Engineered Biomaterials via Molecular (Nanoscale) Surface Modifications

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Introduction: Surface modifications of materials to alter or enhance interactions between synthetic materials and biological systems date back to the early 1960's and are, if anything, growing in popularity and success. The rationale for surface modification is centered around the idea that medical device manufacturers can take existing, relatively successful devices and enhance performance by a low cost post-treatment of the device surface. Early surface modifications focused on simple chemistry changes (grafting a hydrogel to a surface, for example) that offered some performance advantage, mostly observed *in vitro*. A second generation of surface modifications envisioned bioactive agents such as the RGD peptide immobilized to device surfaces. Also, surface controlled release strategies were evolved in this era. These were brilliant advances because they sought to tap directly into the biology controlling the reaction to the implanted device. In the early 21st century, a new concept will emerge. Tapping into the biology surrounding the implant will still be central to the strategy used by these devices to improve performance. However, the sophistication of this evolving approach will address multiple signals, proper geometric presentation of signals and inhibition of non-specific reactions. Controlled release of signals, genes and siRNA might be important. Signaling molecules on the surface will be properly oriented and appropriately conformational stabilized. This lecture will focus on the path to a third generation of surface modifications that would be seamless with living biological systems to integrate and function. Four specific ideas will be highlighted with data: inhibition of non-specific signals (a bland background); control of molecular orientation and conformation on surfaces; controlled release of bioactive agents from surfaces; and use of specific geometric design ideas to enhance biointegration.

Inhibition of Non-Specific Adsorption: Surfaces can be efficiently engineered to reduce adsorption levels of key proteins affecting bioreaction to <5 ng/cm^2. Plasma deposition of tetraglyme can create surfaces that are PEG-like and show this low adsorption. Such surfaces exhibit good blood contact properties and have potential for biosensors. They can be modified with –OH groups to facilitate the attachment of biomolecules to the "bland" background. Whether such surfaces are useful for inhibiting the foreign body reaction is still a subject of exploration.

Control of Molecular Orientation: Biology delivers signals with the *correct* biomolecules oriented in a geometrically advantageous, conformationally stabilized manner. Two approaches to do this will be reviewed – using charged self-assembled monolayers to orient proteins and using type I collagen to control orientation and conformation. Impressive increases in bioactivity can be realized with proper presentation of the surface biomolecule.

Controlled release of bioactive agents from surfaces: Many options have been explored for controlled release to impact healing. Release of cytokines has been explored to impact the course of bioreaction. Anti-proliferative drugs are routinely released from stents to inhibit restenosis. The release of antisense nucleotides to inhibit thrombospondin 2 at implant sites will be described – such release reduces fibrosis and enhances angiogenesis.

Specific geometric design ideas to enhance biointegration: There has also been a long history in biomaterials science of attempts to understand and harness unique biological reactions associated with porosities and textures. By precisely tuning pore size using sphere templating, materials have been created that exhibit enhanced angiogenesis and reduced fibrosis in implant sites as diverse as subcutaneous soft tissue, skin (percutaneous) and cardiac muscle.