2. History of Photomedicine and biomedical optics: The antique

Man has recognized the relation between light and health for about 3000 years

Ancient medical litterature: treatment of de-pigmented skin areas (vitiligo) by application of plant seeds (psoralea) followed by the exposure to sunlight

1500 BCE
India

500-200 BCE
Buddhism litterature

1000 CE
China

1500 BCE
Egypt
(Ebers Papyrus)

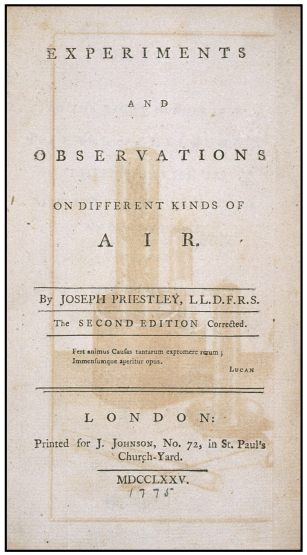
BCE CE

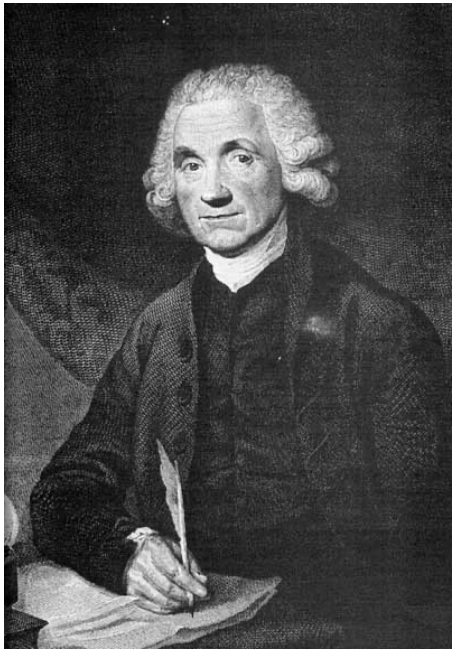
Vitiligo

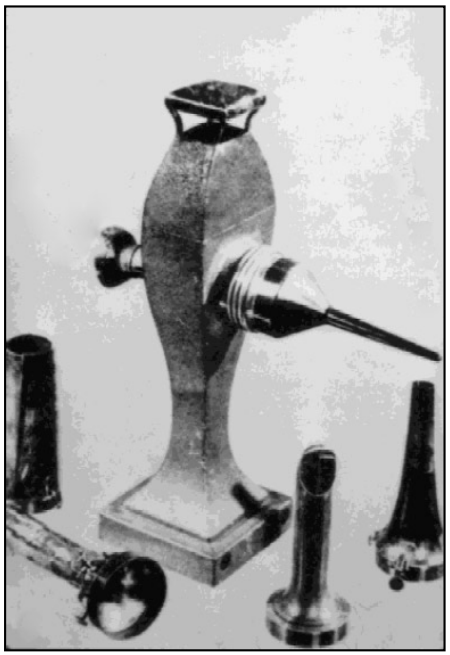

VIENS SUR LE BLOG
20MINUTES-FRIDAY.CH
HORS DU COMMUN Le milieu de la mode célèbre le top canadien, qui s'est fait connaître grâce à sa beauté particulière. Sa maladie de la peau, le vitiligo, est à la fois son fardeau et sa chance.

Later and turn of the 18th century

1775
J. Priestley discovers oxygen


EXPERIMENTS
AND
OBSERVATIONS
ON DIFFERENT KINDS OF
AIR.
By JOSEPH PRIESTLEY, LL.D.F.R.S.
The SECOND EDITION Corrected.
Lucan
LONDON:
Printed for J. Johnson, No. 72, in St. Paul's Church-Yard.
MDCCLXXV.





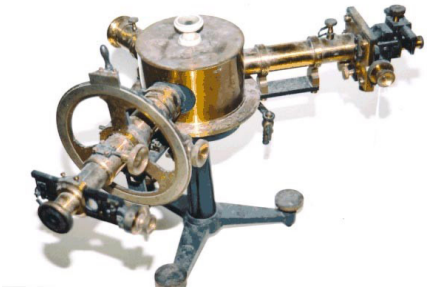
1806

Ph. Bozzini invents a device to "make visible the inner cavities of the body"
=> first endoscope

Early and middle of the 19th century

1841
Johann Joseph Scherer removes iron from blood with concentrated sulfuric acid => Hematoporphyrin

1842 : Louis Pasteur and Paul Bert report phototoxicity in cells and germs
Becquerel and Draper: spectral extent of UV radiation



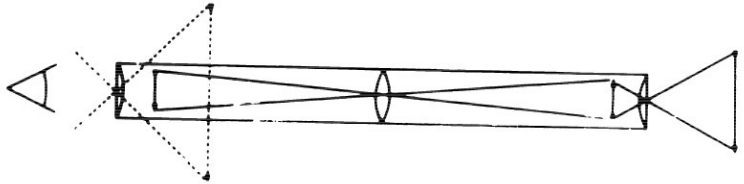
1852 : Georges G. Stokes introduces the term "Fluorescence", interprets the light-emitting phenomenon, and fromulates the "Stokes law"

1859 : Kirchoff and Bunsen invent the spectroscope

Late 19th century (2)

1876/77
Jablochkow and Brush invent the first useful carbon electrode arc lamp

1877 : Nitze develops the first cystoscope based on a telescopic lens system



1879 : Th. A. Edison invents the incandescent lamp

The Beginning of modern Photomedicine

1893-1903
N.R. Finsen develops the phototherapy

(Finsen lamp)

1893
Treatment of smallpox (variole) with red light

1895
Treatment of lupus vulgaris (skin tuberculosis) with artificial UV light from the "Finsen lamp"

(Phototherapy for tubeculosis, Finsen Institute, ~1900)

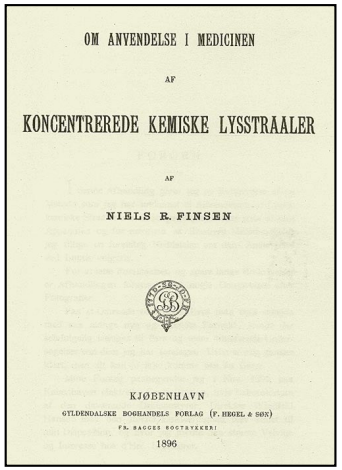
Niels Rysberg Finsen

(*15.12.1860, +24.9.1904)

"Pioneer of Phototherapy"

1893 Finsen discovered that UV light aggraved smallpox (la variole), but that red light improved healing

1895 treatment of lupus vulgaris (dermal tuberculosis) first with sunlight and then with artificial UV light (Finsen light)


OM ANVENDELSE I MEDICINEN

AF

KONCENTRERede KEMISKE LYSSTRAALER

AF

NIELS R. FINSEN

KJØBENHAVN

GYLDENDALSKE BOGHANDELS FORLAG (F. HEGEL & SØN)

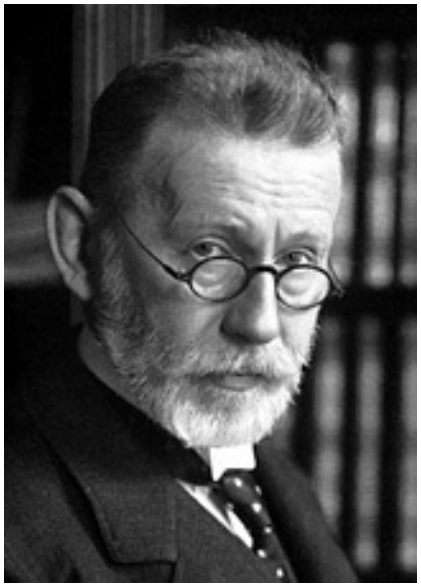
1896

1903 Nobel Prize *"in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science"*

Paul Ehrlich (*14.3.1854, + 20.8.1915)

Paul Ehrlich "Father" of the chemotherapy

1897 Idea of cell-targeting therapy:



*"If we picture an organism as infected by a certain species of bacterium, it will…be easy to effect a cure if substance have been discovered which have a specific affinity for these bacteria and act…on these alone…while they possess no affinity for the normal constituents of the body…such substances would then be…**magic bullets**"*

1908 Nobel Prize in Physiology and Medicine for his scientific work in immunology

Discovery of Photosensitization

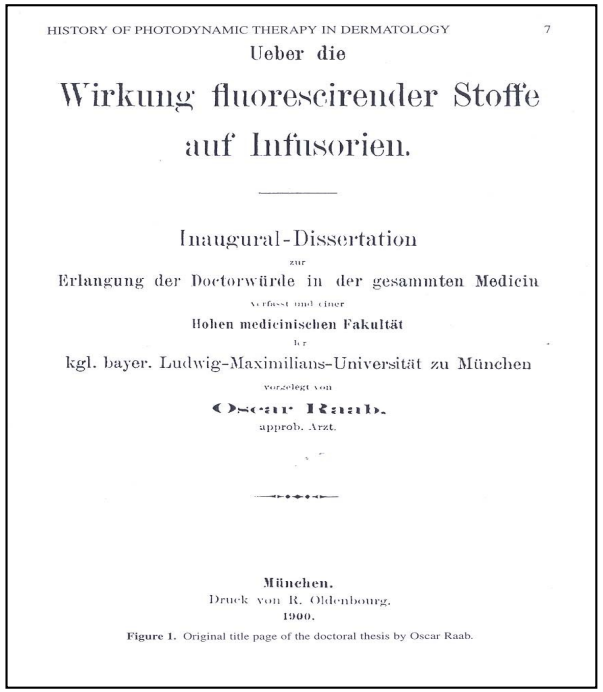
1900

J. Prime (french neurologist) used eosin orally in the treatment of epilepsy and showed that this induced dermatitis in sun-exposed areas of skin

[Prime J. (1900)"Les accidents toxiques par l'eosinate de sodium." Jouve and Boyer, Paris]

1900

Oscar Raab discovers the biological photosensitisation using chemical substance followed by exposure to light (acridine red on bacteria)



HISTORY OF PHOTODYNAMIC THERAPY IN DERMATOLOGY 7

Ueber die

Wirkung fluorescirender Stoffe auf Infusorien.

Inaugural-Dissertation

zur

Erlangung der Doctorwürde in der gesammten Medicin

verfasst und einer

Hohen medicinischen Fakultät

der

kgl. bayer. Ludwig-Maximilians-Universität zu München

vorgelegt von

Oscar Raab,

approb. Arzt.

München.

Druck von R. Oldenbourg.

1900.

Figure 1. Original title page of the doctoral thesis by Oscar Raab.

Discovery of Photosensitation, cont.

1901 Cooper-Hewitt produce the first commercially available mercury vapor lamp

1903 H. von Tappeiner and A. Jesionek treat skin cancers with eosin dye followed by exposure of the lesions to sunlight

1904 H. von Tappeiner introduces the term "photodynamic action" and conclude that the presence of oxgen is a necessary requirement to obtain photosensitization

[H. von Tappeiner, A. Jodlbauer, "Über Wirkung der photodynamischen (fluoreszierenden) Stoffe auf Protozoen und Enzyme", Dtsch Arch Klin Med 80, 427 (1904)]

Early 20th century

1906

Coolidge invents the Tungsten lamp

1911/1913

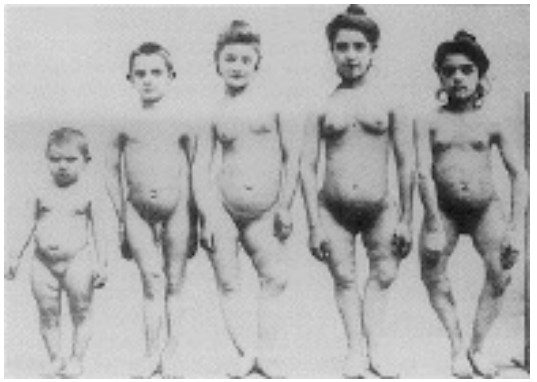
Otto Heimstaedt and Heinrich Lehmann develop the first fluorescence microscope

Rickets (Rachitisme)

1919 K. Huldschinsky first cures children of rickets using artificially-produced UV light following the observations of T. Palm (1848–1928)

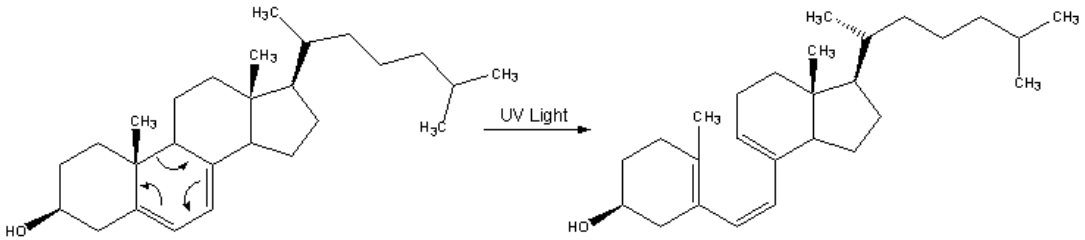
Leg deformation due to rickets

Rickets (osteomalacia): a frequent childhood disease in developing countries
Origin: vitamin D (calcium) deficiency
Symptoms: bone pain and tenderness; skeletal deformity
(bowed legs, cranial, spinal, and pelvic deformaties)



A family with rickets, France ~1900

Vitamin D can be synthetised in human skin under UV light exposure by photolyzation



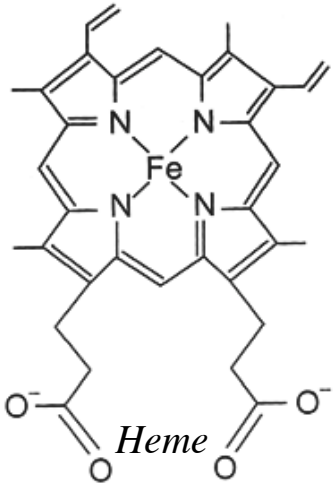
Photolyzation of 7-dehydrocholesterol to pre-vitamin D3

Hans Fischer (*27.7.1881, +31.5.1945)

German Chemist and MD

1925 studies the structure and constituents of porphyrins

1926 first synthesis of porphyrins



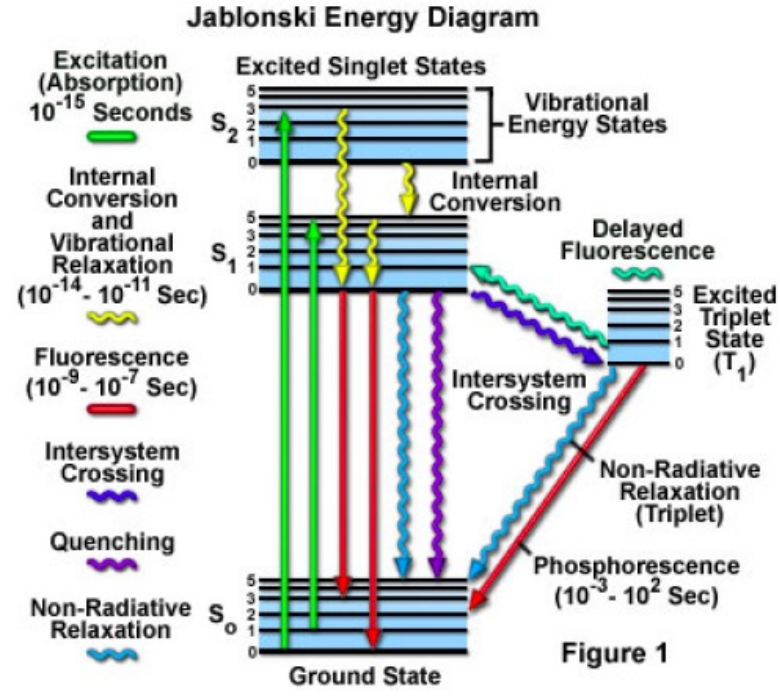
1928 first synthesis of heamin

1930 Nobel Prize "for his researches into the constitution of haemin and chlorophyll and especially for his synthesis of haemin".

Fondamental and Medtech progresses

1935

Alexander Jablonski establishes his Jablonski diagram



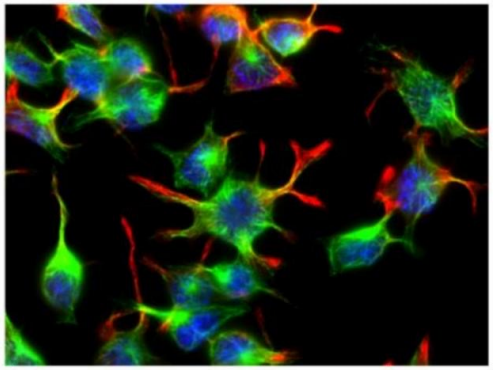
1936

Schindler and Wolf introduce a semi-flexible gastroscope

Middle of the 20th century

1950

A. Hewett Coons and Melvin Kaplan develop the immuno-fluorescence technique in biology



Immunofluorescence:
Rat basophilic leukemia cells

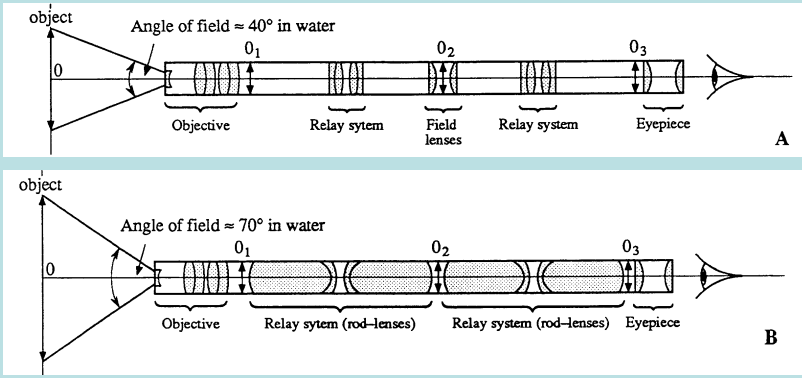
1952

Forestier uses a quartz rod inserted into a steel tube placed inside a rigid endoscope to guide light to the endoscopic site => external light source)

Progresses in endoscopic optics

1954

H.H. Hopkins develop an improved optical system based on glass rods interspaced by air lenses, instead of standard lenses (Hopkins optics)



1954

A. van Heel and H.H. Hopkins: imaging fiber bundles

1954

A. van Heel invents the cladding of fiber-optical cables

Endoscopy and Neonatal Jaundice

1957

Neonatal jaundice: benefit of blue light exposure on neonatal jaundice is discovered by accident

1959

Brian O'Brien and Narinder Kapany: fibroscope

Neonatal Jaundice (Ictère "jaunisse")

Common condition in newborn (about 50%)

Origin:

1. breakdown of fetal hemoglobin (replaced with adult hemoglobin)
2. immature hepatic metabolic pathways
   ⇒ accumulation of unconjugated billirubin
   ⇒ neurotoxicity

Symptoms:
yellow colour of skin and sclera

Phototherapy:
photoisomerization and photooxidation of unconjugated bilirubin to its watersoluble, i.e. excretable, conjugated form

The first lasers

1960

Theodore H. Maiman: first working ruby laser (694 nm, pulsed operation)

1961

A. Javan: first HeNe laser

Tissue imaging and lasers in medicine

1961
Novotny and Alvis: retina angiography with fluorescein

1961
L. Goldman, MD "Father of laser surgery" recognises the potential for lasers in medical applications
"If you don't need a laser – don't use it."

1962
first black and white television camera for endoscopy

Major "Medtech" breakthrough

1965

first surgical CO_2 laser

1968

S. Ikeda: flexible bronchoscope

1969

W. Boyle and G. Smith invent the CCD (Camera)

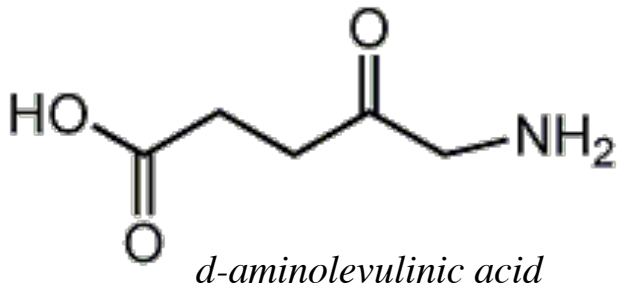
"Medtech" and Pharma progresses

1985

First videoendoscopy system with CCD detectors at the distal tip are investigated for clinical use

1987

Malik and Lugaci use d-aminolevulinic acid (ALA) as photosensitising and tumor photodetection agent.



d-aminolevulinic acid

"Medtech" and Pharma progresses

1990

633 nm diode laser commercialised

1990/92

Kennedy: first clinical use of topical aminolevulinic acid (ALA) for fluorescence detection and Photodynamic Therapy (PDT)

"Medtech" progress

1990

First Optical Coherent Tomography (OCT) image

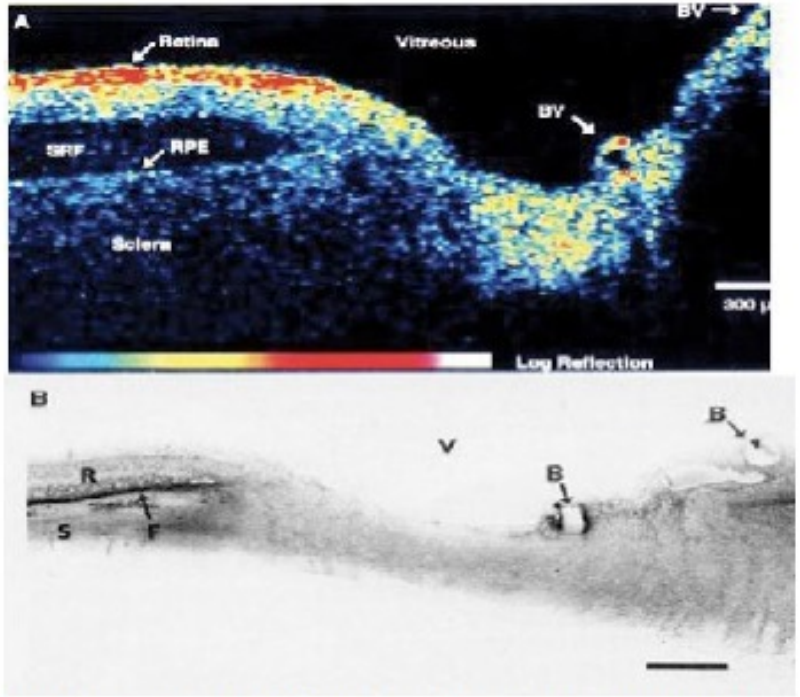


Figure 1. The first OCT image of the retina *ex vivo* and corresponding histology. Note the detachment of the retina, common in post-mortem eyes.

Actinic Keratosis and basocellular carcinoma treated by PDT

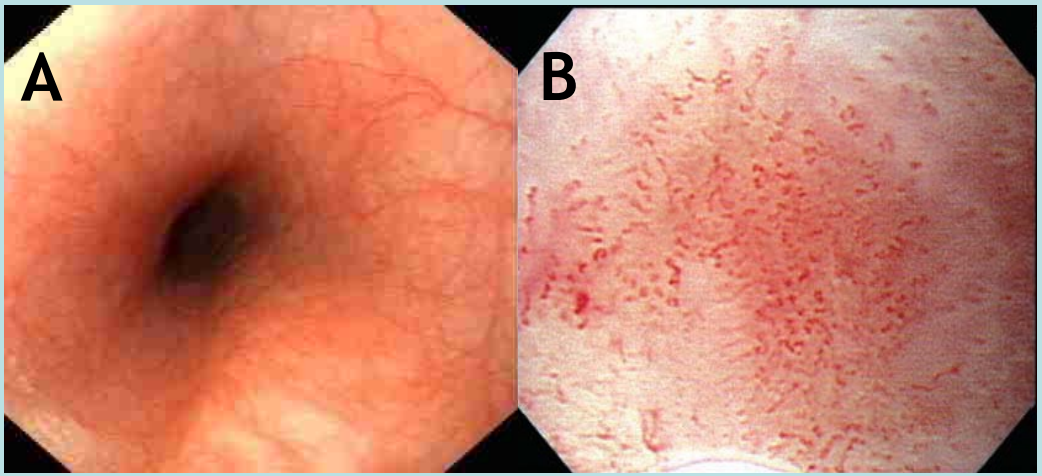
2000
Levulan®
(ALA) topically

2001
Metvix®
(methyl-ester ALA)
topically

Other present/future fields include: High magnification endoscopy (gastroenterology)

- Observation of the intrapapillary loops (IPCL)
  - dilatation
  - weaving
  - changes in caliber
  - differences in shape

XEC300 & XE120, Olympus Corp., Tokyo, Japan



A) Normal view of the esophagus.
B) Magnification view of carcinoma in situ (m1; 100X).

Kumagai et al. (2006) Digestive Endoscopy 18, 165–172

Other present/future fields include: Narrow band imaging (NBI)

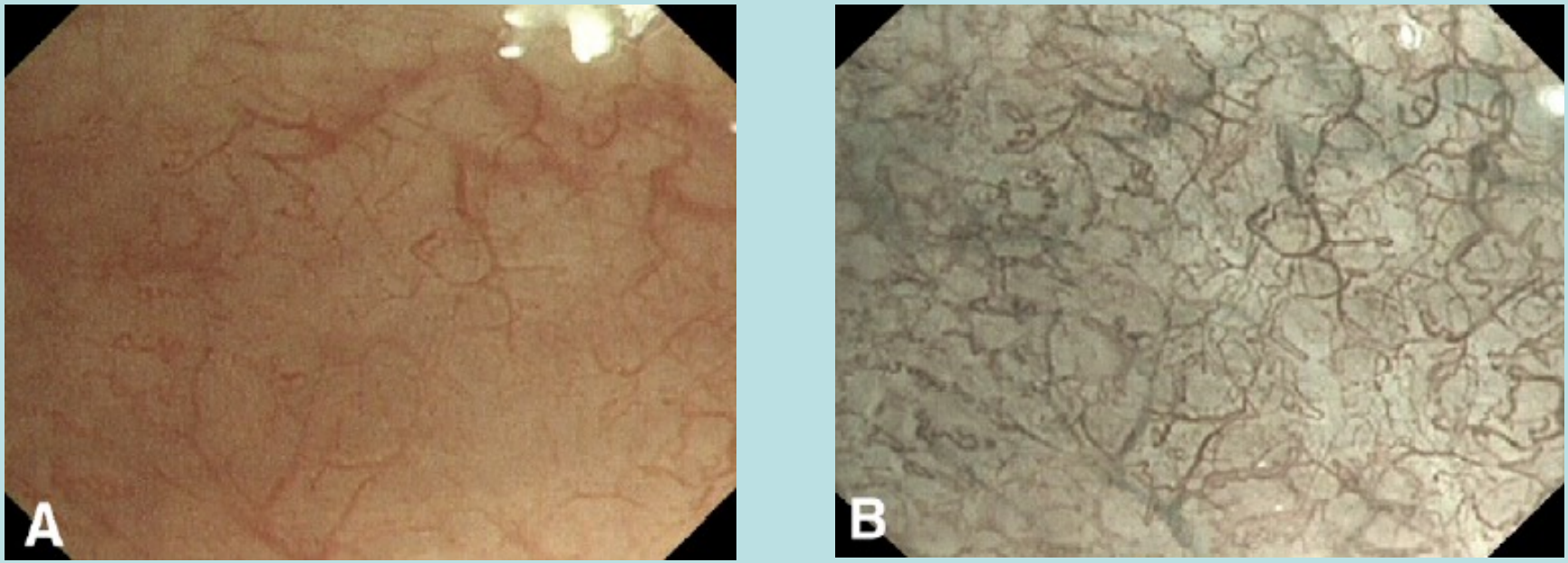
TABLE 1. Narrow band filters and display of 2-band versus 3-band NBI systems

NBI systems	NBI filters (center wavelength) (bandwidth)	Video channels used for image display
2-Band RGB sequential and color CCD NBI	415 nm (30 nm)	Blue and green
	540 nm (20 nm)	Red
3-Band RGB sequential NBI*	415 nm (30 nm)	Blue
	445 nm (30 nm)	Green
	500 nm (30 nm)	Red

*Prototype.

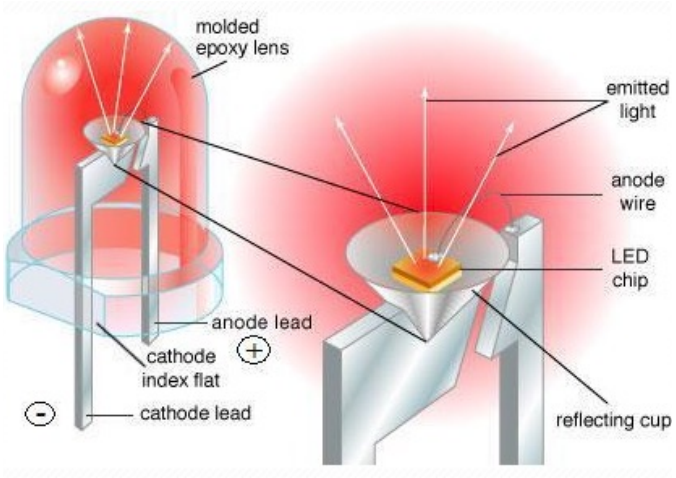
Other present/future fields include: Narrow band imaging (NBI)

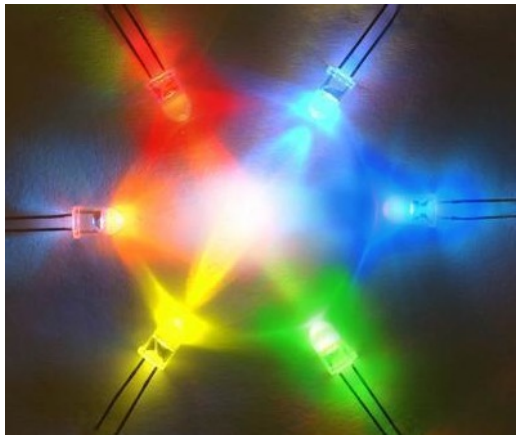
Figure 1. Magnified (**A**) white-light versus corresponding (**B**) NBI images of nondysplastic Barrett's mucosal vascular pattern. Under NBI, capillaries appear brown, whereas deeper vessels appear cyan.



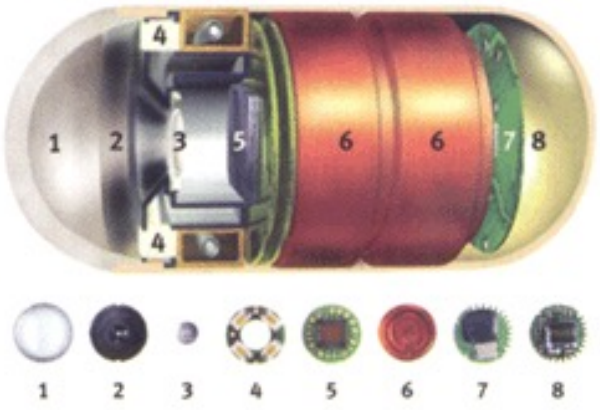
Wong Kee Song et al., GASTROINTESTINAL ENDOSCOPY, Volume 67, No. 4 : 2008

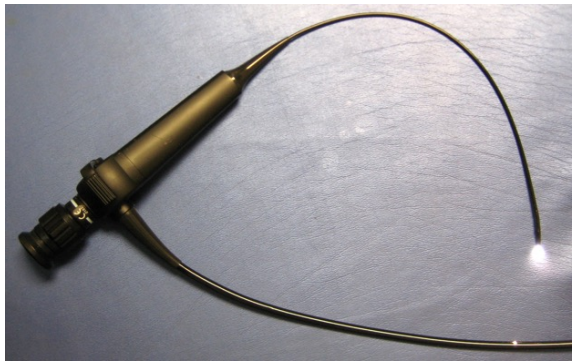
Other present/future fields include: Light Emitting Diodes (LEDs)



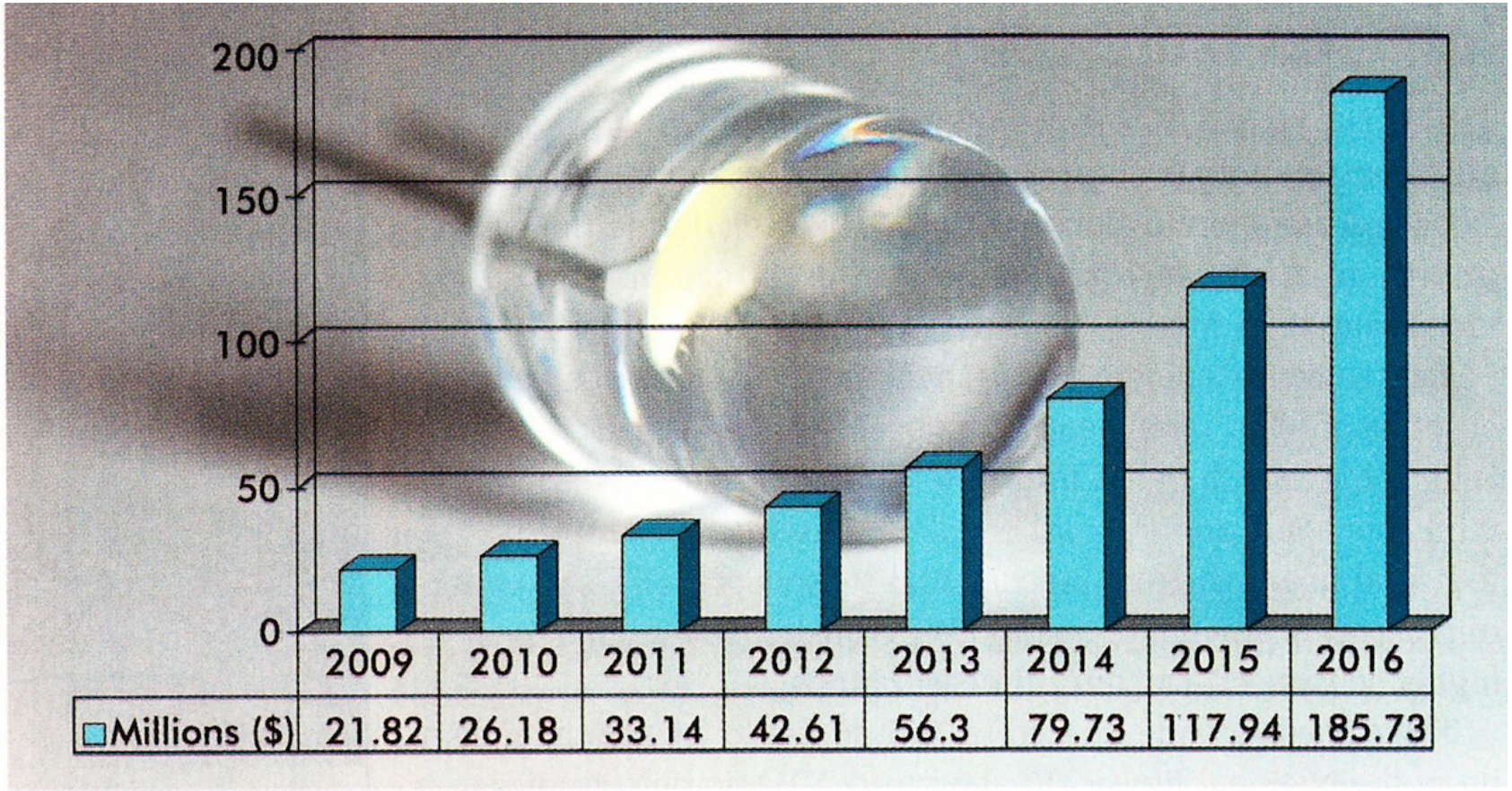


- ✓ Small
- ✓ Powerful
- ✓ High efficiency
- ✓ Cheap
- ✓ Robust
- ✓ Long lifetime
- ✓ Different wavelengths
- ✓ Relatively bright





Other present/future fields include: Light Emitting Diodes (LEDs)



The global consumption value of LEDs in test/measurement and medical/science devices is expected to rise to $185.73 million in 2016, with an average annual growth rate of 35.8 percent over the period from 2009. Courtesy of ElectroniCast Consultants.

Partial list of some of the biomedical applications for laser diodes

Applications	Type	Wavelength (nm)																		
		405	450	635	652	670	689	752	766	794	810	915	940	980	1064	1210	1320	1470	1550	1940
Aesthetics	Acne Treatment		X															X		
	Hair and Wrinkle Remover								X		X	X			X	X				
	Laser Skin Resurfacing										X	X								
	Lipolysis														X	X				
	Pigmented Lesions										X		X	X						
	Tooth Whitening										X			X						
	Varicose Vein Removal												X							
Diagnostics	MRI									X										
Photodynamic Therapy	Aged-Related Macular Degeneration						X	X												
	Cancer Treatment			X	X	X														
	Wound Healing	X												X						
Surgical Treatment	Dental Treatment													X						
	Endovenous Treatment												X							
	General Surgery													X	X		X	X	X	X
	Microsurgery													X	X					
	Urology													X			X	X		

..... to be continued ..... !

- Nanoparticles-based delivery of photosensitizers
- Light-induced immunomodulation
- Photobiomodulation (LLLT)
- 2 hν tissue characterization
- …

The availability of lasers, sensitive detectors and/or advanced signal acquisition/processing/analysis techniques are at the origin of numerous approaches used in microscopy !

- Fluorescence Correlation Spectroscopy (FCS)
- Fluorescence Lifetime Imaging (FLIM)
- Fluorescence Recovery After Photobleaching (FRAP)
- Light sheet fluorescence microscopy (LSFM)
- Confocal microscopy (CFM)
- …

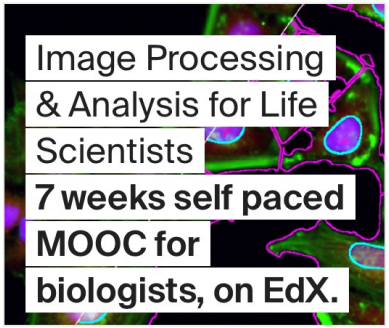
The availability of lasers, sensitive detectors and/or advanced signal acquisition/processing/analysis techniques are at the origin of numerous approaches used in microscopy ! (Cont.)

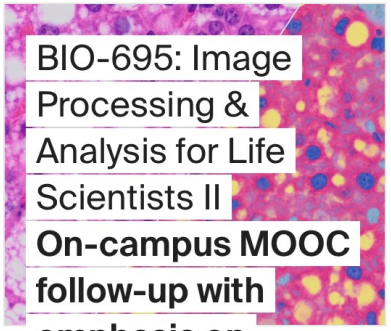
Super-resolution techniques have gained momentum over the last few years, pushing the limits of light microscopy beyond the classical diffraction limit.

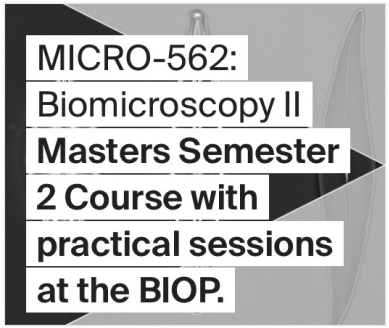
- Structured Illumination (SIM)
- Stimulated Emission Depletion (STED)
- Stochastic Optical Reconstruction (STORM)
- ….

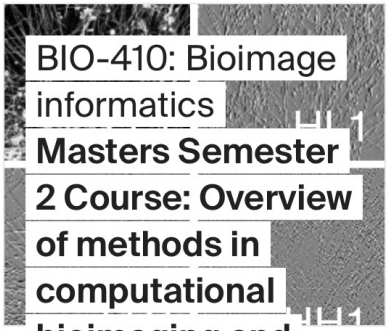
The BioImaging and Optics Core Facility (BIOP-EPFL) is active through multiple teaching programs.

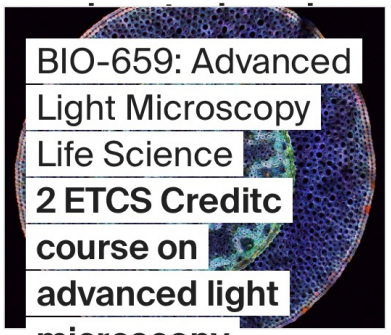
Therefore, these microscopy approaches will not be adressed in this course!

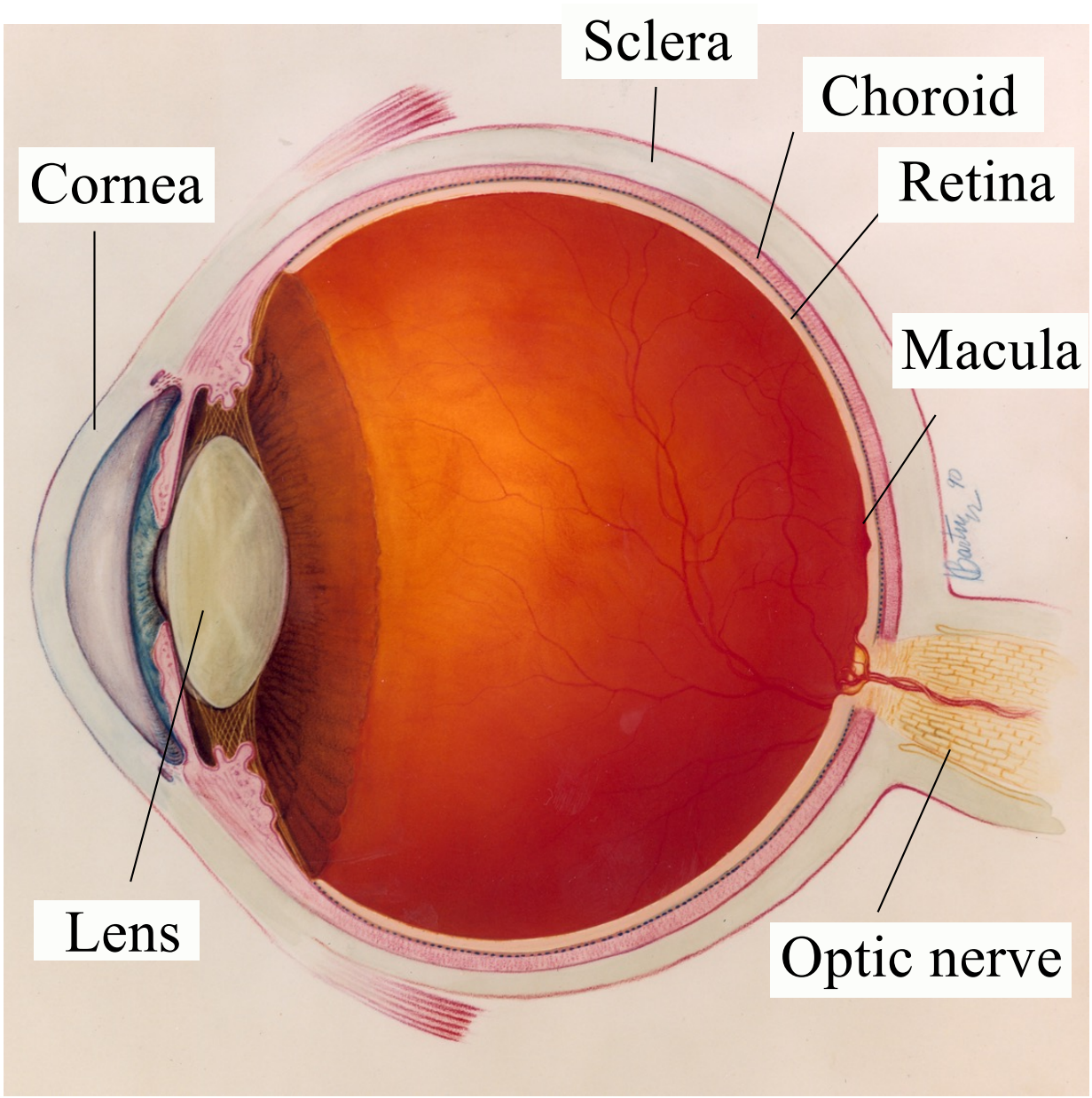












An interesting case:

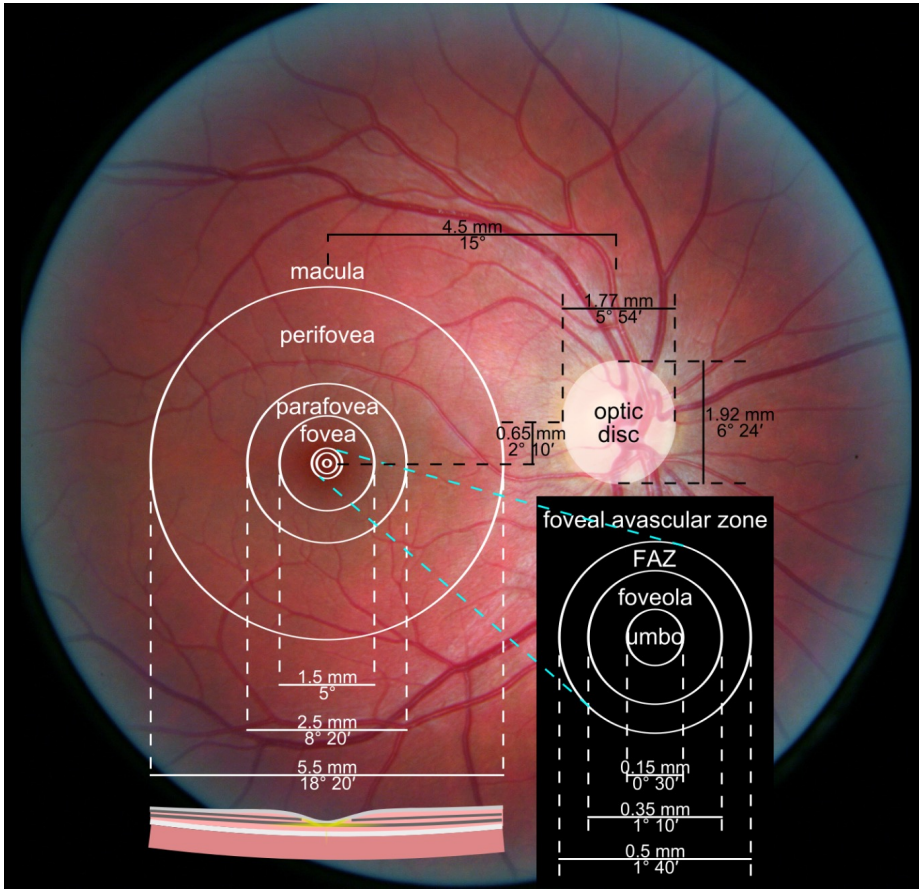
(A **therapeutic** application of photomedicine)

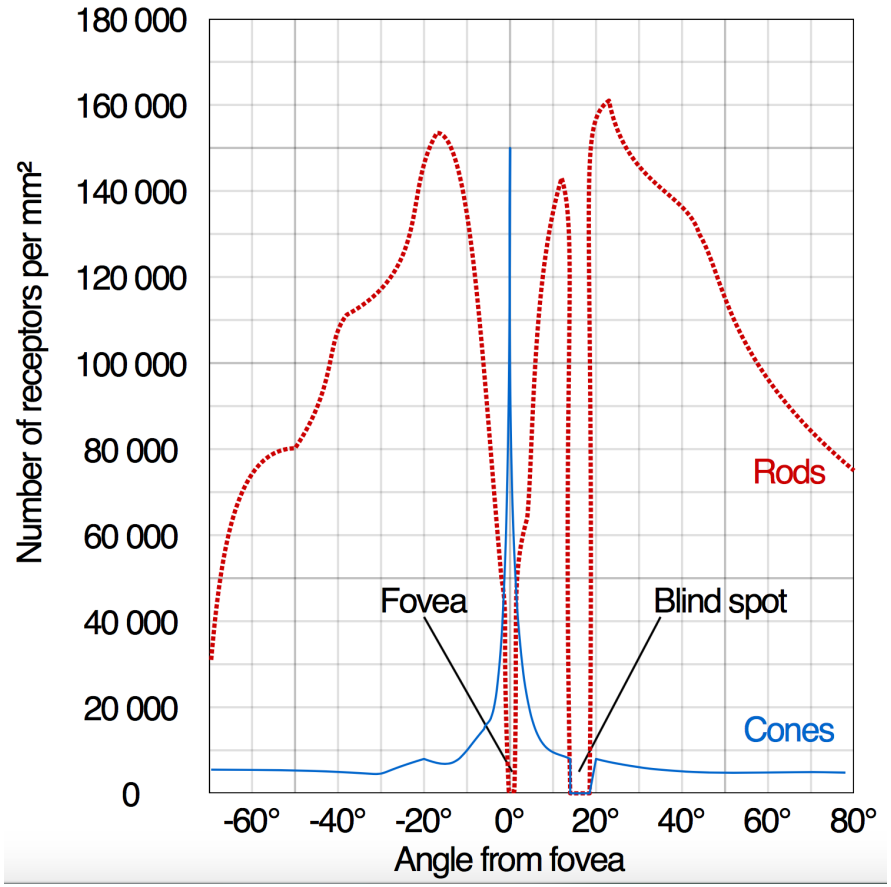
Treatment of age-related Macular degeneration by photodynamic therapy With Visudyne®

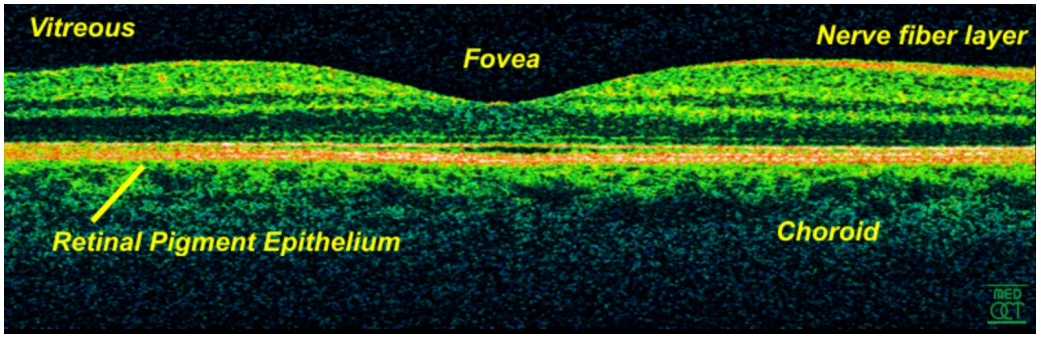
First studies: early 90's
First approval: 1999

Anatomy of the human eye

Location of the macula

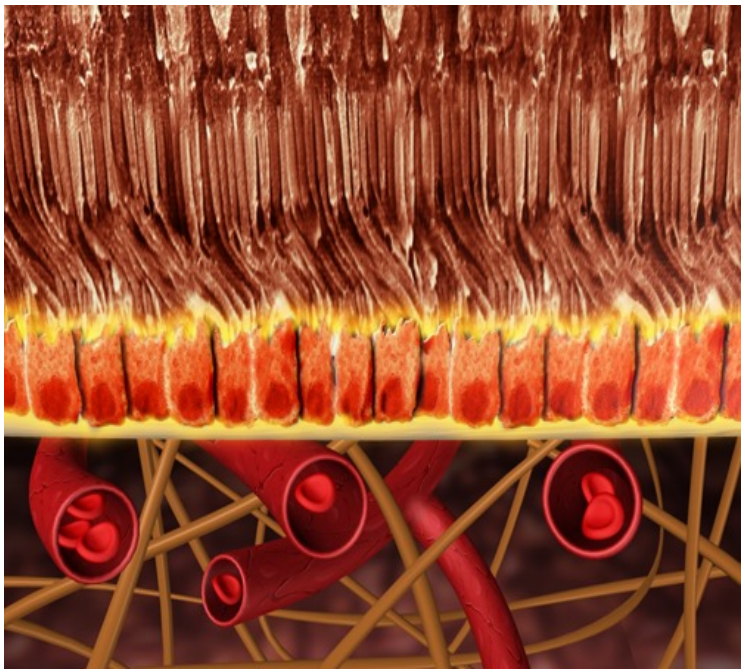






OCT cross-section image at 800 nm

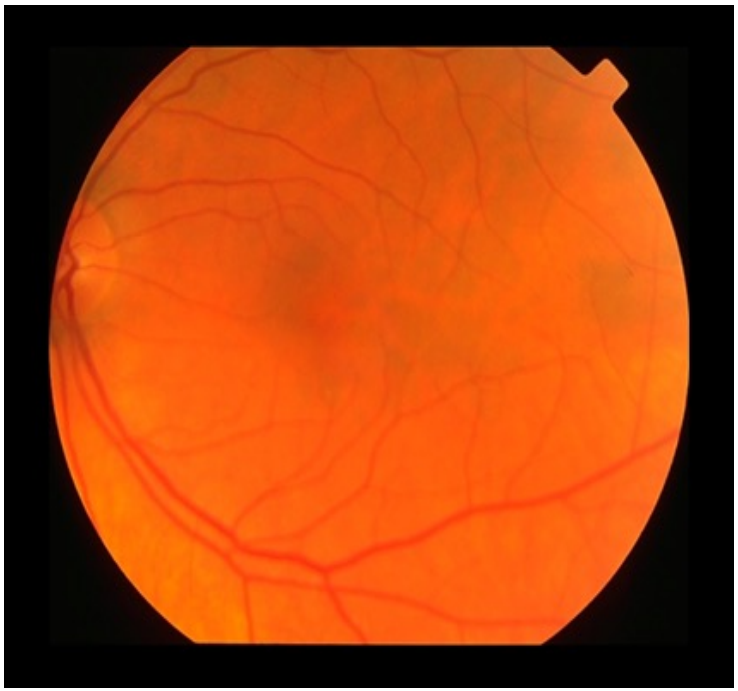
Normal retina



Photoreceptors

RPE

Choroid



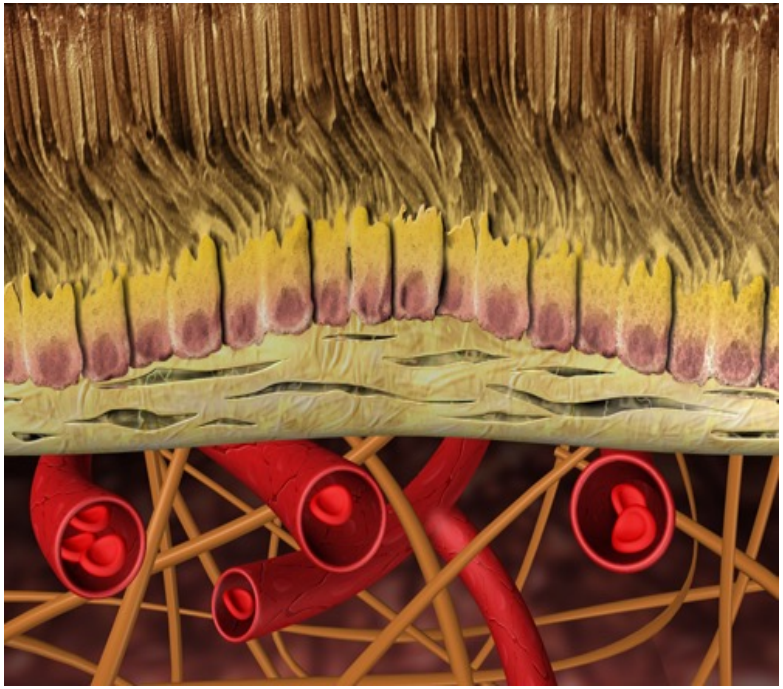
fundus photograph

Vision = high metabolic activity

Retinal Pigmented Epithelium (RPE): major role in nutrition + protection

Source: Novartis Ophthalmics

Aging of macula



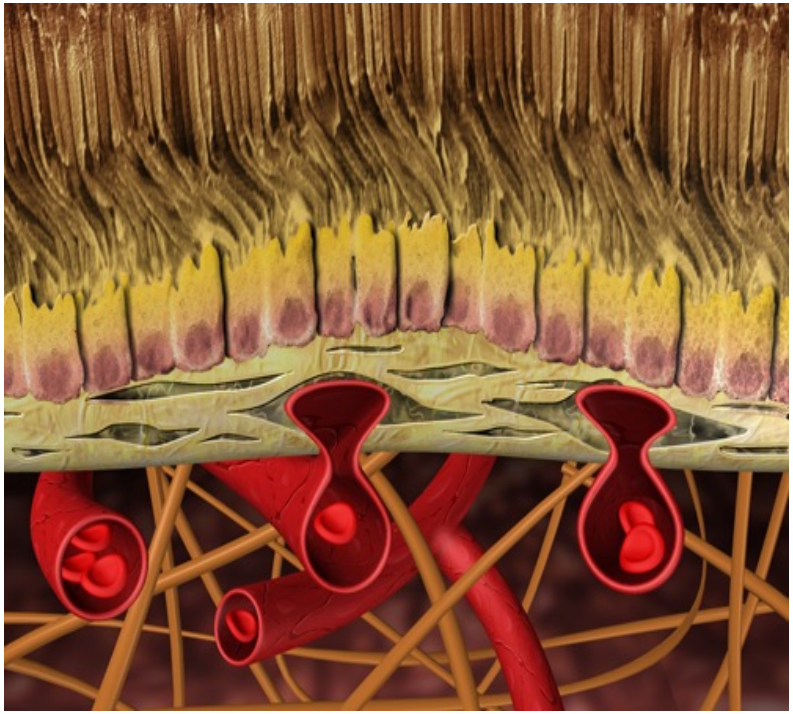
fundus photograph

Drusen: accumulation of lipofuscin
Bruch's membrane thickens + calcification
Less choriocapillaris
Rupture of blood-retina barrier

Source: Novartis Ophthalmics

Aging of macula

One form of AMD:
Bruch's membrane penetration
by choroidal neovessels (CNV)

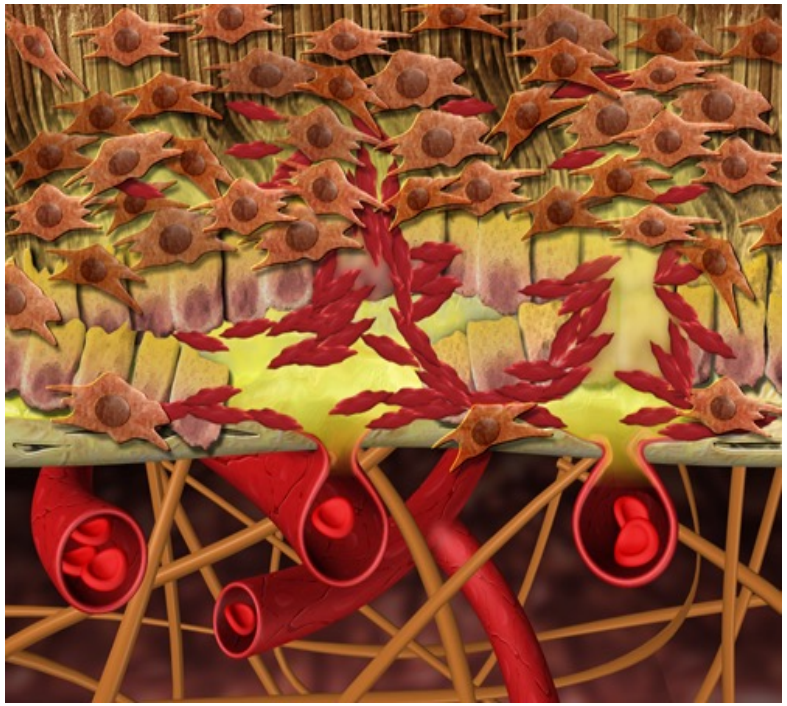


fundus photograph

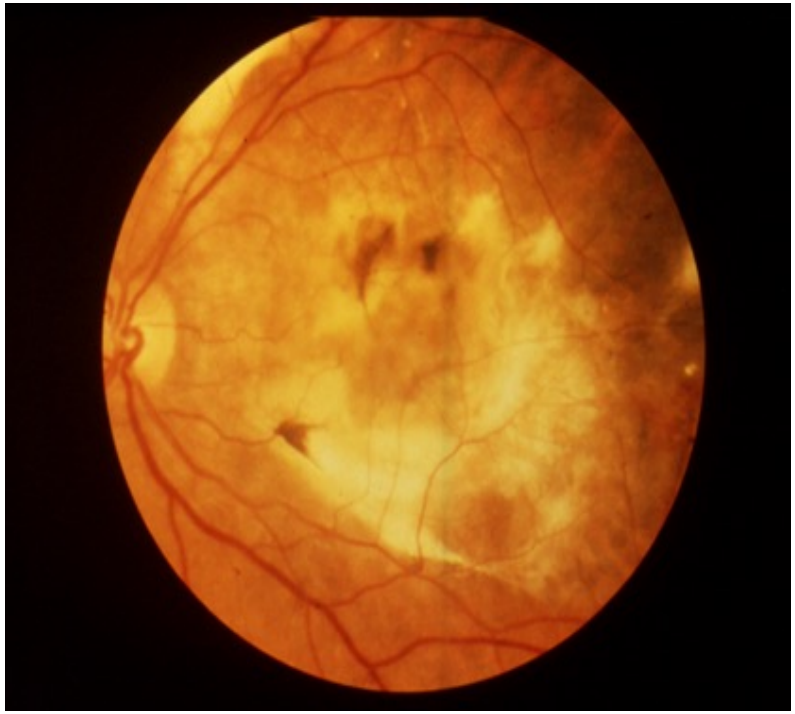
Source: Novartis Ophthalmics

Formation of disciform scar

⟹ **Vision loss**



Fibroblasts
+
Neovascular Endothelial cells

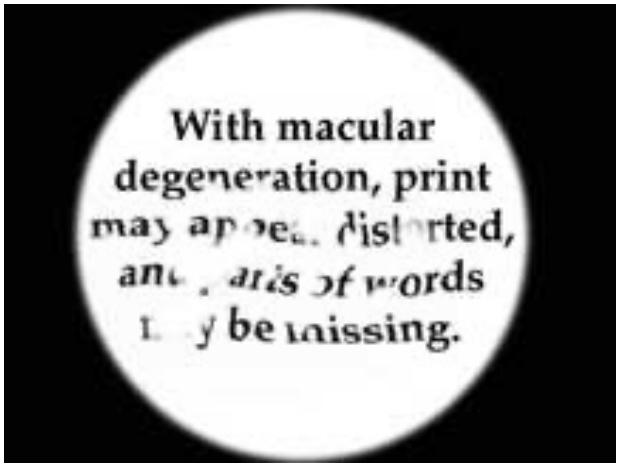


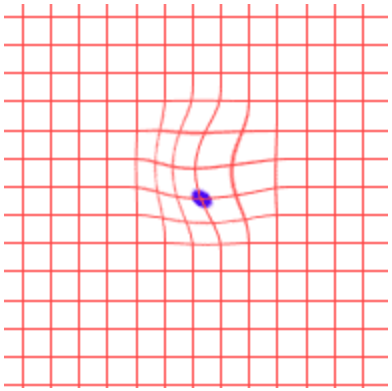
fundus photograph

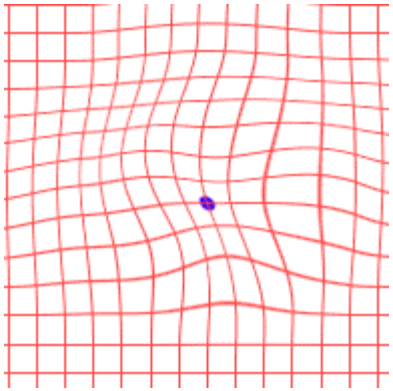
Source: Novartis Ophthalmics

Normal vision

Vision with (AMD)



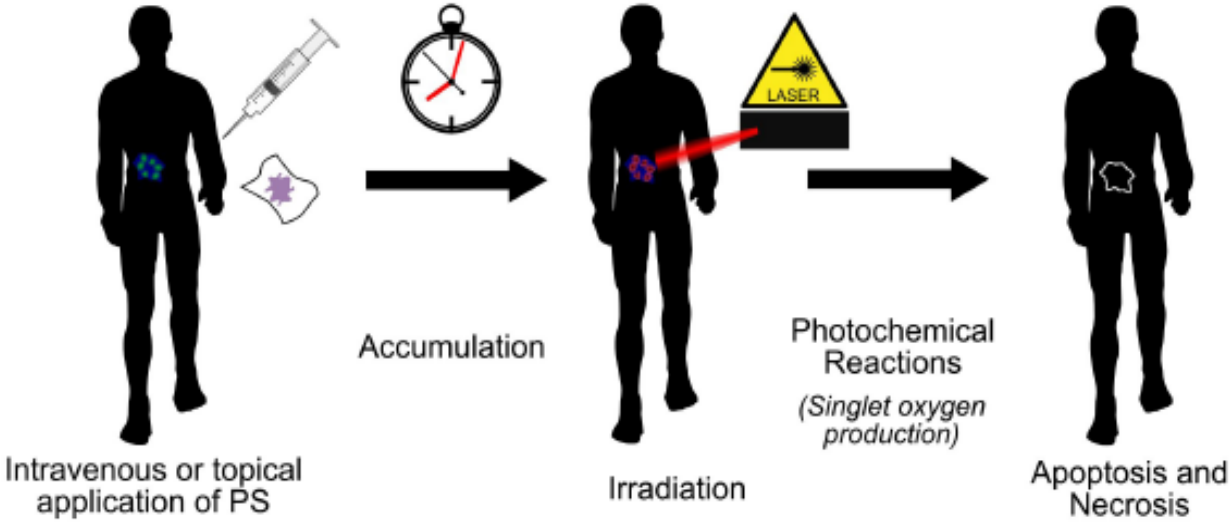




Amsler grid

Photodynamic Therapy (PDT)

PDT is a well extablished technique that is effective in treating several non malignant and malignant conditions



Three main components:

1. **Drug**: photosensitizer (PS)
2. **Light**: energy source that activates the drug
3. **Oxygen**: interacting with the excited PS, induce cell death

Advantages:

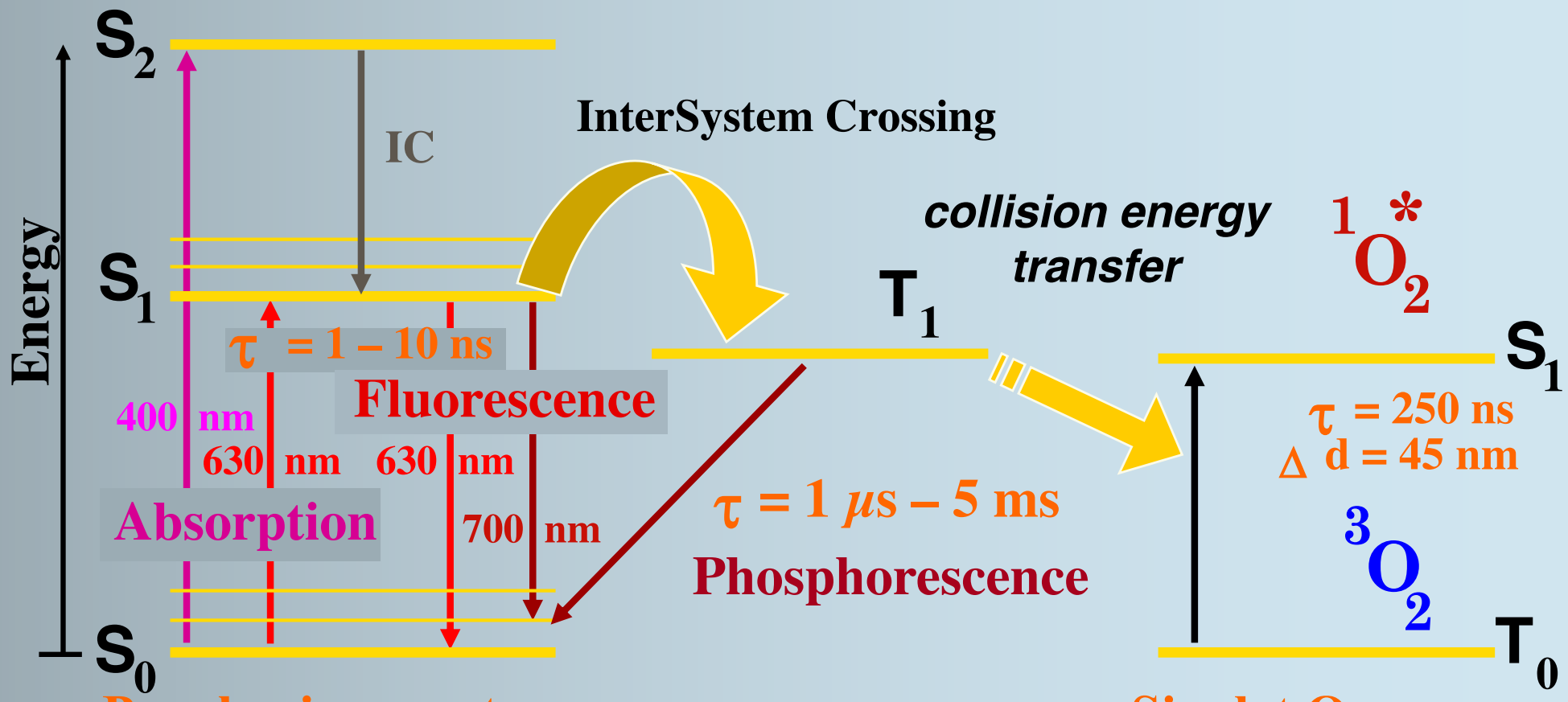
- *Good selectivity in certain cases*
- *Can be repeated*
- *Minimally invasive*
- ...

Drawbacks:

- Delayed response
- Skin photosensitization
- Only small/superficial volumes can be treated
- Inter and intra patient fluctuation
- …

Photophysical Processes in:

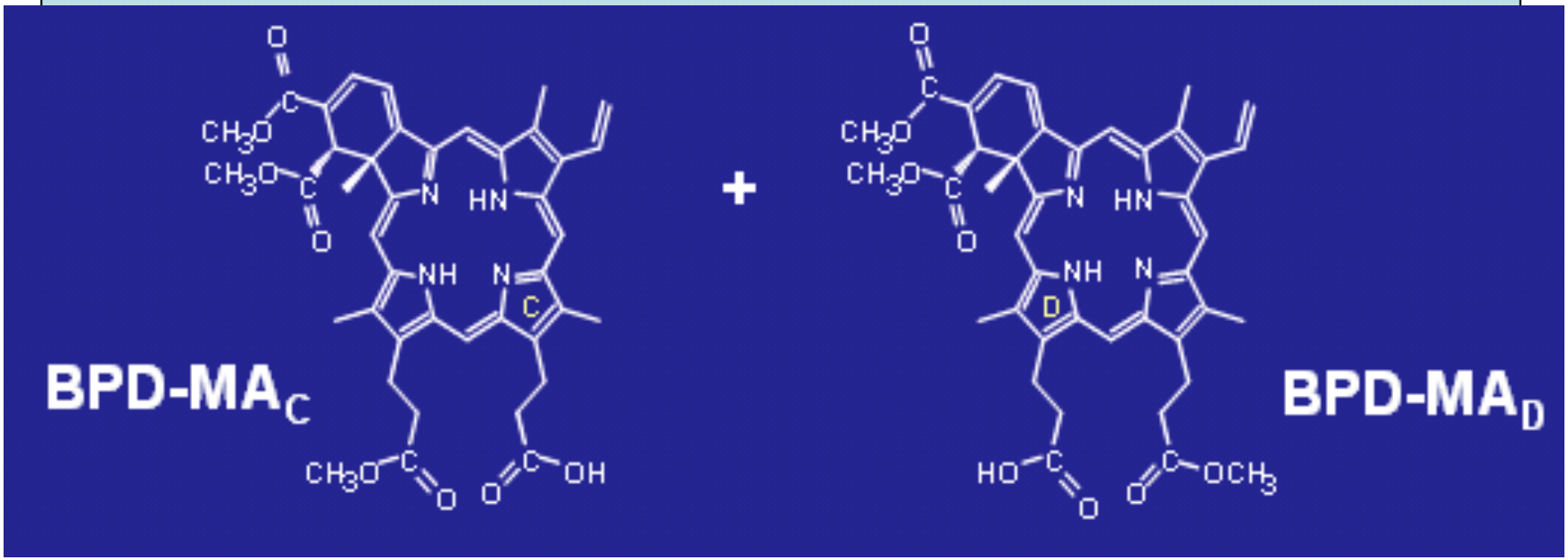
Fluorescence detection *Photodynamic Therapy*



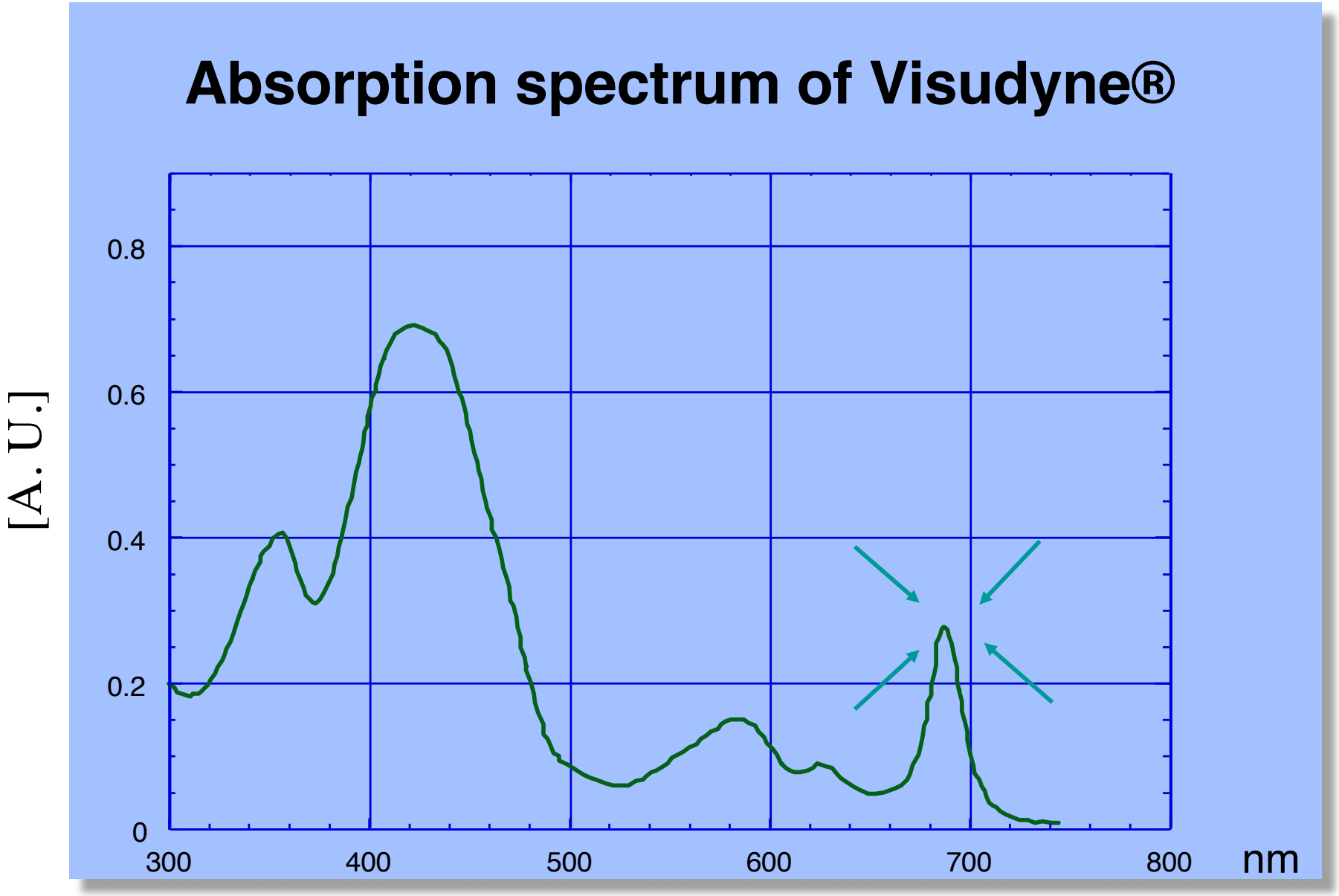
Collisions with O_2 shorten the PS's triplet state lifetime τ

Visudyne® is an angio-occlusive photosensitizer

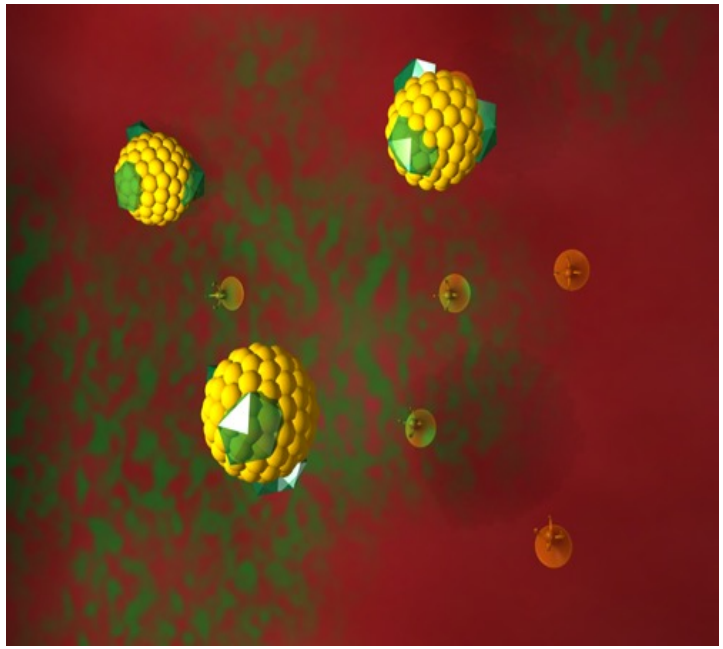
Visudyne (verteporfin) exists in an equal mixture of two pharmacologically active benzoporphyrin-derivative monoacid (BPD-MA) regioisomers



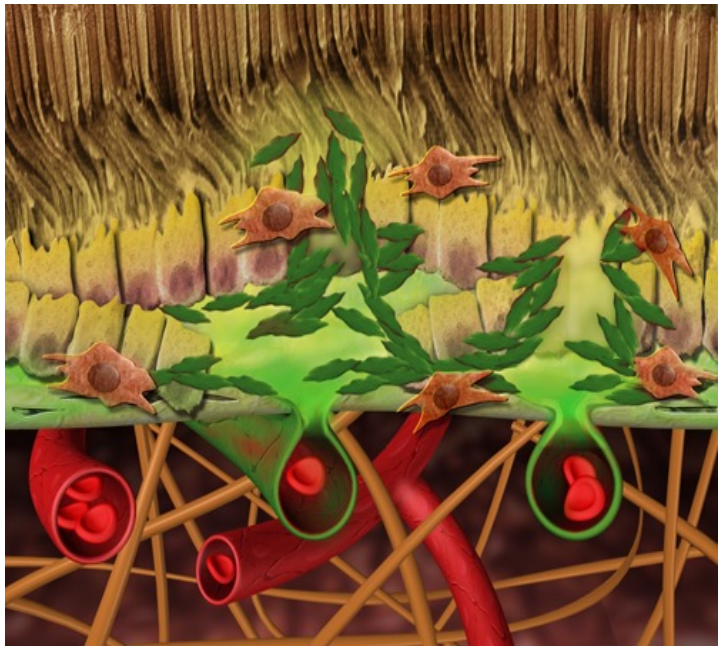
Houle JM, Strong A. *J Clin Pharmacol.* 2002;42:547–557.


Absorption spectrum of Visudyne®
[A. U.]
0.8
0.6
0.4
0.2
0
300
400
500
600
700
800
nm

Verteporfin: Mechanism of action



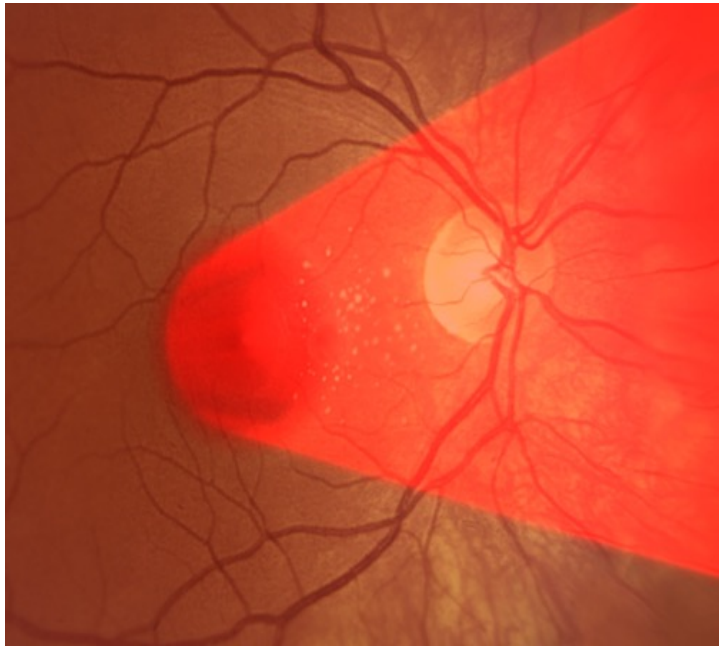
Verteporfin complexes with LDL



Dye accumulates in neovascular tissue

Source: Novartis Ophthalmics

PDT with Visudyne™
Treatment procedure

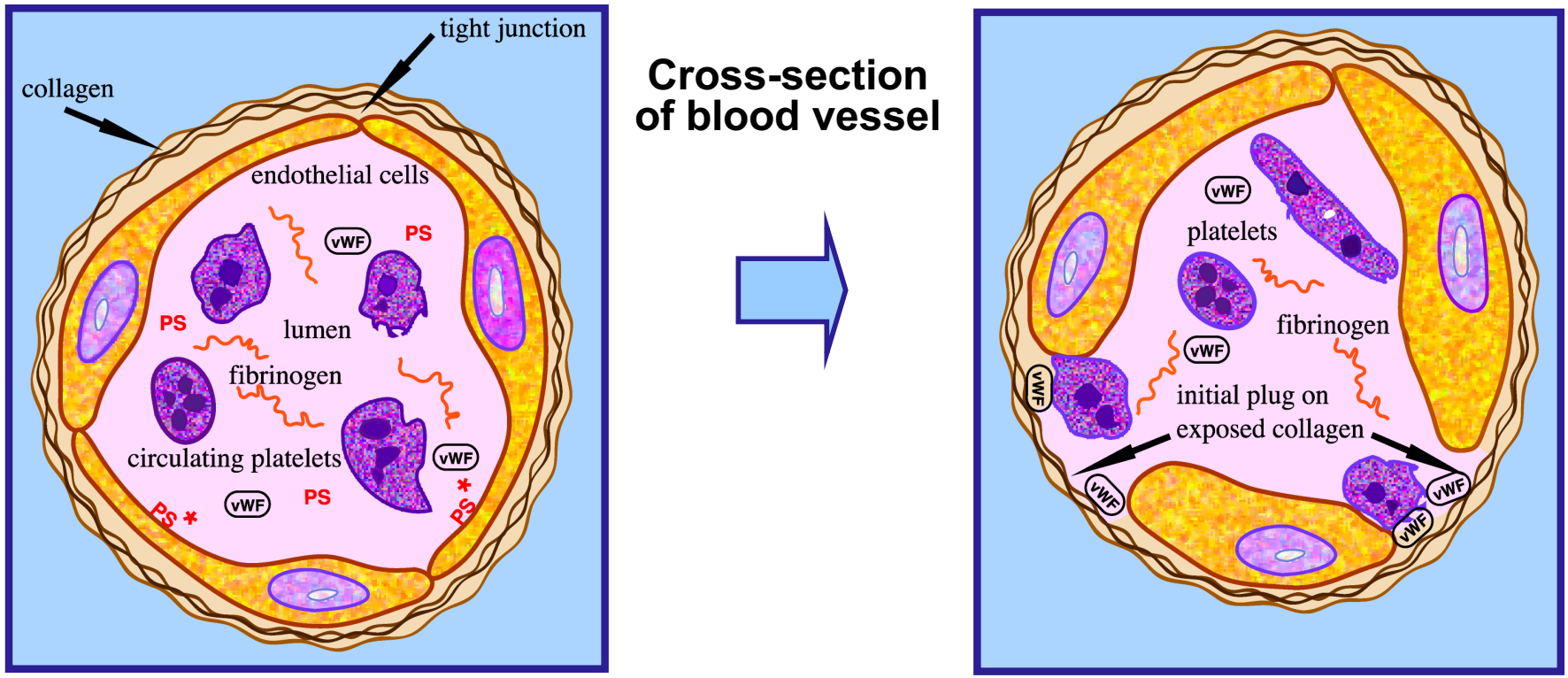


- Drug dose: 6 mg/m^2
- Light dose: 50 J/cm^2 @ 690 nm
- Light dose rate: 600 mW/cm^2
- Outpatient procedure

Laser started 15 min
after infusion begins

Source: Novartis Ophthalmics

The short-lived reactive oxygen species cause endothelial cell changes



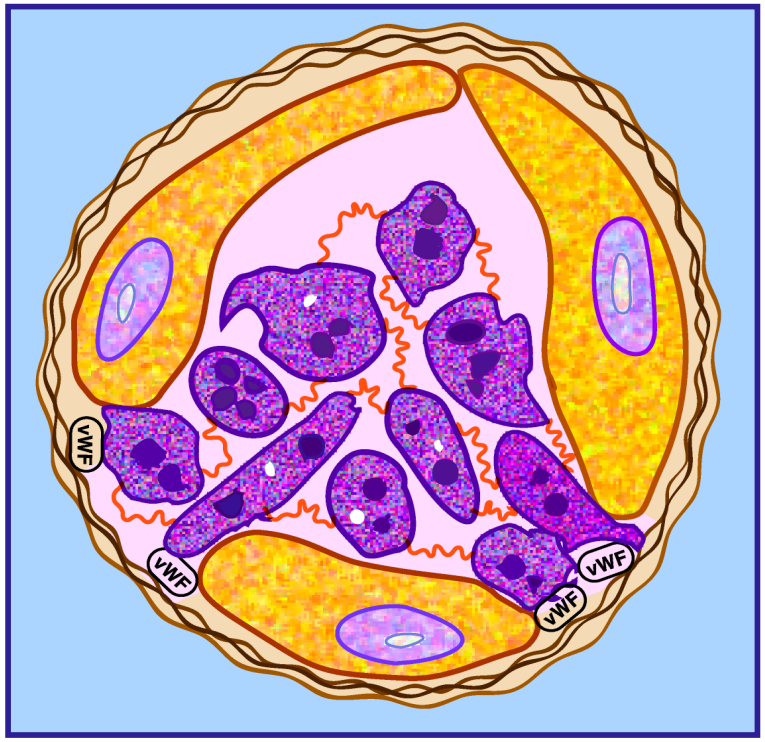
- **Cytoskeleton changes cause rounding and contraction of the vascular endothelial cells.**
- **Exposure of the subendothelial basement membrane triggers platelet binding and aggregation.**

Beaumont P *et al. Arch Ophthalmol.* 2004;122:1546–1547.
Schmidt-Erfurth U, Hasan T. *Surv Ophthalmol.* 2000;45:195–214.

Verteporfin therapy triggers a process leading to neovascular angioocclusion

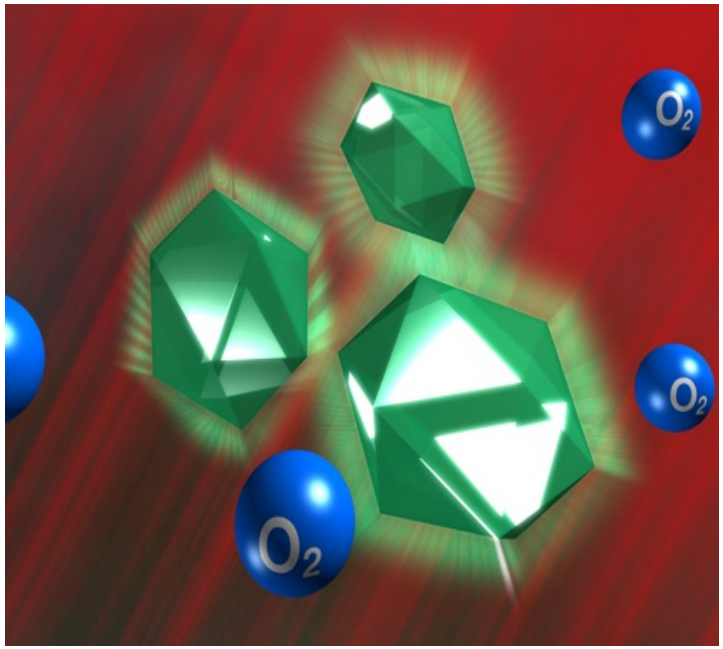
- **The activated platelets adhere to the collagen of the exposed basement membrane**
- **A fibrin-stabilized plug is formed as the blood clots**
- **Complete closure of the choroidal neovasculature occurs within 1 day**

Cross-section of blood vessel

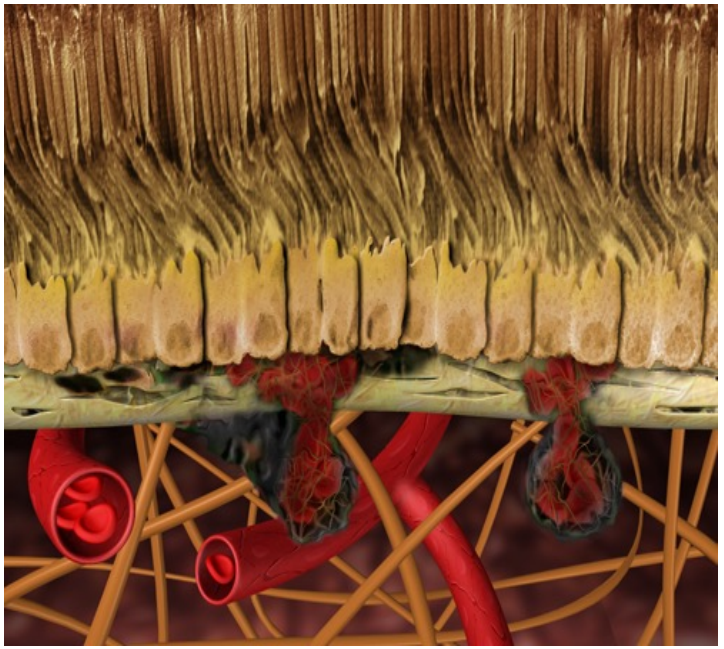


Beaumont P *et al. Arch Ophthalmol.* 2004;122:1546–1547.
Michels S, Schmidt-Erfurth U. *Invest Ophthalmol Vis Sci.* 2003;44:2147–2154.
Visudyne US Package Insert. 2005.
Michels S *et al. Invest Ophthalmol Vis Sci.* 2006;47:371–376.

Verteporfin: Mechanism of action



Verteporfin reacts with oxygen after absorption of light

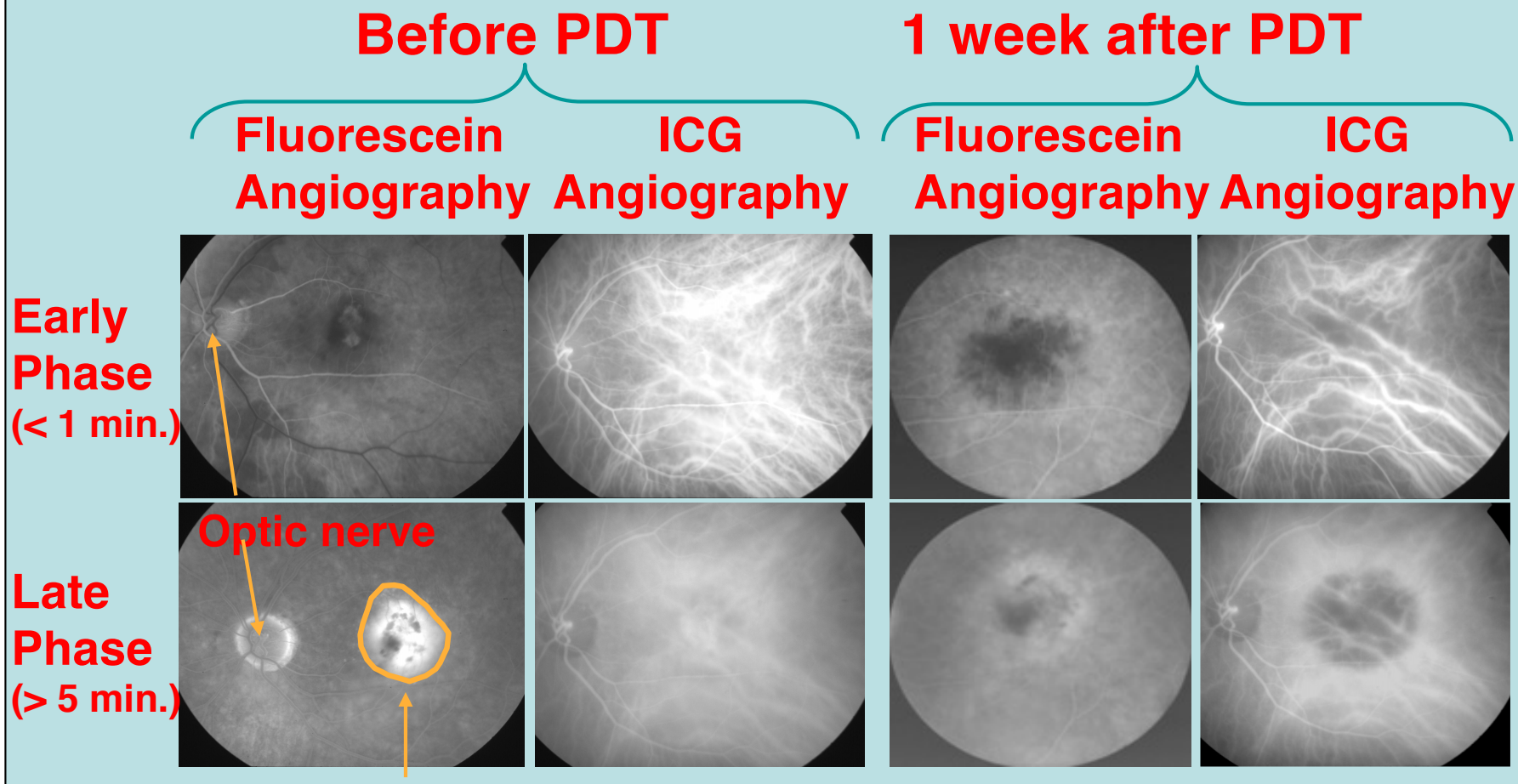


Damaged Choroidal neo-vessels (thrombosis)

Source: Novartis Ophthalmics

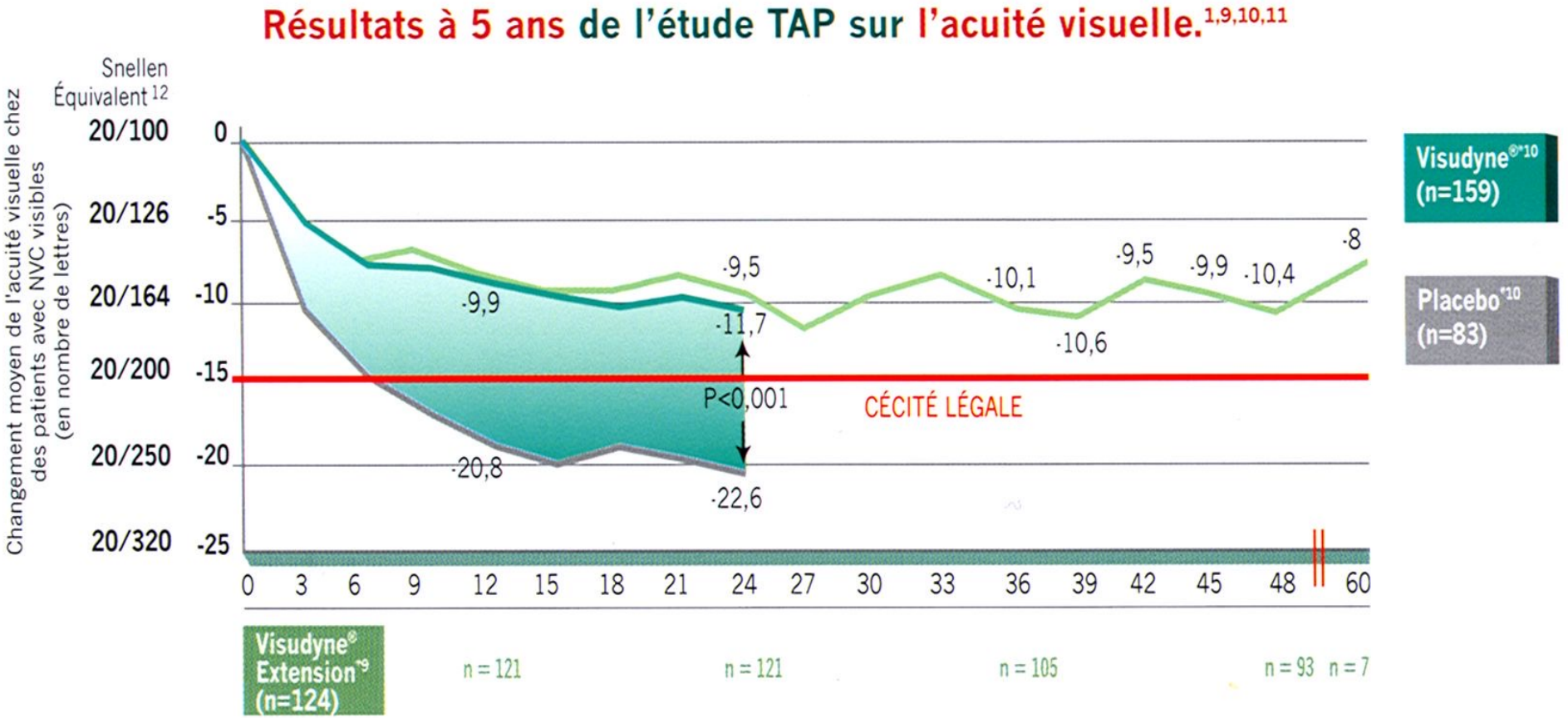
Fluorescence angiographies showing the PDT effects

Swissmedic **1999** and FDA **2000** approvals of Visudyne™ for the treatment of Age-related Macular Degeneration (AMD)

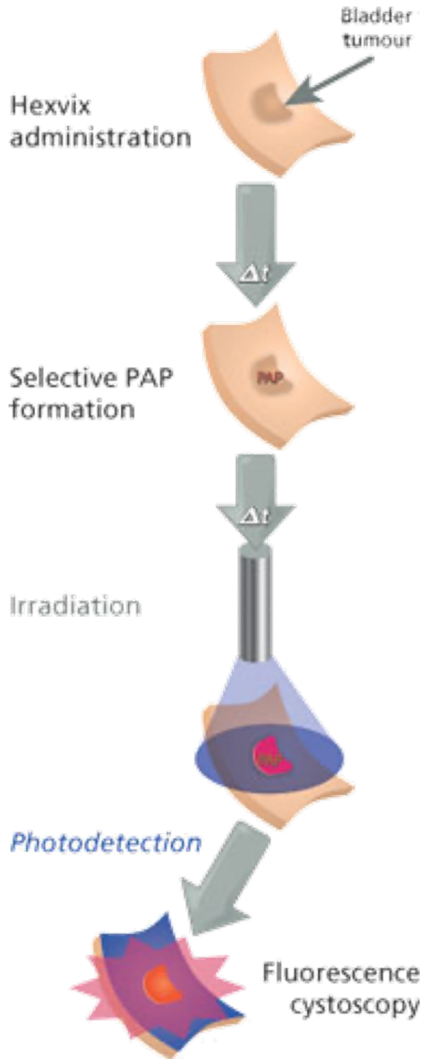


Source: Dr. M. Sickenberg, Lausanne

Visudyne® 5 years Follow up



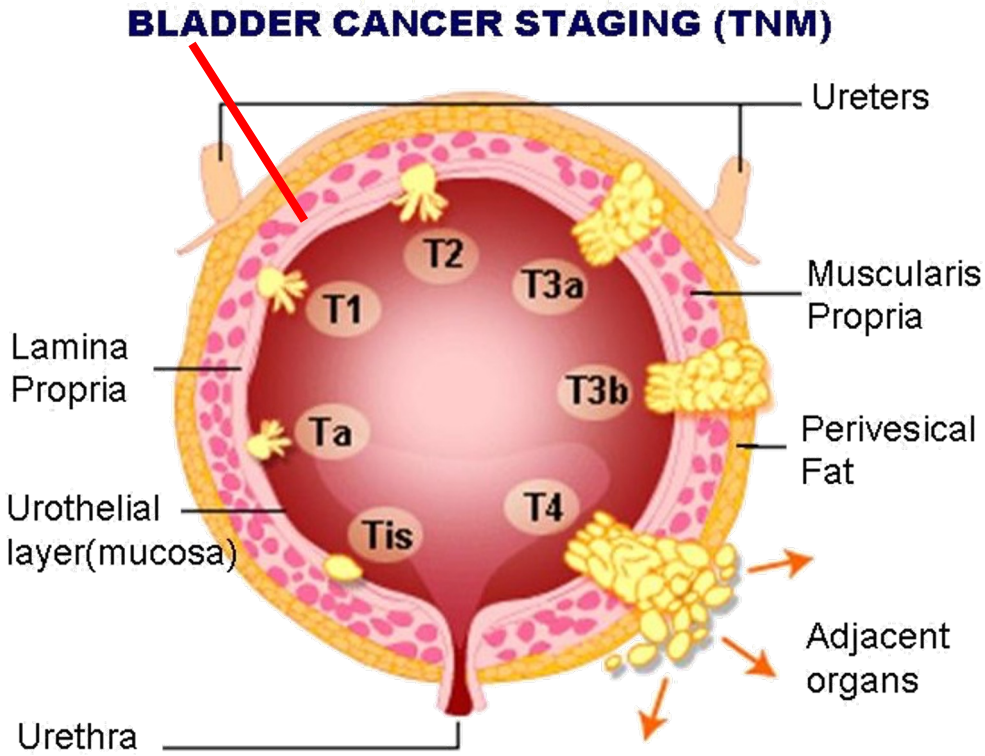
An interesting case:
(A **diagnostic** application of photomedicine)



The detection of early bladder cancer by fluorescence cystoscopy with Hexvix®

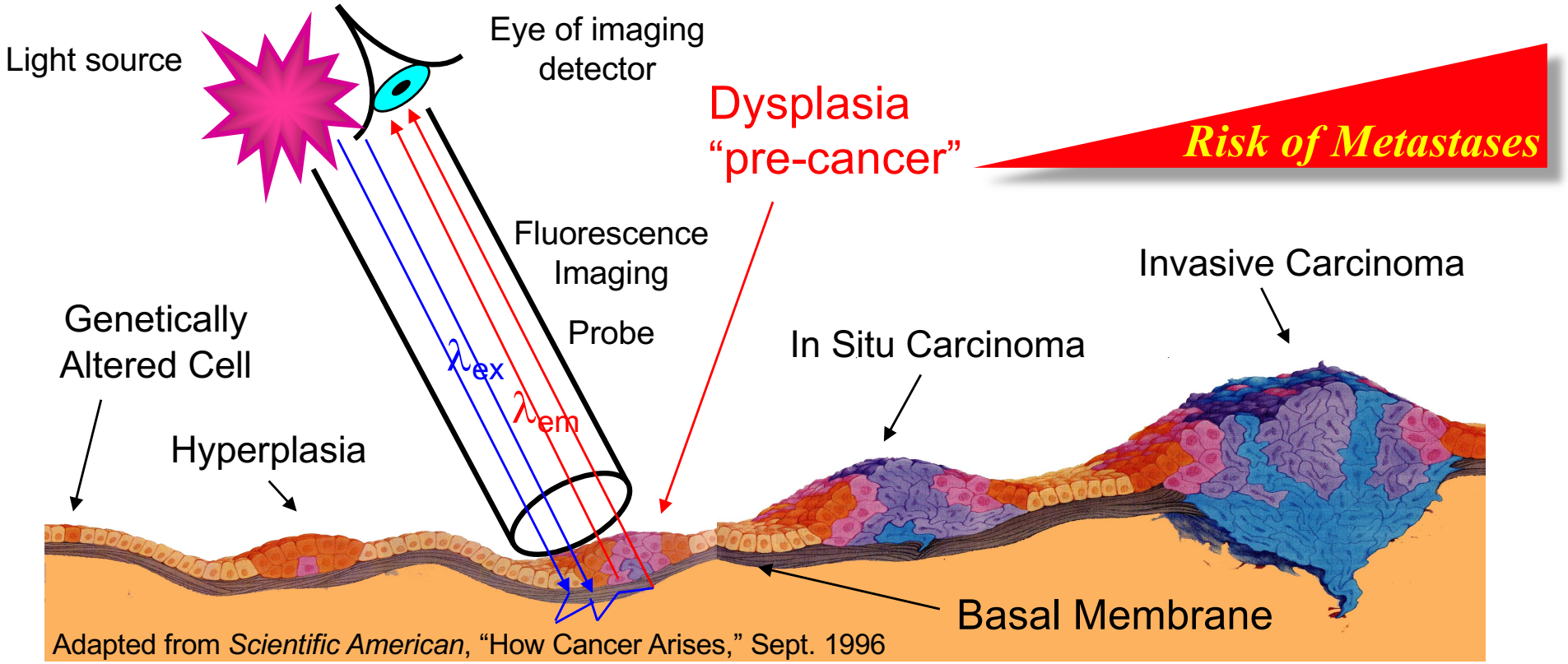
First studies: early 90's

First approval: 1999



Tis, Ta, T1: superficial, non-invasive
T2,T3,T4: invasive

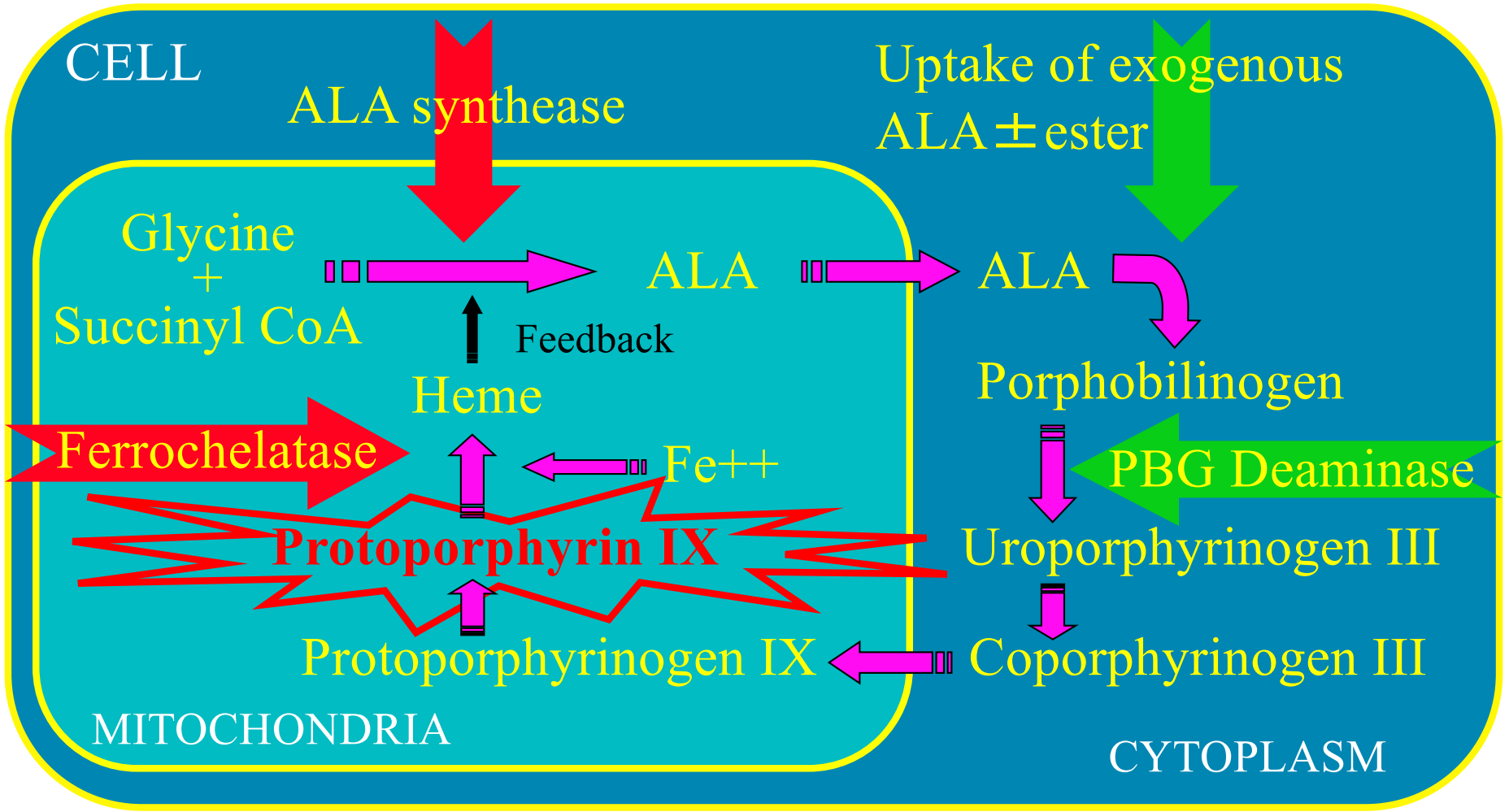
Localization of early carcinoma by fluorescence imaging: Principle



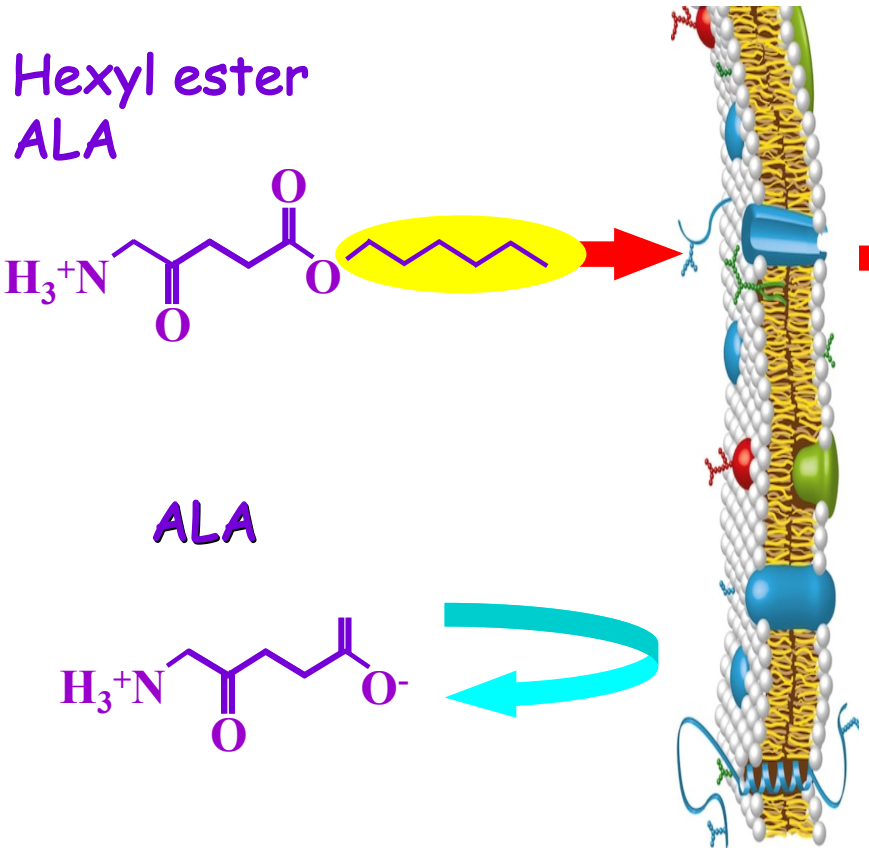
Stages detectable by conventional methods →

Fluorescence imaging →

Aminolevulinic acid (ALA)-induced production of protoporphyrin IX in the biosynthetic pathway of heme



Advantage of Esters of Aminolevulinic Acid



More lipophilic,
improved membrane permeability
Selective for certain cancer cells

Hexvix® produced by Photocure
(Cysview® in the USA)

Too hydrophilic,
weak membrane permeability

Lange et al., BJC, 1999 Uehlinger et al., JP&P, 2000 Uehlinger et al., P&P, 2006

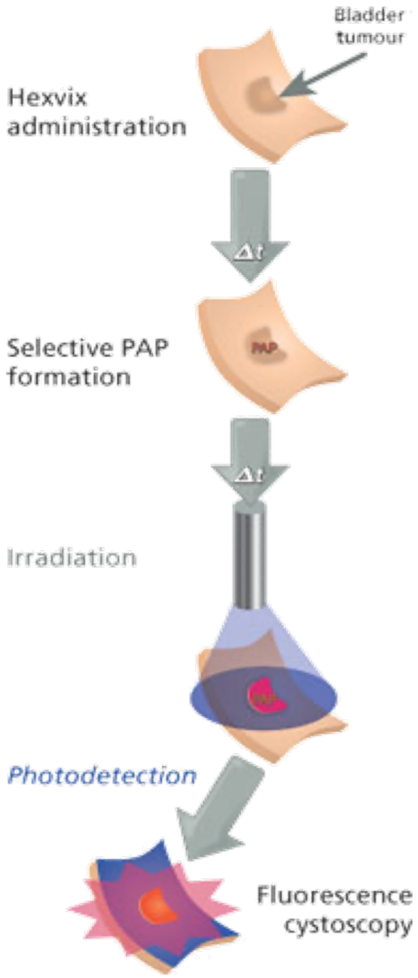
Fluorescence cystoscopy using Hexvix®

Principes:

- Instillation (50 ml; 8 mM) of an exogenous precursor (hexylester of aminolevulinic acid, Hexvix®) of protoporphyrin IX (PpIX) during one hour prior to examination

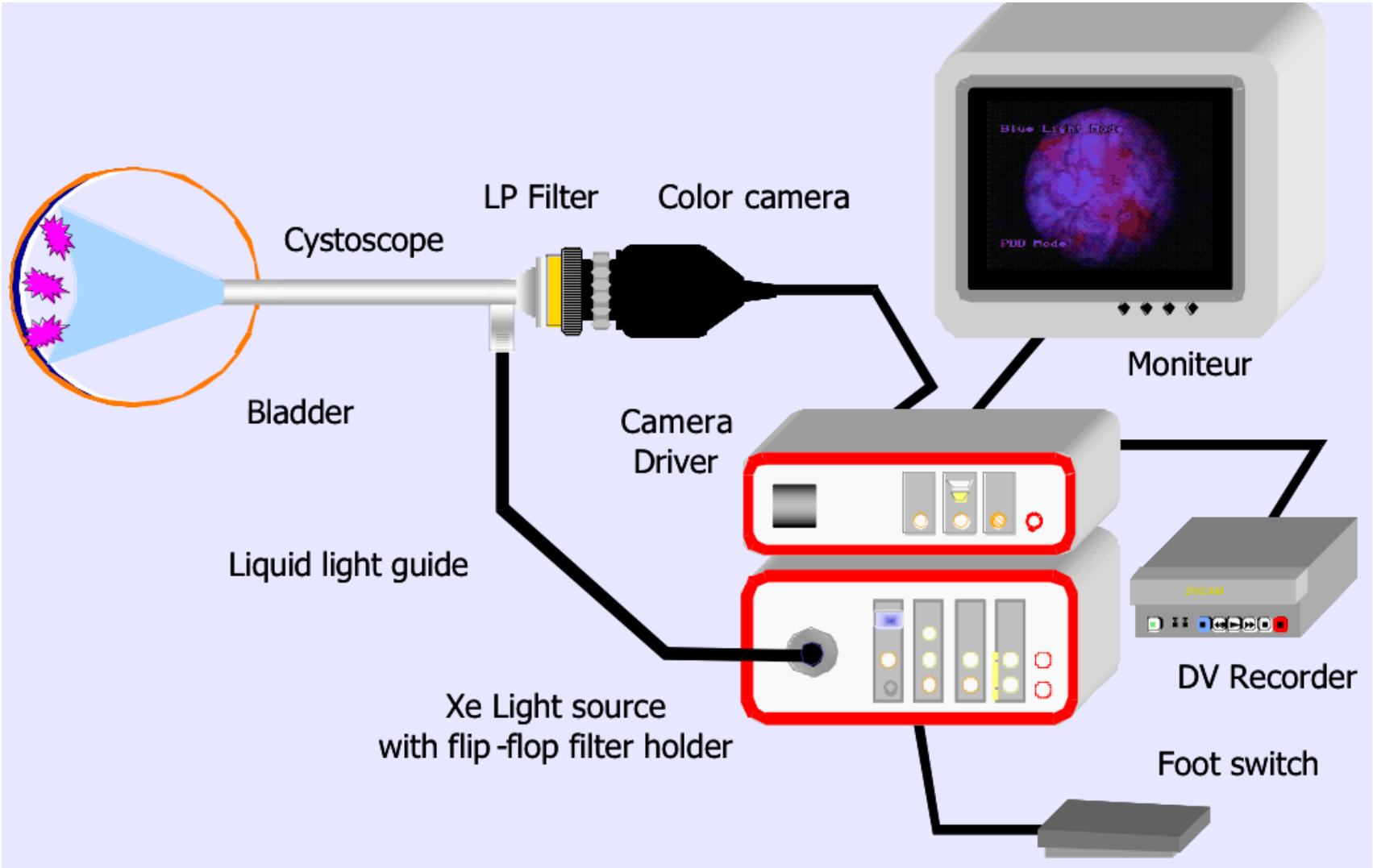
- Detection of the red (peak @ 635 nm) fluorescence produced by the lesions under violet (410 nm) light excitation.

Ideal for the detection of non muscle-invasive bladder cancers !

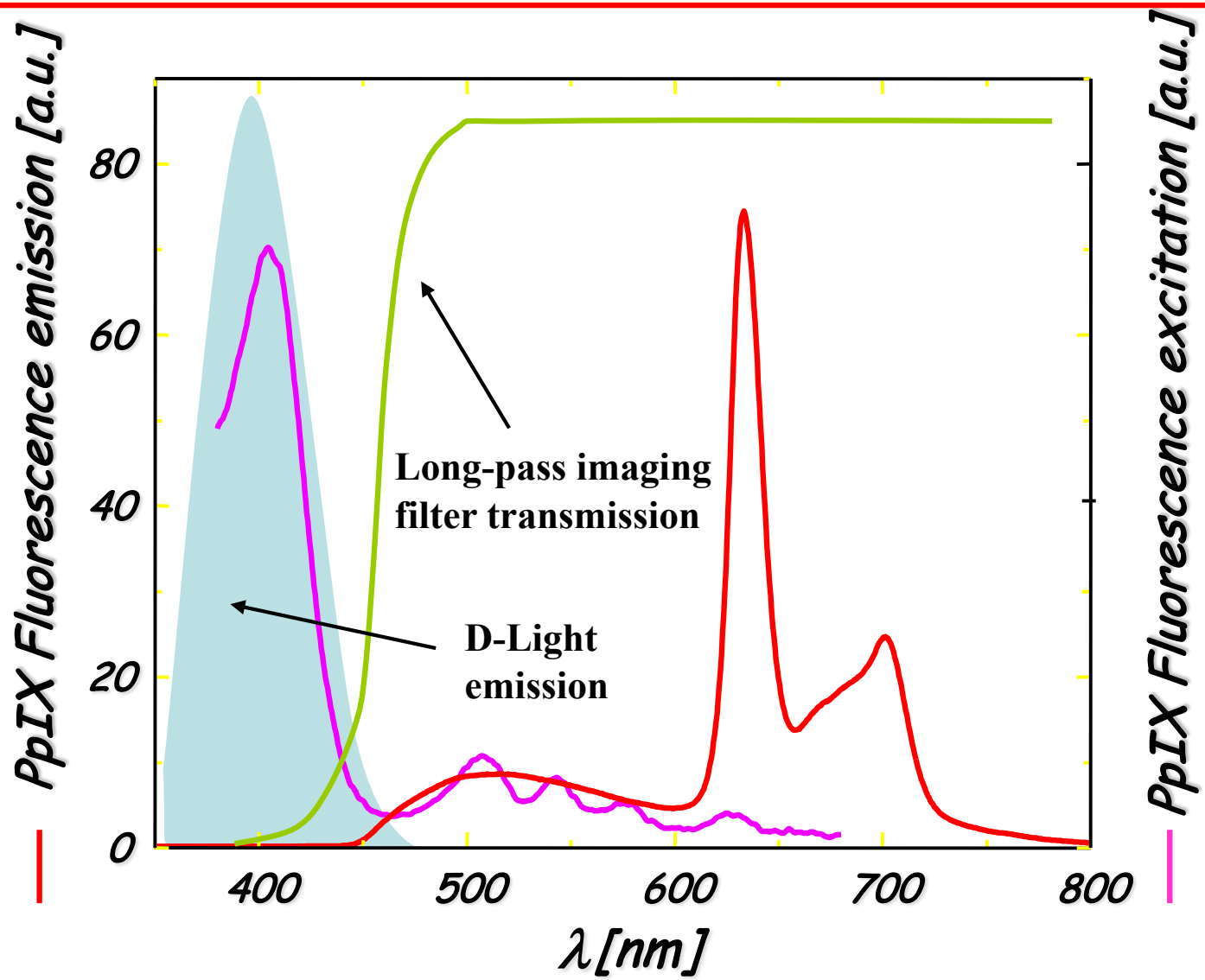


© Photocure ASA

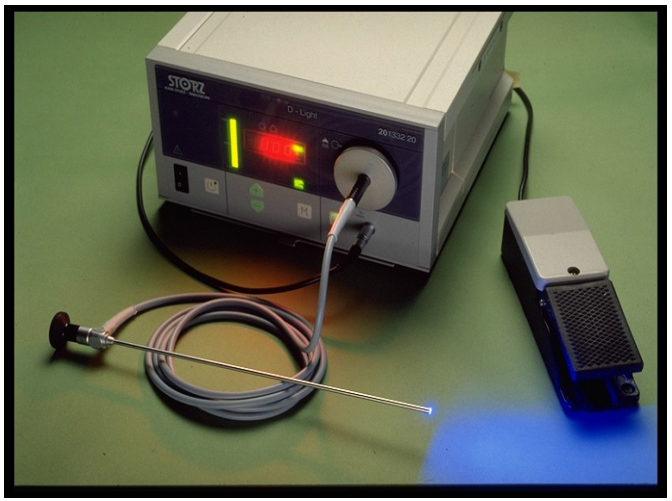
Fluorescence imaging photodetection instrumental setup

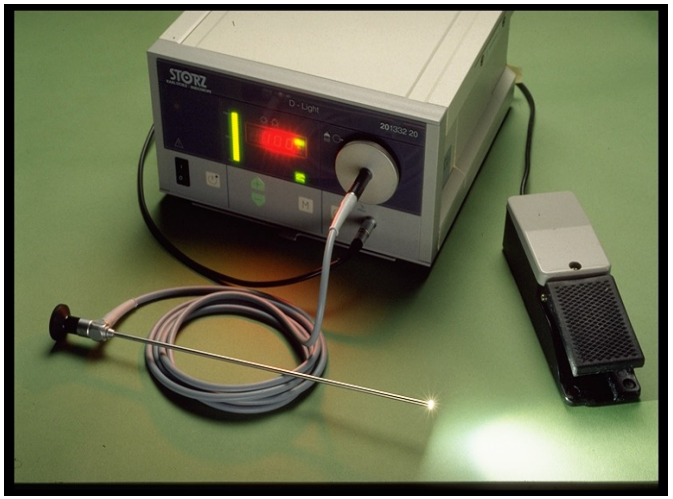


Spectral design of the fluorescence imaging photodetection setup

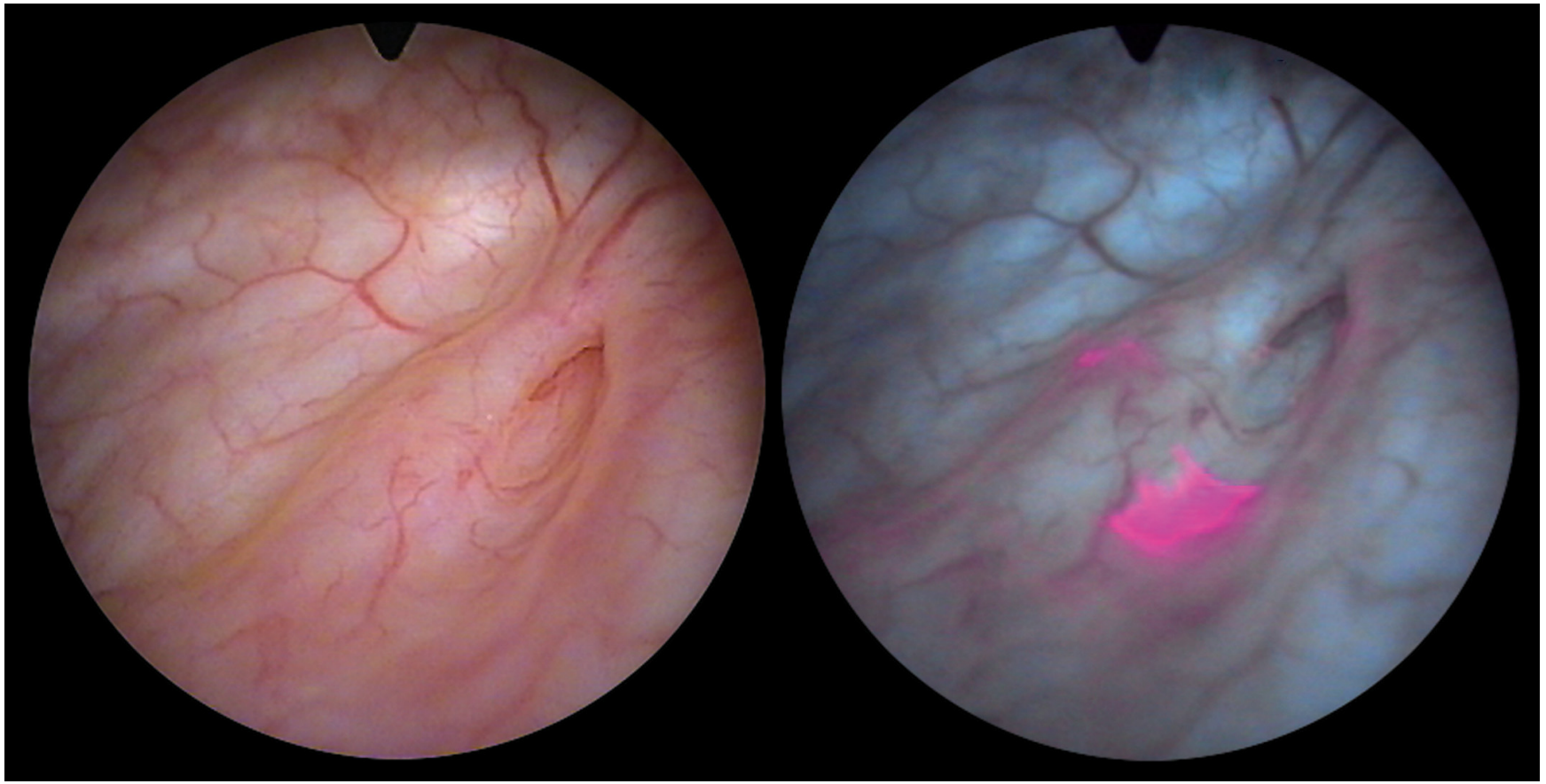


Combined development of Medtech and Pharma technologies





Photodetection of flat lesions (Carcinoma in situ) in the bladder



White light Cystoscopy

ALA-Hexylester Cystoscopy

Hexvix® Fluorescence vs White Light Cystoscopy: Key Clinical Benefits

- **Very good sensitivity** (93%) vs. WL (73%)

  Indeed, fluorescence cystoscopy (FC) detects :

  At least one more CIS detected in 41.5% of the patients.
  Fradet et al., J. Urol 2007

  One more pTa or pT1 in ~30% of the patients
  Grossman et al., J. Urol 2007

- **Limited specificity** (61%) vs. WL (65%)

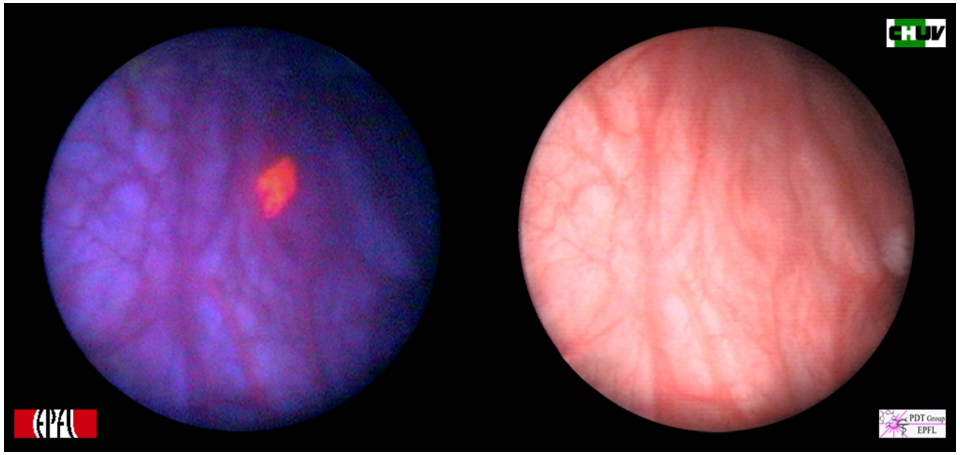
  mainly due to high rate of false positive :

  inflammation, hyperplasia, metaplasia are often cause of false-positive intravesical therapy (BCG), geometrical aspects.

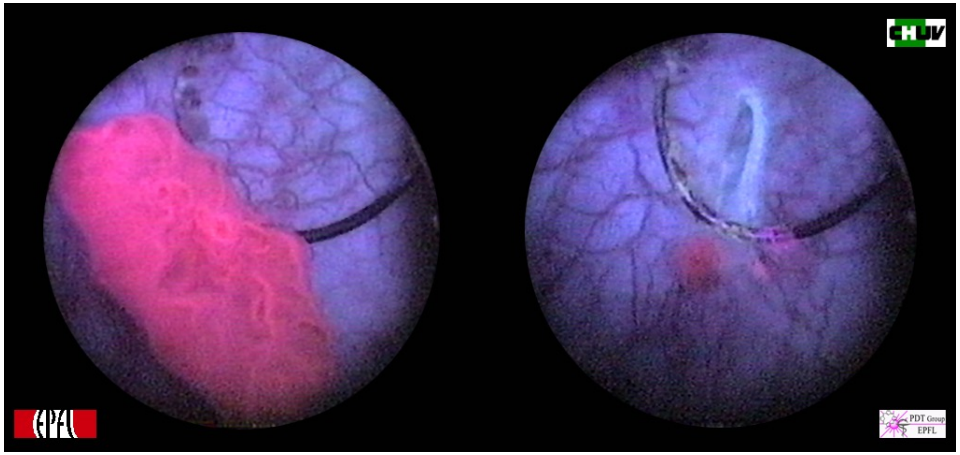
  Draga et al. Eur Urol 2009; Jichlinski et al. J.Urol 2003;
  Lerner et al., Urologic Oncology 2011.

Cancer detection by endoscopic fluorescence imaging with a contrast agent (bladder cancer)

2003 Hexvix® (hexyl-ester ALA) topically



Fluorescence detection of small CIS



Fluorescence guided resection

Hexvix® and Cysview® are now commercialized by Photocure and Ipsen

Between 50'000 and 100'000 procedures / year at present

- Approved in all EU/EEA countries in 2005.
- Recommended in 2005 as standard method by the European Association of Urology
- Reimbursement obtained in many European countries since 2007
- Approval of Cysview® by the US FDA in May 2010
- Approval of the fluorescence cystoscopy system from Karl Storz by the US FDA in May 2012
- Approval of the extension of Cysview® to include Flexible Cystoscopes, which are used in the ongoing surveillance of patients with bladder cancer in 2018

PHOTOCURE™

HEXVIX®
HEXAMINOLEVULINATE

IPSEN
Innovation for patient care