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Visualization and Photodynamic Therapy in Malignant Glioma - An Overview and Perspectives

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1. Introduction

Photodynamic therapy (PDT) is a relatively new modality of cancer treatment. Actual ongoing clinical era started with the studies of Dougherty in the 1970s. PDT is based on the application of a so called photosensitizer (PS), which preferably enriches in the tumor tissue. The application of light at an appropriate wavelength excites the PS molecules from their ground state S_0 to an electronically excited singlet state S_x. The energy of the excited state can be dissipated via several relaxation pathways. By this, so called cytotoxic reactive oxygen species (ROS) are generated. ROS react with various biomolecules inducing cell death by different mechanims.(Dougherty et al. 1998b)

2. History of PDT

The newer history of PDT starts with the observations of Von Tappeiner and Raab at the Maximilian Ludwig University in Munich. In 1900, Raab first reported on the chemical sensitisation of tissue by light.(Raab 1900) Von Tappeiner described in 1904 the so called "photodynamic reaction".(Tappeiner & Jodlbauer 1904) He believed that this effect was based on fluorescence. In contrast Neiser (Breslau) and Dreyer (Finsen Institue in Kopenhagen) described a sensitisation by light for photodynamic reaction.(Dreyer 1903;Neisser & Halberstaedtter 1904) At this time Ledoux-Lebards already proved the concept of the presence of oxygen as a condition for PDT at the Institute Pasteur in Paris (1902).(Ledoux-Lebards 1902) In this era skin diseases were treated with chinidin, acridin and eosin with unsatisfying results.

Already from the beginning of PDT, haematoporphyrin (Hp) was of special interest. Hausmann used Hp for photodynamic investigations in mice in 1911.(Hausmann 1911) In 1913, Meyer-Betz studied Hp to determine its biological effects on himself. After exposition to sunlight he suffered from extensive phototoxic reactions.(Meyer-Betz 1913) Policard detected 1924 in rat sarcoma a red fluorescence after Hp administration.(Policard 1924) In 1942 Auler and Banzer reported on the affinity of neoplastic tissues for Hp in tumor, metastases and lymphatic vessels in patients suffering cancer.(Auler & Banzer 1942) Further investigations were performed by Figge et al. in 1948; they demonstrated the properties of Hp to localize tumors.(Figge, Weiland, & Manganiello 1948) Due to high toxic reactions of

Hp, in 1955 a hematoporphyrin derivat (HpD) was developed by Schwartz et al..(Schwartz, Absolon, & Vermund 1955) This derivat also contained many components of hematoporphyrins. Lipson et al. used the HpD *in vivo* and in patients for tumor detection and localisation in the early sixties.(Lipson, Baldes, & Olsen 1964)

A milestone in PDT was done by Dougherty in 1973.(Dougherty 1973) Dougherty postulated the criteria for PSs and for PDT. Essential for a successful PS is less or no toxicity without light, selective enrichment in the tumor or affected tissue and activation by light with a wavelength of 600 nm or more.(Dougherty et al. 1978;Dougherty et al. 1998a) HpD was further purified by Dougherty's group to Photofrin®. Photofrin is up to now for PDT drug approved.

2.1 First and second generation photosensitizers

HpD and Photofrin® are first generation PSs. The maximum of absorption of HpD is 628 to 632 nm. Penetration depth is about 5 mm. *In vivo* the concentration of HpD is twelve times higher compared to normal brain tissue. In clinical investigations the concentration was 1:2.5 to 1:4 fold. (Kostron, Obwegeser, & Jakober 1996) This first generation PSs have some disadvantages, e.g. high impurity, prolonged skin photosensitivity about several weeks and low absorbance at 630 nm, where tissue penetration of light is low. To improve this, second generation photosensitizers (phthalocyanines, naphthalocyanins, benzoporphyrins, chlorines, purpurins, texaphyrins, porphycenes, pheophobides, bacteriochlorins, etc.) were introduced (Juzeniene, Peng, & Moan 2007). Second generation PSs have a high absorbance in the region of 650-850 nm and produce adequate singlet oxygen. Meta-tetra hydroxyphenylchlorin (m-THPC; Foscan®, Biolitec AG) and benzoporphyrin derivative monoacid A (BPD-MA; Visudyne®, QLT Inc. and Novartis Opthalmics) are approved drugs for clinical use. The second generation PS mTHPC has its maximum absorption at 652 nm. Phototoxic reaction had been observed up to a depth of 15 mm. For meta-tetrahydroxyphenylchlorin (mTHPC) a ratio tumor to normal tissue of more than 80:1 has been described *in vivo* after implantation of C6 glioma in Spraque-Dawley rats. In clinical applications the ratio tumor to normal brain tissue was 20:1.(Dougherty, Gomer, Henderson, Jori, Kessel, Korbelik, Moan, & Peng 1998a;Obwegeser, Jakober, & Kostron 1998) Several more PSs are available, but have been less usage in neurosurgery. Third generation PSs are second generation photosensitizers bound to carriers for selective accumulation in the tumor.

2.2 Prodrug: 5-aminolevulinic acid derived protoporphyrin IX

5-aminolevulinic acid (5-ALA) a prodrug transformed to 5-aminolevulinic acid-derived protoporphyrin IX (5-ALA PpIX) is especially used for photodiagnosis (PD) although properties for as a PS are known. In 1955 Scott described the transitory hypersensitivity to sunlight following exogenous administration of 5-ALA.(Scott 1955) First description about the use of 5-ALA as a porphyrin precursor in PDT was done by Malik and Lugaci, who demonstrated, that exogenous 5-ALA PpIX in combination with light led to inactivation of leukemic cells.(Malik & Lugaci 1987) Kennedy et al. reported about successful treatment of malignant and precancerous skin diseases in 1990.(Kennedy, Pottier, & Pross 1990) The use of 5-ALA PpIX in neurosurgery for fluorescence guided resection of glioblastoma was a milestone. Stummer et al. demonstrated convincingly that the radicality of tumor resection and thus the outcome of patients improves significantly by intraoperative tumor

visualisation.(Stummer et al. 2000;Stummer et al. 2006;Stummer et al. 2008) 5-ALA is a precursor, converted in malignant cells to PpIX, the fluorescent substance. 5-ALA is the first substrate in the heme biosynthesis. Heme biosynthesis consists of eight discrete enzymes catalysed steps which involve the mitochondrial (the first and the last three steps) and cytosolic (the other four intermediate steps) compartments of the cell. In the first step 5-ALA is produced by ALA synthetase in the mitochondria. This is the rate-limiting step in heme biosynthesis. 5-ALA is actively transported to the cytoplasm. After reentry into the mitochondrion, PpIX is produced. PpIX is the last step in the heme pathway before forming heme by insertion of ferrous iron by the enzyme ferrochelatase. Mitochondrial ferrochelatase is dependent on mitochondrial energy generation. In malignant tissue ferrochelatase is reduced, therefore PpIX, a strongly fluorescent and effective tissue PS accumulates in higher concentrations after application of 5-ALA in gliomas.(Kemmner et al. 2008) Some more reasons for higher accumulation of PSs should be mentioned. On the surface of tumour cells more low-density lipoprotein (LDL) receptors are found than on the surface of normal cells.(Maziere, Morliere, & Santus 1991) Increased porphobilinogendeaminase activity in malignant glioma cells also leads to higher PpIX concentration. (Berkovitch-Luria et al. 2011;Greenbaum et al. 2002) At least slightly elevated temperature increases also the rate of biosynthesis of PpIX.

3. Photodiagnosis and photodynamic therapy in neurosurgery

Currently, standard treatment of glioblastoma is based on microsurgical tumour resection, radiation and chemotherapy. Overall prognosis of glioblastoma patients remains poor; therefore, new therapeutical options are necessary. Glioblastomas are diffuse infiltrating tumors, with growth patterns according to Scherer as follows: (i)perineuronal growth (perineuronal satellitosis); (ii) surface (subpial) growth; (iii) perivascular growth and (iv) intrafascicular growth.(Peiffer & Kleihues 1999) Due to the fact that tumor recurrence occurs most frequently at the resection margins, PDT of malignant glioma might be a promising treatment option as a local therapy. Additionally PDT might be able to reach the so called Guerilla cells(Claes, Idema, & Wesseling 2007), tumor cells localized in the brain adjacent to tumor region (BAT region) by local therapy at the end of the resection and perhaps by PDT stimulated anti-tumor immunity. Stimulation of anti-tumor immunity by PDT is off increasing relevance, an opportunity for PDT to become quite more than another local glioma treatment method. This topic will be discussed later in the chapter.
In the 1970s, when lasers and optical light delivery systems became available, the therapeutic use of Hp maintained interest also in neurosurgery. In 1972, Diamond et al. studied the photodynamic effects of Hp in glioma cell cultures where addition of 10^{-5} M Hp and exposure to light caused cell death.(Diamond et al. 1972) In 1975 the same group investigated the photodynamic effect of Hp *in vivo* in Fisher rats and subcutaneous implanted glioma cells; the authors demonstrated a time dependent cell death of glioma cells increasing by time of light exposure. For clinical use of PDT in Neurosurgery mainly HpD and mTHPC are currently in use.

3.1 Photodiagnosis (PD) and PDT with 5-ALA PpIX
Introduction of 5-ALA fluorescence guided resection was a milestone in neurosurgery in the last fifteen years. Great contribution was done by Stummer and coworkers. 5-ALA is orally applied about 4 hours before surgery. Surgery is performed under operating

microscope, during resection the surgeon is able to switch between the white light mode and the fluorescent mode (blue light), where the tumour appears red fluorescent, see also figure 1.
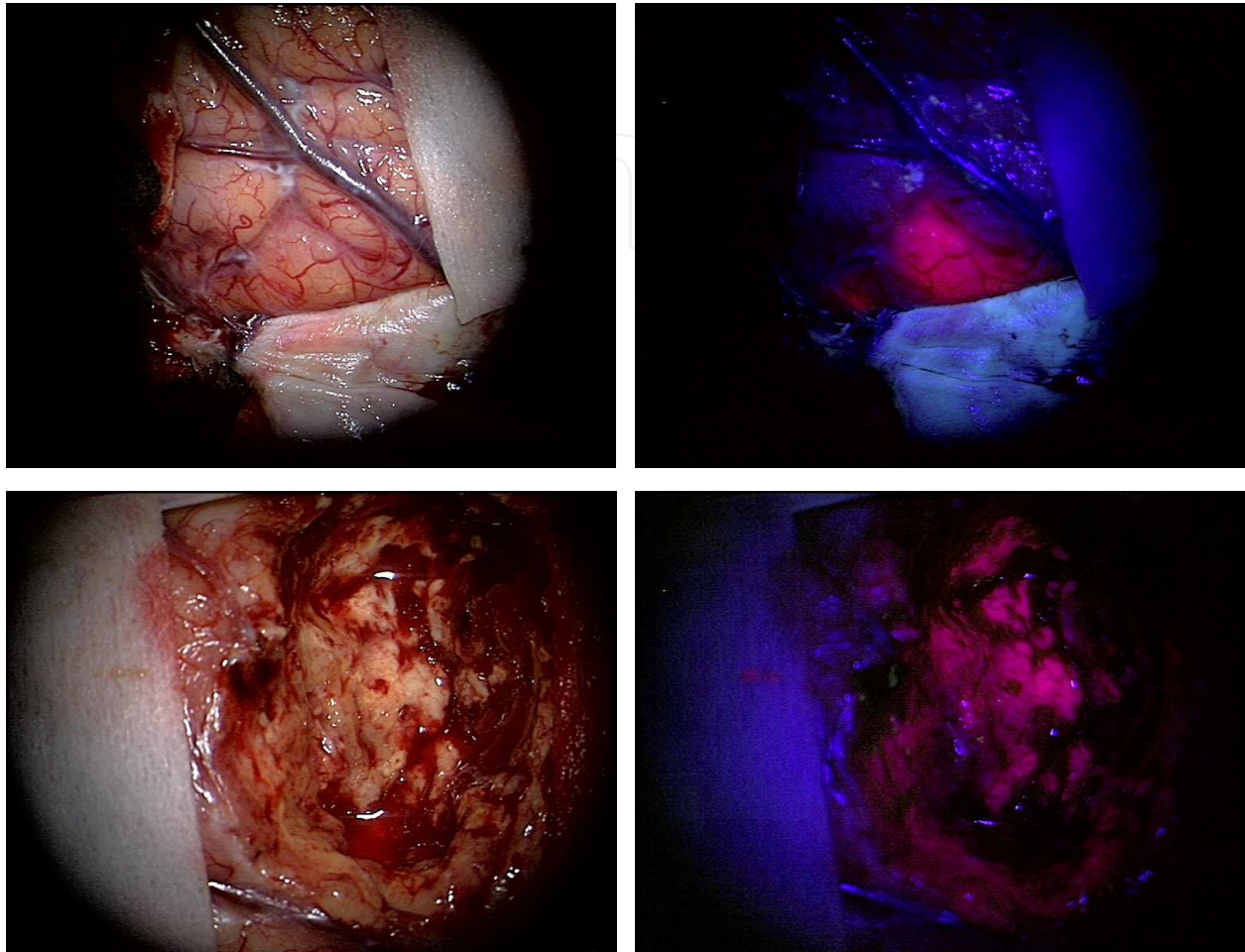

Fig. 1. Glioblastoma WHO IV at the beginning of resection in white light mode (upper row left) and under fluorescence mode (upper row right) after opening of the dura. Note the red shining PpIX fluorescence. During resection under white light conditions residual tumor (bottom row left) can be clearly detected under fluorescence mode (bottom row right).

The first results of improvement of the radicality of resection by 5-ALA fluorescence guided surgery were published in the nineties. The results of a randomised controlled multicentre phase III trial performed are summerized. The German study group investigated 322 patients enrolled by 32 investigators at 17 study centres. 161 patients were treated by fluorescence-guided surgery with 5-ALA, (20 mg/kg bodyweight; medac, Wedel, Germany), 161 were resected under conventional white light mode. In the fluorescence guided resection group tumor was resected completely in 65%, in the white light group complete tumor resection was achieved only in 36% of patients, as investigated by early postsurgical MRI. The difference between the groups was 29% [95% Confidence interval (CI) 17-40], p<0.0001. Table 1 gives a short overview about the results depending to surgery (5-ALA fluorescence guided vs. resection under white light mode).(Stummer, Pichlmeier, Meinel, Wiestler, Zanella, & Reulen 2006)

	5-ALA	White light
PFS (median)	5.1 mon.	3.6 mon.
PFS-6 months	41.0 %	21.1 %
SR age > 55 years	14.1 mon.	11.5 mon.
SR age < 55 years	18 mon.	17.5 mon.
SR 5-ALA vs. whitelight	17,9 mon.	12,9 mon
PFS: progression free survival; SR: survival rate		

Table 1. Summary of the randomised controlled multicentre phase III trial, fluorescence-guided surgery with 5-ALA versus white light surgery. Stummer et al. 2006

Stratification by postoperative MRI findings showed that patients without residual contrast-enhancing tumor had higher overall median survival than did those with residual-enhancing tumour (**17.9** months [CI 14.3-19.4] vs **12.9** months [CI 10.6-14.0]). Although *in vivo* experience demonstrated the feasibility to perform 5-ALA PDT, 5-ALA PDT is not established up to now in clinical practice without exceptions of some groups. Beck et al. 2007 treated 10 patients with small and circumscribed recurrent malignant gliomas by implantation of up to six light diffusers with a distance of 9mm.(Beck et al. 2007) By this method a mean tumor volume of 5.9 cm^3 could be treated. The median survival was 15 months, without side effects in the treated patients.

3.2 PDT in neurosurosurgery clinical studies – an overview

Currently Kostron (2010) reviewed clinical investigations of PDT in a meta analysis, median survival of primary GBM with PDT was 22 months vs 15, in recurrent GBM 9 months vs. 3 months.(Kostron 2010) A brief overview about the relevant clinical investigations in the last decade is given by table 2. For PDT the PSs Hpd (Photofrin®) and mTHPC (Foscan) were

Author, Publication year	Photosensitizer	Light dose	Number of patients	Results
Stylli 2005 (Stylli et al. 2005)	HpD 5 mg/kg bw	70-260 J/cm^2	145	Mean survival 14.3 mon. 2-year survival 28% for newly diagnosed GBM
Kostron 2006(Kostron, Fiegele, & Akatuna 2006)	mTHPC 0.15 mg/kg bw	20 J/cm^2	26	Median survival 9 mon. Control 3.5 mon.
Muller 2006(Muller & Wilson 2006)	HpD 2 mg/kg bw		96	Survival time 7.5 mon., 1-year survival 44%, 2-year survival 22%
Eljamel 2008 (Eljamel 2008)	ALA and Photofrin (HpD)	500 J/cm^2	27, 13 study group 14 control group	Tumor progression 8.6 mon. vs. 4.8 mon.

Table 2. Short overview - clinical investigations with PDT

used, the survival time was enlarged in newly and also in patients with tumor recurrence. Side effects of PDT were modest, including skin sensitivity against sunlight and sometimes increased intracranial pressure.

Due to the small penetration depth of 5-ALA derived PpXI of 2-3mm, Eljamel et al. combined fluorescence guided resection and PDT.(Eljamel 2008) They used 5-ALA PpXI for resection and HpD for PDT. In respect to the limitation of these PSs we were encouraged to investigate a new PS combining both positive properties.

4. Hypericin – high potential for PD and PDT

Hypericin, a Naphtodianthron is a naturally occurring compound of the plant *Hypericum perforatum*, better known as St. John's wort. St. John's wort is a plant that has been used since the Middle Ages to treat wounds and depression. It grows bushy and has its peak season between May and August, see figure 2. St. John's wort contains the following active ingredients: essential oils, flavonoids (Biapigenin, hyperoside, Isoquercitin, rutin), tannins, glycosides, resins, Naphtodianthrone (hypericin, Pseudohyericin) and phloroglucinol (hyperforin). In 1942 by Pace a pronounced sensitization of the skin by light for grazing animals taken St. John's wort containing feed was described. The changes in the skin were reversible after the animals were protected from sun exposure. The phenomenon was described as hypericism.(Pace 1942) Hypericin is a lipophilic molecule that is incorporated into the phospholipid bilayer of cell membranes and has already in the dark versatile pharmacological activities. These include antiviral, anticancer and antiangiogenic properties. Takahashi et al. could show an inhibitory effect on proteinkinase C, which is involved in cell proliferation.(Takahashi et al., 1989) Malignant gliomas have, compared to glial cells, a high proteinkinase C activity.(Couldwell et al. 1991) Hypericin has excellent properties as a PS. It has a high triplet quantum yield and a high efficiency in the formation of ROS.(Diwu & Lown 1993;Ehrenberg, Anderson, & Foote 1998;Hadjur et al. 1996)

The excessive production of the so called ROS leads to oxidative stress to many biomolecules, e.g. proteins, causing cell death by induction of apoptosis, necrosis or autophagy associated cell death.(Buytaert, Dewaele, & Agostinis 2007)

Fig. 2. *St. John's wort, also known as Hypericum perforatum*;
[www.awl.ch/heilpflanzen/hypericum-perforatum/index.htm].

4.1 Hypericin differentiating neurons and glioma cell lines in vitro

For selective PDT it would be advantageous when the PS enriches in the malignant cells more compared to neurons or glial cells. In 2005 we investigated eight human glioma cell lines (L; LN-18,LN-229, U87MG, U373MG, D247MG, U251MG, U251MG,T98G) and twelve primary human glioma cell cultures (P) and compared the hypericin uptake with human astrocytes (AC; SV-FHAS) and cerebellar granule neurons (N) prepared from 8-day-old Sprague-Dawley rat pups (Charles River, Sulzfeld, Germany). Long term glioma cell lines and primary human glioma cell cultures showed significant higher hypericin uptake compared to neurons. Hypericin uptake in astrocytes was higher compared to glioma cells and to neurons.(Ritz et al. 2005) Another investigation done by fluorescence microscopy showed that hypericin was predominately localized in the glial envelope surrounding the neuron in a model with crayfish neuron and surrounding glia. Uzdensky et al. found a minor fraction of hypericin in the neuron compared to the glia in this model.(Uzdensky et al. 2003)

4.2 Subcellular distribution of hypericin

Predominantly perinuclear localization of hypericinis is in common concordance.(Uzdensky et al. 2001) The more detailed description of subcellular distribution of hypericin is not uniform. Due to the very short life span of the singlet-oxygen for cytotoxic reactions, the subcellular distribution of hypericin is off interest to understand PDT mechanisms in more detail. Many investigators studied in different cultured cell lines with different methods the subcellular hypericin localisation. According to our studies hypericin enriches particularly in the endoplasmatic reticulum (ER) and the Golgi apparatus (GA) in U37MG glioblastoma cells after incubation with noncytotoxic hypericin (1µM, 2h incubation time). ER is predominantly found in the perinuclear region while the GA is more distant to the nucleus, see figure 3.(Ritz et al. 2007b;Ritz et al. 2008)
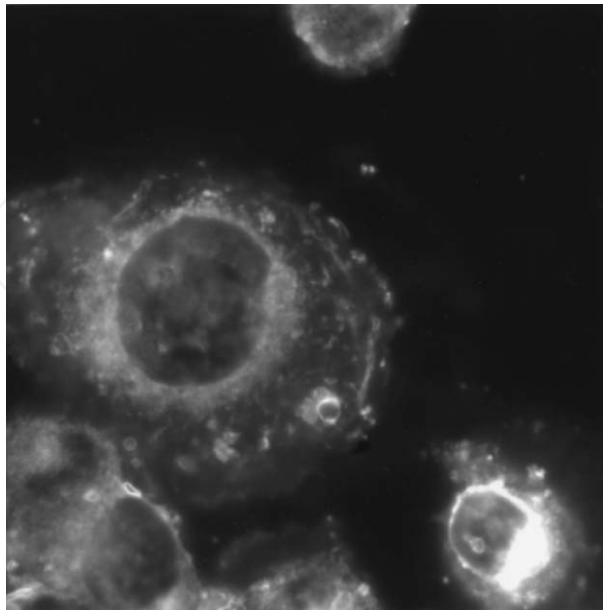

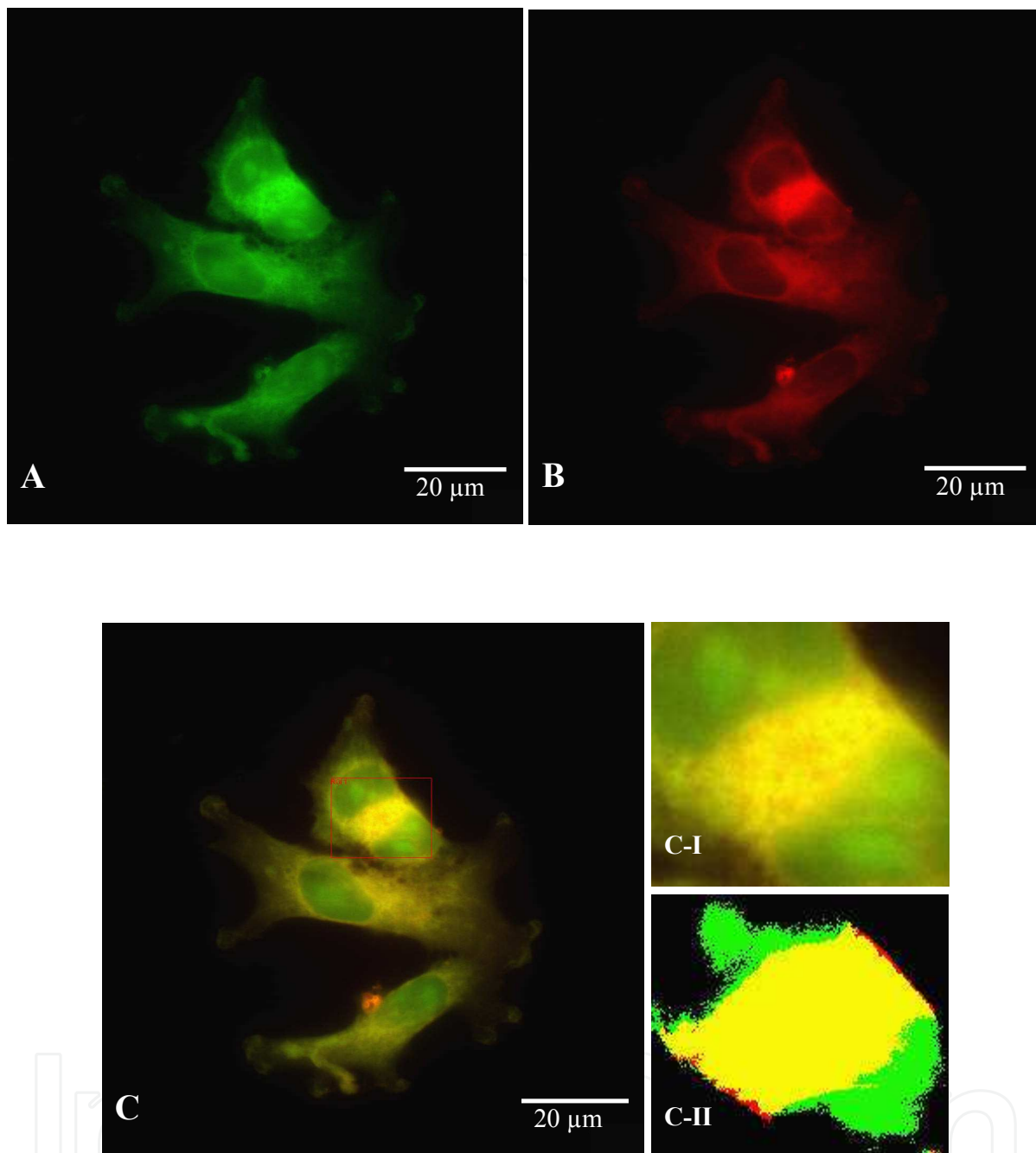Fig. 3a. Long-term glioblastoma, incubated with 20µM Hypericin. Note the perinuclear granular enrichment.

Fig. 3b. Fluorescence microscopic images of U373 MG glioblastoma cells, co stained with ER-Tracker (2 M/20 min) and Hypericin (1µM/2h). (A) staining for ER, (B) hypericin fluorescence. (C) demonstrates the costaining image. C-I original image, C-II after image processing.

4.3 Kinetic of intracellular accumulation of hypericin

The cellular accumulation of hypericin in glioma cell culture is time and concentration dependent. Short incubation times of 2 h lead to saturation up to 5µM hypericin, higher concentrations do not increase hypericin accumulation. Cellular hypericin uptake is subjected by active temperature dependent transport mechanism, although details are not clear at all (Fig. 4).(Ritz, Wein, Dietz, Schenk, Roser, Tatagiba, & Strauss 2007b)
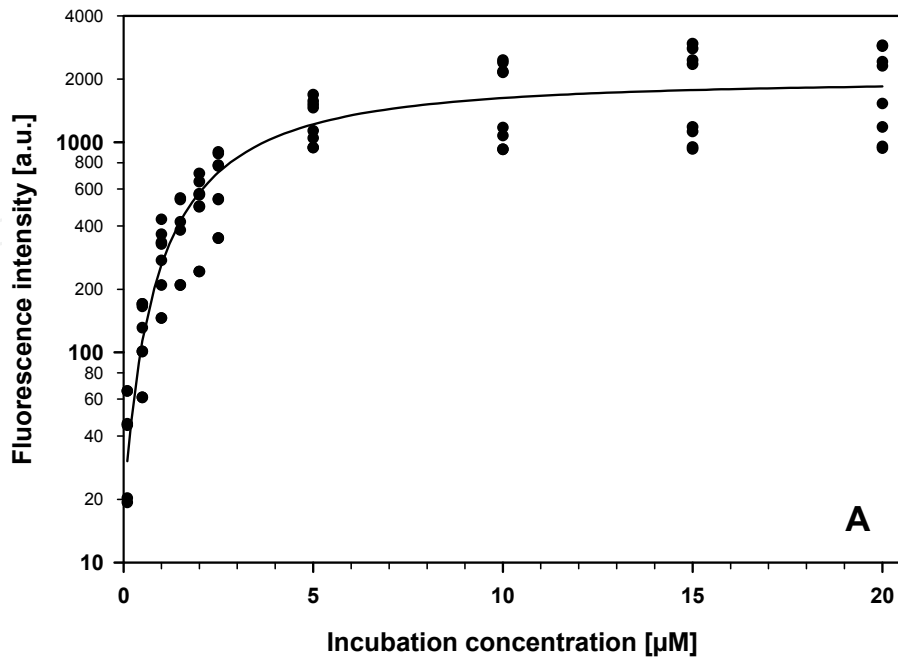
Fig. 4a. Incubation concentration dependent hypericin uptake in U373 MG cells. Cells were incubated for 2 hours; up to 5 µM cellular fluorescence increased. No further increase was found at higher incubation concentrations.
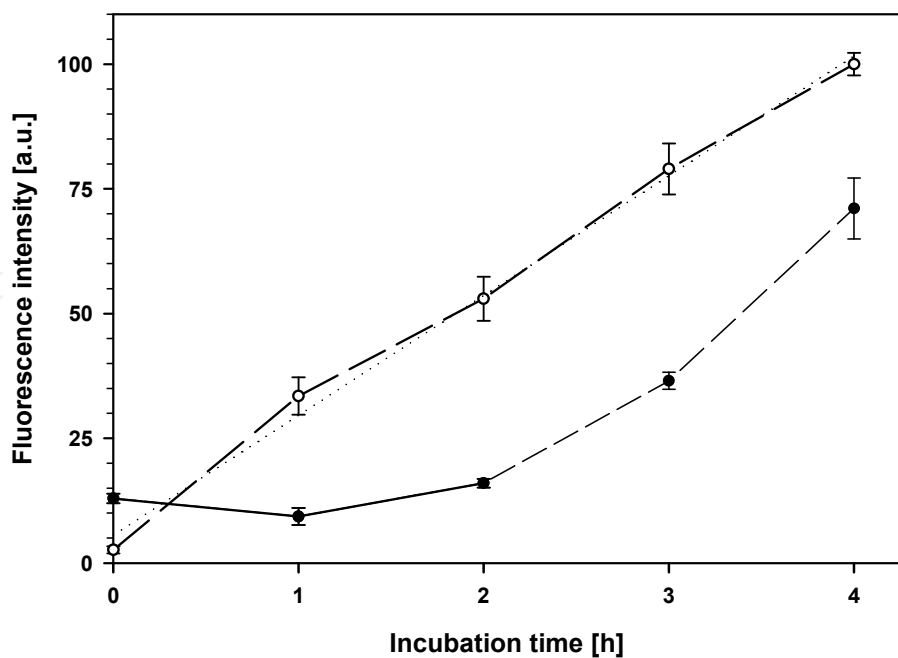

Fig. 4b. Cellular accumulation of hypericin in U373MG glioblastoma cells (incubation concentration 2.5µM) dependent on incubation temperature [(4°C for 2h and subsequently 37°C for further 2 h (●) vs. 37°C for 4h (o)] measured by flow cytometry.

4.4 Photodynamic therapy with hypericin in glioma

Hypericin exhibits high phototoxicity combined with weak to negligible dark cytotoxicity, as reported previously.(Ritz et al. 2007a) Optimal illumination wavelength for PDT is at 595nm. In our *in vitro* studies on glioma cells, a dosis of 0.15-0.2 J/cm^2 resulted in cell survival to 50% (ID_{50}-value); after exposure to 0.4 J/cm^2 cell survival was reduced to about 10% as compared to non-illuminated controls. In comparison other investigators applied light doses between 2 J/cm^2 (ID_{50} in U373 MG) up to 15J/cm² for 5-ALA PDT.(Blake & Curnow 2010)
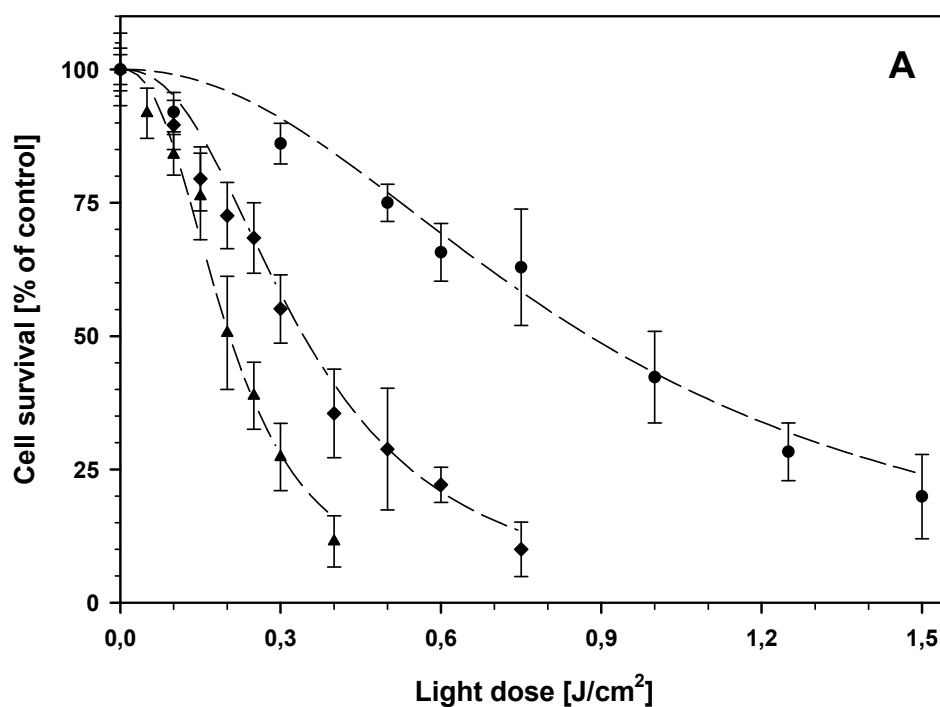

Fig. 5. Phototoxicity of hypericin in T98G cell line. Phototoxicity depends on incubation concentration (incubation time of 2h) and light dose. Cells were incubated with 0.5 μM (●) 1.5 μM (♦) and 2.5 μM (▲). Illumination was performed at 595 nm, light was delivered at 5-10 mW/cm². Cell viability is given on the ordinate.

4.5 Tumor selectivity of hypericin *in vivo*

Basical for a successful clinical application of hypericin for fluorescence guided resection and PDT is a selective enrichment in tumor tissue without enrichment in normal brain tissue. For this we evaluated in a C6 rat glioma model selective hypericin accumulation in tumor tissue compared to BAT zone and normal brain tissue. By these experiments it could be demonstrated that ratios of hypericin in rat glioma compared to BAT and normal brain tissue were 19.8:2.5:1 (Fig. 6).(Noell et al. 2011) Hypericin was found in a high concentration in tumor tissue, BAT zone was also enriched by hypericin in contrast to normal brain tissue were no hypericin was found.

Our first clinical results demonstrated also a high potential of hypericin for fluorescence guided surgery in malignant glioma, data are submitted for publication.
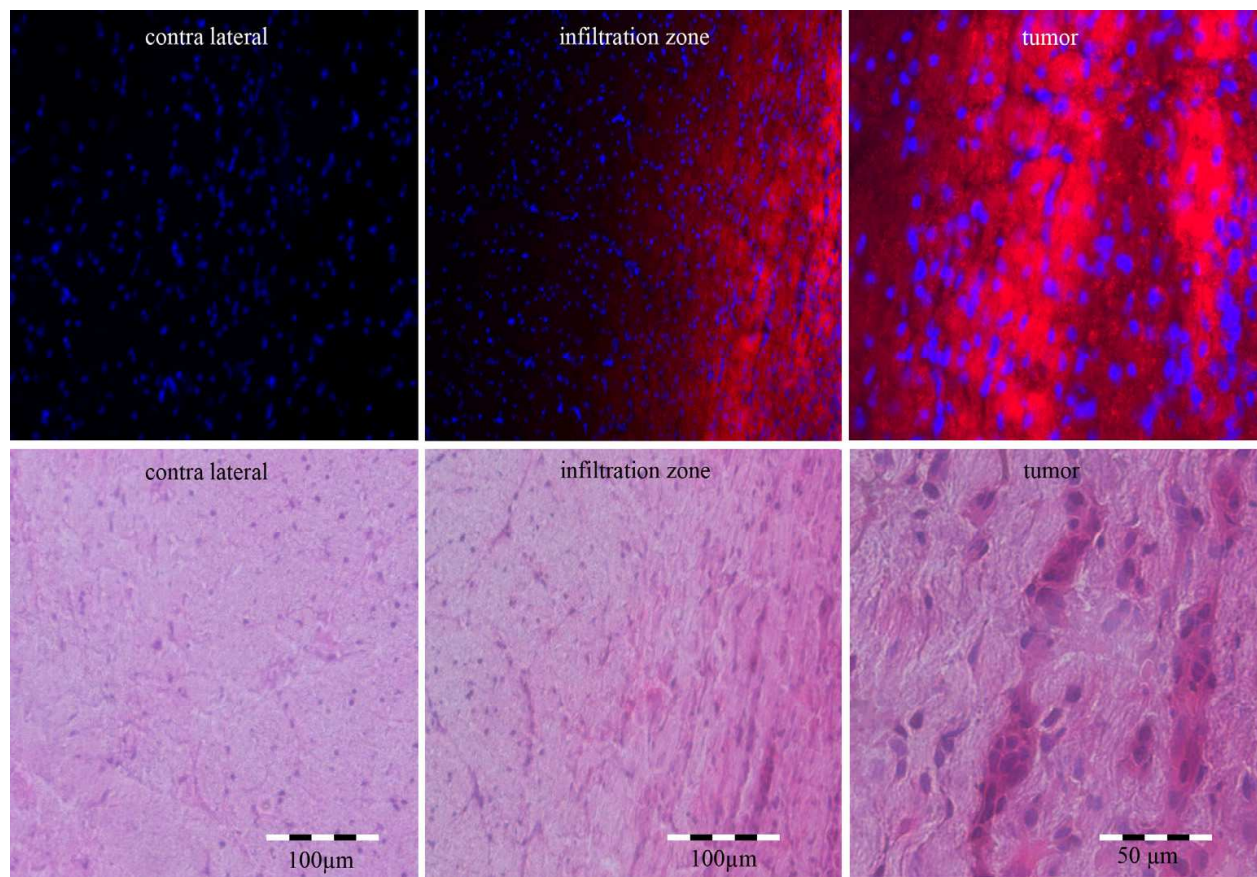
Fig. 6. Cryosections of the C6 glioma in rat brain. Contralateral hemisphere without tumor (left), BAT zone (middle) and tumor (right). Selective hypericin accumulation (red fluorescence) in the tumor and tumor infiltration zone co-stained with DAPI (blue) is demonstrated in the upper row. Corresponding sections stained by hematotoxylin and eosin (lower row).

5. Photodynamic therapy and anti-tumor immunity – A chance for PDT to be more than a local cancer therapy?

In malignant brain tumors standard therapy is based on surgery, radiation and chemotherapy. The prognosis of patients is still dismal. There is no doubt about the necessitiy of other treatment options. As mentioned in this chapter PDT represents an interesting therapy option in addition to the modern therapeutical strategies described in this book. At the first moment PDT seems only as one additional tool of local tumor treatment, with all advantages, e.g. low costs compared to modern biotechnical products, selective and repetitive application. Therapy resistancy has been seldom observed. PDT is able to occluse tumor associated vessels, mainly PDT induces apoptosis and necrosis, also autophagy plays a role. Great hope lies in the modulation of immune system by PDT. Fluorescence guided tumor resection is able to eradicate tumor locally. In combination with

induced systemic anti-tumor immune reactions distant tumor cells, e.g. Guerilla cells could be treated. Several mechanisms contribute therefore. Cells killed by PDT produce signals, increasing antigen presentation by dendric cells (DCs) and recruit antigen-specific cytotoxic T lymphocytes (CTLs).(Mroz et al. 2011)

Great importance is also given to so called damage-associated molecular patterns (DAMPs). DAMPs are intracellular molecules in living cells, exposed by sudden cell damage as initialized for example by PDT. Up to date it is generally accepted that PDT activates the immune system. Complete understanding of the processes and how to influence them for improvement the immune responses is mandatory and could be advanced by closer cooperation of researchers in PDT and immunology.

6. Conclusion and future directions

PDT for malignant gliomas is an interesting additional therapeutic tool with low side effects. By fundamentally distinct mechanisms compared to radiochemotherapy PDT also offers new opportunities for patients with tumor relapse. Hypericin seems to be a quite effective fluorescence marker for the detection of glioma. Since hypericin exhibits excellent photosensitizing properties, as demenostrated in detail *in vitro,* it might also be a promising PS in glioma therapy. Further *in vivo* investigations will proof this hypothesis in future. Due to high induction of apoptosis by hypericin mediated PDT, further investigations should focus on anti-tumor immunity by hypericin PDT, a chance to be more than only a local therapeutic tool.

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       Ref Type: Journal (Full)

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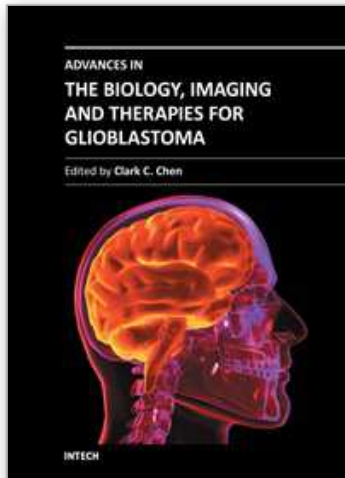
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