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Spring 2018
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Letter from President Chris Jenney

Hello Friends of the Foundation,

Time marches on. Our spring edition of SurFACTS is here and planning for BioInterface 2018 is in full swing by the dedicated volunteers of the Conference Committee. As a reminder, this year's meeting will be held Oct. 1 through 3 at the St. Julien Hotel in Boulder, Colorado, an amazing venue perfect for our unique and impactful event. I want to thank all our members, supporting members, and sponsors, who make it possible for the Foundation to serve the surface science and biomaterial communities and organize this very special conference.

Registration is now open at a discounted early bird rate, so hurry up and take advantage. The attendees at BioInterface are some of the most influential and knowledgeable in the fields of biomaterials and surface science. Please consider the possibility of your organization becoming a meeting sponsor or exhibitor. These are exclusive and powerful ways to network and highlight what your organization has to offer the biomaterials community. In the coming months we will send out a call for student posters, which will be featured during an evening reception at BioInterface. Posters will be judged by Foundation board members and an award given for the top poster. All conference information can be found on our website, which I encourage you to visit right away.

Lastly, I encourage all of you to submit news and articles to SurFACTS Executive Editor Melissa Reynolds (Melissa.reynolds@colostate.edu) for consideration in future SurFACTS issues. This is a great way to share the innovation and progress achieved by you and your organization.

I look forward to seeing you all in Boulder this fall. If you have any questions, comment, or suggestions regarding the Surfaces in Biomaterials Foundation or the upcoming BioInterface 2018 meeting, please email me at chris.jenney@abbott.com.

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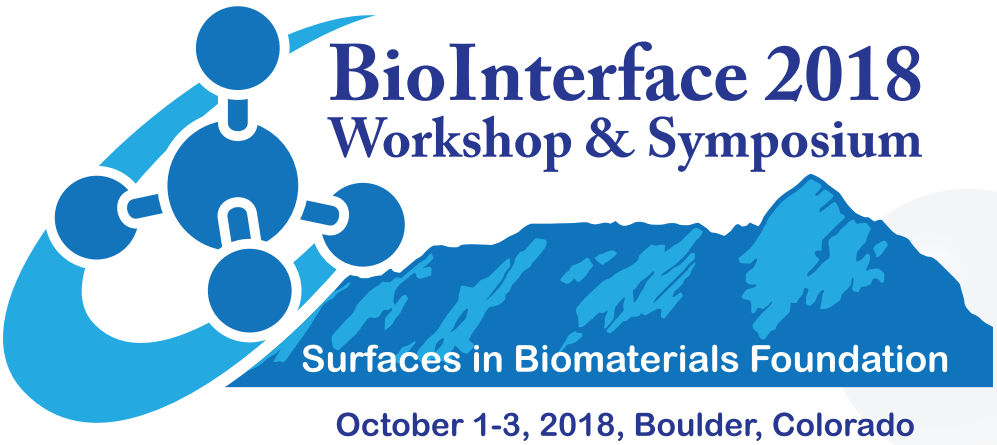

October 1-3, 2018, Boulder, Colorado

October 1-3, 2018, Boulder, Colorado

Workshops/Sessions

MONDAY October 1

BIOINTERFACE WORKSHOP

Theme:
3D Printing in Medical Devices
Co-Chairs: Angela DiCiccio
Verily Life Sciences
Dan Gostovic
Thermo Fischer Scientific

TUESDAY October 2

BIOINTERFACE SYMPOSIUM

Session 1 Topic:
Surface Functionalization and Thin Film Coatings
Co-Chairs: Daniel Higgs
ALD Nano Solutions
Lijun Zou
W.L. Gore & Associates

Session 2 Topic:
Neurological Devices
Chair: Tim Becker
Northern Arizona University

Session 3 Topic:
Adhesion of Soft Tissues
Chair: Terry Steele
Nanyang Technological University

Session 4:
Point Counterpoint Debate

WEDNESDAY October 3

BIOINTERFACE SYMPOSIUM

Session 5 Topic:
Metallurgy
Co-Chairs: Mallika Kamarajugadda,
Medtronic, plc
Siobhan Carroll, *G. Rau Inc.*

Session 6 Topic:
Metallic Devices
Co-Chairs: Mallika Kamarajugadda,
Medtronic, plc
Siobhan Carroll, *G. Rau Inc.*

Session 7 Topic:
Bioresorbable Materials
Chair: Norman Munroe
Florida International University

Session 8 Topic:
Tissue Engineering and Regenerative Therapies
Co-Chair: Rob Diller
Axolotl Biologix
Roy Biran
W.L. Gore & Associates

For more information and to register go to http://www.surfaces.org/page/2018BioInterface.

Role of Design and Microstructure on the Corrosion of Modular Hip Prosthesis

Norman Munroe, Vishal Musaramthota, Jose Gonzalez, and Kinzy Jones

Introduction

Prosthetic joint implantation has improved the quality of life for many individuals for more than a century by restoring satisfactory, pain-free joint function [4]. From ivory implants in the 1890s, the design of artificial hip prostheses has progressed to revolutionary modular metallic implants [1, 2] that require superior materials with superior performance [3]. However, prosthetic failure and joint infection remain major concerns [5]. Improper material manufacturing methods and prosthetic design lead to fretting corrosion, aseptic loosening and stress shielding [6]. The incidence of implant failure is further exacerbated by the increasing number of young patients undergoing total hip replacement (THR), whose more active lifestyles place greater demands on their prosthetic joints [7].

In an effort to alleviate stress shielding, modular prostheses were developed so that the femoral stem can be manufactured from a material with a modulus of elasticity close to that of bone. This resulted in a modular two-piece design overwhelmingly adopted over the past three decades instead of the previous mono-block design. However, the introduction of lower modulus materials has increased the incidence of aseptic loosening. Furthermore, fretting corrosion at the interface between the femoral head and the stem causes metal ion release [8, 9]. The prevalence of material degradation at modular interfaces has been widely reported [10, 11] and although the exact cause of aseptic loosening in some cases is difficult, an increasing number of studies have confirmed severe modular interface corrosion co-occurring with adverse local tissue reaction including soft tissue damage and loss of implant fixation [8 -11].

This article discusses the role of material microstructure and prostheses design on their biocompatibility with the hope of contributing to the development of a new generation of hip prostheses with even lower modulus of elasticity, less wear debris and metal-ion release. This will ultimately enable implantable devices to outlive patients and reduce revision surgeries.

Significance

The femoral head has traditionally been considered the primary source of metal ion release as a result of tribo-corrosion. In fact, any change in material composition, microstructure or design of the prosthetic could significantly affect its performance. It is well established that different manufacturing methods and material heat treatments result in different microstructures that affect a material's properties. However, there is a lack of comprehensive dimensional analysis to delineate whether the damage observed on explanted prostheses resulted from their design, the material's properties or from clinical factors. This article focuses on several design parameters such as Morse taper, neck and taper diameter, trunnion-head interface and femoral head dimension and their relationship to corrosion behavior.

Material Characterization

In this study, 48 explanted modular total hip prostheses made of titanium-aluminum-vanadium and cobalt-chromium-

Table 1: Femoral head and femoral stem dimensional variables

Dimension	Name	Description
A	Stem Length	Axis is determined using any available markers, lower stem symmetry and/or stem driver bore.
B	Stem Width	Taken at one inch from the bottom of the stem.
C	Neck Length	Taken from proximal end of taper to porous coating or below collar. Use taper symmetry to find axis and extrapolate.
D	Neck axis length	Length of neck from proximal taper to stem axis intersection. Can be calculated from *sqrt* (E^2 + F^2)
E	Stem X-Offset	
F	Stem Y-Offset	
G	Full Stem Height	
H	Minimum Neck thickness- A/P View	Thickness at narrowest point along neck when viewed in anterior/posterior view.
I	Minimum Neck thickness- Top View	Thickness at narrowest point along neck when viewed from top view
J	Proximal Width A/P view	
K	Proximal Width M/L view	
L	Neck Angle (deg)	As determined directly or by $\tan^{-1}$ E/F
M	Taper length	Length of in-contact taper surface
N	Taper Axis Length	Length of taper axis length
O	Proximal Taper Diameter	Diameter of proximal taper diameter
P	Distal Taper Diameter	Diameter of distal taper diameter, ending in contact.
Q	Taper Angle (deg)	2* (90 – α_{distal})
R	Axial skirt length	

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molybdenum were acquired after revision surgeries as a result of implant failures such as aseptic loosening, acetabular liner degradation and dislocation. The explants were sterilized, sectioned and cleaned to remove any organic residue. An effort was made to correlate the materials' properties with corrosion observed on retrieved implants.

Dimensional Measurements and Design Features

The explanted prostheses were catalogued according to their surface finish as shown in Figure 1. The dimensional measurements of a typical total hip prosthesis are shown in Figure 2 and the femoral head and femoral stem dimensions are shown in Table 1.

Another key dimensional aspect that is of paramount importance is the head-trunnion mating surface as shown in Figure 3. The dimensions associated with the head-trunnion mating surface as shown in the Figure 3 are described in Table 2.

Microstructure of Alloys used for the Manufacture of Prostheses

The Co-Cr samples (as cast; wrought low carbon; wrought high carbon; solution treated) and Ti-6Al-4V samples were mettallographically prepared to a high smooth finish and observed for their microstructure. The morphology as well as grain size were determined as shown in Figure 4.

Table 2: Modular junction dimensional variables

Dimension	Description	Example
HS	Head Size	
HH	Head Height	
TD	Top of Head to Distal End of Taper	
CL	Center Coverage	Distance from the center of the in-contact taper axis to the rotational center of the head.
MA	Trunnion-Head Moment Arm	
PN	Penetration	HH-TD
PR	Relative Penetration	(HH-TD) / (HH/2)
NL	Effective Neck Length	
SA	Taper in-contact Surface Area	$\pi(O/2+P/2)\sqrt{(N^2+(O/2-P/2)^2)}$
CV	Taper in-contact Volume	

Discussion

The Co-Cr as-cast microstructure exhibited severe corrosion as compared to solution treated samples. The wrought low carbon and high carbon Co-Cr alloy was slightly prone to corrosion. The solution treated Co-Cr alloy had non-equiaxed grains of diameter >300 µm, with secondary phases at the grain boundaries. This sample exhibited severe to moderate fretting corrosion.

A low carbon Co-Cr wrought explanted prosthesis of grain size ~5µm with a 32 mm skirted femoral head had a moment arm of 5.2mm, which was the 5th largest moment arm of the 32 implants examined. It had the fourth largest in-contact surface area of 117 mm^2 which was greater than the value of the median. The fretting corrosion was uniformly distributed throughout the head and trunnion

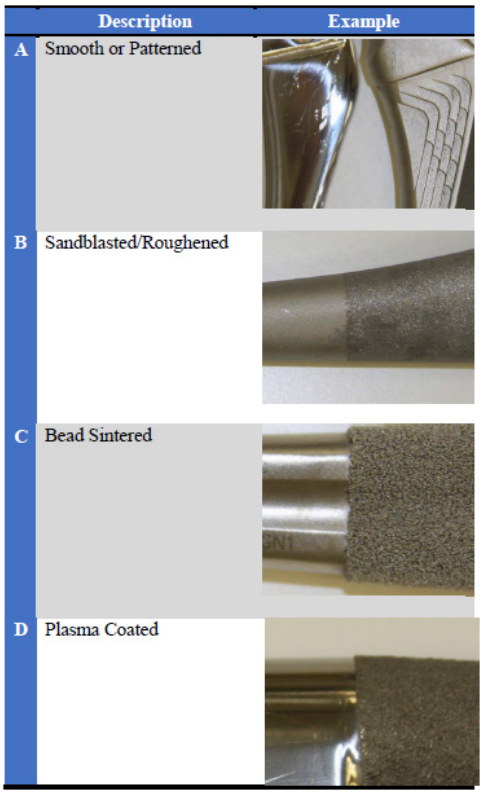

Figure 1. Porous Surface Coating Types

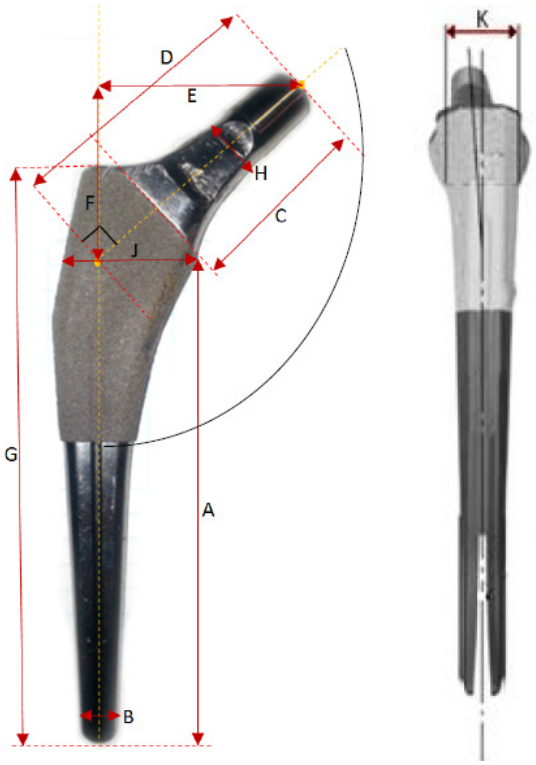

Figure 2. Dimensions for Typical Total Hip Prosthesis. Left: Anterior/Posterior view. Right: Mediolateral view

Role of Design and Microstructure ... continues on pg. 5

tapers for this sample as compared with localized pitting corrosion observed when there was taper angle mismatch. It seems plausible that the high offset coupled with the 32mm head size might be responsible for the fretting corrosion observed in Figure 5.

The Ti-6Al-4V samples were received with trunnions engaged and were separated post-sectioning. This ruled out the occurrence of any damage to the surface during disengagement. These samples exhibited variable microstructures (see Figure 4 (e) but both surfaces of the trunnions exhibited similar corrosion patterns. The samples had identical taper features called flattened neck notches that are intended for increased range of motion. The notches extended far into the femoral head with a taper contact area that was 2-fold in symmetry. This resulted in variable taper contact length, which created taper edges in a tortuous crevice that extended deep into the femoral head. Together these features enabled stagnant fluid to be in contact with reactive edge surfaces, thus creating prime conditions for crevice corrosion as shown in Figure 6.

The effect of moment arm (the distance from the center of pressure of the femoral head to the proximal taper contact) was also investigated and appeared to have some influence on the degree of fretting corrosion. At lower moment arms where the taper extended beyond the center of the femoral head, fretting corrosion was non-existent or mild and vice versa for higher moment arms. Samples with the largest moment arms (≥ 4.11mm) required a skirted femoral head to maintain high contact surface area at such low head penetrations. Nevertheless, contact surface area alone did not correlate with fretting corrosion. While some of the worst performing prostheses possessed high offsets, those manufactured from high carbon wrought heads on low carbon wrought femoral stems were excellent performers.

Conclusions

The effect of microstructure, material composition, manufacturing method, heat treatment and design on fretting corrosion of numerous explanted prostheses were investigated in an effort to understand the role each played, which lead to revision surgery. As far as microstructure is concerned, prostheses manufactured from alloys with appreciable grain boundary segregation exhibited severe fretting corrosion.

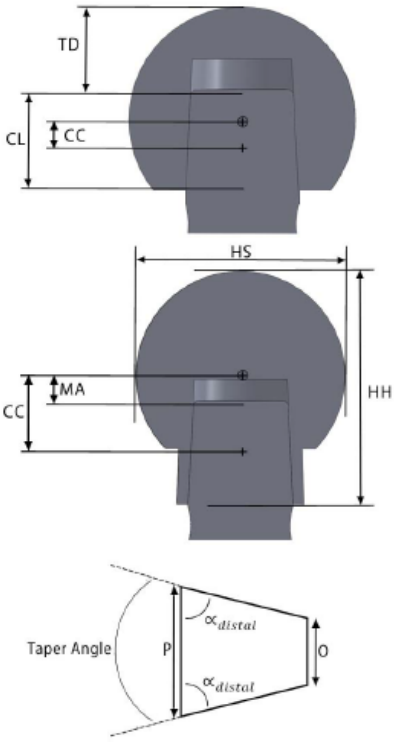

Figure 3. Dimensions for Femoral Head and Head — Trunnion mating. Top — Typical skirtless head with engaged taper. Center —Skirted head with engaged taper. Bottom — Taper dimensions.

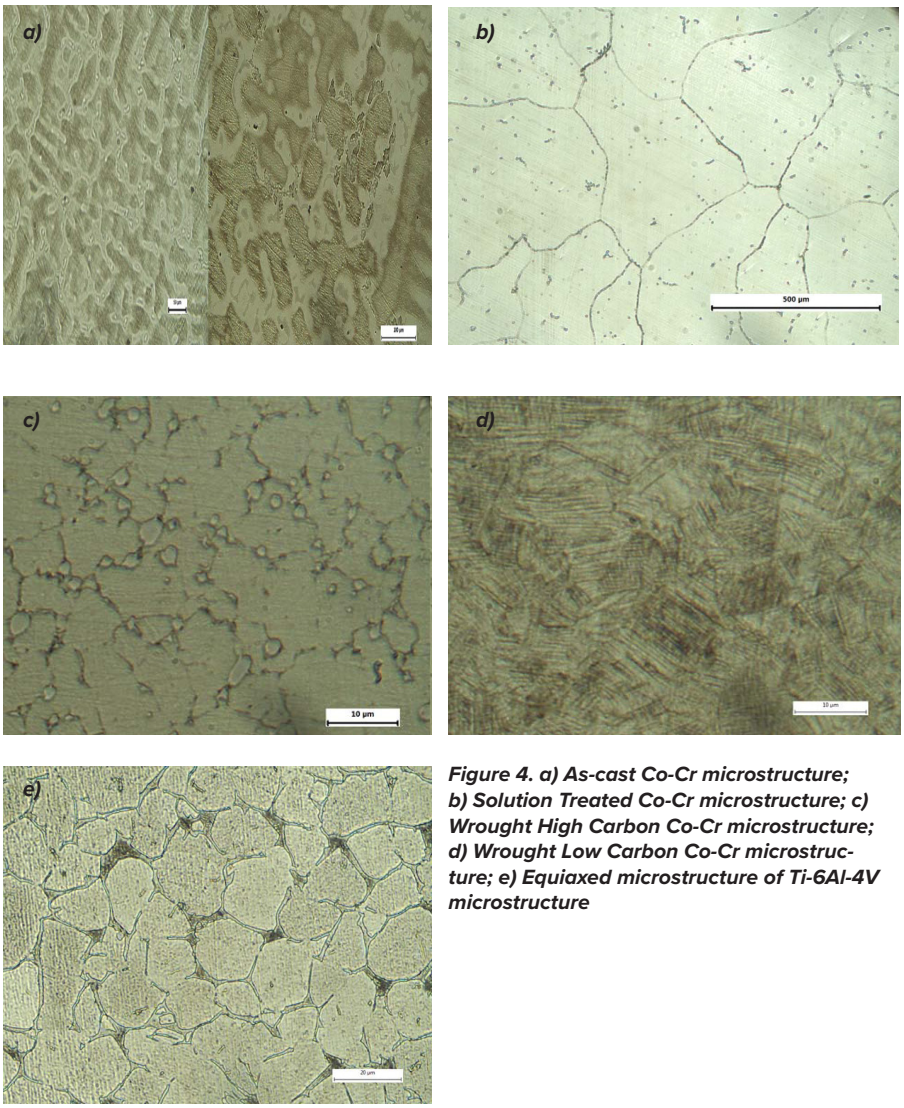

Figure 4. a) As-cast Co-Cr microstructure; b) Solution Treated Co-Cr microstructure; c) Wrought High Carbon Co-Cr microstructure; d) Wrought Low Carbon Co-Cr microstructure; e) Equiaxed microstructure of Ti-6Al-4V microstructure

Role of Design and Microstructure ... continues on pg. 6

With regard to the design of prostheses, fretting corrosion occurred in those prostheses with crevices at the trunnion-head interface, high offsets and large moment arms, although it could be mitigated in some cases by usage of the appropriate combination of metals, such as high carbon wrought heads on low carbon wrought femoral stems. This investigation revealed that there are several factors that must be considered in the design and manufacture of prostheses with the hope of reducing revision surgery and medical costs.

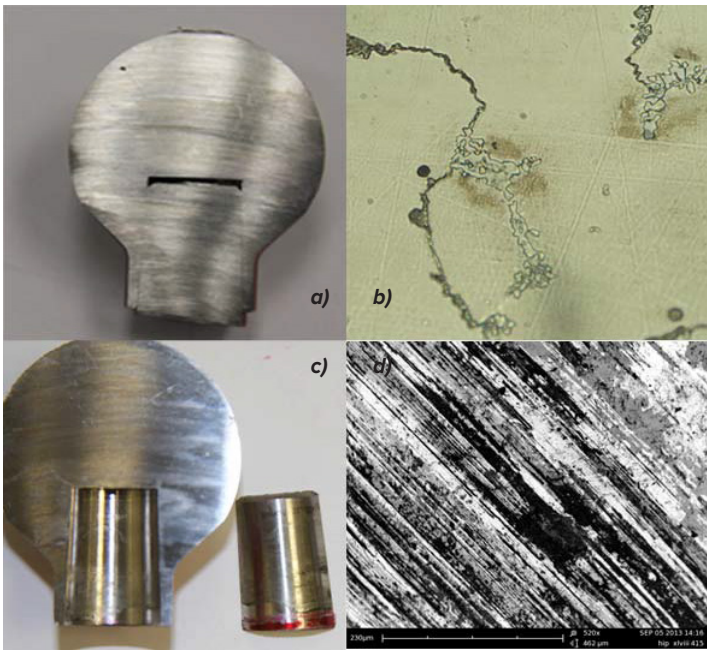

Figure 5. a) Trunnion-head assembly. Note very high offset; b) Etched solution treated Co-Cr microstructure revealing secondary phases at grain-boundaries; c) Disengaged trunnion revealing uniformly distributed corrosion (black corrosion products on both tapers); d) SEM image of striations illustrating extensive fretting corrosion.

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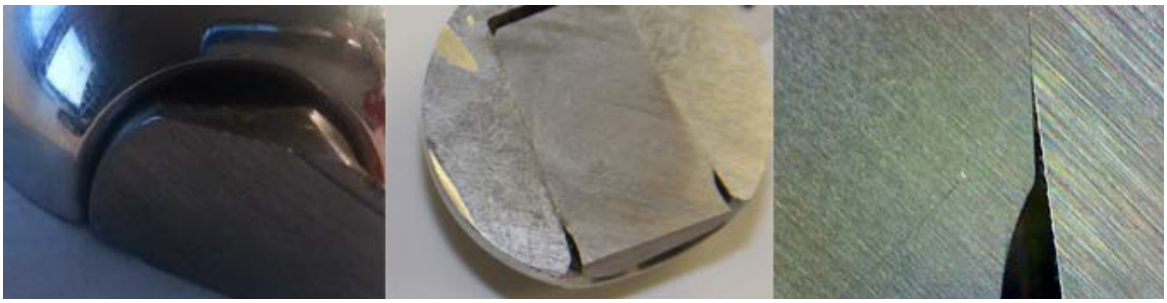

Figure 6. a) Notch extending deep into the femoral head; b) and c) Crevice at the trunnion-head interface.

Identifying Failure Mechanisms for Biologically Driven Surface Modifications

Carolyn Harris, Ph.D.; Department of Chemical Engineering and Materials Science, Wayne State University, Detroit, MI

One area of focus in the Harris lab at Wayne State University is the development and improvement of shunt systems used to treat hydrocephalus. The shunt system (Figure 1, (1)) reduces intracranial pressure by creating an artificial pathway to drain excess cerebrospinal fluid from the brain's ventricles. However, the shunt system is not physiologic in the way it drains, can disconnect, become infected, and repetitively blocks with infiltrating tissue as a result of the foreign body reaction. How these responses occur and what we can do to reduce the incidence of shunt blockage are keys to improving patient care.

The cells and tissues which block shunt systems are widely misunderstood, likely because the cell types can range anywhere from meningeal cells pulled into the shunt system during insertion, to whole tissue choroid plexus, to inflammatory cells. The activity of the cell, likely dictating what the cell is doing and how it interacts with the shunt material and the other cells, can also vary across patient subpopulations and is an area of further exploration in the lab. As has been observed by Harris and others, the degree of inflammatory response is inconsistent across patient cohorts and varies over time. Finding identifiable correlations across these datasets is key to understanding blockage mechanisms. Astrocytes and microglia are leading contributors in the response to the shunt; they bind directly to the protein-adsorbed catheter surface and create an interface in which other cells can bind.

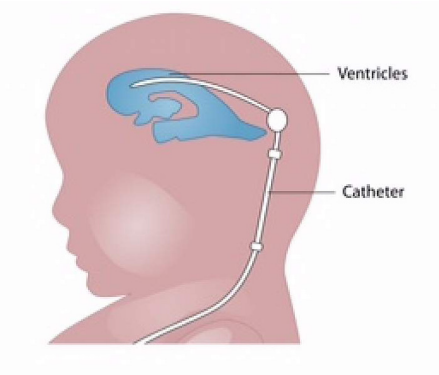

Figure 1. Abnormal excess CSF accumulation in the brain's ventricles can elevate intracranial pressure and cause neurologic decline if not treated. The shunt system commonly drains this excess fluid to the peritoneal cavity. Credit: National Institutes of Health

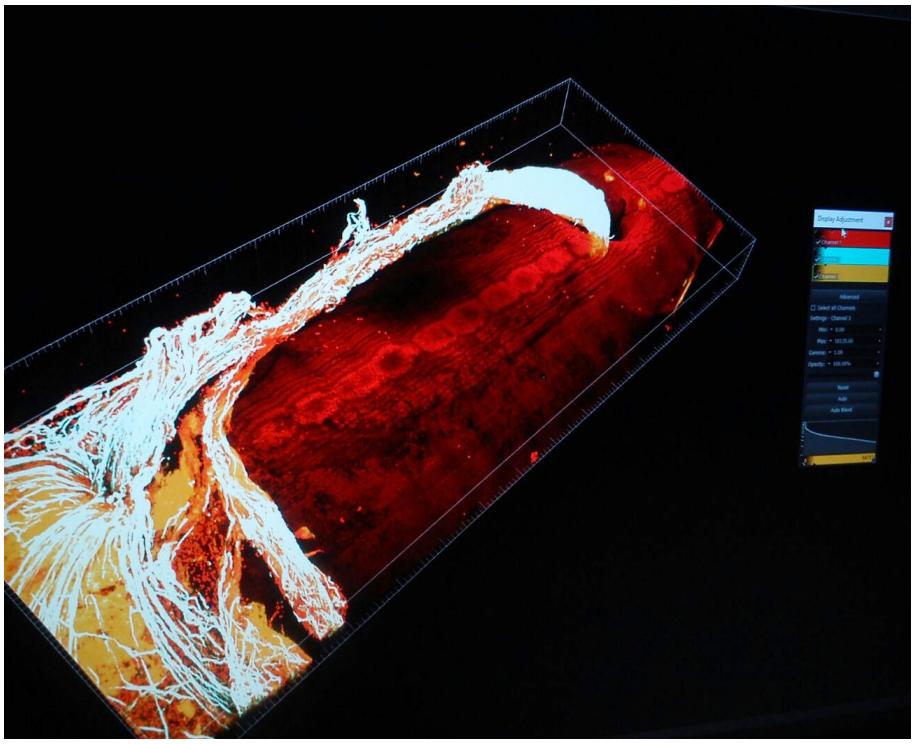

Figure 2. Infiltration of the ventricular catheter of the shunt system used to treat hydrocephalus (Glial Fibrillary Acidic Protein in Cyan; Microglia/Macrophage lineage in yellow; shunt background represented in red). When we know the mechanisms that drive cell attachment and activity on the shunt, we will be able to define strategies for biology-driven engineering improvements.

Microglia appear to dominate the response to shunt systems that have been removed early, with astrocytes dominating the more chronic response.(2) This is similar to the response to other chronically implanted neural implants,(3) but the microenvironment around the shunt certainly plays a role in cell attachment and activity: cells attach to different surface chemistries when exposed to static or dynamic cultures.(4)

To understand the mechanisms of the astrocyte and microglial response to shunt systems, we look to new-age techniques, including imaging and quantification of failed shunt systems from patients (Figure 2). This end-point analysis is paired with analysis over time, performed in vivo and in vitro. While in vivo modeling gives systemic response and clinically-relevant variables, multi- or single-cell in vitro systems can begin to help us decipher what the cell is doing at any given time point. Cell cytoskeleton organization, elasticity, cell shape, and adhesion strength are all areas of exploration in the lab when in the presence of the shunt system and microenvironment of the cerebral ventricles. Recently, Harris and colleagues recorded shunt system blockage with astrocytes in an alginate 3D scaffold in as short as eight weeks

Identifying Failure Mechanisms ... continues on pg. 8

Integrated Approach to Materials-Assisted Bone Regeneration

Sujit Kootala, Ph.D, University of Pau & Pays de l'Adour, France & Uppsala University, Sweden

Introduction

It is estimated that approximately 9 million women across the world suffer from osteoporosis (fractures caused due to extreme loss of bone density) after menopause. This roughly translates to one fracture every three seconds world-over, resulting in trauma, compromised lifestyle and risk of secondary fractures. Hip and limb fractures alone account for more than half of fracture incidences worldwide. This imposes an equally huge social-economic burden on healthcare systems, both in developed and developing economies. Traditional standard treatments include surgical implants, protective casts and/or the administration of pro-bone formation drugs to counter the deterioration in bone density and promote new bone formation. A traditional line of treatment that has proved to be useful in medicine is the administration of a class of drugs called bisphosphonates (BPs). Due to their inherent capacity to mute the activity of bone resorbing osteoclasts, several generations of bisphophonates are still in clinical use today. However, reduced solubility, nonspecific interactions with healthy cells and hazards associated with long-term use of these drugs have resulted in the urgent need for better therapeutic replacements.

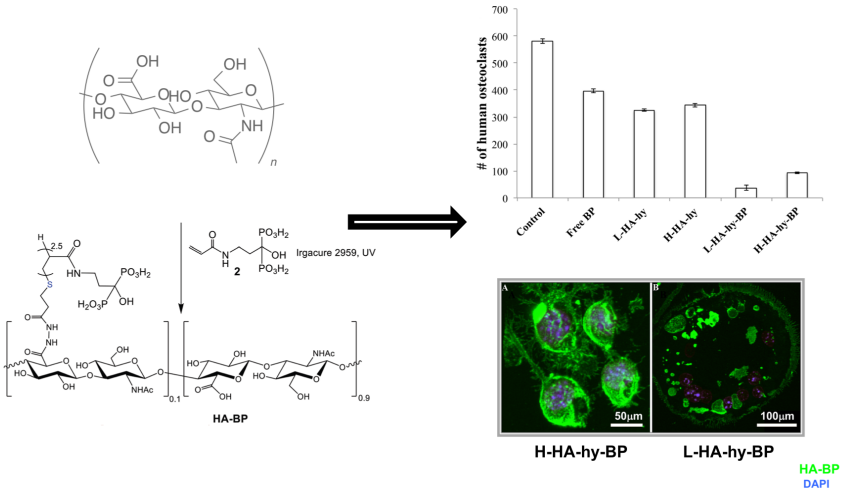

Figure 1. Grafting BP to low-molecular-weight hyaluronic acid (HA) enhances selevtive delivery of BP to osteoclasts.

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Identifying Failure Mechanisms ... continued from pg. 7

in culture.(5) These data indicated that cell migration may occur around the shunt inlet holes, binding on the rougher inlet hole walls, extending and retracting in a progressive cyclic fashion, ultimately leading to shunt blockage.(5)

Significant modifications have been made to the pressure- and flow-regulation of the shunt system. Still, shunt obstruction persists. Since the inception of the shunt in 1955, less than 40 substantial modifications have been implemented to inhibit blockage, but none have yet yielded dramatic improvements in treatment. (6) Manipulations to other devices, specifically other neuroprosthetics, tell us that initial cell attachment is dictated by the surface characteristics and the adsorbed protein layer. Polyethylene glycol, polytetrafluoroethylene, and poly(2-hydroxyethyl methacrylate) are among some that have been recently tried. Still, surface changes have not yet been able to modify long term failure rates,(7) perhaps because passive surface treatments may discourage acute cell attachment, but may not have the desired impact of deterring pro-inflammatory cytokine release from attached cells.(8) It will likely be an approach of surface treatments: passive coatings and active releasing agents targeting specific attachment mechanisms, combined with changes to the shunt catheter's architecture that will ultimately improve shunt failure rate.

This project is funded, in part, by the NIH 1R01NS094570-01A1.

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The efficacy of delivering poorly soluble drugs at significantly lower effective doses can be achieved by hybridizing drugs with bioactive polymers such as hyaluronan, collagen, mucins etc. derived from the extracellular matrix (ECM). Although the stimulation of new bone through the action of osteoblasts is definitely a key requirement for fracture healing, the reduction of hyperactive osteoclast numbers is equally important for healthy bone turnover. In fact, both these goals can be simultaneously achieved using a single bioactive delivery vehicle, thereby increasing availability of active bone forming growth factors like Bone Morphogenetic Protein (BMP-2) on the one hand as well as delivery of osteoclast inhibitory drugs like bisphosphonates on the other. In our approach we chose to use hyaluronic acid as a model delivery vehicle. Hyaluronic acid (HA) is found as a viscous jelly in the body's synovial spaces and functions as a natural lubricant dampening the effects of external shock. It is a natural polymer produced by cells in the body to fill the space in the ECM and function as a cell scaffold and anchor.

Formulation

In the first study[1], we developed a new approach in which chemically functionalized hyaluronic acid chains with hydrazides were linked to BP's to reduce the vigor of osteoclast activity. Comparisons were carried out between unbound BP's, low molecular weight (8 kDa) HA, HA-hydrazide, HA-hydrazide-BP and high molecular weight (150 kDa) HA, HA-hydrazide and HA-hydrazide-BP. It was found that viability or function of mouse osteoblast was not affected in any negative way by free or bound BP. The most potent molecule in the test group was found to be the low molecular weight HA-hy-BP, in which the number of both rat and human osteoclasts were found to be reduced by almost 90 percent. Following the track of these prodrug molecules in osteoclasts, it was found that the high molecular weight HA--hy-BP variant were localized on the cell surface and the low molecular weight HA-hydrazide-BP variant crossed the cell membrane and localized in the endosomal compartment, indicating successful intra-cellular transfer of the prodrug. This method facilitates an otherwise poorly soluble drug to be recognized by CD44 cell surface receptors which display affinity towards HA and assist in receptor mediated endocytosis rather than diffusion mediated processes, thereby allowing lower doses of the drug to be more effectively used for therapy (figure 1).

In a concurrent second study[2], the affinity of BP's to divalent cations such as Ca2+ and growth factors such as BMP-2 was studied with the same delivery vehicle. This dual functionality in a single molecule (HA-BP) allows the integration of concepts such as reduced osteoclast fueled resorption and growth factor aided recruitment of bone cells for new bone formation within a single delivery strategy. In this study, HA was conjugated with BP using a thiol linker. The presence of BMP-2 showed a dose-dependent response with respect to alkaline phosphatase (a key osteoblast enzyme involved in mineralization). One of the problems related to the release of biomolecules and their activity is the lack of suitably precise tools to follow this process in situ.

To overcome this problem, the release of BMP-2 was done by radioactively labeling BMP with Iodine131 and following the release of labelled BMP-2 in vitro. In parallel, in another set of samples without radioactive labeling, the release medium was collected and supplied to C2C12 cells that produce ALP in response to BMP-2. The presence of active growth factor showed dose dependence and cells in this test group showed clear differences in cell attachment and survival when encapsulated into 3D hydrogels formed with these materials. Control gels without BP were not able to match this performance (figure 2).

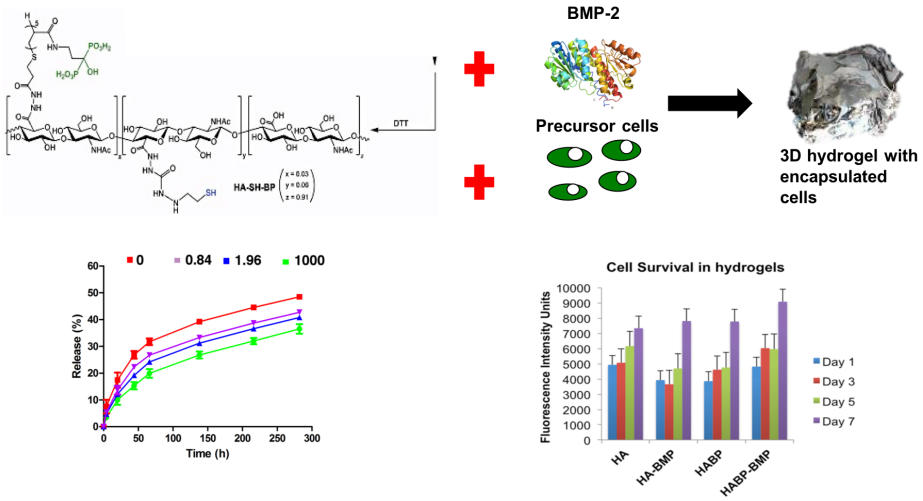

Figure 2. BP functionalized hyaluronan hydrogels can sequester, actively releas BMP-2 and sustain cells over time.

Summary

These two studies demonstrate the value of a dual therapy approach could prove far more effective for patients with osteoporosis. Such an approach could also prove useful in other pathologies where simultaneous interventions are necessary or where two drugs with different release rates or mechanisms need to be employed.

Integrated Approach ... continues on pg. 10

Integrated Approach to Materials-Assisted Bone Regeneration ... continued from pg. 9

References

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