Photodiagnosis/therapy for specific treatment of ovarian cancer

Attila L. Major, MD, PhD

Presentation Plan

- Introduction ovarian cancer and photomedicine
- Photodetection
- Therapy
- Current research
- Conclusion / Perspective

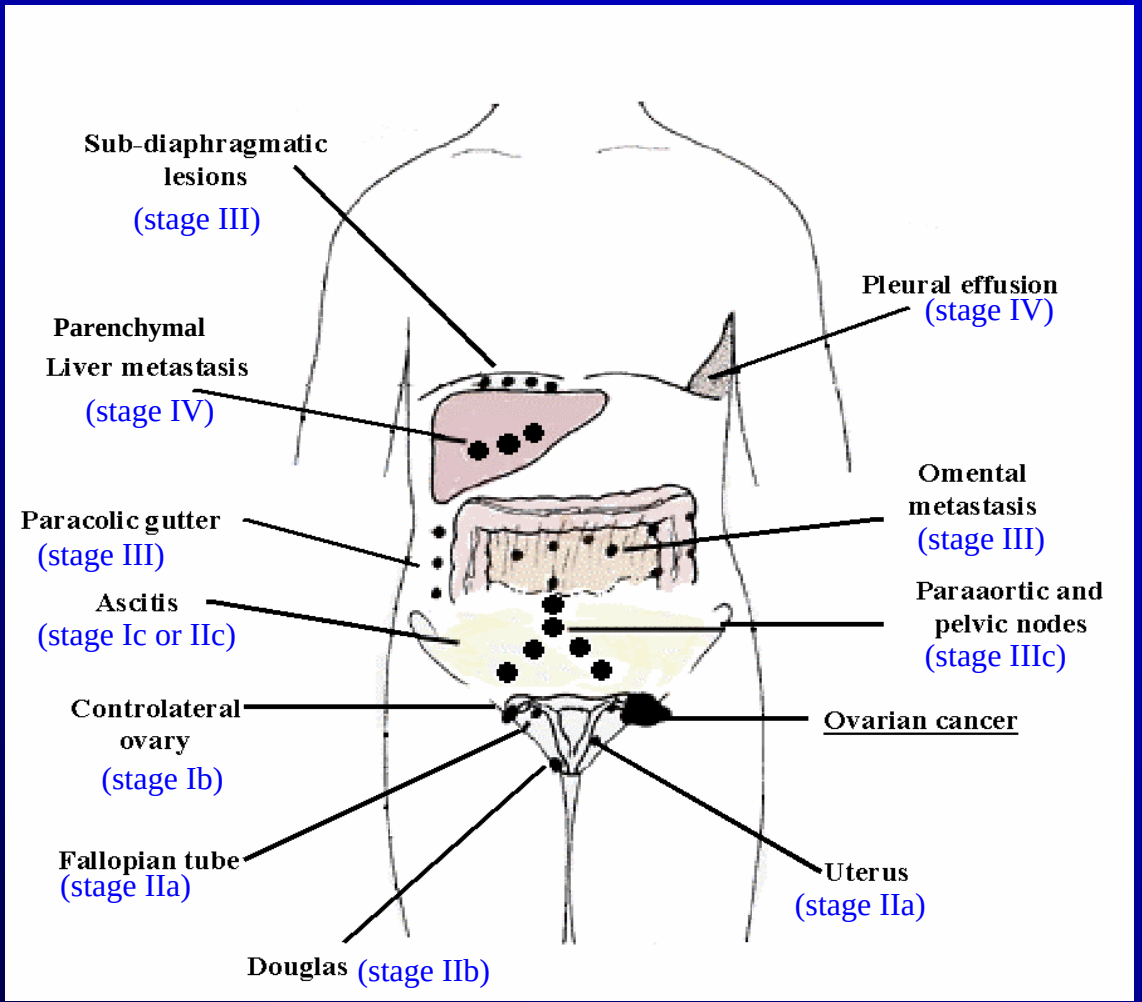


Figure 1

Common sites of ovarian cancer metastases.

Ovarian cancer spreads fast to the whole abdominal cavity by exfoliation

Epithelial Ovarian Cancer

- Fourth most frequent cause of “cancer-related” death
- 65% diagnosed with stage III-IV disease

- 80% chemo-sensitive (initial response)
- 5 year survival rate: 15-20%
- 50% of “cured” patients (negative second look laparotomy) will recur

RATIONAL

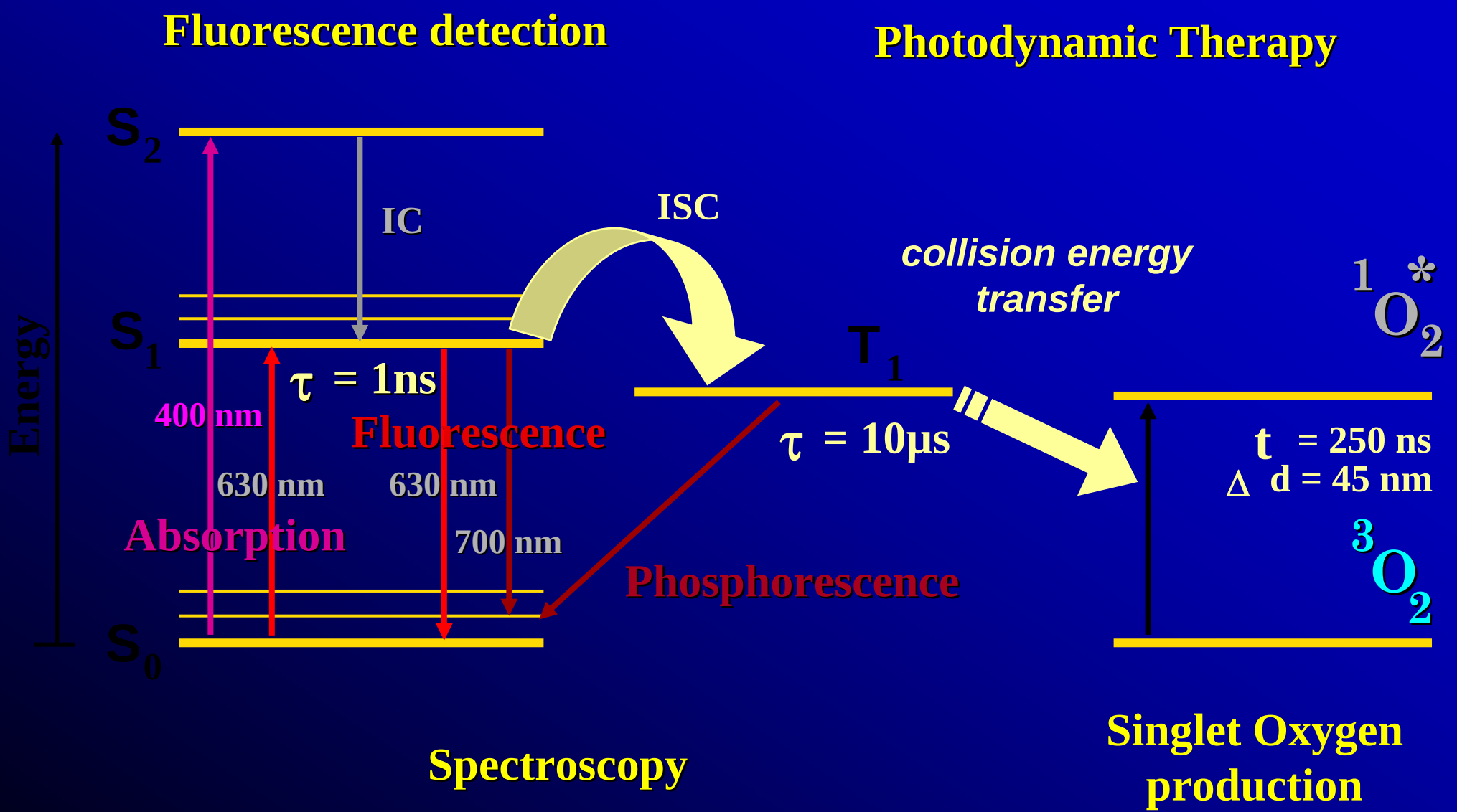
“The facts remains that a large number of patients are being treated almost to the point of “cure” and an additional stroke of some sort is needed.”

(DiSaia, Clinical Gynecological Oncology, Mosby-Year Book, 1997)

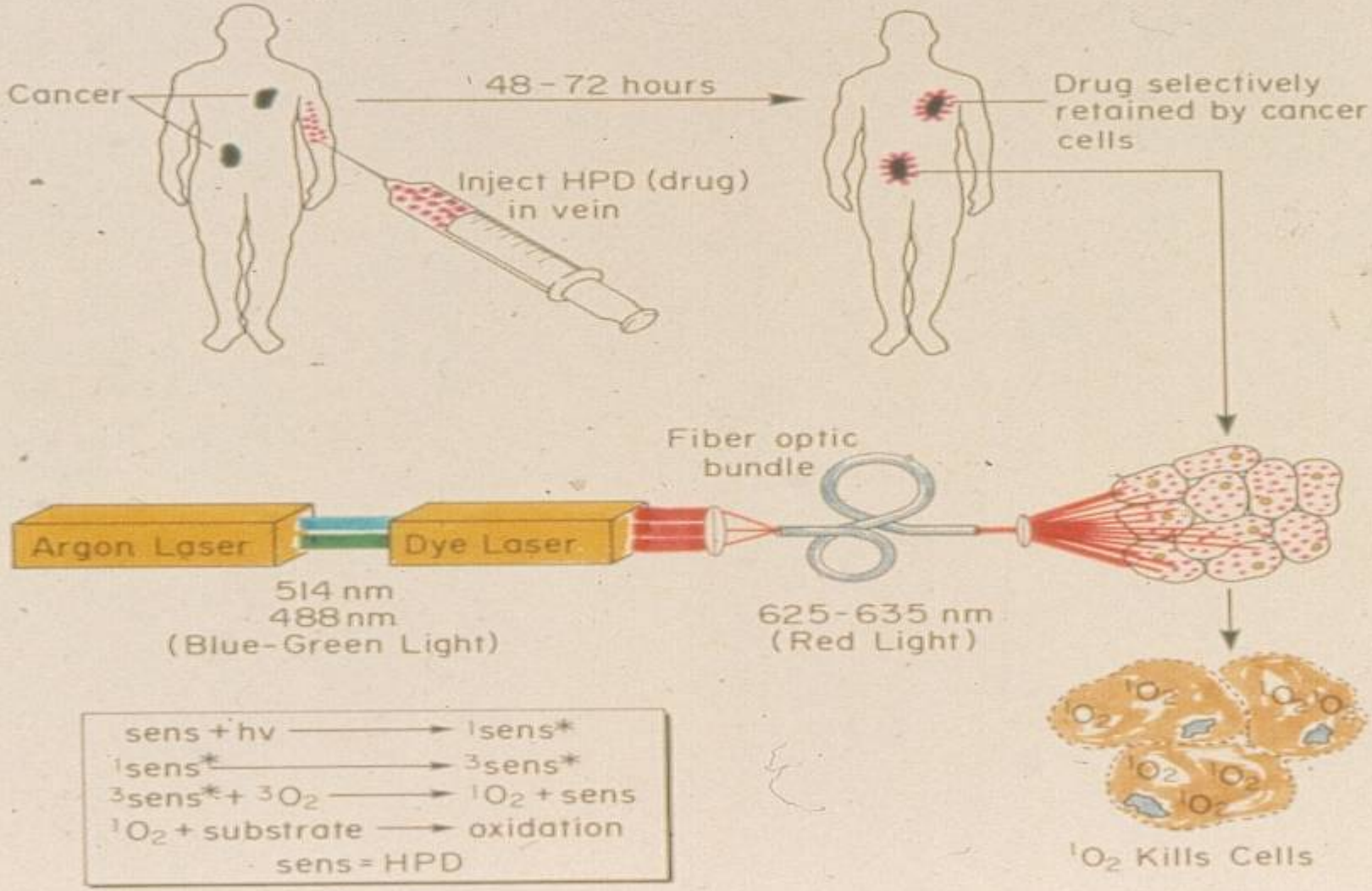
Photodynamic Principle

- Use of a photo-enhancing or photo-sensitizing chemical to aid in the diagnosis or treatment of a target cell

Photophysical Processes



PHOTORADIATION THERAPY OF CANCER
(Laser–Hematoporphyrin Derivative)

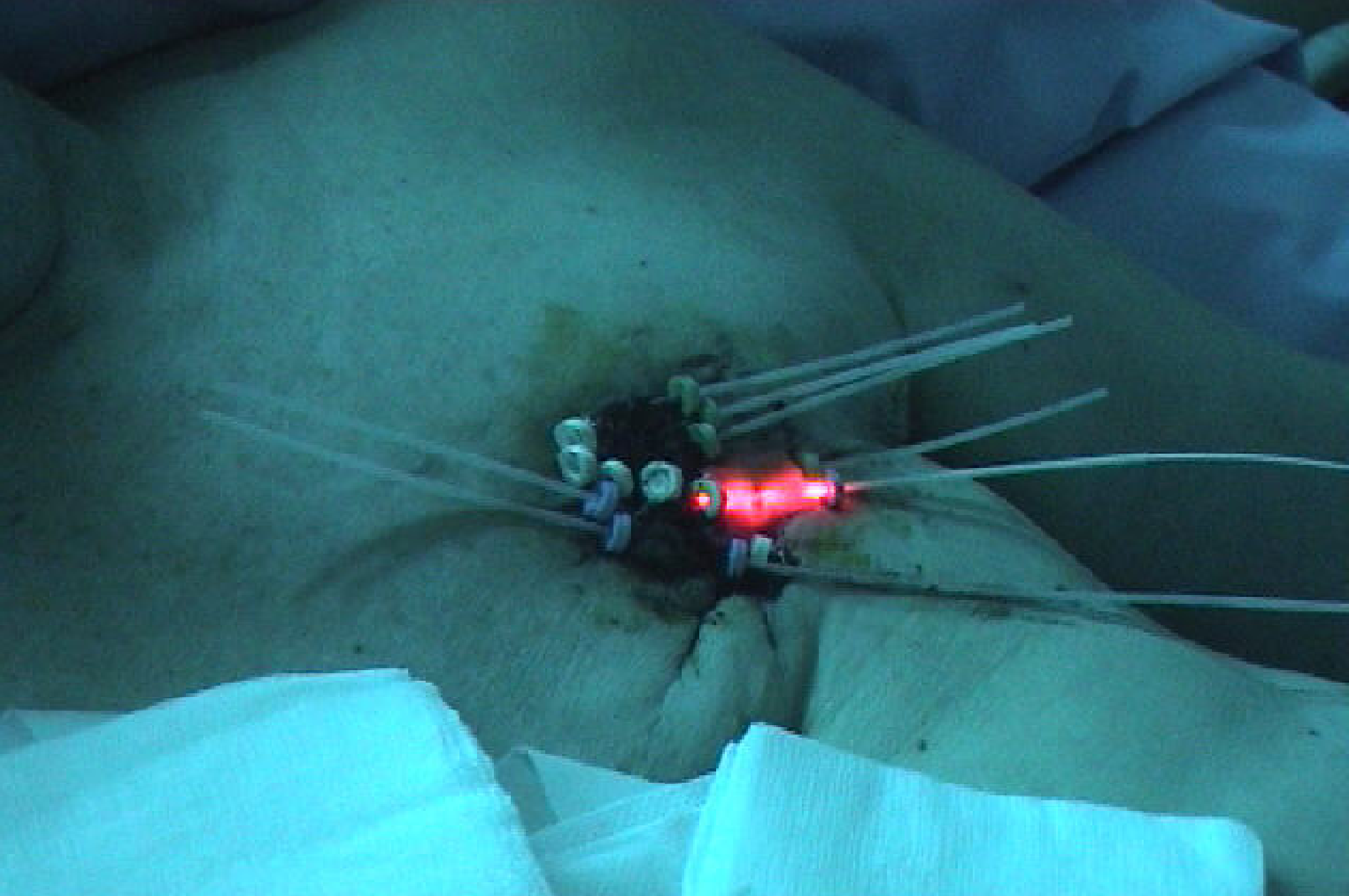


$$\text{sens} + h\nu \longrightarrow {}^1\text{sens}^*$$
$${}^1\text{sens}^* \longrightarrow {}^3\text{sens}^*$$
$${}^3\text{sens}^* + {}^3O_2 \longrightarrow {}^1O_2 + \text{sens}$$
$${}^1O_2 + \text{substrate} \longrightarrow \text{oxidation}$$

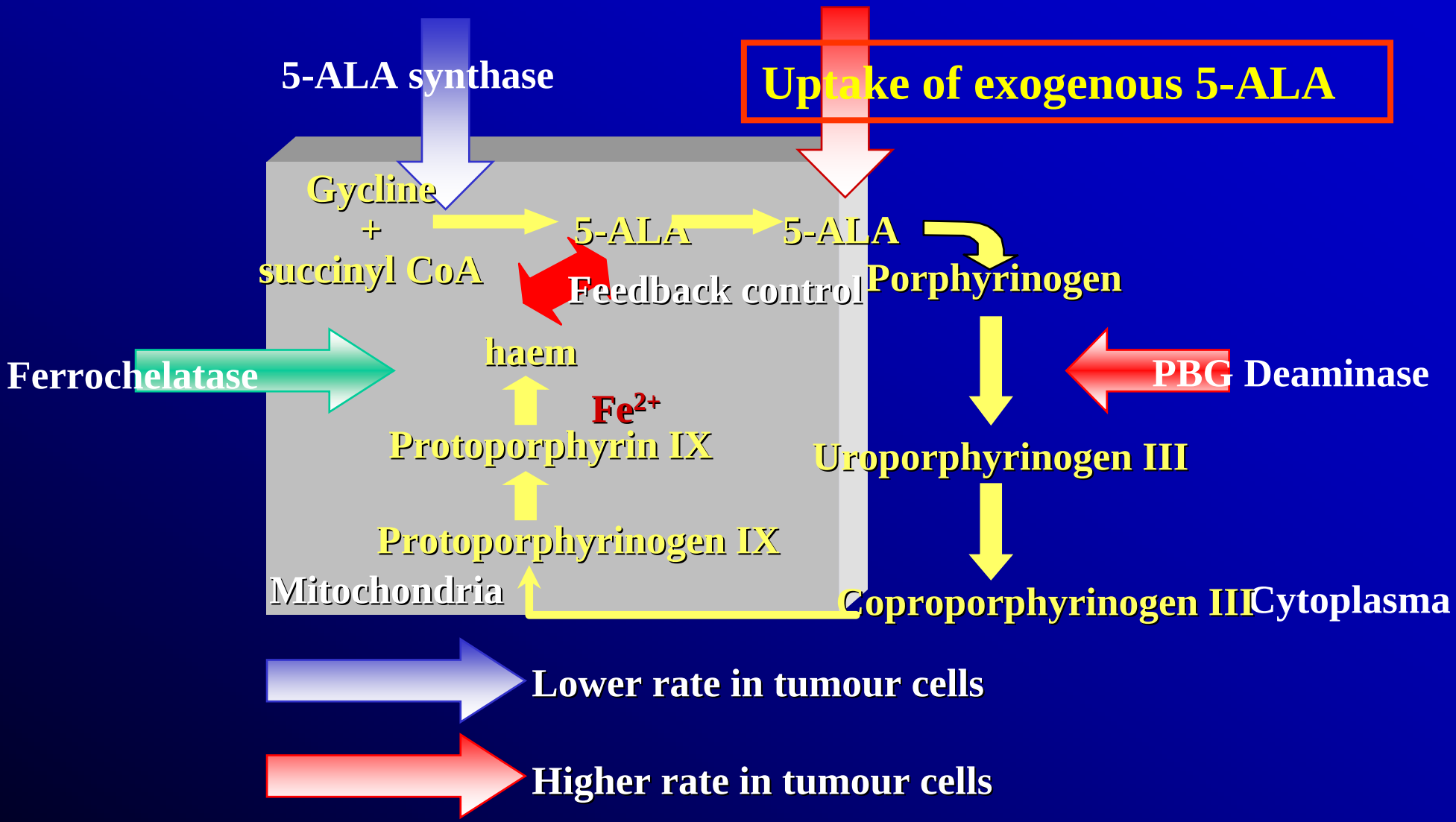
sens = HPD

Photosensitizers

- Porphyrins
  - Photofrin (PF)
  - "Aminolevulinic acid (ALA)", Protoporphyrin IX (PpIX)
- Chlorins
  - m-Tetrahydroxyphenyl chlorin (mTHPC)
  - Benzoporphyrin derivative mono-acid (BPD)
  - Tin ethyl etiopurpurin (SnET2)
- Phtalocyanines



Haem Biosynthesis



AIMS

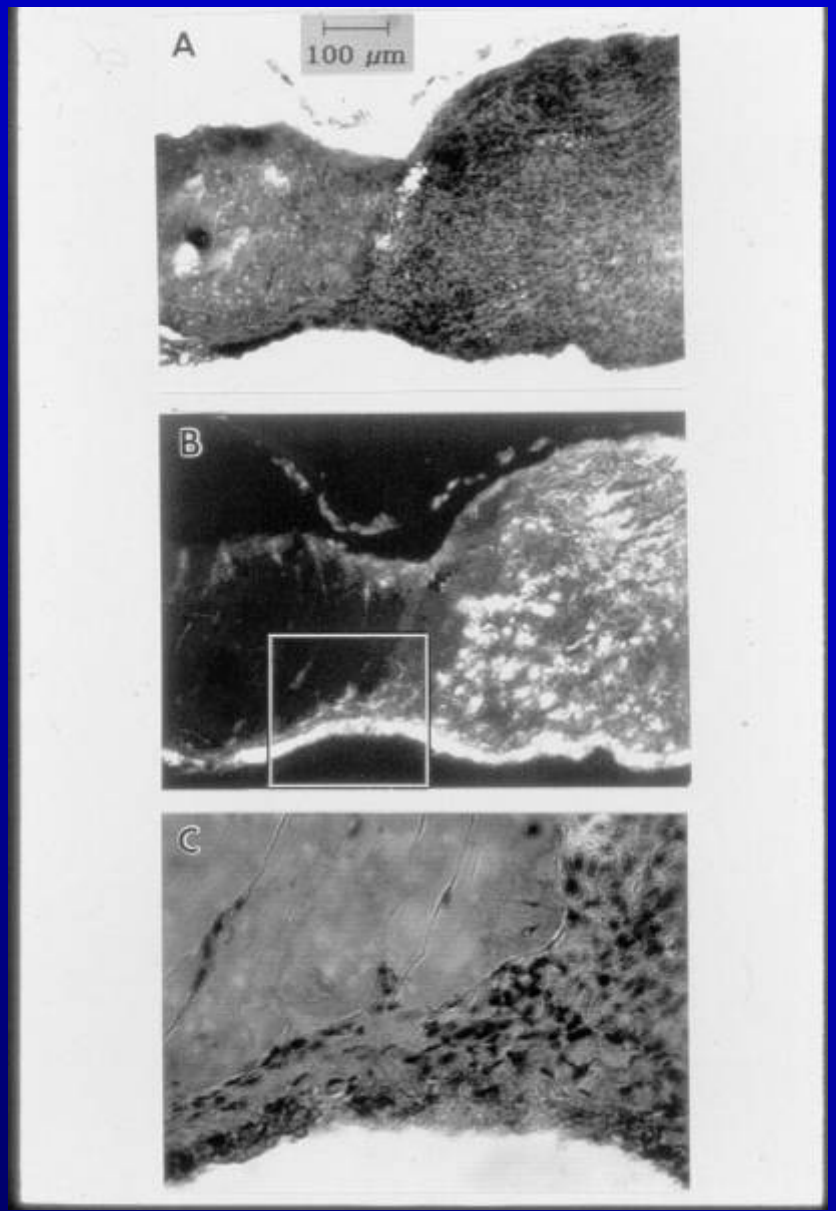
- To evaluate *photodetection* of ovarian cancer peritoneal implants in the animal model
- To evaluate *photodetection* of ovarian cancer peritoneal implants in patients
- To analyse toxicity of ALA *photodynamic therapy* (PDT) in the animal model

NuTu-19 Ovarian Cancer Animal Model

- **Completely analogous to human epithelial ovarian cancer**
- **Cell line - NuTu-19 - Spontaneous mutation**
- **Histology - Poorly differentiated ovarian adenocarcinoma with papillary features**
- **Growth pattern - I.P. serosal nodules with local tissue invasion (omentum, diaphragm, liver, peritoneum)**
- **Malignant ascites - average vol. 50-70ml in 6 weeks**
- **Survival - 10^6 cells I.P are 100% fatal, mean survival of 50 days**
- **Non-immunogenic tumor developed in an immunocompetent host**

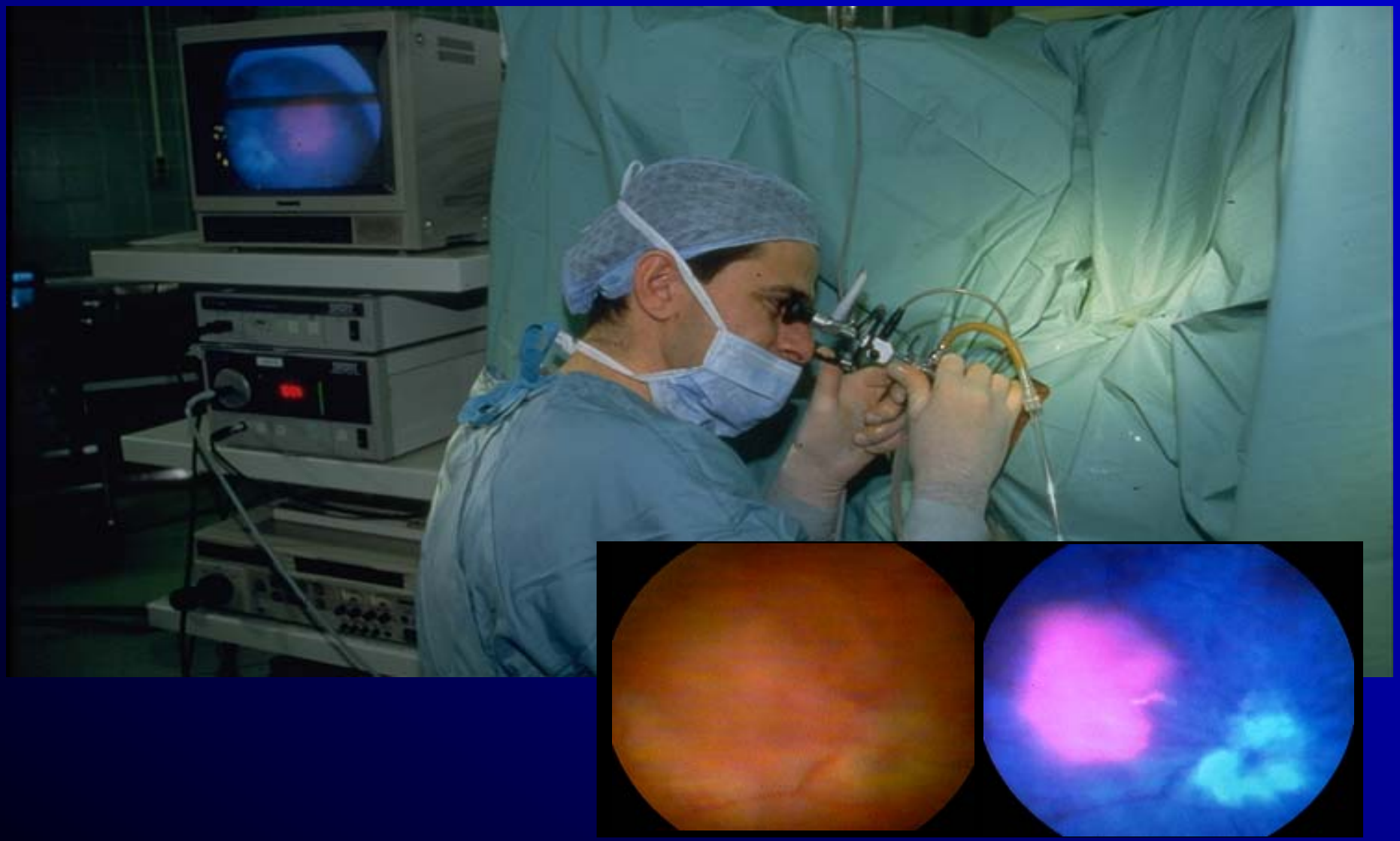
Rose et al AJOG 9/96

Light micrographs (A) and fluorescence (B) of a peritoneal nodule (size < 0.5 mm) 6 hr after ip ALA administration. Magnification (C) of the peritoneal serosa (boxed area in B) showing a thin layer of tumor matching with the fluorescence

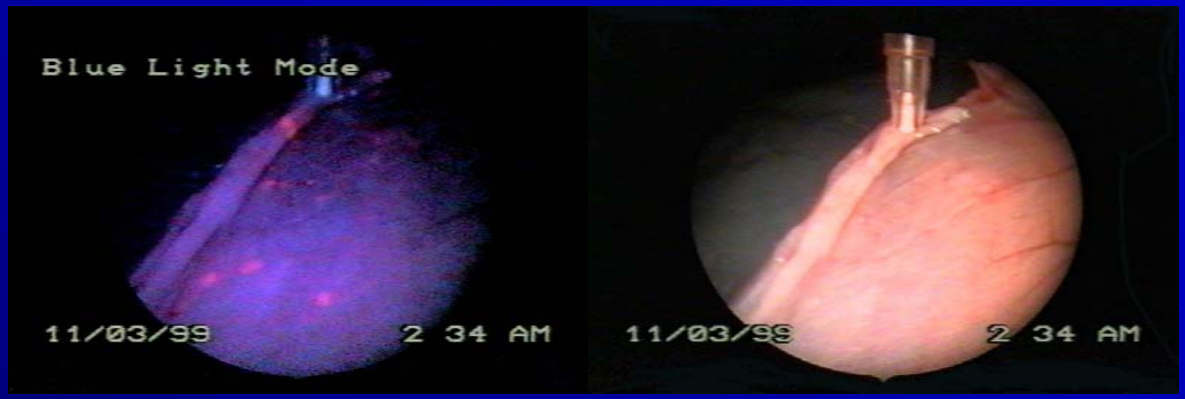


Major A. et al Gynecol Oncol 1996, 66 : 122-32.

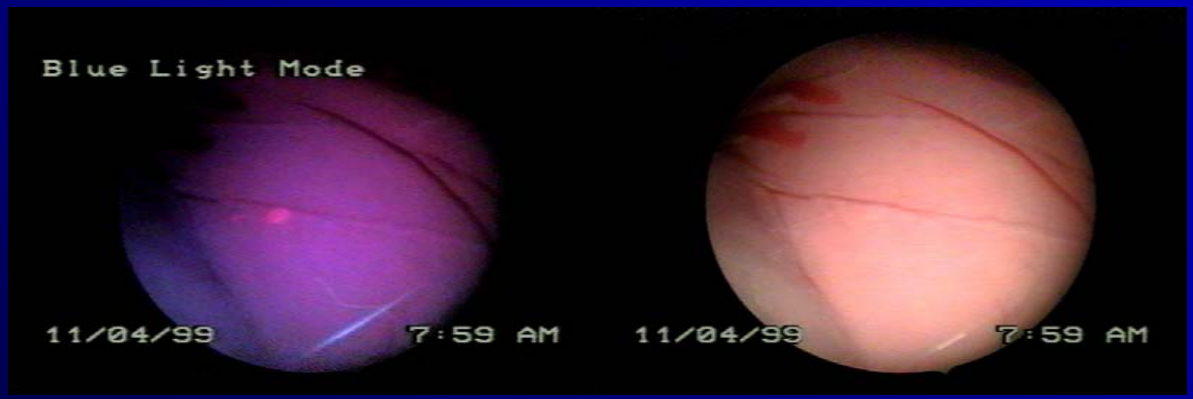
P HOTODETECTION



Epithelial ovarian cancer PDD in NuTu-19 rat model



A

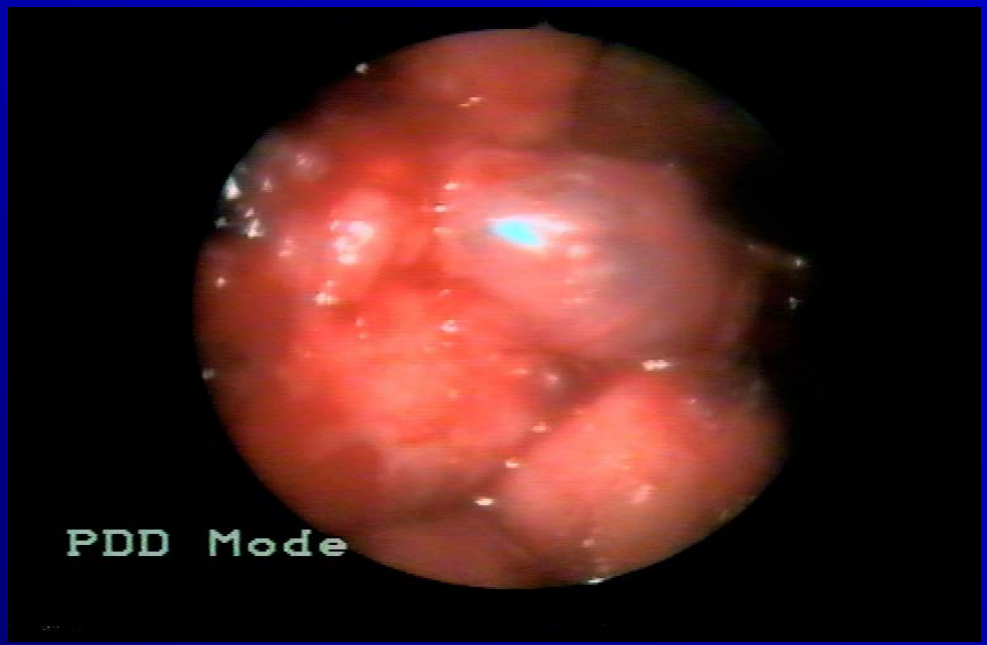


B

8mM h-ALA IV prior to photodetection 2 hours later

Ludicke F et al, Br J Cancer 2003

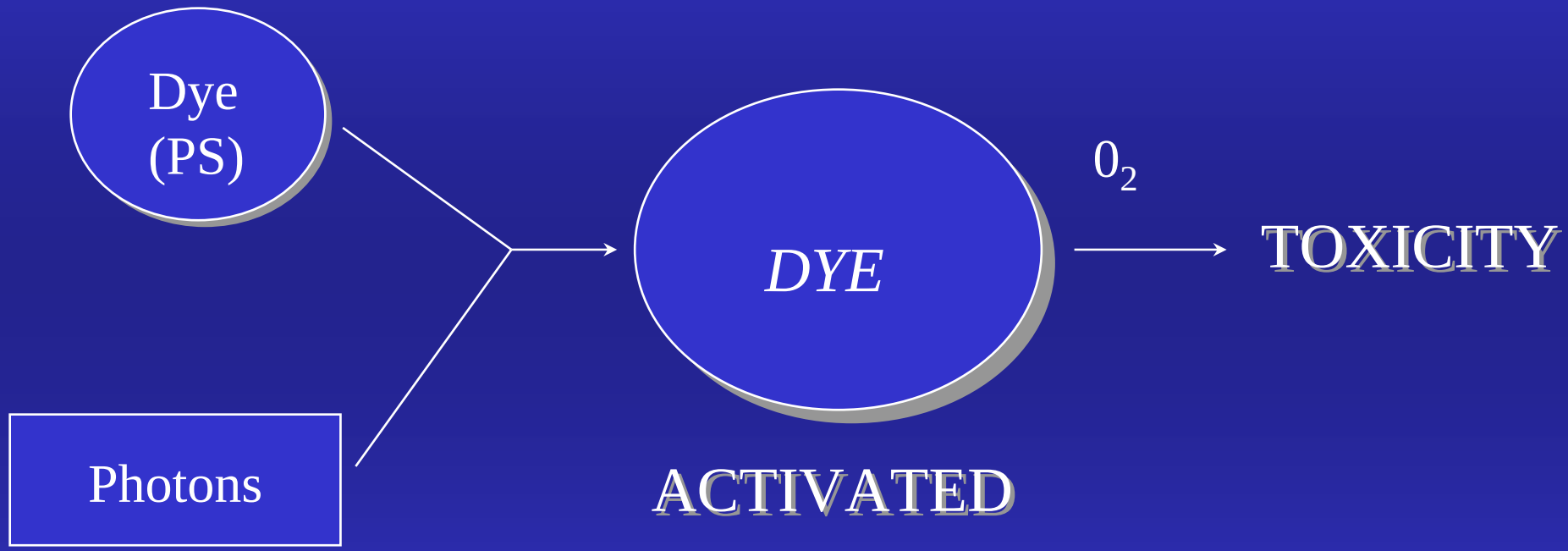
Human Epithelial Ovarian cancer PDD

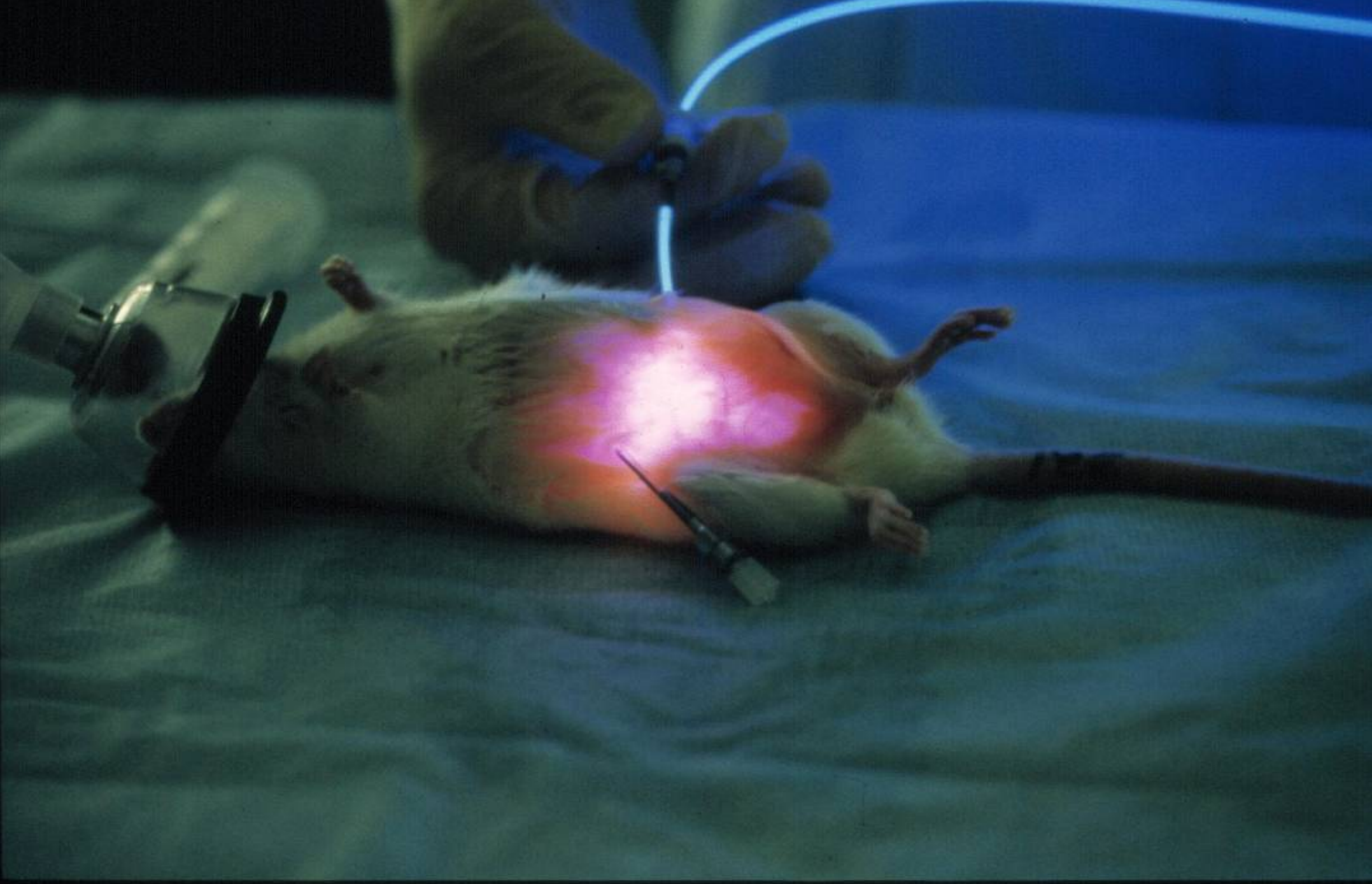


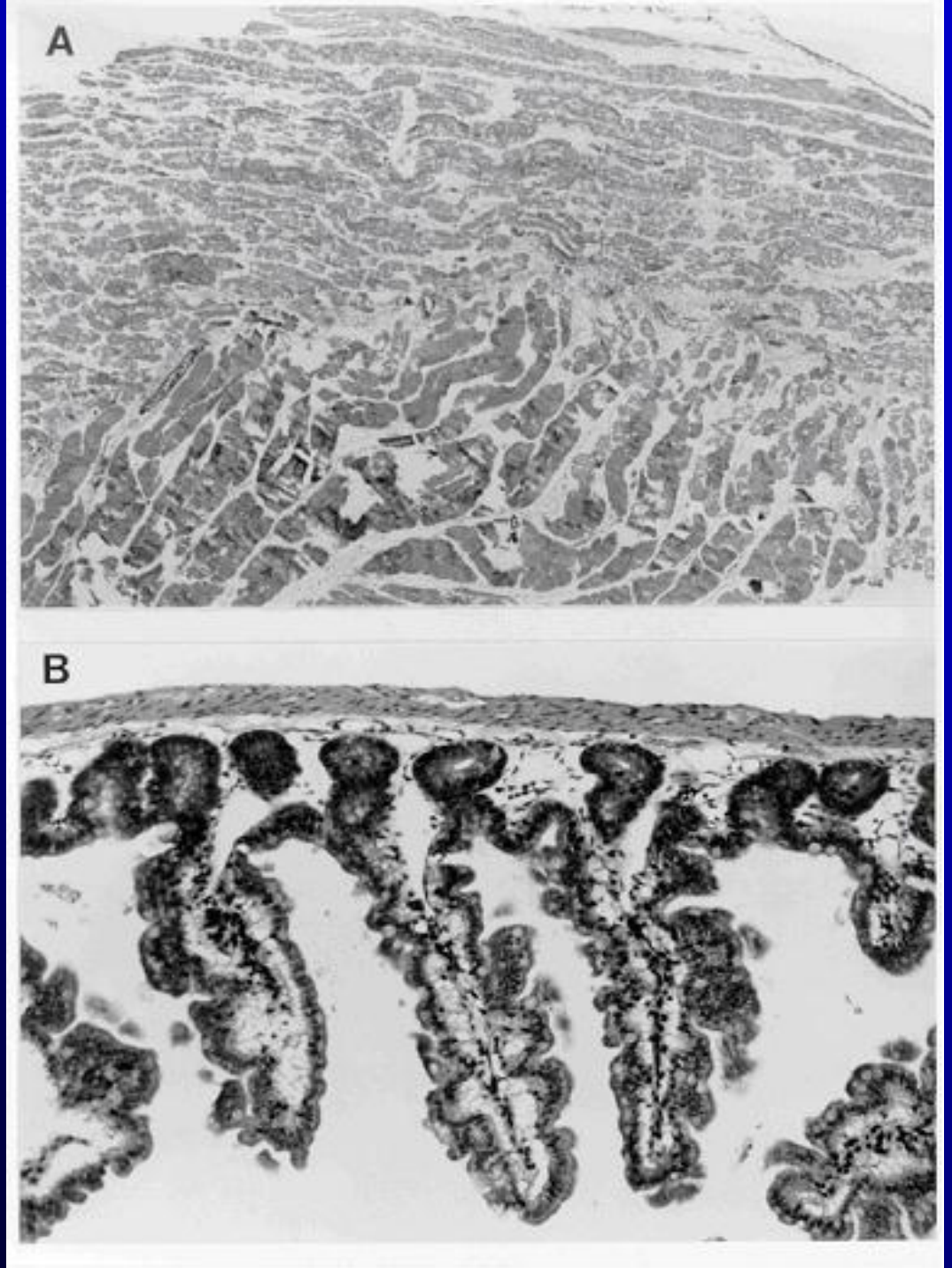
10mg/ml ALA applied topically prior to photodetection

Major AL et al, Laser Med Sci 2002

PHOTODYNAMIC THERAPY






A
B

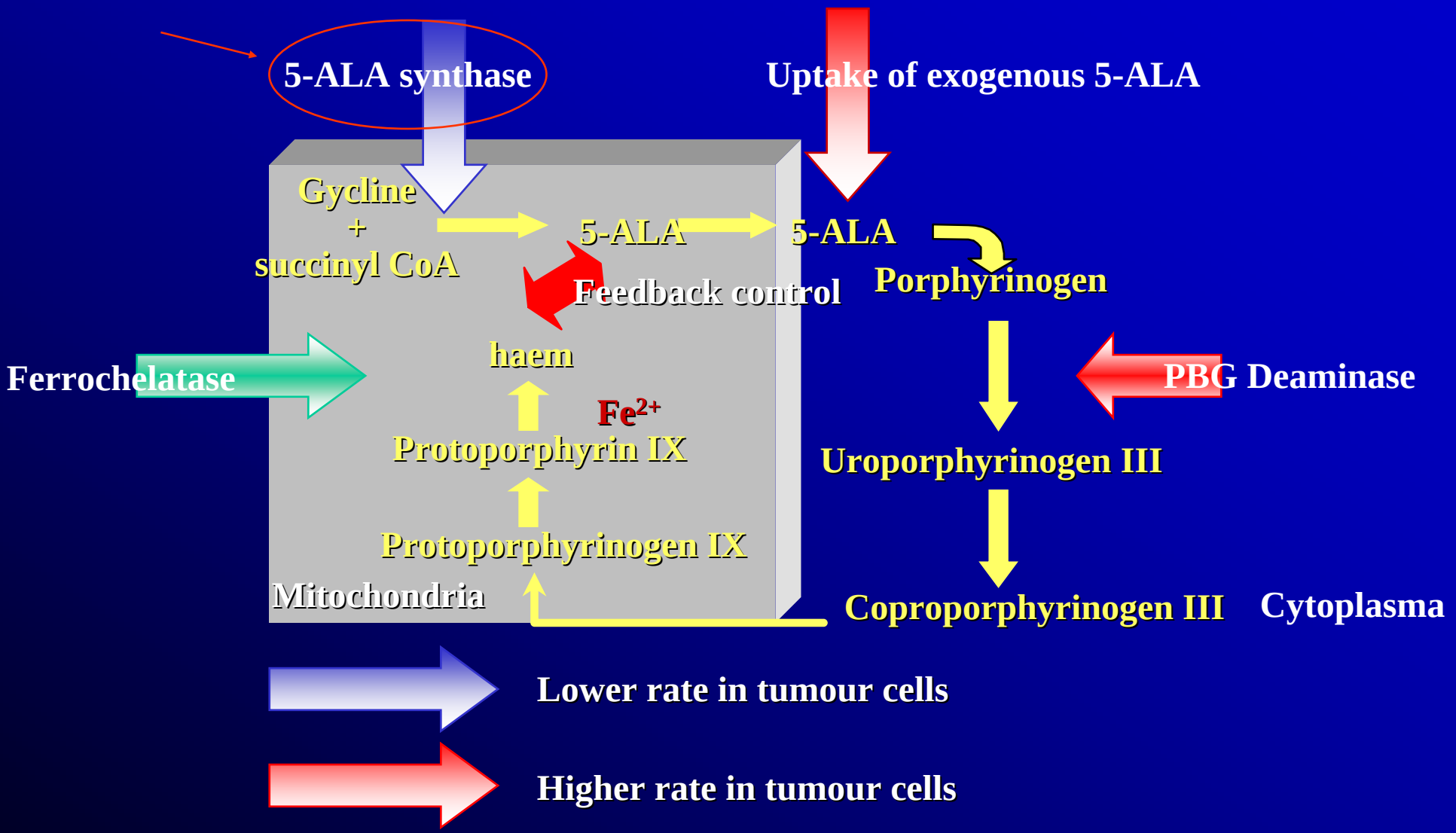
CONCLUSIONS

- Photodetection has been shown to be efficient in the animal model and feasible in patients
- Photodetection of ovarian cancer peritoneal implants, not visible by other methods, is a conceivable goal for the future

- ALA-PDT did not succeed in our animal model

Phototherapy for specific treatment of ovarian cancer

Haem Biosynthesis



Issues in gene therapy

- Vectors (plasmid, virus, nanoparticle)
- Side effects
- Tissue penetration
- Immune reaction
- Specificity

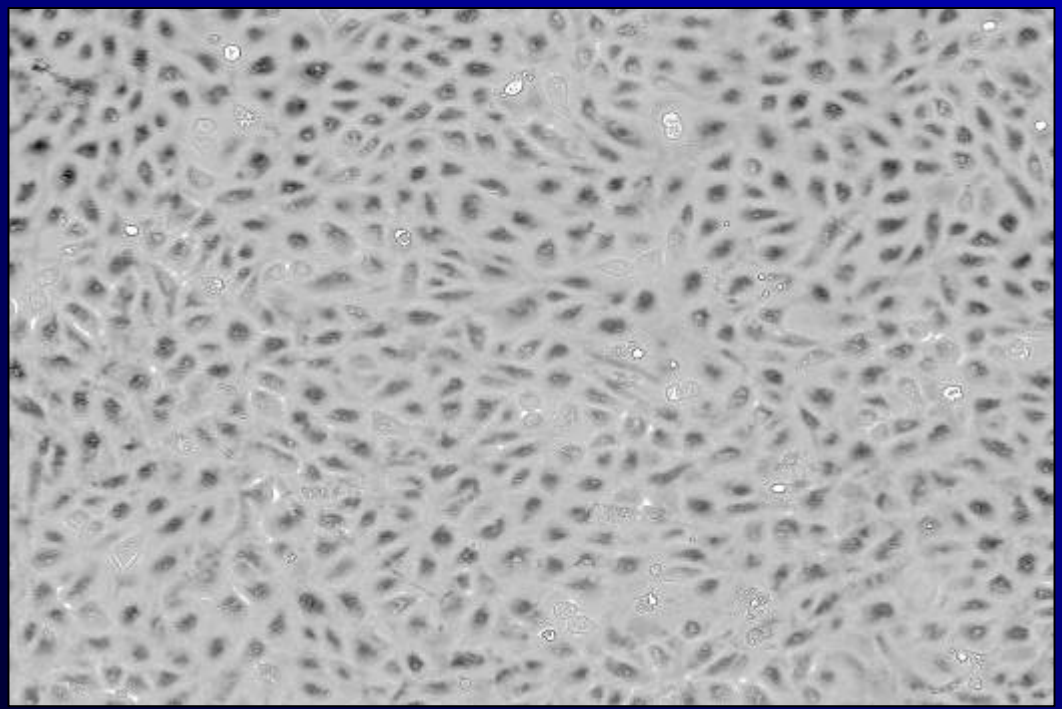
AIM

- Proof of principle of photodynamic therapy of the peritoneal cavity .

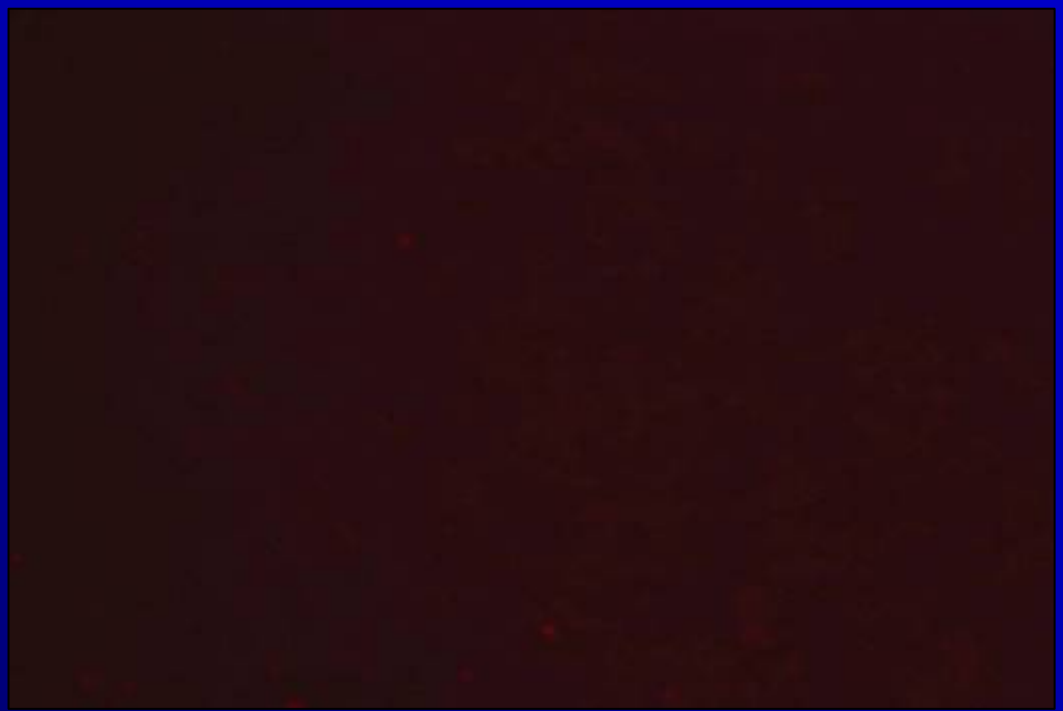
STRATEGY

- Establishment of a stable NuTu 19 ALA-S cell line with a doxycyclin ON system:

NuTu-19

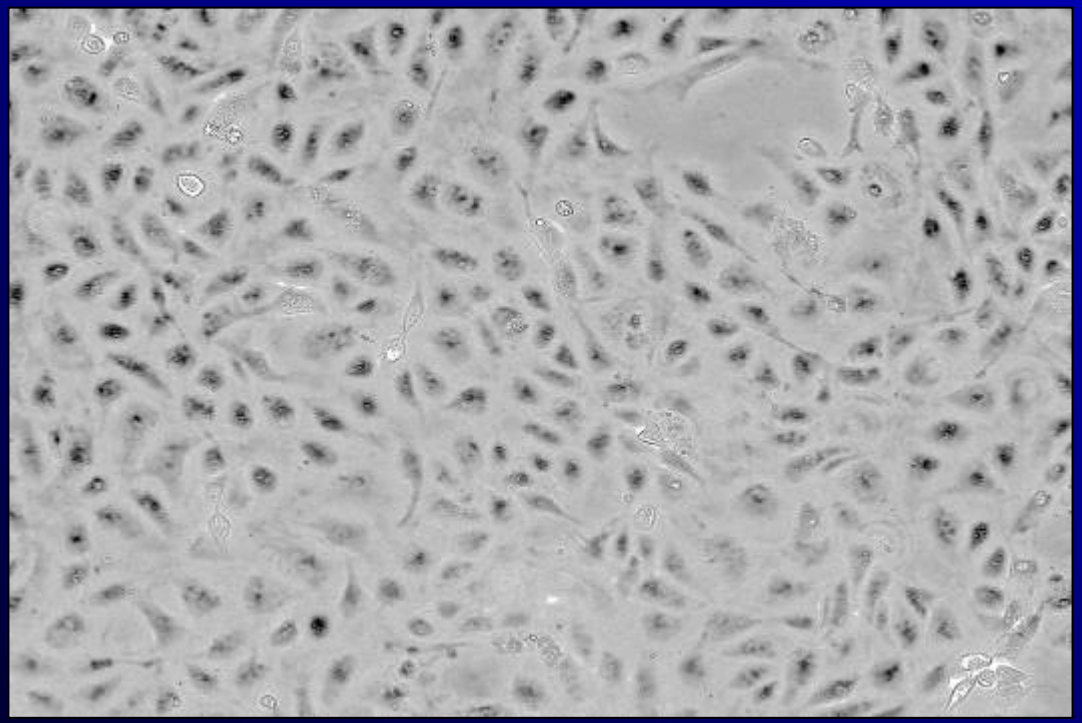


Bright field

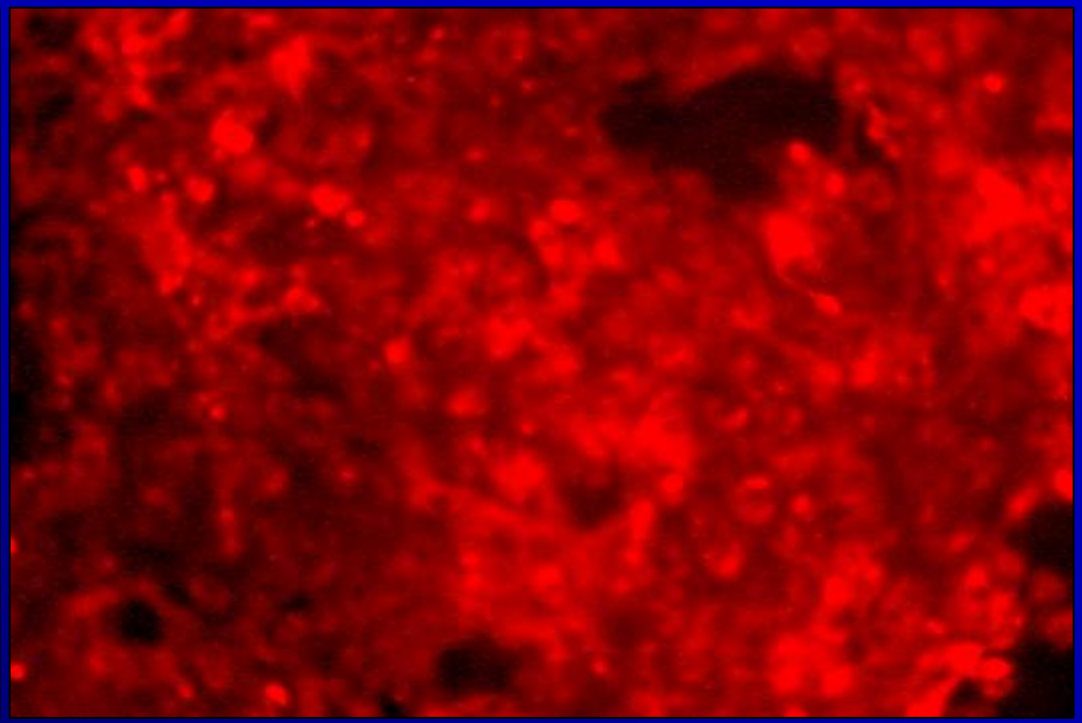


PDT filter

NuTu-19 treated with 5’ALA

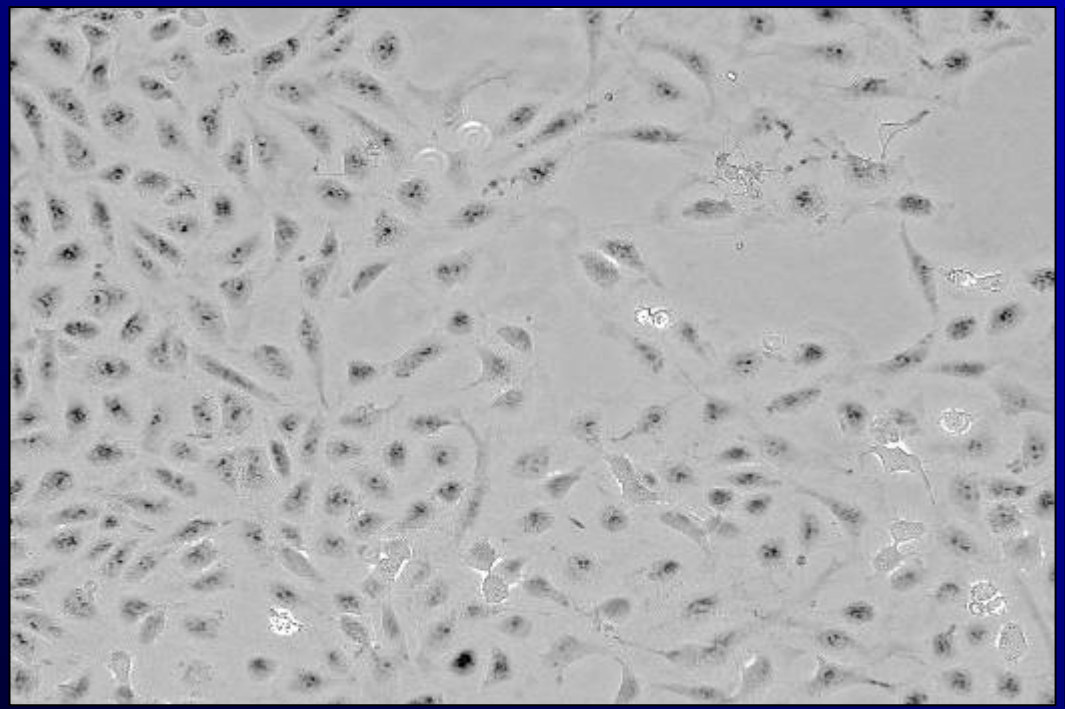


Bright field

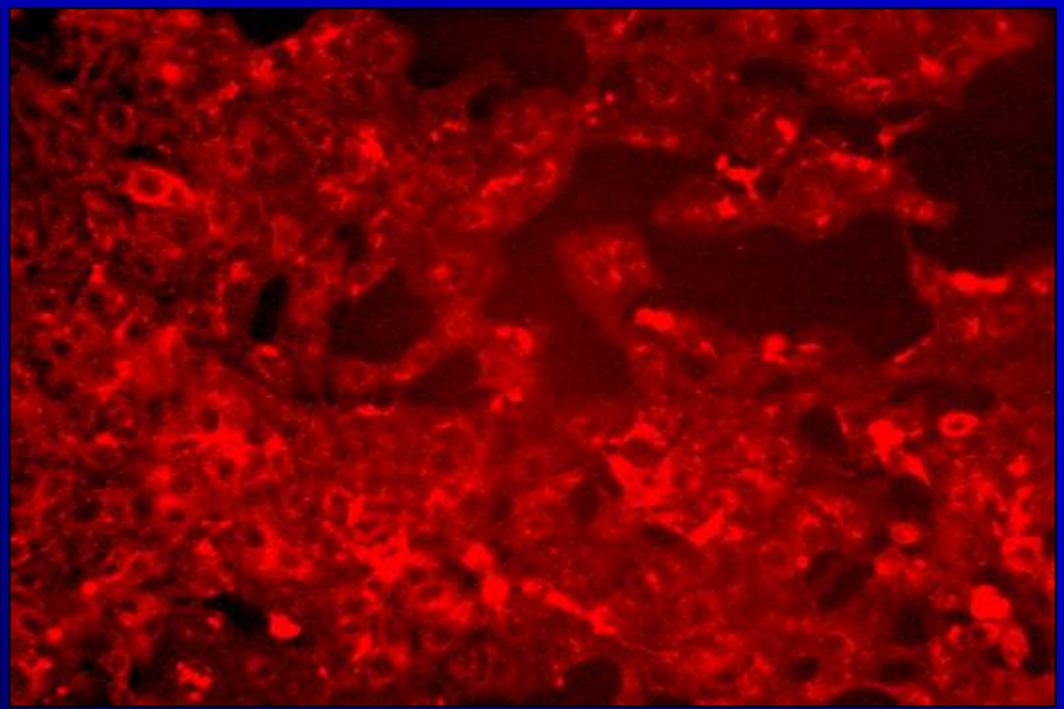


PDT filter

ALA-synthase-NuTu-19



Bright field



PDT filter

CONCLUSIONS

- Efficient Pp IX production and PDT effects after application of ALA-S virus (CMV) on normal NuTu 19 cells
- Good PpIX production in ALA-S NuTu cells after doxycyclin application
- Efficient photodynamic therapy of ALA-S NuTu 19 ovarian cancer cells after doxycyclin application

Perspective

- Establishment of the ALA-S NuTu 19 ovarian cancer model
- Proof of efficient photodynamic therapy in the animal model after doxycyclin administration, impact on survival
- Studies with different vectors and promoters
- Achieve cancer specific expression of the transgene

FONDATION POUR RECHERCHES MÉDICALES

Hubert van den Bergh

Georges Wagnières

Norbert Lange
Jean-Pierre Ballini

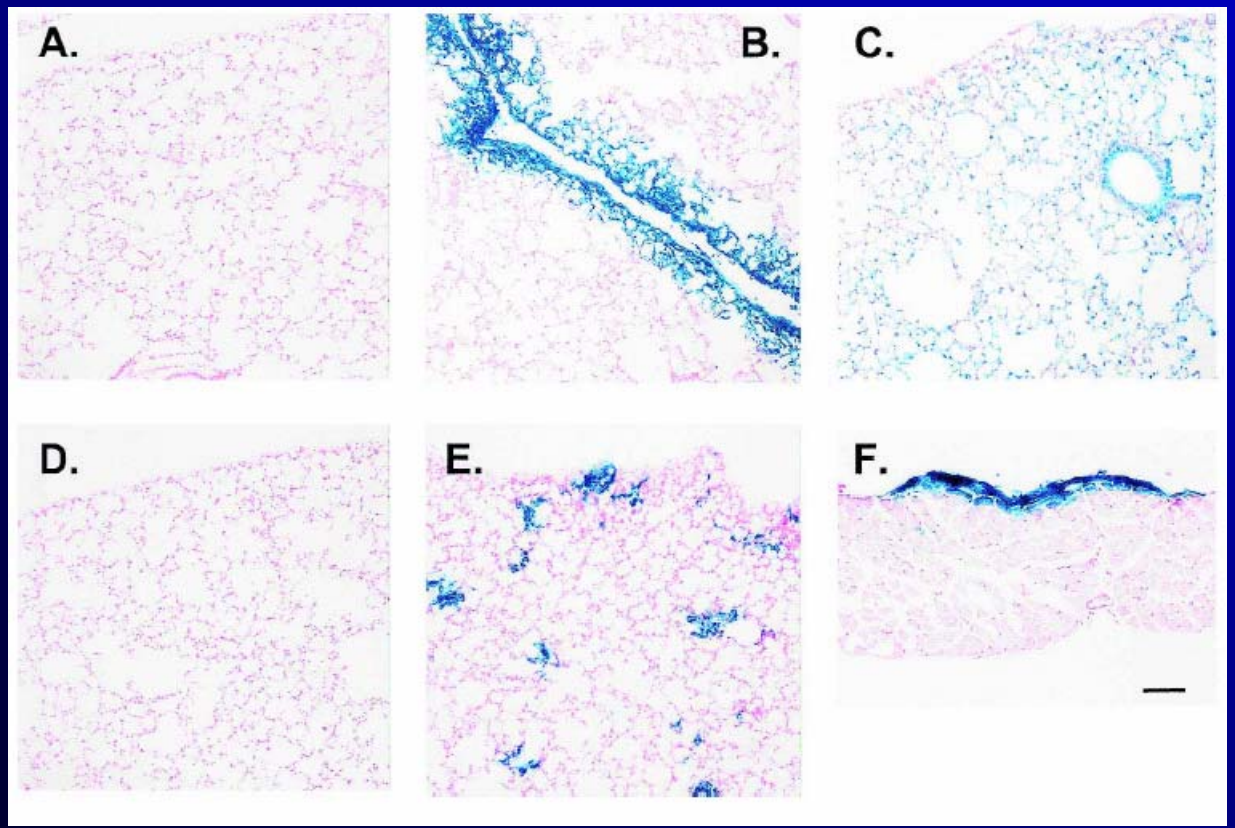
Werner Schlegel

Attila L. Major
Pierre-Marie Tebeu
Bianca Mottironi

Magali Zeisser
Anis Fekih

Igor Bondarev

COLOR PLATE 1. Transfer of genes to pleural mesothelial cells after intrapleural administration of an adenovirus gene transfer vector encoding an intracellular protein. The lungs and diaphragm were harvested 3 days after right intrapleural or, for comparison, intratracheal and intravenous administration of 109 PFU of an Ad vector encoding *b*-galactosidase (Ad*b*gal) to BALB/c mice. Control animals received 100 *m*l of phosphate-buffered saline by the intrapleural route. All sections were stained with the X-Gal reagent and counterstained with nuclear fast red; a blue color indicates cells expressing *b*-galactosidase activity. (**A**–**E**) Lung tissue. (**A**) Right intrapleural administration of PBS as control. (**B**) Right intrapleural administration of Ad*b*gal. (**C**) Intratracheal administration of Ad*b*gal. (**D**) Intravenous administration of Ad*b*gal. (**E**) Intravenous administration of 3 3 105 CT26.CL25 tumor cells expressing *b*-Gal as control to demonstrate *b*-Gal activity within the vascular compartment. (**F**) Right diaphragm from the same animal as in (**B**). Magnification bar: 50 *m*m. Mae et al, Hum Gene Ther 2002.



A photosensitising adenovirus for photodynamic therapy

J Gagnebin1,2, M Brunori1, M Otter1, L Juillerat-Jeanneret3, P Monnier2 and R Iggo1

1*Swiss Institute for Experimental Cancer Research (ISREC), Epalinges;* 2*Otorhinolaryngology and* 3*Pathology Service, University Hospital (CHUV), Lausanne, Switzerland*

Gene Therapy (1999) 6, 1742–1750