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CONTRACTING ORGANIZATION: Thomas Jefferson University
Philadelphia, Pennsylvania

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13. ABSTRACT (Maximum 200 Words) Decorin is a prototype member of a family of the so-called small leucine-rich proteoglycans. Recent evidence has shown that decorin down-regulates the growth of a variety of tumor cells including breast carcinoma cells. Specifically, we have previously shown that decorin blocks the ErbB2 activity and, therefore, we believe that this is the mechanism that is utilized by decorin-induced growth inhibition. In the past funded year, we have made an attempt to generate adeno-associated viral vector (AAV2) containing decorin. After several negative attempts, we were successful in generating an AAV1-decorin vector. In preliminary studies, we have shown that this vector is capable of transducing various tumor cell lines and generating decorin. We have requested and obtained a one-year, no cost extension to pursue the AAV1 transduction experiments both in vitro and in vivo, in an animal model of orthotopic breast cancer.				
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INTRODUCTION

Decorin, a prototype member of the small leucine-rich proteoglycan gene family, is emerging as a powerful modulator of cell growth because of its ability to affect matrix assembly, growth factor binding and receptor tyrosine kinase activity. The central hypothesis of our research is that the decorin gene, delivered by adenoviral or adeno associated virus (AAV2) vectors directly to the tumor site, will reduce the growth of solid tumors such as breast, colon and squamous carcinomas (1-5).

BODY OF WORK

In the past year we have worked actively on generating an AAV2 vector containing the human decorin gene. We have obtained the AAV2-decorin vector and tested on two breast carcinoma cell lines, namely MDA-468 and MDA-453. Unfortunately, after several attempts of transduction with the AAV2-decorin vector, we could not find any expression of decorin either by RT-PCR or Western immunoblotting. We then made another construct in which the vector was changed to AAV1 and was modified to include a 400 bp deletion. Just recently, we found the first evidence for the presence of decorin. Thus we plan to test AAV1-decorin vector in the next year.

We have requested and obtained a one year, no-cost extension from the Department of the Army, in order to continue this project.

KEY RESEARCH ACCOMPLISHMENTS

We were able to generate a vector that could be used in future studies to target breast cancer cells *in vivo*. This vector is based on the latest generation of AAV1, adeno associated virus 1, which can conceivably induce the expression of decorin in the tumor cells and thus retard the growth of breast carcinoma.

This vector could potentially be delivered systemically

REPORTABLE OUTCOMES

At this moment there are no reportable outcomes.

CONCLUSIONS

We have demonstrated that it is possible to generate an AAV1 vector containing decorin and that this vector can efficiently transduce tumor cell lines. These preliminary studies are encouraging and suggest that we will be able to pursue the study of breast cancer cells *in vitro* and the treatment of animal models of breast cancer as originally planned.

REFERENCES

1. Iozzo, R.V. 1998. Matrix proteoglycans: from molecular design to cellular function. *Annu. Rev. Biochem.* 67:609-652.

2. Iozzo, R.V., F. Chakrani, D. Perrotti, D.J. McQuillan, T. Skorski, B. Calabretta, and I. Eichstetter. 1999. Cooperative action of germline mutations in decorin and p53 accelerates lymphoma tumorigenesis. *Proc. Natl. Acad. Sci. USA* **96** :3092-3097.
3. Santra, M., D.M. Mann, E.W. Mercer, T. Skorski, B. Calabretta, and R.V. Iozzo. 1997. Ectopic expression of decorin protein core causes a generalized growth suppression in neoplastic cells of various histogenetic origin and requires endogenous p21, an inhibitor of cyclin-dependent kinases. *J. Clin. Invest.* **100**:149-157.
4. Iozzo, R.V., D. Moscatello, D.J. McQuillan, and I. Eichstetter. 1999. Decorin is a biological ligand for the epidermal growth factor receptor. *J. Biol. Chem.* **274**:4489-4492.
5. Santra, M., I. Eichstetter, and R.V. Iozzo. 2000. An anti-oncogenic role for decorin: downregulation of ErbB2 leads to growth suppression and cytodifferentiation of mammary carcinoma cells. *J. Biol. Chem.* **274**:35153-35161.



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