Progress Report for NIH Grant 5R21AR054339-02

A. Summary of Progress

The objective of this grant work was to use shape memory polymers to develop minimally invasive soft-tissue orthopedic fixation devices with enhanced short- and long-term fixation strength and reliability. To be a successful orthopedic implant material, the polymer must exhibit good mechanical properties and elicit an appropriate biological response. These two characteristics served as the primary focus for studies carried out under this funding project.

Shape memory acrylate-based networks were synthesized with various combinations of monomers and crosslinkers to control crosslinking density, modulus, and glass transition temperature (Tg) and tested under different environmental conditions relevant to *in vivo* conditions. Toughness was chosen as the primary focus of the mechanical testing as this property has been associated with improved material durability, but there had been little previous studies examining ways to toughen biomedical polymers, particularly shape memory polymers. During the first year of this funding project, After characterizing the effect of testing temperature and chemical structure on network toughness was characterized and the results discussed in the first annual progress report. In the final year, the effect of phosphate buffered saline (PBS), a fluid used to simulate physiological conditions, on network toughness was investigated in relation to how water absorption affects the material properties of copolymer networks. Stress-strain behavior and toughness were determined by performing tensile strain to failure tests at temperatures spanning the glassy and rubbery regimes of each system in both air and in phosphate buffered saline (PBS). Other thermo-mechanical properties were assessed through dynamic mechanical analysis (DMA), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) while chemical characterization was performed using fourier transform infrared spectroscopy (FTIR). The ultimate outcome of this objective was identifying compositions that would exhibit the appropriate mechanical behavior to ensure improved implant viability under the harsh loading conditions inherent to most orthopedic applications.

Concurrently, the biological response of acrylate-based shape memory polymer networks was evaluated using an *in vitro* cell culture model developed by Dr. Barbara Boyan, co-PI. MG63 pre-osteoblast cells were plated on acrylate copolymer surfaces having different chemistries and elastic moduli. Cell number and the production of several osteogenic markers were measured to assess the level of differentiation on each surface. The fundamental objective was to understand how the osteogenic response is affected by polymer chemistry and stiffness in an attempt to design SMP networks that can promote an optimal osteogenic response towards promoting bone formation over bone resorption. Limiting bone resorption is critical in ensuring the success of many orthopedic implants as the implant usually serves to provide fixation or stability to the physiological site with the material acting in direct contact with bone tissue.

B. Results

Initial work focusing on optimizing the mechanical properties revealed that network toughness is dependent upon the monomer chemistry and network structure (i.e. crosslinking density), where networks that contained phenyl rings in their pendant group and had around 10 wt% crosslinker achieved the highest toughness. In addition, the addition of two structurally-similar monofunctional monomers in combination with 10wt% crosslinker were found to exhibit enhanced toughness, possibly due to increased intermolecular bonding. Follow-up work examined the effects of environmental conditions, specifically temperature and moisture, on the mechanical properties of acrylate-based networks. Results demonstrated that network toughness is highly dependent on temperature and that toughness reached a maxima at a temperature equal to or slightly less than the material's glass transition temperature (Tg). This finding was significant with regards to using these materials in biomedical applications by indicating that polymer toughness at room temperature might not transfer to the same level of toughness *in vivo*. The immersion of these networks in phosphate-buffered saline (PBS), a physiologically-simulated fluid, also altered the mechanical properties of the network by causing a shift in the toughness maxima to a lower temperature. This shift was attributed to a decrease in the network Tg due to water molecules penetrating the network and disrupting the intermolecular interactions, including hydrogen bonds and hydrophobic interactions. A ternary network composed of two monofunctional monomers and a crosslinker at specific concentrations was identified as exhibiting enhanced toughness at body temperature in PBS. The toughness of this network fell within the range of other commonly-used biomedical polymers including polyetherether ketone (PEEK). The toughness of this copolymer network as a function of immersion time (up to 9 months) was further evaluated to verify that toughness could be maintained for long term. The effect of immersion time on toughness was found to be dependent upon the viscoelastic state of the polymer in that networks initially acting in their viscoelastic state are affected the least by long term immersion.

Results examining the *in vitro* osteogenic response on acrylate-based copolymers revealed that MG63 cells respond in a differential manner on acrylate-based shape memory polymer surfaces depending upon the surface chemistry and stiffness of the polymer substrate. In particular, MG63 cells reached a more differentiated state on surfaces whose stiffness aligned closely with native immature bone matrix. Given that bone formation is regulated by the differentiation of immature cells to adult osteoblasts, these results signify that osseointegration of an implant material with surrounding could be controlled through modifications in material stiffness. The ternary copolymer deemed to have long term toughness was also evaluated in this *in vitro* cell model and found to elicit a comparable osteogenic response suggesting the cells are reaching a more differentiated state on the surface. The combination of mechanical and biological results indicate that certain shape memory acrylate-based copolymers have the potential to serve as implant materials in soft-tissue orthopedic fixation devices.

C. Publications

Below is a list of publications produced from this funding:

1. **Smith KE**, Trusty P, Wang B, Gall K. Long Term Toughness of Photopolymerizable (Meth)Acrylate Networks in Aqueous Environments. *Acta Biomaterialia*, 2010 (*available online; DOI# 10.1016/j.actbio.2010.09.001).*

2. **Smith KE**, Hyzy SL, Sunwoo M, Gall K, Schwartz Z, and Boyan BD. The dependence of MG63 osteoblast response to (meth)acrylate-based networks on chemical structure and stiffness. *Biomaterials*, 2010; 31(24): 6131-6141.

3. **Smith KE**, Parks SS, Hyjek MA, Downey SE, and Gall K. The effect of the glass transition temperature on the toughness of photopolymerizable (meth)acrylate networks under physiological conditions. *Polymer*, 2009; 50(9): 5112-5123.

4. **Smith KE**, Temenoff JS, Gall K. On the Toughness of Photopolymerizable Meth(arylate) Networks for Biomedical Applications. *Journal of Applied Polymer Science*, 2009; 114(5): 2711-2722.