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Optimization of Concentration and Activity in the Production of Radioactive Gold Nanoparticles for Cancer Treatment

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1. Introduction

Cancer is a major global health concern with increasing incidence, expected to reach over 25 million new cases by 2030. Various treatment options exist, including surgery, chemotherapy, and radiation therapy, but alternatives like brachytherapy are needed due to the risk of organ damage. Brachytherapy delivers localized radiation with minimal healthy tissue exposure, making it suitable for various anatomical sites. Advances in nanotechnology, particularly with nanoparticles, offer promising avenues for targeted cancer therapy through mechanisms like the enhanced permeability and retention effect. [1–7]

In previous studies we have demonstrated the effectiveness of radioactive gold nanoparticles[8–10], in terms of radioactivity and concentration we have reached the limit and have obtained good results. By 2024, the EA-R1 reactor here at IPEN has opened the possibility of increasing the irradiation time, which has opened new possibilities in terms of optimizing the activity (A)/ concentration (C) relationship.

2. Methodology

Radioactive gold nanoparticles ^{198}Au

The synthesis of the goldnanoparticles (AuNPs) follows the methodology reported in previous works [8], the difference lies in the optimization of the A/C ratio. In previous experiments, we reported in vivo studies with two groups of camundongs (BALB/C Nude strain rodents) where each animal was injected with 30 ul of nanoparticle solution with 400 and 500 uCi of activity respectively per group. The results were optimal, however, given the possibility of reducing the concentration, which has represented a great challenge to achieve a relationship where the activity (dose) would be sufficient to generate damage to cancer cells, the development has been proposed. The present work, which has been possible by extending the irradiation time of the EA-R1 reactor of the IPEN. Going from working 16 hours per week to a little more than 60 hours per week, greatly expanding our possibilities.

Production of ^{198}Au

In the so-called method 1, previously reported, the amount of gold sent to the reactor was 3 mg of gold, which was irradiated for 16 hours, with hours being 8 per day. In 2024 the reactor will allow irradiation for 60 hours in a row without interruptions, thus which the expected activity is tripled by sending only 1 mg, which is equivalent to 1/3 of the initial mass, this is method 2, the results of which will be reported for this version of the INAC (2024). The obtaining method follows the same parameters already reported in already published works.

Coating

In cancer therapy, the tumor microenvironment guides tailored strategies due to its unique characteristics compared to normal tissue, including vascular abnormalities and metabolic states[11]. Nanoparticle coatings modulate interactions with proteins in the bloodstream and enable tumor-specific targeting through passive and active methods. While nanoparticles offer promising medical potential, their behavior in living systems depends on surface coatings. Interactions with living systems lead to protein corona formation, directly affecting biological behavior, highlighting the importance of surface coating properties[12].

3. Results and Discussion

This study aims to refine concentration and activity parameters based on prior findings. The extension of irradiation periods facilitated by the IEA-R1 reactor has been instrumental in enabling this research. Synthesis of AuNPs is accomplished through the Turkevich method, utilizing a citrate solution (NaCit) as a reducing agent and HAuCl4 solution. The ensuing reaction conducted under vigorous stirring and elevated temperatures, manifests a transition from a yellow-clear to a red-wine hue within three minutes. Subsequent functionalization involves the incorporation of a stabilizing and functionalizing agent, gum arabic, with additional agents such as Polyethylene glycol (PEG) and Bovine Serum Albumin (BSA) introduced under stirring to the obtained AuNPs.

The nanoparticles obtained by method 1 allowed results such as those shown in Figure 1. For method 2, similar results are expected in terms of tumor reduction and elimination, but with a lower concentration and higher activity, the volume to be injected will be smaller, and therefore the distribution of the radioactive solution can be greater, being able to achieve a reduction and elimination of the tumor in a shorter time, as well as reducing the risk of agglomeration of the nanoparticles which at high concentrations can occur, making the internalization of the nanoparticles difficult in the cells.

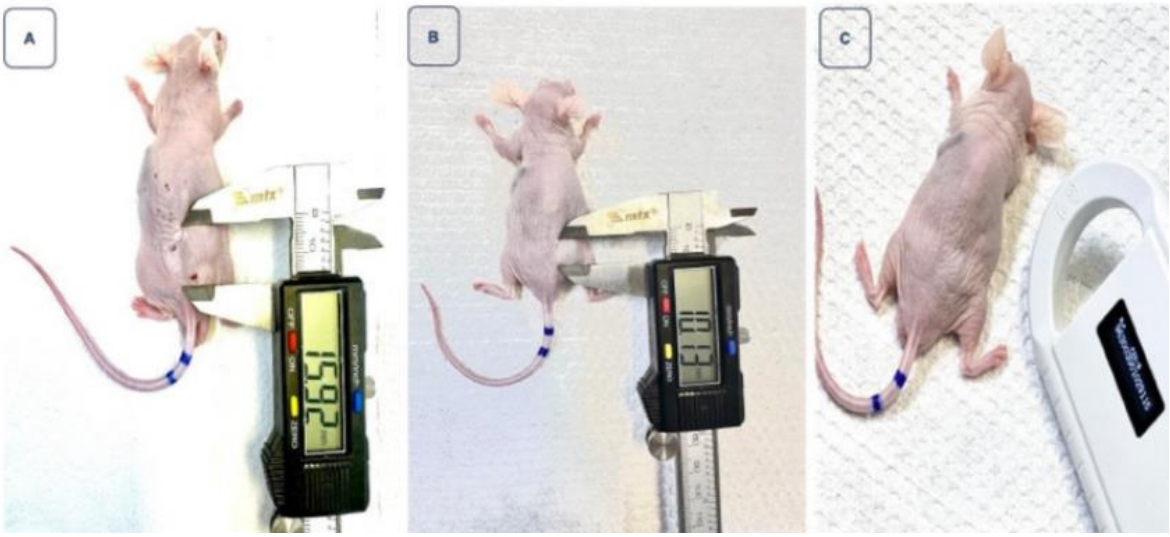

Figure 1: Monitoring of tumor regression in animal 2, ID 9115, after receiving 417 μCi of BSA-coated AuNPs. Image A illustrates the tumor measurement on the day of treatment, with a volume of 107.63 mm³. In image B, a reduction in volume is observed on the seventh day after treatment. Finally, image C highlights that on the 14th day; the reduction was so significant that measurement with a digital caliper became unfeasible.

Activation in the reactor

To send material to the reactor and calculate the approximate activity, equation 1 is used. Being A (activity), P (molecular weight g/mol), M (mass g), N (Avogadro's number), Θ (abundance isotopic %), σ (cross section $cm^2 – 10^{—24}$ cm), ϕ (reactor flow $n/cm^2 * s$), λ (decay) and t (irradiation time).

$$A = \frac{M*N*\theta*\sigma*\phi}{P}\left(1 - e^{-\lambda t}\right) \qquad (1)$$

The parameters used are presented in table 1.

Table I : Irradiation parameters

Parameters	Method 1	Method 2
M	3 mg	1 mg
N	$6.022*10^{23}$ atoms/mol	$6.022*10^{23}$ atoms/mol
Θ	100 %	100 %
σ	$2.3*10^{-27}$ cm^2 (14.5 Mev)	$2.3*10^{-27}$ cm^2 (14.5 Mev)
ϕ	$3.19*10^{13}$ n/cm^2 s	$3.19*10^{13}$ n/cm^2 s
P	196.97 g/mol	196.97 g/mol
t	57600 s	216000 s
A	0.11 Ci	0.31 Ci

As expected, longer irradiation time, higher expected activity, with which promising results are expected for method 2.

4. Conclusions

Being able to reduce the concentration of the radioactive solution of gold nanoparticles allows an improvement in terms of stability of the nanoparticles, since with the decrease in concentration, the probability of nucleation decreases, and on the way to producing an effective treatment that can reach to be applied, stability is one of the most important characteristics, maintaining the size of around 5 nm of the nanoparticles allows their internalization in the cancer cell and with it cell mortality and therefore tumor reduction will occur. In terms of volume, the reduction in concentration with an increase in activity allows us to think about modifying the methodology for injecting the radioactive nanoparticle solution into the tumor, and a method similar to that of brachytherapy with iridium seeds can be applied. In prostate tumor, where each one is inserted in a different location of the tumor, thus the number of irradiated cells is greater and possibly the reduction of the tumor occurs in a shorter time.

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