Tracking gold nanoparticles in the body

Article *in* SPIENewsroom · January 2009

DOI: 10.1117/2.1200907.1619

CITATIONS
4

READS
355

1 author:

George S Terentyuk
Saratov State University
59 PUBLICATIONS **899** CITATIONS

SEE PROFILE

10.1117/2.1200907.1619

Tracking gold nanoparticles in the body

Georgy Terentyuk, Galina Maslyakova, Leyla Suleymanova, B. Kogan, Nicolai Khlebtsov, Boris Khlebtsov, Garif Akchurin, Irina Maksimova, Alexander Shantrokha, and Valery Tuchin

Characterizing how nanoparticles affect organs and accumulate in tissue may provide insight into their safety as a potential cancer therapy

Functionalized nanoparticles are of great clinical interest because they hold promise as a cancer treatment.[1–6] Therefore, it is important to study how they circulate through the body and are distributed in different organs and tissues. To understand this process better, the field needs systematic studies in multiple animal models.

Several publications have investigated the organ distribution of particles in animals. The functionalization of gold nanoparticles with polyethylene glycol (PEG)-thiols resulted in prolonged circulation. De Jong et al.[7] performed a kinetic study to evaluate the effects of size on gold nanosphere tissue distribution in rats. Katti and co-workers[8] published detailed in vitro analysis and used pigs to study the pharmacokinetic effects of gold nanoparticles housed within a nontoxic phytochemical gum-arabic matrix.

To add to this body of work, we investigated the in vivo organ and tissue distribution of functionalized nanoparticles in rats. As part of our work, we tracked their blood kinetics at intravenous administration.[9] We also performed a histological study of morphological tissue changes that could be caused by the treatment. We used both nanospheres (15nm and 50nm) and silica/gold nanoshells (160nm). We then attached PEG molecules (using end thiol groups) to the particle surface to protect them from the animals' reticuloendothelial systems. We injected the animals with a 57μg/ml gold concentration solution. We measured the concentration of the solution in blood and visceral organs using an atomic absorptive spectrometer.

We monitored the concentration of gold nanoparticles in different organs after intravenous injection and found the highest level of PEGylated 15nm particles (2.5μg/ml) in the blood 30min after administration (see Figure 1). After this time, the concentration gradually falls. (This decrease in the blood occurs because the particles have migrated to the inner organs.)

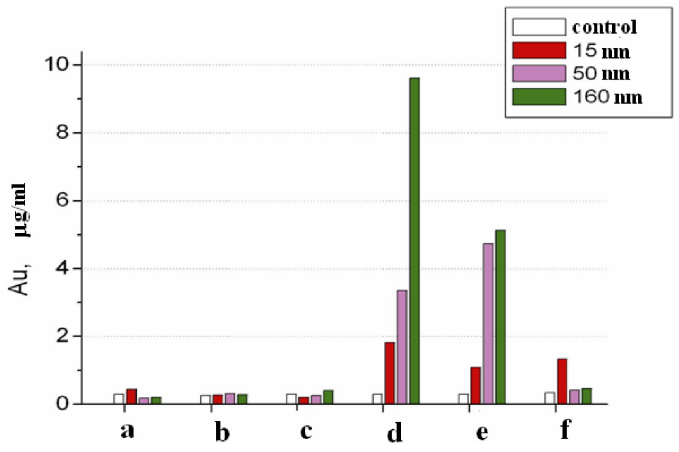

Figure 1. *Gold concentration in rat organs 24hr after intravenous administration. a: brain, b: kidney, c: lung, d: liver, e: spleen, f: blood.*

During 24 hours after intravenous administration, we observed maximal gold accumulation in the liver and spleen. This pattern can be explained by the fenestrated structure of capillaries in these organs. (Although the endothelium of the glomeruli in the kidney is also fenestrated, the basal membrane of the glomeruli forms a barrier that prevents nanoparticle accumulation.) Distribution in the inner organs was size-dependent, with larger ones accumulating more. The brain concentration was similar to that of the control group, because the blood brain barrier blocks their entry.

The results confirmed that concentration of gold in tumors is elevated in comparison with surrounding normal tissue by means of passive delivery. We found two peaks of gold accumulation in the tumor (see Figure 2). We speculated that the first spike in accumulation (30–45min) occurs because the concentration of gold in the bloodstream peaks. The second one (24hr) occurs due to passive accumulation of gold in the tumor tissue.

Continued on next page

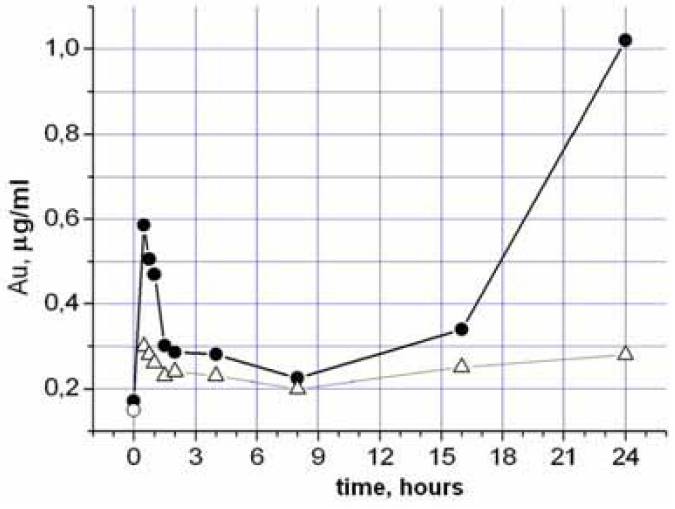

Figure 2. *Passive accumulation of nanoshells in the tumor. •- Au concentration in tumor, Δ - Au concentration in normal skin and muscle tissue.*

In addition, we observed separation of the blood cells and plasma and moderate degeneration of the parenchymatous cells. We could not determine the mechanism of blood separation, but noticed deposits of black pigment on the border between separated plasma and the erythrocytes (see Figure 3).

We also determined that changes in the inner organs depend on the size of the particle. For instance, 160nm particles affected the vessel wall, leading to vacuolar degeneration of the endothelial cells, and 50nm nanoparticles caused more expressed changes in the inner organs. In the spleen, for instance, lymphoid nodules showed an indistinct peripheral zone and no germinal centers. The majority of lymphocytes had indistinct outlines and light-blue cytoplasm. Between normal lymphocytes we noticed multiple bodies (which look apoptotic). In the liver, we found severe degeneration of hepatocytes and moderate blood congestion. We found less blood separation with smaller particles than for 160nm ones. Examination of lung tissue revealed more developed congestion and focal hemorrhages. The kidneys exhibited moderate hyperemia and changes in the glomeruli—specifically, the presence of single erythrocytes and the proliferation of the epithelial cells of Bowmen's capsule. The 15nm particles caused moderate degeneration of parenchymatous cells of inner organs and moderate hemodynamic disorders (as well as severe liver degeneration).

Our study of in vivo nanoparticles characterized their behavior in the body and tissue changes associated with them. One day after administration, the nanoparticles mainly accumulated in the spleen and liver in a size-dependent manner. Maximal

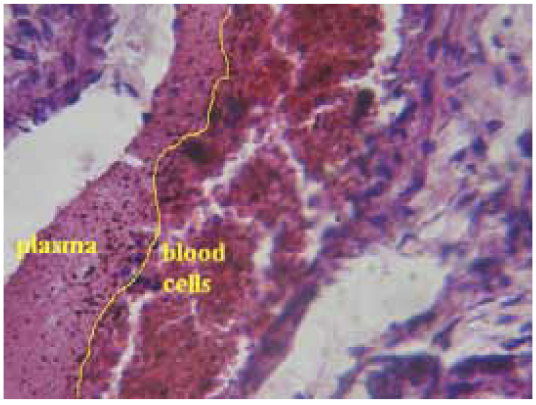

Figure 3. *Blood vessel containing separated blood cells and deposits of black-brown pigment (Hematoxylin and eosin stain ×150).*

concentration was found for 160nm nanoparticles, while smaller nanoparticles (15nm) stayed in the bloodstream much longer due to recirculation. We also demonstrated histological changes, not only in the liver and spleen, but also in the organs that showed less accumulation. Future work will investigate chronic toxicity and the quantitative dynamic characteristics of gold accumulation in tumor by targeted delivery.

This research was supported by grants No 224014 PHOTONICS4LIFE of FP7-ICT-2007-2, RFBR (Nos. 07-02-01434a and 08-02-00399a), NSHA-208.2008.2, the Ministry of Science and Education of RF (RNP 2.1.1/4989 and 2.2.1.1/2950). BK was supported by grants from the RF President (MK) and RFBR (Nos. 07-04-00301a, 07-04-00302a, and 09-02-00496-a). NK was supported by a grant from the Presidium of RAS (Program 'The Basic Sciences – to Medicine').

Author Information

Georgy Terentyuk, Garif Akchurin, Irina Maksimova, Alexander Shantrokha, and Valery Tuchin
Saratov State University
Saratov, Russia

Galina Maslyakova and Leyla Suleymanova
Saratov Medical State University
Saratov, Russia

B. Kogan
Federal State Unitary Enterprise
State Scientific Center

Continued on next page

Research Institute of Intermediate Products and Dyes
Moscow, Russia

Nicolai Khlebtsov and Boris Khlebtsov
Institute of Biochemistry and Physiology of Plants and Microorganisms
Saratov, Russia

References

1. X. Huang, I. El-Sayed, W. Qian, and M. El-Sayed, *Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods*, **J. Am. Chem. Soc. 128**, pp. 2115–20, 2006.
2. P. Jain, I. El-Sayed, and M. El-Sayed, *Au nanoparticles target cancer*, **Nanotoday 2**, pp. 18–29, 2007.
3. D. Pissuwan, S. Valenzuela, and M.Cortie, *Therapeutic possibilities of plasmonically heated gold nanoparticles*, **Trends in Biotechnol. 24**, pp. 62–67, 2006.
4. R. Visaria, J. Bischof, M. Loren, B. Williams, E. Ebbini, G. Paciotti, and R. Griffin, *Nanotherapeutics for enhancing thermal therapy of cancer*, **Int. J. Hyperthermia 23** (6), pp. 501–511, 2007.
5. T. Huff, L. Tong, Y. Zhao, M. Hansen, J.-X. Cheng, and A. Wei, *Hyperthermic effects of gold nanorods on tumor cells*, **Nanomed. 2**, pp. 125–132, 2007.
6. J. Chen, D. Wang, J. Xi, L. Au, A. Siekkinen, A. Warsen, Z.-Y. Li, H. Zhang, Y. Xia, and X. Li, *Immuno gold nanocages with tailored optical properties for targeted photothermal destruction of cancer cells*, **Nano Lett. 7**, pp. 1318–1322, 2007.
7. W. De Jong, W. Hagens, P. Krystek, M. Burger, A. Sips, and R. Geertsma, *Particle size-dependent organ distribution of gold nanoparticles after intravenous administration*, **Biomater. 29** (12), pp. 1912–1919, 2008.
8. V. Kattumuri, K. Katti, S. Bhaskaran, E. Boote, S. Casteel, G. Fent, D. Robertson, M. Chandrasekhar, R. Kannan, and K. Katti, *Gum arabic as a phytochemical construct for the stabilization of gold nanoparticles: In vivo pharmacokinetics and x-ray-contrast-imaging studies*, **Small 3**, pp. 333–341, 2007.
9. G. Terentyukl, G. Maslyakova, L. Suleymanova, B. Khlebtsov, B. Ya. Kogan, G. Akchurin, A. Shantrocha, I. Maksimova, N. Khlebtsov, and V. Tuchin, *Circulation and distribution of gold nanoparticles and induced alterations of tissue morphology at intravenous particle delivery*, **J. Biophoton. 3**, 2009. (accepted)