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[15] Crystal structure data: monoclinic, space group $C2/c$, $a = 25.484(18)$, $b = 13.219(8)$, $c = 18.109(11)$ Å, $\beta = 120.400(17)^\circ$, $V = 5262(6)$ Å^3, $Z = 4$, $\rho = 1.565$ g cm^{-3}, $\mu = 0.842$ mm^{-1}, $F(000) = 2512$, crystal size $= 0.2 \times 0.2 \times 0.1$ mm. Crystals were mounted on a glass capillary with perfluorinated hydrocarbons and immediately chilled to 203 K. Data collection was performed with a Bruker axs SMART diffractometer ($Mo_{K\alpha}$ grahite monochromator). A total of 11158 reflections ($1.80 < \theta \leqslant 25.37^\circ$) were collected, of which 4690 unique reflections ($R_{int} = 0.100$) were used. The structure was solved using the program SHELXS-97 and refined (326 parameter) using the program SHELXL-97 to $R1 = 0.0525$, w$R2 = 0.1137$ (all data) ($I > 2\sigma(I)$; both programs from G. M. Sheldrick, Universität Göttingen, **1997**). The positions of the Zr-H hydrogen atoms were localized in the difference fourier map and refined; non-hydrogen atoms were anisotropically refined. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication no. CCDC-116996. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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Lectin-Mediated Drug Targeting: Discrimination of Carbohydrate-Mediated Cellular Uptake between Tumor and Liver Cells with Neoglycoconjugates Carrying Fucose Epitopes Regioselectively Modified in the 3-Position**

Hans-Georg Lerchen,* Joerg Baumgarten, Norbert Piel, and Victoria Kolb-Bachofen

Dedicated to Dr. Pol Bamelis on the occasion of his 60th birthday

The specific interaction between carbohydrate epitopes and corresponding endogenous cell-surface lectins plays a fundamental role in a variety of intercellular recognition processes such as sperm–egg adhesion, leucocyte adhesion to platelets and endothelium, cancer metastasis, and microorganism adhesion to host cells.[1] Various lectins have been identified and characterized with respect to carbohydrate specificity on rat, mice, and mammalian tissues, particularly on the liver.[2] The utility of these carbohydrate–lectin interactions for receptor-mediated drug targeting has already been explored mainly focussing on liver targeting.[3] Also tumor cells express a distinct lectin pattern on their surfaces.[4] However, to our knowledge, so far no tumor-specific lectins have been described, and a lectin-mediated drug targeting to tumor cells is extremely challenging.[5] Prerequisites are the discrimination of the targeting moiety between tumor cells and healthy tissue and the circumvention of an efficient scavenging of glycoconjugates by liver cells as described for Kupffer cells and hepatocytes.[6]

The goal of this work was the identification of carbohydrate residues appropriate for tumor targeting. A fucose-binding receptor has been identified on colon cancer cells such as SW480 and was considered to be an appropriate target mediating tumor cell binding and uptake.[7] However, fucose also efficiently binds to lectins in the liver, particularly on Kupffer cells.[2] Therefore a discrimination between the recognition of tumor and liver cell had to be achieved. Neoglycoconjugates such as glycoconjugates of bovine serum albumin (BSA) are appropriate tools for studying lectin–carbohydrate interactions and carbohydrate-mediated cellu-

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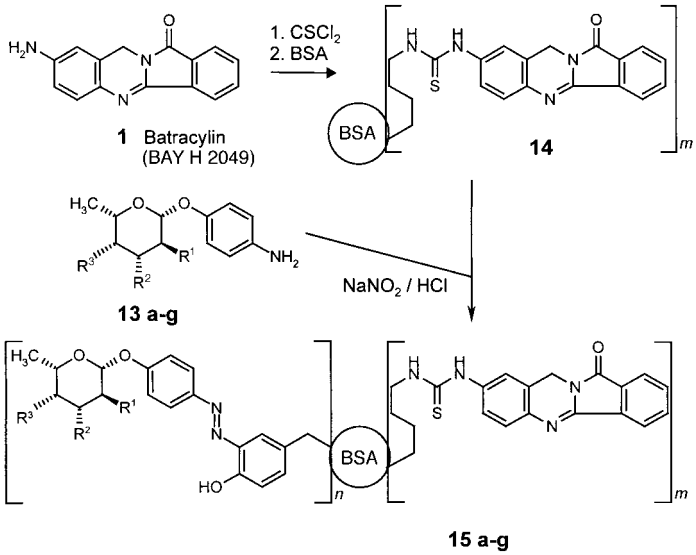
lar uptake.[4a] A couple of methods have been described for the attachment of carbohydrate residues to different amino acid side chains of the protein.[4a, 8] The clustered carbohydrate epitopes on the BSA molecule effect a multivalent and efficient binding to corresponding receptors on cellular membranes.[8, 9] To investigate potential differences of cellular uptake of tumor and liver cells, we designed novel BSA conjugates with modified fucose epitopes which were subsequently labeled with colloidal gold particles for electron microscopic detection of cellular uptake. This functional endocytosis assay rather than studies at isolated lectins was considered to be most significant in exploring the targeting potential of these carbohydrate residues, because of the expression of a variety of lectins on cellular membranes with overlapping carbohydrate specificities. BSA conjugates carrying unmodified fucose residues are expected to be endocytosed by both tumor and liver cells. Previous studies from other groups with distinct lectins have demonstrated a strong impact of chemical modifications of the carbohydrate hydroxyl functionalities on lectin binding.[10] Therefore, the rationale of this work was a systematic investigation of BSA conjugates carrying regioselectively modified fucose residues to identify a particular modification of the carbohydrate epitope that is tolerated by receptors on tumor cells and at the same time decreases receptor mediated uptake into liver cells. For this purpose a straightforward synthesis of regioselectively modified *p*-aminophenyl β-L-fucoside derivatives starting from readily available *p*-nitrophenyl β-L-fucoside has been developed. These modified fucose derivatives were attached to the tyrosine side chains of BSA, and the uptake of these neoglycoconjugates into the tumor cell line SW480 and into different liver cells was investigated. Furthermore, an additional attachment of a toxophore moiety to the lysine side chains allowed the measurement of cytotoxic activity of these BSA conjugates against the tumor cell line SW480.

As a toxophore moiety the fluorescent cytostatic agent batracylin (BAY H 2049; **1**) was selected.[11] The anilinic amino group of **1** was activated with thiophosgene to provide the corresponding isothiocyanate, which in a second step reacted with the lysine side chains of BSA to give the conjugate **14** (Scheme 1). Appropriate carbohydrate moieties for attachment to BSA are *p*-aminophenyl glycosides such as the *p*-aminophenyl β-L-fucoside (**13a**) and its modified derivatives



Scheme 1. Synthesis of BSA conjugates with batracylin and modified fucose residues.

13b–g. They were diazotated with sodium nitrite and subsequently attached to the tyrosine side chains that show the highest reactivity under these acidic reaction conditions.[4a, 8] In the obtained BSA conjugates **15a–g** about 15–30 lysine side chains are linked to the toxophore moiety and 10–22 tyrosines are modified with carbohydrate residues (Table 1).

For the synthesis of regioselectively modified *p*-aminophenyl β-L-fucosides **13b–g** readily available *p*-nitrophenyl β-L-fucoside **2** was used as a convenient starting material. Conversions of the hydroxyl groups without the placement of protecting groups at the anomeric center are possible. Furthermore, after completion of the conversions hydrogenolytic reduction of the nitro group quickly generates the *p*-aminophenyl fucosides **13b–g** suitable for attachment to BSA.

An efficient access to a series of 3-O-modified *p*-aminophenyl β-L-fucosides is shown in Scheme 2 utilizing tin chemistry.[12] The *cis* hydroxyl groups **2** were converted into the tin acetal **3** with dibutyltin oxide in methanol. After evaporation of methanol the addition of alkylating agents such as methyl iodide or methyl bromoacetate in DMF or

Table 1. Substitution pattern of *p*-aminophenyl fucosides **13a–g** as well as the constitution and biological data (cellular uptake and cytotoxic activity) of BSA conjugates **15a–g**.

Entry	modified fucoside residue				BSA conjugate		Uptake[a] into			Cytotoxicity against
	compd	R^1	R^2	R^3	compd	*n*	Kupffer cells	hepato-cytes	SW480 cells	SW480 cells [μM][b]
1	**13a**	OH	OH	OH	**15a**	9	+++	++	+	7
2	**13b**	OH	OMe	OH	**15b**	20	(+)/++[c]	+	++	12
3	**13c**	OH	OCH_2-COOH	OH	**15c**	22	−	(+)	++	7
4	**13d**	OH	OCH_2-CH_2OH	OH	**15d**	21	(+)	+	n.d.	15
5	**13e**	OH	H	OH	**15e**	14	(+)/++[c]	n.d.	n.d.	25
6	**13f**	OMe	OH	OH	**15f**	15	+++	n.d.	n.d.	>60
7	**13g**	OH	OH	H	**15g**	4	+++	(+)	n.d.	25

[a] Uptake was assessed against the uptake of gold-adsorbed asialofetuin, which was defined as highly efficient (++) in all three cell types. +++ = highly efficient uptake, similar to that of the control; ++ = good uptake; + = weak uptake; (+) = uptake in a few events; − = no uptake; n.d. = not determined. [b] Assay detecting cellular growth using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT assay). Concentrations for 50% growth inhibition. [c] Heterogeneous uptake repeatedly seen with a smaller subpopulation demonstrating good uptake.

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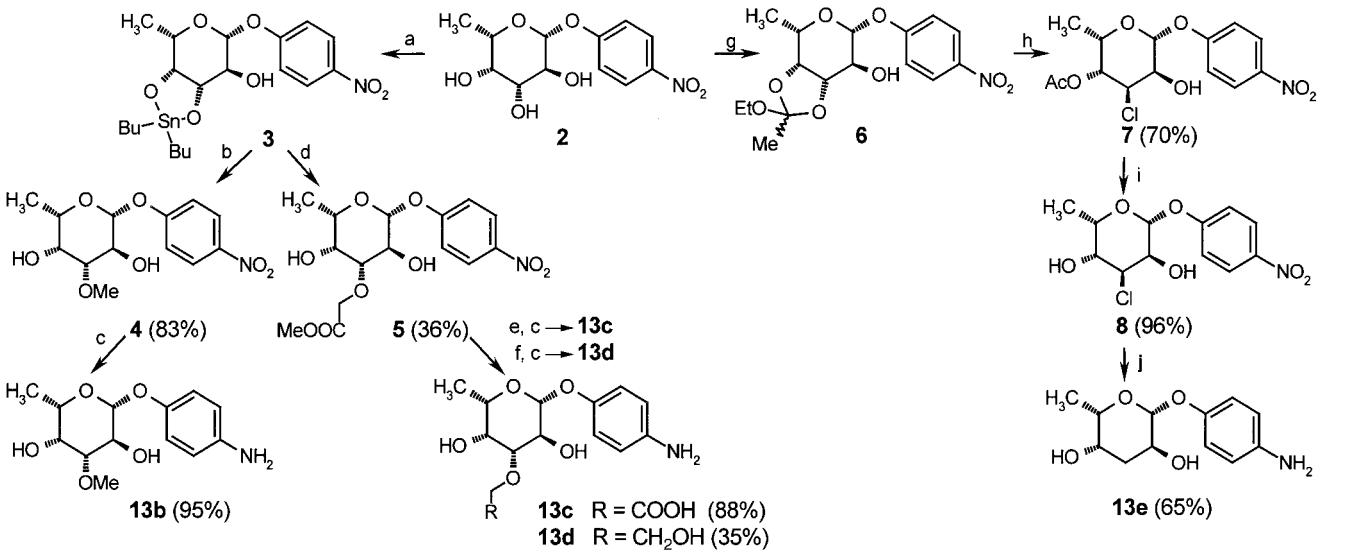


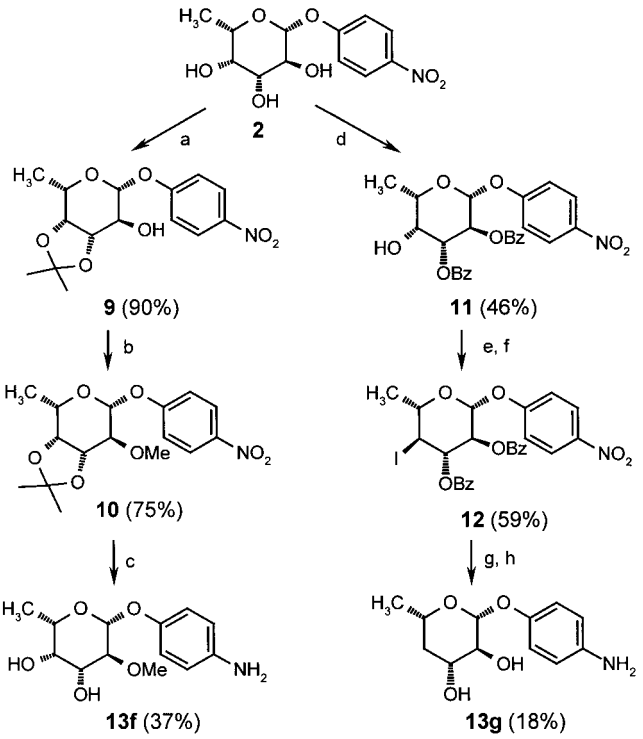
Scheme 2. Synthesis of 3-O-modified *p*-aminophenyl fucosides. a) Bu_2SnO/MeOH; b) MeI/DMF; c) H_2/Pd-C, MeOH; d) $BrCH_2COOMe/Bu_4NI$ in dioxane; e) LiOH, MeOH, then Lewatit SC108; f) $NaBH_4$, THF/H_2O 40 °C; g) triethyl orthoacetate, *p*-TosOH, THF; h) HCl/CH_2Cl_2; i) MeOH/NaOMe; j) H_2/Pd-C, MeOH, NEt_3. Tos = toluene-4-sulfonyl.

dioxane resulted in an opening of the tin acetal and an alkylation of the more reactive equatorial position with high regioselectivity. Particularly the 3-O-methylated derivative **4** was obtained in 83 % yield and was subsequently reduced with hydrogen on palladium/charcoal to yield *p*-aminophenyl 3-*O*-methyl-β-L-fucoside (**13b**).

The alkylation of **3** with methyl bromoacetate proceeded most efficiently at 100 °C in dioxane in the presence of catalytic amounts of tetrabutylammonium iodide. The intermediate methyl ester **5** was cleaved with lithium hydroxide in methanol. The carboxylate was acidified with the ion-exchange resin Lewatit SC108 [H^+] and subsequently reduced to give *p*-aminophenyl 3-*O*-carboxymethyl-β-L-fucoside (**13c**). Alternatively, **5** could be transformed in two reduction steps with sodium boranate in THF/water at 40 °C and subsequent hydrogenolysis to *p*-aminophenyl 3-*O*-hydroxyethyl-β-L-fucoside (**13d**).

Ortho esters of *cis* hydroxyl groups in carbohydrates have been shown to open preferentially to the axially acylated derivatives.[13] Compound **2** was converted into a mixture of diastereomeric ortho esters **6** (Scheme 2). During the efforts to convert the 2-hydroxyl group of **6** with benzoic acid chloride into the benzoate, a side reaction of an opening of the ortho ester with chloride ions was observed. Upon treatment of **6** with hydrogen chloride in dichloromethane this reaction was the main reaction, giving the 3,6-dideoxy-3-chloro-L-gulose derivative **7** in 70 % yield. This reaction should open an efficient access to *p*-aminophenyl 3-deoxy-β-L-fucoside (**13e**). The acetyl group was removed with catalytic amounts of sodium methoxide in methanol under Zemplén conditions to avoid epoxide formation and to give the gulose derivative **8**. Hydrogenolysis of **8** in methanol in the presence of triethylamine as acid scavenger gave **13e** in one step.

Selected procedures for a regioselective modification of the 2- and 4-hydroxyl groups of *p*-nitrophenyl β-L-fucoside are exemplified in Scheme 3: For access to the 2-hydroxyl group the *cis*-configured 3- and 4-hydroxyl groups were protected as



Scheme 3. Synthesis of 2- and 4-O-modified *p*-aminophenyl fucosides. a) 2-methoxypropene, *p*-TosOH in dioxane/DMF; b) MeI (5 equiv) in THF, then NaH (1.5 equiv); c) 80 % AcOH, H_2/PtO_2, d) BzCl (2 equiv), CH_2Cl_2, pyridine, −35 °C; e) $(CF_3SO_2)_2O$, CH_2Cl_2; f) NaI, DMF; g) H_2/PtO_2, MeOH, NEt_3; h) NaOMe, MeOH. Bz = benzoyl.

isopropylidene acetal (→**9**) with methoxypropene in dioxane/DMF in the presence of *p*-toluenesulfonic acid. Subsequently the 2-hydroxyl group was deprotonated with 1.5 equivalents of sodium hydride in the presence of a fivefold excess of methyl iodide, giving the 2-alkylated derivative **10** in 75 % yield. Hydrogenolysis with hydrogen on platin oxide in 80 % acetic acid gave *p*-aminophenyl 2-*O*-methyl-β-L-fucoside (**13f**) in one step in 37 % yield.

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The axial 4-hydroxyl group in the fucose moiety is the least reactive with respect to acylations.[14] It was possible to acylate selectively the 2- and 3-hydroxyl groups of **2** with benzoic acid chloride in dichloromethane in the presence of pyridine at low temperatures (−35 °C). The 4-hydroxyl group of **11** was allowed to react with trifluoromethanesulfonic acid anhydride, and the corresponding triflate was substituted by iodide. Hydrogenolysis in the presence of triethylamine followed by alcoholysis of the benzoates with sodium methoxide in methanol gave *p*-aminophenyl 4-deoxy-β-L-fucoside (**13g**).

Each of the modified *p*-aminophenyl β-L-fucoside derivatives **13b**–**g** was treated, in analogy to **13a**, with the batracylin–BSA conjugate **14** to give the conjugates **15b**–**g** (Scheme 1). Subsequently, these conjugates were adsorbed onto colloidal gold particles of 5 or 17 nm in diameter for electron microscopic detection of cellular uptake.[15] Gold sols were prepared by reduction of a chloroauric acid solution with phosphoric acid (for 5-nm particles) or sodium citrate (for 17-nm particles). These gold sols were mixed with conjugate solutions at a final concentration of 10 μg of protein per mL of gold sol, stabilized with addition of polyethylene glycol, and washed by centrifugation to remove excess protein. Saturation of the adsorption was monitored by color changes after addition of excess NaCl. Freshly isolated or cultured cells were incubated with the coated gold particles at 4 °C for monitoring the binding or at 37 °C for studying uptake, and processed for electron microscopy after removal of unbound ligands. The uptake into the tumor cell line SW480 and into liver cells such as Kupffer cells and hepatocytes was semiquantitatively assessed in comparison to the endocytosis of gold-adsorbed asialofetuin as a control. Furthermore, cytotoxic activity of the conjugates **15a**–**g** against SW480 tumor cells has been measured using the MTT assay (Table 1).

The BSA glycoconjugate **15a** carrying unmodified β-L-fucose epitopes was endocytosed by SW480-tumor cells, but even more efficiently by Kupffer cells and hepatocytes (Table 1, entry 1). The analogues BSA glycoconjugates with 2-*O*-methyl- and 4-desoxyfucoside epitopes (**15f** and **15g**) did not show any decrease of cellular uptake into Kupffer cells compared to **15a** (Table 1, entries 6 and 7). In contrast, BSA conjugates with various fucose epitopes modified in the 3-position, **15b**–**e** (Table 1, entries 2–5), exhibited a marked decrease of liver cell endocytosis compared to **15a**.

Furthermore, as shown for **15b** and **15c**, the tumor cell line SW480 apparently tolerated a modification of the fucose epitopes in this particular position and exhibited an efficient endocytosis of those glycoconjugates. The desired discrimination between tumor and liver cells was most pronounced with the BSA conjugate **15c**, carrying 3-*O*-carboxymethylfucoside epitopes.

Owing to the attached batracyline residues the neoglycoconjugates with fucose residues which are unsubstituted or modified in the 3- or 4-position also demonstrated a significant cytotoxic activity. Concentrations for 50% growth inhibition were in the range of 7-25 μM, which is expected in the case of cellular uptake (Table 1). In contrast, the carbohydrate-free batracyline–BSA conjugate **14** did not show any cytotoxic activity at SW480, and also the cytotoxic activity of **15f** was markedly decreased, indicating a carbohydrate-mediated uptake and cytotoxicity of the glycoconjugates **15a**–**e** and **15g**.

These results indicate that in particular the modification of the 3-position of fucose residues leads to the desired discrimination of cellular uptake between tumor and liver cells. Furthermore, the detected uptake into tumor cells correlates with a cytotoxic activity of these neoglycoconjugates.

Thus, BSA neoglycoconjugates have proven to be powerful tools for identifying carbohydrate residues which might be suitable for tumor targeting. However, its use in vivo might be limited because of the immunogenic potential. Therefore, the investigation of the tumor targeting potential of the identified carbohydrate residues using low molecular weight glycoconjugates of cytotoxic agents is ongoing.

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