PW065

Effect of different injection routes in tumor accumulation and biodistribution of radiolabeled Pluronic P94 unimers

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Introduction

Pluronic P94 unimers (P94) are amphiphilic tri-block copolymers of poly(ethylene oxide) and poly(propylene exide) (PEO-PPO-PEO) (Fig 1a) with high in vivo stability and relatively long circulation times. Due to the enhanced permeability and retention (EPR) effect, P94 can accumulate in the tumor tissue and therefore be potentially used as drug carrier. For various macromolecules it has been shown that following intravenous (IV) administration (Fig 1b) , limited tumor accumulation occurs versus undesired high liver uptake and clearance via the mononuclear phagocyte system. Intratumoral (IT) administration (Fig 1c) might overcome this limitation by avoiding the systemic circulation and therefore improving the retention in the tumor.

Aim of the study

In this study we compared IT versus IV administration routes of radiolabeled P94 in terms of biodistribution profiles and tumor accumulation and retention over time in a mouse tumor model.

Fig 1. Schematic rapresentation of radiolabeled tracer and injection routes (a) Schematic representation of ^{111}In-DTPA-P94 pluronics; (b) IV injection in the tail vein which provide systemic circulation of tracer and passive targeting in the tumor; (c) IT injection is carried out injecting directly in the tumor core allowing for local retention and low systemic involvement

Material and Methods

H69 tumors were grown subcutaneously for approximately 3 weeks in Balb/c nude mice (N=20).

P94 were modified by adding an -NH_2 teminal, a DTPA chelator and labeled with ^{111}In reaching a lebeling efficiency of 96%. ^{111}In-DTPA-P94 unimers were injected in tumor-bearing mice following two injection routes:

- IV: N=8, 0.2 mg/mouse, ~ 10 MBq/animal
- IT: N=8, 0.1 mg/mouse, ~ 5 MBq/animal

For a negative control in IT condition, ^{111}In-DTPA (200 pmol/mouse ~3MBq) was injected in 4 tumor bearing mice.

Molecular SPECT/CT imaging was performed at different time points post injection (pi): early (30 min or 4 h pi), intermediate (24 h pi), late time points (48 h pi).

Ex vivo biodistribution was determined in isolated organs at 48 h and 96 h pi.

Results

SPECT/CT images of ^{111}In-DTPA-P94 after IV injection (Fig 2a-c) show sustained accumulation in the liver, and little uptake in the tumor, which is also confirmed by the ex vivo biodistribution (Fig 2d).

After IT injection both the SPECT/CT images and ex vivo biodistribution shows that tumor has elevated retention while liver and off-target organs show a limited uptake (Fig 2e-i)

Different injection routes of ^{111}In-DTPA-P94 depicts discordant retention in critical organs, namely tumor and liver (Fig 3a).

Ex vivo biodistribution, at two different time points indicates the general trend of each organs to reduce the retention over time (Fig 2d and 2i). The retention of ^{111}In-DTPA-P94 over time was estimated by the calculation of tumor to tissue ratio (TTR) (Fig 3 b).

For both injection routes, although the effect is more visible after IT injection, the TTR increases. This finding suggest that there is a generalized trend of retention of the traced in the tumor, in contrast with a progressive clearance in other organs.

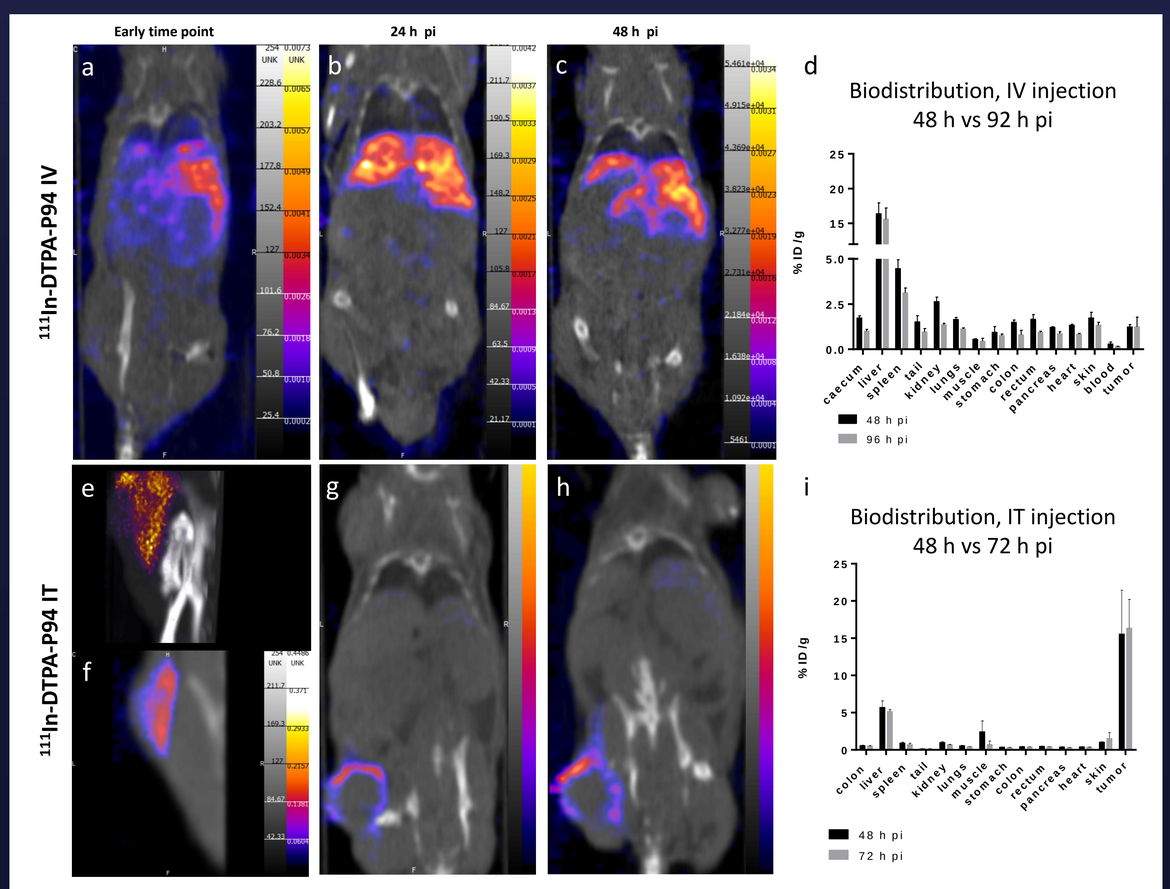

Fig 2. In vivo SPECT/CT imaging and ex vivo biodistribution of H69 tumor bearing mice after IV or IT administration of ^{111}In-DTPA-P94 unimers. (a-c) Whole body SPECT/CT imaging of one representative mouse after IV injection 4 h (a), 24h (b) and 48 h (c) pi. (d) Ex vivo biodistribution 48 h pi (N=4) and 92 h pi (N=4) after injection. The bar represent the average of uptake ± SEM. (e-h) SPECT/CT imaging of one representative mouse after IT injection. Focus scan on the tumor region, 30 min pi (e: maximum intensity projection , f: coronal view); whole body scan 24 h (g) and 48 h (h) pi. (i) Ex vivo biodistribution 48 h pi (N=4) and 72 h pi (N=4) after injection. The bar represent the average of uptake ± SEM.

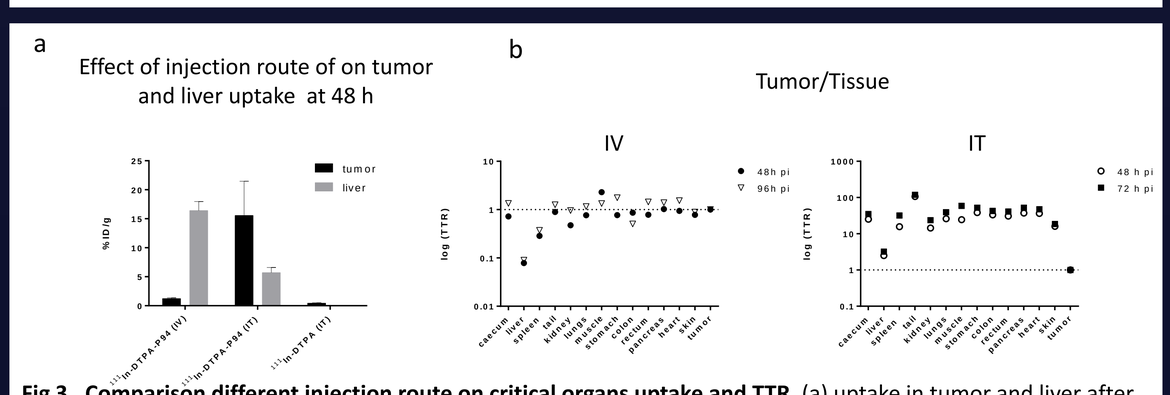

Fig 3. Comparison different injection route on critical organs uptake and TTR. (a) uptake in tumor and liver after ^{111}In-DTPA-P94 administration IV and IT and after IT injection of ^{111}In-DTPA . The bar represents the average of the uptake (N=4) ± SEM. (b) Tumor to tissue ratio over time after IV or IT injection. The dots represent the average of uptake for each organ (N=4).

Conclusions

IV injection of ^{111}In-DTPA-P94 resulted in limited tumor uptake, whereas IT administration substantially increased the uptake in the tumor. The minimal involvement of off-target tissue, including liver, and the tracer retention over time especially for IT administration, confirmed the potential of ^{111}In-DTPA-P94 to be used as a carrier for therapeutic radionuclides.