Potent Antibody-Drug Conjugates for Cancer Therapy: From Early Stage Research to a Clinically Approved Drug

Peter Senter, Seattle Genetics, 21823 30th Dr. SE, Bothell WA

Monoclonal antibodies (mAbs) have played a major role in cancer medicine, with active drugs such as trastuzumab (Herceptin), cetuximab (Erbitux), bevacizumab (Avastin) and rituximab (Rituxan) in a wide range of therapeutic applications. The mechanism of activity of these agents once they bind to tumor associated antigens may involve direct signaling, interactions with Fcγ receptor positive cells on effector cells, and complement fixation. Several approaches have been explored to improve antibody-based therapies for cancer treatment by optimizing these activities and by using antibodies as delivery agents for highly potent cytotoxic drugs. These areas have advanced significantly in the past few years, leading to the approval of two antibody drug conjugates (ADCs) and a glyco-engineered antibody with enhanced binding to endogenous natural killer cells.

New insights into how ADCs can be effectively developed have been gained through studies on cancer antigen targets and their expression on normal tissues, drug potency and mechanism, and linker stability and conditional drug release. Adcetris (brentuximab vedotin, SGN-35, approved in 2011 for use in relapsed or refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma) is an example an ADC designed with these parameters in mind. Since then, significant new developments have been made many areas of ADC technology, including new antigen targets, new drugs, new linkers, and new recombinant carriers. An overview will be provided of where the field has been and where it is going.