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PII: S0168-3659(18)30548-0
DOI: doi:10.1016/j.jconrel.2018.09.018
Reference: COREL 9470

To appear in: *Journal of Controlled Release*

Received date: 20 June 2018
Revised date: 17 September 2018
Accepted date: 20 September 2018

Please cite this article as: Tomáš Etrych, Lenka Daumová, Eva Pokorná, Diana Tušková, Ondřej Lidický, Věra Kolářová, Jan Pankrác, Luděk Šefc, Petr Chytil, Pavel Klener , Effective doxorubicin-based nano-therapeutics for simultaneous malignant lymphoma treatment and lymphoma growth imaging. Corel (2018), doi:10.1016/j.jconrel.2018.09.018

Effective doxorubicin-based nano-therapeutics for simultaneous malignant lymphoma treatment and lymphoma growth imaging

Tomáš Etrych[1,*], Lenka Daumová[2], Eva Pokorná[2], Diana Tušková[2], Ondřej Lidický[1], Věra Kolářová[3], Jan Pankrác[3], Luděk Šefc[3], Petr Chytil[1], Pavel Klener[2,4]

[1] Institute of Macromolecular Chemistry, Czech Academy of Sciences, Heyrovského nám. 2, 162 06 Prague 6, Czech Republic

[2] Institute of Pathological Physiology, First Faculty of Medicine, Charles University in Prague, U Nemocnice 5, 128 53 Prague 2, Czech Republic

[3] Center for Advanced Preclinical Imaging (CAPI), First Faculty of Medicine, Charles University in Prague, Salmovská 3, 128 53 Prague 2, Czech Republic

[4] First Dept. of Internal Medicine - Hematology, Charles University General Hospital in Prague, Czech Republic, U Nemocnice 2, 128 08 Prague 2, Czech Republic

* Corresponding author. Tel.: +420-296 809 231; fax: +420-296 809 410

E-mail address: etrych@imc.cas.cz (T. Etrych).

Abstract: In this study, we report the *in vivo* anti-lymphoma efficacy and diagnostic potential of newly designed near-infrared fluorescent dye containing polymer-doxorubicin conjugates using murine models of malignant lymphomas including one cell line-derived xenograft (RAJI) and two patient-derived lymphoma xenografts (VFN-D1 and VFN-M2). Two types of passively targeted conjugates differing in architecture of the polymer backbone were synthesized. One of the conjugates was designed using a single linear polymer chain, and the second was more sophisticated with a star-shaped high-molecular-weight (HMW) polymer employing a dendrimer core. The linear HPMA copolymers were linked to the dendrimer core via a one-point attachment, thus forming a hydrophilic polymer shell. Both polymer-doxorubicin conjugates were long-circulating with reduced side effects. Both polymer prodrugs were designed as stimuli-sensitive systems in which the anti-cancer drug doxorubicin was attached to the hydrophilic copolymers via a pH-labile hydrazone linkage. Such polymer prodrugs were fairly stable in aqueous solutions at pH 7.4, and the drug was readily released in mildly acid environments at pH 5-6.5 by hydrolysis of the hydrazone bonds. In addition, polymers were labelled with near-infrared fluorescent dye enabling long term *in vivo* visualization. Malignant lymphomas represent the most common type of haematological malignancies. Therapy for the majority of malignant lymphomas consists of multi-agent chemotherapy based on an anthracycline doxorubicin, the most prominent side effect of which is cardiotoxicity. We have demonstrated significant anti-lymphoma efficacy of the polymer-doxorubicin conjugates when