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**. Many such radioisotopes are at present produced only in the few high flux nuclear reactors operating worldwide. Therefore, this limits their widespread use due to the current (and probably worse future) lack of availability of nuclear reactors for medical applications. Furthermore, the intense γ-heating typical of nuclear reactors could induce damages in some samples such as injectable preparations of nanoparticles suspensions.

Starting from the **Adiabatic Resonance Crossing** concept proposed by C. Rubbia in 1998 (**ARC patent**), the AAA company has developed a **compact cyclotron-driven neutron activator** capable of efficiently activating injectable suspensions of nanoparticles carrying β-emitting radioisotopes for **brachytherapy applications**.

Figure 1: concept of the neutron activator

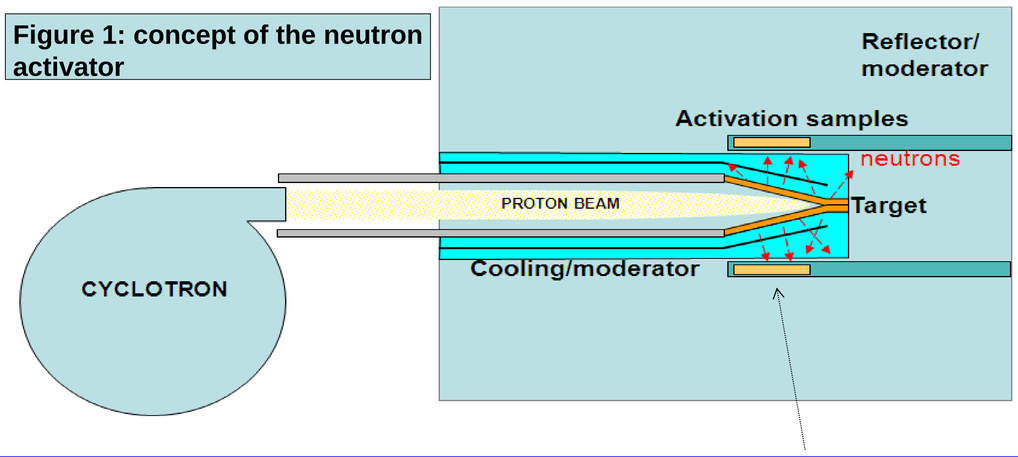


Figure 2: the INBARCA activator at JRC

In the framework of the **INBARCA project** (INnovative Brachytherapy through Adiabatic Resonance Crossing using Accelerators) funded by ANVAR-OSEO (EUREKA project), a **prototype** of the activator has been realised in collaboration with IHCP-JRC and is currently operational on beam line 5 of the Scanditronix MC40 at JRC Ispra (Italy).

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.**

Following the results obtained with the INBARCA prototype (see below), the **THERANEAN project** (THERApy through NEutron Activation using Nanoparticles, funded by the French government) has been launched for the realisation of a **high-power neutron activator** coupled with the **70 MeV–350 μA** (protons) cyclotron installed in the ARRONAX centre in Nantes (France).

The project also foresees the exploitation of preclinical tests of an innovative **brachytherapy technique using multi-functional lanthanide-oxide nanoparticles** locally injected using a dedicated medical device (**Targeted Multi Therapy injector**), as well as the development of a **Monte Carlo based dosimetry technique**

Figure 3: the THERANEAN concept

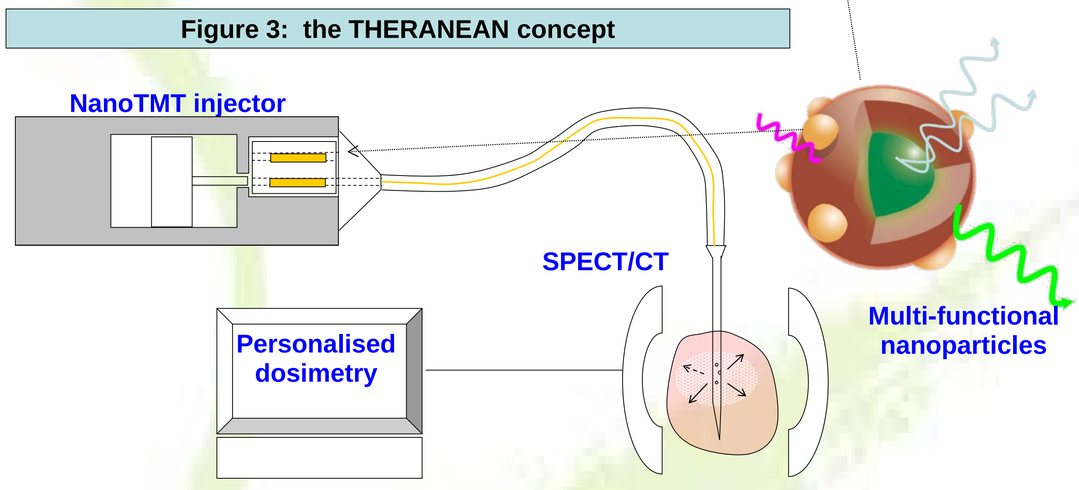
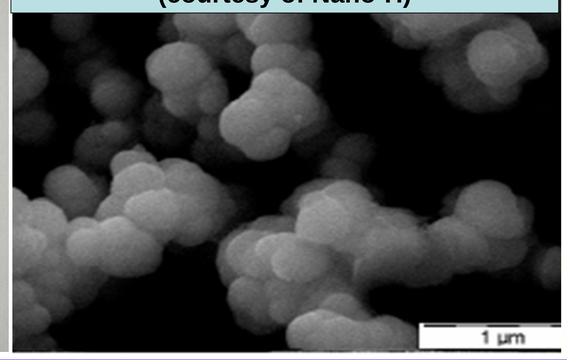


Figure 4: Activation samples

Figure 5: Ho-oxide nanoparticles (courtesy of Nano-H)



Experiments. The activator set-up was optimised by using **Monte Carlo codes** (FLUKA, MCNPX) for the neutronic design and **CFD codes** for the thermal-hydraulic design of the target.

An **extensive experimental campaign** (24 runs) has been carried out on the JRC activator prototype 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 high resolution **γ-ray spectrometry** with HPGe detectors.

Various 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** after intra-tumoral high-pressure injection of nanoparticles in tumours grafted in rats.

Results and discussion. The comparison of experimental and simulated results of activation yields shows a reasonably good agreement for most of the considered reactions (see Table 1). Also the neutron spectrum simulated with MCNPX and the spectrum deduced through the experimental results of the activation yields are in good agreement (Fig. 6) confirming the **reliability of Monte Carlo codes for the neutronic design and optimisation of the activator**. With respect to results presented in *Abbas et al., NIMA 601 (2009) 223–228,* a yield gain of a factor 1.5 (e.g. on Ho foils) is obtained thanks to an improved activator configuration.

Evident neutron **self-shielding effects** were observed when irradiating different quantities of nanoparticles (Fig. 7). The rationale of the proposed brachytherapy methodology (THERANEAN method) is to irradiate previously prepared injectable doses in the range 10 - 20 mg of **Ho oxide nanoparticles** (size distribution range 100 - 300 nm, 87.3% Ho content). In these conditions **a maximum specific (per g of particles) ^{166}Ho saturation yield of about 130 MBq/μA/g can be considered at 36 MeV**.

Nanoparticles activated in the JRC activator were used to carry out **biodistribution studies based on SPECT imaging** (Fig. 8). 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 20 h of irradiation at 40 MeV and 50 μA.

In order to obtain higher therapeutic doses/lower irradiation time the **THERANEAN 70 MeV-350 μA activator** is being designed, for which an increase of the specific activity of a factor 10-15 is expected.

The main challenges in the realisation of the THERANEAN activator are the thermal-hydraulic and structural design of the 24.5 kW proton target and the optimisation of the activator components in order to obtain a neutron spectrum suitable for the considered isotopes.

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	215	83.8	2.6
^{197}Au(n,2n)^{196}Au	0.38	0.29	1.3
^{98}Mo(n, γ)^{99}Mo	0.87	1.63	0.53
^{165}Ho(n, γ)^{166}Ho	153	78.7	1.9
^{185}Re(n, γ)^{186}Re	78.6	130	0.6
^{187}Re(n, γ)^{188}Re	82.9	68.8	1.2

Figure 6: Simulated and unfolded neutron spectra

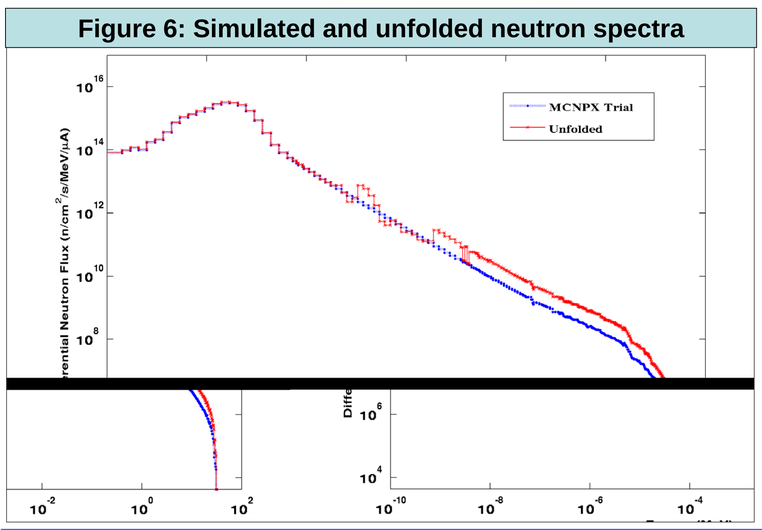


Figure 7: Experimental results on Ho nanoparticles

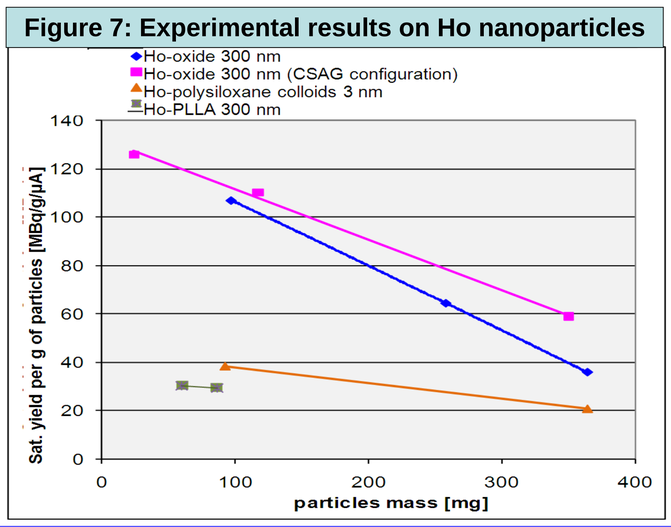
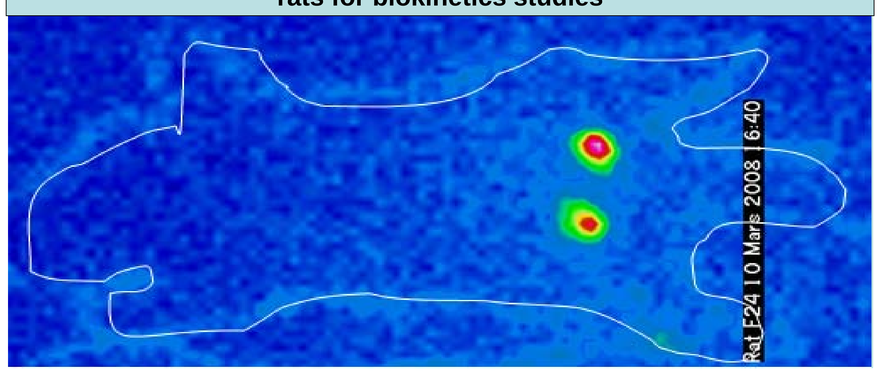


Figure 8: SPECT visualisation (performed at Université Claude Bernard, Lyon, France) of Ho_2O_3 nanoparticles activated in the JRC neutron activator and injected at high pressure in tumours grafted in rats for biokinetics studies



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 based nanoparticle suspensions** make the neutron activator concept illustrated in this work a promising methodology for brachytherapy.

The exploitation of the THERANEAN program in the next 3 years will allow the realisation of the high-power activator and its use for the **pre-clinical validation of the proposed methodology.**