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TARGETING GRANULOCYTIC TUMOR CELLS WITH CHOLIC ACID PRODRUG CONJUGATES

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Introduction

While investigating the antitumor compounds based on N-alkylaminoferrocene prodrugs, which enhance reactive oxygen species production in the tumor cells and thus killing them we wanted to add the targered delivery of feature to these next-generation antitumor compounds. The prodrugs were investigated in mouse leukemia induced by myeloid cells of the NK/Ly line.

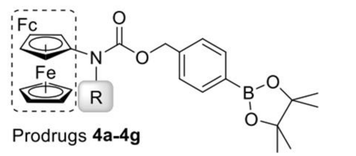
Material & Methods

These tumor cells express high levels of myeloblastic antigens CD11b, Ly6C, as well as attributable to granulocytes, in particular neutrophils, markers CD16, Ly6G and neutrophil elastase enzyme.

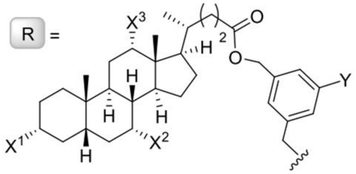
We used flow cytometry to immunophenotype cells and determine their viability, fluorescence microscopy to determine accumulation of compounds in cells and determine their sublimated localization, induction of tumors in laboratory animals and evaluation of antitumor activity in vivo

Results

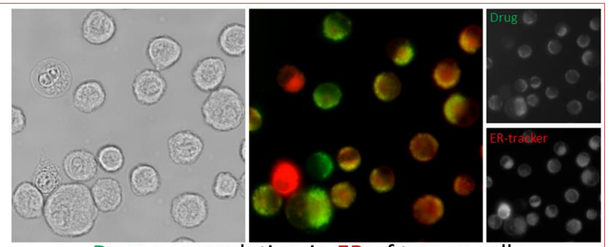
Selectioned NK/Ly cells were co-incubated with N-alkylaminophericen-7-hydroxycoumarin-cholic acid conjugate and fluorescence of 7-hydroxycoumarin residue was observed in the cells by fluorescence microscopy. The signal was localized around the nucleus in the area inherent to the endoplasmic reticulum. The use of dye ER-tracker dye confirmed the co-localization of the signal in the endoplasmic reticulum. Upon entering the cells, the compounds caused an increase in the level of reactive oxygen species, which was sufficient to induce cell death. Intraperitoneal administration of the compound to mice (1uM every other day, a total of 10 injections) with NK/Ly-RB-induced myeloma resulted in a significant almost twofold reduction in tumor growth rate (as assessed by animal weight), starting on day 9 of the experiment



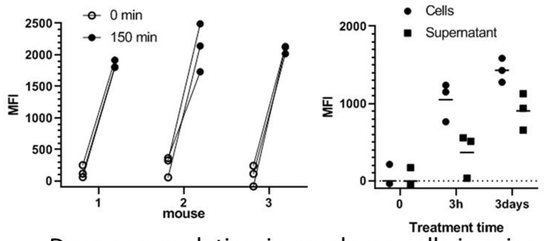
Prodrugs **4a-4g**



Cholic-acid conjugated ROS amplifier



Drug accumulation in ER of tumor cells



Drug accumulation in myeloma cells in mice

Conclusions

The ability of neutrophilic granulocytes to interact with cholesterol-derived lipids, such as cholic acid, can be successfully used to target specific compounds to these cells. We have successfully targeted ROS-amplifying anticancer prodrugs resulting in inhibition of myeloma development in mice.

Details in Mokhir et al., Angew. Chem. Int. Ed., 2021, 10.1002/anie.202100054