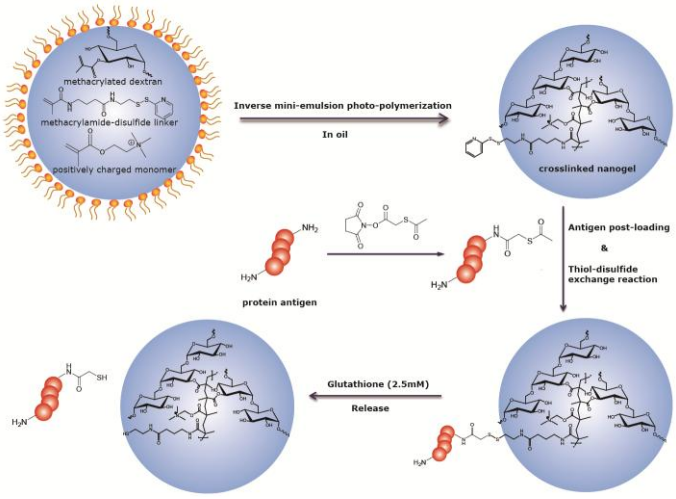
Reduction-Sensitive Dextran Nanogels aimed for Intracellular Delivery of Antigens

Dandan Li, Tina Vermonden, Wim E. Hennink, Cornelus F. van Nostrum
Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences, Utrecht University,Utrecht, The Netherlands

Contact : D.Li@uu.nl

An attractive approach to induce a strong immune response against a certain antigen is targeting it to dendritic cells (DCs). Targeting can be established by loading the antigen in a nano-sized carrier and keeping the antigen encapsulated or associated with the particles until they are internalized by DCs. [1-2]
We aim to develop a technology in which an antigen is reversibly immobilized in nanogels via disulfide bonds. These bonds are stable in the extracellular environment but are reduced in the cytosol of DCs due to the presence of glutathione.
Ovalbumin (OVA, a frequently used model antigen) is negatively charged at pH 7 because of its pI of 5.1. Therefore, cationic dextran nanogels also containing thiol-reactive groups were prepared and OVA, derivatized with succinimidyl S-acetylthioacetate groups, was almost quantitatively absorbed in these particles exploiting the electrostatic interactions between protein and carrier.[3] Subsequently, OVA was covalently immobilized in the gel particles by a reaction of the thiolated OVA with pyridyldithio groups present in the nanogels. [4]



In this study, we have developed nanogels in which OVA was immobilized via disulfide bonds. The protein was not released in extracellular space, however release inside the DCs occurred. These particles can boost the MHC class I antigen presentation in vitro. In line with those results, mice treated with OVA nanogels showed stronger anti-cancer effect than soluble OVA with TLR3 ligand (poly I:C).

References:

1. L. J. Thomann-Harwood, P. Kaeuper et al, Journal of Controlled Release 2013, 166, 95-105.
2. A. E. Gregory, R. Titball et al, Front Cell Infect Microbiol 2013, 3, 13.
3. J. P. Schillemans, E. Verheyen et al, Journal of Controlled Release 2011, 150, 266-271.
4. E. Verheyen, L. Delain-Bioton et al, Macromolecular Bioscience 2010, 10, 1517-1526.