بسم الله الرحمن الرحيم

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تم رفع هذه الرسالة بواسطة / سلوي محمود عقل

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات:
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The In Vivo Expression of Gamma Secretase Catalytic Subunit (Presenilin) in Patients with Chronic Lymphocytic Leukemia)

Thesis

Submitted for Partial Fulfillment
of Master Degree in **Internal Medicine**

By

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قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

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Engy Alaa Eldin Loly Abbas

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List of Abbreviations

Abb.	Full term

ADCC ..... *Antibody dependent cell-mediated cytotoxicity*
AEs ..... *Adverseevents*
ALL ..... *Acute lymphoblastic leukemia*
AML ..... *Acute myeloid leukemia*
APP ..... *Amyloid –protein precursor*
ATM ..... *Ataxia telangiectasia mutated*
BCL2 ..... *B cell lymphoma 2*
BCR ..... *B cell receptor*
CDC ..... *Complement-dependent cytotoxicity*
CLL Chronic ..... *lymphocytic leukaemia*
CLL-IPI ..... *Chronic Lymphocytic Leukemia Inter national Prognostic Index*
DDR ..... *DNA damage response*
DLBCL ..... *Diffuse large B-cell lymphoma*
EBMT ..... *European Society for Blood and Marrow Transplan tation*
EMA ..... *European Medicines Agency*
FISH ..... *Fluorescence in situ hybridization*
GS ..... *Gamma-secretase*
GSI ..... *Secretase inhibitors*
HCT-CI ..... *Hematopoietic Cell Transplantation-Specific Comorbidity Index*
HSV ..... *Herpes simplex virus*
IC ..... *Inhibitory concentration*
ICD ..... *Intracellular domain*
IGHV Immunoglobulin heavy-chain genes
LPL ..... *Lymphoplasmacytic lymphoma*
MALT ..... *Mucosa-associated lymphoid tissue*
MBL Monoclonal B-cell lymphocytosis
MCL ..... *Mantle cell lymphoma*

List of Abbreviations (Cont...)

Abb.	Full term
MRD	*Minimal residual disease*
MZL	*Marginal zone B-cell lymphoma*
NCT	*Nicastrin*
NGS	*Next generation sequencing*
NICD	*Releases the NOTCH intracellular domain*
NIH	*National Institutes of Health*
NRM	*Non relapse mortality*
ORR	*Overall response rate*
OS	*Overall survival*
PDAC	*Pancreatic adenocarcinoma*
PEN2	*Presenilin enhancer 2*
PFS	*Progression-free survival*
PI3K	*phosphoinositide 3-kinase*
PS	*Presenilin*
R/R	*Relapsed/refractory*
RB1	*Retinoblastoma gene*
RIC	*Reduced intensity conditioning*
RS	*Richter syndrome*
SEER	*Surveillance, Epidemiology, and End Results Program*
TLS	*Tumor lysis syndrome*
UVB	*Ultraviolet rays effects*
W&W	*Watch and wait*

INTRODUCTION

Gamma secretases are intramembranous multisubunit protease complexes that are composed of four core components (presenilin, nicastrin, presenilin enhancer 2*(*Pen2*)* and anterior pharynx-defective 1 (Aph1), and several associated proteins ***(De Strooper and Annaert, 2010).***

Two presenilin genes and two Aph genes have been identified in the human genome, so there could be at least 6 different gamma secretase complexes containing different presenilin as Aph1 could exhibit distinct activities ***(Serneels et al., 2009).***

Gamma secretase was primarily identified in Alzehimer's disease as it cleaves amyloid precursor protein (APP) ***(Laguarta, and Pera, 2010).***

Gamma secretase cleaves various type 1 membrane proteins by regulated intramembrane proteolysis. The gamma secretase mediated cleavage releases the C terminal intracellular domain (ICD) of the substrate protein which may perform important signaling functions inside the cells. The group of gamma secretase substrates is large and constantly growing ***(Haapasalo and Kovacs, 2011).***

Many of the identified substrates are intimately involved in tumorigenesis. Those substrates as NOTCH receptors and their ligands, CD 44, ErbB4, E-cadherin, and MUC1. Gamma

secretase may influence on tumorigenic also via its role in angiogenesis as many of substrates are shown to regulate the formation and development of new blood vessels ***(Boulton et al., 2008).***

Many of physiological and pathological activities of gamma secretase is derived from its activity as a protease against NOTCH, a central molecule in the control of growth and differentiation ***(De Strooper et al., 1999).***

NOTCH activation plays an important role in the genesis of T cell acute lymphoblastic leukemia ***(Weng et al., 2004).***

In contrast, the role of NOTCH activation in B cell malignancies is not clear ***(Chiaramnonte et al., 2003).***

However, follicular dendiritic cells leaving NOTCH legand activate NOTCH and protect germinal center B cells from apoptosis ***(Yoon et al., 2009).***

There are several reports of NOTCH activation in Hodgkin's lymphoma, multiple myeloma and chronic B cell lymphocytic leukemia ***(Jundt et al., 2002; Nefedova et al., 2008 and Rosati et al., 2009).***

Due to the central role of gamma secretes in these malignancies, considerable efforts have been made to characterize this unique protease, however, to the best of our

knowledge, all the studies were directed to an exo cell assay of gamma secretase expression and activity and even in vitro inhibition of gamma secretase activity in some cell lines of B cell malignancies ***(Shelton et al., 2009; Ramakrishnan et al., 2012 and Secchiero et al., 2017).***

So, modulation or inhibition of gamma secretase activity and hence altered signal pathways, could be a light path as a line of therapy against various types of tumor cells ***(Selkoe and Walfe, 2007; Shih and Wang, 2007 and Groth and Fortini, 2012).***

Chronic lymphocytic leukaemia (CLL), the most frequent type of leukaemia in adults, is a lymphoproliferative disorder that is characterized by the expansion of monoclonal, mature $CD5^{+}CD23^{+}$ B cells in the peripheral blood, secondary lymphoid tissues and bone marrow. CLL is an incurable disease with a heterogeneous clinical course, for which the treatment decision still relies on conventional parameters (such as clinical stage and lymphocyte doubling time) ***(Bosch and Dalla-Favera, 2019).***

Aim of the Work

The Aim of this work is to evaluate the in vivo expression of gamma secretase catalytic subunit (Presenilin) in patients with B cell lymphocytic leukemia.

Chapter 1

CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults and mainly affects the elderly ***(Zenz et al., 2010).***

CLL is a B cell malignancy, where clonal CD5+CD19+CD23+ B cells accumulate in peripheral blood and infiltrate secondary lymphoid organs such as lymph nodes, spleen, and bone marrow ***(Stilgenbauer et al. 2014)***. The disease is highly heterogeneous clinically mostly due to hyper mutations of the immunoglobulin heavy-chain genes (IGHV), genomic aberrations, and recurrent gene mutations which associate with the clinical course.

Epidemiology

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER), the estimated number of new cases of CLL in the United States in 2018 was 20,940, representing 1.2% of new cancer diagnoses and the number of deaths from CLL was 4510. 7% of all cancer deaths (SEER Cancer Stat Facts: Chronic Lymphocytic Leukemia, National Cancer Institute, Bethesda, MD. Median age at diagnosis was 70, with the highest numbers of cases identified in the 65–74 yr age group.