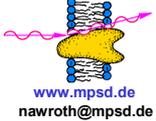


Indirect Radiation Therapy of Cancer IRT with Target Nanoparticles

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Indirect radiation therapy : secondary radiation products hit DNA



Fig.1: Indirect radiation therapy IRT inactivates tumor cells by secondary radiation products and free radicals after specific absorption of synchrotron X-ray photons at the K-edge (PAT/PXT) or neutrons (NCT) at a target material.

Cancer in the EU:

- one of three people get cancer in the life
- one of five die by the disease, i.e. > 1 000 000 / year

Methods of cancer treatment : surgery, radiation therapy, chemotherapy

- the methods decrease in effect by three in the sequence to 50%, 20%, 5-10% healing

The power of radiation therapy can be extended by **indirect radiation therapy IRT** using **heavy metal targets** with synchrotron X-ray and neutron radiation, as shown in figure 1 & 4-7.

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 **magnetic target nanoparticles** which are based on two principles (figure2, 3):

- **concentration** of about 1,000,000 target atoms in nanoparticles
- **local enrichment** of the nanoparticles by magnetic forces at the tumor site

We use two kinds of **magnetic target nanoparticles**, as shown in figure3: **i) magnetic target liposomes**, which bear the **water soluble target** in the entrapped lumen, and **ii) double-shell poly-Ferofluids**, containing the target in a surface layer by partial iron-lanthanide replacement. Our target nanoparticles are biocompatible. The heavy metal is applied as extremely stable metal-DTPA complex (no metabolism; renal excretion; Gd-DTPA is usual in MRT imaging (2g)).

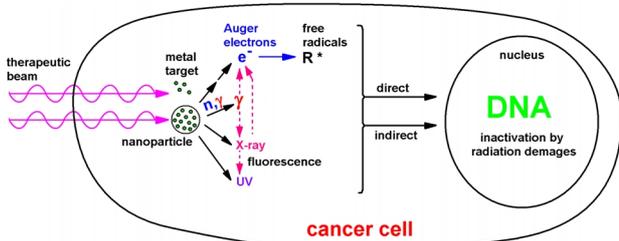
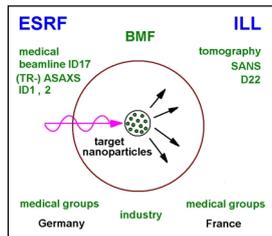


Fig4.: Indirect radiation therapy IRT inactivates cancer cells by secondary radiation products of **short range** upon specific absorption at the target. The tumor DNA is hit directly or indirectly.

Fig5.: Indirect radiation therapy with target nanoparticles is an object of european and institutional cooperations.



Parallel-serial feedback strategy : saves life by speed

Sequence	level / step	sublevel
<div style="display: flex; align-items: center;"> <div style="writing-mode: vertical-rl; transform: rotate(180deg);">feedback</div> <div style="margin: 0 10px;"> <div style="border-left: 1px solid black; border-right: 1px solid black; height: 100px; position: relative;"> <div style="position: absolute; top: 0; right: 0; width: 100%; height: 100%; background: linear-gradient(to top, transparent 49%, black 49%, black 51%, transparent 51%);"></div> </div> </div> <div style="writing-mode: vertical-rl; transform: rotate(180deg);">sequential</div> </div>	1. Target nanoparticles, application devices, structure and dynamics	1.1. target formulations, mixtures 1.2. nanoparticles (liposomes, Ferofluids) 1.3. manipulation, dynamic properties
	2. Cell experiments	2.1. bacteria (carrier, no endocytosis) 2.2. mammalian cells (endocytosis uptake) 2.3. tumor cells (endocytosis, altered)
	3. Animal tests	3.1. Animal dummy experiments 3.2. small animals : rats 3.2. large animals : dogs, pigs
	4. Human treatment	4.1. human dummy experiments 4.2. individual early therapy trials 4.3. therapy trials with different tumors (4.4. clinical application) ... after 3-4 years

Fig7.: The parallel-serial strategy speeds up medical application on cost of effort (~ factor 2).

Nano-therapy : target concentration and local enrichment

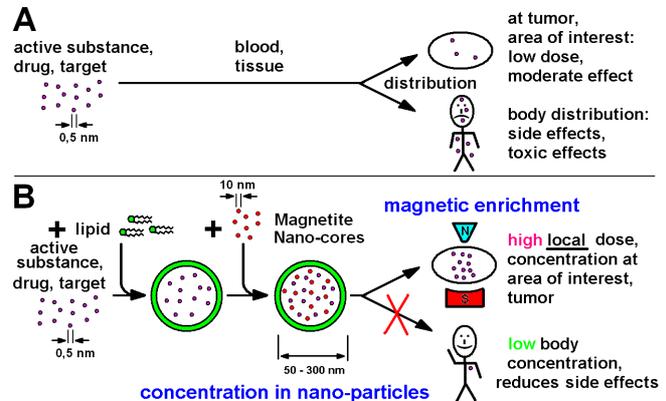


Fig.2: Nanotherapy (B) improves the effect of molecular active substances (drug, target) twice: ~1,000,000 molecules are concentrated in nanoparticles, which are enriched at the tumor locally.

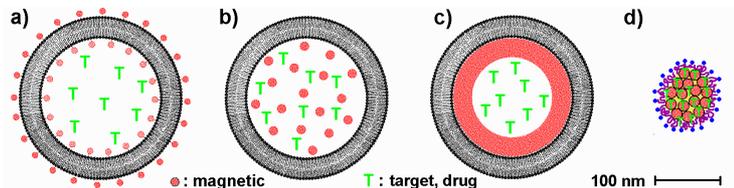


Fig.3: Magnetic and target entities (T) for nano-therapy can be introduced in magnetic liposomes (a-c: metal-lipid, entrapped core, double-shell liposomes), or in double-shell poly-Ferofluids (d).

The **target nanoparticles** have for the medical application to fulfill **eight critical demands**:

- 1) The **structure** has to be smaller than 500 nm, because of embolic risks (blocking blood capillaries);
- 2) The **particle shape** has to be free of cell damaging edges;
- 3) The **nanoparticle size** has to be large enough to entrap a sufficient amount of target material;
- 4) The nanoparticles must contain **biocompatible material** only, or an **excretion path** has to exist;
- 5) The nanoparticles have to be **cell- and tissue-compatible** for in vivo applications.
- 6) The **target concentration** has to exceed a threshold limit for therapy success (metastasis risk);
- 7) **Nanoparticles & superstructures** need a high macroscopic **magnetic moment** for local enrichment;
- 8) The **physical target properties** (energy, cross section) have to yield a significant **specific radiation absorption** at an acceptable level of unspecific body absorption (water absorption, radiation damages)

Lutetium photon absorption

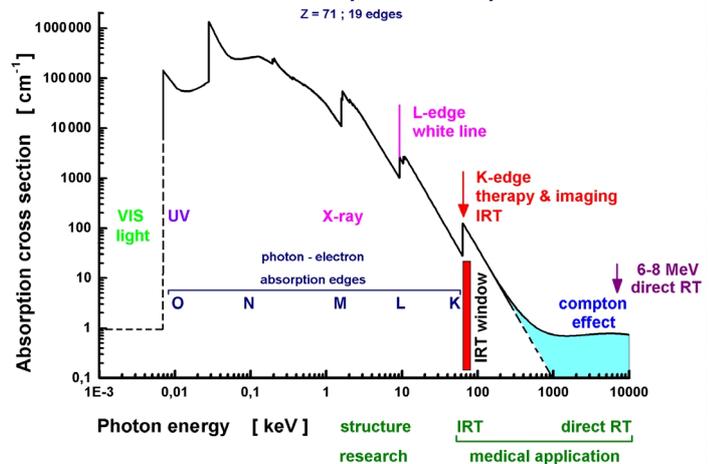


Fig6.: The photon absorption spectrum of Lutetium is the key for research and medical applications.

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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“
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Abbreviations :

PAT = Photon Activation Therapy; PXT = Photodynamic X-ray Therapy; NCT = Neutron Capture Therapy
DTPA = Di-ethylene-Triamine-Penta-Acetic acid (Complexon V); LuDTPA was a gift of www.ferro-med.de