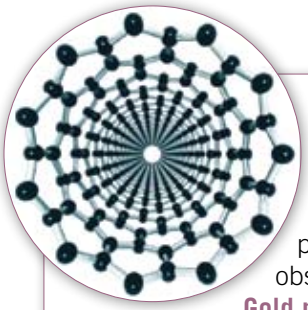
Tiny particles one billionth of a meter in diameter could offer hope to the estimated 45 million people in the United States who are allergic to nickel. In a vivid example of the exciting ways that nanotechnology is being used in dermatologic settings, scientists at Boston's Brigham and Women's Hospital have found that nanoparticles containing calcium—when applied to the skin in a cream—efficiently capture nickel, preventing it from entering the body. The nanoparticles can't penetrate the skin, and the cream itself can be easily washed off with water. The research was reported in the April 3, 2011 issue of the journal *Nature Nanotechnology*, and is—according to nanodermatology experts—exactly where dermatology-based research on these tiny molecules is headed.

Tiny WONDERS

By Russell A. Jackson

Nanoparticles already play a role in dermatology and cosmetic products, and that role is likely to expand rapidly in the coming years.

Tiny Wonders



Glossary of Nanodermatology Terms

Nanoparticles. Particles sized between 1nm and 100nm that behave as whole units in terms of their transport and properties; they may or may not exhibit nanosize-related properties that differ significantly from those observed in bulk materials.

Gold nanoshells. Particles of silica in the 90nm to 130nm size range coated with a thin layer of gold. Gold has unusual optical features, such that the coating can absorb and scatter light at specific frequencies. This allows the gold nanoshells to respond to near-infrared light frequencies that can pass through human tissue. The nanoshells can be coupled with targeting agents like melanocyte-stimulating hormone to deliver them to specific cells, such as melanoma cells.

Solid lipid nanoparticles and nanostructured lipid carriers. Particulate systems for topical drug administration with mean particle diameters ranging from 50nm to 1,000nm.

Nanocrystals. Drug nanoparticles with crystalline characteristics that are composed of 100% drug—meaning there's no carrier material, as in polymeric nanoparticles. Dispersion of drug nanocrystals in liquid media leads to nanosuspensions.

Semiconductor nanowires. Wires made from nanotubes that allow a much lower current to flow when compared to metal wires.

Carbon nanotubes. Molecular tubes that consist of rolled-up sheets of carbon hexagons that can be used, for example, as a matrix for the growth of bone cells. They are single molecules measuring a few nanometers in diameter and several microns in length.

Gold nanorods. Nanostructures shaped like dowel rods, often used to target tumors for radiation.

Quantum dots. Nanoparticles made of a semiconductor material that display unique optical and electrical properties—including the emission of photons under excitation, which are visible to the human eye as light.

Nanocantilevers. Nanostructures resembling tiny diving boards made of silicon that vibrate at different frequencies when contaminants stick to them.

"Certainly, some of the early leaders in nanodermatology have been the cosmetic companies," says Adnan Nasir MD PhD, president of the Raleigh, North Carolina-based Nanodermatology Society (nanodermsociety.org). Now, the medical and device side of the research and development equation is catching on.

The theory behind the development of nanodermatology products is to use engineered molecules of reactive substances—and the unique ways that they interact on a one-to-one basis with each other and with their environment—to create products that offer an advantage over their precursors, whether in delivery, efficacy or toxicity.

> "If we can use these nanoshells for melanoma, then we may be able to use them on cancers deeper in the body."

What's the Buzz?

The buzz around nanodermatology is growing thanks, in part, to President Obama. In his 2011 State of the Union address, the President "discussed recent research related to nanotechnology-based treatment for melanoma," Dr. Nasir reports, noting how rare it is for a chief executive to discuss individual scientific studies in that annual speech to the Congress. "It was a very profound gesture to mention the treatment based on gold nanoshells that are activated by infrared light," says Dr. Nasir. "Dermatologists are very excited about it because if we can use these nanoshells for melanoma, then we may be able to use them on carcinomas and other cancers deeper in the body and still spare healthy tissue." If it comes to fruition, he states, the technique "will revolutionize surgery and skin cancer treatment."

Maximum Benefit, Minimal Harm

Melanoma is not the only area where nanotechnology is being used in the diagnosis and treatment of dermatologic disease. The thrust of innovation involves targeting just the tissue that needs to be treated without destroying healthy surrounding tissue—the "maximize benefit, minimize harm" approach. In the topical realm, for example, researchers are studying ways to apply a nanotechnologic approach to what are now systemic drug delivery systems—cyclosporine for atopic dermatitis, antiandrogens for hair loss, retinoids for acne or wrinkles, and topical steroids for inflammatory disease or eczematic diseases. Scientists are studying ways to encapsulate those systemic treatments and release the active ingredients only where they're needed. As an example, Dr. Nasir points to one oral psoriasis treatment on the market that can negatively affect liver function. "The nano-version

would only work where the psoriasis is, and people are looking into that," he explains. A lot of this work, he adds, is based on research into chemotherapy drugs. Encapsulated methotrexate, for example, is currently used for cancer treatment, but would be very useful and less toxic for treatment of dermatologic disease, too. Another area of study is small inhibitor RNA. Scientists can encapsulate those molecules to turn off the genes that drive the development of melanoma—an approach that has already proven beneficial in treating pachyonychia congenita.

"The nanoparticles themselves do not exert a magnetic field, but rather respond to external magnetic forces for improved imaging."

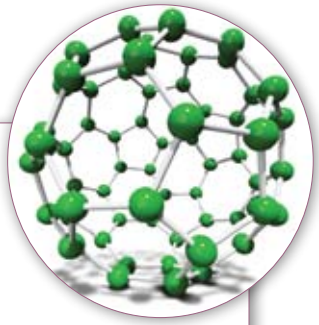
Adam Friedman MD, FAAD, director of dermatologic research and the Basic Science/Translational Research Fellowship in the Albert Einstein College of Medicine division of dermatology, and head of the Center for Dermatology, Cosmetic & Laser Surgery at the Montefiore Medical Center, knows clinical nanodermatology firsthand. "I personally am working on several nanoparticle technologies, one of which allows for controlled and sustained release of nitric oxide for the topical treatment of skin infections, poor wound healing and even erectile dysfunction," he says. "Another has paramagnetic properties, meaning that the nanoparticles themselves do not exert a magnetic field, but rather respond to external or outside magnetic forces for improved imaging of tumors as well as targeted cancer therapy."

More Elegant and Efficacious Formulations

Some of the activity in the nanodermatology space is more a hybrid of clinical and cosmetic applications. "As laser technologies continue to develop in the medical arena, there is a greater need for post-care formulas to repair and regenerate cells and nourish the skin," notes Rhonda Allison, founder and CEO at Rhonda Allison Cosmeceutical and RAW skin care for men (www.rhondaallison.com). "Nanotechnology allows for deeper penetration and can drastically improve product efficacy."

And there's no shortage of cosmetic nanodermatology applications. "Nanotechnology is employed in many cosmetic products, including moisturizers, hair care products, makeup and sunscreen," says Dr. Friedman. "In fact, a large number of major cosmetics manufacturers use nanomaterials in their products." L'Oréal (www.loreal.com), for example, has multiple nanotechnology-related products on the market, and is ranked as a Top 10 holder of nanotech-related patents, he reports. In 2006, the European Commission estimated that 5% of cosmetic products in Europe contained nanoparticles and predicted that number "to exponentially increase over time."

The Safety of Nanoparticles



The elephant in the nanotechnology room is, of course, the safety of the nanoparticles themselves. As particles shrink, their interactivity and ability to penetrate the body may grow, leading to questions of biocompatibility and biodegradability.

"The FDA has yet to give the green light on the safety of nanotechnology," says Rhonda Allison, founder and CEO at Rhonda Allison Cosmeceutical. "As it stands, there haven't been any safety or efficacy standards established, either."

This is one reason the Nanodermatology Society has released a position statement on the safety of nanotechnology in sunscreens. "To address concerns, the NDS conducted a rigorous review of the scientific literature regarding the use and safety of nano-sized ultraviolet-blocking ingredients," the organization's statement reads. "The picture is clear. To date, the data show that the nanotechnology used in sunscreens is safe." The nanoparticles in that usage are coated to minimize reactivity, to clump in aggregates or to stay on the surface of the skin, the statement reads.

But, as Dr. Nasir points out, "with any new technology, there's always concern, perhaps even a little fear." Just look at in-home electricity, he says. "People were very concerned about the safety of electricity at first. But we've developed codes for wiring, currents, transformers and generators and we've developed safety guidelines for the people who work around electricity and use it at home." Radiation for use in X-rays and cell phones is another example. Similarly, Dr. Nasir says, nanodermatology likely won't be derailed by a smoking safety gun. "We'll need to study the risks, understand them and try to minimize them," he says. "That's why, if we have some simple rules for nano-materials, we can harness them safely and make sure the risks are commensurate with the benefits."

Tiny Wonders

In cosmetics, the two main uses for nanoparticles are as sunblocking agents and for agent delivery. Titanium dioxide and zinc oxide are the main compounds used as blockers. Structures—such as solid lipid nanoparticles and nanostructured lipid carriers—have been shown to enhance skin hydration and bioavailability of ingredients, improve stability of the encapsulated agent and allow for controlled delivery, Dr. Friedman points out. Nanocrystals and nanoemulsions are also being investigated for similar purposes. One company, Nanobio (www.nanobio.com), offers a nanoemulsion product derived from soybean oil with indications including the treatment of herpes labialis and onychomycosis, and vaccine delivery, says Dr. Friedman.

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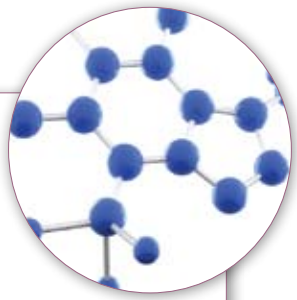
Broad Applications for Small Wonders



Nanotechnology already plays a larger role than many realize in both our health care and personal hygiene. Following are some products that already contain nanoparticles as well as some recent nano-innovations.

- Shampoos for dermatitis and lotions for eczema and psoriasis
- Silver-based antibacterial surface coatings for salon implements—including trimmers and shavers—that help to reduce the risk of infection
- Clothing that incorporates nanotechnology to make it more highly compressive, including post-liposuction corsets and stockings to help keep varicose veins in check
- Bandage fabrics with antibacterial properties that release a dye only in the presence of bacteria, thus signaling treatment of a wound only if it's infected
- New imaging methodologies, including X-rays, ultrasound and MRIs, that use nanoparticles—such as quantum dots or gold nanorods—tagged for various tissues (one such use allows for visualization of sentinel lymph nodes in the staging of melanoma)
- Diagnostic tools including nanocantilevers, quantum dots and gold nanorods that require far less tissue to diagnose skin disease
- Small, magnetic nano-"cages" that can be guided from outside the body to collect tissue samples. These cages—with their tissue molecules inside—are released in urine and captured, allowing for minimally invasive tissue recovery and analysis
- Abrasive nano-ceramics in toothpaste for whitening teeth and filling surface imperfections that could lead to cavities
- Clothing impregnated with silver that doesn't need to be washed as often, as well as hydrophobic nano-whiskers that are resistant to spills and boron that's resistant to radiation
- Emollients that incorporate solid lipid nanostructures so people with dry skin can reduce transepidermal water loss and reduce the risk of acne

Guided Therapy and e-Skin

Because nanodermatology is a relatively new area of study—Nasir's organization was founded just last year—potential uses for nanotechnology in this specialty are still being discovered. Researchers are learning both what nanotechnology is, precisely, and what nanoparticles can be made to do. In one recent development, for example, researchers in the NanoRobotics Laboratory of École Polytechnique de Montreal's Department of Computer Engineering and Institute of Biomedical Engineering guided—*in vivo* and via computer control—a ferromagnetic 1.5-millimeter-diameter sphere inside the carotid artery of a living animal in a magnetic resonance imaging system. In another, engineers at the University of California at Berkeley recently developed a pressure-sensitive electronic material from semiconductor nanowires that functions like human skin. Called "e-Skin," it's the first such material made out of inorganic single crystalline semiconductors. It could some day restore the sense of touch to patients with prosthetic limbs. With major players like Merck, Schering-Plough and Johnson & Johnson providing funding, and major research institutions across the globe devoting time and effort to its study, what seemed like science fiction just a few years ago could well be the nanotechnology-based realities of tomorrow.

Russell A. Jackson is a West Hollywood, California-based freelance writer specializing in healthcare, clinical research and small business management.