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Promising Pre-clinical Validation of Targeted Radionuclide Therapy Using a [¹³¹I] Labelled Iodoquinoxaline Derivative for an Effective Melanoma Treatment

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Abstract

Targeted internal radionuclide therapy (TRT) would be an effective alternative to current therapies for disseminated melanoma treatment. At our institution, a class of iodobenzamides has been developed as potent melanoma-seeking agents. This review described the preclinical validations of a quinoxaline derivative molecule (ICF01012) as tracer for TRT application. It was selected for its high, specific and long-lasting uptake in tumour with rapid clearance from non-target organs providing suitable dosimetry parameters for TRT. Extended *in vivo* study of metabolic profiles confirmed durable tumoural concentration of the unchanged molecule form. Moreover melanin specificity of ICF01012 was determined by binding assay with synthetic melanin and *in vivo* by SIMS imaging. Then, we showed *in vivo* that [¹³¹I] ICF01012 treatment drastically inhibited growth of B16F0, B16Bl6 and M4Beu tumours whereas [¹³¹I] NaI or unlabelled ICF01012 treatment was without significant effect. Histological analysis showed that residual tumour cells exhibit a significant loss of aggressiveness after treatment. This anti-tumoural effect was associated with a lengthening of the treated-mice survival time and an inhibition of lung dissemination for B16Bl6 model.

Results presented here support the concept of TRT using a [¹³¹I] labelled iodoquinoxaline derivative for an effective melanoma treatment.

Introduction

Melanoma is a poor prognosis skin cancer that affects about 150000 new patients per year in world. Despite recent advances in prevention and early diagnosis, malignant melanoma remains an increasingly prevalent cancer worldwide (Lorigan et al., 2008; Thompson et al., 2005). It is notably the second most common cancer among patients aged 20-39 years (Garbe and Leiter, 2009; Jennings and Murphy, 2009; Thompson et al., 2005). This aggressive disease displays a strong tendency to metastasize. Although localized disease is frequently curable by surgical removal, there is no effective treatment for metastatic melanoma. Patients with metastatic malignant melanoma have an average median survival rate of 6 months and a 5-year survival rate of less than 15% (Balch et al., 2001; Miller and Mihm, 2006). There are several approved therapies

for malignant melanoma treatment as dacarbazine (an alkylating agent) and interleukin-2. However, the response rate obtained with these therapies remains low (less than 20%) and contributes little to overall patient survival (Tarhini and Agarwala, 2006). A higher response rate of up to 40% may be obtained with combined treatment schedules, but without significant prolonged survival in randomized studies (Hauschild et al., 2001; Tarhini and Agarwala, 2006). Globally, the response rate is still rather low and there has been no progress in systemic palliative melanoma treatment for three decades partly due to their high toxicity (Eigentler et al., 2003; Garbe and Eigentler, 2007). In this context, there is an urgency to develop more effective therapy and to find new more specific ways to treat disseminated melanoma.

Identification of signalling pathways that are central to melanoma initiation and progression, provides opportunity to develop targeted therapies. Several clinical investigations are under way in patients with melanoma testing these novel agents (Bcl-2 antisense, BRAF inhibitors as BAY 43-9006, heat shock protein 90 inhibitor, angiogenesis inhibitor, melanoma vaccine strategies...) (Carlson et al., 2007; Gray-Schopfer et al., 2007). At this time, it seems difficult to transpose the encouraging results obtained in preclinical studies and no real benefit in term of global survival has been demonstrated with these agents (Bedikian et al., 2006; Fecher et al., 2008; Gray-Schopfer et al., 2007). Involvement of these different targeted pathways in the melanoma development as well as their interactions must be better understood to exploit these new strategies.

Targeted radionuclide therapy (TRT) is a potentially important alternative to conventional therapeutic agents. In comparison with standard therapies (external beam

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radiotherapy or monochemotherapy), TRT offers the potential of tumour-selective radio-therapeutic treatment of tumours and distal metastases. This approach is under development for several tumoural pathologies with success. First radio-immunotherapy with name Zevalin® was approved by FDA in 2002 for treatment of non-Hodgkin's lymphoma (Conti et al., 2005; Wiseman et al., 2000).

Different carriers for radionuclides and melanoma targets are being investigated. Peptide analogues of α -melanocyte stimulating hormone (α -MSH) targeting melanocortin-1 receptor have been developed and provide good quality imaging in melanoma-bearing mice (Miao et al., 2008; Miao and Quinn, 2007; Ren et al., 2009). For a systemic radionuclide therapy, promising experimental results in melanoma-bearing mice have been reported (Miao et al., 2005; Miao and Quinn, 2008). However, high kidney concentration may result in a restricting renal toxicity.

Melanin pigment itself can be a target for melanoma tissue. Melanin is an amorphous, irregular polymer composed of intimate mixtures of two separated but biogenetically related pigments: eumelanins and pheomelanins (Prota, 2000). Recently, radioimmunotherapy using mAb against melanin has been developed and evaluated on nude mice bearing human melanoma. Significant anti-tumoural effect has been obtained but important renal uptake is also detected with this treatment (Dadachova et al., 2004; Dadachova et al., 2008).

Many drugs bind to melanin both *in vivo* and *in vitro*: polycyclic aromatic compounds such as methylene blue (MTB), chloroquine or acridine orange. An extended experimental work has been done with ¹³¹I or ²¹¹At labelled MTB giving some promising data but without further clinical development (Link, 1999).

Another class of aromatic compounds with a cationic site such as *N*-(2-diethylaminoethyl) iodobenzamide was developed as potent melanoma-seeking agents. Two of these compounds named respectively BZA and BZA₂ have been clinically evaluated as suitable imaging agents in nuclear medicine with very encouraging results for metastases imaging (Michelot et al., 1993; Moins et al., 2002). The BZA intracellular localization within melanin-containing structures has been clearly visualized with analytical imaging by secondary ion mass spectrometry (Guerquin-Kern et al., 2005). Various iodinated benzamides have been evaluated showing *in vivo* distribution profiles with a high and specific tumour uptake that was promising for imaging (Eisenhut et al., 2000; Moins et al., 2001; Pham et al., 2007). However biodistribution profiles of these tracers were not compatible for radiotherapy strategy in term of potential delivered dose to the tumour.

Selection of ICF01012 tracer for targeted radionuclide therapy of melanoma

Pharmacomodulation study: To discover new molecular derivatives for targeted radionuclide therapy with strong,

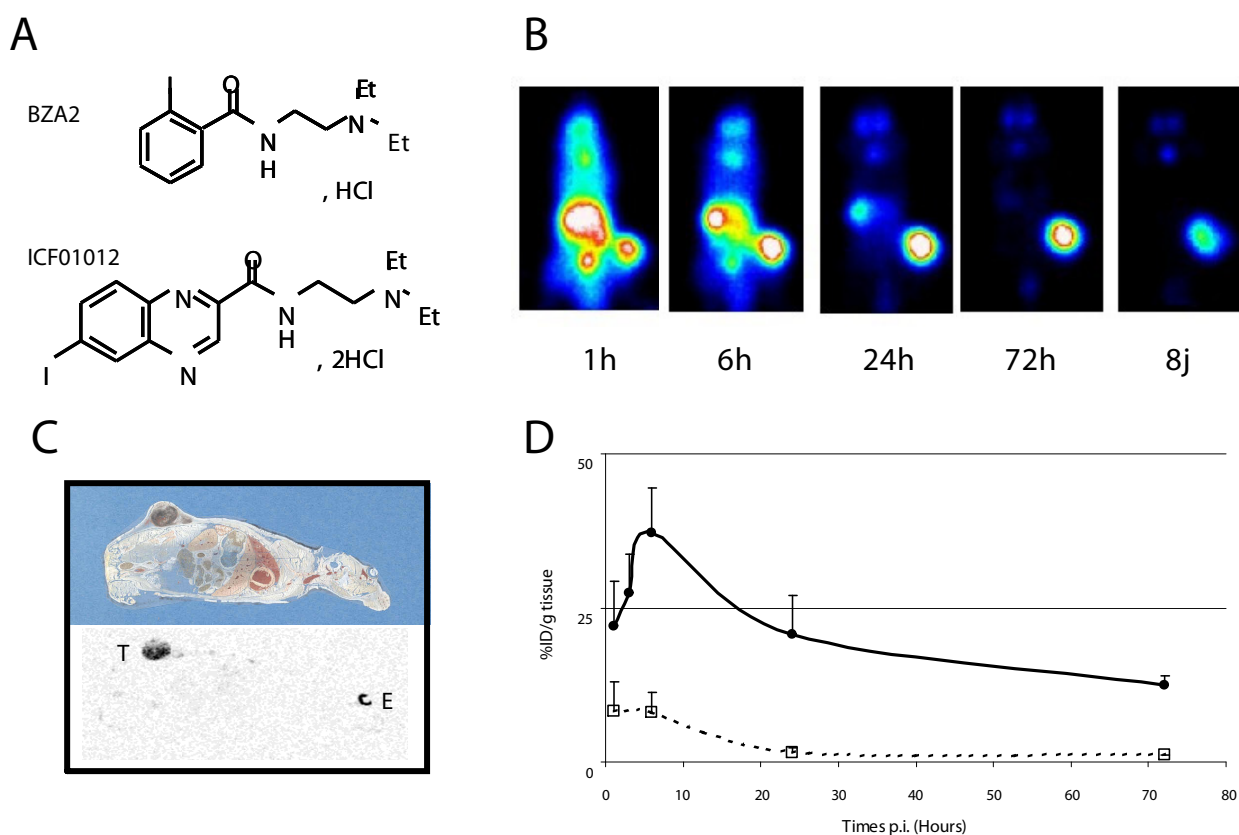


Figure 1: (A) Chemical structure of BZA₂ and ICF01012. (B) Representative scintigraphic planar images of a B16F0-bearing C57Bl6 mouse. Mice were injected intravenously with 3.7 MBq [¹²⁵I] ICF01012. Images were acquired at 1, 6, 24, 72 hours and 8 days after injection. Tumours were easily visualized (T) suggesting a significant [¹²⁵I] ICF01012 tumoural concentration. Moreover rapid systemic elimination was quite complete from non target organs 24 hours p.i. (Miot-Noirault et al., 2009) (C) Representative whole-body autoradiography of a mouse bearing B16F0 melanoma cell xenograft, 72 h after i.v. injection of 1.7 MBq (0.1 μmol) [¹²⁵I] ICF01012. T: Tumour; E: eyes. (D) Tumoural distribution radioactivity in nude mice bearing B16F0 melanoma cell xenograft after i.v. injection of [¹²⁵I] ICF01012 and [¹²⁵I] BZA₂.

specific and long-lasting uptake in melanoma tissues, a large pharmacomodulation study was performed (Chezal et al., 2008). This strategy involved the incorporation of aromatic or heteroaromatic structures in place of the phenyl moiety of BZA₂ to take advantage of polycyclic aromatic compounds that display a strong affinity for melanin, while the lipophilic side chain was kept identical. Then, various iodo (hetero) aromatic fused ring systems with a carboxamide part were synthesized and radioiodinated. Biodistribution of these compounds radiolabelled with ¹²⁵I was performed in B16F0 melanoma bearing C57BL6 mice after i.v. injection. The radioactivity biodistribution was analysed by quantitative whole body autoradiography using an AMBIS 4000 detector on whole body slices of mice obtained by cryosection. The radioactivity was quantified in different organs including tumour and expressed as percentage of injected dose/g of tissue (%ID/g). Dosimetry parameters for a ¹³¹I utilization were extrapolated using an adaptation of the MIRD program. From this study a quinoxaline derivative molecule (N-(2-diethylaminoethyl)-6-iodoquinoxaline-2-carboxamide dihydrochloride salt named ICF01012) was selected for its high, specific and long-lasting uptake in B16F0 tumour with a rapid clearance from non-target organs (Figure 1) (Chezal et al., 2008). In comparison with [¹²⁵I] BZA₂ (Chezal et al., 2008; Moins et al., 2001), we observed for [¹²⁵I] ICF01012 a more elevated and durable concentration on B16F0 tumour (Figures 1A and 1B). At the stage 72 h p.i., the tumour concentration was increased up to 11 fold as compared to BZA₂ (Figure 1D). In term of dosimetry, for a ¹³¹I labelling, the tumour absorbed dose was increased by more than 5 fold.

Pharmacokinetic profiles: [¹²⁵I] ICF01012 biodistribution in B16F0-bearing C57BL6 mice to 1 hour from 8 days post-injection was analysed by quantitative whole body autoradiography (AMBIS 4000) (Chezal et al., 2008). Radioactivity quantifications expressed as percentage of injected dose/g of tissue (%ID/g) were reported for different organs including tumour in Table 1. [¹²⁵I] ICF01012 tumoural concentration was significantly observed as early as 1 hour p.i and a significant and durable accumulation until 8 days p.i demonstrating a very high tumour uptake. Moreover the cumulative urinary and fecal

excretions collected up to 72 h showed that elimination was almost total (88%) with a mainly urinary route (70%) (Chezal et al., 2008). SPECT imaging of B16F0-bearing C57BL6 mice injected intravenously with [¹²⁵I] ICF01012 confirmed this pharmacokinetic profile (Figure 1B). Indeed tumours were easily visualized suggesting a significant [¹²⁵I] ICF01012 tumoural concentration (Miot-Noirault et al., 2009). Moreover systemic elimination was quite complete from non target organs 24 hours p.i confirming the rapid clearance from non target tissues obtained with autoradiography quantitation (Table 1). 24 hours post-injection, radioactivity concentration was very low within liver (<1.5% ID/g), and undetectable in spleen, kidneys, lungs, blood (Table 1). This led to high tumour to nontarget organ activity ratios rapidly unquantifiable when organ concentration was within the range of the background value (Table 1). Interestingly, [¹²⁵I] ICF01012 renal uptake is very low (undetectable 24 hours after injection) by comparison with other targeting-melanin molecules as antibodies and α -MSH peptide analogues (Dadachova et al., 2008; Miao et al., 2005).

To trace and quantify the metabolic fate of [¹²⁵I] ICF01012 in B16F0 melanoma bearing mice, high-performance liquid chromatography (HPLC) analysis were performed on tumour (Denoyer et al., 2008). Many HPLC peaks were identified in tumoural extracts with the major peak corresponding to the non-metabolized form of [¹²⁵I] ICF01012. Eight days post-injection, 83.6% of the remaining radioactivity is under [¹²⁵I] ICF01012 unchanged form.

All these promising data made this tracer a strong melanoma seeking agent for both scintigraphic imaging and radionuclide therapy (Chezal et al., 2008).

Melanin specificity: In experiments presented above, we observed B16F0 melanoma targeting using our quinoxaline analogue tracer. We verified the melanin specificity of [¹²⁵I] ICF01012 using a binding assay with synthetic melanin. We showed that [¹²⁵I] ICF01012 displayed a strong affinity for synthetic melanin in water and in PBS (Chezal et al., 2008). Additional study was performed to visualised in vivo ICF01012 melanin specificity by Secondary ion mass spectrometry

Hours p.i.	Ratio Tumour vs organ							Ratio Tumour vs organ	
	1	3	6	24	72	120	192	6	24
Tumour	21,99±7,25	27,38±6,27	37,24±7,12	20,67±6,38	12,45±1,61	5,37±3,18	3,77±0,43	1	1
Brain	2,17±0,83	0,52±0,73	0,39±0,47	0,06±0,08	UD	UD	UD	95,5	344,5
Stomach	22,06±5,35	20,6±4,98	21,35±3,02	0,96±1,12	2,23±0,38	UD	UD	1,7	21,5
Liver	13,95±1,32	8,77±1,11	7,69±0,65	1,51±0,08	UD	UD	UD	4,8	13,7
Bone Marrow	4,7±0,45	ND	0,34±0,69	UD	UD	UD	UD	109,5	ND
Muscle	2,06±0,06	0,88±0,17	0,84±0,07	0,00±0,05	UD	UD	UD	44,3	5167,5
Lung	7,96±0,74	5,7±0,31	3,91±0,71	0,18±0,26	UD	UD	UD	9,5	114,8
Spleen	15,6±14,99	2,35±3,32	1,39±1,62	0,11±0,14	UD	UD	UD	26,8	187,9
Kidney	16,03±0,54	8,95±2,44	7,23±0,64	0,49±0,57	UD	UD	UD	5,2	42,2
Blood	2,89±0,67	2,9±0,06	3,19±0,19	0,4±0,12	UD	UD	UD	11,7	51,7
Uvea	30,75±4,78	24,79±0,08	30,52±5,27	30,06±3,58	25,26±8,38	17,21±6,67	15,34±1,44	1,2	0,7

ND: Not Determined; UD: Undetected

Table 1: Biodistribution of radioactivity (%ID/g) in C57BL6 mice bearing B16 melanoma at various time after i.v. injection of [¹²⁵I] ICF01012. Melanoma/Organ Ratios of [¹²⁵I] ICF01012 at 6 and 24 hours p.i.

(SIMS) imaging (Bonnet-Duquennoy et al., 2009). With this technique, we observed a perfect co-localization of ICF01012 signal with melanin confirming the melanin binding properties of this tracer and its internalization in melanoma cells.

Moreover, we noted on biodistribution study (Table 1) an important radioactivity concentration on uvea confirming the high ICF01012 specificity for pigmented structures and so for melanin (Chezal et al., 2008). However fixation of tracer on normal pigmented tissues in these pre-clinical experiments should not be considered as a limit for our strategy. Indeed these experiments were performed on the heavily pigmented C57BL/6J mice associated with an important uveal melanin content which is not predictive for human status of uvea. On a clinical imaging study with [¹²³I] BZA₂, the parental benzamide analogue of ICF01012, no significant uveal uptake was imaged excepted for an ocular melanoma case while important uveal uptake was observed with the same tracer on this mouse model (Moins et al., 2002; Sillaire-Houtmann et al., 2004). Because of murine and human differences on ocular geometry and melanin content, ICF01012 accumulation within C57Bl6 mice eyes should not be considered as hampering for clinical transfer of this radiotherapy concept. Nevertheless this point has to be taking into account in our studies.

In vivo anti-tumoural efficacy of TRT

Several radionuclides are developed for the treatment of oncological diseases. Various approaches using ¹³¹I for TRT were developed to treat different cancers because of its relatively low beta energy with a maximum range of 3 mm in tissue which is effective for treatment (Kassis and Adelstein, 2005). Some of them have resulted in very good curative responses like ¹³¹I treatment of thyroid cancer and its micrometastases (Nijssen et al., 2007; Verburg et al., 2005). Biodistribution properties of [¹²⁵I] ICF01012 molecule provide suitable dosimetry parameters using a labelling with ¹³¹I. Indeed an administered dose of 37 MBq will allow the delivery of 49 Gy to the tumour, a usefully high dose for a good therapeutic efficacy (Chezal et al., 2008).

We investigated the *in vivo* therapeutic efficacy of [¹³¹I] ICF01012 as a radionuclide therapeutic agent (Bonnet-Duquennoy et al., 2009) on murine melanoma models B16F0 and on the metastatic B16Bl6 cell lines grafted s.c. into syngenic C57Bl/6J mice (Poste et al., 1980). [¹³¹I] ICF01012 was administered i.v. at days 6 and 10 (2x18.5 MBq). Control groups received [¹³¹I] Na or unlabelled ICF01012 (equimolar dose). All groups contained at least 10 animals and experiments were performed twice. The survival of [¹³¹I] ICF01012-treated mice, with a median of 39 days, was significantly (p=0.006) better than that of untreated group whereas that of [¹³¹I] NaI-treated mice was similar (p=0.3). These results suggested that [¹³¹I] ICF01012 treatments showed low toxicity confirming precedent pharmacokinetic experiments and rapid systemic elimination.

We observed that the treatment with unlabelled ICF01012 was without any significant effect whereas [¹³¹I] ICF01012 treatment drastically suppressed the growth of both B16F0 (p=0.001) and B16Bl6 (p=0.009) tumours. Figure 2A illustrates the strong difference on B16Bl6 tumour size at day 19 between control and treated animals. [¹³¹I] NaI alone did not have any

efficacy against tumour growth showing interest of targeting strategy with [¹³¹I] ICF01012 for an efficient therapeutic effect (Bonnet-Duquennoy et al., 2009).

In term of proliferation, the tumour volume doubling time (DT) was determined to quantify precisely the tumoural growth. After [¹³¹I] ICF01012 treatment, DT was significantly increased (range +44 to +147%) confirming inhibition of tumoural growth. Histological analysis showed that after targeted radiotherapy treatment, residual tumoural cells exhibited a decrease of mitotic index and microvessel numbers and an increase of anisocytosis. This effect was associated with a significant decrease of the tumoural PCNA proliferation marker expression after treatment. All these results suggested a loss of aggressiveness of residual tumour cells after [¹³¹I] ICF01012 treatment (Bonnet-Duquennoy et al., 2009).

After macroscopic analysis, we observed that 55% of the untreated mice bearing B16Bl6 tumours had lung metastases whereas no metastasis was counted on [¹³¹I] ICF01012 treated group (Figure 2B) suggesting an inhibitory effect of this treatment on lung dissemination (Bonnet-Duquennoy et al.,

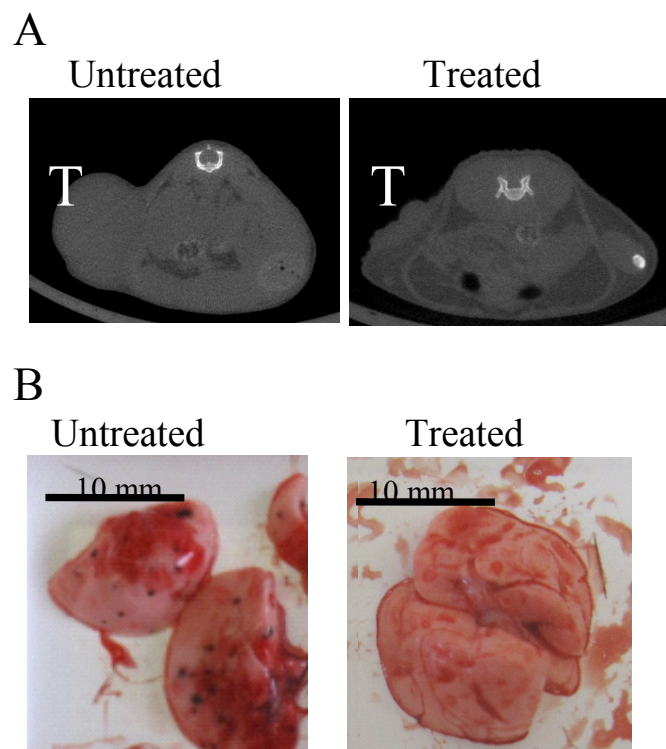


Figure 2: Illustrations of significant anti-tumoural effect of TRT using [¹³¹I]ICF01012 treatment on B16Bl6 tumoural growth (A) and B16Bl6 dissemination on lung (B). [¹³¹I]ICF01012 treatment was administered intravenously at days 6 and 10 (2x18.5MBq) in C57Bl6 mice bearing B16Bl6 palpable tumours. (A) Observation of untreated and treated mice bearing B16Bl6 by computed tomography. Animal imaging was performed by using the GE eXplore CT 120 micro-CT scanner (GE Healthcare, London, Canada). The micro-CT image acquisition consisted of 220 views were acquired in 0.88° increments around the animal collected in one full rotation of the gantry, with 32 ms exposure per view. The X-ray tube settings were 70 kV and 50 mA. The resulting raw data were reconstructed to a final image volume of 0.989 x 0.989 x 0.989 μm. The reconstructed slices were output in the CT manufacturer's raw format and were corrected equal to Hounsfield units. (B) Macroscopic observation of representative lung of untreated and treated mice. No metastasis was detected on treated animals (0/25) whereas 55% of untreated mice exhibited dissemination (12/22).

2009). We demonstrated a strong and similar anti-tumoural effect of [¹³¹I] ICF01012 on both nonmetastatic B16F0 tumour and the more aggressive metastatic B16Bl6 model and a complete inhibition of B16Bl6 dissemination towards lungs. These results provide useful data for support our approach to treating all melanoma forms including disseminated disease.

Because B16F0 and B16Bl6 tumours were highly pigmented, we assessed radiotherapy experiment on human melanoma cells which exhibit lower melanin content (Bonnet-Duquennoy et al., 2009). Tumour distribution of radiotracer was evaluated on nude mice bearing M4Beu melanoma which contain a lower melanin concentration than B16F0 tumour (ratio: 1/2.8) (Bonnet-Duquennoy et al., 2009). We observed that M4Beu tumour uptake of [¹²⁵I] ICF01012 was consistent with 6.3±1.3% and 2.3±0.5% ID/g 6 and 24 hours after injection respectively but lower than B16F0 tumour uptake (Bonnet-Duquennoy et al., 2009). Then targeted radiotherapy was evaluated using 2 injections of 18.5 MBq [¹³¹I] ICF01012 into nude mice bearing M4Beu tumours. In term of proliferation, the tumor DT were significantly increased (range +46%) after [¹³¹I] ICF01012 treatment. These results showed that treatment significantly slowed the M4Beu tumoural growth (p=0.003) confirming strong efficacy of this TRT strategy even in melanoma containing lower target concentration.

Discussion

Our data demonstrated a strong anti-tumoural efficacy associated with low toxicity of [¹³¹I] ICF01012 for radionuclide therapy on murine and human pigmented melanoma models whatever their dissemination profiles and their melanin content be. In melanoma, melanin is observed within tumoural cells, into extracellular space and in melanophages (Lazova et al., 2009; Revskaya et al., 2009). In this project we proved that ¹³¹I radionuclide physical proprieties associated with this melanin target distribution was able to deliver efficient cytotoxic irradiation (Bonnet-Duquennoy et al., 2009; Chezal et al., 2008). Considering that melanin is detected in more than 90% of melanoma cases, strategy targeting this pigment could be used in the majority of patients.

Optimization of the therapy protocol in mice with lower doses and other schedules of injections will be explored in order to define the better balance between the anti-tumoural effect and the safety on normal pigmented tissues. Interestingly histological evaluation of B16F0 and B16Bl6 tumours in treated mice revealed an increased of extracellular melanin content after radiotherapy providing more abundant target for new injection. [¹³¹I] ICF01012 treatments used in this strategy showed low toxicity with an increase of median survival time confirming in vivo pharmacokinetic profile of ICF01012 which demonstrated a rapid clearance of tracer from non-target organs as liver, brain and lung. Additional dosimetric studies are in progress to evaluate the delivery dose in the different organs in these therapeutic conditions by taking into account evolution of the tumoural size. This work should allow to better manage the future protocol and to predict the anti-tumoural response for clinical transfer of this strategy. Furthermore, an imaging clinical trial will be performed to evaluate tumour and possible normally pigmented organ fixation of ICF01012 and to determine dosimetric parameters in human.

Results presented here support the concept of targeted radionuclide therapy using a [¹³¹I] labelled iodoquinoline derivative for an effective melanoma treatment.

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References

- Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, et al. (2001) Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol* 19: 3622-3634. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
- Bedikian AY, Millward M, Pehamberger H, Conry R, Gore M, et al. (2006) Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol* 24: 4738-4745. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
- Bonnet-Duquennoy M, Papon J, Mishellany F, Labarre P, Guerquin-Kern JL, et al. (2009) Targeted radionuclide therapy of melanoma: anti-tumoural efficacy studies of a new ¹³¹I labelled potential agent. *Int J Cancer* 125:708-716. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
- Carlson JA, Linette GP, Aplin A, Ng B, Slominski A (2007) Melanocyte receptors: clinical implications and therapeutic relevance. *Dermatol Clin* 25: 541-557. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
- Chezal JM, Papon J, Labarre P, Lartigue C, Galmier MJ, et al. (2008) Evaluation of radiolabeled (hetero)aromatic analogues of N-(2-diethylaminoethyl)-4-iodobenzamide for imaging and targeted radionuclide therapy of melanoma. *J Med Chem* 51: 3133-3144. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
- Conti PS, White C, Pieslor P, Molina A, Aussie J, et al. (2005) The role of imaging with (111)In-ibritumomab tiuxetan in the ibritumomab tiuxetan (zevalin) regimen: results from a Zevalin Imaging Registry. *J Nucl Med* 46: 1812-1818. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
- Dadachova E, Nosanchuk JD, Shi L, Schweitzer AD, Frenkel A, et al. (2004) Dead cells in melanoma tumors provide abundant antigen for targeted delivery of ionizing radiation by a mAb to melanin. *Proc Natl Acad Sci USA* 101: 14865-14870. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
- Dadachova E, Revskaya E, Sesay MA, Damania H, Boucher R, et al. (2008) Pre-clinical evaluation and efficacy studies of a melanin-binding IgM antibody labeled with ¹⁸⁸Re against experimental human metastatic melanoma in nude mice. *Cancer Biol Ther* 7: 1116-1127. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
- Denoyer D, Labarre P, Papon J, Miot-Noirault E, Galmier MJ, et al. (2008) Development of a High-Performance Liquid Chromatographic method for the determination of a new potent radioiodinated melanoma imaging and therapeutic agent. *J Chromat B* 875: 411. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
- Eigentler TK, Caroli UM, Radny P, Garbe C (2003) Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. *Lancet Oncol* 4: 748-759. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
- Eisenhut M, Hull WE, Mohammed A, Mier W, Lay D, et al. (2000) Radioiodinated N-(2-diethylaminoethyl)benzamide derivatives with high melanoma uptake: structure-affinity relationships, metabolic fate, and intracellular localization. *J Med Chem* 43: 3913-3922. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)

12. Fecher LA, Amaravadi RK, Flaherty KT (2008) The MAPK pathway in melanoma. *Curr Opin Oncol* 20: 183-189. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
13. Garbe C, Eigentler TK (2007) Diagnosis and treatment of cutaneous melanoma: state of the art 2006. *Melanoma Res* 17: 117-127. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
14. Garbe C, Leiter U (2009) Melanoma epidemiology and trends. *Clinics in dermatology* 27: 3-9. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
15. Gray-Schopfer V, Wellbrock C, Marais R (2007) Melanoma biology and new targeted therapy. *Nature* 445: 851-857. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
16. Guerquin-Kern JL, Wu TD, Quintana C, Croisy A (2005) Progress in analytical imaging of the cell by dynamic secondary ion mass spectrometry (SIMS microscopy). *Biochim Biophys Acta* 1724: 228-238. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
17. Hauschild A, Garbe C, Stolz W, Ellwanger U, Seiter S, et al. (2001) Dacarbazine and interferon alpha with or without interleukin 2 in metastatic melanoma: a randomized phase III multicentre trial of the Dermatologic Cooperative Oncology Group (DeCOG). *Br J Cancer* 84: 1036-1042. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
18. Jennings L, Murphy GM (2009) Predicting outcome in melanoma: where are we now. *Br J Dermatol* 161: 496-503. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
19. Kassis AI, Adelstein SJ (2005) Radiobiologic principles in radionuclide therapy. *J Nucl Med* 1: 4S-12S. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
20. Lazova R, Klump V, Pawelek J (2009) Autophagy in cutaneous malignant melanoma. *J Cutan Pathol*.
21. Link EM (1999) Targeting melanoma with ²¹¹At/¹³¹I-methylene blue: preclinical and clinical experience. *Hybridoma* 18: 77-82. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
22. Lorigan P, Eisen T, Hauschild A (2008) Systemic therapy for metastatic malignant melanoma—from deeply disappointing to bright future. *Exp Dermatol* 17: 383-394. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
23. Miao Y, Figueroa SD, Fisher DR, Moore HA, Testa RF, et al. (2008) ²⁰³Pb-labeled alpha-melanocyte-stimulating hormone peptide as an imaging probe for melanoma detection. *J Nucl Med* 49: 823-829. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
24. Miao Y, Hylarides M, Fisher DR, Shelton T, Moore H, et al. (2005) Melanoma therapy via peptide-targeted {alpha}-radiation. *Clin Cancer Res* 11: 5616-5621. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
25. Miao Y, Quinn TP (2007) Alpha-melanocyte stimulating hormone peptide-targeted melanoma imaging. *Front Biosci* 12: 4514-4524. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
26. Miao Y, Quinn TP (2008) Peptide-targeted radionuclide therapy for melanoma. *Crit Rev Oncol Hematol* 67: 213-228. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
27. Michelot JM, Moreau MF, Veyre AJ, Bonafous JF, Bacin FJ, et al. (1993) Phase II scintigraphic clinical trial of malignant melanoma and metastases with iodine-123-N-(2-diethylaminoethyl 4-iodobenzamide). *J Nucl Med* 34: 1260-1266. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
28. Miller AJ, Mihm MC Jr (2006) Melanoma. *N Engl J Med* 355: 51-65. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
29. Miot-Noirault E, Papon J, Gardette M, Bonnet-Duquennoy M, Labarre P, et al. (2009) The use of [(125)I] scintigraphic in vivo imaging in melanoma-bearing mice for a rapid prescreening of vectors to melanoma tissue. *Cancer Biother Radiopharm* 24: 629-636. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
30. Moins N, D'Incan M, Bonafous J, Bacin F, Labarre P, et al. (2002) ¹²³I-N-(2-diethylaminoethyl)-2-iodobenzamide: a potential imaging agent for cutaneous melanoma staging. *Eur J Nucl Med Mol Imaging* 29: 1478-1484. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
31. Moins N, Papon J, Seguin H, Gardette D, Moreau MF, et al. (2001) Synthesis, characterization and comparative biodistribution study of a new series of p-iodine-125 benzamides as potential melanoma imaging agents. *Nucl Med Biol* 28: 799-808. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
32. Nijsen JF, Krijger GC, van Het Schip AD (2007) The bright future of radionuclides for cancer therapy. *Anticancer Agents Med Chem* 7: 271-290. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
33. Pham TQ, Berghofer P, Liu X, Greguric I, Dikic B, et al. (2007) Preparation and biologic evaluation of a novel radioiodinated benzylpiperazine, ¹²³I-MEL037, for malignant melanoma. *J Nucl Med* 48: 1348-1356. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
34. Poste G, Doll J, Hart IR, Fidler IJ (1980) In vitro selection of murine B16 melanoma variants with enhanced tissue-invasive properties. *Cancer Res* 40: 1636-1644. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
35. Prota G (2000) Melanins, melanogenesis and melanocytes: looking at their functional significance from the chemist's viewpoint. *Pigment Cell Res* 13: 283-293. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
36. Ren G, Liu Z, Miao Z, Liu H, Subbarayan M, et al. (2009) PET of malignant melanoma using ¹⁸F-labeled metallopeptides. *J Nucl Med* 50: 1865-1872. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
37. Revskaya E, Jongco AM, Sellers RS, Howell RC, Koba W, et al. (2009) Radioimmunotherapy of experimental human metastatic melanoma with melanin-binding antibodies and in combination with dacarbazine. *Clin Cancer Res* 15: 2373-2379. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
38. Sillaire-Houtmann I, Bonafous J, Veyre A, Mestas D, D'Incan M, et al. (2004) Phase 2 clinical study of ¹²³I-N-(2-diethylaminoethyl)-2-iodobenzamide in the diagnostic of primary and metastatic ocular melanoma. *J Fr Ophtalmol* 27: 34-39. » [PubMed](#) » [Google Scholar](#)
39. Tarhini AA, Agarwala SS (2006) Cutaneous melanoma: available therapy for metastatic disease. *Dermatol Ther* 19: 19-25. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
40. Thompson JF, Scolyer RA, Kefford RF (2005) Cutaneous melanoma. *Lancet* 365: 687-701. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
41. Verburg FA, de Keizer B, Lips CJ, Zelissen PM, de Klerk JM (2005) Prognostic significance of successful ablation with radioiodine of differentiated thyroid cancer patients. *Eur J Endocrinol* 152: 33-37. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)
42. Wiseman GA, White CA, Stabin M, Dunn WL, Erwin W, et al. (2000) Phase I/II ⁹⁰Y-Zevalin (yttrium-90 ibritumomab tiuxetan, IDEC-Y2B8) radioimmunotherapy dosimetry results in relapsed or refractory non-Hodgkin's lymphoma. *Eur J Nucl Med* 27: 766-777. » [CrossRef](#) » [PubMed](#) » [Google Scholar](#)

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