Historical Perspective of PDT Light Sources

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Presentation Outline

- **Background of PDT and production of singlet oxygen**
- **Early light sources and observation**
- **Large frame laser sources**
- **Miniature diode lasers**
  - Fiber coupled devices
  - Singlet oxygen dosimetry
- **Other sources discussed at this conference**
  - Light emitting diodes
  - Two photon sources
  - Radiation sources (x-ray and Cherenkov)
  - Solar radiation
- **Summary**

Early Sources and Observations

- **In 1900, Oscar Raab, a medical student studying the effect of acridine on parmecia observed that light was required to inactivate paramecia.**

- **In 1924, Policard observed red fluorescence from UV excited hematoporphyrin in sarcoma of laboratory rats, implying that fluorescence might be able to visualize tumors.**

- **In 1976, using a red filtered slide projector in an *in-vitro study*, Weishaupt et al. observed that cancer cell killing required singlet oxygen.**

- **Since these early observations numerous excitation sources have been applied to laboratory and clinical studies. Dosimetry continues to be a major challenge in terms of treatment outcome prediction**

Production of Singlet Oxygen

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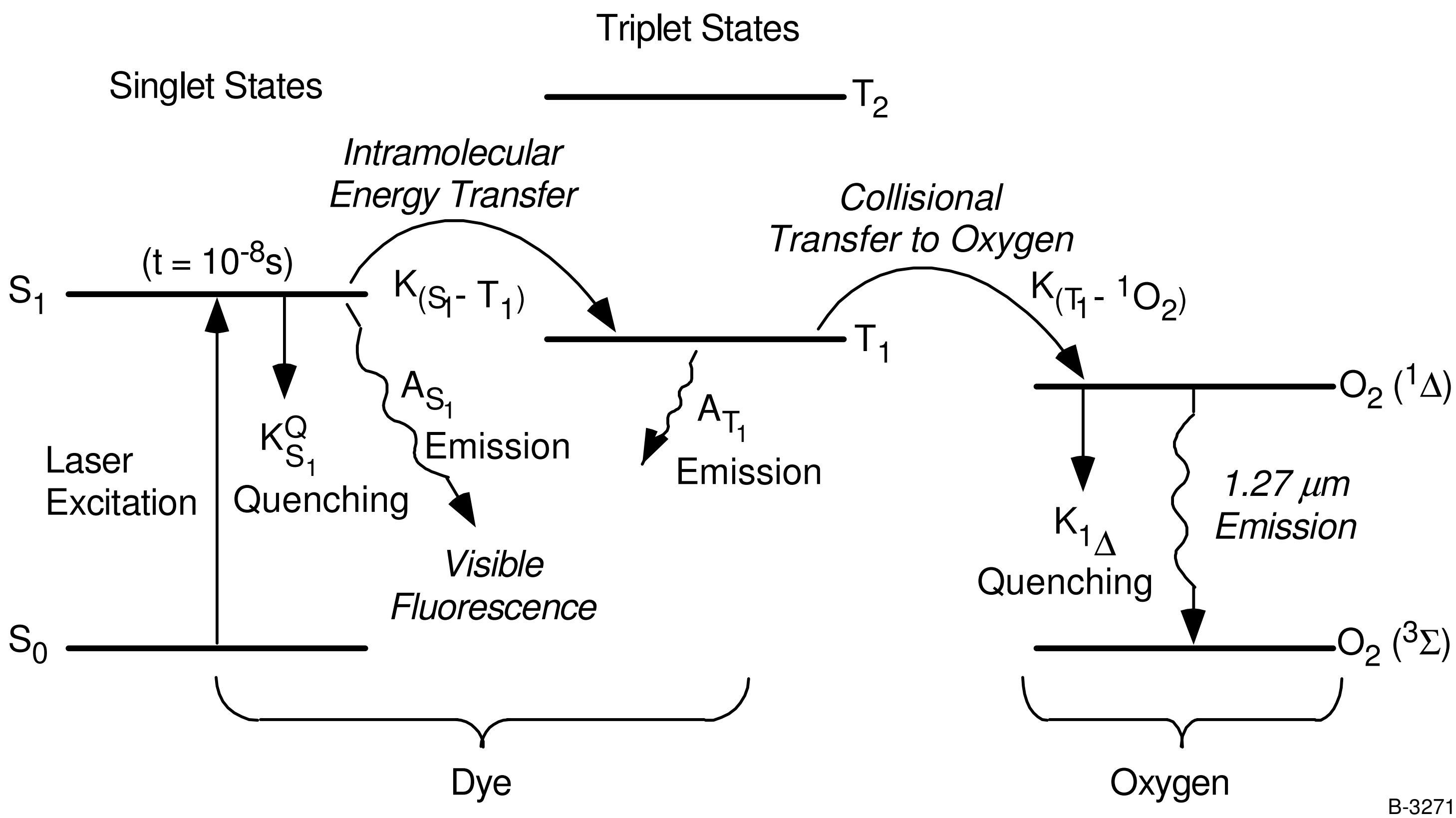
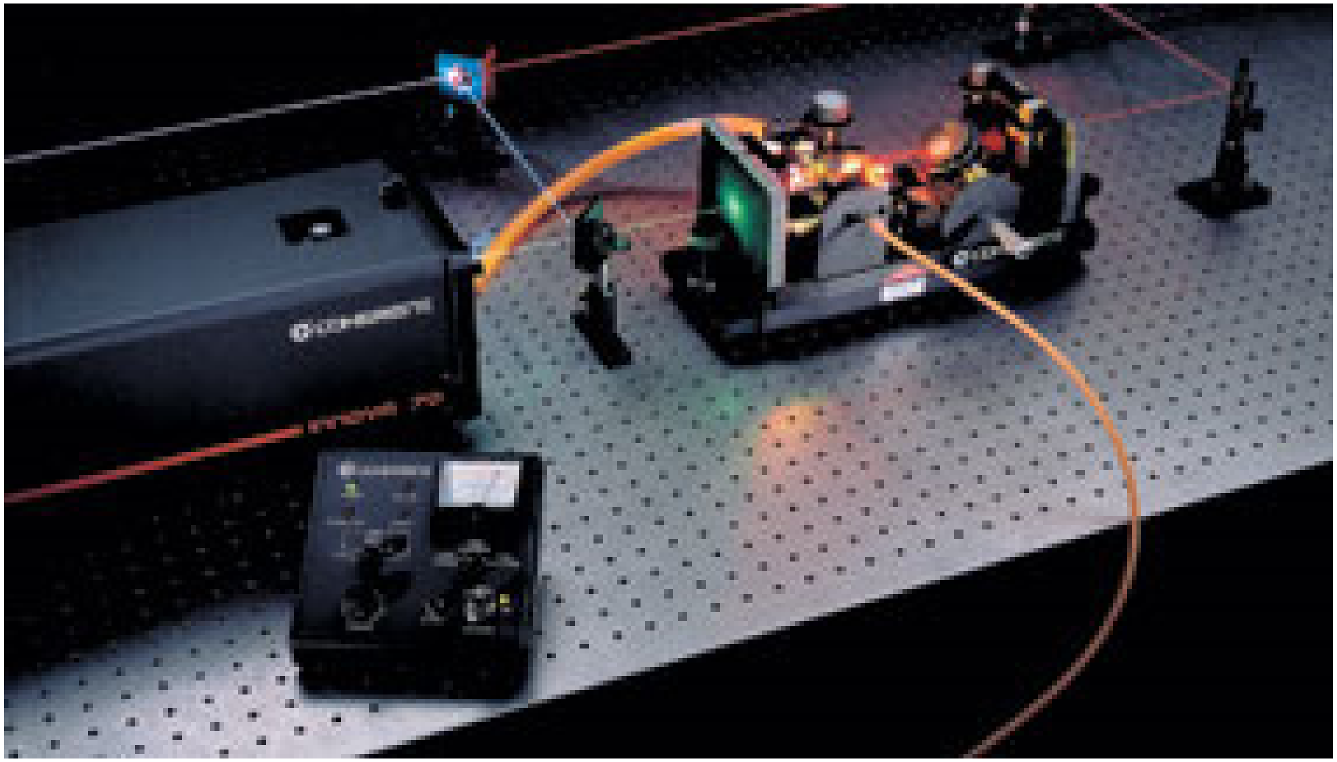
Type II PDT Mechanism



"Prompt" dye fluorescence
+
Energy Transfer

Singlet oxygen emission

Example of Argon Ion Laser-pumped Dye Laser



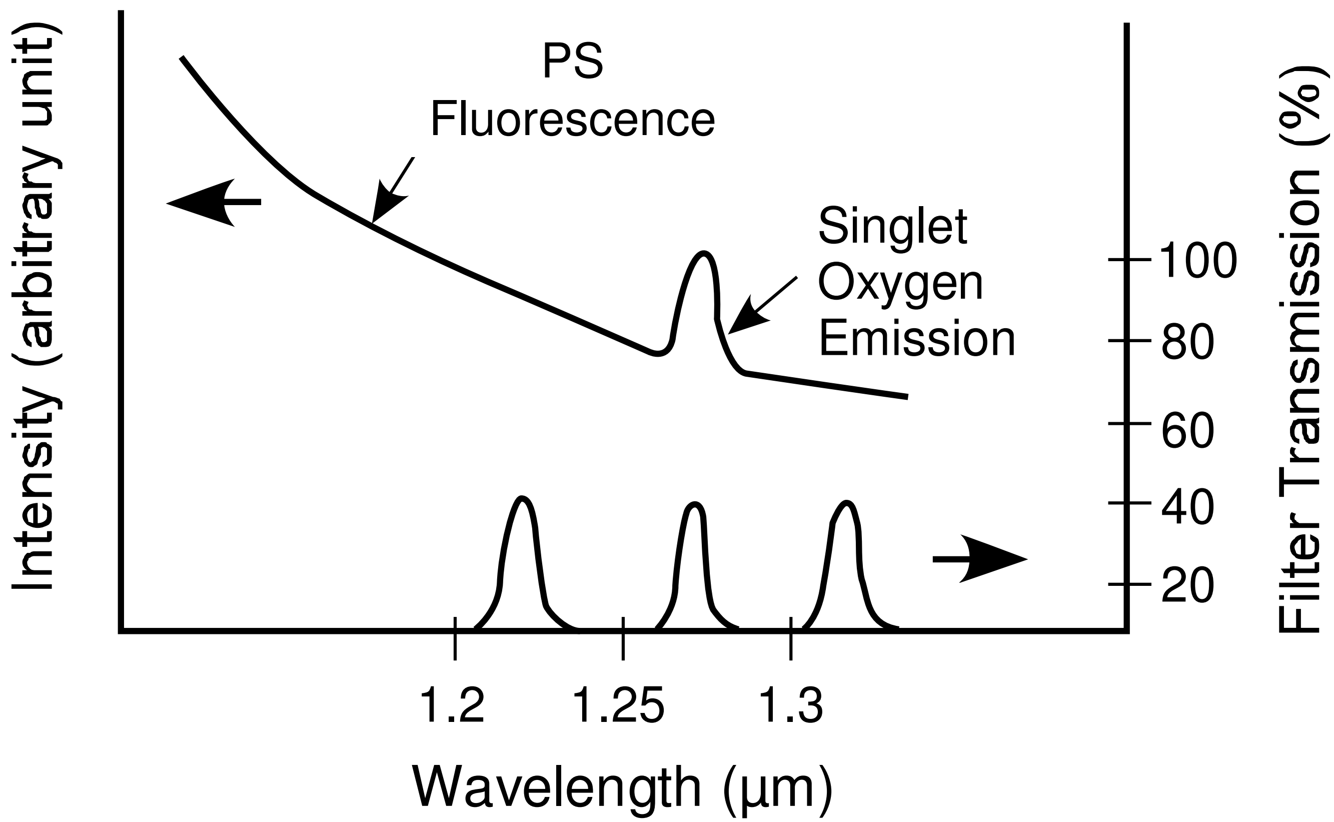
- Large and required “care and feeding”
- Provided tunable CW output from 570-700 nm
- Required ~ 50kW of electrical power and high volume water cooling
- System costs ≥ $50K

Diode Lasers Bring Unique Capabilities to PDT

- Compact, electrically efficient
- Fiber coupled
- Multiple wavelengths that cover PDT photosensitizers
- Pulsed and CW operation
- Extremely reliable and stable output
- Appropriate for laboratory and clinical applications
- Inexpensive ~ $1K

Application of Diode Lasers to PS and Singlet Oxygen Dosimetry

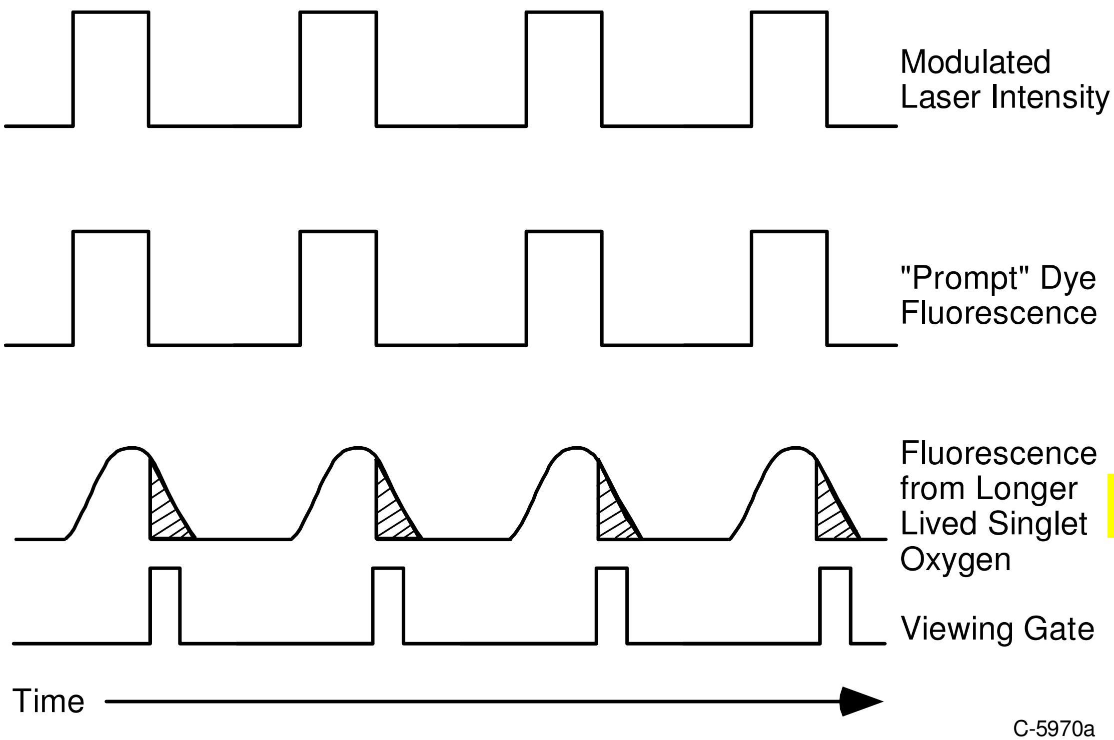
Spectral Discrimination of Singlet Oxygen from PS



Use three bandpass filters to extract the singlet oxygen signal from the PS

Time-resolved Detection for Singlet Oxygen

- **Pulsed Diode Laser → "Prompt" Dye fluorescence**
- **Photon Counter with optical filtering → Singlet Oxygen Monitor**



Optical filtering ~1.27 μm

Method we and others have used in the past to detect singlet oxygen *in-vivo*

Singlet Oxygen Emission Profiles

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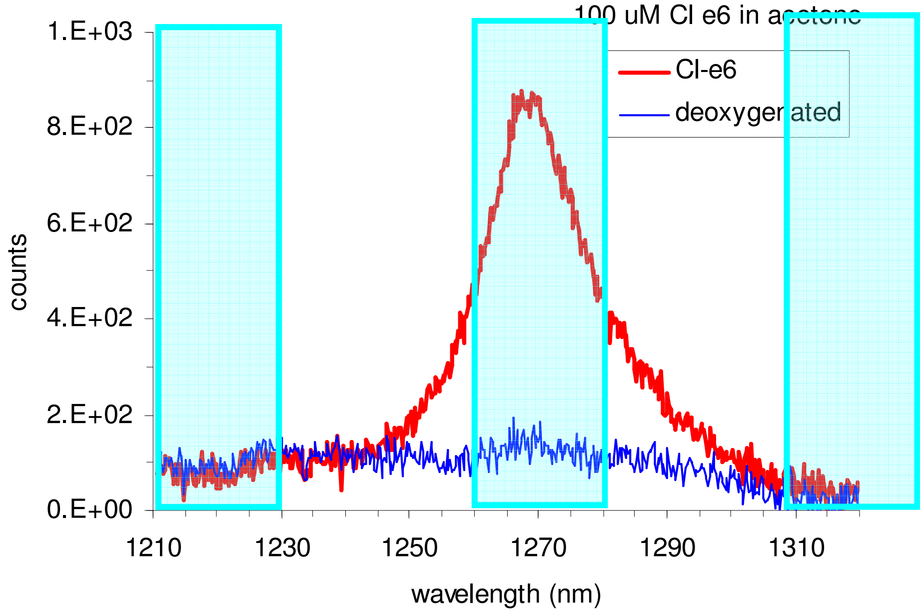
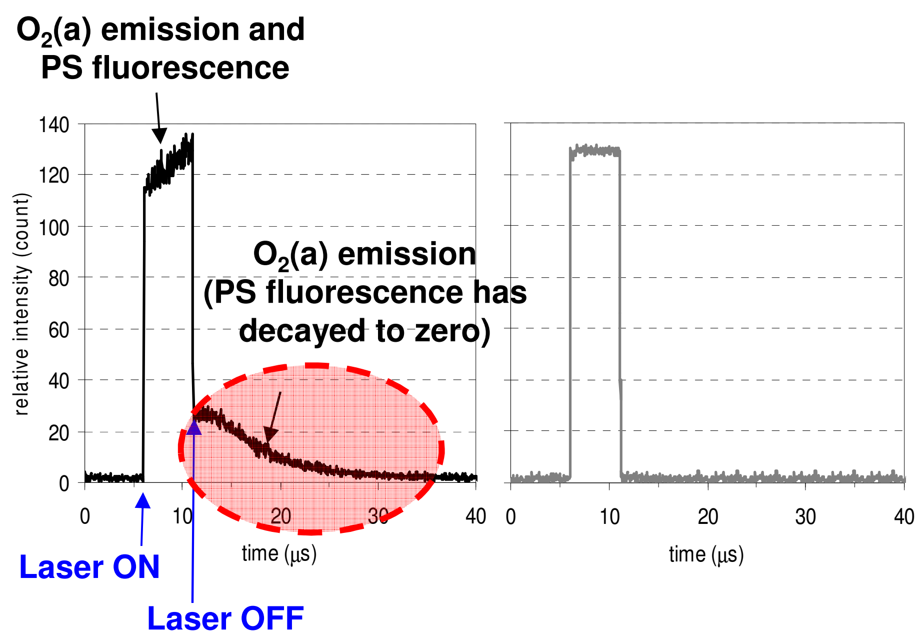
Spectral Profile



Temporal Profile



- **Point sensor**: Spectral and Temporal discrimination methods
- **2D Imager**: Spectral discrimination method

Prediction of PDT Temporal Profiles

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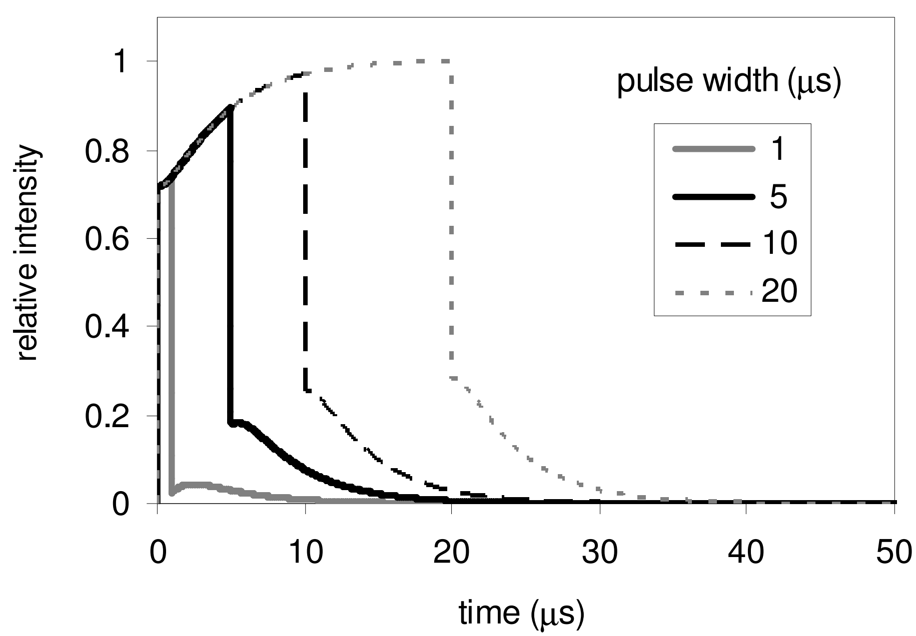
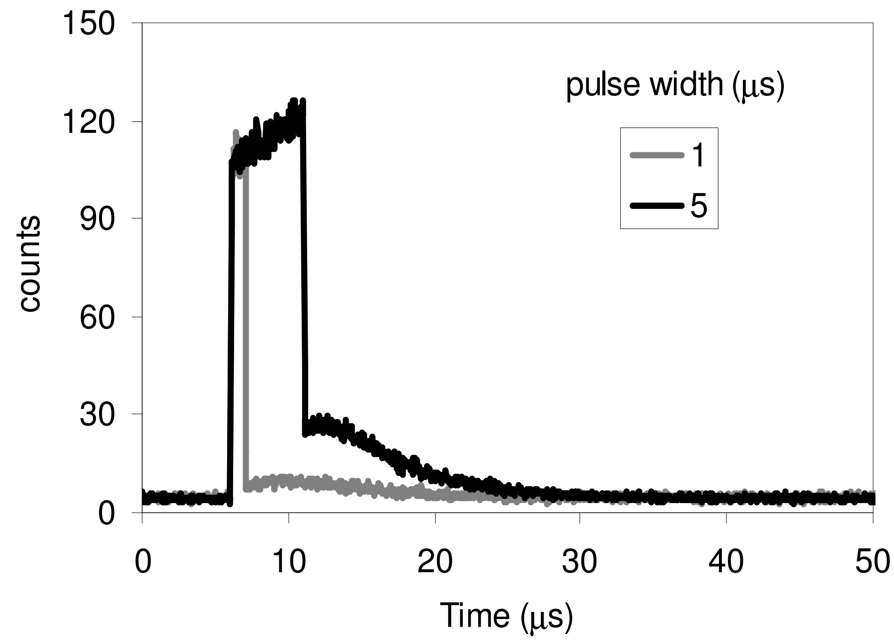
Cl e6 in water with various diode laser pulse widths





Prediction

with parameters:
Diode Laser intensity
State lifetimes, Transfer rates

Measurement

DL: pulse width of 1 & 5 μs
Cl e6: 100 μM

Singlet oxygen production during diode laser pulse is apparent

In-vitro Data Showing Temporally- and Spectrally-Resolved Detection of both PS and Singlet Oxygen (10 uM BPD in PBS)

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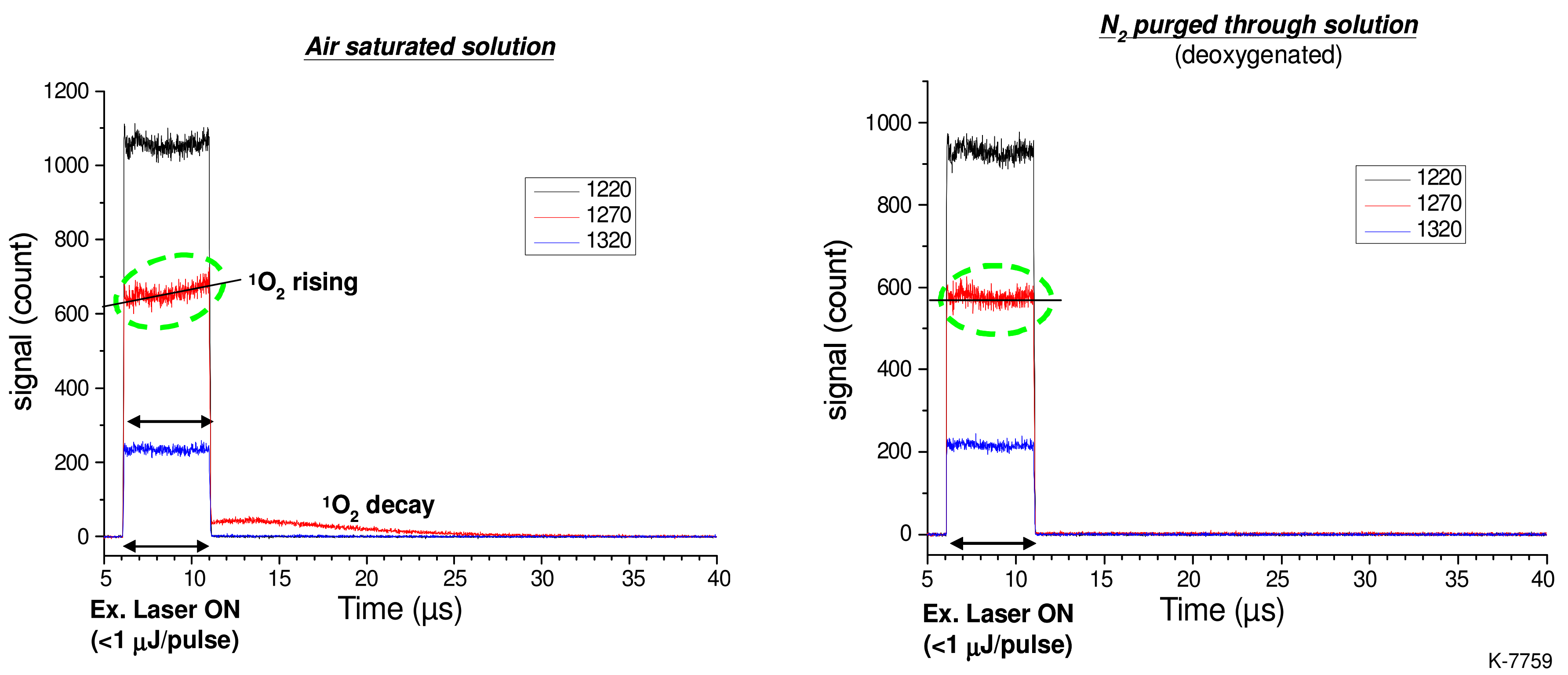

Singlet oxygen is observed only when sample is oxygenated

Studies with an Avalanche Photodiode (APD) Camera for 2D Imaging of Singlet Oxygen

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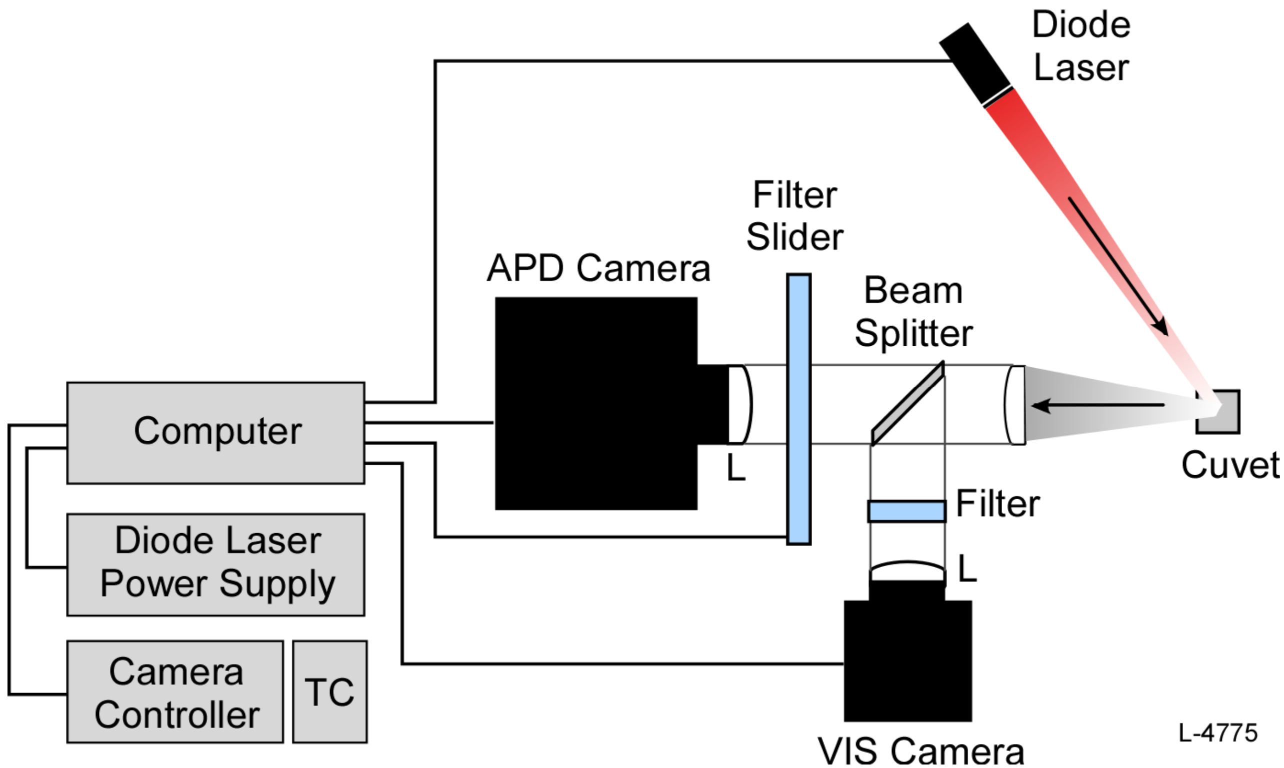

Camera can be gated up to 100kHz framing rate

Image and Time-resolved Intensity Observed with APD Camera for 5 us Laser Pulse (3µM BPD in methanol)

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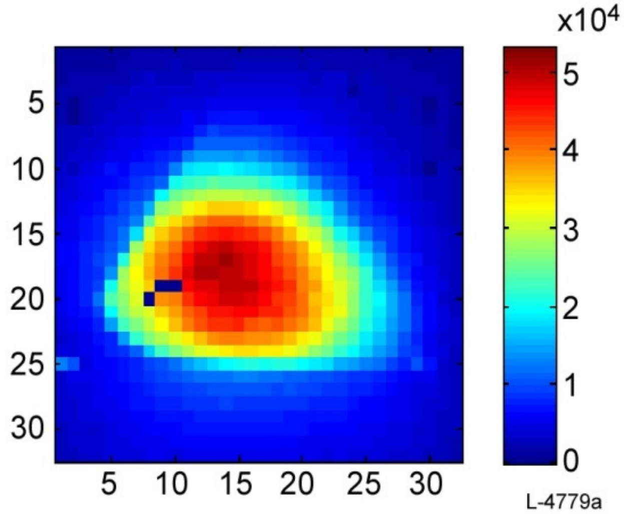

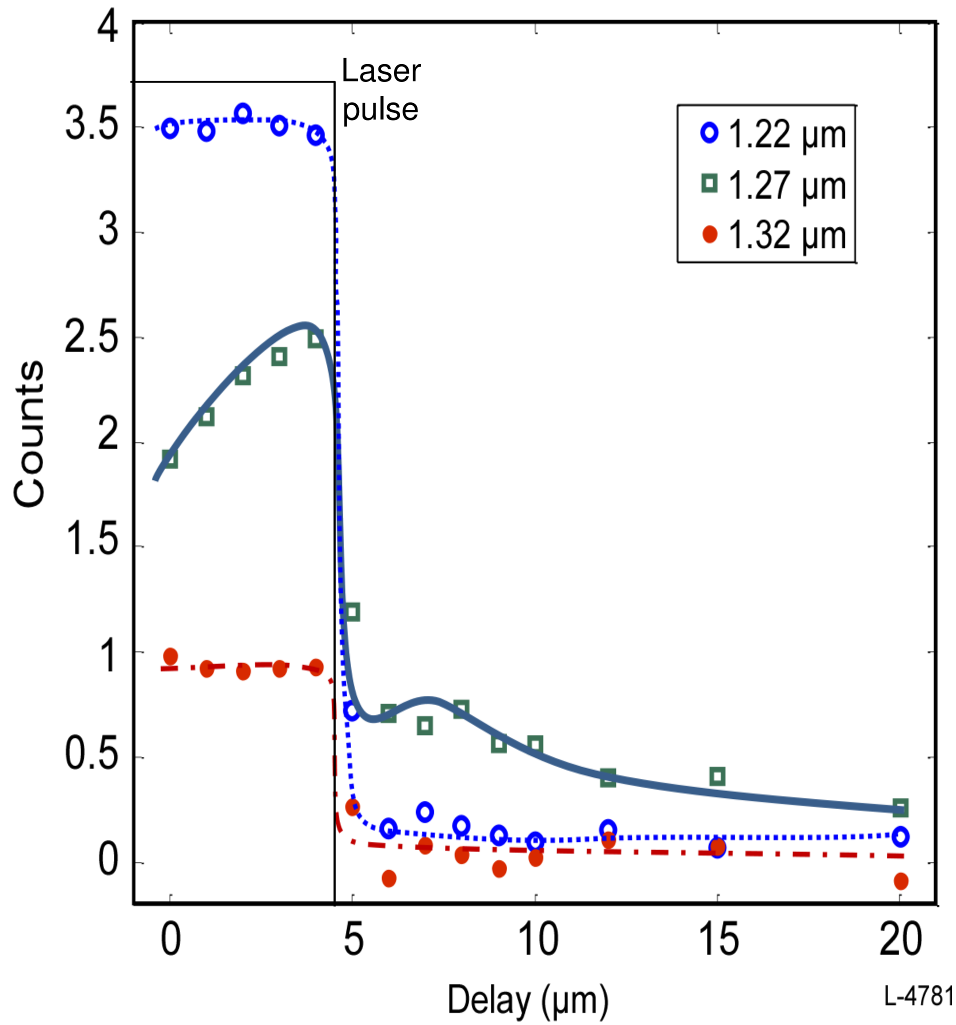

- Cuvette was masked with 3mm triangle
- Delay of 0.5 us camera gate was varied from 0 to 20 us
- Time profile similar to that obtained with PMT and agrees with model

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In-vivo Images of PS and Singlet Oxygen from Two Tumor-laden Mice

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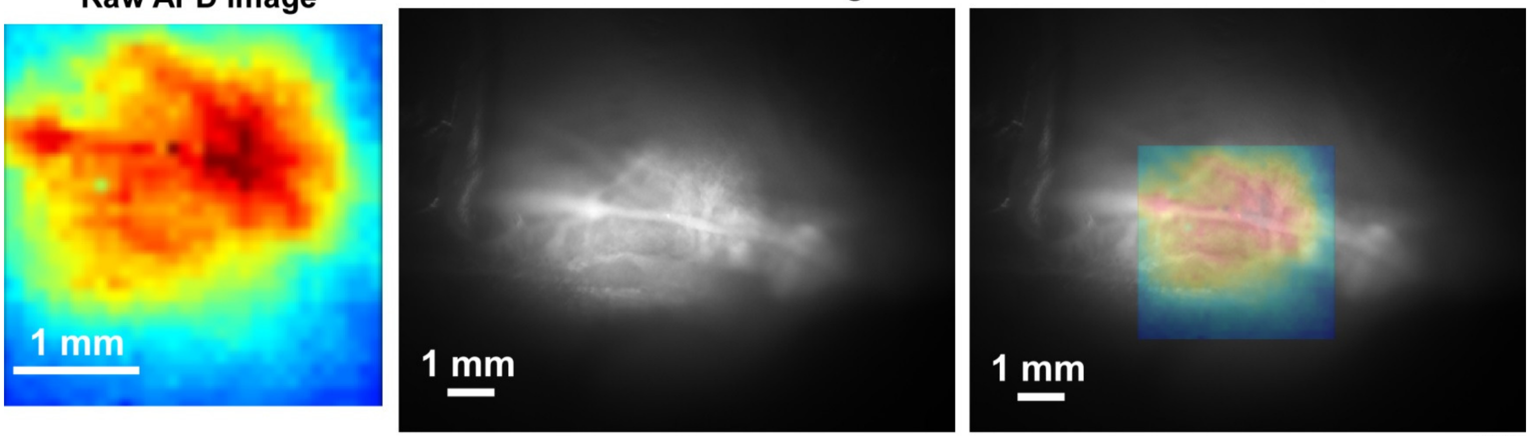
First image: Pulsed diode laser used, camera viewed both within and after laser pulse

Raw APD image | Raw fluorescence image | Overlaid image



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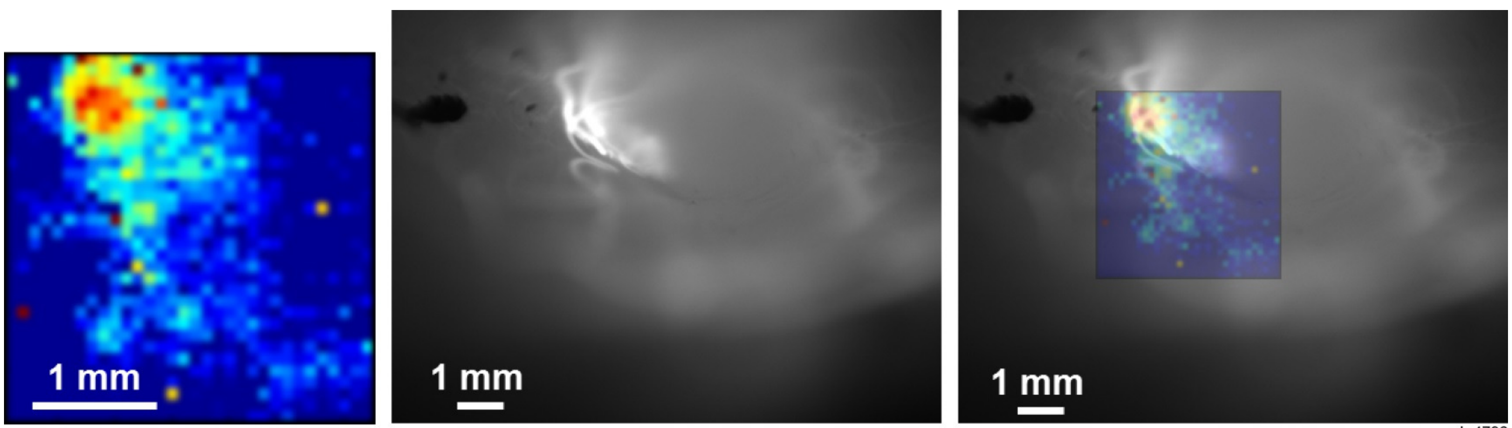
Second image: CW diode laser used, camera gated to 100 kHz, essentially cw viewing



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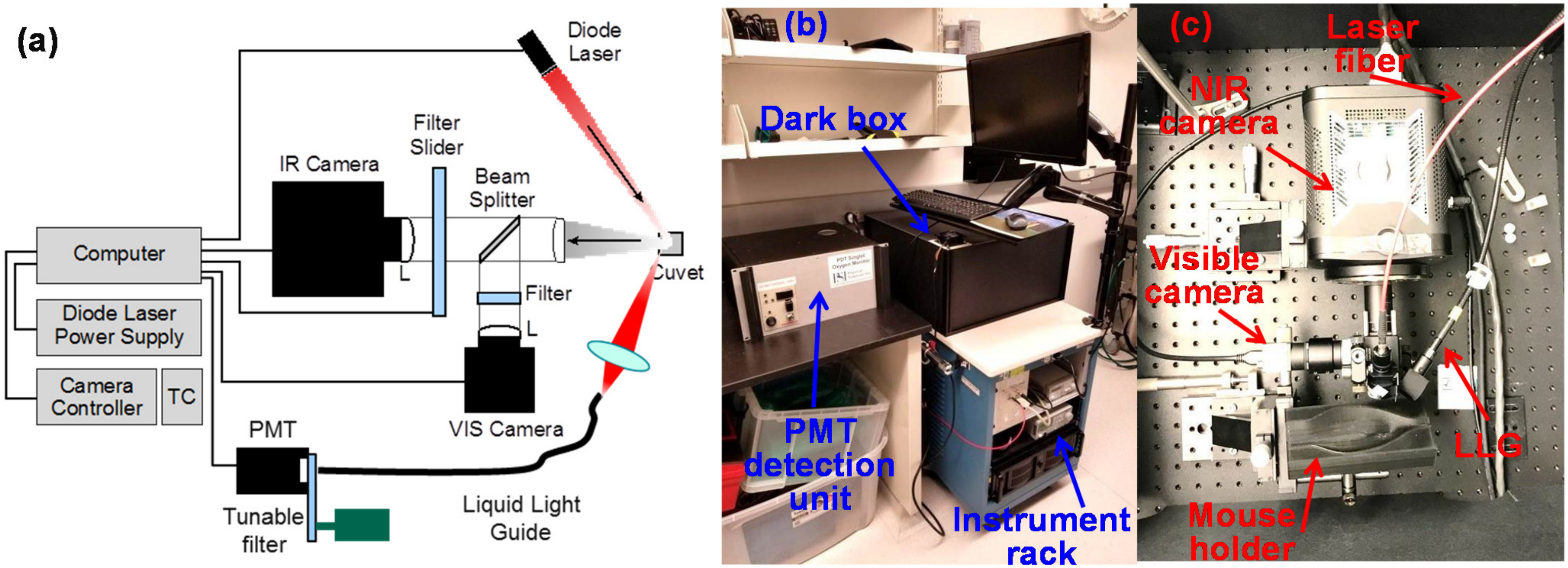
Integrated Imaging and Point Sensors



- New camera, cooled to -80 C (low dark count), 85% QE, and resolution < 50 µm
- Filtered to observe singlet oxygen at 1.27 um
- PMT channel provides simultaneous spectra of PS and singlet oxygen

In-vivo Measurements of PS and Singlet Oxygen

- **PMT used to determine the PS emission spectrum**
- **Visible wavelength camera used to obtain PS image**
- **IR camera used to image PS + Singlet Oxygen (1.27 μm)**
- **All three detectors operate simultaneously**
- **A 2-D image with cw diode laser PDT source obtained in ~30s**

PS and Singlet Oxygen Spectrum from a Mouse 7 minutes after Injection of BPD (2mg/kg) Laser Power: 39 mW

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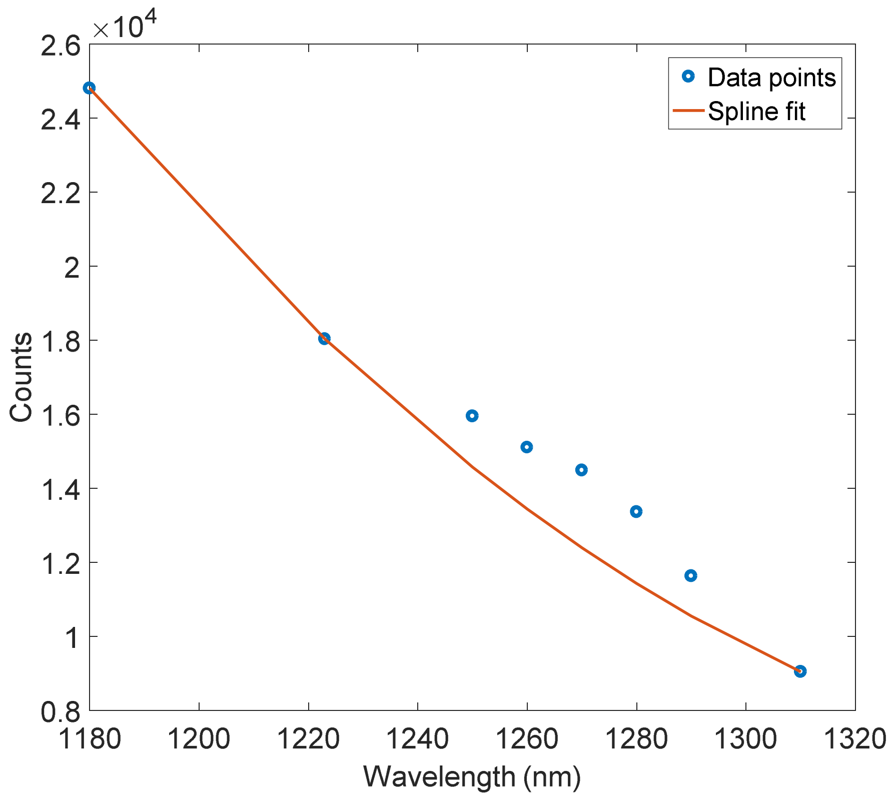

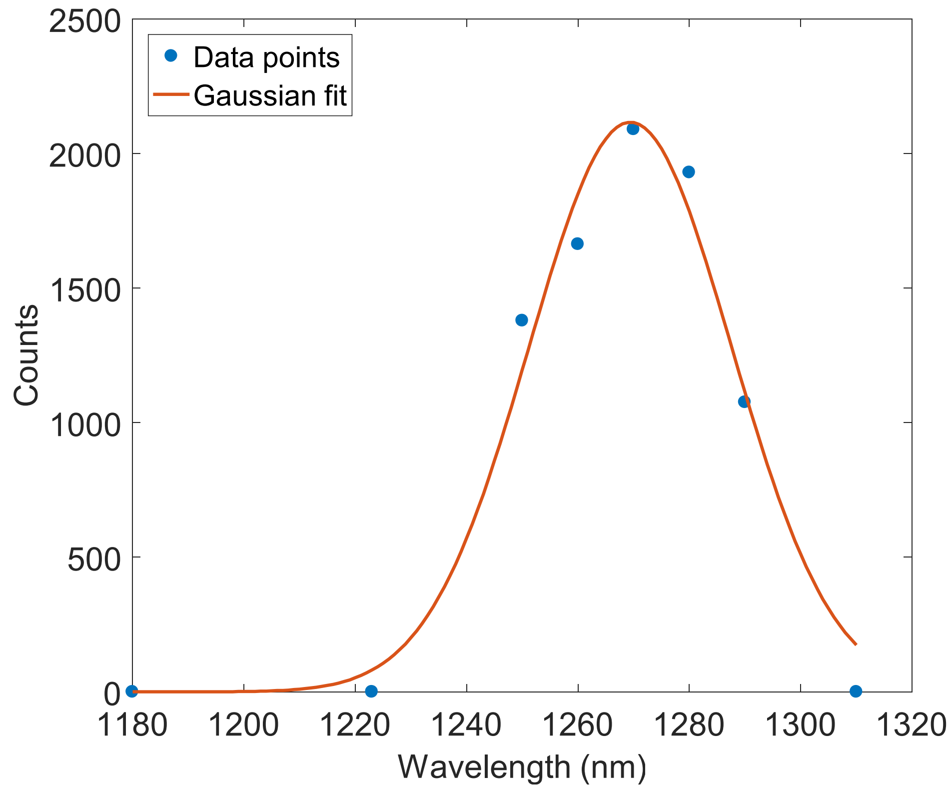

PS spectrum in the spectral region of singlet oxygen determined using a cubic spline fit

PS and $^1O_2$ Images of a Mouse after BPD Injection

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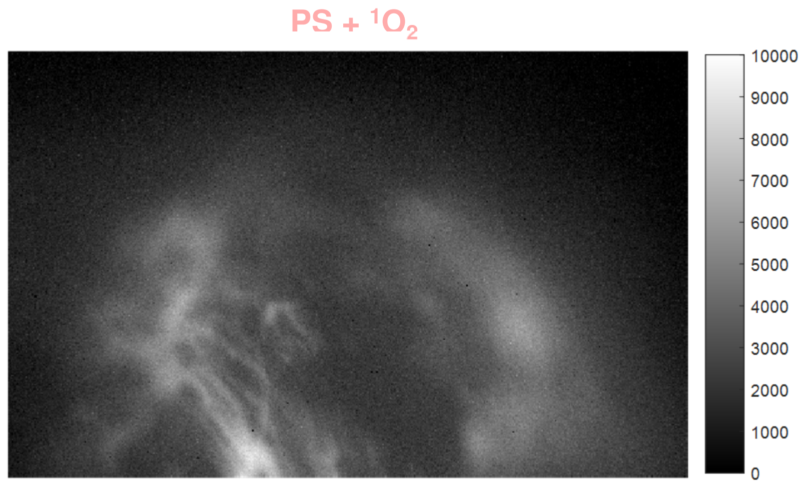

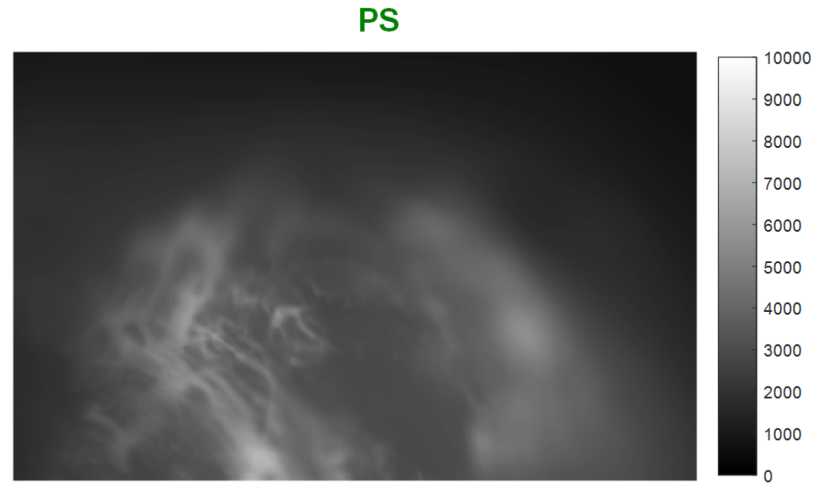

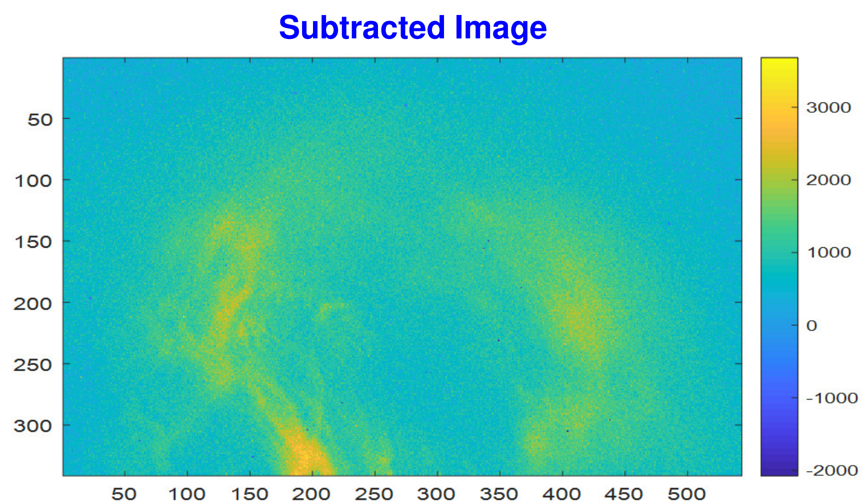

Other PDT Light Sources Discussed at IPA

- **Two photon excitation**
  - Deeper penetration
- **X-ray sources**
  - Synergistic effects of ionizing radiation and PDT
  - Deep in tissue treatment
- **Cerencov radiation**
- **Solar radiation**
  - Longer duration treatments may offer less painful treatments for skin lesions
- **Light Emitting Diodes**
  - Low cost, appropriate wavelengths, compact

Summary

- **PDT light sources have advanced from high power discharge lamps to miniature coherent and incoherent fiber-coupled devices**
- **Progress in these light sources have greatly advanced both our understanding of the PDT mechanisms and kinetics**
- **Modern light sources are facilitating both laboratory studies and clinical treatments**

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