Electrostatic interactions of nanoparticles with cells for drug/gene delivery

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***Abstract*— Multilayered "programmable" (controlling a multi-step sequence of events) "nanodrug" (nanomedical) systems are being developed for diagnostic and therapeutic applications. These nanomedical systems (NMS) promise to revolutionize medicine by precise targeting and huge reductions in total initial dose with potentially 10-fold higher specific delivery to the targeted disease cells while sparing normal bystander cells. Simpler NMS are designed to eliminate by "nanosurgery" diseased single cells by either direct killing or inducing programmed cell death (apoptosis). Advanced NMS can partially "reprogram" diseased cells to alter the diseased cell's most harmful characteristics (e.g. proliferation rate, differentiation pathway, or ability to metastasize).**

NMS interactions with their target cells are driven by electrostatic interactions usually through their "zeta potentials" (ZP). Their ZP varies as atomic or molecular layers are added and is a strong function of local pH and ionic strength microenvironments which can vary considerably in different tissues and organs and especially in intracellular environments. The ZP may need to adapt to different microenvironments as the NMS travel throughout the body.

Targeted, as opposed to passive, NMS frequently use an opposing negative ZP to prevent non-specific sticking to cells which are almost always zeta potential negative. But this means that the targeting molecules (antibodies, peptides, aptamers, small molecule ligands (e.g. folate)) must overcome these electrical potential barriers to bind to their receptors and be delivered inside cells by receptor-mediated uptake.

Many NMS are "theranostic" meaning that they function as both therapeutic and diagnostic systems. Currently designed NMS in our laboratory consist of superparamagnetic iron oxide (SPIO) core nanoparticles (a magnetic resonance imaging (MRI) T2 contrast agent) and other layers of polymer materials containing near infrared fluorescence (NIRF) probes (e.g. Cy5.5) suitable for real-time, fluorescence-guided surgery. Such guided-surgery permits surgeons to "light up" the diseased cells and permit better discrimination between normal and diseased cells.