

Session 2: Cancer – I

Wednesday 8 October 2003. Moderators: Zdenka L. Jonak and Murk Glassy

[11.30–12.00]

A human antibody to CTLA-4: In vivo data from animal models and human clinical trials

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CTLA-4 is a negative signaling receptor on T cells. Extensive animal model data demonstrates that CTLA-4 reactive antibodies can enhance immune responses, and may be useful for therapeutic applications in oncology and infectious diseases. MDX-010 is a fully human high-affinity antibody that specifically binds to human CTLA-4 and augments immune responses. Medarex is developing MDX-010 for therapy in melanoma, prostate cancer, and other indications. The preclinical and clinical progress of this novel therapeutic will be presented.

[12.00–12.30]

Recombinant anti-CEA diabody and minibody production for radiolabeled pre-clinical and clinical studies

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Recombinant antibodies and radiolabeled forms have proven clinical utility as high-affinity protein based therapeutics against cancer. Recombinant fragments due to their smaller molecular size offer several potential advantages over intact antibodies for *in vivo* imaging of solid tumors. Radiolabeled anti-carcinoembryonic antigen (CEA) T84.66 minibody

(scFv-C_H3 dimer) and the T84.66 diabody (scFv dimer) have displayed rapid tumor targeting and blood clearance in animal models and substantial improvement in tumor:blood ratios over intact antibodies. These smaller recombinant fragments offer a more uniform tumor distribution, and a lower potential to elicit an immune response. Optimization for imaging of these mini-antibodies has included the selection of radionuclides with complementary properties. However, the predominant limiting factor in the evaluation of these antibody-derived proteins in humans has been the ability to produce the quantities necessary for clinical trials.

To proceed toward clinical studies, the T84.66 minibody and T84.66 diabody have been expressed using a high-level mammalian expression system. A number of small-scale production systems were evaluated, including cell culture bags, WAVE bioreactor, and hollow fiber bioreactors. Productions of the minibody in a small scale hollow fiber bioreactor resulted in 137 to 307 milligrams. This system was scalable, producing 3.4 grams for clinical studies. The design of these Fc-deleted antibodies does not allow purification by standardized affinity capture methods. A purification protocol was developed employing ceramic hydroxyapatite and anion exchange chromatography. As result of this successful pathway, a ¹²³I-minibody imaging study for CEA positive disease has been completed, while the manufacture of the diabody is in process. The pilot study showed the ¹²³I-minibody was well tolerated and demonstrated tumor targeting in colorectal cancer. Blood clearance was rapid but slower than predicted by animal models. These studies will help evaluate the clinical utility of these rapid targeting agents based on their molecular size, structure and radionuclide.