Supplementary material

Structures of some antitumor lipophilic prodrugs (Fig. 1) [1-3] and glycoconjugates (Fig. 2) [2,4,5] synthesized in IBC RAS are shown.

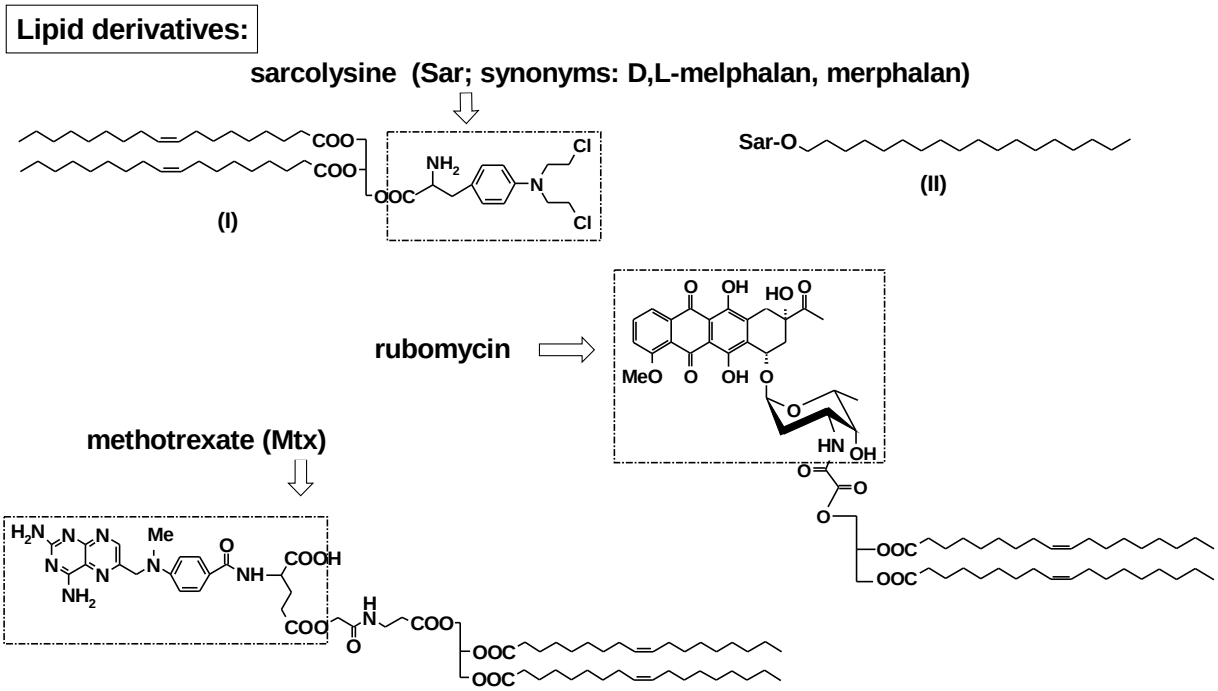

Fig. 1. Some lipid derivatives of antitumor drugs.

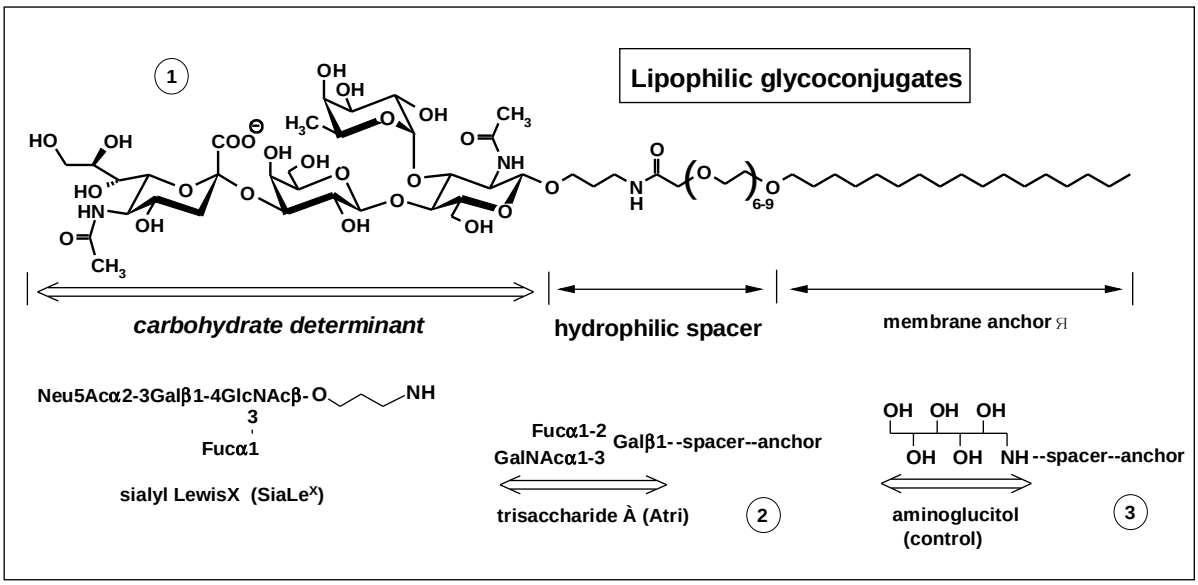

Fig. 2. Some carbohydrate-bearing liposomal addresses (lipophilic glycoconjugates) synthesized on the basis of Lubrol: 1, SiaLe^{X}-conjugate; 2, Atri-conjugate; 3, control analog bearing inactive carbohydrate residue.

Figure 3 shows the structure of liposome prepared by extrusion of all the components suspended in physiological buffer through membrane filters with pores of ca 100 nm.

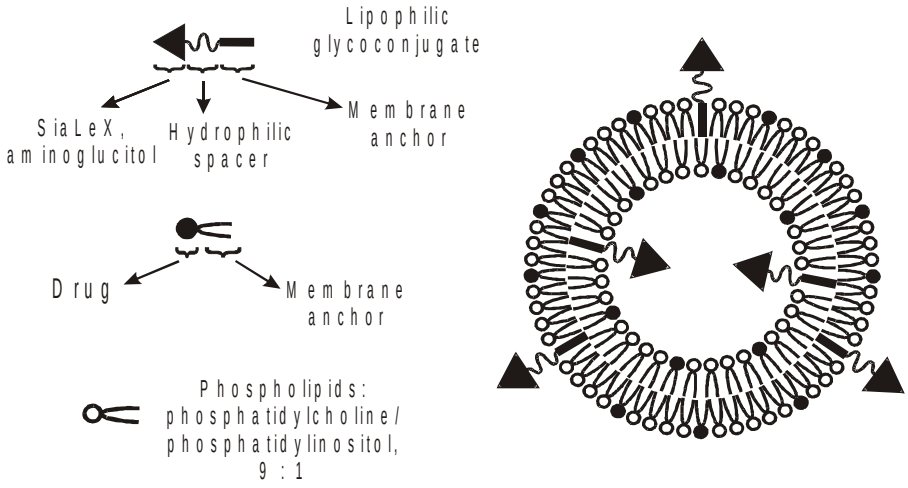

Fig. 3. Scheme of a drug-loaded addressed liposome.

Therapeutic effect of targeted cytotoxic liposomes is represented by the survival dynamics of mice with grafted mammary adenocarcinoma in different experimental groups [6] (Fig. 4).

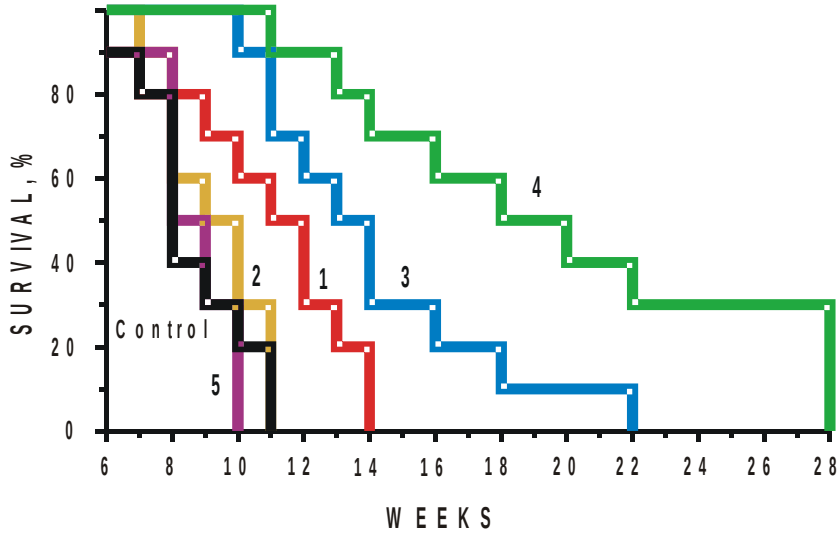

Fig. 4. Weekly survival dynamics for different experimental groups. Mice of each group (20-w. age; 10 in each group) were given two i.v. injections on the 3rd and 7th days after mammary adenocarcinoma cell inoculation: 1, sarcolysine (merphalan, Mrph; 7 mg/mg); 2, empty liposomes; 3, liposomes with C_{18}-Mrph (**II**); 4, liposomes with C_{18}-Mrph (**II**) + SiaLeX-conjugate; 5, liposomes with SiaLeX-conjugate only; control, phosphate-buffered saline.

Testing of the antitumor activity of addressed liposomes bearing the sarcolysine *LP* (**I**), on mouse model BLRB-Rb (8.17)1Iem with spontaneous mammary adenocarcinoma were carried out; such tests simulate closely the tumor treatment in humans. The animal survival data are shown in Fig. 5.

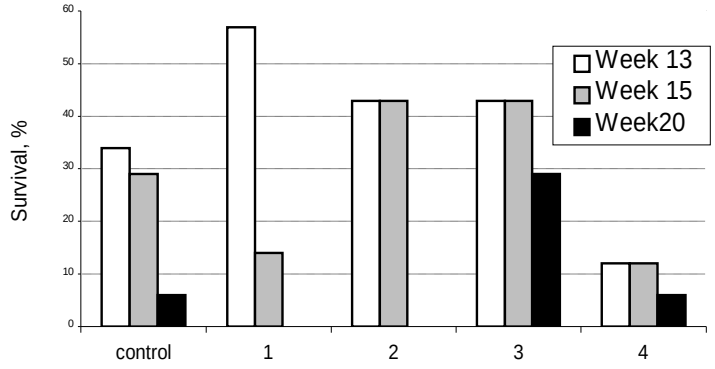

Fig. 5. Survival of female BLRB mice with spontaneous mammary carcinoma at the 13th, 15th and 20th week after visual detection of tumor (4–5 mm). Animals were given two i.v. injections: 1st group (7 mice), liposomes with sarcolysine *LP* (**I**); 2nd group (7 mice), liposomes with sarcolysine *LP* (**I**) and SiaLe^x-ligand on PEG(9–16)-diglyceride; 3rd group (8 mice), liposomes with sarcolysine *LP* (**I**) and SiaLe^x-ligand on PEG(9–16)-C17 (Lubrol); 4th group (16 mice), sarcolysine; control, 35 mice.

Obviously, treatment with different liposomal forms of sarcolysine *LP* (**I**) is more effective as compared to intact initial drug (4th group), the targeted drug liposomes (2nd and 3rd groups) surpassing non-targeted (1st group). Cytotoxic liposomes equipped with SiaLe^x-ligand on Lubrol (3rd group) have more expressed durable action than the preparation bearing SiaLe^x-determinant on PEG(9–16)-diglyceride (2nd group). It was shown also that survival improvement after the addressed liposome treatment was brought about not only and rather than by tumor eradication of initial tumor but more precisely by metastasing prevention. A paper will be submitted soon on this matter.

References

1. Vodovozova E.L., Nikolskii P.Yu., Mikhalev I.I., Molotkovsky J.G. Lipid derivatives of sarcolysine, methotrexate, and rubomycin. *Russ. J. Bioorgan. Chem.* 1996, **22**, 468-475.
2. Vodovozova E.L., Khaidukov S.V., Gayenko G.P., Bondarchuk T.N., Mikhalyov I.I., Grechishnikova I.V., Molotkovsky J.G. The transport of cytotoxic liposomes to malignant cells by means of carbohydrate determinants. *Russ. J. Bioorg. Chem.* 1998, 24, 676-682.
3. Vodovozova E.L., Yevdokimov D.V., Molotkovsky J.G. A synthesis of the lipid derivative of antitumor agent methotrexate. *Russ. J. Bioorg. Chem.* 2004, 30, 663-665.
4. Korchagina EYu, Bovin NV. Synthesis of spacered trisaccharides with blood group specificities A and B, their fragments and structural analogs. *Russ. J. Bioorgan. Chem.* 1992, **18**, 283-298.
5. Nifant'ev N.E., Tsvetkov Y.E., Shashkov A.S., Kononov L.O., Menshov V.M., Tuzikov A.B., Bovin N.V. Selectin receptors 4: synthesis of tetrasaccharides sialyl Lewis A and sialyl Lewis X containing a spacer group. *J. Carbohydr. Chem.* 1996, **15**, 939-953.
6. Vodovozova E.L., Moiseeva E.V., Gayenko G.P., Nifant'ev N.E., Bovin N.V., Molotkovsky J.G. Antitumour activity of cytotoxic liposomes equipped with selectin ligand SiaLeX, in mouse mammary adenocarcinoma. *Eur. J. Cancer* 2000, **36**, 942-947.