News

Research Highlights

New approach may improve nanoparticle assembly

New template integrating supramolecular nanochemistry and rational drug design shows promise for drug development.

Researchers from Brigham and Women's Hospital (MA, USA) used cisplatin as a model drug to illustrate the synthesis of platinum (II) tethered to a cholesterol backbone via a unique monocarboxylate and O → Pt coordination environment. The team found that the template facilitated nanoparticle assembly. The team evaluated the efficiency of these self-assembling cholesterol–succinic acid–cisplatinum II-based nanoparticles (SACNs) *in vitro* using Lewis lung carcinoma and 4T1 breast cancer cell lines. The SACNs had lower IC_{50} values compared with carboplatin or cisplatin *in vitro*. In the cisplatin-resistant hepatocellular carcinoma cell line, the SACNs were found to overcome the resistance with again a lower IC_{50} value than that of free cisplatin.

The team, led by Shiladitya Sengupta, senior author of the study, then went on to study the efficacy of the rationally designed nanoparticles in animal models of breast and ovarian cancer. The nanoparticles exhibited significantly enhanced antitumor activity *in vivo*, with decreased systematic and nephrotoxicity.

The researchers describe, in their article published ahead of print in *Proceedings of the National Academy of Sciences,* that the traditional processes used for nanoformulation are often incompatible with the physiochemical properties of chemotherapeutic drugs, which can ultimately limit their entrapment efficiency and release kinetics. Cisplatin, for instance, is the drug of choice as a first- or second-line chemotherapy for most cancers; however, its clinical efficacy is dose-limited because of nephrotoxicity. By using a rational design strategy of molecules that facilitates supramolecular assembly in the nanoscale dimension, the Brigham and Women's Hospital researchers hope to avoid these problems. Sengupta and colleagues conclude their study optimistically, stating that their results could indicate that nanostructures constructed by this method could translate into the next-generation platinum-based agent in the clinics.

– Written by Hannah Stanwix

Source: Sengupta P, Basu S, Soni S et al. *Cholesterol-tethered platinum II-based supramolecular nanoparticle increases antitumor efficacy and reduces nephrotoxicity.* Proc. Natl Acad. Sci. USA *109, 11294–11299 (2012).*

Nanolipogels could offer two-pronged attack against tumors

A novel immunotherapy system has been described that simultaneously prevents resistance of, and activates, an immune response against tumorous cells.

In a recent *Nature Materials* paper, a group of scientists from Yale University (CT, USA) has described the development of nanoscale liposomal polymeric gels termed 'nanolipogels', which have shown efficacy in mice models for the immunotherapeutic treatment of metastatic melanoma.

Immunotherapy is described as the treatment of disease by inducing the body's immune response. In cancer

Future Medicine part of fsg

immunotherapy, tumor cells can often bypass this effort by producing agents that prevent this local immune response. One such example is TGF-β. In their paper, the group describes its efforts to overcome this phenomena. By delivering both IL-2, a cytokine often used as an immunotherapeutic agent, and a novel TGF-β inhibitor, the group hoped to both suppress the tumors' ability to resist the cytokine and stimulate the body's immune response to attack the tumor.

The team encapsulated the two molecules in nanoscale liposomal polymeric gels synthesized from cyclodextrins and biodegradable polymers. These nanolipogels were shown to deliver both agents over a prolonged period. The researchers investigated their efficacy in mice models, injecting the nanolipogels both intravenously and direct to the tumor site. After administration of this novel therapeutic system, a significant delay in tumor growth and an increased survival of the mice was shown. This response was attributed to an increased activity of natural killer cells and T-cell infiltration into the tumor site.

– Written by Alice O'Hare

Source: Park J, Wrzesinski SH, Stern E et al. *Combination delivery of TGF-β inhibitor and IL-2 by nanoscale liposomal polymeric gels enhances tumour immunotherapy.* Nat. Mater. *doi:10.1038/nmat3355 (2012) (Epub ahead of print).*

Nanozyme for antiviral therapy causes targeted RNA cleavage in mice

Nanoparticle-based enzyme system shows potential for hepatitis C treatment through RNA cleavage.

A group of scientists from Florida University (FL, USA) has recently published their results on a new antiviral therapy. Their research offers a novel method for the inhibition of HCV utilizing a 'nanozyme' – the nanoparticle-based enzyme system developed by the team.

RNA silencing is an integral process in the normal functioning of cells, carried out in part by the RNA-induced silencing complex (RISC). This process can be synthetically exploited in the treatment of HCV infection, since if a key HCV RNA sequence can be targeted and destroyed, such a therapeutic can effectively destroy HCV molecules while leaving the host's cells unharmed.

The research team have produced a synthetic system to mimic the RISC system – the nanozyme system. This nanoparticle contains both a ribonuclease enzyme (to destroy RNA within the virus) and an oligonucleotide to target this ribonuclease to the correct RNA sequence within the HPV cell.

The nanozyme was tested in both cultured human hepatoma cells and a mouse model infected with HPV. The researchers observed a greater than 99% decrease in HCV RNA levels in these mice models, indicating the potential of this system for HPV treatment. The team also hypothesize that by altering the targeted genetic sequence, this system could be used in the future to target any 'protein expression-related' disease – for example, other viral infections and cancers.

– Written by Alice O'Hare

Source: Wang Z, Liub H, Yang SH et al. *Nanoparticle-based artificial RNA silencing machinery for antiviral therapy.* Proc. Natl Acad. Sci. USA *doi:10.1073/pnas.1207766109 (2012) (Epub ahead of print).*

Radioactive nanoparticles show promise in prostate cancer treatment

A combination of gold nanoparticles and a compound found in tea leaves could lead to more efficient targeting of prostate tumors.

Researchers from the University of Missouri (MO, USA) have designed a new treatment for prostate tumors using radioactive gold nanoparticles (AuNPs) and epigallocatechin-gallate (EGCg), a compound found in tea leaves. The team, led by Professor Kattesh Katti (University of Missouri), synthesized biocompatible nanoparticles (NPs) utilizing the redox chemistry of EGCg, which converts gold salt into AuNPs. These radioactive NPs were derived from the ^{198}Au isotope. Katti explained to *Nanomedicine* the rationale behind the use of EGCg in the study: "EGCg, which is abundantly present in tea, is a strong antioxidant. We therefore hypothesized that this phytochemical will have capabilities in transforming gold salts into the corresponding AuNPs. EGCg has a high affinity toward laminin receptors that are overexpressed on prostate tumor

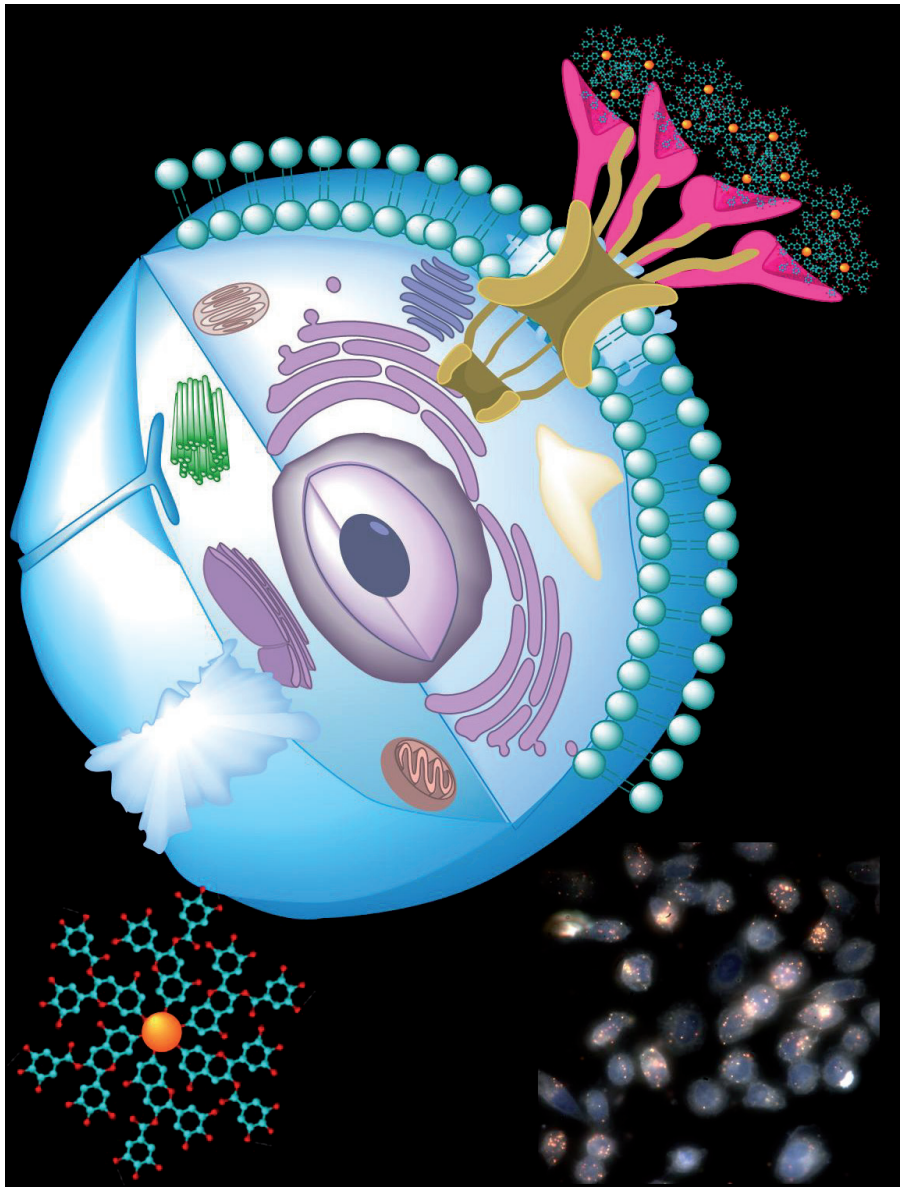
cells. This means that the AuNPs decorated with EGCg can selectively target prostate tumors for imaging and therapy applications." The use of radioactive NPs also had additional benefits for the system, as Katti noted, "Radioactive gold isotope is inherently therapeutic because its β-emission is ideal for the destruction of tumor cells and tumor tissue."

The current treatment for prostate cancer involves the injection of hundreds of radioactive 'seeds' into the prostate. However, the size of the seeds (~50–100 µm) hampers their ability to treat very aggressive forms of prostate cancer, as the tumor vasculature only allows sizes of 150–300 nm to penetrate. Katti and his team created NPs of specific size to treat the tumors. Pharmacokinetic studies in mice showed approximately 72% retention of the NPs in tumors, 24 h after intratumoral administration. A total of 28 days following administration of the NPs, the researchers saw an 80% reduction of tumor volumes. Katti commented on the significance of the findings to *Nanomedicine*; "Singular injections of EGCg-AuNPs in prostate tumor in mice has shown that the injected dose resided within the tumor and did not leak to other organs, while most other therapy agents are not retained to this high level of retention within the tumors. The unprecedented high retention of therapeutic dose of EGCg-AuNP within tumors has translated into excellent therapeutic efficacy."

Looking forward, prior to human studies the team will study their treatment in dogs with prostate cancer. As Katti explained to *Nanomedicine,* this trial will be key to the eventual clinical translation of the treatment: "Prostate tumors in dogs mimic human prostate tumors in terms of tumor morphology and genetic characteristics. Therefore, our future studies in dogs will allow us to collect important safety and efficacy data which will help in the clinical translation of our findings for use of EGCg-AuNP in treating human prostate cancer patients."

– Written by Hannah Stanwix

Source: Shukla R, Chanda N, Zambre A et al. *Laminin receptor specific therapeutic gold nanoparticles (^{198}AuNP-EGCg) show efficacy in treating prostate cancer.* Proc. Natl Acad. Sci. USA *109(31), 12426–12431 (2012).*



Laminin receptor expression in prostate tumor cells showing affinity and receptor specificity resulting in the endocytosis of gold nanoparticles (saffron balls conjugated with epigallocatechin gallate [EGCg-AuNP] shown in the lower left hand corner). The cartoon shows endocytosis of EGCg-AuNP within prostate tumor cells to reflect the actual dark field microscopic images (lower right hand corner), which provide experimental evidence on the highly efficient receptor-specific internalization of EGCg-AuNPs within prostate tumor cells**.** The specific prostate tumor cellular uptake of EGCg-AuNPs may lead to improved treatment outcomes for patients with prostate cancer.
AuNP: Gold nanoparticle; EGCg: Epigallocatechin-gallate.
Figure courtesy of Kattesh Katti (University of Missouri, MO, USA).