CHAPTER I: INTRODUCTION

Neuroblastoma is one of the most common extracranial childhood cancers, in which 90% of its occurrence is found in children below the age of four. By 2009, there are approximately new 1,500 cases every year in Europe and 700 cases in the USA and Canada (Heck et al., 2009). Although there are no known risk factors, Neuroblastoma is more often found in males rather than females, and also in Caucasoid rather than Negroid infants.

Neuroblastoma arises from the disrupted development of sympathoadrenal neural crest lineage from the ectodermal layer during embryogenesis. As such, 30% of neuroblastoma cases were found to be starting from the adrenal medulla, 60% from the paraspinal ganglia of the stomach, and 10% from the sympathetic ganglia along the head, neck, chest, and pelvis. This type of development, combined with the fact that the developmental disturbance can be caused by disruption of multiple signaling axes, causes the myriad of Neuroblastoma phenotypes. Thus, it is tough to pinpoint a mutual genetic mutation across all Nerobloastoma phenotypes (Louis and Shohet, 2015).

The outcome of Neuroblastoma varies according to its phenotypes and degree of differentiation. Patients with more neural crest-like tumor have a worse prognosis than those with a more differentiated tumor. By applying this concept, retinoid therapy has been utilized to induce differentiation and cell cycle arrest of Neuroblastoma (Louis and Shohet, 2015).

Among many causes of neural crest developmental arrest, one of them is the downregulation of Peroxisome proliferator-activated receptor (PPAR) gamma coactivator (PGC)-1α. PGC-1α is a transcription coactivator of PPARG, permitting the interaction of PPARG protein with multiple transcription factors. It is a master regulator of metabolic processes, mainly but not limited to

mitochondrial biogenesis (Liang & Ward, 2006; St-Pierre & Austin, 2012). PGC-1α provides positive signaling for mitochondrial respiration and has a reactive oxygen species (ROS) scavenging function, interacting with many ROS-detoxifying enzymes (Lin, Handschin, and Spiegelman, 2005; St-Pierre & Austin, 2012).

The antitumor role of PGC-1α lies in its ROS-scavenging ability. However, this also results in resistance against redox-based cancer treatment regimens (Pagliei et al., 2013; Ye et al., 2015). Not only that, but PGC-1α also induces inducing mitochondrial biogenesis to fulfill the energy requirements of cancer cells (Pagliei et al., 2013). Numerous suggestions have been made regarding the significance of understanding the underlying mechanism of PGC,-1α including its utilization as a target to mediate chemoresistance and as a biomarker, as the level of PGC-1α expression might correlate with the stages of tumor progression.

Considering the fact that the role of PGC-1α at different cancer will also be different and the degree of differentiation of Neuroblastoma also affect its prognosis, the author plans to elucidate the role of PGC-1α in undifferentiated and differentiated Neuroblastoma cells, by assessing its tumorigenic characteristics, such as cell proliferation and migration. To reach the stated objective, MTS colorimetric assay and BrdU incorporation assay will be used to assess the proliferative capability and scratch migration assay to assess the migration capability. Immunocytochemistry will also be done to assess the characteristics of the undifferentiated and differentiated cells. These investigations will use undifferentiated and all-trans retinoic acid (atRA)-induced differentiated SH-SY5Y neuroblastoma cell line as its subject, inhibiting and upregulating the transcriptional activity of PGC-1α with small molecular modulator SR-18292 and ZLN005, respectively.