From Nano Shape & Self Recognition to Flexibility in Cancer Treatment and Stem Cell Differentiation

Dennis E. Discher, Ph.D.
Robert D. Bent Professor, NanoBioPolymers Lab, School of Eng'g & Applied Science
Physical Sciences in Oncology Center @ Penn (psoc.seas.upenn.edu)
University of Pennsylvania, Philadelphia, PA, USA

From viruses to tissue matrices, biology is filled with remarkable polymeric structures that motivate mimicry with goals of both clarifying and exploiting biological principles. Filamentous viruses inspired our development and computations of worm-like, flexible polymer micelles – 'filomicelles' – that reveal non-spherical nano-therapeutics can persist in the circulation and deliver even better than spheres [Geng *Nat Nanotech* 2007]. However, particles, implants, and cells of any type interact with the innate immune system, especially phagocytes that try to 'eat' everything. At the same time, 'Self' cells are spared due to a polypeptide found on all cells that marks cells (as well as engineered viruses and particles) as 'Self', limiting their phagocytic clearance *in vitro* and *in vivo* [Rodriguez *Science* 2013]. The phagocyte's cytoskeleton drives the decision downstream of adhesion. If an injected cell is recognized as 'Self' *and* if it has stem-like properties, then further interactions with the surrounding tissue can influence its differentiation. Matrix elasticity is one physical feature that directs stem cell fate [Engler *Cell* 2006; Swift *Science* 2013] and reflects the fact that tissues can be very soft like fat and brain, or increasingly stiff like striated muscle and rigid like bone. What unifies these mechanisms of immune or matrix recognition is a convergence of decision-making pathways on cytoskeletal force generation.

Y. Geng, P. Dalhaimer, S. Cai, R. Tsai, M. Tewari, T. Minko, and D.E. Discher. Shape effects of filaments versus spherical particles in flow and drug delivery. ***Nature Nanotechnology*** 2: 249-255 (2007).

P.L. Rodriguez, T. Harada, D.A. Christian, D.A. Pantano, R.K. Tsai, and D.E. Discher. Minimal 'Self' peptides that inhibit phagocytic clearance and enhance delivery of nanoparticles. ***Science*** 339: 971-975 (2013).

A. Engler, S. Sen, H.L. Sweeey, and D.E. Discher. Matrix elasticity directs stem cell lineage specification.
Cell 126: 677-689 (2006).

J. Swift, I.L. Ivanovska, … and D.E. Discher. Nuclear Lamin-A Scales with Tissue Stiffness and Enhances Matrix-directed Differentiation. ***Science*** 341: 1240104-1 to 15 (2013).