

1 cotransfection, the mice were divided into two groups. One group ($n = 2$) was injected i.v.
2 with 100 μL Na^{124}I (1.85 MBq) and sacrificed 2 h later. The other group ($n = 2$) was injected
3 i.p. with 100 μL NaI (57 mM). After 15 min, 100 μL Na^{124}I (1.85 MBq) was injected i.v. and
4 the mice were sacrificed 2 h later. The TA muscles were then processed for autoradiography.

5 **PET imaging**

6 The Fine Structure Imaging PET (Fine-PET) scanner has the sensitivity of 40 cps/kBq/mL.
7 The FOV diameter is 64 mm and its axial length is 26 mm. The energy window setting was
8 250 keV - open ended (17). Six of 40 BALB/c mice were used as controls (6 weeks old,
9 weight 22–25 g), 5 arthritis and vasculitis disease model mice (16 weeks old, weight 32–24
10 g), and 3 muscular dystrophy model mice (5 weeks old, weight 12–15 g). The TA muscle in
11 the left leg was cotransfected with pGL3 and hNIS in the presence of US. The TA muscle in
12 the right leg was injected with saline alone as control. Four days after cotransfection, mice
13 were injected i.v. with 100 μL Na^{124}I (74 MBq). The dose concentration was chosen to be
14 certain to obtain informative images. The dose concentration was chosen to obtain secure
15 gene expression images. Then the mice were anesthetized with isoflurane (1.0–1.5 L/min),
16 ventilated (1.0 L/min) through a nose cone in the bed of the scanner. A camera was used to
17 monitor the lack of movement of the anaesthetized mice as well as their breath to check that
18 they were alive during the scanning period. The detector of the Fine-PET is CdTe. Its

1 performance characteristics are independent from temperature. In the present study, the room
2 temperature was kept at constant ($20 \pm 2^\circ\text{C}$) using air controllers in the PET scanning room.
3 Thirty minutes after injection, the PET scan was performed and the data were acquired for 2
4 h. The Fine-PET has a three-dimensional mode with a spatial resolution of $0.6 \text{ unit} \times 0.6 \text{ unit}$
5 $\times 0.6 \text{ unit}$ (unit: mm/pixel). The images were reconstructed by the Fourier rebinning +
6 Maximum-Likelihood Expectation-Maximization (FORE + ML-EM) method. In a pilot
7 study, we have shown that integrated average pixel values in the ROI of a mouse tumor
8 gradually increase with increasing iteration number. However, from 30 iterations onwards,
9 these values are saturated (data not shown). Therefore, 30 iterations were chosen. PET
10 images were obtained and visualized with image analysis software (Image J). After PET
11 imaging, the mice were sacrificed and the TA muscle was removed from the mice for
12 autoradiography.

13 **Autoradiography**

14 After the mice were sacrificed, the TA muscles were quickly removed and frozen using
15 powdered dry ice. Cryostat sections ($10 \mu\text{m}$) were serially cut for each frozen sample. The
16 sections were exposed to universal-type imaging plates. Autoradiographic images with a
17 $25\text{-}\mu\text{m}$ pixel size were obtained using an imaging plate system (Fuji Bio-Imaging Analyzer
18 BAS5000).

1 **Statistical analysis**

2 All measurements are expressed as the mean \pm S.E.M. (standard error of the mean). Overall
3 differences between the groups were determined by one-way analysis of variance (one-way
4 ANOVA). When the one-way ANOVA results were significant for 3 samples, the differences
5 between each group were estimated using the Tukey–Kramer test. Simple comparisons of the
6 mean and S.E.M. of the data were performed using the Student's *t*-test. The differences were
7 considered to be significant at $P < 0.05$.

8

9 **Results**

10 **Kinetics of gene expression induced by US and NBs**

11 To investigate the kinetics of transgene transfection in the TA muscle induced by the US/NB
12 method, bioluminescence imaging was performed (Fig. 1). Luciferase activity was detectable
13 when pGL3 + US were administered but the combination of pGL3 + US + NBs showed an
14 enhanced luciferase activity on each day ($P < 0.01$). The luciferase gene expression reached a
15 peak 4 d after transfection. These results demonstrate the transient nature of
16 US/NB-mediated gene transfer.

17 **Cotransfection with pGL3 and hNIS genes in the TA muscle**

18 Transgene expression was analyzed by RT-PCR 48 h after US/NB-mediated cotransfection of

1 pGL3 and hNIS. Figure 2 demonstrates that both transgenes were co-expressed in the same
2 TA muscle.

3 **Biodistribution of ^{124}I**

4 To confirm the disposition of ^{124}I in mice and to determine whether the NIS expression
5 detected by RT-PCR resulted in the expression of a functional protein, TA muscles of
6 BALB/c mice were cotransfected with pGL3 and hNIS using the US/NB method, while
7 saline solution was injected into the right TA muscle as a control. For most organs and tissues,
8 the accumulation of ^{124}I reached its maximum value at 60 min, and decreased at 180 min (Fig.
9 3). The highest accumulation of ^{124}I was in the thyroid, and the lowest accumulation was in
10 the brain. There was significant accumulation of ^{124}I at 60 min ($P < 0.05$) and 180 min ($P <$
11 0.01) in the TA muscle transfected with hNIS compared to the control TA muscle. These data
12 suggest that the transfection procedure results in the synthesis of an active protein. In
13 addition, we demonstrate here that US/NB-mediated transfection is restricted to the site of
14 US administration as no ectopic NIS-mediated iodide accumulation was detected.

15 **Blocking of ^{124}I in the TA muscle**

16 To confirm that the ^{124}I accumulation observed in the TA muscle was indeed due to the
17 expression of NIS, we used autoradiography to determine the accumulation of ^{124}I in the TA
18 muscle, in the presence or absence of a large excess of cold iodide. Figure 4B shows that the

1 accumulation of ^{124}I (Fig. 4A) was completely blocked by the injection of non-radioactive
2 NaI (Fig. 4B).

3 **Visualization of gene expression**

4 To determine whether the NIS expression detected on biopsies (by RT-PCR (Fig. 2),
5 biodistribution (Fig. 3), and autoradiography (Fig. 4)) could also be detected by PET imaging,
6 BALB/c mice were subjected to US/NB-mediated gene transfer (day 0) and subjected to
7 bioluminescence imaging on day 3 and PET imaging (Fig. 5). The data presented in Figure 5
8 show a specific signal in the transfected TA muscle (left muscle), while no signal was
9 observed in the right muscle injected with saline. Autoradiographic analysis performed on
10 muscle biopsies confirmed the PET imaging results (Fig. 5A). These data, obtained with
11 “normal” BALB/c mice were repeated on mice suffering from arthritis and vasculitis disease
12 (Fig. 5B), and muscular dystrophy model mice (Fig. 5C) with very similar results.

13

14 **Discussion**

15 Ultrasound and nano/microbubbles have been developed for applications in experimental
16 therapeutics. In gene therapy, this methodology has been exploited to increase the infectivity
17 of adeno-associated viruses (24), adenoviruses (25), and retroviruses (26). In addition,
18 US/NB-mediated gene transfer has been used in non-viral approaches to deliver plasmid

1 DNA to experimental tumors (27), the pancreas (28), to antigen-presenting cells (29), and the
2 kidneys (30).

3 Skeletal muscle is a key target for many gene therapy applications, including
4 peripheral ischemia, secreted protein production, cancer and infection vaccines, and
5 Duchenne muscular dystrophy (31). In this context, our results demonstrate that the US/NB
6 gene transfer technology is very effective. Considering the low toxicity, ease of use, and
7 flexibility of this methodology, US/NB-mediated gene transfer should be considered as the
8 method of choice for the TA muscle. We also demonstrated that the signal is transient and
9 reaches a peak 4 d after transfection (Fig. 1). Our results are in agreement with another recent
10 report, demonstrating that muscle is more amenable to US/NB-mediated gene transfer than
11 subcutaneous or orthotopic tumors (32). In addition, we demonstrated that gene transfer
12 mediated by US and NB can also be performed on arthritic mice or mice suffering from
13 muscle degeneration, suggesting that these pathologies do not impair the transduction
14 potential of the methodology.

15 We cotransfected pGL3 and hNIS into the TA muscle using the US/NB method
16 (Figs. 2, 3, 4, and 5). This cotransfection method is based on the hypothesis that two plasmids
17 have the same backbone and promoter. The promoter of pGL3 is the Simian virus 40 (SV40),
18 while that of the hNIS gene is the cytomegalovirus (CMV). It has been reported that the gene

1 expression levels differed (SV40 < CMV) when plasmids with the SV40 and CMV promoter
2 both expressed the same gene product (33). So et al. showed a correlation between the ¹²⁵I
3 uptake of the hNIS gene and the bioluminescence activity induced by the luciferase gene
4 when a plasmid with both the luciferase and hNIS genes was transfected *in vitro* (34).
5 Therefore, it is reasonable to select mice and to visualize the gene expression of hNIS using
6 PET based on the expression of the luciferase gene. In addition, Figure 2 clearly showed that
7 both genes were expressed after cotransfection in the TA muscle. Extrapolated to a
8 physiopathological situation and based on these data, it is possible to envisage therapeutic
9 strategies combining the action of at least two transgenes carried by different expression
10 plasmids. This flexibility may provide the means for a “mix-and-match approach” to provide
11 optimal therapeutic efficiency.

12 The biodistribution study was important to confirm the radiation exposure before
13 PET imaging. Figure 3 demonstrates that specific accumulation of ¹²⁴I was observed in the
14 thyroid and stomach when endogenous NIS was expressed (35), and in the bladder as a result
15 of iodide excretion (36). Low levels of ¹²⁴I accumulation were observed in the brain,
16 indicating that iodide does not pass the blood–brain barrier (37). In addition, we
17 demonstrated that US/NB-mediated transfection is restricted to the site of US administration
18 as no ectopic NIS-mediated iodide accumulation was detected in sites not subjected to the

1 transfection procedure. These results are agreement with a previous ^{125}I study that suggested
2 ^{124}I is available as well as ^{125}I (38). In addition, the radioiodide activity of the TA muscle
3 transfected with the hNIS gene indicated a twofold accumulation compared to the control TA
4 muscle. This result demonstrates that the specific accumulation of ^{124}I in the TA muscle
5 occurred by the ectopic expression of the hNIS gene. Since accumulation of ^{124}I in the blood
6 was observed until 180 min, the residual ^{124}I internal exposure should be investigated in a
7 future study.

8 To confirm the specific binding of ^{124}I in mouse TA muscle, we injected
9 non-radioactive NaI before administration of ^{124}I (Fig. 4). The uptake of ^{124}I was blocked by
10 NaI, indicating that hNIS was actually transfected in the TA muscle. The results of the
11 biodistribution and blocking studies showed that the hNIS gene was transfected in the TA
12 muscle by the US/NB method and the accumulation of ^{124}I was due to its expression.

13 In this study, we verified the effectiveness of gene delivery using the US/NB
14 method and the visualization of gene expression using PET towards the development of gene
15 therapy. Expression of the hNIS gene was confirmed at the peak of gene transfer determined
16 by bioluminescence imaging. However, longitudinal studies are required for this to be
17 applicable as a clinical endpoint. We administered ^{124}I (74MBq i.v.) for PET imaging (Fig. 5).
18 This dose is ten times larger than used in previous studies (39) and is similar to that used in a

1 clinical study (40). Acute radiation injury in mice will occur at this dose and longitudinal
2 studies are not possible under these conditions. We administered this amount of dose for the
3 following reasons: (1) this was the first study using ^{124}I and Fine-PET, (2) the sensitivity of
4 the Fine-PET is 40 cps/kBq/mL (17) (one tenth of that of the commercially available
5 micro-PET imaging system). In future studies, we will conduct a longitudinal analysis of
6 gene expression with a lower injected dose of ^{124}I .

7

8 **Conclusion**

9 This study demonstrates for the first time the proof of principle that PET imaging can be used
10 to visualize US/NB-mediated gene transfer. This technology provides a new platform to
11 detect non-viral-mediated gene transfer and, extrapolated to patients, a new clinical endpoint
12 for future clinical trials that may include patients suffering from genetic disorders (i.e.,
13 vascular diseases and muscular dystrophy). In this perspective, we are developing a new
14 plasmid that combines a therapeutic gene and the hNIS gene to visualize the therapeutic
15 effect; we are also improving the US/NB-hNIS/PET system to improve the levels of
16 transfection and expression.

17

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11

12 **Figure legends**

13 **Figure 1. Peak of gene expression in mouse TA muscle**

14 Kinetics of luciferase gene expression in the TA muscles by the US/NB method. (A)
15 Luciferase activity after transfection. (B) Bioluminescence imaging. pGL3 + US ($n = 3$),
16 pGL3 + US + NB ($n = 4$). The bars represent the mean \pm S.E.M. $P < 0.01$ (**).

17

18 **Figure 2. RNA isolation and RT-PCR for luciferase and NIS**

1 Gel electrophoretic analysis of an RT-PCR reaction for luciferase and/or hNIS expression in
2 mice TA muscle induced by NBs and US. Lane M: 0.1–2 kbp size ladder. Lane 1: β -actin
3 (739 bp), Lane 2: Luciferase (689 bp), Lane 3: hNIS (581 bp).

4
5 **Figure 3. Biodistribution of ^{124}I**

6 pGL3 and hNIS were cotransfected into the left TA muscle of BALB/c mice using the US/NB
7 method, while saline solution was injected into the right TA muscle as a control. The
8 distribution of ^{124}I (370 kBq) is observed 30 (thyroid: $n = 1$, the others $n = 4$), 60 ($n = 6$), and
9 180 (thyroid: $n = 3$, the others: $n = 4$) min after the injection. The radioactivity of the tissues
10 was expressed as the percentage of the injected dose per gram (%ID/g). The bars represent
11 the mean \pm S.E.M. $P < 0.01$ (**) and $P < 0.05$ (*).

12

13 **Figure 4. Blocking ^{124}I in the TA muscle**

14 Autoradiography localization of ^{124}I in mouse TA muscle axial slices. Mice cotransfected
15 with pGL3 and hNIS were divided into 2 groups 4 d after transfection. (A) One group was i.v.
16 injected with Na^{124}I (1.85 MBq) and scarified 2 h later. (B) The other group was i.p. injected
17 with NaI. After 15 min, Na^{124}I (1.85 MBq) was i.v. injected and the group was scarified 2 h
18 later. The color bar shows logarithmic radioactivity.

1

2 **Figure 5. Visualization of gene expression**

3 We used three types of mice: control (A); arthritis and vasculitis disease (B); and muscular
4 dystrophy model mice (C). In all images, the left TA muscle (L) was cotransfected with pGL3
5 and hNIS by the US/NB method, while the right TA muscle (R) was injected with saline. In
6 all images, upper show the Bioluminescence image on 3 d after transfection, middle show
7 PET images on 4 d after transfection (Na^{124}I 74 MBq i.v.), and bottom show
8 Autoradiography of the TA sections. Radioactive tracer accumulated in the left TA section,
9 while it did not accumulate in the right TA section. The color bar shows logarithmic
10 radioactivity.

11

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