ANTIBODY-BASED THERAPEUTICS FOR CANCER THERAPY

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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 involves cell signaling, effector functions through interactions with Fcγ receptor positive cells, and complement fixation. In order to improve activity, attention has turned towards enhancing mAb ADCC activity by selecting stronger Fcγ receptor binders. This has been accomplished using engineered cell lines that generate mAbs with optimized Fc regions designed for enhanced receptor binding (Xencor technology), or by changing the carbohydrate structures on the heavy chains of mAbs (Glycart and Biowa technologies). We have discovered an alternative approach involving the identification of biochemical inhibitors of the enzymes fucosyl transferase and GDP-d-mannose dehydratase (GMD). The inhibitors are fucose analogues, and can be added to cells that not only produce mAbs, but other proteins in which fucosylation is important for activity. Several applications of this technology will be discussed, both in vitro and in vivo.

mAb activity can also be enhanced by appending highly potent cytotoxic drugs to them. While this area has been investigated for many years, it has only been recently that mAb-drug conjugates have demonstrated the potential for playing a convincing role in cancer chemotherapy. The field has advanced significantly, with new insights gained into the roles that antigen target, normal tissue expression, drug potency, drug mechanism, linker stability, and mechanism of drug release play in generating active antibody drug conjugates (ADC) with acceptable safety profiles. ADCETRIS (Brentuximab vedotin, SGN-35) is an example an ADC designed with these parameters in mind. In August 2011, ADCETRIS was approved by the US Food and Drug Administration for use in relapsed or refractory Hodgkin lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma, two diseases with significant unmet medical needs. An overview will be provided of how this drug was developed, and how we are extending the technology.