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Murine Model of Multiple Myeloma**

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► **To cite this version:**

A. Navarro, T. Le Bihan, Patricia Remaud-Le Saëc, Sébastien Gouard, N. Le Bris, et al.. Biodistribution, Imaging and Metabolism Studies of 64-Copper Radiolabelled Monoclonal Antibody : Comparison of DOTA and TE1PA Chelating Agents in a Murine Model of Multiple Myeloma. *European Journal of Nuclear Medicine and Molecular Imaging*, Springer Verlag (Germany), 2018, 45 (1), pp.S119-S120. inserm-02344286

HAL Id: inserm-02344286

<https://www.hal.inserm.fr/inserm-02344286>

Submitted on 4 Nov 2019

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Biodistribution, Imaging and Metabolism Studies of 64-Copper Radiolabelled Monoclonal Antibody: Comparison of DOTA and TE1PA Chelating Agents in a Murine Model of Multiple Myeloma

A. Navarro^{1,2}, T. Le Bihan³, P. Le Saëc¹, S. Gouard¹, N. Le Bris³, C. Bailly^{1,2}, C. Sai-Maurel¹, B. Chalopin¹, J. Gestin¹, M. Chérel^{1,4}, R. Tripier³, A. Faivre-Chauvet^{1,2,4}; ¹Inserm 1232 CRCINA, University of Nantes, Nantes, FRANCE, ²University Hospital, Nantes, FRANCE, ³CNRS 6521 / IBSAM, University of Brest, Brest, FRANCE, ⁴Cyclotron Arronax, Saint-Herblain, FRANCE.

Purpose: TE1PA is a C-functionalized monopicolinate cyclam designed for 64-copper chelation. It was proven to have excellent Cu(II) and Cu(I) chelation properties, with fast kinetics, high thermodynamic stability and resistance to transchelation *in vitro*, and a usefulness for phenotypic imagery when coupled to antibodies. This work presents *in vivo* studies (biodistribution, metabolism and imaging) of TE1PA in a syngenic multiple myeloma model on mice, compared to DOTA, its main competitor.

Materials and methods: *p*-SCN-Bn-TE1PA and DOTA-NHS ester were grafted on 9E7.4 rat IgG_{2a} antibody, targeting murine CD-138. Immunoconjugates were then radiolabelled with ⁶⁴Cu. Both ⁶⁴Cu-9E7.4-*p*-SCN-Bn-TE1PA and ⁶⁴Cu-9E7.4-NHS-DOTA were injected in 12 mice previously grafted with 5T33 cells, allowing the development of subcutaneous tumors expressing CD-138. Each mouse was injected with 100 µg of radioimmunoconjugates corresponding to 10 MBq of ⁶⁴Cu. For each time studied (2h, 24h and 48h post-injection), a biodistribution and a liver metabolism studies were conducted on mice for both radiolabelled antibodies. Additionally, a micro-PET scan was performed on 4 mice injected with ⁶⁴Cu-9E7.4-*p*-SCN-Bn-TE1PA at those 3 times. **Results:** Biodistribution study shows an excellent hepatic clearance of the ⁶⁴Cu-9E7.4-*p*-SCN-Bn-TE1PA over time. Significantly higher radioactivity was found in blood, lungs and heart at 48h PI for ⁶⁴Cu-9E7.4-NHS-DOTA, which suggests a release of ⁶⁴Cu from antibody, in parallel with a higher intestinal elimination. This was correlated by the liver metabolism study, which shows a better *in vivo* resistance to transchelation for ⁶⁴Cu-9E7.4-*p*-SCN-Bn-TE1PA. The imaging study of ⁶⁴Cu-9E7.4-*p*-SCN-Bn-TE1PA shows an increasing targeting of the tumors over time and confirms the hepatic clearance at 24h and 48h PI.

Conclusion: ⁶⁴Cu-9E7.4-*p*-NCS-Bn-TE1PA has shown a very high tumor targeting, associated to an increasing of tumor-to-tissues ratio over time that suggests an overall clearance from healthy tissues. Compared to DOTA, TE1PA displays an *in vivo* stability and resistance to transchelation significantly superior. This confirms the previous results obtained *in vitro* and ⁶⁴Cu-labelled TE1PA proved once again its usefulness for immuno-PET imaging in a preclinical model.