

# Unprecedented, Verified Roadmap for Material-Dependent Field Enhancement of Lanthanide Doped Upconverters to be utilized in Biomedical Applications

Noha S. A.

The American University in Cairo, Egypt, [noha.abouqara@gmail.com](mailto:noha.abouqara@gmail.com), [nohaaboqara@aucegypt.edu](mailto:nohaaboqara@aucegypt.edu),

*Abstract-B-NaYF<sub>4</sub>:Yb<sup>3+</sup>, Er<sup>3+</sup> was synthesized hydrothermally to yield 100 nm average sized nanoparticles, according to their TEM. The absorption peak was found by UV-VIS-NIR spectroscopy to be at 980 nm. Upon excitation with this wavelength, emission peaks in the UVC were observed, confirming the concept of 6-photon nonradiative energy transfer between these lanthanide ions. Then, a generic approach for the optimization of upconverting nanoparticles is proposed to enhance the field by several orders of magnitude, for the first time, using all biodegradable materials and without the use of any metals. The approach was then verified by synthesizing B-NaGdF<sub>4</sub>:Yb<sup>3+</sup>, Er<sup>3+</sup> and B-NaGd<sub>2</sub>F<sub>7</sub>:Yb<sup>3+</sup>, Er<sup>3+</sup> to yield a field enhancement of 2x the visible band and 1.5x in the UVC band. All of the nanoparticles synthesized were confirmed to have an emission band in the UVC band and another band in the visible, allowing for both virus killing and imaging, respectively for biomedical applications.*

**Keywords:** UVC, optimization roadmap, NIR, 6-photon upconversion

## I. INTRODUCTION:

NIR-UVC upconverting nanoparticles have represented an important objective for multiple biomedical applications for their capability to emit in the UVC region that is mostly absorbed by viruses and bacteria nucleotides, leading to their destruction. Another important advantage of it is their dual emission bands not only in the UVC but also in the VIS, allowing for biomedical imaging [1], [2]. Furthermore, their thermal effect in the biological medium can be effectively utilized in theranostic medicine [4], the thing that has motivated researchers to focus on their use in cancer targeting and treatment [5], [6].

Other motivations behind their use in biomedical applications include their acceptable level of cytotoxicity and other side effects which have been extensively reviewed [7], [8], [9], biocompatibility of the most commonly used lanthanide ions Er, Tm, Dy, Tb [10], FDA approval of Yb [11], and their safe effect even on macrophages. Focusing specifically on the NIR to the UVC upconversion process advantages, the NIR is the band of the electromagnetic spectrum [800-830] or [830-980] that has minimum absorption and body losses, multiple therapeutic effects,

without any harm imposed on the body and while abiding by the dose exposure limits [8].

However, one of the main challenges that hinder this significant approach from being practically utilized is the need for a real excitation band in the NIR that guarantees an emission in the UVC band. This has never been practically proved in literature except once by Qin group and it had some contradictory results. So, the concept of 6-photon nonradiative energy transfer between Er<sup>3+</sup> and Yb<sup>3+</sup> has to be practically proved, which is the first thing done in this work. The second most intricate challenge that has always faced researchers is field enhancement so that the excitation intensity, power, time at the excitation wavelength abides by the safe dose exposure limits while achieving the required biomedical effect within the human cells, considering the tissue losses at these parameters, the commercial availability of such resources and other technical limitations on the material itself and the biomedical application specific requirements such as targeting. All of these requirements have always imposed an unresolvable challenge, under the constraint of using all biodegradable, biocompatible materials, despite the innumerable trials to do field enhancement. Nevertheless, here we report an optimization roadmap for the upconverting nanoparticles of interest for the first time that achieve the required quantum efficiency, while respecting all of these constraints with their complex interplay. Moreover, we verify this approach by making two samples that follow the first two steps of this roadmap. It is also worth mentioning that Yb is chosen for its good absorption in the NIR band and Er is well-known for its emission band in the UVC, as well. Not only for that but also because of their commercial availability in Egypt.

## II. MATERIALS AND METHODS

### 1) NaYF<sub>4</sub>:Er<sup>3+</sup>, Yb<sup>3+</sup> UC NPs Synthesis:

Ethylene diamine tetraacetic acid (EDTA), NaF, nitric acid (HNO<sub>3</sub>), Yttrium nitrate (Y(HNO<sub>3</sub>)<sub>3</sub>, 99.99%), ytterbium nitrate (Yb(NO<sub>3</sub>)<sub>3</sub>, 99.999%), and erbium nitrate (Er(HNO<sub>3</sub>)<sub>3</sub>, 99.999%) were supplied by Alpha Company. Yb<sub>2</sub>O<sub>3</sub> were dissolved in dilute HNO<sub>3</sub> while heating them at 90 C and 400 rpm till the solute is dissolved to get the

Y(NO<sub>3</sub>)<sub>3</sub>. So, 2.06 g of Yb<sub>2</sub>O<sub>3</sub> was dissolved in 15 mL of nitric acid and 10 mL of water. In another container, EDTA and NaF were added together. EDTA solution consisted of 40 mL of H<sub>2</sub>O and 2 mmol of EDTA. 1 mmol of NaF and 40 mL of water constituted the solution of NaF. Then, the remaining nitrates were added altogether to the EDTA solution and the solutions were left to react for three hours while the temperature was raised to 130 C. Then it was left in two 50 mL Teflon autoclaves for 18 hours at 160 C. Then, the sample was left to cool to room temperature after which it was centrifuged at 1400 rpm for 15 minutes in each washing trial with ethanol and H<sub>2</sub>O and then the precipitate was left to dry for 2 days at 40 C. Finally, the sample was calcined at 400 C for two hours.

2) Coating Synthesis:

The nanoparticles were coated according to the method mentioned in other work [12].

3) Roadmap for Field Enhancement of the Chosen Upconverter:

Based on the review and the roadmap done in a previous work, the first material dependent approach was exhausted based on all relevant theories and prior

experimental research [13]. A summary of the tables of the parameters that can be manipulated and a future plan are summarized in tables (1) and (2) below. Table (1) shows each parameter and the dependent variables or considerations. Table (2) shows a proposed implementation of an enhancement plan for the chosen upconverters based on the suggested parameters. Besides, it highlights the judging criterion, other than photoluminescence measurement, if needed. This plan is optimized to be cost efficient, picking the most promising conditions for the parameters listed in table (1), which are selected based on the feasibility predicted based upon an exhaustive review for each synthesis condition manipulated in literature and working out a correlation between it and the resulting optical properties of the material. For the budget constraints, only the 3 approaches are tried out in this work and verified. The plan is made in decreasing order because the latter procedures (such as milling or applying a magnetic field) won't require material based iterations. Thus, the order is wisely chosen not to be altered.

Action	Increasing Yb Concentration > 20%	Calcination temp	Core-shell	NaF amount	Synthesis medium [EDTA]	Autoclave time	Dopant amount
Consequences	red-shifted emission with optimum concentration being 20% sensitizer (S) ,5% activator ions (A) in the VIS.	600 C for 5 hrs -increasing to 700 for hrs enhanced the green/red by 1000 x [thermal coupling]	Lower excitation intensity	Morphology, size, emission peak [slightly]	Affect particle size Best is a molar ratio of 1/ Ln # mols	Synthesis method dependent	-G has accumulated levels in the UV
Milling	Relative concentrations of the host material to the dopants	Effect of magnetic field	All possible combination of dopants	Amount of precursors	Optimizing a shell host+ dopants		
Debatable; milling coils reduce the size and thus reduces the QM efficiency based on theoretical expectations yet the symmetry of the crystal field gets broken and proved practically to increase the efficiency	Changes luminescence intensity	Human exposure dose limits constraint	no available theoretical guiding info and some of them have never been used	Changes morphology and PL intensity	-low lattice mismatch -absorber -to protect the luminescent ions from the nonradiative decay and - to tailor the local crystal field and tune the spatial distance of sensitizer and activator		

Table (1): the main parameters that are feasible to be optimized and the considerations for each of them

1-Incorporating Gd	
<u>Reference case</u>	NaYF <sub>4</sub> , 2%Er <sup>3+</sup> , 20% Yb <sup>3+</sup>
<u>A) instead of Y</u>	Done in this work
B) Equal amount to Y	Done In this work
<u>C) Doping the best of all with Fe<sup>2+</sup> [30% if NaGdf<sub>4</sub>] note f caused down conv</u>	You should do XRD here to verify Gd is in the host not free ion
D) Doping the best of all with Ca <sup>2+</sup> [25 %	
E) Doping the best of all with Zn <sup>2+</sup> [25 %	
F) Doping the best of all with a combination of the best 2 dopants [Zn, Ca, Fe]	
G) Doping the best of all with a combination of the best 3 dopants [Zn, Ca, Fe]	
<u>2-Calcination Temp [starting 600- 700] but note this s oxide, harder than oursbest was 900 here tho for a different host; ET digaram wz levels also provided at end but no UVC; Er.02, Gd 1.98, O 3-delta</u>	
3-NaF amount	
A) double what we are using i.e 8 times Ln	
B) 6 ties total Ln mol #	
4-introducing a shell	
A) optimized host doped with Yb	
5-milling	
6-magnetic field variation	

Table (2) proposed Optimization Roadmap for the Chosen Upconverter and the required tests other than photoluminescence measurement

#### 4) Characterization:

First, the crystal structure was examined by an X-ray powder diffractometer (XRD) using a nickel-filtered Cu-K $\alpha$  radiation ( $\lambda = 1.5406 \text{ \AA}$ ). The size and morphology were investigated by a high resolution transmission electron microscope (HRTEM).

Absorption spectrum was checked by a NIR-UV spectroscope in the reflectance mode. The impurities were checked using Fourier transform infrared spectroscopy (FT-IR).

The optimum thickness and relative concentration of the targeting ligand to the host in the coating was explored by measuring the refractive index using a variable angle ellipsometry for 30 iterations of various targeting ligands to host concentrations.

To verify the coating and to ensure the lack of negative influence on the targeting ability of the nanoparticles, FTIR was repeated as well as TEM, which will be used in further work.

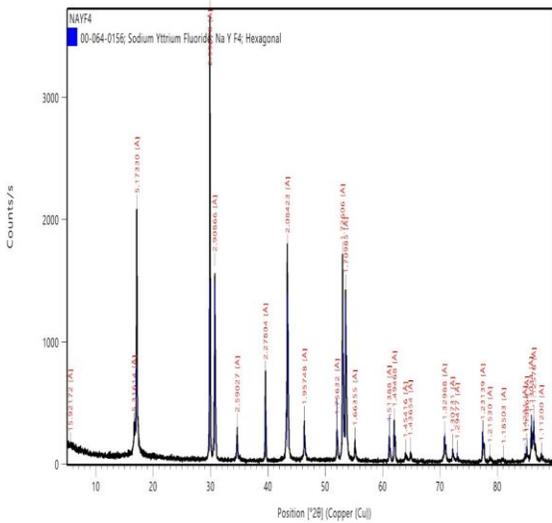
Photoluminescence measurements were conducted in air using a NIR laser source, photodetector and converging lenses. To verify that that coating thickness did not affect

the PL properties, NIR-UV absorption was repeated after coating as well as the photoluminescence measurement.

### III. RESULTS

Figure (1) shows the XRD results confirming the crystal structure of NaYF<sub>4</sub> in the hexagonal phase, doped with 2% Erbium 3<sup>+</sup> and 20% Yb3<sup>+</sup>. NIR-UV spectroscopic results in figure (2) shows an absorption peak at 976 nm, as expected based on prior literature. FT-IR results in figure (3) confirms core layer synthesis with no impurities attached during the synthesis. In figure (4). FTIR for the coated material confirmed the coating chemical binding to the core layer, yet the electromagnetic properties were kept intact, which is evident from the same relative maxima in the NIR-UV absorption spectra for the coated material. This

confirms the optimum coating thickness predicted from the aforementioned experimental iterations not included in this work. Another proof was the PL spectra before and after coating, yet this work is only concerned with the relative PL spectra of the reference sample (where the host is NaYF<sub>4</sub>) and the other two samples proposed in the first stages of luminescence enhancement plan shown in table (2), where the Gd represented half the Y weight in the reference case and finally, where it represented the total weight as presented in figure (5-7). Thus, only the TEM of the core layer is shown in this work -in figure (8) and that of the coated sample would be mentioned in the other work referred to earlier. Similarly, the NIR-UV spectroscopy, zeta potential and other coating related characterizations will be mentioned in that work



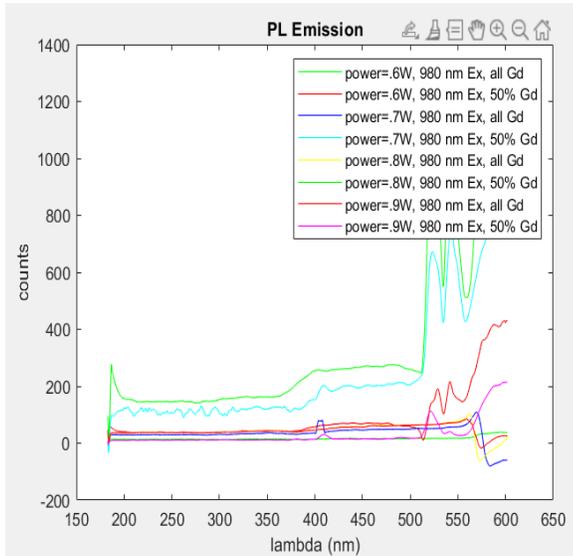


Figure (5) Shows the related PL emission of the two samples having 100 Gd and 50% Gd respectively upon excitation with 980 nm laser source at different powers

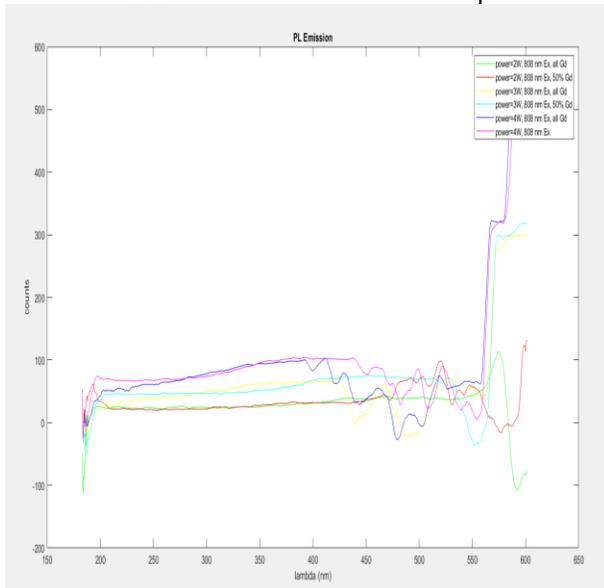
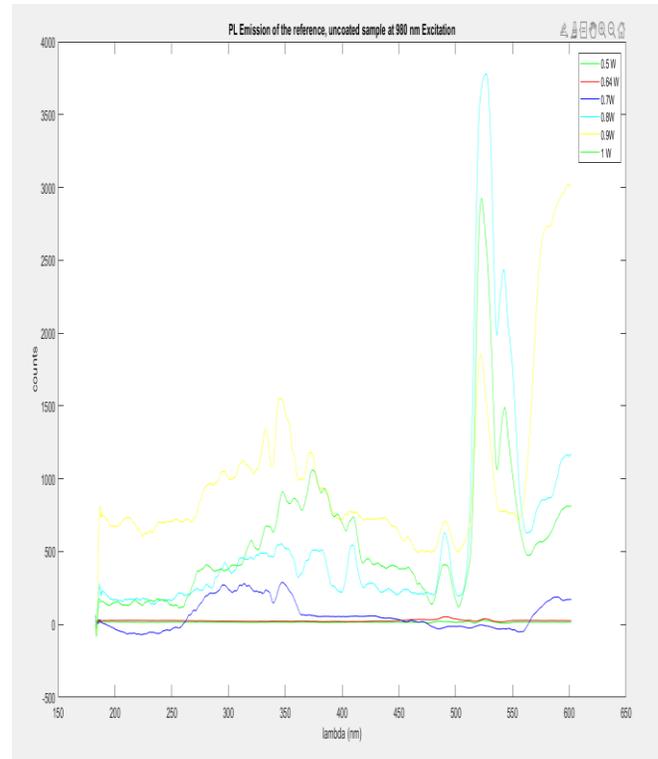


Figure (6) Shows the related PL emission of the two samples having 100 Gd and 50% Gd respectively upon excitation with 808 nm laser source at different powers

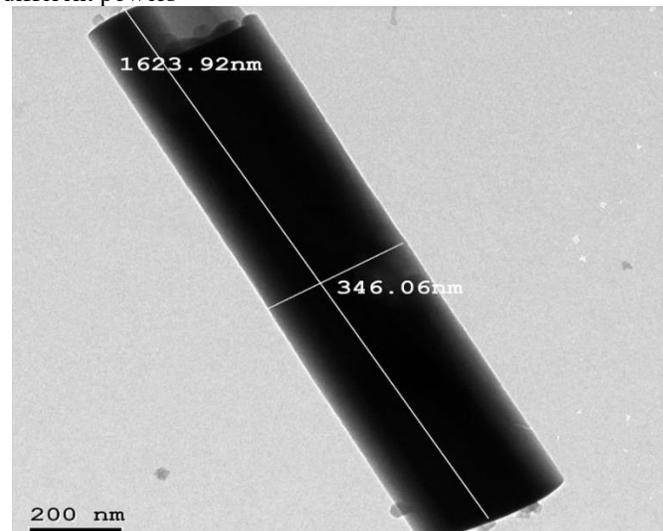
#### IV. Discussion:

The XRD measuring technicians were made blind to the doping completely to ensure the accuracy of the results, yet the XRD report detected an accurate doping concentration as desired.

The FTIR for the uncoated sample was important for the use of EDTA, which could have attached to the UCNPs or



Figure(7) Shows the relative spectra of the reference case at different powers



.Figure (8) shows the TEM of the core layer

any other organic impurity. The FTIR of the coated material was further analyzed, not only to ensure the successful attachment of the coating to the core layer, but also to ensure that the function groups required to target the virus are kept intact without taking part in the chemical reaction between the core layer and the coating. Only FTIR was included in this work as the bare minimum proof of successful coating but further analysis of the coating influence on the PL will be explored in other work.

Despite the debatable concept of 6-photon upconversion between the Ln ions  $\text{Er}^{3+}$  and  $\text{Yb}^{3+}$  hosted by  $\text{NaYF}_4$ , here with a slight deviation of the peak positions from the sole research work cited for similar works. The absorption peak was recorded to be at 976 nm -as compared to the absorption peak of 980 nm recorded in literature- and the emission peaks were also shifted from those in literature. The upconversion setup was only the laser source, the nanoparticles stuck on a holder and a photodetector. Despite the lack of use of a filter (due to low gain of the available UV filters in the required UVC band), the reference was taken to the case where the nanoparticles are not yet stuck on the holder to eliminate the source and background effect. Besides, the same emission will be exposed to the human cells in the desired biomedical applications. Thus, it is practical to expose the same radiation to it. Using isolated fibers to detect the UV emission could have been another feasible alternative but we could not find a fiber with a negligible loss to be used in our case, for the broad band emission spectra from the NIR to the UVC.

The reference sample is the  $\text{NaYF}_4@2\% \text{Er}^{3+}, 20\% \text{Yb}^{3+}$ . The other two samples are the ones where Gd replaces Y once by 50% of the weight and another time by 100% of the weight. The reason why we excited the samples once by 980 nm and another by 808 nm is that  $\text{Gd}^{3+}$  has an absorption peak at 808 nm, while Yb is still there and has an absorption peak at 980nm. Thus, one cannot determine what would the transition probability be in either case practically.

Conventionally, researchers who dealt with  $\text{Gd}^{3+}$  as a dopant, excited the UCNPs with 808 nm only. Here, we can find, unexpectedly, the the UVC emission of 980 nm excited UCNPs reaches double that of the 808 nm excited one and even at tenth of the excitation power, which is a huge turning point to the conventional expectations. This reveals that the absorption is dominant at 980 nm. Figure (7) shows the reference case and proves that the reference case is the best considering the emission in the UVC band of the spectrum or, in other words, the quantum efficiency of the upconversion process. This is in complete contradiction to what was known in literature considering the exact same doping conditions and everything else.

Although the size seems non-biodegradable, further processing in the coating work will reduce the size even more.

## V. CONCLUSION:

In this work, 6-photon upconversion no-radiant energy transfer between the Ln ions  $\text{Yb}^{3+}$  and  $\text{Er}^{3+}$  is proved. The desired material was characterized and made sure to be purely in the required chemical and physical state. Second, an unprecedented, cost and time optimized roadmap for field enhancement utilizing the material dependent approach

is presented and verified. Coating was also optimized in other work and was verified chemically only in this study while the physical characterization was deferred to other work. Multiple design tricks which are crucial to PL measurement have been also highlighted in the discussion. The verified proposed material based field enhancement plan suggests an extremely high potential for the rest of unimplemented stages, which paves the way for other research groups to reach a higher PL by multiple orders of magnitude. Although the work done is sufficient for the biomedical application of concern, which broke a worldwide everlasting challenge that was imposed on the utilization of UCNPs in biomedical applications for the inability to find a healthy PL enhancement method, the verified plan suggests even a more huge breakthrough in that aspect.

## VI. ACKNOWLEDGEMENTS

First and foremost, thanks God, the supporter of every single step in that project. Second, I would like to thank Dr. I. Elsherbiny, Dr. N. Shehata, Dr. M. Kandeel, Dr. M. Hussein, my friend S. Saeed, Dr. M. Saleh, Dr. I. Y. Zahran, Dr. M. Rashad, Dr. A. Mohammad, Dr. BA Anis, and every single person who provided any sort of advice, recommendation, financial support or permission to use his/her lab resources.

## VII. CONFLICT OF INTERESTS:

The authors declare no conflict of interests

## REFERENCES

- [1] Dai, Y., Kang, X., Yang, D., Li, X., Zhang, X., Li, C., ... & Lin, J. (2013). Platinum (IV) pro-drug conjugated  $\text{NaYF}_4:\text{Yb}^{3+}/\text{Er}^{3+}$  nanoparticles for targeted drug delivery and up-conversion cell imaging. *Advanced healthcare materials*, 2(4), 562-567.
- [2] Tang, Y., Pei, F., Lu, X., Fan, Q., & Huang, W. (2019). Recent Advances on Activatable NIR-II Fluorescence Probes for Biomedical Imaging. *Advanced Optical Materials*, 7(21), 1900917.
- [3] Wang, H., Yin, X., Xing, M., Fu, Y., Tian, Y., Feng, X., ... & Luo, X. (2018). Thermal effects of  $\text{Er}^{3+}/\text{Yb}^{3+}$ -doped  $\text{NaYF}_4$  phosphor induced by 980/1510 nm laser diode irradiation. *Journal of the American Ceramic Society*, 101(2), 865-873.
- [4] Wang, W. (2016). Upconversion Nanomaterials for Tumor Targeting Theranostics. In *Nanomaterials for Tumor Targeting Theranostics: A Proactive Clinical Perspective* (pp. 299-326).
- [5] Liu, S., Li, W., Gai, S., Yang, G., Zhong, C., Dai, Y., ... & Suh, Y. D. (2019). A smart tumor microenvironment responsive nanoplatform based on upconversion

nanoparticles for efficient multimodal imaging guided therapy. *Biomaterials science*, 7(3), 951-962.

[6] Gnach, A., Lipinski, T., Bednarkiewicz, A., Rybka, J., & Capobianco, J. A. (2015). Upconverting nanoparticles: assessing the toxicity. *Chemical Society Reviews*, 44(6), 1561-1584.

[7] Gnach, A., Lipinski, T., Bednarkiewicz, A., Rybka, J., & Capobianco, J. A. (2015). Upconverting nanoparticles: assessing the toxicity. *Chemical Society Reviews*, 44(6), 1561-1584.

[8] Gu, X. N., Li, S. S., Li, X. M., & Fan, Y. B. (2014). Magnesium based degradable biomaterials: A review. *Frontiers of Materials Science*, 8(3), 200-218.

[9] [Drugs@FDA: FDA-Approved Drugs](#)

[10] Sojka, B., Liskova, A., Kuricova, M., Banski, M., Misiewicz, J., Dusinska, M., ... & Tulinska, J. (2017). The effect of core and lanthanide ion dopants in sodium fluoride-based nanocrystals on phagocytic activity of human blood leukocytes. *Journal of Nanoparticle Research*, 19(2), 68.

[11] Frigerio, F., Borra, M., Cottica, D., Grignani, E., Militello, A., Mansi, A., ... & Sisto, R. (2020). Interim indications for the use of UV germicidal irradiation in the conjuncture of covid-19 pandemic.

[12] Aboqara N. (2021), Novel, Broadband, Material-independent Theory on Near-field Enhancement; A Special Focus on UVC Microlasers for Biomedical Applications

[13] Aboqara N. (2021), Unprecedented, Exhaustive Review and Roadmap for Upconverting Nanoparticles Field Enhancement Mechanisms to be utilized in Biomedical Applications.