Drug Design

**Major finding:** An antibody–drug conjugate linking anti-CD276 to PBD dimers has antitumor and antimetastatic activity.  

**Concept:** CD276 is expressed by multiple tumor types and angiogenic and nonangiogenic tumor vasculature.  

**Impact:** Dual targeting of the tumor cells and tumor vasculature may be effective in multiple tumor types.

AN ANTI-CD276 ANTIBODY–DRUG CONJUGATE KILLS TUMOR CELLS AND VASCULECTURE

The use of antibody–drug conjugates (ADC) has emerged as a potential therapeutic strategy to improve the efficacy of monoclonal antibodies in cancer therapy. The ADCs in clinical use target the tumor cells, and their efficacy is thereby limited by tumor cell heterogeneity and genomic instability that can promote acquired resistance. To overcome these challenges, Seaman and colleagues sought to develop an ADC targeting both tumor cells and the tumor vasculature. The cell-surface tumor endothelial cell marker CD276 was investigated as a therapeutic target, as it may distinguish pathologic angiogenesis from physiologic angiogenesis and is frequently overexpressed on tumor cells. CD276 was expressed on the angiogenic and nonangiogenic tumor vasculature, and despite broad expression of CD276 on multiple tumor types, it was not required for tumor cell growth. Treating tumor xenografts with anti-CD276 linked to the antimitic drug monomethyl auristatin E (MMAE) resulted in tumor regression followed by relapse, and tumor cells expressing low levels of CD276 were more resistant to treatment. Although anti-CD276–MMAE effectively targeted tumor cells, the tumor endothelium was unaffected. Endothelial cells were found to be more sensitive to DNA-damaging pyrrolobenzodiazepine (PBD) dimers than MMAE. Thus, anti-CD276 was conjugated to PBD, and the ADC selectively targeted both CD276 tumor cells and tumor endothelial cells, resulting in tumor regression in mouse xenografts with CD276 tumor cells and tumor vessels. Further, anti-CD276–PBD was well tolerated and had broad antitumor and antimetastatic activity in lung, breast, and colon cancer xenografts. In addition to developing an anti-CD276–PBD ADC that induces tumor regression, this study demonstrates that dual targeting of tumor cells and tumor vasculature may be an effective therapeutic strategy in many solid tumor types.

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Chemotherapy

**Major finding:** Bacteria alter the response to the chemotherapeutics 5-FU, FUDR, capecitabine, and CPT in *C. elegans*.  

**Concept:** Bacterial RNA pyrimidine metabolism is essential for pro-drug conversion to active metabolites.  

**Impact:** Bacterial metabolism can enhance or diminish the host response to chemotherapeutics.

BACTERIAL METABOLISM ALTERS THE EFFICACY OF CHEMOTHERAPEUTICS

Chemotherapy is associated with a range of responses, toxicities, and pharmacokinetics in patients with colorectal cancer, but genetics is not sufficient to explain these differences. Two independent studies hypothesized that gut bacteria may influence response to chemotherapy and used *C. elegans*, which have a bacterial diet, as a model system to investigate host–microbiome–drug interactions. García-González and colleagues showed that chemotherapeutics 5-fluorouracil (5-FU), 5-fluoro-2′-deoxyuridine (FUDR), and camptothecin (CPT) impaired fecundity in *C. elegans* fed either *E. coli* or *Comamonas*. There was no difference in 5-FU efficacy between the two diets. FUDR caused nematodes to lay dead embryos when fed *E. coli*, but they fared better when fed *Comamonas*. Conversely, CPT promoted a mild increase in dead embryos laid by nematodes fed *Comamonas* compared with *E. coli*. Active metabolism of FUDR by *E. coli* enhanced the drug’s efficacy, whereas *Comamonas* increased CPT efficacy through a passive mechanism. A genetic screen using mutant *E. coli* and *Comamonas* strains identified mutations that positively and negatively influence the efficacy of chemotherapeutics, including multiple nucleotide metabolism genes. In a related study, Scott and colleagues also found that *C. elegans* fed different human commensal bacteria strains exhibited differences in fluoropyrimidine (e.g., 5-FU, capecitabine, and FUDR) activity. A three-way high-throughput chemical-genomic screen revealed a complex network of host-microbe–drug interactions, and found that bacterial vitamins B6 and B9 were required for 5-FU efficacy in *C. elegans*. Vitamins B6 and B9 worked in concert with pyrimidine metabolism to regulate pro-drug bioconversion to active metabolites. Further, disrupting the bacterial pools of deoxynucleotides promoted 5-FU-induced autophagy and cell death of quickly dividing embryonic nematode cells. Together, these studies demonstrate that bacterial metabolism alters chemotherapeutic response in *C. elegans*, highlight that the host and microbe act together to metabolize and mediate the action of chemotherapeutics, and raise the possibility of the gut microbiome influencing chemotherapeutic efficacy in gastric cancer.

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An Anti-CD276 Antibody–Drug Conjugate Kills Tumor Cells and Vasculature


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