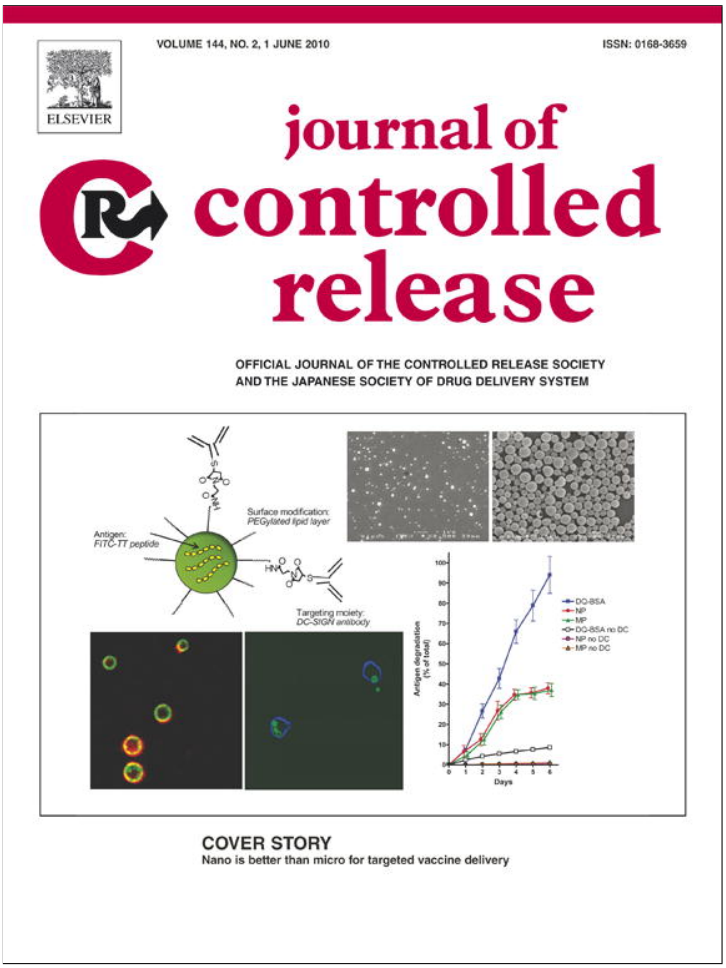

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Cover Story

Nano is better than micro for targeted vaccine delivery

Since the first experimental vaccination by Edward Jenner in 1796, immunization has become one of the most effective means of preventing diseases. While vaccine development in the beginning was largely based on trial and error, the current vaccine design relies on more rational approach. The rapid advancements in the field of immunology have had major implications for vaccine design, including those to combat tumors and infectious diseases that were so far difficult to treat.

One of the turning points in vaccine design is the identification of dendritic cells (DCs) as key antigen presenting cells instructing the immune system to which antigens immune responses should be directed. Naturally, many strategies were developed to specifically guide antigens to DCs. Initially, antigens were conjugated to ligands for receptors whose expression is relatively restricted to specific antigen presenting cell (APC) subsets. Alternatively, antigens were entrapped within nanoparticles (NPs) or microparticles (MPs), which are preferentially taken up by APCs. Over the last decade various studies have shown that antigenicity is markedly enhanced by specifically targeting antigens to surface receptors that are preferentially expressed by DCs [1]. However, these studies also showed that the delivery of antigen to DCs is not sufficient to induce antigen-specific cytotoxic T cell responses, which ultimately clear virus infected and tumor cells. Additional stimuli were required to activate DCs resulting in expression of co-stimulatory molecules and proinflammatory cytokines. This led to the hypothesis that vaccine efficacy might be enhanced by simultaneously targeting multiple vaccine components towards DCs. For this purpose, vaccine components might be entrapped within controlled release NPs or MPs carrying DC-specific antibodies on their surface.

NPs are known to display excellent tissue penetration, access the lymphatics, and freely drain to the lymph nodes, where they reach a large number of lymph node-resident DCs. In contrast, MPs remain at the injection site and require active transport by phagocytic cells to reach the lymph nodes [2]. This suggests that NPs are more favorable over MPs for targeted vaccination strategies, since they have greater access to their target cells. In this issue, the article by Carl Figdor and his group examined the interactions of targeted NP and MP vaccine carriers with human DCs [3]. Their vaccine carriers were composed of poly(lactide-co-glycolide) (PLGA), which has been used widely in clinical applications and is the most extensively studied polymer for encapsulating vaccine components [4]. The PLGA particles were surface-coated with a lipid-PEG layer to prevent nonspecific interactions with proteins and cells, and to introduce humanized DC-specific antibodies to the functionalized groups present on the PEG-moiety. The humanized targeting antibody carried a composite IgG2/IgG4 Fc domain to prevent interactions with Fc receptors. While the degradation kinetics of encapsulated antigen was strikingly similar for NPs and MPs following uptake by human DCs, there were marked differences in the mode of particle uptake. Despite the presence of lipid-PEG on the surface, MPs were taken up rather nonspecifically and uptake was hardly affected by the introduction of the DC-specific antibody. In contrast, NPs were only efficiently internalized by DCs when carrying the DC-specific antibody. This shows that specific, antibody-mediated delivery of particulate vaccines to DCs requires the use of nano-sized delivery systems.

NP vaccine carriers, such as the ones described in this issue by Carl Figdor, become a valuable tool for further development of targeted vaccination strategies. These NP carriers can be used to deliver not only antigens, but also a wide range of biomolecules, such as immunostimulatory molecules and siRNAs that suppress immune dampening pathways. This will allow extensive manipulation of the DC activation status *in vivo* to drive antigen-specific immune responses into the desired direction. This is indeed a big step toward achieving the goal of preventing/treating various diseases that are extremely difficult to treat. It will be interesting to see whether simultaneous delivery of DC-targeted antigens and tumor-targeted anticancer agents proves to be a viable mode of cancer treatment.

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