Functional nanomaterials in cancer therapy

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"*The contributors to this special focus issue represent early carreer researchers to experts in their respective research areas and came from across the globe. Their collective contributions provide a past and up to date research overview of functional nanomaterials in cancer therapy from targeted drug delivery to localized heating using hyperthermia and their effects on possible cellular pathways both in vitro and in vivo. In addition, a range of diagnostic tools from magnetic resonance imaging (MRI) and fluorescence, to novel terahertz imaging modalities have been covered. The theme of this Special Issue was the main research theme of the second international symposium "Functional Nanomaterials in Industrial & Clinical Applications: Academia -Industry-Clinicians Meet (14-16th July 2020)", organized by the University of Central Lancashire (Preston, UK) via Zoom platform during the global coronavirus pandemic.*

This *Nanomedicine* Special Issue has been divided into two issues in May 2021 (volume 16, issues 11 and 12). The first issue comprises four original research articles [1-4] focusing on magnetic, and plasmonic nanoparticles for potential cancer therapy *in vitro*, along with a review article [5] covering only *in vivo* applications of magneto-optical nanoparticles of iron oxide as magnetic and organic dyes as optical probes. The second issue comprises five original research articles [5-10] focusing on functional nanoparticles for both *in vitro* and *in vivo* cancer therapy and a novel terahertz imaging technique [10] as a potential future diagnostic platform along with a review article [11] covering various non-apoptotic pathways in cellular toxicity during cancer therapy.

These two issues (11 and 12) showcase selected original research works presented by the invited and keynote speakers at the International symposium, organized as a part of the dissemination event of an international project "Functional Nanoparticles in Cancer Therapy (Grant Ref: IND/Cont/G 16-17/62)" funded by UK-India Education and Research Initiative (UKIERI). The symposium aimed to discuss three major thematic areas *viz*. (i) Nano-energy / environment for a better society; (ii) Nanomedicine in health & diagnostics and (iii) Nano-catalysis for green technology. Around 110 abstracts were received altogether, of which 60 were on Nanomedicine in Health & Diagnostics. After the strict intensive blind

peer-review process, only 9 original research articles and 2 review articles have been processed for publication in this Special Issue. An overview of international UKIERI project and the symposium full abstract proceedings can be found by browsing the links provided in the reference section [12,13]. Specifically, the scope of this special focus issue is to inform readers from academia, industries and hospital clinicians about the latest status of a range of multifunctional nanomaterials, such as superparamagnetic iron oxide nanoparticles (SPIONs) of various shapes and sizes, plasmonic and lipid nanoparticles with biologically (i.e. human serum and cisplatin) modified forms for *in vitro* and *in vivo* cancer therapy, surface enhanced Raman scattering (SERS) guided photothermal therapy, monitoring Eddy currents on optimizing magnetic hyperthermia treatment, along with a terahertz (THz) imaging technique.

In issue 11, we focused only on magnetic, optical and plasmonic nanoparticles in cancer therapy. Iron oxide nanoparticles with magnetic properties have been utilized for decades in nanomedical areas such as targeted drug delivery to tumor sites under the influence of an externally applied magnetic field while their localization at target sites can be monitored by MRI contrasting. However, the combination of iron oxide nanoparticles with optical probes such as organic photosensitizers can provide major advantages as multimodal theranostic agents by combining multiple therapeutic applications such as (i) targeted drug delivery and (ii) localized heating at tumor sites by applying both alternating magnetic field (AMF) and shining laser light of certain wavelengths, along with diagnostic applications via monitoring their distribution in cancer cells by a combination of MRI and fluorescence imaging. Organic dyes (e.g. fluorescein) are well known for bioimaging, however, the combination of fluorescein with iron oxide based magnetic liposomes for photodynamic therapy by activating reactive oxygen species (ROS) with the exposure of laser light during *in vitro* cellular toxicity study of cancer cell lines is novel [1]. Localized heating of tumor cells by applying AMF using magnetic nanoparticles is an important area of research in cancer therapy, however, optimizing their performance by mitigating eddy currents is unique and provides an important step towards cancer therapy by selecting optimized frequency and field during the hyperthermia treatment [2]. Similarly, plasmonic nanoparticles based on noble metals such as gold, silver etc. are beginning to be explored due to their photothermal effects under laser light to create localized heat. However, monitoring their distribution in cellular system can be difficult. In this context, a well-known technique SERS has been utilized for guiding / monitoring via surface mapping followed by photothermal effect using Ag nanoparticles capped copper sulfide (CuS) *in vitro* cancer cell lines [3]. An important step towards finding the right wavelength for excitation and emission bands in the near infrared (NIR) region by theoretical calculation and applied the values *in vitro* human HeLa cell lines is once again a unique work. This has huge potential for targeted cancer therapy using plasmonic nanoparticles via photothermal treatment [3]. Iron oxide nanoparticles with various sizes and morphologies are common and correlating physicochemical properties with heating efficiency (hyperthermia treatment) under AMF has become an important issue before applying them in cancer

theranostics. In this context, cubic iron oxide nanoparticles with a biocompatible diamagnetic coating DMSA improved magnetic properties and cellular toxicity *in vitro* using human HeLa cell lines [4]. In addition, a comprehensive up to date information of iron oxide based magnetic nanoparticles in conjugation with a range of photosensitizers for only *in vivo* cancer theranostics is reviewed [5].

In issue 12, we focused mainly on novel methodologies and a diagnostic tool for *in vivo* and *in vitro* cancer theranostics. CRISPR technology is a well-known technique and the inventors have been awarded Nobel Prizes in Chemistry in 2020 [14]. In this context, the CRISPR/Cas9 system is a promising gene editing tool for various anti-cancer therapies. However, biocompatible, non-viral and efficient delivery of CRISPR/Cas9 expression systems remains a challenge. The use of a solid lipid nanoparticulate system as a delivery mode for a reliable non-viral carrier system has been successfully demonstrated [6] which could pioneer widespread use of CRISPR/Cas9 technology in pre-clinical studies in the near future. Ovarian cancer is a resilient cancer with a high death rate and a huge negative impact to the aging populations of Asian countries. Cisplatin (Cis) was the first platinum-based drug approved by the US Food and Drug Administration for use against cancers including ovarian cancer. Regardless of its anti-tumor activity, the clinical efficacy of Cis is limited owing to resistance and severe side effects. Cis loaded nanostructured lipid carriers (Cis-NPC) have been utilized for finding connectivity between biotoxicity and efficacy in sensitizing Cis resistant ovarian cancer cells [7]. Personalized medicine is going to be the next generation of medical treatment. In this context, developing total serum nanoparticles using protein molecules from human serum and loaded with anticancer drugs such as paclitaxel or piperlongumine for drug delivery has been successfully demonstrated [8]. In short, drug-loaded nanoparticles formed from the patient's own blood serum could act as a personalized nanomedicine platform for the better, safe delivery of chemotherapeutic agents. Porous silica nanoparticles have been utilized as drug delivery vehicles due to their controlled pore sizes, internal porosity and their biocompatibility. Mesoporous silica nanoparticles with variable sizes and with or without thiol functionalized (-SH) forms have been efficiently prepared and utilized in drug, 5-fluorouracil) loading for breast cancer therapy using both *in vitro* (MCM-7 cell lines) and *in vivo* [9]. It has been demonstrated that small thiol-functionalized mesoporous sMCM-41 nanoparticles altered genes that were predominantly associated with inhibiting tumor invasion and growth. Issue 11 has already mentioned the importance of monitoring nanoparticles in tumor cells via MRI or fluorescence imaging before applying therapies. In this context, a new diagnostic platform using a terahertz (THz) radiation source for biomedical imaging has been explored and compared with an MRI study in cancer cells [10]. The apoptosis pathway is a universally accepted pathway for the toxicity of nanoparticles in biomedical application. However, there are several non-apoptotic pathways such as necroptosis, autophagy and ferroptosis are beginning to explore. In this Special Issue, various non-apoptotic pathways have been comprehensively reviewed in *in vivo* biomedical studies [11].

The contributors & their work

This Special Issue has been fully managed by Tapas Sen (University of Central Lancashire, UK) chairperson of the symposium [13] and the coordinator of UKIERI project [12] along with the partial help from Morteza Mahmoudi (Michigan State University, MI, USA). Sen's group, with that of Indian project lead Indrajit Roy, highlight the importance of multifunctional nanoparticles involving magnetic and optical probes in photodynamic therapy in cancer [1]. In addition, Sen and Roy's groups have contributed a review article involving multifunctionality of both magnetic and optical organic molecular probes in *in vivo* biomedical studies [5]. Lastly, Sen and Roy's groups, along with Anita Verma's group in India have also reviewed various non-apoptotic pathways in cellular toxicity using multifunctional nanoparticles [11].

Indrajit Roy (Delhi University, India) was the Indian project lead of UKIERI project [12] and has been working in the area optical nanoparticles in biomedical applications for the last 2 decades. His group has contributed one original article [1] and two review articles [5,11] in collaboration with Sen's group in the UK and Verma's group in India.

Mavroeidis Angelakeris's group (Center for Interdisciplinary Research and Innovation - Aristotle University of Thessaloniki, Greece) has been working on the physics aspects of magnetic nanoparticles and contributed an article on the importance of eddy currents on optimizing magnetic hyperthermia treatment [2].

Hsieh-Chih Tsai (National Taiwan University of Science and Technology, Taipei, Taiwan), in collaboration with the research group of Rakesh S Moirangthem (Indian Institute of Technology, Dhanbad, India) has been working on a joint international project on plasmonic nanoparticles for biomedical application. SERS guided plasmonic nanoparticles for photothermal therapy has been shown to be promising for next generation of cancer therapy [3].

Nguyen T K Thanh (University College London, UK) leads a research team focusing on the design, synthesis and biomedical application of various nanomaterials. Cubic iron oxide nanopaticles for improved magnetiations and cellular toxicity study have been successfully repoted [4]. These nanomaterials could be potential nanomedical agents for multimodal cancer theranostics.

Hasan Akbaba (Ege University, Bornova, Turkey), in collaboration with various academic organizations in Turkey, has contributed an article covering an important area of cancer therapy using CRISPR/Cas9 technology by incorporating solid lipid nanoparticles [6].

Anita Kamra Verma (Kirori Mal College, Delhi University, India) is the co-investigator of the UKIERI project and has been working on the biological aspects of nanoparticles for the last two decades. Her group has contributed one original article on Cis-platin capped nanocomposites lipid carriers for ovarian cancer [7] and a review article [11] on the non-apoptotic pathways of cellular toxicity in collaboration with Roy's group in India and Sen's group in UK.

Manzoor Koyakutty (Amrita Vishwa Vidyapeetham University, Kochi, India) leads the group dedicated to cancer nanomedicine and his group has contributed an important research article using the concept of personalized medicine involving protein nanoparticles as total serum particles for drug delivery both *in vivo* and *in vitro* [8].

Uma Maheswari Krishnan (SASTRA Deemed-to-be-University, Thanjavur, India) is a leading nanomedicine researcher in India and her group has contributed mesoporous nanomaterials (functionalized and non-functionalized forms) for drug delivery application in breast cancer therapy [9].

Hiroshi Inokawa (Shizuoka University, Japan) and Amit Banerjee (National University of Singapore, Singapore) are well known for their work on device fabrication using terahertz (THz) radiation. They have contributed, in collaboration with groups in India, research on a new generation of THz imaging platform for cancer cells diagnosis [10] and compared their results with already published MRI data.

The special focus issue's particular benefit to readers

The Second International Symposium, which took place during the global health crisis of the Covid-19 pandemic, has been a great success for connecting the international nanotechnology community from academia, industries, and healthcare professionals. Several commercial entities (i) Hosokawa Micron Ltd (Cheshire, UK), (ii) Feedwater Ltd., (Birkenhead, UK), (iii) Magnetic Insight (USA), (iv) Tata Chemical Ltd. (Pune, India) along with the National Health Service of the UK (iv) Royal Blackburn Teaching Hospital, (v) University Hospital of Warwickshire & Coventry were involved in the program. During the forum discussion, a large number of audiences from across the globe joining for finding the right pathways to transform academic research from laboratory to bedsides in hospital. This Special Issue has been focused on those aspects. Finally, the Special Issue highlights the significance and importance of international collaborations typified by those brokered and funded by UKIERI [12].

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activity. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Dedication:

This Special Issue is dedicated to the people across the globe who have lost their lives during the global Covid-19 pandemic, and to the researchers who have tirelessly worked to develop vaccines in a short period of time for the benefit of the human race.

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