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GUEST SPEAKER

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TOPIC

Polymeric Nanoparticles for the Intracellular Delivery of Biotherapeutics

ABSTRACT

Many biotherapeutics among which nucleic acid based drugs, pharmaceutical proteins and antigens, have to be delivered intracellularly to exert their biological effects. However, these therapeutics, because of their hydrophilic character and large size, do not spontaneously pass cellular membranes. An attractive approach to deliver these therapeutic in the target cell is to load them in nano-sized carriers.

As first example, we designed reduction-sensitive cationic dextran nanogels in which an antigen (ovalbumin, OVA) was reversibly immobilized to the hydrogel network via disulfide bonds. These bonds are stable in the extracellular environment but are cleaved in the cytosol of dendritic cells due to the presence of glutathione resulting in triggered released of the loaded antigen. These OVA-loaded nanogels indeed showed intracellular release of OVA up on internalization by DCs and subsequently boost the MHC class I antigen presentation leading to activation of T-cells. In a prophylactic model, 90% of the mice vaccinated with OVA conjugated nanogels + poly I:C) as adjuvant were protected against tumor formation for 55 days. In a therapeutic model, 40% of the mice eliminated their tumor cells, which was remarkable compared to other groups in which none of the mice showed tumor cell killing [1, 2].

In another approach, cationic polymers containing either azide or strained alkyne groups were synthesized as electrostatic glue which complexed charged single stranded RNA (PolyU) to form a self-crosslinked polyplex core. An azide-modified model antigen (ovalbumin, OVA) and a BCN-modified mannosylated or galactosylated polymer were sequentially conjugated to the RNA core via disulfide bonds using copper free click chemistry to form the shell of the polyplexes. The generated reducible virus mimicking particles (VMPs) with a diameter of 200 nm and negatively surface charge (−14 mV) were colloidally stable in physiological conditions. The mannosylated VMPs (VMP-Man) showed 5 times higher cellular uptake by bone marrow

derived DCs (BMDCs) compared to their galactosylated VMP (VMP-Gal) counterpart. Moreover, VMPMan efficiently activated DCs and greatly facilitated MHC I Ag presentation *in vitro*. Vaccination of mice with VMP-Man elicited strong OVA-specific CTL responses as well as humoral immune responses [3].

In another study, we reported on PEGylated NPs based on a hydroxylated PLGA polyester for the selective delivery of saporin, a cytotoxic protein, in the cytosol of HER2 positive cancer cells. This selective uptake was achieved by decorating the surface of the NPs with the 11A4 nanobody that is specific for the HER2 receptor. Confocal microscopy observations showed rapid and extensive uptake of the targeted NPs (11A4-NPs) by HER2 positive cells, but not by HER2 negative cells. Importantly, a dose dependent cytotoxic effect was only observed on HER2 positive cells when these were treated with saporin-loaded 11A4-NPs in combination with photochemical internalization (PCI), a technique that uses a photosensitizer and local light exposure to facilitate endosomal escape of entrapped nanocarriers and biomolecules. The combined use of saporin-loaded 11A4-NPs and PCI strongly inhibited cell proliferation and decreased cell viability through induction of apoptosis. These results suggest that the combination of the targeting nanobody on the NPs with PCI are effective means to achieve selective uptake and cytotoxicity of saporin loaded NPs [4].

In conclusion, polymeric nanoparticles are attractive carrier systems for the targeted intracellular delivery of biotherapeutics.

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BIO

Wim E. Hennink, obtained his Ph.D. degree in 1985 at the Twente University of Technology on a thesis with a biomaterials research topic. From 1985 until 1992 he had different positions in the industry. In 1992 he was appointed as professor at the Faculty of Pharmacy of the University of Utrecht. From 1996 on he is head of the Pharmaceutics division. At present he is the head of the Department of Pharmaceutical Sciences, Utrecht University. His main research interests are in the field of polymeric drug delivery systems. He published over 600 papers and book chapters and is the inventor of 20 patents.

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