Best Ten Original Research Publications with brief description of important contributions with Illustrations

S No.	Publication Details	I.F
1	PratikshaTiwari, Ravi Prakash Shukla Krishna Yadav, Neha Singh, Disha Marwaha, Shalini Gautam, Avijit Kumar Bakshi Nikhil Rai, Ankit Kumar, Deepak Sharma, **Prabhat Ranjan Mishra***, Dacarbazine-primed carbon quantum dots coated with breast cancer cell-derived exosomes for improved breast cancer therapy ***J. Controlled Rel.*** 365; 43-59 (2024) ***(Corresponding author)***	**10.80**
2	Ravi Prakash Shukla, Pratiksha Tiwari, Anirban Sardar, Sandeep Urandur, Shalini Gautam, Disha Marwaha, Ashish Kumar Tripathi, Nikhil Rai, R. Trivedi, **Prabhat Ranjan Mishra*** Alendronate-functionalized porous nano-crystalsomes mitigate osteolysis and consequent inhibition of tumor growth in a tibia-induced metastasis model ***J. Controlled Rel.*** 372 (2024) 331–346 ***(Corresponding author)***	**10.80**
3	Venkatesh Teja Banala, Shweta Sharma, Puja Barnwal, Sandeep Urandur, Ravi P Shukla, Naseer Ahmad, Naresh Mittapalley, Gitu Pandey, Monika Dwivedi, Navodayam Kalleti, Kalyan Mitra, Srikanta Kumar Rath, Ritu Trivedi, **Prabhat Ranjan Mishra*** Synchronized Ratiometric Co-Delivery of Metformin and Topotecan Through Engineered Nanocarrier Facilitate In-Vivo Synergistic Precision Levels at Tumor Site ***Adv. Healthcare Mater.*** 7(19):e1800300 (2018). ***(Corresponding author)***	**11.12**
4	Sandeep Urandur, Venkatesh TejaBanala, Ravi Prakash Shukla, Naresh Mittapelly, Gitu Pandey, NavodayamKalleti, Kalyan Mitra, Srikanta Kumar Rath, Ritu Trivedi, Pratibha Ramarao, **Prabhat Ranjan Mishra*** Anisamide Anchored Lyotropic Nano Liquid Crystalline Particles with AIE Effect-A Smart Optical Beacon for Tumor Imaging and Therapy ***ACS Appl. Mater. Interfaces*** 10(15) 12960-12974 (2018) ***(Corresponding author)***	**10.38**
5	Shweta Sharma, Ashwni Kumar Verma, Jyotsana Singh, B Venkatesh Teja, Naresh Mittapelly, Gitu Pandey, Sandeep Urandur, Ravi Shukla, Rituraj Konwar, **Prabhat Ranjan Mishra*** Vitamin B6 Tethered Endosomal pH-Responsive Lipid Nanoparticles for Triggered Intracellular Release of Doxorubicin ***ACS Appl. Mater. Interfaces*** 8 (44), 30407–30421 (2016) ***(Corresponding author)***	**10.38**
6	Sandeep Urandur, Venkatesh Teja Banala, Ravi Prakash Shukla, Shalini Gautam, Disha Marwah, Nikhil Rai, Madhu sharma, Shweta Sharma, Pratibha Ramarao, **Prabhat Ranjan Mishra*** Theranostic lyotropic liquid crystalline nanostructures for selective breast cancer imaging and therapy ***Acta Biomater.*** 113, 522-540 (2020) ***(Corresponding author)***	**10.63**
7	Gitu Pandey, Naresh Mittapelly, Venkatesh Teja Banala, and **Prabhat Ranjan Mishra*** Multifunctional Glycoconjugate Assisted Nanocrystalline Drug Delivery for Tumor Targeting and Permeabilization of Lysosomal Mitochondrial Membrane ***ACS Appl. Mater. Interfaces*** *10* (20), 16964–16976 (2018) ***(Corresponding author)***	**10.38**
8	S Sharma, A Verma, G Pandey, N Mittapelly, **and PR Mishra*** Investigating the role of Pluronic-g-Cationic polyelectrolyte as functional stabilizer for nanocrystals: Impact on Paclitaxel oral bioavailability and tumor growth ***Acta Biomater.*** 26, 169-183 (2015). ***(Corresponding author)***	**10.63**
9	Ashwni Verma,Shweta Sharma, Pramod Kumar Gupta, Awadhesh Singh, B Venkatesh Teja, Pankaj Dwivedi, Girish Kumar Gupta, Ritu Trivedi, **Prabhat Ranjan Mishra*** Vitamin B12 functionalized layer by layer calcium phosphate nanoparticles: A mucoadhesive and pH responsive carrier for improved oral delivery of insulin ***Acta Biomater.*** 31:288-300. doi: 10.1016/j.actbio (2016). ***(Corresponding author)***	**10.63**
10	S Kansal, R Tandon, A Verma, P Misra, AK Choudhary, R Verma, PRP Verma, A Dube, **PR Mishra*** Coating doxorubicin loaded nanocapsule with alginate enhances therapeutic efficacy against *Leishmania* in hamsters by inducing Th1 type immune responses ***Br. J. Pharmacol.*** 171(17):4038-50. (2014)**.** ***(Corresponding author)***	**7.30**

Journal of Controlled Release 365 (2024) 43–59

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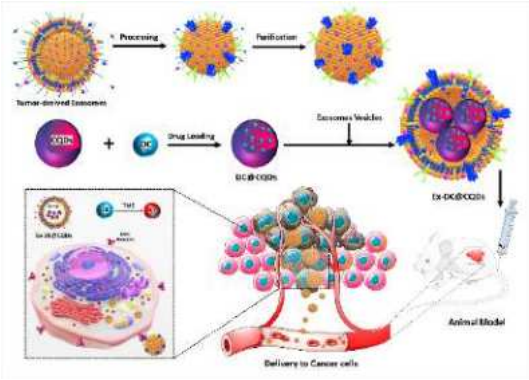
Dacarbazine-primed carbon quantum dots coated with breast cancer cell-derived exosomes for improved breast cancer therapy

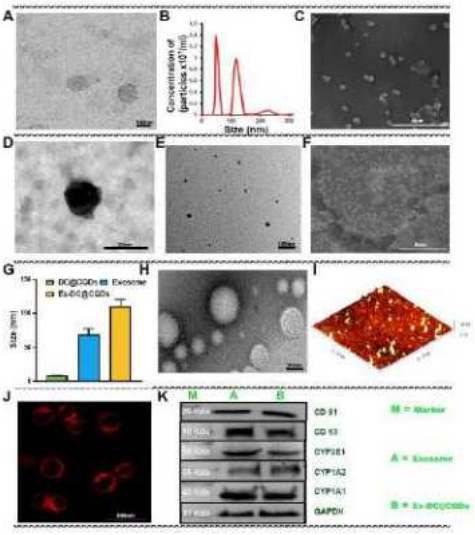
Pratiksha Tiwari [a,c], Ravi Prakash Shukla [a], Krishna Yadav [a], Neha Singh [a], Disha Marwaha [a], Shalini Gautam [a], Avijit Kumar Bakshi [a], Nikhil Rai [a], Ankit Kumar [a], Deepak Sharma [a], Prabhat Ranjan Mishra [a,b,*]

J. Controlled Rel 365, 43-59 (2024) ***(Corresponding author)*** **(I.F. 10.80)**

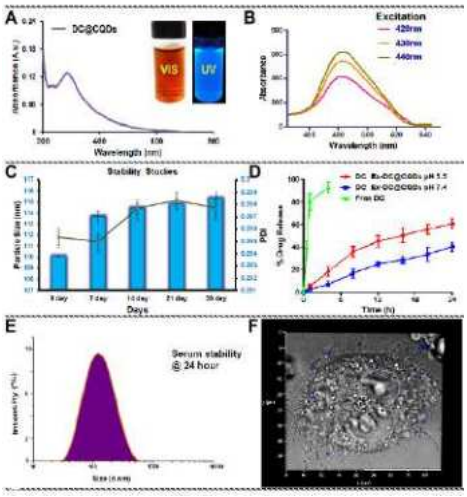
Imprecise targeting of chemotherapeutic drugs often leads to severe toxicity during breast cancer therapy. To address this issue, we have devised a strategy to load dacarbazine (DC) into fucose-based carbon quantum dots (CQDs), which are subsequently coated with exosomes (Ex-DC@CQDs) derived from breast cancer cells. Nanoparticle tracking analysis and western blotting revealed that Ex-DC@CQDs retained the structural and functional characteristics of exosomes. We found that exosomes facilitated the transport of DC@CQDs to cancer cells via heparan sulfate proteoglycan (HSPG) receptors, followed by an augmented depolarization of the mitochondrial membrane potential, ROS generation, and induction of apoptosis leading to cell death. In vivo imaging and pharmacokinetic studies demonstrated enhanced antitumor targeting and efficacy compared to free DC which we attribute to an improved pharmacokinetic profile, a greater tumor accumulation via exosome-mediated- HSPG receptor-driven cell uptake, and sustained release of the Ex-DC@CQDs. Our findings may pave the way for the further development of biologically sourced nanocarriers for breast cancer targeting.

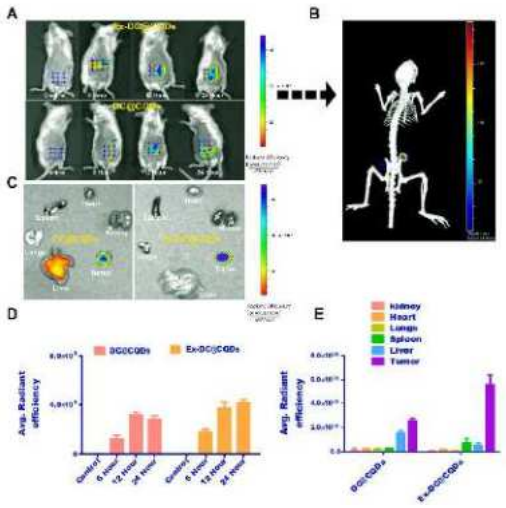


In the present study, we have successfully developed an exosome (Exo) derived bioengineered quantum dots-based system to address the issue of complicated imprecise targeting that often leads to clinical toxicity with breast cancer therapy. We devised a strategy that involved loading DC into Fucose-based CQDs, which were then coated with cancer cell isolated Exosomes, resulting in Ex-DC@CQDs. The studies confirmed the formation and characteristics of the CQDs and demonstrated that the Exosome retained their structural and functional properties within the system. The use of Exosome facilitated the targeted delivery of the DC@CQDs to cancer cells through HSPG receptors, thereby enhancing therapeutic efficacy. The study showed that Ex-DC@CQDs exhibited precise targeting and increased cellular uptake, and induced cell death in BC cells through



the generation of ROS, depolarization of MMP, and apoptosis. In vivo imaging demonstrated sustained fluorescence intensity at the tumor site, indicating efficient targeting through the exosome-mediated HSPG receptor-driven cell uptake. Additionally, the study evaluated the pharmacokinetic profile and antitumor efficacy of Ex-DC@CQDs compared to free DC and DC@CQDs. The results revealed a significant increase in the AUC0-∞ and a substantial reduction in tumor weight in the Ex-DC@CQDs-treated group, indicating improved pharmacokinetics, higher tumor accumulation, and sustained release of the carrier. Overall, our findings feature the potential of exosome-specific targeting and DC@CQD-mediated delivery as an effective intervention for BC. The use of Exo as nanocarriers offers advantages such as precise targeting, enhanced therapeutic efficacy, and reduced toxicity, facilitating the development of a new approach to biologically sourced nanocarriers for cancer targeting. Therefore, it was hypothesized that cytochrome enzymes, particularly CYP1A1, CYP1A2, and CYP2E1, being integral parts of the Exo would facilitate direct activation of DC within the tumor microenvironment (TME) after HSPG-mediated spatial targeting of Ex-DC@CQDs into tumor cells, thereby engendering improved efficacy while minimizing untoward effects on normal cells [12]. Thus, Exo co-loaded with CQDs and DC can provide significant therapeutic effects against BC while avoiding the many risks associated with the free DC. Moreover, Exo possess an intrinsic ability to cross biological barriers, enabling them to encounter the phagocytosed drug lost during circulation. To achieve this, CQDs were initially prepared using the microwave method [13,14]. Subsequently, the developed CQD was loaded with DC, and the formulations were optimized to develop pharmaceutical specifications with higher loading and then characterized extensively both in-vitro and in-vivo. This amalgamation of DC@CQDs within BC cell-derived Exo is anticipated to emerge as a promising modality for the precise and targeted delivery of pharmaceutical agents to BC cells. Ex-DC@CQDs have the potential as an innovative therapeutic avenue for BC treatment.





Journal of Controlled Release 372 (2024) 331–346

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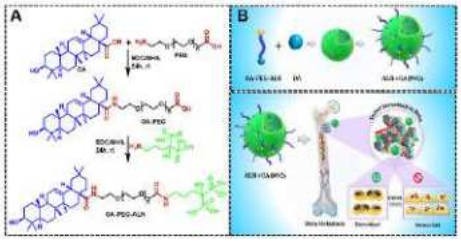
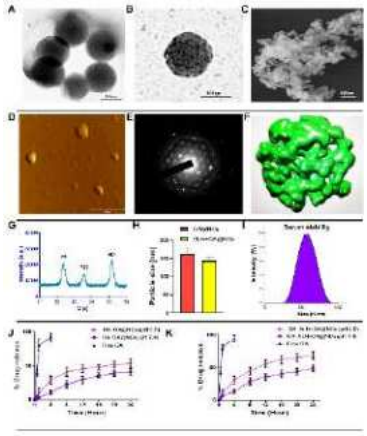
Alendronate-functionalized porous nano-crystalsomes mitigate osteolysis and consequent inhibition of tumor growth in a tibia-induced metastasis model

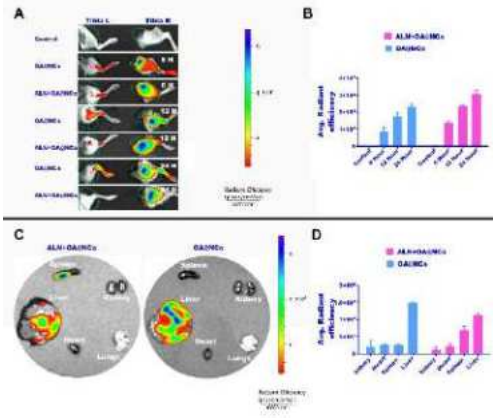
Ravi Prakash Shukla [a,1], Pratiksha Tiwari [a], Anirban Sardar [b,c], Sandeep Urandur [a], Shalini Gautam [a], Disha Marwaha [a], Ashish Kumar Tripathi [b], Nikhil Rai [a], Ritu Trivedi [b,c,**], Prabhat Ranjan Mishra [a,c,*]

J. Controlled Rel 372, 331-346 (2024) ***(Corresponding author)*** **(I.F. 10.80)**

Bone is one of the most prevalent sites of metastases in various epithelial malignancies, including breast cancerand this metastasis to bone often leads to severe skeletal complications in women due to its osteolytic nature. To address this, we devised a novel drug delivery approach using an Alendronate (ALN) functionalized selfassembled porous crystalsomes for concurrent targeting of Oleanolic acid (OA) and ALN (ALN + OA@NCs) to bone metastasis. Initially, the conjugation of both PEG-OA and OA-PEG-ALN with ALN and OA was achieved, and this conjugation was then self-assembled into porous crystalsomes (ALN + OA@NCs) by nanoemulsion crystallization. The reconstruction of a 3D single particle using transmission electron microscopy ensured the crystalline porous structure of ALN + OA@NCs, was well aligned with characteristic nanoparticle attributes including size distribution, polydispersity, and zeta potential. Further, ALN + OA@NCs showed enhanced efficacy in comparison to OA@NCs suggesting the cytotoxic roles of ALN towards cancer cells, followed by augmentation ROS generation (40.81%), mitochondrial membrane depolarization (57.20%), and induction of apoptosis (40.43%). We found that ALN + OA@NCs facilitated inhibiting osteoclastogenesis and bone resorption followed by inhibited osteolysis. In vivo activity of ALN + OA@NCs in the 4 T1 cell-induced tibia model rendered a reduced bone loss in the treated mice followed by restoring bone morphometric markers which were further corroborated bone–targeting effects of ALN + OA@NCs to reduce RANKL-stimulated osteoclastogenesis. Further, In vivo intravenous pharmacokinetics showed the improved therapeutic profile of the ALN + OA@NCs in comparison to the free drug, prolonging the levels of the drug in the systemic compartment by reducing the clearance culminating the higher accumulation at the tumor site. Our finding proposed that ALN + OA@NCs can effectively target and treat breast cancer metastasis to bone and its associated complications.







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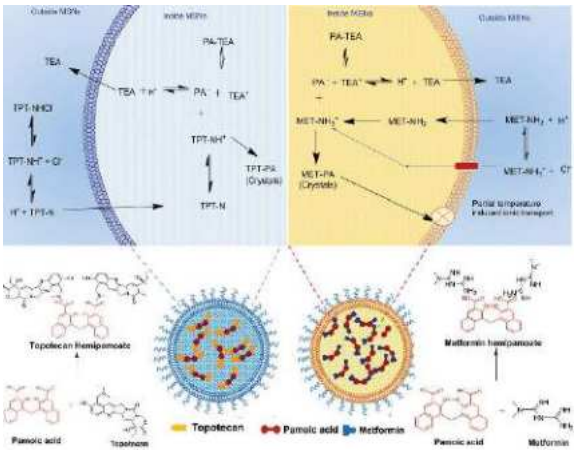
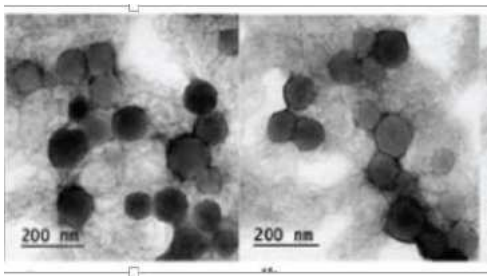
Synchronized Ratiometric Codelivery of Metformin and Topotecan through Engineered Nanocarrier Facilitates In Vivo Synergistic Precision Levels at Tumor Site

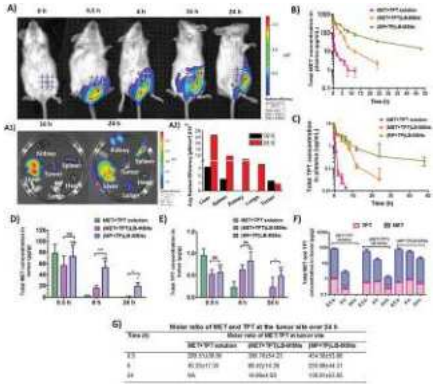
*Venkatesh Teja Banala, Shweta Sharma, Puja Barnwal, Sandeep Urandur, Ravi P. Shukla, Naseer Ahmad, Naresh Mittapelly, Gitu Pandey, Monika Dwivedi, Navodayam Kalleti, Kalyan Mitra, Srikanta Kumar Rath, Ritu Trivedi, and Prabhat Ranjan Mishra**

7(19):e1800300 (2018). ***(Corresponding author)*** **(I.F. 11.12)**

Highlights: The combination of metabolic modulators with chemotherapy holds vast promise for effective inhibition of tumor progression and invasion. Herein, a ratiometric co-delivery platform is developed for metformin (MET), a known metabolic modulator and topotecan (TPT), a chemotherapeutic drug, by engineering lipid bilayer–camouflaged mesoporous silica nanoparticles (LB-MSNs). In an attempt to deliver and maintain high tumor site concentrations of MET and TPT, a novel ion pairing–assisted loading procedure was developed using pamoic acid (PA) as an in situ trapping agent. PA, a hydrophobic counterion, increases the hydrophobicity of MET and TPT and facilitates MSNs with exceptionally high payload capacity (>40 and 32 wt%, respectively) and controlled release profile. Further, the synergy between MET and TPT determined by a modeling approach helps to afford synchronized delivery of both the drugs. Co-loaded MET and TPT LB-MSNs present synergistic cytotoxicity against MDA-MB-231/4T1 cells and effectively promote apoptosis via mitochondrial membrane depolarization and cell cycle arrest. Extended pharmacokinetic profiles in preclinical models with fourfold to sevenfold longer circulation half-life and 7.5–100 times higher tumor site concentrations correspond to a significant increase in pharmacodynamics efficacy. Taken together, the developed co-delivery approach effectively addresses the challenges in the chemotherapeutic efficacy of MET and TPT collectively.







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Cite This: ACS Appl. Mater. Interfaces 2018, 10, 12960−12974
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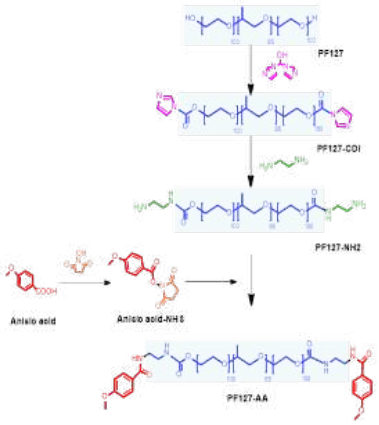
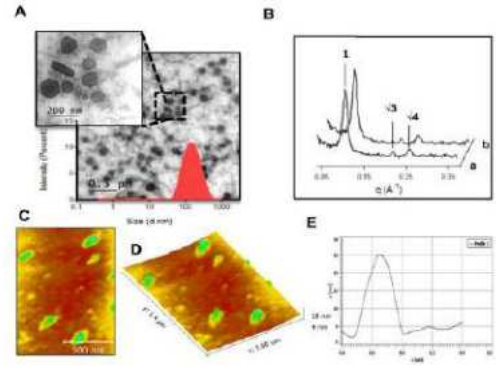
Anisamide-Anchored Lyotropic Nano-Liquid Crystalline Particles with AIE Effect: A Smart Optical Beacon for Tumor Imaging and Therapy

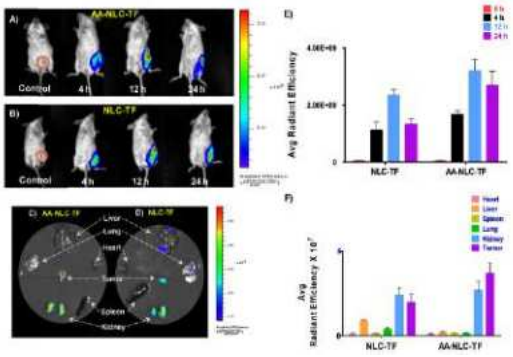
Sandeep Urandur,[†] Venkatesh Teja Banala,[†] Ravi Prakash Shukla,[†] Naresh Mittapelly,[†] Gitu Pandey,[†] Navodayam Kalleti,[‡] Kalyan Mitra,[§] Srikanta Kumar Rath,[‡] Ritu Trivedi,[∥] Pratibha Ramarao,[⊥] and Prabhat Ranjan Mishra*[,†]

ACS Appl. Mater. Interfaces 10(15) 12960-12974 (2018) **(Corresponding author) (I.F. 10.38)**

Highlights: To overcome exposure to harmful ionizing radiation and poor diagnostic accuracy, multifunctional nanoparticles (as theranostics) was developed for synchronized imaging and tumor-targeted non-invasive therapy through optical imaging. A novel optical beacons with distinct aggregation-induced emission (AIE) property in combination with therapeutic functions into one theranostic systems has been exploited as all-in-one approach. We have developed inverse hexagonal nano-liquid crystalline (NLC) particles that are able to host formononetin (FMN), a phytoestrogen with known anticancer activity, and tetraphenylethene (TPE), an iconic optical beacon with aggregation-induced emission (AIE) signature, simultaneously. The developed nanoparticles having three-dimensional mesoporous structure was covalently anchored with anisamide (AA), a novel sigma receptor targeting ligand. The existence of AIE effect in the nanoparticles was evidenced through the photophysical studies that advocate the application of NLC NPs in fluorescence-based bio imaging. Moreover, confocal microscopy illustrated the single living cell imaging ability endowed by the NLC NPs. *In vitro* and *in vivo* studies supported the enhanced efficacy of targeted nanoparticles (AA-NLC-TF) in comparison to non-targeted nanoparticles (NLC-TF) and free drug. The data provide the evidence that this critically designed multimodal NLC NPs may establish a promising platform for targeted and image-guided chemotherapy for breast cancer.







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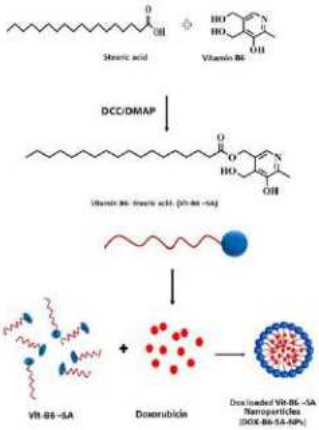
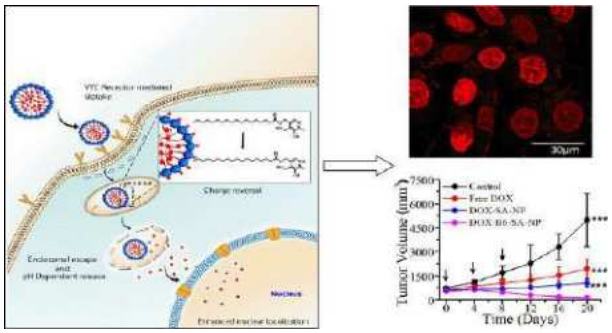
Vitamin B6 Tethered Endosomal pH Responsive Lipid Nanoparticles for Triggered Intracellular Release of Doxorubicin

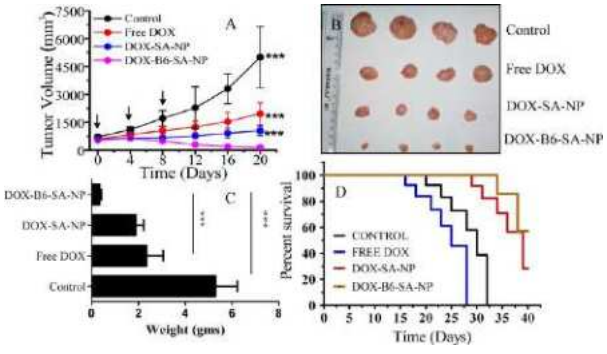
Shweta Sharma,[†,§] Ashwni Verma,[†] Jyotsana Singh,[‡,§] B. Venkatesh Teja,[†] Naresh Mittapelly,[†,§] Gitu Pandey,[†,§] Sandeep Urandur,[†] Ravi P. Shukla,[†] Rituraj Konwar,[‡] and Prabhat Ranjan Mishra*[†,§]

ACS Appl. Mater. Interfaces 8 (44), 30407–30421 (2016) ***(Corresponding author)*** **(I.F. 10.38)**

Highlights: This study reports the development of Vitamin B6 (VitB6) modified pH sensitive charge reversal nanoparticles for efficient intracellular delivery of Doxorubicin (DOX). Herein, VitB6 was conjugated to stearic acid, and the nanoparticles of the lipid were formulated by solvent injection method (DOX-B6-SA-NP). Because of the pKa (5.6) of VitB6, DOX-B6-SA-NP showed positive charge and enhanced release of DOX at pH 5. Confocal microscopy illustrated that DOXB6- SA-NP treatment kept higher DOX accumulation inside the cells than conventional pH insensitive lipid nanoparticles (DOX-SA-NP). The cationic charge of nanoparticles subsequently facilitated the endosomal escape and promoted the nuclear accumulation of DOX. Furthermore, in vitro cytotoxicity, apoptosis, cell cycle arrest, and mitochondrial membrane depolarization studies supported the enhanced efficacy of DOX-B6-SA-NP in comparison to free DOX and DOX-SA-NP. The enhanced tumor efficacy in in vivo tumor models was consistent with in vitro apoptosis of tumor cells, which was being mediated through increased cell cycle arrest in the G2/M phase. This enhanced efficacy was owing to the high cellular uptake, subsequent stimuli-triggered intracellular release, and charge conversion nature of the delivery system. Intravenous pharmacokinetics and bio-distribution investigations indicated that pH-sensitive nanoparticles can significantly prolong the blood circulation time of DOX in a biological system and increase the drug accumulation to tumor site. Consequent to this, DOX-B6-SA-NP also exhibited much enhanced therapeutic efficacy and lower toxicity in tumor-bearing rats compared to free DOX. The reduction in toxicity was confirmed by histological and survival analysis. In conclusion, these results suggest that the VitB6 modified charge reversal nanoparticles can be a novel platform for the successful delivery of anticancer drugs.







Acta Biomaterialia 113 (2020) 522–540

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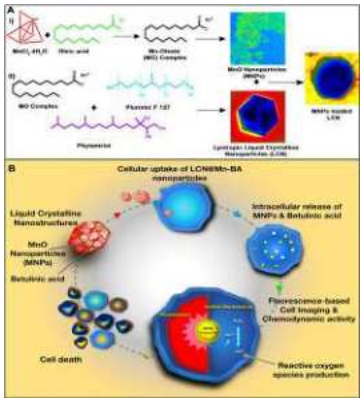
Full length article

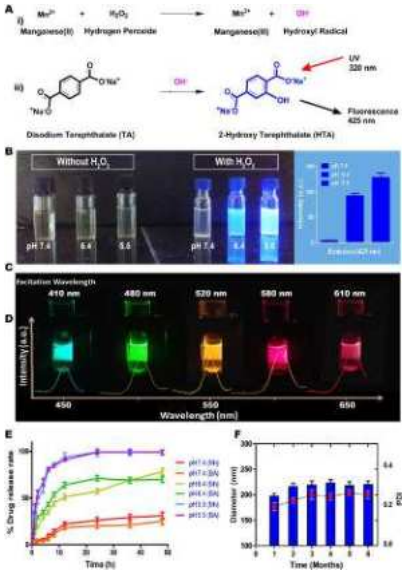
Theranostic lyotropic liquid crystalline nanostructures for selective breast cancer imaging and therapy

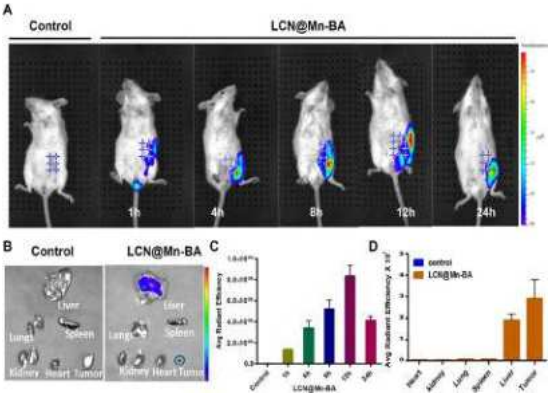
Sandeep Urandur[a], Venkatesh Teja Banala[a], Ravi Prakash Shukla[a], Shalini Gautam[a], Disha Marwaha[a], Nikhil Rai[a], Madhu Sharma[a], Shweta Sharma[a], Pratibha Ramarao[b], Prabhat Ranjan Mishra[a,*]

Acta Biomaterialia 113, 522–540 (2020) **(Corresponding author) (I.F. 10.63)**

Highlights: Compared to radiation, photodynamic and photothermal therapy, the specific and selective activation of tumor microenvironmental endogenous stimuli for the logical generation of cytotoxic OH ·free radicals serves as an efficient therapeutic strategy for chemodynamic-cancer treatment. Herein, we report the development of theranostic lyotropic liquid crystalline nanostructures (LCN's) loaded with unique MnO nanoparticles (MNPs) for selective cancer imaging and therapy. MNPs serves as a fluorescent agent as well as a source of manganese (Mn^{2+}) and enables localized oxidative stress under the hallmarks of cancer (acidosis, high H_2O_2 level). In pursuit of synergistic amplification of Mn^{2+} antitumor activity, betulinic acid (BA) is loaded in LCN's. In this investigation, nano-architecture of LCN's phase interface is established via SAXS, Cryo-TEM and Cryo-FESEM. Intriguing *in vitro* studies showed that the LCN's triggered hydroxyl radical production and exhibited greater selective cytotoxicity in cancer cells, ensuring the safety of normal cells. Significant tumor ablation is realized by the 96.5 % of tumor growth inhibition index of LCN's as compared to control group. Key insights into on-site drug release, local anti-cancer response, and tumor location are gained through precise guidance of fluorescent MNPs. In addition, comprehensive assessment of the safety, pharmacokinetics and tumor distribution behavior of LCN's is performed *in vivo* or *ex vivo*. This work emphasizes the promise of modulating tumor microen- vironment with smart endogenous stimuli sensitive nano systems to achieve advanced comprehensive cancer nano-theranostics without any external stimulus. In this investigation, MnO nanoparticles fulfill two needs (fluorescence- based optical imaging and a source of Mn^{2+} based chemodynamic therapy) in one unit. This approach also ensures the safety of normal cells, as the toxic OH ·free radical activity is substantially suppressed under the mild alkaline/H_2O_2 conditions in normal cell microenvironment.







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Cite This: ACS Appl. Mater. Interfaces 2018, 10, 16964−16976
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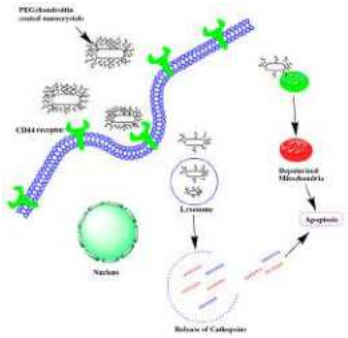
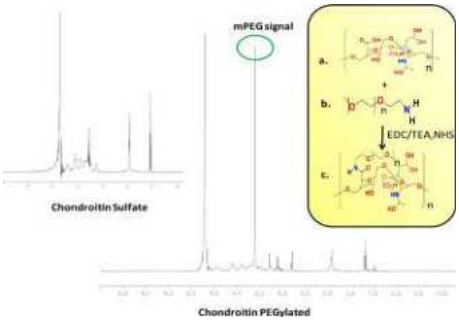
Multifunctional Glycoconjugate Assisted Nanocrystalline Drug Delivery for Tumor Targeting and Permeabilization of Lysosomal-Mitochondrial Membrane

Gitu Pandey,[†,‡] Naresh Mittapelly,[†,‡] Venkatesh Teja Banala,[†] and Prabhat Ranjan Mishra*[,†,‡]

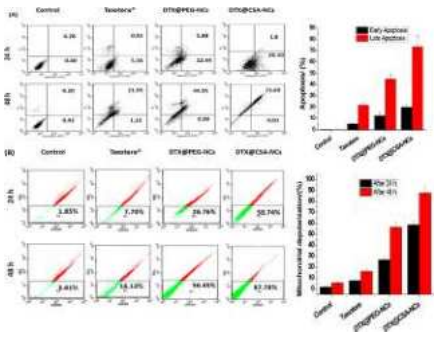
ACS Appl. Mater. Interfaces *10* (20), 16964–16976 (2018) ***(Corresponding author)*** **(I.F. 10.38)**

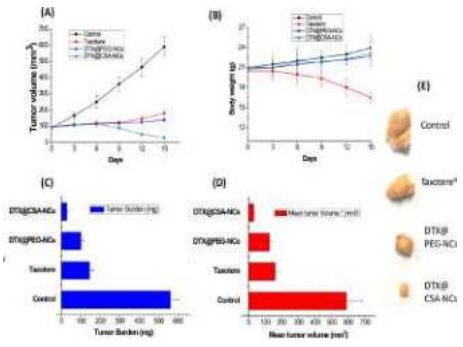
Highlights: To address the practical issues associated with docetaxel delivery like low aqueous solubility and proclivity toward P-gp efflux pump render it unsuitable for administration as a purely water based solution and necessitate the administration with polysorbate 80 (PS 80) based solution. This adds to the woes as PS 80 itself is associated with various adverse reactions like severe hypersensitivity due to histamine release from mast and basophil cells and severe hypotension.





Nanotechnology has emerged as the most successful strategy for targeting drug payloads to tumors with the potential to overcome the problems of low concentration at the target site, nonspecific distribution, and untoward toxicities. In this study we synthesized chondroitin sulfate A−polyethylene glycol conjugate and exploited its subsequent application in the fabrication of docetaxel nanocrystals. We further employed this glycoconjugate possessing the propensity to provide stability, stealth effects, and tumor targeting via CD44 receptors, all in one, to develop a nano-crystalline system of docetaxel (DTX@CSA-NCs) with size < 200 nm, negative zeta potential, and 98% drug content. Taking advantage of the enhanced permeability and retention effect coupled with receptor mediated endocytosis, the DTX@CSA-NCs cross the peripheral tumor barrier and penetrate deeper into the cells of tumor mass. In MDA-MB-231 cells, this enhanced cellular uptake was observed to exhibit a higher degree of cytotoxicity and arrest in the G2 phase in a time dependent fashion. Acting via a mitochondrial-ly sosomotropic pathway, DTX@CSA-NCs disrupted the membrane potential and integrity and outperformed the clinically used formulation. Upon intravenous administration, the DTX@CSA-NCs showed better pharmacokinetic profile and excellent 4T1 induced tumor inhibition with significantly less off target toxicity. Overall, the results obtained with in vitro experiments corroborated well with in vivo results where the DTX@CSANCs showed higher plasma concentration and higher tumor regression in 4T1 induced mice tumor model. Thus, this glycoconjugate stabilized nanocrystalline formulation has the potential to take nano-oncology a step forward.





Acta Biomaterialia 26 (2015) 169–183

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Investigating the role of Pluronic-g-Cationic polyelectrolyte as functional stabilizer for nanocrystals: Impact on Paclitaxel oral bioavailability and tumor growth

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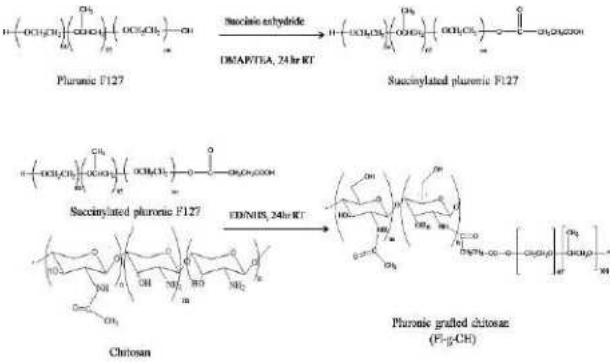
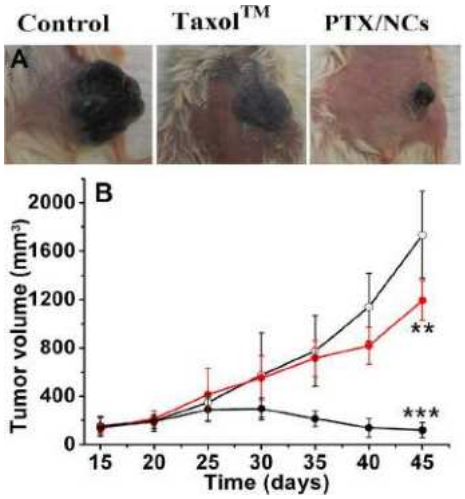
Acta Biomaterialia 26, 169-183 (2015) ***(Corresponding author)*** **(I.F. 10.63)**

Highlights: Paclitaxel (PTX) is a potent anticancer drug which suffers limitations of extremely low oral bioavailability due to low solubility, rapid metabolism and efflux by P-gp transporters. The main objective of this study was to overcome the limitation of PTX by designing delivery systems that can enhance the absorption using multiple pathways. A novel Pluronic-grafted chitosan (Pl-g-CH) copolymer was developed and employed as a functional stabilizer for nanocrystals (NCs) and hypothesized that it would improve PTX absorption by several mechanisms and pathways. Pl-g-CH was synthesized and characterized using 1H NMR and then used as a stabilizer during nanocrystal development. To establish our proof of concept the optimized formulation having a particle size 192.7 ± 9.2 nm and zeta potential (+) 38.8 ± 3.12 mV was studied extensively on in vitro Caco-2 model. It was observed that nanocrystals rendered higher PTX accumulation inside the cell than TaxolTM. P-gp inhibitory potential of Pl-g-CH was proved by flow cytometry and fluorescence microscopy where the much enhanced fluorescence intensity of Rhodamine 123 (Rho-123, P-gp substrate) was observed in the presence of Pl-g-CH. In addition, a significant decrease in Trans Epithelial Electrical Resistance (TEER) of Caco-2 cell monolayers was observed with nanocrystals as well as with TaxolTM (in the presence of free Pl-g-CH compared to only TaxolTM). This supports the role of the stabilizer in reversible opening of tight junctions between cells which can allow paracellular transport of drug. The in vivo results were in complete corroboration with in vitro results. Nanocrystals resulted in much enhanced absorption with 12.6-fold improvement in relative bioavailability to that of TaxolTM. Concomitantly efficacy data in B16 F10 murine melanoma model also showed a significant reduction in tumor growth with nanocrystals compared to TaxolTM and control. Based on the results it can be suggested that nanocrystals with functional stabilizers can be a promising approach for the oral delivery of anticancer drugs which are P-gp substrates.





Acta Biomaterialia 31 (2016) 288–300

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

Vitamin B12 functionalized layer by layer calcium phosphate nanoparticles: A mucoadhesive and pH responsive carrier for improved oral delivery of insulin

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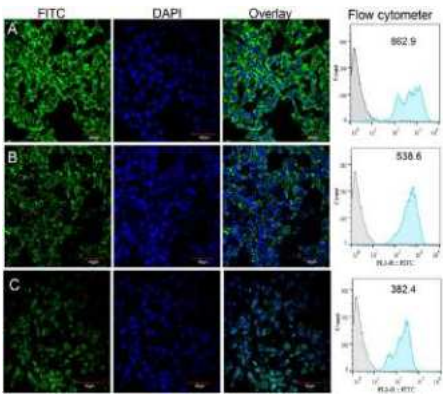
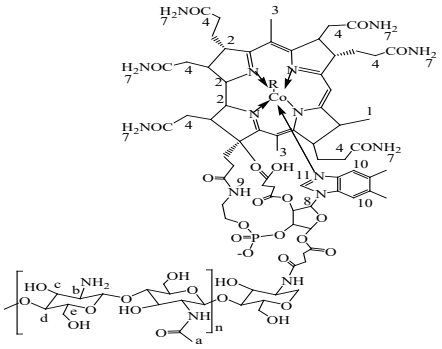
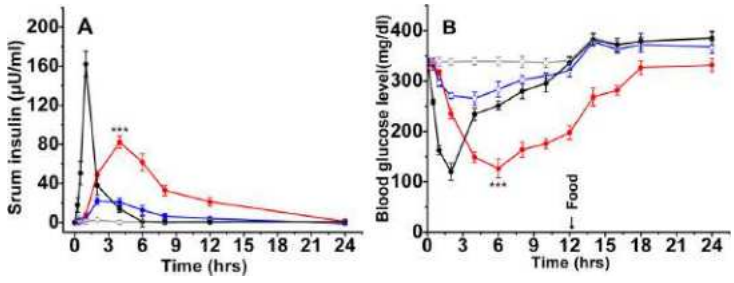
31:288-300 (2016). ***(Corresponding author)*** **(I.F. 10.63)**

Highlights: The present study investigates the potential of layer by layer coated calcium phosphate nanoparticles-for oral delivery of insulin where Vitamin B12 grafted chitosan and sodium alginate have been used as cationic and anionic polyelectrolyte respectively. The major emphasis has been given on the role Vitamin B12 conjugated chitosan as cationic polyelectrolyte (VitB12-Chi) in the delivery system. VitB12-Chi conjugate was prepared by carbodiimide reaction. The formulated VirB12-Chi-CPNPs were tested for in vitro and in vivo efficacy studies carried out in Caco-2 monolayers and diabetic rats. VitB12-Chi-CPNPs with particle size <250 nm and zeta potential + 32.56(±2.34) exhibited pH responsive insulin release at simulated gastric fluid and simulated intestinal fluid. Fluorescence microscopy and flow cytometry studies revealed higher uptake of VitB12-Chi-CPNPs in Caco-2 monolayer in comparison to Chi-CPNPs. Further reduction in TEER supported paracellular transport of insulin because of opening of tight epithelial junctions. In vivo intestinal uptake of FITC tagged Vit-B12-Chi-CPNPs from different intestinal segments supported paracellular and receptor mediated uptake of VitB12-Chi-CPNPs. Plasma insulin and blood glucose levels were measured in diabetic rats and showed about four fold increases in insulin bioavailability and sustained hypoglycemic effects up to 12 h of administration with VitB12-Chi-CPNPs in comparison to Chi-CPNPs. Results of the study revealed the potential of layer by layer nanoparticles for oral insulin delivery. The study also specifically highlighted the role of VitB12 as a pH sensitive and targeting ligand which significantly participated in enhancing insulin oral bioavailability.







BJP British Journal of Pharmacology

DOI:10.1111/bph.12754
www.brjpharmacol.org

RESEARCH PAPER

Coating doxorubicin-loaded nanocapsules with alginate enhances therapeutic efficacy against *Leishmania* in hamsters by inducing Th1-type immune responses

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Received
14 November 2013
Revised
9 April 2014
Accepted
23 April 2014

171(17):4038-50. (2014). ***(Corresponding author)*** **(I.F. 9.47)**

The aim of the present study was to evaluate the immunomodulatory and chemotherapeutic potential of alginate-(SA) coated nanocapsule (NCs) loaded with doxorubicin (SA-NCs-DOX) against visceral leishmaniasis in comparison with nano-emulsions containing doxorubicin (NE-DOX). NE-DOX was prepared using low-energy emulsification methods. Stepwise addition of protamine sulphate and SA in a layer-by-layer manner was used to form SA-NCs-DOX. SA-NCs-DOX, NE-DOX and Free DOX were compared for their cytotoxicity against *Leishmania donovani*-infected macrophages *in vitro* and generation of T-cell responses in infected hamsters *in vivo*. Size and ζ potential of the NE-DOX and SA-NCs-DOX formulations were 310 ± 2.1 nm and (−)32.6 ± 2.1 mV, 342 ± 4.1 nm and (−)29.3 ± 1.2 mV respectively. SA-NCs-DOX was better (1.5 times) taken up by J774A.1 macrophages compared with NE-DOX. SA-NCs -DOX showed greater efficacy than NE-DOX against intramacrophagic amastigotes. SA-NCs-DOX treatment exhibited enhanced apoptotic efficiency than NE-DOX and free DOX as evident by cell cycle analysis, decrease in mitochondrial membrane potential, ROS and NO production. T-cell responses, when assessed through lymphoproliferative responses, NO production along with enhanced levels of iNOS, TNF-α, IFN-γ and IL-12 were found to be up-regulated after SA-NCs-DOX, compared with responses to NE-DOX *in vivo*. Parasitic burden was decreased in *Leishmania*-infected hamsters treated with SA-NCs-DOX, compared with NE-DOX. Our results provide insights into the development of an alternative approach to improved management of leishmaniasis through a combination of chemotherapy with stimulation of the innate immune system.