Long-Term Radioiodine Retention and Regression of Liver Cancer after Sodium Iodide Symporter Gene Transfer in Wistar Rats

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ABSTRACT

Radioiodine therapy of nonthyroid cancers after sodium iodide symporter (NIS) gene delivery has been proposed as a potential application of gene therapy. However, it seems to be precluded by the rapid efflux of taken up iodine from most transduced xenografted tumors. We present an in vivo kinetic study of NIS-related hepatic iodine uptake in an aggressive model of hepatocarcinoma induced by diethyltinlarsmine in immunocompetent Wistar rats. We followed the whole-body iodine distribution by repeated imaging of live animals. We constructed a rat NIS (rNIS) adenoviral vector, Ad-CMV-rNIS, using the cytomegalovirus (CMV) as a promoter. Injected in the portal vein in 5 healthy and 25 hepatocarcinoma-bearing rats and liver tumors in 9 hepatocarcinoma-bearing rats, Ad-CMV-rNIS drove expression of a functional NIS protein by hepatocytes and allowed marked (from 20 to 30% of the injected dose) and sustained (>11 days) iodine uptake. This contrasts with the massive iodine efflux found in vitro in human hepatic tumor cell lines. In vivo specific inhibition of NIS by sodium perchlorate led to a rapid iodine efflux from the liver, indicating that the sustained uptake was not attributable to an active retention mechanism but to permanent recycling of the effluent radioiodide via the high hepatic blood flow. Radioiodine therapy after Ad-CMV-rNIS administration achieved a strong inhibition of tumor growth, the complete regression of small nodules, and prolonged survival of hepatocarcinoma-bearing rats. This demonstrates for the first time the efficacy of NIS-based radiotherapy in a relevant preclinical model of nonthyroid human carcinogenesis.

INTRODUCTION

Radioiodine (131I) therapy is a recognized, well-tolerated approach in the treatment of human thyroid cancer. Thyrocytes are physiologically capable of accumulating iodide attributable to the presence of the sodium iodide symporter (NIS) at their plasma membranes (1–4). Recently, NIS protein was found to be expressed in a large variety of cancers but was not located at the plasma membrane and had no capacity of accumulating iodide attributable to the presence of the sodium iodide symporter (NIS) at their plasma membranes (1–4). The sodium iodide symporter (NIS) was proposed a few years ago (7–9). Various nonthyroid cancer cells (breast, cervix, lung, myeloma, and prostate) were transduced with NIS using plasmid-mediated transfection or virus-mediated gene transfer. High iodine uptake levels have indeed been achieved in these transduced cells both in vitro and in xenografted mice (10–12). Other studies report an almost total efflux of iodine from the cells, occurring less than 1 hour after the NIS-related uptake (13–16). Efflux was not significantly reduced by enzymatic or pharmacological means (14, 17–22). Interestingly, two studies have demonstrated a long retention time for 125I and significant tumor reduction after the application of a high dose of 131I in NIS-transduced mice (23, 24). However, all of these studies were performed in xenografted mice and not in the cancerous organs themselves, which limits their predictive potential for humans. The rapid efflux of iodine from nonthyroid cancer cells thus remains a major concern regarding the therapeutic applications of NIS gene transfer.

It should be noted that, in vivo, the tumor residence time of iodine results from a dynamic equilibrium between tumor cell uptake, efflux, and possible reuptake via the local blood supply and that this reuptake may compensate for a rapid efflux. On the basis of this observation, we have conjectured that the high hepatic blood flow in human liver and the hypervascular character of liver tumors might favor the reuptake of iodine and thereby increase significantly the lifetime of iodine in transduced hepatocytes. Therefore, in vivo quantitative organ-specific kinetic studies are required to validate NIS-based cancer gene therapy (25, 26). More specifically, it is necessary to perform quantitative follow-ups of the iodine distribution in transduced organs in pertinent preclinical models of cancer.

We report on a detailed study of NIS gene delivery via an adenovirus vector in the liver using a combination of in vitro experiments and in vivo investigations of rats presenting with chemically induced hepatocellular carcinoma induced by diethyltinlarsnine. We found, for the first time, strong and sustained (several days) NIS-related radioiodine uptake in both normal and tumor-affected livers and an efficient inhibition of liver tumor growth after 131I therapy. Both in vitro and in vivo, and taking advantage of the specific inhibition of the NIS function by sodium perchlorate, we demonstrated that the prolonged uptake of iodine in the liver is not attributable to any active, liver-specific retention mechanism but is of a dynamic nature, meaning that it results from the balance between rapid efflux and intense reuptake promoted by high hepatic blood flow and NIS transduction. Taken overall, our results provide a new paradigm, which accounts for the in vivo efficacy of NIS gene delivery, and, thus, opens new prospects for the treatment of cancer using 131I therapy.

MATERIALS AND METHODS

Animals. Experiments were performed under the institutional and European Union guidelines for laboratory animal care. Hepatocarcinoma was induced in 6-week–old male Wistar rats weighing 150–180 g by the daily intake of diethyltinlarsnine (Sigma-Aldrich, St. Louis, MO) in their drinking water (100 mg/L) for 8 weeks (27). The rats had received thyroxin (T4) supplementation (50 µg/L) in their drinking water to reduce unwanted thyroid iodine uptake. The litter was changed every other day to avoid fur contamination.

In vivo Gene Transfer. Rats were anesthetized with intraperitoneal ketamine (120 mg/kg; Merck and Co., Inc., Whitehouse Station, NJ) and xylazine (20 mg/kg; Bayer AG, Leverkusen, Germany) and then laparotomized. Intraportal adenovirus vector expressing NIS [adenovirus (Ad)-cytomegalovirus (CMV)]-rNIS (NIS); ref. 10] was administered to 30 rats (5 healthy and 25 diethyltinlarsnine-treated rats bearing tumor nodules with a diameter <5 mm). The rNIS vector was directly injected into 15, 5- to 10-mm diameter nodules.
tumor nodules in 9 diethylnitrosamine-treated rats using a 30-gauge needle. In both cases, the administered dose was of 5 × 10^7 infectious particles. Control animals received either 5 × 10^7 infectious particles of empty vector (Ad-DL324) or 500 μL of saline buffer.

**In vitro Iodine Uptake and Efflux Experiments.** Huh7 and hepG2 liver cells were maintained in DMEM glutamax and a 50:50 mix of DMEM/F12K Ham’s (Invitrogen Corp., Carlsbad, CA), respectively, supplemented with 10% bovine calf serum. The day before infection, 3 × 10^5 cells were seeded into 24-well dishes. Cells were incubated with Ad-CMV-rNIS at a multiplicity of infection of 10 for 24 hours. Iodine uptake and efflux studies were then performed as described previously (10, 28). The radioactive B-HBSS (Invitrogen) contained 1 μCi (37 kBq) of 123I and 0.5 μmol/L of NaI per well. For NIS inhibition studies, NaClO4 was added at a concentration of 30 μmol/L.

**In vivo Iodine Uptake Experiments.** Planar scintigraphic imaging. Na123I (Schering AG, Berlin, Germany) was injected intraperitoneally (6 to 12 MBq/ rat). From 2 to 4 rats were imaged simultaneously using a high-resolution parallel collimator of either low or high energy for 123I or 131I imaging, respectively. Scintigraphic 256 × 256 images were obtained using a DSX gamma camera (GE, Waukesha, WI). The same procedure was applied serially for kinetic studies. We obtained higher resolution images by using a 4-mm hole pinhole collimator and increasing acquisition times and numerization.

**Image Quantification.** We used the region of interest method with appropriate background correction to calculate biological and effective uptake values. Organ half-lives were calculated using a mono-exponential fit.

**Planning of Therapy.** During a preliminary study, we had administrated a fixed escalating schedule of 131I activities (100, 300, and 650 MBq) in control and infected rats. Dosimetric data were obtained from early and late (≥7 days) uptakes. We set the dose absorbed in the liver at 40 Gy, because this dose had proved to be effective in the treatment of human hepatocarcinoma (29). The corresponding therapeutic activities were ~650 MBq for a mean liver weight of 20 g. This level of activity was well tolerated in control animals. No deaths had occurred after 3 months of follow-up, indicating that the bone marrow had not been ablated. Indeed, whole-body 131I clearance followed a two-compartment model in our rats with a first effective half-life of ~30 hours (data not shown). We administrated 650 MBq of 131I to hepatocarcinoma-bearing rats intraperitoneally 2 weeks after the injection of Ad-CMV-rNIS.

**In vitro Uptakes.** Organ samples were weighed, radioactivity was measured in a well gamma counter, and the results expressed as a percentage of the injected dose per gram of tissue (%ID/g).

**Histology, Immunofluorescence, Microautoradiography.** Formalin-fixed tissue sections were embedded in paraffin, stained with H&E, and examined under a light microscope. For immunofluorescence, cryosections, 4 μm, were fixed in 4% paraformaldehyde for 15 minutes and incubated with a polyclonal antibody directed against amino acid 600 to 618 of rNIS diluted at 1:1000. The antibody was purchased from Jackson ImmunoResearch Laboratories, Inc., West Grove, PA. Fluorescence was examined by UV fluorescence microscopy. 123I-labeled liver sections were analyzed with a Micro-Imager (24 × 32 mm² field of view and 25 μm resolution; Biospace Mesures, Paris, France).

**Statistics.** Statistical comparisons were performed using variance analysis and a PLSD Fischer test at risk 5% (StatView 5.0 software SAS system).

**RESULTS**

**In vitro Analysis of Iodine Uptake in Liver Cell Lines.** Firstly, we evaluated the NIS function in vitro in hepatoma cells expressing rNIS, using radiiodine uptake assays. Fig. 1 demonstrates that CMV-rNIS-infected liver cells but not uninfected control cells were capable of taking up large quantities of iodine (≤100 times as much as control cells). The cellular concentration of 123I reached its maximum 15 minutes after the start of incubation. This uptake was inhibited by sodium perchlorate, a potent inhibitor of active iodide transport, confirming that iodide uptake is essentially NIS dependent. However, an almost complete (>90%) efflux of radioactivity was observed 5 minutes after withdrawal of the 123I-containing medium. Thus, the uptake and release kinetics of iodine in NIS-expressing human cancer liver cell lines are essentially similar to those observed in transformed cell lines derived from other organs (14, 15).
images of the liver and stomach in NIS-infected rats (Fig. 2B; comparison of rat N4 with control C1). The pattern of liver uptake was always diffuse and homogeneous. The animals were sacrificed 1,900 minutes after 123I injection, and the %ID/g was measured in liver samples (Fig. 2C). The liver 123I concentration was high and virulose dependent, reaching 1.3 ± 0.53% ID/g for 10^5 infectious particles (column 2) and 2.5 ± 0.64% ID/g for 5 × 10^5 infectious particles (column 3) compared with the uptake reported in normal human thyroid glands of ~1% ID/g (31). In contrast, control rats (column 1) only exhibited low (0.26 ± 0.05% ID/g, P < 10^-4) 123I concentrations in the liver, which mainly reflected overall 123I blood activity. We checked that rNIS protein was expressed at the surface of infected hepatocytes by immunofluorescence analysis in normal (Fig. 2D) and diethylnitrosamine-treated (Fig. 3C) rats. Thus, the iodine uptake observed was caused by a high level of NIS expression related to the strong transcriptional activity of the CMV promoter and adequate targeting of NIS to the plasma membrane of liver cells. On histologic examination at 3 weeks, the treated livers were normal without inflammatory infiltrates, apoptosis, or necrosis, indicative of the relatively strong radiosistance of normal hepatocytes to 111In β particles (mean energy 606 keV; data not shown). Serial 111In scintigraphy studies yielded similar, long-lasting (>11 days) iodine distributions in the livers of NIS-expressing rats, whereas distribution remained diffuse, with only a slight accumulation in the stomach, in control rats (Fig. 2E). The weak thyroid contrast (the residual uptake was 0.3% at day 5 and <0.03% at day 11) indicates stunning or destruction of the gland by 111In attributable to the incomplete inhibition of thyroid uptake by thyroxin. Summarily, the delivery of Ad-CMV-rNIS to the normal liver through the portal vein drove the expression of a functional NIS protein in vivo and led to strong, sustained iodine uptake after infection.

In vivo Analysis of Iodine Uptake in NIS-Transduced Livers in Hepatocarcinoma-Bearing Rats. We then examined rats bearing diethylnitrosamine-induced hepatocarcinoma (Fig. 3). As in normal rats, we injected 5 × 10^5 infectious particles of Ad-CMV-rNIS via the intraportal route. Fig. 3A shows a 24-hour serial whole-body 123I scintigraphy of two NIS-expressing hepatocarcinoma-bearing rats (D1 and D2), presenting with multinodular hepatocarcinoma. Fig. 3B shows a supplementary 131I scintigraphy performed at 72 hours in 2 other hepatocarcinoma-bearing rats (D3 and D4) and a control rat (C3). The iodine uptake pattern exhibited specific hepatic and gastric contrast, similar to that observed in infected healthy rats. The hepatic contrast remained strong in late (≥72 hours) 111In images, being even stronger than the gastric contrast (see rat D4), but was inhomogeneous, which was not surprising in view of the difficult, heterogeneous penetration of recombinant viruses in tumor cells (32). In control rats, only a weak gastric contrast appeared (see rat C3). Correlative in vitro 111In counts demonstrated prolonged and strong uptake in tumor areas (Fig. 3D). The values observed (8 × 10^-3% ID/g at day 8 and 10^-2% ID/g at day 12, column 4) were 16 to 36 times higher than those measured in the plasma and normal liver (<3 × 10^-5% ID/g, P < 10^-1, columns 1 and 5, respectively).

Time Evolution of Liver Iodine Uptake in Healthy and Hepatocarcinoma-Bearing Rats. We calculated the values of liver iodine uptake as a function of time using scintigraphy image quantification. The results obtained with 111In are given in Fig. 4. Early (120 minutes) biological liver uptakes reached 36 ± 6% ID in infected healthy rats and 20 ± 2% ID in infected hepatocarcinoma-bearing rats versus 1.5 ± 0.5% ID in control rats (P < 10^-4). The cumulated uptakes were very high in infected healthy and hepatocarcinoma-bearing rats (572 ± 110% hours and 294 ± 50% hours, respectively; P < 0.016) compared with control rats (26 ± 5% hours; data not shown). It can be seen that the liver activity was lower in hepatocarcinoma-bearing than in healthy rats (but still much higher than in control rats), which was probably attributable to a relatively low transduction of tumor hepatocytes. However, even in hepatocarcinoma-bearing rats, liver uptake accounted for most of the whole-body 111In activity at all times (Fig. 4B). Kinetic measurements were performed at late stages (3 to 11 days) by 123I scintigraphy. We found a late biological half-life of iodine of 53 ± 9.2 hours in NIS-transduced liver. The cumulated uptakes were definitely higher in NIS-expressing rats (1706 ± 297%...
shows that hepatic contrast in Ad-CMV-rNIS-infected, hepatoiodine uptake kinetics after the injection of sodium perchlorate. Fig. 5 lines. We additionally investigated this issue hepatic tumor cell lines (Fig. 1) and others in nonhepatic tumor cell clearly contrasts with the massive iodine efflux found in injected tumor; 4, in injected tumor: P<0.0012; data not shown). The very strong radioiodine uptake in the liver of rNIS-infected rats. The hepatic area of the control rat showed no significant activity. Natural routes of I elimination (colon and stomach; C, colon; Bl, bladder. Note the strong radiiodine uptake in the liver of rNIS-infected rats. The hepatic area of the control rat showed no significant activity. Natural routes of I elimination (colon and stomach) exhibited strong activity in rat D3. C, NIS expression in the liver of rat D1 visualized by immunofluorescence using an antibody anti-NIS. Scale bar, 20 μm. D, percentage of the ID/g 8 and 12 days after 131I injection. Average values of a batch of 10 transduced hepatocarcinoma-bearing rats. I, blood; 2, gastric mucosa; 3, gastric content; 4, injected tumor; 5, liver from three normal rats treated with 131I. Gastric content versus injected tumor: P<0.0012; data not shown).

Thus far, we had demonstrated a long-term retention of iodine in normal and cancerous liver after transfer of the NIS gene. This result clearly contrasts with the massive iodine efflux found in vitro by us in hepatic tumor cell lines (Fig. 1) and others in nonhepatic tumor cell lines. We additionally investigated this issue in vivo by studying liver iodine uptake kinetics after the injection of sodium perchlorate. Fig. 5 shows that 123I hepatic contrast in Ad-CMV-rNIS-infected, hepatocarcinoma-bearing rats disappeared almost totally 6 minutes after drug injection. This establishes the absence of an active retention mechanism in transduced hepatocytes and strongly suggests that the long-term retention of iodine observed was mainly attributable to 123I recirculation and reappraisal.

Tumor Growth Inhibition in Hepatocarcinoma-Bearing Rats. We investigated the inhibition of tumor growth after an intranodular injection of Ad-CMV-rNIS followed by intraperitoneal 131I therapy (650 MBq or 18 mCi). The volume of injected and noninjected nodules was measured 2 weeks after 131I administration (Fig. 6A). The volume of injected nodules decreased or remained stationary (average decrease of 30%), whereas the volume of noninjected nodules grew significantly (average increase of 400%). Empty vector-injected nodules also exhibited a high growth rate (data not shown). Moreover, we observed that diffusion of the viral vector from the injected nodules prevented the development of new tumor nodules in the surrounding tissue, whereas this development was abundant in noninjected areas. This accounts for the relatively slow tumor growth observed in 2 rats (3 and 8), in which the noninjected nodules were all close to the injected nodule. Histologic analysis demonstrated apoptotic bodies and ballooning of hepatocytes in the Ad-CMV-rNIS-injected nodules (Fig. 6B). Micro-imager-based analysis showed heterogeneous low contrast inside the injected nodule, reflecting both reduced nodular vascularization and the loss of 131I uptake activity in apoptotic cells (Fig. 6C). Doppler ultrasonography revealed dense vascularization in the perinodular area (data not shown), which may account for the enhanced contrast appearing in this area in Fig. 6C. The homogeneous labeling seen around the injected nodule illustrates diffusion of the NIS viral vector to nontumor liver.

Finally, we investigated the survival of hepatocarcinoma-bearing rats after treatment consisting of an injection of 5 x 10^7 infectious particles of Ad-CMV-rNIS via the portal vein followed by 131I therapy (650 MBq or 18 mCi). In the absence of the latter, our diethylnitrosamine-treated rats exhibited the same median survival time as in previous studies (5 months after the onset of diethylnitrosamine administration; ref. 33). Eighteen diethylnitrosamine-treated rats were infected with Ad-CMV-rNIS, and 131I was administered intraperito-
obtained a late biological half-life for iodine in the liver of these rats of 2.2 ± 0.4 days, which is adapted to the physical half-life of the widely used therapeutic radioisotope $^{131}$I (8.05 days). On the other hand, we also showed in vivo that the iodine captured by hepatocytes rapidly left the liver cells when the symporter activity of NIS was inhibited by sodium perchlorate. Therefore, it is possible to conclude that the sustained radioiodine concentration in NIS-transduced hepatocytes was the result of a dynamic equilibrium among uptake, efflux, and reuptake. This high stationary liver iodine concentration was attributable, at least partly, to the high hepatic blood flow, which allows the rapid recycling of plasmatic radioiodine to the liver. Such a dynamic equilibrium between uptake and reuptake of the released drug, leading to high intracellular levels, has been reported for metiodobenzylguanidine, a structural analogue of noradrenaline, which targets neuroblastoma cells (34–36). Moreover, the large mass of NIS-expressing hepatocytes, attributable to the use of a strong ubiquitous promoter (CMV), favors cell-to-cell iodine reuptake. Another interesting aspect of our findings is that, in our experimental hepatocarcinoma model, long-term iodine retention in the liver occurred without the expression of thyroperoxidase, indicating that the cotransfer of thyroperoxidase with NIS would be unnecessary.

We also demonstrated that, in hepatocarcinoma-bearing rats, tumor growth was strongly inhibited and survival improved by $^{131}$I therapy after NIS gene transfer. In fact, our results even suggest that a complete regression can be obtained in some cases. It is plausible that the immune response to the expressed NIS followed by $^{131}$I therapy played a role in the survival of our treated immunocompetent animals, but this hypothesis will need to be specifically studied. The increased survival of our treated rats is highly significant given the extreme rapidity of spontaneous tumor progression in this hepatocarcinoma experimental model. We established the safety of this therapeutic procedure in both normal and hepatocarcinoma-bearing rats; all of the animals survived the maximum applied dose of 650 MBq of $^{131}$I without developing bone marrow aplasia.

One of the current major challenges of gene therapy for cancer is the generally low transduction efficacy of tumor cells by the vectors used (37, 38). This has led to the concept that, regardless of the therapeutic approach proposed, a strong bystander effect will be necessary to allow the destruction of neighboring nontransduced tumor cells (39, 40). The intermediate path length of $^{131}$I $\beta$ emission (815 $\mu$m in water) may render $^{131}$I an attractive candidate for such a bystander effect, because cross-fire irradiation can reach even nontransduced tumor hepatocytes. Our results support the validity of this concept by showing that hepatocarcinoma nodules with a diameter of <5 mm cease to grow and are partly destroyed by the presence of $^{131}$I in some of the cells. Interestingly, micro-imager–based analysis of $^{131}$I showed a marked strengthening in peritumor iodine uptake, a finding consistent with $^{131}$I acting against tumor extension. Naturally, this beneficial effect was weaker in larger tumors in which the deposed dose was highly heterogeneous, although intranodular injection did evidence local antitumor action. Thus, our findings suggest that NIS-based, intraarterial gene therapy is indicated in cirrhotic livers with dysplastic and small tumor nodules, as well as in tumor recurrence after hepatocarcinoma resection; interestingly, in the latter case, intra-arterial lipiodol–$^{131}$I has been shown to be efficient in reducing hepatocarcinoma recurrence and enhancing survival when administered after tumor resection (41). We did not observe any apparent $^{131}$I-related liver damage in Wistar rats, although we were using a strong ubiquitous promoter (CMV), and the iodine liver uptake of normal transduced hepatocytes was higher than that of tumor ones (Fig. 4). Interestingly, the dose of 40 Gy used in our study is well tolerated by humans treated with $^{131}$I-lipiodol (41). These results therefore suggest an increased sensitivity of liver tumor cells to the bystander effect.
131I compared with normal hepatocytes. Such conclusions might lead to use the strong CMV promoter when designing preclinical and clinical studies. However, we cannot exclude a late radiotoxicity occurring after our 2-month follow-up period, as observed in some clinical studies. Moreover, this may improve the efficacy of our treatment in the case of large tumors by allowing selective increase of the irradiation dose in the tumor.

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REFERENCES


Fig. 6. Antitumor effect of 131I therapy in hepatocarcinoma-bearing rats infected with 5 × 105 infectious particles of Ad-CMV-rNIS. A, left, tumor volume progression in injected and noninjected cancer nodules (9 rats). Right, changes to average tumor volumes. B, liver histology. Arrows, apoptotic bodies and ballooning of hepatocytes in an Ad-CMV-rNIS-injected nodule. The empty vector-injected nodule (T) exhibited basophilic staining and a high nucleocytoplasmic index. NT, noninjected tissue around the tumor. Scale bar, 20 μm. C, micro-imager–based analysis of 131I distribution in liver sections of rats infected via the intranodular route. Left, empty vector-injected nodule. Middle, Ad-CMV-rNIS-injected nodule (arrow). Ad-CMV-rNIS yielded heterogeneous intranodular targeting with peri-nodular reinforcement. Right, liver histology of the same liver section. Scale bar, 1 mm. D, macroscopic views of a non-131I-treated (left) and 131I-treated (right) rat liver 5 months after the initiation of diethylnitrosamine administration. The 131I-treated liver was apparently cured of hepatocarcinoma nodules. Scale bar, 1 cm.


Corrections

p53 and BCNU Resistance in Astrocytes

In the article on p53 and BCNU Resistance in Astrocytes in the June 15, 1996 issue of Cancer Research (1), the title was incorrect. The title should have read “Wild-Type p53 Renders Mouse Astrocytes Resistant to 1,3-Bis(2-chloroethyl)-1-nitrosourea Despite the Absence of a p53-dependent Cell Cycle Arrest.”


AChE in Apoptosis

In the article on AChE in Apoptosis in the April 15, 2004, issue of Cancer Research (1), there is an error on page 2652, in the section under “Materials and Methods” on “siRNA Transfection”. The AChE target sequence should have read 5’-AAGAGUGUCUGCUAC-CAAUAU-3’.


Depletion of Methionine Aminopeptidase 2

In the article on Depletion of Methionine Aminopeptidase 2 in the May 1, 2004, issue of Cancer Research (1), there is an error on page 2984, in the section under “Materials and Methods” on “Cell and Enzyme Assays”. The text near the end of the section should have read the following; “The targeting sequence was AAUGCCGGUGACACAACAGUA (Dharmacon Research). The control mismatch sequence was AAUGCCGGCGCUACAACAGUA.”


NIS Gene Therapy of Hepatocarcinoma

In the article on NIS Gene Therapy of Hepatocarcinoma in the November 1, 2004, issue of Cancer Research (1), a note should have been included indicating that J. Faivre and J. Clerc contributed equally to the study.


Novel Functions of BRAK

In the article on Novel Functions of BRAK in the November 15, 2004, issue of Cancer Research (1), the following grant support information should have appeared:

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