FUNDACION INSTITUTO DE INMUNOLOGIA DE COLOMBIA

FIDIC

CIENCIA CON CONCIENCIA

THE SEARCH FOR

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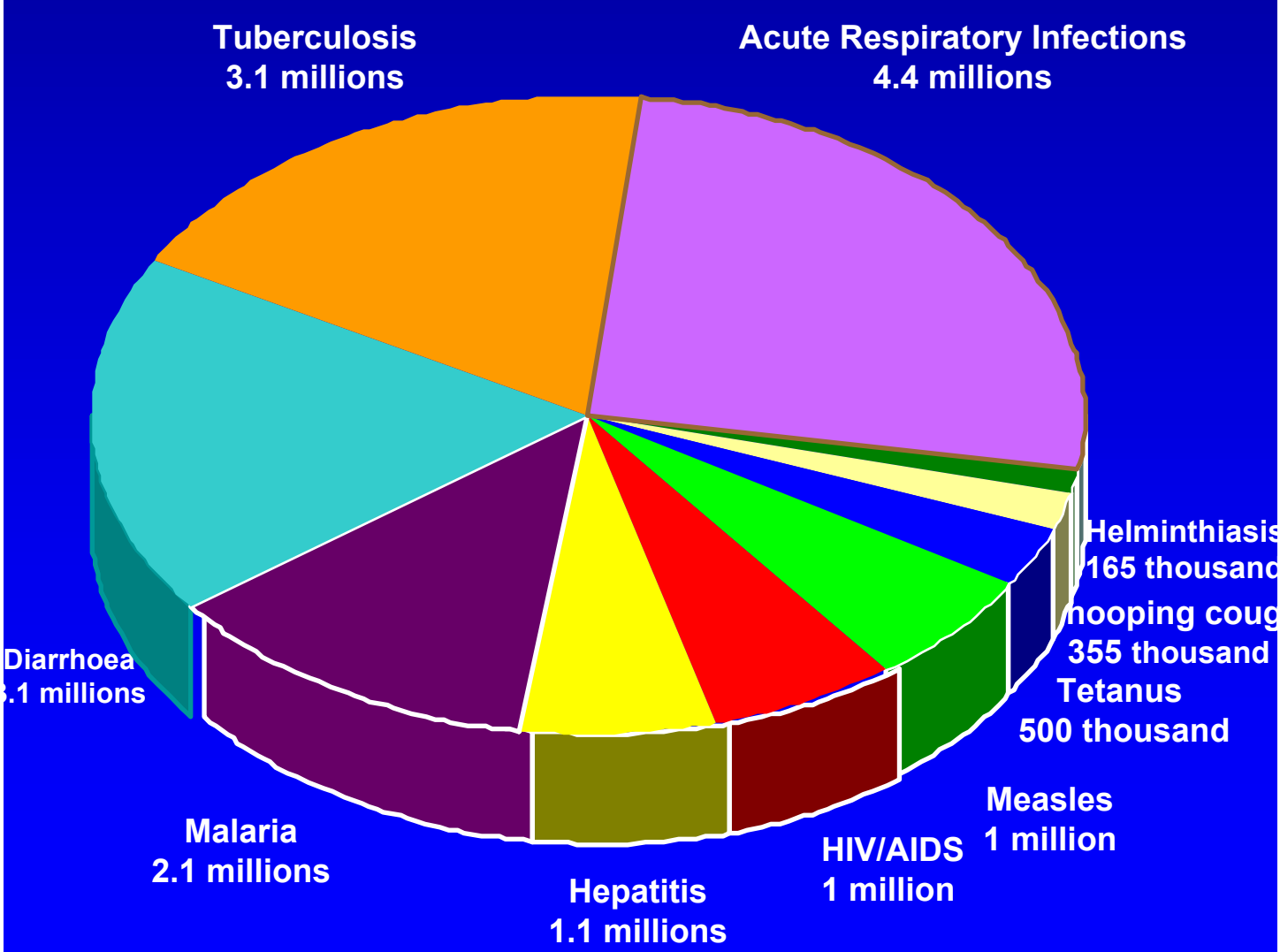
Or

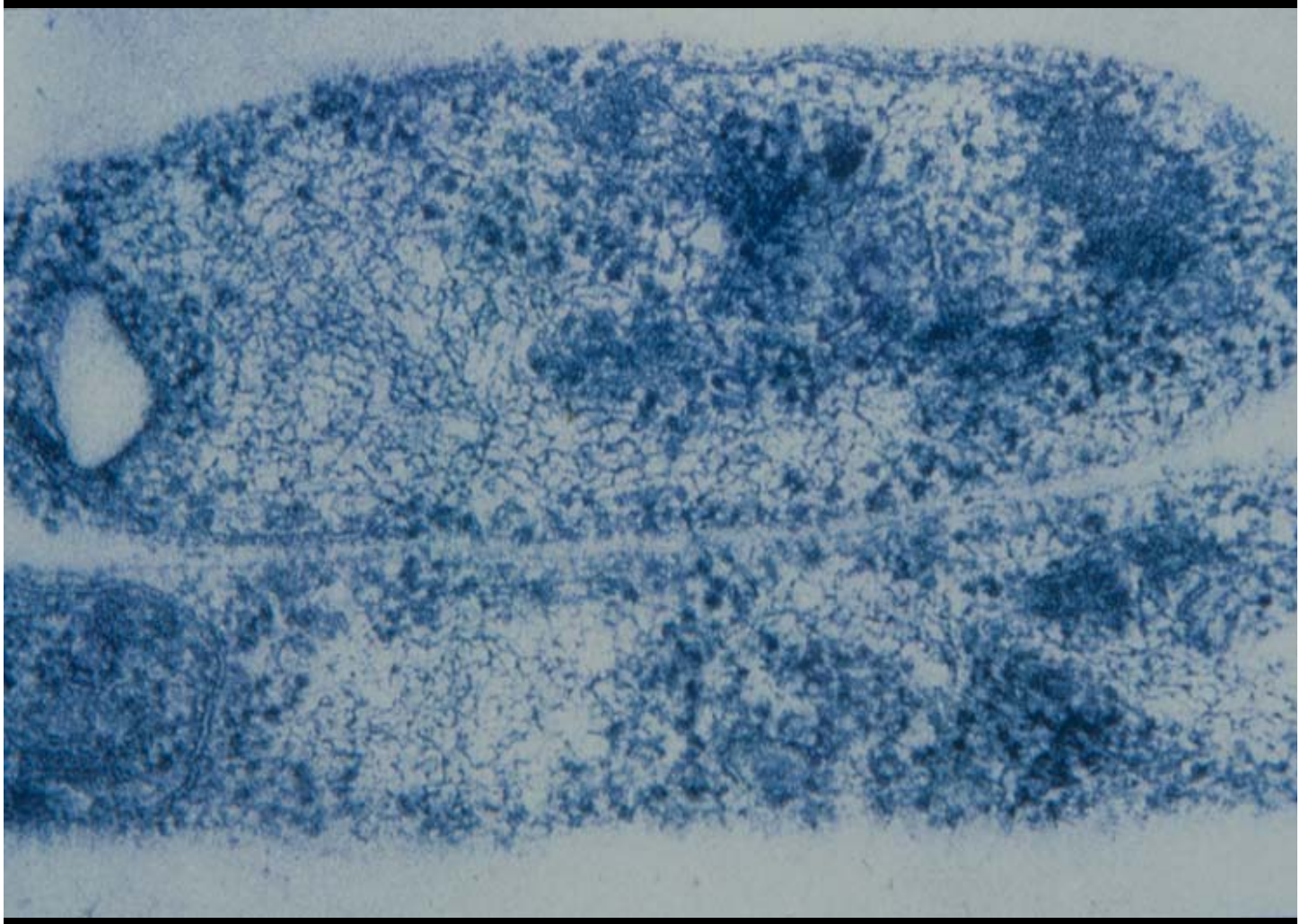
A MATHEMATICAL METHOD FOR DEVELOPING VACCINES

TEN LEADING CAUSES OF MORTALITY IN THE WORLD INDUCED BY TRANSMITTABLE DISEASES

WHO-1995



BIOLOGICAL VACCINES



ACTUAL VACCINES

SMALL POX
POLIO
MEASLES
PAROTIDITIS
GERMAN MEASLES
CHICKEN POX

HEPATITIS A & B
YELLOW FEVER
RABIES
BCG
DPT

VACCINES IN PROGRESS

MALARIA
AIDS
TYPHUS
CHOLERA
MENINGITIS
DENGUE
HERPES
S.T.D.
LEISHMANIA

SCHISTO
CARIES
LYME
STREPTOCOCCUS
RICKETS
INFLUENZA
ROTAVIRUS
RSV
PAPILOMA, ETC

PURPOSE :

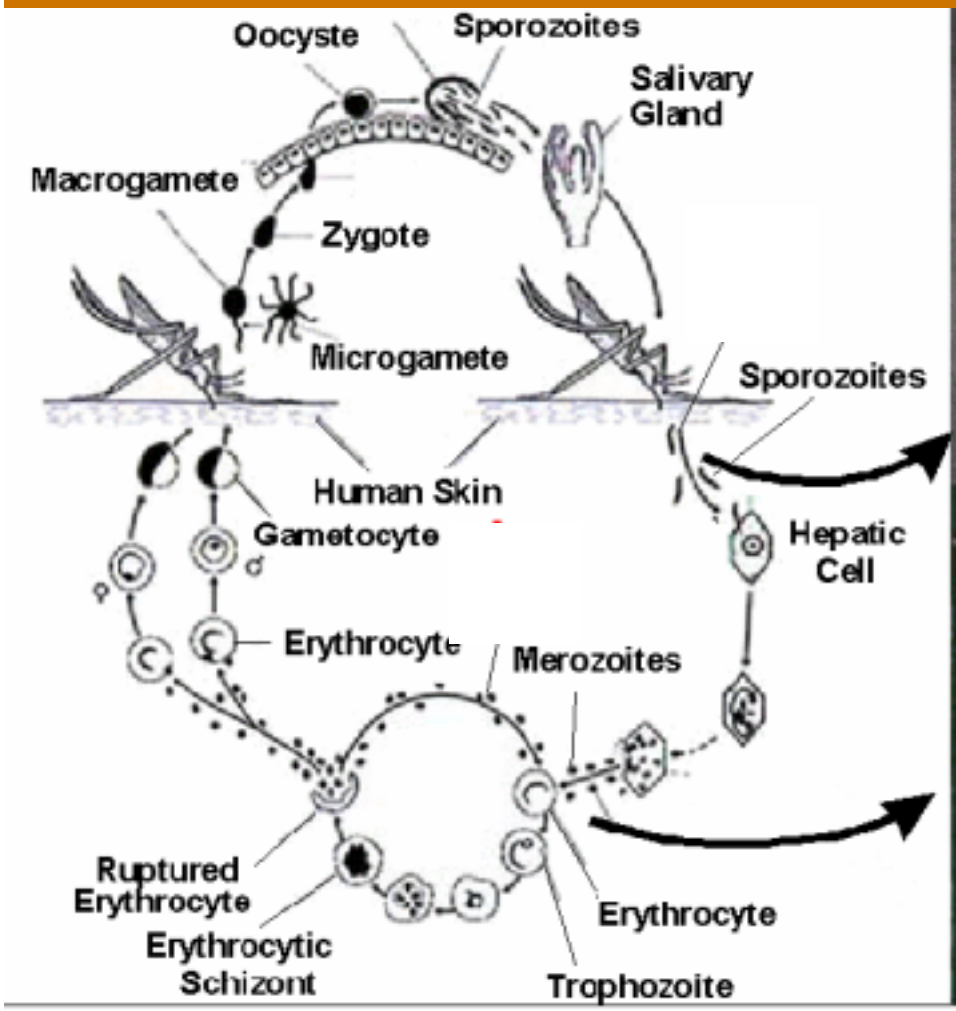
To find a rational approach for the development of chemically synthetized vaccines.

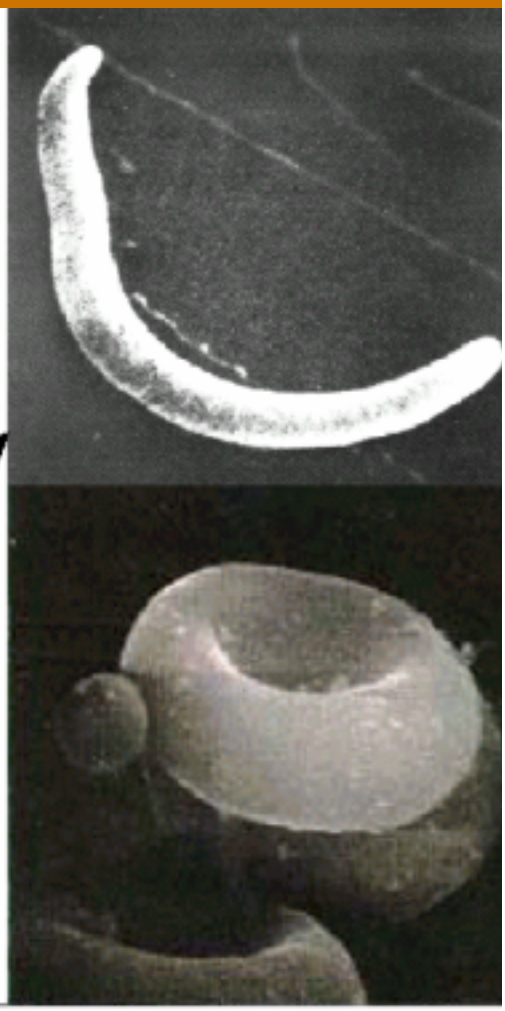
10 April 1997

International weekly journal of science

nature

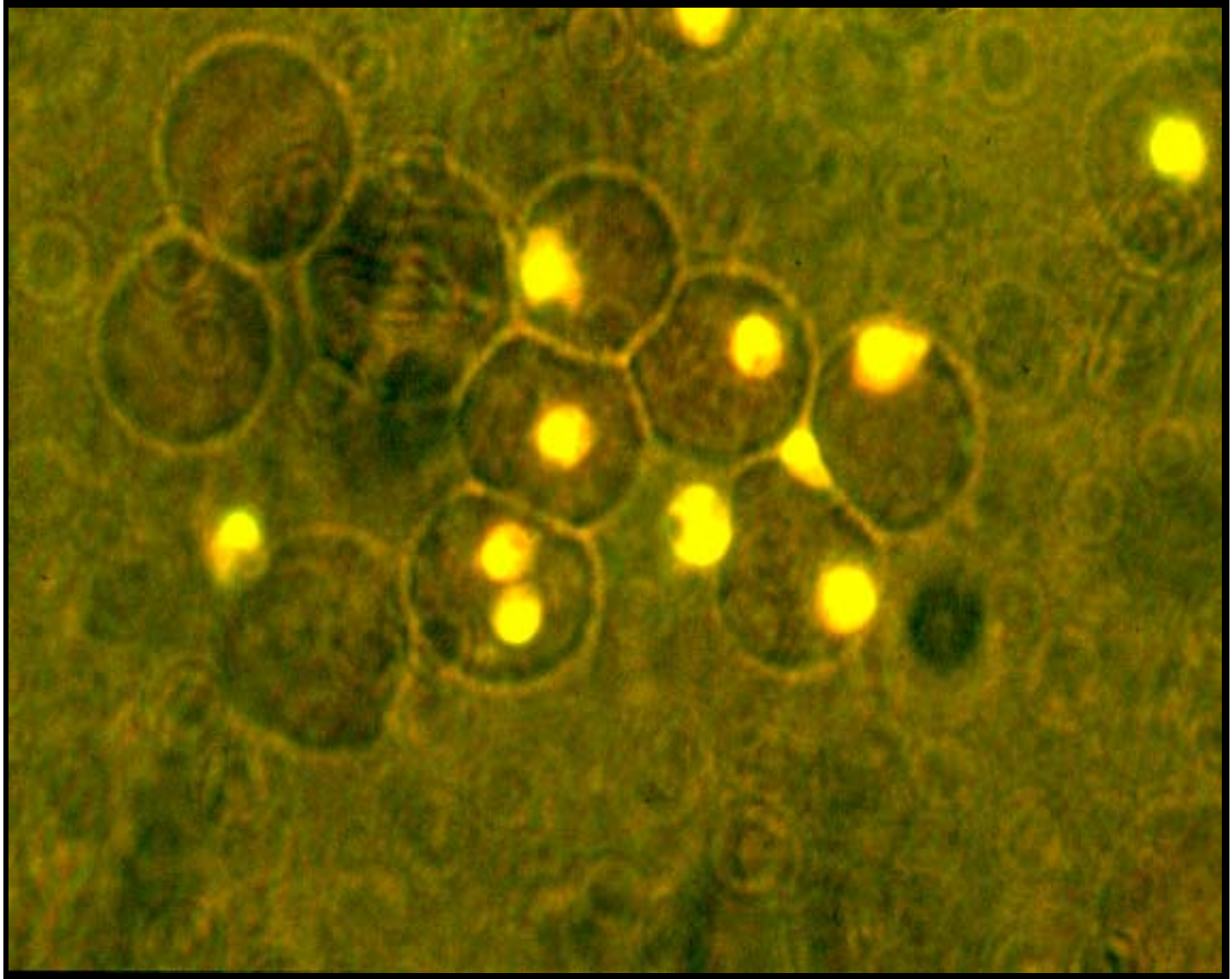
Plasmodium falciparum
PARASITE'S LIFE CYCLE

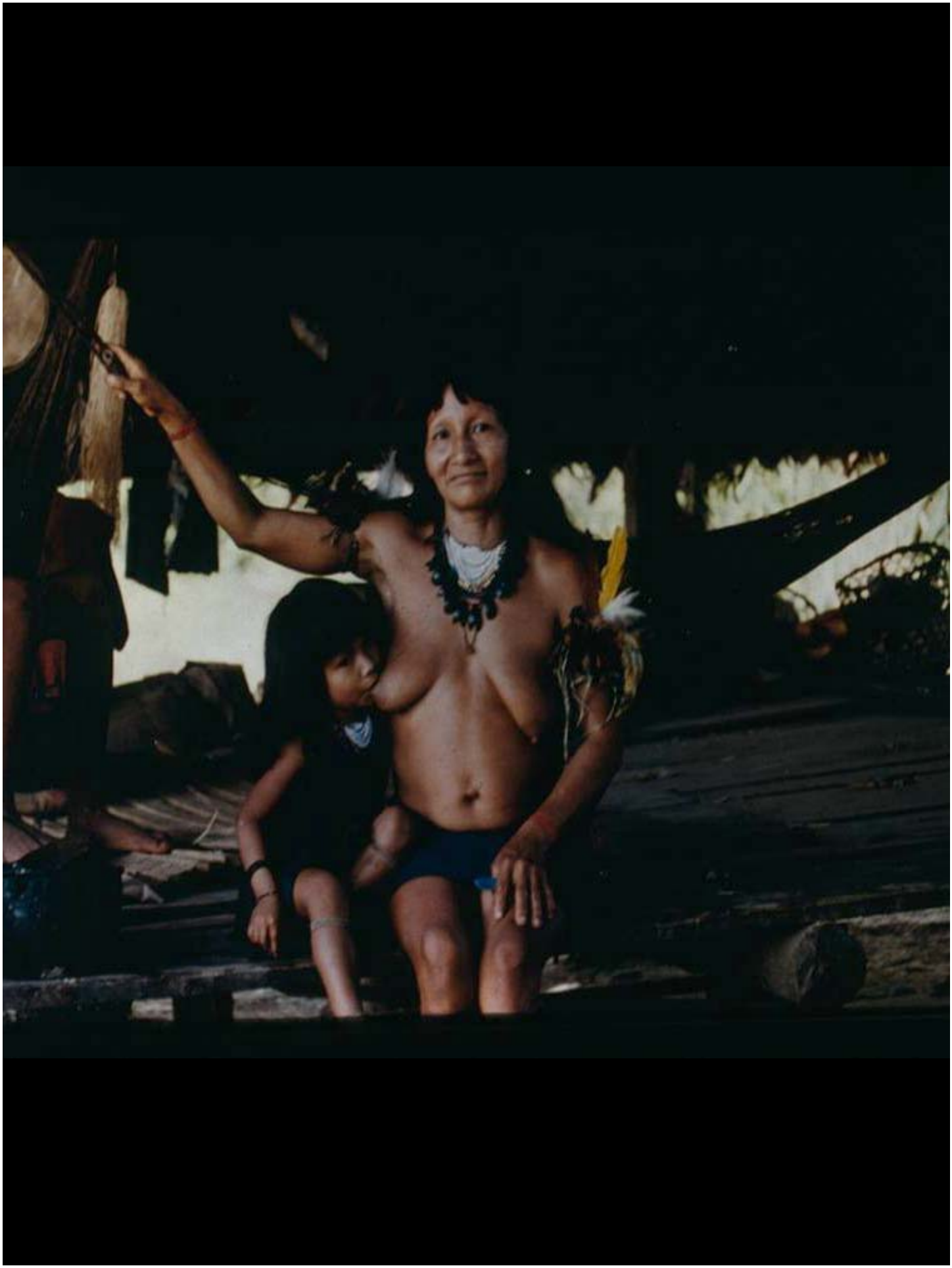




Why malaria?

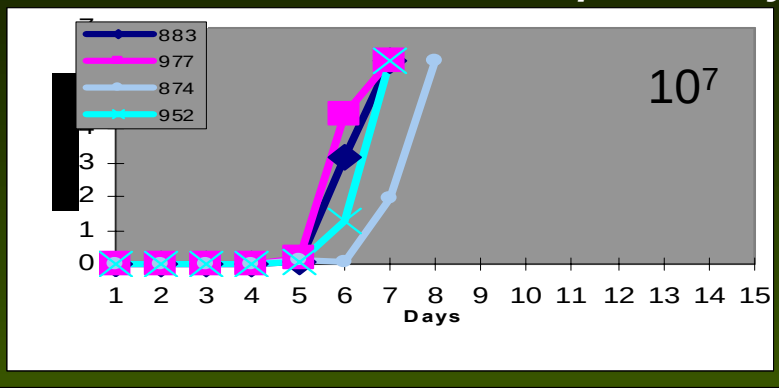
- 300 million people are infected and 3 million die annually
- Acute disease
- Easy diagnosis
- Curable with treatment
- Experimental model: the Aotus monkey
- Heavy economic burden for the developing world

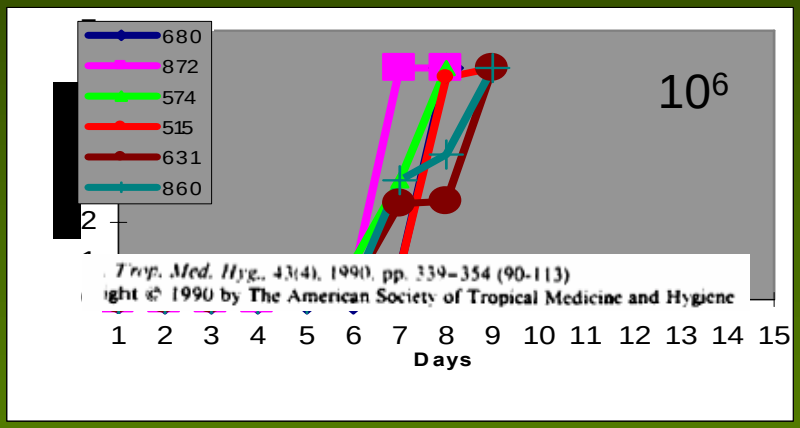


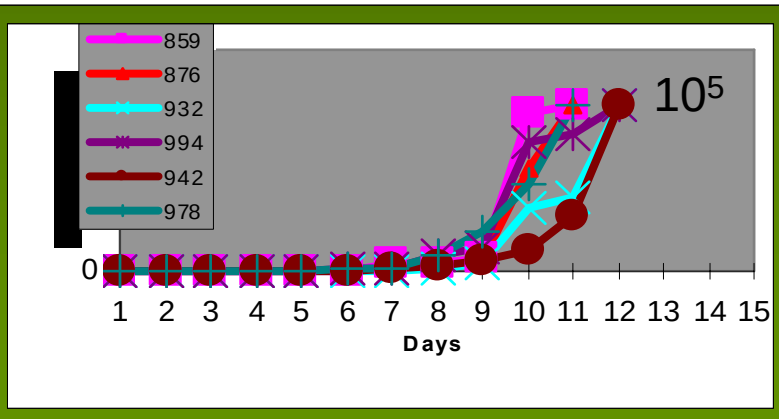


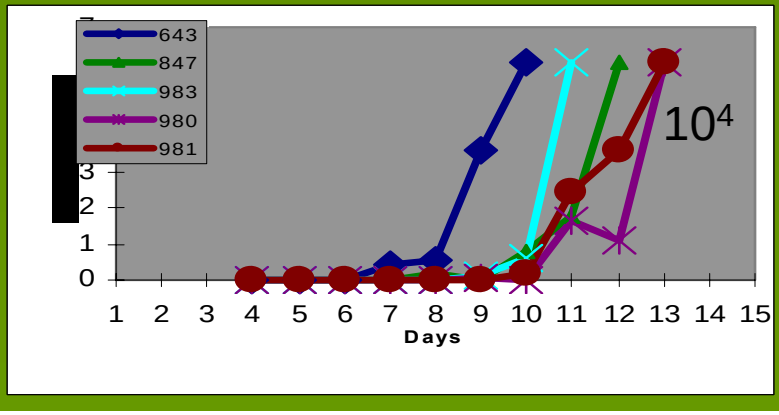
TITRATION OF THE FVO P. *falciparum* STRAIN IN AOTUS MONKEYS

Rodriguez R. et al. 1990. *Am. J. Trop. Med. Hyg* 43:339









Immunogenetics (2000) 51:212–218 © Sprin

ORIGINAL PAPER

Olga L. Diaz · Claudia A. Daubenberger
Raul Rodriguez · Martin Naegeli · Alberto Moreno

Immunoglobulin kappa light-chain *V*, *J*, and *C* gene sequences of the owl monkey *Aotus nancymaae*

Identification and sequencing of genes from constant and variable regions (VH3 and VH4 families) of the heavy-chain of Immunoglobulin in Owl monkeys (*Aotus nancymaae*)

EC HERNÁNDEZ, CF SUÁREZ, CA PARRA, OL DIAZ AND ME PATARROYO.
Fundación Instituto de Inmunología de Colombia (FIDIC). Bogotá- Colombia. Calle 50 No. 26-00.

Immunogenetics (2002) 54:645–653
DOI 10.1007/s00251-002-0512-2

ORIGINAL PAPER

Edith C. Hernández · Carlos F. Suárez
Jairo A. Méndez · Sandra J. Echeverry
Luis A. Murillo · Manuel E. Patarroyo

Identification, cloning, and sequencing of different cytokine genes in four species of owl monkey

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American Journal of Primatology 57:1–11 (2002)

RESEARCH ARTICLE

Partial Characterization of the CD45 Phosphatase DNA in the Owl Monkey (*Aotus vociferans*)

GLADIS E. MONTOYA[1], JEAN-PAUL VERNOT[1,2*], and MANUEL E. PATARROYO[1,2]
[1]*Fundación Instituto de Inmunología de Colombia, FIDIC, Bogotá, D.C., Colombia*
[2]*Facultad de Medicina, Universidad Nacional de Colombia, Bogotá, D.C., Colombia*

J Med Primatol 2003: 32: 31–38

JOURNAL OF MEDICAL PRIMATOLOGY
ISSN 0047-2565

Proliferative response of peripheral blood lymphocytes to mitogens in the owl monkey *Aotus nancymae*

Pinzón-Charry A, Vernot JP, Rodríguez R, Patarroyo ME. Proliferative response of peripheral blood lymphocytes to mitogens in the owl monkey *Aotus nancymae*. J med Primatol 2003; 32:31–38. © Blackwell Munksgaard, 2003

Alberto Pinzón-Charry[1], Jean Paul Vernot[1,2], Raul Rodríguez[1], Manuel Elkin Patarroyo[1,2]

C. F. Suárez*
P. P. Cárdenas*
E.J. Llanos-Ballestas
P. Martínez
M. Obregón
M.E. Patarroyo
M.A. Patarroyo

α_1 and α_2 domains of *Aotus* MHC Class I and Catarrhini MHC Class Ia share similar characteristics

Tissue Antigens 2003: **61:** 362–373

Accepted in IMMUNOGENETICS

Unusual Variability in *Aotus* monkey MHC-E quences

Paula P. Cárdenas1, Carlos F. Suárez1, Consuelo P. Martínez, Eugenio J. Llanos, Mateo Obregón, Manuel E. Patarroyo, Manuel A. Patarroyo *

J. E. Guerrero
D. P. Pacheco
C. F. Suárez
P. Martínez
F. Aristizabal
C. A. Moncada
M. E. Patarroyo
M. A. Patarroyo

Characterizing T-cell receptor γ-variable gene in *Aotus nancymaae* owl monkey peripheral blood

Tissue Antigens 2003 **61:** 1–11

Functional and Structural Similarity of Vγ9Vδ2 T Cells in Humans and *Aotus* Monkeys, a Primate Infection Model for *Plasmodium falciparum* Malaria[1,2]

The Journal of Immunology, 2001, 167: 6421–6430.

Claudia A. Daubenberger,[3]* Maxence Salomon,* William Vecino,† Beatrice Hübner,* Heike Troll,‡ Raul Rodriques,† Manuel E. Patarroyo,† and Gerd Pluschke*

Immunogenetics (2000) 51:219–230

ORIGINAL PAPER

J. Javier Nino-Vasquez · Denise Vogel
Raul Rodriguez · Alberto Moreno
Manuel Elkin Patarroyo · Gerd Pluschke
Claudia A. Daubenberger

Sequence and diversity of *DRB* genes of *Aotus nancymaae*, a primate model for human malaria parasites

Immunogenetics (2000) 51: 528–537
Digital Object Identifier (DOI) 10.1007/s002510000189

ORIGINAL PAPER

Diana Diaz · Martin Naegeli · Raul Rodriguez
J. Javier Nino-Vasquez · Alberto Moreno
Manuel Elkin Patarroyo · Gerd Pluschke
Claudia A. Daubenberger

Sequence and diversity of MHC *DQA* and *DQB* genes of the owl monkey *Aotus nancymaae*

Immunogenetics (2002) 54:251–259
DOI 10.1007/s00251-002-0466-4

ORIGINAL PAPER

Diana Diaz · Claudia A. Daubenberger · Tatjana Zalac
Raul Rodriguez · Manuel Elkin Patarroyo

Sequence and expression of MHC-DPB1 molecules of the New World monkey *Aotus nancymaae*, a primate model for *Plasmodium falciparum*

Immunogenetics (1998) 48: 253–259

ORIGINAL PAPER

Nicolas Favre · Claudia Daubenberger · Jutta Marfurt
Alberto Moreno · Manuel Patarroyo · Gerd Pluschke

Sequence and diversity of T-cell receptor alpha *V*, *J*, and *C* genes of the owl monkey *Aotus nancymaae*

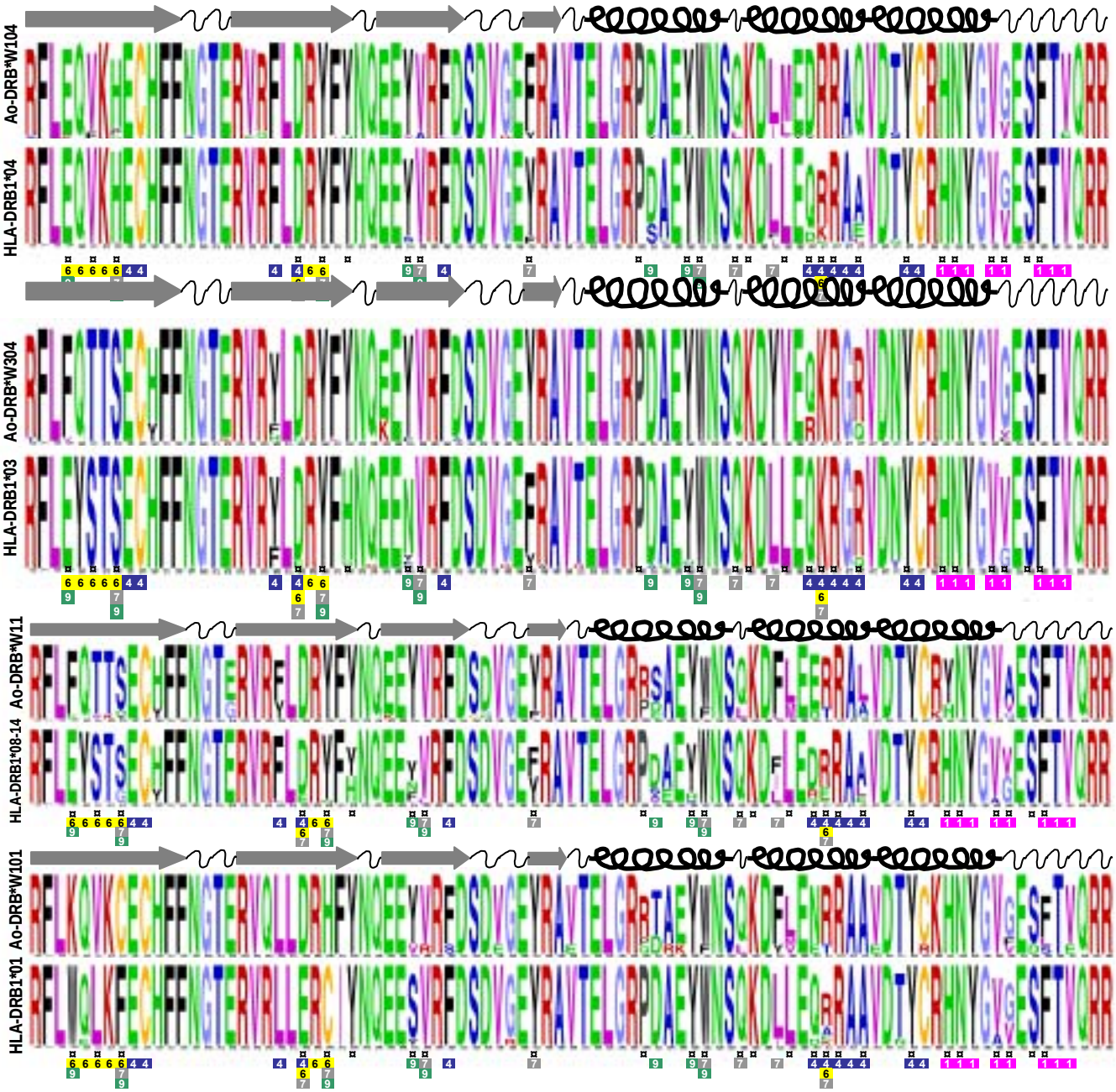
Immunogenetics (1999) 49: 792–799

ORIGINAL PAPER

William Vecino · Claudia Daubenberger
Raul Rodriguez · Alberto Moreno
Manuel Patarroyo · Gerd Pluschke

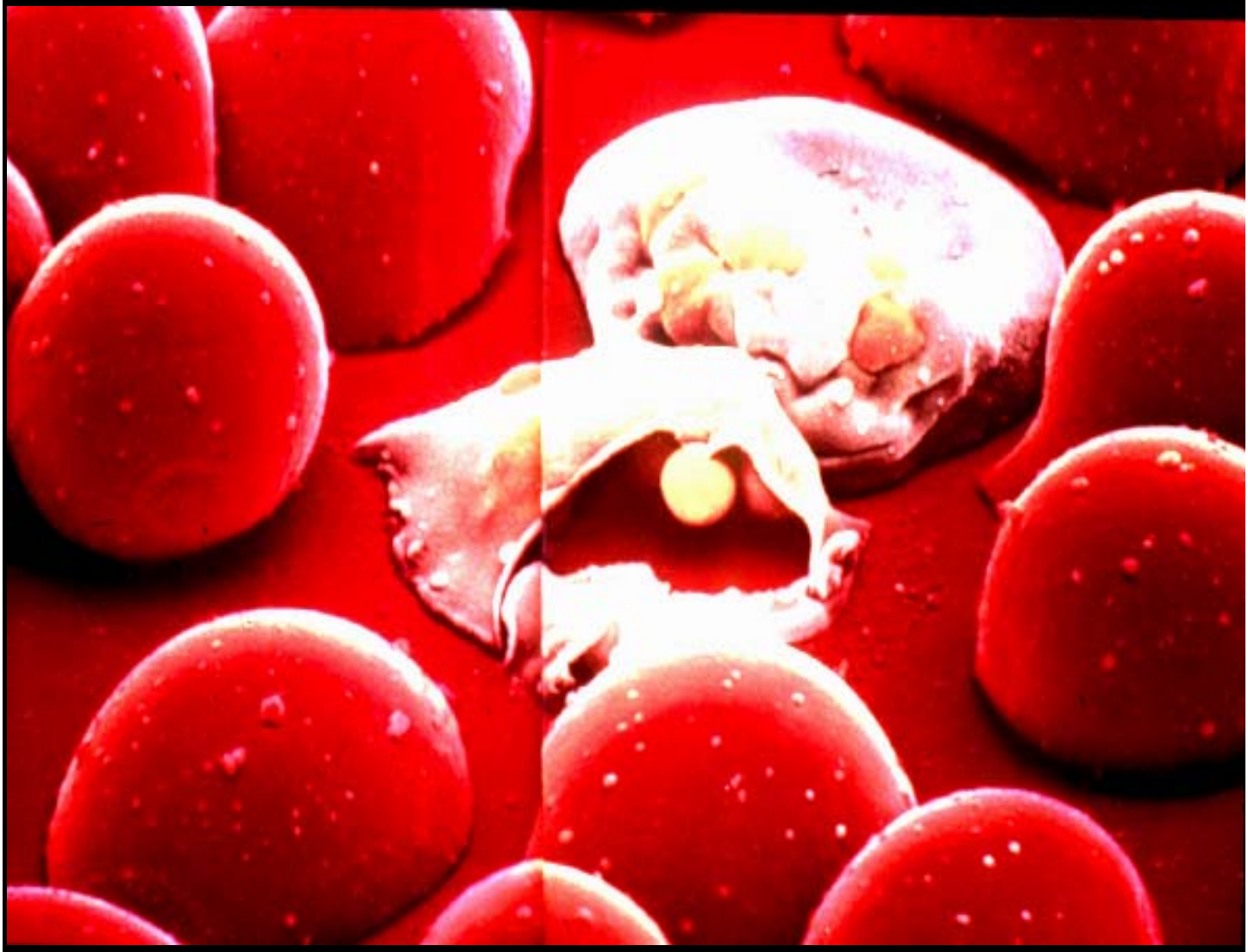
Sequence and diversity of T-cell receptor β-chain *V* and *J* genes of the owl monkey *Aotus nancymaae*

Logos obtenidos a partir de las secuencias de los *Aotus* (Ao-DRB*W) y de las secuencias de humanos (HLA-DRB)



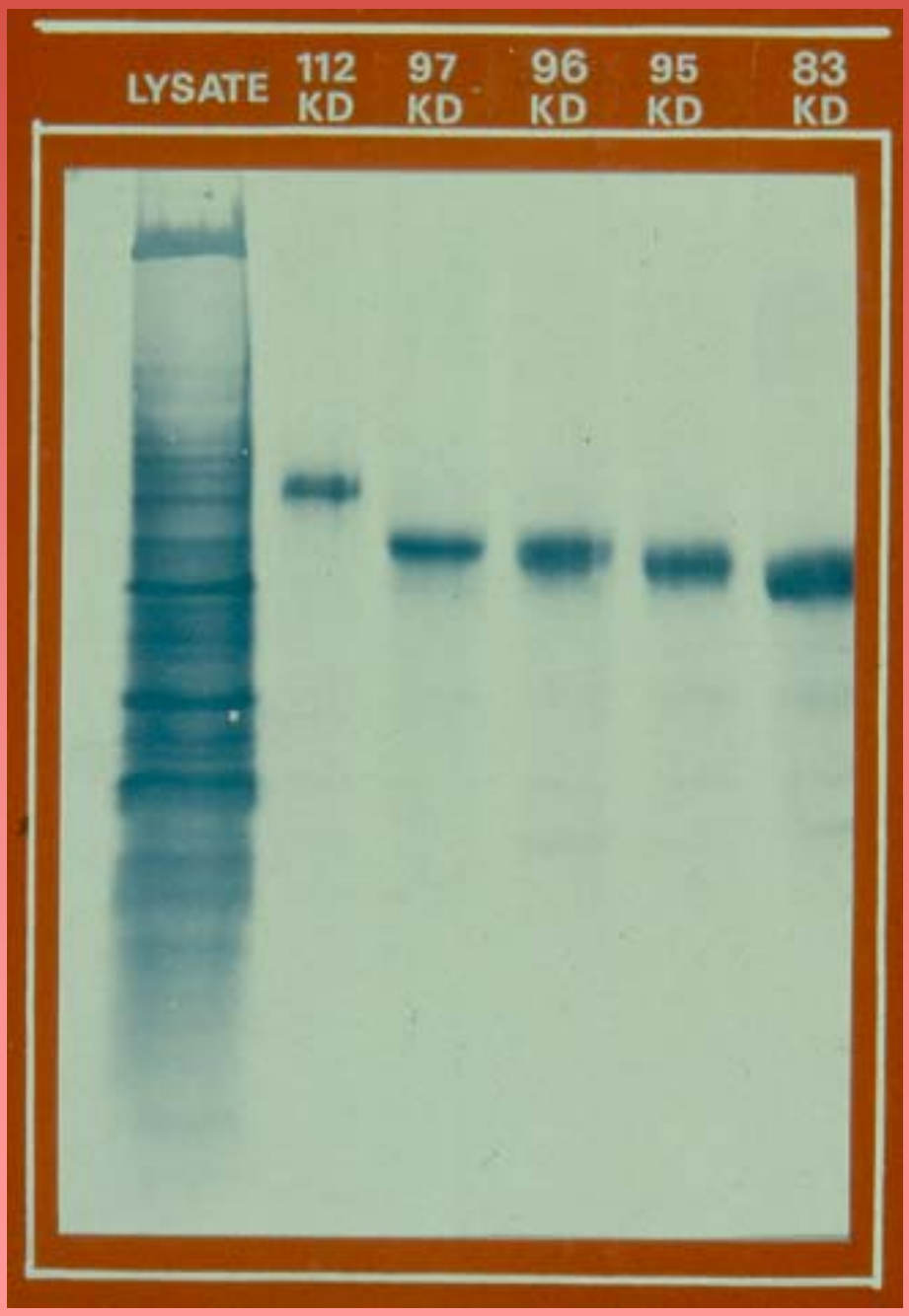
Promedio y Rango de homología entre Ao-DRβ y HLA-DRβ en el dominio β y posiciones de los Pockets

Owl Monkey		Human	β domain			Pockets		
			% mean	% min	% max	% mean	% min	% max
Ao-DRB*W104	vs.	HLA-DRB1*04	95	91	98	93	80	100
Ao-DRB*W304	vs.	HLA-DRB1*03	92	88	95	85	77	91
Ao-DRB*W302	vs.	HLA-DRB3	92	89	94	84	77	91
Ao-DRB*W11	vs.	HLA-DRB1*08	92	88	96	83	74	91
Ao-DRB*W303	vs.	HLA-DRB3	91	86	94	83	71	91
Ao-DRB*W301	vs.	HLA-DRB3	90	86	93	84	74	91
Ao-DRB*W11	vs.	HLA-DRB1*11	90	85	95	83	71	91
Ao-DRB*W11	vs.	HLA-DRB1*13	90	85	96	81	71	91
Ao-DRB*W701/02	vs.	HLA-DRB1*07	90	87	93	80	74	88
Ao-DRB*W101	vs.	HLA-DRB1*01	90	84	94	80	74	88
Ao-DRB*W11	vs.	HLA-DRB1*14	89	85	96	80	68	91
Ao-DRB*W4	vs.	HLA DRB1*10	88	84	89	74	68	80
Ao-DRB*W4	vs.	HLA DRB4	88	83	91	72	65	80



IMMUNOBLOT OF *P. falciparum* ISOLATED PROTEINS

Patarroyo M. E. et. al. 1987. *Vaccines*. 117-124

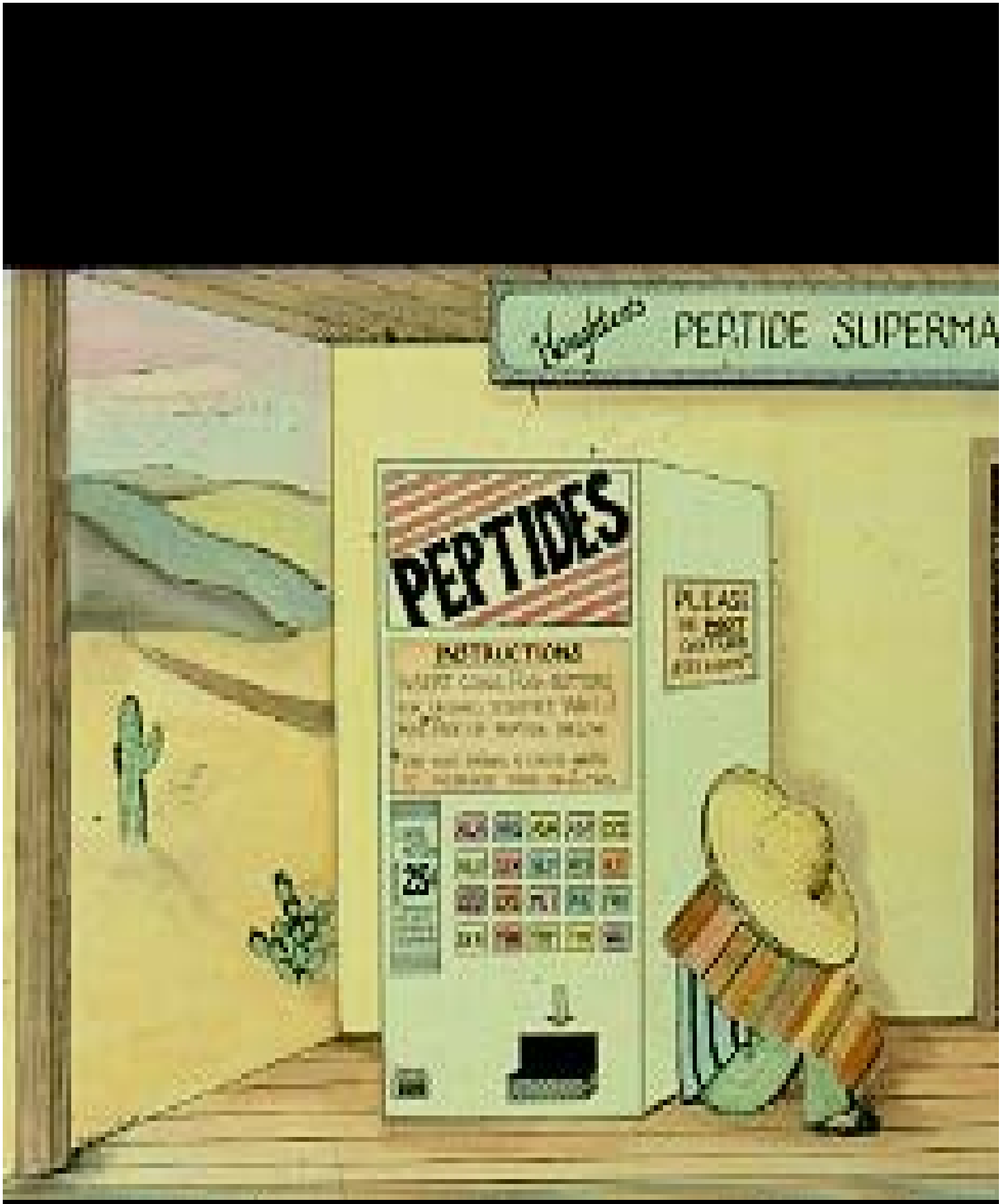


PARASITAEMIA IN MONKEYS IMMUNISED WITH MEROZOITE PURIFIED PROTEINS

Patarroyo M. E.. et al. 1987. *Vaccines 87:*117

Immunizing molecule	Monkey number	Percentage of parasitemia on days (after challenge)													
		6	7	8	9	10	11	12	13	14	15	16	17	18	19
155K	087	0	0	0	0	0.88	0.30	2.0	3.0	5.35	8.8	Q			
	090	0	0	0	0	0	0	0.8	0.2	0.45	0.9	1.5	1.6	2.0	3.4
115K	085	0	0.46	0.84	3.48	3.0	9.93	Q							
	150	0	0.05	0.20	1.12	1.67	nd	6.57	Q						
105K	165	0	0.33	1.92	3.72	10.9	Q								
	168	0	0.81	1.64	3.33	11.5	Q								
90K	160	0	0.13	1.2	3.39	4.14	13.65	Q							
	170	0	0.10	1.1	1.20	5.09	5.40	14.7	Q						
83K	125	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	130	0	0	0	0.6	0.2	0.3	3.63	1.6	1.1	0.6	nd	0	0	0
	144	0	0	0	0	0	0	0	0.1	0.05	0.5	0.3	0.07	0.03	0.01
60K	119	0	0	0	0.1	0.80	0.15	4.5	1.25	15.3	Q				
	122	0	0.13	0.25	0.15	0.80	2.5	17.5	Q						
55K	0.81	0	0	0	0	0	0.18	0.24	0.8	1.57	3.0	3.5	4.4	7.4	Q
	102	0	0	0	0	0	0.05	0.05	0.5	0	0.1	0.6	0.9	5.4	7.3
50K	0.29	0	0.40	1.50	3.6	4.67	10.0	Q							
	0.56	0	0.66	5.6	4.43	6.42	4.20	11.3	Q						
	131	0	0.31	1.50	0.50	3.93	2.0	16.5	Q						
40K	111	0	0	0	0	1.02	0.20	2.7	3.2	14.3	Q				
	114	0	0	0	0	0.8	0.5	2.0	2.0	2.0	7.6	Q			
35K	135	0	0	0	0	0	0	0.01	0.03	0.03	0.1	0.012	0.01	0	0
	159	0	0.25	0.25	1.3	2.23	1.03	2.5	2.1	4.0	2.1	1.6	0.7	0.08	0.01
30K	093	0	0.05	1.52	2.5	4.75	3.45	2.54	4.8	9.4	Q				
	171	0	0.1	2.5	1.6	2.63	2.05	13.0	Q						
23K	112	0	0.06	0	1.0	0	3.60	6.37	6.60	12.0	Q				
	137	0	0.05	0.05	0.20	0	1.1	3.2	nd	+					
Controls	501	0.40	0.76	3.0	2.0	7.82	9.07	Q							
	502	0.03	0.06	0.43	0.47	3.6	3.4	5.9	8.92	Q					
	199	1.0	4.3	3.11	9.8	26.0	Q								

nd indicates not determined


PEPTIDE SUPERMA
PEPTIDES
INSTRUCTIONS

NATURE VOL. 328 13 AUGUST 1987

Induction of protective immunity against experimental infection with malaria using synthetic peptides

Manuel E. Patarroyo, Pedro Romero, Martha L. Torres, Pedro Clavijo, Alberto Moreno, Alberto Martínez, Raul Rodríguez, Fanny Guzman & Edelmira Cabezas

Instituto de Inmunologia, Hospital San Juan de Dios, Universidad Nacional de Colombia, Bogota, Colombia

	Monkey no.	Parasitaemia after challenge on days																										
		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	2	22	24	26	28	30	35	40	45	60	75	90
Controls	358	0.1	0	0.9	0.9	5.3	7.9	10.2	28.4	Q																		
	357	0	0	0.1	0	0.5	1.6	2.8	4.0	7.4	19.0	Q																
	359	0.1	0	0.5	0.9	0.9	2.4	2.5	5.4	9.0	9.0	4.5	11.5	12.0	19.0	Q												
Mixture of SPf 35.1 and SPf 55.1 and SPf 83.1	229	0	0	0.8	0.5	1.5	5.0	6.6	32.5	Q																		
	255	0	0	0.6	1.0	3.7	6.7	10.9	31.0	Q																		
	287	0	0	0.8	0.8	1.0	1.6	4.1	6.0	11.8	9.6	9.8	10.0	10.5	Q													
	251	0	0	0	0	0	0	0	0.2	0.2	1.2	3.2	ND	11.6	Q													
	275	0	0	0	0.1	0.5	0.5	0.5	2.0	4.0	6.5	6.0	6.6	ND	8.3	0.9	0.6	0.5	0.4	0.1	0	0	0	0	0	0	0	0
	288	0	0	0	0	0.2	0.1	0	1.0	0.8	2.3	ND	4.5	5.7	3.1	1.0	1.0	0.5	0.1	0	0	0	0	0	0	0	0	0
	289	0	0	0	0.2	0.1	0.2	1.0	2.3	5.4	10.4	6.8	2.7	5.4	ND	0.2	0.2	0.2	0.1	0	0	0	0	0	0	0	0	0
	286	0	0	0.1	0	0.1	0.4	0.4	3.5	3.7	3.2	ND	0.2	0.2	0	0.2	0.2	0.2	0.2	0	0	0	+					
Mixture of SPf 35.1 and SPf 55.1	295	0	0	0	0	0	0	0	0	0	0	0	0	0	0.1	0	0.3	4.4	5.5	2.1	0.2	0	0	0	0	0	0	0
	298	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3	1.3	4.8	0.9	0.4	0.1	0	0	0	0	0	0	0	0
	290	0	0	0	0.1	0	0	0	0.3	0	0.7	0.1	0.7	0.4	2.5	1.1	0.6	0	0	0	0	0	0	0	0	+		
	291	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	00
	297	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	300	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NATURE VOL. 328 13 AUGUST 1987

Induction of protective immunity against experimental infection with malaria using synthetic peptides

Manuel E. Patarroyo, Pedro Romero, Martha L. Torres, Pedro Clavijo, Alberto Moreno, Alberto Martínez, Raul Rodríguez, Fanny Guzman & Edelmira Cabezas

Instituto de Inmunologia, Hospital San Juan de Dios, Universidad Nacional de Colombia, Bogota, Colombia

Synthetic peptides are potential vaccine candidates because they may be able to induce high antibody titres and specific cellular immune responses against native proteins and thus the whole invading organism[1]. In a previous study we showed that immunization with molecules of relative molecular mass (M_r) 155,000 (155K) 83K, 55K and 35K, specific for the late schizont and merozoite stages of *Plasmodium falciparum*, could elicit either partial or total protection in *Aotus trivirgatus* monkeys experimentally infected with *P. falciparum*[2]. Here we have chemically synthesized 18 peptides corresponding to different fragments of these proteins to immunize *Aotus trivirgatus* monkeys. Some peptides gave partial protection from challenge with *P. falciparum* parasites, but none provided complete protection individually. A combination of three partially protective peptides gave complete or almost complete protection, however, suggesting that this particular combination of peptides is a good candidate for a malaria vaccine.

AMINOACID SEQUENCE OF THE SYNTHETIC MALARIA VACCINE SPf66

Patarroyo M. et al. 1988. *Nature.* 332:158

NATURE VOL. 332 10 MARCH 1988

A synthetic vaccine protects humans against challenge with asexual blood stages of *Plasmodium falciparum* malaria

Manuel E. Patarroyo*, Roberto Amador*, Pedro Clavijo*, Alberto Moreno*, Fanny Guzman*, Pedro Romero*, Ricardo Tascon*, Antonio Franco*, Luis A. Murillo*, Gabriel Ponton† & Gustavo Trujillo†

* Instituto de Inmunologia, Hospital San Juan de Dios, Universidad Nacional de Colombia, Bogota, Colombia SA.
† Hospital Militar Central de Colombia, Fuerzas Militares de Colombia, Bogota, Colombia S.A.

We have previously shown that a mixture of three synthetic peptides (83.1, 55.1, 35.1), corresponding to fragments of the relative molecular mass 83,000 (83K), 55K and 35K *Plasmodium falciparum* merozoite-specific proteins, induces protection in *Aotus trivirgatus* monkeys experimentally infected with *P. falciparum*[1,2]. Here we describe two polymeric synthetic hybrid proteins based on these peptides that delay or suppress the development of parasitaemia in immunized human volunteers.

Clin. exp. Immunol. (1991) **84**, 122-128

Studies on the humoral immune response to a synthetic vaccine against *Plasmodium falciparum* malaria

M. SALCEDO, L. BARRETO, M. ROJAS, R. MOYA, J. COTE & M. E. PATARROYO
Institute of Immunology, Hospital San Juan de Dios, Universidad Nacional de Colombia, Bogotá, Colombia

(*Accepted for publication 9 October 1990*)

SUMMARY

A synthetic vaccine against the asexual blood stages of *P. falciparum*, the SPf 66 synthetic hybrid polymer, composed of peptides derived from three merozoite membrane proteins as well as one peptide from the sporozoite CS protein, has been developed by our group and tested in different protection assays in *Aotus* monkeys as well as in human volunteers. This study evaluates the humoral immune response induced by the SPf 66 protein vaccination in adult human volunteers from the Colombian Pacific coast as follows: determination of specific IgG antibody levels against SPf 66 by FAST-ELISA after each immunization; analysis of antibody reactivity with *P. falciparum* schizont lysates by immunoblots; and determination of the *in vitro* parasite growth inhibition. A clear boosting effect, dependent on time and dose, was observed in the antibody production kinetics. These antibodies also specifically recognize three proteins of the *P. falciparum* schizont lysate corresponding to the molecular weights of the proteins from which the amino acid sequence was derived. These sera were also capable of markedly inhibiting *in vitro* parasite growth.

Vaccine, Vol. 10, Issue 3, 1992 175

Study of the safety and immunogenicity of the synthetic malaria SPf66 vaccine in children aged 1–14 years

Gloria Patarroyo, Lina Franco, Roberto Amador, Luis Angel Murillo, Claudia Lucia Rocha, Mauricio Rojas and Manuel Elkin Patarroyo*

Safety and immunogenicity tests of the SPf66 malaria vaccine have been carried out on a population of children, aged 1 to 14 years, in the town of Tumaco, Colombia. Adverse reactions measured after each vaccination were local and minimal, and observed in only a small percentage of the vaccinated children. One year later, no delayed reaction was evident. The majority of the child population developed high antibody titres against SPf66 and the degree of response did not vary with age. These induced antibodies recognize the native parasite proteins, in particular the molecules from which the amino acid sequence of this vaccine was deduced. These studies demonstrate that the SPf66 vaccine is safe and highly immunogenic for use in children >1 year old.

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Safety and Immunogenicity of the Synthetic Malaria Vaccine SPf66 in a Large Field Trial

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In the first field trial with synthetic malaria vaccine SPf66 in a large population naturally exposed to malaria, 9957 persons >1 year old and residing on the Colombian Pacific coast received three doses of the vaccine. To evaluate vaccine safety, clinical observations were made 30 min and 48 h after each immunization. There were no adverse reactions in 95.7% of cases. In the 4.3% of cases with adverse reactions, local induration and erythema were the most frequent. In a randomly selected group of vaccinees, anti-SPf66 antibody titers were measured after the third dose: 93% of the vaccinees raised antibodies to SPf66. Among these, 55% had titers >1:1600. These results demonstrate the safety and immunogenicity of the SPf66 vaccine in a large field trial.

THE LANCET

Vaccination with SPf66, a chemically synthesised vaccine, against *Plasmodium falciparum* malaria in Colombia

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M. S. Bello L. A. Murillo A. L. Mora G. Patarroyo
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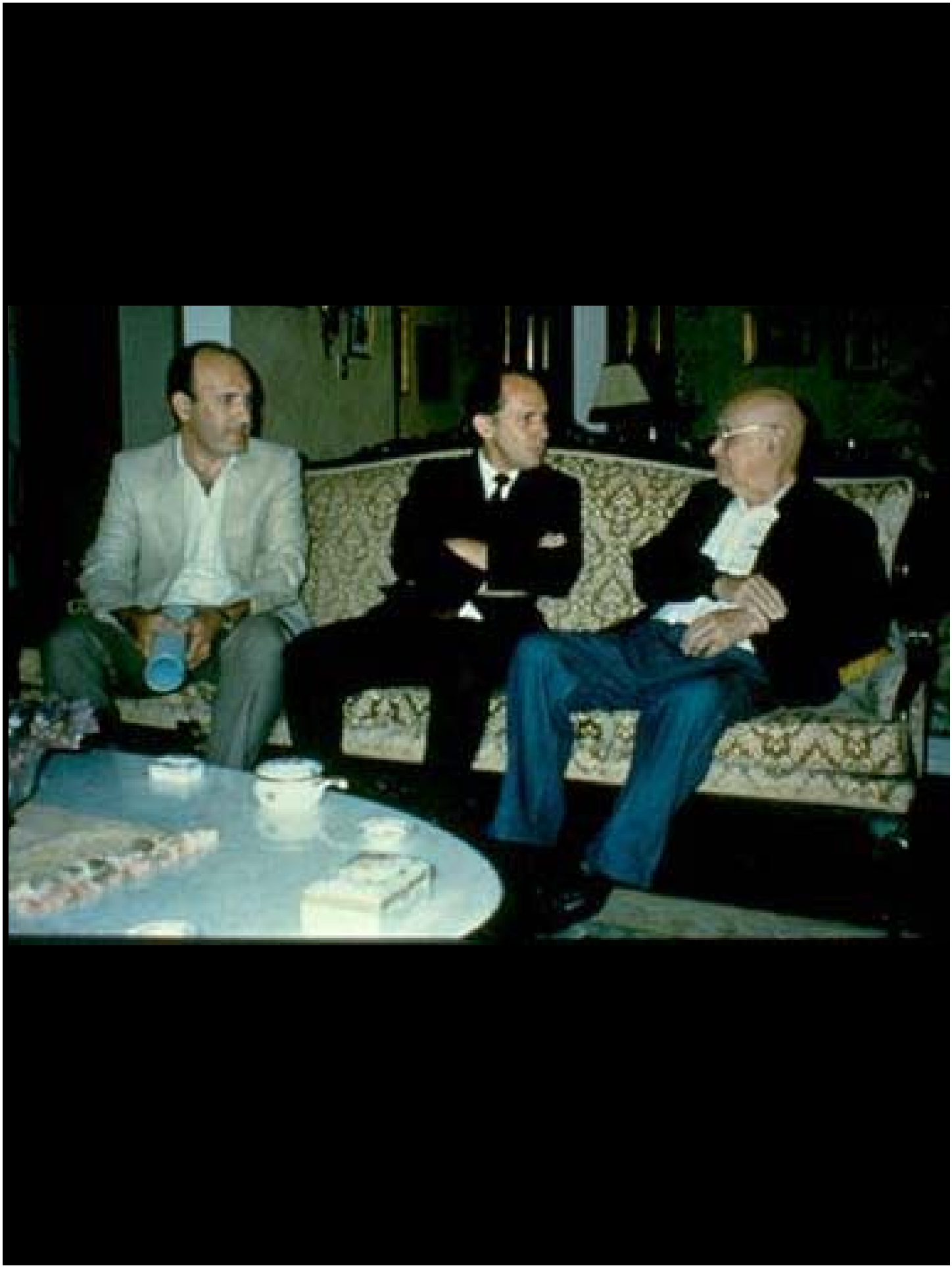
Preclinical and clinical studies have established the safety and immunogenicity of the chemically synthesised SPf66 malaria vaccine. The present study is a phase III randomised, double-blind, placebo-controlled, efficacy trial completed in La Tola, Colombia. 1548 volunteers over one year of age received three doses of either the vaccine (n = 738) or placebo (n = 810).

Active and passive case detection methods were used to document clinical episodes of malaria among the study population. The follow-up period began one month after the third dose and lasted for one year. 168 and 297 episodes of *Plasmodium falciparum* malaria were documented in the SPf66 group and the placebo group, respectively; this corresponds to a crude protective efficacy of 38·8%. Incidence rates for first or only *P falciparum* malarial episodes were 22·3% per annum among the v efficacy against second episodes was 50·5% (95% group (RR = 1·5; 95% CI 1·23, 1·84). Therefore, the protective efficacy of SPf66 against first or only e efficacy against second episodes was 50·5% (95% highest in children aged 1–4 years (77%) and adults older than 45 years (67%). The estimated protective efficacy against second episodes was 50·5% (95% CI 12·9–71·9).



The Journal of Infectious Diseases 1994;170:396–402

A Population-Based Clinical Trial with the SPf66 Synthetic *Plasmodium falciparum* Malaria Vaccine in Venezuela

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A phase III malaria vaccine trial in 13 villages in an endemic area, South Venezuela, compared incidence rates of *Plasmodium falciparum* and *Plasmodium vivax* infections in 1422 vaccinated and 938 nonvaccinated subjects over 18 months. The SPf66 vaccine was given in three doses, on days 0, 20, and 112. Vaccination was complete in 976 subjects (68.7%). Minor side effects requiring no treatment were reported by 123 (12.6%), with an apparent increase in frequency from the first to the third vaccine dose. No autoimmune evidence was observed in a sample of subjects. Antibodies against SPf66 were present at low titers in 24.7% of tested subjects before vaccination, increasing to 53.6% after the second dose and to 73.6% after the third dose; 26.4% of subjects initially seronegative never seroconverted. The SPf66 malaria vaccine showed a protective efficacy of 55% (95% confidence interval, 21%–75%) t *P. falciparum* and of 41% (19%–57%) against *P. vivax* malaria.

Vaccine 1994 Volume 12 Number 4 337

Safety, immunogenicity and protective effect of the SPf66 malaria synthetic vaccine against *Plasmodium falciparum* infection in a randomized double-blind placebo-controlled field trial in an endemic area of Ecuador

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A total of 537 subjects were randomized to receive either SPf66 malaria vaccine against Plasmodium falciparum *or placebo in three doses (days 0, 30 and 180). Subjects completing the course of vaccination (230 in the vaccine and 238 in the placebo group) were followed up for a further 12 months. Case detection surveillance was implemented by parasitological cross-sectional surveys every 2 months and by monthly household visits to each participant. Symptomatic subjects were also diagnosed in a local health centre. Minor local side-effects were observed mainly after the second dose in about 19% of the vaccinated subjects and in 3.7% of the placebo group. Thirty days after the third dose the prevalence of anti-SPf66 antibodies was 57% in the vaccine and 8.8% in the placebo groups. The prevaccination prevalence of antibodies measured by indirect immunofluorescence assay increased with age and seemed to be inversely related to anti-SPf66 antibody production. Immune response to SPf66 was independent of age. Vaccine efficacy was calculated based on person-time of exposure. The protective effect considering any malaria episode was 66.8% (95% confidence interval = −2.7–89.3%) and considering only one episode per individual was 60.2% (95% confidence interval = −26–87.5%).*


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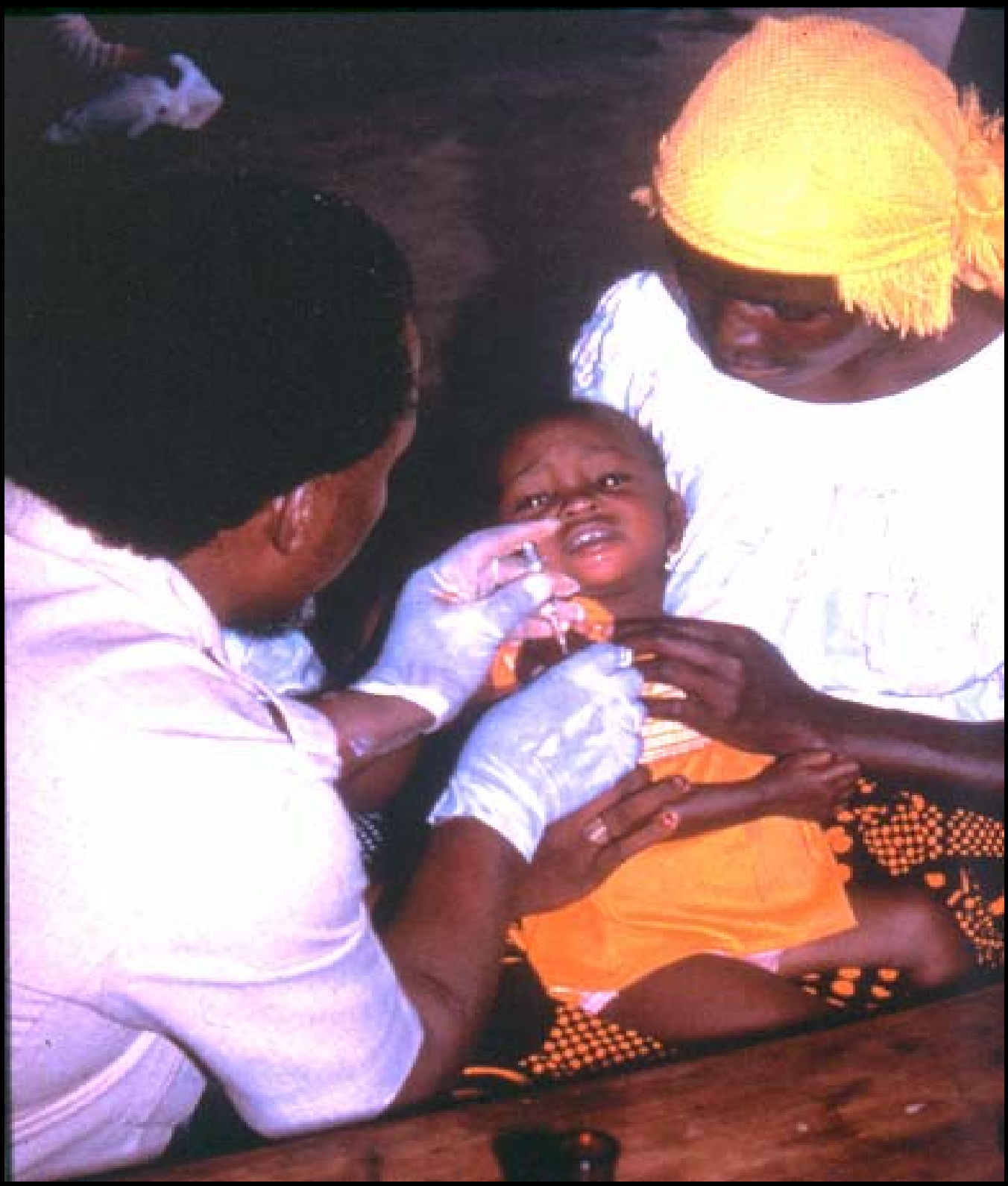
Evaluation of SPf66 malaria vaccine during a 22-month follow-up field trial in the Pacific coast of Colombia

M.V. Valero*, R. Amador*, J.J. Aponte*, A. Narvaez*, C. Galindo*, Y. Silva*, J. Rosas*, F. Guzman* and M.E. Patarroyo*†

A double-blind randomized placebo-controlled field trial with the SPf66 malaria vaccine was carried out in an endemic area consisting of 14 small villages with exclusive fluvial access, in a rain forest area along the Rosario River, Colombia. A total of 1257 subjects completed the full three dose vaccination schedule on days 0, 30 and 180 (643 vaccinated group/623 placebo group) and were followed-up by passive and active surveillance over a period of 22 months. One hundred and thirty-four Plasmodium falciparum *malaria episodes were detected (53 in vaccinated group/81 in placebo group), yielding an attack rate of 5.47 cases/100 person years of follow-up (pyears) in the vaccine group and 8.44/100 pyears in the placebo group. The estimated vaccine protective efficacy was 35.2% (95% CI 8.4–54.2%,* P=*0.01). This result supports earlier findings that the SPf66 malaria vaccine diminishes the risk of infection by* P. falciparum *in endemic areas of South America. Copyright © 1996 Elsevier Science Ltd.*



Lancet 1994; **344**: 1175–81

Randomised trial of efficacy of SPf66 vaccine against *Plasmodium falciparum* malaria in children in southern Tanzania

P L Alonso, J Smith, J R M Armstrong Schellenberg, H Masanja, S Mwankusye, H Urassa, I Bastos de Azevedo, J Chongela, S Kobero, C Menendez, N Hurt, M C Thomas, E Lyimo, N A Weiss, R Hayes, A Y Kitua, M C Lopez, W L Kilama, T Teuscher, M Tanner

Summary

Effective, safe antimalarial vaccines have proved elusive. The synthetic polypeptide SPf66 vaccine is based on pre-erythrocytic and asexual blood-stage proteins of *Plasmodium falciparum*. We report here a randomised double-blind placebo-controlled trial of the efficacy of the SPf66 vaccine against clinical *P falciparum* malaria in Idete, southern Tanzania, an area of intense perennial malaria transmission.

586 children aged 1–5 years received three doses of vaccine (n=274) or placebo (n=312). The incidence and density of parasitaemia were assessed through repeated cross-sectional surveys on subgroups of children. Morbidity was monitored over a 1 year period through passive case detection in all children plus active case detection in a subgroup of 191. An episode of clinical malaria was defined as measured fever (≥37·5°C) and parasite density >20 000/μL.

No severe side-effects were seen and the frequency of mild side-effects after the third dose was less than 6%. The vaccine was highly immunogenic and after three doses all vaccine recipients had detectable anti-SPf66 antibodies: the geometric mean index of response was 8·3 in the vaccine group and 0·7 in the placebo group. The incidence of parasitaemia was similar in both groups. 123 children had at least one episode of clinical malaria during the follow-up period after the third dose and annual incidence rates were 0·25 in the vaccine group and 0·35 in the placebo group. Estimated vaccine efficacy was 31% (95% confidence interval 0–52%; p=0·046). After the third dose there were 6 deaths among the study cohort (1 vaccine, 5 placebo). This study confirms that SPf66 is safe, immunogenic and reduces the risk of clinical malaria among children exposed to intense *P falciparum* transmission.

Lancet 1994; **344**: 1175–81

The Journal of Infectious Diseases 1996; 174:367–72

Duration of Protection and Age-Dependence of the Effects of the SPf66 Malaria Vaccine in African Children Exposed to Intense Transmission of *Plasmodium falciparum*

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The SPf66 synthetic vaccine is safe and partly efficacious against *Plasmodium falciparum* malaria among children 1–5 years old. The estimated vaccine efficacy [VE] for all clinical episodes over a period of 18 months after the third dose is 25% (95% confidence interval [CI], 1%–44%; $P = .044$). The observed temporal variations in efficacy could have been due to chance (likelihood ratio $\chi^2 = 13.8$, 8 *df*; $P = .086$). Efficacy against clinical malaria did not vary significantly with age ($\chi^2 = 1.07$, 4 *df*; $P = .90$). Overall parasite density was 21% lower in vaccine recipients than in the placebo group (95% CI, 0%–38%; $P = .044$). Further development of SPf66 may require trials to evaluate safety, immunogenicity, and efficacy when administered in the first year of life, together with other vaccines contained in the Expanded Programme of Immunization schedule.

The Journal of Infectious Diseases 1997;175:921–6

Analysis of Multiple *Plasmodium falciparum* Infections in Tanzanian Children during the Phase III Trial of the Malaria Vaccine SPf66

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In the first phase III efficacy trial of the malaria vaccine SPf66 in Africa, MOIs in SPf66- and placebo-vaccinated children were analyzed by polymerase chain reaction–restriction fragment length polymorphism of the *Plasmodium falciparum* merozoite surface antigen 2 (MSA2). MOIs were significantly reduced in asymptomatic vaccine recipients compared with those in asymptomatic placebo recipients; however, no differences were observed among symptomatic children in the vaccine and control groups. These results show that immunization with SPf66 modulates the course of naturally occurring infections, as reflected by reduced MOIs. In placebo recipients, however, there was a significant negative correlation between numbers of infecting genotypes, as identified by MSA2, and morbidity. Asymptomatic placebo recipients had an average of 5 concurrent infections, whereas children with clinical cases had an average of 3.4 infections. These data provide further evidence that premunition from concurrent infections is important in immunity against clinical malaria. No such effect of multiple infections was found in the vaccinated group.

Randomised double-blind placebo-controlled trial of SPf66 malaria vaccine in children in northwestern Thailand

*François Nosten, Christine Luxemburger, Dennis E Kyle, W Ripley Ballou, Janet Wittes, Eh Wah, Tan Chongsuphajaisiddhi, Daniel M Gordon, Nicholas J White, Jerald C Sadoff, D Gray Heppner, and the Shoklo SPf66 Malaria Vaccine Trial Group**

Summary

Background Previous efficacy trials of SPf66 malaria vaccine have produced conflicting results in different populations. We report a randomised double-blind trial of the SPf66 vaccine conducted in Karen children aged 2–15 living in a malarious region of northwestern Thailand. Recombinant hepatitis B vaccine was used as a comparator.

Methods The study had a power of 90% to detect an efficacy of 30%, defined as a reduction in the incidence of first cases of symptomatic falciparum malaria after three doses of vaccine. 1221 children received three immunisations and were eligible for the primary efficacy analysis. Intense active and passive case detection continued over 15 months of follow-up.

Findings The SPf66 vaccine was well tolerated, although 26 children had mild or moderately severe local or systemic allergic reactions, compared with none in the comparator group. The vaccine was immunogenic; after three doses, 73% of recipients had seroconverted. There were no deaths due to malaria during the study. During the 15-month period of evaluation there were 379 first cases of symptomatic falciparum malaria (195 in the SPf66 recipients, 184 in the comparator group); an SPf66 efficacy of −9% (95% CI −33 to 14, p=0·41). No significant differences between the two study groups in parasite density or any other measure of malaria-related morbidity were detected.

Interpretation These findings are consistent with a recent study showing lack of efficacy of SPf66 among Gambian infants and differ from earlier positive reports from South America and evidence of borderline efficacy from Tanzania.

We conclude that SPf66 does not protect against clinical falciparum malaria and that further efficacy trials are not warranted.

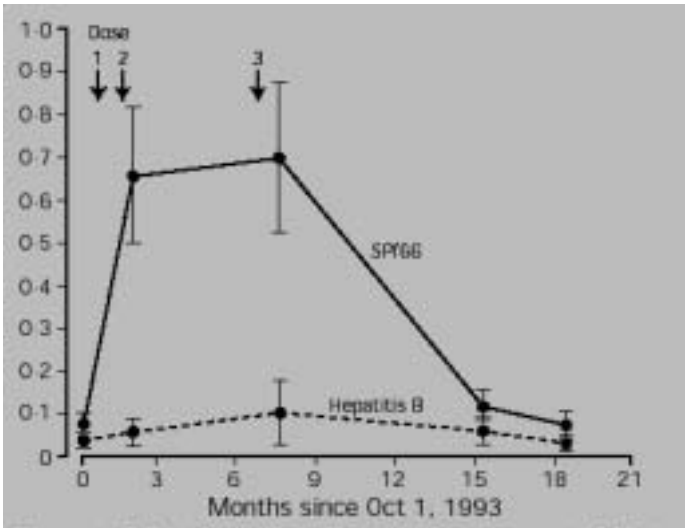

Figure 1: **Cohort I group mean antibody response to SPf66 after the first dose of vaccine**
Bars are standard errors.

The vaccine lots used in this study were produced and formulated in the USA, whereas the previous studies used vaccine produced in Colombia. At the request of the WHO, samples from both sources have undergone extensive independent characterisation by the National Institute of Biological Standards and Controls, UK, and remarkable consistency has been found between lots of bulk and formulated vaccine produced by the two laboratories.

In our hands, the ratio of monomer to polymer was found to be important in the context of peptide binding to alum and thus to immunogenicity. Our SPf66 formulations were prepared with a higher alum concentration per dose than used in Colombia to achieve optimum peptide binding ratios (>50%). The seroconversion rates with standard

A pilot safety and immunogenicity study of the malaria vaccine SPf66 in Gambian infants

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SUMMARY

A pilot safety and immunogenicity trial of the malaria vaccine SPf66 has been undertaken in 150 Gambian infants. No significant systemic side effects were recorded but modest local reactions were seen after the administration of a third 1·0 mg dose. SPf66 produced in Colombia was more immunogenic than SPf66 produced in the USA and a 1·0 mg dose of each vaccine gave higher antibody levels than a 0·5 mg dose. However, antibody levels fell rapidly after administration of the third dose of vaccine and showed little change over the following malaria transmission season.

Comment

The SPf66 Malaria Vaccine:
What is the Evidence for Efficacy?

P. Graves, H. Gelband and P. Garner

Results of individual trials were combined using the Peto odds ratio (OR), for which the trials are weighted by the inverse of their variance[6]. The weighting thus takes into account the number of participants in a trial and the number of outcomes observed. The OR result may be interpreted as the relative risk in the vaccinated group compared with the control group. An OR significantly less than 1.0 (shown as the vertical line in Table 1) indicates a protective effect of the vaccine. The OR is converted to vaccine efficacy (%) by the following formula: Efficacy= (1−OR)×100.

Systematic review findings. In the current edition of the Cochrane malaria vaccine review, six trials of SPf66 met the inclusion criteria: three from South America[7–9], two from Africa[10,11] and one from Thailand[3] (Table 2). Two other trials in South America were excluded due to lack of proper randomization. Results are presented in Table 1 (upper part) for the incidence of the first or only attack of clinical malaria. The Peto OR was 0.77 [95% confidence interval (CI) = 0.68–0.88], giving a combined estimate of vaccine efficacy of 23% (95% CI = 12–32%). During the follow-up period, some participants had more than one episode of clinical malaria, and five of the six SPf66 trials reported the total number of episodes. The results from these five trials suggest that vaccine efficacy was greater against second or subsequent clinical episodes than it was in preventing malaria completely. The overall (unweighted) incidence of the first or only episode of malaria was reduced from 240 per 1000 in the placebo groups to 191 per 1000 in the [illegible] whereas the incidence of subsequent attacks was reduced from 62 per 1000 to 41 per 1000 (a reduction of 34%). Only two trials reported on the most

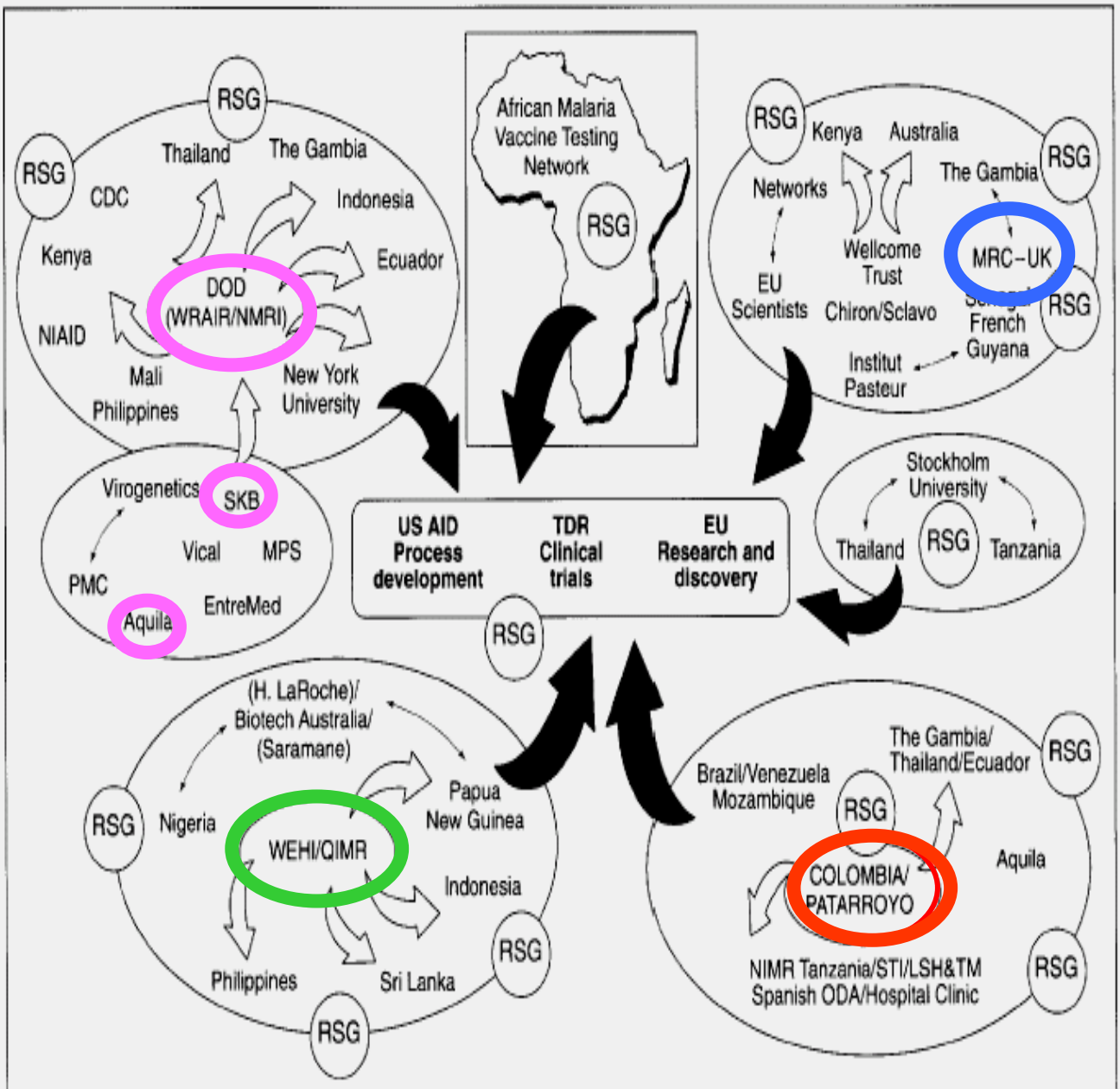

Fig. 2. A global strategy for malaria vaccine development. This schema illustrates the major contributors to malaria vaccine development. Abbreviations: CDC, Centers for Disease Control; DOD, Dept of Defence; EU, European Union; LSH&TM, London School of Hygiene and Tropical Medicine; MPS, Mimiotope Peptide Systems; MRC, Medical Research Council; NIAID, National Institutes of Allergy and Infectious Diseases; NIMR, National Institute for Medical Research, Tanzania; NMRI, Naval Malaria Research Institute; ODA, Overseas Development Agency; PMC, Pasteur/Merieux/Connaught; QIMR, Queensland Institute for Medical Research; RSG, Research Strengthening Group of TDR; SKB, SmithKline Biologicals; STI, Swiss Tropical Institute; TRAP, thrombospondin-related anonymous protein; WEHI, Walter and Elisa Hall Institute; WRAIR, Walter Reed Army Institute for Research.

Papers

Safety, immunogenicity and limited efficacy study of a recombinant *Plasmodium falciparum* circumsporozoite vaccine in Thai soldiers

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Thai soldiers were vaccinated with a recombinant protein derived from the central repeat region of the circumsporozoite (CS) protein of Plasmodium falciparum *conjugated to Toxin A (detoxified) of* Pseudomonas aeruginosa *(R32Tox-A) to evaluate its safety, immunogenicity and efficacy. In a randomized, double-blind manner 199 volunteers received either R32Tox-A or a control vaccine at 0, 8 and 16 weeks. Immunization was performed in a malaria non-transmission area, after completion of which volunteers were deployed to an endemic border area and monitored closely to allow early detection and treatment of infection. The vaccine was found to be safe and to elicit antibody responses in all vaccinees. Peak CS antibody (IgG) concentrations in malaria-experienced vaccinees exceeded those in malaria-naive vaccinees (mean 40.6 versus 16.1 μg ml^{-1}; p = 0.005) as well as those induced by previous CS protein-derived vaccines and observed in association with natural infections. A low rate of falciparum malaria revealed no differences between vaccinated and non-vaccinated subjects. Secondary analyses revealed that CS antibody levels were lower in vaccinee malaria cases than in non-cases, 3 and 5 months after the third dose of vaccine (p = 0.06 and p = 0.014, respectively). Because antibody levels had fallen substantially before peak malaria transmission occurred, the question of whether high levels of CS antibody are protective remains to be resolved.*

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Plasmodium falciparum circumsporozoite vaccine immunogenicity and efficacy trial with natural challenge quantitation in an area of endemic human malaria of Kenya

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It has been hypothesized that antibody induced by Plasmodium falciparum *circumsporozoite protein vaccine would be effective against endemic human malaria. In a malaria endemic region of Kenya, 76 volunteers, in 38 pairs sleeping adjacently, were immunized with subunit circumsporozoite protein Asn-Ala-Asn-Pro tetrapeptide repeat-pseudomonas toxin A, or hepatitis B vaccine. After quinine and doxcycycline, volunteers were followed for illness daily, parasitemia weekly, antibody, T-lymphocyte responses, and treated if indicated.* Anopheles *mosquitoes resting in houses were collected, and tested for* P. falciparum *antigen, or dissected for sporozoites and tested for blood meal ABO type and* P. falciparum *antigen. Vaccine was safe, with side-effects similar in both groups, and immunogenic, engendering IgG antibody as high as 600 μg ml^{-1}, but did not increase the proportion of volunteers with T-lymphocyte responses. Estimation of* P. falciparum *challenge averaged 0.194 potentially infective* Anopheles *bites/volunteer/day. Mosquito blood meals showed no difference in biting intensity between vaccine and control groups. Both groups had similar malaria-free survival curves, cumulative positive blood slides, cumulative parasites mm^{-3}, and numbers of parasites mm^{-3} on first positive blood slide, during three post-vaccination observation periods. Every volunteer had* P. falciparum *parasitemia at least once. Vaccinees had 82% and controls 89% incidences of symptomatic parasitemia (*P*=0.514, efficacy 9%, statistical power 95% probability of efficacy <50%). Vaccine-induced anti-sporozoite antibody was not protective in this study. Within designed statistical precisions the present study is in agreement with efficacy studies in Colombia, Venezuela and Tanzania.*

The Journal of Infectious Diseases 1998; 177:1664–73

Phase I/IIa Safety, Immunogenicity, and Efficacy Trial of NYVAC-Pf7, a Pox-Vectored, Multiantigen, Multistage Vaccine Candidate for *Plasmodium falciparum* Malaria

Christian F. Ockenhouse, Pei-fang Sun, David E. Lanar, Bruce T. Wellde, B. Ted Hall, Kent Kester, Jose A. Stoute, Alan Magill, Urszula Krzych, Linda Farley, Robert A. Wirtz,* Jerald C. Sadoff, David C. Kaslow, Sanjai Kumar, L. W. Preston Church,* James M. Crutcher,* Benjamin Wizel,* Stephen Hoffman, Ajit Lalvani, Adrian V. S. Hill, John A. Tine, Kenneth P. Guito, Charles de Taisne, Robin Anders, Toshihiro Horii, Enzo Paoletti, and W. Ripley Ballou

Department of Immunology, Walter Reed Army Institute of Research, Washington, DC; Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, and Malaria Program, Naval Medical Research Institute, Bethesda, Maryland; Institute of Molecular Medicine, University of Oxford, Headington, Oxford, United Kingdom; Virogenetics Corp., Troy, New York; Connaught Laboratories, Inc., Swiftwater, Pennsylvania; Pasteur Mérieux Connaught, Marcy l'Étoile, France; Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia; Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

Candidate malaria vaccines have failed to elicit consistently protective immune responses against challenge with *Plasmodium falciparum*. NYVAC-Pf7, a highly attenuated vaccinia virus with 7 *P. falciparum* genes inserted into its genome, was tested in a phase I/IIa safety, immunogenicity, and efficacy vaccine trial in human volunteers. Malaria genes inserted into the NYVAC genome encoded proteins from all stages of the parasite's life cycle. Volunteers received three immunizations of two different dosages of NYVAC-Pf7. The vaccine was safe and well tolerated but variably immunogenic. While antibody responses were generally poor, cellular immune responses were detected in >90% of the volunteers. Of the 35 volunteers challenged with the bite of 5 *P. falciparum*–infected *Anopheles* mosquitoes, 1 was completely protected, and there was a significant delay in time to parasite patency in the groups of volunteers who received either the low or high dose of vaccine compared with control volunteers.

Effect of vaccination with 3 recombinant asexual-stage malaria antigens on initial growth rates of *Plasmodium falciparum* in non-immune volunteers

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Abstract

A placebo controlled, randomised, double blind trial was conducted in human volunteers to test a mixture of three recombinant *Plasmodium falciparum* blood stage antigens for its ability to reduce the initial growth rates of parasites. The vaccine contained recombinant MSP2 (3D7 allele), a portion of MSP1 (190LCS.T3) and part of the RESA antigen (C terminal 771 amino acids) in the Montanide ISA 720 adjuvant (SEPPIC). Twelve volunteers received two doses of the vaccine, 6 weeks apart. The five participants in the placebo group received an equivalent volume of the adjuvant emulsion using the same schedule. Antibody responses were low, as has been reported in earlier studies with this combination, while T cell responses were stronger. All the volunteers were challenged with approximately 140 ring infected red cells of the 3D7 cloned line, 4 weeks after the second dose. Parasitaemia was determined once daily from day 4 using a sensitive and quantitative PCR assay. All the volunteers were infected and were treated on day 8, before any developed symptoms. There was no significant difference in initial parasite growth rates between the verum and placebo groups, nor was there any significant correlation between parasite growth rates and any of the measured immunological responses. These results suggest that the formulation tested in this trial did not generate immune responses that were strong enough to reduce parasite growth in naive volunteers.

Vaccine Volume 18, Issue 18 , March 2000 , Pages 1925-1931

nature medicine

Enhanced T-cell immunogenicity of plasmid DNA vaccines boosted by recombinant modified vaccinia virus Ankara in humans

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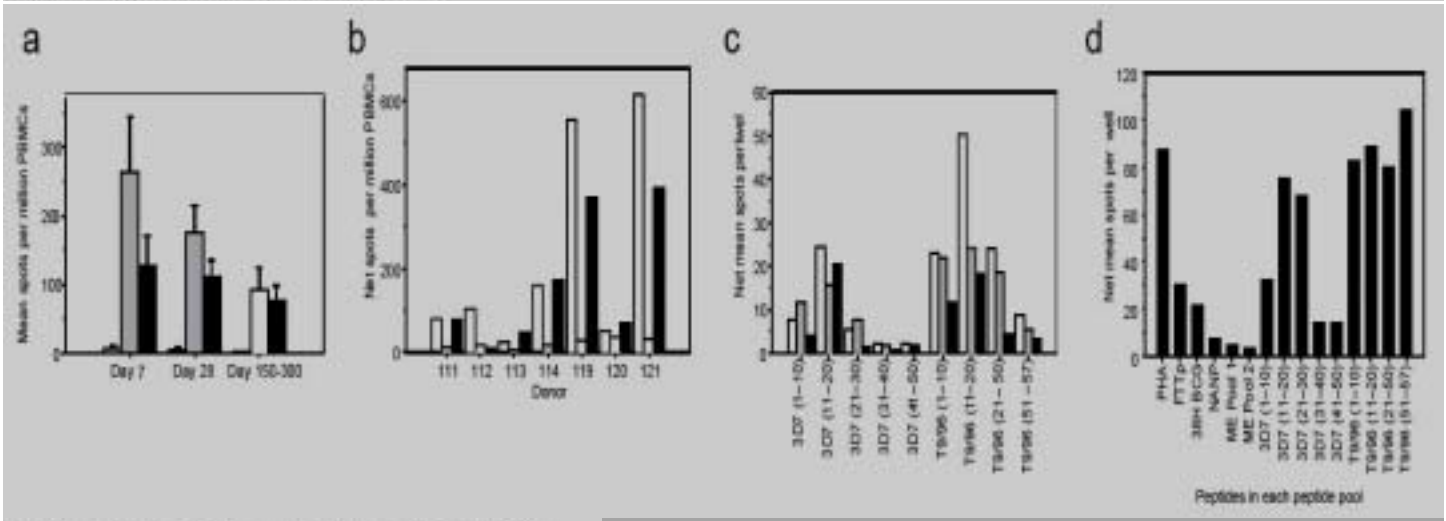
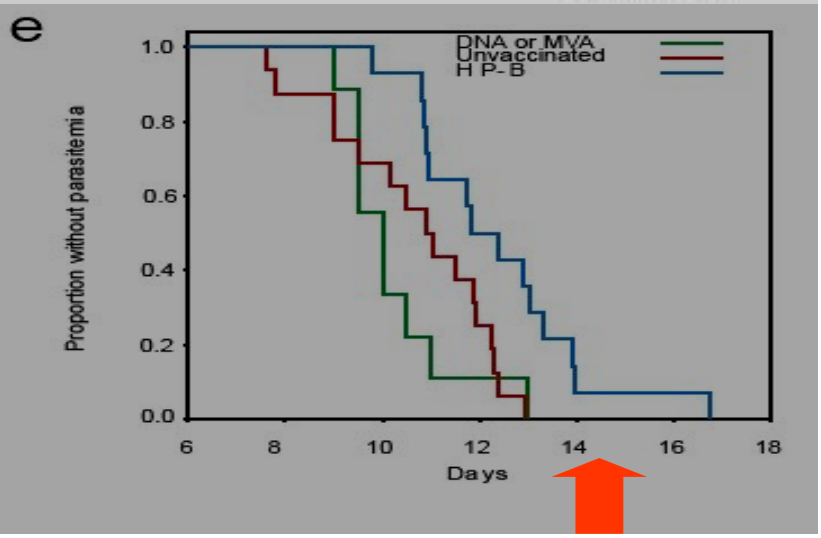


Figure 3 Characteristics of induced T-cell responses and protective efficacy. (**a**) Time course at 7, 28 and 150–350 d after vaccination for six subjects in group GGMM(3). □, ME epitopes; ▨, TRAP TW96 peptides; ■, TRAP 3D7 peptides. The arithmetic mean and standard error are shown. (**b**) The results of $CD4^+$ and $CD8^+$ T-cell depletion experiments from DDD_MM(1.5) and DDDMM(1.5) groups 7 d after the last vaccine. □, undepleted; ▨, CD4-depleted; ■, CD8-depleted. (**c**,**d**) Breadth of the induced responses. The responses to each peptide pool shown in c are from the same subjects and time points as in a. □, day 7; ▨, day 28; ■, days 150–300. Data in d are 7 d after the first MVA booster dose of 1.5×10^7 PFU, for those who had three priming doses of 2 mg of DNA.ME-TRAP intramuscularly. The nomenclature of the peptide pools is described in **Fig. 3b** and in the footnote to **Table 3**. (**e**) Kaplan-Meier curves of time from sporozoite challenge to parasitemia detected on thick blood film for three groups: 16 unvaccinated control subjects, 14 heterologous prime-boost vaccinated subjects who received either GGMM(3) ($n = 6$), DDDMM(1.5) ($n = 4$) or DDD_MM(1.5) ($n = 4$, these being the groups with the strongest immune responses), and 9 vaccinated subjects who received just one of the vaccines, either MMM(3) ($n = 4$) or DDD(1) ($n = 5$; **Table 1**). HP-B, heterologous prime-boost. Development of parasitemia is delayed significantly in the heterologous prime-boost immunization group (log rank test, $P = 0.013$) compared with the unvaccinated controls, but there is no significant difference in time to parasitemia when comparing the volunteers who received DNA only or MVA only and the unvaccinated group.



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Vaccine xxx (2004) xxx–xxx

Vaccine

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Safety, immunogenicity and efficacy of a pre-erythrocytic malaria candidate vaccine, ICC-1132 formulated in Seppic ISA 720

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Abstract

ICC-1132, a recombinant protein comprising a modified hepatitis B core protein with a B cell (NANP) and twp T cell epitopes of *Plasmodium falciparum* circumsporozoite protein (CSP), was administered i.m. as a single 50 μg dose in Seppic ISA 720 11 volunteers. Local reactogenicity and systemic side effects were acceptable with the predominant finding being mild pain at the injection site. This regimen induced anti-NANP antibodies in 10/11 and modest T cell response There was no evidence of protection from experimental challenge with *P. falciparum* sporozoites. Other formulations and/or multi-dose regimens will be required to enhance the immunogenicity and efficacy of ICC-1132.

Lancet 2004; 364: 1411–20

Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial

Pedro L Alonso, Jahit Sacarlal, John J Aponte, Amanda Leach, Eusebio Macete, Jessica Milman, Inacio Mandomando, Bart Spiessens, Caterina Guinovart, Mateu Espasa, Quique Bassat, Pedro Aide, Opokua Ofori-Anyinam, Margarita M Navia, Sabine Corachan, Marc Ceuppens, Marie-Claude Dubois, Marie-Ange Demoitié, Filip Dubovsky, Clara Menéndez, Nadia Tornieporth, W Ripley Ballou, Ricardo Thompson, Joe Cohen

Summary

Background Development of an effective malaria vaccine could greatly contribute to disease control. RTS,S/AS02A is a pre-erythrocytic vaccine candidate based on *Plasmodium falciparum* circumsporozoite surface antigen. We aimed to assess vaccine efficacy, immunogenicity, and safety in young African children.

Methods We did a double-blind, phase IIb, randomised controlled trial in Mozambique in 2022 children aged 1–4 years. The study included two cohorts of children living in two separate areas which underwent different follow-up schemes. Participants were randomly allocated three doses of either RTS,S/AS02A candidate malaria vaccine or control vaccines. The primary endpoint, determined in cohort 1 (n=1605), was time to first clinical episode of *P falciparum* malaria (axillary temperature ≥37·5°C and *P falciparum* asexual parasitaemia >2500 per μL) over a 6-month surveillance period. Efficacy for prevention of new infections was determined in cohort 2 (n=417). Analysis was per protocol.

Findings 115 children in cohort 1 and 50 in cohort 2 did not receive all three doses and were excluded from the per-protocol analysis. Vaccine efficacy for the first clinical episodes was 29·9% (95% CI 11·0–44·8; p=0·004). At the end of the 6-month observation period, prevalence of *P falciparum* infection was 37% lower in the RTS,S/AS02A group compared with the control group (11·9% *vs* 18·9%; p=0·0003). Vaccine efficacy for severe malaria was 57·7% (95% CI 16·2–80·6; p=0·019). In cohort 2, vaccine efficacy for extending time to first infection was 45·0% (31·4–55·9; p<0·0001).

Interpretation The RTS,S/AS02A vaccine was safe, well tolerated, and immunogenic. Our results show development of an effective vaccine against malaria is feasible.

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Malaria vaccine: 3 or 6 months' protection?

The results of the trial of the RTS,S/AS02A malaria vaccine reported by Alonso and colleagues (Oct 16, p 1411)[1] are exciting and show clearly a protective effect against severe malaria and delays in the time to a first attack of clinical malaria and to the appearance of parasites in the blood after vaccination. However, the authors' conclusions that protection against clinical disease showed no evidence of waning during the 6 month follow-up and that there was only limited waning of the efficacy against malaria infection during this period should be interpreted with caution, particularly since an earlier trial[2] with this vaccine in adults in The Gambia showed evidence of a protective effect against malaria infection that lasted for only 2–3 months. Although the new data are compatible with sustained protection over 6 months, they are also compatible with there being little protection against clinical malaria or malaria infection for more than 3 months after vaccination. The data in figure 4 in the report, for example, show that among those who had not developed clinical disease by 3 months after vaccination, the risk of an episode of malaria in the next 3 months was similar (about 7–8%) in vaccinated and unvaccinated groups. Also, the risk of acquiring infection by 6 months among those not infected at 3 months was similar in both groups (about 65%) and, overall, during the 6-month period similar numbers of children were infected (157 and 166, respectively).

Additionally, there is little evidence of protection against clinical episodes of malaria other than the first. After a first episode the rate of subsequent episodes was slightly higher in the vaccinated group than in the unvaccinated group (deduced from table 3: 30 episodes in 19·4 person years at risk [PYAR; rate 1·5 per year] in the vaccinated group compared with 31 episodes in 27·2 PYAR [rate 1·1 per year] in the unvaccinated group).

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1 Alonso PL, Sacarlal J, Aponte JJ, et al. Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial. Lancet 2004; 364: 1411–20.

2 Bojang KA, Milligan PJ, Pinder M, et al. Efficacy of RTS,S/AS02 malaria vaccine against *Plasmodium falciparum* infection in semi-immune adult men in The Gambia: a randomised trial. Lancet 2001; 358: 927–34.

Efficacy of RTS,S/AS02 malaria vaccine against *Plasmodium falciparum* infection in semi-immune adult men in The Gambia: a randomised trial

*Kalifa A Bojang, Paul J M Milligan, Margaret Pinder, Laurence Vigneron, Ali Alloueche, Kent E Kester, Ripley Ballou, David J Conway, William H H Reece, Philip Gothard, Lawrence Yamuah, Martine Delchambre, Gerald Voss, Brian M Greenwood, Adrian Hill, Keith P W J McAdam, Nadia Tornieporth, Joe D Cohen, and Tom Doherty, for the RTS,S Malaria Vaccine Trial Team**

Findings 250 men (131 in the RTS,S/AS02 group and 119 in the control group) received three doses of vaccine and were followed up for 15 weeks. RTS,S/AS02 was safe and well tolerated. *P falciparum* infections occurred significantly earlier in the control group than the RTS,S/AS02 group (Wilcoxon's test p=0·018). Vaccine efficacy, adjusted for confounders, was 34% (95% CI 8·0–53, p=0·014). Protection seemed to wane: estimated efficacy during the first 9 weeks of follow-up was 71% (46–85), but decreased to 0% (–52 to 34) in the last 6 weeks. Vaccination induced strong antibody responses to circumsporozoite protein and strong T-cell responses. Protection was not limited to the NF54 parasite genotype from which the vaccine was derived. 158 men received a fourth dose the next year and were followed up for 9 weeks; during this time, vaccine efficacy was 47% (4–71, p=0·037).

Comment

The SPf66 Malaria Vaccine:
What is the Evidence for Efficacy?

P. Graves, H. Gelband and P. Garner

Results of individual trials were combined using the Peto odds ratio (OR), for which the trials are weighted by the inverse of their variance[6]. The weighting thus takes into account the number of participants in a trial and the number of outcomes observed. The OR result may be interpreted as the relative risk in the vaccinated group compared with the control group. An OR significantly less than 1.0 (shown as the vertical line in Table 1) indicates a protective effect of the vaccine. The OR is converted to vaccine efficacy (%) by the following formula: Efficacy= (1−OR)×100.

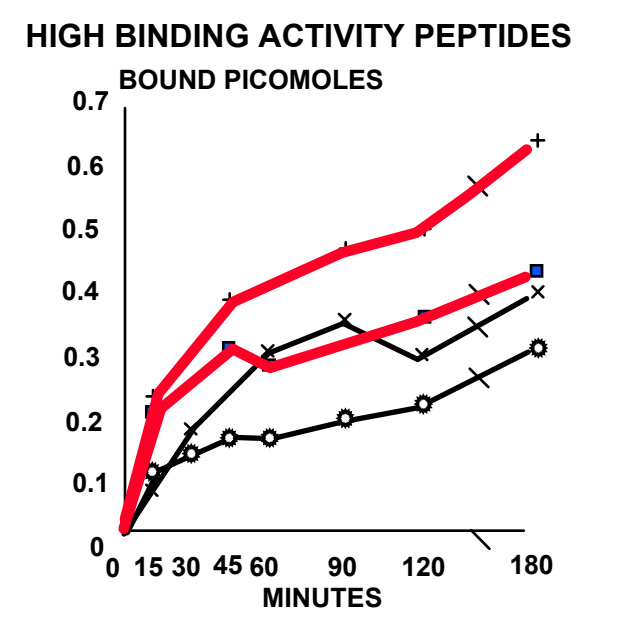
Systematic review findings. In the current edition of the Cochrane malaria vaccine review, six trials of SPf66 met the inclusion criteria: three from South America[7–9], two from Africa[10,11] and one from Thailand[3] (Table 2). Two other trials in South America were excluded due to lack of proper randomization. Results are presented in Table 1 (upper part) for the incidence of the first or only attack of clinical malaria. The Peto OR was 0.77 [95% confidence interval (CI) = 0.68–0.88], giving a combined estimate of vaccine efficacy of 23% (95% CI = 12–32%). During the follow-up period, some participants had more than one episode of clinical malaria, and five of the six SPf66 trials reported the total number of episodes. The results from these five trials suggest that vaccine efficacy was greater against second or subsequent clinical episodes than it was in preventing malaria completely. The overall (unweighted) incidence of the first or only episode of malaria was reduced from 240 per 1000 in the placebo groups to 191 per 1000 in the [illegible] whereas the incidence of subsequent attacks was reduced from 62 per 1000 to 41 per 1000 (a reduction of 34%). Only two trials reported on the most

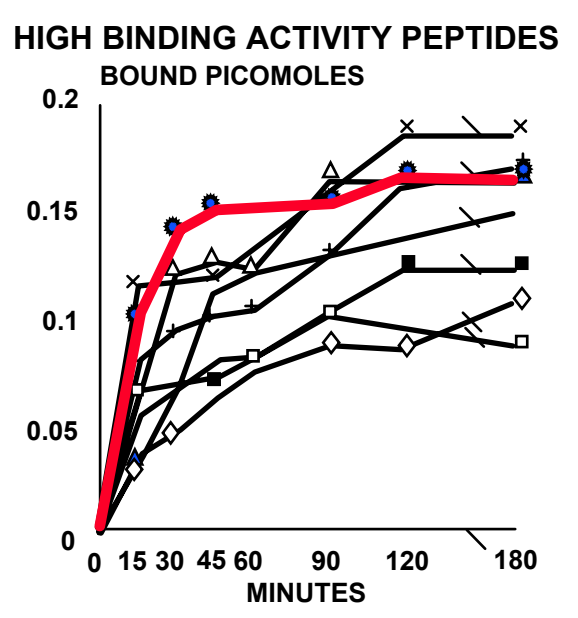
COLFAVAC

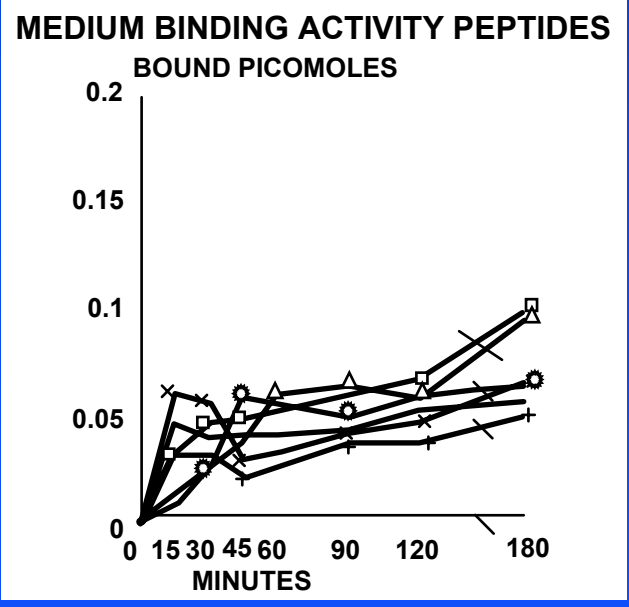
The COLombian FAlciparum VACcine

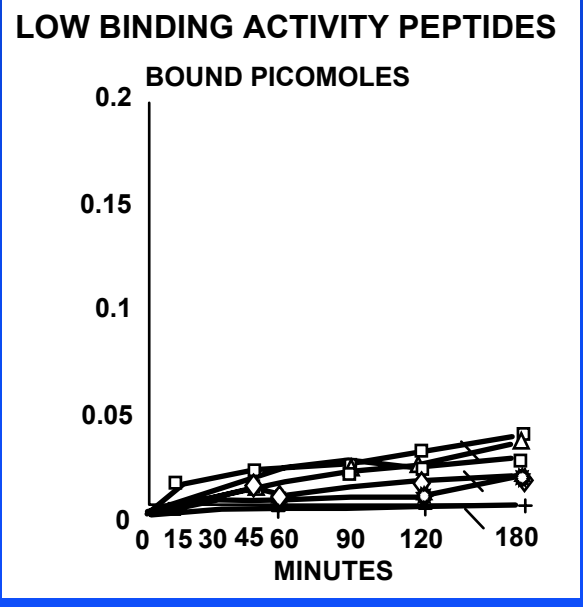
SPECIFIC UPTAKE OF THE DIFFERENT PEPTIDES BY HUMAN R.B.C.

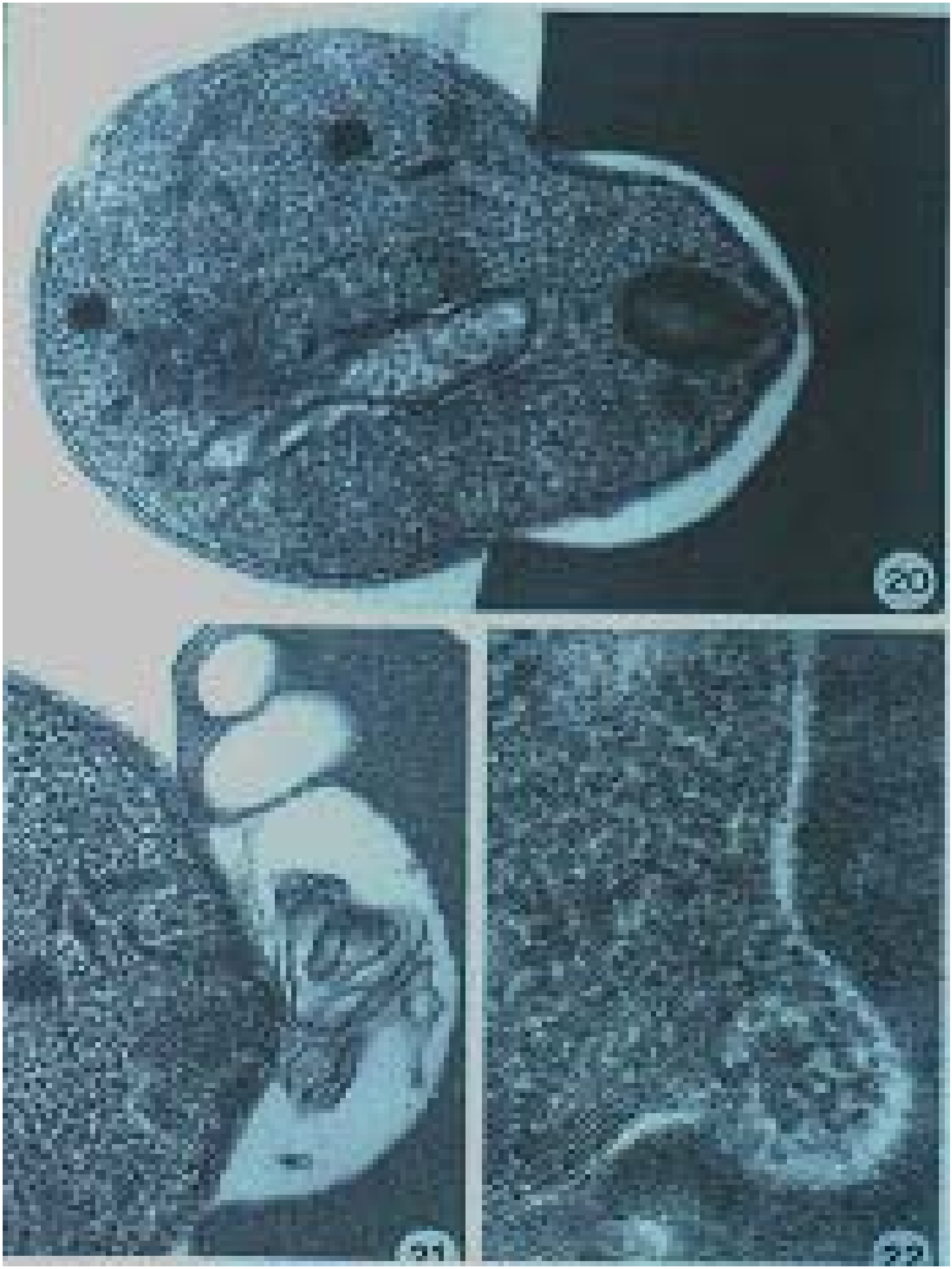
Calvo M. et al. Peptide Research, 1991, 4, 324-333











PRINCIPLES FOR VACCINE DEVELOPMENT

Receptor **Ligand**

Host Cell **Parasite**

INDUCE IMMUNITY

Blocking Receptor- Ligand

Vaccine

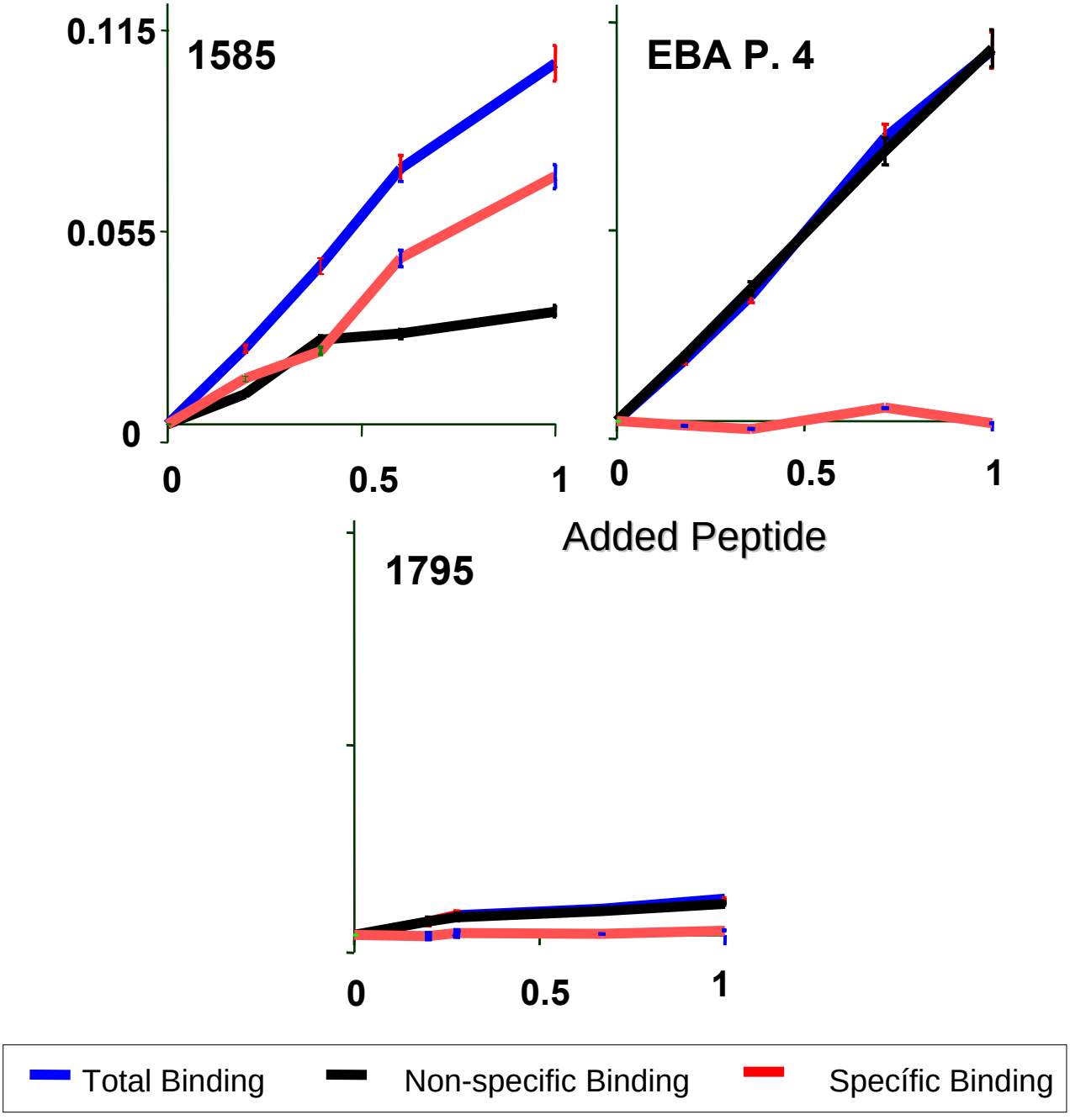
AMINO ACID SEQUENCE OF THE *EBA-175* SYNTHETIC PEPTIDES

Peptide number			
1755	20	KARNEYDIKENEKFLDVYKE	39
1756	40	KFNELDKKKYGNVQKTDKKI	59
1757	60	FTFIENKLDILNNSKFNKRW	79
1758	80	KSYGTPDNIDKNMSLINKHN	99
1759	100	NEEMFNNNYQSFLSTSSLIK	119
1760	120	QNKYVPINAVRVSRILSFLD	139
1761	140	SRINNGRNTSSNNEVLSNCR	159
1762	160	EKRKGMKWDCKKKNDRSNYV	179
1763	180	CIPDRRIQLCIVNLSIIKTY	199
1764	200	TKETMKDHFIEASKKESQLL	219
1765	220	LKKNDNKYNSKFCNDLKNSF	239
1766	240	LDYGHLAMGNDMDFGGYSTK	259
1767	260	AENKIQEVFKGAHGEISEHK	279
1768	280	IKNFRKEWWNEFREKLWEAM	299
1769	300	LSEHKNNINNCKNIPQEELQ	319
1770	320	ITQWIKEWHGEFLLERDNRS	339
1771	340	KLPKSKCKNNTLYEACEKEC	359
1772	360	IDPCMKYRDWIIRSKFEWHT	379
1773	380	LSKEYETQKVPKENAENYLI	399
1774	400	KISENKNDAKVSLLLNNCDA	419
1775	420	EYSKYCDCKHTTTLVKSVLN	439
1776	440	GNDNTIKEKREHIDLDDFSK	459
1777	460	FGCDKNSVDTNTKVWECKNP	479
1778	480	YILSTKDVCVPPRRQELCLG	499
1779	500	NIDRIYDKNLLMIKEHILAI	519
1780	520	AIYESRILKRKYKNKDDKEV	539
1781	540	CKIINKTFADIRDIIGGTDY	559
1782	560	WNDLSNRKLVGKINTNSKYV	579
1783	580	HRNKKNDKLFRDEWWKVIKK	599
1784	600	DVWNVISWVFKDKTVCKEDD	619
1785	620	IENIPQFFRWFSEWGDDYCQ	639
1786	640	DKTKMIETLKVECKEKPCED	659
1787	660	DNCKSKCNSYKEWISKKKEE	679
1788	680	YNKQAKQYQEYQKGNNYKMY	699
1789	700	SEFKSIKPEVYLKKYSEKCS	719
1790	720	NLNFEDEFKEELHSDYKNKC	739

Peptide number			
1791	740	TMCPEVKDVPISIIRNNEQT	759
1792	760	SQEAVPEENTEIAHRTETPS	779
1793	780	ISEGPKGNEQKERDDDSLSK	799
1794	800	ISVSPENSRPETDAKDTSNL	819
1795	820	LKLKGDVDISMPKAVIGSSP	839
1796	840	NDNINVTEQGDNISGVNSKP	859
1797	860	LSDDVRPDKKELEDQNSDES	879
1798	880	EETVVNHISKSPSINNGDDS	899
1799	900	GSGSATVSESSSSNTGLSID	919
1800	920	DDRNGDTFVRTQDTANTEDV	939
1801	940	IRKENADKDEDEKGADEERH	959
1802	960	STSESLSSPEEKMLTDNEGG	979
1803	980	NSLNHEEVKEHTSNSDNVQQ	999
1804	1000	SGGIVNMNVEKELKDTLENP	1019
1805	1020	SSSLDEGKAHEELSEPNLSS	1039
1806	1040	DQDMSNTPGPLDNTSEETTE	1059
1807	1060	RISNNEYKVNEREDERTLTK	1079
1808	1080	EYEDIVLKSHMNRESDDGEL	1099
1809	1100	YDENSDLSTVNDESEDAEAK	1119
1810	1120	MKGNDTSEMSHNSSQHIESD	1139
1811	1140	QQKNDMKTVGDLGTTHVQNE	1159
1812	1160	ISVPVTGEIDEKLRESKESK	1179
1813	1180	IHKAEEERLSHTDIHKINPE	1199
1814	1200	DRNSNTLHLKDIRNEENERH	1219
1815	1220	LTNQNINISQERDLQKHGFH	1239
1816	1240	TMNNLHGDGVSERSQINHSH	1259
1817	1260	HGNRQDRGGNSGNVLNMRSN	1279
1818	1280	NNNFNNIPSRYNLYDKKLDL	1299
1819	1300	DLYENRNDSTTKELIKKLAE	1319
1820	1320	INKCENEISVKYCDHMIHEE	1339
1821	1340	IPLKTCTKEKTRNLCCAVSD	1359
1822	1360	YCMSYFTYDSEEYYNCTKRE	1379
1823	1380	FDDPSYTCFRKEAFSSMIFK	1399
1824	1400	FLITNKIYYYFYTYKTAKVT	1419
1825	1420	IKKINFSLIFFFFFSF	1435

PEPTIDE RBC BINDING BEHAVIOUR

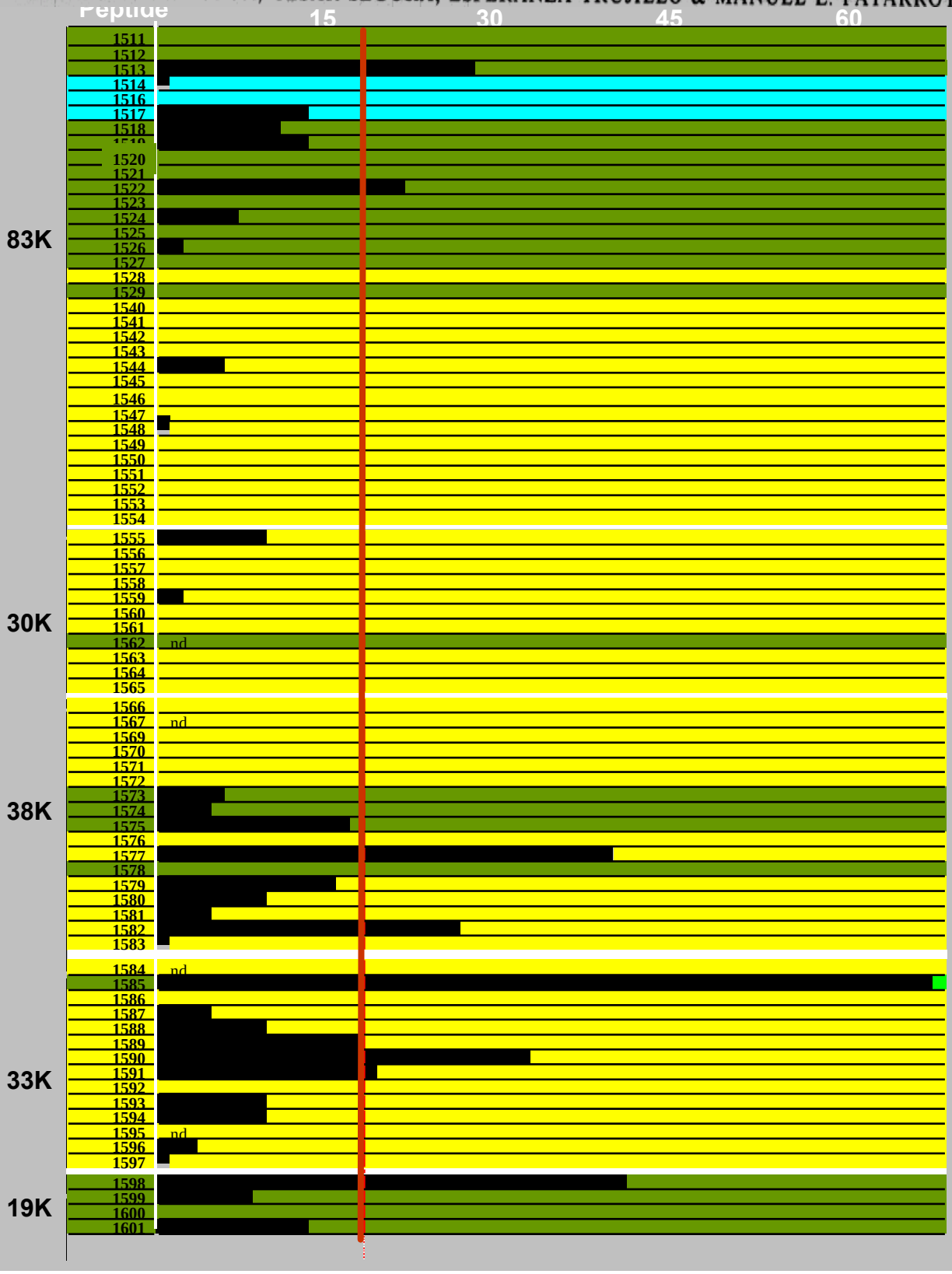
Peptide Binding activity is the curve's specific slope



Parasite Immunology, 1996: **18:** 515–526

Identification of *Plasmodium falciparum* MSP-1 peptides able to bind to human red blood cells

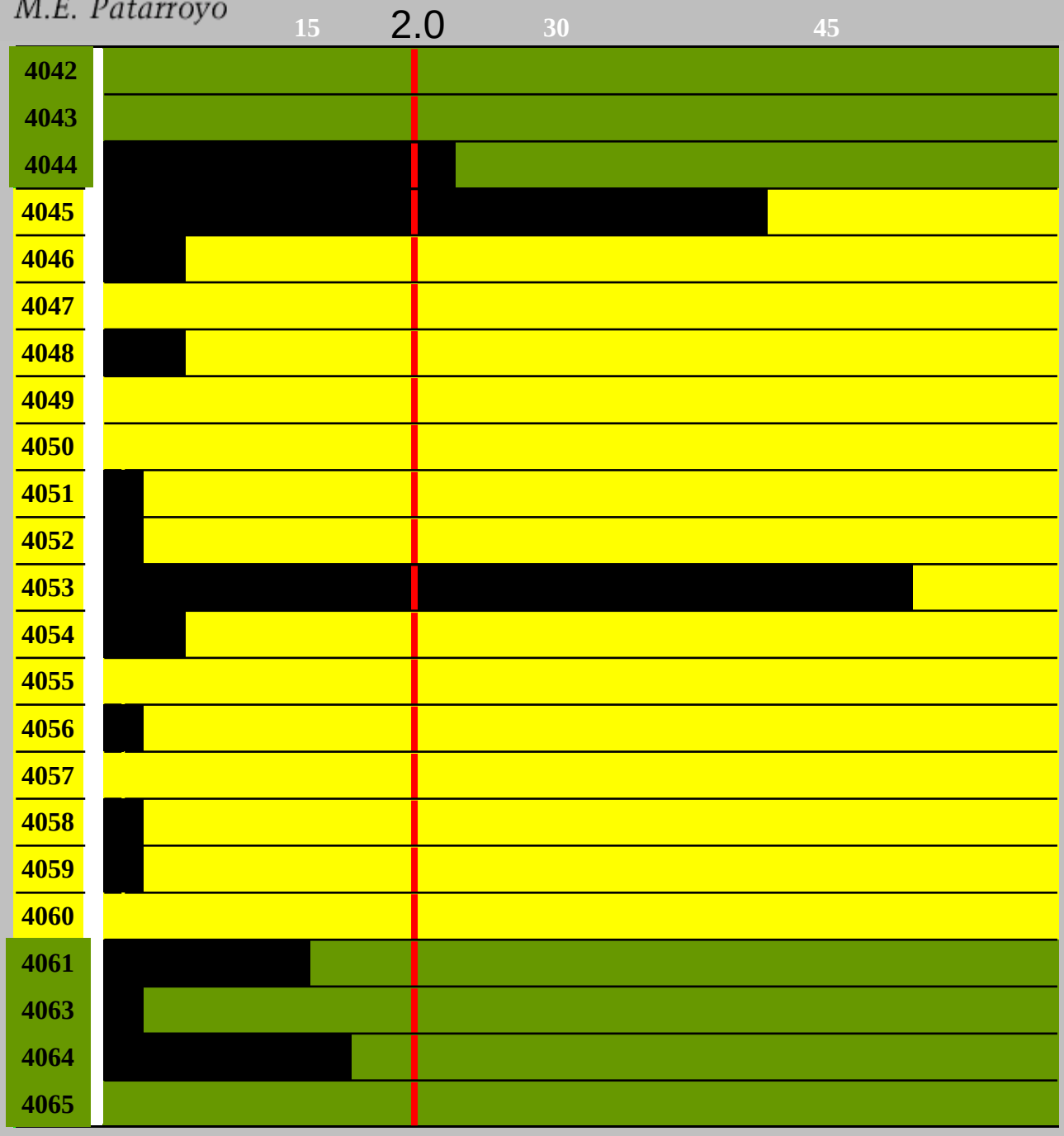
MAURICIO URQUIZA, LUIS E. RODRIGUEZ, JORGE E. SUAREZ, FANNY GUZMÁN, MARISOL OCAMPO, HERNANDO CURTIDOR, CESAR SEGURA, ESPERANZA TRUJILLO & MANUEL E. PATARROYO



J. Peptide Res., 2000, **55**, 216–223.

Two MSA 2 peptides that bind to human red blood cells are relevant to *Plasmodium falciparum* merozoite invasion

M. Ocampo
M. Urquiza
F. Guzmán
L.E. Rodriguez
J. Suarez
H. Curtidor
J. Rosas
M. Diaz
M.E. Patarroyo



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Plasmodium falciparum normocyte binding protein (PfNBP-1) peptides bind specifically to human erythrocytes

John Jairo Valbuena, Ricardo Vera, Javier García, Alvaro Puentes, Hernando Curtidor, Marisol Ocampo, Mauricio Urquiza, Zuly Rivera, Fanny Guzmán, Elizabeth Torres, Manuel Elkin Patarroyo*

Normocyte Binding Protein PfNBP-1				Binding Activity
Peptide		Sequence		1 % 2%
26327	1	LINIETEMKHKQKQLINKMNY	20	
26328	21	DIEKDNITDQYMHDVQQNIFY	40	
26329	41	EPITLKMNEYNTLLNDNHNN	60	
26330	61	NINNEHQFNHLNSLHTKIFSY	80	
26331	81	HNYNKEQQQEYITNIMQRID	100	
26332	101	VFINDLDTYQYEYYFYEWNQ	120	
26333	121	EYKQIDKNKINQHINNIKNN	140	
26334	141	LIHVKKQFEHTLENIKNNENY	160	
26335	161	IFDNIQLKKKDIDDIIININY	180	
26336	181	NTKETYLKELNKKKMLQNKK	200	
26337	201	KVDEKSEINNHHTLQHDNQNY	220	
26338	221	VEQKNKIKDHNLITKPNNNSY	240	
26339	241	SEESHQNEQMKEQNKNILEKY	260	
26340	261	QTRNIKPHHVHNHNHNHNHNY	280	
26341	281	HNQNQNQKDSTKLQEQDISTY	300	
26342	301	HKLHNTIHEQQSKDNHQGNRY	320	
26343	321	EKKQKNGNHERMYFASGIVV	340	
26344	341	SILFLSSLGFVINSKNNKQEY	360	
26345	361	YDKEQEKQQQNDFVCDNNKM	380	
26346	381	DDKSTQKYGRNQEEVMEISF	400	
26347	386	QKYGRNQEEVMEISFDNDYI	405	

AMA-1

Urquiza M., *et al.*, 2001, **Vaccine**, 19: 508

FIDIC

Peptide		Sequence		2.0
4307	14	EFTYMINFGRGQNYWEHPYQ	33	
4308	34	KSDVYHPINEHREHPKEYQY	53	
4309	54	PLHQEHTYQQEDSGEDENTL	73	
4310	74	QHAYPIDHEGAEPAPQEQNL	93	
4311	94	FSSIEIVERSNYMGNPWTEY	113	
4312	114	MAKYDIEEVHGSGIRVDLGE	133	
4313	134	DAEVAGTQYRLPSGKCPVFG	153	
4314	154	KGIIIENSNTTFLTPVATGNY	173	
4315	174	QYLKDGGFAFPPTEPLMSPM	193	
4316	194	TLDEMRHFYKDNKYVKNLDE	113	
4317	214	LTLCSRHAGNMIPDNDKNSNY	233	
4318	234	YKYPAVYDDKDKKCHILYIA	253	
4319	254	AQENNGPRYCNKDESKRNSM	273	
4320	274	FCFRPAKDISFQNYTYLSKN	293	
4321	294	VVDNWEKVCPRKNLQNAKFGY	313	
4322	314	LWVDGNCEDIPHVNEFSAIDY	333	
4323	334	LFECNKLVFELSASDQPKQY	353	
4324	354	EQHLTDYEKIKEGFKNKNAS	373	
4325	374	MIKSAFLPTGAFKADRYKSH	393	
4326	394	GKGYNWGNYNTETQKCEIFN	413	
4327	414	VKPTCLINNSSYIATTALSH	433	
4328	434	PIEVEHNFPCSLYKNEIMKE	453	
4329	454	IERESKRIKLNDNDDEGNKK	473	
4330	474	IIAPRIFISDDKDSLKCPCDY	493	
4331	494	PEIVSNSTCNFFVCKCVERRY	513	
4332	514	AEVTSNNEVVVKEEYKDEYA	533	
4333	534	DIPEHKPTYDKMKIIIASSA	553	
4334	554	AVAVLATILMVYLYKRKGNA	573	
4335	574	EKYDKMDEPQHYGKSNSRND	593	
4336	594	EMLDPEASFWGEEKRASHTTY	613	
4337	603	WGEEKRASHTTPVLMEKPYY	622	

Peptide	Kd (nM)
4313	120 ± 12
4315	120 ± 10
4316	150 ± 14
4322	700 ± 21
4325	100 ± 09
4328	140 ± 11

Parasitology (2000), 120, 225–235.

Plasmodium falciparum EBA-175 kDa protein peptides which bind to human red blood cells

L. E. RODRIGUEZ*, M. URQUIZA, M. OCAMPO, J. SUAREZ, H. CURTIDOR, F. GUZMAN, L. E. VARGAS, M. TRIVIÑOS, M. ROSAS *and* M. E. PATARROYO*

ELSEVIER

Vaccine

Vaccine 18 (2000) 1289–1293

Amino terminal peptides of the ring infected erythrocyte surface antigen of *Plasmodium falciparum* bind specifically to erythrocytes

Ricardo Vera Bravo, Viviana Marín, Javier García, Mauricio Urquiza, Elizabeth Torres, Mary Trujillo, Jaiver Rosas, Manuel Elkin Patarroyo*

ELSEVIER

Parasitology International 49 (2000) 105–117

Serine repeat antigen peptides which bind specifically to red blood cells

A. Puentes*, Javier Garcia, Ricardo Vera, Q. Ramses Lopez, Mauricio Urquiza, Magnolia Vanegas, Luz Mary Salazar, Manuel Elkin Patarroyo

L.E. Rodriguez
M. Ocampo
R. Vera
A. Puentes
R. Lopez
J. Garcia
H. Curtidor
J. Valbuena
J. Suarez
J. Rosas
Z. Rivera
M. Urquiza
M.E. Patarroyo

Plasmodium falciparum EBA-140 kDa protein peptides that bind to human red blood cells

J. Peptide Res., 2003, 62, 175–184.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Biochimie 00 (2004) 000-000
BIOCHIMIE
www.elsevier.com/locate/biochi

Plasmodium falciparum: red blood cell binding studies using peptides derived from rhoptry-associated protein 2 (RAP2)

Ramsés López [a,b], John Valbuena [a,b], Hernando Curtidor [a,b], Alvaro Puentes [a,b], Luis E. Rodríguez [a,b], Javier García [a,b], Jorge Suárez [a,b], Ricardo Vera [a,b], Marisol Ocampo [a,b], Mary Trujillo [a,b], Luis E. Ramirez [a,b], Manuel E. Patarroyo [a,b,*]

ELSEVIER
Acta Tropica 75 (2000) 349–359
ACTA TROPICA

Plasmodium falciparum: red blood cell binding studies of peptides derived from histidine-rich KAHRP-I, HRP-II and HRP-III proteins

Ramsés López *, Mauricio Urquiza, Hemando Curtidor, Jorge Eduardo Caminos, Hemando Mora, Alvaro Puentes, Manuel Elkin Patarroyo

ELSEVIER
Vaccine 18 (2001) 1486–1504
Vaccine

Plasmodium falciparum acid basic repeat antigen (ABRA) peptides: erythrocyte binding and biological activity

H. Curtidor, M. Urquiza, J.E. Suarez, L.E. Rodriguez, M. Ocampo, A. Puentes, J.E. Garcia, R. Vera, R. Lopéz, L.E. Ramirez, M. Pinzon, M.E. Patarroyo *

ELSEVIER
Vaccine 21 (2003) 2404–2411
Vaccine
www.elsevier.com/locate/vaccine

Identification of specific Hep G2 cell binding regions in *Plasmodium falciparum* sporozoite–threonine–asparagine-rich protein (STARP)

Ramsés López, Javier Garcia, Alvaro Puentes, Hernando Curtidor, Marisol Ocampo, Ricardo Vera, Luis Eduardo Rodriguez, Jorge Suarez, Mauricio Urquiza, Ana Liliana Rodríguez, Claudia Alexandra Reyes, Carmen Giovana Granados, Manuel E. Patarroyo*

R. López
H. Curtidor
M. Urquiza
J. Garcia
A. Puentes
J. Suarez
M. Ocampo
R. Vera
L.E. Rodriguez
F. Castillo
G. Cifuentes
M.E. Patarroyo

Plasmodium falciparum: binding studies of peptide derived from the sporozoite surface protein 2 to Hep G2 cells

J. Peptide Res., 2001, 58, 285–292.

Available online at www.sciencedirect.com
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Vaccine xxx (2003) xxx–xxx
Vaccine
www.elsevier.com/locate/vaccine

Sporozoit Liver Stage Antigen igen *Plasmodium falciparum* peptides bind specifically to human hepatocytes

Alvaro Puentes, Javier García, Ricardo Vera, Ramsés López, Jorge Suarez, Luis Rodríguez, Hernando Curtidor, Marisol Ocampo, Diana Tovar, Martha Forero, Adriana Bermudez, Jimena Cortes, Mauricio Urquiza, Manuel E. Patarroyo*

Available online at www.sciencedirect.com
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Parasitology International xx (2003) xxx–xxx
www.elsevier.com/locate/parint

Identification of *Plasmodium falciparum* reticulocyte binding protein RBP-2 homologue a and b (*Pf*RBP-2-Ha and -Hb) sequences that specifically bind to erythrocytes

Marisol Ocampo[1], Ricardo Vera[1], Luis Eduardo Rodríguez, Hernando Curtidor, Jorge Suárez, Javier García, Alvaro Puentes, Ramsés López, John Valbuena, Diana Tovar, Claudia Reyes, Sandra Vega, Manuel Elkin Patarroyo*

Available online at www.sciencedirect.com
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Vaccine xxx (2003) xxx–xxx
Vaccine
www.elsevier.com/locate/vaccine

Specific erythrocyte binding capacity and biological activity of *Plasmodium falciparum*-derived rhoptry-associated protein 1 peptides

Hernando Curtidor, Marisol Ocampo, Diana Tovar, Ramses López, Javier García, Jhon Valbuena, Ricardo Vera, Jorge Suárez, Luis E. Rodríguez, Álvaro Puentes, Fanny Guzmán, Elizabeth Torres, Manuel E. Patarroyo*

Vaccine 19 (2001) 508–513
Vaccine
www.elsevier.com/locate/vaccine

Plasmodium falciparum AMA-1 erythrocyte binding peptides implicate AMA-1 as erythrocyte binding protein

Mauricio Urquiza, Jorge E. Suarez, Constanza Cardenas, Ramses Lopez, Alvaro Puentes, Francisco Chavez, Julio Cesar Calvo, Manuel Elkin Patarroyo*

Instituto de Inmunología, Hospital San Juan de Dios, Universidad Nacional de Colombia, AA 44709 Bogota, Colombia

Available online at www.sciencedirect.com
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BIOCHIMIE

Plasmodium falciparum: red blood cell binding studies using peptides derived from rhoptry-associated protein 2 (RAP2)

Ramsés López [a,b], John Valbuena [a,b], Hernando Curtidor [a,b], Alvaro Puentes [a,b], Luis E. Rodríguez [a,b], Javier García [a,b], Jorge Suárez [a,b], Ricardo Vera [a,b], Marisol Ocampo [a,b], Mary Trujillo [a,b], Luis E. Ramirez [a,b], Manuel E. Patarroyo [a,b,*]

ELSEVIER
Vaccine
Vaccine 19 (2001) 4487–4495

Plasmodium falciparum circumsporozoite (CS) protein peptides specifically bind to HepG2 cells

Jorge E. Suarez *, Mauricio Urquiza, Alvaro Puentes, Javier E. Garcia, Hernando Curtidor, Marisol Ocampo, Ramses Lopez, Luis E. Rodriguez, Ricardo Vera, Marcia Cubillos, Maria H. Torres, Manuel E. Patarroyo

ELSEVIER
Available online at www.sciencedirect.com
SCIENCE DIRECT
PEPTIDES
Peptides xxx (2003) xxx–xxx
www.elsevier.com/locate/peptides

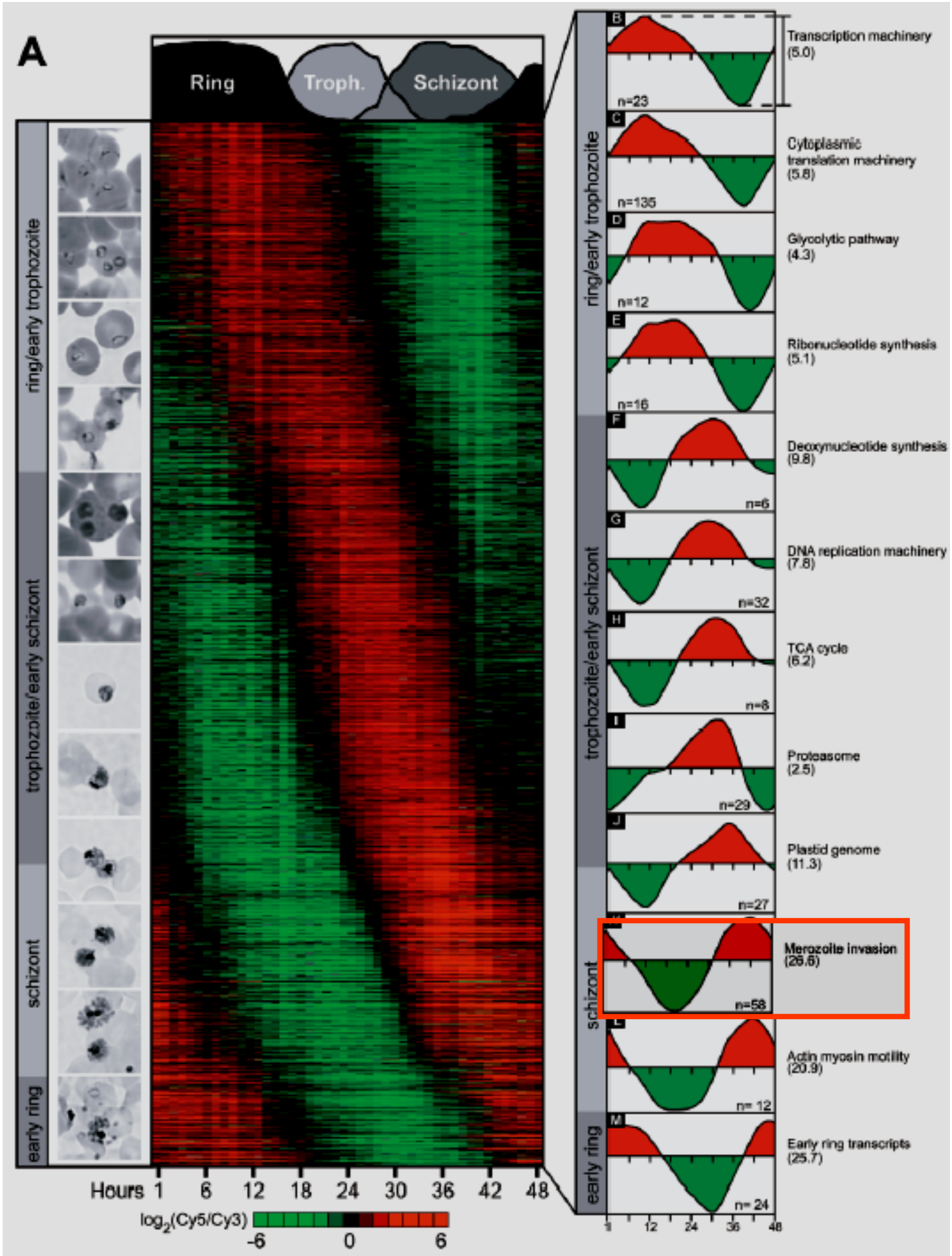
P. falciparum: merozoite surface protein-8 peptides bind specifically to human erythrocytes

Alvaro Puentes, Javier García, Marisol Ocampo, Luis Rodríguez, Ricardo Vera, Hernando Curtidor, Ramsés López, Jorge Suarez, John Valbuena, Magnolia Vanegas, Fanny Guzman, Diana Tovar, Manuel E. Patarroyo*

ELSEVIER
Available online at www.sciencedirect.com
SCIENCE DIRECT
PEPTIDES
Peptides 24 (2003) 647–657
www.elsevier.com/locate/peptides

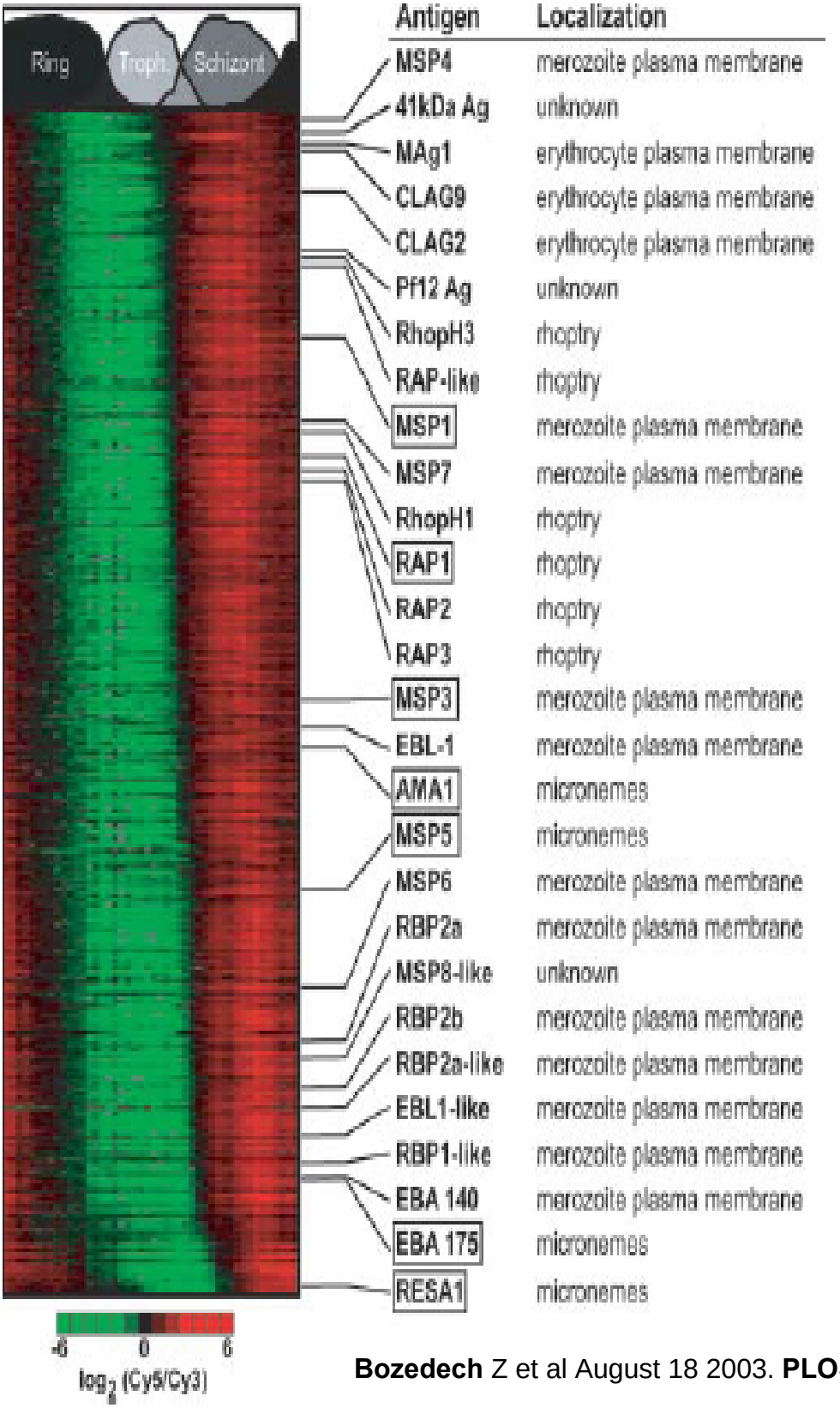
Peptides of the liver stage antigen-1 (LSA-1) of *Plasmodium falciparum* bind to human hepatocytes

Javier E. García, Alvaro Puentes, Ramsés López, Ricardo Vera, Jorge Suárez, Luis Rodríguez, Hernando Curtidor, Marisol Ocampo, Diana Tovar, Martha Forero, Adriana Bermudez, Jimena Cortés, Mauricio Urquiza, Manuel E. Patarroyo*


A
Ring
Troph.
Schizont
ring/early trophozoite
trophozoite/early schizont
schizont
early ring
Hours 1 6 12 18 24 30 36 42 48
log2(Cy5/Cy3)
-6 0 6
B
Transcription machinery (5.0)
n=23
C
Cytoplasmic translation machinery (5.8)
n=135
D
Glycolytic pathway (4.3)
n=12
E
Ribonucleotide synthesis (5.1)
n=16
F
Deoxynucleotide synthesis (9.8)
n=6
G
DNA replication machinery (7.8)
n=32
H
TCA cycle (6.2)
n=8
I
Proteasome (2.5)
n=29
J
Plastid genome (11.3)
n=27
Merozoite invasion (26.6)
n=58
Actin myosin motility (20.9)
n= 12
M
Early ring transcripts (25.7)
n= 24
1 12 24 36 48

PHASEOGRAM OF PUTATIVE VACCINE TARGETS

FIDIC



Bozedech Z et al August 18 2003. **PLOS Biology** 1, 001

High RBC binding activity peptides

FIDIC

PROTEIN	C	V	Reference
MSP1	3	6	Urquiza M. *et. al* . 1996. *Parasite Immunology* . 18: 515-526
RESA	2	–	Vera R. *et al* . 2000. *Vaccine.* 18: 1289-1293
SERA	6	1	Puentes A. *et. al* . 2000. *Parasitology International.* 49: 105-117
MSA2	1	2	Ocampo M. *et. al* . *J. Peptide Research.* 55: 216-233
EBA175	6	–	Rodríguez L.E *et. al.* 2000. *Parasitology.* 120: 225-235
GBP130	1	–	Suárez J. *et. al* . 2000. *Mem. Inst. Oswaldo Cruz* . 95: 495-501
HRP I, II, II	3	1	López R. *et a* l. 2000. *Acta Tropica.* 75: 349-359
ABRA	5	–	Curtidor H. *et. al* . 2001. *Vaccine.* 19: 4496-4504
AMA1	4	3	Urquiza M. *et. al* . 2001. *Vaccine.* 19: 508-513
EBA140	6	–	Rodríguez L.E.. *et. al* . 2003. *J. Peptide Research.* 62: 175-184
NBP1	2	–	Valbuena J. *et al* . 2003. *Peptides* . 24: 1007-1014
MSP8	5	–	Puentes A. *et. al.* 2003. *Peptides* .24: 1015-1023
MAEBL	9	–	Ocampo M. *et al* . 2004. *Biochem. Biophys. Res. Comm. 315: 319-329*
RAP2	4	–	López R. *et al.* 2004. *Biochemie* . 86: 1-6
RBP2 Ha/Hb	9	3	Ocampo M. *et. al* . 2004. *Parasitol. Int.* 53: 77-88
RAP1	4	–	Curtidor H. *et. al* . 2004. *Vaccine* . 22: 1054-1062
EBA160	5	–	Valbuena J. et al. 2004. *Biochem. Biophys. Res. Comm* . 321: 835-844
CLAG3	5	–	Ocampo M. et. al. 2005. *Proteins Science* . 14: 504-513
EBL1	5	–	Curtidor H. *et. al.* 2005. *Protein Science* . 14: 464-473
JESEBL	5	–	Vera R. *et al* . 2004. *Biochemie. In press*
STEVOR	–	3	García J. *et al.* 2004. *Peptides. In press*
MSP10	3	–	Puentes A. *et al* . 2004. *Biochemie. In press*
MSP3	3	–	Rodríguez L.E. *et. al.* 2004. *Submitted to Protein Science*
SORTILIN	6	–	Vera R. *et al.* 2004. *Submitted to Biochemistry*
RESA-LIKE	3	–	Rodríguez L.E. *et. al.* 2004. *Submitted to J. Int. Parasitol.*
TryThrA	4	–	Curtidor H. *et. al.* 2004. *Submitted to Chembiochem*
HAP	2	–	Valbuena J. *et. al* . 2004. *Submitted to Biol. Chem.*
MSP6	2	1	López R. *et al.* 2004. *Submitted to Peptides*

C : CONSERVED

V: VARIABLE

Synthetic vaccines - Emerging principles

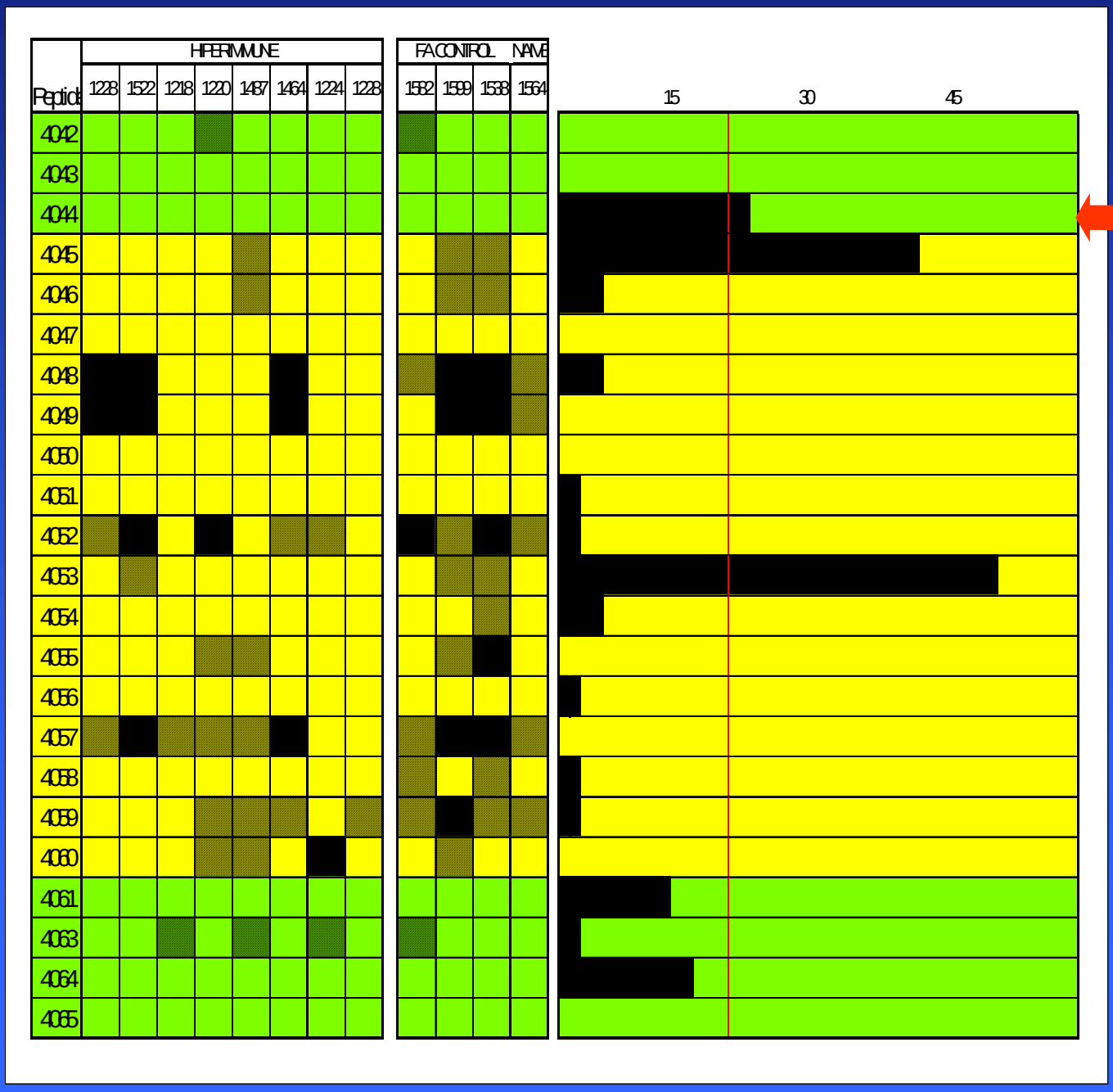
1. Plasmodia (falciparum & vivax) use CONSERVED as well as VARIABLE sequences to bind to host cells.

ANTIGENICITY STUDIES

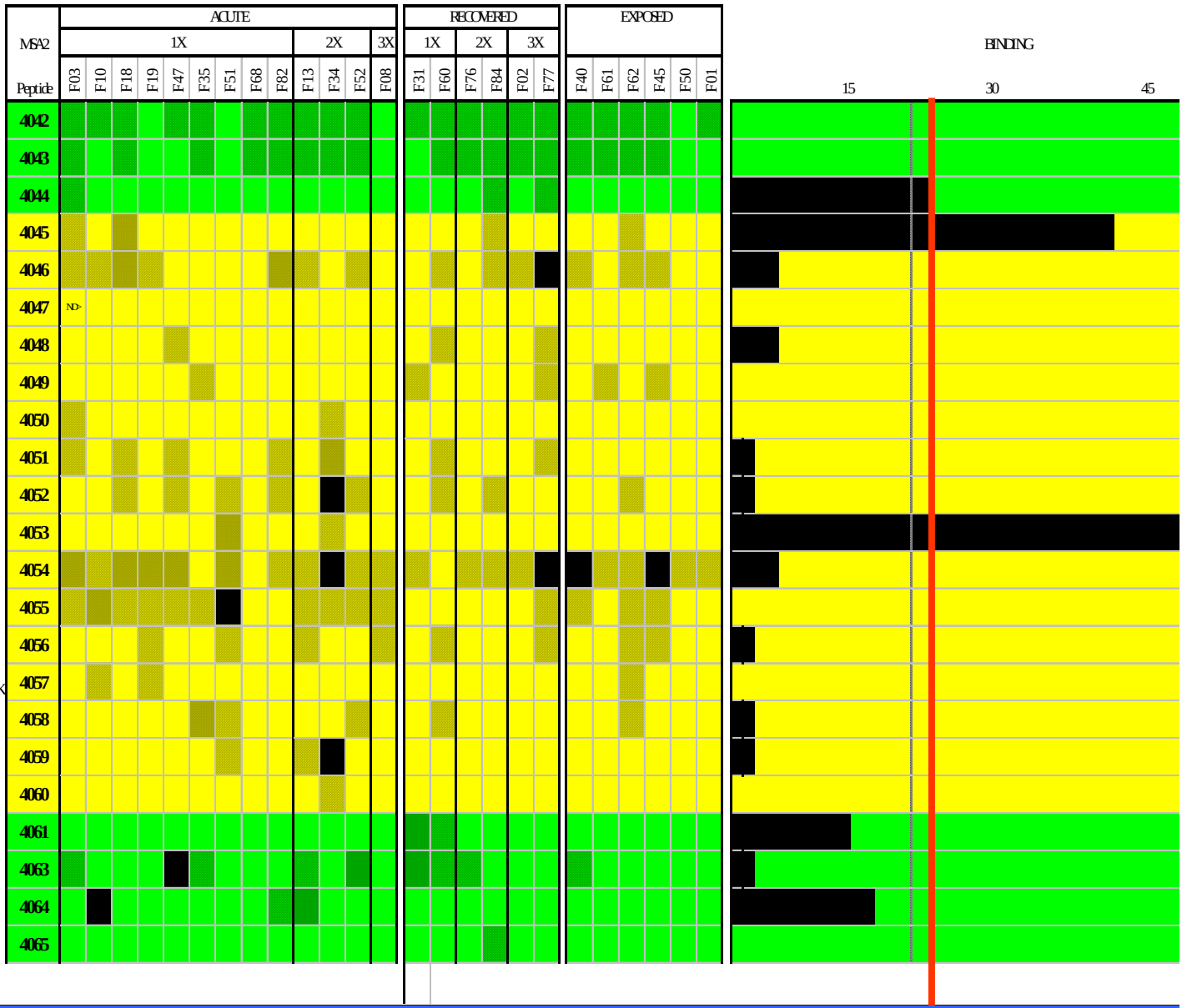
HYPERIMMUNE MONKEYS

Aotus Monkeys develop resistance to reinfection after being infected several times with 5 to 500 X 10^6 P. *falciparum* FVO infected erythrocytes and treated with chloroquine

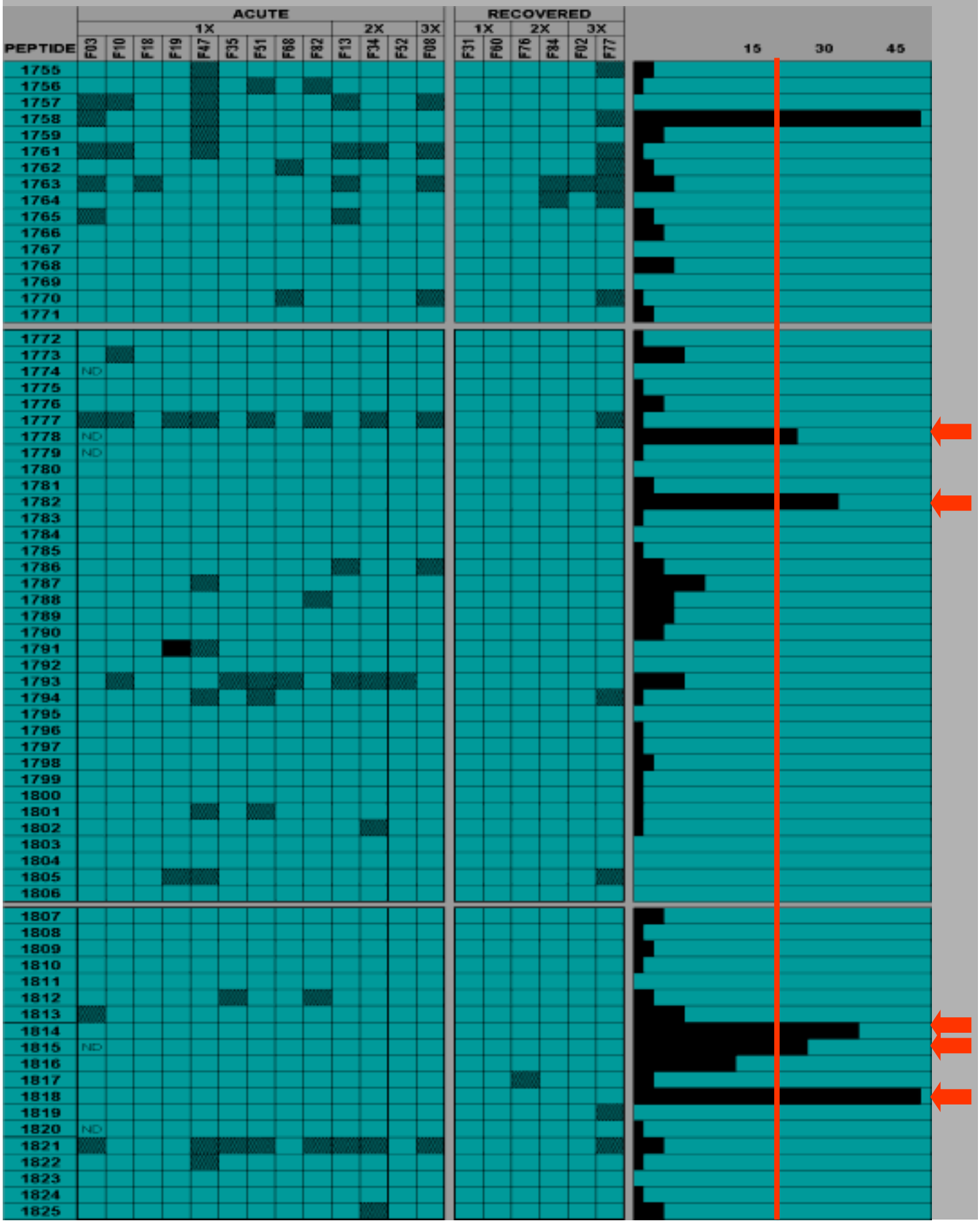
AOTUS ABS AGAINST MSP-2 PEPTIDES Vs. BINDING ACTIVITY



HUMAN ABS AGAINST MSP-2 PEPTIDES Vs. BINDING ACTIVITY



HUMAN Abs AGAINST EBA-175 PEPTIDES vs. BINDING



Synthetic vaccines - Emerging principles

1. Plasmodia (falciparum & vivax) use CONSERVED as well as VARIABLE sequences to bind to host cells.
2. CONSERVED binding sequences are NOT antigenic, but VARIABLE sequences are

IMMUNOGENICITY AND PROTECTION STUDIES

PROTOCOL FOR IMMUNIZATION OF AOTUS MONKEYS

Monkeys were immunized with 125 μgr of peptide in FA on days 1, 20, and 40, bled on day 60 for immunological studies, and challenge on day 65.

AOTUS SERA REACTIVITY AGAINST ORIGINAL EBA-175 IMMUNIZING PEPTIDES

EBA 175 Kd

GROUP H	1678	1692	1713	1730	1737
1758	0	0	0	200	0
1º779	0	0	0	0	0
1783	0	100	0	100	0

EBA 175 Kd VARIABLE

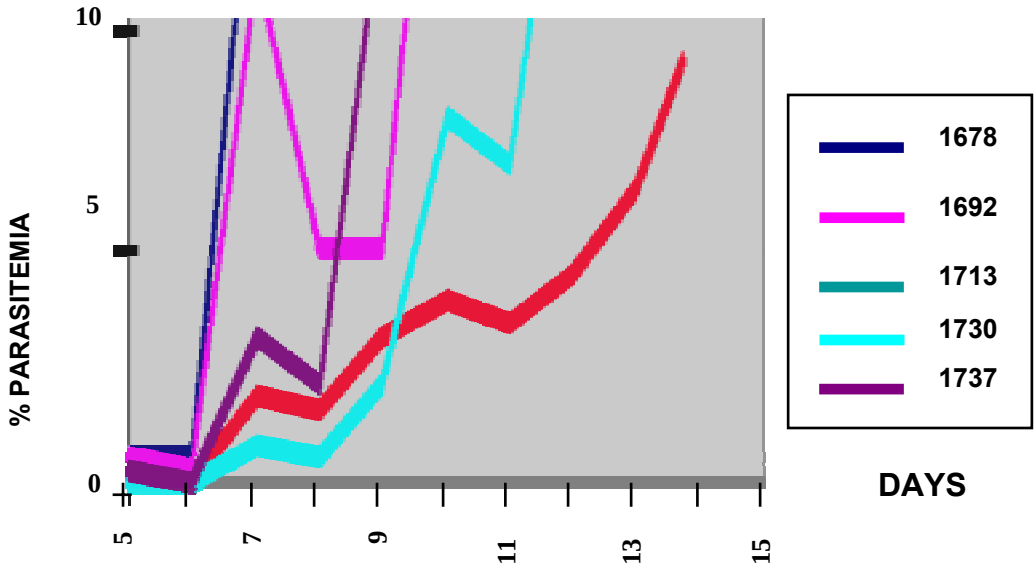
GROUP I	1679	1693	1714	1731	1738
1814	100	200	12800	6400	6400
1815	12800	25600	51200	12800	1600

EBA 175 Kd C&V

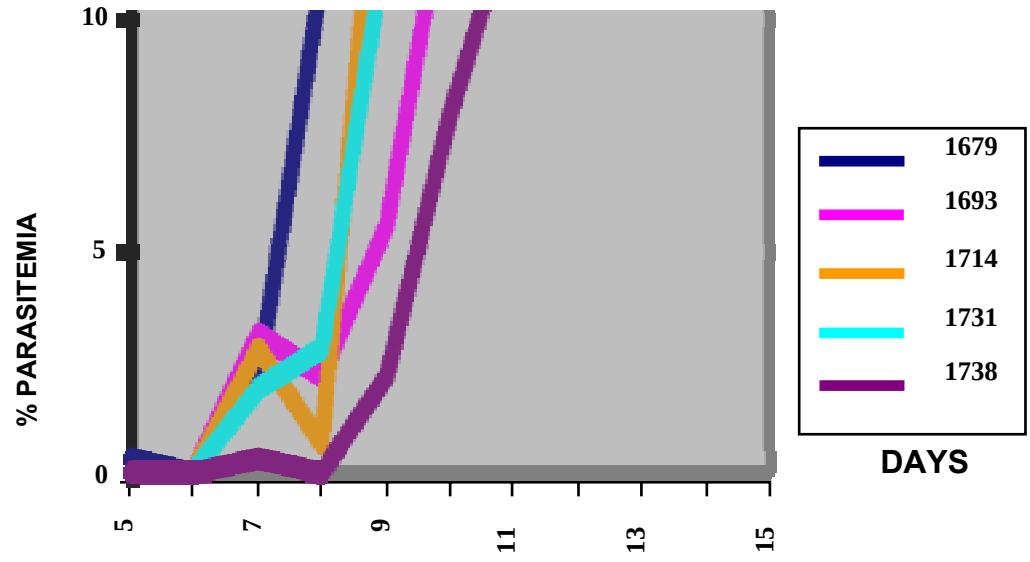
GROUP J	1681	1694	1715	1732	1739
1758	0	0	0	400	100
1779	0	0	0	0	0
1783	0	0	0	800	0
1814	200	100	100	100	0
1815	25600	204800	25600	3200	6400

AOTUS MONKEYS IMMUNIZED WITH EBA UNMODIFIED PEPTIDES

GROUP H: IMMUNIZED WITH CONSERVED HBAP
1758, 1779, 1783.

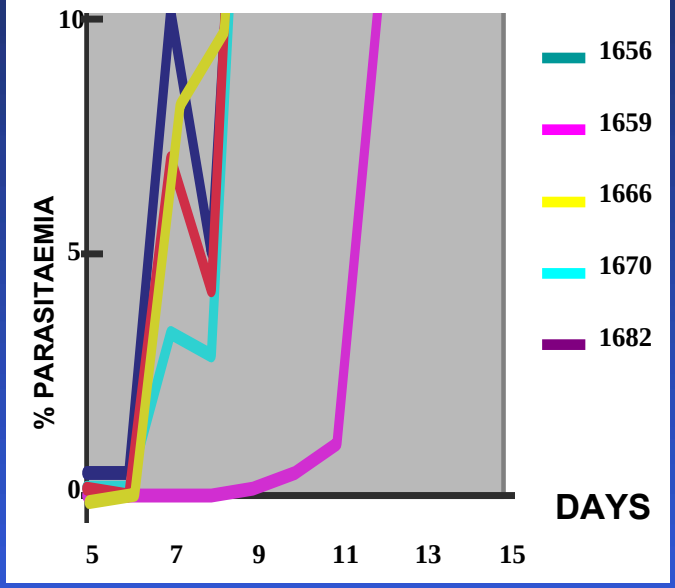


GRUPO I: IMMUNIZED WITH VARIABLE HBAP
1814, 1815.

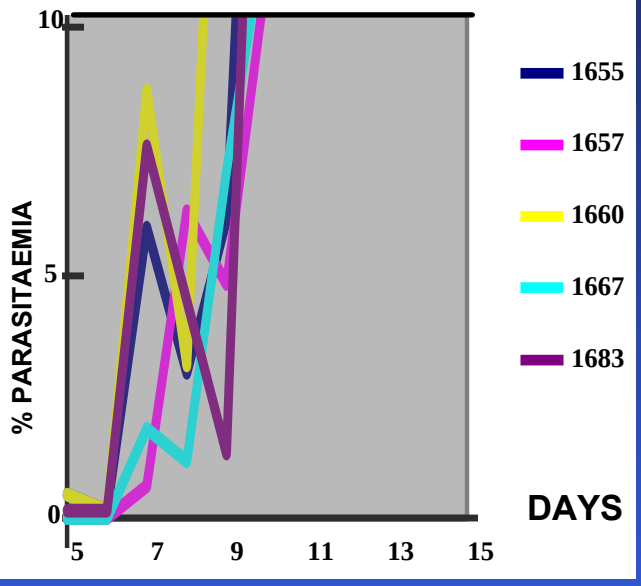


AOTUS MONKEYS IMMUNIZED WITH MSP-1 UNMODIFIED PEPTIDE MIXTURES

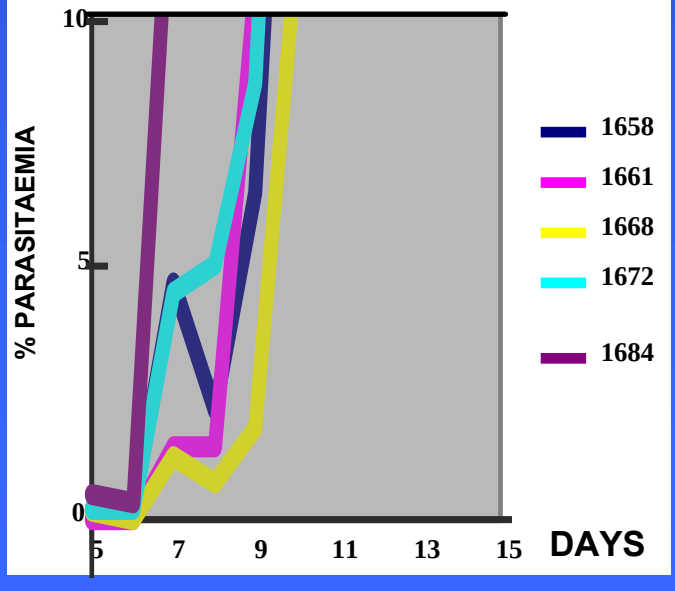
GROUP A: IMMUNIZED WITH PEPTIDES FROM 83 Kd :
1513, 1517, 1522



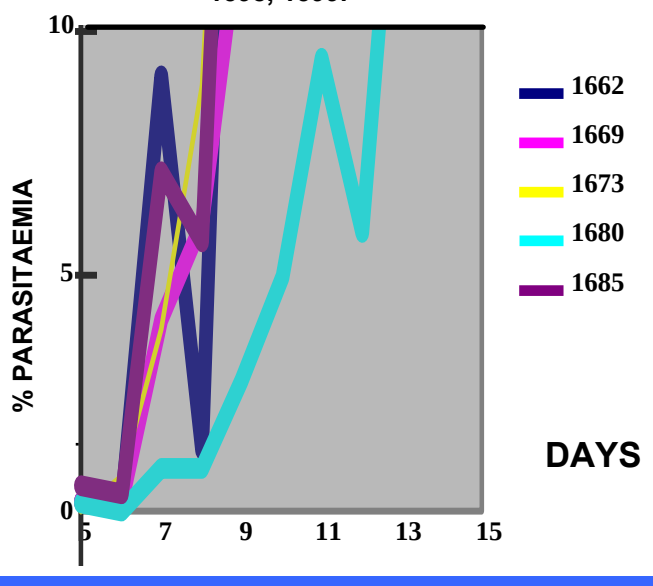
GROUP B: IMMUNIZED WITH PEPTIDES FROM 38 Kd :
1577, 1582.



GROUP C: IMMUNIZED WITH PEPTIDES FROM 33 Kd:
1585, 1590, 4017.



GROUP D: IMMUNIZED WITH PEPTIDES FROM 19 Kd:
1598, 1599.



MAPS USED IN THE MONKEY TRIALS

MAP 5A 1512 (HESYQELVKKLEALEDAVLT)$_4$-P_3C

MAP 5B 1513 (GYSLFQKEKMVLNE)$_4$-P_3C

MAP 6A 1522 (QIPFNLKIRANELDVLKKLV)$_4$-P_3C

MAP 6B 1523 (FGYRKPLDNIKDNVGKMEDY)$_4$-P_3C

MAP 8B 1584 (LGQVVTGEAVTPSVIDNILSKIENEY)$_4$-P_3C

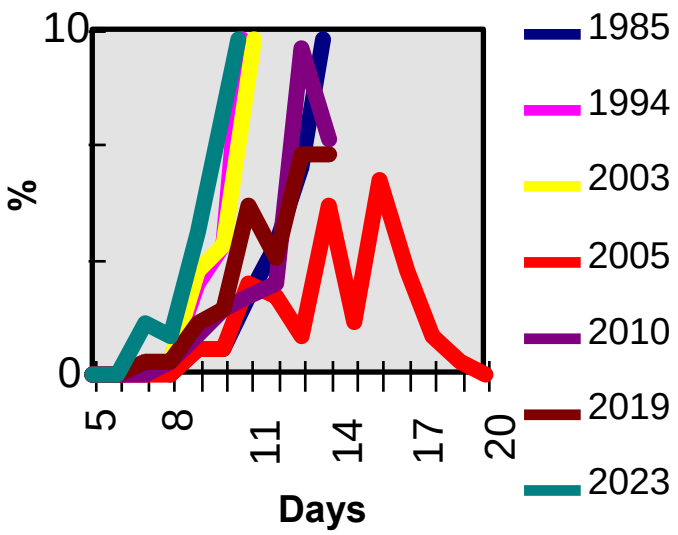
MAP 9B 1585 (DVIYLKPLAGVYRSLKKQIE)$_4$-P_3C

MAP 11A 1596 (IADLSTDYNHNNLLTKFLSTG)$_4$-P_3C

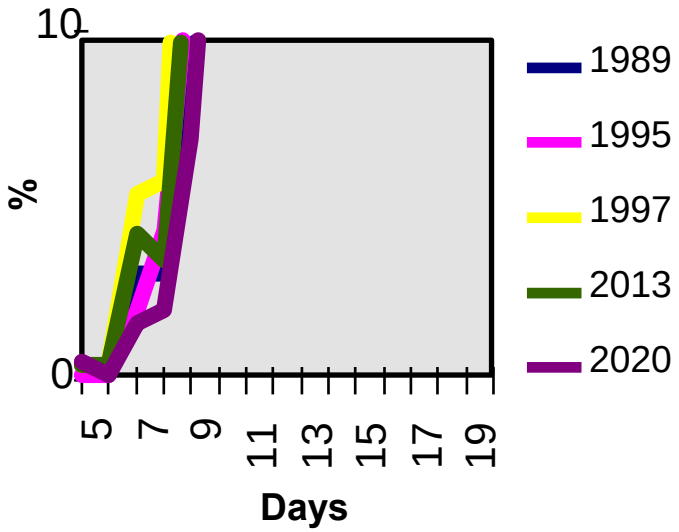
MAP 11B 1597x (MVFENLAKTVLSNLLDNLQGMLNISQHQ)$_4$-P_3C

AOTUS MONKEYS IMMUNIZED WITH MAP MIXTURES

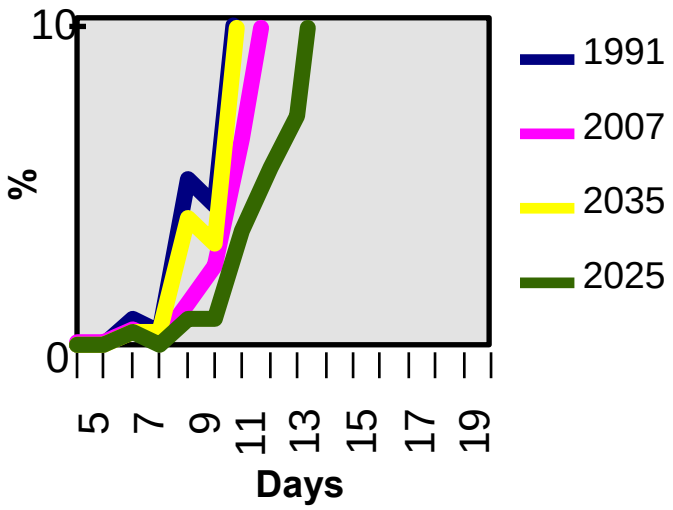
MAPS 3X



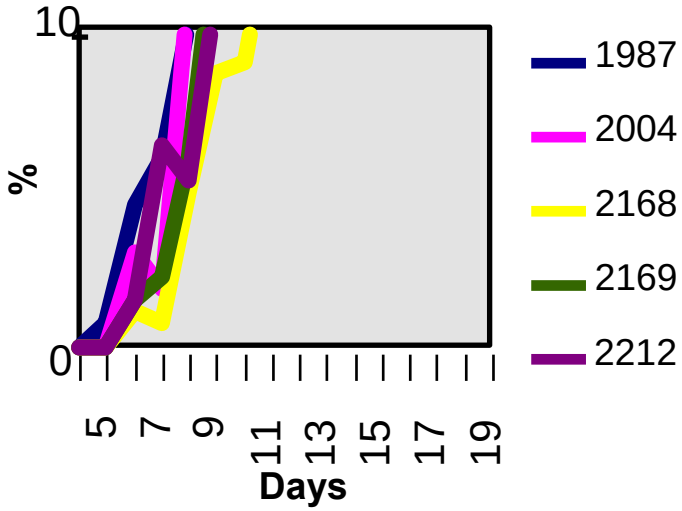
MAPS 5X



CONTROLS



CONTROLS



Aminoacid Sequence of the MSP-1, EBA-175, GBP-130, and MSP-2 Expanded Peptides

Patarroyo M. E. et al. Summitted to *J. Structural Biology*

1512	HESYQELVKKLEALEDAVL	1513	TGYSLFQKEKMVLNE	A
1522	QIPFNLKIRANELDVLKKLV	1523	FGYRKPLDNIKDNVGKMEDY	B
1576	LKTLSEESIQTEDNYASLEN	1577	FKVLSKLEGKLKDNLNLEKK	C
1582	AESNTITTSQNVDDEVDDVILGQ	1584	VVTGEAVTPSVIDNILSKIENEY	D
1584	LDQVVTGEAISVTMDNILSGFENEY	1585	DVIYLKPLAGVYRSLKKQIE	E
1596	IADLSTDYNHNNLLTKFLSTGM	1597	VFENLAKTVLSNLLDNLQGMLNISQHQ	G
1757	FTFIENKLDILNNSKFNKRW	1758	KSYGTPDNIDKNNSLINKHN	H
1779	LGNIDRIYDKNLLMIKEHILAIAI	1780	YESRILKRKYKNKDDKEV	I
1782	YWNDLSNRKLVGKINTNSK	1783	YVHRNKKNDKLFRDEWWKVIKKD	J
1814	DRNSNTLHLKDIRNEEMERH	1815	LTNQNINISQERDLQKHGFH	K
2208	IFHKILTNTDPNDEVERRNA	2209	ADPEYRKHLEVFHKILTNTD	L
2219	EGQIMREYASDPEYRKHLEI	2220	FYKILTNTDPNDDVERRNAD	M

AOTUS SERA REACTIVITY AGAINST *EBA-175 EXPANDED* PEPTIDES

Patarroyo M. E. et al. Summitted to *J. Structural Biology*

GROUP E

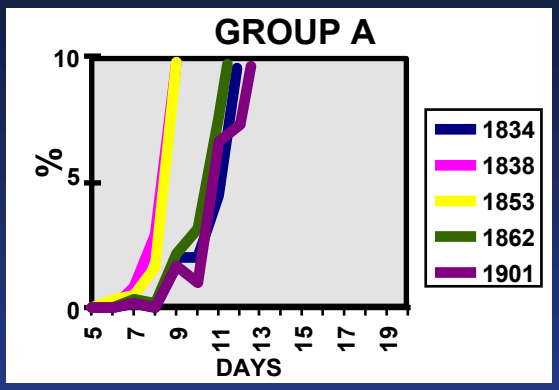
	1843	1873	1902	1912	1917	1918
1779	0	0	0	0	0	0
1780	800	0	6400	0	100	1600
1782	12800	800	3200	12800	12800	400
1783	0	0	100	100	200	100

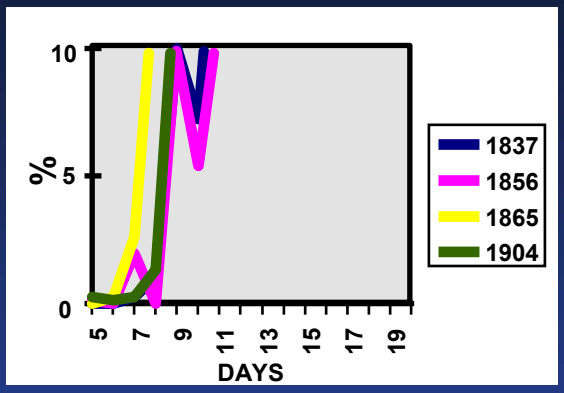
GROUP F

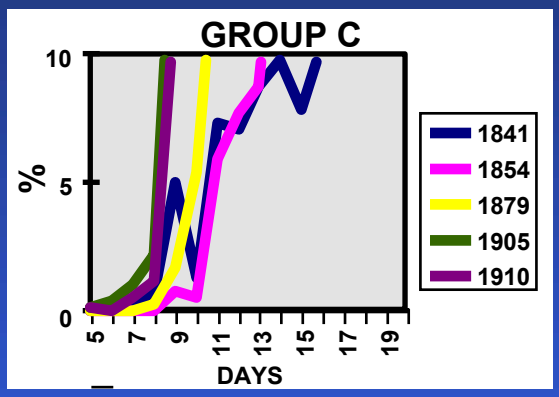
	1845	1874	1903	1919	1934
1757	25600	3200	0	12800	0
1758	0	100	0	100	0
1814	400	100	100	200	800
1815	51200	6400	6400	25600	6400

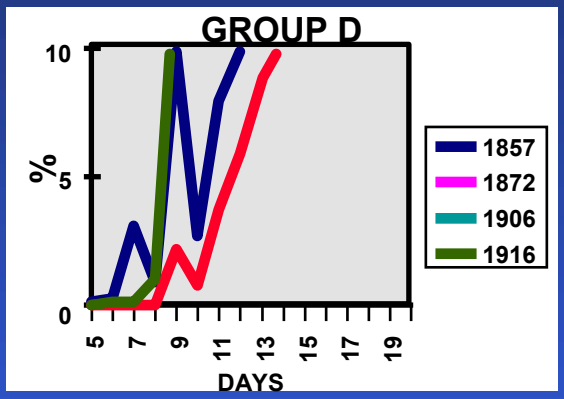
AOTUS MONKEYS IMMUNIZED WITH MSP-1 EXPANDED PEPTIDES

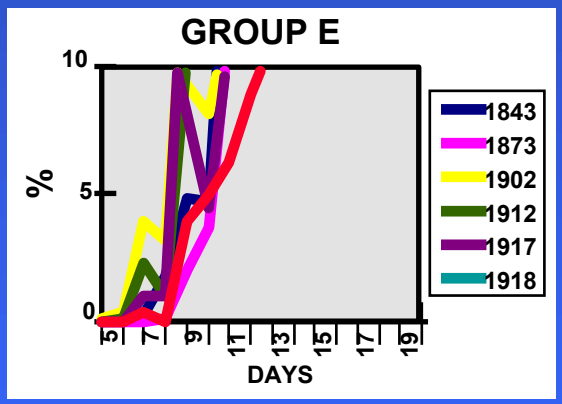
Patarroyo M. E. et al. Summitted to *J. Structural Biology*

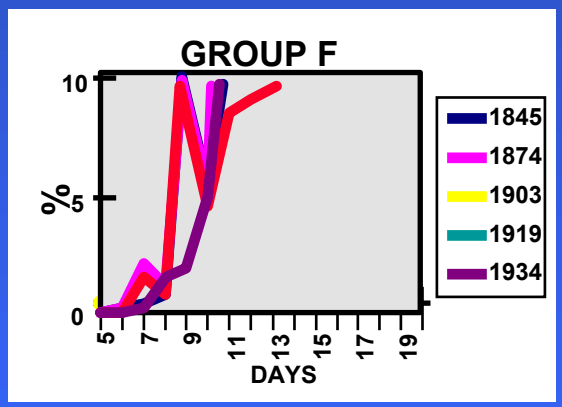


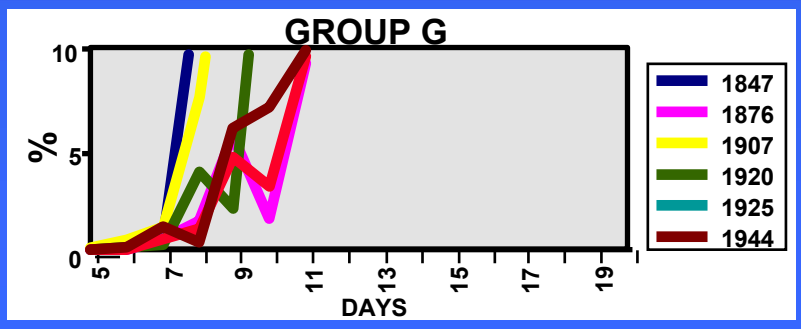












IMMUNOGENICITY OF THE BINDING PEPTIDES IN RABBITS

	CONSERVED			DIMORPHIC		
	PEPTIDE Nr.	RABBIT Nr.	Ab TITER	PEPTIDE Nr.	RABBIT Nr.	Ab TITER
	1513	182	1600	1589	205	12800
	1522	190	0	1525	207	204800
MSA-1	1577	180	800	1590	193	1600
	1585	189	0	1561	228	102400
	1598	181	0	1565	218	6400
MSP-2	4045	195	800	4053	192	12800
	1758	200	800	1814	199	25600
	1779	185	800	1815	184	204800
EBA-175	1783	186	0	1818	222	25600
				1756	209	102400
				1782	210	12800
GBP-130	2220	172	1600	2202	204	12800
				2204	216	12800

IMMUNOGENICITY OF THE CONSERVED BINDING PEPTIDES

For the production of Mo Abs groups of 4 Balb/c mice were immunized i.p. 5x with 15 μgr of the individual MSP1 (1513, 1522, 1585, 5501) EBA - 175 (1758, 1779, 1783, 1818) GBP - 130 (2220) or MSP_2 (4044) conserved peptides. After the 3rd immunization NOT EVEN A SINGLE MOUSE, showed antibodies against the corresponding immunizing peptide, as assessed by ELISA western blots or IFA. The same was also true for mice of the AKR and DBA strains.

Synthetic vaccines - Emerging principles

1. Plasmodia (falciparum & vivax) use CONSERVED as well as VARIABLE sequences to bind to host cells.
2. CONSERVED binding sequences are NOT antigenic, but VARIABLE sequences are
3. CONSERVED binding sequences are NOT immunogenic in ANY of the tested species when administered as monomers, polymerized, associated with T helper epitopes or presented as MAPs. While VARIABLE sequences can be immunogenic they are strain-specific

AN EMPIRICAL APPROACH

Changing some residues.

- To convert putative alpha helices into beta II or beta VII turns.
- To modify putative aromatic composition.

STRUCTURALLY REPLACED ANALOGUES OF THE 1513 PEPTIDE

PEPTIDE	GROUP	SEQUENCE
1513		TGYSLFQKEKMVLNEGTSGTA
4863	1	TGMSLPQKEKMVLNE
4865	2	TGHSLFQKEKMVLNE
4887	3	TGYSLHQKEKMVLNE

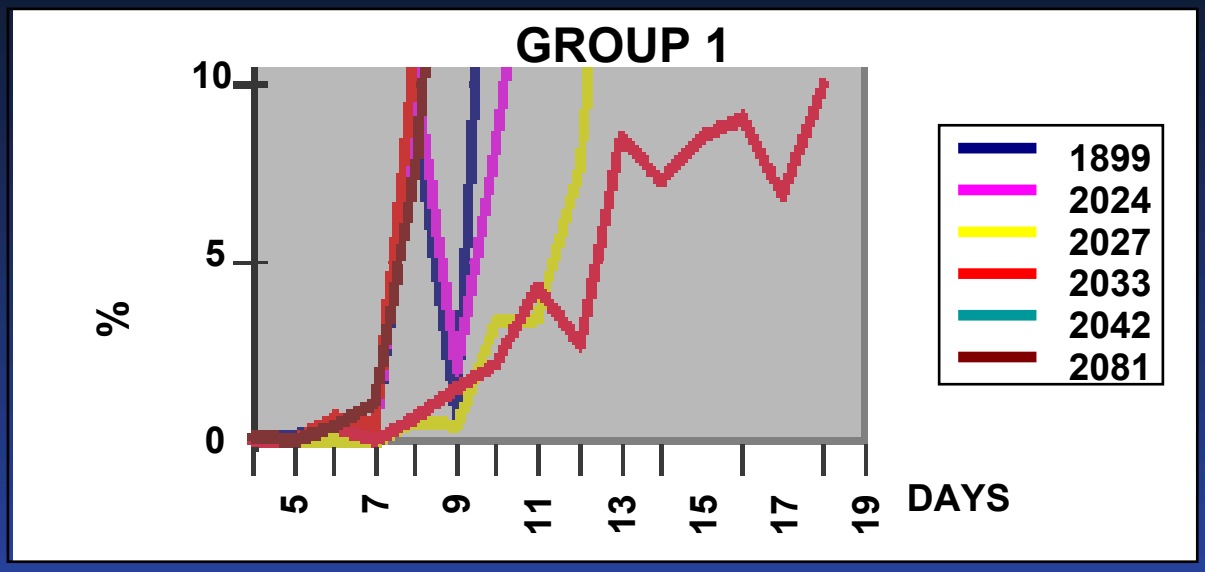
AOTUS SERA REACTIVITY AGAINST THE STRUCTURALLY REPLACED IMMUNIZING PEPTIDES

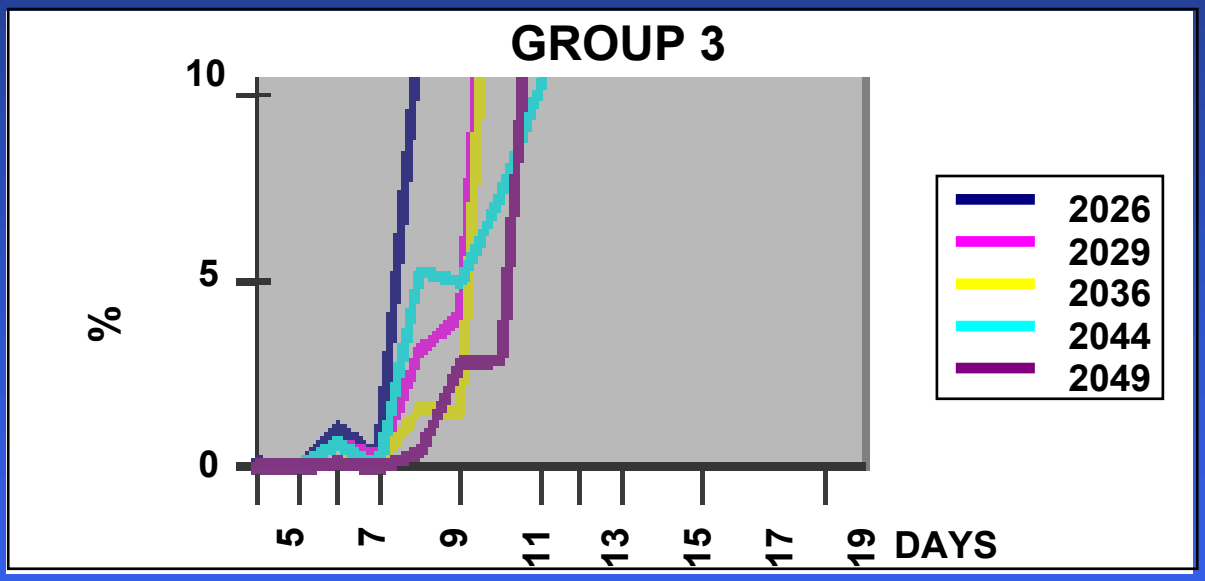
GROUP 1	2024	2027	2033	2042	2081
1513	0	0	0	0	0
4863	0	0	0	0	0
4865	0	0	0	0	100
4867	0	0	0	0	0

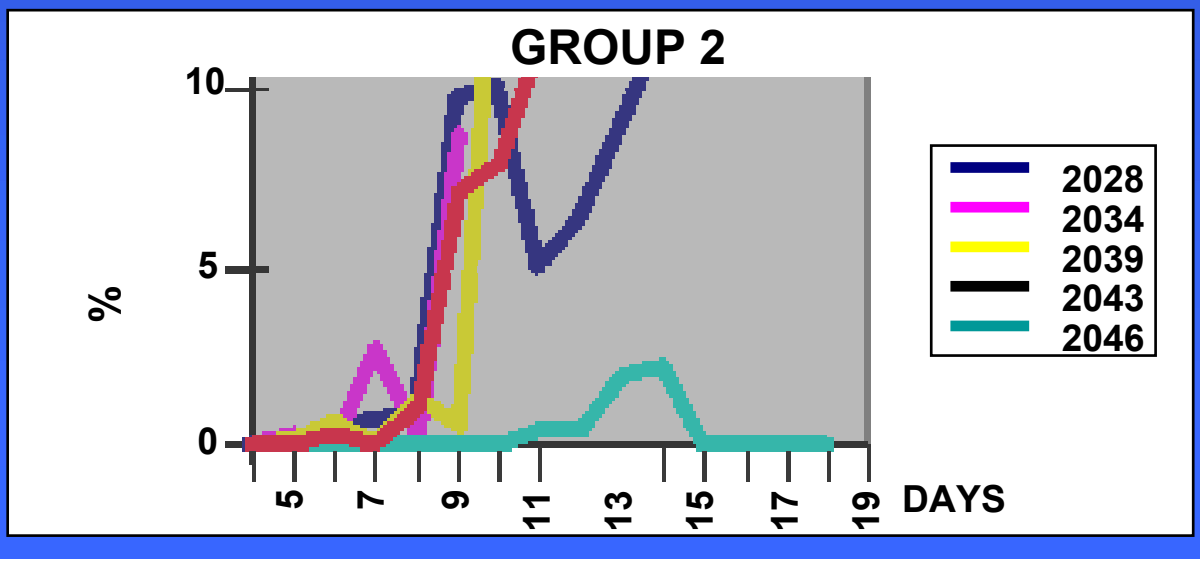
GROUP 2	2028	2034	2039	2043	2046
1513	800	0	0	1600	400
4863	0	0	0	25600	0
4865	800	100	0	3200	200
4867	0	0	0	6400	6400

GROUP 3	2026	2029	2036	2044	2049
1513	0	200	0	1600	100
4863	0	100	0	6400	0
4865	200	100	0	6400	0
4867	200	200	200	12800	0

AOTUS MONKEYS IMMUNIZED WITH MSP-1 STRUCTURALLY MODIFIED PEPTIDES







STRUCTURALLY REPLACED ANALOGUES OF THE 1598_M PEPTIDE

PEPTIDE	GROUP	SEQUENCE
4847	14	FPNTIISKLIEGKFQDMLNISQHQ
4871	4	**M**PN**P**IISKLIEGKFQDMLNISQHQ
4873	5	FPNTIISKLIEGKFQDM**P**N**P**SQHQ
4879	6	FPNTIISKLIEGK**P**QDM**P**N**P**SQHQ

AOTUS SERA REACTIVITY AGAINST THE STRUCTURALLY REPLACED IMMUNIZING PEPTIDES

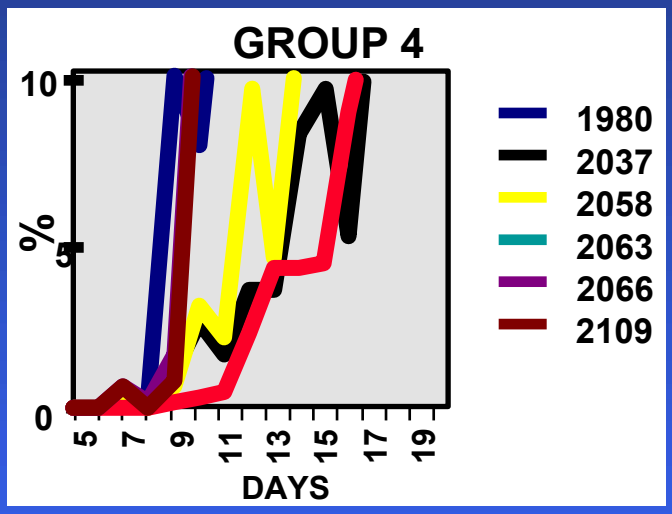
GROUP 4	1980	2037	2058	2063	2066	2109
4869	100	200	200	12800	51200	200
4871	1600	102400	800	102400	102400	25600
4873	100	ND	0	ND	ND	200
4879	3200	12800	6400	51200	6400	3200

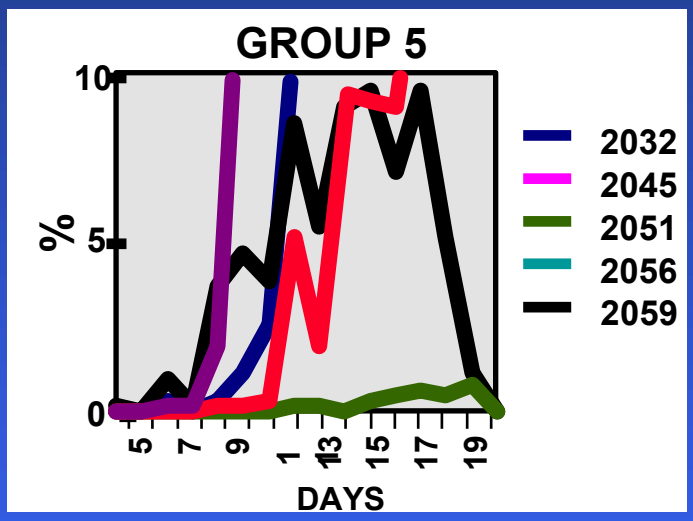
GROUP 5	2032	2045	2051	2056	2059	2047
4869	100	3200	1600	51200	3200	200
4871	200	800	200	1600	200	25600
4873	200	ND	ND	ND	ND	ND
4879	51200	51200	12800	12800	25600	12800

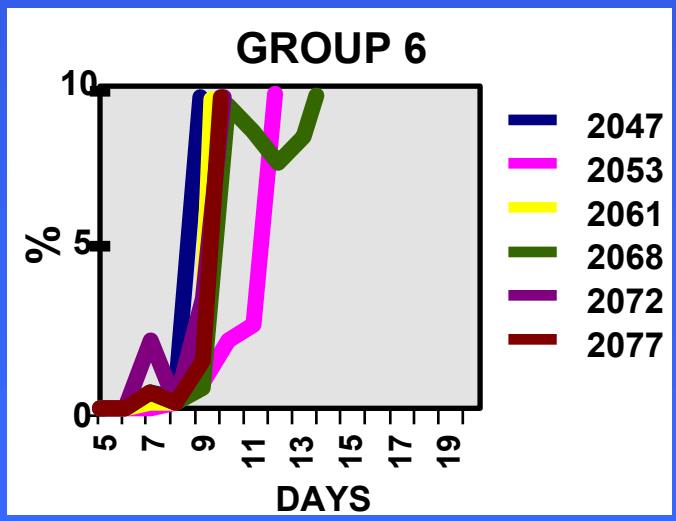
GROUP 6	2053	2061	2068	2072	2077
4869	51200	102400	12800	25600	102400
4871	25600	51200	3200	6400	12800
4873	ND	ND	ND	ND	ND
4879	51200	25600	800	102400	204800

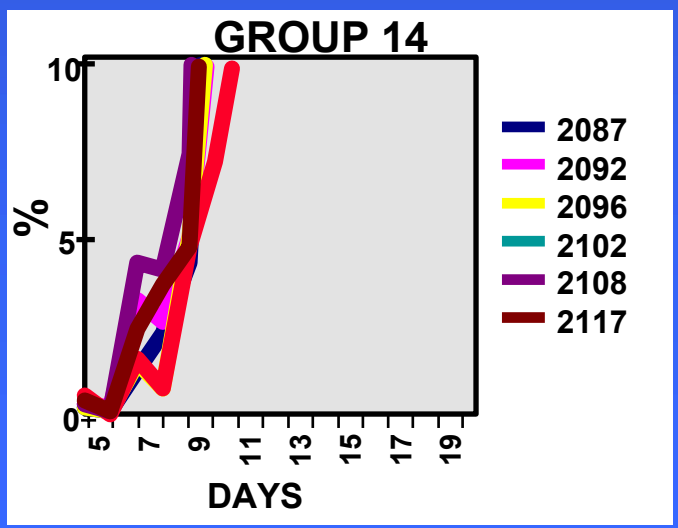
GROUP 14	2087	2092	2096	2102	2108	2117
4869	0	0	0	0	0	0
4871	0	0	0	0	0	0
4873	0	0	0	0	0	0
4879	0	0	0	0	0	0

AOTUS MONKEYS IMMUNIZED WITH MSP-1 STRUCTURALLY MODIFIED PEPTIDES









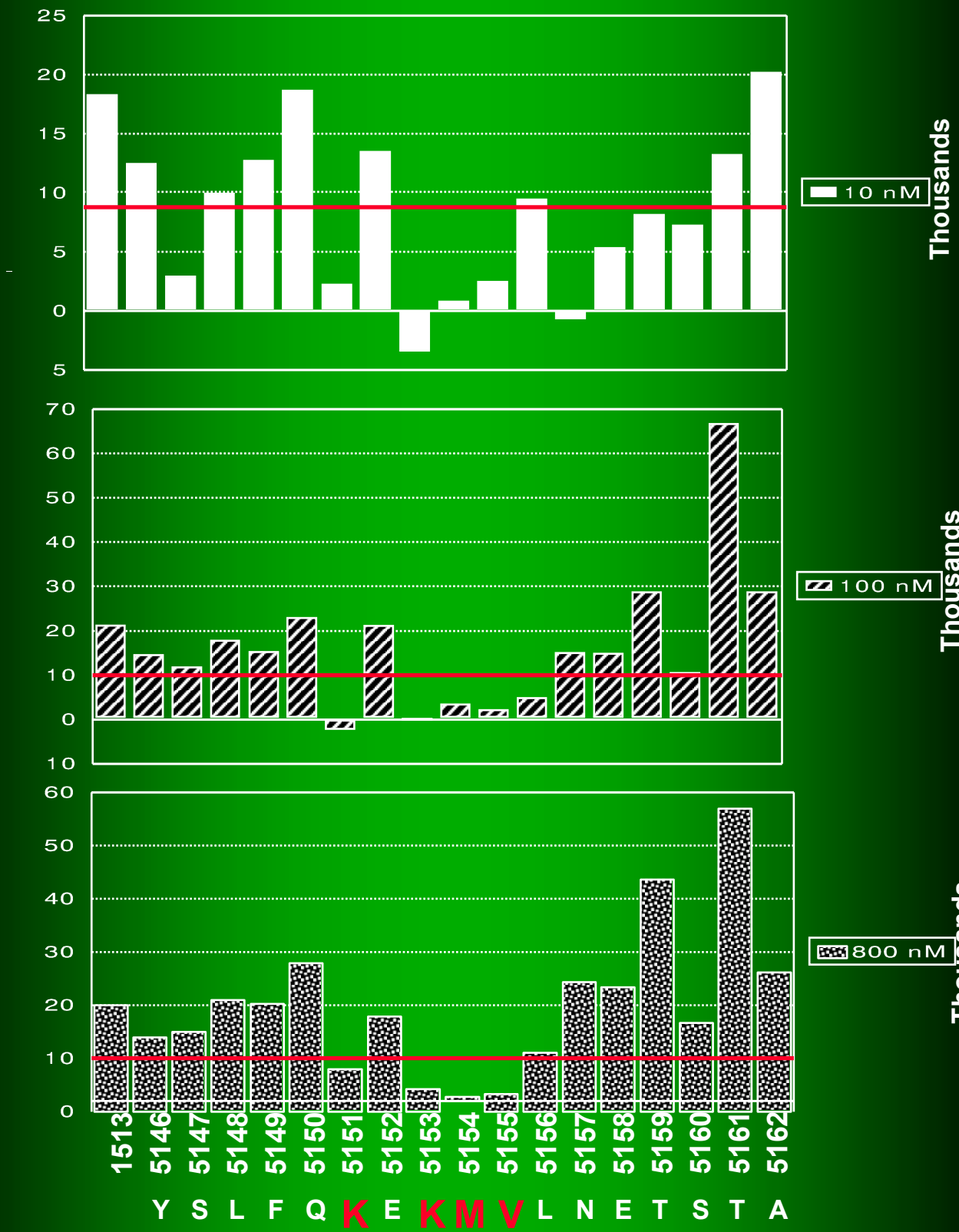
ANALOGUES OF PEPTIDE 1513 FOR BINDING ASSAYS

Urquiza M. et al. 1996. *Parasite Immunology* 18:515-526

1513	G	Y	S	L	F	Q	K	E	K	M	V	L	N	E	G	T	S	G T A Y
5146	G	G	S	L	F	Q	K	E	K	M	V	L	N	E	G	T	S	G T A Y
5147	G	Y	G	L	F	Q	K	E	K	M	V	L	N	E	G	T	S	G T A Y
5148	G	Y	S	G	F	Q	K	E	K	M	V	L	N	E	G	T	S	G T A Y
5149	G	Y	S	L	G	Q	K	E	K	M	V	L	N	E	G	T	S	G T A Y
5150	G	Y	S	L	F	G	K	E	K	M	V	L	N	E	G	T	S	G T A Y
5151	G	Y	S	L	F	Q	G	E	K	M	V	L	N	E	G	T	S	G T A Y
5152	G	Y	S	L	F	Q	K	G	K	M	V	L	N	E	G	T	S	G T A Y
5153	G	Y	S	L	F	Q	K	E	G	M	V	L	N	E	G	T	S	G T A Y
5154	G	Y	S	L	F	Q	K	E	K	G	V	L	N	E	G	T	S	G T A Y
5155	G	Y	S	L	F	Q	K	E	K	M	G	L	N	E	G	T	S	G T A Y
5156	G	Y	S	L	F	Q	K	E	K	M	V	G	N	E	G	T	S	G T A Y
5157	G	Y	S	L	F	Q	K	E	K	M	V	L	G	E	G	T	S	G T A Y
5158	G	Y	S	L	F	Q	K	E	K	M	V	L	N	G	G	T	S	G T A Y
5159	G	Y	S	L	F	Q	K	E	K	M	V	L	N	E	G	G	S	G T A Y
5160	G	Y	S	L	F	Q	K	E	K	M	V	L	N	E	G	T	G	G T A Y
5161	G	Y	S	L	F	Q	K	E	K	M	V	L	N	E	G	T	S	G G A Y
5162	G	Y	S	L	F	Q	K	E	K	M	V	L	N	E	G	T	S	G T G Y

BINDING OF 1513 PEPTIDE ANALOGUES TO RBCs

Urquiza M. et al. 1996. *Parasite Immunology* 18:515-526



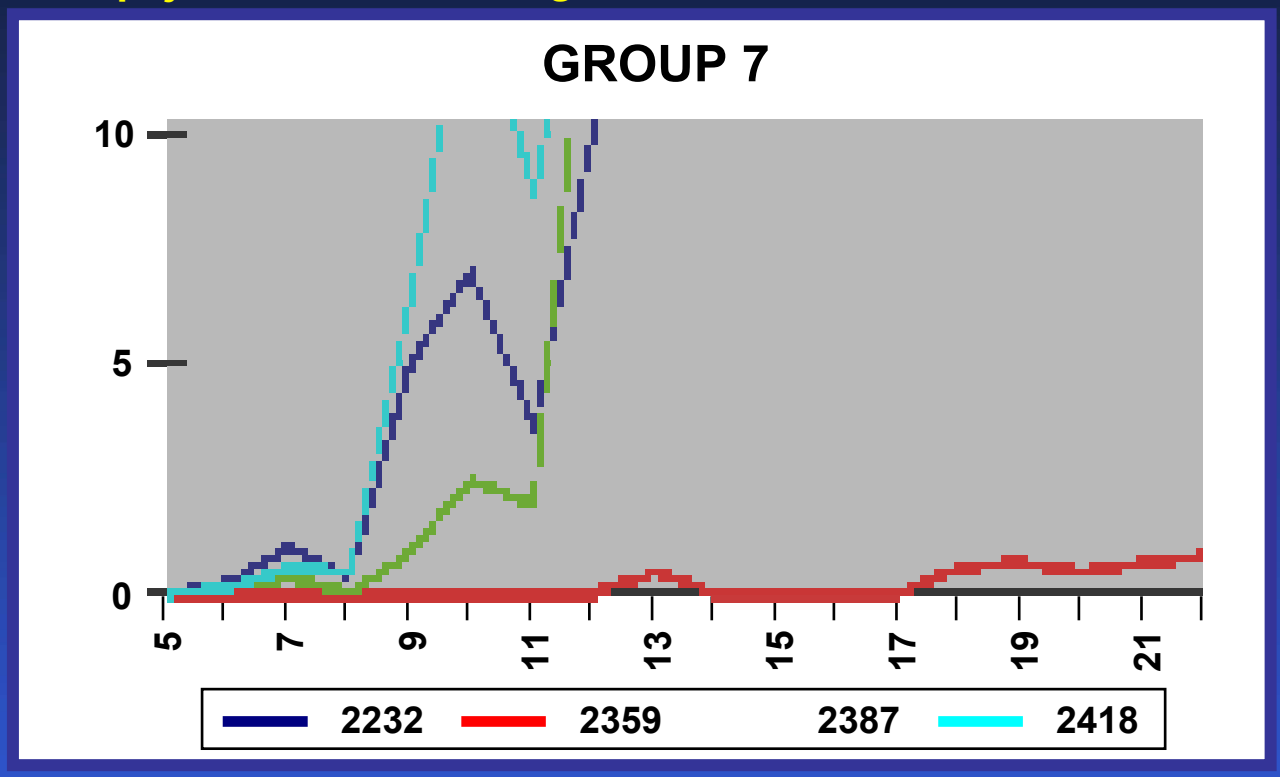
SPECIFICALLY REPLACED ANALOGUES OF THE 1585 PEPTIDE TO IMMUNIZE AOTUS MONKEYS

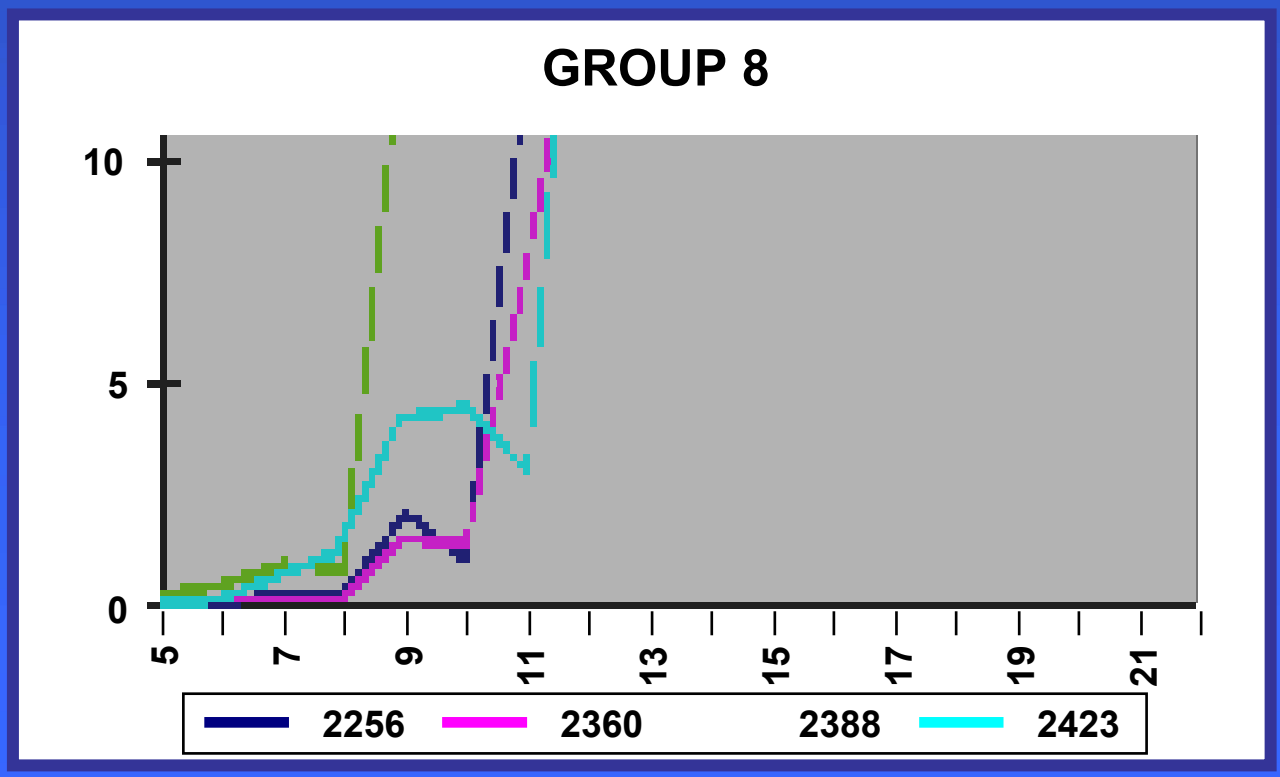
Espejo F. et al. 2001. *Angewandte Chemie Int. Ed*. 40:2631

PEPTIDE	SEQUENCE
1585	EVLY**LKP**L**A**GVYYRSLKKQLE
5187	EVLY**G**KPLAGVYYRSLKKQLE
5190	EVLYLKP**G**AGVYYRSLKKQLE

AOTUS MONKEYS IMMUNIZED WITH 1585 SPECIFICALLY MODIFIED PEPTIDES

Espejo F. et al. 2001. *Angewandte Chemie Int. Ed*. 40:2631





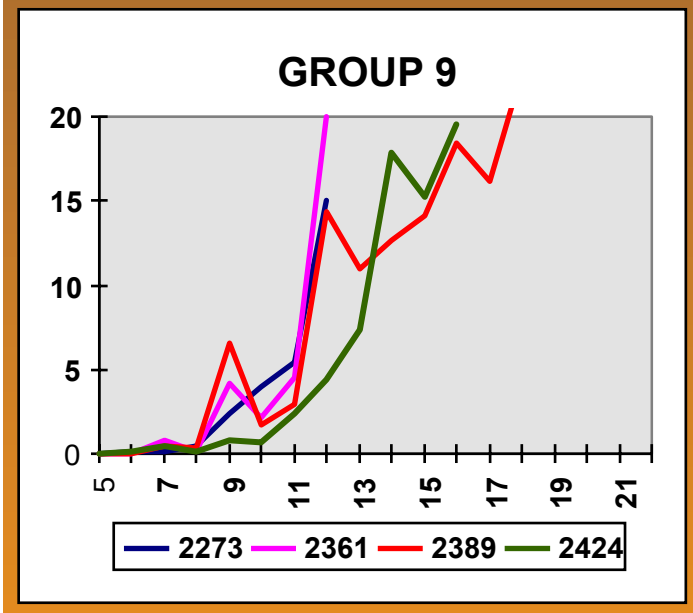
SPECIFICALLY REPLACED ANALOGUES OF THE 5501 PEPTIDE TO IMMUNIZE AOTUS MONKEYS

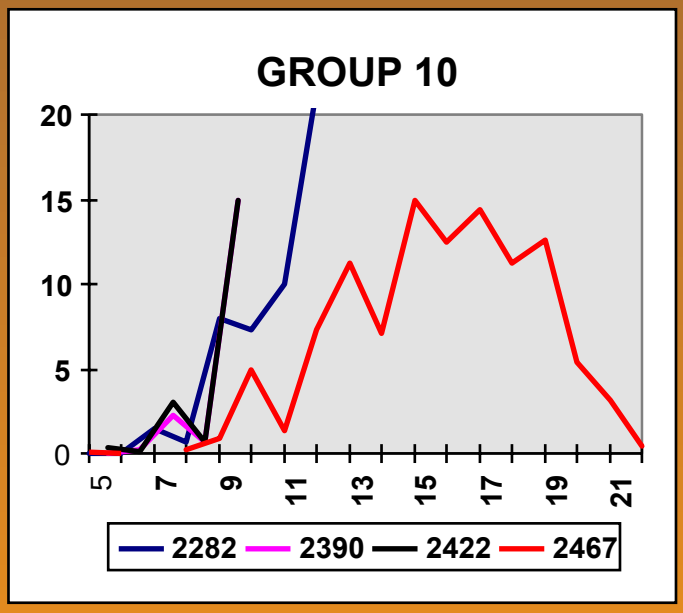
Torres M. H. et al. 2003. *European J. Biochemistry* 270:3946

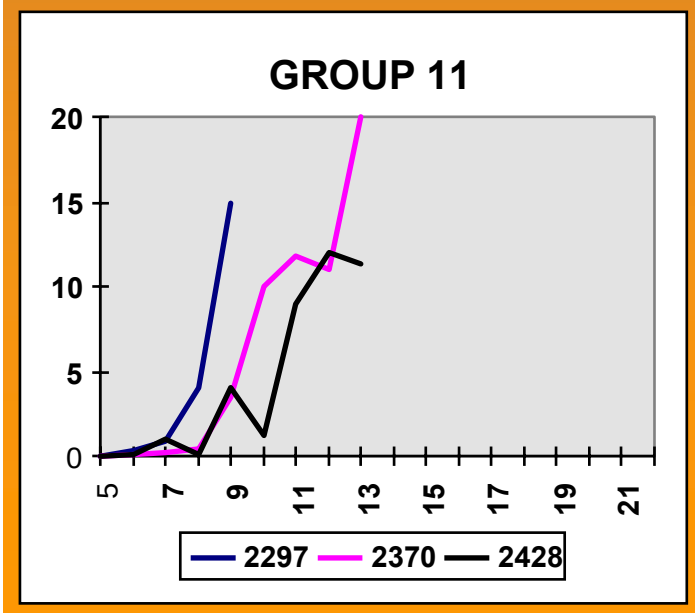
PEPTIDE	SEQUENCE
5501	MLNISQHQCVKKQCPQNSY
5503	MGNISQHQCVKKQCPQNSY
5512	MLNISQHQCVGKQCPQNSY
5513	MLNISQHQCVKGQCPQNSY
5516	MLNISQHQCVKKQCGQNSY

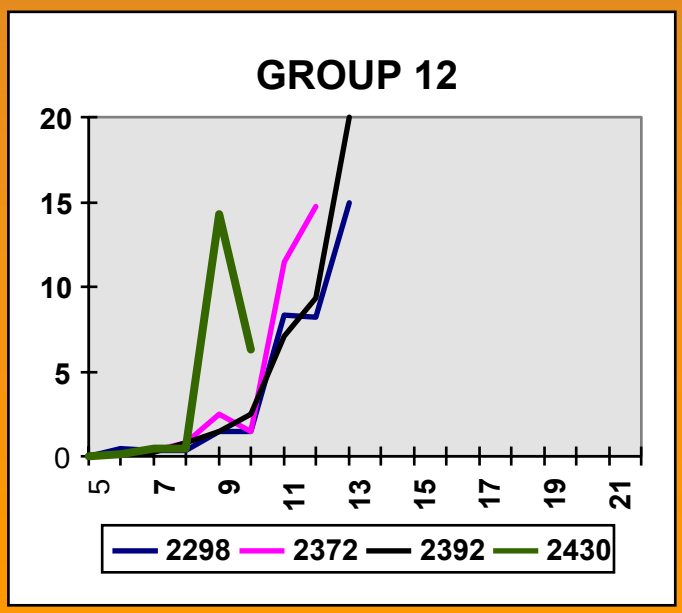
AOTUS MONKEYS IMMUNIZED WITH 5501 SPECIFICALLY MODIFIED PEPTIDES

Torres M. H. et al. 2003. *European J. Biochemistry* 270:3946









Synthetic vaccines - Emerging principles

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2. CONSERVED binding sequences are NOT antigenic, but VARIABLE sequences are
3. CONSERVED binding sequences are NOT immuno-genic in ANY of the tested species when administe-red as monomers, polymerized, associated with T helper epitopes or presented as MAPs. WhileVARIABLE sequences can be immunogenic they are strain-specific
4. To overcome this problem the critical contact residues in the binding interaction have to be identified and changed

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COMMUNICATIONS

Structure, Immunogenicity, and Protectivity Relationship for the 1585 Malarial Peptide and Its Substitution Analogues

Fabiola Espejo,* Marcia Cubillos, Luz Mary Salazar, Fanny Guzman, Mauricio Urquiza, Marisol Ocampo, Yolanda Silva, Raul Rodriguez, Eduardo Lioy, and Manuel Elkin Patarroyo*

Polymerized peptide Nr.	Peptide Sequence	IFA TITERS ≥320 II 15	III 20	PROT	
1585	E V L Y **L K P** L **A** G V Y R **S** L K K Q L E	0	0	0/5	
5187	- - - - **G K P A** - - - - **S** - - - - - -	ND.	**1(320)**	**1/4**	GROUP A
5188	- - - - **L G P** - **A** - - - - **S** - - - - - -	ND.	**1(320)**	**1/4**	
5189	- - - - **L K G** - **A** - - - - **S** - - - - - -	ND.	**1(1280)**	**1/4**	
6187	- - - - **L K P G A** - - - **S** - - - - - -	0	0	0	
6177	- - - - **L K P** - **A** - - - - **G** - - - - - -	0	0	0	
13450	- - - - **L L D A** - - - - **S** - - - - - -	**2(2560)**	**1(2560)**	**2/4**	GROUP B
22806	- **L L D** - **A** - - - - **S** - - - -	**3(1280)**	**1(1280)**	**2/9**	
10014	- - - - **H V P** - **A** - - - - **S** - - - - - -	**2(640)**	**1(640)**	**2/4**	
22768	- **H L P** - **A** - - - - **A** - - - -	**0**	**1(5120)**	**1/10**	
11860	- - - - **H M P** - **G** - - - - **A** - - - - - -	**1(1280)**	**1(2560)**	**2/6**	
22770	- **H L P** - **G** - - - - **A** - - - -	**1(1280)**	**1(1280)**	**2/9**	
13454	- - - - **L M S** - **A** - - - - **S** - - - - - -	0	0	0/5	GROUP C
14448	- - - - **H M D** - **G** - - - - **V** - - - - - -	0	0	0/3	
14496	- - - - **H M D** - **S** - - - - **V** - - - - - -	0	0	0/4	
13724	- - - - **H V T** - **S** - - - - **S** - - - - - -	0	0	0/5	
12896	- - - - **H V P** - **S** - - - - **A** - - - - - -	0	0	0/5	
12898	- - - - **H V P** - **G** - - - - **A** - - - - - -	0	0	0/5	
15954	- - - - **L M D** - **A** - - - - **S** - - - - - -	0	0	0/3	
15956	- - - - **L M P** - **A** - - - - **S** - - - - - -	0	0	0/4	
15958	- - - - **L K D** - **S** - - - - **S** - - - - - -	0	0	0/6	
15960	- - - - **L M D S** - - - - **S** - - - - - -	0	0	0/4	
13728	- - - - **N** L **D** - **G** - - - - **S** - - - - - -	0	0	0/5	
13452	- - - - **L I D** - **A** - - - - **S** - - - - - -	0	0	0/5	
CONTROLS		0	0	0/50	

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Protection against experimental *P. falciparum* malaria is associated with short AMA-1 peptide analogue α-helical structures

Marcia Cubillos [a,1], Luz Mary Salazar [a,1], Libardo Torres [b], Manuel Elkin Patarroyo [a,b,*]

Polymerized peptide No.	Peptide Sequence	IFA ≥1:160 Post 2nd	IFA ≥1:160 Post 3rd	No. of protected monkeys	Group
4325	M I K **S A** F **L** P T G A F **K A D** R **Y** K S H	0	0	0/6	
13486	– – – **A S** – **D** – – – – – – **S P** – – – – –	3(2560)	2(1280)	2/5	A
15516	– – – **A** – – **H** – – – – – **M S** – – **W** – – –	1(1280)	1(160)	1/4	A
20034	– – – **A** – – – – – – – – **M** – – – – – – –	2(320)	1(160)	2/8	A
20032	– – – **A** – – – – – – – – – – – – – – –	1(160)	1(160)	1/8	A
22784	– – – **V G** – **D** – – – – – – **S P** – – – – –	1(2560)	ND	1/10	A
23404	– – – **V S** – **D** – – – – – **M S** – – – – – –	2(320)	ND	1/10	A
23406	– – – **V S** – **D D** – – – – **M S** – – – – – –	1(320)	ND	1/10	A
14518	– – – **V G** – **H** – – – – – – **S P** – **W** – – –	1(320)	0	0/3	B
14520	– – – **V G** – **H** – – – – **M S P** – – – – –	2(640)	0	0/3	B
17934	– – – **A S** – **H V** – – – – **M S** – – – – – –	2(320)	0	0/7	B
17936	– – – **A S** – **H V** – – – – **M S P** – **W** – – –	2(640)	0	0/5	B
9192	– – – – **G** – – – – – – – – – – – – – –	0	0	0/5	C
9196	– – – – – – – – – – – – – **G** – – – – –	0	0	0/5	C
10100	– – – **R G** – – – – – – – – – – – – – –	0	0	0/5	C
10102	– – – **F G** – – – – – – – – – – – – – –	0	0	0/5	C
10104	– – – **G T** – – – – – – – – – – – – – –	0	0	0/5	C
12708	– – – – – – – – – – – – – – – **W** – – –	0	0	ND	C
15512	– – – **A** – – – – – – – – **S** – – **W** – – –	0	0	0/4	C
15510	– – – **A** – – – – – – – – **S** – – – – – –	0	0	0/4	C
16000	– – – – **S** – – – – – – – – – – – – – –	0	0	0/5	C
16008	– – – – – – **H** – – – – – – – **P** – – – – –	0	0	0/4	C
16002	– – – – **S** – **H** – – – – – – – – – – – –	0	0	0/5	C
16004	– – – – **S** – **H** – – – – – – – **P** – – – – –	0	0	0/5	C
16006	– – – – **S** – – – – – – – – – **P** – – – – –	0	0	0/5	C
17932	– – – **A S** – **D** – – – – – – **S P** – **W** – – –	0	0	0/7	C
23178	– – – **V S** – **D** – – – – – – – – – – – – **G** –	0	ND	0/9	C
23774	– – – **V S** – **H D** – – – – **M S** – – – – – –	0	ND	0/9	C
22424	– – – **S S** – **H V** – – – – – – – **P** – – – – –	0	ND	0/8	C
23000	– – – **V** – – **D** – – – – – – – **S P** – – – – –	0	ND	0/7	C
CONTROLS		0/60	0/60	0/60	

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Plasmodium falciparum SERA protein peptide analogues having short helical regions induce protection against malaria

Marcia Cubillos [a], Martha Patricia Alba [a], Adriana Bermúdez [a], Mary Trujillo [a], Manuel Elkin Patarroyo [a,b,*]

Polymerized peptide No.	Peptide Sequence	IFA ≥1:320 Post 2nd	IFA ≥1:320 Post 3rd	No. of protected monkeys	Group
6737	D **N** I **L** V K M F K **T** **N** **E** N N D K S E L I	0/10	0/10	0/10	
12748	* – – – – – – – – – – **V** **I** – – – – – – – *	1(2560)	1(2560)	1/4	A
13840	* – – – – – – – – – **V** **I** **M** – – – – – – – *	3(640)	1(320)	1/5	A
22834	* – – **H** – – – – – **V** **I** – – – – – – – – *	1(2560)	ND	2/9	A
22796	* – – – – – – – – – **V** **I** – – – – – – – – *	1(5120)	ND	2/9	A
13844	* – – **H** – – – – – **V** **I** **M** – – – – – – – *	1(320)	0/6	1/6	A
24096	* – – **H** – – – – – **V** **I** **M** – – – – – – – *	1(5120)	ND	2/8	A
14094	* **I** – – – – – – – – **V** **I** **M** – – – – – – – *	1(320)	2(320)	0/5	B
14096	* – – **H** – – – **R** – **V** **I** **M** – – – – – – – *	3(640)	1(640)	0/4	B
24308	* – – **H** – – – – – – **P** **M** – – – – – – – *	1(640)	ND	0/8	B
9228	* **G** – – – – – – – – – – – – – – – – – – – *	0/5	0/5	0/5	C
9230	* – – **G** – – – – – – – – – – – – – – – – – *	0/5	0/5	0/5	C
9234	* – – – – – – – – – – **G** – – – – – – – – *	0/5	0/5	0/5	C
10154	* – – – – – – – – – – **M** **I** – – – – – – – *	0/5	0/5	0/5	C
10152	* – – – – – – – – – – **M** **L** – – – – – – – *	0/5	ND	0/5	C
10150	* – – – – – – – – – – **M** **F** – – – – – – – *	0/5	0/5	0/5	C
16016	* – – – – – – – – – **V** **D** – – – – – – – – *	0/5	0/5	0/5	C
17970	* – – **H** – – – – – – **I** – – – – – – – – *	0/8	0/7	0/7	C
22460	* – – – – – – – – – – **I** – – – – – – – – *	0/10	0/10	0/10	C
10148	* – – – – – – – – – – **R** **A** – – – – – – – *	0/5	0/5	0/5	C
12754	* – – **H** – – – – – **V** **V** **I** – – – – – – *	0/5	0/5	ND	C
23418	* – – **H** – – – – – – **I** **M** – – – – – – – *	0/10	ND	0/10	C
24392	* – – **H** – – – – – – **A** **M** – – – – – – – *	0/6	ND	0/6	C
CONTROLS		0/50	0/50	0/50	

Synthetic vaccines - Emerging principles

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Biochimica et Biophysica Acta 1571 (2002) 27–33

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NMR structure of *Plasmodium falciparum* malaria peptide correlates with protective immunity

Jindra Purmova, Luz Mary Salazar, Fabiola Espejo, Mary Helena Torres, Marcia Cubillos, Elizabeth Torres, Yolanda Lopez, Raul Rodriguez, Manuel Elkin Patarroyo*

Fundación Instituto de Inmunología de Colombia (FIDIC), Carrera 50, No. 26-00, Bogotá, Colombia

Received 6 November 2001; received in revised form 12 February 2002; accepted 26 March 2002

FEBS 26417

FEBS Letters 527 (2002) 95–100

Protection against experimental malaria associated with AMA-1 peptide analogue structures

Luz M. Salazar, Martha P. Alba, Maria H. Torres, Martha Pinto, Ximena Cortes, Libardo Torres, Manuel E. Patarroyo*

2250

J. Med. Chem. **2003**, *46*, 2250−2253

Distorting Malaria Peptide Backbone Structure to Enable Fitting into MHC Class II Molecules Renders Modified Peptides Immunogenic and Protective

Gladys Cifuentes,† Manuel Elkin Patarroyo,*,†,‡ Mauricio Urquiza,†,‡ Luis E. Ramirez,† Claudia Reyes,† and Raul Rodriguez†

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Peptides 24 (2003) 999–1006

PEPTIDES

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6746 SERA peptide analogues immunogenicity and protective efficacy against malaria is associated with short α helix formation: Malaria protection associated with peptides α helix shortening

Martha Patricia Alba[a], Luz Mary Salazar[a], Alvaro Puentes[a], Martha Pinto[a], Elizabeth Torres[a], Manuel Elkin Patarroyo[a,b,*]

Available online at www.sciencedirect.com
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Biochemical and Biophysical Research Communications 315 (2004) 418–427
BBRC
www.elsevier.com/locate/ybbrc

Shortening and modifying the 1513 MSP-1 peptide's α-helical region induces protection against malaria

Fabiola Espejo,[1] Adriana Bermúdez,[1] Elizabeth Torres, Mauricio Urquiza, Raúl Rodríguez, Yolanda López, and Manuel Elkin Patarroyo*

Biol. Chem., Vol. 384, pp. 000–000, October/November 2003 · Copyright © by Walter de Gruyter · Berlin · New York

Adriana Bermúdez[1], Gladys Cifuentes[1], Fanny Guzmán[1], Luz Mary Salazar[1] and Manuel Elkin Patarroyo[1,2]*

Immunogenicity and Protectivity of *Plasmodium falciparum* EBA-175 Peptide and Its Analog Is Associated with α-Helical Region Shortening and Displacement

Eur. J. Biochem. **270**, 1–7 (2003) © FEBS 2003 doi:10.1046/j.1432-1033.2003.03780.x

Modified merozoite surface protein-1 peptides with short alpha helical regions are associated with inducing protection against malaria

Mary H. Torres[1]*, Luz M. Salazar[1]*, Magnolia Vanegas[1], Fanny Guzman[1], Raul Rodriguez[1], Yolanda Silva[1], Jaiver Rosas[1] and Manuel E. Patarroyo[1,2]

PROTEINS:Structure,Function,and Genetics 50:400 –409 (2003)

Alpha Helix Shortening in 1522 MSP-1 Conserved Peptide Analogs is Associated with Immunogenicity and Protection Against *P. falciparum* Malaria

Marcia Cubillos,[1] Fabiola Espejo,[1] Jindra Purmova,[1] Juan C. Martinez,[2] and M.E. Patarroyo[1,2]*

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Available online at www.sciencedirect.com
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Journal of Structural Biology 141 (2003) 115–121

Journal of Structural Biology

www.elsevier.com/locate/yjsbi

Analysis of a *Plasmodium falciparum* EBA-175 peptide with high binding capacity to erythrocytes and their analogues using ^{1}H NMR

Gladys Cifuentes, Fanny Guzmán, Martha Patricia Alba, Luz Mary Salazar, and Manuel Elkin Patarroyo*

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Available online at www.sciencedirect.com
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Vaccine xxx (2003) xxx–xxx

Vaccine

Induction and displacement of an α helix in the 6725 SERA peptide analogue confers protection against *P. falciparum* malaria

Martha Patricia Alba[a], Luz Mary Salazar[a], Jindra Purmova[a], Magnolia Vanegas[a], Raul Rodriguez[a], Manuel Elkin Patarroyo[a,b,*]

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Life Sciences 71 (2002) 2773–2785

Life Sciences

www.elsevier.com/locate/lifescie

^{1}H-NMR structures of the *Plasmodium falciparum* 1758 erythrocyte binding peptide analogues and protection against malaria

Fanny Guzman[a,1], Katherine Jaramillo[a,1], Luz M. Salazar[a], Angela Torres[a], Augusto Rivera[b], Manuel E. Patarroyo[a,b,*]

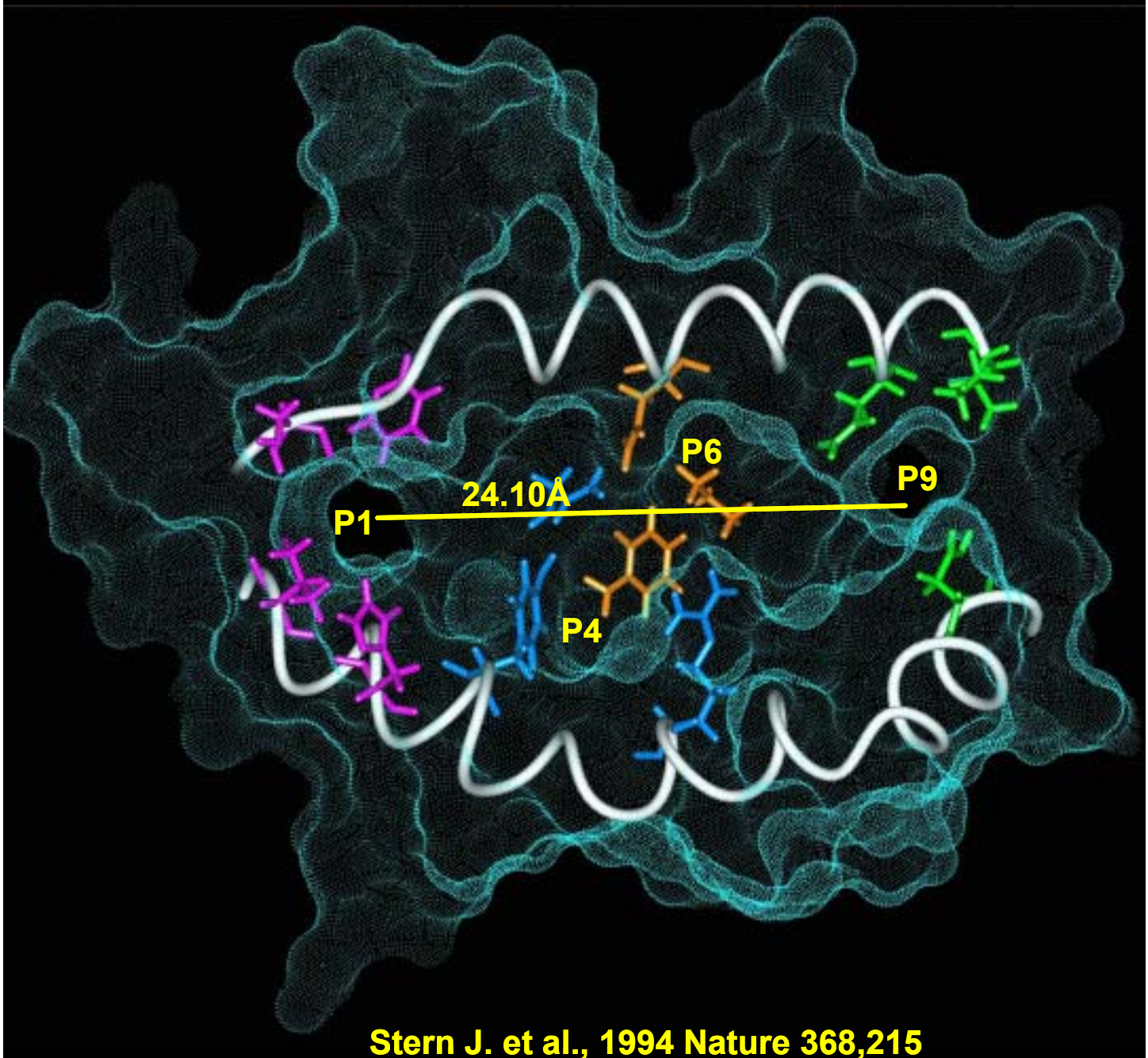
Orientating Peptide Residues and Increasing the Distance between Pockets to Enable Fitting into MHC–TCR Complex Determine Protection against Malaria

Gladys Cifuentes,[§] Fabiola Espejo,[§] Luis Eduardo Vargas,[§] Carlos Parra,[§,‡] Magnolia Vanegas,[§] and Manuel Elkin Patarroyo*[,§,‡]

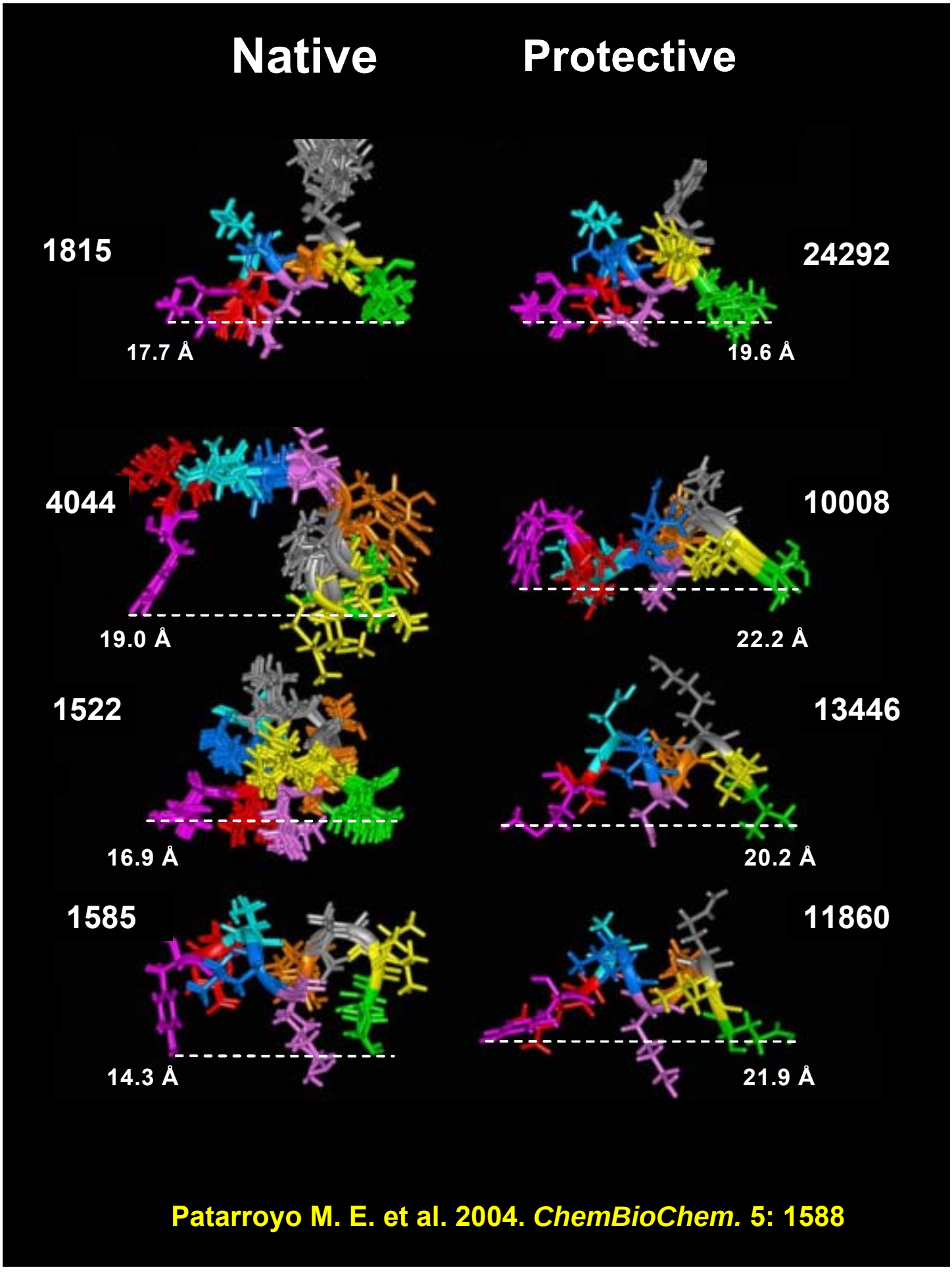
Received February 10, 2004; Revised Manuscript Received March 24, 2004

The MHC molecules the peptide and the T cell receptor complex

Class-II Molecule



Stern J. et al., 1994 Nature 368,215

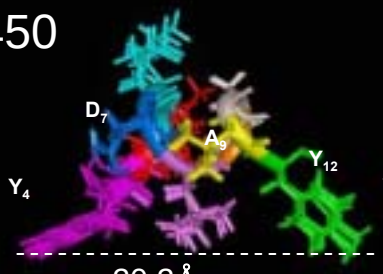


Patarroyo M. E. et al. 2004. *ChemBioChem.* 5: 1588

Inmunogenic and Protection inducers

Short-lived antibodies inducers

13450



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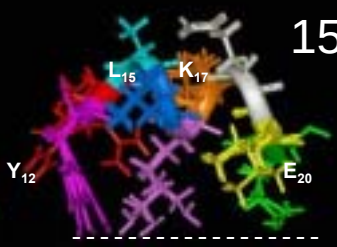
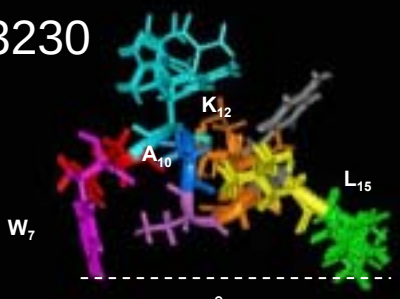


13.3Å

23230



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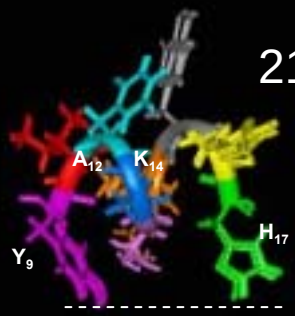
21742

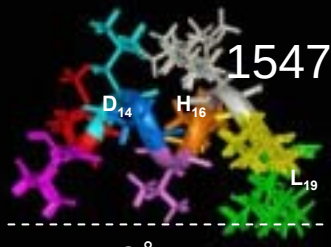


12.7Å

9782

22.1Å

15474



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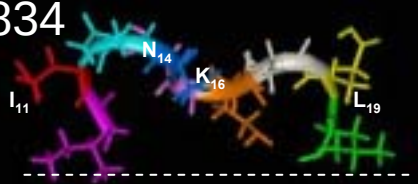
22834



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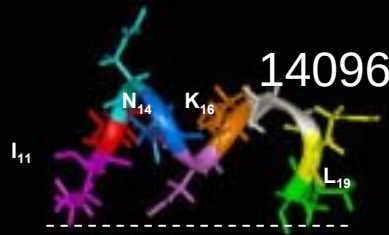

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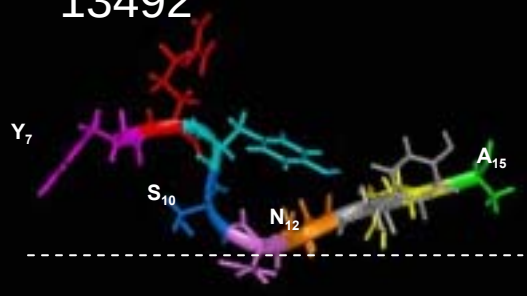

24.7Å

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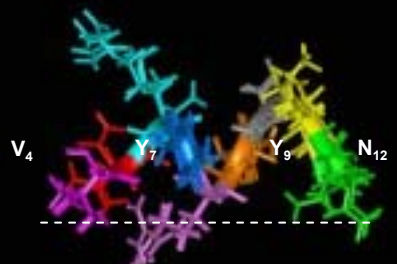
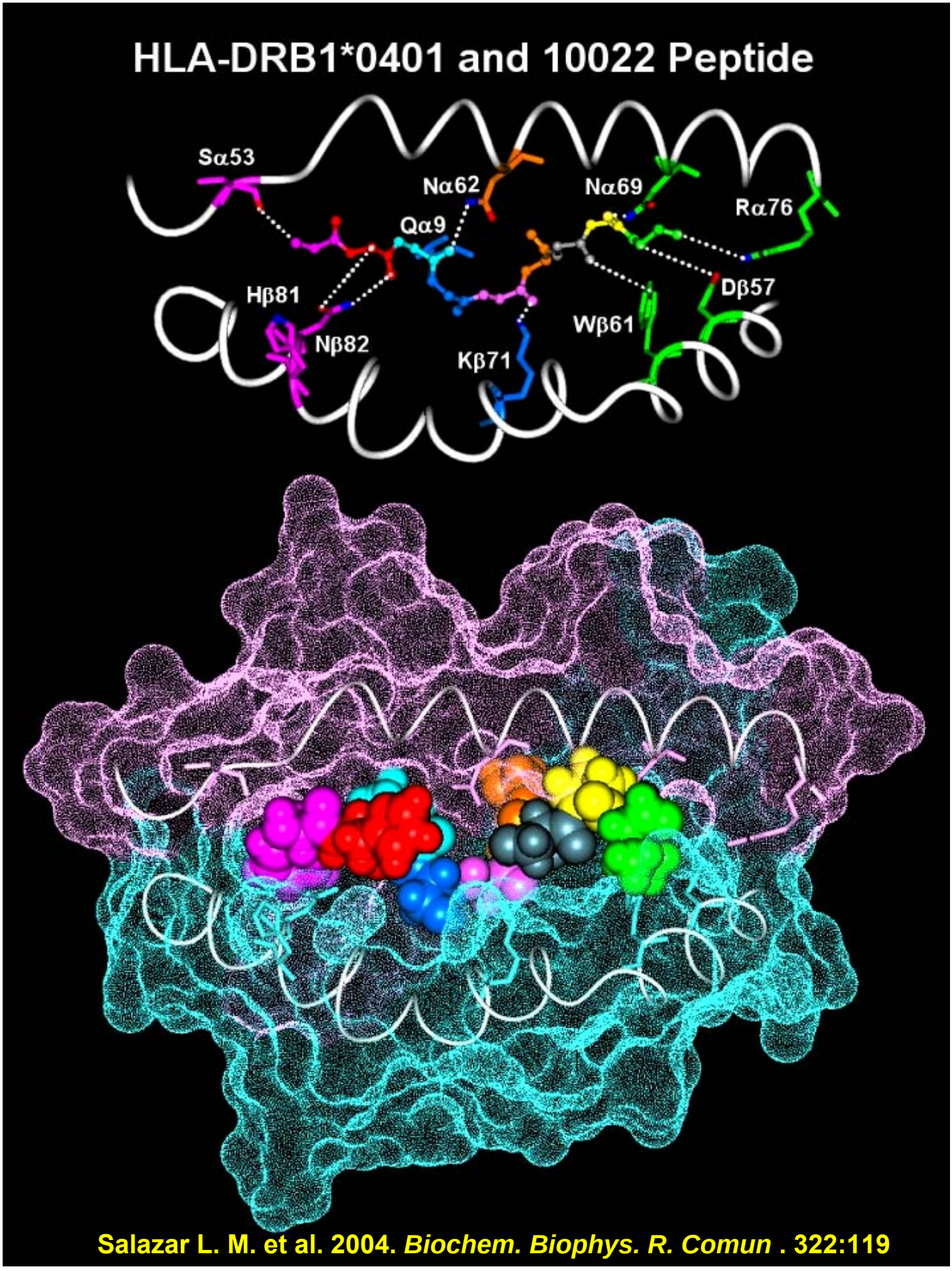


18.9 Å

Patarroyo M. E. et al. 2005. *Biochemistry* In press



Salazar L. M. et al. 2004. *Biochem. Biophys. R. Comun* . 322:119

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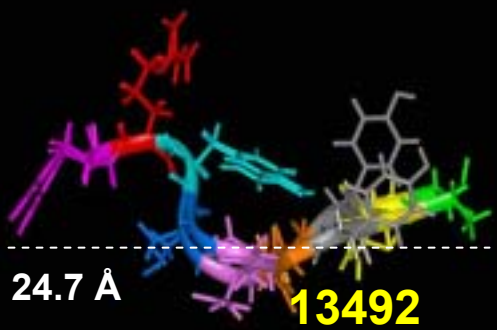
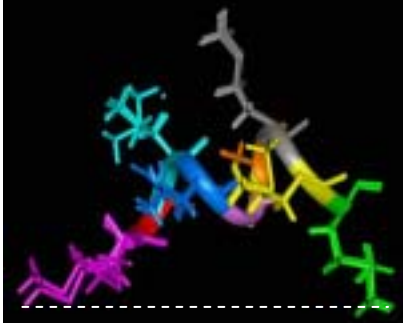
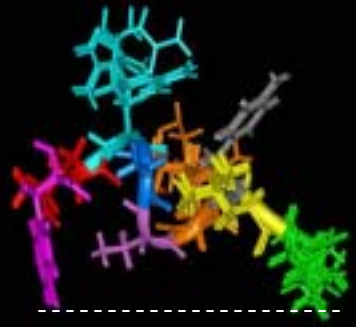
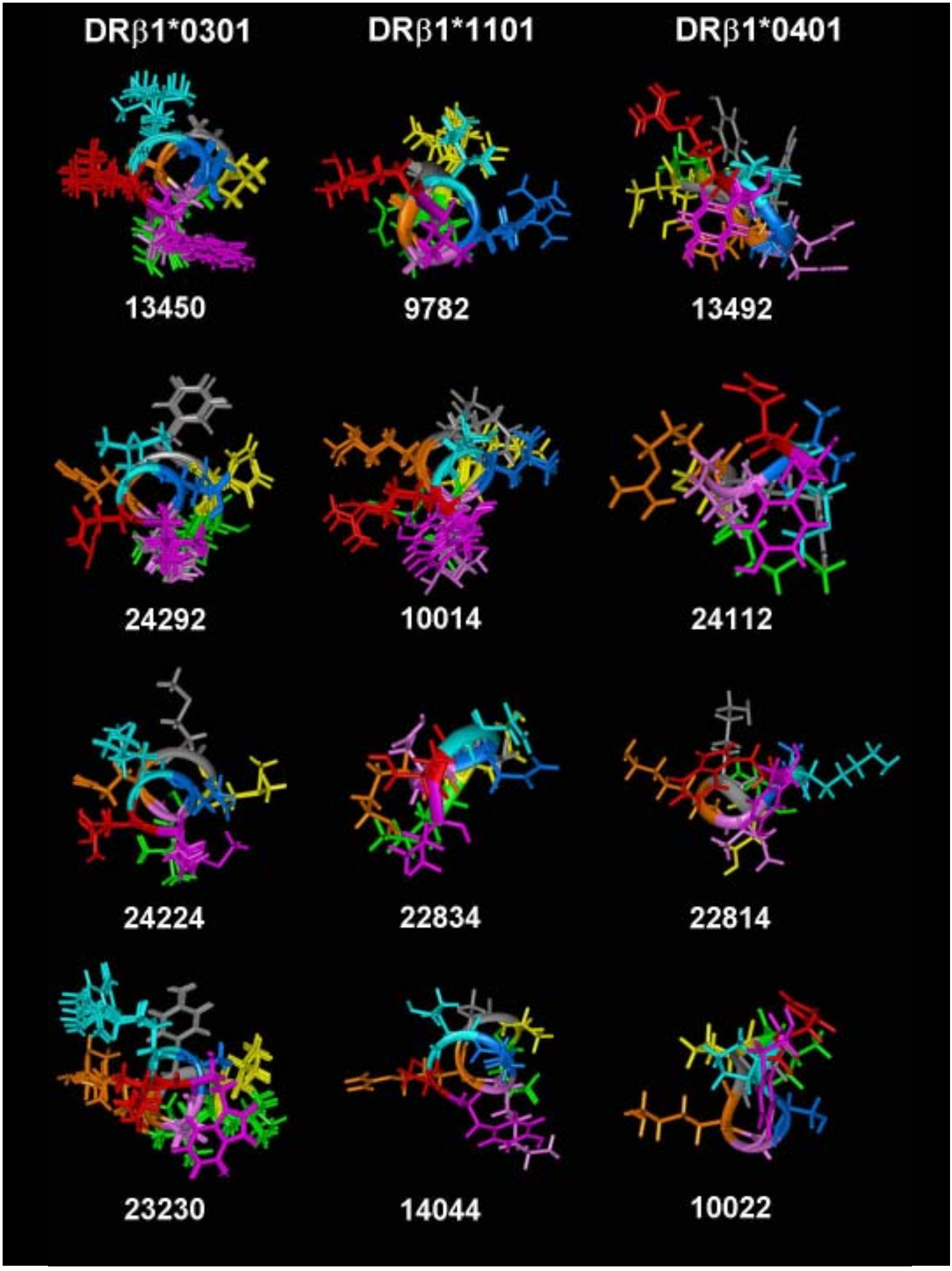
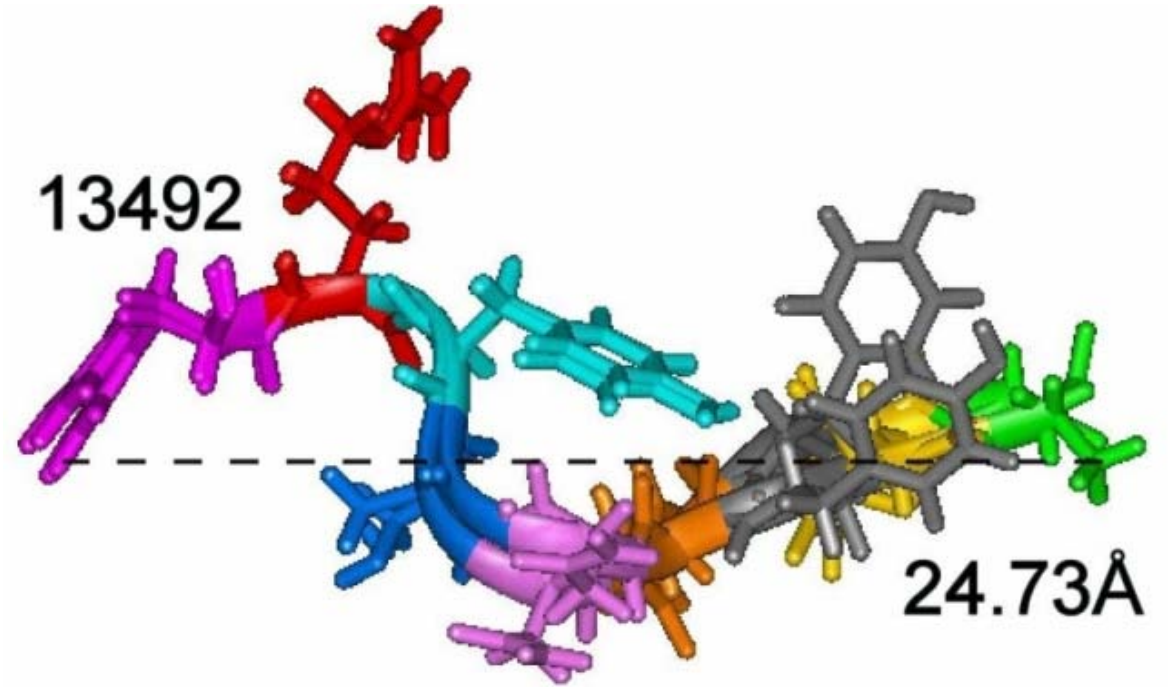
7. **There must be a 23.5 Å ± 3.5 Å distance between those residues fitting into Pockets 1-9 of Class II molecules.**

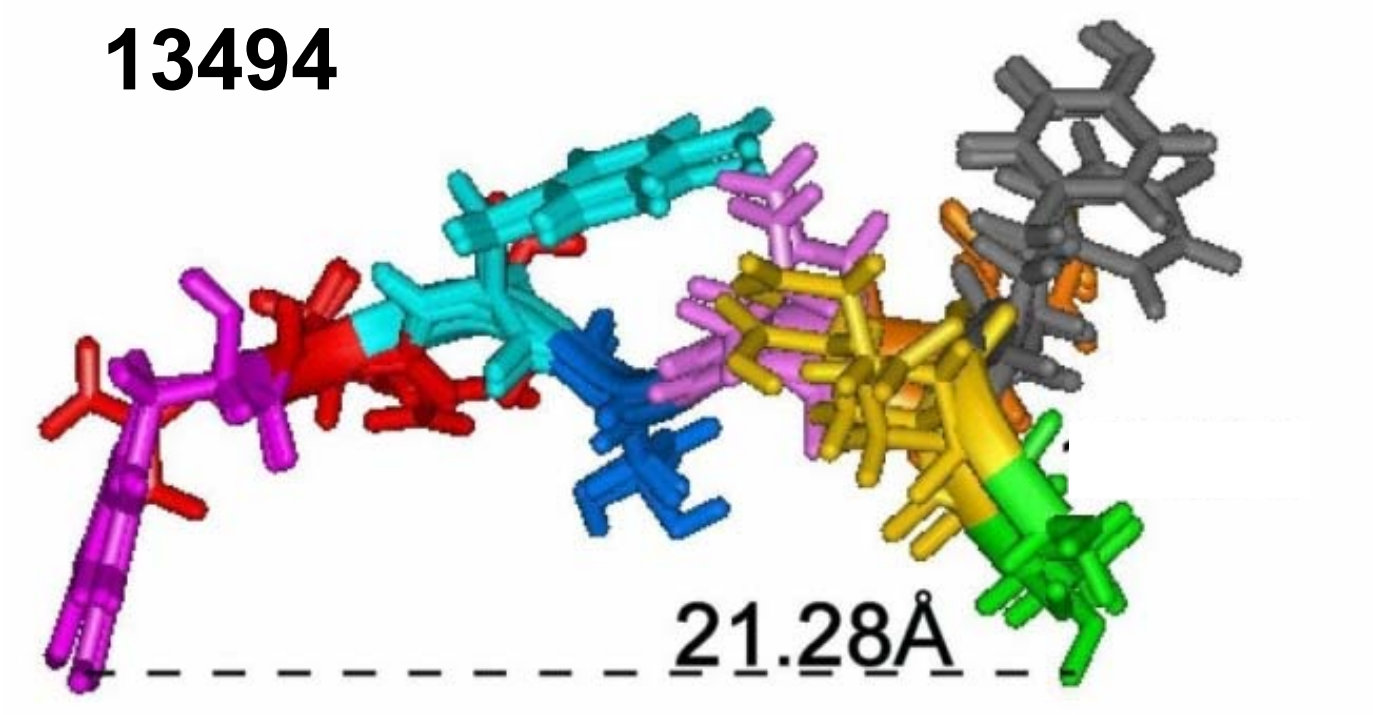
DRβ1*0301	DRβ1*1101	DRβ1*0401
		
20.2 Å 13450	22.1 Å 9782	24.7 Å 13492
		
19.6 Å 24292	20.9 Å 10014	26.5 Å 24112
		
20.3 Å 24224	21.0 Å 22834	25.3 Å 22814
		
20.0 Å 23230	20.2 Å 14044	25.0 Å 10022


DRβ1*0301
DRβ1*1101
DRβ1*0401
13450
9782
13492
24292
10014
24112
24224
22834
22814
23230
14044
10022

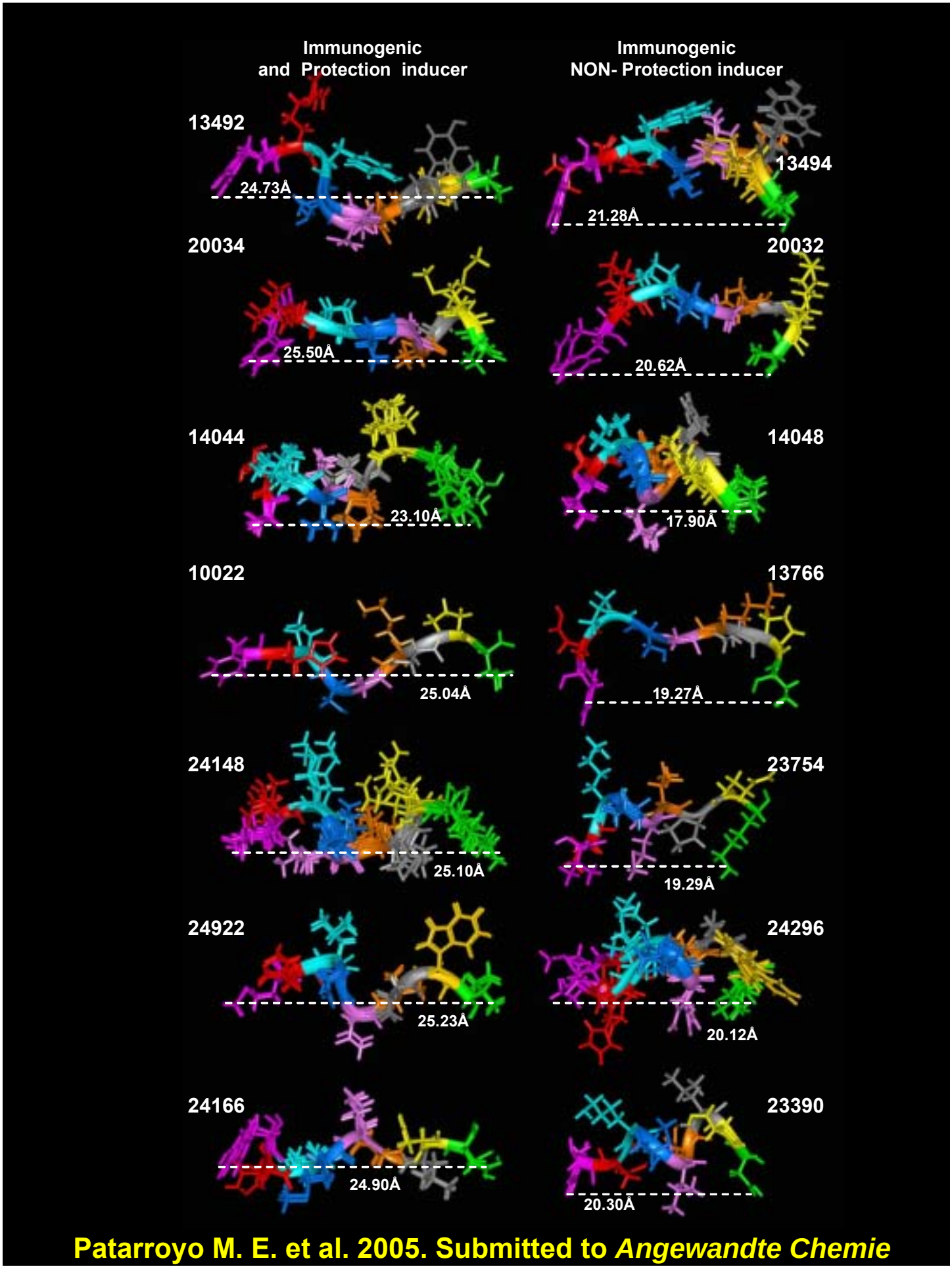
Immunogenic and Protection Inducer



Immunogenic and NON-Protection Inducer



Patarroyo M. E. et al. 2004, Submitted to *Science*



Patarroyo M. E. et al. 2005. Submitted to *Angewandte Chemie*

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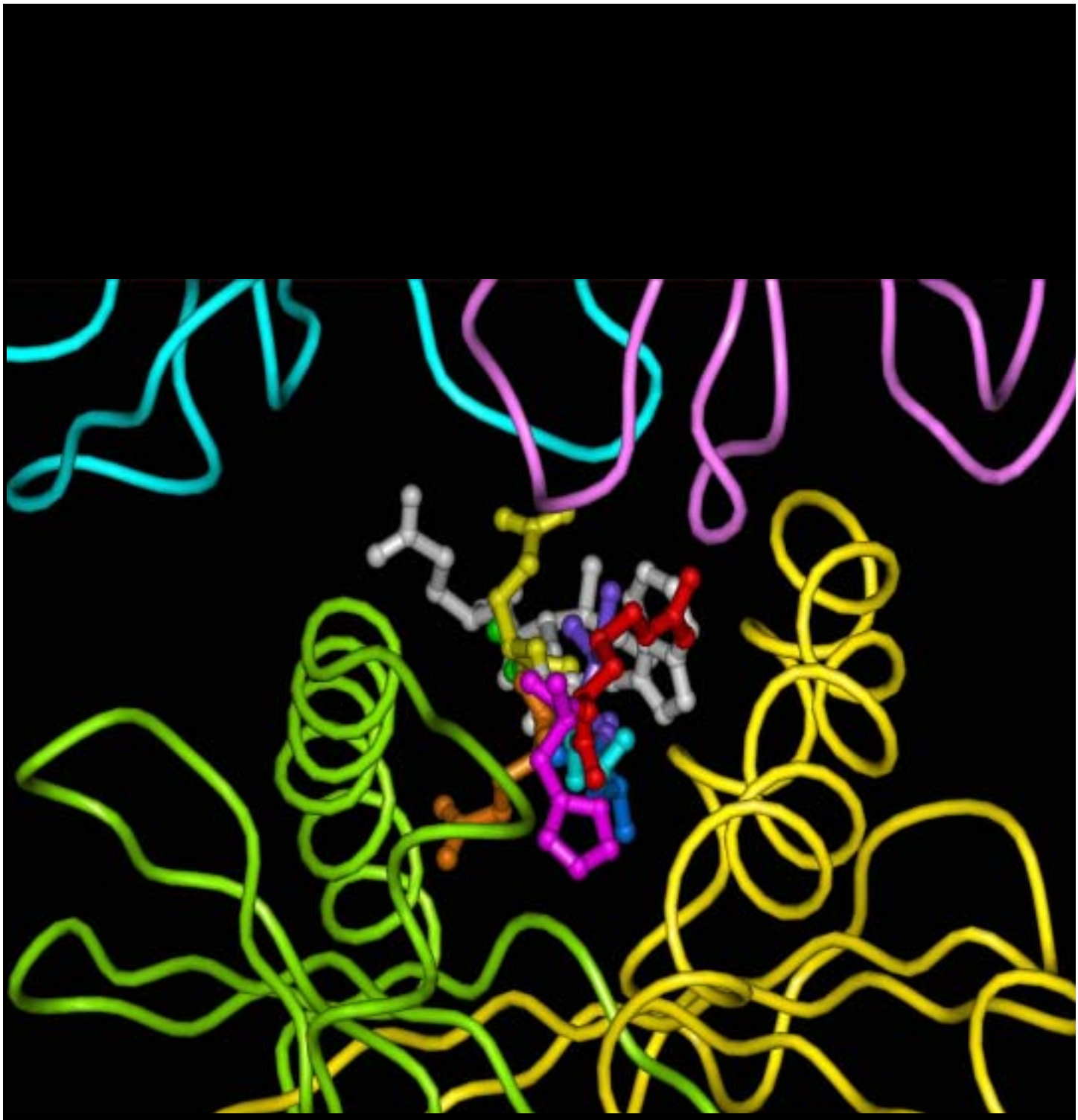

Reinherz E. L. et al., 1999 Science 286, 1973

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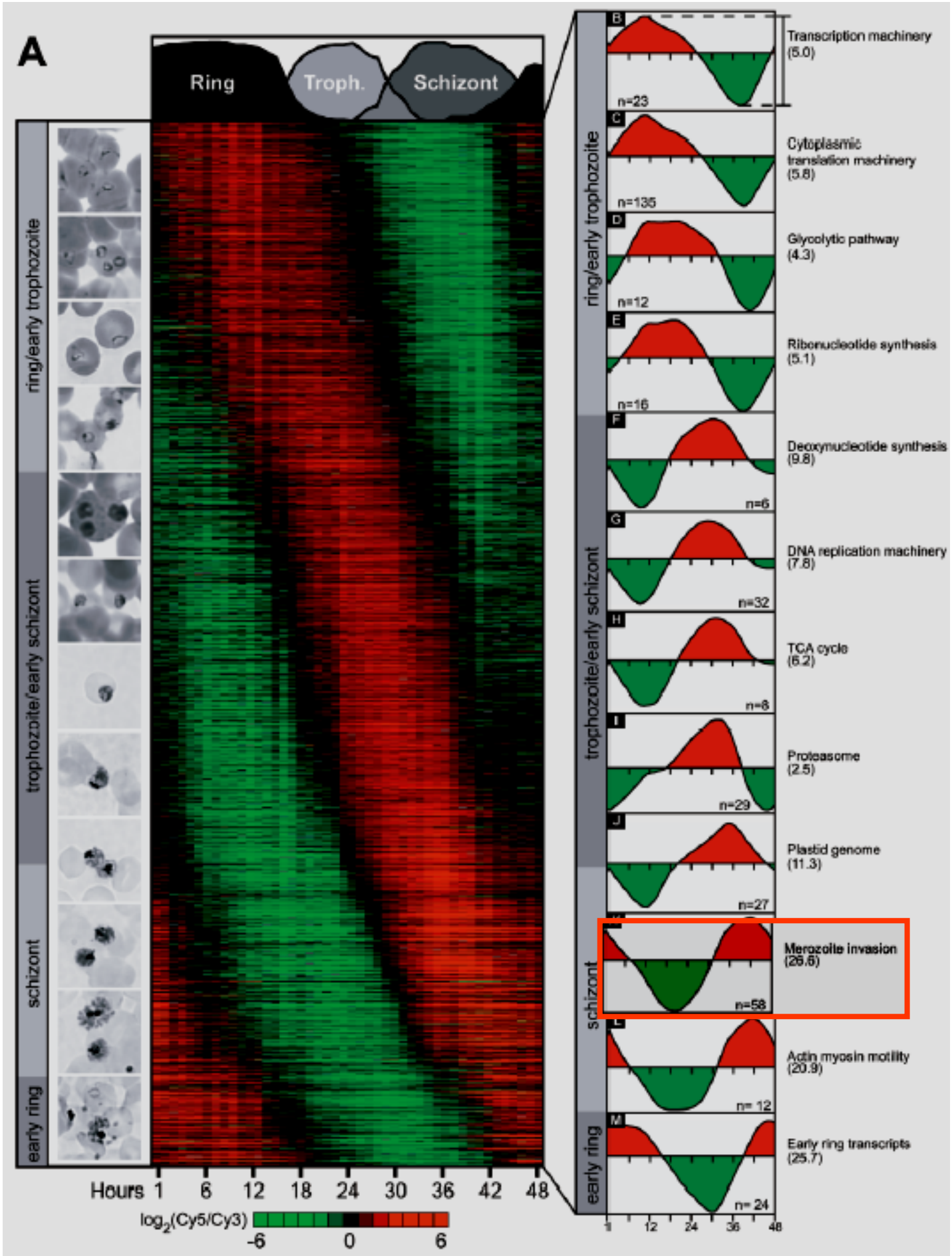
9 **Structural considerations together with affinity, biological and Immunological activities should guide the design of synthetic peptide vaccines.**

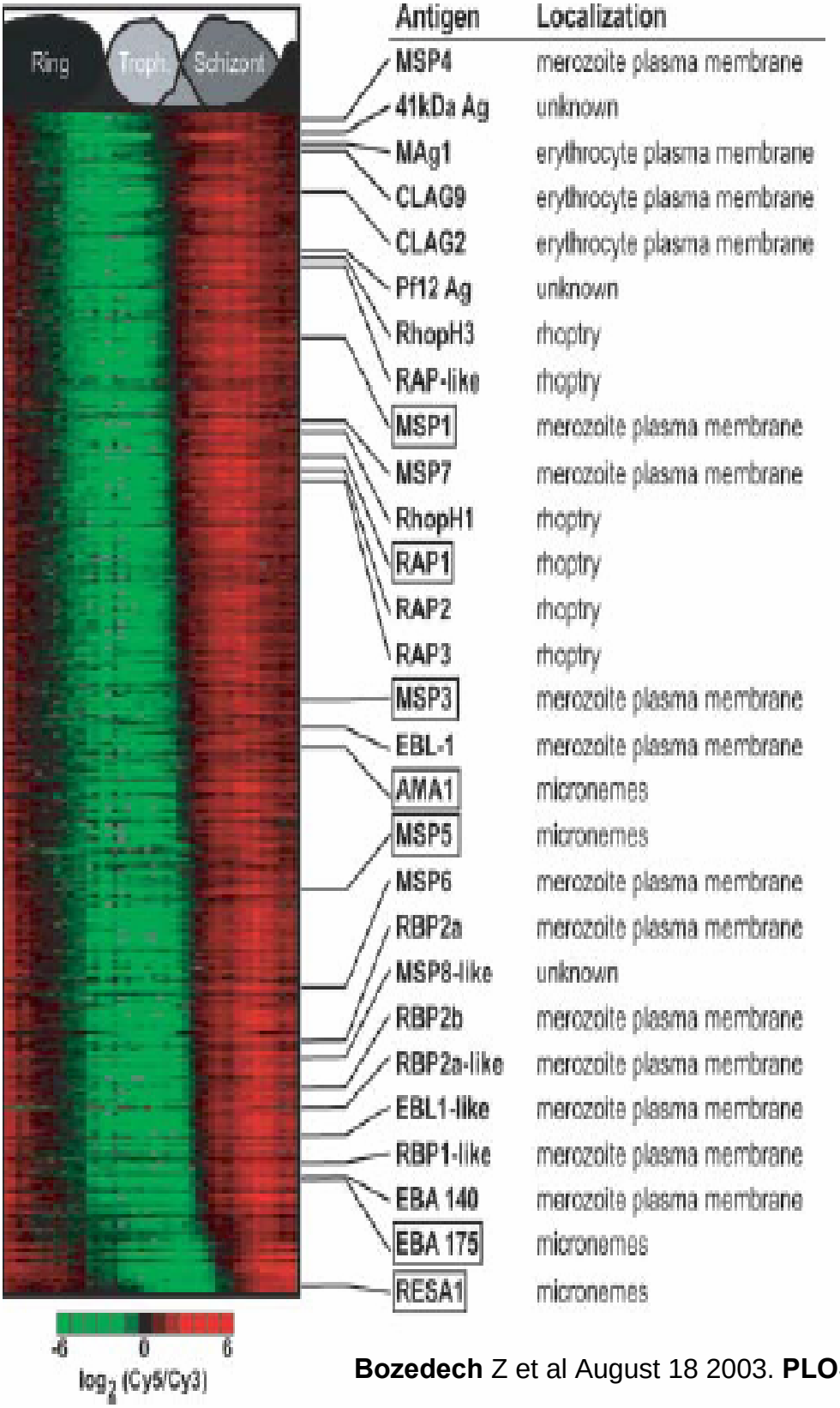
COLFAVAC®

PEP	SEQUENCE	HLA-DR
24148	MLNISMLQTVMMMTPQK	DR1
24150	WKSYSVDDNIPMNMSLIHKH	DR3
22812	NNDRIYDMNHLMIKMHILAI	DR4W4
22814	NDKLYRMEYWKTIKKDVW	DR12
24292	LTNQNINIDQEFNLMKHGFH	DR3
24166	FNNIPSRYNLYDKMLPLDD	DR11
23394	KKMNMHMENVIYIMKNQNLFK	DR12
24112	SKYSNTFNINAYNMVIRRSM	DR12
22782	GEDAEVAGTQWFVPSGKVPVFG	DR1
23406	MIKVSFDDTGAFMSDRYKSH	DR3
22822	HTTYSEEKRASHTTPVLKEK	DR11
24300	ATADYFRHLVTPQNLE	DR15
22720	TDVNRYRYVNNYESNPHK	DR4W10
23422	KETNNAISFMSNAGSLEKK	DR4W10
24096	DNIHVKMFKVIMNNDKSELI	DR12
24216	DQGNTITAMNRAAKFHLETI	DR4W14
23426	KKVQNLTGDDTADLATNIVG	DR3
24224	KSKKHMDLDGEMMMAKKLKD	DR3
24228	SAFDDNLTAMNAMGLILNKR	DR1
24239	VAFNRFHVGTHPAPGKTNLY	DR11
24244	VWDEWSFVSTAVAMGTRSRK	DR1
24246	SPTSVTVGKGAFSFKRE	DR1
24254	GAATPYSGEPSPFDEVLGEE	DR4W15
24310	HNMPNDDIRPVDEPANAN	DR4W13


A
Ring
Troph.
Schizont
ring/early trophozoite
trophozoite/early schizont
schizont
early ring
Hours 1 6 12 18 24 30 36 42 48
log2(Cy5/Cy3)
-6 0 6
B
Transcription machinery (5.0)
n=23
C
Cytoplasmic translation machinery (5.8)
n=135
D
Glycolytic pathway (4.3)
n=12
E
Ribonucleotide synthesis (5.1)
n=16
F
Deoxynucleotide synthesis (9.8)
n=6
G
DNA replication machinery (7.8)
n=32
H
TCA cycle (6.2)
n=8
I
Proteasome (2.5)
n=29
J
Plastid genome (11.3)
n=27
Merozoite invasion (26.6)
n=58
Actin myosin motility (20.9)
n= 12
M
Early ring transcripts (25.7)
n= 24
1 12 24 36 48

PHASEOGRAM OF PUTATIVE VACCINE TARGETS

FIDIC



Bozedech Z et al August 18 2003. **PLOS Biology** 1, 001

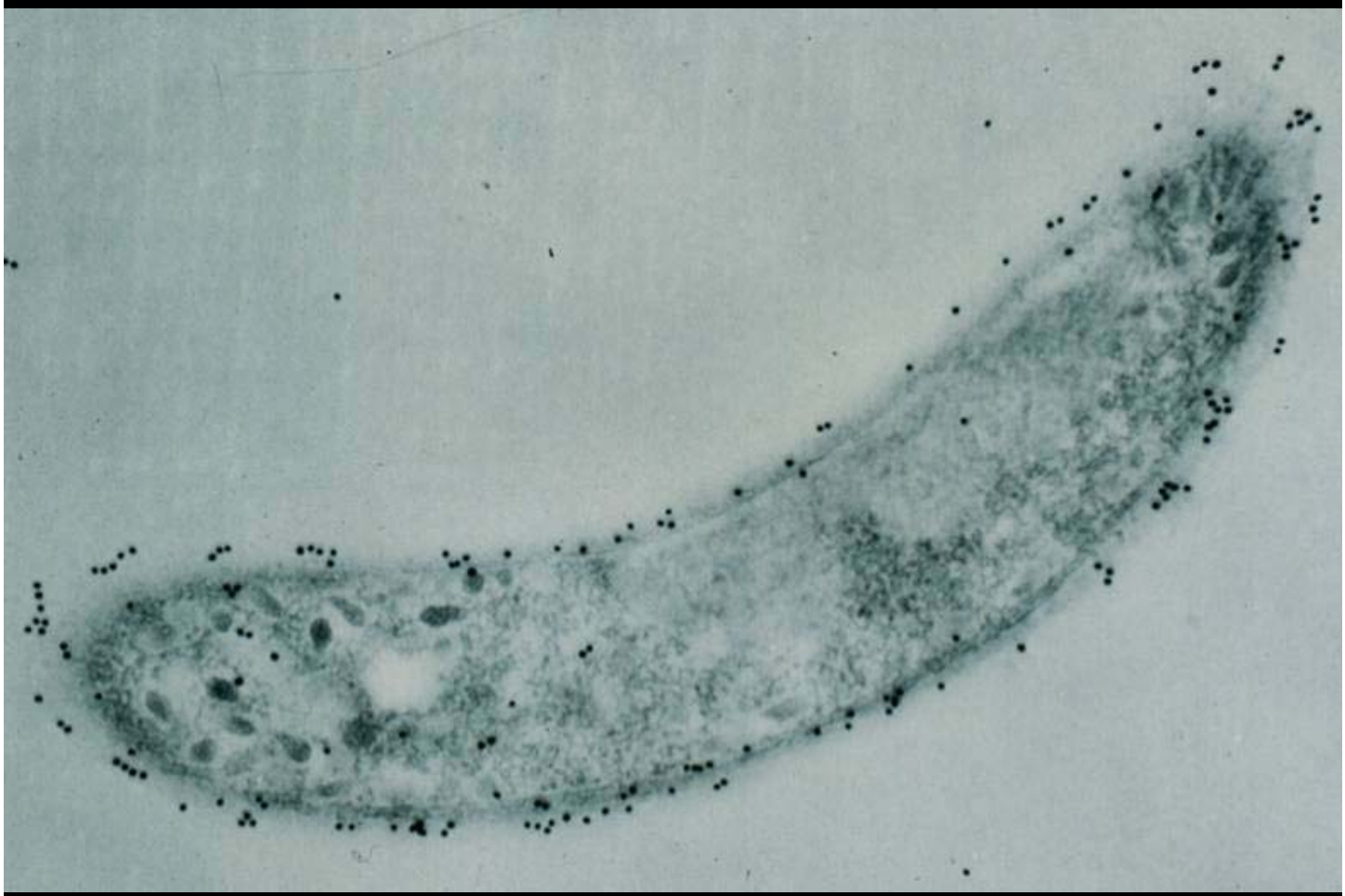
High RBC binding activity peptides

FIDIC

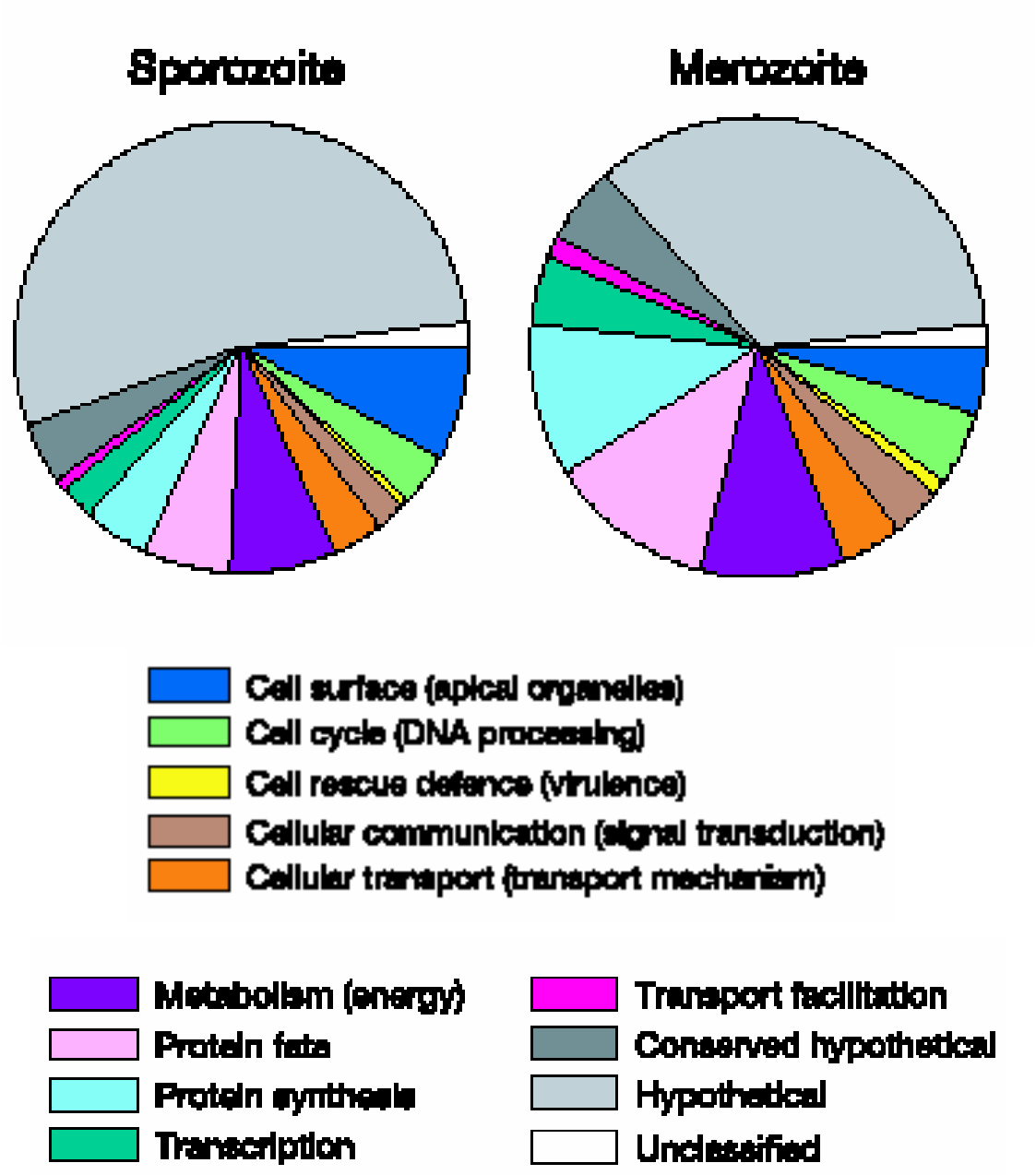
PROTEIN	C	V	Reference
MSP1	3	6	Urquiza M. *et. al* . 1996. *Parasite Immunology* . 18: 515-526
RESA	2	–	Vera R. *et al* . 2000. *Vaccine.* 18: 1289-1293
SERA	6	1	Puentes A. *et. al* . 2000. *Parasitology International.* 49: 105-117
MSA2	1	2	Ocampo M. *et. al* . *J. Peptide Research.* 55: 216-233
EBA175	6	–	Rodríguez L.E *et. al.* 2000. *Parasitology.* 120: 225-235
GBP130	1	–	Suárez J. *et. al* . 2000. *Mem. Inst. Oswaldo Cruz* . 95: 495-501
HRP I, II, II	3	1	López R. *et a* l. 2000. *Acta Tropica.* 75: 349-359
ABRA	5	–	Curtidor H. *et. al* . 2001. *Vaccine.* 19: 4496-4504
AMA1	4	3	Urquiza M. *et. al* . 2001. *Vaccine.* 19: 508-513
EBA140	6	–	Rodríguez L.E.. *et. al* . 2003. *J. Peptide Research.* 62: 175-184
NBP1	2	–	Valbuena J. *et al* . 2003. *Peptides* . 24: 1007-1014
MSP8	5	–	Puentes A. *et. al.* 2003. *Peptides* .24: 1015-1023
MAEBL	9	–	Ocampo M. *et al* . 2004. *Biochem. Biophys. Res. Comm. 315: 319-329*
RAP2	4	–	López R. *et al.* 2004. *Biochemie* . 86: 1-6
RBP2 Ha/Hb	9	3	Ocampo M. *et. al* . 2004. *Parasitol. Int.* 53: 77-88
RAP1	4	–	Curtidor H. *et. al* . 2004. *Vaccine* . 22: 1054-1062
EBA160	5	–	Valbuena J. et al. 2004. *Biochem. Biophys. Res. Comm* . 321: 835-844
CLAG3	5	–	Ocampo M. et. al. 2005. *Proteins Science* . 14: 504-513
EBL1	5	–	Curtidor H. *et. al.* 2005. *Protein Science* . 14: 464-473
JESEBL	5	–	Vera R. *et al* . 2004. *Biochemie. In press*
STEVOR	–	3	García J. *et al.* 2004. *Peptides. In press*
MSP10	3	–	Puentes A. *et al* . 2004. *Biochemie. In press*
MSP3	3	–	Rodríguez L.E. *et. al.* 2004. *Submitted to Protein Science*
SORTILIN	6	–	Vera R. *et al.* 2004. *Submitted to Biochemistry*
RESA-LIKE	3	–	Rodríguez L.E. *et. al.* 2004. *Submitted to J. Int. Parasitol.*
TryThrA	4	–	Curtidor H. *et. al.* 2004. *Submitted to Chembiochem*
HAP	2	–	Valbuena J. *et. al* . 2004. *Submitted to Biol. Chem.*
MSP6	2	1	López R. *et al.* 2004. *Submitted to Peptides*

C : CONSERVED

V: VARIABLE



Functional profile of proteins expressed in different *P. falciparum* life-cycle stages



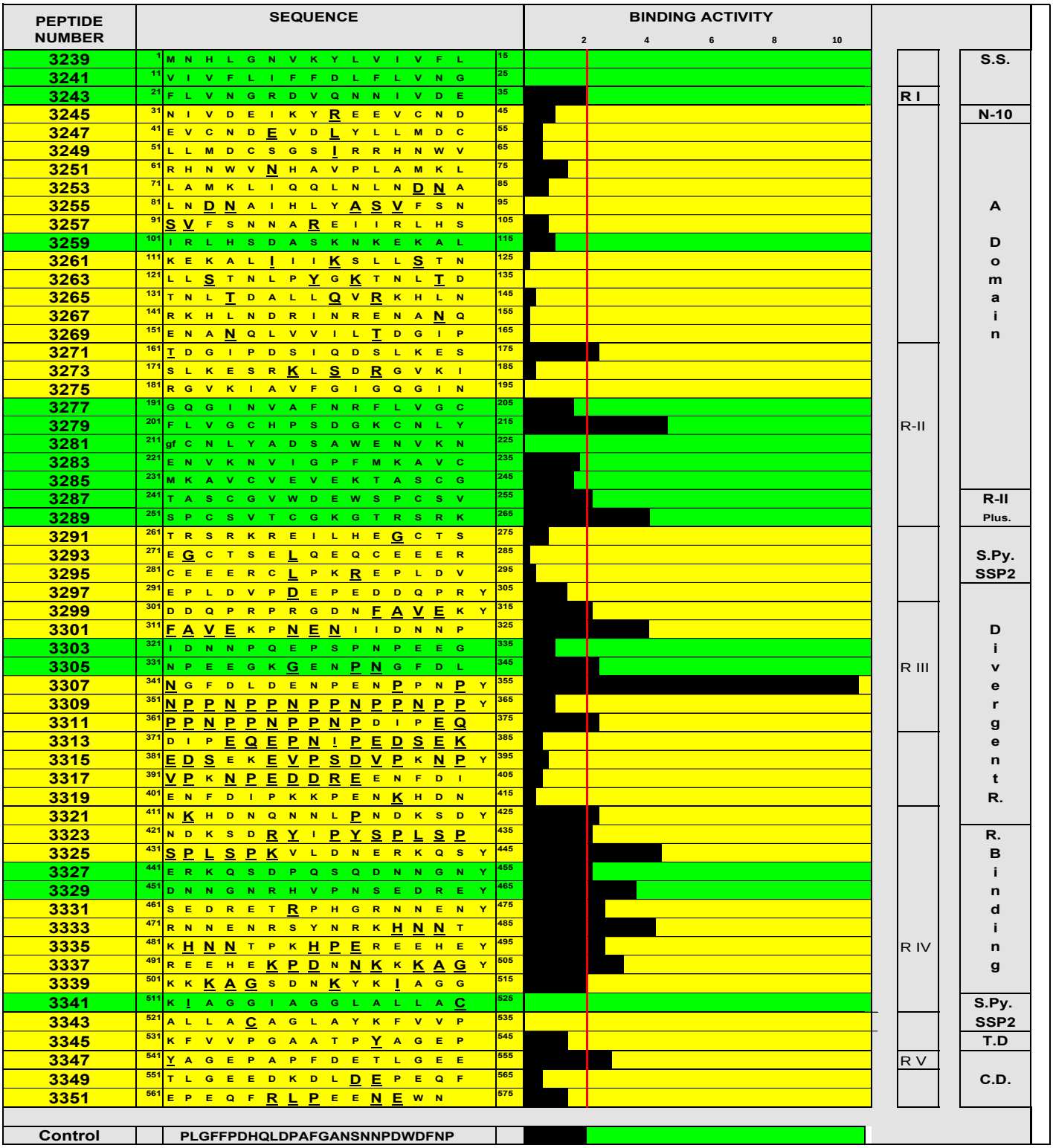
Plasmodium sporozoite surface and/or apical organelle proteome

Protein	Other stages	Subcellular Localization	Conserved pep
Cs	-	Surface	2
TRAP	-	Surface, micronemes	7
STARP	RBC, LS	Surface	5
SALSA	RBC, LS	Surface	2
LSA3	LS	Surface	11
LSA1	LS		1
EBA175	Mz	Surface, micronemes	
AMA1	Mz	Surface, micronemes	
MAEBL	-	Surface, micronemes	
MCP1	MZ	?	
PEMP3	RBC, LS	Surface	
SPATR	RBC	Surface	
PfEMP1	¡RBC		
STEVOR	¡RBC		
RIFINS	¡RBC		
P52	-	?	
P235	Mz		
PPLP1	-	Micronemes	
SPECT	-	Micronemes	

Adapted of :Baldacci P et al. 2004 ***Mol. Microbiol***. 54:298

Plasmodium falciparum binding studies Of peptide derived from the sporozoite surface protein 2 to Hep G2 cell

Ramsés López *et al* 2001**, J. Pept. Res**, 58: 285



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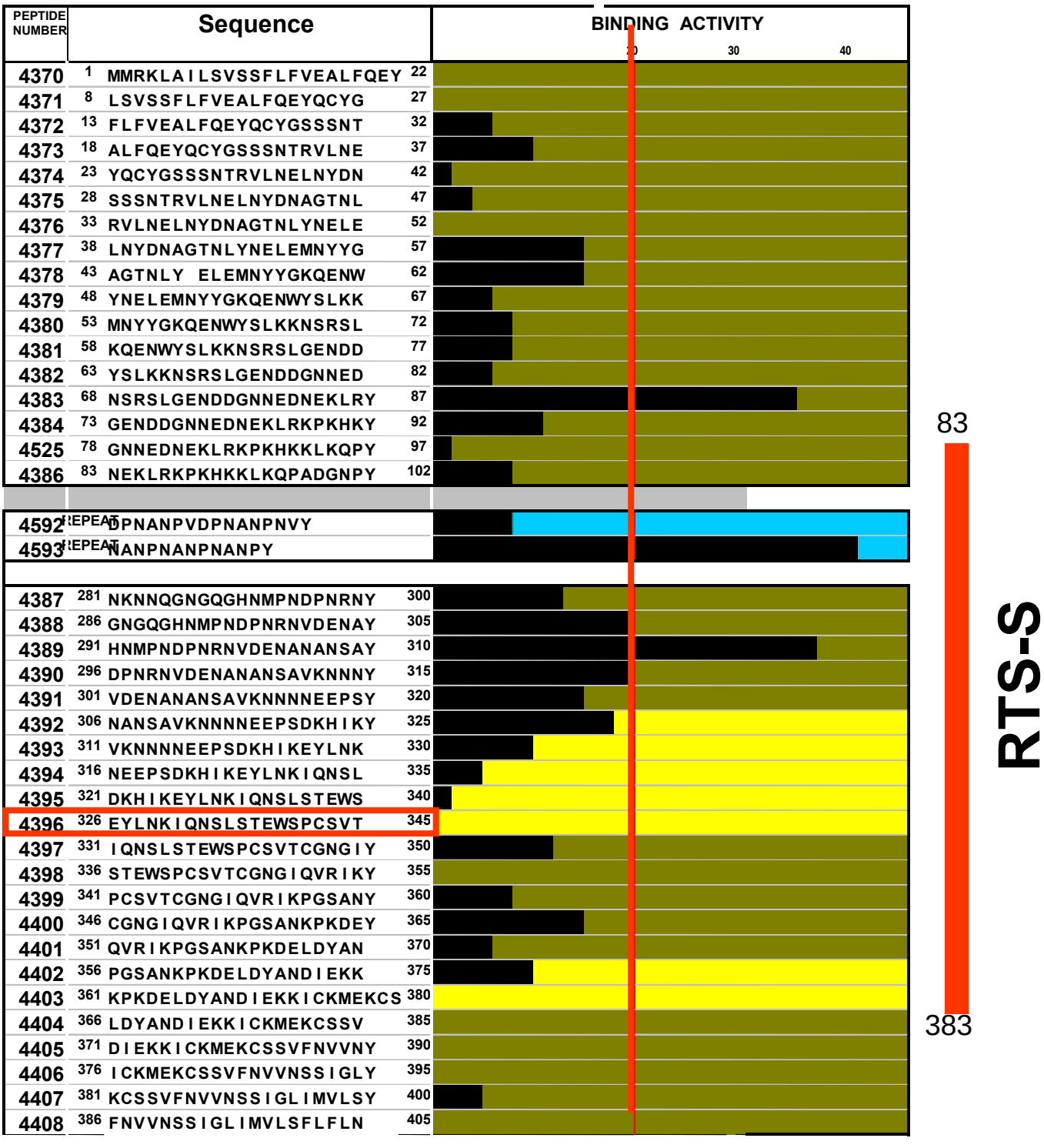
Vaccine 19 (2001) 4487–4495

Vaccine

Plasmodium falciparum circumsporozoite (CS) protein peptides specifically bind to HepG2 cells

Jorge E. Suarez *, Mauricio Urquiza, Alvaro Puentes, Javier E. Garcia, Hernando Curtidor, Marisol Ocampo, Ramses Lopez, Luis E. Rodriguez, Ricardo Vera, Marcia Cubillos, Maria H. Torres, Manuel E. Patarroyo



Polimorphic sequence found in different *P. falciparum* isolates Corresponding to amino acids 326 to 345 Of the NF54 *P. falciparum*

Moreno A. et al. 1993 **J Immunol**. 151:489.

Isolates	Origin	Sequence
NF54,$XP_{8,9}$, $X_{10,11}$,$427_{1-4,6-10}$ 3D7	Wets Africa, Honduras, The Netherlands	**E Y L N K I Q N S L S T E W S P C S V T**
ltG2G1	Brazil	**K K**
MS2,SO6	Thailand, Brazil	**K K R**
LE5, 366_{9}	Liberia, Gambia	**K K T**
366_{t}, 399_{1-10}, 406_{1-9}, 419_{10}	Gambia	**K K T K**
$366_{8,10}$	Gambia	**K Q**
406_{10}, 419_{1-9}	Gambia	**K Q K**
366_{2-7}	Gambia	**K Q R**
Xs,$XP_{12,13}$ HB3, D10, T4, T9-101, WEL, B11, PA, FCR3	Honduras, The Netherlands, Papua New Guinea, Thailand, West Africa, Uganda, Gambia	**Q K**
S24, T9-98	Angola, Thailand	**Q K T K**
7G8	Brazil	**Q K K I**

[a]Amino acids numbering is based on the CS protein of the NF54 strain of *P. falciparum* . The polimorphic residues are underline, and only amino acids that differ from the NF54 sequence are shown for each strain or isolate. The subscript numbers correspond to the isolate name described in materials and methods

SOME OTHER VACCINES IN PROGRESS AT FIDIC

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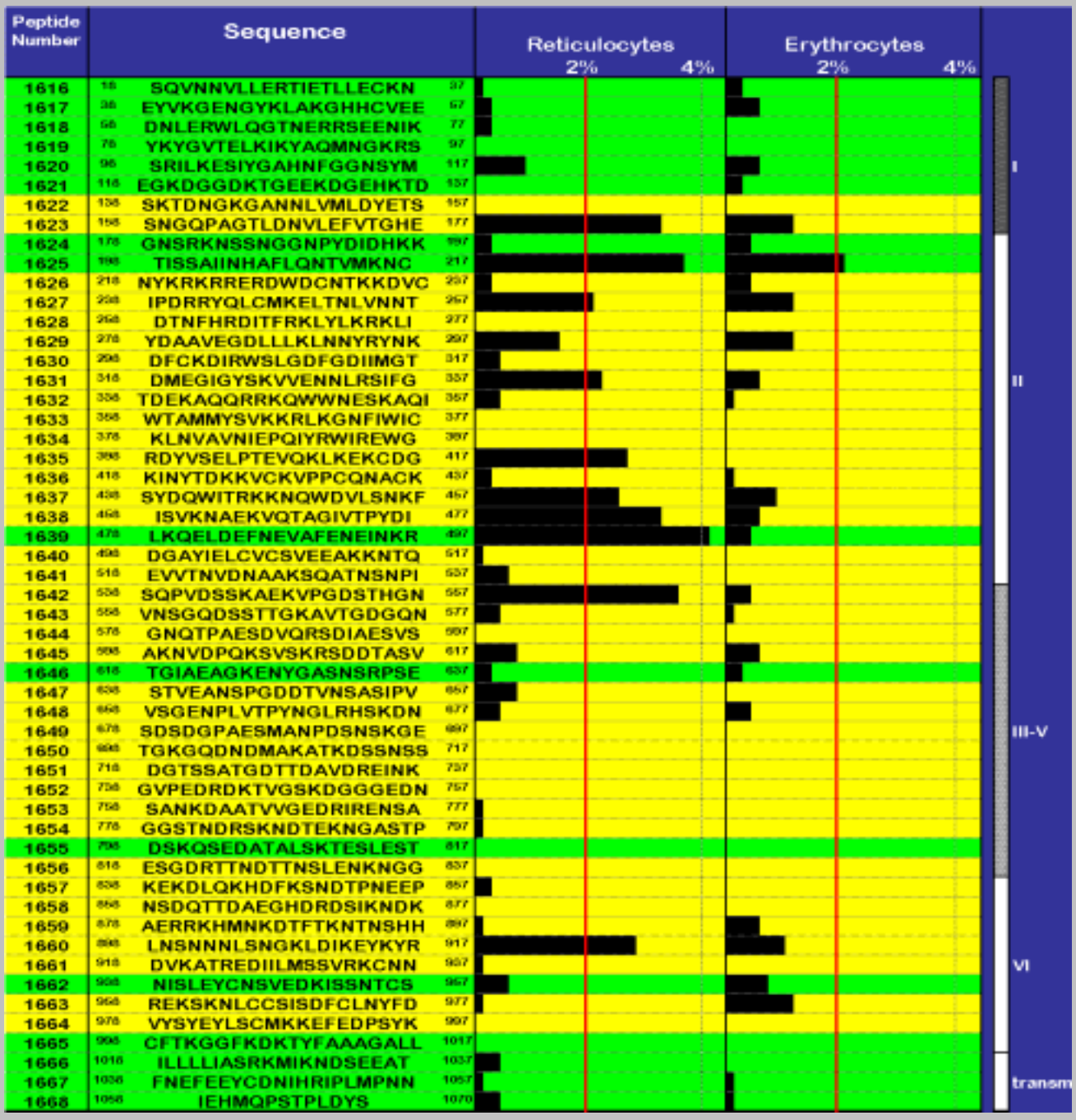
PEPTIDES

Peptides 23 (2002) 13–22

Plasmodium vivax Duffy binding protein peptides specifically bind to reticulocytes

Marisol Ocampo*, Ricardo Vera, Luis Eduardo Rodriguez, Hernando Curtidor, Mauricio Urquiza, Jorge Suarez, Javier Garcia, Alvaro Puentes, Ramsés Lopez, Mary Trujillo, Elizabeth Torres, Manuel Elkin Patarroyo



Available online at www.sciencedirect.com
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Vaccine xxx (2003) xxx–xxx
Vaccine
www.elsevier.com/locate/vaccine

A highly infective *Plasmodium vivax* strain adapted to *Aotus* monkeys Quantitative haematological and molecular determinations useful for *P. vivax* malaria vaccine development

Yago Pico de Coaña[a], Josefa Rodríguez[a], Eduar Guerrero[a], Carlos Barrero[a], Raúl Rodríguez[a], Marcela Mendoza[b], Manuel Alfonso Patarroyo[a,*]

Experimental Parasitology 100 (2002) 131–134
Experimental Parasitology
www.academicpress.com

Research Brief

Plasmodium vivax: parasitemia determination by real-time quantitative PCR in *Aotus* monkeys

Juan Carlos Polanco, Josefa Antonia Rodríguez, Vladimir Corredor, and Manuel Alfonso Patarroyo*

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Vaccine 21 (2003) 4133–4144
Vaccine
www.elsevier.com/locate/vaccine

Review

Splenectomised and spleen intact *Aotus* monkeys' immune response to *Plasmodium vivax* MSP-1 protein fragments and their high activity binding peptides

Adriana Yanett Sierra, Carlos Alberto Barrero, Raul Rodriguez, Yolanda Silva, Camilo Moncada, Magnolia Vanegas, Manuel Alfonso Patarroyo*

Carrera 50B 26-00, Fundación Instituto de Inmunología de Colombia, Bogotá, Colombia

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CYTOKINE

www.elsevier.com/locate/jnlabr/ycyto

Cytokine ■■ (2004) ■■■–■■■

Quantifying *Aotus* monkey cytokines by real-time quantitative RT-PCR

Yago Pico de Coaña[a,b], Carlos Barrero[a], Isabela Cajiao[a], Catalina Mosquera[a], Manuel Elkin Patarroyo[a,c], Manuel Alfonso Patarroyo[a,c,*]

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[b]*Pontificia Universidad Javeriana, Bogotá, Colombia*
[c]*Universidad Nacional de Colombia, Bogotá, Colombia*

Received 27 October 2003; received in revised form 12 April 2004; accepted 15 April 2004

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Vaccine 21 (2003) 1033–1043

Vaccine

www.elsevier.com/locate/vaccine

Expression, polymorphism analysis, reticulocyte binding and serological reactivity of two *Plasmodium vivax* MSP-1 protein recombinant fragments

Ana María Espinosa, Adriana Yanett Sierra, Carlos Alberto Barrero, Libia Alexandra Cepeda, Elvia María Cantor, Tania Bibiana Lombo, Fanny Guzmán, Sandra Julieta Avila, Manuel Alfonso Patarroyo*

Fundación Instituto de Inmunología de Colombia, Bogotá, Colombia

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M.A. Patarroyo

Characterizing T-cell receptor γ-variable gene in *Aotus nancymaae* owl monkey peripheral blood

Received 10 May 2003, revised 19 June 2003, accepted for publication 15 July 2003

Tissue Antigens.

Tissue Antigens 2003 **62:** 472–482

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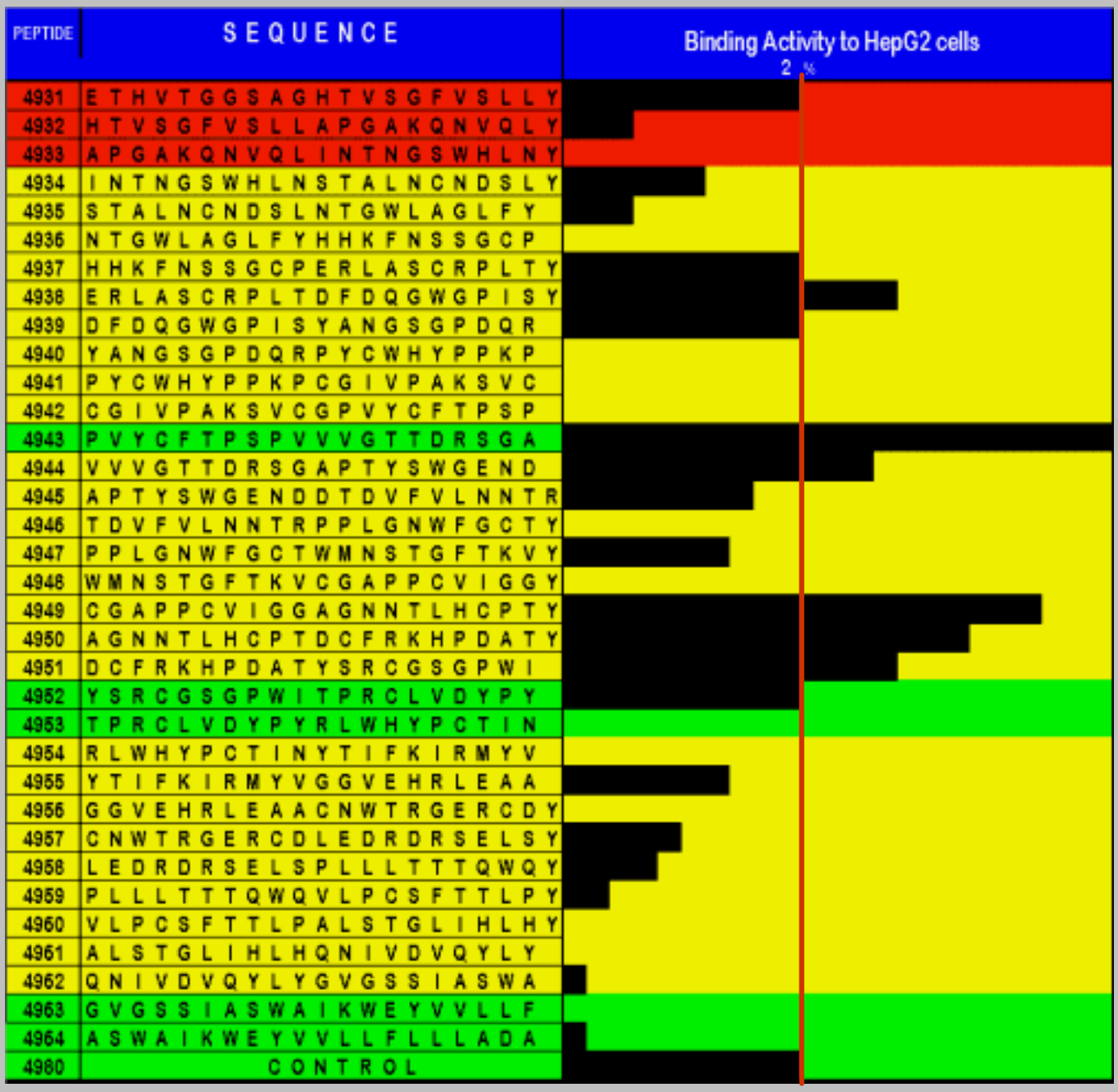
Journal of Hepatology 36 (2002) 254–262

Journal of Hepatology

www.elsevier.com/locate/jhep

Hepatitis C virus (HCV) E1 and E2 protein regions that specifically bind to HepG2 cells

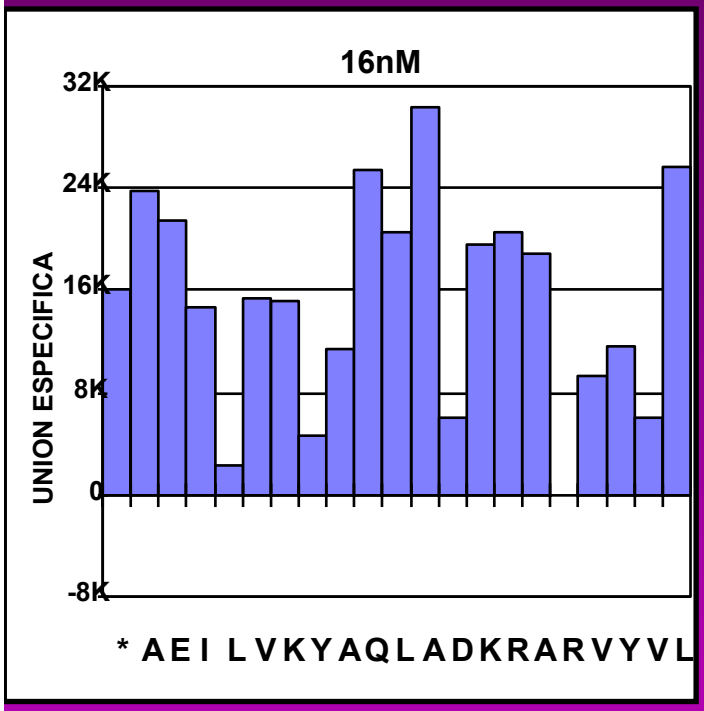
Javier Eduardo Garcia*, Alvaro Puentes, Jorge Suárez, Ramses López, Ricardo Vera, Luis Eduardo Rodríguez, Marisol Ocampo, Hernando Curtidor, Fanny Guzmán, Mauricio Urquiza, Manuel Elkin Patarroyo

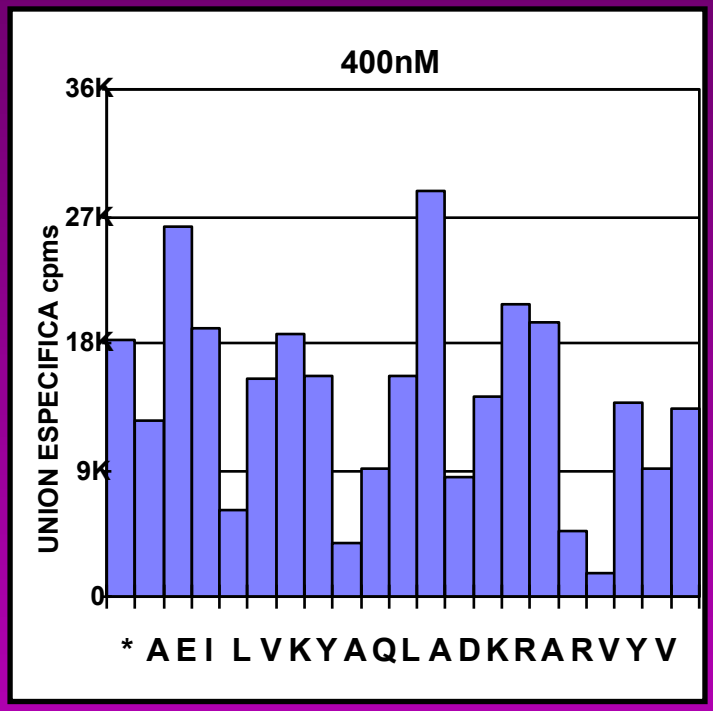


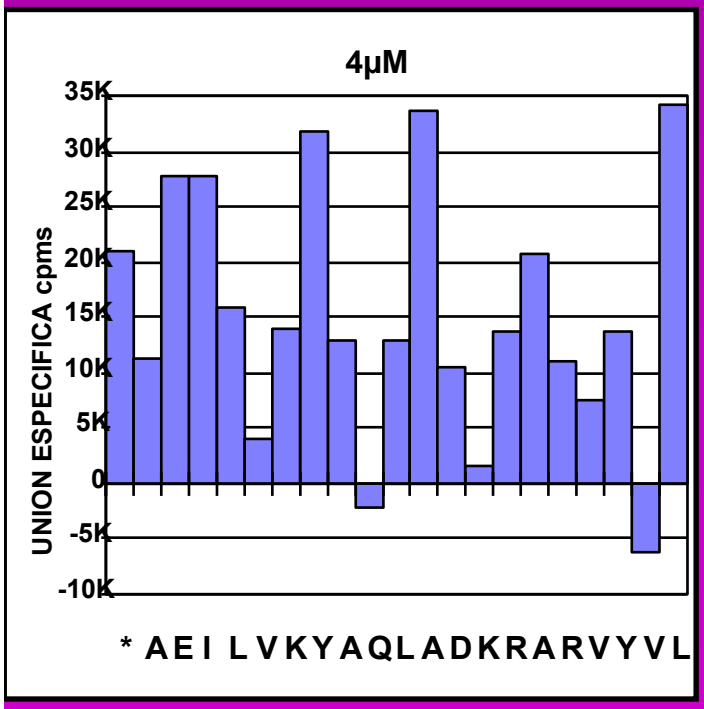
PERFIL DE UNION DE PEPTIDOS DERIVADOS DEL CLON MTCY04C12.18c DE M. *tuberculosis*

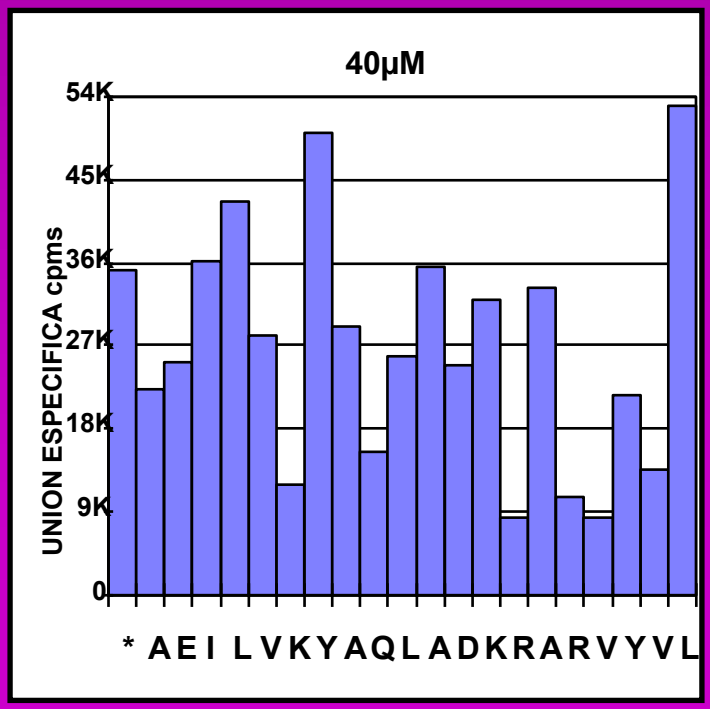
PEPTIDO		SEQUENCE		1%
11175	1	MI ATTRDREGATMI TFRLRLY	20	
11176	21	PCRTI LRVFSRNPLVRGTDRY	40	
11177	41	LEAVVMLLAVTVSLLTI PFAY	60	
11178	61	AAAGTAVQDSRSHVYAHQAQ	80	
11179	81	TRHPATATVI DHEGVI DSNTY	100	
11180	101	TATSAPPRTKI TVPARWVNY	120	
11181	121	GI ERSGEVNAKPGTKSGDRVY	140	
11182	141	GI WWDSAGQLVDEPAPPARAY	160	
11183	161	I ADAALAALGLWLSVAAVAGY	180	
11184	181	ALLALTRAI LI RVRNASWQHY	200	
11185	191	I RVRNASWQHDI DSLFCTQRY	210	

MYCOBACTERIUM TUBERCULOSIS: ANALOGOS DEL PEPTIDO 11060 DE LA PROTEINA PUTATIVA DE MEMBRANA MTCY277.12



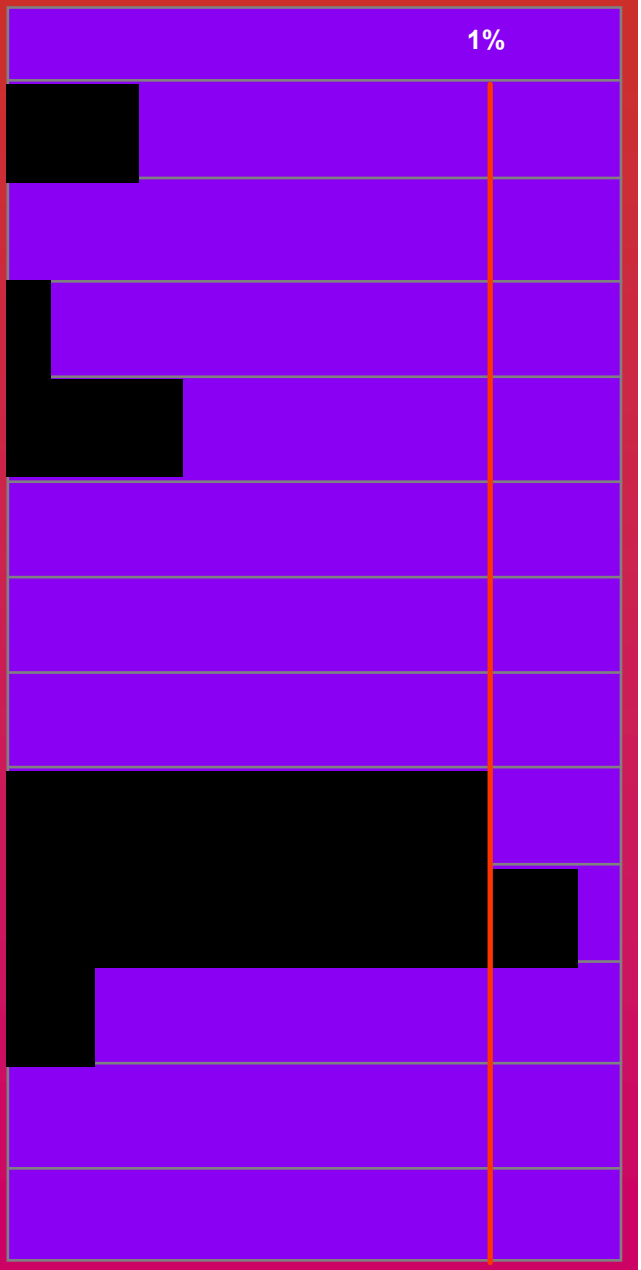




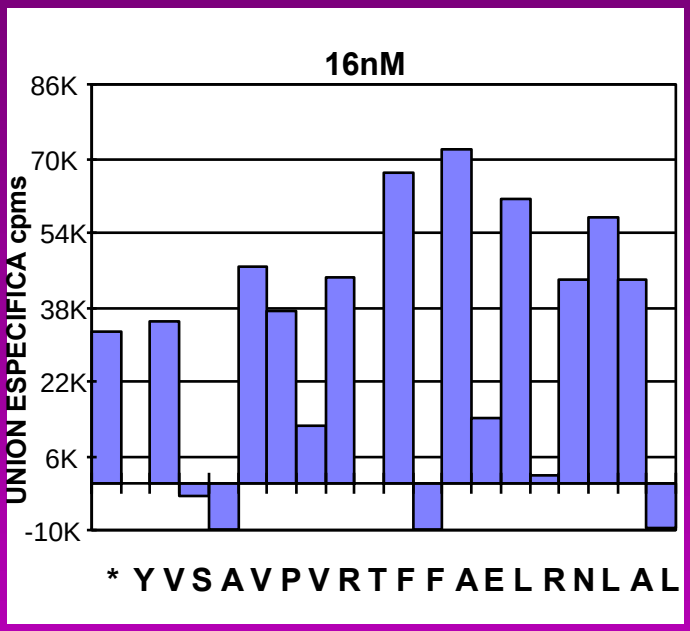


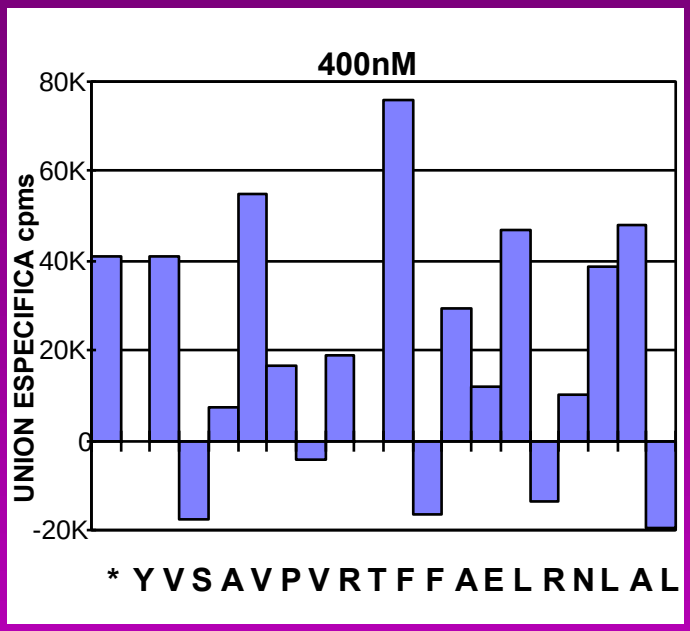
PERFIL DE UNION DE PEPTIDOS DERIVADOS DEL CLON MTCY159.20c DE M. *tuberculosis*

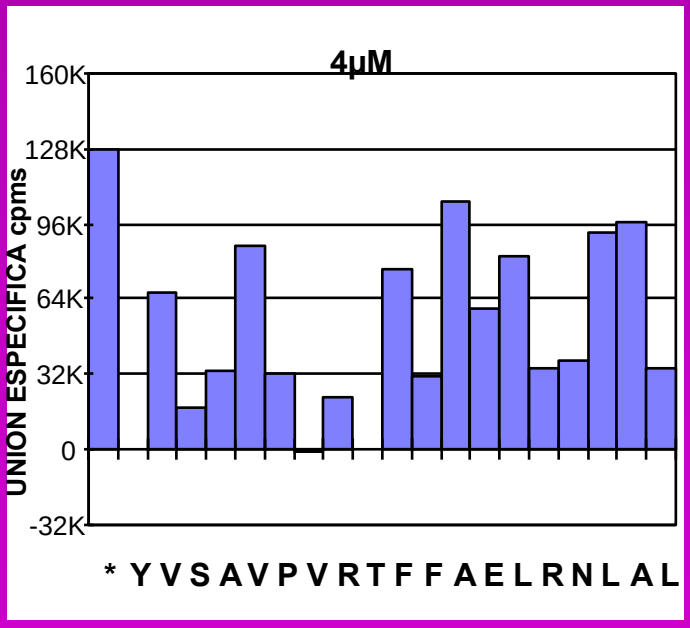
PEPTIDO	SEQUENCE	
11199	1 MTNWMLRGLAFAAAMVVLRL	20
11200	21 FQGALINAWQMLSGLISLVL	40
11201	41 LLLFAIGGVVWGVMDGRADA	60
11202	61 KASPDPDRRQDLAMTWLLAGY	80
11203	81 LVAGALSGAVAWLISLFYKA	100
11204	101 IYTGGPINELTTFAAFTALI	120
11205	121 VFLVGIVGVAVGRWLVDRQLY	140
11206	141 AKAPVRHHGLAAEHERAADTY	160
11207	161 DVFSAVRADDSPTGEMQVAQY	180
11208	181 PEAQTAAVATVEREAPTEVIY	200
11209	201 RTTESDTPTEVIRTDTEADQY	220
11210	211 VIRTDTEADQTKPGDEPKKDY	230

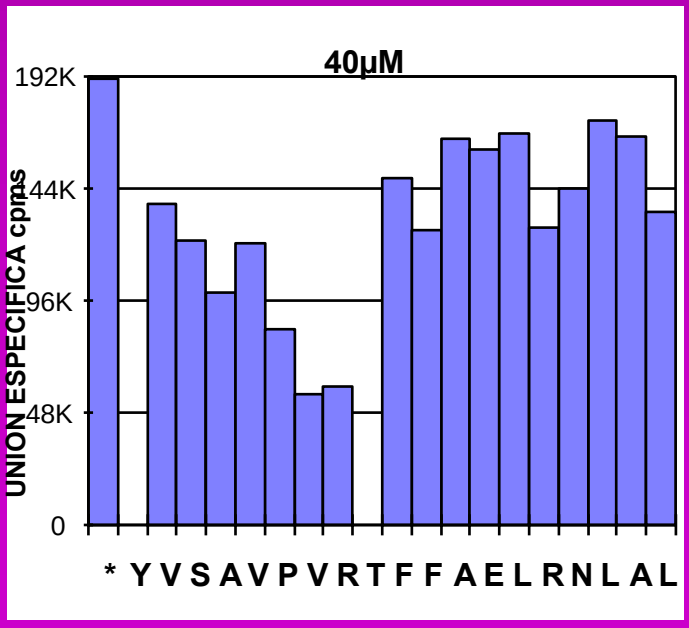


MYCOBACTERIUM TUBERCULOSIS: ANALOGOS DEL PEPTIDO 11076 DE LA PROTEINA PUTATIVA DE MEMBRANA MTCY277.12

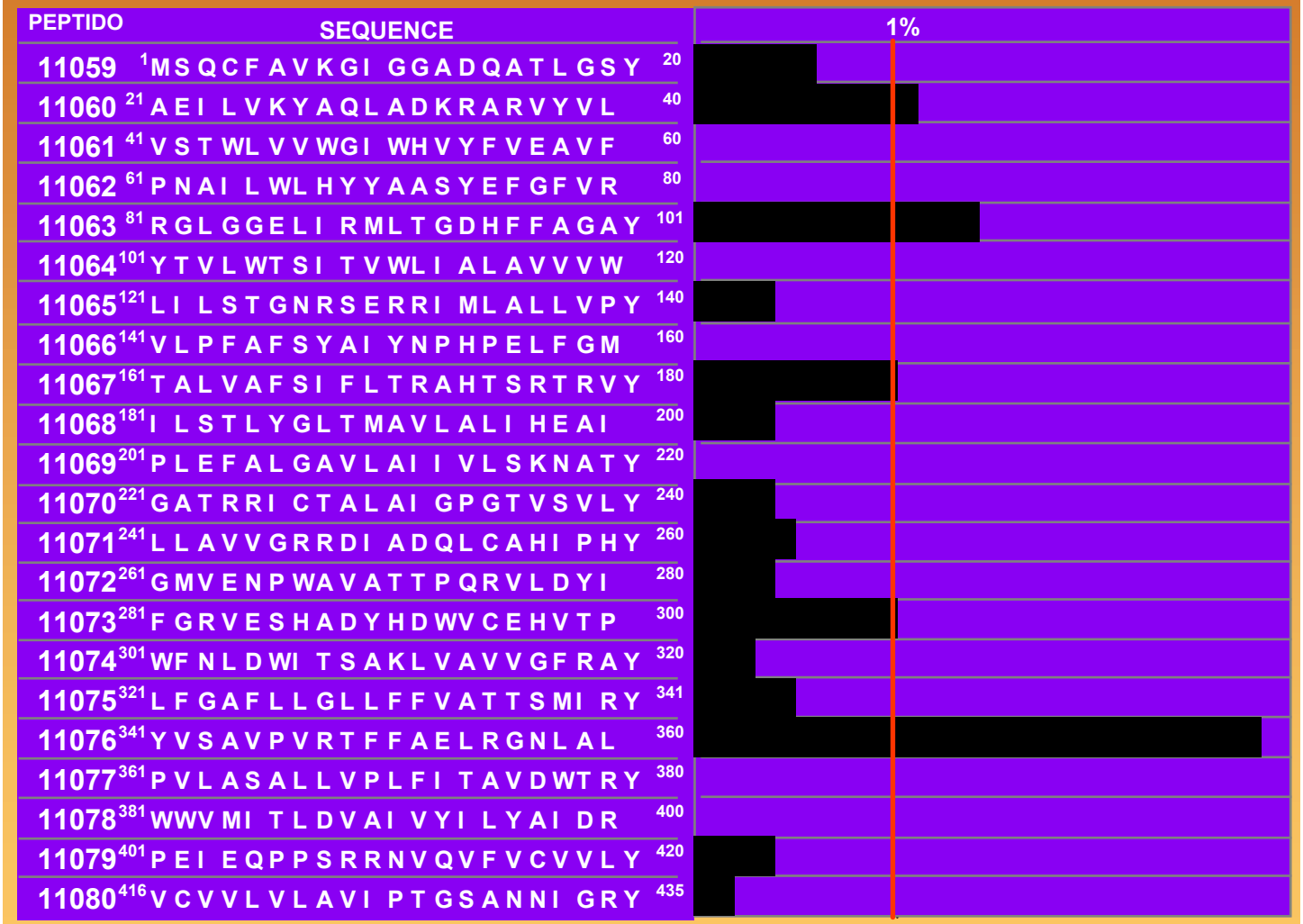




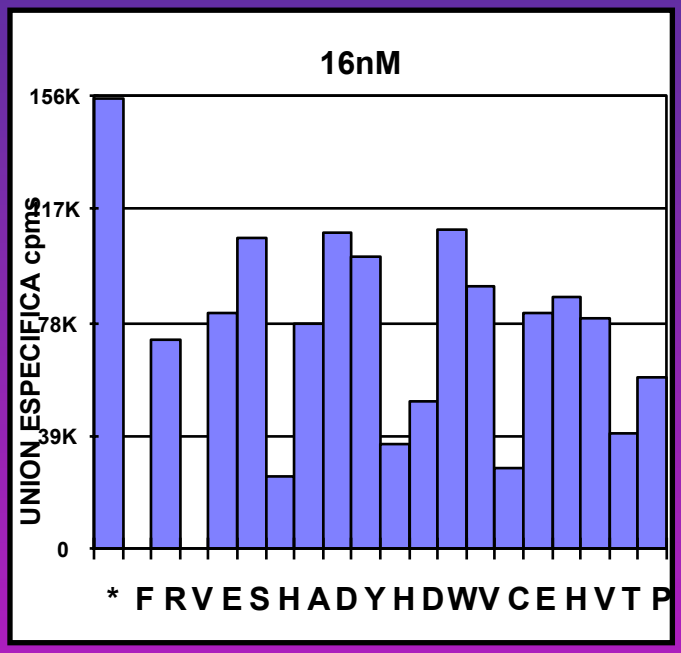


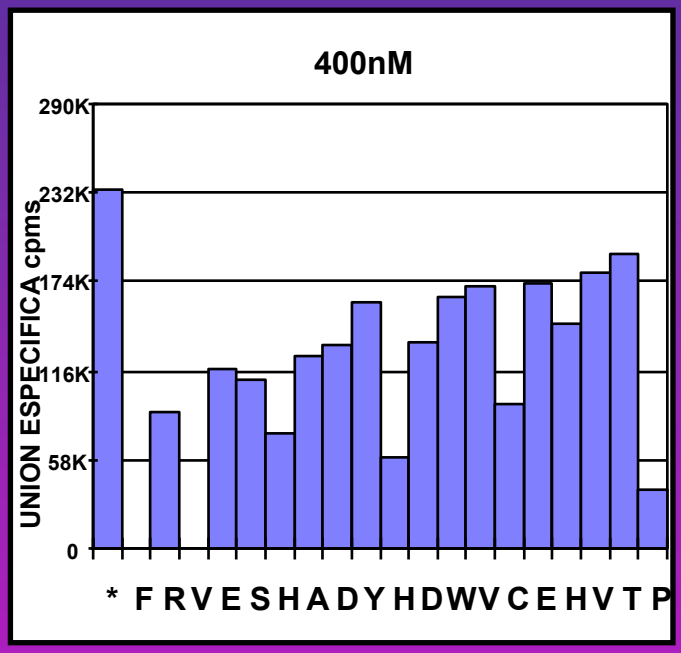


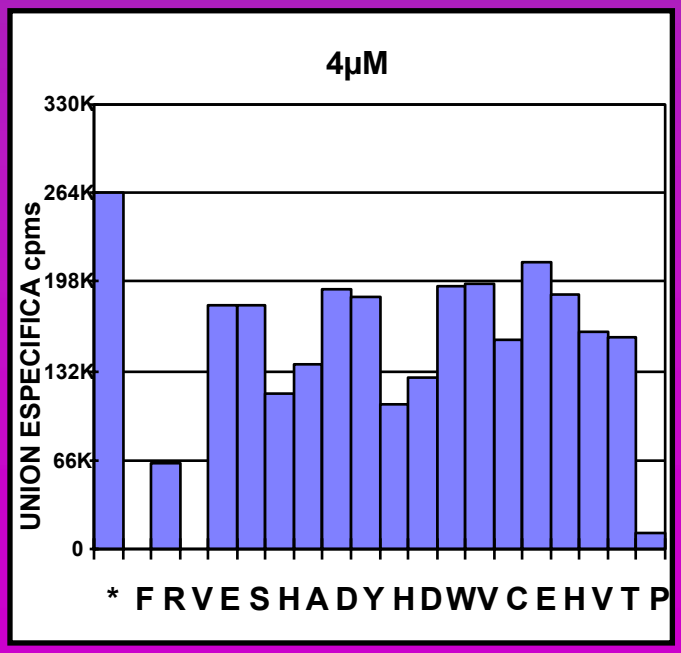
PERFIL DE UNION DE PEPTIDOS DERIVADOS DEL CLON MTCY277.12 DE M. *tuberculosis*

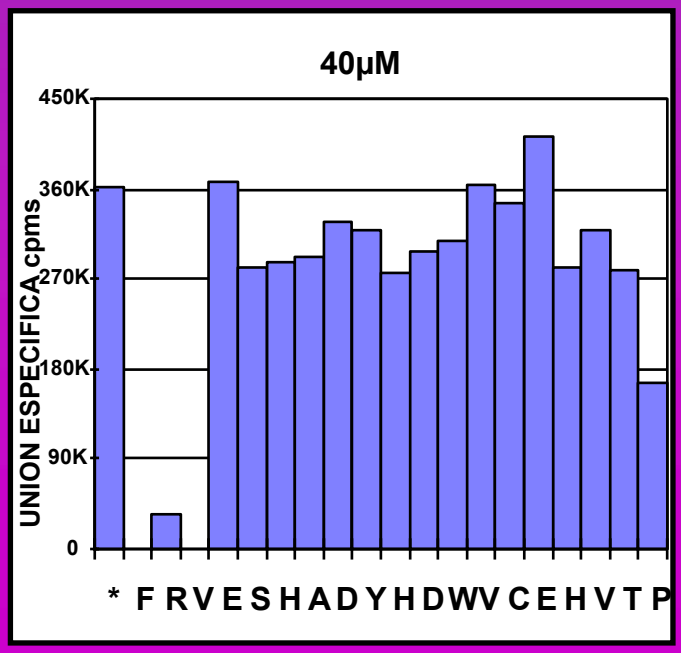


MYCOBACTERIUM TUBERCULOSIS: ANALOGOS DEL PEPTIDO 11073 DE LA PROTEINA PUTATIVA DE MEMBRANA MTCY277.12









Int. J. Cancer: **107**, 416–424 (2003)

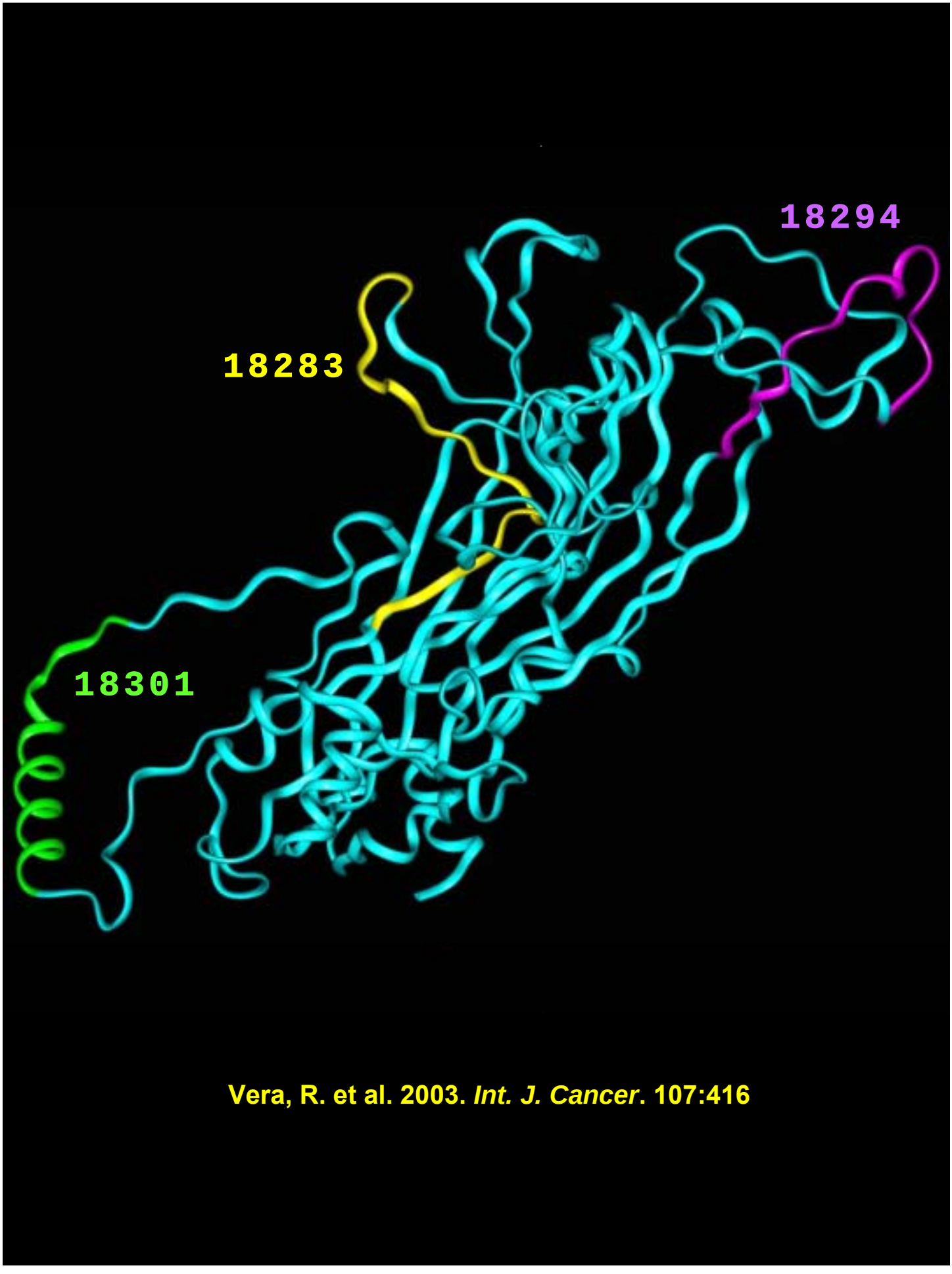
Publication of the International Union Against Cancer

HUMAN PAPILLOMAVIRUS TYPE 16 AND 18 L1 PROTEIN PEPTIDE BINDING TO VERO AND HELA CELLS INHIBITS THEIR VLPS BINDING

Ricardo Vera-Bravo, Marisol Ocampo, Mauricio Urquiza, Javier E. García, Luis E. Rodríguez, Alvaro Puentes, Ramses López, Hernando Curtidor, Jorge E. Suárez, Elizabeth Torres, Fanny Guzmán, Diana Díaz, Jimena Cortes, María M. Bravo, Alba L. Cómbita, Oscar Orozco and Manuel E. Patarroyo*

Fundación Instituto de Inmunologia de Colombia, Instituto Nacional de Cancerología and Universidad Nacional de Colombia, Bogotá, Colombia

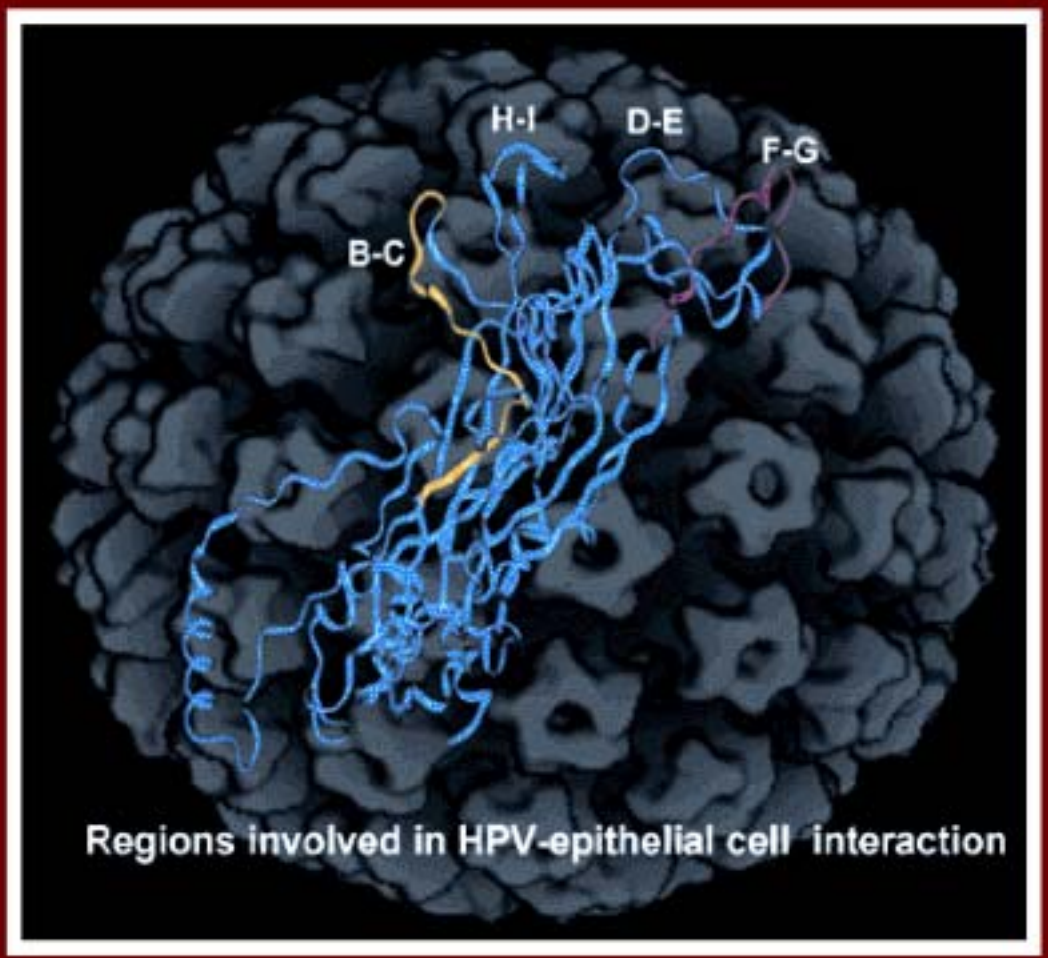
PEPTIDE NUMBER		SEQUENCE		High Specific Binding Activity (VERO CELLS) 2	High Specific Binding Activity (HeLa CELLS) 2
18306	1	MCLYTRVLILHYHLLPLYGP	20		
18307	21	LYHPRPLPLHSILVYMVHII	40		
18308	41	ICGHYILFLRNVNVFPIFLI	60		
18309	61	QMALWRPSDNTVYLPPPSVA	80		
18310	81	RVVNTDDYVTPTSIFYHAGS	100		
18311	101	SRLLTVGNPYFRVPAGGGNK	120		
18312	121	**QDIPKVSAYQYRVFRVQLPD**	140		
18313	141	PNKFGLPDTSIYNPETQRLV	160		
18314	161	WACAGVEIGRGQPLGVGLSGY	180		
18315	181	HPFYNKLDDTESSHAATSNV	200		
18316	201	SEDVRDNVSVDYKQTQLCIL	220		
18317	221	GCAPAIGEHWAKGTACKSRPY	240		
18318	241	LSQGDCPPLELKNTVLEDGDY	260		
18319	261	MVDTGYGAMDFSTLQDTKCE	280		
18320	281	VPLDICQSICKYPDYLQMSA	300		
18321	301	DPYGDSMFFCLRREQLFARH	320		
18322	321	**FWNRAGTMGDTVPQSLYIKG**	340		
18323	341	TGMPASPGSCVYSPSPSGSI	360		
18324	361	VTSDSQLFNKPYWLHKAQGH	380		
18325	381	NNGVCWHNQLFVTVVDTTPSY	400		
18326	401	TNLTICASTQSPVPGQYDAT	420		
18327	421	KFKQYSRHVEEYDLQFIFQL	440		
18328	441	CTITLTADVMSYIHSMNSSI	460		
18329	461	LEDWNFGVPPPPTTSLVDTY	480		
18330	481	RFVQSVAITCQKDAAPAENKY	500		
18331	501	DPYDKLKFWNVDLKEKFSLD	520		
18332	521	LDQYPLGRKFLVQAGLRRKP	540		
18333	541	TIGPRKRSAPSATTSSKPAKY	560		
18334	561	APSATTSSKPAKRVRVRARKY	580		



Vera, R. et al. 2003. *Int. J. Cancer*. 107:416

10 November 2003 Vol. 107 No. 3

INTERNATIONAL Journal of Cancer



Regions involved in HPV-epithelial cell interaction

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Articles published online in Wiley InterScience
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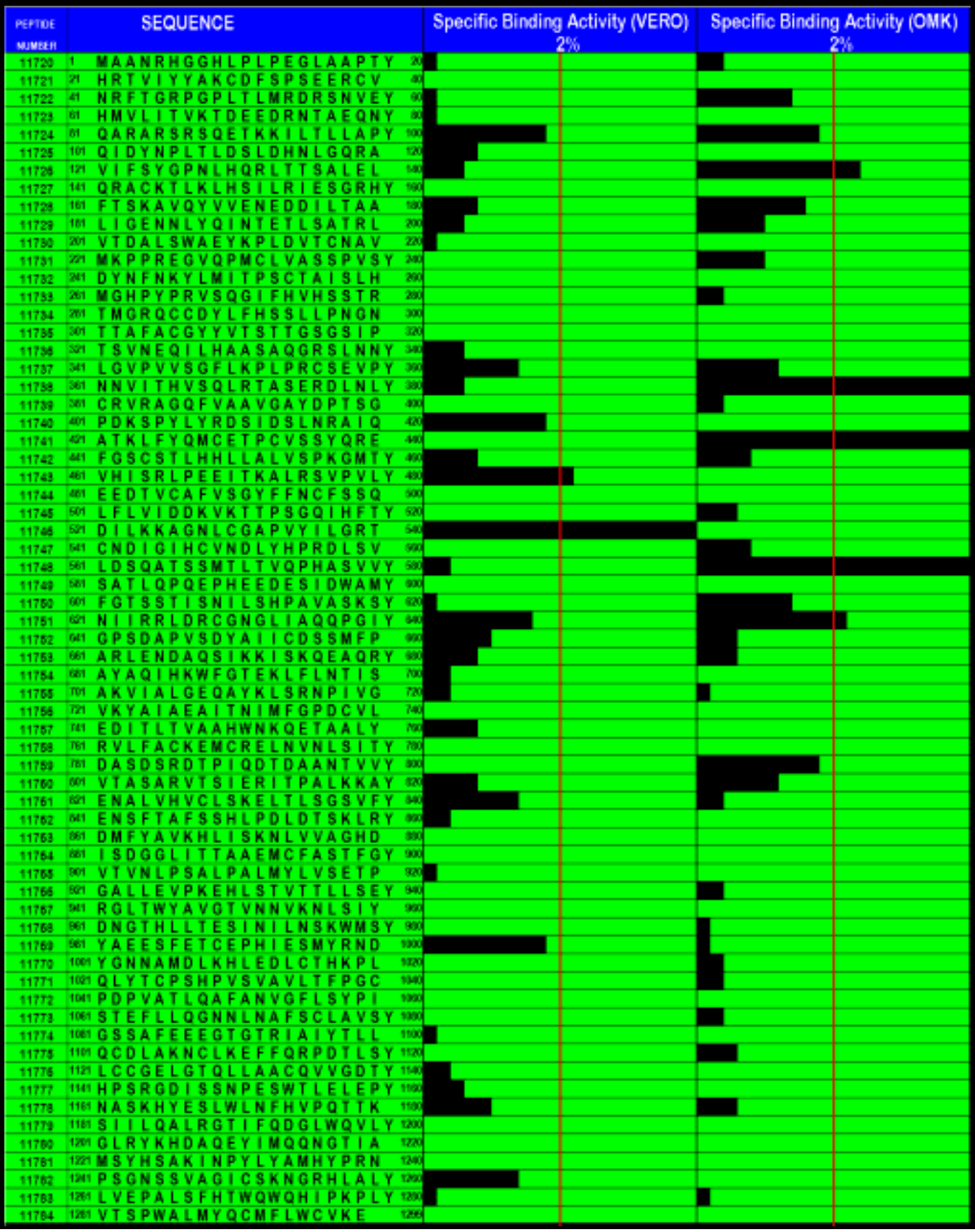
Herpes Virus Saimiri

Peptide Sequence and Binding Activity of Probable Antigen 75

Curtidor H. et al. Manuscript in preparation



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Computers & Chemistry 26 (2002) 667–682

Computers & Chemistry

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Constructing a useful tool for characterizing amino acid conformers by means of quantum chemical and graph theory indices

Constanza Cárdenas [a,b,*], Mateo Obregón [a], Eugenio-José Llanos [a,b], Eduardo Machado [a], Hugo-Javier Bohórquez [a], Jose-Luis Villaveces [b], Manuel-Elkin Patarroyo [a,b]

21 índices de mecánica quántica

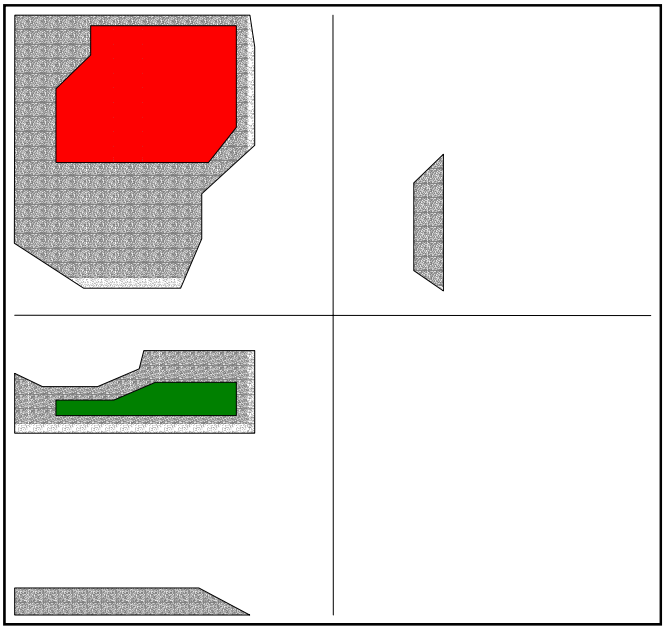
19 índices grafo-teóricos

Ala-X-Ala

NH2-X-CHO

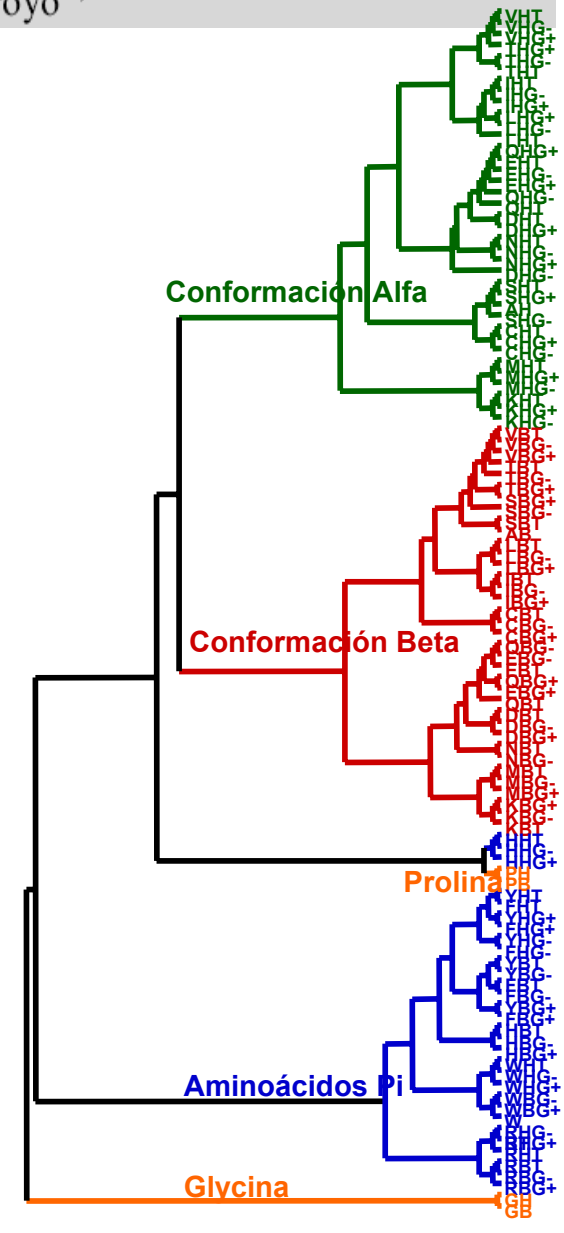
- **2 conformaciones (alfa y beta)**
- **3 rotámeros (g+, g-, t)**

540 moléculas



φ

ϕ



Electronic Energy and Multipolar Moments Characterize Amino Acid Side Chains into Chemically Related Groups

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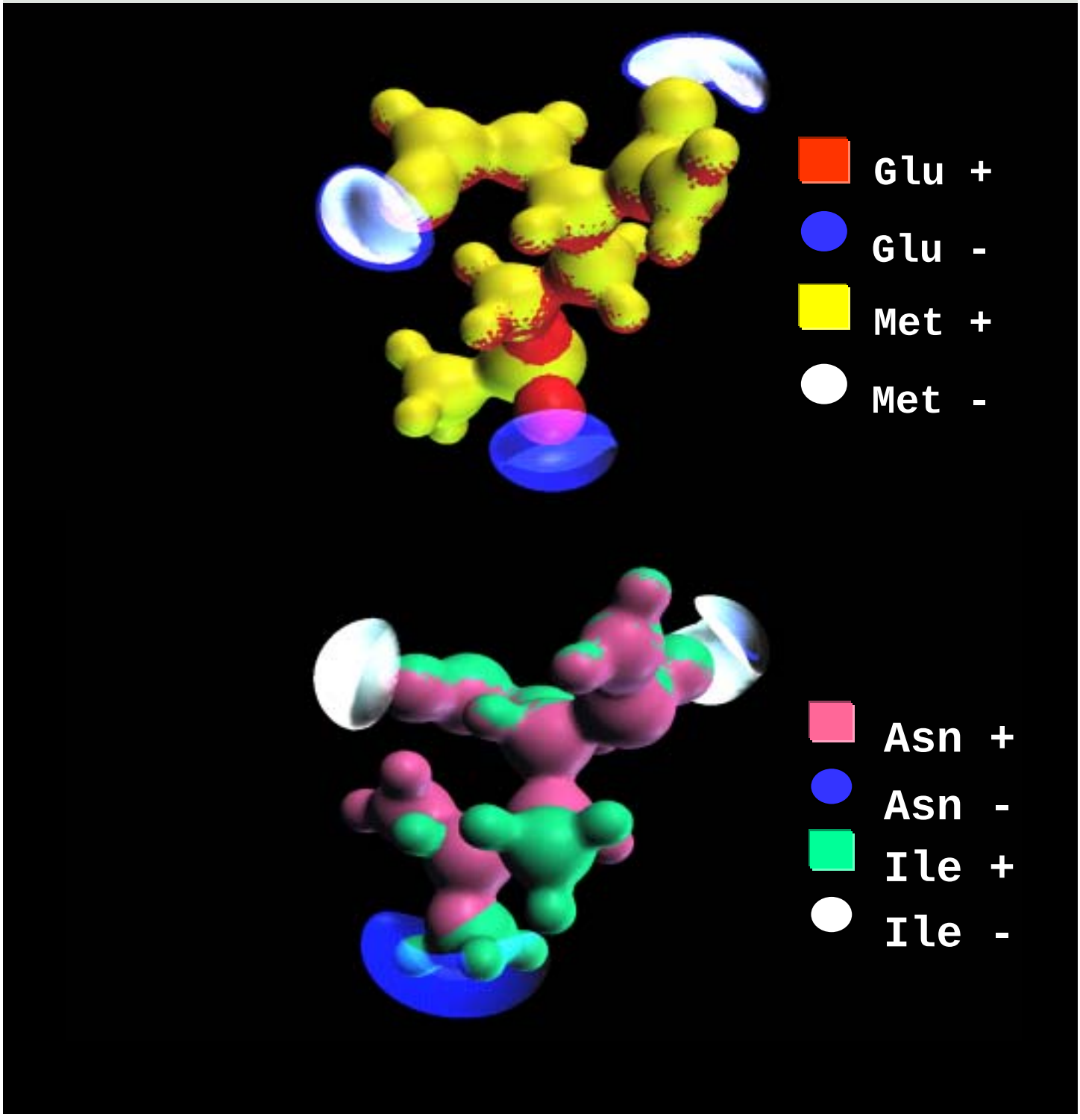

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Quantum chemical analysis explains hemagglutinin peptide–MHC Class II molecule HLA-DRβ1*0101 interactions

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A comparative study of MHC Class-II HLA-DRβ1*0401-Col II and HLA-DRβ1*0101-HA complexes: a theoretical point of view

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Synthetic vaccines - Emerging principles

1. Plasmodia (falciparum & vivax) use CONSERVED as well as VARIABLE sequences to bind to host cells.
2. CONSERVED binding sequences are NOT antigenic, but VARIABLE sequences are
3. CONSERVED binding sequences are NOT immuno-genic in ANY of the tested species when administe-red as monomers, polymerized, associated with T helper epitopes or presented as MAPs. While VARIABLE sequences can be immunogenic they are strain-specific
4. To overcome this problem the critical contact residues in the binding interaction have to be identified and changed
5. The critical contact residues have to be changed for aminoacids that ARE NOT commonly used during the mutational process in the variable sequences
6. Physicochemical characteristics such as size, charge and volume have to be considered. Therefore A↔S; P↔D; F↔R; H↔L, K↔M; N↔I; Q↔E; C↔T; Y↔W; can be exchanged. G and C have special properties.
7. There must be a 23.5 Å + 3.5 Å distance between those residues fitting into Pockets 1-9 of Class II molecules.
8. All the changes made to the CONSERVED binding peptides are designed to achieve a perfect fit with the MHC molecules and the TCR
9. Structural considerations together with affinity, biological and Immunological activities should guide the design of synthetic peptide vaccines.
10. This methodology elicits protective immunity against NON ANTIGENIC, NON IMMUNOGENIC CONSERVED BINDING PEPTIDES, providing a new and powerful tool for the rational development of synthetic vaccines

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Receptor-Ligando

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Quimica Cuantica

Inmunoquímica

Biologia Molecular

NMR y Estructura 3D

Síntesis Quimica de Macro-moleculas