**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
**DIRECCIÓN DE NUEVAS CREACIONES**

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Act. 519 TRASLADOINFORME Folios: 1

Abogada
ALICIA LLOREDA RICAURTE

ASUNTO

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| Radicación | 07 032 109 |
| Trámite | 011 |
| Evento | 378 |
| Actuación | 519 |
| Oficio | |
| Folios | 003 |

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|---|---|---|---|---|---|
| Patente de Invención | ☑ | | | Patente de Modelo de Utilidad | ☐ |
| Vía Nacional | ☐ | | | | |
| Vía PCT (Fase Nacional) | ☑ | Capítulo I | ☑ | Capítulo II | ☐ |

| | |
|---|---|
| No. Solicitud Internacional | PCT/EP2005/009995 |
| Fecha de Presentación Internacional | 14/Septiembre/2005 |

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

## 1. Documentos estudiados

| | | |
|---|---|---|
| Descripción: | Folios 47 a 88 | 29/Marzo/2007 |
| Reivindicaciones: | Folios 89 a 91 | 29/Marzo/2007 |
| Dibujos: | Folios 92 a 99 | 29/Marzo/2007 |
| Prioridad: | GB 0420634.8 | 16/Septiembre/2004 |

## 2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque:
Esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486).
Y su contenido técnico corresponde con el de la prioridad reivindicada.

## 3. Objeto de la invención

Título de la solicitud: "Vacunas que comprenden antígenos de *Plasmodium*"

El problema planteado en esta solicitud consiste en la necesidad de proporcionar una proteína recombinante útil contra el *Plasmodium falciparum* y adyuvantes que estimulan la respuesta inmune en células Th1.

Para resolver este problema técnico la solicitud en estudio proporciona composiciones que contienen una proteína expresada por *Plasmodium falciparum* cuando se encuentra en su fase pre-eritocítica fusionada con un antígeno de

superficie de la hepatitis B. Las proteínas pueden ser del tipo circumesporozoito (CS), antígeno- 1 de merozoíto apical (AMA-1), antígeno Exp-1, antígeno-1 de la fase hepática LSA-1 y antígeno-3 de la fase hepática LSA-3. Las composiciones adicionalmente presentan adyuvantes como 3D-MLP, QS21 (solos o combinados (cuando están combinados se denomina la mezcla AS02)) y otros adyuvantes para una emulsión aceite en agua y liposomas.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 39/002: A 61 K 39/015

**4. Reivindicaciones relativas a un uso o a un segundo uso** (Art 14 y 21 D 486)

Debido a que se esta reclamando el uso de un antígeno para la preparación de un medicamento todo el capítulo reivindicatorio es decir las reivindicaciones 1 - 15 no son patentables de acuerdo con el artículo citado.

A pesar que lo reclamado corresponde a materia no patentable, en el estado de la técnica se encuentran divulgadas composiciones de vacuna que contienen un antígeno del *Plasmodium falciparum* como se muestra a continuación:

| Item | Documento | Título | Fecha de Publicación |
|---|---|---|---|
| D1 | *American Journal of Tropical Medicine and Hygiene*, vol. 71, no. 2 Suppl , pp. 239-47 | Update on the clinical development of candidate malaria vaccines | Agosto/2004 |
| D2 | WO 93/10152 | Hybrid protein between Cs from *Plasmodium* and HBsAG | 27/Mayo/1993 |
| D3 | *American Journal of Tropical Medicine and Hygiene*, vol. 69, no. 3 Supplement, p. 339 | Safety and immunogenicity of RTS,S/AS02 a malaria vaccine in gambian children | Septiembre/2003 |
| D4 | WO 96/33739 | Vaccines containing a saponin and a sterol | 31/Octubre/1996 |

D1 http://www.ajtmh.org/content/71/2_suppl/239.full divulga (páginas 240-244) antígenos candidatos a vacuna expresados en la fase pre-eritrocítica del *Plasmodium falciparum* como CS, LSA-1, LSA-3, Exp-1, y el antígeno AMA-1 expresado en la fase eritrocítica, adicionalmente menciona ensayos clínicos en niños en Gambia de 1 a 5 años, 6 a 11 años y en Mozambique de 1 a 4 años con vacunas basadas en RTS,S/AS02A.

D2:http://worldwide.espacenet.com/publicationDetails/biblio?DB=worldwide.espacenet.com&II=0&ND=3&adjacent=true&locale=en_EP&FT=D&date=19930527&CC=WO&NR=9310152A1&KC=A1 divulga (páginas 1-35) el procedimiento por el cual se produce la proteína hibrida RTS,S y se evalúa su efecto en ratones y monos cuando en la preparación de la vacuna se tiene como adyuvante el monofosforil lípido desacilado presentado en una emulsión aceite en agua.

D3 http://www.ajtmh.org/content/69/3_suppl/185.full.pdf+html divulga (página 339) estudios de fase I de una vacuna contra la malaria en niños de 6 a 11 años y en niños de 1 a 5 años de la preparación basada en RTS,S/AS02A.

D4:http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=0&ND=3&adjacent=true&locale=en_EP&FT=D&date=19961031&CC=WO&NR=9633739A1&KC=A1 divulga (páginas 6-14) preparaciones de vacunas conteniendo adyuvantes como QS21, MLP y liposomas.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante para sesenta (60) días y presentarla por escrito

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

**JOSÉ LUIS SALAZAR LÓPEZ**
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

Elaborado por: Jorge Eduardo Cortázar Gómez
Revisado por: Ana Delia Pinzón García
Aprobado por: Jose Luis Salazar López

Industria y Comercio
SUPERINTENDENCIA

**DIRECCIÓN DE NUEVAS CREACIONES**

RADICACIÓN EXPEDIENTE No. PCT 08-32109

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **587** DE

FECHA **18 DE ENERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **16 DE ABRIL DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ___X___

*Am. J. Trop. Med. Hyg.*, 71(Suppl 2), 2004, pp. 239–247
Copyright © 2004 by The American Society of Tropical Medicine and Hygiene

# UPDATE ON THE CLINICAL DEVELOPMENT OF CANDIDATE MALARIA VACCINES

W. RIPLEY BALLOU, MYRIAM ARÉVALO-HERRERA, DANIEL CARUCCI, THOMAS L. RICHIE, GIAMPIETRO CORRADIN, CARTER DIGGS, PIERRE DRUILHE, BIRGITTE K. GIERSING, ALLAN SAUL, D. GRAY HEPPNER, KENT E. KESTER, DAVID E. LANAR, JEFF LYON, ADRIAN V. S. HILL, WEIQING PAN, AND JOE D. COHEN

*Clinical Research and Development, and Research and Development, GlaxoSmithKline Biologicals, Rixensart, Belgium; Malaria Vaccine and Drug Testing Center, Cali, Columbia; Malaria Program, Naval Medical Research Center, Silver Spring, Maryland; University of Lausanne, Lausanne, Switzerland; Malaria Vaccine Development Program, U.S. Agency for International Development, Washington, District of Columbia; Institut Pasteur, Paris, France; Malaria Vaccine Development Unit, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; Departments of Immunology and Clinical Trials, Walter Reed Army Institute of Research, Silver Spring, Maryland; Centre for Clinical Vaccinology and Tropical Medicine, Oxford University, Oxford, United Kingdom; Second Military Medical University, Shanghai, People's Republic of China*

*Abstract.* The recent availability of significantly increased levels of funding for unmet medical needs in the developing world, made available by newly created public-private-partnerships, has proven to be a powerful driver for stimulating clinical development of candidate vaccines for malaria. This new way forward promises to greatly increase the likelihood of bringing a safe and effective vaccine to licensure. The investigators bring together important published and unpublished information that illuminates the status of malaria vaccine development. They focus their comments on those candidate vaccines that are currently in or expected to enter clinical trials in the next 12 months.

## INTRODUCTION

The development of a safe and effective malaria vaccine remains an urgent unmet medical need for vast populations living in malaria-endemic regions. Because severe morbidity and death due to *Plasmodium falciparum* disproportionately occurs in infants and young children living in sub-Saharan Africa, this target population has been the principal focus of malaria vaccine development. Recently, significantly increased funding through private and public partnerships has encouraged the industrial sector to become more involved in the development of candidate malaria vaccines. This process in turn has led to more clearly articulated target product profiles and clinical development plans that have facilitated decision-making and promoted rapid progress on several fronts. This review will update the status of development of malaria vaccine development, focusing in particular on those candidate vaccines that will soon be or are currently in clinical trials (Figure 1). A summary of the vaccines discussed in this review is shown in Table 1. All volunteers were recruited using non-coercive means under clinical protocols and informed consent documents reviewed and approved by local and region ethical review boards.

## PRE-ERYTHROCYTIC VACCINES

Pre-erythrocytic vaccines are designed to target sporozoites or schizont-infected liver cells and thus prevent the release of primary merozoites from infected hepatocytes. Preclinical studies in rodents and humans immunized with radiation-attenuated sporozoites indicated that this may be achieved by antibodies that target sporozoites and block their ability to infect liver cells or by cell-mediated responses that kill parasite-infected hepatocytes before they can release infectious merozoites.[1,2] Relative to the number of circulating blood stage parasites that result in clinical disease, the number of sporozoites or liver stage schizonts is quite small; however, the window of opportunity to interrupt the pre-erythrocytic stage of the life cycle is rather brief. Protective responses against pre-erythrocytic stages must be 100% effective to translate into sterile immunity in non-immune individuals. Protective responses that are 80–90% effective may have biologically meaningful consequences: thus, a two-day delay in the time to patent parasitemia has been estimated to reflect an approximately eight-fold reduction in the number of infectious sporozoites that develop into liver stage schizonts or the number of infectious merozoites released from infected liver cells. Whether a substantial reduction in initial parasite load will translate into a medically significant impact on the occurrence of clinical or severe disease in an endemic setting is unclear, but this is one possible mechanism by which insecticide-treated bed nets may act to reduce severe malaria morbidity.[3] Indirect evidence from vaccines studies is limited; however, a field trial of one pre-erythrocytic vaccine candidate (RTS,S/AS02A), which indicated significant protection from infection over two seasons, also showed a promising trend towards reducing episodes of clinical malaria during the same period.[4]

The circumsporozoite (CS) protein is the pre-erythrocytic antigen against which immune responses are most clearly

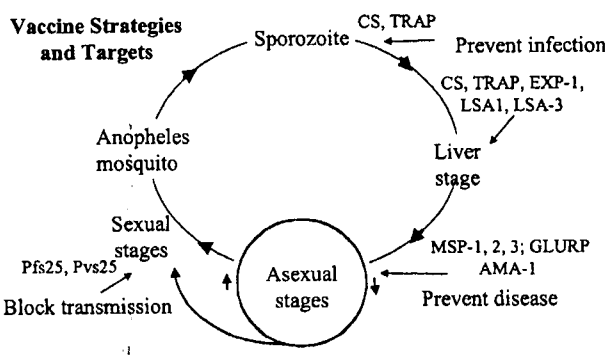


FIGURE 1. Malaria life cycle and vaccine targets. CS = circumsporozoite; TRAP = thrombospondin-related adhesive protein; EXP-1 = exported antigen 1; LSA1 = liver stage antigen 1; MSP-1 = merozoite stage protein 1; GLURP = glutamate-rich protein; AMA-1 = apical membrane antigen 1; Pf = *Plasmodium falciparum*; Pv = *P. vivax*.

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| C07K 15/00, C12N 7/04 | A1 | (43) International Publication Date: | 27 May 1993 (27.05.93) |

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(22) International Filing Date: 11 November 1992 (11.11.92)

(30) Priority data:
9124390.7 16 November 1991 (16.11.91) GB
07/842,694 27 February 1992 (27.02.92) US

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM BIOLOGICALS S.A. [BE/BE]; 89, rue de l'Institut, B-1330 Rixensart (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : DE WILDE, Michel [BE/BE]; COHEN, Joseph [US/BE]; SmithKline Beecham Biologicals s.a., 89, rue de l'Institut, B-1330 Rixensart (BE).

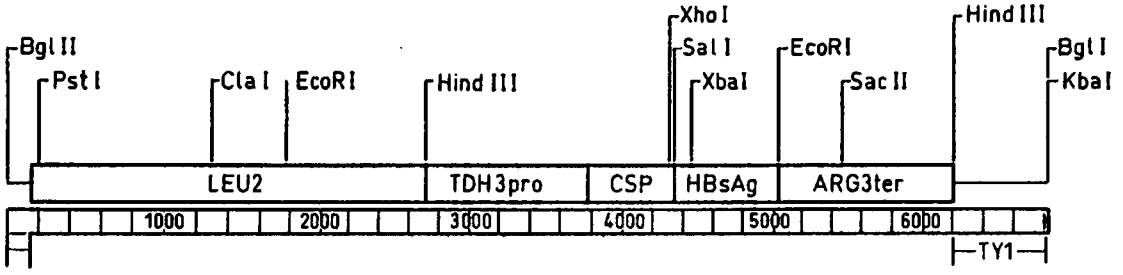
(74) Agent: DALTON, Marcus, Jonathan, William; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).

(81) Designated States: AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

Published
*With international search report.*

(54) Title: HYBRID PROTEIN BETWEEN CS FROM PLASMODIUM AND HBsAG

**Restriction map of the 6.8 Kb linear Bg1II fragment from pRIT13539**
The linear fragment contains the LEU2 gene for selection of transformed yeast cells together with the RTS expression cassette.




(57) Abstract

A novel hybrid protein is provided which comprises a portion of the CS protein of P. falciparum and the surface antigen of Hepatitis B virus. The use of this protein for vaccination purposes is disclosed.

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Safety and Immunogenicity of RTS,S/AS02D Malaria Vaccine in Infants

Salim Abdulla, M.D., Ph.D., Rolf Oberholzer, M.D., Omar Juma, M.D., Sulende Kubhoja, M.D., M.M.E.D., Francisca Machera, A.M.O., Christopher Membi, A.D.M.L.S., Said Omari, D.M.L.T., Alwisa Urassa, B.P.A., Hassan Mshinda, Ph.D., Ajuza Jumanne, M.D., Nahya Salim, M.D., M.M.E.D., Mwanjaa Shomari, B.Sc., Thomas Aebi, M.D., David M. Scheifenberg, M.D., Ph.D., Terrell Carter, M.H.S., Tonya Villafana, Ph.D., M.P.H., Marie-Ange Demoitié, M.Sc., Marie-Claude Dubois, M.Sc., Amanda Leach, M.R.C.P.C.H., Marc Lievens, M.Sc., Johan Vekemans, M.D., Ph.D., Joe Cohen, Ph.D., W. Ripley Ballou, M.D., and Marcel Tanner, Ph.D., M.P.H.

## ABSTRACT

### BACKGROUND

The RTS,S/AS malaria vaccine is being developed for delivery through the World Health Organization's Expanded Program on Immunization (EPI). We assessed the feasibility of integrating RTS,S/AS02D into a standard EPI schedule for infants.

### METHODS

In this phase 2B, single-center, double-blind, controlled trial involving 340 infants in Bagamoyo, Tanzania, we randomly assigned 340 infants to receive three doses of either the RTS,S/AS02D vaccine or the hepatitis B vaccine at 8, 12, and 16 weeks of age. All infants also received a vaccine containing diphtheria and tetanus toxoids, whole-cell pertussis vaccine, and conjugated *Haemophilus influenzae* type b vaccine (DTPw/Hib). The primary objectives were the occurrence of serious adverse events during a 9-month surveillance period and a demonstration of noninferiority of the responses to the EPI vaccines (DTPw/Hib and hepatitis B surface antigen) with coadministration of the RTS,S/AS02D vaccine, as compared with the hepatitis B vaccine. The detection of antibodies against *Plasmodium falciparum* circumsporozoite and efficacy against malaria infection were secondary objectives.

### RESULTS

At least one serious adverse event was reported in 31 of 170 infants who received the RTS,S/AS02D vaccine (18.2%; 95% confidence interval [CI], 12.7 to 24.9) and in 42 of 170 infants who received the hepatitis B vaccine (24.7%; 95% CI, 18.4 to 31.9). The results showed the noninferiority of the RTS,S/AS02D vaccine in terms of antibody responses to EPI antigens. One month after vaccination, 98.6% of infants receiving the RTS,S/AS02D vaccine had seropositive titers for anticircumsporozoite antibodies on enzyme-linked immunosorbent assay (ELISA). During the 6-month period after the third dose of vaccine, the efficacy of the RTS,S/AS02D vaccine against first infection with *P. falciparum* malaria was 65.2% (95% CI, 20.7 to 84.7; P=0.01).

### CONCLUSIONS

The use of the RTS,S/AS02D vaccine in infants had a promising safety profile, did not interfere with the immunologic responses to coadministered EPI antigens, and reduced the incidence of malaria infection. (ClinicalTrials.gov number, NCT00289185.)

From the Bagamoyo Research and Training Centre of Ifakara Health Institute, Bagamoyo, Tanzania (S.A., R.O., O.J., F.M., C.M., S.O., A.U., H.M., A.J., N.S., M.S., T.A., D.M.S., M.T.); Swiss Tropical Institute, Basel, Switzerland (R.O., T.A., M.T.); Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania (S.K.); London School of Hygiene and Tropical Medicine, London (D.M.S.); Program for Appropriate Technology in Health (PATH) Malaria Vaccine Initiative, Bethesda, MD (T.C., T.V.); GlaxoSmithKline Biologicals, Rixensart, Belgium (M.-A.D., M.-C.D., A.L., M.L., J.V., J.C.); and Bill and Melinda Gates Foundation, Seattle (W.R.B.). Address reprint requests to Dr. Abdulla at the Bagamoyo Research and Training Centre, Ifakara Health Institute, Box 74, Bagamoyo Tanzania, or at sabdulla@ihi.or.tz.

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N Engl J Med 2008;359:2533-44.
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(30) Priority Data:

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|---|---|---|
| 9508326.7 | 25 April 1995 (25.04.95) | GB |
| 9513107.4 | 28 June 1995 (28.06.95) | GB |

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM BIOLOGICALS S.A. [BE/BE]; Rue de l'Institut 89, B-1330 Rixensart (BE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GARCON, Nathalie, Marie-Josephe, Claude [FR/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE). FRIEDE, Martin [GB/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B-1330 Rixensart (BE).

(74) Agent: DALTON, Marcus, Jonathan, William; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(54) Title: VACCINES CONTAINING A SAPONIN AND A STEROL

(57) Abstract

The invention relates to a vaccine composition comprising an antigen, an immunologically active saponin fraction and a sterol.