

**Significance of cyclin D,  
overexpression in patients with  
Non-Hodgkin's lymphoma.**

*Thesis*

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٢٠٠٦

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿ قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا  
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ  
الْعَلِيمُ الْحَكِيمُ ﴾

صدق الله العظيم

سورة البقرة / الآية { ٣٢ }

**I dedicate this Thesis to  
my loving and  
supportive family  
to them I owe everything**

## **List of Abbreviations:**

ATM: Ataxia telengectasia mutated gene

AR: androgen receptor

AL: light chain amyloidosis

BL: Burkitt's lymphoma

CKIs: Cyclin kinase inhibitors

CDKs: Cyclin dependent kinases

CAK: CDK-activating kinase

C/EBP: CCAAT/enhancer binding protein

CT: computerized tomography

CLL: chronic lymphocytic leukemia

CD: cluster of differentiation.

CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone)

DLBCL: Diffuse large B cell lymphoma

ECM: Extracellular matrix

ER: estrogen receptor

FL: Follicular lymphoma

HL: Hodgkin's lymphoma

HRS: Hodgkin/ReedSternberg cell

HCL: Hairy cell leukemia

HCV: Hepatitis C virus

IPI: International prognostic index

ICAM: Intercellular adhesion molecule

IL- $\gamma$ : Interleukin- $\gamma$

INK $\epsilon$ A: Inhibitor of cyclin-dependent kinase  $\epsilon$

IGF: insulin like growth factor

JAK: Janus Associated Kinase

JH: Immunoglobulin heavy chain joining region

LPL: Lymphoplasmacytic Lymphoma

MALT: Mucosa associated lymphoid tissue

MCL: Mantle Cell Lymphoma

MM: Multiple Myeloma

MGUS: monoclonal gammopathy of undetermined significance

NHL: Non Hodgkin's lymphoma.

PCNA: proliferating cell nuclear antigen

P/CAF: p300/CBP-associated factor

PPAR: peroxisome proliferator-activated receptor

pRB: RB protein

PLL: Prolymphocytic leukemia

RT-PCR: reverse transcriptase–polymerase chain reaction

REAL classification: Revised European-American Lymphoid classification

SLL: Small lymphocytic lymphoma

SLL: small lymphocytic lymphoma

SMZL: Splenic marginal zone lymphoma

STAT: Signal transducer and activator of transcription

TdT: terminal deoxynucleotidyl transferase.

TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ .

TNF: tumor necrosis factor

VEGF: Vascular endothelial growth factor

TSGs: tumor suppressor genes

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## **Introduction:**

Cyclins are very important components of the cell cycle machinery because their levels regulate cell proliferation. Cyclin D1 is one of the G<sub>1</sub> cyclins that control cell cycle progression by allowing G<sub>1</sub> to S transition. Overexpression of cyclin D1 has been postulated to play an important role in the development of human cancers. Cyclin D<sub>1</sub> is a proto-oncogene that is overexpressed in mantle cell lymphomas and several other hematolymphoid malignancies (**Zukerberg et al., 1990**).

Cyclin D1 also plays a key role in cell cycle regulation by cooperating with cyclin-dependent kinases (CDKs). It can function as an oncogene, the overexpression of which may lead to growth advantage for tumor cells by way of cell cycle progression. They have also been found to be prognostic factors in various cancers (**Jaroslav et al., 2000**). Among hematolymphoid

malignancies, cyclin D $\alpha$  overexpression has been recognized in mantle cell lymphoma, subset of B-chronic lymphocytic leukemia (B-CLL), multiple myeloma, splenic marginal zone lymphoma, and hairy cell leukemia (Yatabe et al., 2000).

Cyclin D $\alpha$  expression appears to be a useful diagnostic adjunct to discriminate mantle cell lymphoma from other non-Hodgkin's lymphomas. Mantle-cell lymphomas (MCL) are associated with a characteristic chromosomal translocation, t(11;14)(q13;q32). This translocation involves rearrangement of the bcl-2 proto-oncogene from chromosome 11 to the immunoglobulin heavy chain gene on chromosome 14, resulting in an overexpression of cyclin D $\alpha$  mRNA. Clinically, mantle-cell lymphoma is more aggressive than many other so-called small B-cell lymphomas. Because cyclin D $\alpha$  expression is not seen in normal hematopoietic cells, the demonstrated expression of cyclin D $\alpha$  in lymphomas other than MCL