

26th International Conference on
Nanotechnology and Nanomedicine

May 13, 2022 | Webinar

Received date: 03-11-2021 2 | Accepted date: 06-11-2021 | Published date: 25-05-2022



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Rationally designed smart nanomedicine augments site-specific chemoradiotherapy of aggressive malignant niches

Limited therapeutic gain with neoadjuvant chemotherapy of locally advanced inoperable cancers can be improved with concomitant use of chemoradiotherapy owing to their spatial cooperation and synergistic cytotoxicity. However, poor circulation half-life, limited passive bioavailability and dose-limiting systemic toxicities of clinically approved radiosensitizers significantly affect the treatment efficacy and patient's quality of life. Incorporation of clinical radiosensitizers into smart nanomedicine can overcome these limitations; however location of the malignant niche is imperative to their rational designing. To target deep-seated malignancies like triple negative breast cancer (TNBC) or metastatic niches, we designed an ultrasound and tumor microenvironment responsive 'stealth' theranostic nano-conjugate platform for contrast enhanced imaging and on-demand spatiotemporal delivery of combinatorial radiosensitizers i.e. curcumin and paclitaxel post systemic administration. Developed strategy imparted site-specific focussed ultrasound mediated infiltration of nano-conjugates at the orthotopic TNBC xenograft in NOD-SCID mice followed by low pH and hyperthermia dependent release of drugs at the tumor interstitium to ameliorate fractionated radiotherapy with improved survival in comparison to commercial paclitaxel formulation and radiotherapy alone. In contrast, locally accessible mucosal malignancies (head and neck cancer, cervical, vulval and anal cancer) requiring concurrent chemoradiotherapy as definitive treatment can be managed more efficiently through a rationally designed regional delivery platform. Thus, we developed a dual radiosensitizing nanocarrier-in-hydrogel as a drug eluting local depot for enhanced and prolonged bioaccumulation of drugs at the tumor with minimal systemic absorption. It helped improve the in vivo chemoradiotherapeutic efficacy and safety of synergistic radiosensitizers (cisplatin and paclitaxel) approved for clinical chemoradiotherapy of head

and neck cancers. Conclusively, our findings suggest the clinical potential of the malignant niche-specific platforms for the rational management of radio-responsive cancers in neoadjuvant settings.

Recent Publications

1. Prateek Bhardwaj, Vikram Gota, Komal Vishwakarma, Venkatesh Pai, Pradip Chaudhari, Bhabani Mohanty, Rahul Thorat, Subhash Yadav, Murari Gurjar, Jayant Sastri Goda, Rinti Banerjee, et al. Loco-regional radiosensitizing nanoparticles-in-gel augments head and neck cancer chemoradiotherapy. *J Control Release*. 2022; 343: 288-302
2. Prateek Bhardwaj, Eshant Bhatia, Shivam Sharma, Nadim Ahamad, Rinti Banerjee. Advancements in prophylactic and therapeutic nanovaccines. *Acta Biomater*. 2020; 108: 1-21
3. Prateek Bhardwaj, Nadim Ahamad, Abhinanda Kar, Sourabh Mehta, Mahima Dewan, Vasanthan Ravichandran, Shivam Sharma, Rinti Banerjee, et al. Immunomodulatory nanosystems for treating inflammatory diseases. *Biomaterials*. 2021; 274: 120875.

Speaker Biography

Prateek Bhardwaj works as a Postdoctoral Associate in the Department of Therapeutic Radiology, Yale School of Medicine. After obtaining a Ph.D. in nanomedicine, he is now keenly interested in developing personalized medicine for leukemia by understanding and exploiting the synthetic lethal interactions between the genes involved in DNA damage response. Pertaining to his doctoral research on developing smart biomaterial-based theranostic nano-platforms and hydrogels for effective site-specific chemoradiotherapy of superficially accessible and deep-seated malignancies like oral cancer and Triple-negative breast cancer respectively, he has been granted a patent and published several peer-reviewed research and review articles in esteemed international journals like *Nanoscale*, *Journal of Controlled Release*, *Biomaterials*, *Acta Biomaterialia* and *Biomacromolecules*. He strongly believes that amalgamating basic science with nanomedicine can bring a revolutionary improvement in existing healthcare technologies by discovering next-generation therapeutics along with their effective delivery for better patient compliance.

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