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Applications of Nanotechnology in Dermatology

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Abstract

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 unintended 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, out weigh 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 different 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.

Nanotechnology and Nanomedicine

Nanoparticles are defined as any material with at least one dimension that is <100 nm (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 (Dubina and Goldenberg 2009; Baker *et al.*, 1991), 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 September 11, 2001 attacks on the World Trade Center are being investigated as a contributing factor to the adverse health affects 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.*, 2005). Some of the most important engineered nanoparticles exploited in an expanding number of commercial products and technological applications include; carbon nanotubes, fullerenes, quantum dots, metals (Ag, Au), metal oxides (TiO_2, ZnO, Fe_2O_3, SiO_2) and lipophilic

nanoparticles. Liposomes are nano-sized vesicles comprised of lipid bi-layers (Kirjavainen *et al.*, 1999; Immordino *et al.*, 2006) formulated with naturally-derived phospholipids and/or other lipophilic molecules. Solid lipid nanoparticles (SLN) are made from lipids that are solid at room temperature (Muller *et al.*, 2000). Both lipophilic nanoparticle types have been designed for transcutaneous drug delivery. Many SLN 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; Immordino *et al.*, 2006; Muller *et al.*, 2000; Prow *et al.*, 2011), 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.*, 2010; Ilbasmiş-Tamer *et al.*, 2010; Huang *et al.*, 2011). Nanomaterials can be designed for passive tumor targeting, relying on the phenomenon of enhanced permeability and retention (EPR) (Iyer *et al.*, 2006; Huang *et al.*, 2010), or active targeting designed with tethered homing ligands (Reubi, 2003; Schottelius and Wester, 2009). Fluorescent quantum dots (Gao *et al.*, 2004; Kosaka *et al.*, 2009; Hild *et al.*, 2008), particularly near infra red (NIR) quantum dot nanoparticles that can over-come tissue background autofluorescence (Ma and Su, 2010; Mortensen *et al.*, 2010; Mortensen *et al.*, 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 immunologic 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), cyto- and genotoxicity (AshaRani *et al.*, 2009; Xu *et al.*, 2009; Nakagawa *et al.*, 1997; Wamer *et al.*, 1997; Jin *et al.*, 2008). In vitro cell studies find that most nanoparticles produce dose dependent cytotoxic or cytokine responses (Ryman-Rasmussen *et al.*, 2006; Zhang and Monteiro-Riviere, 2009; Cui *et al.*, 2010; Pedata *et al.*, 2011; Jin *et al.*, 2008; Pan *et al.*, 2007) as was reported in this journal for keratinocytes exposed to quantum dots with difference surface coatings (Figure 1). Therefore, understanding the fate and transport of nanomaterials that contact the body are critical for optimizing translational applications and therefore constitute areas of active research. Progress made in understanding nanoparticle skin interactions and their therapeutic applications are 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 (Adiseshaiah *et. al* 2010; Baroli 2010; Burnett and Wang 2011; Colvin 2003; Elder *et al.,* 2009; Gwinn and Vallyathan 2006; Nel *et al.,* 2006; Nohynek et al., 2007; Nohynek *et al.,* 2008; Schneider *et al.,* 2009; Smijs and Bouwstra JA, 2010; Stern and McNeil 2008; Tsuji *et al.,* 2006). 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. Nonetheless, 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 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 (Filipe *et al.,* 2009; Sadrieh *et al.,* 2010; Schulz *et al.,* 2002; Lopez *et al.,* 2011; Monteiro-Riviere *et al.,* 2011) and quantum dots (Gopee *et al.,* 2009; Zhang *et al.,* 2008a; Prow *et al.,* 2011) consistently find negligible penetration through barrier intact skin, independent of species. In contrast, small Au metal nanoparticles (5 nm) were reported to diffuse though stratum corneum barrier of intact mouse skin (Huang *et al.,* 2010a) and 15 nm Au nanoparticles penetrated *ex vivo* rat skin to a greater extent than 102 nm and 198 nm (Sonavane *et al.,* 2008). Nanoparticle accumulation in hair follicles occurs in many species (Vogt *et al.,* 2006;

Lademann *et al.*, 2001; Lademann *et al.*, 2007; Lademann *et al.*, 2011; Todo *et al.*, 2010; Patzelt *et al.*, 2011) and stratum corneum penetration through barrier impaired skin (Mortensen *et al.*, 2008; Zhang *et al.*, 2008a; Gopee *et al.*, 2009; Ravichandran *et al.*, 2010; Monteiro-Riviere *et al.*, 2011) are common trends. Studies report detectable penetration of quantum dots through mouse skin treated with ultraviolet B radiation (UVB) (Mortensen *et al.*, 2008; Mortensen *et al.*, 2011) and *ex vivo* human skin treated with a hair removal agent (Ravichandran *et al.*, 2010), which is a common use cosmetic product. The effect of UVB to slightly enhance nanoparticle stratum corneum penetration was corroborated in a recent *in vivo* study of TiO_2 and ZnO nanoparticles applied to pigs formulated in typical sunscreen formulations (Monteiro-Riviere *et al.*, 2011). Others report more significant nanoparticle penetration through dermabraded skin (Zhang *et al.*, 2008a; Gopee e*t 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 *et al.*, 2008a; Gopee *et al.*, 2009) to some detected (Ravichandran *et al.*, 2010; Jeong *et al.*, 2010; Prow *et al.*, 2011) 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 quantum dots (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 quantum dot (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 application to UVB 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 % 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.*, 2011) including the specialized topic of drug targeting through the pilosebaceous unit (Chourasia *et al.*, 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.

1. 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 as 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; Benezra *et al.*, 2011; Li *et al.*, 2010) and selectively deliver drugs (Camerin *et al.*, 2010; Yao *et al.*, 2011) or small-interfering RNA (Davis *et al.*, 2010; Chen *et al.*, 2010; Chen *et al.*, 2010a) specifically to melanoma cells. Many potential drugs fail clinically due to 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; De Jong and Borm, 2008; Cho *et al.*, 2008; Nasir, 2008; Zhang *et al.*, 2008 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; Choi *et al.*, 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 bi-functional methoxy-terminated polyethylene glycol chains (PEG ~0.5 kDa). The neutral charged PEG limits uptake by noncancer cells and the bi-functional group enabled attachment of the integrin targeting RGDY peptide labeled with ^{124}I, a long-lived positron emitting radionuclide, for quantitative 3-D PET 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 (Sarfati *et al.*, 2011; Schottelius and Wester, 2009). 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 non-toxic silicic acid and its subsequent excretion by the kidneys (Rosenholm *et al.*, 2011; Low *et al.*, 2009).

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), quantum dots (Zhou *et al.*, 2007; Zheng *et al.*, 2010), and polymeric liposomes (Zhu *et al.*, 2010; Chen *et al.*, 2010a). Tethering the melanocyte stimulating hormone (αMSH) peptide and/or its derivatives to the nanoparticle is a strategy widely investigated to target the melanocortin 1 receptor (MC1R) (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 (GPCR) that is over expressed 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-MSH 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). While targeting GPCRs with peptide agonists or antagonists is considered to offer many advantages over protein targeting with antibodies (Hild *et al.*, 2010), targeting the MC1R 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 MC1R (Carlson *et al.*, 2007; Hoch *et al.*, 2007; Li and Taylor, 2008; Neumann *et al.*, 2001), and αMSH 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 siRNA to B16F10 melanoma tumors using a mouse model (Chen *et al.*, 2010a). Results showed tumor size was decreased by 2–4X relative to a PBS 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 receptor expression and/or trafficking that may result *in vivo* due to the effects of the tissue microenvironment that are not captured in 2D *in vitro* cell culture studies (Ghosh *et al.*, 2005; Cukierman *et al.*, 2002).

2. Immuno-modulation 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 *et al.*, 2004; Paus *et al.*, 2006; Gallo and Nakatsuji, 2011). Almost every substance that contacts skin has the potential to penetrate and/or produce physiologic 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 (DCs) 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 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 (~$1\times10^6/cm^2$) 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; Geusens *et al.*, 2010; Özbaş-Turan and Akbuğa 2011; Jang *et al.*, 2010; Zolnik *et al.*, 2010) and to deliver vaccines through skin (Nasir, 2008; Nasir, 2009; Fernando *et al.*, 2010; Huang *et al.*, 2010a) are active research areas of increasing importance as recently reviewed (Prow *et al.*, 2011).

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; Tinkle *et al.*, 2003; Vogt *et al.*, 2006; Lademann *et al.*, 2007; Rouse *et al.*, 2007; Mahe *et al.*, 2009; Schneider *et al.*, 2009; Lademann *et al.*, 201), has spurred interest their use for transcutaneous immune modulation. Studies report that the amount and depth to which nanoparticles can penetrate along the follicular duct strongly depend on 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 DCs (CD205+) and transported to local draining lymph nodes via LC and DC migration (Figure 4).

While 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 to hard insoluble nanoparticles that maybe retained longer periods of times in skin. Studies must be done to confirm this as well as to determine the potential effect of skin pretreatments 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 DCs from the skin (Holzmann *et al.*, 2004; Streilein *et al.*, 1982). These effects must be considered in optimizing vaccination strategies. Other fundamental questions that must be investigated include; (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 while the positive use of nanoparticles for vaccine delivery is promising application, there is also the possibility for unintentional nanoparticle skin exposure which could potentiate negative immunological effects, such as a contact hypersensitivity (CHS) 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 subcutaneous injected in NC/Nga mice were shown to exacerbate 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); but 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 AD 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, while transcutaneous immunomodulation with nanoparticles constitutes a promising application (Jang *et al.*, 2010; Zolnik *et al.*, 2010; Prow *et al.*, 2011); 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 co-morbidities such as obesity, diabetes, and atopic dermatitis. Diabetics 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* (MR*SA*), 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) (Elliott, 2010; Chaloupka *et al.*, 2010; Dastjerdi and Montazzer, 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 (Weller and Finnen, 2006; Luo and Chen, 2005; Fang, 2004). Friedman and co-workers describe the design of NO releasing nanoparticles (10 nm) made from tetramethylorthosilicate, polyethylene glycol and chitosan (Friedman *et al.*, 2008). NO 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 MR*SA* infection in a mouse model, as illustrated in Figure 5 (Martinez *et al.*, 2009). The authors suggest that these nanoparticles maybe 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 nanoAg has lead to the rapid commercialization of nanoAg containing products including socks (Benn *et al.*, 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 therapeutic use. It is known that the human body can accumulate silver with overuse of silver sulphadiazine causing Argyria, a bluish graying of skin (Wang *et al.*, 1985; Fun and Bowen 1996). This has raised human health and safety concerns for nanoAg skin exposure particularly since

these products maybe applied to 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 nanoAg *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 nanoAg 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 Conclusions

This review provides a general overview of the nanotechnology and its therapeutic applications in dermatology. This is a growing research area that has lead to the establishment of The Nanodermatology Society (NDS) 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 one that may provoke potential negative side effects. Motivated by the wide use of nanoparticles in UVB protective sunscreens and topical cosmetics, metal oxide nanoparticles are one of the most studied (Nohynek *et al.*, 2007; Nohynek *et al.*, 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.*, 2010a). Zinc is an essential mineral and therefore poses minimal toxicity concern. TiO_2 nanoparticles are highly insoluble and 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 nanoparticles that may contact barrier defective skin, and the effect of UVR skin exposure, remain important open questions. Limited data exists 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.*, 2011a) 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 if nanoparticle therapeutics can be delivered more effectively through diseased skin or if 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 effect LC function by preventing antigen uptake, or altering antigen presentation or migration have yet to be fully explored. Therefore, while the imaging and therapeutic applications of nanotechnology to dermatology are promising areas, there are many interesting unanswered questions and technical challenges, which provide significant opportunity for further investigative studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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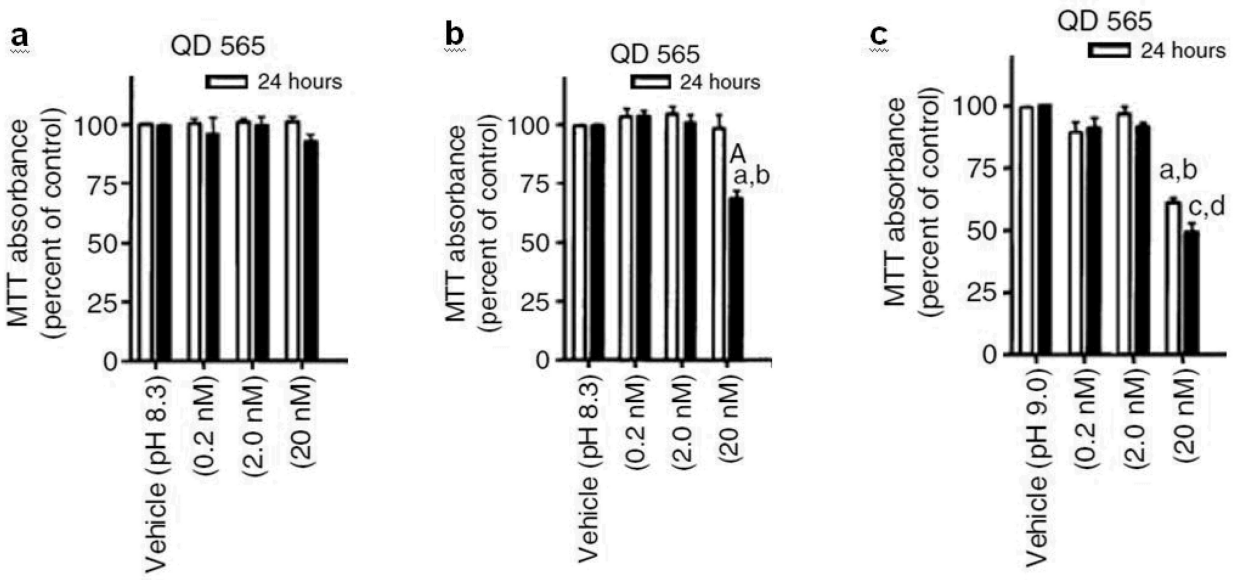

Figure 1. Quantum dot (QD565) surface coating affects keratinocyte concentration dependent cytotoxicity at 24 h exposure

(a) PEG-coated. (b) PEG-amine coated. (c) Carboxylic acid coated QD. Figure adapted from Ryman-Rasmussen *et al.*, 2006.

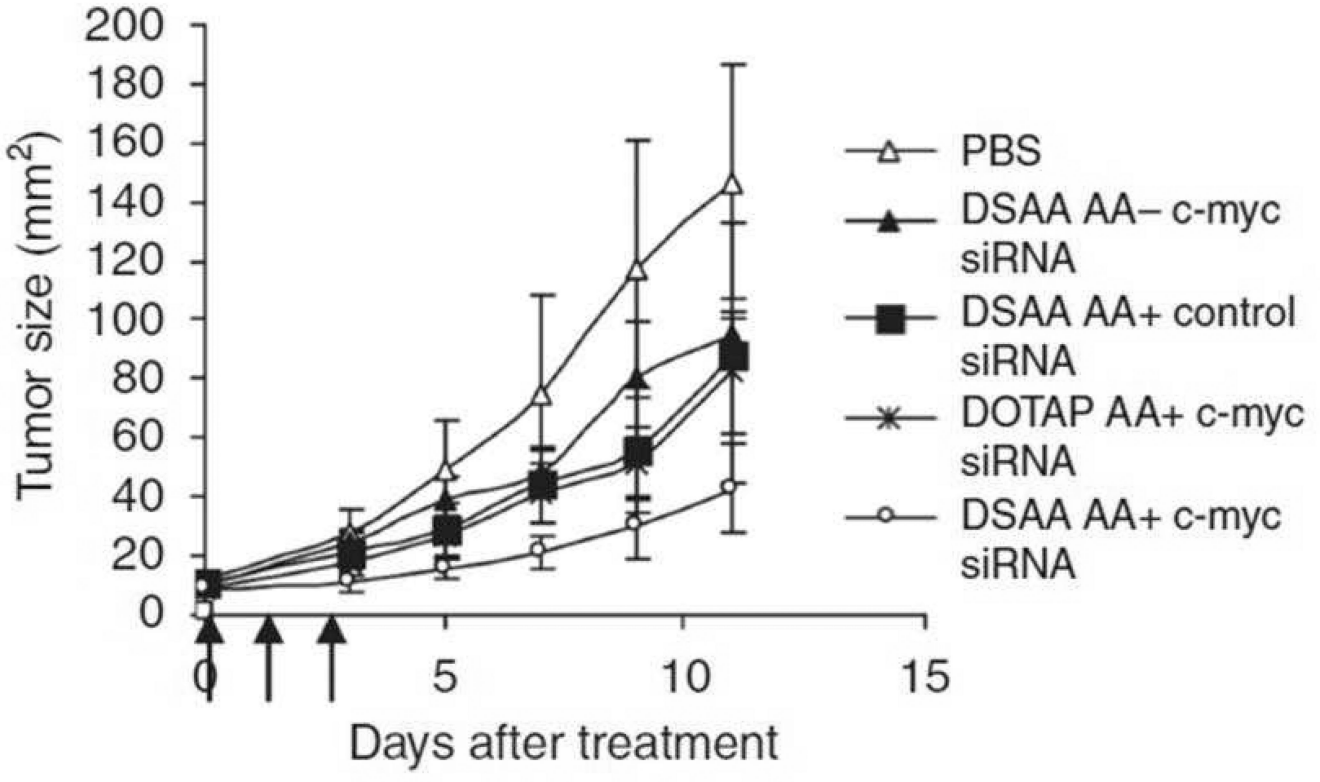

Figure 2. Nanoparticles can be used for targeted drug delivery

Nanoparticle (100 nm) targeting the sigma 1 receptor on melanoma cells are formulated with anisamide (AA) to deliver c-Myc siRNA. DOTAP and DSAA are lipids used in the nanoparticle formulation. Solid arrows indicate the i.v. administration of siRNA nanoparticles. Results show significant reduction in B16F10 melanoma tumor size murine syngeneic model. Figure adapted from Chen *et al.*, 2010a.

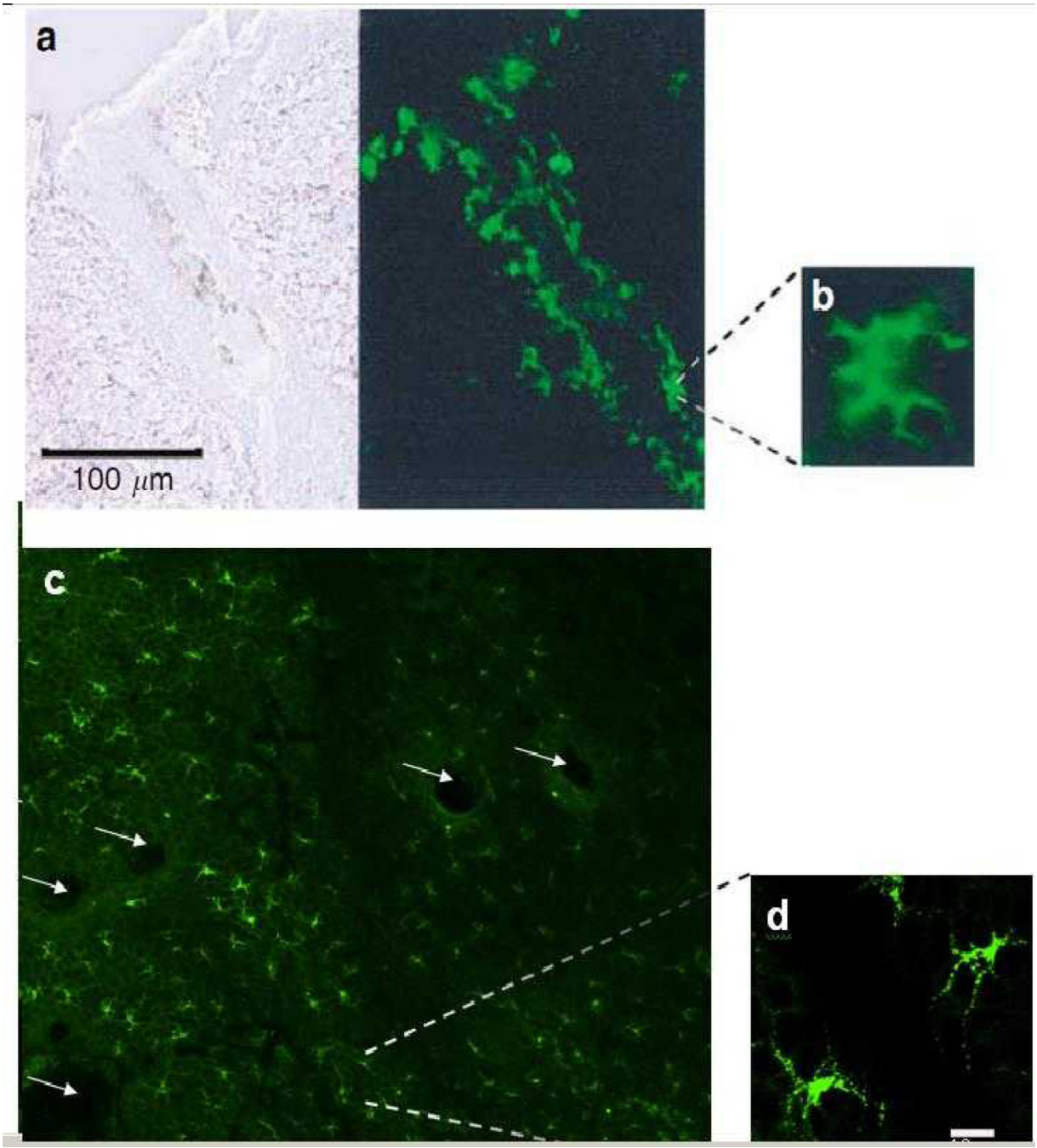

Figure 3. Dendritic cell localization patterns in skin

(a) Bright field image of hair follicle and (b) corresponding immunofluorescent staining with anti-CD1a-FITC antibody showing high concentration of CD1a + cells in human epithelium around hair follicle infundibulum. Scale 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. Scale bar 50 μm (d) CD207+ cells exhibit

dendritic morphology. Scale bar 10 μm. Figures (a) and (b) adapted from Vogt *et al.*, 2006. Figures (c) and (d) provided by Samreen Jatana, University of Rochester.

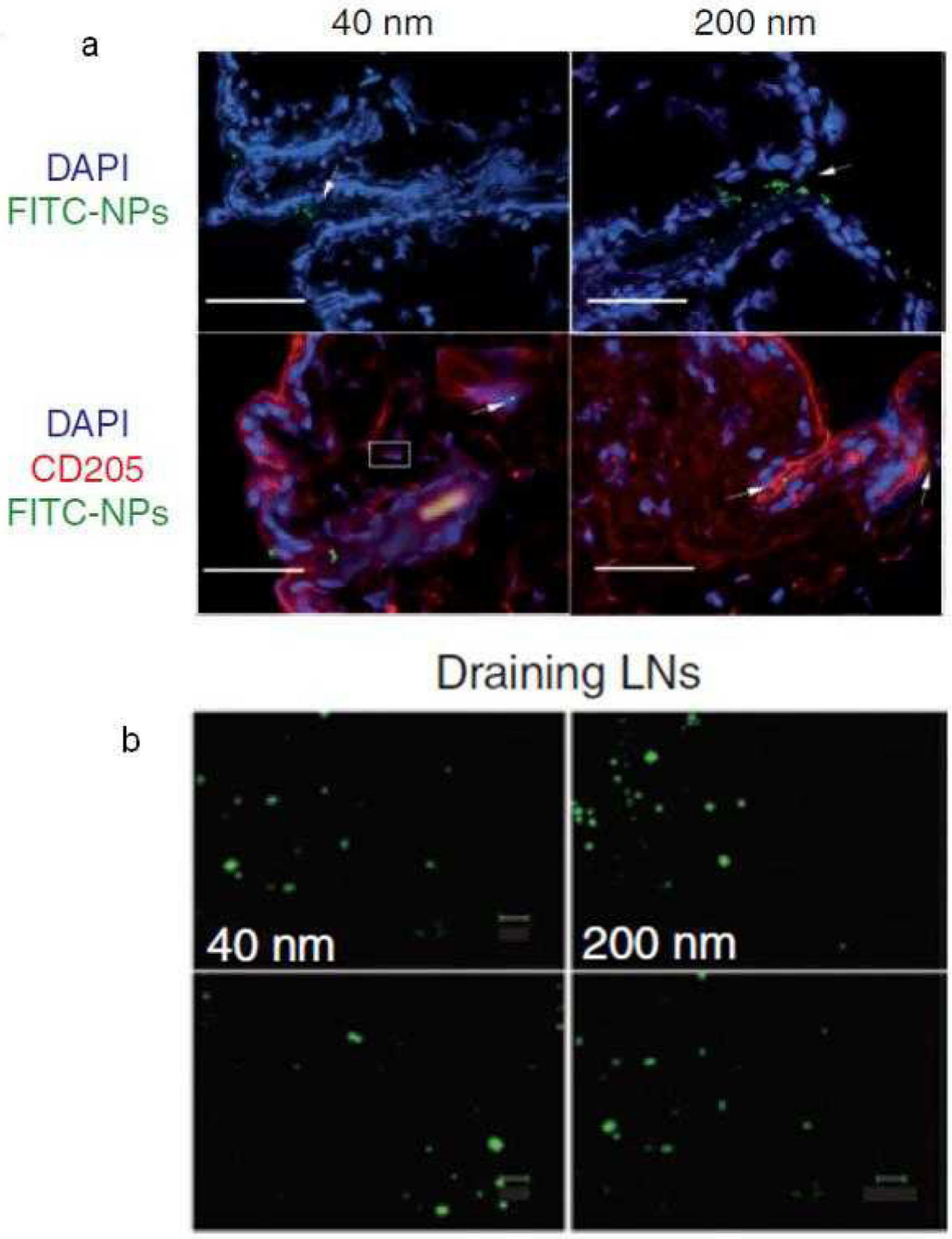

Figure 4. Nanoparticles translocate through skin to local draining lymph node

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) twenty-four hours following topical application the draining lymph nodes were analyzed by fibered confocal fluorescence microscopy (FCFM). Fluorescent spots were observed for

both particle sizes indicating that the fluorspheres penetrated perifollicular tissue and were taken up by epidermal and dermal DC and trafficked to the lymph nodes. Figure adapted from Mahe *et al.*, 2009.

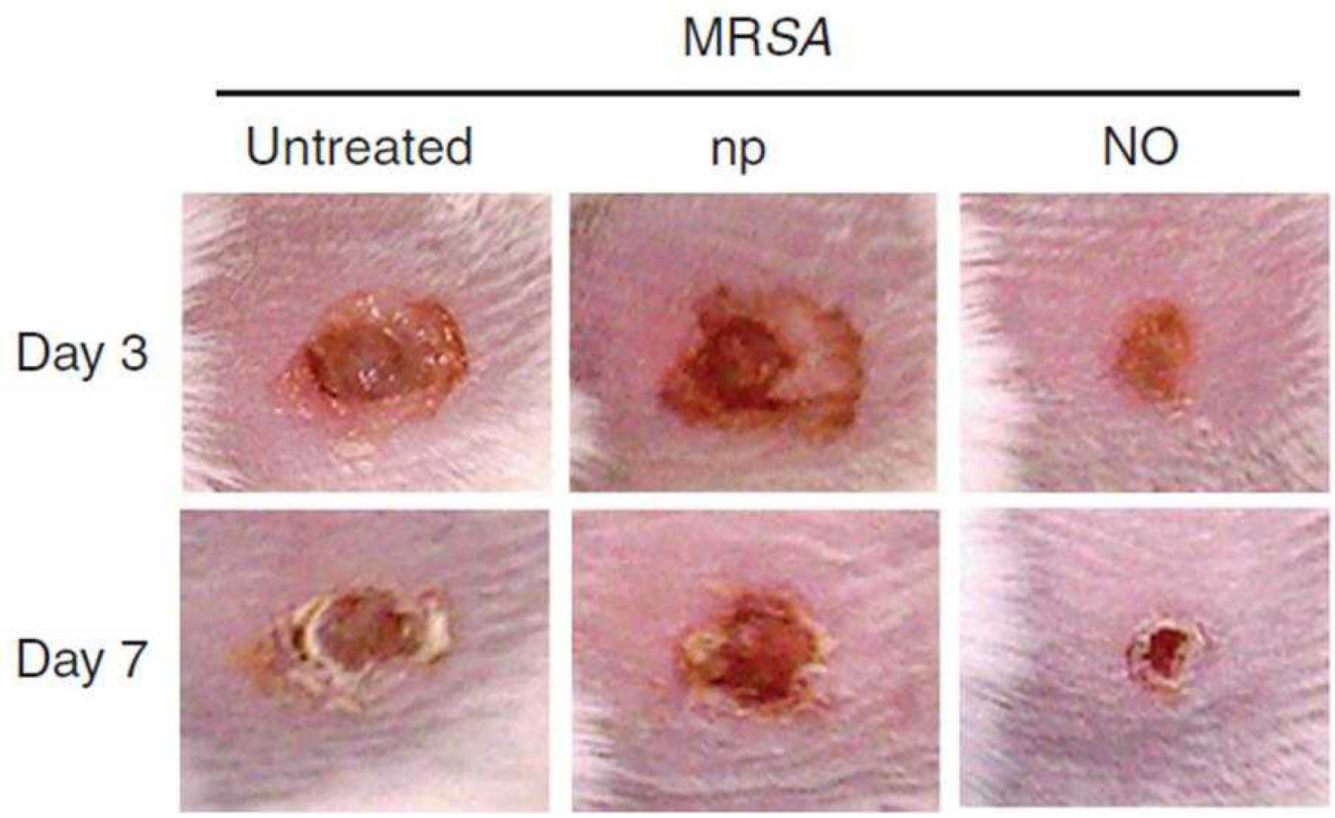

Figure 5. Antimicrobial properties of nanoparticles accelerate wound healing

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