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Neutron-Activatable Needles for Radionuclide Therapy of Solid Tumors

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Abstract

Various approaches have been undertaken to enhance the delivery of therapeutic agents, including tissue-killing radionuclides, into solid tumors. Here we describe the preparation of conical needles composed of Ti and Mo coated by pulsed laser deposition or chemical vapor deposition with elements (Ho and Re) that can readily yield radioactive isotopes following irradiation in a neutron flux. The radioactive needles, whose design were based on solid microneedle arrays used in transdermal drug delivery, can be produced with minimal handling of radioactivity and subsequently inserted into tumors as a means of internal radiation therapy. Ho and Re, were specifically chosen because of their large neutron capture cross-sections as well as the desirable radiotherapeutic properties of the resultant radionuclides. Neutron-absorbing shields were also developed to prevent the production of unwanted radionuclides after neutron irradiation of the needle base materials. Neutron activation calculations showed that therapeutically significant amounts of radionuclides can be produced for treating solid tumors. Stability studies demonstrated that Re did not leach off the Mo needles. These coated neutron-activatable needles offer a new approach to internal radiation therapy of tumors that allows precise tailoring of the absorbed radiation dose delivered to the tumor by controlling the coating thickness and the irradiation time.

Keywords

Neutron-Activation; Brachytherapy; Rhenium-molybdenum alloy; Pulsed laser deposition; Chemical vapor deposition

INTRODUCTION

The treatment of solid tumors, which continue to account for a significant number of deaths worldwide, remains a challenge. In order to deliver therapeutic agents to solid tumors, approaches that have been successfully used in the transdermal drug delivery field that do not involve simple passive diffusion have been investigated for intra-tumoral delivery of

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drugs, proteins and other therapeutics. These approaches include the use of focused ultrasound, iontophoresis and electroporation.^{1–3} One approach that has not been previously explored is the use of microneedle technology. Microneedles have been fabricated in solid form to allow transport of therapeutics across the stratum corneum, in hollow form to allow delivery of drugs through a small orifice in the tip of the needle, and in a form composed of dissolvable materials that permit extended release of therapeutics. Instead of the current cylinder-shaped brachytherapy applicator, the focus of the current work is to fabricate a conical-shaped needle that would deliver therapeutic doses of radiation to tumors after penetration of the needle into solid tumors. This approach involves making the needle itself radioactive by coating them with elements that are readily activated to therapeutic radionuclides following irradiation in a neutron flux. Because the thickness of most solid tumors is much greater than the thickness of the stratum corneum (~15 μm), our design involved needles of much greater length (300 μm - 1 cm) than seen with most microneedle assemblies.

The use of therapeutic (particle-emitting) radionuclides to treat solid tumors remains as a prominent therapeutic option. Internal radiation therapy with sealed radioactive sources (brachytherapy) involves the delivery of high doses of targeted radiation with minimal off-target effects by applying radioactive sources directly to or into the target tumors. Brachytherapy sources containing ^{192}Ir or ^{103}Pd are used in the treatment of prostate cancer, the second leading cause of cancer death in men in the United States, and cervical cancer, the second leading cause of cancer-related deaths in women in developing countries.^{4,5} In addition, ocular plaques containing ^{125}I and ^{106}Ru are used to treat tumors of the eye.⁶

Neutron-activation is an attractive method of generating radioactivity while minimizing radioactive exposure during preparation. Holmium (Ho) is a promising neutron-activatable element as it is 100% naturally abundant (^{165}Ho) and has a large neutron capture cross-section (59 barns; 1 barn = 10^{-24} cm^2).⁷ After irradiation in a neutron flux, ^{166}Ho is produced, which decays by the emission of high energy, tumor-killing β^- particles ($E_{\text{max}} = 1.86$ MeV, half-life = 26.8 h; maximum tissue penetration = 8.7 mm). This neutron-activation approach has been used to produce ^{166}Ho -nanoparticles composed of mesoporous silica, mesoporous carbon and graphene oxide.^{8–10} This method demonstrated the generation of sufficient radioactivity to induce tumoricidal effect as not handling any radioactivity during the formulation preparation steps.

Radiotherapeutic rhenium (Re) radioisotopes can also be produced by neutron activation of natural abundance Re. It is a refractory metal with a very high melting point (3180 $^{\circ}\text{C}$) and is resistant to wear and corrosion even at low pH and high salt condition.^{11–13} Among the refractory metals (niobium, molybdenum, tantalum and tungsten), Re element exhibits the greatest tensile and creep-rupture strength.^{11,14} In addition, Re does not form carbides, nor does it have a ductile-to-brittle transition temperature as it is ductile over a wide range of temperatures.¹³ Thus, it has the capability to be utilized in various applications.¹² In nature, Re exists as two stable isotopes: 37.4% as ^{185}Re (neutron capture cross-section = 112 barns) and 62.6% as ^{187}Re (neutron cross-section = 73 barns).⁷ As such, neutron-activation generates ^{186}Re ($E_{\text{max}} = 1.07$ MeV, half-life = 89.2 h, maximum tissue penetration = 5 mm) and ^{188}Re ($E_{\text{max}} = 2.12$ MeV, half-life = 17.0 h, maximum tissue penetration = 11 mm).^{15,16}

The properties of Ho and Re (e.g., high natural abundance and short half-life) are not only desirable for producing maximal amounts of radioactivity compared to commonly used radioisotopes, but the radioisotopes of produced by neutron activation of natural abundance Ho and Re also emit photons (γ -rays and x-rays). These allows these radionuclides to be used a theranostic agents whereby the disposition of ^{166}Ho , ^{186}Re and ^{188}Re can be monitored by Single Photon Emission Computed Tomography (SPECT).^{15–17} This is not the case for other radionuclides used in brachytherapy, e.g., ^{192}Ir and ^{103}Pd , both of which have low photon yields with γ -ray energies not optimal for SPECT imaging. In addition, the stable isotopes for producing these radionuclides (^{191}Ir and ^{102}Pd) have lower natural abundances (37% and 1%, respectively). The shorter half-lives of the Ho and Re radioisotopes do not limit their ability to be distributed to clinical sites as some diagnostic isotopes routinely used in nuclear medicine have considerably shorter half-lives, e.g., ^{123}I ($t_{1/2} = 13.2$ h). Here we report on the production of custom-sized radiotherapeutic needles coated with neutron-activatable elements (Ho and Re) with the goal of minimizing the handling of radioactive material and improving internal radiation therapy (Fig. 1).

MATERIALS AND METHODS

Materials

Holmium foil (1 mm thick, 99.9% trace rare earth metal basis), methanol (HPLC grade) and acetone (HPLC grade) were purchased from Sigma-Aldrich (St. Louis, MO). Phosphate buffered saline (PBS pH 7.4) was obtained from Fisher Chemical (Fair Lawn, NJ). Acetate buffer (USP heavy metal testing grade, pH 3.5) was acquired from Ricca Chemical (Arlington, TX). Holmium ICP-MS standard (pure single-element standard, 1,000 $\mu\text{g/mL}$ in 2% HNO_3) and rhenium ICP-MS standard (pure single-element standard, 1,000 $\mu\text{g/mL}$ in 2% HNO_3) were received from PerkinElmer (Waltham, MA). Gadolinium sputtering target (76.2 mm diameter, 3.18 mm thick) was purchased from Alfa Aesar.

Pulsed laser deposition (PLD) of Ho on Titanium (Ti) needles

Ti needles were prepared by the North Carolina State University (NCSU) precision instrument machine shop. Prior to deposition of Ho, needles were placed in an ultrasonic bath for 10 minutes in acetone and 10 minutes in methanol to remove impurities. Substrates were then placed in the PLD chamber. Ho foil was utilized as the PLD target. A KrF Lambda Physik LPX 200 excimer laser was operated at a wavelength of 248 nm and an output energy of 450 mJ. A thin Ho film was deposited on the Ti needles using 10,000 shots, with a shot frequency of 20 Hz and a target frequency of 1 Hz.

Characterization of Ho-coated Ti needles

Scanning electron microscopy (SEM; Hitachi S-4700) was used for imaging of the micro-sized needles. Ho deposition was confirmed by energy-dispersive X-ray spectroscopy (EDS; Oxford instruments, INCA PentaFET). The thickness of Ho deposition was measured by atomic force microscopy (AFM, Asylum Research MFP3D Atomic Force Microscope).

Chemical vapor deposition (CVD) of Re on molybdenum (Mo) needles

Three Re coatings of varying thickness (25, 75 and 125 μm) were uniformly deposited on Mo needles by CVD. During this process, a precursor vapor containing rhenium pentachloride was passed over a heated needle substrate. CVD deposits were formed on the substrate at the molecular level. Coating thickness was determined through cross-sectional analysis via scanning electron microscopy of witness coupons coated with actual parts, combined with weight gain of the actual parts. In addition, the CVD coating process exhibited the greatest throwing power, i.e., the ability to uniformly deposit materials onto/into intricately shaped or textured substrates. An essentially 100% dense Re coating was deposited on Mo needles through the thermal decomposition of ReCl_5 at 1100°C .

Gadolinium (Gd) neutron shield

A neutron shield made of pure Gd to prevent the formation of undesired Mo isotopes was produced by the NCSU precision instrument machine shop. The shield was designed to prevent exposure of the base material to the neutrons while allowing irradiation of the coated needle.

Stability assessment at different pH

Non-radioactive coated needles were incubated in 20 mL of PBS (pH 7.4) and in acetate buffer (pH 3.5) at 37°C for up to 30 days. The leached amount of Ho and Re was quantified by inductively coupled plasma mass spectrometer (ICP-MS; Agilent 7500cx with Agilent 1260 Infinity Bioinert LC).

Leaching following by neutron-activation

Neutron-activatable radiation needles were irradiated for 10 minutes in the PULSTAR Reactor Facility at NCSU (reactor power = 1 MW; thermal neutron flux = 5.5×10^{12} neutrons cm^{-2} s). The irradiated samples were washed with 20 mL of Milli-Q water 3 times and the amount of radioactive Ho or Re in the washings was quantified with a γ -scintillation counter (PerkinElmer 2470 Wizard γ -counter).

RESULTS AND DISCUSSION

PLD of Ho on Ti needles

In order to tailor the amount of radioactivity produced by neutron activation of the needle, the total amount of Ho loaded onto the needle can be varied by the deposition process. PLD is a widely-adopted method of adhering thin films to a substrate.¹⁸ With this method, when Ho foil was ablated in a vacuum with an intense pulsed laser, it was transformed into a plasma plume that condensed on the needle.¹⁹ Among many candidates, Ti was selected as a base material because of its relatively low material cost, low density, high strength, good biocompatibility, resistance against corrosion and, most importantly, the low amount of radioactive Ti isotopes produced following neutron irradiation.^{20,21} Two prototypes with different needle sizes (300 μm and 1 cm) were manufactured, and Ho was deposited by PLD. Needles with varying dimensions can be prepared and customized to the size of the tumor to be treated (Fig. 2a). Successful deposition of Ho on the needle was confirmed by elemental

analysis using EDS and by morphological changes observed by SEM (Fig. 2b). The thickness of Ho coating was estimated to be 1.19 μm by AFM (Fig. S1). Coating thickness can be easily modified by changing PLD parameters such the number of shots or shortening the frequency to achieve desired amount of metal loading. A thicker Ho coating on the Ti needles would reduce the irradiation time necessary to produce therapeutic quantities of radioactivity (^{166}Ho).

Leaching study of Ho coating on Ti needles

A significant amount of heat is generated during the neutron activation process that could degrade the radiation delivery matrix leading to premature leaching of the radionuclide.²² Therefore, it is important to assess how much radioactivity leaches from the matrix following neutron activation. In these studies, irradiation time was limited to 10 minutes in order to remain in compliance with possession limits of our institution. The leaching studies showed that all of the Ho that had been deposited on the Ti needles by the PLD process remained on the needles following neutron irradiation and did not leach off when incubated and washed with water.

Since the neutron-activatable radiation needle was designed for use in solid tumors, a pH-stability study was conducted at physiological pH (7.4) as well as in a low pH environments that might be encountered with treating some solid tumors, e.g. cervical (pH 3.5).²³ Ho deposition on the Ti needle was found to be stable at pH 7.4, but ultimately detached from the needle at pH 3.5. A change in color of the Ho coating, possibly due to oxidation, was also observed in acidic conditions. Thus, all subsequent efforts focused on the Re-coated Mo needles.

CVD of Re on Mo needles and evaluation of Re leaching

Mo is another refractory metal that is a reasonable choice for use as a needle base material due to its mechanical strength, resistance to corrosion, excellent machinability and biocompatibility.²⁴ We considered making entire needles of Re, but it is much more expensive than Mo and does not possess many of the desirable characteristic of Mo.¹³ Mo-Re alloys are often formed to offer protection against oxidation, wear and corrosion. Different compositions of Re-Mo alloys have been extensively investigated and employed for various applications, including biomedical, e.g., artificial heart valves.^{25,26}

Based on the capacity for Mo to alloy favorably with Re, a needle was made of Mo and coated with Re by CVD. The size of this needle was 4 mm which was selected specifically for use in tumor-bearing mice models (Fig. 3a). Like PLD, CVD is often utilized for preparing elemental films via chemical deposition of a vapor-phase target onto a heated substrate.²⁷ Due to a faster and more homogenous deposition at a lower cost, CVD is generally considered to be more suitable for large-scale commercial production versus PLD. Based on these factors as well as from previous publications that reported success with CVD methods, the current study used CVD for Re deposition onto a Mo substrate (Fig. 3b,c).^{13,19} Stability testing indicated that the Re coating stayed intact without leaching from the Mo needle even after incubation in different pH buffers for up to 30 days (Table 1). Only

minimal leaching of radioactive Re was observed following neutron irradiation of the Re-coated Mo needles.

Production of Mo radioisotopes and daughters

Although the Re-coated Mo needle was readily machinable, scalable and did not exhibit leaching of Re under diverse conditions, a new issue arose in terms of the production of undesirable radioisotopes of Mo following neutron irradiation. Compared to a Ti needle base, the Mo base generates a number of detectable isotopes, some of which are produced in substantial amounts (Table 2). ^{101}Mo and ^{101}Tc resulting from irradiation of Mo are produced in the greatest amounts, measuring 13.8 mCi and 11.5 mCi, respectively, under simulated conditions (1h irradiation in a flux of 5.5×10^{12} neutrons cm^{-2} s). However, these isotopes decay quickly and activities become negligible within a few hours due to their short half-lives (14.6 minutes for ^{101}Mo , 14.2 minutes for ^{101}Tc). An additional isotope, ^{93}Mo , can also be produced during the irradiation process. Neutron activation calculations revealed that non-negligible amounts (48.6 pCi) of ^{93}Mo ($t_{1/2} = 3500$ y) could be produced under the standard irradiation conditions. Although this amount of radioactivity is not very great, it must be taken into consideration when calculating radiation dosimetry for patients. The most noteworthy isotope resulting from Mo irradiation is $^{99\text{m}}\text{Tc}$, which is a commonly used radionuclide in nuclear medicine for SPECT imaging. Contrary to previously discussed radioisotopes, the radioactivity of $^{99\text{m}}\text{Tc}$ increases with time from the decay of ^{99}Mo until transient equilibrium is established (after ~24 h).

Neutron absorbing shield

In order to avoid the production of these radioisotopes, a neutron shield was manufactured that would allow irradiation of the Re-coated needle, but not the Mo base. Gd was chosen as the shielding material because it has a very high neutron cross-section (49,700 barns), and thus could shield the base of the needle by absorbing neutrons before they reach the base.^{28,29} As shown in Fig. 4, the Gd neutron shield was customized to the size of Mo needle and was comprised of two separate compartments (top and bottom) for easy separation following irradiation. Since the Gd shield itself will become radioactive following neutron-activation, this facile shield removal method is desirable to minimize the handling time. Originally, only the needle itself was to be coated with the Re film, but during the process, some Re was unavoidably deposited on the base as well. (Fig. 3c). Therefore, the Gd shield was designed so that only the needle itself was exposed to neutrons.

Calculation of radioactivity produced by neutron-activatable needles

Neutron-activation of Ho and Re was simulated and compared to yttrium (Y) (Fig. 5a), a therapeutic radionuclide used in commercial products (e.g., Zevalin® and TheraSphere®) due to the energetic beta particles ($\beta_{\text{max}} = 2.28$ MeV) it emits.^{7,30} In spite of the 100% natural abundance of ^{89}Y , its low neutron capture cross-section (1.28 barns) results in the production of small amounts of ^{90}Y compared to ^{166}Ho , ^{188}Re and ^{186}Re when neutron-activated under the same conditions. Although ^{185}Re and ^{187}Re both have larger neutron capture cross-sections than ^{165}Ho , the 100% natural abundance of ^{165}Ho results in significantly larger amounts of radioactivity that can be produced. The difference between ^{166}Ho and ^{188}Re in the amount of radioactivity that can be produced by neutron

activation is not very different for irradiation times up to 20 h; longer irradiation times yield a greater amount of ^{166}Ho that is produced.

Calculations were also performed to assess the time at which elements reached the maximum theoretical amount of radioactivity that could be produced under identical conditions (1 mg of natural abundance Ho, Re and Y irradiated in a thermal neutron flux of 5.5×10^{12} neutrons cm^{-2} s). The properties of the stable and radioactive isotopes of these elements are shown in Table 3. Radionuclides with relatively short half-lives, such as ^{166}Ho and ^{188}Re , reached 90% of their maximum theoretical amount after 100 h of irradiation whereas ^{186}Re and ^{90}Y reached only 54.0% and 66.1%, respectively. Fig. 5b depicts the amount of Ho, Re and Y radioisotopes produced under a protocol feasible for clinical utility, i.e., 10 h of neutron irradiation followed by a decay period of up to 2 days. It can be seen that similar amounts of ^{166}Ho and ^{188}Re are available at the end of irradiation, but ^{188}Re decays faster than ^{166}Ho . Although a much smaller amount of ^{186}Re is present at the end of irradiation, if a 48 h period is necessary to process and ship the neutron-activated needles, the amount ^{186}Re would be essentially equal to the amount of ^{188}Re after this time period due to the longer half-life of the former.

The amount of Re isotopes that can be produced from Re-coated Mo needles can be controlled by varying the amount of Re deposited on the needles. The different thicknesses of Re coating (25, 75, and 125 μm) correspond to depositions of 5.04 mg, 15.6 mg and 26.9 mg of Re, respectively. Fig. 5c shows the calculated amounts of ^{186}Re and ^{188}Re produced after irradiation of needles coated with varying Re thickness for 10 h followed by an extended decay period.

CONCLUSION

The use of neutron-activated materials that can be inserted into tumors offers the possibility of customizing internal radiation therapy by selecting needle geometries, coating thicknesses and irradiation times for solid tumors of specific sizes and shapes. Ti and Mo were selected as base materials for the needles because of their machinability, while Ho and Re were selected as the neutron-activatable materials to be coated on the needles because of their favorable nuclear properties (high neutron capture cross-sections, isotopic natural abundance, half-lives and decay properties of the resultant radionuclides). The ultimate dose of radiation produced by neutron activation of Ho or Re can be also easily controlled either by varying the thickness of the Ho/Re coating or selecting an appropriate neutron-irradiation time. The stability of the coatings, which was accomplished using PLD for Ho deposition on Ti needles and CVD for Re deposition on Mo needles, was assessed following irradiation in a nuclear reactor and incubation in solutions of varying pH, including those anticipated at tumor sites. The irradiation of the Ti base material produces very small amounts of short-lived Ti radioisotopes. However, when Mo is used as the base material, Mo radioisotopes and daughters ($^{99\text{m}}\text{Tc}$) can be produced by neutron activation. Thus, a neutron absorbing shield comprised of Gd was used during the irradiation of the Re-coated Mo needle to minimize the production of non-rhenium radioisotopes that could complicate the calculation of absorbed radiation dose to the tumors and non-target other tissues. The implementation of a neutron-activatable needles would create new opportunities for tailoring the internal

radiation of solid tumors. A design similar to microneedles was investigated in these studies instead of the cylinder-shaped applicators currently used in brachytherapy because we envision that the next generation of this technology will involve the use of true microneedles that can deliver soluble radionuclides into tumor cells in a manner that transdermal microneedles deliver drugs across the skin through the stratum corneum layer. Such a system would involve neutron activation of stable isotopes in solution that are contained in the interior portion of a hollow microneedle. Following irradiation in a neutron flux, the microneedle assembly (e.g., a 16×16 array of microneedles) could be physically applied to a solid tumor. The microneedles would penetrate the tumors after which time the activated radionuclides could diffuse into the tumor, thus delivering the nuclear payload deep into the tumor for more effective and uniform dosimetry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Illustration of neutron-activatable coated needles for internal radiation therapy.

Figure 2.
Ho deposition on Ti needles by PLD. a) Ho-coated Ti needles: 300 μm (left) and 1 cm (right). b) SEM image of 300 μm Ti needle showing surface morphology before and after Ho deposition.

Figure 3.
Mo needle coated with Re by CVD. a) Mo needle b) Re-coated Mo needle (25 μm coating).
c) SEM image of Re-coated Mo needle (red mark indicates area of Re coating).

Figure 4.

Gd neutron shield for Re-coated Mo needle. a) Schematic design of Gd neutron shield. b) Customized two-compartment Gd neutron shield (top and bottom). c) Re-coated Mo needle covered with the Gd neutron shield.

Figure 5.

Calculated amounts of radioactivity produced in a thermal neutron flux of 5.5×10^{12} neutrons cm^{-2} s as a function of irradiation time.⁷ (a) Irradiation of 1 mg of natural abundance Ho, Re and Y (the dotted lines denote the maximum theoretical amount of the individual radionuclides that can be produced under these conditions). (b) The amount of Ho, Re and Y radioisotopes produced by a 10 h neutron irradiation followed by a 48 h

decay. (c) The amount of Re radioisotopes produced by a 10 h neutron irradiation of Re-coated needles of various Re-coating thickness followed by a lengthy decay period.

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Table 1

Leaching of Re and Mo from Re-coated Mo needles when incubated in buffers of different pH values, and after neutron irradiation and three 20 mL washing with Milli-Q water.

Testing Condition		Mo leaching (%)	Re leaching (%)
Acetate Buffer (pH 3.5)	Day 1	0.006	0.001
	Day 2	0.006	0.000
	Day 3	0.007	0.000
	Day 30	0.133	0.001
PBS (pH 7.4)	Day 1	0.032	0.001
	Day 2	0.029	0.001
	Day 3	0.031	0.000
	Day 30	0.627	0.002
Neutron Irradiation	Wash 1	–	0.109
	Wash 2	–	0.009
	Wash 3	–	0.011

Calculation of radioactivity generated by irradiation of 900 mg of natural abundance Mo for 1h in a thermal neutron flux = 5.5×10^{12} neutrons cm^{-2} s and allowing for decay for up to 240 hours after the end of irradiation.⁷

Table 2

Radionuclides	Half-life	Radioactivity after x h Delay				
		0 h	10 h	24 h	168 h	240 h
⁹³ Mo	3500 y	48.6 pCi	48.6 pCi	48.6 pCi	48.6 pCi	48.6 pCi
⁹⁹ Mo	65.9 h	264 µCi	237 µCi	205 µCi	45.1 µCi	21.2 µCi
^{99m} Tc	6.01 h	12.8 µCi	152 µCi	182 µCi	43.5 µCi	20.4 µCi
¹⁰¹ Mo	14.6 m	13.8 mCi	6.09E-15 Ci	0	0	0
¹⁰¹ Tc	14.2 m	11.5 mCi	1.23E-13 Ci	0	0	0

Table 3

Properties of stable neutron-activatable nuclides and resultant radionuclides following neutron irradiation.⁷

Stable Isotope	Natural abundance (%)	Thermal Neutron-Capture Cross-Section (barn)	Radioactive Isotope	Half-life (h)
¹⁶⁵ Ho	100	59	¹⁶⁶ Ho	26.8
¹⁸⁷ Re	62.6	73	¹⁸⁸ Re	17.0
¹⁸⁵ Re	37.4	112	¹⁸⁶ Re	89.2
⁸⁹ Y	100	1.28	⁹⁰ Y	64.1