

## BRIEF REVIEW ΒΡΑΧΕΙΑ ΑΝΑΣΚΟΠΗΣΗ

# Recent patents related to malaria vaccine formulation

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Πρόσφατες πατέντες σε σχέση με τη δημιουργία εμβολίων ελονοσίας

*Περίληψη στο τέλος του άρθρου*

### Key words

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## 1. INTRODUCTION

Several classical infectious diseases continue to cause major problems in medicine. Malaria, caused by four species of the *Plasmodium* parasite, *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*, can produce human febrile illness which in the worst case can result in death. Malaria is still considered to be a global public health problem. This classical tropical mosquito borne disease needs to be targeted as millions of the world's population live in the tropical regions which are endemic for malaria, and numerous cases of malaria infection are recorded annually. Despite the many anti-malarial drugs available, the treatment of malaria is often impaired by the problem of drug efficacy. Because of drug resistant malaria,<sup>1–3</sup> new methods for the treatment and control of malaria are required. The continued search for new drugs and vaccines is the hope for management of malaria in the future.

Malaria vaccine is an important advent in malariology.<sup>4</sup> Greenwood and Targett noted that "malaria vaccines with transmission-blocking properties could play a key role in future elimination programmes".<sup>5</sup> Malaria vaccine is presently expected to be the tool for success in eradication of malaria.<sup>6</sup> To date there has been concerted research on malarial vaccine and a variety of concerns related to malaria vaccination are being addressed. Due to the current advances in biotechnology, the number of patent applications related to malaria vaccine is growing rapidly.<sup>7</sup>

Several malaria vaccine candidates have been recently identified and the genetic manipulation of these candidates is possible.<sup>7</sup> Various basic patents on antigen, epitope and recombinant processing are available for further malaria vaccine development.<sup>7</sup> Adding to the previous review,<sup>7</sup> this article discusses the new patents related to malaria vaccine delivery and novel formulations.

## 2. PATENTS RELATING TO MALARIA VACCINE DELIVERY

There have been many studies on malaria vaccine production, among which the molecular vaccines are of great interest.<sup>8</sup> Focusing on the development of malaria molecular vaccine, apart from the molecular aspects of antigen design and adjuvant advancement, the vaccine delivery systems is an important topic of discussion.<sup>8</sup> Indeed, the key to success for any molecular-based therapy is the design of a safe vector with an efficient delivery system.<sup>9</sup> Suitable approaches include the development of non-viral DNA-mediated gene-transfer techniques, such as the use of liposomes, virosomes, microspheres and nanoparticles.<sup>9</sup> A stable carrier system for the development of antimalaria vaccines is still required.<sup>9</sup> Some live bacteria and viral vectors have proved to hold special promise for malaria vaccine delivery.<sup>10</sup> Various antigen-delivery systems, particularly viral vectors, are presently in use as new malaria vaccine delivery systems.<sup>11</sup>

Some interesting patented works on malaria antigens are listed in table 1. Hoffman et al registered a patent on a vector for delivering polynucleotide vaccines against malaria in 2000.<sup>12</sup> This patent described a specific plasmid vector, pDIP/PyCSP.1, which is pharmaceutically acceptable, and a method of controlling malaria comprising injecting this polynucleotide delivery vector was proposed.<sup>12</sup> Hoffman et al claimed that injection of the new polynucleotide delivery vector could result in the production of an immune response to the malaria protein and a reduction in malaria parasites at the pre-erythrocytic, erythrocytic, and gametocyte stages of infection.<sup>12</sup> Doolan and Hoffman further applied this new polynucleotide delivery vector for further development of multistage, multivalent, multi-immune response malaria vaccine.<sup>13</sup> Based on the concept of this referencing patent, some new vectors for malarial vaccine delivery such as NYVAC-Pf7<sup>14</sup> and PyHsp60<sup>15</sup> have been produced and successfully tried out in experimental studies.

In addition to the standard vaccine injection, a new patent describes an alternative method for vaccination delivery. Tang et al patented a new noninvasive form of genetic immunization that involves skin contact with a vector in an amount sufficient to induce a systemic immune or therapeutic response.<sup>16</sup> This is in line with the new concept of epidermal delivery of molecular based vaccines.<sup>17</sup> Tang et al reported that the administered vector can include and express an exogenous nucleic acid molecule encoding an epitope or gene product of interest.<sup>16</sup> It was also proved that this technique is applicable for other pathogenic molecules, such as molecules of HIV, influenza etc.<sup>16</sup>

### 3. PATENTS RELATING TO MALARIA VACCINE FORMULATIONS

Vaccine formulation is an interesting aspect in vaccinology. The formulation is an important process, designed to enhance and increase the efficacy of the vaccine. Recent advances in parasite immunology and cell biology have

been utilized to improve the design of vaccine formulations, including that of malaria vaccine.<sup>18,19</sup> One promising area is the conjugation of malarial vaccine. The process for preparing conjugate vaccines by a special delivery technique, and the new conjugate vaccines, were first patented by Lees and Mond.<sup>20</sup> The hapten-protein-polysaccharide conjugate is registered in this patent.<sup>20</sup> Based on this original concept of conjugation, many further applications have been developed. Employing advanced nanomedical technology, the application of new peptides promising for malaria vaccine formulations has recently been described. Carbon nanotube,<sup>21</sup> virosome,<sup>22</sup> liposome<sup>23</sup> and nanoceramic mannose<sup>24</sup> conjugates are the main conjugations that are presently under clinical trail; for example, Yandar et al recently reported on the success of using *P. vivax* AMA-1 N-terminus peptide-carbon nanotube conjugate in an animal model.<sup>21</sup>

In addition to the conjugation concept, another promising area is the adjuvant form. Malaria vaccines formulated in various different adjuvants have been reported to have inducing ability of strong immunogenicity.<sup>25</sup> Recently, many new adjuvants have been introduced to increase the efficacy of malaria vaccine, including that of Xue et al, who introduced the use of montanide ISA720 adjuvant, which can increase the efficacy of malaria vaccine candidate.<sup>26</sup> Cummings et al reported the use of a malaria vaccine formulated with ASO1 or ASO2<sup>27</sup> which proved to be safe and capable of inducing high immunity.<sup>27</sup> The other new adjuvants in malarial vaccine formulations include Freund's adjuvant and aluminum hydroxide.<sup>28</sup> Giraldo et al, however, reported that although strong antibody production could be observed in the experimental situation, none of the formulations protected immunized study animals on experimental challenge.<sup>25</sup> Focusing on patented work, Clements and Humphreys reported on a new "Malaria MSP-1 C-terminal enhanced subunit vaccine" that used two adjuvants, montanide and monophosphoryl lipid A derived adjuvants, as immunomodulating agents.<sup>29</sup>

**Table 1.** Patents related to malaria vaccine formulations and delivery.

Publication number	Reference no and title	Inventors	Publication record
US6066623	[12] Polynucleotide vaccine protective against malaria, methods of protection and vector for delivering polynucleotide vaccines	Hoffman SL, Hedstrom RC, Sedegah M	23.12.1993
US6716823	[16] Noninvasive genetic immunization, expression products therefrom, and uses thereof	Tang DC, Marks DH, Curiel DT, Shi Z	9.11.2000
US7166708	[20] Process for preparing conjugate vaccines and the conjugate vaccines	Lees A, Mond J	23.1.2007
WO006052	[29] Malaria MSP-1 C-terminal enhanced subunit vaccine	Clements DE, Humphreys T	11.1.2007

#### 4. CURRENT AND FUTURE DEVELOPMENTS

As noted, some new patents have been registered relating to malaria vaccine delivery and formulations. The current patents are mainly new methods that constitute the basic concepts for ongoing experimental studies on malaria vaccination. More experimental work is needed to perfect the techniques in order to fulfill the present needs for malaria protection and to overcome the identified problems in order to provide more effective malaria vaccine delivery systems and formulations.

#### 5. CONCLUSIONS

Many new promising patents have been registered related to malaria vaccine delivery and formulations. Experimental application of these patents is reported to

be successful. Focusing on malaria vaccine delivery, the patents are usually related to new vector development and administration techniques. Focusing on malaria vaccine formulations, conjugation appears to be the best approach at present. These new patents will be useful for developing suitable therapeutic approaches to fight against malaria in practice.

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#### CONFLICT OF INTEREST

*The author declares no conflict of interest.*

#### ΠΕΡΙΛΗΨΗ

##### Πρόσφατες πατέντες σε σχέση με τη δημιουργία εμβολίων ελονοσίας

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Η ελονοσία θεωρείται παγκόσμιο πρόβλημα υγείας και απαιτούνται προσπάθειες για τη θεραπευτική της αντιμετώπιση. Λόγω του προβλήματος της ανάπτυξης αντοχής στα φάρμακα απαιτούνται νέες μέθοδοι ελέγχου και αντιμετώπισης της ελονοσίας. Η ανάπτυξη εμβολίων κατά της νόσου αποτελεί μια πολύ σημαντική πρόοδο και τελευταία έχουν πραγματοποιηθεί σημαντικές έρευνες και πρόοδοι στην παραγωγή νέων εμβολίων κατά της νόσου. Στο παρόν άρθρο ανασκοπούνται οι νέες πατέντες που σχετίζονται με τη δημιουργία και την κυκλοφορία εμβολίων κατά της ελονοσίας.

**Λέξεις ευρητήριο:** Δημιουργία πατέντας, Εμβόλιο ελονοσίας, Παράδοση εμβολίων

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