Session 10: Infectious Diseases

[11.00–11.30]

'Harnessing the human immune response to fight infectious disease'

Roger Beerli

Intercell AG, Schlieren, Switzerland

Abstract not provided.

[11.30–12.00]

'The usage of the VH5-51 gene by human anti-HIV-1 V3 monoclonal antibodies determines their specificity to a conserved antigenic structure'

Mirek Gorny

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The immunoglobulin (Ig) genes used to encode antibodies (Abs) have a critical impact on Ab specificity and function. We have analyzed the relationship between the usage of particular pairs of the heavy and light chain genes coding for human anti-V3 monoclonal antibodies (mAbs) neutralizing HIV-1 and the structure of their antigen-binding site which determines the antigen recognition. Study of Ig gene usage by a panel of human anti-V3 mAbs produced in our laboratory using cellular methods revealed that 18 of 51 mAbs (35%) preferentially used the VH5-51 gene paired in restricted fashion with VL lambda genes, mainly 1-47 and 3-1 genes. Interestingly, these VH5-51-encoded V3 mAbs were generated from individuals living in disparate geographic locations, North America, Africa and Asia, and infected with different HIV-1 strains from subtypes B, AG, and C, respectively. Crystallographic analysis of five VH5-51-encoded Fabs complexed with various V3 peptides revealed a common three dimensional shape of the antigen-binding sites. The data suggest that the shape of the binding pocket is determined mainly by the four complementarity determining regions (CDR) for the heavy (H) and light (L) chains: H1, H2, L1 and L2 domains. This conclusion is based on the observation that these four CDR domains (H1, H2, L1 and L2) superimposed closely in all five Fabs in contrast to CDR H3 regions (and partly also to L3), which has different length, sequence and conformation for each mAb. The conserved structure of the binding site is additionally documented by the presence, in all five VH5-51 Fabs, of the same key contact residues in the heavy and light chain variable fragments, most of which are germline-encoded. Moreover, a close superimposition of the backbone conformation of the V3 peptides in complex with the five Fabs indicates their complete adaptation to the antigen-binding site, conforming to the same shape. The data demonstrate that preferentially used Ig genes encode a canonical three-dimensional paratope which recognizes a V3 conserved epitope conformation suggesting that this shared conformation may provide a template for immunogens eliciting cross-neutralizing HIV Abs.

[12.00–12.20]

'The role of glycosylation in mAb mediated protection against Ebola virus: Continuing development of an Ebola immunoprotectant for human use'

Larry Zeitlin, Natasha Bohorova, James pettitt, Lori Long, Steve Hume, Barry Bratcher, Michael Pauly, Herta Steinkellner, Gene Olinger and Kevin Whaley

MAPP Biopharmaceuticals, San Diego, CA, USA

Currently no countermeasures exist for the prevention or treatment of the severe sequelae of Filoviruses. Passive immunization has historically been a successful strategy for a wide variety of infectious diseases, and antibodies against smallpox and anthrax are part of the Strategic National Stockpile for use in the event of a biological warfare event. As part of the product development of a monoclonal antibody (mAb) immunoprotectant for Ebola virus, we have evaluated the efficacy of three versions of a humanized mAb (h-13F6) with different glycosylation patterns in a lethal mouse challenge model. A version of h-13F6 mAb with a high percentage of the G0 glycoform provided the most potent protection (ED50 = 3 μg). h-13F6 with typical heterogenous mammalian glycoforms provided less potent

protection (ED50 = 11 μg), with potency similar to the original murine 13F6. Aglycosylated h-13F6 provided the least potent efficacy (ED50 = 33 μg). The binding of these mAbs to FcγRI (CD64), FcγRIII (CD16), and c1q was also evaluated. Together the results suggest the presence of Fc glycans enhances the protective efficacy of h-13F6, and that specific glycoforms may result in further potency enhancement through increased affinity for Fcγ receptors. In addition to these data, the results of challenge studies in non-human primates and progress in cGMP manufacturing of the mAb product will be presented.

[12.20–12.40]
'KBSA301 – a novel human monoclonal antibody for treatment of acute S. Aureus infections'
Holger Koch
Kenta Biotech AG, Bern, Switzerland

Based on believe that the human immune system creates the best antibodies in fighting against infections, the source for antibody selection were isolated B-cells of a convalescent MRSA bacteremia patient. Hybridomas were generated through cell fusions with Kenta Biotech's proprietary cell line LA55, leading to subsequent selection of target specific antibodies through an antigen-specific screening process.

The resulting antibody KBSA301 demonstrated high specificity and affinity for a S. aureus derived exotoxin. Upon binding to its target antigen KBSA301 mediates potent toxin neutralization and protection of various human cell types from toxin dependent destruction. KBSA301 was used as well to confirm toxin expression from an extensive panel of MRSA and MSSA clinical isolates comprising most of the major types of Staphylococcal infections. Beside the extensive in vitro characterization, KBSA301 was also tested in several murine models of systemic and localized S. aureus infections, resulting in a significant survival benefit in therapeutic applications. Interestingly, these beneficial therapeutic effects were reproducibly observed with MSSA, CA-MRSA and HA-MRSA isolates. The positive results justify the development of the antibody for therapeutic intervention in humans as adjunct therapy in combination with antibiotics.

[12.40–13.00]
'Monoclonal antibodies against hepatitis C virus (HCV) receptors show broad range blocking of HCV infection'
John Thompson
Aldevron Freiburg GmbH, Freiburg, Germany

Abstract not provided.