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Session 8: Infectious Diseases II

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[17.10–17.30]

'A non-glycosylated plant-produced human monoclonal antibody against anthrax protective antigen protects mice and non-human primates from an aerosolized challenge'

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The unpredictable nature of infectious diseases in general and bio-terrorism in particular necessitates the development of medical countermeasures. One proven approach to contain outbreaks and prevent spread of disease causing agents is treatment with monoclonal antibodies (mAb) which act by neutralizing pathogens or inhibiting the biological activity of toxins, such as anthrax lethal toxin (LeTx). Here we report the biological characteristics of plant-produced glycosylated (pp-mAb^{PA}) and non-glycosylated (pp-mAb^{PANG}) versions of a human mAb against the protective antigen (PA) of *Bacillus anthracis* produced in *Nicotiana benthamiana* plants. Both versions of the antibody were able to neutralize anthrax LeTx activity *in vitro* and protect mice against an intraperitoneal challenge with spores of *B. anthracis* Sterne strain. Further evaluation of these antibodies in non-human primates demonstrated that both versions provided protection against an aerosolized anthrax spore challenge, however pp-mAb^{PANG} provided greater protection than pp-mAb^{PA}. In addition, pp-mAb^{PANG} had a significantly longer terminal half-life in non-human primates compared to pp-mAb^{PA}. This study suggests the potential of pp-mAb^{PANG} as a promising countermeasure reagent for treatment against inhalation anthrax.

[17.30–17.50]

'Antibodies generated by genetic immunisation against hepatitis C virus (HCV) receptor proteins block infection of human liver cells for all HCV genotypes'

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Approximately 150–200 million people worldwide are infected with Hepatitis C virus (HCV) with approximately 3–4 million new infections each year. The majority of infected individuals develop chronic HCV infection, which frequently leads to serious liver disease. About 20% of these patients develop liver cirrhosis, which progresses to hepatocellular carcinoma in 5% of those cases. Current therapies, even in combination, lead to persistent viral clearance in only 50% of patients and often reveal severe side effects. No vaccine is currently available.

HCV is a positive strand RNA virus which mutates continuously and can thus become immune to therapies focussing on the virus itself. Our approach has been to develop monoclonal antibodies by genetic immunisation against three of four known protein receptors on the surface of human liver cells. Our technology allows presentation of the native tetra-spanning receptor molecules in a native conformation and has successfully allowed development of antibodies that recognise the extracellular loops of these receptors. We have successfully generated antibodies against each of these three receptors which individually block HCV infection of human liver cells *in vitro*. In contrast to the virus, these receptors are not polymorphic and further tests with antibodies directed against one receptor have been shown to block entry of all 6 known HCV genotypes and infection of all HCV quasi-species from two chronic HCV sufferers. *In vitro* studies reveal no toxicity of these antibodies, which not only protect liver cells from HCV infection when added prophylactically, but they have also been shown to drastically reduce the viral load on

liver cells already infected with the virus. Thus, these antibodies offer an exciting potentially new therapeutic drug, not only as a prophylactic drug to protect e.g. liver transplantation patients against re-infection, but for possible treatment of all chronic HCV sufferers.

[17.50–18.10]
'The use of immune complex vaccines to enhance antibody responses against neutralizing epitopes on HIV-1 envelope gp120'
Catarina E. Hioe, Maria Luisa Visciano, Rajnish Kumar, Jianping Liu, Ethan A, Mack, Rachel E. Simon, David N. Levy and Michael Tuen
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The capacity of immune complexes to augment antibody (Ab) responses is well established. However, the enhancing effects of immune complexes have been attributed mainly to Fc-mediated adjuvant activity, while the ability of Abs to induce antigenic alterations of specific epitopes as a result of immune complex formation have been less well studied. In our study, we have shown that the interaction of anti-CD4-binding site (CD4bs) Abs with HIV-1 gp120 induces conformation changes that lead to enhanced antigenicity and immunogenicity of neutralizing epitopes in the V3 loop. The significant increases in the antigenicity of the V3 and C1 regions of gp120 were attained for several subtype B gp120s and a subtype C gp120 upon immune complex formation with the anti-CD4bs monoclonal Ab (mAb) 654-D. Such enhancement was observed with immune complexes made with other anti-CD4bs mAbs and anti-V2 mAbs, but not with anti-C2 mAbs, indicating this activity is determined by antigen specificity of the mAb that formed the immune complex. When immune complexes of $gp120_{LAI}$/654-D and $gp120_{JRFL}$/654-D were tested as immunogens in mice, serum Abs to gp120 and V3 were generated at significantly higher titers than those induced by the respective uncomplexed gp120s. Notably, the anti-V3 Ab responses had distinct fine specificities; $gp120_{JRFL}$/654-D stimulated more cross-reactive anti-V3 Abs than $gp120_{LAI/}$654-D. Neutralizing activities against pseudoviruses with heterologous envelope were also detected in sera of mice immunized with $gp120_{JRFL}$/654-D, although the neutralization breadth was still limited. Overall this study shows the potential use of gp120/Ab complexes to augment the immunogenicity of HIV-1 envelope gp120, but further improvements are needed to elicit virus-neutralizing Ab responses with higher potency and breadth.

[18.10–18.40]
'Prevention of GBS disease by monoclonal antibodies directed against proective surface antigens'
Eszter Nagy, Beatrice M. Senn and Zehra Visram
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Group B streptococcus remains an important neonatal pathogen in spite of widely adopted intrapartum antibiotic administration, therefore immune prophylaxis for GBS infections in highly warranted.

In passive immunization and lethal challenge studies with multiple GBS strains, we characterized the protective effect of rabbit polyclonal and murine monoclonal antibodies specific for four cell wall anchored adhesins, FbsA, BibA, PilA and PilB and a hypothetical protein gbs0233. While single specificity rabbit sera or mAbs were associated with strain dependent protection, their combination resulted in superior and broad efficacy against all six tested strains. Fab fragments of the FbsA and BibA mAbs fully protected animals, suggesting that blocking the function of these proteins was the major mode of action. These data are supportive for the development of immune prophylaxis with human mAbs for prematurely born neonates who receive low levels of antibodies by maternofetal transport and characterized with not fully developed phagocytic and complement activity.