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Passive and specific targeting of lymph nodes: influence of the administration route

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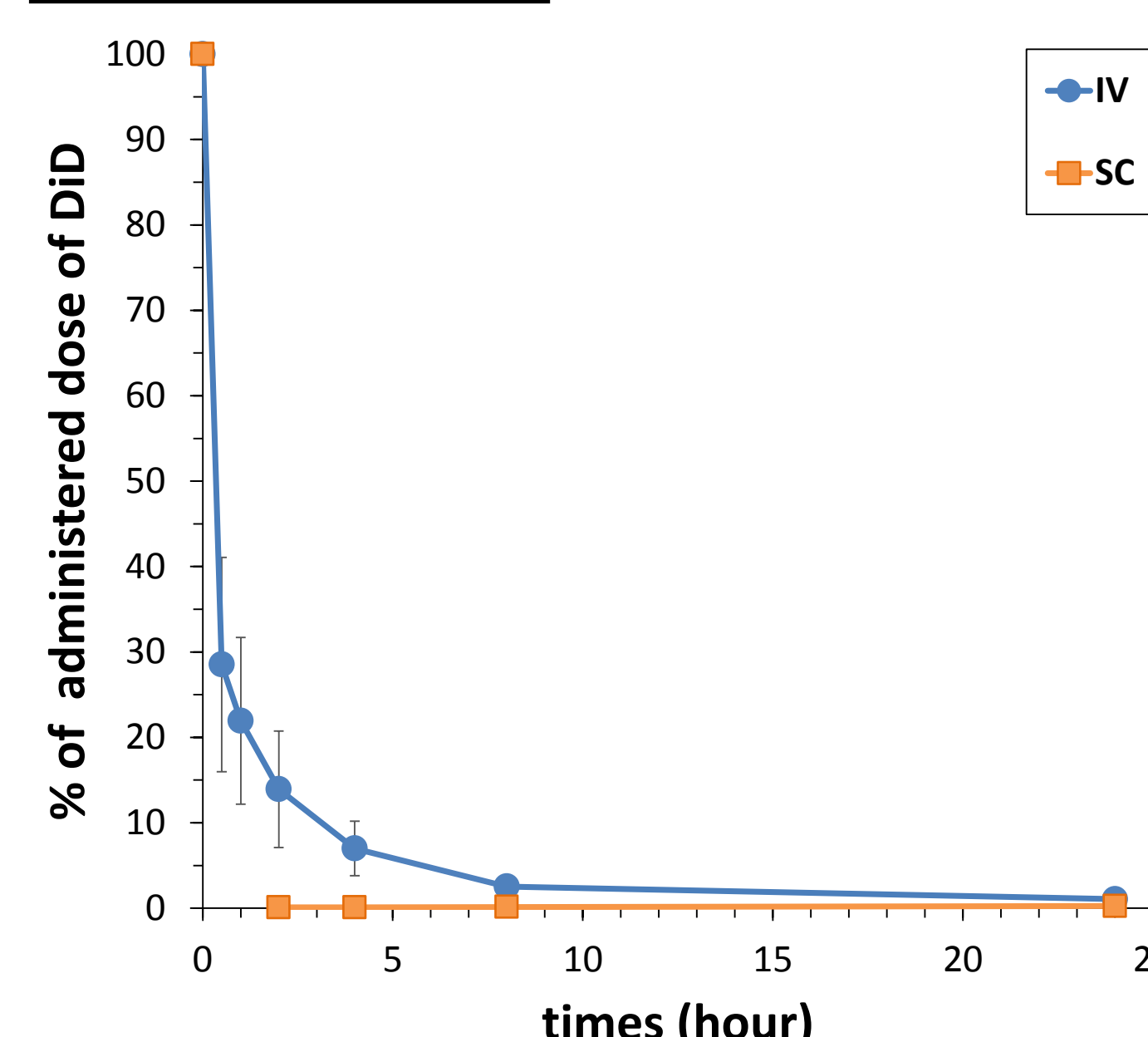
Introduction

Patients with cancer, diagnosed in advanced stage with the presence of metastases in lymph nodes, present a dismal prognosis. Therefore, the targeting of lymph nodes and/or metastases need to be improved in the design of future chemotherapy. Using a lymphogenous metastatic model, the tumor cells (human Ma44-3 cells) implanted in lung were spontaneously disseminated to mediastinum. Using lauroyl modified gemcitabine-loaded lipid nanocapsules (LNCs) to treat the tumor, an accumulation of nanocarriers in mediastinum and associated lymph nodes was observed, after subcutaneous (SC) and/or intravenous (IV) administration.¹ In this study, a correlation between SC sites for LNC administration and specific lymph node accumulation was achieved.

Materials & methods

LNCs were prepared as previously reported with a size of 30 nm (Z-Average) and with the encapsulation of 1,1'-dioctadecyl-3,3,3',3'-tetramethylindodicarbocyanine 4-chlorobenzenesulfonate (DiD) for fluorescence labeling.^{1,2} LNC suspensions were IV (tail vein) and SC (behind the neck, left and right flanks, above the tail) administered to Sprague Dawley rats (9-week females). Blood samples and specific organs (liver, spleen, left and right cervical, axillary, inguinal lymph nodes) were recovered vs. time (until 28 days) to establish pharmacokinetic and biodistribution profiles using fluorescence techniques (spectroscopy and imaging). Fluorescence-labeling of the nanocarriers was performed with the encapsulation of DiD inside LNCs to follow the *in vivo* LNC future. This labeling presents a great stability.³

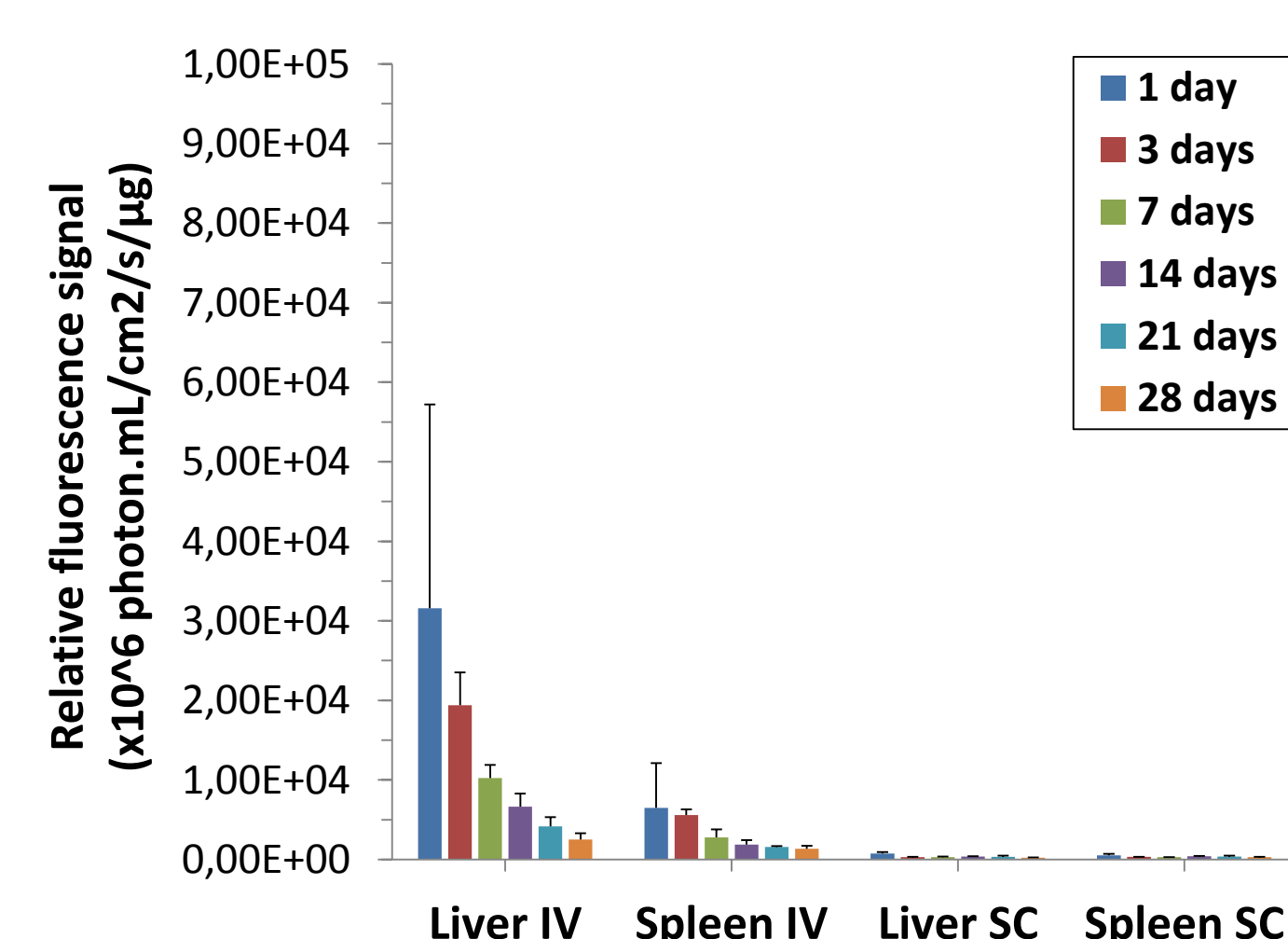
Pharmacokinetics



After SC administrations, no LNC was observed in systemic circulation whatever the injection site while a typical pharmacokinetic profile was obtained after IV administration.

fig. 1 Pharmacokinetic profiles (% of administered dose of DiD vs. time) of DiD-LNC in healthy rats, after (●) intravenous (IV) injection (tail vein) and (■) subcutaneous (SC) injection (on the left flank). (n=4, mean ± SD).

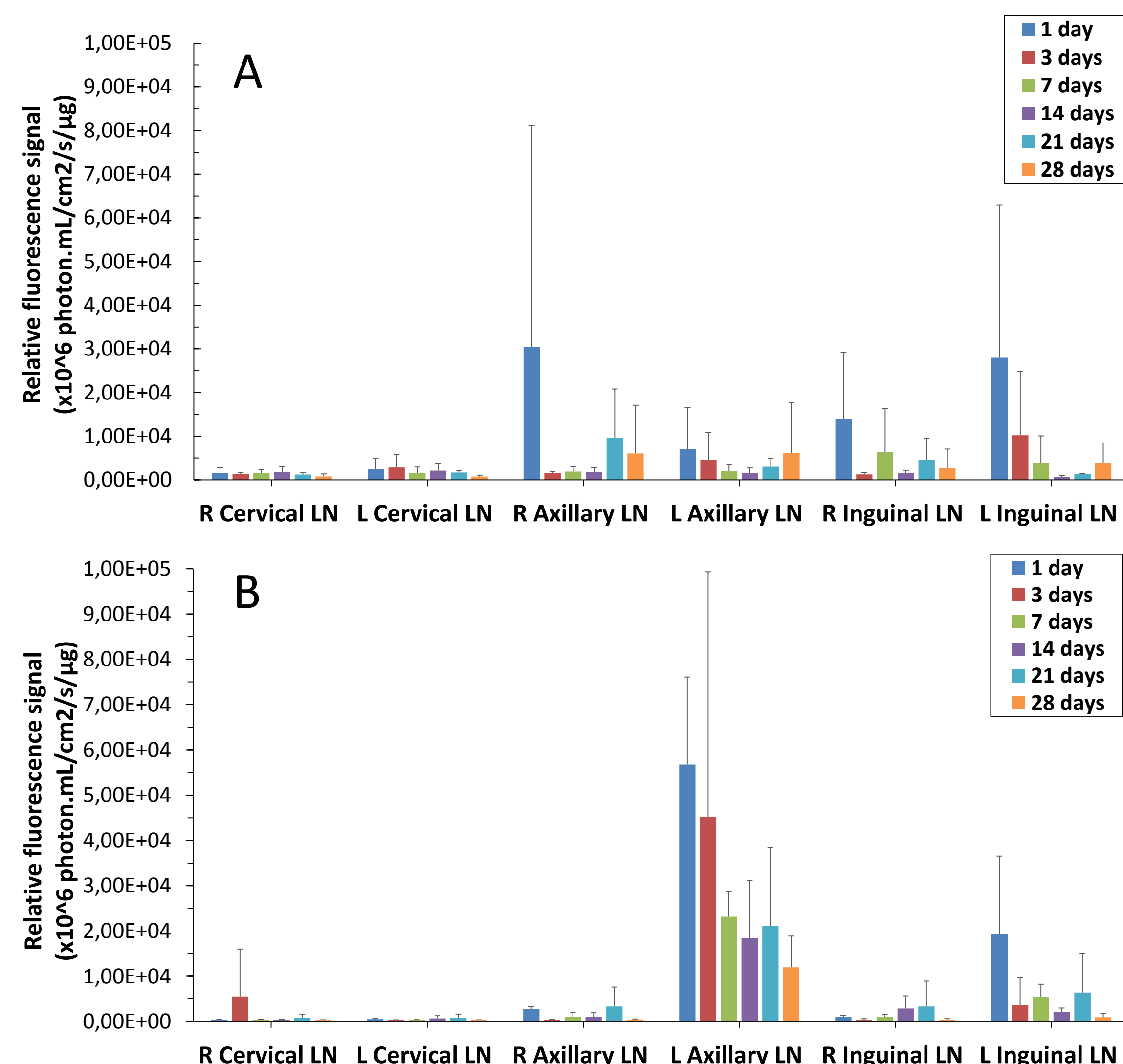
In vivo biodistribution in liver and spleen



LNCs accumulated in liver and spleen after IV administration while no LNC was observed in these organs after SC administrations. These results confirmed the absence of LNC in systemic circulation after SC injection, observed in the pharmacokinetics part.

fig. 2 *In vivo* biodistribution of DiD-LNC suspension in healthy rats, after intravenous injection (tail vein) and subcutaneous injection (on the left flank). Semi-quantification of the fluorescence signals (relative to DiD injected dose) of the removed liver and spleen using fluorescence images (10 ms integration time) at various times post LNC administrations (1, 3, 7, 14, 21 and 28 days) (n=4, mean ± SD).

In vivo biodistribution in lymph nodes



The IV administered LNCs are spread in all lymph nodes. The SC administration in left flank showed a specific distribution of LNCs only in the left axillary and the inguinal lymph nodes.

Fig. 3 *In vivo* biodistribution of DiD-LNC suspension in healthy rats, after intravenous injection (tail vein) (A) and subcutaneous injection (on the left flank) (B). Semi-quantification of the fluorescence signals (relative to DiD injected dose of the removed left (L) and right (R) cervical, axillary and inguinal lymph nodes (LN) using fluorescence images (10 ms integration time) at various times post LNC administrations (1, 3, 7, 14, 21 and 28 days) (n=4, mean ± SD).

In vivo biodistribution overview

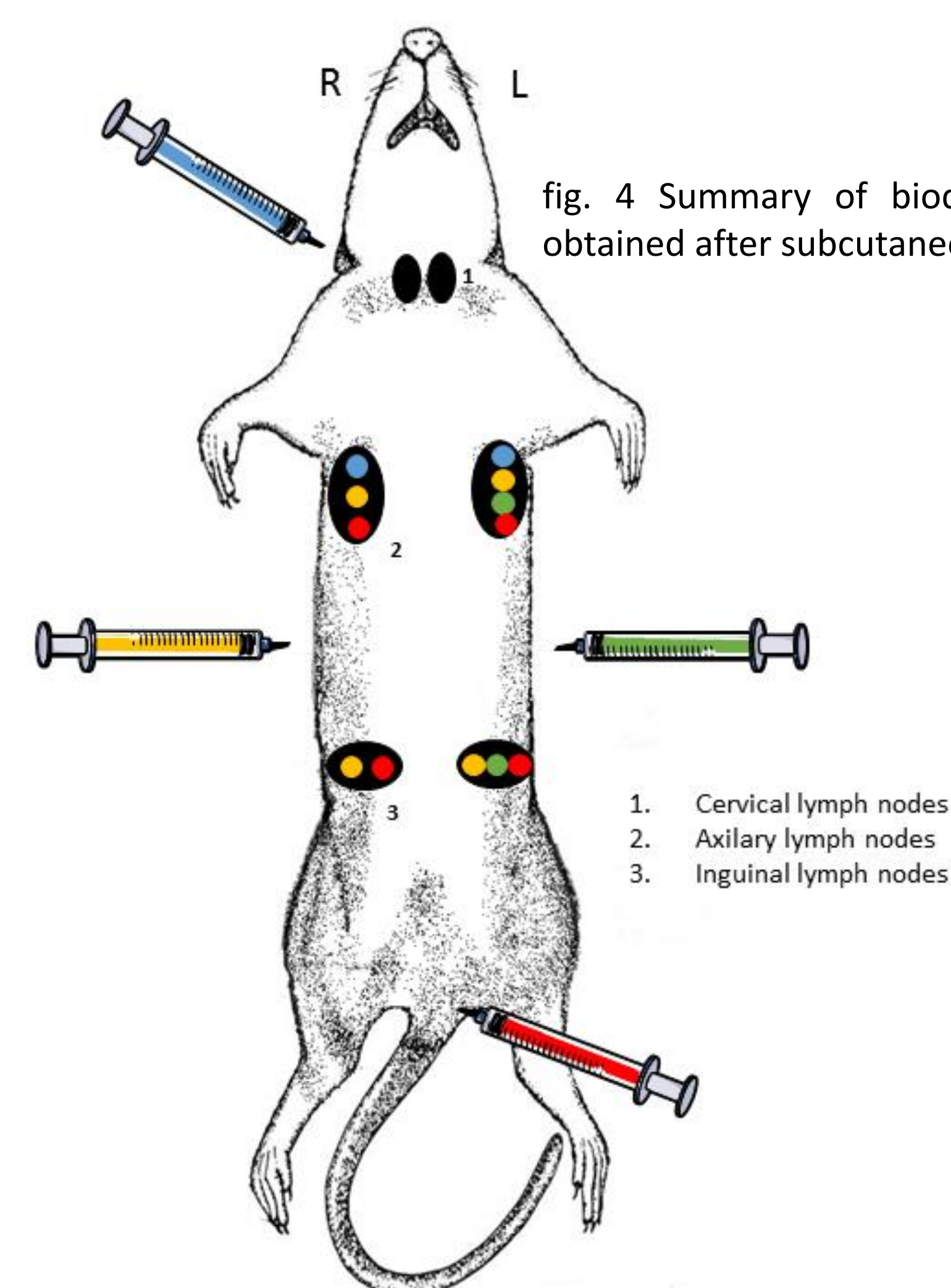


fig. 4 Summary of biodistribution results obtained after subcutaneous injections

After IV administration, a passive targeting was observed in all the studied lymph nodes (left and right cervical, axillary, inguinal ones).

On the other hand, after SC administration, a specific targeting of lymph nodes was observed, depending on the injection site. Whatever the SC injection site, no LNC accumulated in the cervical lymph nodes (left and right).

After SC administration above the tail, LNCs accumulated in all the other lymph nodes (left and right) while after SC administration behind the neck, only the axillary (left and right) lymph nodes (and not the inguinal ones) were targeted. After SC administration in the left flank, only the left lymph nodes (axillary and inguinal ones) were targeted while after SC administration in the right flank, LNCs accumulated in the right lymph nodes but also the left ones.

Conclusion

Passive but specific targeting of lymph nodes was observed, depending on the administration site. With an appropriate SC administration, LNCs can accumulate in specific lymph nodes, while IV administration led to an accumulation of LNCs in overall lymph nodes. A personalized therapeutic scheme for patients could be envisaged when specific lymph node targeting is needed.

References

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