PLENARY LECTURE 1:

Trends in Biomedical materials. Where Physics can help

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Biomedical materials are multidisciplinary field and in focus of intensive research for decades. Often modern advances in Physics might have impact of development of biomaterials of new generation. Exploring physics influence we may alter the materials while they are already in biological matter such as cells or entire organism. Some of applications as remote controlled drug delivery using magnetic field, light or ultrasound are well elaborated and are on the way to clinic. Tracking of individual cells can be processed in cell population, but there is a potential to go to track cells in tissues or in body. In this talk we review recent advances and possible step forwards as well as foreseen obstacles on the way to bring biomedical materials with physically controlled properties to clinical practise.

PLENARY LECTURE 2:

Advances in the design of mucoadhesive polymers for drug delivery

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Drug delivery via mucosal surfaces offers a number of advantages including improved drug bioavailability and possibility of targeting particular organs [1]. Water-soluble and water-swellable polymers have been traditionally used to develop mucoadhesive dosage forms, capable of adhering to mucosal surfaces, resulting in better retention on the mucosa and hence facilitated drug absorption [2]. These are usually considered as mucoadhesives of first generation and their adhesion to mucosa is due to physical interactions such as electrostatic attraction, hydrogen bonding, hydrophobic effects as well as formation of interpenetration layer with the mucus gel. Thiolated polymers have been introduced as mucoadhesives of second generation because of their capability to form covalent S-S bonds with mucins [3]. For the last 5 years, we have been working on the design of several new classes of mucoadhesives of second generation by introducing unsaturated functional groups into water-soluble polymers or nano-/micro- gels and particles. These functional groups include maleimide, acryloyl and methacryloyl. Polymers functionalised with these groups exhibited strong mucoadhesive properties and potential to retain on mucosal tissues due to in situ thiol-ene click reactions occurring between their macromolecules and thiol groups present in mucins. This lecture will consider our advances in the synthesis of these polymers and nanomaterials, including maleimide-functionalised nanogels [4] and nanoparticles [5], methacryloylated chitosan [6], gellan gum [7], hydroxyethylcellulose [8] and poly(2-ethyl-2-oxazoline) [9]. Other functional groups, such as aldehydes and phenylboronic acid, introduced into polymers can also form covalent linkages with mucins via Schiff base chemistry [10] and dynamic covalent bonds with the 1,2-diol-functional sugar groups [11], respectively. The application of these novel polymeric systems in transmucosal drug delivery to the eye, nose and urinary bladder will be discussed. The advantages of the polymers bearing reactive groups (maleimide, acryloyl, methacryloyl, aldehyde and phenylboronic acid) groups over thiolated polymers will be highlighted.

PLENARY LECTURE 3:

Nanostructured Membranes and Process for Separation Technology

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Nanomaterials which are defined as materials with at least one dimension in the range of 1 to 100 nanometers and have the potential to achieve a breakthrough in membranes performances with new exceptional properties for membrane development. Nanomaterials have remarkable capabilities for preventing the worldwide water crisis through their outstanding performance in membrane development technology such as in the realm of water desalination, research has demonstrated that porous graphene, featuring uniform pore diameters of approximately 10 Å, can effectively eliminate salts from seawater while maintaining water flow rates many times higher than those achievable with current polyamide membranes. Notably, the categories of nanomaterials that have garnered considerable attention in laboratory-scale research for environmental and energy applications can be categorized as follows: (i) 2D materials like graphene, graphene oxide, hexagonal boron nitride, and transition metal dichalcogenides (TMDs), (ii) artificial water channels such as carbon nanotubes and other 1D systems, (iii) nanostructured oxides and some polymers, (iv) zeolites, and (v) metal-organic frameworks (MOFs).

Despite the promising findings in recent research, the practical application of nanomaterials (NM) in real membrane systems is still in its early stages, and a complete realization of the potential offered by these innovative material classes remains elusive. This presentation summarizes recent research findings, the application of nanomaterials (NM) to real membrane systems and their applications for the water treatment process. The focus will be on the nanomaterial-based membrane structure design and potential modifications contribute to the vision of nanomaterial-based membranes evolving into the epitome of separation membranes in the foreseeable future.

PLENARY LECTURE 4:

Soft dendritic microparticles with unusual adhesion and structuring properties - Designing material functionality beyond chemistry & composition

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It is challenging to find a conventional nanofabrication technique that can consistently produce soft polymeric matter of high surface area and nanoscale morphology in a way that is scalable, versatile, and easily tunable. Here, the capabilities of a universal method for fabricating diverse nano- and micro-scale morphologies based on polymer precipitation templated by the fluid streamlines in multiphasic flow are explored. It is shown that while the procedure is operationally simple, various combinations of its intertwined mechanisms can controllably and reproducibly lead to the formation of an extraordinary wide range of colloidal morphologies. By systematically investigating the process conditions, 12 distinct classes of polymer micro- and nano-structures including particles, rods, ribbons, nanosheets, and soft dendritic colloids (dendricolloids) are identified. The outcomes are interpreted by delineating the physical processes into three stages: hydrodynamic shear, capillary and mechanical breakup, and polymer precipitation rate. The insights into the underlying fundamental mechanisms provide guidance toward developing a versatile and scalable nanofabrication platform. It is verified that the liquid shear-based technique is versatile and works well with many chemically diverse polymers and biopolymers, showing potential as a universal tool for simple and scalable nanofabrication of many morphologically distinct soft matter classes.

LECTURE 1:
Plant-Based Microcapsules for Biomedical Applications

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Plant-based pollens are some of the most robust and complex biomaterials in nature due to their diverse chemical properties and versatile applications. Unmodified spores and their sporopollenin shells (exine) are highly stable, and show outstanding uniformity in size, shape, and composition, which makes them versatile candidates that offer several advantages over man-made as well as other natural polymers. We aim to design and evaluate natural biomaterials-based drug-loaded microparticles and their composites comprising pollens, and sporopollenin derived from different species (e.g., *Lycopodium clavatum*, *Phoenix Dactylifera L.* and *Sunflowers*, etc..) and investigate their improved drug delivery potential. The versatile nature of these carriers offers broad range of therapeutic applications. We present the in vitro and in vivo release properties of different actives ingredients (e.g., antibiotics, folic acid, metformin, diclofenac sodium, etc.) that belong to different Biopharmaceutics Classification System (BCS) classes where modified drug release is desired. Therapeutic efficacy, bioavailability, and safety are investigated for administration of different formulations. Since there is only limited number of commercial pharmaceutical products that utilize micro- and nano-sized carriers worldwide, the room for improvement is wide enough to allow the introduction of new biomaterials that meet some of the requirements currently unfulfilled by common biomaterials in terms of therapeutic efficacy, large scale production feasibility, and commercialisation costs. This justifies the compelling need to exploit novel biomaterials with improved properties as legitimate alternatives to conventional polymers.

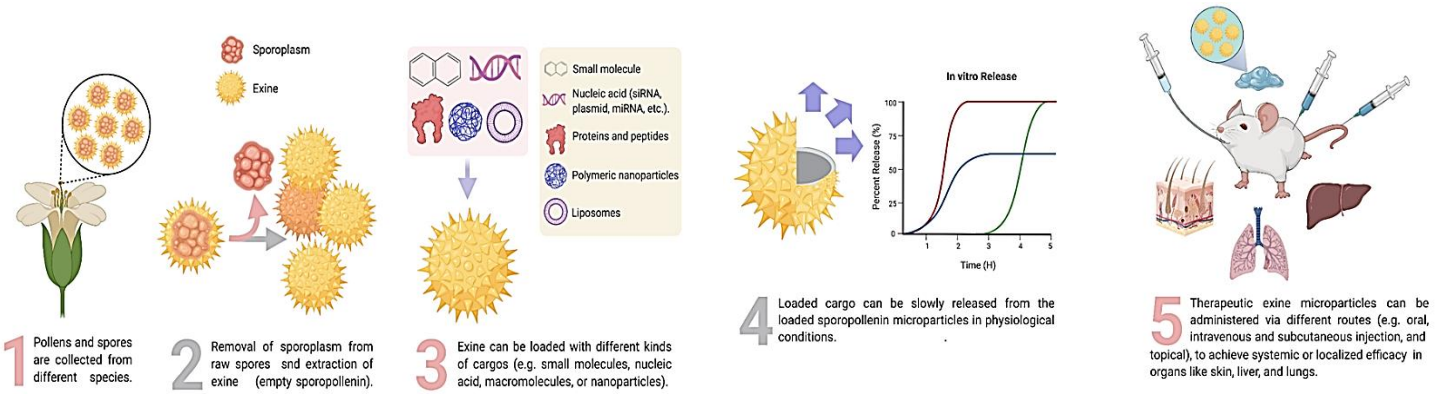

Figure 1: Schematic for protocol used for encapsulation, release and therapeutic applications of different actives loaded into pollen-derived microcapsules.

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LECTURE 2:

Metformin: an old drug with new tricks.

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The glucose-lowering drug, metformin has been widely used for more than half a century.

A of preclinical and clinical data has stimulated interest in re-purposing metformin to treat a variety of diseases including cancer. However, the underlying mechanisms of metformin in the treatment of cancer and potential influencing factors are not fully understood. Therefore, this presentation discusses the antiproliferative activity and putative mechanism of action of metformin. It will also discuss the role of its anti-hyperglycaemic effects on cellular proliferation.

LECTURE 3:

The effect of PEGylation on nanoparticle functionality in biomedical applications.

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Keywords: PEGylation, polyethylene glycol (PEG), organosilica nanoparticles, drug delivery system, toxicity, *in vitro* localization, *in vivo* biodistribution, live cell imaging.

Nanoparticles (NPs) have significant potential for drug delivery due to their unique physicochemical properties, including their ultra small size, high reactivity and large surface area to mass ratio which can offer significant benefits compared to traditional therapeutic and diagnostic agents. Due to these reasons, nanoparticles have been successfully applied as drug carriers, diagnostic tools, labelling and tracking agents. However, there are some significant limitations, including the possibility that nanoparticles can be easily detected by the immune system once in the blood stream, and may be cleared by the mononuclear phagocyte system (MPS) (liver, spleen, lungs and bone narrow) via opsonization (a binding enhancer for the process of phagocytosis) before they can deliver the drug to the target site[1,2]. One of the most widely applied approaches to prolong circulation of nanoparticles is to modify their surfaces with polyethylene glycol (PEG). Grafting or adsorption of PEG or PEG-containing copolymers to the surface of nanoparticles prolongs blood circulation half-life up to several orders of magnitude and provides a hydrophilic protective layer which limits recognition by opsonin proteins due to steric repulsion forces[2]. However, "the more the better" approach does not apply to PEGylation, and the studies show the degree of PEGylation has to be carefully controlled ensuring the most effective drug delivery system with possibilities to get eliminated from the body eventually. The effect of PEGylation on different functions of nanoparticles both *in vitro* and *in vivo* was studied using organosilica nanoparticles and their PEGylated counterparts with PEG of different molecular weights (750 and 5000 Da). Organosilica nanoparticles were synthesized from (3-mercaptopropyl)tri-methoxysilane (MPTS) using aprotic solvent, producing thiolated nanoparticles, two portions of which were then PEGylated with PEG 750 and PEG 5000. *In vitro* cytotoxicity tests revealed that PEGylated nanoparticles exhibit lower cell viability in cancer cells at concentrations higher than 400 μg/mL even after 24 hours of exposure, which can be related to the greater permeation ability through the cell membrane due to screening functional groups on the surface of organosilica nanoparticles provided by PEG (Figure 1A).

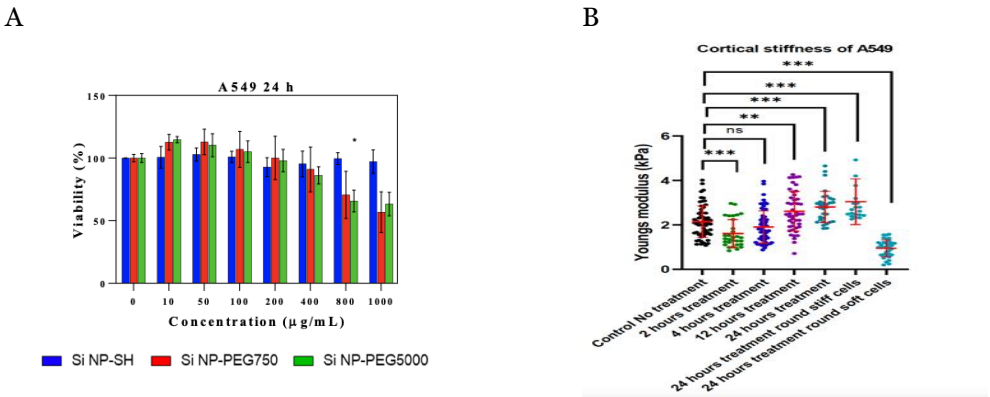

Figure 1: Viability of A549 cell line after 24 hours of exposure to thiolated, PEGylated (750) and PEGylated (5000) organosilica NPs (A). Cortical stiffness of A549 cells upon exposure to PEGylated (750) organosilica nanoparticles (B).

This was in a good correlation with Atomic Force Microscopy data allowing to assess biomechanical properties (cortical stiffness) of healthy and cancer cells using live imaging. These data suggest PEGylation with lower molecular weight PEG (750 Da) enhances nanoparticles permeation through the cell membrane. However, when larger molecular PEG (5000 Da) is employed, the size becomes a limiting factor (Figure 1B). The *in vivo* nanoparticle biodistribution tests studied on mice demonstrated longer circulation of organosilica NPs in the blood stream provided by PEGylation (5000 Da) with the high signal detection in spleen at 28 days. This project has also addressed another important issue in the field of nanoparticles for biomedical applications such as the interaction of nanoparticles with the living cells and their fate after fulfilling their main function in the body.

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LECTURE 4:

TAM receptor tyrosine kinases in bladder cancer: insights into signalling and therapeutic implications

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Bladder cancer (BC) is the most common cancer of the urinary tract and, in its muscle-invasive form, is associated with a poor prognosis. The disease primarily affects older adults, so the incidence rates of BC are increasing in countries with aging populations, such as Kazakhstan. Moreover, BC is the most expensive cancer to treat, and the recommended international guidelines for managing BC remained mainly unchanged for decades. Therefore, developing novel treatment schemes for muscle-invasive BC is considered an unmet need in oncology.

Literature data and our unpublished results suggest that the molecular pathways activated by the proteins belonging to the TAM (TYRO3, AXL, MER) family of the Receptor Tyrosine Kinases are promising therapeutic targets in BC. In normal physiological conditions, TAM receptors are present in professional phagocytes, such as dendritic cells or tissue macrophages, where they are implicated in the clearance of apoptotic cells via efferocytosis. In addition, TAM receptors activate prosurvival pathways, such as PI3K, MAPK, or NF kB, to secure the survival of phagocytes operating in toxic conditions. When hijacked by cancer cells, a TAM family member AXL stimulates cell migration and processes of epithelial-mesenchymal transition, likely by utilizing some elements of efferocytotic pathways operating in dendritic cells. Moreover, cancer cells often rely on TAM signaling to gain therapy resistance. We found that TAM receptors are highly expressed in bladder cancer cell lines, tumor organoids and tumor tissues, and expression of AXL correlates with cancer aggressiveness. We studied the cytotoxic effects of small molecule AXL inhibitors in bladder cancer cells and found paradoxical activation of MAPK and JNK signaling. Underlying mechanisms will be discussed.

LECTURE 5:

Generation of tumour organoid cultures from bladder cancer tissues

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3D tumour organoids represent an in vitro model closely resembling physiological tissue organization. Organoid technology has become a popular tool to study cancer biology and drug response. Tumour organoid cultures demonstrate high levels of histopathological similarity with tumours from which they were generated. They recapitulate molecular characteristics of parental tumours, expression of specific differentiation markers, and mutational spectra. In collaboration with Drs Sha Shalekenov and his team (National Oncology Research Centre, NORC), we established a protocol for the generation of tumour organoids from operation material obtained from patients admitted to the Urology Department at NORC. Tumours are obtained from the operation theatre, submerged in the media containing collagenase, mixed with Matrigel, and cultured in DMEM/F-12 media supplemented with growth factors, such as FGF2, FGF7, FGF10, ROCK, and ALK inhibitors. We freeze the cultures at passages 1-5, and use them for the analysis of tumour response to TAM inhibition.

LECTURE 6:

Targeting bacterial biofilms with multi enzyme functionalized antibiotic-loaded nanogel particles

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Infections of pathogenic bacteria are causing hundreds of thousands of deaths annually worldwide due to antimicrobial resistance and their biofilm formation capabilities. Among these bacteria is Staphylococcus epidermidis which is commonly found on skin and mucous membranes of humans and animals. Its virulence depends on biofilm formed in medical devices-related infections and chronic wounds causing severe health complications and impeding wound healing while resisting traditional antibiotic treatments [1,2]. To overcome S. epidermidis biofilm-based resistance to antibiotics, three types of active nano-formulations were developed based on surface functionalizing antibiotic-encapsulated nanoparticles (NPs) with enzymes that can degrade the extracellular polymeric substance (EPS) matrix components of the biofilm [1-5]. This approach allows the enzyme coated NPs-loaded with antibiotic to penetrate the bacterial biofilm where they can reach the residing bacterial cells and deliver therapeutic concentration of antibiotic directly onto the cell walls of the residing cells, hence killing them. In this study, polysaccharide, protein and eDNA hydrolytic enzymes were used to functionalize antibiotic-loaded polyacrylic acid copolymer nanogel particles separately, their biofilm clearing, and bactericidal effect were investigated and compared. Generally, all the three enzyme-coated nanogel particle formulations loaded with antibiotic were found to be more effective against S. epidermidis biofilm than the equivalent concentration of free antibiotic when compared to untreated biofilms. We also examined the cytotoxic effect of these formulations using several human cell lines and found that they have low-to moderate cytotoxicity. These smart antibiotic nanocarriers are promising nano-formulations for overcoming biofilm based antibiotic resistance as well as other bacterial biofilms resistant mechanisms and may find potential applications in chronic wound treatment.

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LECTURE 7:

TBA

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LECTURE 8:

Surface enhanced spectroscopies, SERS and SEF on Al foil and silicon: when more affordable substrates may be at least as efficient as noble metal substrates

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SERS (Surface Enhanced Raman Spectroscopy/Scattering) is a sensitive vibrational spectroscopic technique increasingly tested in bioanalytical and biomedical applications. SERS has significant advantages over fluorescence, such as relatively narrow peaks that may be used for multiplex detection, resistance to photobleaching and no need to modify the analyte molecule with fluorophore (label free nature). In spite of several 10000s of publications about SERS in the last 40 years, there is still a relatively limited number of clinical/analytical applications of this method in everyday life. Among challenges to its applications are relatively high cost and low shelf life/stability of substrates, sometimes insufficient reproducibility of performance, including one due to substrate contamination. The sandwich SERS immunoassays have used gold film as a default substrate by at least several research groups. Our research group tested silicon and then Aluminum foil as the substrate for this sensitive bioanalytical method. Silicon and aluminum foil are not only far more economical substrates than gold, but also substrates that has demonstrated at least comparable LOD and better selectivity / lower non-specific signal in detection of human IgG on Al foil and on Si wafers in comparison to the same performance parameters in simultaneous assays on gold film. There is some improvement in sensitivity/ decrease in LOD for Al foil vs gold film and Si vs Au film as substrates in sandwich SERS immunoassays, particularly with 4-parameter fit calibration. It is likely to come from a decrease in nonspecific protein binding to the surface of aluminum and silicon relative to this kind of binding to the gold film surface. The same substrates (Al and Si) along with gold and silver films were comparatively tested in Surface Enhanced Fluorescence (SEF) spectroscopy of bacteria labelled with commercial quantum dots. In those SEF experiments the comparative performance on Al foil was nearly or about as good as SEF performance on Au film in terms of both SEF enhancement factor and SEF contrast, while SEF on Al foil had some advantage in reproducibility of the enhancement. SEF of those QD labeled bacteria on both gold and Al foil produced very high enhancement (x 400-500) and high contrast (x 300-370) . Overall we demonstrated that relatively cost efficient substrates such as silicon and especially such as Al foil, have significant, but so far underdeveloped potential for applications in surface enhanced spectroscopies, particularly in biodetection/biosensing applications.

LECTURE 9:

Nano-Molecularly Imprinted Polymers (nanoMIPs) as a novel approach for targeted drug delivery in nanomedicine

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Molecularly imprinted polymers – MIPs – denote synthetic polymeric structures that selectively recognize the molecule of interest against which MIPs are templated. A number of works have demonstrated that MIPs can exceed the affinity and selectivity of natural antibodies, yet operate by the same principle of "lock and key". In contrast to antibodies, which have certain limitations related to the minimal size of the antigen, nanoMIPs can be fabricated against almost any target molecule irrespective of its size and low immunogenicity. Furthermore, the cost of MIP production is much lower compared to the cost of antibody production. Excitingly, MIPs can be used as nanocontainers for specific delivery of therapeutics both in vitro and in vivo. The adoption of the solid phase synthesis rendered MIPs precise reproducible characteristics and, as a consequence, improved the controlled release of therapeutic payloads. These major breakthroughs paved the way for applicability of MIPs in medicine as a novel class of therapeutics.

LECTURE 10:

Carbon nanodots as fluorescent and radiological contrast agents

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Recently, there has been a growing interest in carbon nanodots (CDs) because of their excellent fluorescent properties, low price, simplicity of preparation, and biocompatibility. In this talk, we will discuss recent advances in the synthesis and testing of CDs at Nazarbayev University, as well as the global advancements in the fabrication of multifunctional CDs. The main focus of this talk will be on metal- and nonmetal-doped CDs suitable for use as radiocontrast agents in MRI and CT. In particular, we will discuss the basics of CD formation, how dopant elements are chosen, process scalability, the importance of biocompatibility, and production cost minimization.

LECTURE 11:

How does a cell regulate focal contacts?

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Cell migration is a fundamental process underlying both normal development and pathological processes such as tumour metastasis. Central to cell migration on the solid substrate are focal contacts (FCs), integrin-based complexes that connect the cytoskeleton to the extracellular matrix and provide traction force necessary for cell motility. The dynamics of the formation and turnover of FCs remains poorly elucidated.

Evaluating FC dynamics in cultured cancer cells crawling on the adhesive substrate (fibronectin covered glass) by time-lapse microscopy, we observed formation of numerous small, short-living adhesions at the leading edge, in contrast to the presence of only few large FCs at the trailing edge. Mostly new adhesions formed within 2 μm from the edge, with the majority disassembling within several minutes and some growing to form larger mature FCs with larger area and longer lifespan.

FCs at the trailing edge originated mainly within lateral protrusions and only rarely formed directly at the trailing edge. Intuitively, cell preparing for translocation should disassemble remaining FCs before the retraction of the cell rear. However, some FCs at the trailing edge were enlarging and even merging with neighboring FCs as they slowly slid along with the trailing edge relative to the substrate. As a result, a portion of FCs was forcibly detached and rapidly disassembled only upon retraction edge reached them.

In summary, FCs role in migrating cells are primarily regulated via differential formation and maturation in protruding and retracting cell edges, while disassembly at the rear edge before retraction is not a requirement.

LECTURE 12:

Impact of nanoparticles on the biophysical properties of cell for biomedical applications

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The emergence and rapid spread of multidrug-resistant bacterial strains constitutes a public health problem. This occurrence is due to the overuse and abuse of antibiotics leading to the development of antibiotic-resistant strains. Research on organic and inorganic nanoparticles (NPs) with enhanced antibacterial activity as alternatives to antibiotics has grown substantially due to the increasing incidence of nosocomial and community-acquired infections caused by pathogens. The effects of sulfur and nitrogen co-doped carbon nanoparticles (SN-CNPs) and silica-based nanoparticles (SiNPs) on the proliferation and inhibition of bacterial and animal cells were examined in this study. While live cell imaging and atomic force microscopy were utilized to assess the impact of these nanoparticles on the physical and mechanical properties of the cells, the microtiter plate assay was used to measure the effects of NPs on the growth and inhibition of bacterial cells. Both SN-CNPs and SiNPs exhibited excellent antibacterial activities, with MIC values of less than 200 μg/mL. Our live cell imaging data showed that SN-CNPs induced hyperactive actomyosin contraction, resulting in actin cytoskeleton separation from the cell membrane and subsequent collapse. It also led to a rise in cell size, the depolymerization of microtubules, and finally the bursting of the membrane. The outcomes of the biochemical experiments also revealed that SN-CNPs exhibit strong ATPase and GTPase activity. Thus, SN-CNPs possessed two crucial biological enzymatic activities commonly observed in cells: ATPase and GTPase activities. Due to elevated level of ATPase and GTPase activities, the cell's internal osmotic pressure increases, resulting in uncontrolled expansion and ultimately cell explosion. Both SN-CNPs and SiNPs exhibit potential for utilization in antibacterial applications, whilst SN-CNPS can also be employed in targeted therapy.

LECTURE 13:

In Vitro Evaluation of Strontium and Copper-doped Tricalcium Phosphate Ceramic Granules for Bone Regeneration

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Bioceramics, especially those based on calcium phosphate, are renowned for their superior biocompatibility, osteoconductivity, and biomineralization induction capabilities. In this study, we aim to develop tricalcium phosphate (TCP) ceramic porous granules enhanced with Strontium (Sr) and Copper (Cu). The integration of Sr is inspired by its documented benefits in osteogenesis and bone regeneration. Moreover, mammalian bones contain Sr in their mineral phase, suggesting its role in early bone formation, osteogenesis, osteoclastogenesis, and angiogenesis enhancement. On the other hand, the inclusion of Cu is proposed by its essentiality as an enzyme cofactor and its notable antibacterial attributes. This study evaluated Sr and Cu doped TCP granules for cell cytotoxicity(LDH assay), cell proliferation(CCK8), and osteogenic differentiation in mesenchymal stem cells in vitro. Additionally, an angiogenesis assay with human HUVEC cells was performed to assess angiogenic potential. Several concentrations were tested to reveal the optimal condition. Further, Sr and Cu-doped TCP granules will be tested to enhance bone regeneration in case of critical non-union bone fractures in vivo.