

**New Approaches for Primary Diagnosis and
Screening of Nasopharyngeal Carcinoma by
Using Epstein-Barr virus Markers**

Jajah Fachiroh

VRIJE UNIVERSITEIT

New Approaches for Primary Diagnosis and
Screening of Nasopharyngeal Carcinoma by Using
Epstein-Barr virus Markers

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof. dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Geneeskunde
op woensdag 1 juli 2009 om 10.45 uur
in de auditorium van de universiteit,
De Boelelaan 1105

door

Jajah Fachiroh

Geboren te Sungguminasa (Gowa), Indonesië

The work in this thesis was performed within the framework of "teach the teachers program" and fully supported by The Netherlands Cancer Foundation (KWF) grants IN2000-03 and IN2004-17

ISBN :

Promotor : prof. dr. Jaap M. Middeldorp

Copromotor : prof. dr. Sofia Mubarika

List of Abbreviations

ADCC	antibody-dependent cellular cytotoxicity	LELC	lymphoepithelioma-like carcinoma
AIDS	acquired immunodeficiency syndrome	LMP	latent membrane protein
AJC/UICC	american joint committee/ international union against cancer	NK	natural killer
ARL	AIDS-related lymphoma	NPC	nasopharyngeal carcinoma
BARF1	BamH1-A rightward reading frame 1	mRNA	messenger RNA
BART	BamH1-A rightwards transcript	miRNA	micro-RNA
BL	burkitt's lymphoma	MS	multiple sclerosis
BS	blood spot	OHL	oral hairy leukoplakia
C-EBV	chronic-EBV	ORC	origin recognition complex
CMV	cytomegalovirus	ORF	open reading frame
CoV	cut-off value	PAGE	polyacrylamide gel electrophoresis
CSF-1	colony stimulating factor 1	P13K	phosphatidylinositol 3-kinase
CTL	cytotoxic T cell	PCR	polymerase-chain reaction
CST	complementary strand transcripts	PDT	photodynamic therapy
DB; DBS	dried blood; dried blood sampling	PKR	dependent protein kinase
DC	dendritic cells	PPV; NPV	positive predictive value; negative predictive value
dsRNA	double stranded RNA	PTLD	post transplant lymphoproliferative disorder
DS	dyad symmetry	RISC	RNA-inducing silencing complex
DRiPs	defective ribosomal products	RISH	RNA in-situ hybridization
E; IE	early; Immediate early	RT-PCR	reverse transcriptase PCR
EBER	EBV-encoded nonpolyadenylated RNAs	SAP	SLAM-associated protein
EBNA	epstein-barr nuclear antigen	Se/ Sp	sensitivity/ specificity
EBV	epstein-barr virus	SAP	SLAM-associated protein
ELISA	enzyme-linked immunosorbent assay	SLAM	signaling lymphocyte activating molecule
ENK/T	extranodal NK/T-cell lymphoma	SLE	systemic lupus erythematosus
ENT	ear, nose and throat	S&S	schleicher and schuell
FR	family of repeats	TAP	transporter-associated with antigen processing
GAr	glycine-alanine repeat	TK	thymidine kinase
GC	gastric adenocarcinoma	TR	terminal repeat
gp	glycoprotein	TRF2	telomere repeat binding factors 2
HCC	hepatocellular carcinoma	Tregs	T regulatory cells
HHV	human herpesvirus	TPA	tetradecanoyl phorbol acetate
HIV	human immunodeficiency virus	TGF- 1	transforming growth factor 1
HL/ HD; NHL	hodgkin's lymphoma/ disease; non hodgkin's lymphoma	U1A snRNP	U1A small nuclear ribonucleoprotein
HLA	human-leucocyte antigens	UICC	union international cancer control
HRP	horse-radish peroxidase	UTR	untranslated region
HSV	herpes simplex virus	VAHS	virus-associated hemophagocytic syndrome
IFA	immunofluorescence assay	VZV	varicella zoster virus
IFN	interferon	VCA	viral capsid antigen
IGF-1	insulin-like growth factor 1	X-LPS	X-lymphoproliferative disorder
IM	infectious mononucleosis	ZEBRA	Z-encoded broadly reactive activator
IR	internal repeat		
IFA	immunofluorescence assay		
Ig	immunoglobulin		
KSVH	kaposi's sarcoma-associated herpesvirus		
LC	langerhans cells		

Contents

1	Chapter 1. General Introduction
47	Chapter 2. Molecular Diversity of Epstein-Barr Virus IgG and IgA Antibody Responses in Nasopharyngeal Carcinoma: A Comparison of Indonesian, Chinese, and European Subjects <i>Journal of Infectious Disease. July 2004. 190 (1): 53-62</i>
61	Chapter 3. Single-Assay Combination of Epstein-Barr Virus (EBV) EBNA1- and Viral Capsid Antigen-p18-Derived Synthetic Peptides for Measuring Anti-EBV Immunoglobulin G (IgG) and IgA Antibody Levels in Sera from Nasopharyngeal Carcinoma Patients: Options for Field Screening <i>Journal of Clinical Microbiology. April 2006. 44(4):1459-67</i>
77	Chapter 4. Combination of Epstein-Barr virus Scaffold (BdRF1/ VCA-p40) and Small Capsid protein (BFRF3/ VCA-p18) into A Single Molecule for Improved Serodiagnosis of Acute and Malignant EBV-driven Disease <i>Submitted</i>
93	Chapter 5. Dried-Blood Sampling for Epstein-Barr Virus Immunoglobulin G (IgG) and IgA Serology in Nasopharyngeal Carcinoma Screening <i>Journal Of Clinical Microbiology, April 2008. 46(4):1374-80</i>
105	Chapter 6. Diagnostic Value of Measuring Epstein-Barr Virus (EBV) DNA Load and Carcinoma-Specific Viral mRNA in Relation to Anti-EBV Immunoglobulin A (IgA) and IgG Antibody Levels in Blood of Nasopharyngeal Carcinoma Patients from Indonesia <i>Journal of Clinical Microbiology. July 2005. 43(7):3066-73.</i>
119	Chapter 7. Noninvasive Diagnosis of Nasopharyngeal Carcinoma: Nasopharyngeal Brushings Reveal High Epstein-Barr virus DNA Load and Carcinoma-specific Viral BARF1 mRNA <i>International Journal of Cancer. August 2006. 119(3):608-14.</i>
134	Chapter 8. General Discussion
153	Summary Samenvatting Intisari
168	Words of Gratitude
170	Curriculum Vitae