National Institute of Biomedical Imaging and Bioengineering
Creating Biomedical Technologies to Improve Health

Radiodynamic Therapy of Cancer through Nanotechnology

Xiaoyuan (Shawn) Chen, PhD

Laboratory of Molecular Imaging and Nanomedicine
National Institute of Biomedical Imaging and Bioengineering
National Institutes of Health
shawn.chen@nih.gov

Outline

- Conventional photodynamic therapy
- Overcoming the Achilles' heel of PDT
  - Depth penetration
  - Oxygen self-supplement
  - Non-photodynamic approaches
- Conclusions

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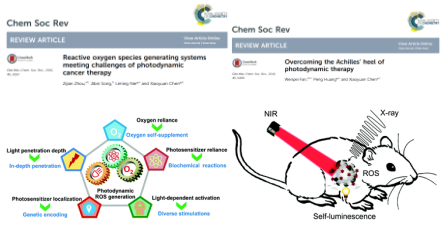
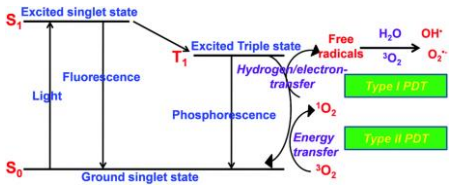
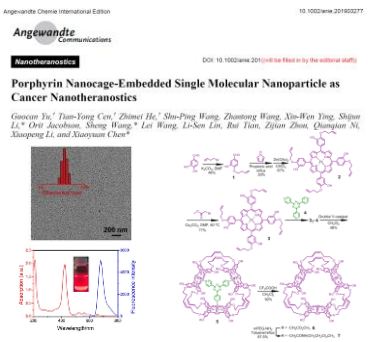


Photodynamic Therapy



PDT procedure is based on the cascade of synergistic effects between light, a photosensitizer (PS) and oxygen



Limitations of Conventional PDT

- The limited penetration depth of light, which restricts traditional PDT to superficial tumors
- Oxygen reliance does not allow PDT treatment of hypoxic tumors
- Light can complicate the phototherapeutic outcomes because of the concurrent heat generation
- Specific delivery of PSs to sub-cellular organelles for exerting effective toxicity remains an issue
- Side effects from undesirable white-light activation and self-catalyzation of traditional PSs.

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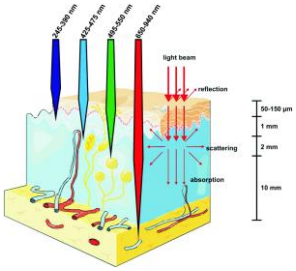
Penetration Depth



Utilizing light as an energy source, photosensitization is an electron transfer (not energy transfer) process from an excited light-absorbing sensitizer to a non-absorbing substrate. The penetration depth and delivery efficiency of light are two major obstacles in PDT of cancers for deep tissue treatment because the light can be largely reflected and decayed upon interacting with tissues (e.g., skin).

Overcoming the Limited Penetration Depth of PDT

- Upconversion system
- Two-photon excitation
- Self-illumination
- X-ray excitation
- Cerenkov irradiation
- Afterglow luminescence

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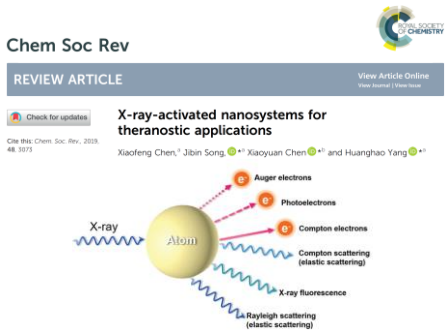
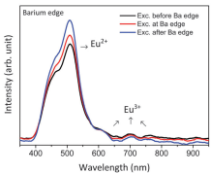


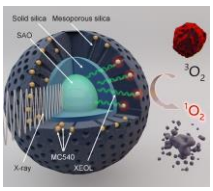
X-Ray Excited Optical Luminescence (XEOL)

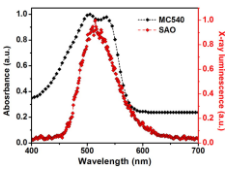
- Scintillation is a kind of radioluminescence (RL) phenomenon where the absorption of high-energy photons or energetic particle beams leads to an observable light emission.
- XEOL is the optical luminescence emitted when the core-level X-ray excitation occurs.



NANO LETTERS

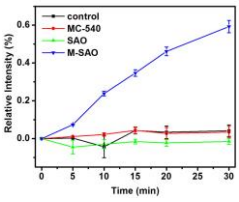
Nanoscintillator-Mediated X-ray Inducible Photodynamic Therapy for In Vivo Cancer Treatment

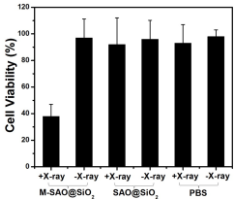




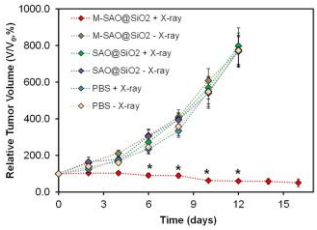
SAO: $SrAl_2O_4:Eu^{2+}$ converts X-ray photons to visible photons (XEOL)
PS: merocyanine 540 (MC540)

M-SAO@SiO_2 Nanoparticles Under X-ray Irradiation Produce $^1O_2$

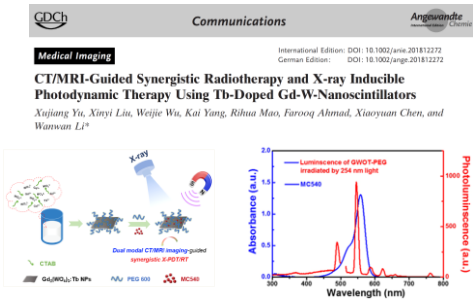




X-PDT for In Vivo Tumor Therapy



1 Gy/h for 30 min, beam diameter 6 mm at 5 min after particle injection.
This irradiation dose is far below those used in clinical radiotherapy (e.g., 60–80 Gy for solid epithelial tumors, 5 Gy per fraction)



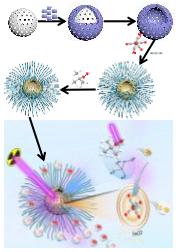
Radiosensitization

- Local availability of molecular oxygen enhances the efficacy of radiotherapy, as DNA lesions caused by ROS produced during water radiolysis react with oxygen to from stable DNA peroxides
  - Dose amplification by high Z atom nanoparticles
  - Enhanced ROS production

ARTICLE

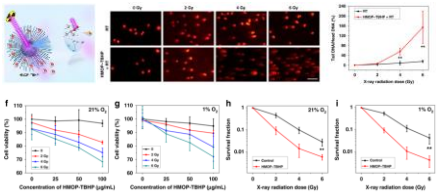
https://doi.org/10.1038/s41467-019-09558-1 OPEN

Generic synthesis of small-sized hollow mesoporous organosilica nanoparticles for oxygen-independent X-ray-activated synergistic therapy



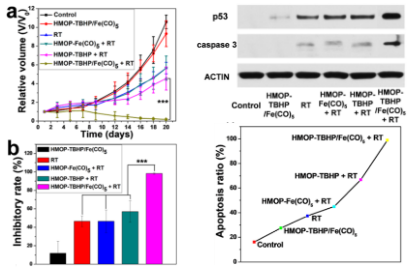
TBHP: tert-butyl hydroperoxide
O-O bond: 146 kJ mol^{-1}
X-ray-activated O–O bond cleavage
Radiodynamic therapy: •OH
•OH reacts with $Fe(CO)_5$ to release CO

In Vitro Evaluation of RDT

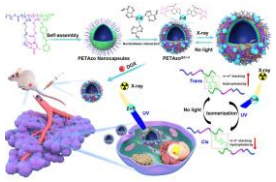


The damaged DNA exhibits long tail of fluorescent stain, and the degree of DNA damage can be determined by the length of tail stain.

HMOP-TBHP/$Fe(CO)_5$ + RT



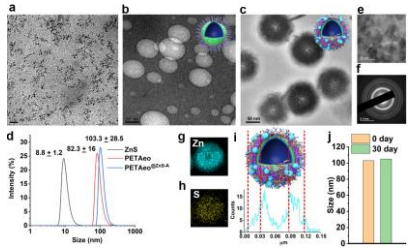
X-ray Controlled Bilayer Permeability of Bionic Nanocapsules Stabilized by Nucleobase Pairing Interactions for Pulsatile Drug Delivery



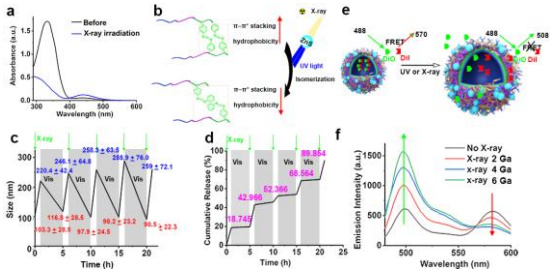
- three-block polymers into nanocapsules
- adenine modified zinc sulfide nanoparticles
- Thymine (T)-Adenine (A) interaction
- Scintillating ZnS NP converts X-ray to UV
- Azobenzene: trans-cis isomerization
- π-π stacking and hydrophobicity ↓
- Nanoparticle swelling

Deng H et al. Adv Mater, in press.

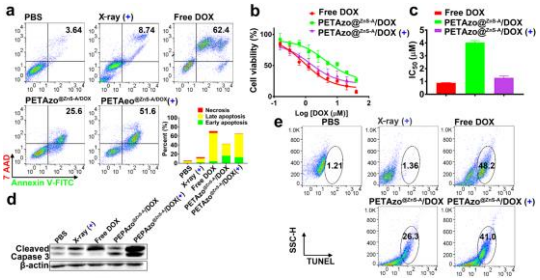
ZnS Nanocapsule



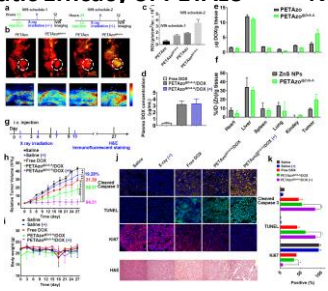
Pulsatile Release by X-Ray



In Vitro Cytotoxicity



Therapeutic Efficacy of PETAzo$^{@ZnS\text{-}A}$ Nanocapsules



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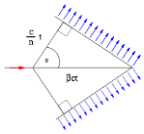
- Afterglow luminescence

Cerenkov radiation is an electromagnetic radiation emitted when a charged particle (such as an electron) passes through a dielectric medium at a speed greater than the phase velocity of light in that medium.

On their way through a medium, charged particles disturb electrons in the medium. When these resume their position, they emit light. Normally this does not produce any light that can be observed, but if the particle moves faster than light, a kind of backwash of light appears.



Pavel A. Cherenkov
(Nobel Prize in Physics 1958)

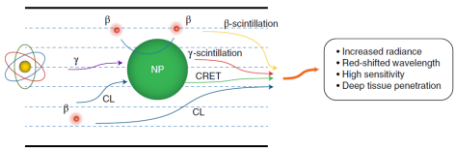
BIOIMAGING

When radionuclides meet nanoparticles

Interaction between radionuclides and nanoparticles expands the in vivo imaging possibilities based on Cerenkov luminescence.

Gang Niu and Xiaoyuan Chen

NATURE NANOTECHNOLOGY | VOL 13 | MAY 2018 | 357–361 |



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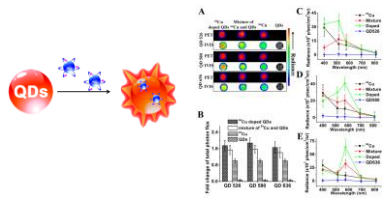
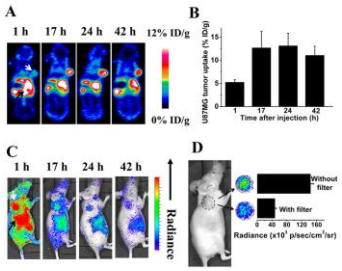
Communication
pubs.acs.org/JACS

Self-Illuminating ^{64}Cu-Doped CdSe/ZnS Nanocrystals for in Vivo Tumor Imaging

Xiaolian Sun,[†,‡] Xinglu Huang,[†,‡] Jinxia Guo,[†,‡] Wenlei Zhu,[‡] Yong Ding,[‡] Gang Niu,[†] Andrew Wang,[⊥] Dale O. Kiesewetter,[†] Zhong Lin Wang,[‖] Shouheng Sun,[§] and Xiaoyuan Chen*[,†]



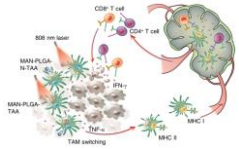
PET vs. Cerenkov Luminescence Imaging



NANO LETTERS
Letter

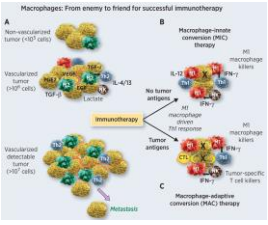
Reprogramming Tumor-Associated Macrophages by Nanoparticle-Based Reactive Oxygen Species Photogeneration

Changrong Shi,[†] Ting Liu,[‡,†] Zhide Guo,[†] Rongqiang Zhuang,[†] Xianzhong Zhang,*[,†] and Xiaoyuan Chen*[,§]



Reprogram TAMs to an antitumor M1 phenotype using nanoparticle-based ROS photogeneration
Reprogrammed TAMs orchestrate CTL recruitment and direct memory T-cells toward tumoricidal response

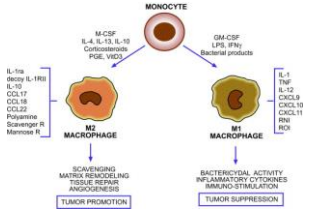
Macrophages Predominate in Cancers and Promote Growth



- Tumor growth is accompanied by the preferential accumulation of M2/repair-type macrophages
- Macrophage-innate conversion from M2 to M1-type (MIC1) can directly cause tumor rejection
- If tumor-specific antigens are present, macrophage-adaptive conversion from M2 to M1-type (MAC1) can directly (non-specifically) and indirectly (specifically) cause tumor rejection.

Adapted from Mills CD et al. Cancer Res. 2016;76(3):513.

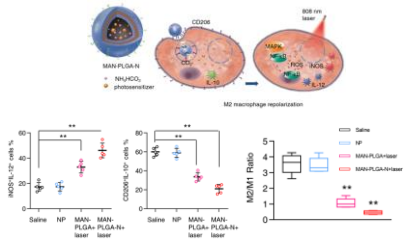
ROS Skews M2 Macrophages to M1 Phenotype



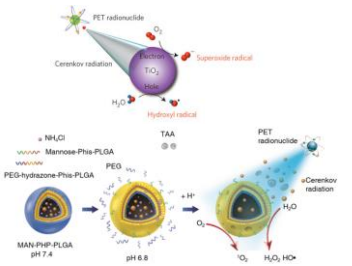
In the presence of granulocyte-macrophage colony stimulating factor (GM–CSF), interferon (IFN)-γ, lipopolysaccharide (LPS) and other microbial products make monocytes differentiate into M1 macrophages.

Adapted from Sica A et al. Eur J Cancer. 2006;42(6):717

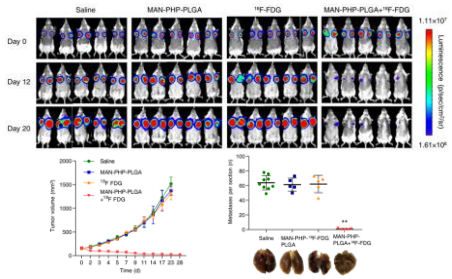
ROS Photogeneration Reprograms TAMs to M1 Phenotype



Cerenkov Radiation Mediated PDT



TiO2 + FDG PDT Prevents Metastasis



Conclusions

- The underlying mechanism of PDT for growth inhibition and shrinkage of tumors is the generation of ROS. Although PDT drugs have been approved for clinical use, they have not gained acceptance as a first-line treatment option.
- Improvement: (i) introducing an engineered light source for in-depth penetration; (ii) constructing oxygen self-supplied formulations; (iii) making photosensitization responsive to stimulations other than light; (iv) utilizing non-photodynamic biochemical reactions to avoid the dependence on PSs, oxygen and light
- Using radiation (both external beam irradiation and internal radionuclide) and nanotechnology can help produce ROS and sensitize cancer treatment, overcoming the limitations of PDT

Acknowledgment

NIH INTRAMURAL RESEARCH PROGRAM