Preface

According with bilateral agreement between the University of Thi-Qar, where I work in Iraq and the University of Magna Graecia in Italy, I was selected to complete the study for a doctorate degree in (Molecular oncology, experimental immunology and the development of innovative therapies).We were three Iraqis students, who came to Italy at the end of 2005 under this convention. During my MSc study in the University of Baghdad in Iraq, I studied the elimination of some pathogenic bacteria like *Salmonella, Shigella* and pathogenic *E. coli* from the water of Tigris River in Baghdad, using biological approaches. I focused on mono cellular bacteriovorous protozoan organisms, capable of engulfing or combating the pathogens by scavenging these harmful bacteria selectively from natural river fresh water microenvironment, thus I got a Master's Degree in pathogenic bacteria. My recent work is no so far from my MSc subject, since here I analyzed the role of defensive NK cells affects during the progression of melanoma, a predator prey scenario, as was in my MSc study. We have discovered that NK cells eliminate lymph nodes metastatic melanoma cells more efficiently than those spreaded via blood stream to liver and pleura. Like *Paramecium caudatum, Euplotes spp*, *Tetrahymena pyriformis, Colpoda culcullus, Cyclidium spp., Halteria grandinella* mono cellular protozoan organisms in the river water community, the immune cell in human body, eliminate metastatic cells within the body. In both systems, the molecular discrimination of the enemies is by their different phenotypic feature.

Our body is offer warm, moist, full of nutrients microenvironments for microorganisms, those fill our world penetrating us when we eat, drink or even breath. Thus these invisible organisms, find the human body a delightful place to live, just our immune system make certain the invasion of these microbial predators doesn't happen, due to its ability to discriminate between self from non self cells and as a resultant, elimination the cells whether of different exotic origin (like bacteria, viruses, parasites, and fungi), exchangeable allogenic transplanted human cells (such as transfused blood cell or transplanted tissue cells) or even self transformed cells which react against the dynamic programmed cellular death laws, while it was compelled to avoid persecution and killing of normal self cells. Immune cells are circulating the body looking for pathogens that are eliminating by wonderful and impressive defensive mechanisms, for instance the sensitive T cell have ability to recognize antigen carried by the transformed or virus infected cell within surface MHC class I and class II TCR complex and lyse foreign antigen carrying cells. While as counter response, virus infected cells or transformed cells have developed mechanisms to avoid the T cells attack by reducing the levels of antigens presentation on their surface so as not easy to fall prey to immune T cells, but these escaped aberrant cells will be recognized by NK lymphocyte. NK which eliminate low or null MHC class I expressing cells.

This thesis is divided into five main sections. **First section** includes a general introduction containing basic information about the immune system, biology, development, distribution of NK cell, their cytolytic functions aiming to provide a detailed review of the molecular mechanism behind the events leading to human NK cell activation, the physiological and clinical significance of NK cells. This section is written to unable the readers outside the field to understand why I chose this subject. **Second section** explained briefly the five studies included in this thesis. Papers I and II deal with NK cell recognition and elimination of melanoma cell line isolated from different metastatic lesions for precise identifying of the contributions of specific receptor expression pattern on NK cell activation. Paper III focus on the role of EHZF/ZNF521 (novel zinc finger protein) transcripts role in up-regulation of HLA class I molecule expression on the tumor cells surface that leads to decreased tumor susceptibility to NK mediated lysis. Paper IV, investigate that mechanical stress approach mediated by a micro-pump, can switch the NK resistant metastases phenotype towards NK susceptible one. In paper V, we studied whether RITA and PRIMA (small molecules that binds p53 and induces its accumulation in tumor cells by disruption of p53-HDM2 interaction) treatment can induce a lymphocytotoxic tumor cells

recognition of NK cell. **Third section** involved the methods and material that used to perform studies included in this thesis. The **fourth section** presented the results and discussed the findings obtained within the work in this thesis. **Last section** briefly summarized some general conclusions and speculates on future prospects and perspectives in relation to the results of the presented work. I think the findings observed here, can provide mechanistic insight into NK cell anti-tumor functions to facilitate applicability of laboratory research findings into the clinical diagnosis and development of immune cells based therapies.

This thesis will take a tour to a very small part of our NK cell functions and show you how it works and how they defend us against progressed tumor cells and which brilliant strategies the evolution have selected to keep us alive.