



BIOENGINEERING

UNIVERSITY of WASHINGTON

A Department of the College of Engineering & School of Medicine

BIOEN 509 – DEPARTMENTAL SEMINAR SERIES

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Foege Bioengineering Building N130

Empowered Antibodies 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 (Erbix), 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 Fc γ receptor positive cells, and complement fixation. In order to improve activity, attention has turned towards enhancing mAb ADCC activity by selecting stronger Fc γ 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 idea has been in existence for many years, it has only been recently that mAb-drug conjugates have the potential of 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 that has been 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 of how this drug was developed and how we are extending the technology will be provided.

Dr. Peter Senter joined Seattle Genetics in August 1998 and has served as Vice President, Chemistry since September 2002. In February 2009, Dr. Senter was recognized as the company's first Distinguished Fellow. He leads Seattle Genetics' chemistry department, which carries out research in antibody-drug conjugate technologies, including the development of potent drug payloads, novel linker systems, conjugation methodology and mechanism of action studies. Prior to joining the company, Dr. Senter was with Cytokine Networks, Inc., the Bristol-Myers Squibb Pharmaceutical Research Institute and the Dana-Farber Cancer Institute, Harvard Medical School. Dr. Senter received a Ph.D. in Chemistry from the University of Illinois, and an A.B. in Biochemistry from the University of California, Berkeley. He is the Senior Editor of Bioconjugate Chemistry and serves on the Editorial Board of four scientific journals. Dr. Senter is an Affiliate Professor of Bioengineering at the University of Washington. His research interests include targeted drug delivery, protein chemistry and biochemistry, and anti-cancer drug design. Dr. Senter has authored more than 120 scientific publications and holds more than 40 patents.

