Nanoapplications – From geckos to human health

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Abstract

Nanotechnology, the manipulation of matter on a molecular scale, is all around us in our everyday lives. Chocolate, non-dairy creamer, and sunscreen are examples of consumer products with a high content of nanoparticles. Nanotechnology holds great potential for environmental applications like wastewater treatment and nanobionic engineering of plants. Due to their unique and adaptable properties for targeted therapeutic payload delivery, nanoparticles are also emerging as promising tools for innovative pharmaceutical treatment. Nevertheless, licensing regulations specifically for nanomaterials are lacking, and the long-term effects of nanoparticles on both the environment and human health need to be further clarified.

Keywords: Nanoparticles, Nanotechnology, Medicine, Gecko, Titanium dioxide

Why does the gecko not fall from the ceiling?

Geckos are able to scurry up walls and stick to ceilings, apparently unaware of the laws of gravity. Why does the gecko not fall from the ceiling? It is not glue, suction, or static electricity that prevents it from falling – it is specific nanostructures. Geckos possess approximately two million 'nanohairs' (setae) that grow from small pads on their toes, terminating as even smaller 'gripping hairs' (spatulas). These nanohairs greatly increase the area that comes into contact with a surface, leading to high van der Waals forces between the gecko and the ceiling (see Figure 1A and B).[1] Pushing down on the feet generates shear forces that bend the setae to further increase the contact area, enabling the gecko to stick to the ceiling. Relaxation of the feet allows the feet to be lifted off the ceiling surface.

Nanostructured surfaces that increase adhesion forces, such as those demonstrated with the gecko, have inspired the development of products including reusable dry glue.[1] This glue uses nanotube bundles as synthetic setae (see Figure 1C and D), and possesses adhesive capacities nearly four times higher than that of gecko feet. It even sticks to Teflon.

What is nanotechnology?

Nanotechnology is generally defined as the manipulation of matter on a molecular scale, typically in the range of nanometres (1 nm = 10^{-9} m). Nanomatter is typically smaller than a cell, but bigger than a small molecule (see Figure 2). The European Union (EU) defines nanomaterials as 'natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm–100 nm'.[2] Nanoparticles can be engineered in specific ways as spherical, cylindrical, rod-, or tube-like forms,[3] consisting of metallic,[4] polymeric,[5] or biological (DNA,[6] amino acids[7]) materials, or as a combination thereof.[8,9]

Several unique properties allow nanoparticles to be used successfully in various practical applications. Nanoparticles have a large surface-to-volume ratio in comparison to their original bulk material, enabling them to strongly interact with their surroundings. Chemical and biological degradation is much faster in nanoparticles than in their original bulk material due to the larger contact surface area. The degradation is, however, much slower in comparison to the smaller molecular structures in solution. Interestingly, for inorganic nanoparticles, the melting point is strongly dependent on the size of the particles.[10]

Nanoparticles can also increase the solubility of hydrophobic compounds[5,11] and be used as delivery vectors in the field of nanomedicine.[11] As they are in the size range of the wavelength of visible light, some nanoparticles exhibit different colours depending on their size.[12] In addition, nanoparticles that interact with light energy are utilised in cancer

DOI: 10.1179/2047480614Z.000000000233

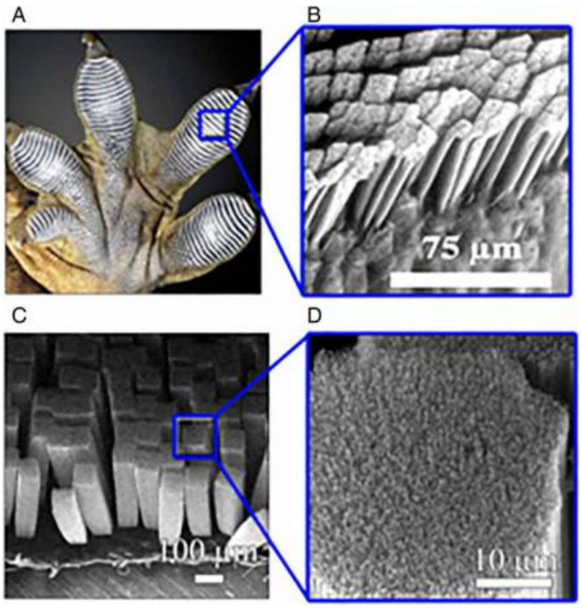

Figure 1: Gecko and synthetic setae. (A) Picture of a gecko foot showing the setae arranged into lobes on the foot. (B) Scanning electron microscope (SEM) image of gecko setae terminating into thousands of smaller spatulas (gripping hairs). Side view (C) and an SEM image (D) of synthetic setae. Image gratefully used with permission from Prof. Dhinojwala.[1] © National Academy of Sciences.

therapy to create localised heat to destroy diseased tissue.[13] The advantageous characteristics of nanomaterials have driven implementation of nanotechnology in various settings including the food industry, consumer products, the medical sector, and environmental fields. Nanoapplications represent a new subject area in need of expert medical writers. This paper, therefore, aims to give an overview of recent scientific findings in the field of nanoapplications and their opportunities for the medical writing community.

Food industry and consumer products: we consume nanotechnology products on a daily basis

The potential uses of nanotechnology have led to its increased presence in food and consumer products. For example, nano-sized titanium dioxide (TiO_2) and zinc oxide (ZnO) particles, typically smaller than 100 nm, are frequently used in sunscreen as an inorganic sun blocker (up to 10% by weight[14]). They reduce the undesired opaqueness usually found in sunscreens containing larger TiO_2 and ZnO particles in the size range of micrometres.[15] Nanoparticles also provide certain properties to food. Due to their ability to absorb UV radiation, they can be used as coating for confectionaries to prolong shelf-life. They also introduce a white colouring to chocolate, non-dairy creamer, and sauces, and improve the flowability of salt. Foods with the highest TiO_2 nanoparticle contents include candies, sweets, and chewing gum,[14] in which TiO_2 nanoparticles are mainly used as a whitener. In the USA, a typical adult may be exposed every day to up to 1 mg of titanium per kilogram of body weight – around 10^{12} particles.[14,16] The potential negative consequences of nanoparticle ingestion in humans will be mentioned later in this article.

Medical sector: therapeutic and diagnostic applications

Nanomedicine describes the application of nanotechnology in medicine. The first generation of nano-oncological therapeutics is already on the market. A characteristic of this first generation is the use of so-called passive targeting. Due to their increased molecular weight compared with small molecules, nanoparticles have a greater tendency

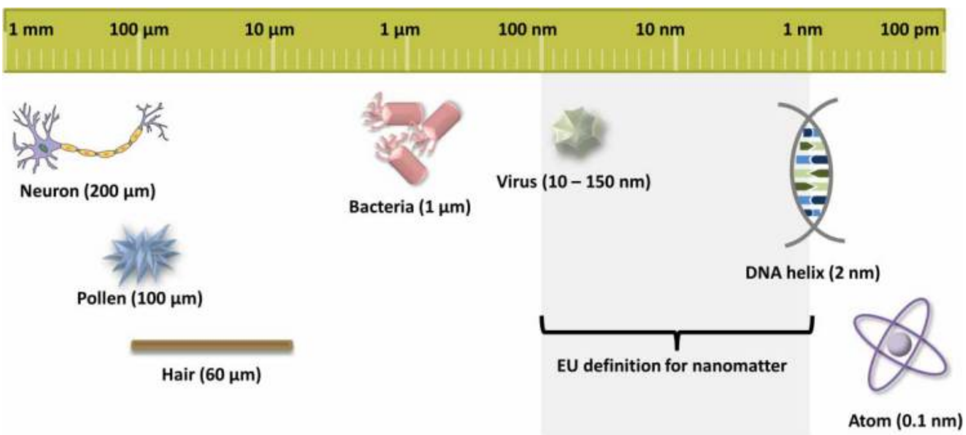

Figure 2: Explanatory scale of typical micro- and nano-sized objects. The EU defines nanomaterials as particles in the range of 1–100 nm.[2]

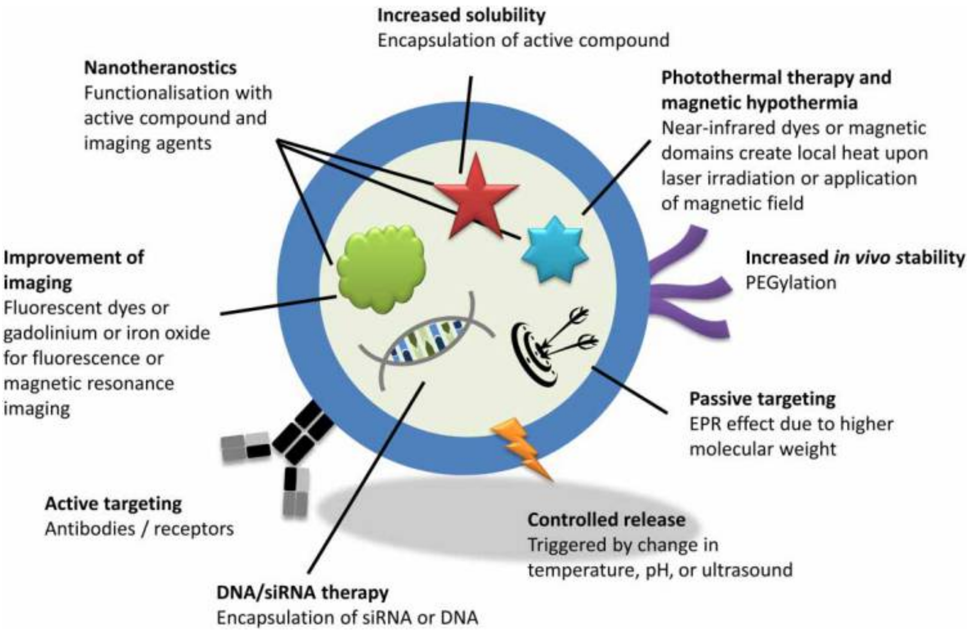

Figure 3: Potential for use of nanotechnology in medicine. Schematic representation of the nano-toolbox: potential modifications for nanoparticles to increase efficacy and safety in medicine.[5,11,13] EPR, enhanced permeability and retention; siRNA, small interfering RNA.

to passively accumulate in tumour tissue that has increased vascular permeability.[17] This is a phenomenon described in the literature as the enhanced permeability and retention effect (see Figure 3).

Albumin-bound paclitaxel and liposomal doxorubicin, pioneer drugs of the first generation of nanotherapeutics, were licensed by the EMA for the treatment of metastatic breast cancer (MBC) in 2000 and 2009, respectively.[5,18,19] Polyethylene glycol (PEG)-functionalised liposomal doxorubicin provided comparable efficacy to doxorubicin in a phase III trial in women with MBC, with significantly reduced cardiotoxicity ($P < 0.001$), myelosuppression, vomiting, and hair loss.[20] In another phase III trial in women with MBC, albumin-bound paclitaxel demonstrated significantly higher response rates compared with standard paclitaxel ($P = 0.001$), longer time to tumour progression, and a favourable safety profile.[21]

Second-generation nanotherapeutics are in development, with the aim to increase the specificity and timely release of the therapeutic agent.[3] Nanoparticles are typically endocytosed by cells into endolysosomal vesicles (see Figure 4) depending on their size, shape, volume, and, particularly, surface characteristics.[3,22] These properties may also be used to specifically guide the nanocompound to a location of interest *in vivo*, thus decreasing the concentration threshold at which these agents have a therapeutic effect.[11] To increase nanoparticle localisation, molecules such as antibodies can be introduced to particle surfaces,

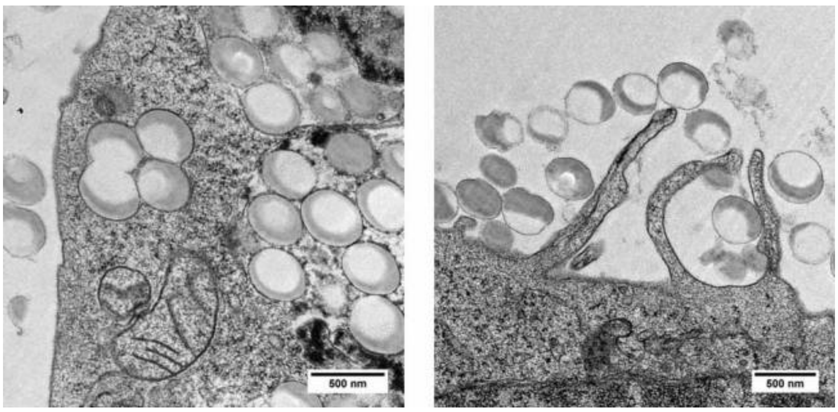

Figure 4: Transmission electron microscope images of HeLa cells after incubation for 24 hours with 603 nm, positively charged, polystyrene particles.[22] Reprinted with permission from Elsevier.

which are then used to target overexpressed cancer cell antigens. Adding a protective layer of macromolecules such as PEG to the nanosurface expands its stability, and encapsulation of active compounds increases solubility *in vivo*.[5]

In addition to chemotherapeutic drugs, DNA and small interfering RNA (siRNA) can also be used as active compounds.[11] For example, a recently published study demonstrated the potential of siRNA-loaded polymeric nanoparticles to target intestinal inflammation. CD98 siRNA-containing nanoparticles demonstrated a therapeutic effect by decreasing artificially induced colitis in a mouse model.[9]

The active and passive accumulation of nanoparticles in tumour tissue can also improve imaging. This is achieved by using nanoparticles to carry cargo (e.g. gadolinium) that is easily detected by magnetic resonance imaging. A nanoparticle with cargo of both active compound and imaging agent (termed a 'nanotheranostic') provides a dual approach for imaging and therapy.[11]

The above modifications to nanoparticles constitute important tools for nanomedical scientists in the development of nanotherapeutics.

Nanomedicine: regulatory status and medical writing

The unique properties of nanomedicines pose additional challenges for regulation and approval.[23] Currently, nanomedicines are regulated by the EMA and FDA under the same procedures used for the assessment of small-molecule pharmaceuticals or medical devices.[23] As the EMA regulates the approval of pharmaceutical products and medical devices differently, the question arises as to how the assessment of nanotheranostics can be integrated into these procedures.[24] In addition, a lack of definitions for nanomaterials and limited standard nomenclature and reference material challenge the regulatory communities.[23] Draft guidance papers that have been issued by the FDA and EMA[23] are expected to represent precursors for regulatory requirements specific for nanomedicines.

The development of generic equivalents to nanomedical products, called 'nanosimilars', is even more ambitious than the development of biosimilars. The nanosimilar needs to express the same complex physicochemical properties as the patented drug (e.g. *in vitro* leakage rate and liposomal size distribution), which in turn require the establishment of sophisticated analysis methods. Three years after the last patent expired for the successful liposomal doxorubicin Doxil®, only one generic (Lipodox®) has been approved by the FDA (but not the EMA).[23]

For the medical writing community, the writing of (regulatory) documents for nanoapplications and nanosimilars demands extensive knowledge, not just of the clinical indication and of specific regulations but also of the relevant physics, chemistry, and material science background. Given the expected increase in nanomedical developments and the complex nature of the topic, 'nanomedical writing' might even evolve as a job specialisation in the medical writing profession.

Environmental fields

Nanoparticles in the environment can stem from natural sources (forest fires or volcanic eruptions), accidental release (vehicle exhaust or industrial processes), or intentional use of engineered products.[25] Industrial applications of engineered nanoparticles include the medical sector, ground water remediation, and nanobionic engineering of plants.

Nanotechnology holds great potential for advancing wastewater treatment.[26] Examples of current and potential applications include the absorption of heavy metals by oxidised carbon nanotubes, the reduction of contamination by addition of metal oxide nanoparticles to filter membranes, and nanophotocatalisation with TiO_2 particles to remove trace amounts of microbial pathogens.[26]

By introducing single-walled carbon nanotubes into chloroplasts of nano-engineered plants, it is possible to promote more than three times higher photosynthetic activity than that of controls. Nanotubes absorb light over a broad range of wavelengths in the ultraviolet, visible, and near-infrared spectra not normally captured by chloroplast antenna pigments.[27] They are also able to transfer electrons to the photosynthetic machinery of the chloroplasts. Nanobionic engineering of plant function can thereby contribute to the development of biomimetic materials to better utilise available light.[27]

Potential adverse effects on human health and the environment

Despite their common occurrence in everyday life, the long-term effects of nanoparticles have not been fully investigated, and guidelines on how to evaluate and quantify these effects are lacking.[25] In an attempt to establish guidelines, stakeholders including the Organisation for Economic Co-operation and Development (OECD) and the EU are attempting to define the impact of nanomaterials on both human health and the environment.[25]

Dietary nanoparticles may detrimentally affect human health. A pilot study found that a reduction in dietary TiO_2 microparticles (including nanoparticles under 0.1 μm in size) led to an increase in disease remission in patients with Crohn's disease.[16] Once ingested, some of the degradation-resistant TiO_2 microparticles were absorbed across the gastrointestinal mucosa and some accumulated in macrophages, potentially causing local inflammation that leads to Crohn's disease. A significant reduction ($P = 0.002$) in the disease activity index was observed in patients with lower numbers of lumen microparticles when compared to controls. This would suggest an association between dietary uptake of nanoparticles and inflammatory bowel diseases.[16]

Once released, nanoparticles may enter the marine environment through the sewer system and accumulate in various consumers throughout the food chain. A recent study reported that polystyrene nanoparticles have an effect on both fat metabolism and the ingestion behaviours of crucian carp.[28] This effect is possibly due to a disturbance in fat metabolism connected to accumulation of apolipoproteins on the nanoparticle corona.

Certain nanoparticles can also negatively affect plants. For example, accumulation of TiO_2 nanoparticles has been associated with reduced hydraulic conductivity (the ease with which water can move through pore spaces) in maize root cell walls, thus leading to reduced transpiration and leaf growth.[29]

Future perspectives

Nanotechnology has found its way into many facets of everyday life, including food and consumer products, the medical sector, and environmental fields. This article outlines some of the trends to date. Nanotechnology is a sophisticated tool that can build, characterise, and utilise nanoscale structures across a range of disciplines to create new and innovative applications.

Exposure of humans, animals, and plants to nanoparticles can be beneficial, but also potentially detrimental. Extrapolation from controlled experiments in an artificial setting should be conservative. Therefore, it is important to determine the quantity of exposure and long-term effects of engineered nanoparticles in ecosystems. Regulation and specific guidance on nanoparticle testing are needed for the future. For medical writers, the anticipated regulatory development and the interplay of several scientific disciplines for nanomedicines demand a broad scientific background, and might provide an opportunity for specialised expert writers in the field.

Acknowledgements

The author thanks nspm ltd, specifically Dr William Archey and Dr Ian Leighton for their support with this article. The author acknowledges Prof. Dhinojwala for his kind permission to use the images of the gecko and synthetic setae, and the working group of Prof. Landfester, specifically PD Dr Mailänder and Dr Dass, for their support on cellular uptake experiments with polymeric nanoparticles.

References

1. Ge L, Sethi S, Ci L, Ajayan PM, Dhinojwala A. Carbon nanotube-based synthetic gecko tapes. Proc Natl Acad Sci USA 2007;104(26):10792–5.
2. European Commission. Definition of nanomaterials (2011) [cited 2014 Feb 11]. Available from: http://ec.europa.eu/nanotechnology/policies_en.html.
3. Caldorera-Moore M, Guimard N, Shi L, Roy K. Designer nanoparticles: incorporating size, shape and triggered release into nanoscale drug carriers. Expert Opin Drug Deliv 2010;7(4):479–95.
4. Mody VV, Siwale R, Singh A, Mody HR. Introduction to metallic nanoparticles. J Pharm Bioallied Sci 2010; 2(4):282–9.
5. Li W, Zhao M, Ke C, Zhang G, Zhang L, Li H, *et al.* Nano polymeric carrier fabrication technologies for advanced antitumor therapy. Biomed Res Int 2013; 2013:305089.
6. Han Z, Conley SM, Naash MI. AAV and compacted DNA nanoparticles for the treatment of retinal disorders: challenges and future prospects. Invest Ophthalmol Vis Sci 2011;52(6):3051–9.
7. Raula J, Lehtimäki M, Karppinen M, Antopolsky M, Jiang H, Rahikkala A, *et al.* Preparation of amino acid nanoparticles at varying saturation conditions in an aerosol flow reactor. J Nanopart Res 2012;14:986.
8. Beutner R, Michael J, Schwenzer B, Scharnweber D. Biological nano-functionalization of titanium-based biomaterial surfaces: a flexible toolbox. J R Soc Interface 2010;7(Suppl 1):S93–105.
9. Laroui H, Geem D, Xiao B, Viennois E, Rakhya P, Denning T, *et al.* Targeting intestinal inflammation with CD98 siRNA/PEI-loaded nanoparticles. Mol Ther 2014;22(1):69–80.
10. Dick K, Dhanasekaran T, Zhang Z, Meisel D. Size-dependent melting of silica-encapsulated gold nanoparticles. J Am Chem Soc 2002;124(10):2312–7.
11. Rizzo LY, Theek B, Storm G, Kiessling F, Lammers T. Recent progress in nanomedicine: therapeutic, diagnostic and theranostic applications. Curr Opin Biotechnol 2013;24(6):1159–66.
12. Eustis S, el-Sayed MA. Why gold nanoparticles are more precious than pretty gold: noble metal surface plasmon resonance and its enhancement of the radiative and nonradiative properties of nanocrystals of different shapes. Chem Soc Rev 2006;35(3):209–17.
13. Melancon MP, Zhou M, Li C. Cancer theranostics with near-infrared light-activatable multimodal nanoparticles. Acc Chem Res 2011;44(10):947–56.

14. Weir A, Westerhoff P, Fabricius L, Hristovski K, von Goetz N. Titanium dioxide nanoparticles in food and personal care products. Environ Sci Technol 2012;46(4):2242–50.
15. Smijs TG, Pavel S. Titanium dioxide and zinc oxide nanoparticles in sunscreens: focus on their safety and effectiveness. Nanotechnol Sci Appl 2011;4:95–112.
16. Lomer MC, Thompson RP, Powell JJ. Fine and ultra-fine particles of the diet: influence on the mucosal immune response and association with Crohn's disease. Proc Nutr Soc 2002;61(1):123–30.
17. Maeda H. Vascular permeability in cancer and infection as related to macromolecular drug delivery, with emphasis on the EPR effect for tumor-selective drug targeting. Proc Jpn Acad Ser B Phys Biol Sci 2012;88(3):53–71.
18. European Medicines Agency. Abraxane® – summary of product characteristics (2014) [cited 2014 Feb 24]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000778/WC500020435.pdf.
19. European Medicines Agency. Myocet® – summary of product characteristics (2014) [cited 2014 Feb 24]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000297/WC500031811.pdf.
20. O'Brien ME, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, *et al.* Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 2004;15(3):440–9.
21. Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, *et al.* Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005;23(31):7794–803.
22. Lerch S, Dass M, Musyanovych A, Landfester K, Mailander V. Polymeric nanoparticles of different sizes overcome the cell membrane barrier. Eur J Pharm Biopharm 2013;84(2):265–74.
23. Tinkle S, McNeil SE, Muhlebach S, Bawa R, Borchard G, Barenholz YC, *et al.* Nanomedicines: addressing the scientific and regulatory gap. Ann N Y Acad Sci 2014;1313(1):35–56.
24. Senjen R. Nanomedicine – new solutions or new problems? (2013) [cited 2014 May 26]. Available from: https://noharm-europe.org/sites/default/files/documents-files/2462/HCWH%20Europe%20Nanoreport.pdf.
25. Smita S, Gupta SK, Bartonova A, Dusinska M, Gutleb AC, Rahman Q. Nanoparticles in the environment: assessment using the causal diagram approach. Environ Health 2012;11(Suppl 1):S13.
26. Qu X, Alvarez PJ, Li Q. Applications of nanotechnology in water and wastewater treatment. Water Res 2013;47(12):3931–46.
27. Giraldo JP, Landry MP, Faltermeier SM, McNicholas TP, Iverson NM, Boghossian AA, *et al.* Plant nanobionics approach to augment photosynthesis and biochemical sensing. Nat Mater 2014;13(4):400–8.
28. Cedervall T, Hansson LA, Lard M, Frohm B, Linse S. Food chain transport of nanoparticles affects behaviour and fat metabolism in fish. PLoS ONE 2012;7(2):e32254.
29. Rico CM, Majumdar S, Duarte-Gardea M, Peralta-Videa JR, Gardea-Torresdey JL. Interaction of nanoparticles with edible plants and their possible implications in the food chain. J Agric Food Chem 2011;59(8):3485–98.

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