Optimization of the biodistribution of 1C1m-Fc, an anti TEM-1 fusion protein antibody, un soft tissue sarcoma model in mice

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Introduction

1C1m-Fc is an anti TEM-1 scFv-Fc fusion antibody developed in Lausanne. Our previous study showed the interest of this new compound radiolabeled with ^{177}Lu for molecular imaging in soft tissue sarcoma.

Purpose :

Even if the TEM-1 positive uptake was specific, we also observed an important liver uptake that was not saturation-dependent. Our hypothesis for this phenomenon was the influence of the number of chelator (DOTA) on the biodistribution.
The aim of this study was to verify this hypothesis and find the best ratio of DOTA per antibody to develop an optimal radiolabeled compound for theranostic applications.

Materials and methods

1C1m was conjugated with six different concentrations of DOTA (evaluated by mass spectrometry).
The different conjugates were radiolabelled with 177Lu and injected in mice bearing TEM-1 positive tumors.
In each group, three animals were euthanized by CO2 inhalation and exsanguinated at 24h after injection of the radiolabeled product.
Blood was collected, organs and tumors were removed, weighed, and the activity was measured by gamma counter.

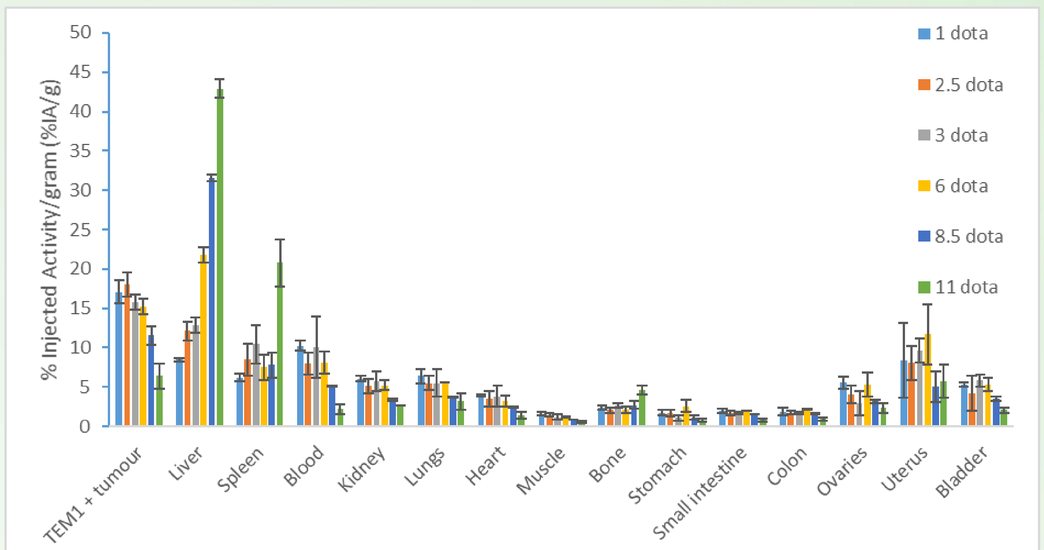
Results

Number of DOTA per 1C1m-Fc	Bmax (cpm)	Total Act (cpm)	Immunoreactivity (%)
1	1742	2046	**85.1**
3	3200	4540	**70.5**
6	2234	2553	**87.5**
8.5	3557	4541	**78**
11	1098	4414	**24**

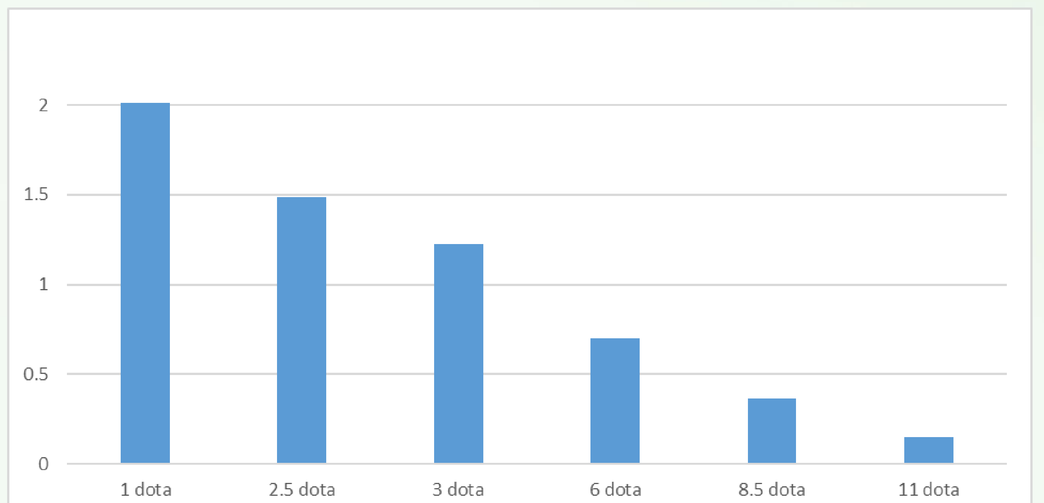
Lindmo assays results for [177Lu]Lu-1C1m-Fc conjugated with 1 to 11 DOTA.
No correlation between the IR and the number of DOTA until 8.5.
Dramatical loose of IR for 1C1m-Fc conjugated with 11 DOTA.

Conclusion :

The number of DOTA molecules attached per antibody moiety plays a significant role in determining successful tumor targeting with radiolabeled antibodies. 1 DOTA per antibody seems to be the best ratio to maintaining a balance between radiochemical yield, immunoreactivity and pharmacokinetic behavior. Our next step would be to measure immunoreactivity to gain more insight about the possible mechanism.



Biodistribution at 24 hours of [177Lu]Lu-1C1m-Fc conjugated with 1 to 11 DOTA in Balb/c nu mice bearing TEM-1 positive tumour. Data are shown as mean ± SD.



Ratio between the tumour and the liver mean uptake at 24 h regarding the number of DOTA per [177Lu]Lu-1C1m-Fc in Balb/c mice bearing TEM-1 positive tumour. Spearman test giving a rho = - 0.99, p < 0.0001

	1 DOTA	3 DOTA
Source organ	Mean Abs Dose (mGy/MBq)	Absorbed dose (mGy/MBq)
Tumor SK-N-AS	2.53E+03	1.82E+03
Liver	1.79E+03	2.23E+03
Kidneys	1.32E+03	7.05E+02
Lungs	9.83E+02	5.39E+02
Spleen	1.18E+03	1.20E+03
Uterus	1.83E+03	1.5 E+03

Mouse dosimetry comparison between [177Lu]Lu-1C1m-Fc conjugated with 1 or 3 DOTA.
Tumor/Liver ratio multiplied by 1.7 with the 1C1m-Fc conjugated with 1 DOTA vs 3 DOTA.

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