TUTORIAL REVIEW

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^{211}At on gold nanoparticles for targeted radionuclide therapy application

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Targeted alpha therapy (TAT) is a methodology that is being developed as a promising cancer treatment using the α-particle decay of radionuclides. This technique involves the use of heavy radioactive elements being placed near the cancer target area to cause maximum damage to the cancer cells while minimizing the damage to healthy cells. Using gold nanoparticles (AuNPs) as carriers, a more effective therapy methodology may be realized. AuNPs can be good candidates for transporting these radionuclides to the vicinity of the cancer cells since they can be labeled not just with the radionuclides, but also a host of other proteins and ligands to target these cells and serve as additional treatment options. Research has shown that astatine and iodine are capable of adsorbing onto the surface of gold, creating a covalent bond that is quite stable for use in experiments. However, there are still many challenges that lie ahead in this area, whether they be theoretical, experimental, and even in real-life applications. This review will cover some of the major developments, as well as the current state of technology, and the problems that need to be tackled as this research topic moves along to maturity. The hope is that with more workers joining the field, we can make a positive impact on society, in addition to bringing improvement and more knowledge to science.

1. Introduction

1.1. Radiotherapy

Radiotherapy is a method of treating cancer by using radiation to kill cancer cells and other tumors.[1] There are various types of radiotherapy but all of them generally fall into two categories: external treatment and internal treatment. External treatment involves utilizing an external radiation source (such as gamma-rays) to provide a concentrated dosage to the target areas. Internal treatment, also known as brachytherapy, involves placing the radioactive source near to the areas to be treated. This method allows for continuous therapy instead of in sessions which are prevalent in the external treatment variant.

Regardless of the type of radiotherapy, all methods will use some sort of particle to provide treatment into the cancer cells.

For external beam radiation therapy (EBRT), it uses either collimated X-ray or gamma-rays, electrons, or protons from outside sources to be fired into the affected areas.[2] A recent iteration, known as heavy ion therapy, uses heavy ions in lieu of electrons or protons for treatment.[3,4] The advantage of this method being that no operation is needed, which could complicate the health of the patients. Additionally, with the advancement of machinery, the target cells could be identified to great accuracy, allowing for a more accurate dosage to be delivered.

On the other hand, brachytherapy uses radioactive materials and implants them in a sealed container nearby the target cells. This procedure is useful for specific cancers, such as breast cancer or prostate cancer, where it is advantageous to apply a higher dosage to a concentrated area. The two treatments can be combined: by using the EBRT to target large cancer masses and brachytherapy to deliver doses to smaller cancer areas, it is possible to improve the efficacy of the overall treatments.

Another variant of the internal treatment is the radionuclide therapy or the unsealed source radiotherapy. It uses chemical and biological compounds to bind to the cancer cells or uses the tendency of the body to absorb it into the system, and thus is a form of targeted radiotherapy. An early example is the use of radioactive iodine (^{131}I) to treat thyroid cancers.[5] Since the thyroid will naturally absorb iodine for its own regulation, when ^{131}I is ingested, the thyroid will absorb the radioactive iodine and the treatment will run its course.

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1.2. Why use astatine-211/[211]At?

A similar treatment, targeted alpha therapy (TAT), is a new method of cancer treatment that is gaining traction in the medical world.[6–10] It uses the radioactive decay of heavy elements as a source of α-radiation to treat cancer cells inside the body.[11–13] Since α particles have short ranges but particularly large energies, this treatment shows promise for smaller cancers and metastatic cancers which are traditionally difficult to treat.[13] Astatine-211 ([211]At) is a promising radionuclide candidate precisely due to its ability to release α particles during its decay.[14] Its decay scheme is such that one [211]At will result in one α particle, which is desirable due to the above-mentioned properties. There are several isotopes of astatine, but all of them are radioactive and have relatively short half-lives (<10 minutes), and only [211]At is deemed feasible for use as an α-radiation source.[15] Additionally, lower mass isotopes do not have the certainty of releasing α particles during their decay and larger mass isotopes mostly decay almost instantaneously.

Due to the number of possible radionuclides that can be used for TAT, and the corresponding benefits and issues, this review will focus more on the use of [211]At as a radionuclide, with other radionuclides being introduced whenever appropriate.

1.3. Gold nanoparticles as carriers in drug delivery systems

The current state of such treatment incorporates targeting compounds that will seek out and adsorb onto cancer-specific receptors. This means that if the radionuclide can be attached to the compound, it will be directed towards the cancer cells and be able to disrupt the growth of the cancer cells while keeping the healthy cells unharmed.

The use of targeting compounds allows for the targeting radiotherapy to be used more in cancer treatments. Cancer cells have their own different receptors, meaning that a specific compound can be developed to bind to those receptors.[11,16] An advantage of using a carrier is the increased amount of radionuclides that the carrier would be able to hold, thereby increasing the dosage to the targeted area. Fig. 1 shows a simple schematic of a comparison between two cases of targeted radionuclide therapy. The left side shows a traditional method with one radionuclide attaching to a targeting compound, while the right side shows the radionuclides being adsorbed on the AuNPs that have targeting compounds attached. From here, it is easy to see that the use of AuNPs would allow for a greater number of radionuclides to provide treatment to the cancer mass. Additionally, the carriers can also be appended with other drugs or imaging agents so that they would act in concert with the radionuclides to deliver an effective treatment. Finally, flexibility in synthesizing these nanoparticles (NPs) in terms of size and shape can be achieved, primarily from synthesis techniques covered in later sections. Smaller NPs have a high surface area to volume ratio, which allows for a higher number of particles for the same mass. Surfaces are crucial for any reaction since this is where all reaction processes take place. The atoms on the surface levels are also more reactive due to them having a lower coordination number.
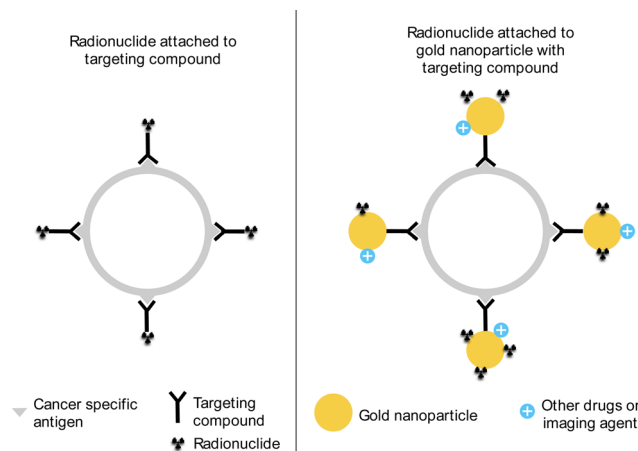

Fig. 1 A simplified schematic of targeted radionuclide therapy with (left) radionuclide with targeting compound and (right) radionuclide on AuNP with targeting compound.

Many studies have looked at gold being used in many biomedical applications due to its biocompatibility.[17–22] This property makes AuNPs a good candidate to be used *in vivo* as carriers for TAT radionuclides. Additionally, there have been experimental studies performed that showed AuNPs being capable of acting as carriers for astatine.[23–26]

Aside from its biocompatibility, there are several advantages to using AuNPs for *in vitro* treatments: among those are surface plasmon resonance (SPR), causing biological radiosensitization to targeted cells, catalyzing the production of reactive oxygen species (ROS), as well as its ability to be labeled with other materials.[10,18,27,28] SPR is a phenomenon that transfers light energy into electron movement, and thereby heat. This allows AuNPs to release concentrated amounts of heat into specified target areas, which damage the surrounding cancer cells. The ability of AuNPs to cause radiosensitization to cancer cells has also been documented.[29–31] By having AuNPs nearby these cells, beam therapies such as X-ray can be tuned to a minimum to avoid damage to healthy cells while at the same time increasing the effect on the targeted areas. Finally, the production of ROS, such as singlet oxygen or superoxide ions, increases biological stress in the cancer cells.[32,33] This oxidative stress can cause the cell's division mechanism to fail or damage the cell in such a way that the affected cell goes into a programmed cell death mode, killing the cell and stopping its proliferation.[32,34–36] There are various works that look at generating or supplementing the production of ROS due to SPR, showing the multidimensional aspect of the utilization of AuNP.[37–39] Additional works have also been included here to provide interested readers with the mechanism of ROS stressing biological systems, as well as the mechanism for dioxygen (O_2) activation.[40–43]

2. Current state of radiotherapy

2.1. Production capability

In order to use this type of treatment, both [211]At and AuNPs would have to be made, and made consistently. A generalized
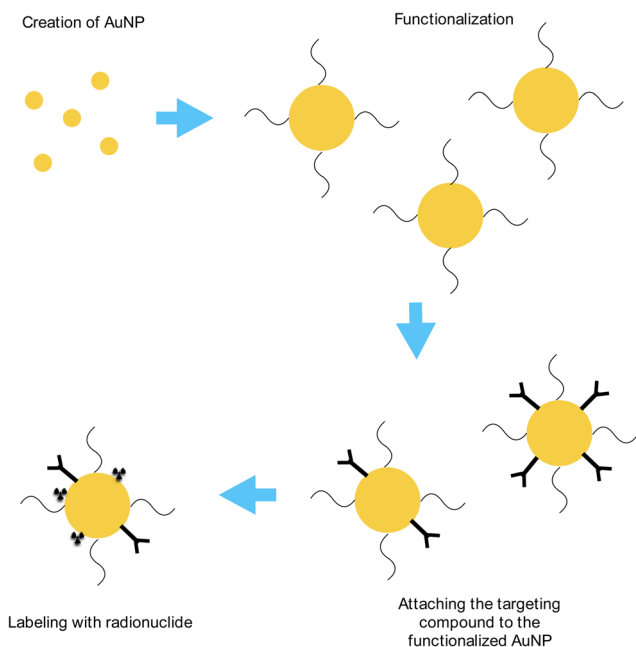
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Fig. 2 Simplified drawings of a general process of labeling of making [211]At-labeled AuNP for TAT.

and simplified diagram has been made to illustrate the process until it is ready to be used *in situ*, shown in Fig. 2. The current technology has to mature in order for trials, and eventually treatment, to be performed in patients reliably. One of the limiting factors in this treatment is the short half-life of [211]At; at 7.2 hours, the production facility has to be close to the treatment centers (such as hospitals or specially designed radioactive wards) in order for the process to retain as much radioactive astatine as possible.[13–15,23–26] As a result, other methods are being developed to extend the time ranges to take into consideration transportation issues as well as possibly short-term storage.

2.1.1. Production of [211]At. Since astatine is extremely rare in nature, all astatine used in medical facilities has to be artificially created. Current production of [211]At involves the use of cyclotrons: the main method is by irradiating a [209]Bi target with a 28 MeV α beam.[13,44,45] The equation for this reaction is given in nuclear notation as follows

$$^{209}Bi(^{4}He,2n)^{211}At \tag{1}$$
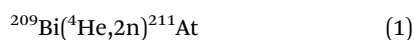
where [209]Bi is the target of the irradiation process, [4]He is the projectile, 2n is the emitted particle(s), and [211]At is the product.

There are several facilities that can produce this, with the majority being located either in the United States or Japan. Trials involving human patients have been few and far between, and there is currently an effort in trying to determine the maximum tolerated dose of such treatment, as well as other side effects that could come about due to the application in patients.[46]

The University of Osaka's RCNP has cyclotrons capable of firing the beam at the aforementioned energy with up to 7 μA of beam current to produce a maximum of 500 MBq of [211]At.[47,48]

Since α particles have a 2+ charge, the beam current is effectively a measure of how many charged particles are being fired into the target. The energy required for producing [211]At varies due to the beam current being used, as well as the time that the production stays online. A rough calculation indicates the surface power density of the beam can be as high as 8 times the power density of an electric kettle (approximately 33 W cm^{-2} *vs.* 4 W cm^{-2}).

Following this, the product [211]At has to be removed from the [209]Bi slab *via* some treatment. There are two methods of separation: wet and dry.[49–54] The wet separation method uses acid (*i.e.*, HNO$_3$ or HCl) to dissolve the solution and another compound to extract the [211]At. The dry separation on the other hand heats the irradiated bismuth slab until the [211]At boils off. The resulting gas is then cooled down before being added into a solution for use. Research is also underway on other methods, which have the potential to increase the yield of [211]At.[55,56]

Another method to obtain [211]At is by irradiating [209]Bi with heavy-ions such as Li to create [211]Rn, with the equations given as follows

$$^{209}Bi(^{7}Li,5n)^{211}Rn \tag{2}$$

$$^{209}Bi(^{6}Li,4n)^{211}Rn \tag{3}$$
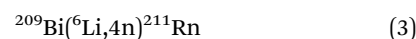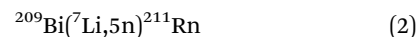
where eqn (2) needs the projectile at around 50–60 MeV while eqn (3) can make do with the projectile energy at 41–42 MeV.[57–59]

The purpose of this alternative method is to both increase the production of [211]At and offset the short lifetime of [211]At for transportation since [211]Rn has a longer half-life of 14.6 hours.[14,57–59] It has been calculated that there is upwards of 80% [211]At activity even after 24 hours due to this [211]Rn/[211]At generator, providing a wider range of distribution of the radionuclide.

2.1.2. Synthesis of gold nanoparticles. AuNPs have been used since ancient times, but modern development started with the discovery of colloidal gold.[60,61] From then on, AuNPs have been developed in various shapes and sizes, each with varying capability and desired uses. Several works have looked at this topic in detail and the reader is directed to them to study the various aspects of synthesizing AuNPs.[26,62–65] This work will briefly cover the methods as well as considerations for using the different AuNPs.

One of the most straightforward methods to synthesize AuNPs is by reducing chloroauric acid (HAuCl$_4$) with reducing agents. The result is Au nanospheres of different sizes depending on the ratio of the acid and the reducing agent. The Turkevich–Frens method produces relatively uniform sized Au nanospheres around 10–20 nm in diameter by reducing HAuCl$_4$ with sodium citrate solution, with bigger NPs resulting from a smaller citrate/acid ratio.[18,66,67] The sodium citrate solution acts both as a reducing agent and a capping agent, which stops the growth of the Au nanospheres.[67,68] A larger amount of citrate solution yields smaller NPs, and *vice versa*.

Another method to synthesize AuNPs is by using humic substances, such as fulvic acid and humic acid, as a reducer and stabilizer for the creation of AuNPs.[69–71] The resulting

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AuNP sizes range from <10 nm to >100 nm in diameter and have been found to be stable. An additional property of this method is the ability to produce silver nanoparticles; the interested reader may want to look at these works, as well as the references contained therein.[71–74]

A third method is the Brust–Schriffin method, which uses sodium borohydride as a reducing agent and organic liquids (such as toluene) as anti-coagulants.[75,76] In this method, the resulting Au nanospheres are <10 nm in diameter which are highly stable and thiol functionalized.

Functionalization is a process of binding some ligands or molecules to the NP, allowing it to have a broader application in the medical field.[77–82] Standard NPs tend to agglomerate, which makes them useless at being created in the first place. By enveloping the surface of the NP with other compounds, it allows the AuNP to stay separated, as well as being able to bind to compounds such as targeting compounds, drugs, *etc.* to be used in the medical society. There are several methods for functionalization, including DNA, peptides, and polyethylene glycol (PEG).[79–82]

Since the body's own reticuloendothelial system (RES) will generally remove any injected NPs, a "covering" substance will be required for those nanoparticles in order to reach the target areas.[83–86] One of these substances is PEG, an inert polymer that is widely used in medicine to allow for the NPs to bypass the RES recognition, and therefore stay in the bloodstream for a longer period.[83–88] Additionally, PEG has been found to improve biocompatibility, as well as cellular uptake of the NPs that the PEG is attached to.

Following synthesis, verifications can be done in several ways, usually by Transmission Electron Microscopy (TEM) imaging or by absorption spectra.[89–91] TEM imaging is easier to understand since the size and 2D shape is visible in the image. The absorption spectroscopy method measures the absorption characteristics of ultraviolet-visible light after passing through the sample. The amount of light at a specific wavelength that is absorbed corresponds to the size of the AuNP found in the sample. Calculations can also then be performed to provide information on the mass concentration of the AuNP as well as particle concentration in the solution.

For gold nanorods, one of the ways to produce them is by using the seed mediated growth method.[92,93] Instead of an aggregation of gold atoms to form a sphere-like structure, this method utilizes an initial seed to grow the NP. The advantage of this method is the ability to control the size and shape of the AuNPs grown, partly depending on the initial size and shape of the seed.[93] This allows for gold nanorods to be developed at high aspect ratios (*i.e.*, high length to width ratio) which is otherwise difficult to obtain using the previous methods.

Gold nanoshells can be produced using several methods; but since they are effectively thin shelled gold nanospheres, the process first requires seedlings to start the growing process. The main types of gold nanoshell are core or hollow. Core gold nanoshells have solid cores in the middle, where the gold will attach and grow, while hollow gold nanoshells are just gold shells with nothing inside them. Several cores that can be used

in creating gold nanoshells are silica, iron oxides, and polymers.[94–96] Hollow gold nanoshells can be made by growing the gold in the acid solution on the silver nanoparticle, by replacing the silver atoms with gold ions.[95–97]

These different types of AuNPs can be used in various treatment or experiments depending on the goal of such applications. To provide even more choice, the AuNPs' size and shapes can have an effect on their end uses. The reader is encouraged to look at review works, such as the ones listed in the reference, for a more comprehensive understanding.[98–102]

2.1.3. Production of [211]At-labeled decorated AuNPs. Before the [211]At can be used in treatment or experiments, it has to be labeled onto a carrier, in this case the AuNP. The labeling process is surprisingly simple, needing only stirring of the [211]At in the solution containing the AuNP.[23–26] These works also show almost complete adsorption of [211]At to the AuNPs, as well as good retention of the radionuclide.

2.2. Biological trials

Since TAT is a promising concept, it is constantly being developed for various treatments, both experimentally and clinically.[8,46,103–105] Experiments fall into two categories: *in vitro* and *in vivo*. *In vitro* experiments use cancer cells and expose them to treatment for a given amount of time to see the effect of the different variables, such as choice of targeting compound, concentration of [211]At-labeled AuNP, size of AuNP, *etc.*[24,26,105] These variables are sometimes permuted to obtain an optimized condition for such treatment.

The setup for the experiment is similar for all the following trials: two sets of groups are prepared. One group is designated the control and is assumed to have 100% growth rate. The other group is divided into several treatment regimes, treated with different solutions containing the [211]At–AuNP. Each treatment regime may have different variables being altered and is administered once to test their efficacies on the cellular material and the results are compared to the control group that received no treatment. The measurement used is the half maximal inhibition concentration or IC_{50}. The data is plotted to provide a relationship between the concentration of [211]At–AuNP *versus* the inhibition value. A smaller concentration value to achieve IC_{50} indicates the treatment is highly effective while a larger concentration value means the treatment is less or not as effective.

In vivo experiments require the use of live-animal testing, such as rats or mice that are implanted with cancer cells. Treatments are then administered based on the variables being tested. The goal is the same: to confirm their efficacy at curing cancers or at least controlling their growth.[24,26,104,105] As can be seen in many works, a control group is set up and provided with a non-radiating solution (*e.g.* saline) and compared to the group that received treatments. These experiments are performed first to ensure [211]At–AuNP's preliminary safety before testing them in human patients.

There are two main methods of delivery: direct injection of radionuclide labeled AuNP to the cancer masses as well as through intravenous injection.[24,26] The first is a direct

application to provide proof of concept that the AuNP can hold the radionuclides in place, as well as for the radionuclide to show its effect on the cancer cells. The second is much more interesting, since it will make real-life applications much easier to perform.

2.3. Experimental and theoretical works

There have been theoretical works that have embarked on understanding both the physics of the adsorption of radionuclides to AuNP as well as obtaining a more accurate model for further simulation use. Since astatine is a relatively newly discovered element, there are some works that look at the bonding characteristics of astatine, specifically at the halogen bonding of astatine and other halogens.[106–109] Due to the importance of [211]At as a future medical substance, more experiments are being carried out.[23–26] One such result is obtained from experimental study by Huang *et al.*, who found that even with a relatively small cumulative adsorption, the effect of targeted radiotherapy is controlling the growth of the tumor (see Fig. 3).[26] This result is mirrored by another *in vivo* study that showed the efficacy of such methodology in rats, whereby the presence of [211]At–AuNP of any size has a positive impact in reducing the growth of cancerous mass (see Fig. 4).[25]

With the promise of TAT treatments being developed in the medical field, the study turns into both finding more effective designs for its application, as well as elucidating the underlying physics that govern the process. The hope is for a better model to be developed before production begins. Due to the highly complex nature of the system, theoretical calculations can only cover a very small scope, such as the adsorption of the radionuclides to the gold surface.

Surface chemistry is crucial since any reaction between AuNPs and radionuclides occur at the surface level. The inside of the NP, termed as the bulk, do not take part in the adsorption process. Additionally, the lower coordination number of surface atoms make them more suited to reacting with other species. The issue comes when we decide how large the NP is. For calculation purposes, NPs, in particular nanospheres, of diameter *circa* 2.7 nm or above can be treated as a surface facet.[110,111] While the majority of the NPs created have diameters above 5 nm, newer findings and control mechanism can produce NPs of 2.5 nm diameter, meaning that finite sized effects will become apparent when calculating systems based on these small sized NPs.

2.3.1. Theoretical calculation of adsorption of astatine on gold surfaces. There are two types of gold systems being considered in theoretical studies: one with gold nanoclusters (extremely small) and one with gold surfaces (large approximation).[112–114] As previously mentioned, there are several works that looked at the bonding characteristics or the properties of the said element.[106–109,115–119] However, there are few theoretical studies for astatine and gold bonding for use in this field.

Owing to its nature as a halogen, a comparison between iodine adsorption and astatine adsorption seems fitting. Iodine is relatively well studied and is being used in its capacity as a radionuclide. It was found that covalent bonding is the primary method of adsorption of both iodine and astatine.[113,114] Both iodine and astatine were found to adsorb on the fcc hollow site of the flat Au(111) surface and the edge-bridge site of Au(211) (adsorption of astatine on gold slab shown in Fig. 5), meaning that both adsorption profiles should be very similar. Additionally, the density of states (DOS) shows the 5d orbital of gold hybridizing with the 5p orbital and 6p orbital of iodine and astatine respectively, as well as the s orbitals of both adsorbates. Fig. 6 shows the local DOS of the adsorbed astatine on the flat Au(111) surface (top) as well as the stepped Au(211)
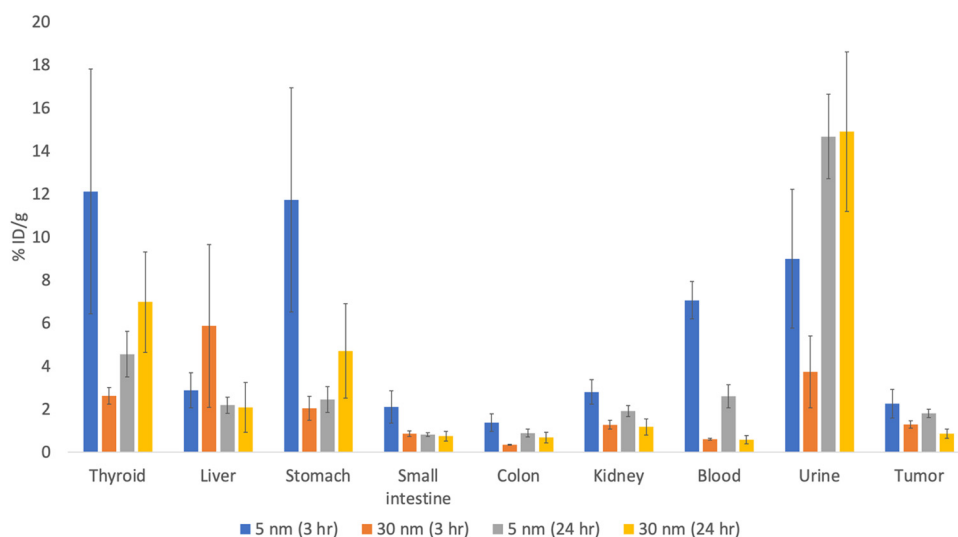

Fig. 3 Percentage of [211]At–AuNP adsorbed per gram of organ weight, adapted from data found in ref. 27. The blue and orange bars represent [211]At-labeled 5 nm and 30 nm AuNPs, respectively, accumulated for 3 hours, whereas the gray and yellow bars represent [211]At-labeled 5 nm and 30 nm AuNPs, respectively, accumulated for 24 hours. The %ID per g stands for the percentage of accumulated radioactive materials per weight of the organ/liquid; a higher value means more of the [211]At–AuNPs are found in that system. Error bars are shown as black bounded vertical lines.
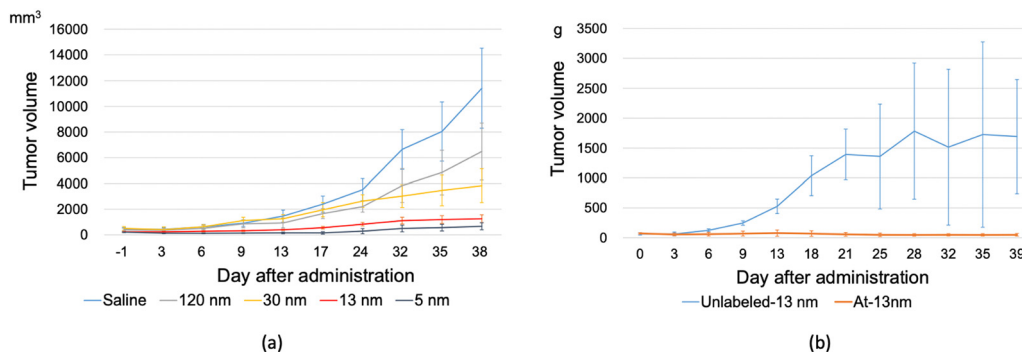
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Fig. 4 An abridged version of *in vivo* data for ^{211}At-labeled AuNP of various diameters.[26] It can be seen that the presence of ^{211}At-labeled AuNP of any size contributes to limiting the growth of cancer cells. (a) The tumor size growth after administration of different sized ^{211}At-labeled AuNP and (b) a comparison of the effect of ^{211}At on the tumor size growth.
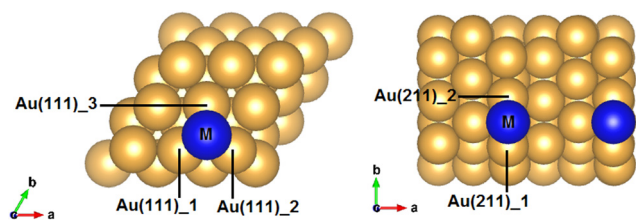

Fig. 5 Most stable adsorption sites of a flat Au(111) and stepped Au(211).[91]

surface (bottom). Comparison between the clean and bond DOS shows the effect of adsorption of At on the Au atom mainly on the large energy band of −4.5 eV to −2 eV. This is the region in which the majority of the 5d gold orbital is overlapping with the 6p orbital of the astatine, and hybridization is visible when looking at the similar peaks between the two DOS of the highlighted orbitals.

However, when charge transfers are analyzed, iodine is clearly an electron recipient while astatine is only weakly affected.[113] This is an interesting finding since astatine falls into the halogen group in the periodic table, and halogens typically have strong electron affinity as they are one electron away from a complete shell. From the standpoint of electronegativity, astatine is less electronegative than Au, meaning that it is more likely for astatine to donate its electrons to Au during bonding.[120,121] However, the amount of electrons transferred is not large since they bond covalently.

So far, theoretical calculations have corroborated the adsorption strength of astatine on Au obtained from experiment, which is a good indication that the system being tested is of sufficient similarity.[113,114,121] The simple equation for adsorption energies can be obtained by

$$E_{ads} = E_{M/Au(X)} - (0.5 \times E_{M_2} + E_{Au(X)}) \qquad (4)$$

where E_{ads} is the adsorption energy, $E_{M/Au(X)}$ is the total energy of a single adsorbate M (in this case At), on a slab of Au of some facet X, E_{M_2} is the energy of the M_2 system, and $E_{Au(X)}$ is the energy of the clean Au slab system without any impurities. A more detailed description can be found in ref. 113 and 114. Note that this is a simplistic approximation of a perfect system

that only has one adsorbate per unit cell or supercell and does not take into account other factors such as temperature, more than one adsorbate on the Au surface, and more complex chemical interactions between the functionalization ligands/molecules, targeting compounds, or possibly other drugs or imaging agents. Furthermore, the AuNP is a slightly different system than just a normal slab, even though the equation for calculating adsorption energies is still the same as eqn (4). Therefore, more investigation is needed to look into the effect of AuNP on the adsorption profile, because of the finite-size effect that will have to be taken into consideration as the size of the system gets smaller.

Since one NP is much larger than an atom, it is fair to assume that there could be more than one radionuclide being adsorbed on its surface. A 2.5 nm diameter AuNP would consist of approximately 500 Au atoms, which could allow several radionuclides adsorbing on its surface. However, as will be explained in the next section, the actual application may not be close to the limit of adsorption due to many factors such as the binding of targeting compounds, functionalization, and the amount of radionuclides in the solution, *etc.*

3. Issues to be tackled

3.1. Increase in production of ^{211}At

With the use of heavy elements for treatment, there are various issues that spring up, such as logistics, safety, ethical aspects in its use for patients, *etc.* One of the primary issues is the limited production of ^{211}At. There are currently very few facilities in the world capable of producing ^{211}At for use.[46,47]

One problem that needs to be solved in order to increase production is the amount of beam current. As the minimum necessary energy to make ^{211}At is 28 MeV, it falls to the beam current to increase its production. Since the beam current is proportional to the amount of α particles (He^{2+}), the higher the beam current, the more α particles are being sent to the ^{209}Bi target. A low beam current would yield a small amount of ^{211}At, and, since ^{211}At itself is radioactive, will result in an even smaller usable product.
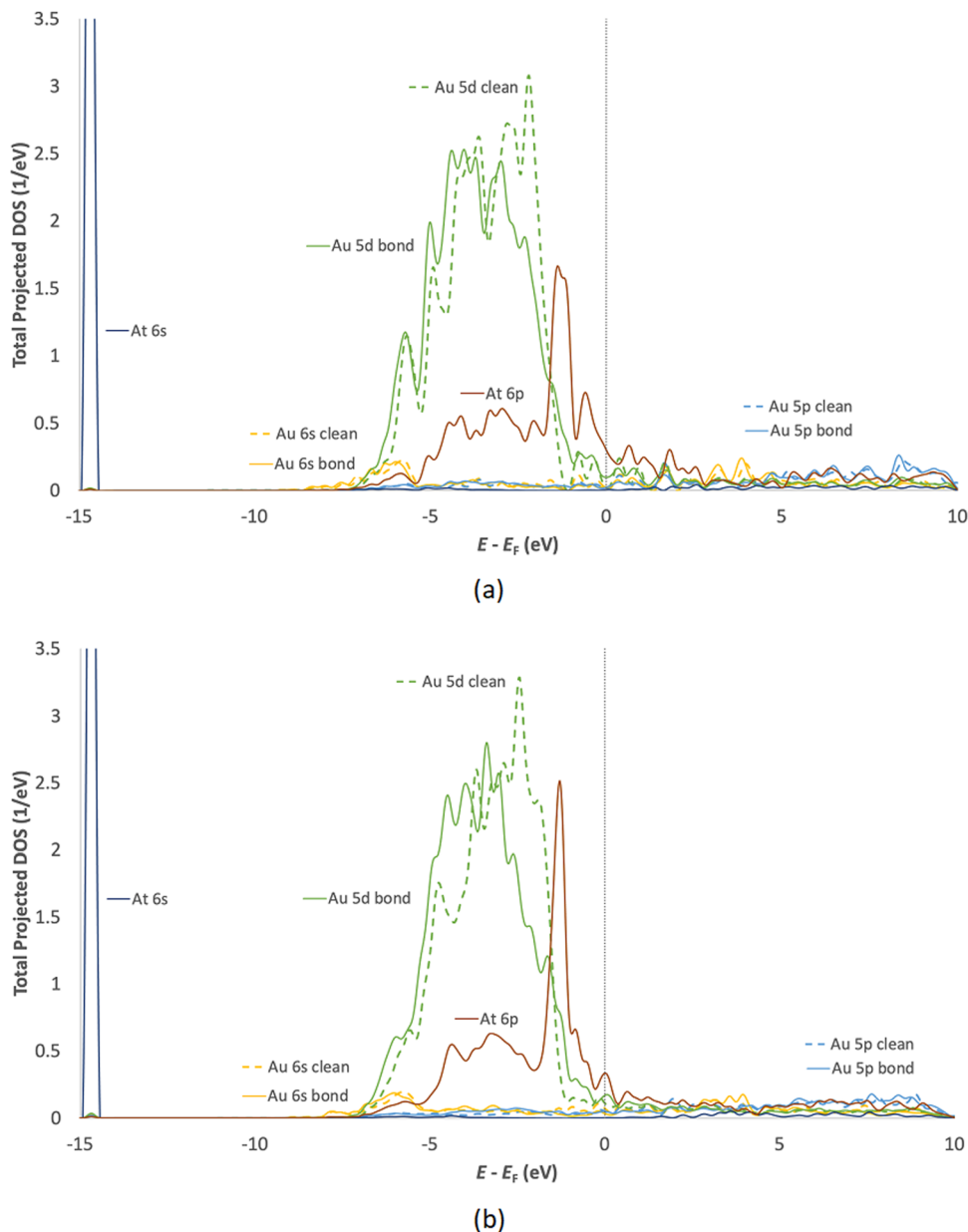
Fig. 6 LDOS plot of (a) At on Au(111) and (b) At on Au(211).

Another problem is the saturation limit for each machine synthesizing the ^{211}At. The saturation limit is a point whereby the rate of ^{211}At being produced is equal to the rate of decay of ^{211}At and is normally reached around 3 times the time for its half-life (*i.e.*, 21 hours).[48] This means that any production batch should not exceed the time limit lest energy is just being used to replenish the decaying radionuclide.

Additionally, engineering aspects must also be taken into consideration due to the heat that the process generates. As alluded to previously, the surface power density of the α beam is very high and causes overheating of the target easily. Currently, the beam is either oscillated on top of the bismuth target or being reduced by adjusting the slits to remove certain areas of the beam.[47,48] More efficient and larger cooling systems

must be developed so that as the beam current increases to accommodate more production capacity, such that the target bismuth does not overheat and melt in the process.

Another consideration is the chemical treatment to obtain the product from its stand/hold. The process takes time and causes a percentage of the ^{211}At to undergo decay. Depending on the time elapsed, this treatment can yield 30% to 80% usable ^{211}At, which necessitates an increase in production capability so that the required amount can be sent to testing. This is a classic "chicken-and-egg" problem that seems to be difficult to solve, unless both production capability and a more efficient and faster process can be found. Currently, developments are taking place on both fronts and hopefully, this issue can be remedied in the next few years.[48,55,56]

3.2. Use in human patients

Currently, there are ongoing clinical trials with [211]At but none with AuNP as the carrier.[46] There are several hurdles regarding this point, one of them being the supply of [211]At. Another issue is the myriad of targeting compounds that can be used.

A targeting compound, as mentioned previously, allows the [211]At-labeled AuNPs to be directed towards the cancer cells and perform their treatment there. Unfortunately, different cancer cells can have different overexpressed genes (such as antigens), which makes the choice of a suitable targeting compound quite difficult.[122] A specific targeting compound may also be targeting multiple different types of cancer cells, which may cause the treatment to go to a different cancer cell. While this may not be a bad thing if the patient's cancer is already at a high stadium level (meaning that the cancer has already spread to other parts of the body), but it may not be ideal if the treatment administered is focused on a particular target area. Preliminary gene tests would need to be done to determine which proteins or molecules can act as the targeting compound, and this further adds complexities to the procedure.

As one of the experiments found, there is an increase of the AuNP injected in the liver and stomach of the experimental subjects.[26] This could be due to the liver breaking down red blood cells as they near their useful timespan. Even though these tests are done in mice, there are possibilities that the same result may arise when tested in humans, which raises the concern that the treatment may irradiate the healthy organs instead of solely going to the target tumor. While the tests show no damage of those organs by the treatment, it remains to be seen whether the human biology will display the same effect.

Another improvement is the small amount of radionuclides that was found in/near the tumor area. As can be seen in Fig. 3, roughly 2% of injected dose per gram of tumor was measured, compared to the large percentage measured in the liver.[26] This is further exacerbated by the larger percentage of radionuclides that is expelled through urine. Given that this small amount of radiation is giving a positive outcome for controlling the cancer growth, the actual amount of radioactivity needed may be much smaller than what was injected into the test subject. This "inefficiency" can vastly increase the necessary amount of [211]At needed for the treatment, creating unnecessary strain on both the patient and the production of the radionuclide. It is worth noting, however, that the experiment was done using passive targeting; other future works are looking at active targeting mechanisms to gauge their effectiveness as well as improve the efficiency of the [211]At–AuNP treatment.[105]

Finally, there is the issue of cost. At the time of writing, while the cost of gold is relatively high, it is dwarfed by the cost of [211]At production, which can be 50 times the cost of the gold being used.[105] Part of this problem comes back to the supply, as well as the production being quite sensitive to the cost of electricity. For such costs to be born, patients will expect that the treatment be very effective and safe to them.

3.3. Gold nanoparticles as carriers

As we have covered before, the use of AuNP as carriers for these radionuclides also provide a source of issues that needs to be understood more clearly. One is the consideration of weight, as Au itself is a heavy element, meaning a small amount of Au atoms can end up having a large mass, which makes it unwieldy for intravenous transport. Another issue that was raised is that in experiments, AuNPs of around a few nanometers would exhibit a phenomenon of "drooping", whereby the cancer receptors are unable to hold the AuNP straight but instead the AuNP would descend to the cancer cell due to its weight.[123]

At a glance, the solution seems to be to use smaller NPs for testing and also eventually for treatment. However, making smaller NPs would require a higher degree of accuracy and control of the synthesis. In many of the experiments, there can still be a large deviation of sizes and imperfect shapes of AuNPs that are produced. While technology is improving, a consistent production capability must be achieved in order to solve these issues.

3.4. Radioactive decay products

One of the major issues of using α-particle treatment is the prevalence of heavy isotopes being the parent nuclide. This means that heavy elements such as lead, bismuth, *etc.* are being produced for every decay process. As we know, lead poses a significant danger to human health, as has been demonstrated by many real-life examples (lead in white paint, tetraethyl lead in leaded petrol, lead contamination of water supply, *etc.*). For TAT to gain acceptance by the greater public, these concerns must be addressed in such a way that is both scientifically rigorous and transparent so that the patients can form their own opinion whether to follow the TAT or seek other treatment methods.

[211]At is known to decay into two possible daughter isotopes: [207]Bi (41.7% probability) and [207]Pb (58.2% probability) *via* different mechanisms.[13,128] These two isotopes are relatively stable ([207]Bi will decay further to [207]Pb, with a half-life of 31.22 years)[124] and since they are in such small concentrations, experimental results are hard to come by. Bismuth has been found to be relatively nontoxic for living organisms, and the toxic threshold in humans is approximately 15 g *versus* a toxic threshold of approximately 1 mg for lead.[125]

Additionally, this decay produces energy, which is transformed mostly into kinetic energy to the two remaining products. The majority of the energy will go into the α-particle which is the crux of the treatment; however, a smaller amount will go to the daughter isotope that may cause the recoil of the said isotope from the AuNP. Depending on the direction of the separation, the daughter isotope may detach from its carrier, bury itself in (or even go through) the gold AuNP, or even be readsorbed on the surface of the AuNP after some event that drains the energy of the daughter isotope.

It is worth noting that since [211]At releases only one α-particle during its decay, there are no problems relating to recoiling radioactive daughters as can be found in other chain decay radionuclides.[125] Some radionuclides, *e.g.* [225]Ac, while capable of releasing multiple α-particles during their decay process, may be harder to control after their detachment from the carriers.[126–128]

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This phenomenon could potentially cause unintended damage to nearby healthy organs or even healthy cells in the cancer mass' vicinity.

These issues must be taken into consideration as the technology matures enough for clinical trials to be held. Currently, clinical trials for ^{211}At–Na are being performed in Osaka University Hospital for refractory thyroid cancer (*i.e.* cancer that does not respond to conventional treatment), which can lay the groundwork for future use of At-labeled AuNP in humans.[129]

3.5. Theoretical aspects

Modeling accurate systems remains an elusive problem that needs to be tackled. As shown here, the complexities of interdisciplinary issues prevent a full simulation from being carried out. Primarily, the various binding ligands, as well as new drugs being developed are too complex for density functional theory (DFT) based software to run. Molecular dynamics may be helpful in bridging some of the gaps, but there remains the issue of radiation of different types to consider.

Additional physical and chemical theories can also be developed from this field. One such example is the filled 4f orbital that astatine has. Lanthanoid contraction, commonly found in the lanthanoid series has generated an interest in the community, due to interesting phenomena that do not occur in lower mass atoms. The presence of 4f electrons has been found to decrease the radius of the atoms with these electrons, making the higher mass atoms more compact than their preceding counterpart.[130,131] Additionally, since the lanthanoid contraction affects heavier elements, relativistic effects are also at play, which alter the characteristics of those elements.

Pyykkö has written extensively about the characteristics of gold, including the effect of the relativistic treatment on orbital radial densities.[132,133] It was found that around 10% of the lanthanoid contraction could be attributed to relativistic effects.[132] Interestingly, while both relativistic effects and lanthanoid contraction would suggest a reduction of bond length for heavy element bonding, not all results point to that conclusion. Rossi *et al.* found that halogen bonding involving astatine, itself a heavier element than gold, has similar or increasing bond length after considering relativistic effects and spin–orbit coupling.[108] Since we are heading into heavier elements, spin–orbit coupling effects will become more pronounced, and can affect the physics and chemistry of the orbitals. Considering these factors and other similar results further highlight the fact that more research needs to be done to verify theoretical results by experiments, which will in turn improve the accuracy of the theoretical model.

Furthermore, due to reasons alluded to earlier, the simulation of heavy elements would require corrections of a relativistic nature to be added into the system. Developments have been made to reduce the computational cost for fully relativistic DFT, and there are also works that have predicted the various characteristics of astatine as well as new compounds that can theoretically be obtained.[109,117,130,134–136] However, as of now, it is still very difficult, due to the lack of supply, for some of these results to be verified experimentally. Interested readers may want to look at theoretical modeling developments in this area, including in superheavy elements ($Z \geq 104$), to become more familiar with them.[137–139]

Since this problem is not purely of nuclear physics, consideration of the interaction of radioactive materials and surface physics are lacking. Studies on the adsorption coverage on the AuNPs are few, as well as the issue of combining two vastly different energy regimes between the adsorption process (on the order of eV) and the decay process (on the order of MeV).[112–114,121,124] There is also the question of modeling multiple adsorptions on AuNPs. Experimental works have reported successful adsorption of ^{211}At on AuNPs, but there are no data on how different concentrations of ^{211}At affect the adsorption strength and stability of the radionuclides adsorbed on the AuNP. A similar theoretical study performed by Fernández and Balbá on multiple NO adsorptions on Au_{10}^- and Au_9Zn^- clusters found that after the first NO molecule is adsorbed, the subsequent adsorptions yield weaker adsorption energies.[140] This result means that a trade-off needs to be found where the adsorption strength is optimized with the amount of adsorbates on the surface. Additionally, different sized AuNPs are made up of different facets, which may yield different adsorption strengths and numbers of possible adsorbates.[141,142] Obtaining information on these can provide more knowledge on the science behind the adsorption characteristics of the radionuclides on AuNPs.

These issues are just some of the challenges that face this field in advancing the development of both technology and best-practices in the hopes of bringing this treatment to a wider scope of patients. It is crucial that both theoretical and experimental knowledge should work in concert so that the medical community can benefit from this cooperation. With the rise of more advanced techniques and fundamental understanding, we are hopeful that the state of development will mature quickly enough to bring a positive impact to many patients struggling with this illness.

3.6. Future plans for ^{211}At on AuNP

As a developing field, the study of ^{211}At on AuNP has potential to contribute to many fields. Aside from improving the medical knowledge and impact of such methodology, we can learn many things in both theoretical side and experimental best practices. Experimentally, we have learned that there are many areas that await both experimental verifications and optimization of best practices. The complex nature of experiments and clinical trials mean that there could be many correlations between variables that are yet unknown. As more ^{211}At producing facilities come online, there would be more experiments and trials being performed, which can hopefully provide more knowledge on the subject matter.

Theoretical advancements are also beneficial for the development of TAT; as we know more about the chemistry and physics of such elements and interactions, we can better model these systems with more confidence. The simulation of ^{211}At-labeled AuNP would be very useful in bridging the gap between theory and experiment, as well as providing a base for future

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development. Additionally, a more complete theory can arise out of the collective knowledge of modeling and experimental verification which will give us a benchmark on the various variables that may affect the use of the [211]At-labeled AuNP.

4. Summary

The development of TAT using [211]At on AuNP has a promising future in the medical community. The present technology, along with future developments ensure that this research will continue to grow and make a big impact on the medical field for a long time to come. Interesting findings and challenges have also been brought up here, although these barely scratch the surface of this topic, along with the myriad of real-life problems that each of these discoveries will have to address before they can be utilized.

As science becomes more complex, we should work together to develop this field in order to improve our quality of life as well as provide more understanding for our own fields. This is a great area of research to go into since the majority of the work done is of biological nature, and not much thought has gone into answering the fundamental questions that this topic offers. As physicists and chemists, we can contribute to the further development of this field *via* problems and issues that they face but do not usually consider. In exchange, we learn more about the science behind certain phenomena, as well as provide understanding for future problems that have yet to arise.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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