Applications of Nanotechnology in Dermatology

Lisa A. DeLouise[1,2]

What are nanoparticles and why are they important in dermatology? These questions are addressed by highlighting recent developments in the nanotechnology field that have increased the potential for intentional and unintentional nanoparticle skin exposure. The role of environmental factors in the interaction of nanoparticles with skin and the potential mechanisms by which nanoparticles may influence skin response to environmental factors are discussed. Trends emerging from recent literature suggest that the positive benefit of engineered nanoparticles for use in cosmetics and as tools for understanding skin biology and curing skin disease outweigh potential toxicity concerns. Discoveries reported in this journal are highlighted. This review begins with a general introduction to the field of nanotechnology and nanomedicine. This is followed by a discussion of the current state of understanding of nanoparticle skin penetration and their use in three therapeutic applications. Challenges that must be overcome to derive clinical benefit from the application of nanotechnology to skin are discussed last, providing perspective on the significant opportunity that exists for future studies in investigative dermatology.

Journal of Investigative Dermatology (2012) **132,** 964–975; doi:10.1038/jid.2011.425; published online 5 January 2012

NANOTECHNOLOGY AND NANOMEDICINE

Nanoparticles are defined as any material with at least one dimension that is <100 nm in size (Dowling *et al.*, 2004). Nanoparticles have many shapes (spheres, rods, dendritic) and they can be soft or hard, soluble or insoluble. Natural sources of nanoparticles include viruses (Baker *et al.*, 1991; Dubina and Goldenberg 2009), allergens (Menetrez *et al.*, 2001), and particulates produced in high-temperature processes such as volcanic eruptions (Buzea *et al.*, 2007). Unintentional man-made sources include atmospheric automobile or industrial exhaust, coal mining, and cigarette smoke (Buzea *et al.*, 2007). Nanoparticles present in the dust created in the 11 September 2001 attacks on the World Trade Center are being investigated as a contributing factor to the adverse health effects suffered by recovery workers (Altman *et al.*, 2010; Cone and Farfel, 2011). In the laboratory, nanoparticles are created via the deliberate manipulation of materials at the atomic, molecular, and macromolecular scales. Nanotechnology is the engineering of materials on the nanoscale for technological or scientific applications (Rittner and Abraham, 1998). Engineered nanoparticles exhibit many novel physiochemical, electronic, optical, mechanical, catalytic, and thermal properties not present in the bulk form (Misra *et al.*, 2008). These properties derive, in large part, from the increased surface area-to-volume ratio (Nel *et al.*, 2006). Some of the most important engineered nanoparticles exploited in an expanding number of commercial products and technological applications include carbon nanotubes, fullerenes, quantum dots (QDs), metals (Ag, Au), metal oxides (TiO_2, ZnO, Fe_2O_3, SiO_2), and lipophilic nanoparticles. Liposomes are nanosized vesicles comprising lipid bilayers (Kirjavainen *et al.*, 1999; Immordino *et al.*, 2006) formulated with naturally derived phospholipids and/or other lipophilic molecules. Solid lipid nanoparticles are made from lipids that are solid at room temperature (Müller *et al.*, 2000). Both lipophilic nanoparticle types have been designed for transcutaneous drug delivery. Many solid lipid nanoparticles and liposomal delivery systems have been commercialized, and many more are in clinical trials (Walve *et al.*, 2011). Historically, many articles on lipophilic nanoparticles appear in this journal and several excellent reviews exist (Schäfer-Korting *et al.*, 1989; Müller *et al.*, 2000; Immordino *et al.*, 2006; Prow *et al.*, 2011a, b), and therefore these will not be explicitly discussed in this review.

The emerging field of nanomedicine seeks to exploit the novel properties of engineered nanomaterials for diagnostic and therapeutic applications (Zhang *et al.*, 2008; Parveen *et al.*, 2011). Nanoparticles can be engineered to carry drug payloads, image contrast agents, or gene therapeutics for diagnosing and treating disease, with cancer being a primary focus (Gao *et al.*, 2004; Moghimi *et al.*, 2005; Al-Jamal *et al.*, 2009; Boisselier and Astruc, 2009; Debbage, 2009; Riehemann *et al.*, 2009; Huang *et al.*, 2010a; Huang *et al.*, 2011; Ilbasmiş-Tamer *et al.*, 2010). Nanomaterials can be designed for passive tumor targeting, relying on the phenomenon of enhanced permeability and retention (Iyer *et al.*, 2006; Huang *et al.*, 2010a), or for active targeting designed with tethered homing ligands (Reubi, 2003; Schottelius and

[1]*Department of Biomedical Engineering, University of Rochester, Rochester, New York, USA and* [2]*Department of Dermatology, University of Rochester Medical Center, Rochester, New York, USA*

Correspondence: Lisa A. DeLouise, University of Rochester, Department of Biomedical Engineering, University of Rochester, 601 Elmwood Avenue, Rochester, New York 14642, USA.
E-mail: Lisa_DeLouise@urmc.rochester.edu

Abbreviations: LC, Langerhans cells; LN, lymph node; nano Ag, silver nanoparticles; QD, quantum dot

Received 7 July 2011; revised 6 October 2011; accepted 24 October 2011; published online 5 January 2012

Wester, 2009). Fluorescent QDs (Gao *et al.*, 2004; Hild *et al.*, 2008; Kosaka *et al.*, 2009), particularly near-infrared QD nanoparticles that can overcome tissue background autofluorescence (Ma and Su, 2010; Mortensen *et al.*, 2010, 2011), have been developed for *in vivo* tumor and sentinel lymph node tracking (Hama *et al.*, 2007; Frangioni, 2008). Superparamagnetic iron oxide nanoparticles have been investigated as contrast agents for magnetic resonance imaging (Huang *et al.*, 2011; Lim *et al.*, 2011).

It has come to light in recent years that there is an increasing need to understand nanomaterial tissue interactions at cellular and systemic levels, not only to optimize the therapeutic/imaging applications but to also minimize potential side effects (De Jong and Borm, 2008). Some lipophilic and polymeric nanomaterials are designed to biodegrade *in vivo,* but many of the important semiconductor, metal, and metal oxides nanoparticles are sparingly soluble. Long-term cellular presence may produce toxic or immunological side effects such as reactive oxygen species generation (Long *et al.*, 2006), leaching of toxic ions (Bottrill and Green, 2011), exposure of cryptic epitopes (Lynch *et al.*, 2006), cytotoxicity, and genotoxicity (Nakagawa *et al.*, 1997; Wamer *et al.*, 1997; Jin *et al.*, 2008; AshaRani *et al.*, 2009; Xu *et al.*, 2009). *In vitro* cell studies find that most nanoparticles produce dose-dependent cytotoxic or cytokine responses (Ryman-Rasmussen *et al.*, 2006; Pan *et al.*, 2007; Jin *et al.*, 2008; Zhang and Monteiro-Riviere, 2009; Cui *et al.*, 2010; Pedata *et al.*, 2011) as was reported in this journal for keratinocytes exposed to QDs with different surface coatings (Figure 1). Therefore, understanding the fate and transport of nanomaterials that contact the body is critical for optimizing translational applications and therefore constitute areas of active research. Progress made in understanding nanoparticle skin interactions and their therapeutic applications is discussed next.

NANOPARTICLE SKIN PENETRATION

Fueled by the expanding commercialization of products that contain engineered nanoparticles such as carbon nanotubes that strengthen everyday products including bicycle frames, tennis, and badminton rackets (Endo *et al.*, 2004), and principally by the use of TiO_2 and ZnO nanoparticles in cosmetics and sunscreens for UVR protection (Robichaud *et al.*, 2009; Nanowerk, 2010), researchers in the nanotoxicology field have sought to determine the conditions under which nanoparticles may penetrate the stratum corneum barrier and how the nanoparticle physiochemical properties may influence penetration, systemic translocation, and toxicity (Colvin 2003; Gwinn and Vallyathan 2006; Nel *et al.*, 2006; Tsuji *et al.*, 2006; Nohynek *et al.*, 2007, 2008; Stern and McNeil 2008; Elder *et al.*, 2009; Schneider *et al.*, 2009; Adiseshaiah *et al.*, 2010; Baroli 2010; Smijs and Bouwstra, 2010; Burnett and Wang 2011). Most work in this area has focused on engineered nanoparticles; however, a link to skin aging from exposure to soot and fine dust nanoparticles associated with traffic-related air pollution has recently been reported in this journal (Vierkötter *et al.*, 2010). The question of nanoparticle skin penetration from unintended exposure is clearly important from an environmental and occupational health and safety standpoint (Teow *et al.*, 2011). Conversely, to be useful in therapeutic applications, nanoparticles must be able to penetrate the skin barrier, deliver their payload, and clear from the body without adverse side effects. Nanoparticle penetration through a severely defective skin barrier (i.e., open wounds) is not contested; however, despite nearly 15 years of active investigation, a debate still lingers on whether nanoparticles can penetrate healthy or a mildly defected skin barrier. This lack of consensus stems, in part, from the wide diversity of *in vivo* and *ex vivo* skin models and nanoparticle types used, as well as limitations in analytical tools and instrument sensitivity to detect isolated nanoparticles. Certainly, epidermal thickness and hair follicle density vary widely among species and anatomical locations (Bronaugh *et al.*, 1982; Otberg *et al.*, 2004), and these differences will affect nanoparticle skin penetration, making it difficult to draw general conclusions from the vast literature base. Nevertheless, trends are beginning to emerge. For example, (1) qualitative studies suggest that healthy human skin constitutes a formable barrier to nanoparticle penetration, (2) hair follicles comprise

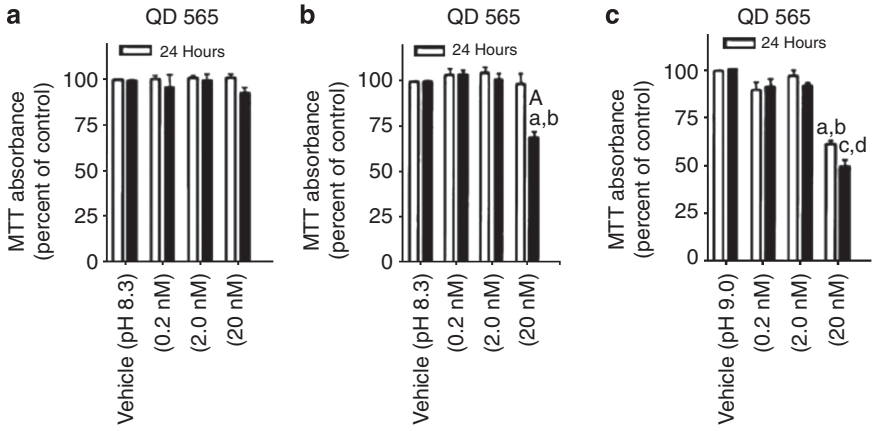

Figure 1. Quantum dot (QD565) surface coating affects keratinocyte concentration–dependent cytotoxicity at 24-hour exposure. (**a**) Polyethylene glycol-coated QD. (**b**) Polyethylene glycol amine-coated QD. (**c**) Carboxylic acid–coated QD. Figure adapted from Ryman-Rasmussen *et al.*, 2006.

important collection sites for nanoparticles, especially when skin is massaged or flexed, and (3) nanoparticle surface charge can significantly influence skin interactions, with neutral charged particles being less hindered from penetration and positively charged particles exhibiting increased cytotoxicity. A brief summary of recent studies that support these conclusions are highlighted below.

Numerous qualitative studies have been published investigating the skin penetration of many types of nanoparticles. Studies of topically applied nanosized TiO_2 (Schulz *et al.*, 2002; Filipe *et al.*, 2009; Sadrieh *et al.*, 2010; Lopez *et al.*, 2011; Monteiro-Riviere *et al.*, 2011) and QDs (Zhang and Monteiro-Riviere, 2008a; Zhang *et al.*, 2008b; Gopee *et al.*, 2009; Prow *et al.*, 2011a, b) consistently find negligible penetration through barrier intact skin, independent of species. In contrast, 5-nm Au metal nanoparticles were reported to diffuse though the stratum corneum barrier of intact mouse skin (Huang *et al.*, 2010b), and 15-nm Au nanoparticles were reported to penetrate *ex vivo* rat skin to a greater extent than 102 nm and 198 nm (Sonavane *et al.*, 2008). Nanoparticle accumulation in hair follicles, which occurs in many species (Lademann *et al.*, 2001, 2007, 2011; Vogt *et al.*, 2006; Todo *et al.*, 2010; Patzelt *et al.*, 2011), and stratum corneum penetration through barrier-impaired skin (Mortensen *et al.*, 2008; Zhang and Monteiro-Riviere, 2008a; Zhang *et al.*, 2008b; Gopee *et al.*, 2009; Ravichandran *et al.*, 2010; Monteiro-Riviere *et al.*, 2011) are common trends. Studies report detectable penetration of QDs through mouse skin treated with ultraviolet B radiation (Mortensen *et al.*, 2008, 2011) and *ex vivo* human skin treated with a hair removal agent (Ravichandran *et al.*, 2010), which is a commonly used cosmetic product. The effect of ultraviolet B radiation to slightly enhance nanoparticle stratum corneum penetration was corroborated in a recent *in vivo* study of TiO_2 and ZnO nanoparticles applied to pigs in typical sunscreen formulations (Monteiro-Riviere *et al.*, 2011). Others report more significant nanoparticle penetration through dermabraded skin (Zhang and Monteiro-Riviere, 2008a; Zhang *et al.*, 2008b; Gopee *et al.*, 2009), which is noteworthy because this too is a popular skin treatment used by consumers for cosmetic reasons (Karimipour *et al.*, 2010). Stratum corneum tape stripping is a well-accepted method of barrier disruption (Bashir *et al.*, 2001), and it is used to enhance the skin permeability of large hydrophilic molecules (Tsai *et al.*, 2003); however, nanoparticle penetration through tape-stripped skin varies qualitatively in magnitude from none (Zhang and Monteiro-Riviere, 2008a; Zhang *et al.*, 2008b; Gopee *et al.*, 2009) to some detected (Jeong *et al.*, 2010; Ravichandran *et al.*, 2010; Prow *et al.*, 2011a, b), and may therefore depend strongly on skin species and/or the number of strips and type of tape used.

Few studies have endeavored to quantify the magnitude of nanoparticle penetration level and to correlate penetration with the magnitude and type of skin barrier defect. One relevant study quantified the penetration of neutral charged polyethyleneglycol-coated nail-shaped QDs (CdSe/CdS core/shell, 37 nm) through dermabraded SKH hairless mice (Gopee *et al.*, 2009). Elemental Cd ion organ analysis suggested that ~2% of the applied dose accumulated in the liver 48 h after exposure. This is considerably higher than the systemic levels of negatively charged dihydrolipic acid–coated sphere-shaped QD (CdSe/ZnS core/shell, 15 nm) quantified to be <0.001% of the applied dose in the lymph nodes of SKH hairless mice following 24 h of ultraviolet B radiation exposure (Mortensen *et al.*, 2011), which may suggest an effect of surface charge. The latter is consistent with a recent *in vivo* human study that quantified systemic Zn ion levels in blood to be <0.001% of the applied dose following repeated application of ZnO nanoparticle containing sunscreen to UVR-exposed skin (Gulson *et al.*, 2010). The main conclusion that can be drawn from these quantitative studies is that nanoparticle skin penetration, even through barrier-disrupted skin, is a minor percentage of applied dose. A key limitation, however, with elemental organ analysis is the inability to distinguish between nanoparticle and soluble ion skin penetration. Therefore, the development of more sensitive techniques and new assays that can be exploited to quantify intact nanoparticle skin and systemic penetration are seen as key challenges to advancing the fields of nanomedicine and nanotoxicology forward as we discuss further in the last section.

NANOPARTICLE-BASED THERAPEUTICS

As highlighted above, for effective therapeutic use, nanoparticles must be able to breach the stratum corneum barrier and enter cells, perhaps through receptor-mediated processes (Zhang and Monteiro-Riviere, 2009). Therefore, many techniques including gene gun, microneedles, ultrasound, electroporation, and tape stripping have been developed to disrupt the stratum corneum to aid in nanoparticle delivery (Lindemann *et al.*, 2003; Polat *et al.*, 2011; Kim *et al.*, 2012). Research investigating therapeutic applications have focused in three main areas: (1) skin cancer imaging and targeted therapeutics, (2) immunomodulation and vaccine delivery, and (3) antimicrobials and wound healing. Many excellent reviews exist in these areas (Bolzinger *et al.*, 2011; Prow *et al.*, 2011a, b), including the specialized topic of drug targeting through the pilosebaceous unit (Chourasia and Jain, 2009). In the following, we highlight some recent findings and emphasize challenges that remain in the clinical translation of nanotechnology to dermatology, thus pointing to the significant opportunity for continued investigative studies in this field.

Skin Cancer Imaging and Targeted Therapeutics

Applications of nanotechnology to skin cancer has seen much effort in the design of new imaging and therapeutic approaches (Stracke *et al.*, 2006; Kosaka *et al.*, 2009; Weiss *et al.*, 2010). The main focus has been on diagnosing and treating metastatic melanoma, which is the deadliest of skin cancers (Lev *et al.*, 2004). Most chemotherapeutics are administered systemically and are cytotoxic to healthy cells; therefore, cancer patients must endure considerable morbidity. Nanomedicine seeks to engineer nanoparticles to image (Schmieder *et al.*, 2005; Boles *et al.*, 2010; Li *et al.*, 2010; Benezra *et al.*, 2011) and selectively deliver drugs (Camerin

et al., 2010; Yao *et al.*, 2011) or small-interfering RNA (Chen *et al.*, 2010, 2010a; Davis *et al.*, 2010) specifically to melanoma cells. Many potential drugs fail clinically because of insolubility. Nanoparticles may overcome this as many more types and higher concentrations of drugs can be loaded on and into nanoparticles (Kaul and Amiji, 2002; Cho *et al.*, 2008; De Jong and Borm, 2008; Nasir, 2008; Zhang and Monteiro-Riviere, 2008a; Zhang *et al.*, 2008b; Dhar *et al.*, 2011).

Design criteria for nanoparticle therapeutics *in vivo* emphasize the need for rapid renal clearance of insoluble particles requiring particle sizes to be less than ~6 nm (Choi *et al.*, 2007, 2010). Recently, multimodal silica nanoparticles (7 nm) have been described for targeting M21 melanomas in a xenograft mouse model (Benezra *et al.*, 2011). Particles were coated with bifunctional methoxy-terminated polyethylene glycol chains (~0.5 kDa). The neutral charged polyethylene glycol limits uptake by noncancer cells, and the bifunctional group enabled attachment of the integrin-targeting RGDY peptide labeled with ^{124}I, a long-lived positron emitting radionuclide, for quantitative three-dimensional positron emission tomography imaging. The RGDY peptide increases tumor retention. The laminin receptor–binding peptide (YIGSR) has also been used to increase nanoparticle retention in B16 melanoma and other types of tumors (Schottelius and Wester, 2009; Sarfati *et al.*, 2011). The positron-emitting silica nanoparticles were successfully demonstrated for tumor targeting and nodal mapping. They are now approved for in-human clinical trials to test for real-time intraoperative detection and imaging of nodal metastases, differential tumor burden, and lymphatic drainage patterns (Benezra *et al.*, 2011). Although rapid clearance of these particles was demonstrated in humans, an added advantage of silica is its biodegradation to nontoxic silicic acid and its subsequent excretion by the kidneys (Low *et al.*, 2009; Rosenholm *et al.*, 2011).

Proof-of-principle studies for specific targeting of metastatic melanoma using homing ligands attached to nanoparticles have been demonstrated using gold nanocages (Kim *et al.*, 2010), gold nanospheres (Lu *et al.*, 2009), QDs (Zhou *et al.*, 2007; Zheng *et al.*, 2010), and polymeric liposomes (Zhu *et al.*, 2010; Chen *et al.*, 2010a). Tethering the melanocyte-stimulating hormone peptide and/or its derivatives to the nanoparticle is a strategy widely investigated to target the melanocortin 1 receptor (Siegrist *et al.*, 1994; Wong and Minchin 1996; Wen *et al.*, 1999; Lu *et al.*, 2009; Kim *et al.*, 2010), a G protein–coupled receptor that is overexpressed on melanoma cells (Loir *et al.*, 1999; Salazar-Onfray *et al.*, 2002). It is interesting to note that melanocortin peptides possess anti-inflammatory properties, and, consequently, α-melanocyte-stimulating hormone–conjugated nanoparticles have been investigated as anti-inflammatory agents in the treatment of endodontic lesions (Fioretti *et al.*, 2010) and colitis using mouse models (Laroui *et al.*, 2009). Although targeting G protein–coupled receptors with peptide agonists or antagonists is considered to offer many advantages over protein targeting with antibodies (Hild *et al.*, 2010), targeting the melanocortin 1 receptor may have limited clinical benefit, as it does not provide sufficient cellular specificity. Melanocytes and melanoma cells are not the only cells in the body that express melanocortin 1 receptor (Neumann *et al.*, 2001; Carlson *et al.*, 2007; Hoch *et al.*, 2007; Li and Taylor, 2008), and α-melanocyte-stimulating hormone can bind to other melanocortin receptors (Srinivasan *et al.*, 2004). Therefore, considerable opportunities exist to identify selective melanoma-targeting receptors. The sigma 1 receptor, as reported in this journal, is a promising candidate that was recently investigated to deliver c-Myc small interfering RNA to B16F10 melanoma tumors using a mouse model (Chen *et al.*, 2010a). Results showed that tumor size was decreased by 2–4 × relative to a phosphate-buffered saline control depending upon the nanoparticle formulation, as illustrated in Figure 2.

Collectively, the existing research on the specific targeting of melanoma cells *in vivo* is limited, and as studies progress it will be critical to take into account cell surface receptor variants, receptor internalization, and recycling, as well as differences in receptor expression and/or trafficking that may result *in vivo* owing to the effects of the tissue microenvironment that are not captured in two-dimension *in vitro* cell culture studies (Cukierman *et al.*, 2002; Ghosh *et al.*, 2005).

Immunomodulation and Vaccine Delivery via Skin

The skin provides both innate and adaptive immune response functions that maintain tissue homeostasis and the ability to react quickly to environmental insults (Iwasaki and Medzhitov, 2004; Paus *et al.*, 2006; Gallo and Nakatsuji, 2011). Almost every substance that contacts skin has the potential to penetrate and/or produce physiological changes. Skin is the main route to allergen sensitization (Beck and Leung 2000; Warbrick *et al.*, 2002; Arts *et al.*, 2003). Langerhans cells (LCs) and dermal dendritic cells are two types of skin-resident antigen-presenting cells that express CD1a, a protein that mediates antigen presentation. It has been reported in this journal that CD1a+ cells concentrate in the epithelium of

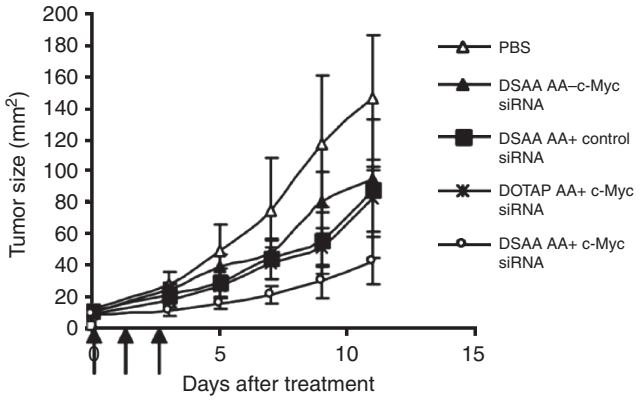

Figure 2. Nanoparticles can be used for targeted drug delivery. Nanoparticles (100 nm) targeting the sigma 1 receptor on melanoma cells are formulated with anisamide (AA) to deliver c-Myc small-interfering RNA (siRNA). DOTAP and DSAA are lipids used in the nanoparticle formulation. Solid arrows indicate the intravenous administration of siRNA nanoparticles. Results show significant reduction in B16F10 melanoma tumor size murine syngeneic model. Figure adapted from Chen *et al.*, 2010a.

the hair follicle infundibulum (Vogt *et al.*, 2006), Figure 3a. LCs also express langerin (CD207), and CD207+ cells in dorsal mouse skin show a distributed presence in the epidermis Figure 3b. LCs comprise ~2–4% of epidermal cells (Maurer and Stingl, 2001; Clark *et al.*, 2006). T cells are also abundantly present in normal skin ($\sim 1 \times 10^6$ cells per cm^2), and they display a diverse receptor repertoire (Clark *et al.*, 2006). The possibility to exploit nanotechnology to modulate the immune system (Chen *et al.*, 2009; Geusens *et al.*, 2009, 2010; Jang *et al.*, 2010a; Zolnik *et al.*, 2010; Özbaş-Turan and Akbuğa 2011) and to deliver vaccines through skin (Nasir, 2008, 2009; Fernando *et al.*, 2010; Huang *et al.*, 2010b) are active research area of increasing importance as recently reviewed (Prow *et al.*, 2011a, b).

The ability of nanoparticles to carry antigen (Lynch *et al.*, 2007), provide adjuvant function (McNeela and Lavelle, 2011), and to accumulate in hair follicles, especially after mechanical stimulation (Lademann *et al.*, 2001, 2007, 2011; Tinkle *et al.*, 2003; Vogt *et al.*, 2006; Rouse *et al.*, 2007; Mahe *et al.*, 2009; Schneider *et al.*, 2009), has spurred interest in their use for transcutaneous immune modulation. Studies report that the amount and depth to which nanoparticles can penetrate along the follicular duct strongly depends on the particle size (Vogt *et al.*, 2006; Mahe *et al.*, 2009; Patzelt *et al.*, 2011). A recent study reported in this journal exemplifies the use of 40 nm and 200 nm polystyrene nanoparticles to target vaccine compounds to skin antigen-presenting cells (Mahe *et al.*, 2009). Tape stripping was used to open hair follicles. The nanoparticles were observed to penetrate into hair follicles, diffuse into the perifollicular tissue where they were taken up by LCs (CD207+) and dendritic cells (CD205+), and transported to local draining lymph nodes via LC and DC migration (Figure 4).

Although lipophilic and polymer particles are commonly used to deliver substances across skin (Choi and Maibach, 2005; Benson, 2009; Rancan *et al.*, 2009), these particle types are typically designed to degrade. Therefore, they may comprise inferior adjuvants compared with hard insoluble nanoparticles that may be retained for longer periods in skin. Studies must be conducted to confirm this, as well as to determine the potential effect of skin pretreatments

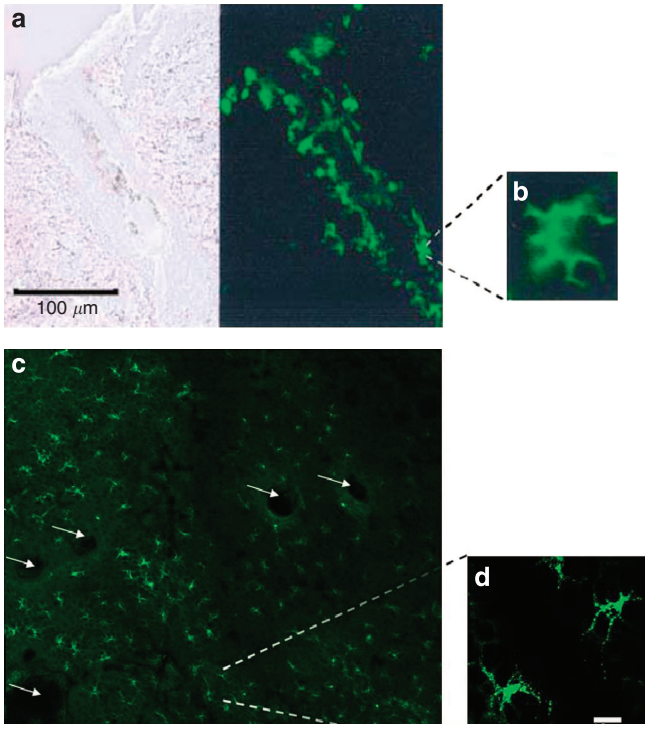

Figure 3. Dendritic cell localization patterns in skin. (**a**) Bright-field image of hair follicle and corresponding immunofluorescent staining with anti-CD1a-FITC antibody showing high concentration of CD1a+ cells in human epithelium around hair follicle infundibulum. Bar = 100 μm. (**b**) CD1a+ cells exhibit dendritic morphology. (**c**) Immunofluorescent staining of dorsal mouse epidermis with anti-CD207-FITC (Langerin), specific for Langerhans cells, showing distributed presence in plan view. White arrows indicate hair follicles. Bar = 50 μm. (**d**) CD207+ cells exhibit dendritic morphology. Bar = 10 μm. Panels **a** and **b** are adapted from Vogt *et al.*, 2006. Panels **c** and **d** are provided by Samreen Jatana, University of Rochester.

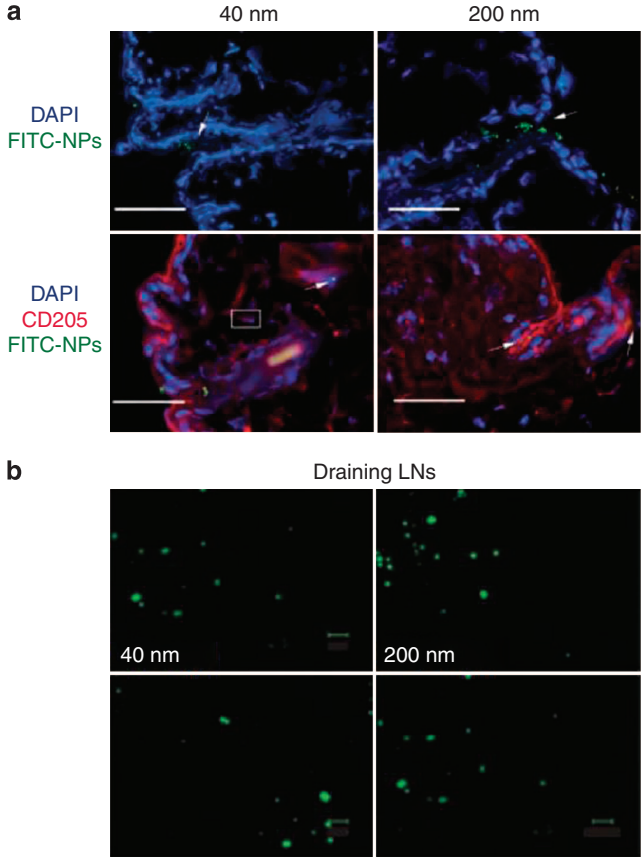

Figure 4. Nanoparticles translocate through skin to local draining lymph node. Application of fluorescent 40- and 200-nm-diameter polystyrene fluorosphere particles onto tape-stripped C57BL/6 mice skin were observed to penetrate into hair follicles and translocate via skin-resident antigen-presenting cells to draining lymph nodes. (**a**) Penetration of both 40 and 200 nm fluorospheres into the hair follicles was analyzed on longitudinal 5 mm cryosections of the skin showing fluorescent signal confined to hair follicle openings. (**b**) At 24 hours following topical application, the draining lymph nodes (LNs) were analyzed by fibered confocal fluorescence microscopy. Fluorescent spots were observed for both particle sizes, indicating that the fluorspheres penetrated perifollicular tissue and were taken up by epidermal and dermal dendritic cells and trafficked to the lymph nodes. Figure is adapted from Mahe *et al.*, 2009.

on immune response. The many methods used to clear follicular openings and to reduce barrier function in healthy skin have the potential to induce inflammatory responses (Reilly and Green, 1999) and cause the emigration of LCs and dendritic cells from the skin (Streilein *et al.*, 1982; Holzmann *et al.*, 2004). These effects must be considered in optimizing vaccination strategies. Other fundamental questions that must be investigated include the following: (1) determining whether nanoparticles themselves are immunogenic, (2) if and where in the epidermis nanoparticle haptinization occurs (Simonsson *et al.*, 2011), and (3) how nanoparticles may alter the way antigen is presented/processed by skin-resident antigen-presenting cells.

It is important to note that although the positive use of nanoparticles for vaccine delivery is a promising application, there is also the possibility for unintentional nanoparticle skin exposure that could potentiate negative immunological effects, such as a contact hypersensitivity response in susceptible people, resulting from the combined skin exposure to nanoparticles and environmental factors such as allergens or UVR. Using an *in vivo* mouse model, carbon nanotubes were shown to be immunostimulatory; inducing macrophage activation, proliferation of antigen-specific and nonspecific T lymphocytes, production of cytokines, and the induction of an antibody response to ovalbumin (Nygaard *et al.*, 2009; Grecco *et al.*, 2011). TiO_2 nanoparticles subcutaneously injected in NC/Nga mice were shown to exacerbate the development of atopic dermatitis (AD)–like skin lesions following co-exposure to mite allergen (Yanagisawa *et al.*, 2009). UVR is an important environmental factor known to induce a skin barrier defect (Holleran *et al.*, 1997) that can slightly increase nanoparticle stratum corneum penetration (Mortensen *et al.*, 2008; Monteiro-Riviere *et al.*, 2011); however, the question of whether nanoparticles could exacerbate allergen sensitization on UVR-exposed skin has not been widely considered. Combined skin exposure to TiO_2 and UVR was reported to exacerbate atopic dermatitis–like symptoms in DS-Nh mice (Kambara *et al.*, 2006). UVR skin exposure is also immunosuppressive (Schwarz, 2008; Schwarz and Schwarz, 2011), and how this may impact nanoparticle immunomodulation has not been investigated. Therefore, although transcutaneous immunomodulation with nanoparticles constitutes a promising application (Jang *et al.*, 2010a; Zolnik *et al.*, 2010; Prow *et al.*, 2011a, b), the field is in its infancy with many unanswered questions about the positive and negative effects and mechanisms by which immunomodulation occurs.

Antimicrobials and Wound Healing

Wound healing can be complicated by common comorbidities such as obesity, diabetes, and atopic dermatitis. Diabetic patients are prone to chronic leg and foot ulcerations and infection (O'Meara *et al.*, 2000), and a high percentage of atopic dermatitis lesions are colonized with *Staphylococcus aureus* (Abeck, 1998; Breuer *et al.*, 2002). Technologies that can facilitate wound healing and prevent microbial invasion, particularly from antibiotic-resistant microbes such as methicillin-resistant *Staphylococcus aureus,* are in high demand. There are several recent studies that describe topical application of nanoparticles for antimicrobial and wound healing applications. Recent reviews focus on the use of silver nanoparticles (nano Ag; Chaloupka *et al.*, 2010; Dastjerdi and Montazer, 2010; Elliott, 2010) and the design of nitric oxide–releasing nanoparticles (Jones *et al.*, 2010; Sortino, 2010). Silver ions have long been used for their inherent antimicrobial properties (Silver and Phung, 1996; Nowack *et al.*, 2011). Silver ions are thought to inhibit bacterial enzymes and bind to DNA (Jung *et al.*, 2008), whereas nano Ag is reported to induce bacterial cell wall and cytoplasmic membrane damage (Chamakura *et al.*, 2011). Literature also supports the antimicrobial activity of nitric oxide (NO) and its use to promote wound healing (Fang, 2004; Luo and Chen, 2005; Weller and Finnen, 2006). Friedman *et al.* (2008) describe the design of nitric oxide–releasing nanoparticles (10 nm) made from tetramethylorthosilicate, polyethylene glycol, and chitosan. Nitric oxide gas was trapped in the hydrogel/glass composite matrix and released upon contact with water. Topical application of these nanoparticles was reported in this journal to be highly effective against cutaneous methicillin-resistant *Staphylococcus aureus* infection in a mouse model, as illustrated in Figure 5 (Martinez *et al.*, 2009). The authors suggest that these nanoparticles may be ideal for applications in combat or disaster situations where emergency personnel could apply them directly to trauma wounds in the field.

The antimicrobial and odor-reducing properties of nano Ag has lead to the rapid commercialization of nano Ag–containing products including socks (Benn and Westerhoff, 2008; Lubick, 2008), food-storage containers (Costa *et al.*, 2011), washing machines (Farkas *et al.*, 2011), soaps (Nanocyclic, 2008), and surgical masks (Li *et al.*, 2006). This has significantly increased the potential for human skin exposure beyond intentional antimicrobial use. It is known that the human body can accumulate Ag with overuse of silver sulphadiazine causing Argyria, a bluish graying of skin (Wang *et al.*, 1985; Fung and Bowen, 1996). This has raised human health and safety concerns for nano Ag skin exposure, particularly as these products maybe applied to

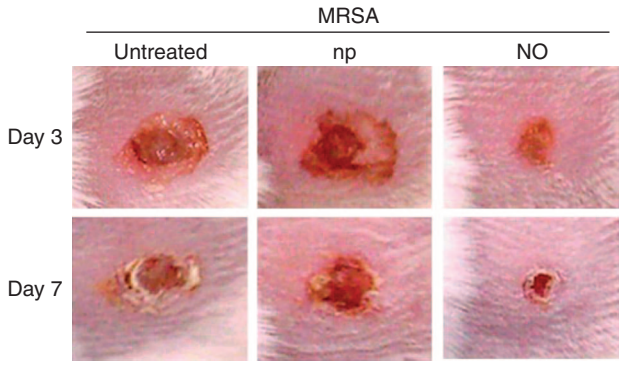

Figure 5. Antimicrobial properties of nanoparticles accelerate wound healing. Nitric oxide (NO)–releasing nanoparticles increase healing rate of wounds infected with methicillin-resistant *Staphylococcus aureus* (MRSA) in Balb/c mice relative to untreated controls and wounds treated with nanoparticles alone (np). Figure is adapted from Martinez *et al.*, 2009.

barrier-defective skin (Lubick, 2008a; Christensen *et al.*, 2010; Jun *et al.*, 2011; Teow *et al.*, 2011). A recent study reported that topical application of nano Ag *in vivo* to pigs daily for 14 consecutive days caused dose-dependent epidermal edema and dermal inflammation, with epidermal hyperplasia at the highest concentration, consistent with a chronic skin irritation response (Samberg *et al.*, 2010). *In vitro* studies showed that nano Ag produced dose-dependent cytotoxicity and cytokine responses in keratinocytes, suggesting the potential for adverse tissue responses, particularly if applied to barrier-defective skin such as on open wounds.

CHALLENGES, PERSPECTIVES, AND CONCLUSION

This review provides a general overview of the nanotechnology and its therapeutic applications in dermatology. This is a growing research area that has led to the establishment of the Nanodermatology Society in 2010 to promote a greater understanding of the scientific and medical aspects of nanotechnology in skin health and disease. In addition to therapeutics, the expanding use of nanomaterials in technological and consumer applications has increased the potential for unintentional human skin exposure. This has generated considerable interest in determining the conditions under which nanoparticles may penetrate skin—an essential property for therapeutic efficacy, but the one that may provoke potential negative side effects. Motivated by the wide use of nanoparticles in ultraviolet B radiation–protective sunscreens and topical cosmetics, metal oxide nanoparticles are one of the most studied (Nohynek *et al.*, 2007, 2008; Burnett and Wang, 2011). From available literature, it is reasonable to conclude that under normal use conditions on healthy skin, the penetration of ZnO and TiO_2 nanoparticles pose minimal health concern. ZnO is soluble in acidic environments, and the acidity of the skin stratum corneum likely induces dissolution and penetration of ionic Zn (Jang *et al.*, 2010b). Zinc is an essential mineral and therefore poses minimal toxicity concern. TiO_2 nanoparticles are highly insoluble and are prone to agglomeration, which may hinder their penetration (Sadrieh *et al.*, 2010). Furthermore, stability and low toxicity of TiO_2 are two properties that have long been exploited in the successful use of Ti metal for dental and orthopedic implants (Geetha *et al.*, 2009). The adjuvant effect of these (Vamanu *et al.*, 2008) and other types of nanoparticles that may contact barrier-defective skin, as well as the effect of UVR induced immunosuppression on nanoparticle skin interactions, remain important open questions. Limited data exist on nanoparticle interaction with diseased skin. Atopic dermatitis and psoriasis are common conditions on the rise (Stensen *et al.*, 2008; Koebnick *et al.*, 2011). Contact hypersensitivity is a common occupational disease (Diepgen and Coenraads, 1999). The effects of these barrier-altering skin conditions on the penetration and transport of nanoparticles are largely unknown. As studies intensify, consistent use of skin models, nanoparticle standards, and exposure conditions will greatly aid our ability to solidify trends from the published literature. More sensitive imaging techniques (Graf *et al.*, 2009; Lin *et al.*, 2011; Mortensen *et al.*, 2011) are needed that can track the biodistribution of nanoparticles systemically. Greater emphasis is needed on quantitative studies that can relate nanoparticle exposure (dose) to nanoparticle penetration and therapeutic efficacy. Quantitative studies are needed to determine whether nanoparticle therapeutics can be delivered more effectively through diseased skin, or whether unintentional nanoparticle exposure may exacerbate symptoms in susceptible individuals. To date, there has been an inconsistent reporting of the detection sensitivity of the techniques used, which can lead to incorrect conclusions about prevalence of nanoparticle skin penetration. From a mechanistic perspective, relatively little is known about nanoparticle transport mechanisms in skin. Transcelluar transport between corneocytes in the stratum corneum (Mortensen *et al.*, 2008; Monteiro-Riviere and Zhang, 2009) has been reported; however, the dominant transport mechanism through the epidermis is not well characterized. Langerhans cells have been identified as an important systemic transport mechanism to lymph nodes (Vogt *et al.*, 2006; Mahe *et al.*, 2009), but the ability of nanoparticles to affect LC function by preventing antigen uptake or altering antigen presentation or migration have yet to be fully explored. Therefore, although the imaging and therapeutic applications of nanotechnology to dermatology are promising areas, there are many interesting unanswered questions and technical challenges that provide significant opportunity for further investigative studies.

CONFLICT OF INTEREST

The author states no conflict of interest.

ACKNOWLEDGMENTS

I acknowledge Drs Beck, Miller, Pentland, and Scott from the University Of Rochester Dermatology Department for their continued support and helpful discussions; Biomedical Engineering graduate student Samreen Jatana for providing the images reported in Figure 3b; and the National Science Foundation (CBET 0837891) and the National Institutes of Health (R21OH009970) for financial support.

REFERENCES

Abeck M (1998) Staphylococcus aureus colonization in atopic dermatitis and its therapeutic implications. *Br J Dermatol* 139:13–6

Adiseshaiah PP, Hall JB, McNeil SE (2010) Nanomaterial standards for efficacy and toxicity assessment. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 2:99–112

Al-Jamal WT, Al-Jamal KT, Tian B *et al.* (2009) Tumor targeting of functionalized quantum dot-liposome hybrids by intravenous administration. *Mol Pharm* 6:520–30

Altman KW, Desai SC, Moline J *et al.* (2010) Odor identification ability and self-reported upper respiratory symptoms in workers at the post-9/11 World Trade Center site. *Int Arch Occup Environ Health* 84:131–7

Arts JH, Bloksma N, Leusink-Muis T *et al.* (2003) Respiratory allergy and pulmonary irritation to trimellitic anhydride in Brown Norway rats. *Toxicol Appl Pharmacol* 187:38–49

AshaRani PV, Mun GLK, Hande MP *et al.* (2009) Cytotoxicity and genotoxicity of silver nanoparticles in human cells. *ACS Nano* 3:279–90

Baker TS, Newcomb WW, Olson NH *et al.* (1991) Structures of bovine and human papillomaviruses. Analysis by cryoelectron microscopy and three-dimensional image reconstruction. *Biophys J* 60:1445–56

Baroli B (2010) Penetration of nanoparticles and nanomaterials in the skin: fiction or reality? *J Pharm Sci* 99:21–50

Bashir SJ, Chew A-L, Anigbogu A *et al.* (2001) Physical and physiological effects of stratum corneum tape stripping. *Skin Res Technol* 7:40–8

Beck LA, Leung DY (2000) Allergen sensitization through the skin induces systemic allergic response. *J Allergy Clin Immunol* 106:S258–3

Benezra M, Penate-Medina O, Zanzonico PB *et al.* (2011) Multimodal silica nanoparticles are effective cancer-targeted probes in a model of human melanoma. *J Clin Invest* 121:2768–80

Benn TM, Westerhoff P (2008) Nanoparticle silver released into water from commercially available sock fabrics. *Environ Sci Technol* 42:4133–9

Benson HA (2009) Elastic liposomes for topical and transdermal drug delivery. *Curr Drug Deliv* 6:217–26

Boisselier E, Astruc D (2009) Gold nanoparticles in nanomedicine: preparations, imaging, diagnostics, therapies and toxicity. *Chem Soc Rev* 38:1759–82

Boles KS, Schmieder AH, Koch AW *et al.* (2010) MR angiogenesis imaging with Robo4- vs. alphaVbeta3-targeted nanoparticles in a B16/F10 mouse melanoma model. *FASEB J* 24:4262–70

Bolzinger M-A, Briancom S, Chevalier Y (2011) Nanoparticles through the skin: managing conflicting results of inorganic and organic particles in cosmetic and pharmaceutics. *WIREs Nanomed Nanobiotech* 3:463–78

Bottrill M, Green M (2011) Some aspects of quantum dot toxicity. *Chem Commun* 47:7039–50

Breuer K, HAussler S, Kapp A *et al.* (2002) *Staphylococcus aureus*: colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. *Br J Dermatol* 147:55–61

Bronaugh RL, Stewart RF, Congdon ER (1982) Methods for *in vitro* percutaneous absorption studies. II. Animal models for human skin. *Toxicol Appl Pharmacol* 62:481–8

Burnett ME, Wang SQ (2011) Current sunscreen controversies: a critical review. *Photodermatol Photoimmunol Photomed* 27:58–67

Buzea C, Pacheco II, Robbie K (2007) Nanomaterials and nanoparticles: sources and toxicity. *Biointerphases* 2:MR17

Camerin M, Magaraggia M, Soncin M *et al.* (2010) The *in vivo* efficacy of phthalocyanine-nanoparticle conjugates for the photodynamic therapy of amelanotic melanoma. *Eur J Cancer* 46:1910–8

Carlson JA, Linette GP, Aplin A *et al.* (2007) Melanocyte receptors: clinical implications and therapeutic relevance. *Dermatol Clin* 25:541–57

Chaloupka K, Malam Y, Seifalian AM (2010) Nanosilver as a new generation of nanoproduct in biomedical applications. *Trends Biotechnol* 28: 580–8

Chamakura K, Perez-Ballestero R, Luo Z *et al.* (2011) Comparison of bactericidal activities of silver nanoparticles with common chemical disinfectants. *Colloids Surf B Biointerfaces* 84:88–96

Chen XF, Prow TW, Crichton ML *et al.* (2009) Dry-coated microprojection array patches for targeted delivery of immunotherapeutics to the skin. *J Control Release* 139:212–20

Chen Y, Bathula SR, Yang Q *et al.* (2010a) Targeted nanoparticles deliver siRNA to melanoma. *J Invest Dermatol* 130:2790–8

Chen Y, Zhu X, Zhang X *et al.* (2010) Nanoparticles modified with tumor-targeting scFv deliver siRNA and miRNA for cancer therapy. *Mol Ther* 18:1650–6

Cho K, Wang X, Nie S *et al.* (2008) Therapeutic nanoparticles for drug delivery in cancer. *Clin Cancer Res* 14:1310–6

Choi HS, Liu W, Misra P *et al.* (2007) Renal clearance of quantum dots. *Nat Biotechnol* 25:1165–70

Choi MJ, Maibach HI (2005) Elastic vesicles as topical/transdermal drug delivery systems. *Int J Cosmet Sci* 27:211–21

Choi HS, Liu W, Liu F *et al.* (2010) Design considerations for tumour-targeted nanoparticles. *Nat Nanotechnol* 5:42–7

Chourasia R, Jain SK (2009) Drug targeting through pilosebaceous route. *Curr Drug Targets* 10:950–67

Christensen FM, Johnston HJ, Stone V *et al.* (2010) Nano-silver - feasibility and challenges for human health risk assessment based on open literature. *Nanotoxicology* 4:284–95

Clark RA, Chong B, Mirchandani N *et al.* (2006) The vast majority of CLA+ T cells are resident in normal skin. *J Immunol* 176:4431–9

Colvin V (2003) The potential environmental impact of engineered nanomaterials. *Nat Biotechnol* 21:1166–70

Cone JE, Farfel M (2011) World trade center health registry—a model for a nanomaterials exposure registry. *J Occup Environ Med* 53(6 Suppl): S48–51

Costa C, Conte A, Buonocore GG *et al.* (2011) Antimicrobial silver-montmorillonite nanoparticles to prolong the shelf life of fresh fruit salad. *Int J Food Microbiol* 148:164–7

Cui HF, Vashist SK, Al-Rubeaan K *et al.* (2010) Interfacing carbon nanotubes with living mammalian cells and cytotoxicity issues. *Chem Res Toxicol* 23:1131–47

Cukierman E, Pankov R, Yamada KM (2002) Cell interactions with three-dimensional matrices. *Curr Opin Cell Biol* 14:633–9

Dastjerdi R, Montazer M (2010) A review on the application of inorganic nano-structured materials in the modification of textiles: focus on anti-microbial properties. *Colloids Surf B Biointerfaces* 79:5–18

Davis ME, Zuckerman JE, Choi CHJ *et al.* (2010) Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. *Nature* 464:1067–70

Debbage P (2009) Targeted drugs and nanomedicine: present and future. *Curr Pharm Des* 15:153–72

De Jong WH, Borm PJA (2008) Drug delivery and nanoparticles: applications and hazards. *Int J Nanomed* 3:133–49

Dhar S, Kolishetti N, Lippard SJ *et al.* (2011) Targeted delivery of a cisplatin prodrug for safer and more effective prostate cancer therapy *in vivo*. *Proc Natl Acad Sci USA* 108:1850–5

Diepgen TL, Coenraads PJ (1999) The epidemiology of occupational contact dermatitis. *Int Arch Occup Environ Health* 72:496–506

Dowling A, Cliff R, Grobert N *et al.* (2004) *Nanoscience and Nanotechnologies: Opportunities and Uncertainties*. London: The Royal Society & The Royal Academy of Engineering. Report 44, 7–10

Dubina M, Goldenberg G (2009) Viral-associated nonmelanoma skin cancers: a review. *Am J Dermatopathol* 31:561–73

Elder A, Vidyasagar S, DeLouise L (2009) Physicochemical factors that affect metal and metal oxide nanoparticle passage across epithelial barriers. *Wiley Interdiscip Rev Nanomed Nanobiotechnol* 1:434–50

Elliott C (2010) The effects of silver dressings on chronic and burns wound healing. *Br J Nurs* 19:S32–6

Endo M, Hayashi T, Kim YA *et al.* (2004) Applications of carbon nanotubes in the twenty-first century. *Phil Trans R Soc Lond A* 362:2223–38

Fang FC (2004) Antimicrobial reactive oxygen and nitrogen species: concepts and controversies. *Nat Rev Micro* 2:820–32

Farkas J, Peter H, Christian P *et al.* (2011) Characterization of the effluent from a nanosilver producing washing machine. *Environ Int* 37: 1057–62

Fernando GJP, Chen XF, Prow TW *et al.* (2010) Potent immunity to low doses of influenza vaccine by probabilistic guided micro-targeted skin delivery in a mouse model. *PLoS ONE* 5:e10266

Filipe P, Silva JN, Silva R *et al.* (2009) Stratum corneum is an effective barrier to TiO_2 and ZnO nanoparticle percutaneous absorption. *Skin Pharmacol Physiol* 22:266–75

Fioretti F, Mendoza-Palomares C, Helms M *et al.* (2010) Nanostructured assemblies for dental application. *ACS Nano* 4:3277–87

Frangioni JV (2008) New technologies for human cancer imaging. *J Clin Oncol* 26:4012–21

Friedman AJ, Han G, Navati MS *et al.* (2008) Sustained release nitric oxide releasing nanoparticles: characterization of a novel delivery platform based on nitrite containing hydrogel/glass composites. *Nitric Oxide* 19:12–20

Fung MC, Bowen DL (1996) Silver products for medical indications: risk-benefit assessment. *Clin Toxicol* 34:119–26

Gallo RL, Nakatsuji T (2011) Microbial symbiosis with the innate immune defense system of the skin. *J Invest Dermatol* 131:1974–80

Gao X, Cui Y, Levenson RM *et al.* (2004) *In vivo* cancer targeting and imaging with semiconductor quantum dots. *Nat Biotechnol* 22: 969–76

Geetha M, Singh AK, Asokamani R *et al.* (2009) Ti based biomaterials, the ultimate choice for orthopaedic implants – A review. *Prog Mater Sci* 54:397–425

Geusens B, Sanders N, Prow T *et al.* (2009) Cutaneous short interfering RNA therapy. *Expert Opin Drug Deliv* 6:1333–49

Geusens B, Van Gele M, Braat S *et al.* (2010) Flexible nanosomes (SECosomes) enable efficient siRNA delivery in cultured primary skin cells and in viable epidermis of *ex vivo* human skin. *Adv Func Mater* 20:4077–90

Ghosh S, Spagnoli GC, Martin I *et al.* (2005) Three-dimensional culture of melanoma cells profoundly affects gene expression profile: a high density oligonucleotide array study. *J Cell Physiol* 204:522–31

Gopee NV, Roberts DW, Webb P *et al.* (2009) Quantitative determination of skin penetration of peg-coated cdse quantum dots in dermabraded but not intact skh-1 hairless mouse skin. *Toxicol Sci* 111:37–48

Graf C, Meinke M, Gao Q *et al.* (2009) Qualitative detection of single submicron and nanoparticles in human skin by scanning transmission x-ray microscopy. *J Biomed Opt* 14:021015

Grecco ACP, Paula RFO, Mizutani E *et al.* (2011) Up-regulation of T lymphocyte and antibody production by inflammatory cytokines released by macrophage exposure to multi-walled carbon nanotubes. *Nanotechnology* 22:265103

Gulson B, McCall M, Korsch M *et al.* (2010) Small amounts of zinc from zinc oxide particles in sunscreens applied outdoors are absorbed through human skin. *Toxicol Sci* 118:140–9

Gwinn MR, Vallyathan V (2006) Nanoparticles: health effects—pros and cons. *Environ Health Perspect* 114:1818–25

Hama Y, Koyama Y, Urano Y *et al.* (2007) Two-color lymphatic mapping using Ig-conjugated near infrared optical probes. *J Invest Dermatol* 127: 2351–6

Hild WA, Breunig M, Goepferich A (2008) Quantum dots–nano-sized probes for the exploration of cellular and intracellular targeting. *Eur J Pharm Biopharm* 68:153–68

Hild W, Pollinger K, Caporale A *et al.* (2010) G protein-coupled receptors function as logic gates for nanoparticle binding and cell uptake. *Proc Natl Acad Sci USA* 107:10667–72

Hoch M, Eberle AN, Wagner U *et al.* (2007) Expression and localization of melanocortin-1 receptor in human adipose tissues of severely obese patients. *Obesity (Silver Spring)* 15:40–9

Holleran WM, Uchida Y, Halkier-Sorensen L *et al.* (1997) Structural and biochemical basis for the UVB-induced alterations in epidermal barrier function. *Photodermatol Photoimmunol Photomed* 13:117–28

Holzmann S, Tripp CH, Schmuth M *et al.* (2004) A model system using tape stripping for characterization of Langerhans cell-precursors *in vivo*. *J Invest Dermatol* 122:1165–74

Huang HC, Barua S, Sharma G *et al.* (2011) Inorganic nanoparticles for cancer imaging and therapy. *J Control Release* 155:344–57

Huang X, Peng X, Wang Y *et al.* (2010a) A reexamination of active and passive tumor targeting by using rod-shaped gold nanocrystals and covalently conjugated peptide ligands. *ACS Nano* 4:5887–96

Huang Y, Yu F, Park YS *et al.* (2010b) Coadministration of protein drugs with gold nanoparticles to enable percutaneous delivery. *Biomaterials* 31:9086–91

Ilbasmiş-Tamer S, Yilmaz S, Banoğlu E *et al.* (2010) Carbon nanotubes to deliver drug molecules. *J Biomed Nanotechnol* 6:20–7

Immordino ML, Dosio F, Cattel L (2006) Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. *Int J Nanomed* 1:297–315

Iwasaki A, Medzhitov R (2004) Toll-like receptor control of the adaptive immune responses. *Nat Immunol* 5:987–95

Iyer AK, Khaled G, Fang J *et al.* (2006) Exploiting the enhanced permeability and retention effect for tumor targeting. *Drug Discovery Today* 11: 812–8

Jang B, McCall M, Korsch M *et al.* (2010b) Small amounts of zinc from zinc oxide particles in sunscreens applied outdoors are absorbed through human skin. *Toxicol Sci* 118:140–9

Jang J, Lim D-H, Choi I-H (2010a) The impact of nanomaterials in immune system. *Immune Netw* 10:85–91

Jeong SH, Kim JH, Yi SM *et al.* (2010) Assessment of penetration of quantum dots through *in vitro* and *in vivo* human skin using the human skin equivalent model and the tape stripping method. *Biochem Biophys Res Commun* 394:612–5

Jin CY, Zhu BS, Wang XF *et al.* (2008) Cytotoxicity of titanium dioxide nanoparticles in mouse fibroblast cells. *Chem Res Toxicol* 21:1871–7

Jones ML, Ganopolsky JG, Labbé A *et al.* (2010) Antimicrobial properties of nitric oxide and its application in antimicrobial formulations and medical devices. *Appl Microbiol Biotechnol* 88:401–7

Jun EA, Lim KM, Kim KY *et al.* (2011) Silver nanoparticles enhance thrombus formation through increased platelet aggregation and procoagulant activity. *Nanotoxicology* 5:157–67

Jung WK, Koo HC, Kim KW *et al.* (2008) Antibacterial activity and mechanism of action of the silver ion in Staphylococcus aureus and Escherichia coli. *Appl Environ Microbiol* 74:2171–8

Kambara T, Aihara M, Matsukura S *et al.* (2006) Effects of photocatalytic agent on DS-Nh mice, developing atopic dermatitis-like eruption with an increase of *Staphylococcus aureus*. *Int Arch Allergy Immunol* 141:151–7

Karimipour DJ, Karimipour G, Orringer JS (2010) Microdermabrasion: an evidence-based review. *Plast Reconstr Surg* 25:372–7

Kaul G, Amiji M (2002) Long-circulating poly(ethylene glycol)-modified gelatin nanoparticles for intracellular delivery. *Pharm Res* 19:1061–7

Kim C, Cho EC, Chen J *et al.* (2010) *In vivo* molecular photoacoustic tomography of melanomas targeted by bioconjugated gold nanocages. *ACS Nano* 4:4559–64

Kim YC, Jarrahian C, Zehrung D *et al.* (2012) Delivery systems for intradermal vaccination. *Curr Top Microbiol Immunol* 351:77–112

Kirjavainen M, Urtti A, Valjakka-Koskela R *et al.* (1999) Liposome–skin interactions and their effects on the skin permeation of drugs. *Eur J Pharm Sci* 7:279–86

Koebnick C, Black MH, Smith N *et al.* (2011) The association of psoriasis and elevated blood lipids in overweight and obese children. *J Pediatrics* 159:577–83

Kosaka N, Ogawa M, Sato N *et al.* (2009) *In vivo* real-time, multicolor, quantum dot lymphatic imaging. *J Invest Dermatol* 129:2818–22

Lademann J, Otberg N, Richter H *et al.* (2001) Investigation of follicular penetration of topically applied substances. *Skin Pharmacol Appl Skin Physiol* 14(Suppl 1):17–22

Lademann J, Richter H, Teichmann A *et al.* (2007) Nanoparticles—an efficient carrier for drug delivery into the hair follicles. *Eur J Pharm Biopharm* 66:159–64

Lademann J, Richter H, Schanzer S *et al.* (2011) Penetration and storage of particles in human skin: perspectives and safety aspects. *Eur J Pharm Biopharm* 77:465–8

Laroui H, Dalmasso G, Nguyen HT *et al.* (2009) Drug-loaded nanoparticles targeted to the colon with polysaccharide hydrogel reduce colitis in a mouse model. *Gastroenterology* 138:843–53

Lev DC, Onn A, Melinkova VO *et al.* (2004) Exposure of melanoma cells to dacarbazine results in enhanced tumor growth and metastasis *in vivo*. *J Clin Oncol* 22:2092–100

Li D, Taylor AW (2008) Diminishment of alpha-MSH anti-inflammatory activity in MC1r siRNA-transfected RAW264.7 macrophages. *J Leukoc Biol* 84:191–8

Li Y, Leung P, Yao L *et al.* (2006) Antimicrobial effect of surgical masks coated with nanoparticles. *J Hosp Infect* 62:58–63

Li Z, Huang P, Lin J *et al.* (2010) Arginine-glycine-aspartic acid-conjugated dendrimer-modified quantum dots for targeting and imaging melanoma. *J Nanosci Nanotechnol* 10:4859–67

Lim SW, Kim HW, Jun HY *et al.* (2011) TCL-SPION-enhanced MRI for the detection of lymph node metastasis in murine experimental model. *Acad Radiol* 18:504–11

Lin LL, Grice JE, Butler MK *et al.* (2011) Time-correlated single photon counting for simultaneous monitoring of Zinc oxide nanoparticles and NAD(P)H in intact and barrier-disrupted volunteer skin. *Pharm Res* 28:2920–30

Lindemann U, Wilken K, Weigmann HJ *et al.* (2003) Quantification of the horny layer using tape stripping and microscopic techniques. *J Biomed Opt* 8:601–7

Loir B, Perez Sanchez C, Ghanem G *et al.* (1999) Expression of the MC1 receptor gene in normal and malignant human melanocytes. A semiquantitative RT-PCR study. *Cell Mol Biol* 445:1083–92

Long TC, Saleh N, Tilton RD *et al.* (2006) Titanium Dioxide (P25) produces reactive oxygen species in Immortalized brain microglia (BV2): implications for nanoparticle neurotoxicity. *Environ Sci Technol* 40:4346–52

Lopez RF, Seto JE, Blankschtein D *et al.* (2011) Enhancing the transdermal delivery of rigid nanoparticles using the simultaneous application of ultrasound and sodium lauryl sulfate. *Biomaterials* 32:933–41

Low SP, Voelcker NH, Canham LT *et al.* (2009) The biocompatibility of porous silicon in tissues of the eye. *Biomaterials* 30:2873–80

Lu W, Xiong C, Zhang G *et al.* (2009) Targeted photothermal ablation of murine melanomas with melanocyte-stimulating hormone analog-conjugated hollow gold nanospheres. *Clin Cancer Res* 15:876–86

Lubick N (2008) Silver socks have cloudy lining. *Environ Sci Technol* 42:3910

Lubick N (2008a) Nanosilver toxicity: ions, nanoparticles or both? *Environ Sci Technol* 42:8617

Luo JD, Chen AF (2005) Nitric oxide: a newly discovered function on wound healing. *Acta Pharmacol Sin* 26:259–64

Lynch I, Cedervall T, Lundqvist M *et al.* (2007) The nanoparticle–protein complex as a biological entity; a complex fluids and surface science challenge for the 21st century. *Adv Colloid Interface Sci* 134-135: 167–74

Lynch I, Dawson KA, Linse S (2006) Detecting cryptic epitopes created by nanoparticles. *Sci STKE* 2006:pe14

Ma Q, Su X (2010) Near-infrared quantum dots: synthesis, functionalization and analytical applications. *Analyst* 135:1867–77

Mahe B, Vogt A, Liard C *et al.* (2009) Nanoparticle-based targeting of vaccine compounds to skin antigen-presenting cells by hair follicles and their transport in mice. *J Invest Dermatol* 129:1156–64

Martinez LR, Han G, Chacko M *et al.* (2009) Antimicrobial and healing efficacy of sustained release nitric oxide nanoparticles against *Staphylococcus aureus* skin infection. *J Invest Dermatol* 129:2463–9

Maurer D, Stingl G (2001) Langerhans cells. In: *Dendritic Cells: Biology and Clinical Applications*. (Lotze MT, Thomas AW (eds), Academic Press, NY, 35–50

McNeela EA, Lavelle EC (2011) Recent advances in microparticle and nanoparticle delivery vehicles for mucosal vaccination. *Curr Top Microbiol Immunol*; e-pub ahead of print 9 September 2011

Menetrez MY, Foarde KK, Ensor DS (2001) An analytical method for the measurement of nonviable bioaerosols. *J Air Waste Manag Assoc* 51:1436–42

Misra SK, Mohn D, Brunner TJ *et al.* (2008) Comparison of nanoscale and microscale bioactive glass on the properties of P(3HB)/Bioglass composites. *Biomaterials* 29:1750–61

Moghimi SM, Hunter AC, Murray JC (2005) Nanomedicine: current status and future prospects. *FASEB J* 19:311–30

Monteiro-Riviere NA, Zhang LW (2009) Assessment of Quantum Dot Penetration into Skin in Different Species Under Different Mechanical Actions. *Nanomaterials: Risks and Benefits, NATO Science for Peace and Security Series C: Environmental Security*. Springer Netherlands, p. 43

Monteiro-Riviere NA, Wiench K, Landsiedel R *et al.* (2011) Safety evaluation of sunscreen formulations containing titanium dioxide and zinc oxide nanoparticles in UVB sunburned skin: an *in vitro* and *in vivo* study. *Toxicol Sci* 123:264–80

Mortensen LJ, Glazowski CE, Zavislan JM *et al.* (2011) Near-IR fluorescence and reflectance confocal microscopy for imaging of quantum dots in mammalian skin. *Biomed Opt Express* 2:1610–25

Mortensen LJ, Oberdorster G, Pentland AP *et al.* (2008) *In vivo* skin penetration of quantum dot nanoparticles in the murine model: the effect of UVR. *Nano Lett* 8:2779–87

Mortensen LJ, Ravichandran S, Zheng H *et al.* (2010) Progress and challenges in quantifying skin permeability to nanoparticles using a quantum dot model. *J Biomed Nanotechnol* 6:596–604

Müller RH, Mäder K, Gohla S (2000) Solid lipid nanoparticles (SLN) for controlled drug delivery - a review of the state of the art. *Eur J Pharm Biopharm* 50:161–77

Nakagawa Y, Wakuri S, Sakamoto K *et al.* (1997) The photogenotoxicity of titanium dioxide particles. *Mutat Res* 394:125–32

Nanocyclic (2008) http://nanocyclic.com/

Nanowerk (2010) Nanowerk, Nanotechnology Commercial Organizations 2010. http://www.nanowerk.com/nanotechnology/nanomaterial/commercial_all.php

Nasir A (2008) Dermatologic toxicity of nanoengineered materials. *Arch Dermatol* 144:253–4

Nasir A (2009) Nanotechnology in vaccine development: a step forward. *J Invest Dermatol* 129:1055–9

Nel A, Xia T, Mädler L *et al.* (2006) Toxic potential of materials at the nanolevel. *Science* 311:622–7

Neumann AG, Nagaeva O, Mandrika I *et al.* (2001) MC(1) receptors are constitutively expressed on leucocyte subpopulations with antigen presenting and cytotoxic functions. *Clin Exp Immunol* 126:441–6

Nohynek GJ, Lademann J, Ribaud C *et al.* (2007) Grey goo on the skin? Nanotechnology, cosmetic and sunscreen safety. *Crit Rev Toxicol* 37:251–77

Nohynek GJ, Dufour EK, Roberts MS (2008) Nanotechnology, cosmetics and the skin: is there a health risk? *Skin Pharmacol Physiol* 21:136–49

Nowack B, Krug HF, Height M (2011) 120 Years of nanosilver history: implications for policy makers. *Environ Sci Technol*; e-pub ahead of print 10 January 2011

Nygaard UC, Hansen JS, Samuelsen M *et al.* (2009) Single-walled and multi-walled carbon nanotubes promote allergic immune responses in mice. *Toxicol Sci* 109:113–23

O'Meara S, Cullum N, Majid M *et al.* (2000) Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration. *Health Technol Assess* 4:1–237

Otberg N, Richter H, Schaefer H *et al.* (2004) Variations of hair follicle size and distribution in different body sites. *J Invest Dermatol* 122:14–9

Özbaş-Turan S, Akbuğa J (2011) Plasmid DNA-loaded chitosan/TPP nanoparticles for topical gene delivery. *Drug Deliv* 18:215–22

Pan Y, Neuss S, Leifert A *et al.* (2007) Size-dependent cytotoxicity of gold nanoparticles. *Small* 3:1941–9

Parveen S, Misra R, Sahoo SK (2011) Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. *Nanomedicine*; e-pub ahead of print 7 June 2011

Patzelt A, Richter H, Knorr F *et al.* (2011) Selective follicular targeting by modification of the particle sizes. *J Control Release* 150:45–8

Paus R, Schröder JM, Reich K *et al.* (2006) Who is really in control of skin immunity under physiological circumstances – lymphocytes, dendritic cells or keratinocytes? *Exp Dermatol* 15:913–6

Pedata P, Boccellino M, La Porta R *et al.* (2011) Interaction between combustion-generated organic nanoparticles and biological systems: *In vitro* study of cell toxicity and apoptosis in human keratinocytes. *Nanotoxicology*; e-pub ahead of print 16 May 2011

Polat BE, Hart D, Langer R *et al.* (2011) Ultrasound-mediated transdermal drug delivery: mechanisms, scope, and emerging trends. *J Control Release* 152:330–48

Prow TW, Grice JE, Lin LL *et al.* (2011a) Nanoparticles and microparticles for skin drug delivery. *Adv Drug Deliv Rev* 63:470–91

Prow TW, Monteiro-Riviere NA, Inman AO *et al.* (2011b) Quantum dot penetration into viable human skin. *Nanotoxicology*; e-pub ahead of print 1 April 2011

Rancan F, Papakostas D, Hadam S *et al.* (2009) Investigation of polylactic acid (PLA) nanoparticles as drug delivery systems for local dermatotherapy. *Pharm Res* 26:2027–36

Ravichandran S, Mortensen LJ, DeLouise LA (2010) Quantification of human skin barrier function and susceptibility to quantum dot skin penetration. *Nanotoxicology* 5:675–86

Reilly DM, Green MR (1999) Eicosanoid and cytokine levels in acute skin irritation in response to tape stripping and capsaicin. *Acta Derm Venereol* 79:187–90

Reubi JC (2003) Peptide receptors as molecular targets for cancer diagnosis and therapy. *Endocrine Rev* 24:389–427

Riehemann K, Schneider SW, Luger TA *et al.* (2009) Nanomedicine—challenge and perspectives. *Angew Chem Int Ed Engl* 48:872–97

Rittner MN, Abraham T (1998) Nanostructured materials: an overview and commercial analysis. *J Miner Met Mater Soc* 50:37–8

Robichaud CO, Uyar AE, Darby MR *et al.* (2009) Estimates of upper bounds and trends in nano-TiO_2 production as a basis for exposure assessment. *Environ Sci Technol* 43:4227–33

Rosenholm JM, Sahlgren C, Linden M (2011) Multifunctional mesoporous silica nanoparticles for combined therapeutic, diagnostic and targeted action in cancer treatment. *Curr Drug Targets* 12:1166–86

Rouse JG, Yang J, Ryman-Rasmussen JP *et al.* (2007) Effects of mechanical flexion on the penetration of fullerene amino acid-derivatized peptide nanoparticles through skin. *Nano Lett* 7:155–60

Ryman-Rasmussen JP, Riviere JE, Monteiro-Riviere NA (2006) Surface coatings determine cytotoxicity and irritation potential of quantum dot nanoparticles in epidermal keratinocytes. *J Invest Dermatol* 127: 143–53

Sadrieh N, Wokovich AM, Gopee NV *et al.* (2010) Lack of significant dermal penetration of titanium dioxide from sunscreen formulations containing nano- and submicron-size TiO_2 particles. *Toxicol Sci* 115:156–66

Salazar-Onfray F, López M, Lundqvist MA *et al.* (2002) Tissue distribution and differential expression of melanocortin 1 receptor, a malignant melanoma marker. *Br J Cancer* 87:414–22

Samberg ME, Oldenburg SJ, Monteiro-Riviere NA (2010) Evaluation of silver nanoparticle toxicity in skin *in vivo* and keratinocytes *in vitro*. *Environ Health Perspec* 118:407–13

Sarfati G, Dvir T, Elkabets M *et al.* (2011) Targeting of polymeric nanoparticles to lung metastases by surface-attachment of YIGSR peptide from laminin. *Biomaterials* 32:152–61

Schäfer-Korting M, Korting HC, Braun-Falco O (1989) Liposome preparations: a step forward in topical drug therapy for skin disease? A review. *J Am Acad Dermatol* 21:1271–5

Schmieder AH, Winter PM, Caruthers SD *et al.* (2005) Molecular MR imaging of melanoma angiogenesis with anb3-targeted paramagnetic nanoparticles. *Magn Reson Med* 53:621–7

Schneider M, Stracke F, Hansen S *et al.* (2009) Nanoparticles and their interactions with the dermal barrier. *Dermatoendocrinol* 1:197–206

Schottelius M, Wester H-J (2009) Molecular imaging targeting peptide receptors. *Methods* 48:161–77

Schulz J, Hohenberg H, Pflücker F *et al.* (2002) Distribution of sunscreens on skin. *Adv Drug Deliv Rev* 54:S157–63

Schwarz T (2008) 25 years of UV-induced immunosuppression mediated by T cells-from disregarded T suppressor cells to highly respected regulatory T cells. *Photochem Photobiol* 84:10–8

Schwarz T, Schwarz A (2011) Molecular mechanisms of ultraviolet radiation-induced immunosuppression. *Eur J Cell Biol* 90:560–4

Siegrist W, Stutz S, Eberle AN (1994) Homologous and heterologous regulation of α-melanocyte-stimulating hormone receptors in human and mouse melanoma cell lines. *Cancer Res* 54:2604–10

Silver S, Phung LT (1996) Bacterial heavy metal resistance: new surprises. *Annu Rev Microbiol* 50:753–89

Simonsson C, Andersson SI, Stenfeldt AL *et al.* (2011) Caged fluorescent haptens reveal the generation of cryptic epitopes in allergic contact dermatitis. *J Invest Dermatol* 131:1486–93

Smijs TG, Bouwstra JA (2010) Focus on skin as a possible port of entry for solid nanoparticles and the toxicological impact. *J Biomed Nanotechnol* 6:469–84

Sonavane G, Tomoda K, Sano A *et al.* (2008) *In vitro* permeation of gold nanoparticles through rat skin and rat intestine: effect of particle size. *Colloids Surf B Biointerfaces* 65:1–10

Sortino S (2010) Light-controlled nitric oxide delivering molecular assemblies. *Chem Soc Rev* 39:2903–13

Srinivasan S, Lubrano-Berthelier C, Govaerts C *et al.* (2004) Constitutive activity of the melanocortin-4 receptor is maintained by its N-terminal domain and plays a role in energy homeostasis in humans. *J Clin Invest* 114:1158–64

Stensen L, Thomsen SF, Backer V (2008) Change in prevalence of atopic dermatitis between 1986 and 2001 among children. *Allergy Asthma Proc* 29:392–6

Stern ST, McNeil SE. (2008) Nanotechnology safety concerns revisited. *Toxicol Sci* 101:4–21

Stracke F, Weiss B, Lehr CM *et al.* (2006) Multiphoton microscopy for the investigation of dermal penetration of nanoparticle-borne drugs. *J Invest Dermatol* 126:2224–33

Streilein JW, Lonsberry LW, Bergstresser PR (1982) Depletion of epidermal langerhans cells and Ia immunogenicity from tape-stripped mouse skin. *J Exp Med* 155:863–71

Teow Y, Asharani PV, Hande MP *et al.* (2011) Health impact and safety of engineered nanomaterials. *Chem Commun (Camb)* 47:7025–38

Tinkle SS, Antonini JM, Rich BA *et al.* (2003) Skin as a route of exposure and sensitisation in chronic beryllium disease. *Environ Health Perspect* 111:1202–8

Todo H, Kimura E, Yasuno H *et al.* (2010) Permeation pathway of macromolecules and nanospheres through skin. *Biol Pharm Bull* 33: 1394–9

Tsai JC, Shen LC, Sheu HM *et al.* (2003) Tape stripping and sodium dodecyl sulfate treatment increase the molecular weight cutoff of polyethylene glycol penetration across murine skin. *Arch Dermatol Res* 295:169–74

Tsuji JS, Maynard AD, Howard PC *et al.* (2006) Research strategies for safety evaluation of nanomaterials, part iv: risk assessment of nanoparticles. *Toxicol Sci* 89:42–50

Vamanu CI, Hol PJ, Allouni ZE *et al.* (2008) Formation of potential titanium antigens based on protein binding to titanium dioxide nanoparticles. *Int J Nanomed* 3:69–74

Vierkötter A, Schikowski T, Ranft U *et al.* (2010) Airborne particle exposure and extrinsic skin aging. *J Invest Dermatol* 130:2719–26

Vogt A, Combadiere B, Hadam S *et al.* (2006) 40 nm, but not 750 or 1,500 nm, nanoparticles enter epidermal cd1a+ cells after transcutaneous application on human skin. *J Invest Dermatol* 126:1316–22

Walve JR, Bakliwal SR, Rane BR *et al.* (2011) Transfersomes: a surrogated carrier for transdermal drug delivery system. *Int J Appl Biol Pharma Technol* 2:204–13

Wamer WG, Yin JJ, Wei RR (1997) Oxidative damage to nucleic acids photosensitized by titanium dioxide. *Free Radic Biol Med* 23:851–8

Wang XW, Wang NZ, Zhang OZ *et al.* (1985) Tissue deposition of silver following topical use of silver sulphadiazine in extensive burns. *Burns Incl Therm Inj* 11:197–201

Warbrick EV, Dearman RJ, Kimber I (2002) Induced changes in total serum IgE concentration in the Brown Norway rat: potential for identification of chemical respiratory allergens. *J Appl Toxicol* 22:1–11

Weiss MB, Andrew E, Aplin AE (2010) Paying ''particle'' attention to novel melanoma treatment strategies. *J Invest Dermatol* 130:2699–701

Weller R, Finnen MJ (2006) The effects of topical treatment with acidified nitrite on wound healing in normal and diabetic mice. *Nitric Oxide* 15:395–9

Wen A, Tao X, Lakkis F *et al.* (1999) Toxin-related a-melanocyte-stimulating hormone fusion toxin. *J Biol Chem* 266:12289–93

Wong W, Minchin RF (1996) Binding and internalization of the melanocyte stimulating hormone receptor ligand [Nle4, D-Phe7] α-MSH in B16 melanoma cells. *Int J Biochem Cell Biol* 28:1223–32

Xu A, Chai Y, Nohmi T *et al.* (2009) Genotoxic responses to titanium dioxide nanoparticles and fullerene in *gpt* delta transgenic MEF cells. *Part Fibre Toxicol* 6:3

Yanagisawa R, Takano H, Inoue K *et al.* (2009) Titanium dioxide nanoparticles aggravate atopic dermatitis-like skin lesions in NC/Nga mice. *Exp Biol Med* 234:314–22

Yao H, Ng SS, Huo LF *et al.* (2011) Effective melanoma immunotherapy with interleukin-2 delivered by a novel polymeric nanoparticle. *Mol Cancer Ther* 10:1082–92

Zhang L, Gu FX, Chan JM *et al.* (2008) Nanoparticles in medicine: therapeutic applications and developments. *Clin Pharmacol Ther* 83:761–9

Zhang LW, Monteiro-Riviere NA (2009) Mechanisms of quantum dot nanoparticle cellular uptake. *Toxicol Sci* 110:138–55

Zhang LW, Monteiro-Riviere NA (2008a) Assessment of quantum dot penetration into intact, tape-stripped, abraded and flexed rat skin. *Skin Pharmacol Appl* 21:166–80

Zhang LW, Yu W W, Colvin VL *et al.* (2008b) Biological interactions of quantum dot nanoparticles in skin and in human epidermal keratinocytes. *Toxicol Appl Pharm* 228:200–11

Zheng H, Chen G, DeLouise LA *et al.* (2010) Detection of the cancer marker CD146 expression in melanoma cells with semiconductor quantum dot label. *J Biomed Nanotechnol* 6:303–11

Zhou M, Nakatani E, Gronenberg LS *et al.* (2007) Peptide-labeled quantum dots for imaging GPCRs in whole cells and as single molecules. *Bioconjug Chem* 18:323–32

Zhu X, Bidlingmair S, Hashizume R *et al.* (2010) Identification of internalizing human single chain antibodies targeting brain tumor sphere cells. *Mol Cancer Ther* 9:2131–41

Zolnik BS, González-Fernández A, Sadrieh N *et al.* (2010) Minireview: nanoparticles and the immune system. *Endocrinology* 151:458–65