Bioceramics: Materials and Applications IV

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It is my privilege and pleasure to edit this volume, containing the proceedings of the Bioceramics symposia of the 2003 Annual Meeting of The American Ceramic Society.

The focus of materials research as applied to medicine, and specifically the human body, is not a new phenomenon. The use of materials as prostheses to human organs dates back to the great river civilizations. Materials and especially ceramics have been chosen and used for their long-term stability and their inertness in the human body over centuries.

What sets apart our times from this tradition, in my opinion, is the change in focus from materials chosen for their inertness, to materials tailored to interact with the body, and its living components, in unique and tailored ways. It is entirely appropriate then, that this symposium honors a pioneer in this field: Larry Hench. Prof. Hench graciously condensed his Sosman Lecture into the keynote paper of this volume.

We planned this symposium to draw together research in the different aspects of bioceramics and illustrate its unifying themes. We hope that these proceedings reflect our intent. Apatites and active bone substitute materials are well represented, as always, with extended analyses of processing effects and variations in making these materials more functional. A series of studies on interactions between ceramics and biological environments with some much needed analysis of why ceramics succeed — or don’t — in vivo.

The pleasure of working with ceramics that could make a material difference in people’s lives is something that enlivens this field. I have often remembered an old conversation with an early mentor of mine, Prof. R. Vasudevan, who got me excited about how materials could be made to mimic humans. Give them memory, he said, and some self-healing capability and you’ve gone a long way to establishing anthropomorphic characteristics in an inert material. We’ve had memory in materials for decades now: shape memory alloys, not to mention silicon and its ferroic cousins, in a purist ceramic sense. Self-healing has been more the province of mechanically resilient materials: hydrothermal dental materials or stabilized zirconia. We live in interesting times, where materials could evolve and combine
these properties into the next stage of beneficial roles in medicine. I hope we'll have an opportunity to edit those proceedings as well!

Richard and I would like to recognize our fellow symposium organizers—Alexis Clare, Gary Fischman, Irene Peterson, Subrata Saha, and Warren Wolf, for their enthusiasm and welcomed help in organizing and conducting this symposium. We are most grateful to the staff of The American Ceramic Society, our sponsoring Divisions (Engineering Ceramic, NICE, Glass & Optical Materials), the Sosman Lecture organizers, student pages, and volunteer session chairs for the hard work that make these meetings possible.

Our colleagues at Dentsply Ceramco, 3M ESPE and CRMA have generously lent us their expertise and guidance. In closing, to our families—for their support and understanding while we juggled these proceedings with our other commitments—our love and thanks.

Veeraraghavan (V) Sundar
for and with Richard P. Rusin and Claire A. Rutiser
Sosman Lecture
THE ROLE OF CERAMICS IN AN AGE OF BIOLOGY

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ABSTRACT

Meeting the healthcare needs of an ageing population is one of the great challenges of this century. This lecture explores the use of ceramics to stimulate the regeneration and repair of human tissues at a genetic level. Approximately 3.5 billion years ago life emerged on earth. This transformation from disorder to order has been passed on by countless generations of descendants in the form of genes, microscopic bundles of DNA. The cells of many present day life forms, including humans, contain as many as 60,000 genes that direct the growth, maintenance and replication of our cells. The genes encode proteins that control all phases of the bone cell cycle; including growth, replication of DNA, repair of DNA, cell division (mitosis), programmed cell death (apoptosis) and differentiation of the cells to form bone matrix and control bone mineralization. Special compositions of silicate based glasses act as gene-activating ceramics. Analysis of the reaction kinetics of the bioactive glass surfaces reveals that it is release of soluble silica and calcia ions in very specific concentrations that activates the genes. Gene activation occurs only when the temporal sequence of the cell cycle is matched by the temporal sequences of the glass surface reactions. When the two are synchronised the bone cells quickly form new bone, even when the cells are obtained from old humans. The implications of this discovery extend from understanding the origin of species that contain mineralised bones to the loss of bone mass in space travel. It also establishes a scientific foundation for designing a personalised, genetic basis for repair and regeneration of tissues in patients and offers hope for eventual inhibition of the deterioration of bones and joints as we age.
It also provides direction for molecular design of ceramics for tissue engineering scaffolds and living cell bio-optical sensor systems for monitoring chemical and biological warfare agents and testing the toxicity of industrial materials and wastes. New types of bioceramics provide an innovative approach to controlling human biology and maintaining a high quality of life for ageing people. First generation biomaterials were developed to be as bioinert as possible to minimise rejection by host tissues. Second-generation biomaterials were designed to be either resorbable or bioactive, achieving positive interactions with the body. The next generation of biomaterials is combining these two properties, with the aim of developing materials that, once implanted, will help the body heal itself. The function of first and second generation biomaterials is to replace diseased or damaged parts of the body. Third generation biomaterials are designed to regenerate tissues.
The understanding of the human genome and the manipulation of DNA also make it possible to influence the nature of a child that is born. The age of biology gives rise to many moral and ethical questions and dilemmas. Many of these ethical uncertainties are addressed in my recent book, "Science, Faith & Ethics"\(^1\). Among the most important of these questions that now face every reader is the ultimate balance between our length of life and our quality of life.

Figure 1. Growth of ceramics field to incorporate physics, chemistry and biology.

During the last 100 years the average age of the population in the developed world has increased by 30 years. This trend will continue. The problem that faces us is that the percentage of the population that generate the resources to maintain life...
are now less than the percentage of the population which depends on others for their quality of life. The number of individuals from infancy until twenty years of age combined with the number of individuals from the age of 65 to 100 is greater than the number of productive individuals from 20 to 65 years of age. Thus the resources to maintain quality of life for all individuals are shrinking. This important shift in the average age and distribution of age has occurred simultaneously with the ability of the medical community to maintain life for long periods of time using life support systems. Living a long life is good. However, living a long life with deteriorating quality of life is bad. It is now well established that the quality of tissues, including skeletal tissues, cardiovascular tissues and nervous tissues, all deteriorate with age. As described in references 1-4 it is well known that by the time people reach the age of 60 years or more that the quality of their tissues has degraded by 20% to 50% compared to their tissues when they were 20 to 30 years of age. The medical community supported by the biomaterials community, including bioceramics, have responded to this need.

During the last 50 years more than 40 different parts of the body have become routinely replaced by prostheses and implants. It is now commonplace to replace tissues with spare parts: more than 3 million people receive implants each year. The use of man made implants to replace living parts of the body was an excellent solution for millions of people. However, people are now outliving their implants. Survivability of replacement parts are typically in the range of 10 to 15 years, whereas the life expectancy of the individuals receiving the implants is increasing from 10, to 20, to 30 years. The consequences of patients outliving their implants is a growing incidence of revision surgery which drains the resources of hospitals, medical staff, private or national insurances and greatly deteriorates the quality of life of the patients. The use of transplants, parts from other patients or animals, does not provide a viable alternative for the problem of survivability of implants. The incidence of viral infections and/or prions combined with the deterioration of transplants over a period of time and the requirement for a lifetime use of immuno-suppressant drugs combined with the difficulty and ethical problems of obtaining sufficient donors limits the use of transplants. Another solution is required. Without another alternative we will, as a society, be faced with a growing in-balance between our infinite desires for a long, healthy, high quality of life versus the finite resources to achieve those aims.

EXPANDING ROLE OF CERAMICS IN HEALTHCARE

Numerous reviews and books have documented that ceramics have played an important part in the maintenance of high quality of life. Medical grade alumina and zirconia are excellent examples. Bioactive glasses heralded the development of a new generation of biomaterials, as did resorbable calcium phosphate ceramics. Recent results, which will follow, show that a third generation of biomaterials, materials that serve to activate the genes of the tissues in contact with the materials, are now feasible. In the remaining sections of this
presentation we will review the first, second and third generation of bioceramics and discuss the potential use of ceramics to control biology.

**First Generation Biomaterials:** The goal of all early biomaterials was to "achieve a suitable combination of physical properties to match those of the replaced tissue with a minimal toxic response in the host". These materials resulted in a revolution in healthcare; i.e., the reliable replacement of diseased or damaged parts of the body. In 1980 there were more than 50 implanted devices (prostheses) in clinical use made from 40 different materials, approximately 3 million prosthetic parts were implanted in patients in the United States and Europe annually. A common feature of most of the materials was their "bioinertness." Tens of millions of individuals have had their quality of life enhanced for 5 to 25 years by use of implants made from first generation, bioinert biomaterials.

**Second-Generation Biomaterials:** During the 1970s the field of biomaterials began to produce bioactive components that could elicit a controlled action and reaction with tissues. Bioactive glasses (composed of Na$_2$O-CaO-P$_2$O$_5$-SiO$_2$) were developed to bond to living tissue. Interfacial bonding involved a sequence of 11 reaction steps. The first five steps occurred on the surface of the material due to rapid ion exchange of Na$^+$ with H$^+$ and H$_3$O$^+$ followed by a polycondensation reaction of surface silanols to create a high-surface area silica gel. These surface reactions provided a large number of sites for heterogeneous nucleation and crystallisation of a biologically reactive hydroxy-carbonate apatite (HCA) layer equivalent to the inorganic mineral phase of bone. The growing HCA layer on the surface of the material is synergistic with six cellular reaction steps that include colonization by osteoblasts, followed by proliferation and differentiation of the cells to form new bone that produces a mechanically strong bond to the implant surface.

By the mid-1980s bioactive materials reached clinical use in many orthopaedic and dental applications. Synthetic hydroxyapatite (HA) ceramics were used as porous implants, powders, and coatings on metallic prostheses to provide bioactive fixation. The HA coatings led to a tissue response (termed osteoconduction) in which bone grew along the coating and formed a mechanically strong interface. Bioactive glasses and glass-ceramics were used as middle-ear prostheses to restore the ossicular chain and treat conductive hearing loss. They were also used as dental implants to preserve the alveolar ridge from the bone resorption that follows tooth extraction. A strong and tough bioactive glass-ceramic, A-W glass-ceramic, was used for replacement of vertebrae in patients with spinal tumors. By the 1990s bioactive composites, composed of HA particles in a polyethylene matrix, became important in the repair and replacement of bones in the middle ear. Another advance achieved in second generation biomaterials was the development of resorbable biomaterials that exhibited controlled chemical breakdown and resorption when implanted in the body.
implant material is ultimately replaced by regenerating tissues, and ultimately there is no discernible difference between the implant site and the host tissue\(^2\). An example of this is the biodegradable suture, in which the polymer composed of polylactic (PLA) and polyglycolic (PGA) acids hydrolytically decomposes into CO\(_2\) and H\(_2\)O. By 1984 clinical use of resorbable polymers as sutures was routine\(^3\). Resorbable fracture fixation plates and screws in orthopaedics and controlled-release drug-delivery systems were in their infancy\(^10\). An important characteristic of this second generation of biomaterials is their design especially for medical applications, in contrast to first generation biomaterials which were selected from "off the shelf" compositions\(^2-5\).

**THE CLINICAL CHALLENGE FOR THE FUTURE**

The clinical success of first and second generation biomaterials has been excellent. However, survival analyses of skeletal prostheses\(^6-11\) and artificial heart valves\(^12\) show that a third to half of prostheses fail within 10 to 20 years. Years of research have had only small effects on failure rates\(^6\). Improvements of first- and second-generation biomaterials are limited in part because all man-made biomaterials used for repair or restoration of the body represent a compromise\(^1\). Living tissues can respond to changing physiological loads and biochemical stimuli, but synthetic materials cannot. This limits the lifetime of artificial body parts. Continuing this path of trial-and-error experiments that require the use of many animals and human clinical trials is prohibitively expensive. We have reached a limit to our current medical paradigm that emphasises replacement of tissues. It is time to emphasize a more biologically based method for the repair and regeneration of tissues. The biological response of cells to bioactive ceramics provides an insight towards creating a third generation of biomaterials\(^8\).

**Third Generation Biomaterials:** Third-generation biomaterials are being designed to stimulate specific cellular responses at the molecular level\(^8\). The separate concepts of bioactive materials and resorbable materials have converged. Bioactive materials are now made resorbable. Resorbable polymers are being made bioactive. Molecular modifications of resorbable polymers and bioactive composite systems elicit specific interactions with cell integrins. Consequently third generation biomaterials can enhance cell proliferation, differentiation, and extracellular matrix production and organization. Recent findings show that third generation bioactive glasses and macroporous foams can be used to activate genes that stimulate regeneration of living tissues. Two alternative routes of repair are now available with the use of these third generation molecularly tailored biomaterials.

**Tissue engineering:** The engineering of tissues starts with the seeding of progenitor cells onto biologically active resorbable scaffolds. The cells grow outside the body and become differentiated and mimic naturally occurring tissues. These tissue-engineered constructs are then implanted into the patients to replace
diseased or damaged tissues. With time the scaffolds are resorbed and replaced by host tissues that include a viable blood supply and nerves. The living tissue-engineered constructs adapt to the physiological environment and should provide long-lasting repair.

**In situ tissue regeneration:** The concept of tissue regeneration involves the use of biomaterials in the form of powders, solutions, or doped microparticles to stimulate local, *in situ*, tissue repair. Bioactive materials release chemicals in the form of ionic dissolution products, or growth factors such as bone morphogenic protein (BMP), at controlled rates, by diffusion or network breakdown, that activate the cells in contact with the stimuli. The cells produce additional growth factors that in turn stimulate multiple generations of growing cells to self-assemble into the tissues *in situ* along the biochemical and biomechanical gradients that are present. For example, when a particulate of bioactive glass is used to fill a bone defect there is rapid regeneration of bone that matches the architecture and mechanical properties of bone at the site of repair. Both *osteogenesis* and *osteoproduction* occur as a consequence of rapid reactions on a bioactive glass surface. The surface reactions release critical concentrations of soluble Si, Ca, P, and Na ions that give rise to both intracellular and extracellular responses at the interface of the glass with its cellular environment.

**CELL CYCLE CONTROL AND GENE ACTIVATION**

Rapid repair of bone requires differentiation as well as proliferation of osteoblasts. A synchronised sequence of genes must be activated in the osteoblasts so that they undergo cell division called mitosis. The bone cells then synthesize an extracellular matrix that is capable of mineralizing to become bone. We now know that there is genetic control of the cellular response of osteoblasts to bioactive glasses. Seven families of genes are up regulated within 48 hours of the exposure of primary human osteoblasts to the ionic dissolution products of bioactive glasses. The activated genes express numerous proteins that influence all aspects of differentiation and proliferation of osteoblasts:

- Transcription factors and cell-cycle regulators;
- Signal transduction molecules;
- Proteins involved in DNA synthesis, repair, and recombination;
- Growth factors and cytokines that influence the inflammatory response to the material;
- Cell-surface antigens and receptors;
- Extracellular-matrix components
- Apoptosis regulators.

Use of the dissolution products of resorbable bioactive gel-glasses to stimulate cellular repair at a molecular level offers promise for creating scaffolds for bone tissue engineering as well as *in situ* regeneration of tissues. Under appropriate