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Targeting of Antiviral Agents to Specific Liver Cell Types by Neoglycoproteins.

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Glycoproteins can in principle be used as carriers for cell specific delivery of ara-AMP and AZT-monophosphate to the various cell types in the liver. These cell types are crucial sites for HBV replication and HIV infection. The specific delivery of the antivirals is based on receptor-mediated endocytosis of the glycoproteins as determined by the terminal sugar, number of sugar groups and overall charge. Endocytosed material was visualized by immunohistochemical staining. Coupling of antiviral drugs had little influence on cell specific targeting. Galactose terminated neoglycoproteins (prepared by reductive amination) with 5-10 drug molecules were shown to be specifically delivered to hepatocytes, while mannose terminated carrier-drug conjugates can be targeted to Kupffer cells, provided that the total negative charge introduced by the drug and the sugar does not exceed a certain threshold. Kupffercells, apart from the mannose-receptor, seem to contain an endocytic receptor recognizing both sugar and negative charge.

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Multivariate Data Analysis in Antiviral Research.

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The objective of multivariate data analysis is to represent visually the most important relationships in a large table of numbers. In antiviral research the relationship under study is the interaction between chemical compounds and the viral target site, resulting in inhibition of viral replication. The mean inhibitory concentration (MIC) is a result of the potency and the specificity of a drug on the one hand, and the susceptibility and specificity of the viral target on the other hand. Irrespective of having a low potency, a compound can be either specifically active against one or more serotypes or exhibit a broad spectrum of antiviral activity.

Spectral Map Analysis (SMA) is a multivariate method which has been designed to analyse and represent these types of interactions in a highly visual way. Technically, the method comprises logarithmic re-expression of the data (MIC-values in this application), subtraction of the row- and column-means from each element in the table, extraction of principal components from the resulting variance-covariance matrix, plot of the viral serotypes and compounds in the plane spanned by the two most important principal components. The method will be illustrated, using the case of 15 antiviral compounds in the panel of 100 rhinoviruses. The multivariate analysis by SMA led to the identification of two distinct groups of rhinoviruses and allowed to select a reduced panel of 17 rhinoviruses to enable antiviral screening of new antiviral compounds for a broad spectrum of activity.