NTP Research Concept: Nanoscale Gold

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Nomination Background and Rationale

The U.S. Food and Drug Administration nominated nanoscale gold (n-Au) for study by the National Toxicology Program (NTP) based on (a) increasing widespread use as a therapeutics platform, availability as a food supplement and (b) the general lack of data on the toxicology and pharmacokinetics of nanoscale materials in general (http://ntp.niehs.nih.gov/go/29287).

The potential for human exposure may be through the use of nanoscale gold based drug delivery vehicles, incorporation into dental and bone implants, through ingestion of colloidal gold as dietary supplement, or by inhalation exposure through the handling of nanoscale gold powders, and via dermal application of nanocrystalline powders.

Nanoscale gold sold in commerce is available in both powders and in colloids with nanoscale gold particles occurring in the range form 1-100 nm. While many of the commercial forms are sold prepared as spherical nanoparticles, nanoscale gold particles can be prepared in variety of shapes including wires, rods, cubes, prisms, disks, and dendrites. Nanoscale gold can be surface functionalized with a variety of groups. These include: dialkyl sulfides, dialkyldisulfides, alkanethiols, peptides, and peptide conjugated drugs and small molecules, antibodies, carbohydrate-like moieties, phosphine and halide ligands, thiols, dextran, polyethylene glycol, biotin, and streptavidin.

While there are several reports examining the effects of nanoscale gold in vitro there have been few studies that have examined the effects of nanoscale gold of defined size and coatings *in vivo* in experimental animals. One study showed that 2 nm gold particles were not acutely toxic after a single i.v. exposure (Hainfeld et al 2006). There are no longer term *in vivo* toxicity studies of nanoscale gold of defined sizes and/or coating in the public literature.

There have been a number of studies that have examined the tissue distribution and kinetics of nanoscale gold after oral and i.v. exposure and including analysis of both particles and rods. Together these data indicate that the size and surface functional group can impact both the uptake and tissue distribution and whole body retention of the nanoscale gold. Hillyer and Albrecht (2001) examined the gastrointestinal uptake and tissue distribution of maltodextrin-stabilized colloidal particles from 4-58 nm, and showed that 58 nm particles were unable to cross the gastrointestinal barrier and remained in the stomach and intestine.

Together these data indicate that any comparison of biological effects of nanoscale gold *in vivo* requires an assessment of the absorption, distribution, metabolism and elimination (ADME) of the respective nanoscale gold preparations.

Key Issues

For nanoscale materials the dose metric related to observed effects is a key issue. Particle number-based and surface area-based metrics increase with decreasing particle size and as such, mass-based potency of nanoscale materials may differ from that of materials of larger size, but surface area-based potency may not. Some studies have shown that surface area-based metrics may be more appropriate for the comparison of potency of pulmonary toxicity of some metal oxides. While this may not be applicable to all nanoscale materials or all routes of exposure, it indicates that other dose metrics that scale with physicochemical properties, rather than the mass of nanoscale material, should be considered in the interpretation of dose-response data. Consequently, experimental approaches may require the comparative analysis of multiple forms of a given nanoscale material of similar composition but varying in particle size, coatings, shape, or other physicochemical parameters.

A major issue for this research program is the number of possible permutations of size, shape and the variety of coatings that are or could be applied to nanoscale gold in a commercial setting. Given that it is an unattainable goal to be able to evaluate all these permutations, this research program will initially focus on the impact of a matrix of two coatings and two sizes to provide initial information on the extent of the impact of these physicochemical properties on the pharmacokinetic and pharmacodynamic properties of nanoscale gold.

Proposed Approach

Hypothesis to evaluate are:

- That the pharmacokinetics and tissue distribution of nanoscale gold particles of different sizes are the same.
- That the pharmacokinetics and tissue distribution of nanoscale gold particles of comparable size but with different surface modifications are the same.
- That the toxicity of nanoscale gold particles of different sizes are the same.
- That the toxicity of nanoscale gold particles of comparable size but with different surface modifications are the same.

Specific Aims

1. Evaluate the effect of particle size and particle coatings on the pharmacokinetic profile of nanoscale gold.

We propose to compare 3 specific nanoscale gold preparations and conduct time course and tissue disposition studies in rodents (rats and mice).

We will evaluate two sizes of "uncoated" citrate-stabilized Au (from 10 nm to 100 nm). In addition, we propose to evaluate one "coated" nanoscale gold particle (surface functionalized with polyethylene glycol [PEG]). This "coated" form will be of comparable size (core + PEG) to the largest of the uncoated nAu particles and equivalent core nanoscale gold size to the smaller of the uncoated nanoscale gold preparations.

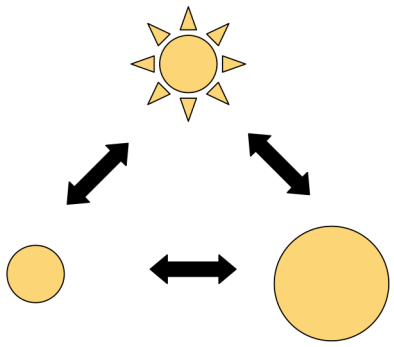

Figure 1: A conceptual matrix of the three nanoscale gold particle preparations and three-way comparisons that will be made to address the hypotheses outlined above

We propose to evaluate pharmacokinetics and tissue disposition after oral and intravenous administration. These studies will include quantitation in tissues using established methods for analyses and, if feasible, location within tissues. The determination of which specific sized nanoscale gold particles will be evaluated will be determined by the study design team through discussion with scientists from the FDA, NIST and NCI.

2. Evaluate the effect of particle size and particle coatings on the toxicological profile of nanoscale gold *in vivo*.

We propose to compare the three nanoscale gold preparations and evaluate and compare the toxicological profile after subacute and subchronic exposure in rodents. Studies should consider an evaluation of potential systemic toxicity and organ specific toxicity and the potential for toxicity to the immune and nervous systems.

Significance and Expected Outcome

The primary NTP principle addressed by this research concept is to increase our science base on the understanding of how physiochemical properties impact on the disposition, metabolism, elimination and toxicity of nanoscale gold. In this regard, this project integrates with other studies being conducted as part of the NTP Nanotechnology Safety Initiative (http://ntp.niehs.nih.gov/go/nanotech). The intent of this initiative is to understand the potential adverse effects of nanoscale materials before widespread exposure has occurred, to identify key physicochemical properties that govern their safety and to examine how they enter, travel through, and deposit in the body. The comparison of data on nanoscale gold to data of other nanoscale materials being evaluated will provide insight into these issues.

While the extent or magnitude of human exposure is not the primary justification for this research program, nonetheless there are known exposures where individuals intentionally ingest colloidal gold dietary supplements or receive treatment with medical devices utilizing nanoscale gold as a "platform" for the device. While the extent of human exposure to nanoscale gold has not been quantified, the increasing use in commerce increases the probability that a larger number of individuals could be exposed in the future.

Since studies of nanoscale gold were identified as research needs by the FDA, it is anticipated that information from these studies will serve to increase the scientific base on which regulatory agencies such as FDA make their interpretations of the potential adverse biological and toxicological events associated with exposure to nanoscale gold and nanotechnology based products in general.

References

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