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# *Nanoparticles: New Medical Potential—Today and Tomorrow*

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**CONTENTS**



## 3.1 Introduction

The history of drug formulations that rely on nanoengineering is quite modern. The launch of products incorporating nanostructure particles is showing clear differentiation across sectors. Materials and products based on nanotechnology are regulated today within the existing network. Nanostructures are evaluated as "chemicals with new uses" or as "new chemicals."

Health-care and life sciences applications, such as nanostructured medical devices and nanotherapeutics, have the longest time to market due to sector-specific regulation. In 2004, the US Food and Drug Administration (FDA) estimated that the proportion of all new drugs entering first-phase trails that ultimately gain approval had fallen to 8% from a historical average of about 14%. The most common factors resulting in project failure are lack of efficacy (25%), clinical safety concerns (12%), and toxicological findings in preclinical evaluation (20%). Proposed Investigational New Drug Application (IND) needs to follow the way to FDA and EC approval, passing through all stages of investigations lasting up to 10–15 years, starting *in vitro* and ending with the third phase of clinical trials with subsequent approval of medication and pharmaceutical market entry.

The current applications of nanotechnology span a wide range of sectors. The current niche for such applications is in the areas where there is an overlap between the medicine and cosmetic sectors. Many products are marketed as a means to enhance performance for different lifestyles and age groups, as an aid to health, beauty, and well-being. Although such applications are relatively new and emergent, they appear to have started to make a global

impact. The number one question is if the quality of life will improve thanks to the synthesis of new materials with new properties. How should people benefit from achievements of nanotechnology and nanoengineering? The answers to these and related questions are controversial, owing to the different approaches of regulation rules before the market entry of new products.

While FDA requirements are strict for novel medications, conversely, regulatory mechanisms for cosmetic products allow earlier market entry. Unlike the medical and health-care sectors, the cosmetic industry outpaces the commercial potential of nanoparticle-containing products. To compare with the rate of released cosmetics, widely distributed worldwide, the situation is quite unequal. Drugs, food packaging, and new chemical compounds require premarket review and approval, whereas in cases related to cosmetics and the majority of consumer products, postmarket surveillance and monitoring are sufficient.[1]

Although the constituent materials used in cosmetic and personal care products should be approved by the FDA, at the same time there is no need for conducting long-running clinical trials, as in the case of pharmaceutical drugs. However, regulatory mechanisms require revision when dealing with ingredients processed to nanoscale dimension, where absolutely diverse chemical and physical properties are revealed. Of particular interest are cosmetics and personal care products. Recently, there is widespread use of nanoparticle gold–containing cosmetics such as skin creams that are used on the whole body surface for the "shining glow" appearance, lipsticks, antiaging face creams, and many other products. Despite the large interest and widespread investigations performed for safety and efficacy studies for nanoparticle gold utilization in medical diagnostics and treatment, it is obvious that few, if any, are approved for these purposes. An overview of the state-of-the-art exploration of nanoparticle gold compounds will provide us with special knowledge about the differences in physical and chemical properties of nanogold, dependent on size, shape, charge, and even the solvent used in processing of this metal.

Gold nanoparticles are widely used in biomedical imaging and diagnostic tests. On the basis of their established use in the laboratory and their chemical stability, gold nanoparticles are expected to be safe. The recent literature, however, contains conflicting data about the cytotoxicity of gold nanoparticles.

## 3.2 Health Monitoring Issues Concerning Nondestructive Use of Nanoparticle Gold Compounds in Medicine and Cosmetology

"All is not gold that glitters"

The postindustrial gold rush reflects the hype of nanotechnologies, already ubiquitous in a wide range of consumer products, as diverse as

electronics, medicine, environmental remediation, cosmetics, and solar energy. Discovering distinctive properties that many materials display at the extremely minuscule scale opens new opportunities for their conventional use.[2] Of particular interest to most nanotechnology applications are engineered nanoparticles (ENPs), which have much larger surface-to-mass ratios. Nanosized ENPs have also been claimed to have a greater uptake, absorption, and bioavailability in the body compared with their bulk equivalents. This makes it possible to reduce the use of solvents in certain applications, such as certain cosmetics and personal care products, to allow the dispersion of water-insoluble colors, flavors, and preservatives in low-fat systems. Nanosized water-insoluble substances can enable their uniform dispersion in aqueous formulations. This aspect alone has attracted a lot of commercial interest in the use of nanosized ingredients.[3]

Among other ENPs, interest in gold has not diminished; on the contrary, it has increased enormously in recent years, particularly since the early 1980s, when the mass production of nanoscaled chemical substances started, owing to the invention of the scanning tunneling microscope and the atomic force microscope. IBM scientists have enabled the manipulation of even individual atoms to design and synthesize materials for attaining desired features. Later in the 2000s, IBM scientists, by precisely placing atom-by-atom 20,000 gold particles, each about 60 nm in diameter, reproduced an image of Robert Fludd's 17th century drawing of the sun—alchemists' symbol for gold. IBM scientists demonstrated a new nano "printing" bottom-up technique, which will lead to breakthroughs in ultra-tiny chips, lenses for optics, and biosensors for health care.

As gold is the most studied chemical element, it is characterized as having the most predictable behavior. However, gold nanoparticles may act absolutely diversely. Bulk gold, which is usually characterized by its yellow color, while being processed to nano-dimensional scale, transforms its color to orange, purple, red, or a greenish tinge owing to different particle sizes. The most well-known cultural artifact in nanotechnology is housed in the British Museum—the Lycurgus Cup (dated 4th century A.D.), which is a glass cup of ruby red color due to its colloidal gold content and changes to a greenish color upon light exposure. Nanogold was already used in medieval times in stained glass materials to attain almost all the colors of the rainbow. Today, nobody will argue that nanosized gold particles do not act like bulk gold.[4]

Traditionally, bulk gold was considered a chemically inert and biocompatible material; owing to these features, it is utilized widely in medical applications, for example, in dental prosthesis and eyelid implants. Throughout history, gold has been used to cure diseases. Finely ground gold particles in the size range of 10–500 nm can be suspended in water. Such suspensions were used for medical purposes in ancient Egypt over 5000 years ago. In Alexandria, Egyptian alchemists used fine gold particles to produce a colloidal elixir known as "liquid gold," which was intended to restore youth.[5] Dating back to the Roman Empire, colloidal gold was thought to have healing

properties. A colloid refers to a substance in which many fine particles are suspended in a stable condition with another substance. Gold nanoparticles was traditionally used in the Indian remedy "curcumin."[6] The German bacteriologist Robert Koch showed that gold compounds inhibit the growth of bacteria. He was awarded the Nobel Prize for medicine in 1905.

With the developments in the pharmaceutical industry, first in 1935, gold salt–containing drugs were reported to be effective for the treatment of rheumatoid arthritis. It is thought that gold affects the entire immune response (phagocytes, leukocytes, T cells) and reduces its potency and limits its oxidizing nature on joint inflammation and erosion. This effect is explained by the fact that administered gold compounds accumulate within the body once absorbed into the cells and are linked to antimitochondrial activity, inducing the apoptosis of proinflammatory cells. The World Health Organization classified gold salt–containing compounds as antirheumatic agents and included such compounds in the basic treatment scheme of the disease.

Because of the long history of the use of gold inside the body, the safety issues seem to have been somewhat easier to assume, despite becoming more and more challenging owing to achievements in the synthesis of new materials enabled by nanotechnology.

The properties of gold molecules processed to nanometer dimension are almost thoroughly studied. Gold attains divergent physical and chemical characteristics while its molecules are being processed to nanoscale dimension. Scientists have revealed the diverse properties of nanoparticle gold, which is dependent on various factors. Particularly, such properties are dependent not only on the size of the gold nanoparticle but also on other characteristics such as particle shape, charge and composition, or surface coating, which are also important. Consequently, the health monitoring aspects are of greater concern than before.

When dealing with constraints of size <100 nm, the laws of quantum physics supersede those of traditional physics, resulting in changes in a substance's properties. Quantum size effects begin to significantly alter material properties, such as transparency, color of fluorescence, electrical conductivity, magnetic permeability, and other characteristics. All these properties are of great interest for the industry and society, as they enable new applications and products. Consequently, more attention is focused on determining the ratio of efficiency versus toxicity, or harm versus benefit. There are some examples of conventional use of nanoscaled gold particles. For instance, the Japanese scientist Dr. Masatake Haruta discovered that while the particle diameter is turned in the size range of 3–5 nm, gold exhibits unique catalytic performance, for example, carbon monoxide (CO) oxidation and direct peroxide ($H_2O_2$) production at a temperature as low as –77°C.[7] In practice, this invention was tested to prevent bad odor in rest rooms and are already in use in Japan. Thus, gold nanoparticles can eliminate odors produced by bacterial action. This is an unusual feature for bulk gold but characteristic for

nanoscaled gold particles. Another application for the catalytic properties of nanosized gold particles is for fuel cells of hydrogen batteries.

One hundred fifty years after one of the founders of chemistry, Michael Faraday, first created gold nanoparticles in the 1850s and observed that these nanoparticles absorb light, researchers in the 20th century rediscovered that a mere flash of light can cause gold particles to melt. Absorbed light is efficiently turned into extreme heat, which is capable of killing cancer cells. The externally applied energy may be mechanical, radiofrequency, laser, optical, or near-infrared light but the resultant therapeutic action is the same. Gold nanoparticles are also recognized by their ability to bind to DNA, which may be exploited for the treatment of diseases, for example, as anticancer agents or gene therapy agents; however, they may also contribute to genotoxicity, or block transcription.[8] Hamad-Schifferli et al.[9] have demonstrated that transmitted radiosignals influence the integrity of the DNA strand while is bound to nanoparticle gold molecules. This discovery opens up the possibility of controlling more complex biological processes of living cells, such as enzymatic activity, protein folding, and biomolecular assembly. Furthermore, the ability of gold nanoparticles to bind to DNA is of concern, owing to their potential cytotoxic or genotoxic consequences, which may be exploited for anticancer drugs or gene therapy, and warrants further investigation. In addition, the ability of gold nanoparticles to interrupt transcription is of concern.[10]

Naomi Halas of Rice University (Houston, TX) developed gold nanoshells in the 1990s. According to the study's lead authors, Rebekah Drezek and Jennifer West, nanoshells have a core of silica and a metallic outer layer of gold, or may be exchanged by cupper or iron. Nanoshells will preferentially concentrate in cancer lesion sites. In her interview with Nova, Naomi Halas describes a nanoshell as "essentially a nanolens" that captures light and then focuses it around itself.[11] A near-infrared laser aimed at the tumor site from outside the body (light can travel through tissue more than 10 cm) induces the nanoshells to absorb the light and focus it on the tumor. The area around the nanoshells heats up and the tumor "cooks" until it is ablated. Halas points out that the nanoshells leave no "toxic trail" in the body the way conventional chemotherapeutic agents do, and stated that "long-term studies have not indicated any toxicity or effect on the immune system."

The structure and properties of gold nanoparticles make them attractive for a wide range of biological applications. Nanoparticle gold is considered a low-toxicity material and is currently widely used in cosmetology.

Actually, nanostructured gold particles possess various properties that are under investigation and need longer time to final approval. Few if any of the fabricated nanoparticle gold–containing medications are yet approved by the FDA. In August 2009, a report of the EU 7th Framework Program, "Engineered Nanoparticles: Review of Health and Environmental Safety," was released.[12]

Particle size has been demonstrated to influence the dermal penetration of gold nanoparticles.[13] Therefore, in general, greater effects are observed for smaller particles. The size of particles has been proven to have a large influence on their behavior. Accordingly, smaller particles have a wider tissue distribution, penetrate further within the skin and become internalized to a greater extent, and have a larger toxic potency. However, more extensive investigations in the future are required to more fully understand the tissue distribution and fate of metal particles after exposure.

It was estimated that the optimal size of nanoparticles for interaction with the skin would be in the range of 50 nm. Smaller particles tend to penetrate the skin more easily than large particles, sometimes being taken up by the lymphatic system and becoming localized in the lymph nodes.[14] Among other factors that should also be considered are particle concentration and charge state, which are in causal relation with their influence on living cells. Goodman et al.[15] demonstrated gold cationic particles of 2 nm size as moderately toxic, whereas anionic particles were relatively non-toxic; their observation data coincide with those obtained in different studies.[16] Toxicity, however, has been observed at high concentrations of these systems.

In one study, the research group headed by Dr. Shuguang Wang[17] demonstrated a cytotoxic effect on human skin keratinocytes of gold nanomaterials of different sizes and shapes. It was shown that spherical gold nanoparticles of different sizes are not inherently toxic to human skin cells; conversely, gold nanorods are highly toxic due to the presence of the coating material cetyltrimethylammonium bromide (CTAB), which is used in the manufacturing process. This toxicity factor caused a limitation on the commercialization of gold nanorods for *in vivo* and *in vitro* applications. It is unreasonable to make generalizations from just a few studies because in recent years the company Nanopartz has announced about a new manufacturing method, replacing the undesirable organic molecule CTAB with polyethylene glycol (PEG). PEG has low toxicity and is used in a variety of products. Nanorods from one supplier may not be necessarily representative of the toxicity of the physical characteristics of all manufactured nanorods. Furthermore, other nanocoating molecules, such as liposomes, dendrimers, biodegradable polymers, or albumin, are capable of reducing the toxicity of the incorporated agent.

The major promise lies on the discovery of thiol (a compound with a functional group composed of a sulfur atom and a hydrogen atom—SH), which protects colloidal gold nanoparticles bound to the cytokine tumor necrosis factor (TNF). ~~Buffering~~ the extreme activity of free TNF, an enhanced antitumor effect is attained by assembling TNF molecules into a complex structure with PEG linked with colloidal gold nanoparticles.[18] This new approach has significant advantages over other alternatives and is under development by the company CytImmune, elaborating the results to achieve final approval.

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Gold nanoparticles are also more biocompatible than other types of optically active nanoparticles, such as cadmium-containing quantum dots. Owing to its toxicity, the use of cadmium is restricted in living cells. This

is why the process of nanofabrication, in particular the preparation of gold nanodots or quantum dots, is well known. In 2007, the National Medal of Science, the United States' highest honor in the field, was awarded to the Egyptian-American chemist Professor Mostafa El-Sayed, director of the Laser Dynamics Laboratory of Georgia Institute of Technology, for his many outstanding contributions, among which using gold nanorods in cancer tumor treatment was the most recent. Gold nanoparticles are very good at scattering and absorbing light. For example, nanoparticles that are 36 nm wide absorb light over 10,000 times better than conventional organic dyes, making them potential candidates for optical imaging applications of small tumors. In the study, researchers found that gold nanoparticles have 600% greater affinity for specific overexpressed surface receptors in cancer cells than in noncancerous cells.

As nanotechnology tended to progress in a most responsible manner from the moment of its foundation, when the US National Nanotechnology Initiative (NNI) was established in 2000, it seems to have the most number of regulatory mechanisms for greener development than any other known technology, and social scientists have been involved from the very beginning.

Green nanotechnology is developed to be environmentally friendly. Dr. Jim Hutchinson's research group at the University of Oregon works at the cleaner and greener production of gold nanoparticles, a process that also reduces the cost of synthesizing these materials from 300,000 to 500 dollars per gram.[19] Actually, cost is one of the determining factors for manufacturing, next to safety and effectiveness.

Recent studies have enabled the synthesis of gold nanoparticles by means of certain bacterial strains; for example, *Stenotrophomonas maltophilia* was incubated for 8 h in a gold salt–containing solution, resulting in the synthesis of gold nanoparticles that were about 40 nm in size.[20] The opportunity of this way of synthesis is that it produces gold nanoparticles that are free of solvent and have hydrophilic properties, and may attain particles of various sizes in industrial quantities. This is a new approach to green technology development.

A recent report by J. Davies, from the Woodrow Wilson International Center of Scholars, strongly criticized the current approach in cosmetics regulation as wholly inadequate in dealing with the risks posed by nanotechnologies: "Although the Food, Drug and Cosmetic Act (FDCA) has a lot of language devoted to cosmetics, it is not too much of an exaggeration to say that cosmetics in the USA are essentially unregulated."[21]

David Rejeski, director of the Project on Emerging Nanotechnologies, Woodrow Wilson International Center of Scholars, gives recommendations: "for building confidence in nanotechnologies it is necessary to achieve greater transparency and disclosure; compulsory requirement is also premarket testing, as well involvement of third party for additional testing and further research."[22] Although some cosmetic manufacturers may differ with regard to such conclusions, based on unpublished propriety research, due diligence is needed in tracing assertions back to primary sources.[23]

In 2007, the United States listed gold and silver nanoparticles among a number of new chemicals and materials that the FDA had asked the National Toxicology Program (NTP) to study. This will seek to determine whether their use causes specific health problems. The NTP should test gold nanoparticles and determine what types of tests are warranted.

## 3.3 Summary

Although bulk gold is considered to be intact and the most inert material used safely for centuries, in addition to being considered the most non-toxic material by chemists, nanoparticulated gold poses certain risks for human health, mainly due to the many aspects of modifications enabled by nanotechnology. Particle shape and the solvent used to obtain gold nanoparticles present some danger to safety. Experiments have shown that gold nanoparticles can result in uptake via the relevant exposure routes. Their properties and the cell types used for their exposure are likely to influence the uptake, subcellular distribution, and toxicity of gold nanoparticles. That is why scientists work to obtain safe and non-toxic forms of nanoparticle gold—examples include ultrasound exposure for the production of gold nanoparticles and the use of certain bacterial strains capable of producing gold nanoparticles that are free of solvent. However, the charge and particle shape characteristics remain a cause for concern with regard to consumer safety. From a thorough analysis of the scientific literature, investigating the divergent features of gold nanoparticles, the concept that some gold nanoparticles pose human health risks can be obviated, as information about the exact physical and chemical properties of gold nanoparticles used in certain cosmetic or health-care products need to be strictly regulated. Until now, relevant control mechanisms are under development. As cosmetic products achieve market acceptance earlier than drugs, there are currently available personal care items in the market that are positioned as nanoparticle gold containing and safe. Actually, many of them must be safe, as manufacturers sell nanogold-containing fluids, the chemical and physical properties of which are presented in product certificates.

However, investigations on metal particulates are still in their infancy at this time and have concentrated on revealing the toxicity, safety, tissue distribution, antibacterial properties, and cellular uptake of gold nanoparticles. Consequently, more comprehensive studies are required to more fully understand the risks associated with metal particulate exposure.

Inevitably, any emerging technology requires extensive safety assessment before coming to market, including diagnostics, medications, and cosmetics. While comparing and evaluating newly established properties at the nanoscale, consumers may experience confusion concerning safety issues.

Mass production and the uncontrolled release of products containing gold nanoparticles may reveal the same consequences as any irresponsible application of a new technology. The 21st century "gold rush" may result in worse consequences than any other emerging technology.

Fortunately, in recent years, the control and regulatory mechanisms for the utilization of nanoparticles in cosmetic products have increased. For instance, in March 24, 2009, the European Parliament (EP) approved an update of the EU legislation on cosmetics. As requested by the EP, the new regulation introduces definition, safety assessment procedure, and labeling requirements for all nanomaterials that are used in cosmetics.

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