New Methods to Treat Cancers by Bi-Functional Molecules Targeting Growth Factors

Summary

Angiogenesis, required for the sustained growth of tumors, requires the secretion of growth factors to stimulate the formation of new blood vessels. Drugs that block growth factors (such as Avastin®, targeting vascular endothelial growth factor (VEGF)) have been shown to render tumors vulnerable to chemotherapy and targeted therapy, highlighting the therapeutic value of this strategy. The UMB inventors, Dr. Mao & Dr. Ren, have reported on another key growth factor, hepatoma-derived growth factor (HDGF), shown to stimulate angiogenesis, promote the survival of cancer stem cells, and suppress anti-tumor immunity [see Refs]. The expression levels of both VEGF and HDGF correlate with poor patient outcomes, suggesting the dual inhibition of both growth factors is a logical therapeutic strategy in oncology. To this end, UMB researchers developed a humanized bifunctional antibody targeting both VEGF and HDGF. This novel molecule shows promising results in patient-derived xenograft (PDX) models of non-small cell lung cancer (NSCLC). In these models, treatment with the VEGF/HDGF bi-functional antibody enhanced the efficacy of chemotherapy (Gemzar and pemetrexed or Gemzar and cisplatin). VEGF/HDGF co-targeting resulted in significantly decreased tumor volume and extended survival compared to control treatments with monovalent antibodies targeting only one growth factor (or chemotherapy alone).

Market

There are ~224,000 Americans diagnosed with NSCLC each year, with more than half dying within a year of diagnosis. Despite treatment with aggressive combination therapy, NSCLC remains a deadly disease, with an overall response rate of 5-25%, depending on the stage of diagnosis and molecular signature of the tumor. Pharmacological treatments often result in the emergence of additional mutations that induce resistance to previous and ongoing therapies, complicating treatment strategies. Currently, there are 11 anti-angiogenic cancer drugs marketed in the US, led by Avastin, with worldwide revenues of over $7 billion. Key patents on the market-leading drugs are due to expire in the next few years, opening up the treatment landscape to competitors and biosimilars. UMB’s bi-functional antibody has the potential to become an important therapeutic option for NSCLC patients, and may also extend disease-free survival by decreasing the rate of metastasis and relapse.

Technology

In a pilot PDX preclinical study using NSCLC patient tumor xenograft models, the combination of the bifunctional antibody and chemotherapy demonstrated enhanced tumor elimination and prevented relapse in several cases. Therefore, when administered in combination with chemotherapy or another targeted therapy, this first-in-class approach could enhance tumor elimination as well as prevent recurrence, leading to longer-lasting benefits for NSCLC patients.

Technology Status

Humanized VEGF/HDGF bifunctional antibody has been tested in vivo in 16 PDX models of NSCLC. Its effect in tumor volume and relapse has been compared with that of mice treated with chemotherapy alone (Gemzar and pemetrexed), as well as compared to co-administration of chemotherapy with HDGF- or VEGF-only antibody.