Abstracts for Oral Presentation

Session 1. Chairman: A.L. Thunberg, Pennsylvania, USA

Molecular modelling of antibodies and antigens

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The amino acid sequences of many antibodies and antigens have been determined. However, three-dimensional information to direct the design of novel antibodies and antigens requires experimental analysis that remains difficult. Molecular modelling using computer graphics can often be used to predict protein conformation from sequence. The approach will be illustrated from our predicted structure of CD4 antigen. The HIV gp120 binding site and antigenic epitopes have been mapped onto the model.

Structural and functional approaches to the study of protein antigenicity

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The antigenic sites of a protein can be defined structurally by X-ray crystallography of the antigen-antibody complexes or functionally by binding measurements (Van Regenmortel MHV, *Immunol Today* 1989, **10**, 266). The structural approach leads to the site being viewed as a "contact epitope" comprising as many as 16 aminoacid residues in the case of a lysozyme epitope (Mariuzza RA *et al. Annu Rev Biophys Chem* 1987, **16**, 139). Computation of free energy changes that accompany complex formation leads to the definition of an "energetic epitope" comprising only about 5 residues (Novotny J *et al. Biochemistry* 1989, **28**, 4735). Immunoassays measure the functional binding activity and usually rely on cross-reactivity for identifying a small number (1–5) of so-called critical residues. These differences between the apparent sizes of an epitope reflect the operational nature of the epitope concept and emphasize the fact that epitopes are not an intrinsic feature of a protein molecule (Van Regenmortel MHV, *TIBS* 1987, **12**, 237). An epitope is a relational concept which depends on a particular paratope for its operational definition.

Case 1—Ovarian carcinoma imaged with humanised indium-labelled macrocycle coupled antibodies

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Two patients with known ovarian cancer have been imaged with indium labelled humanised antibody. The first patient had a positive murine antibody scan 6 weeks previously. She cleared the humanised antibody very rapidly, with no satisfactory images being obtained. The second patient had previously been treated twice with intraperitoneal administration of a different murine antibody, and demonstrated a human antimouse antibody response (HAMA). She did not clear the humanised antibody rapidly, and good images were obtained. Humanised monoclonal antibodies may facilitate repeated treatments, because no HAMA will be generated. However, anti-idiotypic responses may result in faster clearance of repeated administration of antibody.

Case 2—Radioimmunotherapy of rectal carcinoma

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A sixty-four-year-old man was found to have multiple liver metastases 10 months after resection of a carcinoma of the rectum. Intravenous ^{131}iodine (^{131}I) labelled antibody to carcino-embryonic antigen (CEA) occasionally gives short remissions in this condition. These are not sustained because of dose limiting myelosuppression and because human anti-antibodies develop which prevent repeated treatment. Cyclosporin A can prevent human anti-antibody production and a second antibody directed against the anti-CEA can reduce the radiation dose to the bone marrow. To investigate the effect of combining these measures, the patient was given four treatments with this regimen over 134 days. A total of 372 mCi of ^{131}I were given with no myelosuppression. No human anti-antibody production was detected. Partial remission of the liver metastases was shown by serial CT scanning after the first treatment and this persists. This case illustrates that initial obstacles to radioimmunotherapy can be overcome and that useful therapy of colorectal tumours may result.

Case 3—A case of cystic oligodendroglioma treated by intrathecal radiolabelled monoclonal antibodies

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A case is described of a 41-year-old man with a recurrent oligodendroglioma two years after initial debulking and external beam radiotherapy. An ommaya reservoir was inserted through which 21 mCi of ^{131}I labelled UJ13A and 1.0 mCi of ^{125}I labelled 45.6 were injected. Blood, urine and CSF measurements were taken over 4 weeks, at the end of which time tissue biopsies were taken. The results demonstrate firstly a very slow clearance of antibody from the cyst. Secondly 0.74% of the injected dose of UJ13A per gramme of tumour was found on biopsy and the ratio of binding to the tumour of specific UJ13A to non-specific 43.6 was 74:1. This dosage and specificity are 100 times and 75 times better respectively than intravenous administration (Richardson, 1986) and thus represent a considerable improvement in targeted radiation delivery.