WHO: Geneva. p. 9-10.

[10] Yeung, S., et al., Antimalarial drug resistance, artemisinin-based combination therapy, and the contribution of modeling to elucidating policy choices. The American journal of tropical medicine and hygiene, 2004. **71**(2 suppl): p. 179-186.

[11] Klayman, D.L., Qinghaosu (artemisinin): an antimalarial drug from China. Science, 1985. **228**(4703): p. 1049-1055.

[12] White, N.J., Qinghaosu (artemisinin): the price of success. Science, 2008. **320**(5874): p. 330-334.

[13] Ye, R., et al., Distinctive origin of artemisinin-resistant Plasmodium falciparum on the China-Myanmar border. Scientific reports, 2016. **6**.

[14] Davis, T., H.A. Karunajeewa, and K.F. Ilett, Artemisinin-based combination therapies for uncomplicated malaria. Med J Aust, 2005. **182**(4): p. 181-5.

[15] Fairhurst, R.M. and A.M. Dondorp, Artemisinin-resistant Plasmodium falciparum malaria. Microbiology spectrum, 2016. **4**(3).

[16] Straimer, J., et al., K13-propeller mutations confer artemisinin resistance in Plasmodium falciparum clinical isolates. Science, 2015. **347**(6220): p. 428-431.

[17] Golenser, J., et al., Current perspectives on the mechanism of action of artemisinins. International journal for parasitology, 2006. **36**(14): p. 1427-1441.

[18] O'Neill, P.M., et al., Enantiomeric 1, 2, 4-Trioxanes Display Equivalent in vitro Antimalarial Activity Versus Plasmodium falciparum Malaria Parasites: Implications for the Molecular Mechanism of Action of the Artemisinins. ChemBioChem, 2005. **6**(11): p. 2048-2054.

[19] O'Neill, P.M. and G.H. Posner, A medicinal chemistry perspective on artemisinin and related endoperoxides. Journal of medicinal chemistry, 2004. **47**(12): p. 2945-2964.

[20] Ashley, E.A., et al., Spread of artemisinin resistance in Plasmodium falciparum malaria. New England Journal of Medicine, 2014. **371**(5): p. 411-423.

[21] Hott, A., et al., Artemisinin-resistant Plasmodium falciparum parasites exhibit altered patterns of development in infected erythrocytes. Antimicrobial agents and chemotherapy, 2015. **59**(6): p. 3156-3167.

[22] White, N., et al., Averting a malaria disaster. The Lancet, 1999. **353**(9168): p. 1965-1967.

[23] Von Seidlein, L., et al., Treatment of African children with uncomplicated falciparum malaria with a new antimalarial drug, CGP 56697. Journal of infectious diseases, 1997. **176**(4): p. 1113-1116.

[24] Tjitra, E., et al., Therapy of uncomplicated falciparum malaria: a randomized trial comparing artesunate plus sulfadoxine-pyrimethamine versus sulfadoxine-pyrimethamine alone in Irian Jaya, Indonesia. The American journal of tropical medicine and hygiene, 2001. **65**(4): p. 309-317.

[25] Adjuik, M., et al., Amodiaquine-artesunate versus amodiaquine for uncomplicated Plasmodium falciparum malaria in African children: a randomised, multicentre trial. The Lancet, 2002. **359**(9315): p. 1365-1372.

[26] Barennes, H., et al., A randomized trial of amodiaquine and artesunate alone and in combination for the treatment of uncomplicated falciparum malaria in children from Burkina Faso. Tropical Medicine & International Health, 2004. **9**(4): p. 438-444.

[27] Staedke, S.G., et al., Combination treatments for uncomplicated falciparum malaria in Kampala, Uganda: randomised clinical trial. The Lancet, 2004. **364**(9449): p. 1950-1957.

[28] Awab, G.R., et al., Clinical trials of artesunate plus sulfadoxine-pyrimethamine for Plasmodium falciparum malaria in Afghanistan: maintained efficacy a decade after introduction. Malaria journal, 2016. **15**(1): p. 1.

[29] Dondorp, A.M., et al., Artemisinin resistance in Plasmodium falciparum malaria. New England Journal of Medicine, 2009. **361**(5): p. 455-467.

[30] WHO, Status report on artemisinin and ACT resistance - September 2015. 2015 WHO: Geneva.

[31] Duru, V., et al., Plasmodium falciparum dihydroartemisinin-piperaquine failures in Cambodia are associated with mutant K13 parasites presenting high survival rates in novel piperaquine in vitro assays: retrospective and prospective investigations. BMC medicine, 2015. **13**(1): p. 1.

[32] Wang, Z., et al., Prevalence of K13-propeller polymorphisms in Plasmodium falciparum from China-Myanmar border in 2007–2012. Malaria journal, 2015. **14**(1): p. 1.

[33] Escobar, C., et al., Polymorphisms in Plasmodium falciparum K13-Propeller in Angola and Mozambique after the Introduction of the ACTs. PLoS One, 2015. **10**(3): p. e0119215.

[34] Liu, H., et al., Investigation and control of a Plasmodium falciparum malaria outbreak in Shan Special Region II of Myanmar along the China-Myanmar Border from June to December 2014. Infectious diseases of poverty, 2016. **5**(1): p. 1.

[35] Ariey, F., et al., A molecular marker of artemisinin-resistant Plasmodium falciparum malaria. Nature, 2014. **505**(7481): p. 50-55.

[36] Tun, K.M., et al., Parasite clearance rates in Upper Myanmar indicate a distinctive artemisinin resistance phenotype: a therapeutic efficacy study. Malaria journal, 2016. **15**(1): p. 1.

[37] Amaratunga, C., et al., Artemisinin-resistant Plasmodium falciparum in Pursat province, western Cambodia: a parasite clearance rate study. The Lancet infectious diseases, 2012. **12**(11): p. 851-858.

[38] Tripura, R., et al., Persistent Plasmodium falciparum and Plasmodium vivax infections in a western Cambodian population: implications for prevention, treatment and elimination strategies. Malaria journal, 2016. **15**(1): p. 1.

[39] Takala-Harrison, S., et al., Genetic loci associated with delayed clearance of Plasmodium falciparum following artemisinin treatment in Southeast Asia. Proceedings of the National Academy of Sciences, 2013. **110**(1): p. 240-245.

[40] O'Brien, C., et al., Recent clinical and molecular insights into emerging artemisinin resistance in Plasmodium falciparum. Current opinion in infectious diseases, 2011. **24**(6): p. 570.

[41] Bosman, P., et al., Plasmodium prevalence and artemisinin-resistant falciparum malaria in Preah Vihear Province, Cambodia: a cross-sectional population-based study. Malaria journal, 2014. **13**(1): p. 1.

[42] Cheeseman, I.H., et al., A major genome region underlying artemisinin resistance in malaria. Science, 2012. **336**(6077): p. 79-82.

[43] Mita, T., et al., Little polymorphism at the K13 propeller locus in worldwide Plasmodium falciparum populations prior to the introduction of artemisinin combination therapies. Antimicrobial agents and chemotherapy, 2016. **60**(6): p. 3340-3347.

[44] Feng, J., et al., Evaluation of antimalarial resistance marker polymorphism in returned migrant workers in china. Antimicrobial agents and chemotherapy, 2015 a. **59**(1): p. 326-330.

[45] Hawkes, M., et al., Slow clearance of Plasmodium falciparum in severe pediatric Malaria, Uganda, 2011–2013. Emerging infectious diseases, 2015. **21**(7): p. 1237.

[46] Kite, W.A., et al., Alternative methods for the Plasmodium falciparum artemisinin ring-stage survival assay with increased simplicity and parasite stage-specificity. Malaria journal, 2016. **15**(1): p. 1.

[47] Alareqi, L.M., et al., Molecular markers associated with resistance to commonly used antimalarial drugs among Plasmodium falciparum isolates from a malaria-endemic area in Taiz governorate—Yemen during the transmission season. Acta Tropica, 2016. **162**: p. 174-179.

[48] Chenet, S.M., et al., Independent emergence of the Plasmodium falciparum kelch propeller domain mutant allele C580Y in Guyana. Journal of Infectious Diseases, 2015: p. jiv752.

[49] Mbengue, A., et al., A molecular mechanism of artemisinin resistance in Plasmodium falciparum malaria. Nature, 2015. **520**(7549): p. 683-687.

[50] Feng, J., et al., Amplification of pfmdr1, pfcrt, pvmdr1, and K13 propeller polymorphisms associated with Plasmodium falciparum and Plasmodium vivax isolates from the China-Myanmar border. Antimicrobial agents and chemotherapy, 2015 b. **59**(5): p. 2554-2559.

[51] Ghorbal, M., et al., Genome editing in the human malaria parasite Plasmodium falciparum using the CRISPR-Cas9 system. Nature biotechnology, 2014. **32**(8): p. 819-821.

[52] Chatterjee, M., et al., No polymorphism in Plasmodium falciparum K13 propeller gene in clinical isolates from Kolkata, India. Journal of pathogens, 2015. **2015**.

[53] Huang, B., et al., Polymorphisms of the artemisinin resistant marker (K13) in Plasmodium falciparum parasite populations of Grande Comore Island 10 years after artemisinin combination therapy. Parasites & vectors, 2015. **8**(1): p. 1.

[54] Tanabe, K., et al., Spontaneous mutations in the Plasmodium falciparum sarcoplasmic/endoplasmic reticulum Ca2+-ATPase (PfATP6) gene among geographically widespread parasite populations unexposed to artemisinin-based combination therapies. Antimicrobial agents and chemotherapy, 2011. **55**(1): p. 94-100.

[55] Edwards, H.M., et al., Novel cross-border approaches to optimise identification of asymptomatic and artemisinin-resistant Plasmodium infection in mobile populations crossing Cambodian borders. PloS one, 2015. **10**(9): p. e0124300.

[56] Torrentino-Madamet, M., et al., K13-propeller polymorphisms in Plasmodium falciparum isolates from patients in Mayotte in 2013 and 2014. Antimicrobial agents and chemotherapy, 2015. **59**(12): p. 7878-7881.

[57] Ménard, D., et al., A worldwide map of Plasmodium falciparum K13-propeller polymorphisms. New England Journal of Medicine, 2016. **374**(25): p. 2453-2464.

[58] Carter, T.E., et al., Artemisinin resistance-associated polymorphisms at the K13-propeller locus are absent in Plasmodium falciparum isolates from Haiti. The American journal of tropical medicine and hygiene, 2015. **92**(3): p. 552-554.

[59] Siddiqui FA, Boonhok R, Cabrera M, Mbenda HGN, Wang M, Min H, Liang X, Qin J,Zhu X, Miao J, Cao Y, Cui L. Role of Plasmodium falciparum Kelch 13 Protein Mutations in P. falciparum Populations from Northeastern Myanmar in Mediating Artemisinin Resistance.Mbio:2020; 11:e01134–19. https://doi.org/10.1128/mBio.01134-19 PMID:32098812

[60] Tacoli, C., et al., Artemisinin Resistance–Associated K13 Polymorphisms of Plasmodium falciparum in Southern Rwanda, 2010–2015. The American Journal of Tropical Medicine and Hygiene, 2016: p. 16-0483.

[61] Taylor, S.M., et al., Absence of putative artemisinin resistance mutations among Plasmodium falciparum in sub-Saharan Africa: a molecular epidemiologic study. Journal of Infectious Diseases, 2015. **211**(5): p. 680-688.

[62] Kamau, E., et al., K13-propeller polymorphisms in Plasmodium falciparum parasites from sub-Saharan Africa. Journal of Infectious Diseases, 2014: p. jiu608.

[63] Cooper, R.A., et al., Lack of artemisinin resistance in Plasmodium falciparum in Uganda based on parasitological and molecular assays. Antimicrobial agents and chemotherapy, 2015. **59**(8): p. 5061-5064.

[64] Conrad, M.D., et al., Polymorphisms in K13 and falcipain-2 associated with artemisinin resistance are not prevalent in Plasmodium falciparum isolated from Ugandan children. PloS one, 2014. **9**(8): p. e105690.

[65] Muwanguzi, J., et al., Lack of K13 mutations in Plasmodium falciparum persisting after artemisinin combination therapy treatment of Kenyan children. Malaria journal, 2016. **15**(1): p. 1.

[66] Borrmann, S., et al., Genome-wide screen identifies new candidate genes associated with artemisinin susceptibility in Plasmodium falciparum in Kenya. Scientific reports, 2013. **3**: p. 3318.

[67] Bayih, A.G., et al., A Unique Plasmodium falciparum K13 Gene Mutation in Northwest Ethiopia. The American journal of tropical medicine and hygiene, 2016. **94**(1): p. 132-135.

[68] Heuchert, A., et al., Molecular markers of anti-malarial drug resistance in southwest Ethiopia over time: regional surveillance from 2006 to 2013. Malaria journal, 2015. **14**(1): p. 1.

[69] Boussaroque, A., et al., Emergence of Mutations in the K13 Propeller Gene of Plasmodium falciparum Isolates from Dakar, Senegal, in 2013-2014. Antimicrobial agents and chemotherapy, 2016. **60**(1): p. 624-627.

[70] Thriemer, K., et al., Delayed parasite clearance after treatment with dihydroartemisinin-piperaquine in Plasmodium falciparum malaria patients in central Vietnam. Antimicrobial agents and chemotherapy, 2014. **58**(12): p. 7049-7055.

[71] Mohon, A.N., et al., Mutations in Plasmodium falciparum K13 propeller gene from Bangladesh (2009–2013). Malaria journal, 2014. **13**(1): p. 1.

[72] Zhang J, Li N, Siddiqui FA, Xu S, Geng J, Zhang J, He X, Zhao L, Pi L, Zhang Y, Li C,Chen X, Wu Y, Miao J, Cao Y, Cui L, Yang Z. In vitro susceptibility of Plasmodium falciparum isolates from the China-Myanmar border area to artemisinins and correlation with K13 mutations. 2019 International Journal for Parasitology: Drugs and Drug Resistance. DOI: 10.1016/j.ijpddr.2019.04.002

[73] Mok, S., et al., Drug resistance. Population transcriptomics of human malaria parasites reveals the mechanism of artemisinin resistance. Science, 2015. **347**(6220): p. 431-5.

[74] Woodrow, C.J. and N.J. White, The clinical impact of artemisinin resistance in Southeast Asia and the potential for future spread. FEMS Microbiology Reviews, 2016: p. fuw037.

[75] Adams, J., R. Kelso, and L. Cooley, The kelch repeat superfamily of proteins: propellers of cell function. Trends in cell biology, 2000. **10**(1): p. 17-24.

[76] Prag, S. and J.C. Adams, Molecular phylogeny of the kelch-repeat superfamily reveals an expansion of BTB/kelch proteins in animals. BMC bioinformatics, 2003. **4**(1): p. 1.

[77] Mitsuishi, Y., H. Motohashi, and M. Yamamoto, The Keap1-Nrf2 system in cancers: stress response and anabolic metabolism. Frontiers in oncology, 2011. **2**: p. 200-200.

[78] Velichkova, M. and T. Hasson, Keap1 regulates the oxidation-sensitive shuttling of Nrf2 into and out of the nucleus via a Crm1-dependent nuclear export mechanism. Molecular and cellular biology, 2005. **25**(11): p. 4501-4513.

[79] Villeneuve, N.F., A. Lau, and D.D. Zhang, Regulation of the Nrf2–Keap1 antioxidant response by the ubiquitin proteasome system: an insight into cullin-ring ubiquitin ligases. Antioxidants & redox signaling, 2010. **13**(11): p. 1699-1712.

[80] Dogovski, C., et al., Targeting the cell stress response of Plasmodium falciparum to overcome artemisinin resistance. PLoS Biol, 2015. **13**(4): p. e1002132.

[81] Mok, S., et al., Population transcriptomics of human malaria parasites reveals the mechanism of artemisinin resistance. Science, 2015. **347**(6220): p. 431-435.

[82] Mbenda HGN, Zeng W, Bai Y, Siddiqui FA, Yang Z, Cui L. Genetic diversity of the Plasmodium vivax phosphatidylinositol 3-kinase gene in two regions of the China–Myanmar border. Infect Genet Evol. 2018;61:45–52

[83] Mbenda HGN, Wang M, Guo J, Siddiqui FA, Hu Y, Yang Z, Kittichai V, Sattabongkot J,Cao Y, Jiang L, Cui L. Evolution of the Plasmodium vivax multidrug resistance 1 gene in the Greater Mekong Subregion during malaria elimination. 2020. Parasites & vectors 13(1), 67.

[84] Wang, M., Siddiqui, F.A., Fan, Q. et al. Limited genetic diversity in the PvK12 Kelch protein in Plasmodium vivax isolates from Southeast Asia. Malar J 15, 537 (2016). https://doi.org/10.1186/s12936-016-1583-0

[85] Miotto, O., et al., Genetic architecture of artemisinin-resistant Plasmodium falciparum. Nature genetics, 2015. **47**(3): p. 226-234.

[86] Mukherjee, A., et al., Artemisinin resistance without pfkelch13 mutations in Plasmodium falciparum isolates from Cambodia. Malar J, 2017. **16**(1): p. 195.

[87] Siddiqui FA, Cabrera M, Wang M, Brashear A, Kemirembe K, Wang Z,Miao J,Chookajorn T, Yang Z, Cao Y, Dong G, Rosenthal PJ, Cui L. 2018.Plasmodium falciparum falcipain-2a polymorphisms in Southeast Asia and their association with artemisinin resistance. J Infect Dis 218:434 – 442. https://doi.org/10.1093/infdis/jiy188.

[88] Zhao Y, Ziling Liu, Soe MT, Wang L, Soe TN, Wei H, Than A, Aung PL, Li Y, Zhang X, Hu Y, Wei H, Zhang Y, Burgess J, Siddiqui FA, Menezes L, Wang Q, Kyaw MP, Cao Y, Cui L. Genetic Variations Associated with Drug Resistance Markers in Asymptomatic Plasmodium falciparum Infections in Myanmar. 2019 Genes 10 (9), 692. DOI:10.3390/genes10090692

[89] Pradhan, A., et al., Chemogenomic profiling of Plasmodium falciparum as a tool to aid antimalarial drug discovery. Scientific reports, 2015. **5**.

[90] Alam, M.M., et al., Phosphoproteomics reveals malaria parasite Protein Kinase G as a signalling hub regulating egress and invasion. Nat Commun, 2015. **6**: p. 7285.

[91] Dawn A, Singh S, More KR, Siddiqui FA, Pachikara N, Ramdani G, Langsley G, Chitnis CE.2014. The central role of cAMP in regulating Plasmodium falciparum merozoite invasion of human erythrocytes. PLoS Pathog 10:e1004520 https://doi.org/10.1371/journal.ppat.1004520

[92] Balaich, J.N., et al., The Nonartemisinin Sesquiterpene Lactones Parthenin and Parthenolide Block Plasmodium falciparum Sexual Stage Transmission. Antimicrobial agents and chemotherapy, 2016. **60**(4): p. 2108-2117.

[93] Mott, B.T., et al., High-throughput matrix screening identifies synergistic and antagonistic antimalarial drug combinations. Scientific reports, 2015. **5**.

[94] Baragaña, B., et al., A novel multiple-stage antimalarial agent that inhibits protein synthesis. Nature, 2015. **522**(7556): p. 315-320.

[95] Hati S, Madurkar SM, Bathula C, Thulluri C, Agarwal R, Siddiqui FA, Dangi P, Adepally U, Singh A,Singh S, Sen S. Design, synthesis and biological evaluation of small molecules as potent glucosidase inhibitors. Eur J Med Chem. 2015; 100:188–196.https://doi.org/10.1016/j.ejmech.2015.04.059 PMID:26087029

[96] Li J, Zhang J, Li Q, Hu Y, Ruan Y, Tao Z,et al. (2020) Ex vivo susceptibilities of Plasmodium vivax isolates from the China-Myanmar border to antimalarial drugs and association with polymorphisms in Pvmdr1 and Pvcrt-o genes.PLoS Negl Trop Dis 14(6): e0008255. https://doi.org/10.1371/journal.pntd.0008255

[97] Li J, Zhang J, Li Q, Hu Y, Ruan Y, Tao Z, et al. (2020) Ex vivo susceptibilities of Plasmodium vivax isolates from the China-Myanmar border to antimalarial drugs and association with polymorphisms in Pvmdr1 and Pvcrt-o genes. PLoS Negl Trop Dis 14(6): e0008255. https://doi.org/10.1371/journal.pntd.0008255

[98] Pandey AK, Reddy KS, Sahar T, Gupta S, Singh H, Reddy EJ, et al. Identifcation of a potent combination of key Plasmodium falciparum merozoite antigens that elicit straintranscending parasite-neutralizing antibodies.Infect Immun. 2013;81:441–51