

Design and preclinical evaluation of melanoma targeting agents for internal radionuclide therapy.

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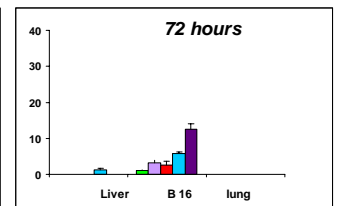
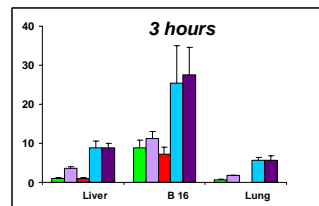
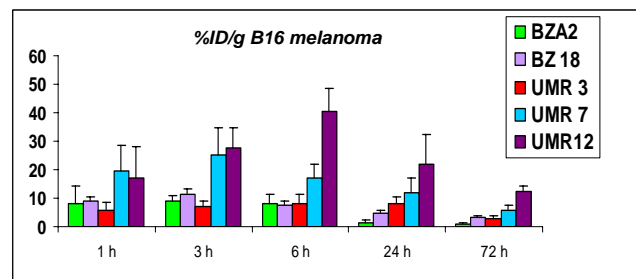
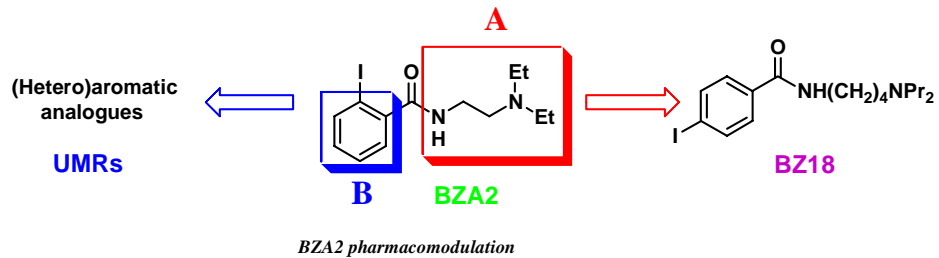
INTRODUCTION

Iodobenzamides are reported to possess a specific affinity for melanoma. A such property gives them a potential application as **radiopharmaceuticals** for the scintigraphic detection of melanoma. *N*-(2-diethylaminoethyl)-2-iodobenzamide (**BZA2**) has been selected for SPECT melanoma imaging with good results and its performances will be compared to ^{18}F -FDG PET.

The limited effectiveness of the conventional therapy on the disseminated melanoma induces a crucial need for effective and specific novel agents for metastases treatment.

Targeted tumour radionuclide therapy may be an alternative by using BZA2 analogues with ^{131}I , β^- emitter or ^{125}I , Auger electron emitter

For this application, a « **structure-activity** » study has been done by variation: first, on the alkyl chain length and the nature of the aminoalkyl substituents (**A**) and secondly, on the aromatic ring (**B**), and the pharmacokinetic profiles have been assessed on B16 melanoma bearing mice.



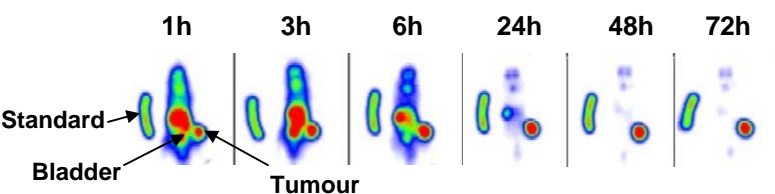
Biodistribution of ^{125}I -BZA2 analogues in B16 melanoma bearing mice at various time after injection (% ID/g \pm SEM) in tumour, liver and lungs, organs supposed to be the site of metastases

For radionuclide therapy, tumoural affinity must be **high, specific and long lasting**.

Four molecules have been firstly selected (**UMR3**, **UMR7**, **UMR12** et **BZ18**) with a pharmacokinetic profile inducing more favourable dosimetry parameters within the tumour.

	Tumour fixation % ID/g		Dosimetry ^{131}I	
	3 h	72 h	Effective Half life h	Absorbed dose cGy/ μCi
BZA2	8,8	1,2	22,4	1,1
BZ18	11,2	3,2	36,4	1,9
UMR3	7,1	2,7	41,3	1,4
UMR7	25,3	5,9	31,8	3,7
UMR12	27,7	12,5	49,3	4,9

Dosimetry parameters determined using the MIRD program

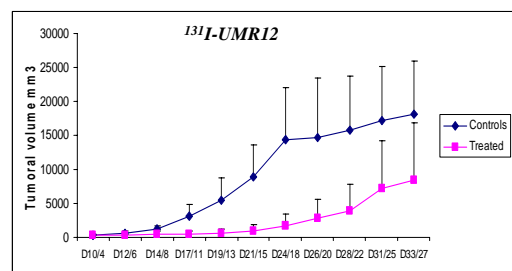


Scintigraphic imaging of B16 melanoma bearing C57BL6 mice with ^{125}I -UMR12.

(γ IMAGER BIOSPACE dedicated for small animal imaging).

^{131}I -UMR12 administered intravenously in B 16 melanoma bearing C57BL6 mice, induced a significant regression in tumoural growth and a lengthening in median survival time from 32 days (controls) to 39 days (treated).

A potential therapeutic efficiency was exhibited.



Effects of ^{131}I -UMR12 i.v. administration on the growth of B16 melanoma subcutaneously grafted on C57BL6 mice (2x18.5 MBq 6 and 10 days after tumour induction).

CONCLUSION

From these promising results the compound UMR12 with the better pharmacokinetic profile has been selected for an application to internal radionuclide therapy. A more complete preclinical study has to be done: kinetic and metabolism, tissular and cellular imaging, antitumoural effects. Different models of melanoma and different administration protocols will be tested (primary tumours and metastases, human melanoma on « nude » mice ...).