Biomaterial Surfaces & Interfaces
Room Milo - Session BI-TuE

Medical Applications

Moderator: Michael Grunze, KIT, Germany

5:40pm **BI-TuE1 Challenges in Translating Surface Designs to Clinical Medical Device Applications**, ***David Grainger***, University of Utah, USA **INVITED**

Surface strategies for translational clinical performance for 1) medical devices with antimicrobial properties, and 2) nanomaterials in imaging and drug delivery are discussed.

1. Antimicrobial medical devices.[1-5] Increasing medical devices are used in clinical implants: in aging populations, diverse patient genetic profiles, ethnicity and health status, and increasing developing countries. Notably, infection related to implanted devices is a primary concern both for patient risk and healthcare cost reasons. Medical device surfaces and interfaces have long been a focus to produce diverse antimicrobial strategies, yet few translate to clinical use. A classic problem is lack of in vitro-in vivo correlation, validation or efficacy for surface methods and antimicrobial approach in vivo. A second issue is lack of commercial enthusiasm to take approaches forward thru regulatory pathways to clinical use. Improved methods are required to assess and validate new antimicrobial technologies that reduce implant-associated infections and risks in translation.

2. Nanomaterials exposure to the human physiome.[6-10] Human exposure to engineered nanotechnology is an increasing concern. Importantly, medical grade standards of purity and contamination validation and analysis are difficult for nanomaterials and not commonly followed in most in vivo studies. Since surface area is critical nanomaterials property, surface analysis is critical but rarely performed.[6] Much published data demonstrate that particles placed in blood circulation are rapidly filtered by the reticuloendothelial system (RES) comprising liver, spleen, lung, kidney, and marrow, performing blood scavenging. Particle removal is mostly independent of size or chemistry, and refractory to targeting strategies by coatings. Wide variations in circulating nanomaterials properties produce quite similar results in mammalian biodistributions and RES clearance (>90% RES filtration). Issues with connecting nanomaterials surface properties to complex biological interactions will be discussed.

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6:20pm **BI-TuE3 Metal Oxides, Hydroxyapatite and Bone Healing**, ***Håkan Nygren***, University of Gothenburg, Göteborg, Sweden; *P. Malmberg, L. Ilver,* Chalmers University of Technology, Sweden

Magnesium alloy, Zinc and Manganese have been explored extensively for application as degradable metal implants, but there is still a lack of understanding of the biological response to the corrosion products and their influence on the local tissue repair process at the implantation site. The approach, in this study is to correlate the effect of corrosion products on human embryonic stem cells *in vitro* and on bone healing with and without stainless steel implants *in vivo* in rat tibia by preparing a paste of MgO or $MgCO_3$, ZnO and MnO. The metals and the formation of mineral were analysed by ToF-SIMS, EDX and XPS. Metal oxides, incubated in tissue culture medium (DMEM), induced the formation of hydroxyapatite (HA), covering the oxide grains. The apatite was low crystalline and carbonated. We found that when cultured human embryonic stem cells were presented with the HA-coated corrosion products they were able to maintain viability and proliferate over time. The presence of HA-coated metal corrosion products resulted in the up-regulation of hydroxyapatite formation by the stem cells *in vitro* and enhanced bone formation *in vivo*, preceded by the formation of hydroxyapatite in the tissue. The results of the present study suggest that metal corrosion products catalyse the formation of hydroxyapatite in the tissue, that the formation of apatitite is amplified by stem cells and that the hydroxyapatite is an active species in promoting osteogenesis.

7:00pm **BI-TuE5 Modulation of Macrophage Polarization Using Surface Immobilized Bioactive Molecules**, ***Alex Chen***, *B.D. Ratner,* University of Washington, USA

Introduction: The polarization of macrophages is highly influential in modulating the foreign body response. Macrophages characterized by the M2 (anti-inflammatory) phenotype are believed to reduce the formation of the foreign body capsule. It is hypothesized that surface immobilizing M2 promoting bioactive molecules will reduce the formation of the foreign body capsule by increasing M2 polarization as well as decreasing M1(inflammatory) polarization of macrophages. Collagen VI (col6) and α-1 acid glycoprotein (AGP) have been shown to induce M2 polarization of macrophages when introduced in solution. This work demonstrates the feasibility of modulating macrophage polarization via immobilization of col6 and AGP onto hydrogel coated surfaces.

Methods: 2-hydroxyethyl methacrylate (HEMA) was plasma deposited onto 10mm circular glass slides. HEMA coated glass slides were washed three times in p-dioxane and then surface activated by incubation with 100mM carbonyl diimidazole (CDI) in dioxane for 2.5 hours at 40°C. CDI activated glass slides were then incubated in either 440µg/mL AGP only or 250µg/mL AGP plus 62.5 µg/mL col6 solutions in pH 10.2 sodium carbonate/bicarbonate buffer for 24 hours at 40°C. Bone marrow derived macrophages (BMDMs) were cultured by harvesting marrow from the femurs of sacrificed mice, which was then dispersed and cultured in RPMI with macrophage colony stimulating factor for 7 days. BMDMs were then transferred to glass slides coated with immobilized bioactive molecules and cultured for 48 hours. CDI activated HEMA coated glass slides without immobilized bioactive molecules was used as a control. Macrophage polarization was assessed via ELISA measurements of tumor necrosis factor-α (TNF-α), a cytokine released by M1 macrophages, as well as RT-qPCR of arginase 1 (Arg1), an enzyme highly expressed by M2 macrophages. ELISA experiments involved the addition of 10uM lipopolysaccharide(LPS) to culture media in order to induce an M1 polarization of macrophages. RT-qPCR experiments did not involve the use of LPS and solely focused on the expression of Arg1.

Results and Conclusions: ELISA experiments showed a decrease of TNF-α expression in macrophages cultured on surfaces with immobilized AGP (~30%). RT-qPCR experiments showed an increase in Arg1 expression of macrophages cultured on surfaces with immobilized AGP (2.6x) or immobilized AGP + col6 (5.85x).

These experiments show the potential of using immobilized bioactive molecules to modulate the polarization of macrophages, which can potentially be used to reduce the foreign body response and foreign body capsule formation.

7:40pm **BI-TuE7 Activatable Molecular Nanoprobes for the Perception of Cancer Activity**, ***Seungjoo Haam***, Yonsei University, Korea, Republic of Korea **INVITED**

Stimuli responsive, i.e. activatable, nanomaterials are capable of providing their conformational or phase changes corresponding to specific environmental stimuli variations in biological systems including temperature, pH and reactive oxygen species (ROS). Further, specific biomolecules such as DNA, RNA and enzymes can represent the biological status, particularly for cancer activity allowing better understanding physiological and pathological processes. These stimuli variations would be small but they can trigger drastic changes in the structures of materials because they interact facilely with sub-nanometre-sized drugs or other nanometres-sized biomolecules. In particular, matrix metalloproteinases (MMPs) are highly attractive targets for molecular imaging because degrading and modifying the extracellular matrix by enzymatic activity is required for the invasive process of cancer cells. On the other hand, microRNAs (miRNAs), small, non-coding RNA molecules, play an important role as negative gene regulators and have been found to control various biological functions, such as cellular proliferation, differentiation, metastasis, and apoptosis. Emerging evidence suggests that miRNAs can also function as a diagnostic biomarker and a therapeutic target for a wide range of diseases, including human cancers, because miRNAs themselves can act as tumour suppressor genes or oncogenes. In this presentation, we describe the case examples of the development of activatable nanoprobes enabling precise recognition of the expression of specific enzyme (MT1-MMP) and miRNA34a which could provide deep perception of cancer activity, metastasis and invasion.

8:20pm **BI-TuE9 Thin Film Metallic Glass: A Novel Coating for Biomedical Applications**, *C. Yu, Y. Tanatsugu, C. Li, C. Lee,* ***Jinn P. Chu,*** National Taiwan University of Science and Technology, Taiwan, Republic of China*; M. Chen, S. Chang,* Mackay Memorial Hospital Tamsui Campus, Taiwan, Republic of China

Thin film metallic glasses (TFMGs) possess exceptional mechanical properties adopted from its bulk form such as high strength, large elastic limits, and excellent corrosion and wear resistances owing to their amorphous structure. In addition, the smooth surface, due to the grain boundary-free structure, and low surface free energy of TFMGs in certain compositions can be achieved and leads to the relatively high hydrophobicity and the low coefficient of friction.

In our studies, TFMG coatings are deposited using RF magnetron sputtering for various biomedical applications, including the property enhancements of dermatome blades and syringe needles, adhesion resistance of platelet, as well as the suppression of cancer cell attachments. The TFMG-coated dermatome blades show great enhancements in sharpness and durability, compared with those of the bare one. For the syringe needle, significant reductions in insertion and retraction forces for TFMG-coated needle are found due to the non-sticky property and relatively low coefficient of friction. For thrombosis reduction, less platelet aggregations are observed on the TFMG than that of on the bare glass in platelets adhesion test, suggesting TFMG-coated catheters is potentially useful to be placed into vessels for long periods of time with reduced numbers of the aggregation of blood platelets. For cancer cell attachment suppressions, TFMG exhibits the least cancer cell attachment among other control groups. Thus, anti-proliferation and anti-metastasis of medical tools can be achieved with TFMG coating.

8:40pm **BI-TuE10 Monitoring Human Physiological Signals Using Artificial Flexible Graphite Thin Films**, ***Takanari Saito****, Y. Kihara, J. Shirakashi,* Tokyo University of Agriculture & Technology, Japan

Recently, wearable health-monitoring devices based on strain sensors have been widely applied in disease diagnosis and health assessment. Various flexible materials, including polymer nanofibers [1], nanowires [2], carbon nanotubes [3], and graphene [4], have high flexibility and sensitivity, and are good potential candidates for the wearable health-monitoring devices. However, the fabrications of the wearable devices are, in many cases, complicated multistep procedures which result in the waste of materials and require expensive facilities. Therefore, we focused on a commercially available pyrolytic graphite sheet (PGS) [5] which is an inexpensive and an artificial flexible graphite sheet. Previously, we have reported that thin graphite films are simply and easily fabricated from PGSs, and are used as wearable strain sensors for monitoring human motions [6, 7]. In this study, we investigated the application of wearable devices based on the thin graphite films for wrist pulse monitoring.

First, the thin graphite films were fabricated by cutting small films from 17-μm-thick PGSs. Then, the thin graphite films were cleaved onto adhesive tapes using the mechanical exfoliation method. Finally, the thin graphite films were wired using silver conducting paste for electrical measurements. The thin graphite films used as strain sensors were attached over the radial artery to monitor the wrist pulse. The peaks of the resistance waveform were periodically observed, and therefore the wrist pulse was successfully detected using these devices. The results suggest that the thin graphite films could be applied as cost-effective health monitoring devices for human physiological signals.

References

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