Indirect Radiation Therapy of Cancer with Synchrotron Radiation at the K-Edges of Heavy Metal Complexes and Target-Nanoparticles

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Indirect radiation therapy and therapeutic imaging

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.

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).

The healing effect of **indirect radiation therapy**, cell inactivation by secondary radiation products after specific beam absorption, is superimposed by unspecific radiation absorption elsewhere, which may cause radiation damages. In our concept the ratio of healing to damage effects is improved with **target nanoparticles** which are based on two principles (figure6,7): **slow diffusion** and **magnetism**

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

We use **target nanoparticles**, which can be locally **concentrated**, as shown in figure3: **i) target liposomes** (magnetic), which bear the **water soluble target** in the entrapped lumen, and **ii) 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-chelate 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 quality factors Q (Equ.1) [1]. The dose can be precisely estimated and predicted by transmission measurements under therapy conditions, i.e. above and below the absorption K-edge (contrast imaging, tomography). This leads us to a **therapeutic imaging** postulate, at least for **adjuvant therapy**, which tries to cure 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 - dose calculation : human head with a brain tumor

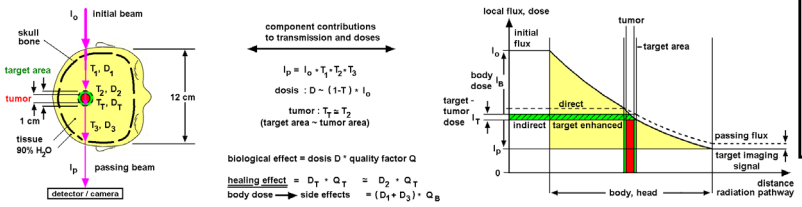
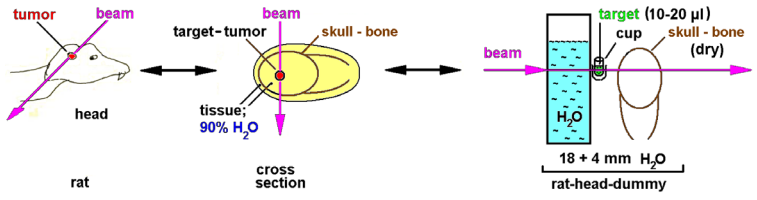


Fig.2: Dose-transmission calculation for a **human head** with a **brain tumor** (1cm) and **Lutetium-target** (2cm).

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



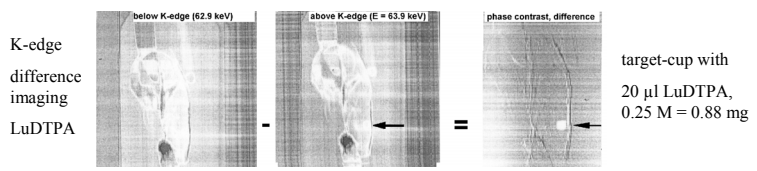


Fig.3,4: A rat head with a **brain tumor** and **Lutetium-target** (4 mm) was simulated by a water-rat-skull dummy. The phase-contrast projection image yielded the detection limit and the suitable therapy conditions.

Therapeutic imaging : first *in vivo* treatment (rat brain)

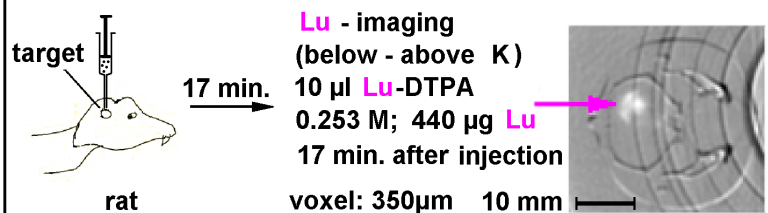


Fig.5: A rat was subjected to therapeutic imaging after intracranial injection of 10 µl **Lutetium-target** (0.44 mg) during anaestesia. The animal survived during subsequent tomography experiments (target kinetics; 5h).

Nano-therapy : target concentration and local enrichment

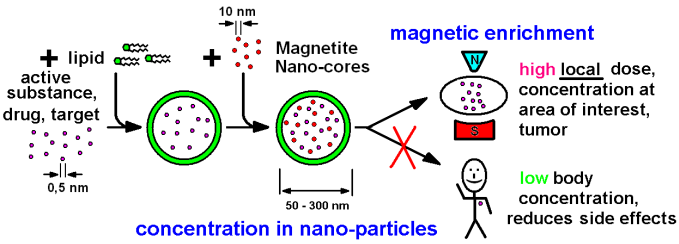


Fig.6: Nanotherapy improves the effect of molecular active substances (drug, target) twice: ~1,000,000 molecules are concentrated in nanoparticles, which are enriched at the tumor locally. Thus unfavorate side effects of conventional therapy are reduced, the healing dose is incresed.

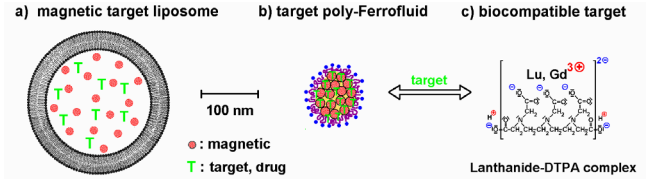


Fig.7: Magnetic and target entities (T) for nanotherapy can be introduced in magnetic liposomes (a), or in double-shell poly-Ferrofluids (b). The Lanthanide-DTPA complexes are biocompatible.

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
I 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

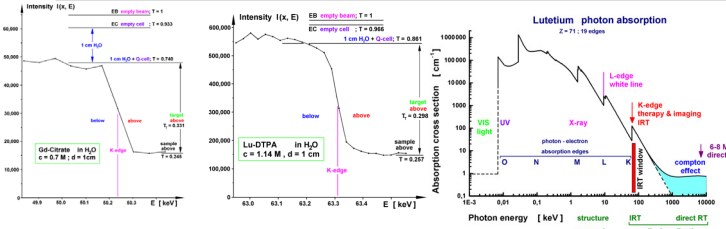


Fig.8-10: Stable Lanthanide-DTPA complexes are suitable for **IRT** and therapeutic imaging due to their biocompatibility and high solubility. The best absorbing is **Lutetium**; E_K = 63 keV; $d_{1/2}$ = 6 cm.

The comparison of possible **target materials** in table1 indicates three important properties: **biocompatibility** (non toxic), high **target solubility** and suitable **K-energy** range, which result in a sufficient **half-path absorption length $d_{1/2}$ in body**. Thus trials with I and Pt were interupted.

-The most specifically absorbing are the rare earth elements **Lutetium**, to **Gadolinium** (fig.8-10).

-Target-irradiation and biocompatibility **cell tests** with living bacteria (*Micrococcus luteus*) and rat . 9L & F98 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 fulfill the therapeutic imaging postulate. The heaviest element is Lutetium-DTPA (biocompatible)

- **Dummy tests** with a water-rat-skull target system (fig.3,4) 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 (fig.5) was successful.

-First **cancer treatment** tests with **tumor rats** (fig.11) resulted in prolonged survival after treatment.

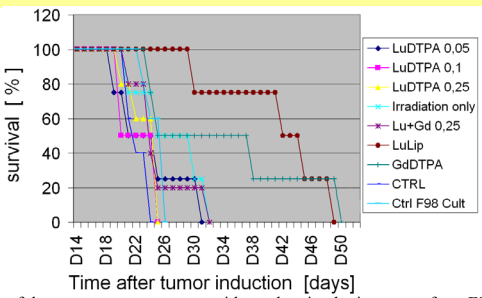


Fig.11: First successful **cancer treatment tests** with rats bearing brain-tumors from F98 cells.

References :

1. T. Nawroth, M. Rusp and R.P. May, Physica **B 350**, e635-638 (2004) "Magnetic liposomes and entrapping : time resolved neutron scattering TR-SANS and electron microscopy"
2. T. Nawroth, Ch. Meesters, H. Decker, M. Rusp, G. Le Duc, St. Corde, A. Bravin, H. Requardt, T. Brochard; ESRF experiment report **MD163-1** (2005) „Imaging of imobilised magnetic target.nanoparticles: liposomes and ferrofluids entrapping target for magneto-photodynamic therapy of cancer M-PXT"
3. T. Nawroth, R. Gebhardt, M. Rusp, I. Grillo, R.P. May; ILL experiment reports **8-03-413** & **9-10-661** (2004) „Time resolved neutron scattering of magnetic liposomes entrapping target"; c) **8-05-394** (2006) „Gd-NCT"
4. International Atomic Energy Agency **IAEA**, status report (2001) „Neutron Capture Therapy" ... This report is sufficiently critical and actual, but limited on Boron therapy (B-NCT).

Abbreviations : NCT = Neutron Capture Therapy; PAT = Photon Activation Therapy; PXT = Photodynamix X-ray Therapy; DTPA = Di-ethylene-Triamine-Penta-Acetic acid (Complexon V); Gd- &Lu-DTPA was produced by the STS method

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