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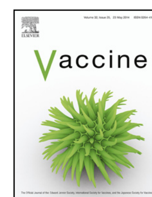

Transmission blocking malaria vaccines: Assays and candidates in clinical development

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ABSTRACT

Stimulated by recent advances in malaria control and increased funding, the elimination of malaria is now considered to be an attainable goal for an increasing number of malaria-endemic regions. This has boosted the interest in transmission-reducing interventions including vaccines that target sexual, sporogenic, and/or mosquito-stage antigens to interrupt malaria transmission (SSM-VIMT). SSM-VIMT aim to prevent human malaria infection in vaccinated communities by inhibiting parasite development within the mosquito after a blood meal taken from a gametocyte carrier. Only a handful of target antigens are in clinical development and progress has been slow over the years. Major stumbling blocks include (i) the expression of appropriately folded target proteins and their downstream purification, (ii) insufficient induction of sustained functional blocking antibody titers by candidate vaccines in humans, and (iii) validation of a number of (bio)-assays as correlate for blocking activity in the field. Here we discuss clinical manufacturing and testing of current SSM-VIMT candidates and the latest bio-assay development for clinical evaluation. New testing strategies are discussed that may accelerate the evaluation and application of SSM-VIMT.

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1. Introduction

Q3 The World Malaria Report 2014 documented major progress with a considerable reduction of the malaria burden in several countries. In sub-Saharan Africa, average infection prevalence in children aged 2–10 years showed a decline of 48% since the year 2000 with similar decreases in malaria-attributed mortality [1]. In addition to the prevention and treatment of clinical cases, reduction of malaria transmission forms a fundamental basis of malaria control and elimination. As new tools are developed, their impact on malaria parasite transmission can be quantified and malaria elimination may become a realistic endeavor for an increasing number of settings. Transmission reduction may thereby become a key metric in measuring the impact of new tools and combinations of intervention methods. Vaccines interrupting malaria transmission (VIMT), introduced in the malaria vaccine roadmap (reviewed in [2]), that effectively interrupt transmission from humans to mosquitoes have the potential to fill a critical gap in the malaria vaccine portfolio. Such vaccines aim to reduce the spread of the parasites among humans by preventing infection of *Anopheles* vectors and represent highly relevant tools for the accomplishment of malaria elimination and eradication. Traditionally only sexual- and sporogonic antigens have been considered transmission blocking vaccine targets but more recently pre-erythrocytic vaccines have been included because these – if highly effective – prevent parasitaemia and thus generation of gametocytes and onward transmission [2,3]. Pre-erythrocytic vaccines have the advantage that they confer direct personal protection while only delayed personal protection can be expected from vaccines directed exclusively against sexual-sporogonic-mosquito stages (SSM-VIMT).

Already in the 1950s, it was shown that immunization of chickens with a mix of asexual-and sexual stages of *Plasmodium gallinaceum* blocked parasite infectivity [4]. Twenty years later, it appeared that antibodies against target antigens on sexual stages were responsible for the observed transmission blocking effects in this model and that these antibodies acted after ingestion by mosquitoes [5,6]. Antibodies can destroy gametes and zygotes up to several hours after a mosquito blood meal and can completely prevent infectivity to mosquitoes. The first description of mosquito feeding assays, that form a cornerstone of assessments of transmission blocking immune responses, dates from the 1950s [7]. In the decades that followed, experimental mosquito membrane feeding systems were optimized and monoclonal antibody technology became available. This resulted in the development of the standard membrane feeding assay (SMFA) and a series of sexual stage proteins were defined as targets for transmission blocking antibodies

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([8–10], reviewed in [11]). The genes encoding Pfs48/45, Pfs230 and Pfs25 in *Plasmodium falciparum* as well as its ortholog Pvs25 in *Plasmodium vivax*, were isolated and these target proteins remained the major candidates for clinical development of transmission blocking vaccines for already for the past three decades [12–15]. During this period, several workshops have been organized by, amongst others, the World Health Organization, the United States National Institutes of Health (NIH), Malaria Vaccine Initiative and the Bill & Melinda Gates Foundation to discuss clinical trial design and endpoints, efficacy evaluation assays, regulatory aspects and application strategies [2,3,16–18]. Major challenges in this endeavor have been (i) incomplete/inadequate conformation of vaccine proteins and the production of clinical grade material; (ii) absence of validated standards and assays for clinical efficacy; (iii) absence of a rapid pipeline of proof-of-principle human trials for testing lead candidates. Here, we will discuss the latest progress in clinical development of SSM-VIMTs and evaluation of biological endpoint measures with suggestions for future steps.

2. SSM-VIMT candidates in clinical development

Transmission blocking immunity relies on functional antibodies against surface membrane proteins on sexual/sporogonic stages or mosquito midgut antigens. Pre-fertilization antigens are expressed in gametocytes in the human host but only become accessible for functional antibody binding once gametocytes emerge from the red blood cells to form gametes in the mosquito midgut. Naturally acquired- or experimentally-induced antibodies can bind to gametes, thereby preventing fertilization and zygote formation. Pre-fertilization antigens expressed in humans can induce antibodies after natural infection thereby creating the possibility to boost and/or enhance vaccine induced antibody titers and longevity [19–21]. Post-fertilization transmission blocking target antigen expression occurs in the mosquito midgut in zygotes and ookinetes [10,22]. There is currently no evidence that these proteins are expressed in gametocytes in the human circulation and therefore the human immune system is not exposed to these proteins and naturally acquired antibodies are not detectable [23,24]. Although a substantial number of targets have been identified and tested in preclinical studies over the past decades, the lead vaccine candidates have not changed and include pre-fertilization proteins Pfs48/45 [8,10] and Pfs230 [25] and post-fertilization antigen Pfs25 [10]. Recombinant P25 proteins have been successfully generated for both *P. falciparum* and *P. vivax* [26,27]. In a very different approach, mosquito derived targets have been identified that are involved in egress of the ookinete stages from the midgut represented by AnAPN1 [28], also forming a starting point for SSM-VIMT development.

2.1. Pfs48/45

*Pf*s48/45 is expressed in gametocytes once the parasite undergoes sexual differentiation in the human host and plays a critical role in male gamete fertility [29]. *Pf*s48/45 is a member of a protein family defined by a disulfide bonding pattern of six conserved cysteine residues and glycosylphosphatidylinositol (GPI) anchored in the membrane [30]. The transmission blocking B-cell epitopes fully depend on tertiary structures [31] with an N-terminal domain with epitope V, a central domain that comprises epitopes II and III, and a C-terminal domain containing the most potent transmission blocking epitope I [32]. The most effective target for transmission blocking antibodies is epitope I, while antibodies against epitopes II and III are less potent but show complementary functionality in suppression of infectivity to mosquitoes [33,34]. Although a well-established SSM-VIMT since the gene was cloned in 1993, *Pf*s48/45 has proven to be a difficult target for production of appropriate conformers in multiple heterologous expression systems [13,35–38]. Significant progress was made with production of the 10-C fragment, containing 10 cysteines (residue 159–428) in fusion with Maltose Binding Protein in *Escherichia coli* [35]. While generating appropriate conformers and inducing transmission blocking antibodies in mice, the yield remained low after purification [35]. These challenges were partly overcome by a correctly-folded functional fragment of *Pf*s48/45 (10C) as a chimeric antigen fused in frame with a section of GLURP (GLURP.RO) in *Lactococcus lactis*. Purified R0.10C induced functional antibodies in rats showing strong transmission blocking activity [37]. A fully current good manufacturing process (cGMP) compatible production and downstream purification process of R0-10C has been established at industrial scale in collaboration with Gennova Biopharmaceuticals (India) (Sauerwein, unpublished). Formulation conditions are currently optimized in preparation for clinical testing.

2.2. Pfs230

Production of Pfs230 starts in immature gametocyte stages as a 363-kD precursor protein of 70 cysteine residues, which is subsequently processed into 300- and 307-kDa fragments [14,39]. In the apparent absence of a GPI anchor, these fragments are expressed in stable complex with Pfs48/45 on the parasitophorous membrane of gametocytes [30,39–41]. Once these parasite forms are activated and transformed into gametes, Pfs230 is readily accessible on the membrane for binding to specific antibodies. Functionality of anti-Pfs230 Mabs is dependent on complement fixing isotypes [25,42,43]. A study by Read et al. demonstrated that Mabs of a complement-fixing isotype prevented infectivity of *P. falciparum* to mosquitoes in the presence of complement whilst none of the tested Mabs of non-complement fixing isotypes had transmission reducing effects [44]. Due to its complexity, recombinant expression of full-length Pfs230 has never been achieved. Pfs230 fragment C (residues 443–1132) contains epitopes for at least partial transmission reduction and subsequently became the focus for clinical vaccine development [45,46]. A purified portion of Pfs230 domain C, 230CMB, (residue 444 to 730) expressed in a plant-based expression system induced fully blocking activity in the presence of complement in rabbits qualifying as potential SSM-VIMT vaccine candidate for clinical development [47].

2.3. Pfs25

Pfs25 has been in the lead position since 1983 when specific and potent mAbs were shown to block transmission [10]. Pfs25 is a 25-kDa GPI-anchored surface protein containing four epidermal growth factor (EGF)-like domains with 22 cysteines and 11 disulfide bonds [12]. The protein is shed from the membrane and likely involved in ookinete adhesion and subsequent penetration of the midgut [10,12]. The potent transmission blocking activity of a panel of Mabs recognizing (linear and conformational) epitopes has greatly boosted subunit vaccine development [26,48]. Recombinant Pfs25 as well as *P. vivax* ortholog Pvs25 proteins expressed in yeast, have been the only SSM-VIMTs tested in clinical trials, first as TBV25H that later became Pfs25H [49]. The first human phase 1 trial occurred in 1994 with *P. falciparum* TBV25H absorbed to Alum where 1/8 volunteers experienced a hypersensitivity reaction. Antibody titers were low with consequently unsatisfactory results in the SMFA (Kaslow, unpublished) [49]. In a second trial, TBV25H/alum was used to boost a prime induced by the virally vectored multi-antigen NYVAC-Pf7 that included Pfs25, resulting in at least 75% oocysts reductions in the SMFA in 3/9 volunteers [49]. Many modifications were employed to overcome problems related to homogeneity and conformational integrity of

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