Isoform-Specific Targeting of Cancer-Associated Genes by Small Interfering RNA in Ovarian Carcinoma

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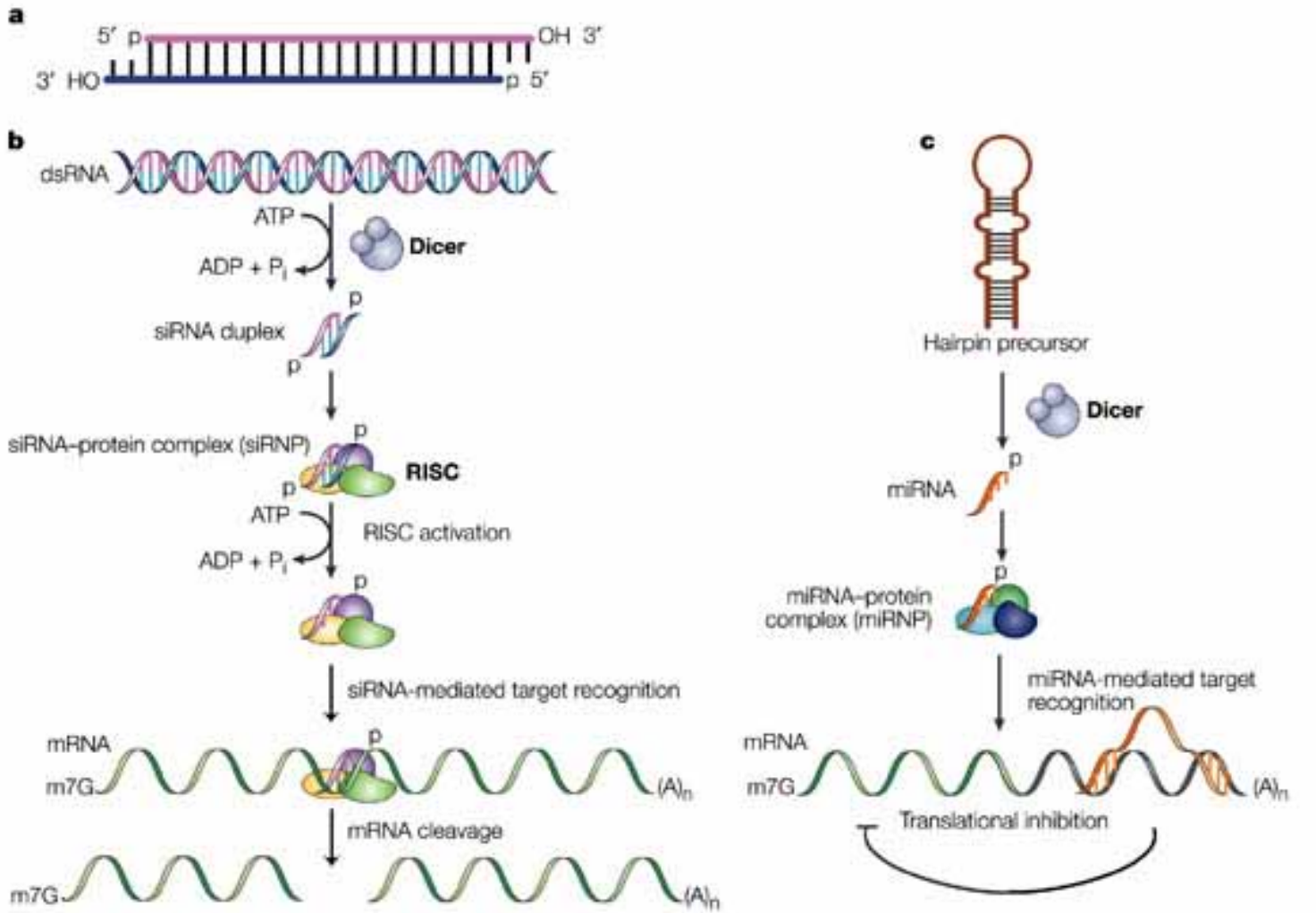
RNA interference (RNAi), a sequence-specific post-transcriptional gene silencing mechanism

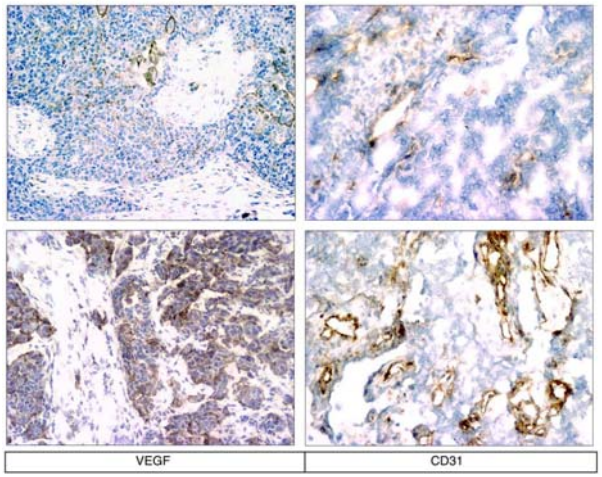


Exon-Specific RNAi

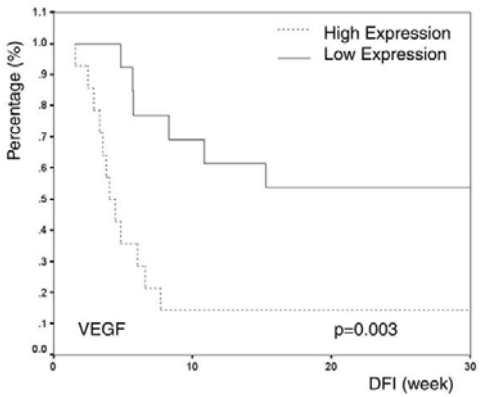
- The majority of metazoan genes encode pre-mRNAs that are subject to alternative splicing.
- As many as 74% of human genes encode alternatively spliced mRNA.
- An alternative spliced gene can generate anywhere from 2 to 38,016 different isoforms.
- Different protein isoforms synthesized from a single gene have distinct functions.
- Multiple isoforms of a large percentage of human proteins associated with cancer are produced by alternative RNA splicing.
- Isoform-specific therapeutic method is very limited.

Vascular Endothelial Growth Factor (VEGF) in Ovarian Carcinoma

Human ovarian cancer



L. Zhang et. al. Cancer Res. 2003

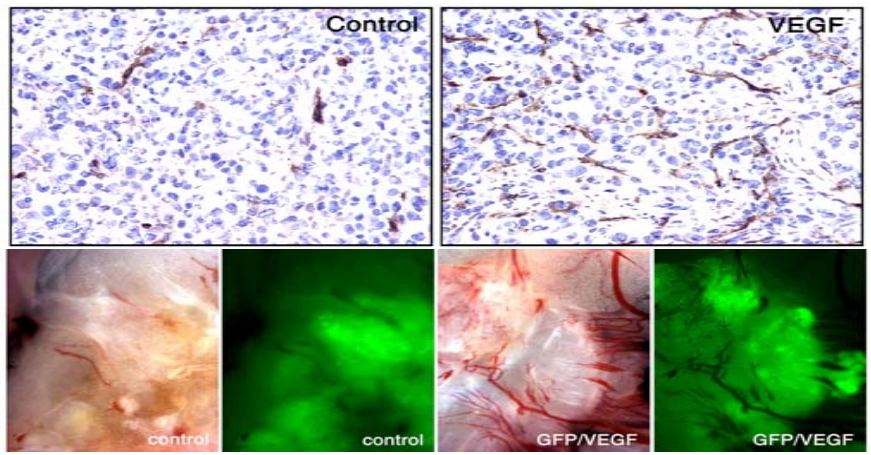


L. Zhang et al. Clin. Cancer Res. 2002

VEGF is associated with poor outcome of ovarian carcinoma.

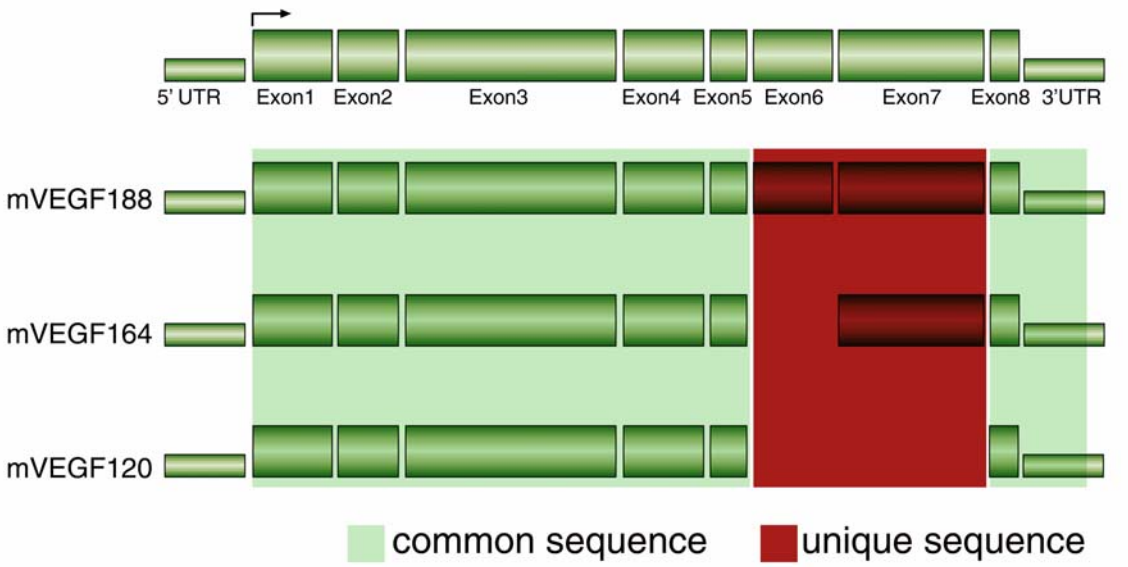
- VEGF promotes tumor angiogenesis;
- VEGF suppresses anti-tumor immune response;
- VEGF exerts autocrine function on tumor cells.

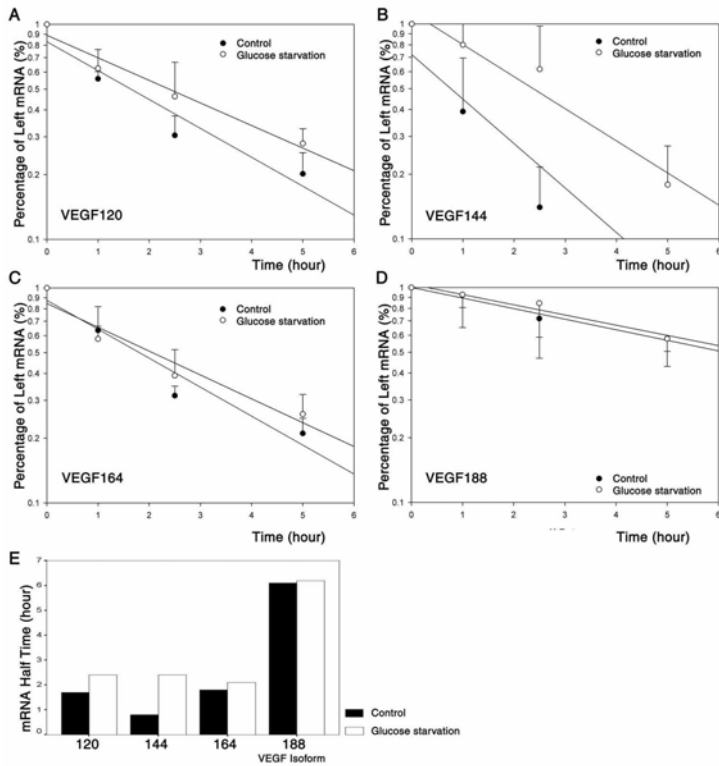
Murine ovarian cancer model



L. Zhang et. al. Am J. Path. 2002

VEGF exists as at least five isoforms produced by alternative splicing



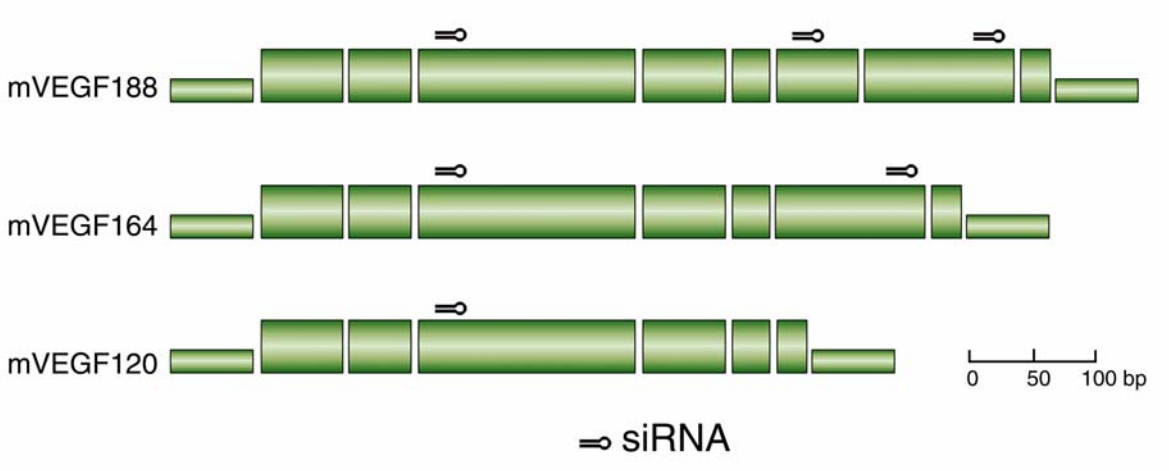


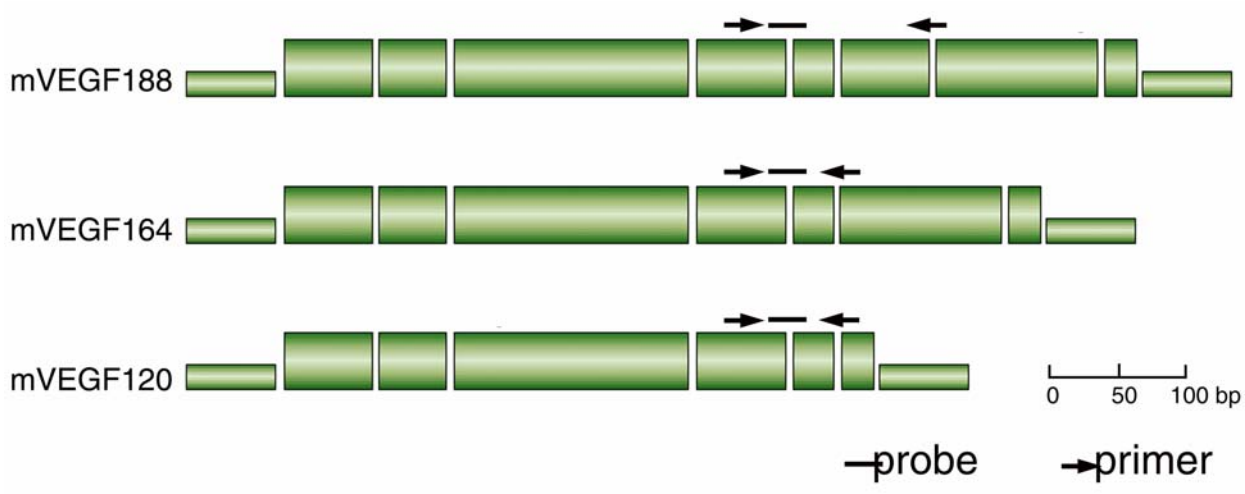
Various VEGF isoforms may perform distinct functions as well as cooperate with each other in tumor development.

E.g. larger molecular weight isoforms are associated with poor outcome in some solid tumors.

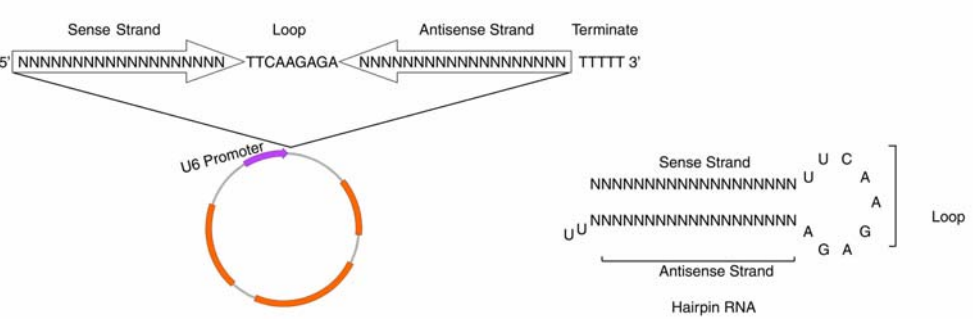
L Zhang, et al. BBRC2002

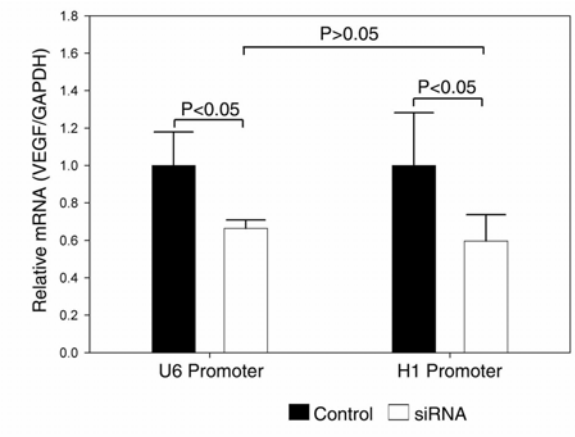
Isoform-specific RNAi and qPCR detection methods

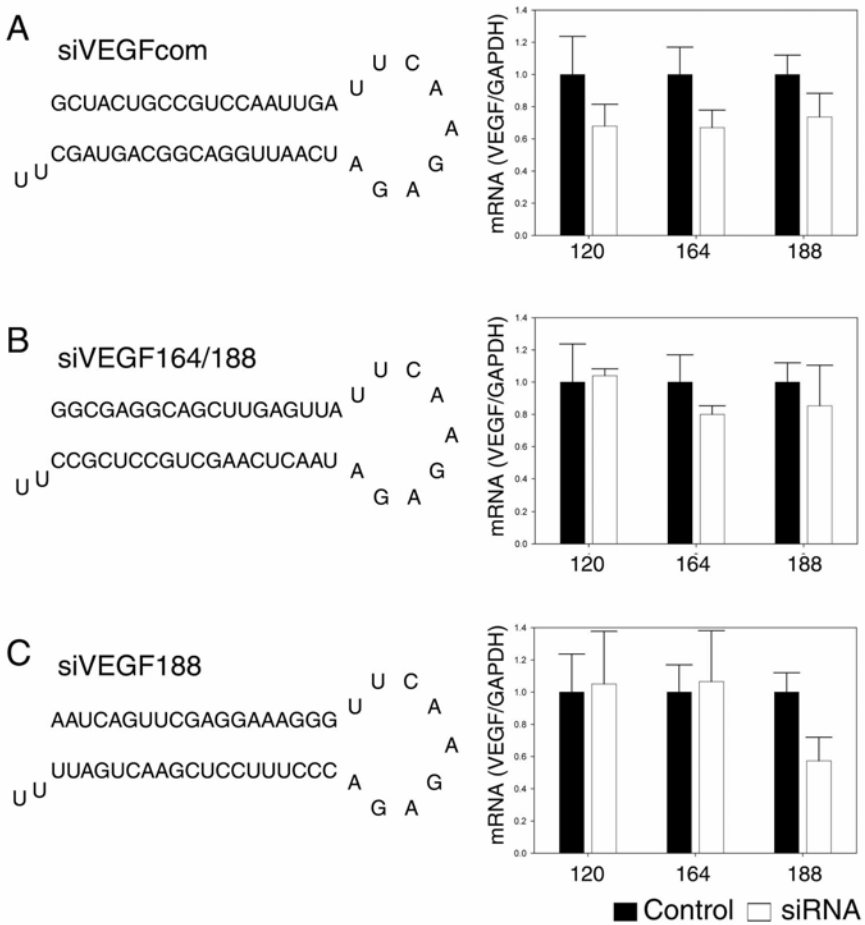




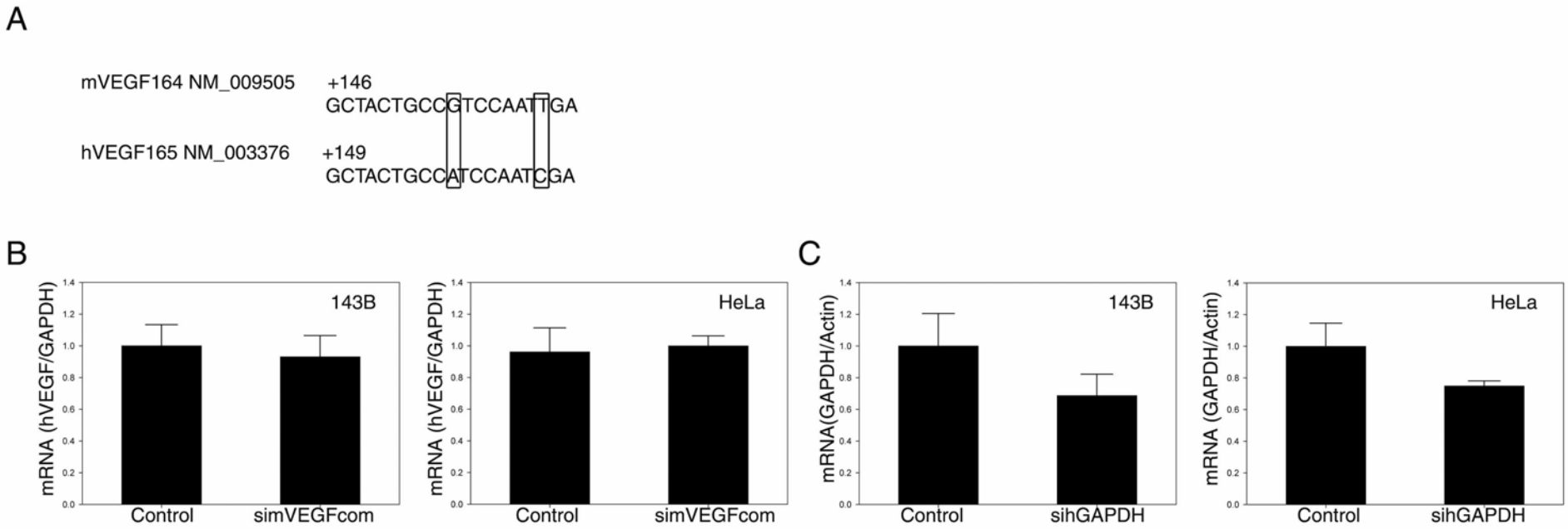
RNAi specifically knocked-down mVEGF isoforms in ID8 cells



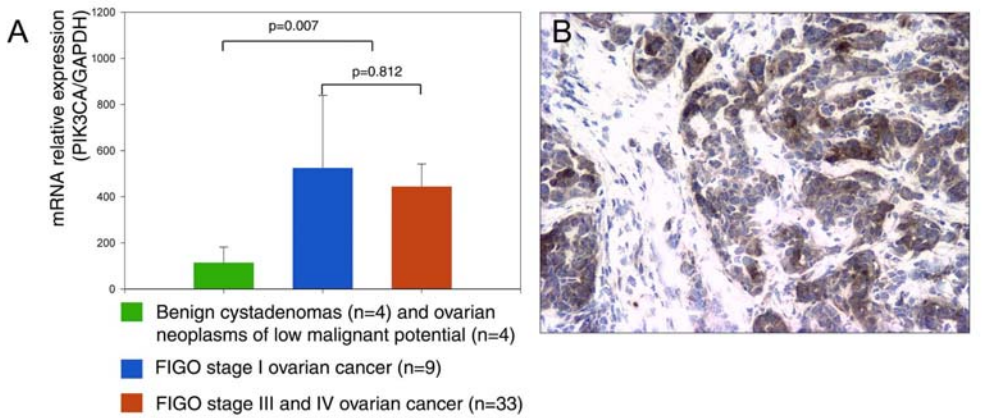


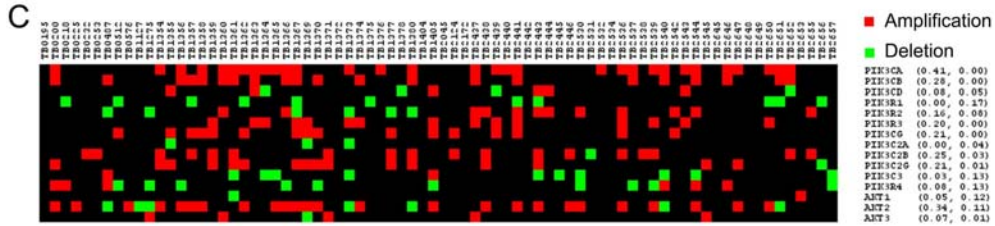


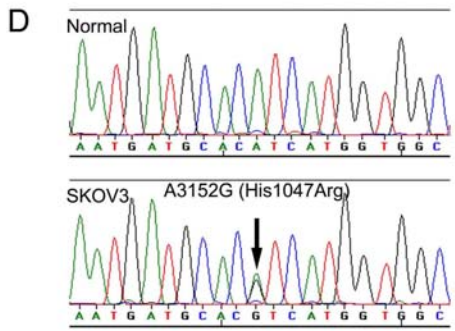
Suppressed gene expression by RNAi is highly target sequence-specific

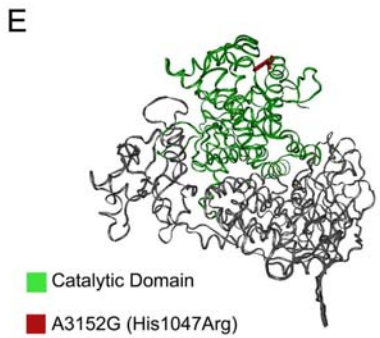


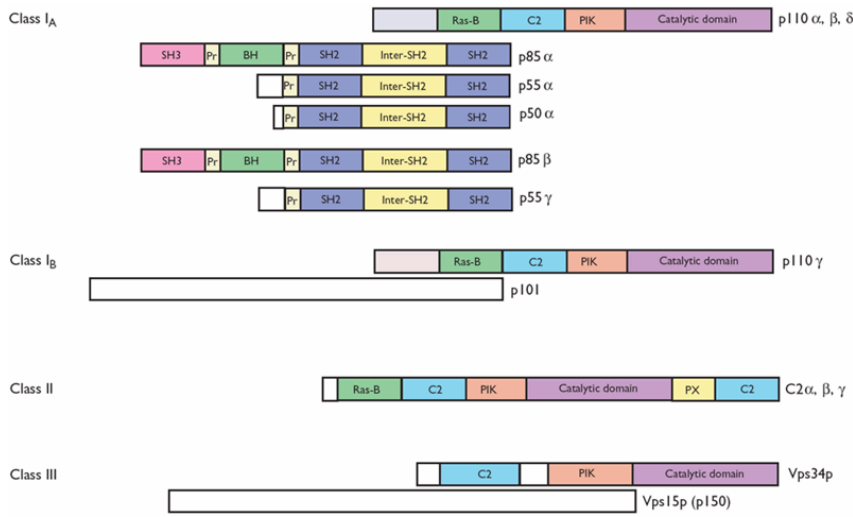
Phosphatidylinositol 3'-kinase catalytic subunit alpha (PIK3CA) is an oncogene in Ovarian Carcinoma





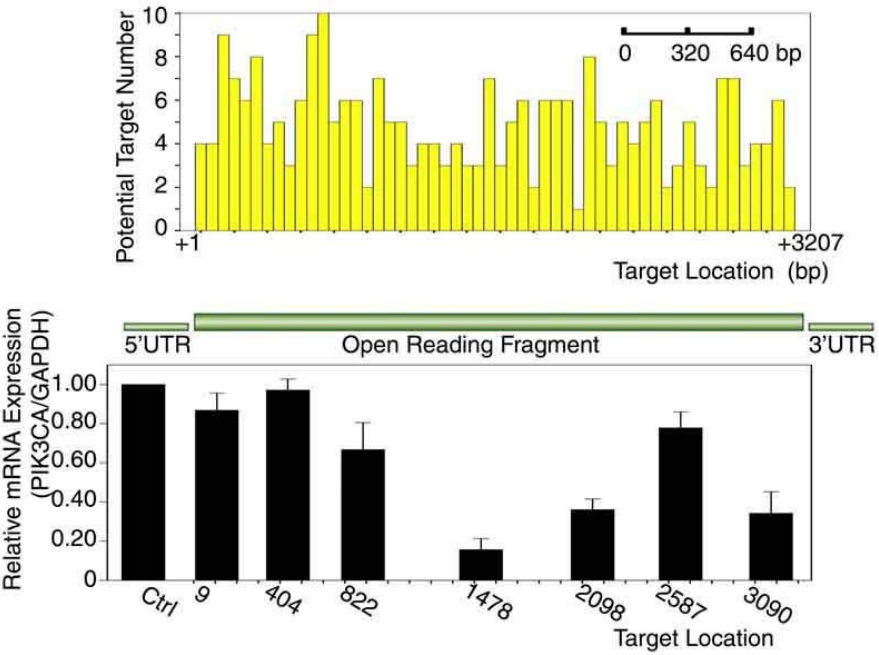


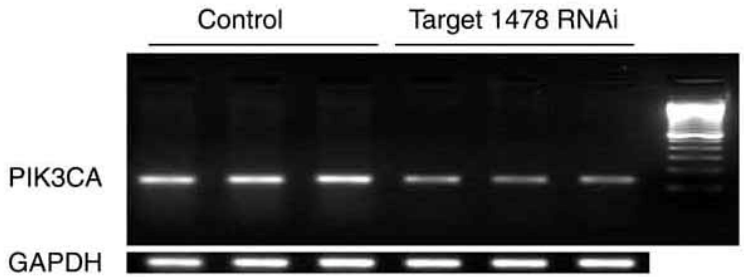


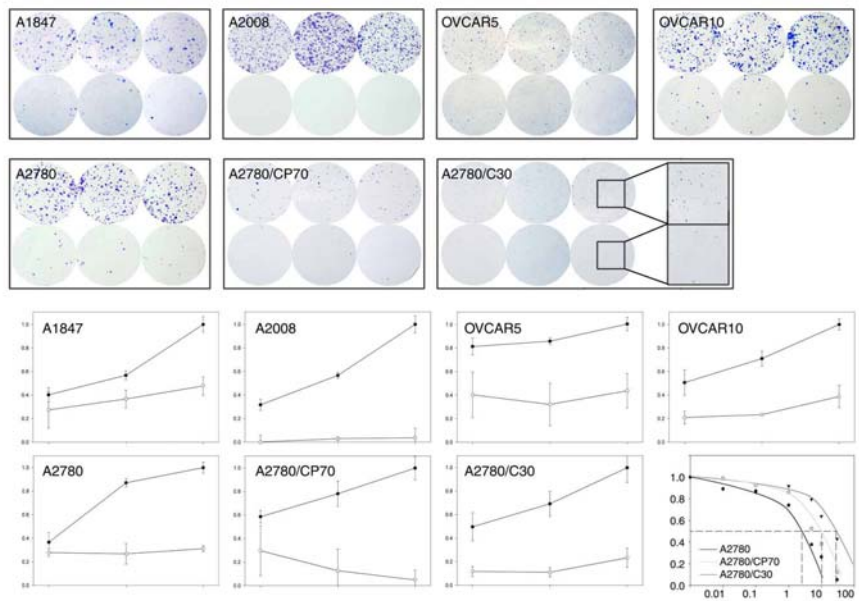


L Zhang, et al. Cancer Res. 2003

RNAi knocked down PIK3CA expression and decreased tumor cell proliferation

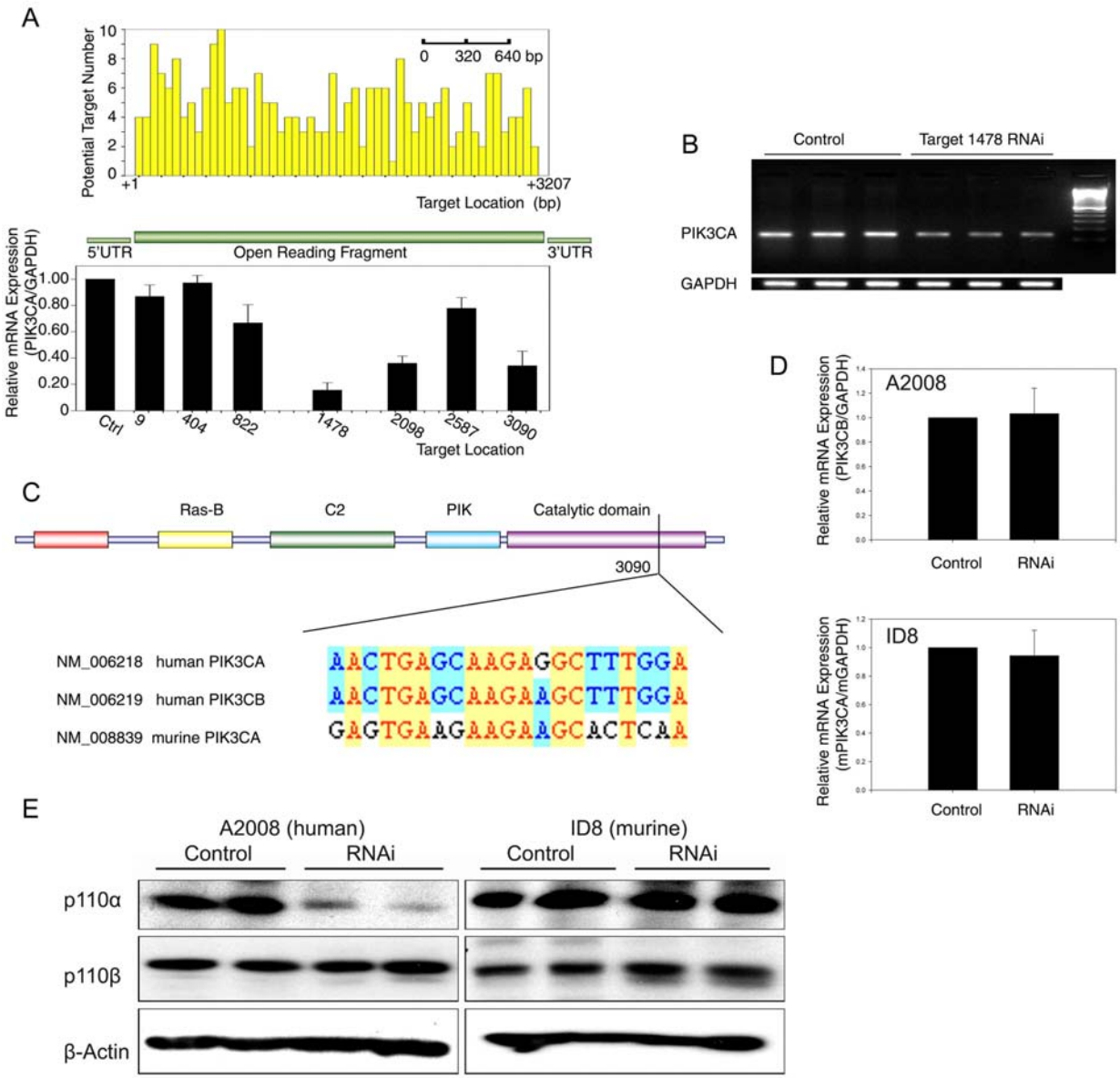






L Zhang, et al. Cancer Biol. & Ther. 2004

Specificity of PIK3CA RNAi targeting



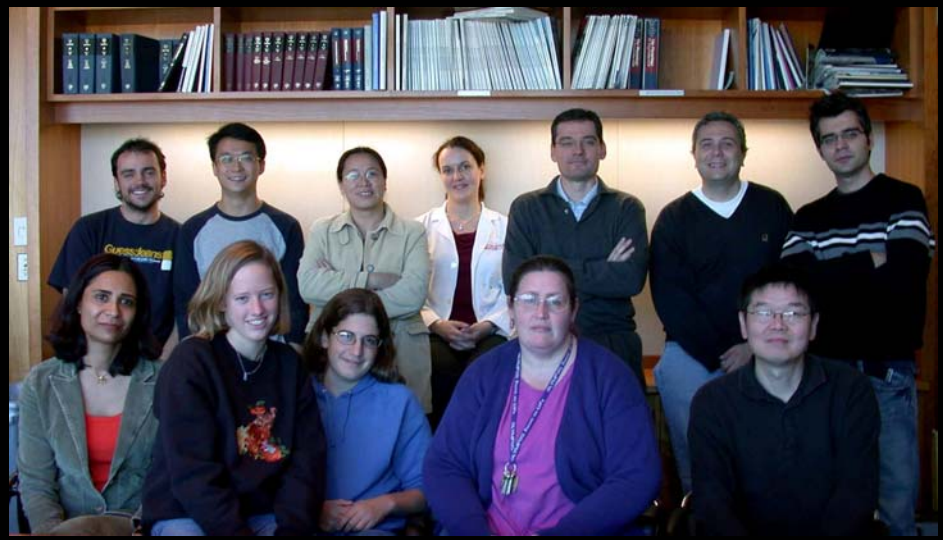
On Going Work

- Efficient delivery systems need to be developed.

- Tissue type and/or cancer specific siRNA strategy needs to be developed.

Acknowledgments

The George Coukos Lab



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