Neutron Activated $^{153}$Sm Sealed in Carbon Nanocapsules for *In Vivo* Imaging and Tumor Radiotherapy

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ABSTRACT: Radiation therapy along with chemotherapy and surgery remain the main cancer treatments. Radiotherapy can be applied to patients externally (external beam radiotherapy) or internally (brachytherapy and radioisotope therapy). Previously, nanoencapsulation of radioactive crystals within carbon nanotubes, followed by end-closing, resulted in the formation of nanocapsules that allowed ultrasensitive imaging in healthy mice. Herein we report on the preparation of nanocapsules initially sealing ‘cold’ isotopically enriched samarium ($^{152}$Sm), which can then be activated on demand to their ‘hot’ radioactive form ($^{153}$Sm) by neutron irradiation. The use of ‘cold’ isotopes avoids the need for radioactive facilities during the preparation of the nanocapsules, reduces radiation exposure to personnel, prevents the generation of nuclear waste and evades the time constraints imposed by the decay of radionuclides. A very high specific radioactivity is achieved by neutron irradiation (up to 11.37 GBq/mg), making the ‘hot’ nanocapsules useful not only for in vivo imaging but also therapeutically effective against lung cancer metastases after intravenous injection. The high in vivo stability of the radioactive payload, selective toxicity to cancerous tissues and the elegant preparation method offer a paradigm for application of nanomaterials in radiotherapy.

KEYWORDS: cancer therapy, nuclear imaging, nanoencapsulation, filled carbon nanotubes, radiooncology, nanooncology.
Advances of nanomedicine in cancer diagnosis and therapy require the production of ‘small’ and ‘smart’ agents that can offer specific targeting, adequate detection sensitivity, efficient therapeutic effects and ideally favorable biocompatibility.\textsuperscript{1-5} Carbon nanotubes (CNTs) have been exploited as delivery systems for theranostic applications.\textsuperscript{6-10} Their needle-like structure enables efficient cell penetration.\textsuperscript{11-14} Moreover, a selected biomedically relevant payload can be loaded onto the CNT structure either by chemical modification of the largely available external surface (exohedral), or by filling their interior space (endohedral). Surface engineering is a more straightforward approach and has been widely investigated.\textsuperscript{15, 16} Although less explored, confinement of imaging and therapeutic agents into CNTs is attracting an increased attention.\textsuperscript{17, 18} After encapsulation, the external walls remain available to anchor biocompatible and/or targeting ligands. One advantage of the nanoencapsulation approach is the protection that the carbon coating (CNT walls) offers to the encapsulated materials from enzymatic degradation once exposed to biological environment. It has been already demonstrated that only highly defective, oxidized CNTs are degraded by peroxidases.\textsuperscript{19} Apart from CNTs, a variety of materials are being employed for the formation of nanocapsules that shield a selected payload.\textsuperscript{20-24} In the vast majority of studies, release of the encapsulated cargo is necessary to achieve a therapeutic effect via the delivery of bioactive agents such as drugs. This is however not the case for nuclear imaging and targeted radiotherapy applications where departure of the encaged imaging and/or therapeutic radionuclides from the nanocapsule is neither required nor desired. From the library of nanocapsules available, the properties of carbon nanotubes make them unparalleled for the permanent sealing of radionuclides.\textsuperscript{25-28} The graphene shells that constitute the walls of the CNTs can perfectly separate the core from the external environment, forming impermeable nanocapsules when the ends of the CNTs are closed.\textsuperscript{29, 30} Having closed ends allows the removal of non-encapsulated material, after
the filling step, under harsh washing conditions\textsuperscript{31} and even the retention of gases in their interior.\textsuperscript{32} Mutual protection is therefore afforded to both biological systems and the nanotube cargo delivered.\textsuperscript{7} When radionuclides are sealed, the action of ionizing particles exerts through the walls of CNTs\textsuperscript{25, 27, 28} and it spans from micron to millimeter distances depending on the characteristics of the chosen isotopes. It is worth noting that the internal radionuclides and external moieties (biocompatible/targeting molecules) can be independently changed thus giving versatility to this approach.

In current clinical cancer therapy, half of all cancer patients are treated with radiation therapy either alone or combined with other types of therapies. Nanotechnology strategies however have been mainly driven by the use of chemotherapeutic agents. Notwithstanding, there is a growing interest in the development of nanomaterials bearing radioisotopes, since they offer a platform not only for molecular imaging but also to enhance the radiation response of tumors while reducing side effects.\textsuperscript{33-36} CNTs have been shown to deliver positron/\(\gamma\)-radioemitters and alpha particles of interest for imaging and therapeutic applications. This has been mainly achieved \textit{via} chelation of radionuclides onto the external walls\textsuperscript{37-39} although the impregnation of radionuclides onto highly defective CNTs, which can be regarded as mesoporous materials, has also been investigated by Wilson \textit{et al.}\textsuperscript{40-42} As just mentioned, an attractive feature of CNTs is the possibility to hermetically seal radionuclides in their interior. The nanocapsule will not only prevent release of the chosen radionuclides into the biological milieu but also of their decay products, which might be of a different chemical nature and detach from the nanocarrier with the previously employed strategies. We have previously reported a pioneering work using hermetically sealed Na\textsuperscript{125}I-filled and externally glycosylated single-walled CNTs (SWNTs).\textsuperscript{25} Specific tissue accumulation (lung) coupled with high \textit{in vivo} stability prevented leakage of radionuclide to high-affinity organs
(thyroid/stomach) or excretion, and resulted in ultrasensitive imaging and delivery of a high radiation dose density.\textsuperscript{25} Pascu \textit{et al.} have recently given versatility to this approach and investigated the behavior of radiometal-filled ($^{64}\text{Cu}$) SWNTs \textit{in vitro} and \textit{in vivo}.\textsuperscript{27} In this study the ends of the CNTs were sealed using fullerenes as corks to prevent release of the encapsulated radioemitter.\textsuperscript{43, 44} In contrast to these previous reports, where ‘hot’ radionuclides, in the form of Na$^{125}$I or $^{64}\text{Cu}$(OAc)$_2$, were directly filled into SWNT, followed by end-closing, herein, we present an approach by which ‘cold’ non-radioactive $^{152}\text{Sm}$ is initially sealed into the cavities of both SWNT and multi-walled CNTs (MWNT) leading to the formation of closed-ended $^{152}\text{Sm}$-filled carbon nanocapsules. The encapsulated and stable $^{152}\text{Sm}$ can then be activated into therapeutically active ‘hot’ $^{153}\text{Sm}$ by neutron irradiation through the walls of the CNTs (Figure 1a; Schematic representations comparing both strategies to achieve ‘hot’ nanocapsules are included in Figure S1). After neutron activation, exceptionally high specific activities were obtained, compared to previous works on direct encapsulation of radionuclides, which allowed not only \textit{in vivo} nuclear imaging but also lung tumor radiotherapy. $^{153}\text{Sm}$ is an attractive radionuclide as it emits beta particles at maximum energy of 810 keV (suitable for cell killing), and also releases gamma energy of 103 keV (allowing clinical imaging).\textsuperscript{45, 46} $^{153}\text{Sm}$ is used clinically in the form of $^{153}\text{Sm}$-ethylene diamine tetramethylene phosphonate chelate ($^{153}\text{Sm}$-EDTMP, Quadramet®) for palliation of bone metastases.\textsuperscript{47} It offers added advantages such as desirable half-life (46.3 h) and lower gamma energy over other therapeutic radionuclides currently being used in clinic such as iodine-131 or yttrium-90.\textsuperscript{48}

The encapsulation of ‘hot’ radionuclides into the cavity of CNTs requires a fast and safe manipulation of the material due to their constant decay. By using the neutron activation strategy (Figure 1a), both the filling and the removal of the non-encapsulated compound do not require the
use of radioactive facilities thus reducing radiation exposure to the personnel. It also alleviates the
time constraints imposed by the constant decay of radionuclides since the ‘cold’ nanocapsules can
be shelf-stored and activated by neutron irradiation on demand. Neutron activation of nanoparticles
incorporating neutron-activatable isotopes is well documented, with initial studies focused on the
use of fullerenes and polymeric nanoparticles.\textsuperscript{49-53} Di Pasqua \textit{et al.} also proposed the use of
inorganic mesoporous silica nanoparticles loaded with neutron-activatable holmium-165.\textsuperscript{54, 55}
Taking advantage of the porosity of the nanocarrier, this was later expanded to
chemoradiotherapy.\textsuperscript{56} Other inorganic materials including holmium iron garnet, mesoporous
carbon nanoparticles and graphene oxide have more recently been explored as holmium
nanocarriers.\textsuperscript{57-59} On the other hand, neutron activation of large particles (\textit{i.e.} holmium-166
containing microspheres) has been employed in clinical trials for the treatment of liver tumor \textit{via}
intra-arterial injection leading to radioembolization.\textsuperscript{60, 61} In this work we propose the use of neutron
irradiation of ‘cold’ isotopically enriched \textsuperscript{152}Sm sealed within carbon nanotubes. The activated
‘hot’ \textsuperscript{153}Sm nanocapsules allow both \textit{in vivo} imaging and tumor radiotherapy.

RESULTS AND DISCUSSION

\textbf{Preparation and neutron activation of \textsuperscript{152}Sm-filled nanocapsules to yield radioactive
\textsuperscript{153}Sm@CNTs.} As-received CNTs were initially purified and shortened by combination of solution
processing with strong acids followed by steam.\textsuperscript{62} High temperature molten phase capillary filling
was employed for the encapsulation of isotopically enriched \textsuperscript{152}SmCl\textsubscript{3} into SWNT and MWNT,
leading to the closing of the nanotube ends on cooling\textsuperscript{29, 30} (Figure 1a). For ease of nomenclature,
we will refer to these nanocapsules as \textsuperscript{152}Sm@SWNT and \textsuperscript{152}Sm@MWNT. We employed enriched
samarium (\textsuperscript{152}Sm) to ensure an efficient activation to the clinically employed \textsuperscript{153}Sm isotope upon
neutron irradiation. After the filling experiment, the excess of $^{152}$SmCl$_3$ external to the walls of the CNTs was removed by repeated washings and filtration of the sample in water. The length and external diameter distribution of the samples was determined after the filling step. The median length turned out to be ca. 200 nm for SWNTs and ca. 330 nm for MWNTs (see Figure S2 and Table S1 for statistical data), and the median external diameters 2.1 nm for SWNTs and 10.7 nm for MWNTs (Figure S3, Table S2). The amount of samarium present was next quantitatively determined by ICP-MS. The analyses revealed ~12.3 w/w% and 17.6 w/w% loading of $^{152}$Sm for $^{152}$Sm@SWNT and $^{152}$Sm@MWNT, respectively. The bigger cavity of $^{152}$Sm in MWNTs with respect to their single-walled counterparts accounts for the larger amount of encapsulated $^{152}$Sm. Due to the large excess of $^{152}$SmCl$_3$ (10 mg) that was employed for the bulk filling of CNTs (1 mg), only a small fraction of the metal halide was encapsulated (ca. 2 % according to the filling yield). With the present strategy, the non-encapsulated $^{152}$SmCl$_3$, dissolved during the washing steps, is recovered by filtration. This compound is an enriched non-radioactive form of samarium which can be dried (from the collected filtrate), stored and employed in further filling experiments. Therefore, no samarium waste is generated in the filling step.

Neutron activation is favored in radionuclide production because of its relatively simple process and the availability of various types of nuclear reactors. It also permits lower radiation exposure to the personnel since the preparation procedures such as encapsulation, purification and characterization can be conducted prior to irradiation. Exceptionally high specific radioactivities (SRA) with respect to the mass of the composite material were obtained after 96 h neutron irradiation of $^{152}$Sm@SWNT (6.33 GBq/mg) and $^{152}$Sm@MWNT (11.37 GBq/mg) (Table 1). The SRA values are two orders of magnitude (differ by a factor of about 100) higher than those previously reported for neutron irradiated nanocarriers loaded with clinically relevant
radiotherapeutic isotopes, which are in the range of ca. 1-80 MBq/mg (Table S3). This is due to the high neutron flux and long irradiation time employed in the present study taking into account the amount of $^{152}\text{Sm}$ loading. In fact, such high SRA are in line of those achieved by neutron irradiation of pure elements or their oxides for industrial applications.

**Structural examination of the nanocapsules before ($^{152}\text{Sm}@$CNT) and after ($^{153}\text{Sm}@$CNT) neutron irradiation.** Instant thin-layer chromatography (ITLC) examination was performed for $^{153}\text{Sm}@$SWNT and $^{153}\text{Sm}@$MWNT to evaluate whether neutron irradiation had caused any structural damage to the carbon nanocapsules that could result in leakage of $^{152}\text{Sm}$ from their interior. Based on recent studies on non-enriched SmCl$_3$ nanocapsules, over 99% of SmCl$_3$ that is not sealed inside the CNTs can be easily dissolved by a short sonication (10 s) of the sample in water. Therefore, to ensure the complete dissolution of $^{153}\text{Sm}$ from the inner cavities of those CNTs that could have undergone structural damage, a longer sonication step (several min) in water was performed. As shown in Table 1 and Figure S4 a large amount of $^{153}\text{Sm}$ remained sealed in the cavities of MWNT (92%) and SWNT (70%), despite the high neutron flux ($1.6\times10^{14}$ n cm$^{-2}$s$^{-1}$) and long neutron irradiation time employed (96 h) to achieve high SRA. Milder irradiation conditions are usually used to prevent/decrease degradation of the carrier during neutron activation. Comparison of SRA under different conditions is included in Table S1. The fraction of $^{153}\text{Sm}$ external to the CNT walls could be either chelated prior to *in vivo* studies or washed from the sample resulting in a minimal amount of radioactive waste, compared to the previously employed strategy where radionuclides were directly filled into CNTs. The presence of several concentric graphene layers resulted in a more stable construct to the flux of neutrons. Therefore, although $^{152}\text{Sm}$ can be activated inside both MWNT and SWNT, the former turned out to be more robust for the preparation of ‘hot’ nanocapsules by neutron irradiation. Even higher fractions of
permanently sealed $^{152}$Sm would be expected in both constructs by decreasing the time and flux of neutron irradiation, with the corresponding reduction of SRA (according to equation (1)).

Transmission electron microscopy (TEM) allowed us to evaluate the effect of neutron irradiation on the $^{152}$Sm-filled CNTs. Encapsulated $^{152}$SmCl$_3$ can be observed in the high resolution TEM (HRTEM) images of $^{152}$Sm@SWNT and $^{152}$Sm@MWNT before irradiation (Figure 1b, top panels). The filled metal halides were still present in both types of CNTs (black arrows) after irradiation without evident damage on the nanotube structure. It is important to note that the ends of the carbon nanotubes remain sealed after neutron irradiation (pointed with white arrows). Additional TEM images for both ‘cold’ and ‘hot’ nanocapsules are included in Figure S5. Structural changes of the encapsulated crystals are sometimes observed during electron microscopy imaging.$^{66-71}$ In the present case we observed that in some cases, SmCl$_3$ nanowires were fragmented into smaller crystals (Figure S6). Preservation of the payload encapsulation was further confirmed by high angle annular dark field (HAADF) scanning transmission electron microscopy (STEM) (Figure 1b, central panels). The SmCl$_3$ filling (bright white lines) aligned nicely within the CNT lumen (dim grey contrast) even following irradiation also indicating the presence of filling material.

Energy dispersive X-ray (EDX) spectroscopy was conducted to assess the preservation of the payload content upon irradiation. The presence of samarium was detected before and after irradiation (Figure 1b, bottom panels). Europium, the decay product of $^{153}$Sm, was not detected by EDX because despite the high SRA less than 1% of $^{152}$Sm nuclei underwent nuclear reaction to radioactive $^{153}$Sm under the employed conditions.

**Whole body SPECT/CT imaging and tissue biodistribution of $^{153}$Sm@CNTs in normal mice following i.v. injection.** The $^{153}$Sm@CNT suspensions underwent different dilutions with
non-irradiated $^{152}$Sm@CNT to contain the appropriate radioactivity for the *in vivo* studies in 1% Pluronic® F-127 saline. As just discussed, stable nanocapsules sealing 70 % (SWNT) and 92 % (MWNT) of $^{153}$Sm were obtained. The sonication step after neutron irradiation ensures no further leakage of $^{153}$Sm from the nanocapsules *in vivo*. The fraction of $^{153}$Sm dissolved during the preparation of ‘hot’ nanocapsules was chelated with EDTA to ensure a fast renal clearance. The pharmacokinetics and biodistribution of $^{153}$Sm@SWNT and $^{153}$Sm@MWNT up to 24 h were next explored by whole body SPECT/CT imaging and quantitative γ-scintigraphy (Figure 2).

SPECT/CT imaging demonstrated that both $^{153}$Sm@CNTs showed similar biodistribution patterns with accumulation mostly in spleen, lung and liver within 30 min (Figure 2a). The uptake in these organs was retained up to 24 h post injection (period of imaging). We have previously observed *in vivo* lung accumulation of filled CNTs bearing targeting and non-targeting groups. This behavior has been attributed to the physical properties of CNTs within physiology. As expected, high signals were detected from kidney and bladder within 30 min after injection, which were attributed to the $^{153}$Sm:EDTA chelate. From quantitative γ-scintigraphy measurements, a progressive clearance from the blood was observed for both $^{153}$Sm@CNTs, in which most of the compounds were cleared out from circulation at 4 h post injection (Figure 2b). Figure 2c shows roughly 20% and 10% of injected dose (ID) were detected in urine in the case of $^{153}$Sm@SWNT and $^{153}$Sm@MWNT, respectively. The results correlated well with the ITLC findings where a higher amount of free $^{153}$Sm was detected after neutron irradiation in $^{153}$Sm@SWNT than in $^{153}$Sm@MWNT (Figure S4). Negligible radioactivity was detected in feces for both $^{153}$Sm@CNTs (< 0.5 %ID). The organ biodistribution profiles established at 4 and 24 h (Figure 2d) paralleled the SPECT/CT imaging results where $^{153}$Sm@CNTs largely accumulated in spleen and showed high uptake in lung and liver. The accumulation in spleen and liver increased over time while the uptake
in lung at 4 h and 24 h remained steady. Biodistribution analyses expressed as %ID per organ are presented in Figure S7.

**Assessment of radiotherapeutic efficacy of $^{153}$Sm@CNTs in B16F10-Luc melanoma lung metastasis.** Taking advantage of the prominent lung accumulation property of CNTs, the radiotherapeutic efficacy of $^{153}$Sm@SWNT and $^{153}$Sm@MWNT was investigated using an experimental B16F10-Luc melanoma lung metastatic tumor model. This syngeneic tumor model is characterized as highly aggressive and metastatic, and has been commonly used for evaluation of cancer regimens.73, 74 The luciferase-expressing feature of this cell line enabled tumor growth monitoring by whole body bioluminescence imaging.

The results demonstrate that single intravenous administration of 20 MBq of $^{153}$Sm@SWNT or $^{153}$Sm@MWNT (200 µg of CNTs per mouse) significantly delayed the tumor growth in lung (Figure 3). Representative bioluminescence images of untreated, $^{153}$Sm@SWNT and $^{153}$Sm@MWNT treated mice on day 10 and day 16 post-tumor inoculation are shown in Figure 3a and images of all mice are shown in Figure S8. From the lung tissues examined at post-mortem (Figure 3b), distinct differences were visualized between the treatment groups. Metastatic melanoma nodules occupied most of the lung tissue from the untreated mice, while lesser number of melanoma nodules were observed in $^{153}$Sm@CNT treated mice. The number of tumor nodules also reflected the lung weights in which lung tissues from untreated mice weighed significantly heavier than $^{153}$Sm@CNT treated mice ($***p<0.001$).

Figure 3c displays the average tumor size (photons/sec) of untreated mice and mice treated with $^{153}$Sm@SWNT or $^{153}$Sm@MWNT over the therapy time course. Treatment responses started to appear on day 13 for both $^{153}$Sm@CNTs showing significant tumor reduction compared to the untreated group (*$p < 0.05$). Although similar amount of radioactivity was administered and both
$^{153}$Sm@CNTs showed comparable % ID in lung, notably smaller tumors were measured in mice treated with $^{153}$Sm@SWNT compared to $^{153}$Sm@MWNT on day 16 ($p < 0.05$). Nevertheless, both $^{153}$Sm@CNT treatments demonstrated substantial tumor growth suppression on day 16 ($p < 0.001$, compared to control) where the therapy study terminated. The reasons behind this more prolonged therapeutic effect of $^{153}$Sm@SWNT are not clear, but there might be differences between the two $^{153}$Sm@CNTs in terms of the interaction with lung tissues/tumor cells which led to the differential therapeutic outcomes.

Histological analysis was carried out on H&E (hematoxylin and eosin stain) and Neutral Red stained lung tissue sections at post-mortem at the end of therapy study on day 16. The lung sections from untreated mice showed an invasion of cancerous mass leading to the disappearance of healthy lung tissues and a clear reduction of alveoli number (Figure 3d, top panels). In contrast, in $^{153}$Sm@CNT treated mice (Figure 3d, middle and bottom panels), lung sections appeared healthier with the presence of fewer colonies of melanoma nodules. Zoom-in images of healthy and cancerous areas from each treatment groups are shown on the right panels with arrows indicating some trapped $^{153}$Sm@CNTs. CNTs were difficult to identify in cancerous regions due to the dark appearance of melanoma. Together with the bioluminescence images, it indicated that $^{153}$Sm@CNT therapies did not fully eradicate tumors but prevented their proliferation.

**Toxicity assessments post $^{153}$Sm@CNT injection and after radiotherapy.** During the radiotherapy period, variable whole body weight changes were observed within groups (Figure 4a). Body weight loss seemed to occur for the $^{153}$Sm@CNT treated mice starting from day 10 post-tumor inoculations but there is no significant difference between the groups including the untreated mice. The weights of major organs were measured at sacrifice. Marginal changes were found between most of the untreated and $^{153}$Sm@CNT treated organs, except for lungs (with tumors,
***p < 0.001) and spleen (***p < 0.01 or ***p < 0.001) (Figure 4b). As previously evidenced in Figure 3b, the aggressively growing tumors increased the weight of lung significantly for the untreated mice. We have previously demonstrated that cold metal-filled CNTs were biocompatible in vivo. The significant weight loss in lungs from mice treated with \(^{153}\)Sm@CNTs compared to untreated mice is likely a result of reduction of tumor nodules. Histological assessment performed on mice treated with low dose radioactivity (200 µg \(^{153}\)Sm@CNTs/mouse, 1 MBq) showed no significant histological abnormalities in the selected major organs (heart, lung, kidneys, liver, and spleen) sampled at 24 h post injection (Figure S9). This further confirms that the reduced lung weights were due to the radiotherapy effect and not from the CNTs per se.

The average weight of spleen of \(^{153}\)Sm@CNT treated mice was reduced compared to untreated tumor-bearing mice. This is less likely to be general toxicity of the CNTs but a consequence of the high spleen uptake of \(^{153}\)Sm@CNTs leading to high radioactivity accumulation. Histological examination on spleen with profound observation of the death of splenocytes could explain the spleen and body weight reduction of \(^{153}\)Sm@CNT treated mice since the malfunction of spleen can debilitate the immune system (Figure 4c). No histological abnormalities were observed for heart, liver, and kidney. The lack of liver toxicity further supports containments of \(^{153}\)Sm within the CNTs in vivo. For example, studies by other groups demonstrated hepatotoxicity with unchelated \(^{153}\)Sm which naturally ends up in reticuloendothelial organs such as the liver and spleen.47, 72 Hematological and inflammatory examinations are needed in future investigations.

**Dosimetry simulation studies.** Since the developed therapeutic \(^{153}\)Sm@CNT nanocapsules achieved promising killing effect on tumor cells, a model was established to simulate the performed radiation therapy. Figure 5 shows the comparison between the experimental (green dots) and simulated tumor growth (blue lines, according to equation (2)) data of untreated mice,
and mice treated with $^{153}$Sm@SWNT or $^{153}$Sm@MWNT. The $^{153}$Sm@CNTs were injected on day 8 which is the reason for the hump on the simulated curve at day 8. For both $^{153}$Sm@SWNT and $^{153}$Sm@MWNT the effect of irradiation was to decrease the rate of tumor growth. Despite the many simplifying assumptions of the model (e.g. mono-exponential uptake, washout, and proliferation rates), the simulations reproduced the general trend of the experimental data for both systems. Moreover, the simulations successfully predicted that, for the particular administered activity, biodistribution features and tumor cell type, the resulting dose rate was not high enough. The performed radiotherapy clearly decreased the rate of tumor growth; however, the cell killing could not dominate over cell proliferation which could lead to complete tumor regression. The simulations suggest that local tumor control (defined here as the eradication of all tumor cells with 95% probability) requires roughly 17-28 times higher administered activities (330 MBq for $^{153}$Sm@MWNT and 550 MBq for $^{153}$Sm@SWNT). Taking into account the obtained SRA values for the prepared nanocapsules, it is indeed possible to administer the required dose for complete eradication of cancer in vivo (ca. 30–90 µg of undiluted $^{153}$Sm@CNT). In view of efficacy and safety, toxicity profiles using higher doses should be further studied. Due to radiation regulation limits, a much lower dose (20 MBq) has been employed herein for the internal radiation therapy studies. Significant delay in tumor growth has been observed even using such small doses.

CONCLUSIONS

The development of radiopharmaceuticals requires a simple and safe handling of raw materials and final products, during both the manufacturing process, at the point of care, and during the intermediate steps. Furthermore, radiopharmaceuticals must be chosen carefully to deliver the correct activity for the particular radionuclide, given its half-life. The current work is an original
concept to produce highly energetic $^{153}\text{Sm}$-encapsulated CNTs via a stable intermediate consisting of $^{152}\text{Sm}$-filled CNT nanocapsules, that may ultimately be used in a therapeutic context. Preparing the CNT nanocapsules in this way enables control over the $^{153}\text{Sm}$ content and consequently, the activity. Furthermore, it reduces the process-complexity and the amount of waste that would be generated if one performed the encapsulation process directly on radioactive isotopes. Finally, the isotopically enriched ‘cold’ nanocapsules can be stored and activated by neutron irradiation when needed. Neutron irradiation of ‘cold’ $^{152}\text{Sm}$-nanocapsules turned out to be robust, especially for MWNT with 92% retention of $^{153}\text{Sm}$. Extremely high SRA were obtained (6.33 GBq/mg for $^{153}\text{Sm}@\text{MWNT}$ and 11.3 GBq/mg for $^{153}\text{Sm}@\text{SWNT}$), which allowed live imaging and therapy in experimental metastatic lung tumor model in mice. The obtained SRA are two orders of magnitude higher than those previously reported for neutron activated nanomaterials bearing clinically relevant radioisotopes.$^{64}$ On the other hand, the activity of a standard dose of clinically employed yttrium-90 microspheres is 2-4 GBq.$^{76-78}$, requiring the administration of over 100 mg (52.0 mCi in 116 mg TheraSphere®).$^{79}$ This activity can be achieved with less than 1 mg of the developed nanocapsules. Dosimetry modelling studies can further optimize the treatment efficacy for potential clinical applications and predict the dose required. The preparation of nanocapsules with enriched isotopes benefits from well established filling and end closing strategies, thus giving versatility in the selection of neutron activatable imaging and/or therapeutic isotopes. The possibility of carrying out further surface functionalization on the irradiated nanocapsules can potentially result in a stable nanoconstruct capable of in vivo targeting, imaging, and therapy.

METHODS

Additional experimental details are included in the Supporting Information.
Preparation of ‘cold’ nanocapsules (\(^{152}\text{Sm}@\text{CNT}\)). Both SWNTs and MWNTs (Elicarb\textsuperscript{®}) were initially treated to shorten the tubes, open their ends and remove carbonaceous and metallic (catalyst) impurities. SWNTs were exposed to a combined piranha-steam treatment, whereas MWNTs underwent a combined \(\text{H}_2\text{SO}_4:\text{HNO}_3\)-steam treatment following previously reported protocols.\textsuperscript{62} Steam is very efficient in removing functional groups and highly defective carbon nanotubes.\textsuperscript{62} Enriched \(^{152}\text{Sm}_2\text{O}_3\) (CIS-Bio International-Ion Beam Applications, France) was transformed to anhydrous \(^{152}\text{SmCl}_3\) following the protocol reported for the synthesis of anhydrous \(\text{SmCl}_3\) with natural isotopic distribution (non-enriched).\textsuperscript{80} The synthesized anhydrous \(^{152}\text{SmCl}_3\) is highly hygroscopic and was handled under an inert atmosphere, and employed for filling CNTs. SWNT or MWNT and \(^{152}\text{SmCl}_3\) were ground together in a weight ratio 1:10 (CNTs:\(^{152}\text{SmCl}_3\)) inside an argon filled glove box, split in smaller fractions, placed inside silica tubes and sealed under vacuum. The mixtures were annealed for 12 h at 900 °C (SWNT) or 1200 °C (MWNT) thus leading to the formation of carbon nanocapsules (closed-ended filled CNTs).\textsuperscript{29, 30} Removal of the non-encapsulated \(^{152}\text{SmCl}_3\) with 0.6 M HCl was followed by UV-Vis, until no more \(^{152}\text{SmCl}_3\) was detected in the washings (0.2 μm Whatman\textsuperscript{®} polycarbonate membranes).\textsuperscript{65} The length distribution of the resulting \(^{152}\text{Sm}@\text{SWNT}\) and \(^{152}\text{Sm}@\text{MWNT}\) was determined from SEM images, following a previously described methodology,\textsuperscript{81} and the external diameter distribution from TEM images. Two hundred CNTs were measured for each of the analyses (see SI).

Neutron activation of \(^{152}\text{Sm}\)-filled CNTs to achieve ‘hot’ nanocapsules (\(^{153}\text{Sm}@\text{CNT}\)). The irradiation protocol was established according to equation (1):\textsuperscript{63} 

\[
A = \frac{0.6\sigma\Phi}{M} \left(1 - e^{-\lambda t}\right) \quad (1)
\]
where $A$ is the predicted activity of the radioisotope produced (Bq g$^{-1}$), $M$ is the atomic mass of the target element (152 g mol$^{-1}$ for $^{152}$Sm), $\Phi$ is the neutron flux of the reactor (1.6x10$^{14}$ n cm$^{-2}$s$^{-1}$), $\sigma$ is the thermal neutron activation cross-section of the target isotope (206 barns for $^{153}$Sm), $\lambda$ is the decay constant (0.693/T$_{1/2}$), (T$_{1/2}$ is the half life of the target isotope, which is 46.27 h for $^{153}$Sm) and $t$ is the irradiation time (96 h). Vacuum sealed silica ampoules containing 30 mg of either $^{152}$Sm@SWNT or $^{152}$Sm@MWNT were placed in an aluminum capsule and irradiated at a neutron flux of 1.6x10$^{14}$ n·cm$^{-2}$·s$^{-1}$ for 96 h in a pool-type reactor (OSIRIS, CEA Saclay, France). $^{153}$Sm@SWNT and $^{153}$Sm@MWNT powders were separately suspended in a volume of 1% Pluronic® F-127 saline (0.9 % NaCl) solution at 0.5 mg/mL.

**Characterization.** HAADF-STEM images were acquired at 20 kV on an FEI Magellan XHR Scanning Electron Microscope (SEM). HRTEM images were acquired on a FEI Tecnai G2 F20 microscope at 200 kV. Samples were dispersed in ethanol and deposited onto lacey carbon Cu grids. $^{153}$Sm@CNT were imaged after the complete decay of radioactivity. EDX was carried out on a FEI Quanta SEM microscope equipped with an EDAX detector at 20 kV. EDX spectra were acquired on large areas of CNTs (> 50 $\mu$m$^2$) to obtain representative data of the composition of the samples. ICP-MS analysis was carried out using an ICP-MS with a quadrupole collision cell (PerkinElmer Sci EX ELAN® DRC II). Samples for ICP-MS were microwave digested (800 W, 40 min) in a 3:1 mixture of nitric:hydrogen peroxide (Suprapur® Merck KGaA, Germany). For ITLC, aliquots of $^{153}$Sm@SWNT and $^{153}$Sm@MWNT were spotted on TLC strips (Agilent Technologies, UK) and then developed in 0.1 M ammonium acetate containing 50 mM EDTA as a mobile phase. Strips were allowed to dry and counted quantitatively using a cyclone phosphor detector (Packard Biosciences, UK).
**In vivo studies.** All *in vivo* experiments were conducted under the authority of project and personal licenses granted by the UK Home Office and the UKCCCR Guidelines (1998). Female C57BL/6 mice aged 6-8 weeks were purchased from Harlan (UK) and used for all *in vivo* studies. Mice were anaesthetized by isoflurane (IsoFlo®, Abbott Laboratorie Ltd, UK) inhalation and injected via a tail vein. Each injection dose contained the same amount of CNT (200 µg), and the necessary radioactivity (for imaging, biodistribution or therapy studies) was a by dilution of the $^{153}$Sm@CNT suspensions with non-irradiated $^{152}$Sm@CNT (2 mg/mL in 1% Pluronic® F-127 saline). Injection suspensions were added with 0.1 M EDTA (one twentieth of the injection volume) to chelate any free $^{153}$Sm. For histological examination, collected organs were fixed in 10% neutral buffered formalin. Harvested fixed organs were paraffin-embedded and sectioned for haematoxylin and eosin (H&E) or Neutral Red staining according to standard histological protocols at the Royal Veterinary College (UK). All stained sections were analysed using a Leica DM 1000 LED Microscope (Leica Microsystems, UK) coupled with a CCD digital camera (Qimaging, UK).

**In vivo imaging, pharmacokinetics and organ biodistribution of $^{153}$Sm@CNTs.** Biodistribution was firstly assessed by 3D whole body SPECT/CT imaging (Nano-SPECT/CT, Bioscan, USA). SPECT images were taken in 24 projections over 30-40 min using a four-head scanner with 1.4 mm pinhole collimators. CT scans were performed at the end of each SPECT acquisition. Images were reconstructed by MEDISO software (Medical Imaging Systems), and SPECT and CT images were merged using the InVivoScope™ software (Bioscan, USA). The radioactivity of tissues, blood, urine or feces was measured by γ-scintigraphy (LKB Wallac 1282 Compugamma, PerkinElmer). Blood (sampled from a tail vein), urine and feces were collected over 24 h. To assess the excretion profiles, animals had free access to water but not food.
**In vivo** $^{153}$Sm@CNT radiotherapy studies on B16F10-Luc lung metastasis tumor model.

Mice were injected with $5 \times 10^5$ B16F10-Luc cells in 0.2 mL of PBS via a tail vein to establish pulmonary melanoma metastases. Following tumor inoculation, *in vivo* quantitative bioluminescence imaging was performed on day 7, 10, 13 and 16 to monitor the tumor growth (IVIS Lumina III, Perkin-Elmer, UK). Mice were subcutaneously injected with luciferin (D-luciferin potassium salt, Perkin-Elmer, UK) at 150 mg/kg and imaged 10 min after injection. To determine the radiotherapeutic action of $^{153}$Sm@CNT, B16F10-Luc tumor bearing C57BL/6 mice were randomly divided into three groups ($n = 9$-$10$): untreated, $^{153}$Sm@SWNT and $^{153}$Sm@MWNT. On day 8 post tumor inoculation, mice were injected with $^{153}$Sm@CNT (ca. 20 MBq). Mice were sacrificed on day 16 post tumor inoculation, and major organs were collected. Tumor growth was monitored by bioluminescence imaging. The tumor growth data was expressed as mean ± SEM (standard error of the mean), with $n$ denoting the number of animals.

**Dosimetry simulation.** For targeted radionuclide therapy, the surviving fraction (SF) of the tumor cell population over time, SF($t$), can be described by equation (2).

\[
SF(t) = \exp\left\{-\alpha r_0 \left(\frac{m-k}{m} + \frac{1}{m} e^{-mt} - \frac{1}{k} e^{-kt}\right) + \lambda \cdot t\right\} \quad (2)
\]

where $\alpha$ is the radiosensitivity parameter (Gy$^{-1}$), $r_0$ is the extrapolated initial dose rate (Gy h$^{-1}$), $m$ is the radionuclide effective uptake rate (h$^{-1}$), $k$ is the radionuclide effective washout rate (h$^{-1}$) and $\lambda$ is the tumor cell proliferation rate (h$^{-1}$). The effective rates of uptake and washout of the radionuclide account for both biological and physical processes and they are defined through

\[
m = \frac{\ln(2)}{T_u} + \frac{\ln(2)}{T_p} \quad \text{and} \quad k = \frac{\ln(2)}{T_u} + \frac{\ln(2)}{T_p},
\]

respectively, where $T_u$ is the biological uptake half-life, $T_w$ is the biological washout half-life, and $T_p$ is the physical half-life of the radionuclide. The values of
and $k$ were obtained from a fit of the experimental tumor biodistribution data for the percentage injected dose (% ID) using equation (3):

$$
\text{ID}(t) = \text{ID}_0 \left( e^{-kt} - e^{-mt} \right)
$$

where $\text{ID}_0$ is the extrapolated % ID in the tumor at time $t = 0$. Note that the physical half-life of $^{153}\text{Sm}$ ($T_p = 46.3$ h) sets a lower limit to the values of $m$ and $k$ which should be larger than $\frac{\ln(2)}{T_p}$. The least square fits yielded $\text{ID}_0 = 16.6\%$, $k = 0.0162$ h$^{-1}$, $m = 2.32$ h$^{-1}$ for SWNTs, and $\text{ID}_0 = 28.0\%$, $k = 0.0160$ h$^{-1}$, $m = 0.826$ h$^{-1}$ for MWNTs (Figure S10).

To obtain the rate constant for tumor cell proliferation ($\lambda$), we assume (following standard practice) that all tumor cells in the population are proliferating. The experimental tumor growth data of the non-irradiated group of mice are fitted in equation (4):

$$
N(t) = N_0 \ e^{\lambda t},
$$

where $N_0$ is the number of tumor cells at $t = 0$. The rate constant $\lambda$ in equation (4) is normally expressed as $\lambda = \frac{\ln(2)}{T_d}$ with $T_d$ being the tumor doubling time. Fit of the experimental data by equation (4) yields $T_d = 39.78$ h (see Figure 7a).

The extrapolated initial dose rate in the tumor, $r_0$, entering equation (2) is estimated from equation (5):

$$
r_0 = A_0 \ \text{ID}_0 \ S \ f_T,
$$

where $A_0$ is the administered activity to the mice (20 MBq), $\text{ID}_0$ is obtained from equation (3), $f_T$ is the fraction of the organ activity that is taken up by the tumor, and $S$ is the radiation absorbed dose to the tumor per radionuclide decay (Gy Bq$^{-1}$ s$^{-1}$). For $^{153}\text{Sm}$ and a tumor mass of 0.07 g, $S = 4.25 \times 10^{-10}$ Gy Bq$^{-1}$ s$^{-1}$. To obtain $f_T$, it is assumed that the activity was distributed uniformly...
in the tumor \(M_{\text{tumor}} = 0.07 \, g\) and the lungs \(M_{\text{lungs}} = 0.12 \, g\), so \(f_T = \frac{M_{\text{tumor}}}{M_{\text{tumor}} + M_{\text{lungs}}} = 0.368\).

Substituting the above parameters in equation (2), the values \(r_0 = 3.158 \, \text{Gy h}^{-1}\) and \(r_0 = 1.872 \, \text{Gy h}^{-1}\) are obtained for MWNTs and SWNTs, respectively.

The radiosensitivity parameter \(\alpha\) was determined empirically from cell survival data using the expression

\[
\alpha = \frac{\ln(SF_2)}{D + D^2 (\alpha/\beta)^{-1}}, \tag{6}
\]

where \(SF_2\) is the measured surviving fraction at \(D = 2 \, \text{Gy}\) and \(\alpha/\beta\) is the dose where the linear and quadratic cell-kill mechanisms (of the linear-quadratic cell survival model) are equal. For B16F10-Luc cells, \(SF_2 = 0.96\).\(^{84}\) Such a high value for \(SF_2\) corresponds to an extremely radioresistant cell line. Thus, to a first approximation, we can assume \(\alpha/\beta = 1 \, \text{Gy}\) which is at the low-end of the range of values observed for the late responding tissues.\(^{85, 86}\) Equation (6) yields \(\alpha = 0.0068 \, \text{Gy}^{-1}\).

From the above dosimetry model we may also obtain a rough estimate of the required administered activity for local tumor control, defined here as the eradication of all (clonogenic) tumor cells with 95% probability. Assuming that 70 mg of tumor contain roughly \(7 \times 10^7\) cells (and all are clonogenic) the above local tumor control probability translates to the condition

\[
SF < \frac{-\ln(0.95)}{7 \times 10^7} \approx 7 \times 10^{-10}
\]

which can be achieved with 670 MBq \(^{153}\)Sm@SWNT and 400 MBq \(^{153}\)Sm@MWNT administered activity. If we consider the (perhaps) more realistic approximation that only 1% of tumor cells are clonogenic \((i.e.,\, \ldots)\) the \(SF < \frac{-\ln(0.95)}{7 \times 10^5} \approx 7 \times 10^{-8}\) corresponding administered activity values are 550 MBq \(^{153}\)Sm@SWNT and 330 \(^{153}\)Sm@MWNT.
FIGURES
Figure 1. Preparation and characterization of carbon nanocapsules. a) Schematic representation of the strategy employed for the preparation of ‘hot’ nanocapsules. A non-radioactive enriched precursor is initially encapsulated ($^{152}$Sm) and it is activated into its radioactive form by neutron irradiation ($^{153}$Sm) in the last step. The wavy lines indicate radioactivity emerging from radionuclides ($^{153}$Sm). b) Structural characterization of Sm-filled CNTs before (‘Cold’ nanocapsules) and after (‘Hot’ nanocapsules) irradiation. HRTEM images are shown in the top panels. Black arrows point to the SmCl$_3$ filling, and white arrows to closed tips of carbon
nanotubes. The crystalline structure of SmCl$_3$ can be better appreciated on the MWNT images, with visible lattice fringes (parallel lines). HAADF-STEM images are shown in the middle panels. The bright lines correspond to the filling of SmCl$_3$, while CNTs appear as a dim grey contrast. EDX analyses confirming the presence of SmCl$_3$ are shown in the bottom panels.
Figure 2. Whole body SPECT/CT imaging and tissue biodistribution of $^{153}$Sm@SWNT and $^{153}$Sm@MWNT in mice up to 24 h. a) SPECT/CT imaging, b) blood circulation, c) excretion profiles and d) tissue biodistribution profiles. C57BL/6 mice were i.v. injected with 200 µg of EDTA-quenched $^{153}$Sm@SWNT or $^{153}$Sm@MWNT containing 10 MBq or ~1 MBq for SPECT/CT imaging or $\gamma$-scintigraphy, respectively. In excretion studies, mice were housed individually in metabolic cages for 24 h immediately after injection. The radioactivity in blood, major organs sampled at specified time points and urine/feces collected at 24 h post injection, was measured by $\gamma$-scintigraphy. The results are expressed as mean ± S.D. (n=3-4).
Figure 3. Tumor growth delay studies in experimental metastatic lung tumor mice model after internal administration of radiotherapy. B16F10-Luc tumor-bearing C57BL/6 mice received a single i.v. injection of $^{153}$Sm@SWNT or $^{153}$Sm@MWNT (20 MBq, 200 µg) on day 8 post-tumor inoculation. a) Average lung weights measured on day 16 post-tumor inoculation, the experimental
endpoint. b) Representative whole-body images of untreated, $^{153}\text{Sm@SWNT}$ and $^{153}\text{Sm@MWNT}$ treated mice captured on days 10 and 16 post-tumor inoculation. c) Tumor growth monitoring over time. Bioluminescence signals correspond to luciferase expressing B16F10 cells in the lung. d) H&E and Neutral Red stained B16F10-Luc tumor-containing lung tissue sections excised on day 16 (left panels). High magnification images of tumor (areas 1) and non-tumor (areas 2) lung tissues are shown on the right. Arrows indicate the presence of CNTs. Scale bars: 200 $\mu$m for H&E and Neutral Red stained sections; 5 $\mu$m for zoom-in images of areas 1 and 2. Results are presented as mean ± S.D. (n=9-10). Significant differences were examined using one-way ANOVA followed by Tukey’s multiple comparison test ($^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).
Figure 4. Toxicity assessments in tumor-bearing mice treated with $^{153}$Sm@SWNT and $^{153}$Sm@MWNT via intravenous injection. B16F10-Luc tumor-bearing C57BL/6 mice received a single i.v. injection of $^{153}$Sm@SWNT or $^{153}$Sm@MWNT (20 MBq, 200 µg) on day 8 post-tumor inoculation. a) Percentage of whole body weight changes of B16F10-Luc tumor-bearing mice after...
radiotherapy. b) Major organ weight and c) histological examination of major organs on day 16 post tumor inoculation. The body weight of individual mouse was measured every 3-4 days post tumor-inoculation. At the experimental endpoint on day 16, major organs including heart, kidney, liver and spleen were excised, weighed and fixed for histological examination. Tissue sections were stained with H&E (examine necrosis) or Neutral Red (track CNTs). Scale bars: 50 μm. Results are presented as mean ± S.D. (n = 9-10). No statistical differences were found in % whole body weight changes between different treatments. Mice treated with $^{153}$Sm@CNTs showed significant weight reduction in lung and spleen. Significant differences were examined using one-way ANOVA followed by Tukey’s multiple comparison test (**$p < 0.01$, ***$p < 0.001$).
Figure 5. Predicted and experimental relative tumor sizes as a function of time in control or $^{153}$Sm@SWNT- and $^{153}$Sm@MWNT-treated mice. B16F10-Luc tumor-bearing C57BL/6 mice received a single dose i.v. injection of $^{153}$Sm@SWNT or $^{153}$Sm@MWNT (20 MBq, 200 µg) on day 8 post tumor inoculation or remained untreated. Green dots represent experiment data and blue lines are simulated results for the three groups: a) untreated control, b) $^{153}$Sm@SWNT treated group, and c) $^{153}$Sm@MWNT treated group. The calculated blue lines are plotted according to equation (2). The values of the coefficients entered in equation (2) are as follows: for all three
cases, the radiosensitivity parameter was $\alpha = 0.0068 \text{ Gy}^{-1}$ and the cell doubling time $T_d$ equals 39.78 h which corresponds to a proliferation rate $\lambda = \ln(2)/T_d = 0.017 \text{ h}^{-1}$. Extrapolated initial dose rate $r_0$, effective uptake rate $m$, and effective washout rate $k$ are specific for each case. Specifically, for the untreated sample (a), the extrapolated initial dose rate $r_0$ equals 0 whereas for SWNT (b) the parameter values are: $r_0 = 1.872 \text{ Gy h}^{-1}$, $k = 0.0162 \text{ h}^{-1}$, $m = 2.34 \text{ h}^{-1}$ and for MWNT (c) the parameter values are $r_0 = 3.158 \text{ Gy h}^{-1}$, $k = 0.0160 \text{ h}^{-1}$, $m = 0.826 \text{ h}^{-1}$. The detailed derivation of the parameter values for each case is given in the Dosimetry simulation section in the Supporting Information.

### TABLES.

**Table 1.** Neutron irradiation of $^{152}\text{Sm@SWNT}$ and $^{152}\text{Sm@MWNT}$ to achieve radioactive $^{153}\text{Sm@SWNT}$ and $^{153}\text{Sm@MWNT}$.

| Starting material | $^{152}\text{Sm @CNT}$ | $^{153}\text{Sm @CNT}$ |
|------------------|--------------------------|--------------------------|
|                  | % $^{152}\text{Sm}$ (ICP-MS) | Neutron irradiation [h] | Predicted SRA [GBq/mg] | Observed SRA [GBq/mg] | ITLC % Purity |
| $^{152}\text{Sm@SWNT}$ | 12.3 | 96 | 7.77 | 6.33 | 70 |
| $^{152}\text{Sm@MWNT}$ | 17.6 | 96 | 11.11 | 11.37 | 92 |
ASSOCIATED CONTENT

Supporting Information.

Schematic representation employed for the development of ‘hot’ nanocapsules. Length distribution of $^{152}\text{Sm@CNT}$ samples. External diameter distribution of $^{152}\text{Sm@CNT}$ samples. ITLC analysis. HRTEM images of Sm-filled SWNTs before and after irradiation. Effect of the electron beam on the filling material. Table with neutron activated isotopes loaded onto nanocarriers. Tissue biodistribution of $^{153}\text{Sm@SWNT}$ and $^{153}\text{Sm@MWNT}$. Live bioluminescence images. Live bioluminescence images of untreated mice or mice treated with $^{153}\text{Sm@CNTs}$. Histological examination of major organs. Fit of the experimental biodistribution data (% ID) in the lung. Additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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