Indirect Radiation Therapy of Cancer by Neutron Capture with dense Gadolinium targets (Gd-NCT)

T. Nawroth[1a], B. Pairet[1b], H. Decker[1b], M. A. Konerding[1c], M. Rusp[2], G. LeDuc[3], St. Corde[4], R. Gähler[5a], B. Lauss[5b], M. Jentschel[5b], R.P. May[5c]

[1] Gutenberg-University Inst.: a) Biochemistry, b) Molecular Biophysics, c) Anatomy; D-55099 Mainz, Germany
[2] Technical University München TUM, Biophysics-E22, Physics Department, D-85748 Garching, Germany
[3] ESRF, BioMedical Facility BMF & ID17, BP220, Rue Jules Horowitz, F-38043 Grenoble Cedex, France
[4] Dep. Hemato-Cancerologie-Radiotherapie, CHRU clinics, B.M. 217X, F-38043 Grenoble Cedex9, France
[5] ILL : a) Neutrograph, b) NP3, c) LSS - D22; BP156, Avenue des Martyrs,F-38042 Grenoble Cedex, France

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www.mpsd.de
nawroth@mpsd.de

Indirect radiation therapy : secondary radiation products hit DNA

PAT / PXT :	Lu, Gd + γ ⇒ n·e⁻	Auger-electrons	(secondary radiation)	⇒ DNA inactivation @	tumor
B - NCT :	^{10}B + n ⇒ ^{7}Li + α	alpha	(secondary radiation)	⇒ DNA inactivation @	tumor
Gd - NCT :	^{157}Gd + n ⇒ ^{158}Gd + e⁻	Auger-electrons	(secondary radiation)	⇒ DNA inactivation @	tumor

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.

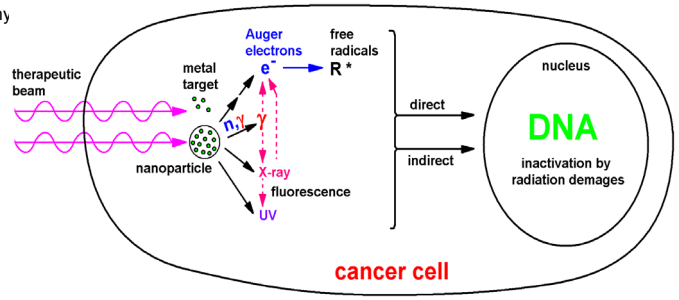


Fig4.: Indirect radiation therapy IRT inactivates cancer cells by secondary radiation products of **short range** upon specific absorption at the target. The tumor DNA is hit directly or indirectly.

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, 5.

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 (figure 3): **slow diffusion** and **magnetism**

– **concentration** of about 1,000,000 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 by partial iron-lanthanide replacement. Our target nanoparticles are biocompatible. The heavy metal is applied as extremly stable metal-DTPA complex (no metabolism; rhenal excremation; Gd-DTPA is usual in MRT imaging (2g)).

Cold Neutron Capture cNCT : complete local beam absorption

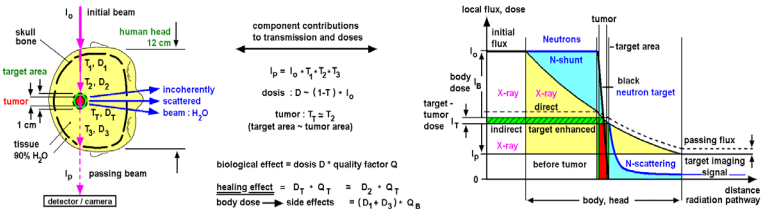


Fig5.: The therapeutic beam of indirect radiation therapy is partially absorption at the **target / tumor**, but may be scattered. **Cold neutrons** are locally absorbed at dense **Gadolinium** targets **completely**.

A) Tentative target materials for NCT

Isotope	σ(n,γ) [barn] + σ(n,α) + σ(n,2n)	$b_{sc,coh}$ [cm^{-10}]	$\sigma_{sc,coh}$ [barn]	$\sigma_{sc,incoh}$ [barn]	total (s + a) σ_{total} [barn]
^{6}Li	940	2.0	0.46	0.51	941
^{10}B	3 835	- 0.1- 1.066i	0.144	3.0	3 838
^{157}Gd	259 000	-1.14 – 71.9i	650	394	260 044
Gd (nat.)	49 700	6.5 – 13.82i	29.3	151	49 880
^{149}Sm	42 080	- 19.2 – 11.7i	63.5	137	42 280
^{1}H	0.3326	- 3.7390	1.7568	80.26	82.35
^{2}D	0.000519	+ 6.671	5.592	2.05	7.64
O (nat.)	0.00019	5.803	4.232	0.0008	4.232
H_2O	0.6654	- 1.675	7.7456	160.521	168.93

B) Nuclear absorption of 50 mM Gd-DTPA

d (mm)	Transmission T(d) native Gd-DTPA (mix)	in D_2O ^{157}Gd-DTPA
1	0.8605	0.4570
2	0.7405	0.2088
3	0.6373	0.0954
4	0.6224	0.0436
5	0.4719	0.0200
10	0.2227	0.0004
15	0.1051	0.000 008
20	0.0456	0.000 000 16

We can make the neutron target black !!!

Fig6.: A) Possible target materials for **neutron capture therapy NCT** (data source: NIST) and B) Absorption of thermal neutrons by a **biocompatible** solution of 50 mM Gd-DTPA.

Neutron capture therapy : experiments for brain and liver cancer

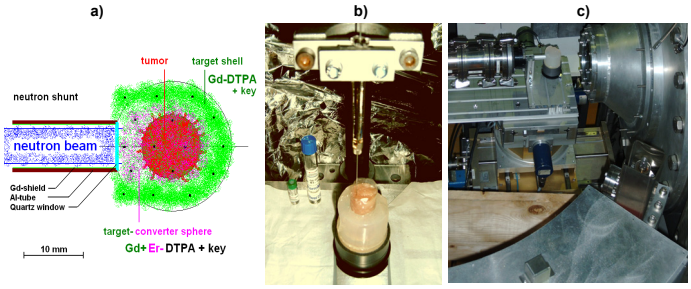
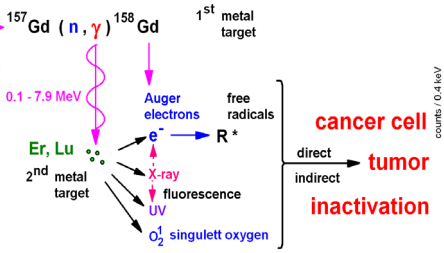


Fig.2: Neutron capture by a dense Gd-target (T<5%): **a)** principle of a fluid **Gd**-target enclosing the **tumor**; **b)** experimental target deposition by multi-injections into a muscle tissue sample inside an agarose dummy; **c)** experiment setup at ILL-D22 with a 2D-camera (right), an extra 1D-detector (front) and **γ**-detection (back).

A) Gamma-Electron conversion by an enhancer



B) Gamma spectra with Gd- ± Er-DTPA

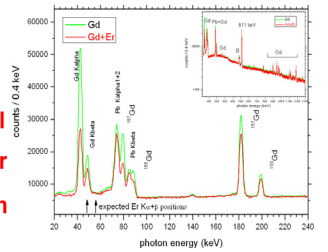


Fig7.: A **double target** improves the yield of cancer inactivating radiation products by re-absorption of the gamma photons produced by neutron capture at Gadolinium. At ILL-D22 we used Erbium-DTPA [3c].

Cancer therapy with neutrons has to fulfill **specific demands:**

1) The **therapeutic beam** has reach the area of interest (tumor) without incoherent scattering by H_2O. This is solved by a **neutron shunt** in our concept, i.e. a neutron guide tube with a quartz window.

2) The **beam absorption** has to be local and specific, enabling indirect radiation therapy at a body-target. In our concept the problems of Boron-NCT are overcome by dense **Gadolinium** targets as Gd-NCT.

3) The **target concentration** in tissue and inside the cancer cells needs to exceed a threshold limit. We use **target nanopaticles** and **lanthanide chelates** in key formulations braking the blood-brain barrier.

4) The **yield of therapeutic useful products** in tissue has to be increased by **gamma re-absorption**.

Nano-therapy : target concentration and local enrichment

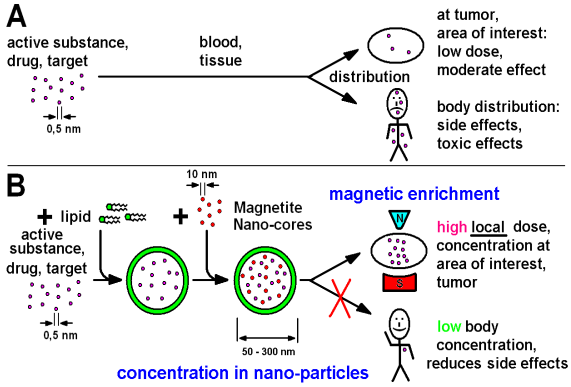


Fig.3: Nanotherapy (B) improves the effect of molecular active substances (drug, target, A) twice: ~1,000,000 molecules are concentrated in nanoparticles, which are enriched at the tumor locally.

The neutron capture therapy of cancer was improved by five developments:

1) The **absorbtion of the therapeutic beam** was improved by **Gadolinium targets** (**Gd-NCT**) by orders of magnitude, in comparison to conventional Boron-therapy (B-NCT). This avoids radiation demages.

2) The absorption was increased by the use of **cold neutrons** instead of an (epi)thermal beam. This increased the cross section by a further factor of 3 (energy gependent) and avoided neutron activation.

3) The target material and nanoparticles must contain **biocompatible material** only, or an **excremation path** has to exist. This was solved by biocompatible DTPA-complexes and entrapping into liposomes;

4) The **beam delivery** to the area of interest (brain, liver tumor) was solved by a **neutron shunt**, which was an implantable tube covered with a Quartz window;

5) The **yield of cancer inactivating products** was improved by a **second target** (Erbium), which partly re-absorbs the gamma photons from Gd-neutron capture. This acts as a **gamma-electron converter**.

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"
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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"; c) **8-05-394** (2006) „Gd-NCT"
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Abbreviations : NCT = Neutron Capture Therapy; PAT = Photon Activation Therapy; PXT = Photodynamix X-ray Therapy; DTPA = Di-ethylene-Triamine-Penta-Acetic acid (Complexon V); LuDTPA was a gift of www.ferromed.de

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