*Session II: Speaker Abstracts*

## Drug Discovery, Collaboration and Partnership

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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. While there are examples of highly successful mAbs in the clinic, many tumor selective antibodies may be devoid of or have suboptimal activities when administered as monotherapy. In order to improve monotherapy or single agent activity, attention has turned towards enhancement of antibody-dependent cellular cytotoxicity (ADCC) by selecting stronger Fcγ receptor binding mAbs. 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 (GDP-mannose 4,6 dehydratase and fucosyltransferases). The inhibitors are fucose analogues and can be added to cells in culture that not only produce mAbs, but other proteins in which fucosylation is important for activity. Several applications of this technology will be discussed.

mAb activity can also be enhanced by appending highly potent cytotoxic drugs to them. While this idea has been in existence for many years, only recently have mAb-drug conjugates (ADCs) gained the potential to play a convincing role in cancer therapy. 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 achieving the goal of generating active antibody drug conjugates with acceptable safety profiles. An example of an ADC that was designed with these parameters in mind will be discussed as well as how we are extending the technology.