Therapeutic Imaging and Indirect Radiation Treatment IRT with Target Nanoparticles for Cancer Therapy at ESRF-ID17

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Indirect radiation therapy and therapeutic imaging

Therapy of cancer and specific imaging can be extended by **indirect radiation therapy IRT** using **heavy metal targets** with synchrotron X-ray radiation, as shown in figure 1, or neutrons (Gd).

In our concept the ratio of healing to radiation damage effects is improved with **magnetic target nanoparticles** which are based on two principles (figures 2):

- **concentration** of about 1000,000 target atoms in nanoparticles
- **local enrichment** of the nanoparticles by magnetic forces at the tumor site

We use **magnetic target nanoparticles**: **magnetic target liposomes**, which bear the water soluble target in the entrapped lumen, and **double shell poly-Ferrofluids**, containing the target in a surface layer. Our target nanoparticles are biocompatible. The heavy metal is applied as extremly stable metal-DTPA complex, e.g. Lutetium-DTPA (fig.3, no metabolism; Gd-DTPA is usual in MRI imaging (2g)).

The **healing effect** of indirect radiation therapy, cell inactivation by secondary radiation products after **specific** beam absorption by the target metal, is superimposed by **unspecific** radiation absorption elsewhere, which may cause **radiation damages**. A therapy quality factor R_{TB} can be defined, which is given by the relation of the radiation absorption contributions of therapeutic target (T, specific) and body (B, unspecific), and the corresponding doses D and qualitiy factors Q (Equ.1) [1]. The dosis can be precisely estimated and predicted by transmission measurements under therapy conditions, i.e. above and below the absotion K-edge (contrast imaging, tomography). This leads us to a **therapeutic imaging** postulate, at least for **adjuvant therapy**, which tries to abolish cancer completely.

Postulate :

Relative therapy effect $R_{TB} = D_T * Q_T \,/\, D_B * Q_B$ (equ.1)

An effective (adjuvant) cancer therapy target should be visible by *in vivo* contrast imaging (therapeutic imaging)

Absorption - dosis calculation : human head with a brain tumor

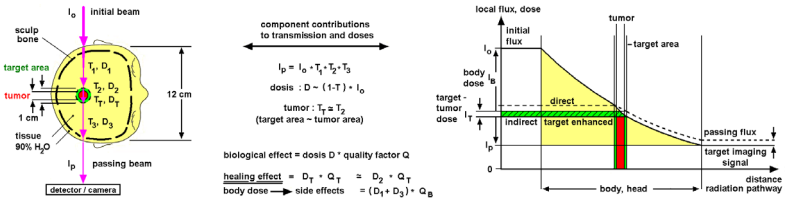


Fig.6: Dose-transmission calculation for a human head (12 cm) with a **brain tumor** (1cm) and **Lutetium-target**.

Therapeutic imaging test : dummy experiment with a rat sculp + water

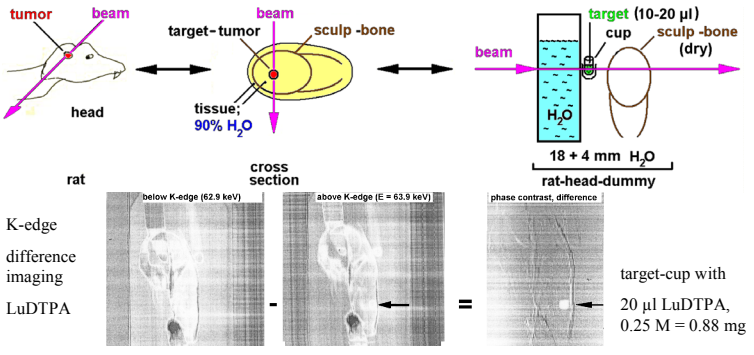


Fig.7,8: A rat head with a **brain tumor** and **Lutetium-target** (4 mm) was simulated by a water-rat-sculp dummy. The phase-contrast projection image yielded the detection limit and indicated the suitable therapy image conditions.

Therapeutic imaging : first *in vivo* treatment (rat under anestesia)

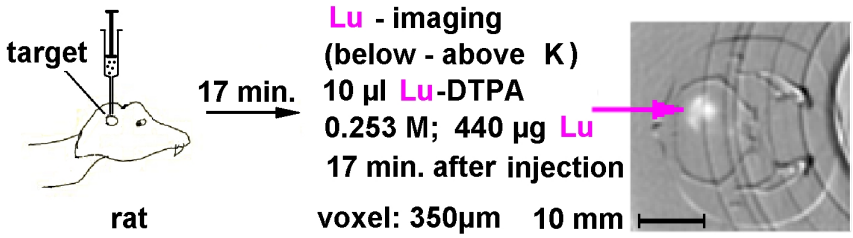


Fig.9: A rat was subjected to therapeutic imaging after intracranial injection of 10 µl **Lutetium-target** (0.44 mg) during anestesia. The animal survived during subsequent tomography experiments (pharmaco - kinetics ; 4.5 h).

Indirect radiation therapy with magnetic target nano-particles

PAT / PXT : Lu, Gd + γ ⇒ n·e⁻ Auger-electrons ⇒ R* radicals ⇒ DNA inactivation @ tumor

Fig.1: Photon activation therapy PAT (PXT) inactivates cancer cells by secondary radiation products after specific absorption of synchrotron X-ray photons at the K-edge of the target material.

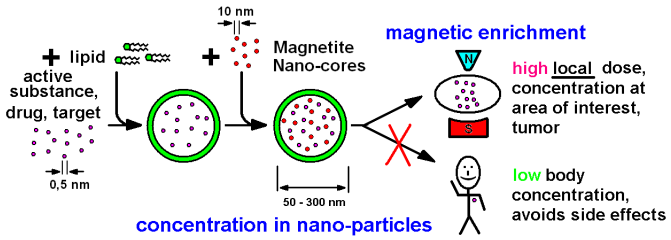


Fig.2: Nanotherapy improves the effect of molecular active substances (drug, target) twice: ~1000,000 molecules are concentrated in nanoparticles, which are enriched at the tumor locally.

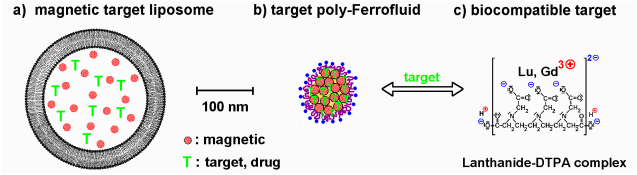
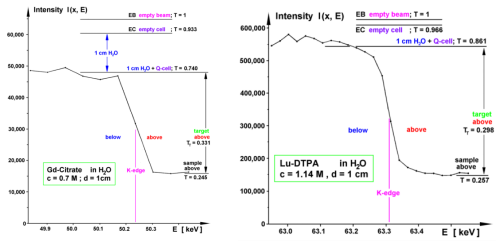


Fig.3: Magnetic and target entities (T) for nanotherapy can be introduced in magnetic liposomes (a), or in double-shell poly-Ferrofluids (b). The Lanthanide-DTPA complexes are biocompatible.

Target materials and properties

Table1: Element	Z	E_K [keV]	$d_{1/2}$ [cm] in H_2O	1-T_{H2O} 1 cm @ K-edge	1-T_{H2O} 12 cm ~ head	Physiol. possible concentr.	1-T_T target-tumor d=1 cm, metal-c= $c_{physiol}$	$R_{TB} = I_T/I_B$, (6+6) cm H_2O-head dummy, 1 cm tumor-target
J Iodine	53	33.17	0.93	0.525	0.9998	1 M	~ 0.6	0.007; before tumor!
Pt cis-Platinum	78	78.39	11.4	0.059	0.518	0.001 M	~ 0.0006	~ 0.0008; conc. low
Hf Hafnium	72	65.35	6.6	0.100	0.716	? (0.2 M)	? (~ 0.12)	? (0.1) tox. unknown
La Lanthanum	57	38.92	1.4	0.370	0.996	0.25 M +	~ 0.2 (calc.)	0.013 // 2x6 cm H_2O
Gd Gadolinium	64	50.24	3.0	0.206	0.938	0.25 M +	0.239, see fig.4	0.063 // 2x6 cm H_2O
Lu Lutetium	71	63.31	6.0	0.109	0.750	0.25 M +	0.154, see fig.5	0.098 // 2x6 cm H_2O

Fig.4,5: The stable Lanthanide-DTPA complexes are suitable to **IRT** and therapeutic imaging due to their biocompatibility and high solubility. The best suitable is **Lutetium**; E_K = 63 keV; tissue half absorption path = 6 cm



The comparison of possible **target materials** in table1 indicates three important properties: **biocompatibility** (non toxic), high **target solubiluty** and suitable **K-energy** range, which leads to a sufficient **half-path absorption length $d_{1/2}$ in body**. Thus trials with Iodine and Pt were interupted. The best suitable is **Lutetium**, the rarest of the rare earth elements (fig.4-5, Lu-DTPA, citrate).

- After target-irradiation and biocompatibility **cell tests** with living bacteria (*Micrococcus luteus*) and rat 9L-tumor cells (not shown), we were successful in therapeutic imaging and treatment:

-**Model calculations** (fig.6) indicated, that only highly concentrated targets of high Z fullfil the therapeutic imaging postulate. The heaviest element is Lutetium-DTPA (biocompatible)

- **Dummy tests** with a water-rat-sculp target system (fig.7,8) yielded the phase contrast detection limit of 10 µl solution of 25 mM **LuDTPA**, and were the pre-requisite for the *in vivo* experiments

- The first ***in vivo* treatment** and **therapeutic imaging** with a rat (under anestesia) was successful. The animal survived the extended tomography experiment after application of 0.44 mg LuDTPA

We are ready for animal tests for tumor treatment now !

References :

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