Background

Through recent discoveries in cancer biology, it has become increasingly evident that tumor growth and normal development share many properties. Both processes involve alterations in cell proliferation and differentiation, alterations in cell death, neovascularization, cell motility, and invasion of surrounding tissue. Genes involved in normal developmental processes may therefore contribute to tumorigenesis if mis-expressed. Dr. Heide Ford of the University of Colorado Cancer Center has done intensive research on the homeobox superfamily of genes, which encode transcription factors that are essential during normal development and are often dysregulated in cancer. In elucidating the molecular mechanisms by which homeobox genes influence cancer, Dr. Ford has developed a number of novel methods to treat carcinomas.

CU1250H: The Use of Inhibitors of Cyclin A1 Activity for Cancer Therapy

Dr. Ford has shown that the tissue-restricted Cyclin A1 is a transcriptional target of the Six1 homeoprotein. Both genes are expressed in the embryonic but not the terminally differentiated mammary gland, and Six1 knockout mice show a dramatic reduction of Cyclin A1 in the embryonic mammary gland. In addition, both genes are re-expressed in breast cancers. Six1 overexpression increases Cyclin A1 mRNA levels and activity, cell proliferation and tumor volume, whereas Six1 downregulation decreases Cyclin A1 mRNA levels and proliferation. Overexpression of Six1 in wild type mouse embryonic fibroblasts, but not in knockout variants lacking the Cyclin A1 gene, induces cell proliferation. What’s more, inhibition of Cyclin A1 in Six1 overexpressing mammary carcinoma cells decreases proliferation. Together these results demonstrate that Cyclin A1 is required for the pro-liferative effect of Six1. CU recently received a notice of allowance with claims around using siRNA against Six1 to inhibit Cyclin A1 activity (see next page).

CU1748H and CU1754H: Methods for Inhibiting Six1 and Eya Proteins

Dr. Ford’s further work on the Six1/Eya-2 transcriptional complex showed that the Six1 transcription factor and its associated and necessary cofactor, the Eya-2 phosphatase, are critical in embryogenesis, lost in most differentiated tissues after development, and re-expressed in a number of different cancers while being expressed in almost no adult cells, making this an ideal cancer target (which has born out in later Ford technologies; see next page). RNA interference against Six1 was shown to decrease cancer cell proliferation and metastasis in a mouse model, and Dr. Ford’s group has now shown that this complex is an ideal drug target whose disruption will inhibit tumor cell proliferation and metastasis with limited side effects. Other groups including Dr. Ford’s have shown that Eya-2 phosphatase has a unique active site making it a much more druggable target than other known phosphatases. CU has filed patent applications around these targets (see next page), and Dr. Ford and Dr. Rui Zhao have proceeded to do high-throughput screening against Eya-2 and the Six1/Eya-2 interface.
building on previous work, Dr. Ford’s research group discovered miRNAs that are both upstream and downstream of Six-1’s signaling. Three of these miRNA’s can target the 3’UTR of the Six1 mRNA, leading to the downregulation of Six1. These miRNAs may be useful as anti-cancer therapies, as Six1 promotes not only tumorigenesis, but also metastasis, through affecting tumor cell growth, survival, stem cell characteristics, epithelial to mesenchymal transition, invasiveness, and lymph angiogenesis. Additional work is ongoing utilizing antimirs and Dr. Ford has begun a project to identify additional miRNA’s in this pathway. See below for relevant IP.

CU2640H: Eya-2 Phosphatase Inhibitors

CU has filed a patent application to compounds that were identified by Dr. Ford’s group through high throughput screens against Eya-2 and which have shown specificity for Eya-2 in both primary and secondary screens. They are currently the subject of medicinal chemistry optimization through a collaboration with the NIH. Further, the State of Colorado has recently awarded Drs. Ford and Zhao a Proof of Concept Grant to seek out additional compounds that would break up the interaction between Six-1 and Eya-2.

Selected Publications

Eya2 is required to mediate the pro-metastatic functions of Six1 via the induction of TGF-β signaling, epithelial-mesenchymal transition, and cancer stem cell properties. Oncogene. 2012 Feb 2;31(5):552-62.


Gene Amplification is a mechanism of Six1 overexpression in breast cancer. Cancer Res. 2005 Apr 1;65(7):2668-75.


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IP Status:
Issued and pending patents; available for licensing.

Intellectual Property


MiRNA Inhibition of Six 1 Expression. PCT filed July 27, 2010.

“Inhibitors of EYA2.” PCT filed January 10, 2012; available under CDA.