Mechnikov, the Macrophage and the Man: James Anderson, Macrophages & Biomaterials and New Results on Macrophage Phenotypes

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Personal Statement: I first met Dr. James Anderson in the early 1970's at a meeting at the Seattle Battelle Conference Center. At that time we were both postdoctoral fellows (from different research) and both had Ph.D. degrees in polymer science. Jim informed me that he was going to medical school, a decision I found unexpected given that he was already publishing important work on the application of poly(amino acids) to medicine. Looking back now, it seems the combination of medical (pathology) training and materials science gave Jim the perspectives and technical skills to make huge contributions to biomaterials science, medical devices and medicine. His science/medicine publications coupled with his leadership in education, editorship, public service and service to the Society For Biomaterials allow me to state without reservation that Jim Anderson's contributions to the field of biomaterials have been nothing short of awesome! This abstract will particularly focus on the role of the macrophage in the body's reaction to biomaterials. Jim Anderson did not make the first observations on this subject. But he clearly educated our community to the central role of the macrophage in the foreign body reaction. I have personally been strongly influenced by Jim Anderson's insights into the macrophage, biocompatibility and many other subjects in biomaterials. I congratulate Jim Anderson for winning the Acta Biomaterialia gold medal – an award most deserved.

Background and Macrophage History: Ilya Mechnikov, in his 1908 Nobel Prize address, described his work with implanting splinters in starfish larvae stating "In small transparent larvae, it can easily be shown that the moving cells, reunited at the damage point do often close over foreign bodies." This may be the first observation of macrophages and the foreign body reaction. There were early papers that pointed out the presence of macrophages in the reaction of implanted foreign objects, for example, "The fate of retained intracerebral shotgun pellets.[1]" The first paper in *Journal of Biomedical Materials Research* to discuss the macrophage was published in 1969[2]. One of Jim Anderson's earliest papers to address the macrophage described the cage implant system[3]. In 1984, Anderson published his highly influential review article, "Biomaterial Biocompatibility and the Macrophage[4]." By the early 1990's, the cell biology behind the commonly observed heterogeneity in macrophage populations was better defined[5]. In 2002, Mantovani and colleagues had further clarified the extremes of macrophage polarization, defining M1 and M2 phenotypes[6]. Our group at the University of Washington has expanded on these ideas and shown that sphere-templated biomaterials (STB) where all pores are 40 microns in diameter and interconnected, upon implantation, exhibit macrophage-driven proangiogenic, anti-fibrotic healing[7-9]. The angiogenic response has been shown to be associated with M2 macrophages[9]. The University of Washington Ph.D. thesis of Eric Sussman (2012) illuminated a surprising aspect of the macrophage reaction to implanted STB and this is the primary subject of this presentation.

Methods Poly(2-hydroxyethyl methacrylate) (pHEMA) STB were implanted in mouse subcutaneous tissue for one week and rat epicardial tissue for four weeks. Macrophage phenotype was characterized using the M1/M2 polarity scale where M1 macrophages are designated pro-inflammatory and M2 are pro-healing. Explanted scaffolds were analyzed using immunohistochemistry for macrophages expressing nitric oxide synthase 2 (NOS2, M1 marker), IL1-R-1 (M1 marker), macrophage mannose receptor (MMR, M2 marker) and Class B scavenger receptors (SR-Bs, M2).

Results: Macrophages expressing both M1 and M2 markers were found at both mouse subcutaneous and rat epicardial implant sites. Unexpectedly, expression of the M2 marker was two-fold greater in macrophages in tissue surrounding implants, and expression of the M1 marker was higher within macrophages in the interior pore structure of the STB implants.

Conclusions: Our expectation was that macrophages within the STB pore structure would be driven to the M2 phenotype. The fact that macrophages immediately external to the scaffold were driven toward the M2 phenotype, while those with the pores were predominantly M1, illustrates that we have much to learn in order to control with precision the macrophage phenotype to effect non-fibrotic, pro-angiogenic healing. Though the cell biology behind such healing is still being explored, from an engineering perspective we can still achieve this desirable healing with STB.

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