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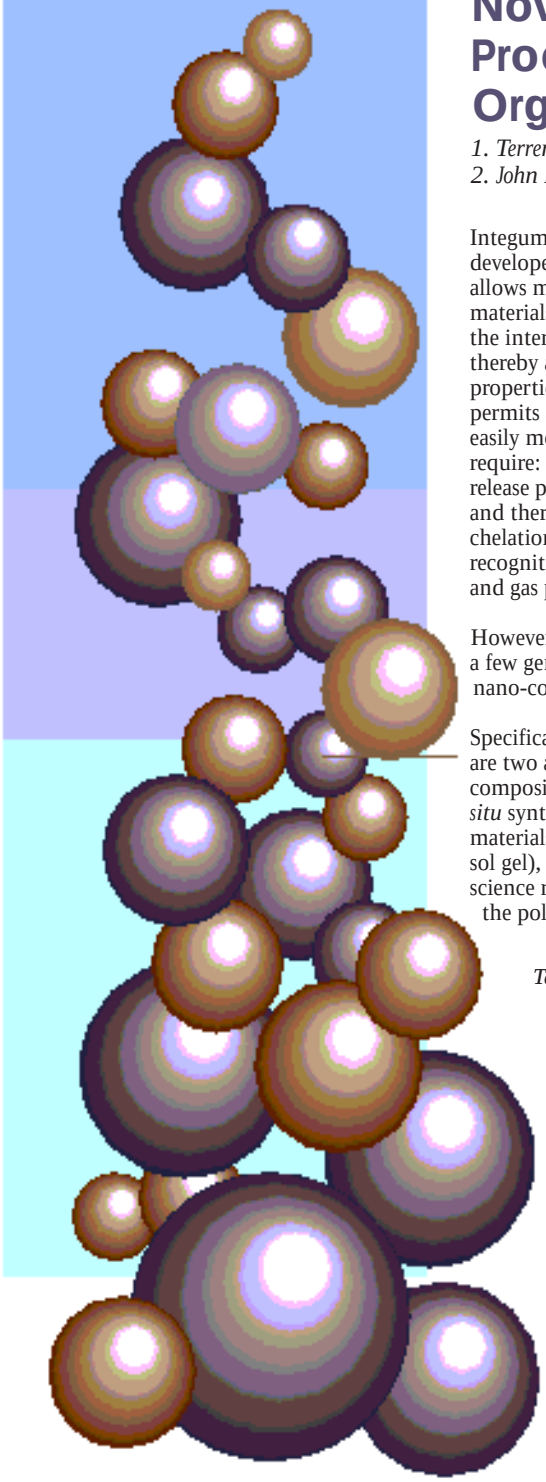

Novel Nano-Technology Fabrication Processes for Constructing Inorganic-Organic Hybrid Materials

1. Terrence G. Vargo, and Timothy S. Koloski, Integument Technologies, Inc.
2. John Brupbacher, Center for Non-Destructive Evaluation, The Johns Hopkins University

Integument Technologies, Inc., (ITI) has developed a new infusion method that allows metals, metal oxides, and organic materials to be controllably grown within the internal structure of almost any polymer, thereby affecting both surface and bulk properties[1]. This new nano-technology permits a polymer composite material to be easily modified for specific uses that may require: (1) Controlled adhesion or foul release properties, (2) Improved mechanical and thermal stability, (3) Surface and bulk chelation of catalysts, anti-microbials, and recognition elements, and (4) Selective ion and gas permeable barriers.

However, before describing this technology a few general comments on synthesis of nano-composites are warranted.

Specifically, with reference to Table 1, there are two approaches to nano-scale polymeric composites: (i) powder blending, and (ii) *in-situ* synthesis [2-4]. In the former, nano-scale materials are formed by wet chemistry (e.g., sol gel), gas phase synthesis or surface science routes and can be combined with the polymeric matrix material in a subsequent blending operation. Although there are advantages to the powder blending approach, working with nano-powders presents materials purity, safety, scale-up, and compositing challenges that will impede the rapid development and transition of nano-technology into biomaterial systems. In particular, the prospects for synthesizing and blending nano-scale metals or other reactive materials into polymers in production quantities are remote. For this reason, it is our belief that for applications where polymeric nano-composites might be desired, development of one step, *in-situ* processing is the preferred route. Another compelling argument for pursuing *in-situ* synthesis is that the transition from "grams-to-kilograms" and "kilograms-to-tons" quantities should not be technologically limited.

A new infusion method that effectively utilizes the inherent free volume contained in a fully cured organic polymer allows us to infuse and then form interpenetrating inorganic metal and metal oxide networks (IPN's) within pre-formed polymeric sheets, films, objects or resins without significantly

Table 1. Comparison of Powder Blending and In-Situ Synthesis Polymeric Nano-Composites

PROCESSING APPROACH		
Variable	***Power Blending***	***In-Situ Synthesis***
Loading	Unlimited	Limited
Particle Size	> 1 micron	Nano-scale to Micron
Particle Shape	Variable	Limted Control
Distribution	Variable, Agglomerates	Uniform, Un-agglomerated
Composition	Considerable Flexibility	Processing Limited
Purity	Contamination Risk High	Contamination Risk Negligible
Interfaces	Often Contaminated	Clean, Un-contaminated

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Surfaces in *Biomaterials* Foundation Elected into AIMBE

By Lise Duran, President

On March 3, the American Institute for Medical and Biological Engineering (AIMBE) granted the Surfaces in *Biomaterials* Foundation membership into its Council of Societies at its annual meeting held in Washington, D.C. AIMBE was established to provide a unifying voice for medical and biological engineering in public policy and science. Its principal activities include participation in the formulation of public policy; the dissemination of information, both to the public and scientific community, through publications and forums; and education.

At this year's annual meeting, four membership groups hosted forums addressing the medical and biological community's response to bioterrorism, the future of education and research in a post-Whitaker Foundation world, the future public policy agenda for AIMBE, and the role of AIMBE in addressing issues of importance to industry. The primary issue discussed in the last forum was the possibility of establishing an Industry Council. The value to industry would be several-fold. First, there would be the ability to speed products to market by leveraging knowledge. This is because AIMBE has peer recognized fellows, including chairmen from almost every prestigious department at major universities and prominent industrial scientists, as well as access to significant databases, e.g., biomaterial databases. In addition, AIMBE would provide a unified scientific voice publicly when controversial issues arise, e.g., reimbursement for new technologies. AIMBE wants to be perceived as the voice that the government turns to for information and opinions. Other benefits discussed were the prestige of being a fellow and the opportunity to network.

This year's AIMBE President is Buddy Ratner, Director, University of Washington Engineered Biomaterials. One of Buddy's goals is to make sure a brochure is disseminated to all of the societies' members that describes what AIMBE is and announces pertinent meetings. He wants to be sure that members understand they are participating at another level, i.e., public issues/policy, and not at the technical level. AIMBE is a society of societies. The members of the Surfaces in *Biomaterials* Foundation will certainly now have a greater voice on issues affecting the biomedical community. We are currently discussing how best to interact with AIMBE and will keep members informed as to the process. Look for AIMBE updates soon on the Foundation web site.

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BioInterface 2002

Annual Symposium & Exhibition

Call For Abstracts and Preliminary Program

The Call For Abstracts and Preliminary Program is now on-line at www.surfaces.org. Look for these highlights:

BioInterface 2002, September 4-6, Fairmont Scottsdale Princess Hotel, Scottsdale, Arizona
Learn about the new name and format changes to reflect the renewed focus of the Foundation.

Call For Abstracts
Discover the new electronic submission process. The abstract deadline is Friday, May 10, 2002.

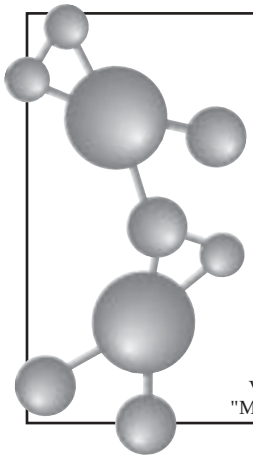
Symposium Preview
This year's presentation topics include:
- Hemocompatible Coatings
- Tissue Engineering
- Animal Models
- Clinical Experience with Drug Eluting Stents
- Designer of Materials for Drug and Gene Delivery

Workshop Preview
Biomineralization in Biomaterials: Prevention, promotion, models, standards, and regulatory concerns. The workshop will be on Wednesday, September 4, 2002. Invited speakers include Brent R. Constanz of Carazón Technologies and Jean-Marie Girardot of Bio Medical Design, Inc.

Registration
Register your attendance at the 2002 BioInterface on line or by using the registration form. The early registration deadline is July 19, 2002.

Hotel Accommodations
Reserve your room at the Fairmont Scottsdale Princess. Rates are effective August 26-September 14, 2002.

1st International BioDevice Interface Science and Technology Workshop
Take advantage of attending two meetings at the same location. The American Ceramic Society is hosting this workshop on September 7-9, 2002, that will also be at the Fairmont Scottsdale Princess. For more information, go to www.ceramics.org and click on the BioDevice Workshop link in the Hot Topics box on the home page.



BioInterface 2002

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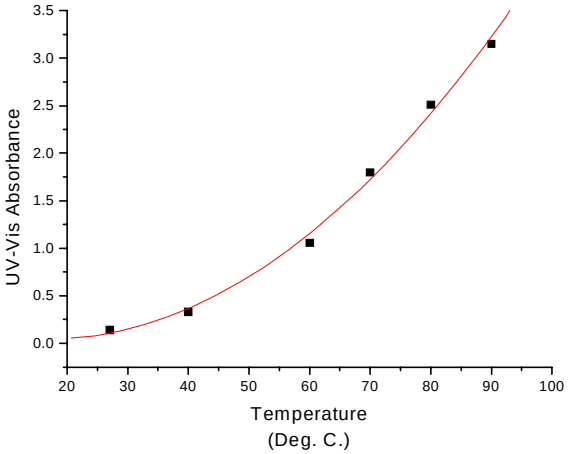


Figure 1. Concentration of Infused V_2O_5 vs. Infusion Temperature

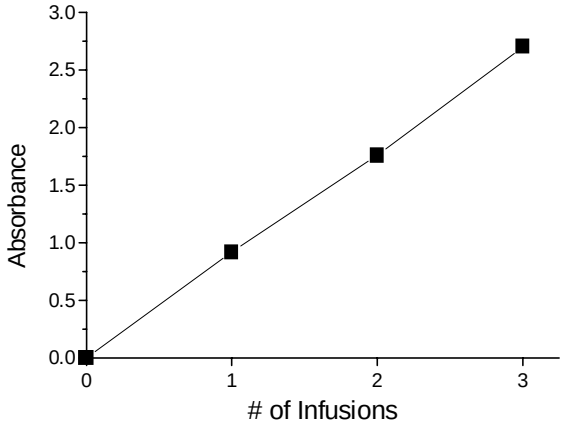


Figure 2. Absorbance of TiO_2 vs. Number of Infusion Cycles

disrupting the initial structure of the polymer. The infusion technique utilizes no solvents or supercritical fluids and is thus not limited to the use of inorganic precursors compatible with the solvents used to either swell or solubilize the starting polymeric material. This enables us to incorporate virtually any metal or metal oxide into any polymeric system, including fluoropolymers and polyolefins. The infusion process is limited by: 1) the free volume contained within the polymer, (i.e., polymers having crystallinity greater than 95% do not lend themselves to this process without using methods that can lower the polymer's crystallinity), and 2) the incorporation of inorganic materials that have precursors (e.g., organometallic complexes) that can be volatilized below the polymer's decomposition temperature [5].

Control of Metal and Metal-Oxide Material into Polymer Free Volume

In practice, the material to be infused is evacuated and a volatile precursor material is introduced, which fills the evacuated free volume. A subsequent thermal or chemical transformation of the infused precursor results in the formation of nano-scale interpenetrating network within the polymer free volume. As previously mentioned, this process requires that the polymeric material possess free volume; i.e., the polymer contains a degree of amorphous character and is not 100% polycrystalline. Thus, in order to gain a full understanding of how this process works it is important to understand the nature of free volume that exists within solid polymers below their glass transition temperatures (Tg). References 6-7 are cited and describe both the theoretical and practical aspects of polymeric free volume and how it relates to diffusional characteristics associated with a particular polymeric system.

Note that polymeric free volume is not the same as unoccupied or empty volume like pores that are produced in materials like filters. The free volume of a polymer relates to the volume in amorphous regions of a polymer that allow the polymeric chains the ability to move depending on how the chains are packed. For example, a solubilized polymer or one that is heated above its Tg has a high degree of free volume due to the fact that the polymeric chains can readily move and fluctuate. By removing the solvent, or decreasing the polymer's temperature below Tg, the polymeric material forms a glassy state where the free volume is decreased but still present to a degree depending on its amorphous character. The free volume of a polymer in its glassy state then determines its diffusional characteristics that allow gaseous molecules to freely diffuse into and out of the polymeric matrix.

By first evacuating the ambient gas that resides within a polymer's free volume other molecules can be transferred into this space with little difficulty as long as the precursor molecules are sufficiently small enough to easily diffuse or infuse into the free volume space. In essence, the polymeric matrix acts as a molecular template that controls: 1) the amount of inorganic precursor that can be added and 2) the physical structure and size of the molecular network that is subsequently formed.

Because an increase in temperature results in an increase in free volume, we have used the infusion temperature to control the concentration of inorganic material formed within a polymeric system. By increasing the temperature during the first step of the process, more free volume is created which allows the infusion of more inorganic precursor into the polymer. This provides the ability to control the amount of inorganic material that is subsequently formed within the polymer after the precursor is converted to a metal or metal oxide. To demonstrate this, $VOCl_3$ was infused into fluorinated ethylene propylene (FEP) at different infusion temperatures, and after subsequent hydrolysis to V_2O_5, the film's absorbance at 225 nm was measured (Figure 1).

The plot shows an increase in V_2O_5 concentration with increasing temperature. Note that the behavior corresponds well with diffusion behavior observed in measurements of polymeric free volume as a function of temperature [6,7].

Step 2 of the infusion process, a thermal, photochemical or chemical transformation of the precursor, also affects the resulting particle size and distribution of the infused metal or metal oxide. TEM results (not shown) have provided images showing particle size and distribution of Pd metal and V_2O_5 incorporated into MFA fluoropolymer and FEP. The hydrolysis used to form V_2O_5 was performed slowly at room temperature. This results in a distribution of particles that average ~ 100 nm in diamter and non-uniform in size, shape, and distribution. The slow hydrolysis allows the hydrolyzed precursor the mobility to form large, irregular shaped aggregates before condensing to the metal oxide. A more rapid hydrolysis using steam results in smaller, more uniform particles, which are uniformly distributed. Alternatively, Pd metal particles formed through thermal decomposition, are ~ 10 nm in diameter with uniform distribution and size. Because the thermal decomposition of the precursor proceeds quickly, there is not significant mobility or agglomeration prior to formation of the metal particle.

The infusion process can also be repeated multiple times in order to controllably increase the amount of infused metal or metal oxide. Figure 2 shows a plot of the measured absorbance of infused TiO_2 in a thin (0.5 mil) film of MFA fluoropolymer vs. number of infusion cycles. Because the free volume is filled with a gaseous precursor, and then condensed via hydrolysis to a solid, most of the original free volume remains after one infusion cycle. Therefore multiple infusion cycles results in an increasing amount of infused material.

Demonstrative Applications of the Infusion Process

To demonstrate the versatility and potential utility of the infusion process, a select number of different materials have been fabricated for applications as described below.

Anti-Fouling and Release Applications

A number of different precursors have been infused into a variety of base polymers to produce resultant materials that possess enhanced release characteristics. For example, 13-FT, a fluoroalkyl-containing organosilane, was infused into silicone rubber. Because of thermodynamics, the fluorinated silicate blooms to the near-surface region during hydrolysis. The resulting material exhibits oleophobic properties not present in the base silicone material. In addition, because the silicate network extends into the bulk of the polymer and is not simply a coating, the oleophobic properties persist even after significant wear of the silicone rubber material. The 13-FT precursor has also been infused into polyester and nylon polymers to produce materials with oleophobic as well as hydrophobic properties.

Alternatively, dimethyldichlorosilane has been infused into MFA fluoropolymers. After hydrolysis, the MFA material contains a network of silicone oligomers – essentially low molecular weight silicone oil. Because the precursor possesses only two hydrolyzable groups, a permanent, three-dimensional network does not form and the silicone oil can slowly exude from the film. The resultant material combines the low surface energy and excellent corrosion protection of the MFA fluoropolymer film with the foul-release characteristics of slowly exuded silicone oil. These materials are currently under evaluation by the U.S. Navy for foul-release appliqués on Navy sea-going vessels.

Enhanced Interfacial Bonding and Adhesion

Many polymers such as polyolefins, silicones and fluoropolymers are difficult to bond because of their low surface energies and lack of bonding sites at the air-polymer interface. Therefore these polymers are often treated by plasma, corona or chemical etchants to facilitate bonding. These treatments can effectively increase surface energies and allow adhesives to wet the surface but, in most cases, they do not provide the necessary functional groups for covalent interaction with the adhesive. The infusion process can be used to introduce functional groups (amine, thiol, vinyl, epoxy and isocyanate) to the surface as well as near-surface region of these treated polymers. Therefore infusion of organosilanes that contain specific functional groups, followed by hydrolysis, creates materials with bonding sites at the air-polymer interface that through a covalent network extends into the bulk of the polymer. These functionalities can facilitate and enhance the bonding of these materials using a variety of adhesives.

One specific example is the use of infusion to tenaciously bond a fluoropolymer to a platinum-catalyzed silicone adhesive. MFA fluoropolymer (5 mil) was infused with vinyltrimethoxysilane and after subsequent hydrolysis, a silicate network containing pendant vinyl groups were formed and extended from the bulk to the surface of the polymer. A platinum-catalyzed silicone adhesive was then used to bond two pieces of the modified fluoropolymer together. During the cure of the adhesive, the platinum catalyzes the covalent coupling of vinyl groups attached to the surface to those in the silicone adhesive. The resulting bond strength was such that attempts to disbond the films resulted in stretching and ultimate tearing of the fluoropolymer films (ca. > 15 PLI).

Anti-microbial Polymers

Ligand-bearing organosilanes have been infused into polymers to form long lasting, dynamic anti-microbial polymeric materials. The ligands, which are covalently attached to the silicate-interpenetrating network, function as chelating sites for reversible attachment of silver ions, which function as anti-microbial agents. After infusion of the ligand-bearing organosilane, such as EDA-Si, and subsequent hydrolysis, the infused polymer is immersed in an aqueous solution of silver ion. Silver ions are abstracted from the solution and are bound to the ligands within the polymer. Although the silicate-ligand network cannot leach out of the infused polymer, the silver-ligand complex slowly releases silver ions out of the polymer resulting in anti-microbial properties. The controlled release of silver ion is governed by the formation constant of the silver-ligand complex and can be tuned by choice of ligand. Because the formation constant for EDA-Ag complex is very large ($K_f \sim 10^{15}$), the rate of release of silver ion is very slow so that anti-microbial properties of the infused polymer are long-lived. Additionally, because the ligand cannot leach, one may simply recharge the polymer with silver ion when necessary. Fabrics made from polypropylene and polyester have each been treated as above and tested for their anti-microbial properties. The treated polymeric fabrics exhibited 100% microbe kill activity even after multiple industrial washing cycles.

Dyeing of Polyolefins

The dyeing of polyolefins is a difficult technological barrier to surpass. Although many polymers such as polyesters may be dyed using aqueous dye solutions, polyolefins cannot be dyed using traditional dye solutions and therefore are pigmented during compounding prior to extrusion. Traditional acidic or basic dyes will indeed migrate into polyolefins, however these dyes readily leach back out again because there are no functional groups available to act as suitable receptor sites for the dye molecules. Attempts have been made to introduce suitable receptor sites in polyolefins, usually by graft or co-polymerizations, so that the polymer may be dyed. These attempts have met with limited success. Polyolefins are low surface energy polymers and any attempt to introduce receptor sites into these materials prior to extrusion, will likely result in the higher energy functionalities being largely segregated to the bulk polymer regions. Therefore these added functionalities are not present at the free volume – polymer interface and cannot effectively interact with the incoming dye molecules.

Because the infusion process specifically takes place within the free volume of the polymer, suitable functional groups introduced by this process should be available to accept the dye molecules. Indeed, the infusion process has been utilized in a number of different permutations to demonstrate the dyeing of polyolefins and, in particular, polypropylene.

Basic functionalities, in the form of amines, can be introduced by infusing any number of amine-functionalized organosilane precursors. After hydrolysis of the precursor to form an IPN within the polypropylene free volume space, the polymer may be effectively dyed using an aqueous acidic dye solution. The electrostatic interaction between the amine receptor and the acidic dye molecule is sufficiently strong to prevent leaching of the dye when immersed for extended periods in boiling water.

Acidic functionalities on suitable organosilane precursors are more difficult to obtain. Alternatively, the infusion of $SiCl_4$ or tetraethoxyorthosilicate, followed by hydrolysis results in an IPN of silica within the polypropylene free volume. The silica thus formed is acidic enough to accept a basic dye molecule that does not leach out when exposed to boiling water.

Lastly, infusion of glycidoxypropyltrimethoxysilane (GOPS) results in, after hydrolysis, an IPN containing an epoxide pendant group on the silica IPN. The epoxide group of GOPS is susceptible to ring-opening attachment of either acidic or basic dyes resulting in a

(continued on page 11)

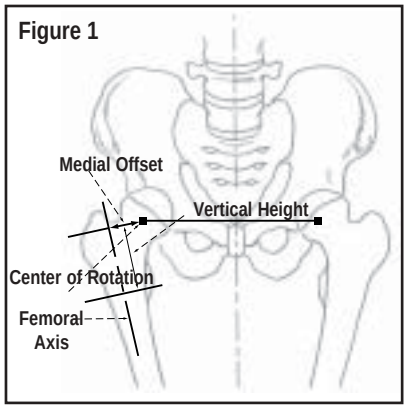
Total Hip Femoral Stem Design Concept that Aids in Fine Tuning the Restoration of Joint Mechanics in THA

By Hugh U. Cameron, M.B. & Timothy McTighe, Ph.D.

Editor's note: Taken from *Joint Implant Surgery & Research Foundation, NOVEMBER 2001*

Restoration of the hip joint mechanics is critical to a long-term successful outcome for total hip arthroplasty.[1] Two important angles need to be considered: the neck shaft angle and the angle of anteversion. In addition to these two angles, femoral head offset affects the joint reaction force.[2]

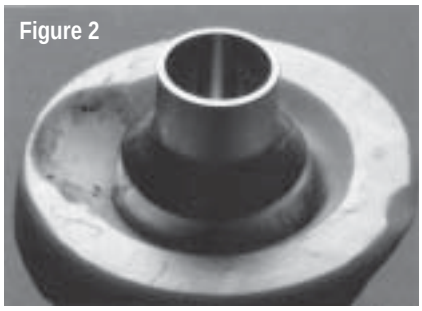
Replacement of the normal position of the femoral head is essential for correction of mechanical balance between abductor forces.[3] If vertical height is too short, joint stability is a problem. If too long, patients are very unhappy. Incorrect version angle can result in reduced range of motion and possible toeing in. Short medial offset will cause shortening of the abductor moments resulting in increased resultant force across the hip joint, and increasing the tendency to limp. Offset too great increases torsional and bending forces on the femoral component.



(Fig. 1)

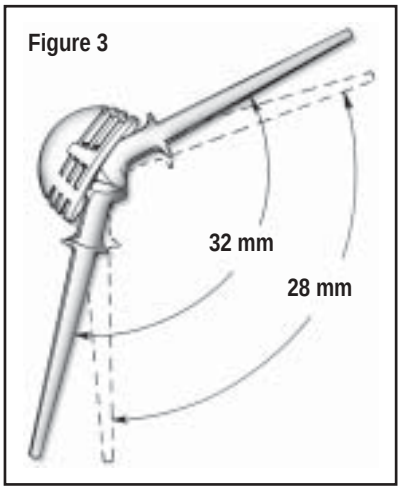
"Technique, technique, technique" as quoted by David Hungerford, M.D. is more important than design or material. With that said, we feel design features can aid in correcting technique related problems.

Surgical approach and technique not only affect soft tissue laxity but also can have a significant influence on component position. The most common surgical errors relate to malpositioning the acetabular component; however, malposition of the femoral component can contribute to increase component impingement and dislocation (Fig. 2).[4,5]



Malpositioning of a cemented stem not only can result in impingement, compromise of cement mantle thickness and dislocation but can significantly impact bone loss by requiring revision of the femoral stem. In addition, malposition can contribute to bone lysis by the increase of articulation wear debris.[6]

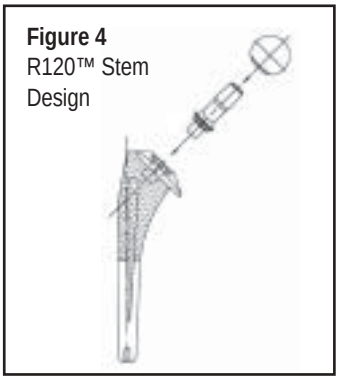
Two factors that affect range of motion are component positioning and component geometry.[4] Although physiological range of motion varies for each patient, an average of 114° of flexion is required for sitting. There is no question that increased range of motion results in better clinical results. Head diameter, neck shape and skirts on femoral heads can all affect hip range of motion (Fig. 3)[1]



The following stem design approach is recommended in an attempt to aid in restoration of joint mechanics and to allow the surgeon a final opportunity to correct for malpostioning of implants due to technique, and /or bony deformity.

R120™ Modular Indexable Neck Cemented Stem

The stem is designed to use standard conventional cementing techniques. The shape of the stem is trapezoidal and with a proportionally designed collar provides for optimal impaction and compression of bone cement. In addition, a teardrop shaped recess on the anterior and posterior portion of the implant increases the cement to prosthesis interface therefore increasing resistances to axial and torsional forces. (Fig. 4)



The proximal stem features a matte surface, which enhances fixation of the implant to the PMMA cement, while the distal portion is polished allowing for ease of retrieval if necessary.
An optional distal PMMA stem centralizer is available depending on each individual's philosophy.

Proximally, R120 stems are designed in five (5) cross sections with three (3) interchangeable modular neck lengths of 32mm, 35mm, and 38mm and two angle variations of 8° and 12°. The proximal stem collar is made with a cavity where a self-locking taper and a positive indexing mechanism are employed to ensure the proper head, length, version and offsets are obtained. (Fig. 5)

This unique design features twelve (12) self-locking positions providing several combinations of neck length version and offset for a closer match to restoring hip joint mechanics.

This innovative approach provides the surgeon with the opportunity to intervene at the last possible surgical moment and fine tune the hip joint mechanics without disruption of the implant-cement-bone interface. In addition, it should provide for increased opportunity to surgically intervene for certain post-op complications, like component malposition, leg length discrepancy, dislocations and replacement of bearing surfaces, with minimal disruption of bony interfaces.

These are just some examples of the flexibility of using this unique Modular Indexable R120™ Neck System (Fig. 6).

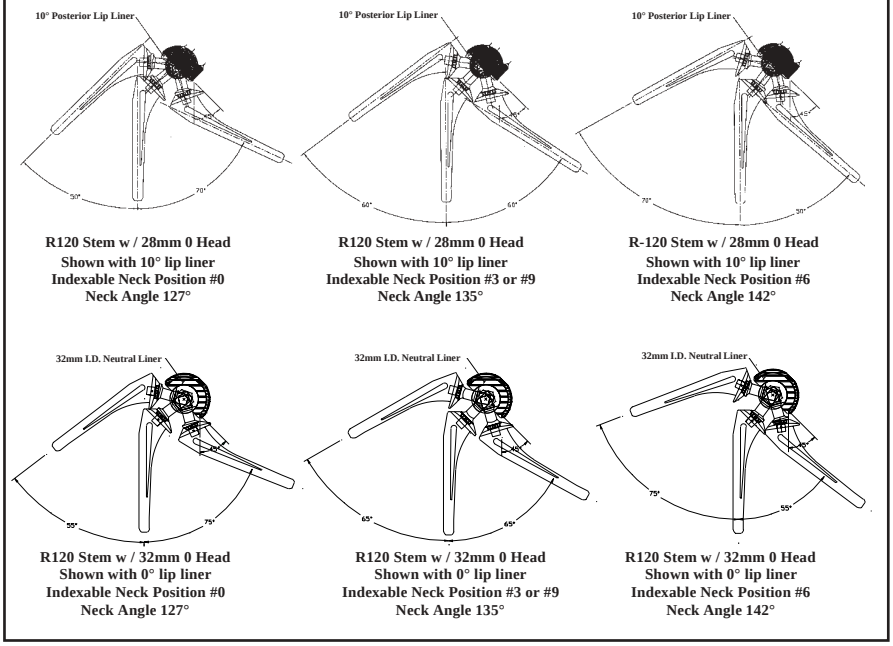
The references for the pros and cons of modular couplings have been well documented and are too numerous to list here. We suggest the basic decision-making be left to the operating surgeon as to the advantages offered by modularity. In addition, we suggest each modular site needs to be evaluated on its own merits.

Modular necks have been used in titanium cementless stems in Europe successfully for years (Fig. 7).

Figure 7

Both mechanical and clinical results have demonstrated the design approach to be safe and effective.[7, 8, 9] However, the authors here feel, for cemented application, cobalt chrome molybdenum alloy is preferable both for interfacing with cement and for providing less risk of fretting and/or corrosion at the modular stem neck junction.[10, 11] The availability of modular necks and heads allow for unprecedented flexibility in restoring hip joint mechanics.

Figure 6



Only long-term outcome data will clearly demonstrate the viability of this modular neck design, however, basic mechanical principals and attention to the design features presented should aid the surgeon in fine-tuning and restoring normal mechanics to the reconstructed hip.
(Source: Press Release)

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Excellence in Surface Science 2002 Awardee Announced

It is with great honor that the Surfaces in *Biomaterials* Foundation presents J. William Costerton the 2002 Excellence in Surface Science Award. Dr. Costerton is the Director of the Center for Biofilm Engineering at Montana State University. He assumed this position in January 1993 after twenty-three years at the University of Calgary. At the University of Calgary he held several positions. He was appointed Associate Professor of Biology in 1970 and became Professor in 1975. In 1980, he was appointed to the AOSTRA Research Chair in Microbiology and to the NSERC Industrial Research Chair in Microbiology in 1990. Prior to his work at Calgary, Dr. Costerton was Assistant Professor of Microbiology at MacDonald College of McGill University (1966-70) and completed a post-doctoral fellowship at Cambridge University (1964-66). From 1960-69 he was Dean of Science at Baring Union College, Punjab India.

Dr. Costerton received his Ph.D. in Bacteriology in 1960 from the University of Western Ontario. His early interest in microbial ecology led him to the study of bacteria attached to surfaces - BIOFILMS. His research since has dealt with biofilms in a broad variety of environments; from mountain streams, to industrial systems, to medical devices implanted in humans. His research has brought honors including the Isaak Walton Killam Memorial Prize for Scientific Achievement in 1990 and the Sir Frederick Haultain Prize from outstanding achievement in the physical sciences in 1986.

Please join the Foundation in congratulating Dr. J. William Costerton on his achievements.

Introducing Surfaces in *Biomaterials* Foundation's Newest Academic Member

Center for Biofilm Engineering Montana State University

The Center for Biofilm Engineering has identified goals in three areas of activity. In the area of research, the CBE's goal is to do leading edge fundamental research to elucidate the mechanisms at work in bacterial biofilms. The CBE has been a leader in defining the structure and function of biofilms on surfaces, in understanding the antimicrobial resistance mechanisms of biofilm, and in identifying the role of signal molecules in controlling bacterial behavior. To the naked eye, biofilms simply look like slimy gunk, but researchers at the CBE have demonstrated that they are actually multicellular attached communities, with primitive circulatory systems and a measure of cellular specialization. Understanding these "biofilm basics" presents opportunities for developing more effective strategies to control biofilms in industrial settings. The second goal of the CBE is to make its research relevant to real systems, where the information can be useful. Industrial partnerships keep the CBE from being a traditional university "ivory tower," collecting information that has no practical application. Industrial needs shape and focus the research efforts. Technology transfer at the CBE involves not only information, but methods and technology development. Key to the Center's success is the CBE's goal to develop an interdisciplinary undergraduate and graduate education program, involving team research on industrially relevant projects.

Gaining Control at the Polymer/Biology Interface: A Recipe for Advanced *in vitro* Cell Culture

By Andrea Liebmann-Vinson, BD Technologies, Research Triangle Park, NC

Excising cells and tissues from living organisms and maintaining them alive *in vitro* is the essence of tissue culture and has first been practiced as early as 1885 [1]. The conventional cell culture technique, practiced routinely in cell culture laboratories today, entails (1) breaking a tissue up into individual cells, for example by digestion with trypsin, (2) suspending the cells in an appropriate medium that will provide the physical conditions of pH, osmotic pressure as well as nutrients required by the cells for their survival, and (3) placing this cell suspension on an appropriate substrate. The choice of substrate is critical and depends on the type of cells to be maintained in culture. Cells whose survival depend on the ability to attach to a substrate, e.g. attachment dependent cells, need a substrate that will allow for effective cell attachment, whereas cells that survive better when kept in suspension do not require a cell adhesion promoting substrate.

The substrate of choice used in the earlier cell and tissue culture attempts was glass because it was readily available, supported cell attachment and growth and due to its transparency also allowed for microscopic studies of the cell culture. Glass cultureware is commonly reused but it requires rigorous cleaning between each use. In the 1950's, Barker and LaRocca reported that polystyrene exposed to a gas plasma discharge supported the attachment and growth of cells equally to a glass surface [2]. Since then, disposable plasma treated (i.e., tissue culture treated) polystyrene culture vessels have remained commonly used for cell culture.

Let us now take a closer look at the events occurring at the surface of a cell culture substrate after the addition of cells suspended in a medium. Cell culture media are balanced salt solutions containing all the essential amino-acids, vitamins and serum proteins. When cells are suspended in such a medium and are placed on a synthetic substrate it is not the cells that immediately interact with the surface but the serum proteins contained in the medium. Instantaneous protein adsorption leads to an adsorbed protein layer consisting of many different proteins in a spectrum of orientations and conformations [3-6]. Within minutes cells arrive and start to interrogate this complex interface which offers many possible sites, e.g. peptide sequences for interactions via transmembrane receptors on the cell surface, e.g. integrins, cell-surface proteoglycans and selectins [7,8]. Cell function and fate strongly depends on binding occurring on these integrins (with proteins/peptides from the surrounding solution as well as the substrate) and subsequent triggering of signaling pathways within the cell. As a consequence, interactions with this randomly adsorbed protein layer will lead to an arbitrary 'biological response', in this case the attachment, spreading, proliferation, migration and differentiation of cells at this interface. It is thus of extreme importance to understand and control those initial stage-setting processes in order to control the biological response, e.g. cell behavior, to a material.

Let nature be our guide to achieve that control. Normal biological reactions are very specific and a ligand interacting with an integrin accurately and specifically triggers particular processes [9]. Let us thus hypothesize that in order to control cell attachment to a synthetic substrate, such as a polystyrene tissue culture surface, the activation of non-specific interactions must be avoided. Instead, cell culture substrates should mimic nature by providing recognition and specificity.

A common strategy to avoid activation of non-specific reactions, e.g. non-specific protein adsorption (NSPA), is through control of the material's surface chemistry. However, early attempts to control NSPA by means of surface chemistry failed and only in the 1980's did it become apparent that the presence of a surface-grafted layer of highly hydrated hydrophilic polymers provides an effective barrier for NSPA. An example for such a hydrated hydrophilic polymers is *poly(hydroxyethyl methacrylate)* (PHEMA). Deposits on contact lenses, mainly consisting of proteins, were found to lead to lens clouding, wearer discomfort and were also linked to a variety of inflammatory responses related to contact lenses. In order to design a contact lens material with minimal protein adsorption, PHEMA and copolymers of PHEMA with poly(methyl methacrylate) (PMMA) were studied [10]. A PHEMA hydrogel coating applied to plastic tissue culture ware is also a common tool to prevent cell adhesion in routine cell culturing [11]. *Phospholipids* are the major component of cell membranes and phospholipid assemblies, such as liposomes, for example, are quite inert for biological systems. Consequently, surfaces coated with phospholipids are thought to resemble a cell's surface thus preventing any non-specific interactions [12]. Similarly to phospholipids, *oligosaccharides* can be used to mimic the non-adhesive properties of the glycocalyx, the external region of a cell membrane [13]. Elimination of mammalian cell adhesion and significantly reduced bacterial cell adhesion was observed with two *polysaccharides*, e.g. alginic acid and hyaluronic acid, immobilized onto the surface of polystyrene dishes [14]. *Self-assembled monolayers* (SAMs) are widely used as model systems of organic surfaces to study relationships between the molecular structure of surfaces and responses resulting when placing this surface in contact with a biological environment. Alkanethiolate SAMs on gold presenting tri(propyl sulfoxide) groups at the surface, a group not commonly used in biomaterials, were reported to entirely resist the *in situ* adsorption of proteins, even "sticky" proteins such as fibrinogen [15]. Recently, four additional functional groups were identified to prevent protein adsorption when present at the terminus of SAMs [16]. These groups have in common that they are all polar, incorporate hydrogen-bond accepting but not hydrogen-bond donating units and possess no net charge, however, elimination of hydrogen bond donor groups seemed to be the key structural element in protein-resistant surfaces.

The most promising material for protein repellent and non-cell adherent surfaces today may well be *polyethylene oxide* (PEO), also commonly called *polyethylene glycol* (PEG). In 1982 Mori et al. reported the ability of long PEO chains to retard protein adsorption to surfaces to which the PEO chains were covalently attached [17]. Since then, grafting of PEO on polymer surfaces has attracted a great deal of attention and a variety of techniques to obtain PEO-rich surfaces have been described.

The last step, after having prevented the activation of non-specific interactions, is to provide sites on the surface that a cell can recognize and specifically interact with. Cell adhesion in tissues is most commonly mediated by adhesion receptors on a cell interacting with a molecule of the extracellular matrix (ECM) or a molecule on a neighboring cell [18]. ECM is a complex mixture of various proteins that is being produced by the cells of a tissue. The main components of ECM are collagens and other glycoproteins, hyaluronic acid, proteoglycans, glycosaminoglycans, and elastins. Specific amino acid motives contained on ECM molecules have been found to bind directly to cell surface receptors. The most prominent examples are the tripeptide RGD isolated first from fibronectin [19], and YIGSR, a peptide sequence found in laminin [20]. The incorporation of such moieties that interact with cells in a specific and directed manner into surfaces that do not provoke non-specific interactions will ultimately lead to control of events at the cell suspension/cell culture substrate interface and present the future of *in vitro* cell culture.

(Source: Press Release)

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(continued on pate 11)

Tissue Engineered Biointerface for BMP-2 Delivery

By Harvey E. McDaniel & Linda Lomax (Systems Technology One Inc.-Biomedical Engineering Group)

Bone morphogenetic proteins (BMP-2) have been under investigation for three decades. Bone and demineralized bone extracts not only are osteoinductive with a temporal sequence of bone induction, but allow native and recombinant BMP's to show growth and differentiative factors to induce denovo bone formation (in vitro and in vivo). Their principle function is to induce transformation of undifferential meschemyal cells into osteoclasts. No effect on bone induction by native and recombinant BMP's when used without carriers (dispersing) after implanation. Metaanalysis and laboratory results provided for the catalysts for the design of the tissue engineered biointerface.

Because of the physical construction we applied osteogenic proteins and through bioinformantics, monitored their progress. Biological and physicochemical properties were adhered to design the optimal delivery system. Target cell attachment was enhanced by the optimized surface providing non-tumorgenic genecity, non-immunogenecity, biosorbability with predictable enzymatic pH reactivity. BMP binding with the proteins provided data on predicted release kinetics, porosity with interconnected voids, protected the BMP from non-specific proteolysis, and promoted vascular and meschemyal invasion. With biological systems having elasticity associated with them, they allowed time dependant biological/biochemical reactions (enzymatic activity) to be observed. The bioelectric phoenomenon that were further associated with charged molecules within a biologic structure caused changes in the distribution resulting from specific processes altering the local anatomy. Bioelectric signal detection involved the interactive ionic charge carriers and transducing ionic current converted into electric current for bioinformantic processing (biointerface-biology based microprocessor). Cohesion and malleability were for contour augmentation and reconstruction of the discontinuity defects prevented dislocation and retained the shape with the replacement of bone.

Calendar of Events

ASM 102nd General Meeting
May 19-23, 2002
Salt Lake City, UT, U.S.A.
www.asm.org/mtgsrc/gm2002prelimprogtopppage.htm

Wound Healing Society 12th Annual Educational Symposium
May 28-June 1, 2002
Baltimore, MD, U.S.A.
www.woundheal.org

Associazione Italiana di Scienza Tecnologia delle Macromolecole (AIM) Europolymer Conference 2002
June 2-6, 2002
Gargnano, Italy
www.dcci.unipi.it/~bea/eupoc02

Medical Design & Manufacturing (MD&M) East
June 3-5, 2002
Jacob K. Javits Convention Center
New York, NY, U.S.A.
www.devicelink.com/expo/east01

International Conference on Advances in Biomaterials for Reconstructive Medicine
June 9-14, 2002
Capri, Italy
www.area.na.cnri.it/itmc

48th Annual ASAIO Conference
June 13-15, 2002
Hilton New York
New York, NY, U.S.A.
www.asaio.com

International Cartilage Repair Society: 4th ICRS Symposium
June 15-18, 2002
MTCC, Toronto, Canada
www.cartilage.org

Controlled Release Society 29th Annual Meeting
July 20-25, 2002
COEX World Trade Center and COEX Inter-Continental Seoul
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The American Ceramic Society 54th Pacific Coast Regional and ACerS Basic Science Division Meeting
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(Novel Nano-Technology...continued from page 5)

covalently bound dye molecule. Dying of polypropylene by this method allows strong covalent anchoring of the dye molecule using either acidic or basic dyes.

Polymerizations Within a Base Polymer's Free Volume

The free volume of a polymer is responsible for the transport of gaseous molecules through the polymer. The infusion process, as described above, adds material to the free volume of polymers. However, the gaseous precursors used for infusion condense to solid materials, and therefore, do not fill a significant portion of the free volume. In fact, the oxygen and water vapor transport properties of an infused polymer do not show significant differences when compared to the base polymer.

Although multiple infusion processes can be used to significantly reduce free volume, another more interesting method involves the use of infused metal oxides as catalysts for polymerizing various organic monomers within the free volume. For example, V_2O_5 was chosen as a catalyst for the initial studies because it provides catalytic sites capable of promoting various anionic polymerizations. Styrene was chosen as the monomer for this investigation. The infusion process places the V_2O_5 catalyst in the free volume and subsequent infusion of styrene monomer results in polymerization of styrene within the free volume. Based on weight gain and IR characterization, approximately 10% by weight of polystyrene polymerized into an MFA film. No unreacted styrene monomer was measured in the IR spectrum of the resulting film. Additionally, a sample of MFA film that did not contain V_2O_5 was infused with styrene monomer. IR did not detect polystyrene in this sample.

Measurement of the oxygen and water vapor transport properties of this sample produced some unexpected results. The rate of water vapor transmission was unaffected by the added polystyrene, but the rate of oxygen transmission increased by a factor of 10. We expected to see an overall decrease in transport rates due to a physical blocking of the free volume. The increase in rate of oxygen transport was unexpected. Work is ongoing to further study these polymer hybrid systems and to determine the selectivity of this effect on different gases.

Conclusion

Nano-technology can be used to fabricate inorganic-organic hybrid materials. The methods described require no solvents or use of supercritical fluid technology and are useful for a wide range of polymeric materials including fluoropolymers and polyolefins.

The infusion process produces materials that exhibit a variety of unique chemical, biochemical, optical, and electrical characteristics that make them commercially attractive for many technological applications. The process allows certain characteristics of a polymer to be enhanced or altered for improved performance, while leaving other polymer properties unchanged. Desirable attributes can be added to polymeric materials with the addition of only 1-2% by weight of infused material.

(Source: Press Release)

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