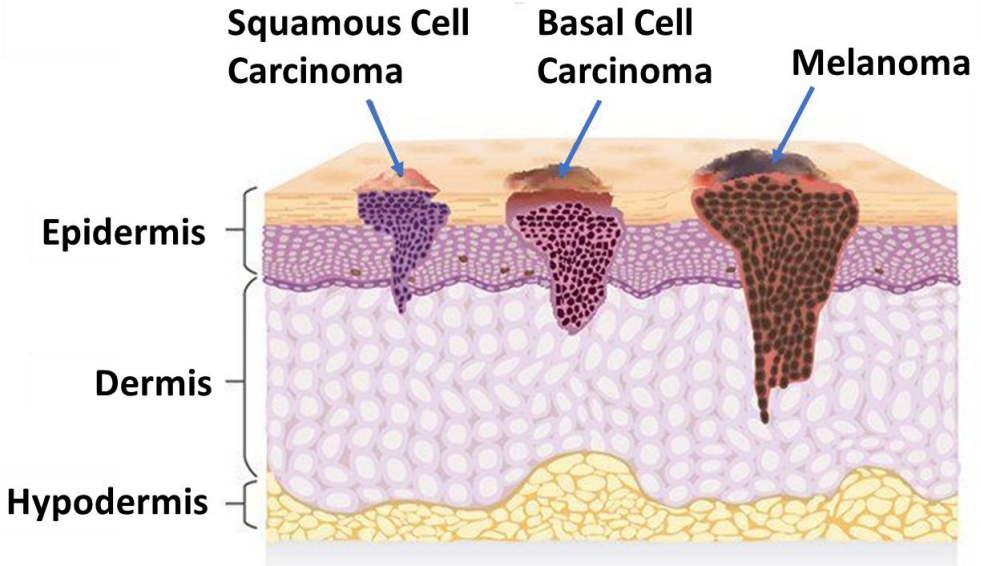
SOLVOTHERMAL FABRICATION OF ROSE BENGAL–TERBIUM THERANOSTIC PARTICLES FOR X-RAY PHOTODYNAMIC THERAPY

Dr. Bunty Sharma
Marie-Curie Fellow
School of Pharmacy, Queen's University Belfast, UK

Skin Cancer



- Challenges with Treatment:
  - Heterogeneity of Skin Cancer types
  - Sex-dependent disparity
  - Resistance to treatment
  - Metastasis
  - Recurrence

*https://www.britishskinfoundation.org.uk

Photodynamic Therapy (PDT)

PDT is a clinical procedure that uses a combination of photosensitizer (PS) drug and the light of a specific wavelength to activate PS which reacts with molecular triplet state oxygen ($^3O_2$) and generates highly toxic reactive oxygen species (ROS)*

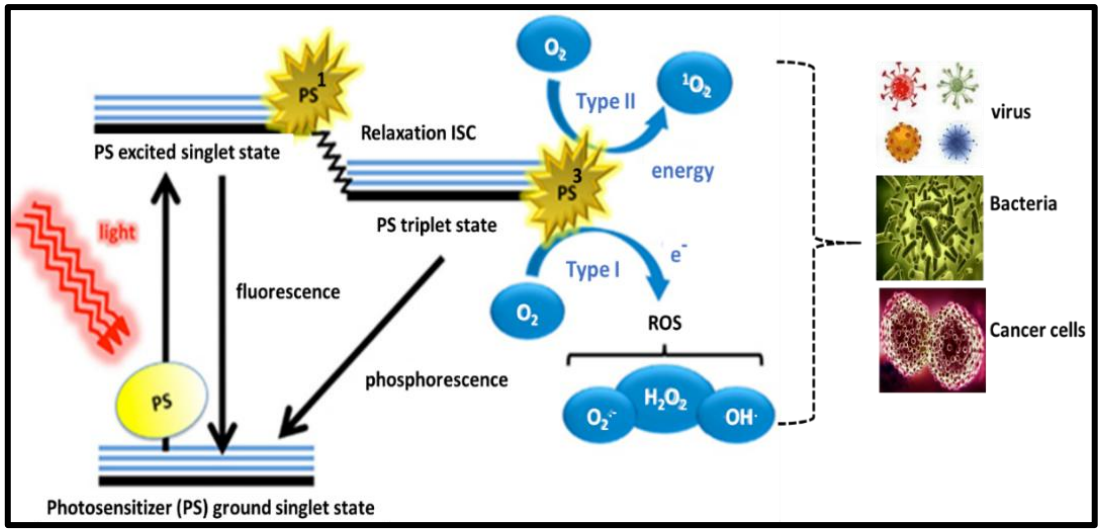


Figure. Pictorial representation of PDT mechanism

*Li et al., Coord. Chem. Rev., 2020, 418, 213355

Challenges with Photodynamic Therapy

1st generation (late 1970)	• Porphyrins and hematoporphyrin derivative
2nd generation (late 1980)	• Derivatives of porphyrins and metalloporpyrins
3rd generation (since 2000)	• Biologic conjugates/ organic and inorganic nanoparticles
4th generation (2011 onwards)	• Nano MOFs/peptide self-assembled photosentizer

Figure. Photosensitizer generation progress**

- Low light penetration through skin tissues
- Non-ideal photosensitizer
- Complex dosimetry
- Some molecules produced through cellular **metabolism (porphyrins and cytochromes)** are also sensitive to certain **wavelengths** of light

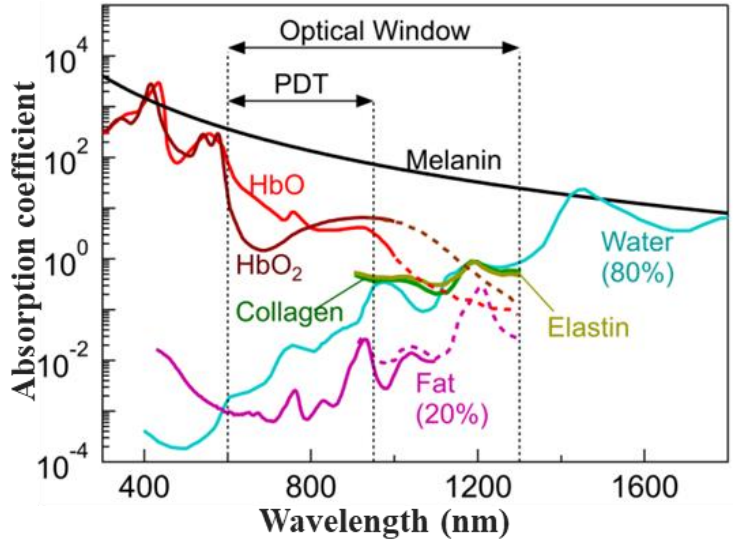


Figure. Absorption coefficient as a function of wavelength for several tissue constituents#

- ❑ Major problems associated with PDT and PSs
  - Poor water solubility
  - Photobleaching
  - Self-aggregation
  - Low Singlet Oxygen generation

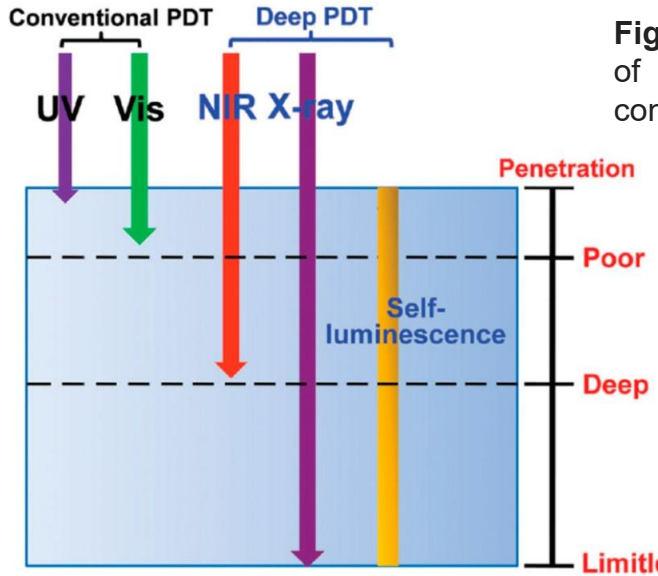


Figure. Comparison of tissue penetration of different excitation sources*

**Josefsen et al., Met. Based Drugs, 2008, 2008, 276109

#Algorri et al, Cancers, 2021, 13(14), 3484,

*Sivasubramanian et al., Molecule, 2019, 24, 520

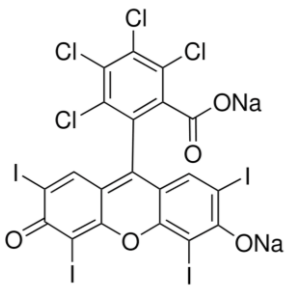
Theranostic approach, Selection of Photosensitizer and Scintillator

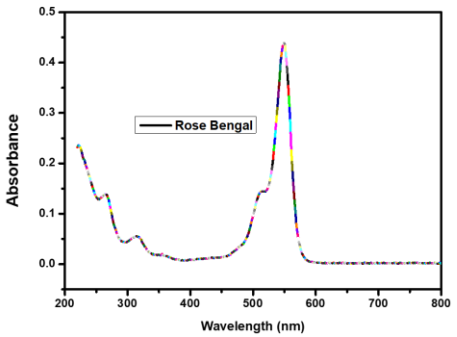
*Theranostic systems combine **imaging** and **therapy** in a single platform for personalized cancer treatment.*

Photosensitizer (PS)	Type/Class	Excitation λ (nm)	Emission λ (nm)	Notes
Rose Bengal	Xanthene dye	550–560	~580–600	High $^1O_2$ yield; hydrophilic

Lanthanide Ion	Main Emission Peaks	Emission Color	Remarks
Tb^{3+}	545 nm (strong), 495 nm, 585 nm	Green	$^5D_4 \rightarrow {}^7F_5$ transition; efficient green emitter

PHOTOSENSITIZER



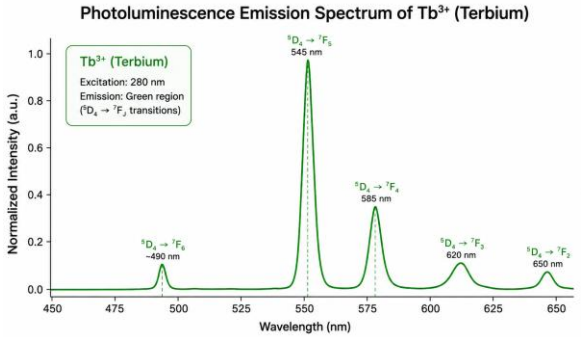


Rose Bengal

- High singlet oxygen ($^1O_2$) quantum yield
- Hydrophilic / water soluble
- Well-established PDT agent
- Easy to functionalize

+

SCINTILLATOR



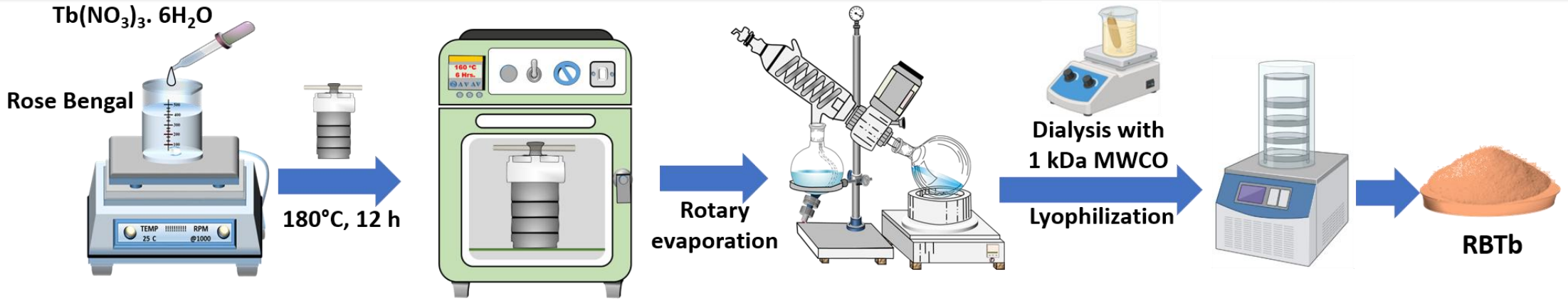
Tb^{3+} (Terbium)

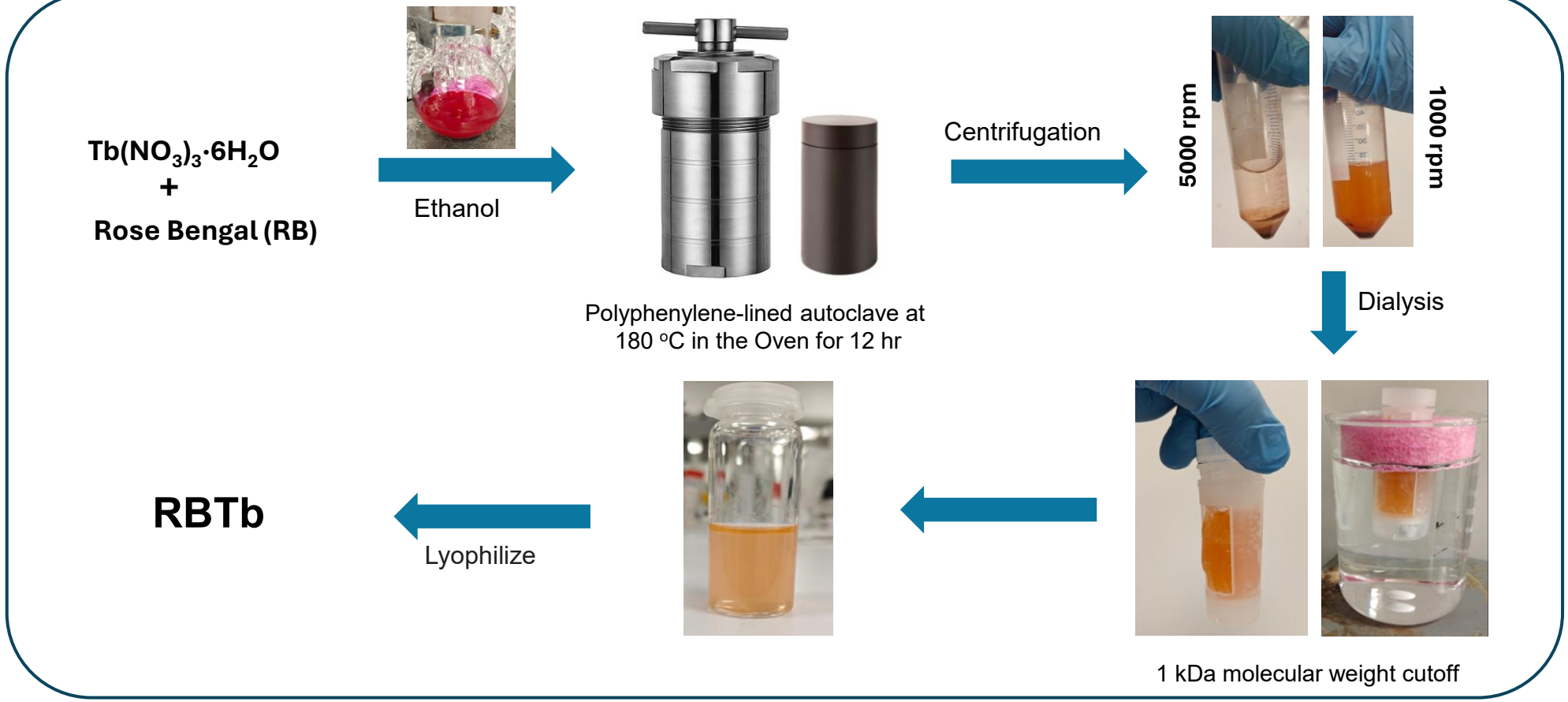
- Strong emission at 545 nm
- Efficient lanthanide scintillator
- Strong green photoluminescence
- Suitable for X-ray excitation

RBTb Theranostic Particles

- Efficient energy transfer (Tb^{3+} → Rose Bengal)
- Strong green emission for imaging
- Responsive to X-ray excitation
- Enhanced singlet oxygen generation under X-ray
- Stable, water-dispersible nanoparticles
- Combines diagnostic and therapeutic functions

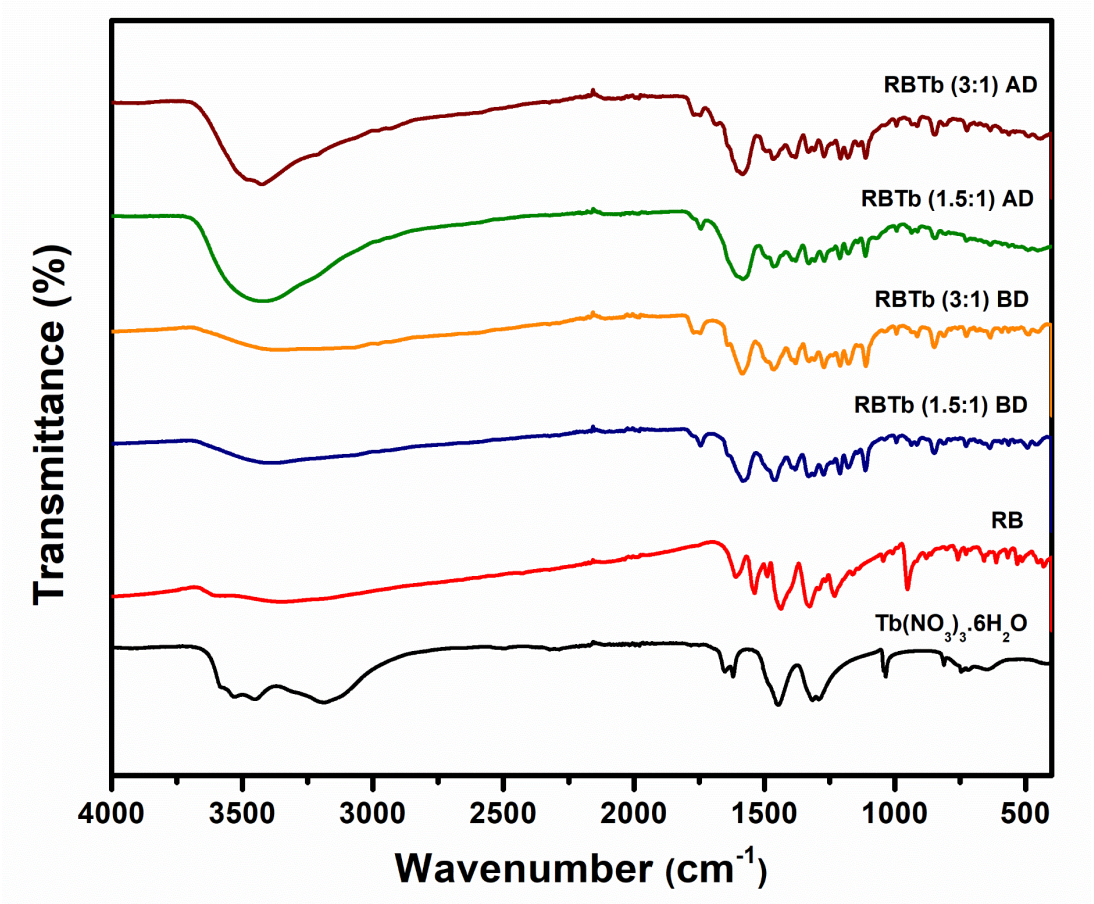
Synthesis of RBTb nanoparticles



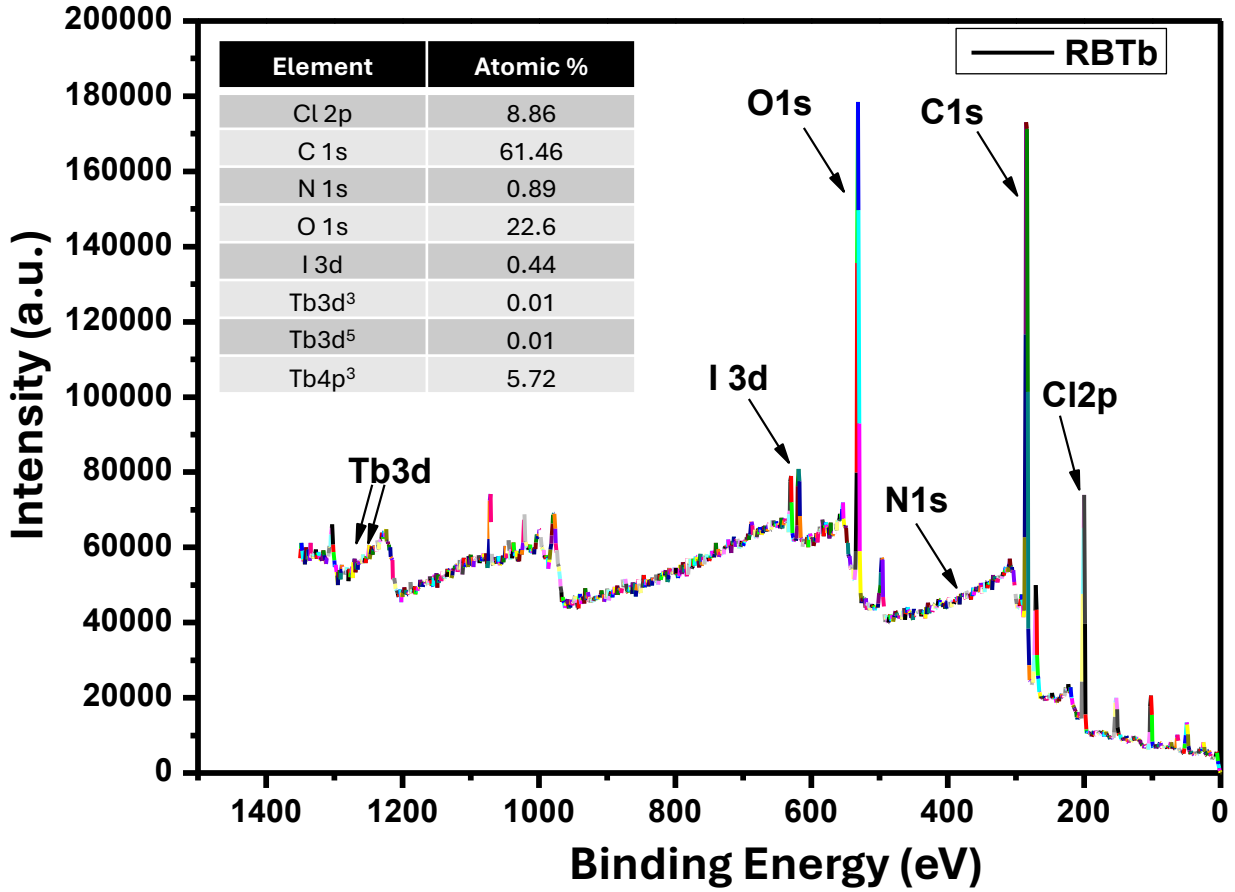


RBTb Characterization

FTIR

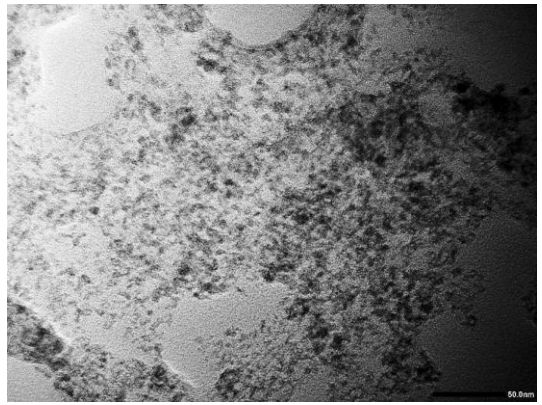


XPS

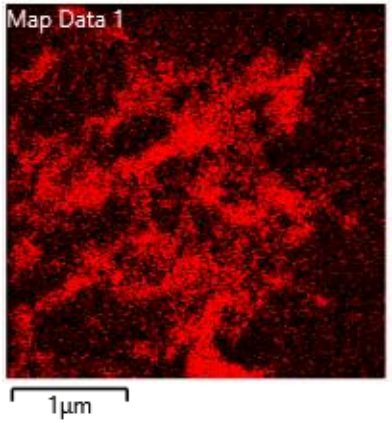


Element	Atomic %
Cl 2p	8.86
C 1s	61.46
N 1s	0.89
O 1s	22.6
I 3d	0.44
$Tb3d^3$	0.01
$Tb3d^5$	0.01
$Tb4p^3$	5.72

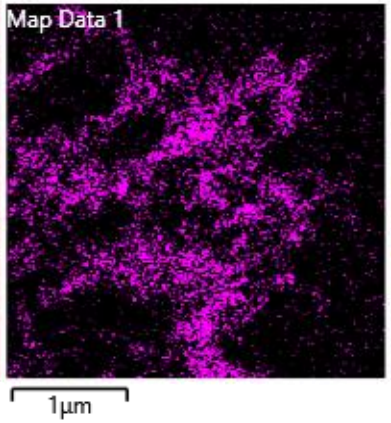
HR-TEM-EDS and Elemental Mapping



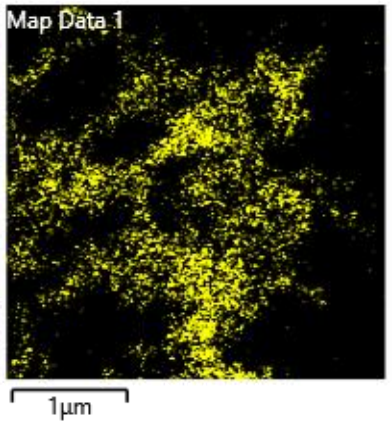
C Kα1_2



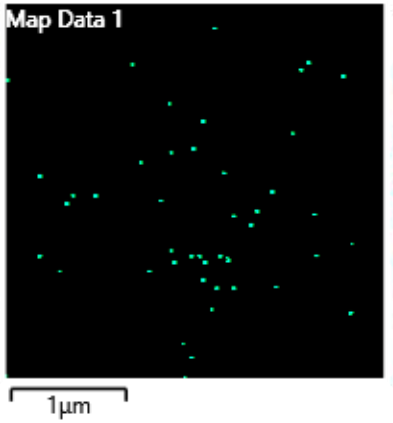
O Kα1



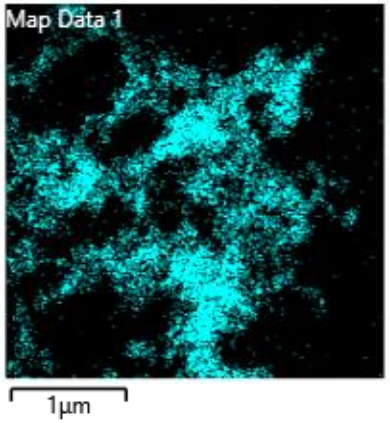
Tb Lα1

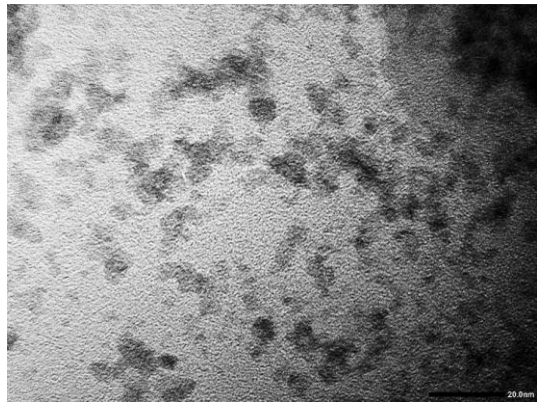


I Kα1

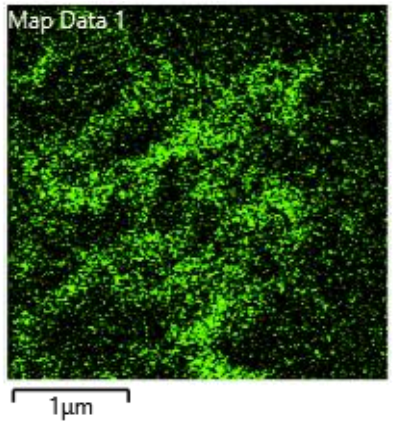


Cl Kα1

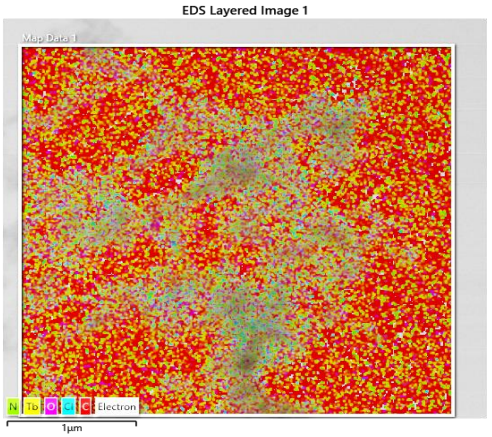


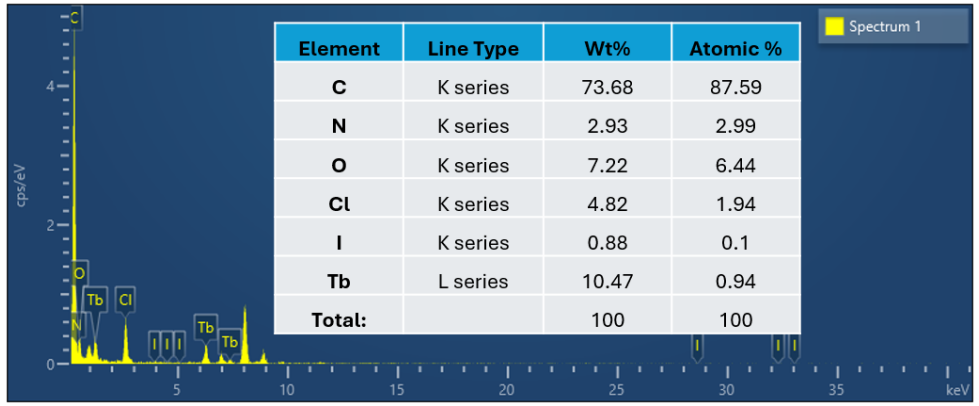


N Kα1_2



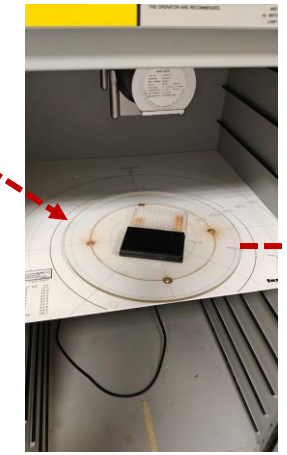
EDS Layered Image 1

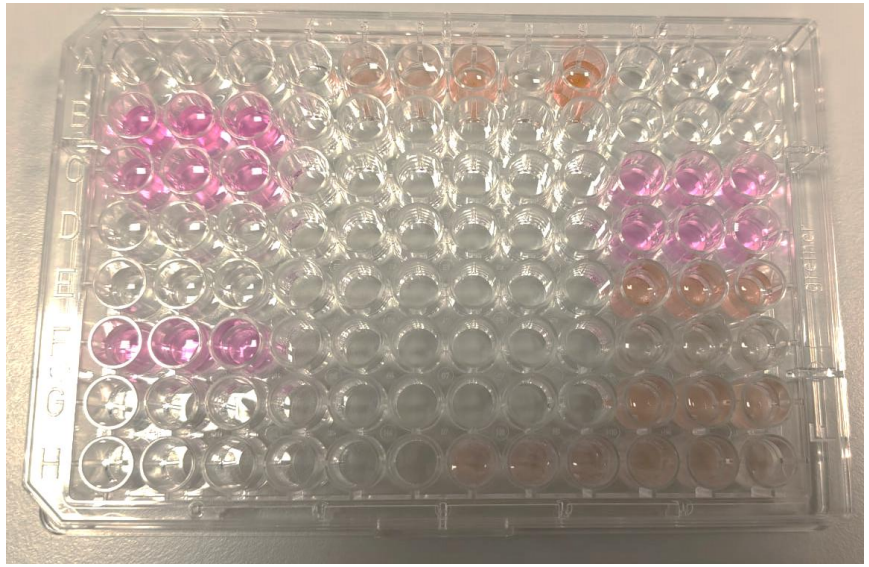




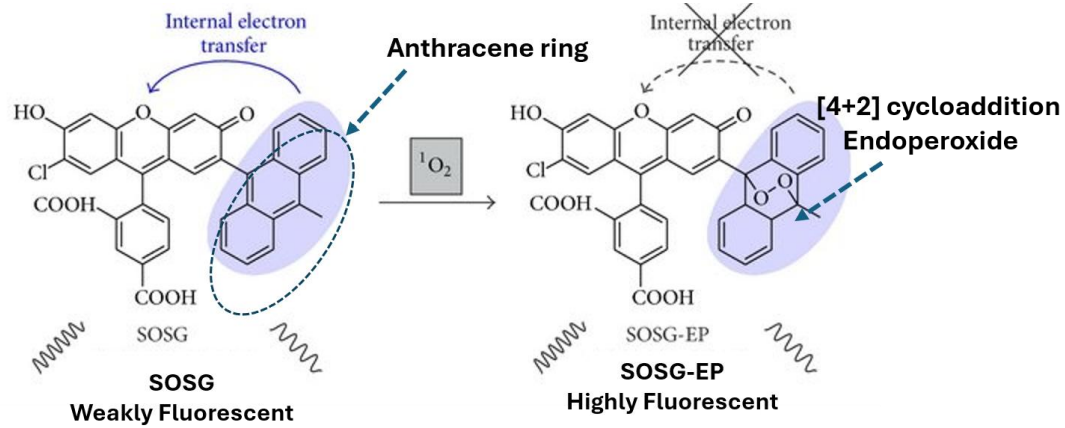
Element	Line Type	Wt%	Atomic %
C	K series	73.68	87.59
N	K series	2.93	2.99
O	K series	7.22	6.44
Cl	K series	4.82	1.94
I	K series	0.88	0.1
Tb	L series	10.47	0.94
Total:		100	100

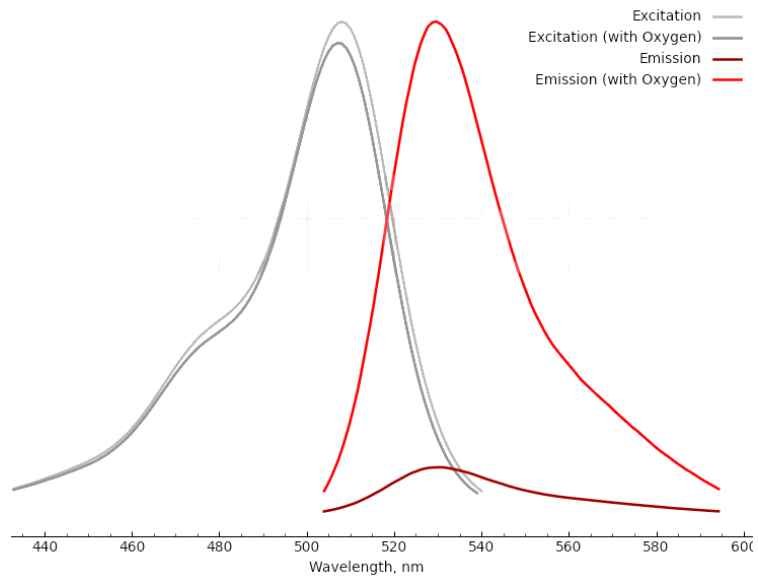
X-ray Photodynamic Therapy

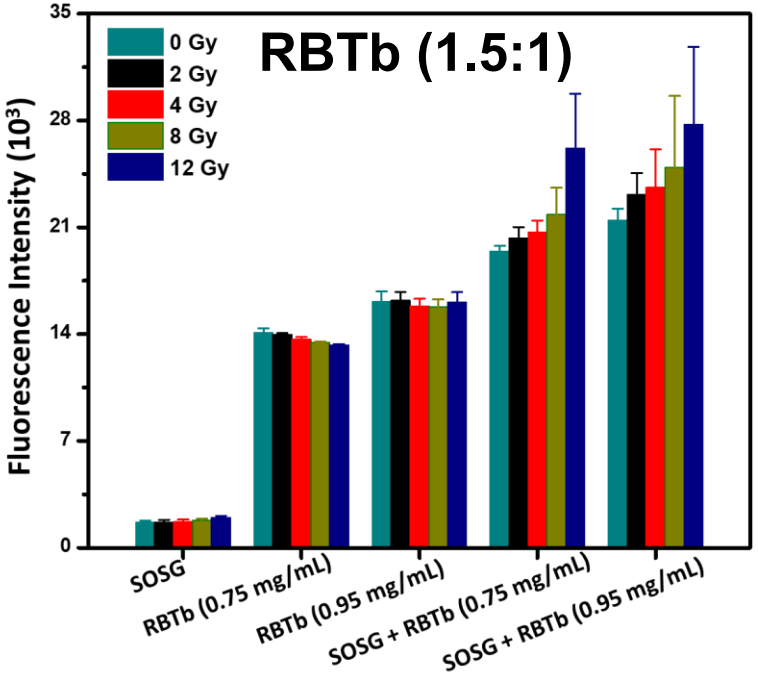


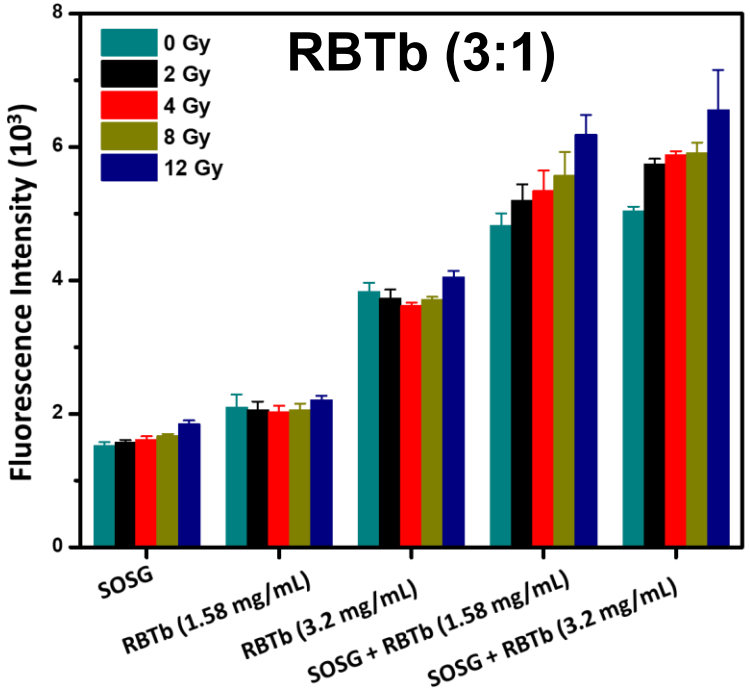


Singlet Oxygen Sensor Green (SOSG) assay for Singlet Oxygen ($^1O_2$) detection









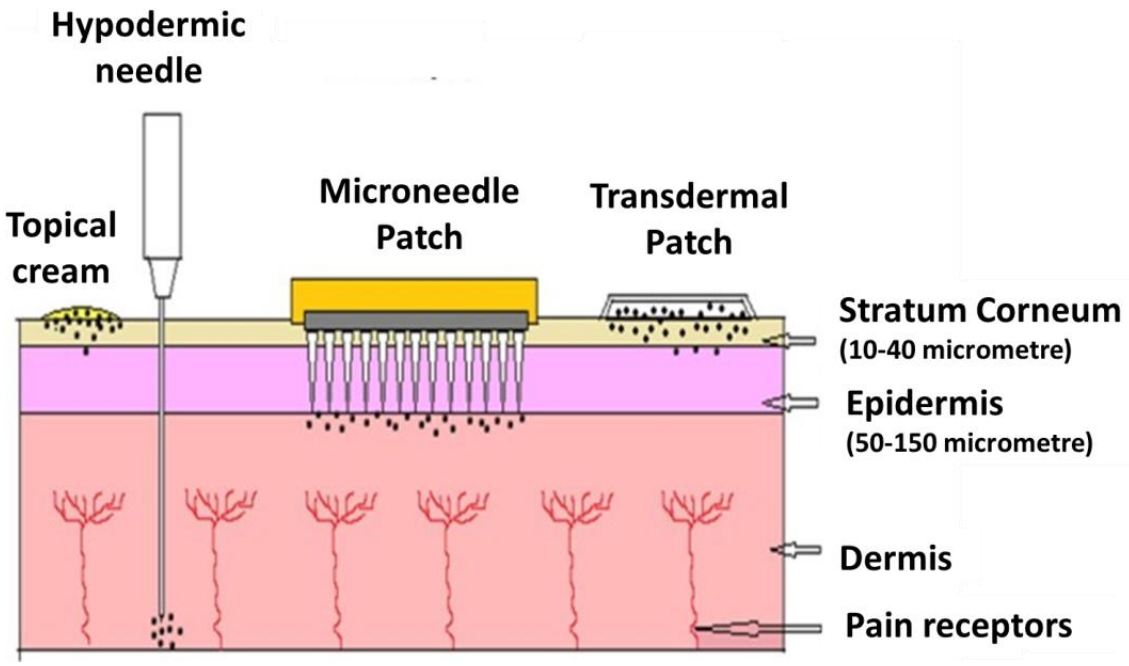
- ✓ RBTb particles increased singlet oxygen production by approximately 4.17-fold at a relatively low dose of 2 Gy and 5.9 times at 12 Gy

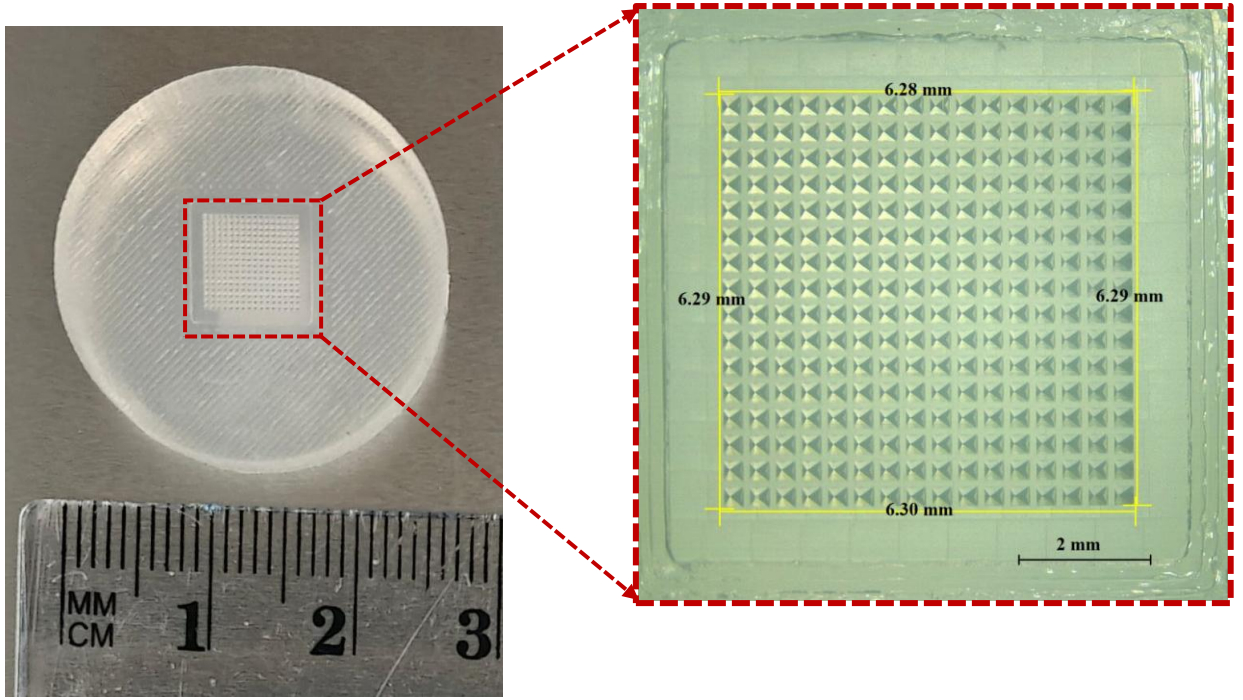
- ✓ RBTb particles increased singlet oxygen production by approximately 2.05 times at a relatively low dose of 2 Gy and 2.16-fold at 12 Gy

Microneedle Array Patches

Microneedle Mold

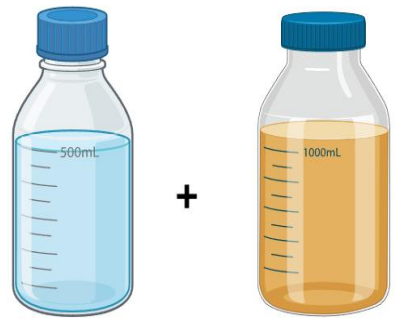
- Microneedles are new form of painless micro-scale delivery system that is used for precise and localized delivery of drugs, vaccine and formulations by crossing the outermost skin layer



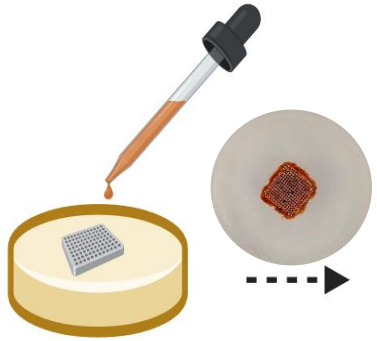


Waghule et al. Bimed. Pharmacother., **2019**, 109, 1249-1258, Himawan et al., Adv. Healthcare Mater., **2022**, 2202066

Synthesis of Microneedle Array Patches (MAP)



40% PVA + 40% PVP

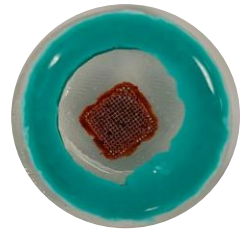


Casting of PVP/PVA mixture in silicone moulds

Positive pressure to cast needles (5 min for 5 bar)

Remove excess formulation

Positive pressure to cast needles (30 min for 5 bar)



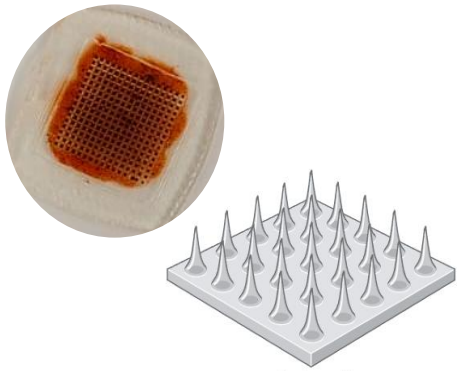
Attachment of silicone rings

24 hr drying

Casting of PVA/ PVP second layer

Centrifugation at 3500 rpm for 15 min

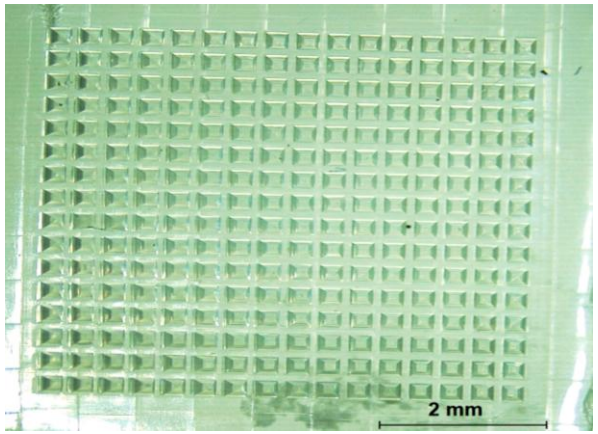
24 hr drying

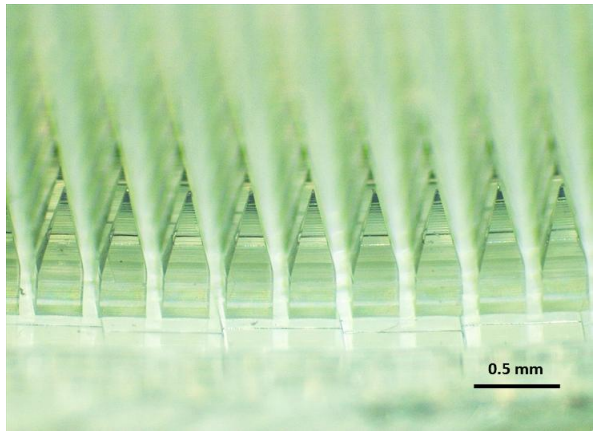


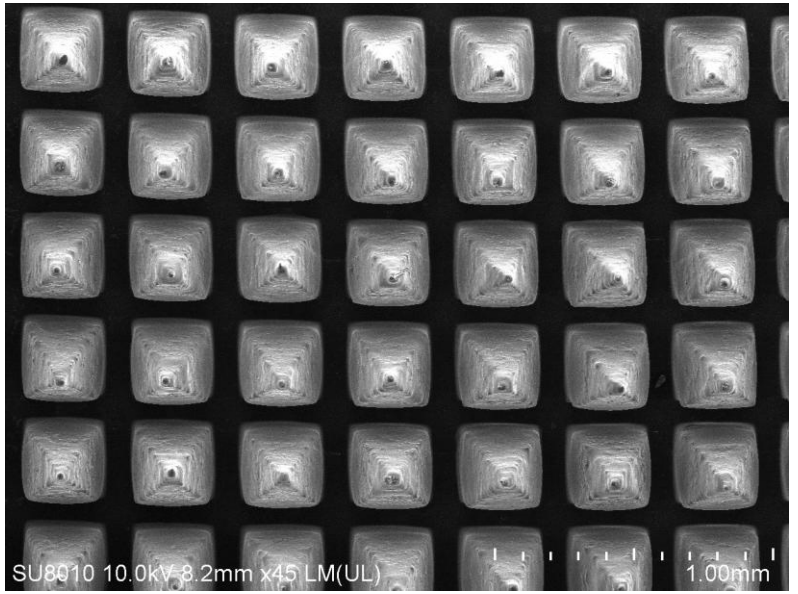
Demoulded DMAP after overnight drying at 37^{O}C

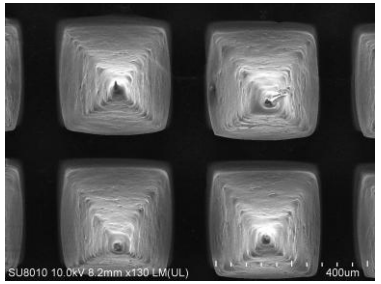
Blank and RBTb loaded MAP

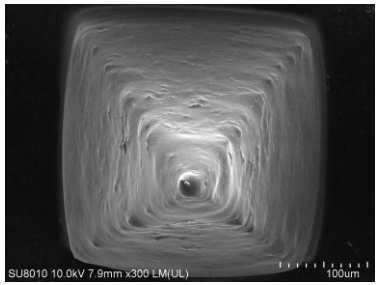
Blank MAP



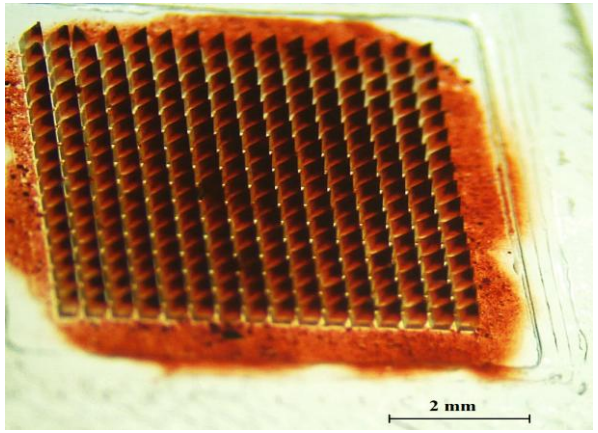


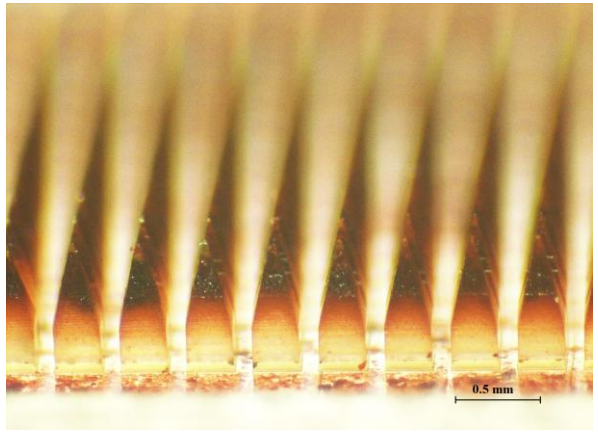


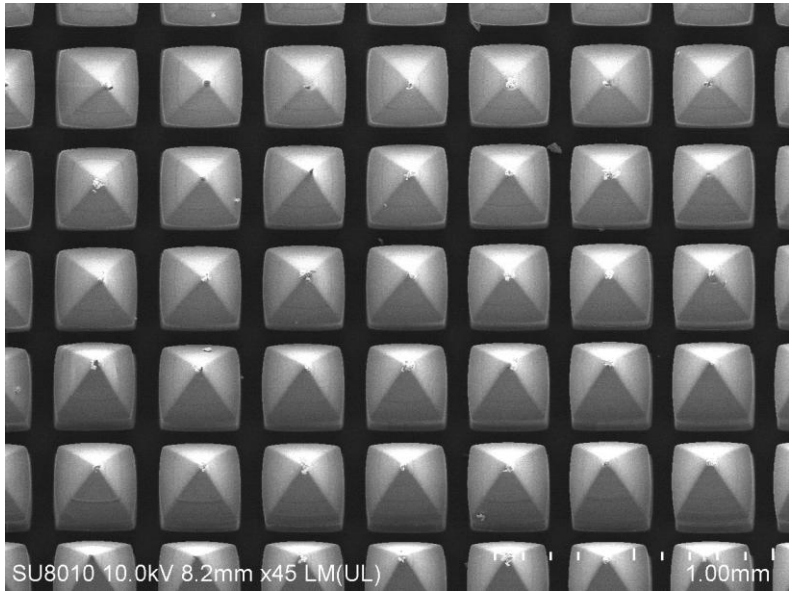


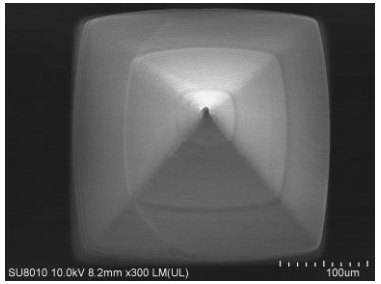


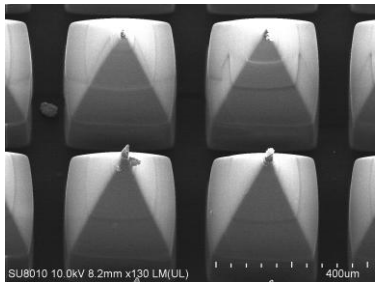
RBTb-MAP



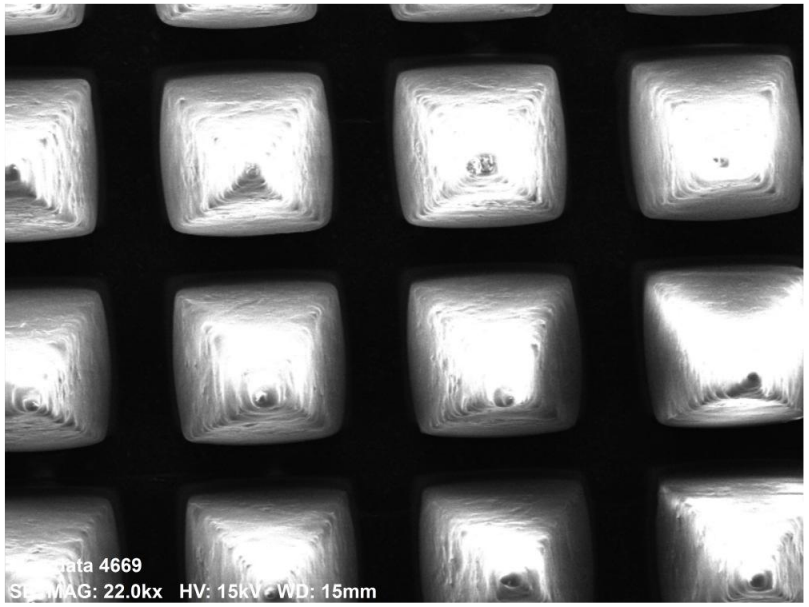


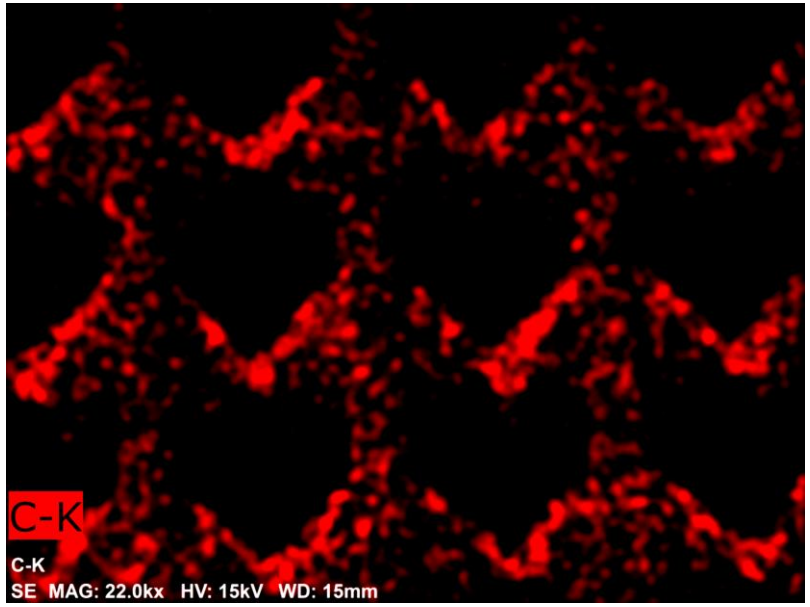


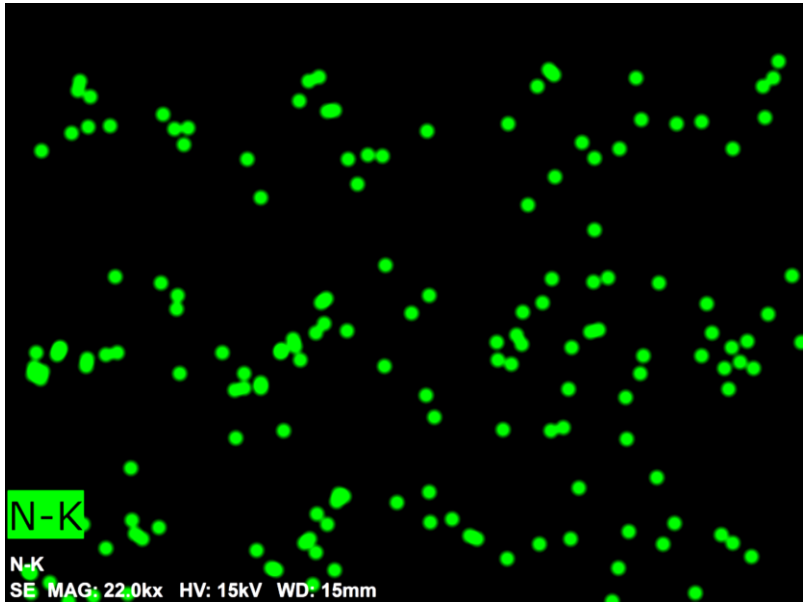


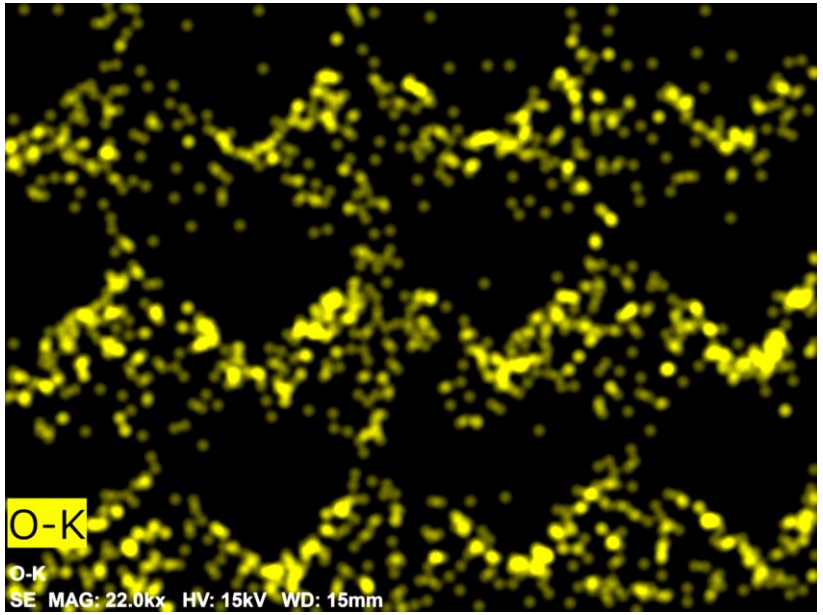


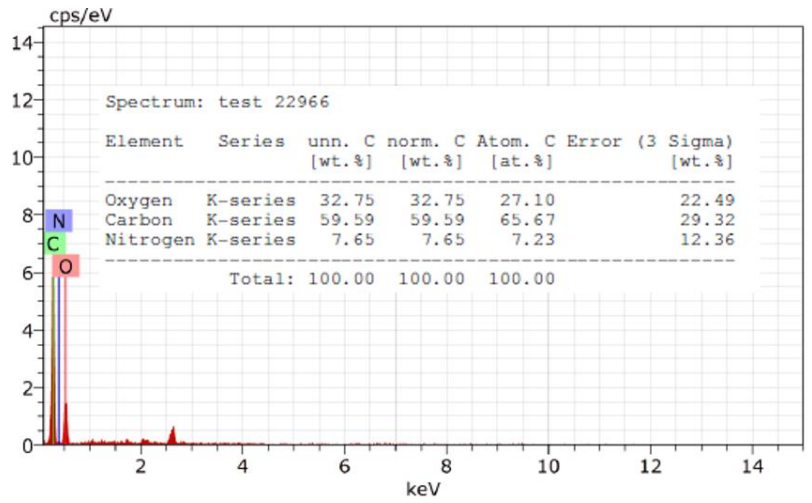
Blank Microneedle FE-SEM-Elemental Mapping



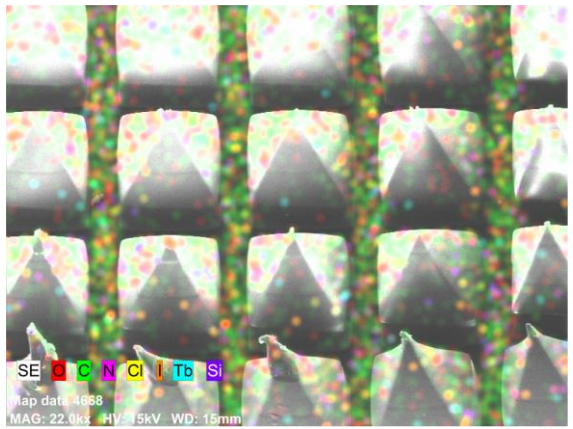


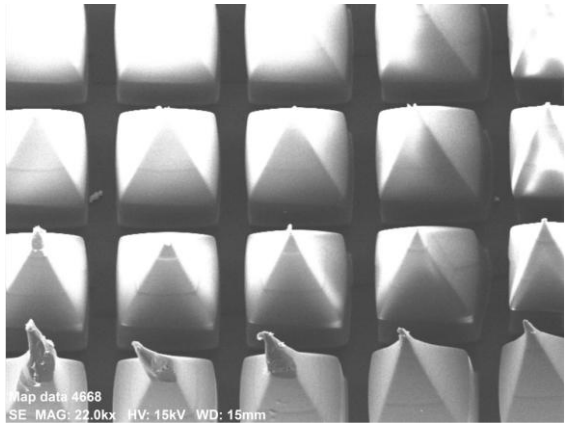


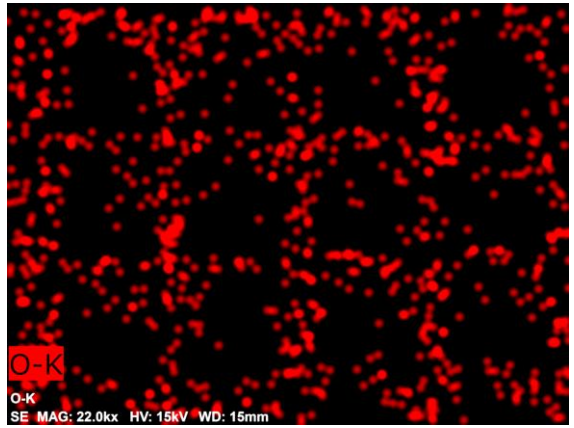


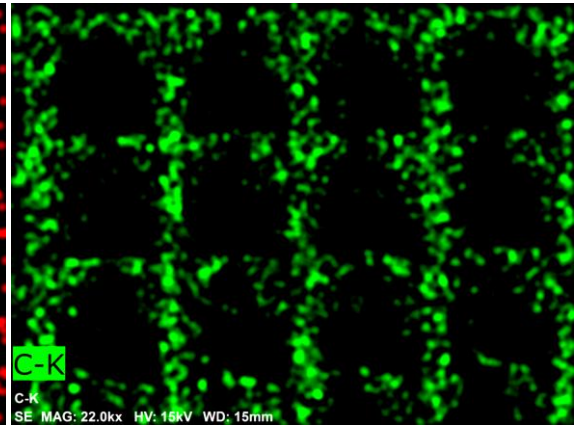


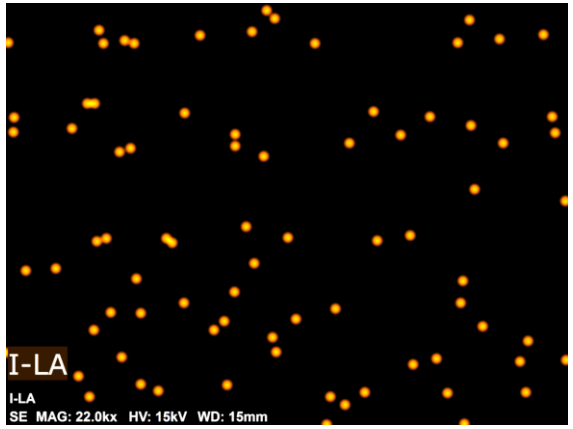
RBTb loaded Microneedle FESEM-Elemental Mapping

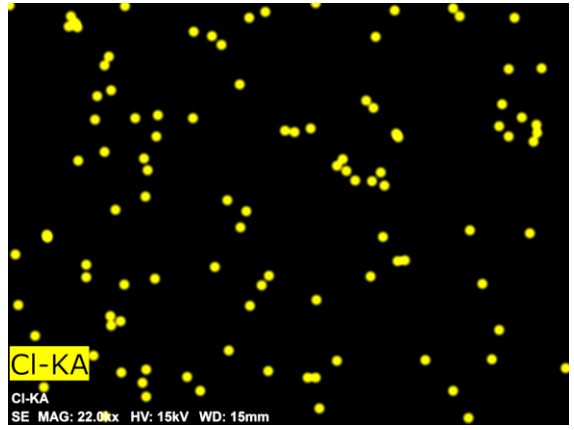


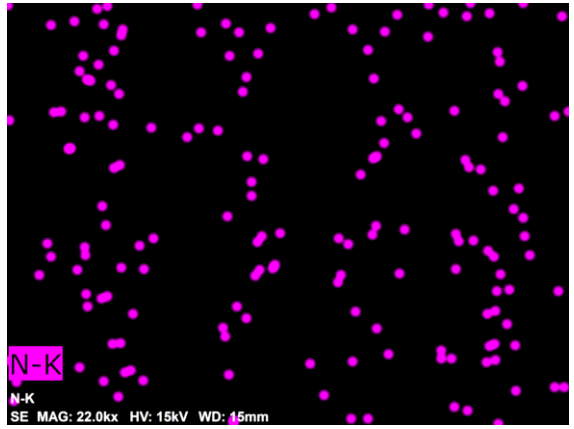


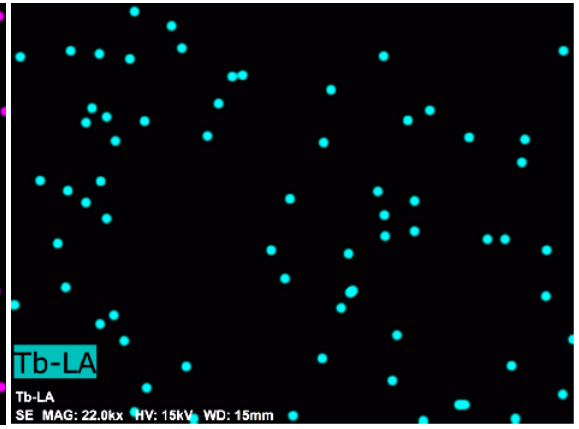


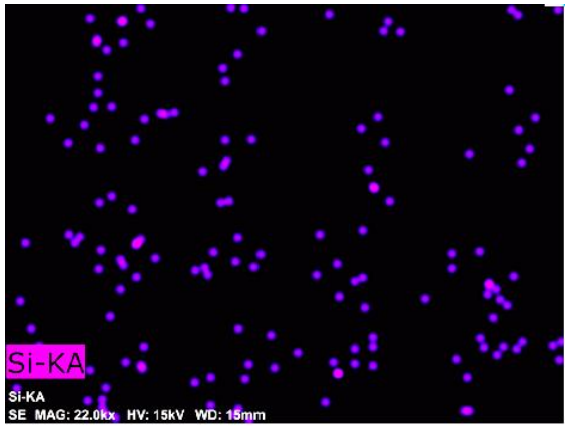


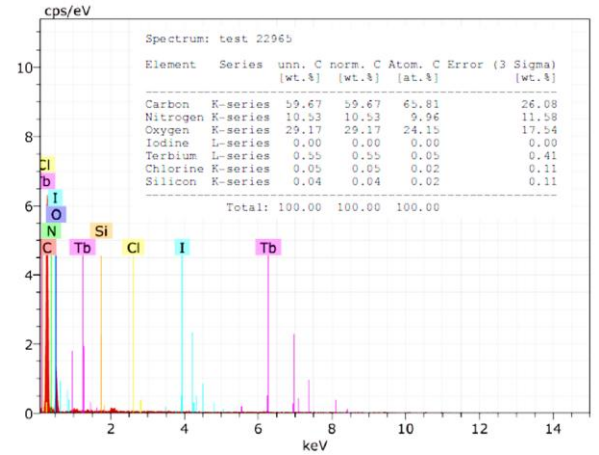




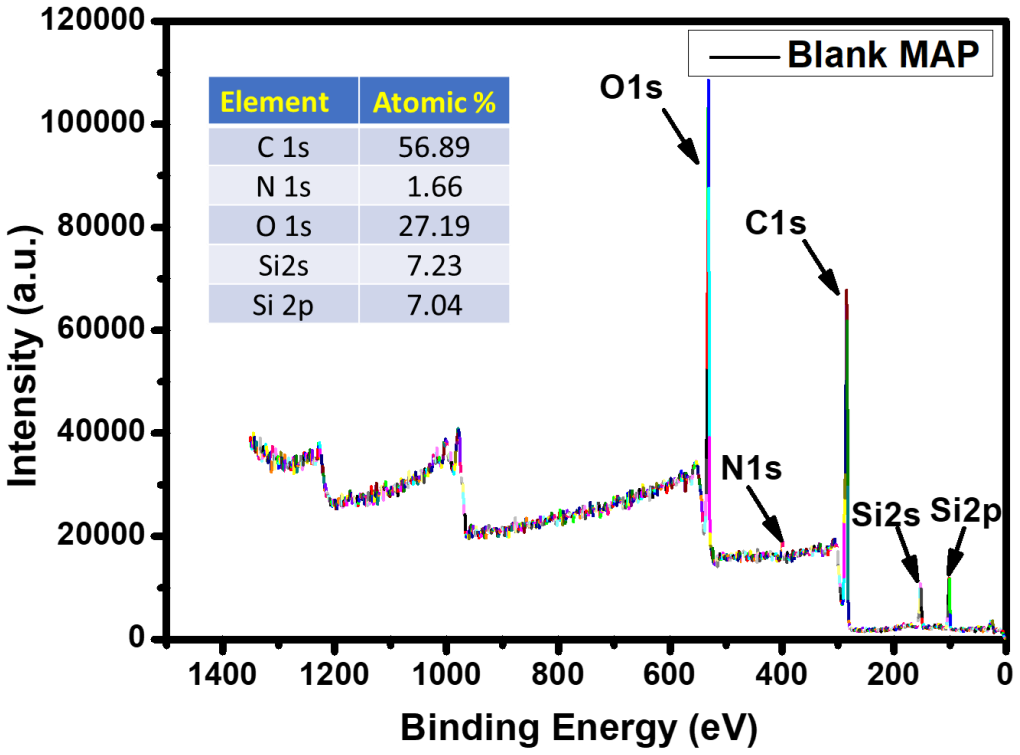


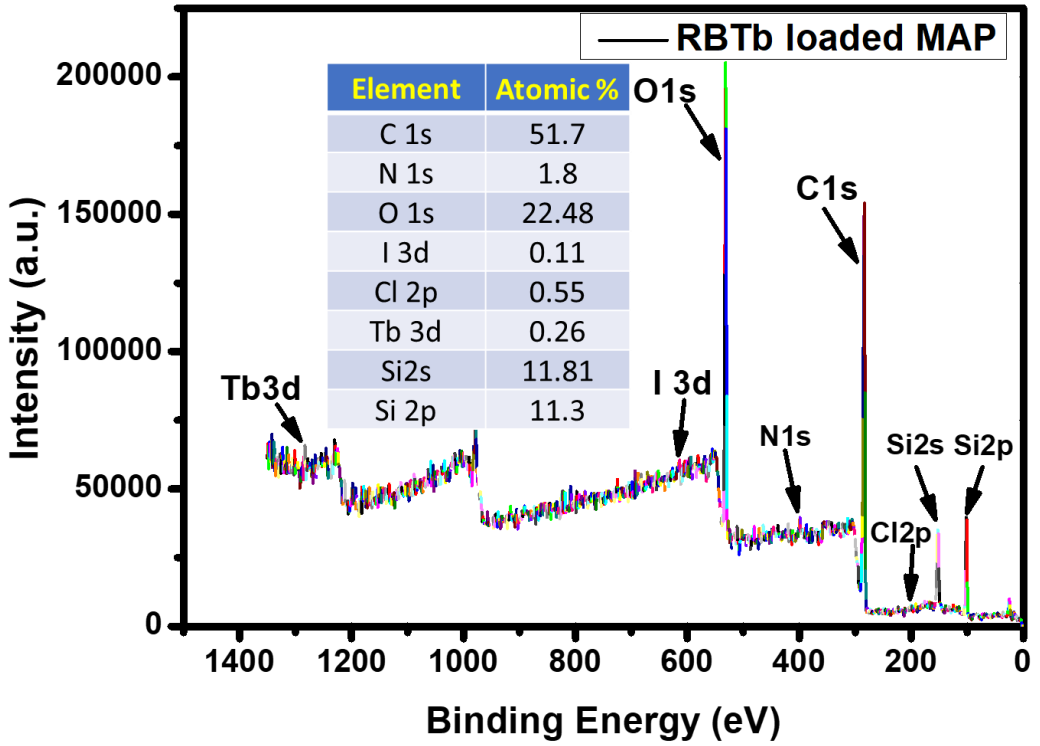




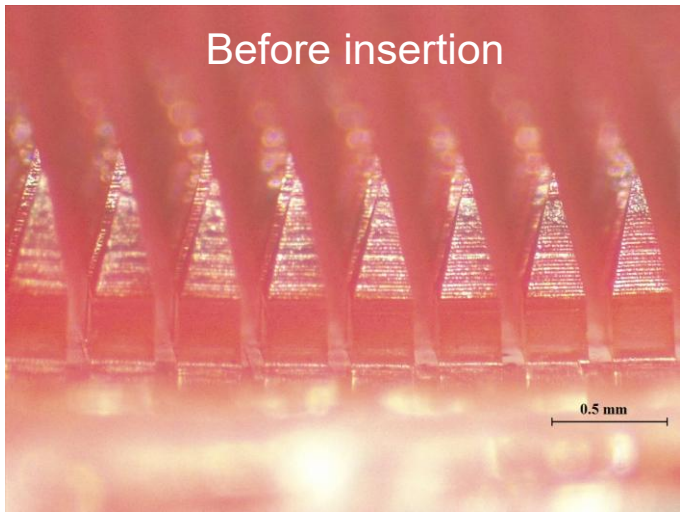


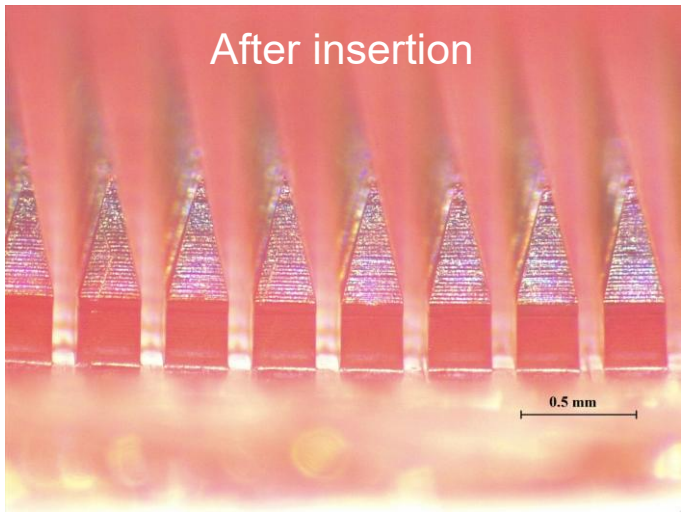
XPS analysis of Blank MAP and RBTb loaded MAP

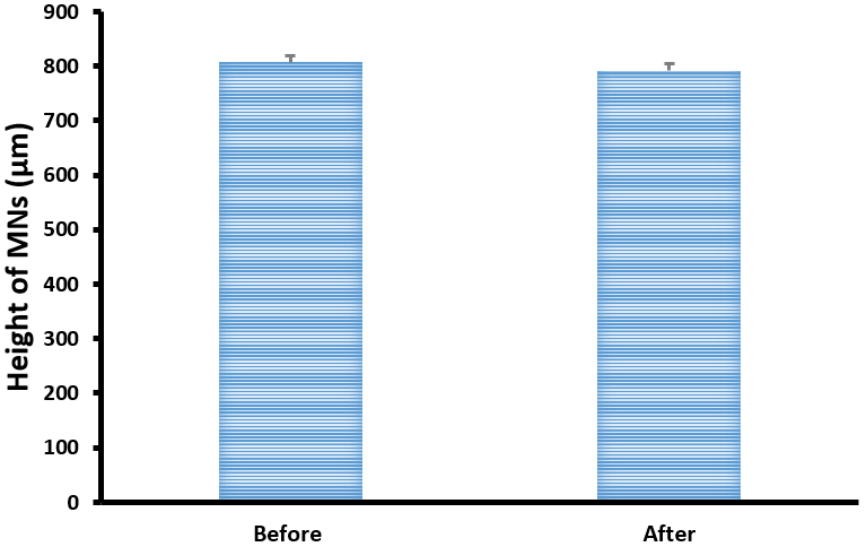




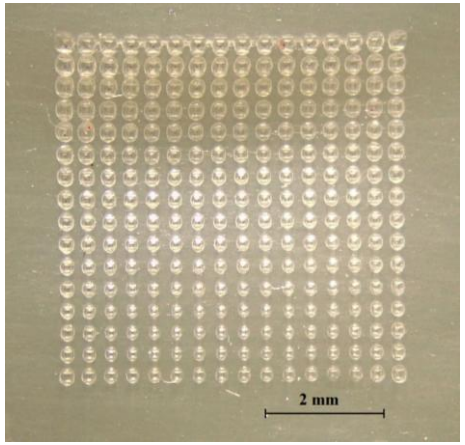
Insertion ability of Microneedle array Patches



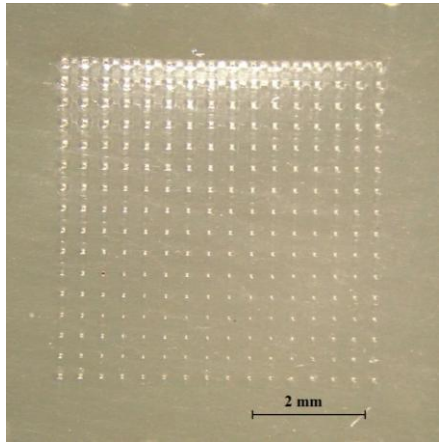




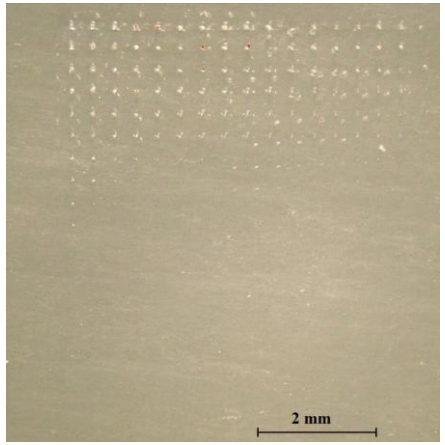
Layer 1

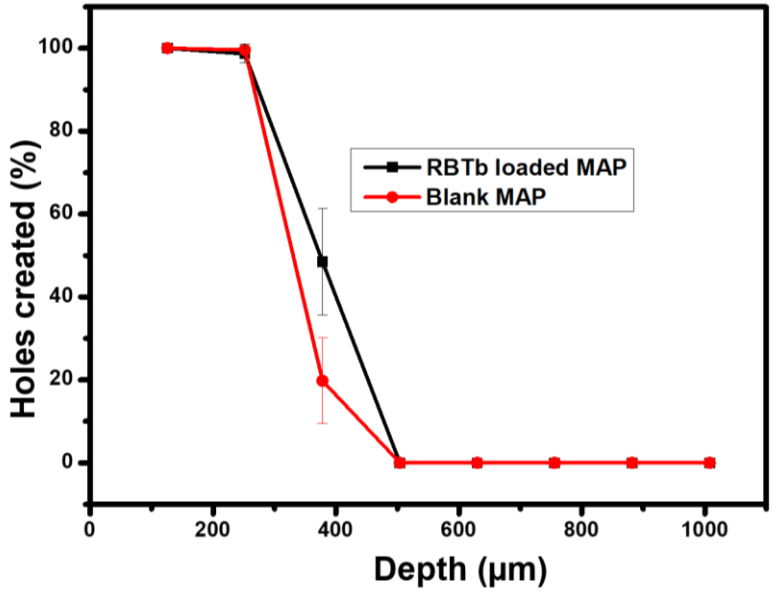


Layer 2



Layer 3

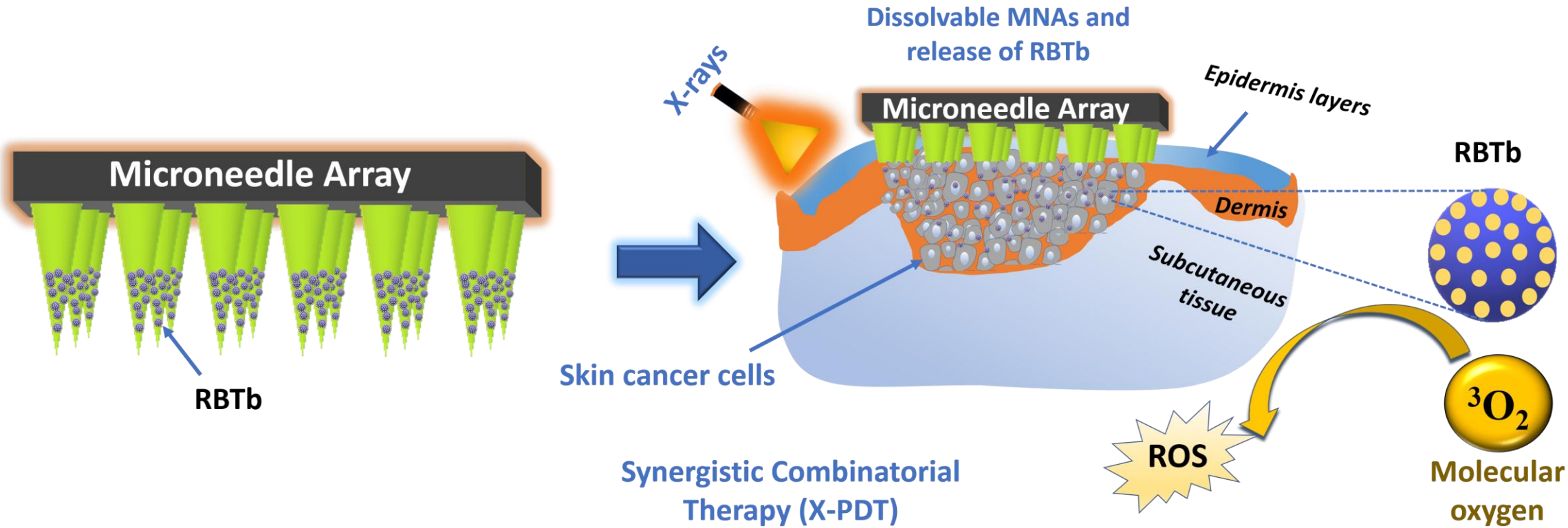




Main Takeaway

✓ Rose Bengal-Terbium nanoparticle was developed using a simple solvothermal strategy.
✓ RBTb significantly enhanced X-ray-induced singlet oxygen generation.
✓ Integration into microneedle array patches provides a clinically translatable approach for localized X-ray photodynamic therapy.

Future work



Acknowledgment

- Prof. Ryan Donnelly, Queen's University Belfast, UK
- Prof. Jonathan Coulter, Queen's University Belfast, UK
- Dr. Lalit Vora, Queen's University Belfast, UK
- EC-Horizon Europe for Marie Sklodowska-Curie Action Postdoctoral Fellowship
- RSC Researcher Development and Travel Grant
- QUB Research and Innovation Conference Fund