News & Analysis

Highlighting the latest news research in therapeutic delivery

Nanoparticles may enable targeted drug delivery to the retina

Steroids attached to dendrimer nanoparticles have been shown to arrest retinal degeneration

A team of researchers from Wayne State University (Detroit, MI, USA), the Mayo Clinic (Rochester, MN, USA) and John Hopkins School of Medicine (Baltimore, MD, USA) have developed dendrimer–drug conjugate nanodevices that may be able to stop retinal degeneration and deliver drugs directly to the cells responsible for retinal neuroinflammation.

> *"The team found that the dendrimers … selectively localized within the activated outer retinal microglia in two different rat models of retinal degeneration, but not in the retina of healthy rats."*

The collaboration of scientists used hydroxyl-terminated polyamidoamine (PAMAM) dendrimers for targeted drug therapy of neuroinflammation in the retina. The team found that the dendrimers themselves selectively localized within the activated outer retinal microglia in two different rat models of retinal degeneration, but not in the retina of healthy rats. This selective biodistribution was then exploited for the targeted drug delivery of fluocinolone acetonide, a steroid that was covalently conjugated to the dendrimer particles. Their research, reported in *Biomaterials*, showed that the drug was released from the PAMAM dendrimers in a sustained manner, over 90 days. An intravitreal injection of 1 μg of the steroid attached to 7 μg of the PAMAM dendrimer nanoparticles was able to arrest retinal degeneration, preserve the number of photoreceptor outer nuclear cells and attenuate the activated microglia for over a month.

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Macular degeneration is caused by neuroinflammation, which leads to damage of the retina and results in a loss of vision in the centre of the visual field and possible blindness. According to the National Institutes of Health, it affects more than 7 million Americans. One of the lead authors of the study, Raymond Iezzi (Mayo Clinic, Rochester, MN, USA) acknowledged the impact this research could have, explaining that as there is no cure for macular degeneration and that an effective treatment could help millions of people worldwide.

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The nanodevices used in this research are a patent-pending technology, which the team think could have significant translational potential.

Written by Hannah Stanwix, Assistant Commissioning Editor. Sources: Iezzi R, Guru BR, Glybina IV, Mishra MK, Kennedy A, Kannan RM. Dendrimer-based targeted intravitreal therapy for sustained attenuation of neuroinflammation in retinal degeneration. *Biomaterials* 33(3), 979–88 (2012); Nanoparticles help researchers deliver steroids to retina; www.physorg.com/news/2011-12-nanoparticles-steroids-retina.html

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Indirect effects: barrier thickness and off-target effects of nanoparticle exposure

A recent *Nature Nanotechnology* study by scientists at the University of Bristol addresses some of the non-targeted effects of nanoparticle therapy, an important consideration given the increasing interest in nanomedicine as a therapeutic option. The study highlights the effect of biological barrier thickness on indirect DNA damage arising from nanoparticle therapy, which could prove useful in understanding and, thus, limiting off-target effects of 'targeted' nanoparticle exposure.

> "*The group have shown in their previous studies that nanoparticles can cause indirect DNA damage to cells through a cellular barrier.*"

The group have shown in their previous studies that nanoparticles can cause indirect DNA damage to cells through a cellular barrier. In their most recent study, they further their work and demonstrate that the extent of indirect DNA damage is dependent on the cellular barrier thickness, the indirect damage being mediated via gap junction proteins in the barrier, the proteins signalling through generation of mitochondrial free radicals.

> "*The researchers observed that signaling across barriers due to nanoparticle exposure only occurred across bilayer and multilayer barriers, not monolayers.*"

The researchers observed that signaling across barriers due to nanoparticle exposure only occurred across bilayer and multilayer barriers, not monolayers. Indirect toxicity across a barrier as a result of nanoparticle exposure was observed across both trophoblast and corneal cellular barriers as well as in *ex vivo* human placenta explants and in an *in vivo* mouse model

The scientists conclude their study postulating that if barrier thickness is an important factor in signalling for all barrier types, their study could offer an insight in to approaches towards limiting the adverse effects of nanoparticle exposure. Reducing the off-target effects of nanoparticle therapy would enhance the clinical applicability of this delivery method and open it up as an efficient, targeted delivery option for new therapeutic approaches.

> "*…if barrier thickness is an important factor in signalling for all barrier types, their study could offer an insight in to approaches towards limiting the adverse effects of nanoparticle exposure.*"

Written by Laura Harvey, Commissioning Editor. Source: Sood A, Salih S, Roh D *et al.* Signalling of DNA damage and cytokines across cell barriers exposed to nanoparticles depends on barrier thickness. *Nat. Nanotechnol.* 6(12), 824–833. doi:10.1038/nnano.2011.188 (2011) (Epub).

Novel approach to target liver cancer cells using glycoconjugated poly(amidoamine) dendrimers

A collaboration between researchers in the USA and China has identified a new approach to targeting liver cancer cells, which utilizes synthesized glycoconjugated poly(amidoamine) dendrimers.

Dendrimers are a class of polymeric materials that are employed as cardiac markers, gene transfection agents, diagnostic tools, solubilizing agents and drug-delivery vehicles.

The researchers synthesized the glycoconjugated poly(amidoamine) dendrimers by conjugating the fluorophore fluorescein isothiocyanate and lactobionic acid using a platform of dendrimers. Once synthesized, confocal microscopy and flow cytometry analysis confirmed the *in vitro* targeting capabilities of the glycoconjugated dendrimers. NMR spectroscopy was also employed to characterize the compounds.

This research presents a novel method for designing compounds to target liver cancer cells and for liver cancer therapies. The glycoconjugated compounds described by Guo and colleagues could also see application as imaging agents for biomedical applications, such as targeted cancer therapy.

> "*The researchers synthesized the glycoconjugated poly(amidoamine) dendrimers by conjugating the fluorophore fluorescein isothiocyanate and lactobionic acid using a platform of dendrimers.*"

Written by Alexandra Hemsley, Assistant Commissioning Editor. Source: Guo R, Yao Y, Cheng C *et al.* Synthesis of glycoconjugated poly(amindoamine) dendrimers for targeting human liver cancer cells. *RSC Advances* 2, 99–102 (2011).

Researchers develop method to stabilize therapeutic proteins

Researchers Andrew Keefe and Shaoyi Jiang at the Department of Chemical Engineering, University of Washington, (Seattle, USA) have developed an approach for stabilizing therapeutic proteins. The new method ensures that drug proteins are not denatured within the body before reaching their target location, an effect that reduces efficacy.

> "*The new approach…employs conjugation with zwitterionic polymers… In this way, the proteins are stabilized by being both positively and negatively charged…*"

Therapeutic proteins are often unstable in physiological conditions and therefore require the use of a stabilizing agent, such as PEG (poly(ethylene glycol)), to ensure they remain efficacious. Current methods of protein therapy require administration of higher drug dosages as the protein is denatured prior to reaching the target location.

The process of associating the therapeutic protein with Poly(ethylene glycol) (PEG) therefore impacts on bioactivity. At present, there is a compromise between protein stability and affinity as a result of the reduction in bioactivity, which generally results from the use of PEG.

The new approach developed by Keefe and colleagues employs conjugation with zwitterionic polymers, such as poly(carboxybetaine) (PCB). In this way, the proteins are stabilized by being both positively and negatively charged, yet the bioactivity of the protein of interest is not affected and target binding remains optimal. "As with PEG, the presence of PCB provides protection through steric hindrance," explained Andrew Keefe.

"This protein conjugate is worthy of further investigation. If it is shown to have demonstrable beneficial pharmacokinetic properties and no adverse effects it may well be of interest to the pharmaceutical industry," added Robert Falconer, of the University of Sheffield, UK.

> "*We think that using these types of conjugates might have advantages, and we are now looking to investigate their use with therapeutic proteins.*"

The research offers the potential for increased drug efficacy: lower doses and reduced cost per treatment. Looking ahead to future research efforts, Keefe said, "We think that using these types of conjugates might have advantages, and we are now looking to investigate their use with therapeutic proteins."

Written by Alexandra Hemsley, Assistant Commissioning Editor. Source: Keefe AJ, Jiang S. Poly(zwitterionic) protein conjugates offer increased stability without sacrificing binding affinity or bioactivity. *Nat. Chem.* doi:10.1038/nchem.1213 (2011) (Epub).

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