

# 'Self' versus 'Foreign' and Soft versus Stiff - Engineering approaches to mechanisms in survival and differentiation

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Tissue cells must survive as well as specialize. We have been studying two broad aspects of both topics with a wide range of experiments and modeling. Our focus on 'survival' centers on the innate immune system, which efficiently terminates – more often than not – all manner of foreign cells and particles while sparing 'Self' cells. A reductionist based materials approach is taken to the decision of macrophages to destroy or not. We simulate, synthesize, and demonstrate in vivo as well as in vitro that a short peptide found in a protein on all cells can mark even plastic particles as 'Self' and prevent their phagocytic clearance. We exploit the peptide in anti-cancer applications and elucidate its folding and function. In a second set of studies, we have focused on the influence in differentiation and systematics of tissue rheology, recognizing that tissues can be very soft like fat and brain, or increasingly stiff like striated muscle and bone [Discher *Science* 2009]. Cells (that survive) feel and respond to the elasticity differences [Engler *Cell* 2006], and we now find the signaling propagates all the way into the lamina of the nucleus, which amplifies matrix cues. Proteomic profiling of tissue nuclei has revealed that Lamin expression increases more than 30-fold and in near-proportion to micro-elasticity of adult tissue. With adherent adult stem cells in vitro, matrix elasticity is shown to affect expression of nucleoskeleton proteins, with low levels of Lamins amplifying soft matrix toward a soft tissue lineage while high levels amplify stiff matrix to promote a rigid tissue lineage.

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2. D.E. Discher, D.M. Mooney, P. Zandstra. Growth factors, matrices, and forces combine and control stem cells. ***Science*** 324: 1673-1677 (2009).
3. Engler, S. Sen, H.L. Sweeney, and D.E. Discher. Matrix elasticity directs stem cell lineage specification. ***Cell*** 126: 677-689 (2006).

**Dennis E. Discher** is the Robert D. Bent chaired Professor at the University of Pennsylvania and an elected member of the US National Academy of Engineering – Bioengineering Section. He received a Ph.D. jointly from the University of California, Berkeley and San Francisco in 1993 for studies in cell and molecular biophysics, and was a US National Science Foundation International Fellow at the University of British Columbia until 1996. He has coauthored more than 150 publications with over 15,000 citations that range in topic from matrix effects on stem cells and biochemical physics of protein folding to self-assembling polymers applied to disease, with papers appearing in *Science*, *Cell*, and various *Nature* journals. Additional Honors and Service include a Presidential Early Career Award for Scientists and Engineers from the US National Science Foundation, the Friedrich Wilhelm Bessel Award from the Humboldt Foundation of Germany, and membership on the Editorial Board for *Science*.

