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13. ABSTRACT (Maximum 200 Words) Breast cancer is the most common malignancy in American women, and its most life-threatening aspect is metastasis. There are presently no effective means to treat metastatic cancer, and novel therapies are required to eliminate metastatic cells and the consequent morbidity and mortality of breast cancer. We are developing polyomavirus gene therapy vectors which are capable of specifically targeting metastatic breast cancer cells. Selective targeting will result from the specific attachment of modified viruses to urokinase plasminogen activator (uPA) expressed on metastatic cells and to the selective expression of genes under the control of promoters which are preferentially activated in metastatic cells. These gene therapy vectors will be assembled from highly purified capsid proteins, histones and DNA and will be tested in human breast cancer cells in culture and in tumors. During the past year, we have modified the polyomavirus VP1 capsid protein to contain sequences of uPA capable of binding to the uPA receptors on tumor cells. We have obtained the requisite enzymes for assembling DNA into chromatin. The next year will be devoted to assembling virus-like particles with the modified capsid proteins and the chromatin, and to preparing to test them for specificity of adsorption to cancer cells.				
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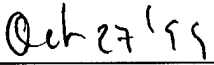
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Foreword

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Introduction

The most life-threatening aspect of cancer is its capacity to invade normal tissue and to establish new foci of tumor cells at distant sites. While there has been some progress in understanding some of the genetic and cellular mechanisms involved in the conversion of normal cells to metastatic tumor cells, little progress has been made in utilizing what has been learned of the molecular mechanisms of metastasis to reduce its impact upon morbidity and mortality. The objective of this work is to do that by developing novel gene therapy vectors selective for metastatic cells. Selectivity of the gene therapy vectors will rely upon metastatic cells expressing receptors to which the vectors can adsorb and upon the metastatic cells expressing signal transduction pathways which will activate vector gene expression.

Key Research Accomplishments — Reportable Outcomes

We are making the progress planned and described in the original application. Specifically:

Technical Objective 1:

We have constructed a polyomavirus vector with the firefly luciferase gene under the control of the viral enhancer and the viral promoters.

Technical Objective 2:

We have modified the polyomavirus VP1 protein to contain high affinity ligands for the uPA receptor. These are being expressed in *E. coli* and will then be placed in vectors capable of expression in insect cells. We will then measure the efficiency of capsomere formation and optimize capsid assembly with these proteins.

Technical Objective 3:

We have obtained the enzymatic machinery required to reconstruct chromatin with DNA containing the LUC gene under the control of the viral enhancer and during the next year will use it to reconstitute chromatin.