شبكة المعلومات الجامعية

# بسم الله الرحمن الرحيم



# شبكة المعلومات الجامعية

# التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

# جامعة عين شمس

## التوثيق الإلكتروني والميكروفيلم

# قسم

## نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
## علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

# يجب أن

## تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

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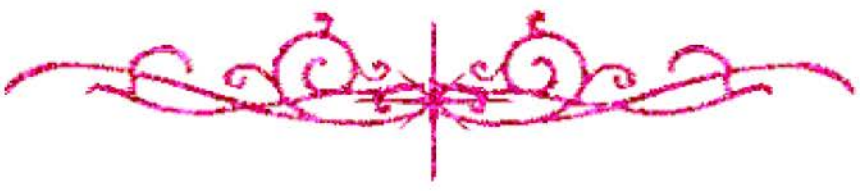
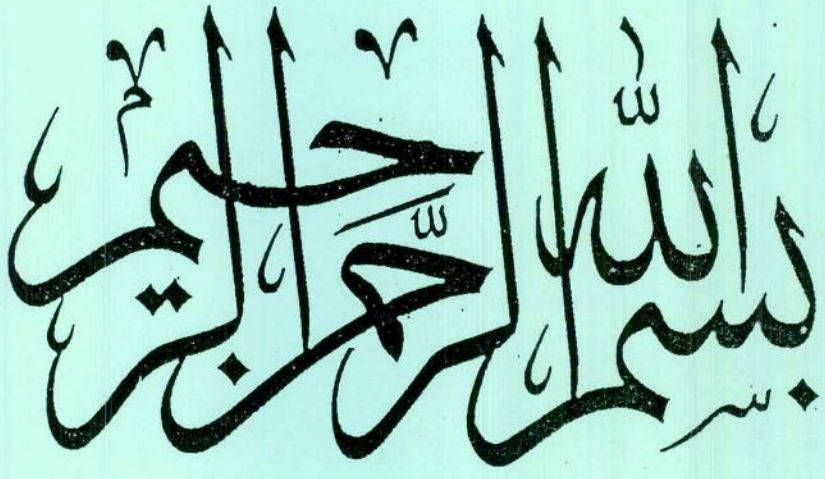
# بعض الوثائق الأصلية تالفة




# بالرسالة صفحات لم ترد بالأصل


بسم الله الرحمن الرحيم

B١٦٧٨٦

# Gene Therapy for Ovarian Cancer

Via Expression Of Intracellular Antibodies To Achieve Targeted Abrogation Of Selected Gene Product, Modulation of apoptosis and Molecular Therapy

**Laboratory and Clinical Study**

**Thesis Submitted to the faculty of Medicine, University of Alexandria,**

**In partial fulfillment of the requirements of the degree of Doctor of Clinical Oncology**

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# INDEX

To the soul of my mother who devoted her life to raise her children
To the soul of my father who taught me how to read and write
To my wife, Laila who makes my life so wonderful
To my daughters, Sarah and Habiba who are my life

# Introduction

## Introduction:

Ovarian carcinoma represents 6.1% of female cancer all over the world. [1] Among women in the United States, cancer of the ovary ranks fifth in incidence. In Alexandria Cancer Registry, cancer ovary accounts for 3% of all malignancies [2]. There are no proven methods of prevention and it often is a rapidly fatal disease were it rank as the fourth most frequent cause of cancer death in women in USA.[3] Surgery is the main modality of treatment for early stage however because most of patients presented in late stages they had to receive chemotherapy and or radiotherapy. The prognosis is still bad with long-term follow-up of suboptimally debulked stage III and stage IV patients reveals a 5-year survival rate of less than 10% even with platinum-based chemotherapy. [4] On the other hand, more advances in the molecular biology technology allow us to understand the molecular pathology of malignancy. More recognition to the genetic lesion responsible for ovarian cancer forced scientist to think in developing gene based treatment for ovarian cancer.[5] In this regard, a number of strategies based on the recognition of the molecular pathological changes in cancer ovary has been developed to accomplish cancer gene therapy. These approaches include, **1) genetic Immunopotentiation, 2) Conditioned viral therapy, 3) Molecular chemotherapy, and 4) Mutation compensation**. Genetic immunopotentiation strategies attempt to achieve active immunization against tumor-associated antigens by gene transfer methodologies. For conditioned viral therapy strategy, replication competent virus has been genetically modified to selectively replicate and destroy only in cancer cells. For molecular chemotherapy, methods have been developed to achieve selective delivery or expression of a toxin gene in cancer cells to achieve their eradication. Also, attempts have been made to deliver genetic sequences that protect normal bone marrow cells from the toxic effects of chemotherapeutic drugs, thus allowing the administration of higher drug doses without reaching otherwise limiting myelosuppression. For mutation compensation, gene therapy techniques are designed to rectify the molecular lesions in the cancer cell etiologic of malignant transformation.

To accomplish any gene therapy approach, certain basic criteria must be achieved to allow an effective genetic intervention:

1- Gene therapy approaches are based upon the fundamental ability to deliver therapeutic nucleic acids to relevant target cells.
2- The delivered genes must be expressed at an appropriate level and for an adequately prolonged period of time. [6]
3- The delivery and expression of the therapeutic genes must not be deleterious to the surrounding normal tissue, nor to the individual as a whole [7].

In practice, two general approaches have been employed to achieve these gene vector criteria: an *ex vivo* approach and an *in vivo* approach. In the former method, target cells are removed from the body and transduced with the genetic vector in vitro, followed by reimplantation. This approach has allowed efficacious transduction of target cells and has also allowed for a safety characterization of modified cells, prior to delivery into the patient. [8] The other approach to achieve therapeutic gene delivery has been the direct, *in vivo* administration into target cells *in situ*. In this regard, both viral and nonviral vectors types have been applied to achieve *in vivo* transduction of relevant target parenchymal cells [9].

Ovarian cancer is a good model to demonstrate the efficacy of gene therapy strategies. In this regard, an examination of the applications of gene therapy for ovarian cancer can exemplify both the rationality and the problems observed in the development of gene therapy, and may serve to illustrate prospects for their solution being refined.

The present study tries to answer some of these questions. How the different strategies of gene therapy can be used to overcome some of the problems of gene delivery. Additionally by knowing some of the genetic alterations behind chemo and radio-resistance of ovarian tumor, the present work tried to exploit the gene therapy machine to serve as enhancer or sensetizer of these conventional therapeutic modalities.

# Review Literature