A cyclotron-driven neutron activator for the production of β⁻ emitting radioisotopes for brachytherapy

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Introduction **β-(electron) emitting radioisotopes** are widely used for radiotherapy purposes, and in particular for **brachytherapy** techniques. Such types of radioisotopes are generated through high-flux neutron irradiation and at present can be efficiently produced only in nuclear reactors. This poses a limit to their widespread use due to the current (and even more future) lack of availability of nuclear reactors for medical applications. Furthermore, the intense γ-heating typical of nuclear reactors poses limitations to the type and conditions of samples to be irradiated (in particular injectable preparations of nanoparticles suspensions). Starting from the Adiabatic Resonance Crossing concept proposed by C. Rubbia in 1998 (ARC patent), AAA has developed a compact cyclotron-driven neutron activator capable of efficiently activating injectable suspensions of nanoparticles carrying β-emitting radioisotopes, to be used for brachytherapy **applications (INBARCA project)**.
A prototype of the activator has been realized in collaboration with JRC-Ispra and is currently operational on beam line 5 of the 40 MeV - 50 μA JRC-IHCP cyclotron. Its main purpose was the demonstration of the **possibility to produce therapeutic doses of activated nanoparticles for brachytherapy applications using medium-size cyclotrons for medical applications.**

Figure 1: concept of the neutron activator

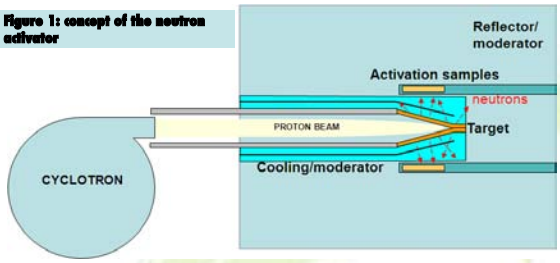


Figure 2: the INBARCA activator at JRC

Subjects and methods The activator prototype has been conceived by using **Monte Carlo codes** (FLUKA, MCNPX) for the neutronic design and **CFD codes** for the thermal-hydraulic design of the target. It is coupled with a variable-energy **(8÷40 MeV) cyclotron** (Scanditronix), capable of a maximum current of **50 μA**.
An **extensive experimental campaign** (24 runs) has been carried out at different proton beam energies and with various activator set-ups in order to characterise the neutron dynamics of the system and its activation capabilities, as well as to validate Monte Carlo codes results. Activation measurements were carried out through **γ-ray spectrometry** with HPGe detectors.
Various activation samples were irradiated: the activation of **high-purity metal foils** (Au, Ag, Al, Ho, Re, Mo, Ni) allowed a precise and repeatable system characterisation, including the experimental derivation of the neutron spectrum in the activation channels through neutron unfolding techniques.
Different types of **Ho and Re loaded nanoparticles** were irradiated, both to determine the achievable specific activities and to carry out **bio-distribution studies** of intra-tumoral high-pressure injection of nanoparticles in tumours grafted in rats (see also C. Billotey et al., *Radionuclide therapy/dosimetry: biological and long-term effects / animal and in-vitro studies,* poster n. *P619* presented in poster session P69).

Figure 3: activation samples

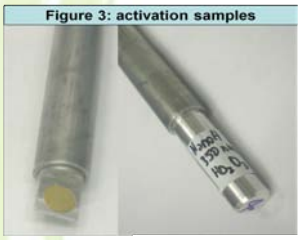


Figure 4: Ho oxide nanoparticles

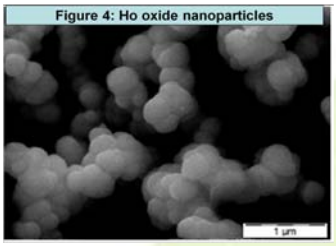
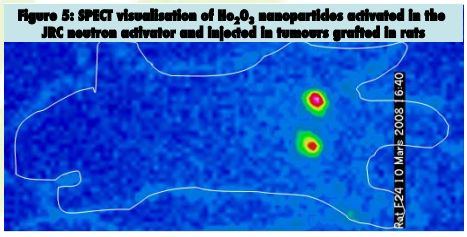


Figure 5: SPECT visualisation of Ho_2O_3 nanoparticles activated in the JRC neutron activator and injected in tumours grafted in rats

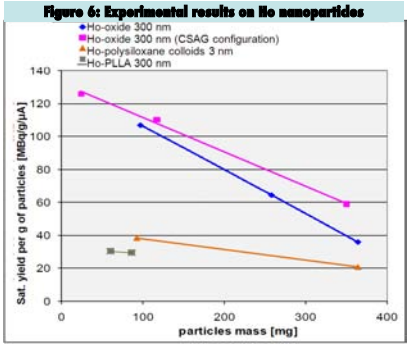


Results and discussion The comparison of experimental and simulation results of activation yields showed a reasonably good agreement for most of the considered reactions (see Tab. 1). **Monte Carlo codes confirm to be a reliable tool for the neutronic design and optimisation of the activator**.
Evident neutron **self-shielding effect** were observed when irradiating different quantities of nanoparticles (Fig. 6). The rationale of the proposed brachytherapy methodology (THERANEAN method) is to irradiate previously prepared injectable doses of 10÷20 mg of **Ho oxide nanoparticles** (100÷300 nm, 87.3% Ho content). In these conditions **a ^{166}Ho saturation yield of about 130 MBq/g/μA can be considered at 36 MeV**.
No irradiations have been done till now at 40 MeV. Available results at 17 and 36 MeV allow estimating an increase in the activation yield from 36 to 40 MeV up to **150 MBq/g/μA**.
Animal tests carried out in the framework of the INBARCA project showed that therapeutic effects on MAT3B tumours (D~1 cm) implanted in rats can be obtained with injected ^{166}Ho activities of the order of 50 MBq, corresponding to the single injection of 20 mg of nanoparticles at 2.5 GBq/g. Such specific activities could be obtained with the JRC activator with 24 h of irradiation at 40 MeV and 50 μA. Higher therapeutic doses/lower irradiation times can be clearly obtained with higher beam energies and currents, available e.g. in the ARRONAX centre in Nantes (70 MeV, 350 μA).
On the other hand, the JRC activator is capable of producing specific activities of Ho nanoparticles largely sufficient to carry out **biodistribution studies based on SPECT imaging** (Fig. 5).

Table 1: Experimental results on activation foils at 36 MeV

Reaction	Saturation yield per sample mass [MBq/μA/g]		
	Experimental	Monte Carlo (MCNPX)	Ratio E/MC
^{197}Au(n, γ)^{198}Au	94.5	52.8	1.8
^{197}Au(n,2n)^{196}Au	0.33	0.29	1.1
^{98}Mo(n, γ)^{99}Mo	0.63	0.36	1.8
^{165}Ho(n, γ)^{166}Ho	99.1	63.1	1.6
^{185}Re(n, γ)^{186}Re	134	33.0	4.1
^{187}Re(n, γ)^{188}Re	83.6	26.1	3.2

Figure 6: Experimental results on Ho nanoparticles



Conclusions The results obtained with the JRC neutron activator prototype indicate **the feasibility of a cyclotron-driven production of β⁻ emitting radioisotopes for brachytherapy applications by using cyclotrons currently commercially available for medical applications**.
Although high-flux nuclear reactors clearly out-perform cyclotron-driven systems (when coupled with medium-size cyclotrons) regarding radioisotope production yields, their increasing lack of availability (due to their ageing and the lack of replacement plans) and the possibility to irradiate **ready-to-inject pharmaceutical preparation of nanoparticles suspensions** make the neutron activator concept illustrated in this work a promising methodology for brachytherapy.