Universität Basel

Research Project

Carbohydrate-Lectin Interactions: ...

Third-party funded project

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Organisation / **Research unit**
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Carbohydrates serve as versatile ligands in numerous biological processes. Many of them are of great pharmaceutical interest, e.g. in the treatment of viral, parasitic, mycotic and bacterial infections, inflammatory diseases, as well as a broad range of human cancers. However, this potential has not been fully exploited to date, because carbohydrates exhibit two inherent drawbacks in respect to their therapeutic potential; they generally show only modest affinities to their targets and, in addition, they do not fulfill even basic requirements in respect to their pharmacokinetic properties, especially their high polarity does not allow an oral application. With our research, we plan to contribute to the basics of carbohydrate-lectin interactions and thereby stimulate new pharmaceutical applications.

In our studies, we are focusing on three pharmaceutically important classes of carbohydrate receptors, the selectins, the siglec family and the asialoglycoprotein receptor. Although all three areas were intensively investigated in recent years, only isolated examples of high affinity antagonists with drug-like properties have been reported so far.

The improvement of the pharmacodynamic and pharmacokinetic properties will be addressed by two approaches: (i) identification of high affinity antagonists by a patented fragment-based *in situ* combinatorial approach and (ii) design and synthesis of carbohydrate mimetics with improved pharmacodynamic and pharmacokinetic properties.

The novel, fragment-based *in situ* combinatorial approach for the identification of high-affinity, low molecular weight antagonists was recently developed in our group. It is especially suited in cases where there is little or no structural information on the binding sites. This new approach was successfully applied in our search of high-affinity MAG antagonists. It is planned to investigate its scope & limitation and to apply it to various other lectins, e.g. selectins or siglecs.

In a second project, various mimetics of hexoses and sialic acid with improved pharmacodynamic and pharmacokinetic properties will be synthesized. One successful example, the replacement of *N*-acetylglucosamine by substituted cyclohexanes was already reported. To test the relevant pharmacokinetic properties of these mimetics, a PADMET-platform (**p**hysicochemical properties, **a**bsorption, **d**istribution, **e**limination, **t**oxicity) will be established. In a first step, oral availability, metabolic stability and renal excretion will be investigated.

With our research, we plan to contribute to an extended understanding of the principles controlling carbohydrate-lectins interactions. In addition, the basis for the identification of high-affinity antagonists with drug-like pharmacokinetic properties will be established.

Keywords E-selectin, sialyl Lewisx, bioactive conformation, conformation in solution, rational design of E-selectin antagonists, myelin-associated glycoprotein (MAG), MAG antagonists, asialoglycoprotein receptor, fragment-based in situ combinatorial approach
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Add publication

Published results

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