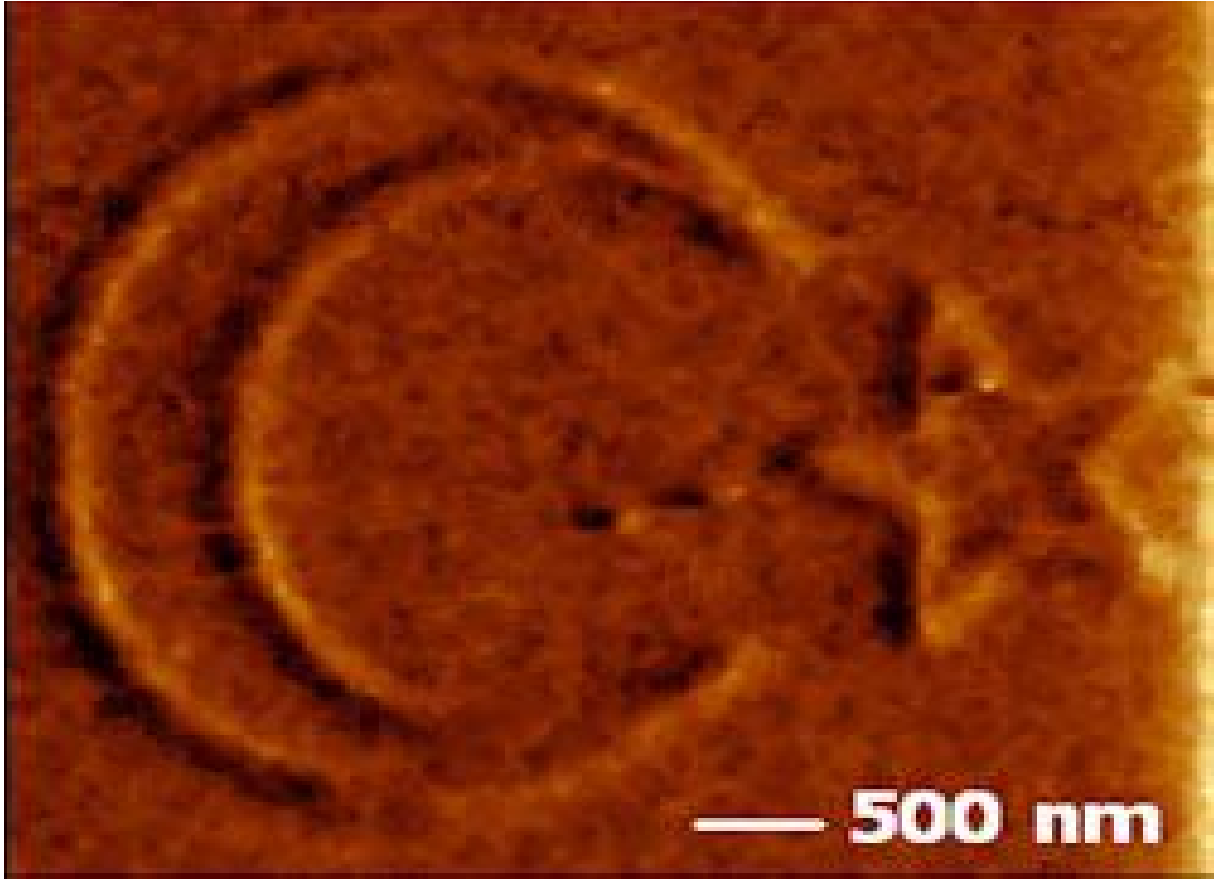


Makale Özetleri

Sağlık Bilimlerinde Nanoteknoloji (*Nanotechnology in Health Science*)



<http://nano-tr.blogspot.com/>

Peculiarities of live cells' interaction with micro- and nanoparticles.

Dukhin AS, Ulberg ZR, Karamushka VI, Gruzina TG.

Adv Colloid Interface Sci. 2010 Aug 11;159(1):60-71. Epub 2010 May 24.

Experimental evidence collected more than 20 years ago in different laboratories suggests that the interactions between live biological cells and micro- and nanoparticles depend on their metabolic state. These experiments were conducted by reputable groups, led by prominent leaders such as H. Pohl of the USA, who was the inventor of dielectrophoresis, and B. Derjaguin of the Soviet Union who was the leading author of DLVO theory. The experiments had been mostly conducted with microparticles in the early 1980s. In the early 1990s, Ukrainian researchers showed that the interaction of live cells with gold nanoparticles consisted of an initial reversible step that also depended on cell metabolism. They found indirect evidence that the ion pumps of the cells were responsible for the reversible step. Ion pumps generate a transmembrane potential, a measurable and widely-used characteristic of the cell's energetic state. The transmembrane potential, in turn, strongly affects the zeta-potential, as was experimentally discovered 40 years ago by several independent groups using cell electrophoresis. This relationship should be taken into account when DLVO theory is considered as the basis for describing the interactions between live cells and micro- and nanoparticles. Unfortunately, detail theoretical analysis indicates that such modification would not be sufficient for explaining observed peculiarities mentioned above. That is why distinguished theoreticians such as Pohl, Frohlich, Derjaguin and others have suggested three theoretical models, presumably to explain these experiments. These theoretical models should be considered to be complementary to the well-established concepts developed on this subject in the molecular biology of cells and cell adhesion. This paper is not a revision of the existing models. It is an overview of the old and forgotten experimental data and discussion of the suggested theoretical models. The unusual interaction mechanisms are only specific for live biological cells and serve a dual role: either as a first barrier to protect the cell from potentially damaging, dispersed particulates, or as a means of accumulating useful substances. Both functions are critical for the modern problem of nanotoxicology.

Nanotechnology in head and neck cancer: the race is on.

El-Sayed IH.

Curr Oncol Rep. 2010 Mar;12(2):121-8.

Rapid advances in the ability to produce nanoparticles of uniform size, shape, and composition have started a revolution in the sciences. Nano-sized structures herald innovative technology with a wide range of potential therapeutic and diagnostic applications. More than 1000 nanostructures have been reported, many with potential medical applications, such as metallic-, dielectric-, magnetic-, liposomal-, and carbon-based structures. Of these, noble metallic nanoparticles are generating significant interest because of their multifunctional capacity for novel methods of laboratory-based diagnostics, in vivo clinical diagnostic imaging, and therapeutic treatments. This review focuses on recent advances in the applications of nanotechnology in head and neck cancer, with special emphasis on the particularly promising plasmonic gold nanotechnology.

Multifunctional magnetic bead-based electrochemical immunoassay for the detection of aflatoxin B1 in food.

Tang D, Zhong Z, Niessner R, Knopp D.
Analyst. 2009 Aug;134(8):1554-60. Epub 2009 May 20.

A sensitive and reusable electrochemical immunoassay for aflatoxin B(1) (AFB(1)) in food has been developed. A multifunctional magnetic bead (MMB) was initially synthesized using magnetic CoFe(2)O(4) nanoparticle as the core and Prussian blue nanoparticle (PBNP)-doped silica as the shell, and then the prepared MMB was used as an affinity support for the immobilization of the AFB(1)-bovine serum albumin conjugate (AFB(1)-BSA). With the aid of an external magnet, the AFB(1)-BSA-conjugated MMBs were attached on the surface of an indium tin oxide (ITO) electrode. Gold nanoparticles, labeled with horseradish peroxidase (HRP)-bound anti-AFB(1) antibodies (HRP-anti-AFB(1)), were employed as detection antibodies. With a competitive immunoassay format, the concentrations of AFB(1) in samples were measured in PBS (pH 7.0) by using PBNP-doped MMBs as the mediator, HRP-anti-AFB(1) as the tracer and hydrogen peroxide (H(2)O(2)) as the enzyme substrate, and the linear range was 0.05-12 ng/mL with a detection limit of 6.0 pg/mL AFB(1) (at 3sigma). Intra- and inter-assay coefficients of variation were less than 7.5%. In addition, the content of AFB(1) in red paprika specimens has been assayed by the developed immunoassay and a commercially available enzyme-linked immunosorbent assay (ELISA) method, respectively, and consistent results were obtained. The as-prepared immunoassay provides a promising approach for the screening of organic pollutants because it is simple, rapid, highly sensitive, specific, and without the need of sample pre-concentration.

Gold nanoparticles for biology and medicine.

Giljohann DA, Seferos DS, Daniel WL, Massich MD, Patel PC, Mirkin CA.
Angew Chem Int Ed Engl. 2010 Apr 26;49(19):3280-94.

Gold colloids have fascinated scientists for over a century and are now heavily utilized in chemistry, biology, engineering, and medicine. Today these materials can be synthesized reproducibly, modified with seemingly limitless chemical functional groups, and, in certain cases, characterized with atomic-level precision. This Review highlights recent advances in the synthesis, bioconjugation, and cellular uses of gold nanoconjugates. There are now many examples of highly sensitive and selective assays based upon gold nanoconjugates. In recent years, focus has turned to therapeutic possibilities for such materials. Structures which behave as gene-regulating agents, drug carriers, imaging agents, and photoresponsive therapeutics have been developed and studied in the context of cells and many debilitating diseases. These structures are not simply chosen as alternatives to molecule-based systems, but rather for their new physical and chemical properties, which confer substantive advantages in cellular and medical applications.

Neuromodulation: advances in the next decade.

Andrews RJ.

Ann N Y Acad Sci. 2010 Jun;1199:212-20.

Many nervous system disorders (e.g., Parkinson's disease, mood disorders) involve neurotransmitters as well as electrical activity. Pharmacologic treatment does not target the precise location(s) where neurotransmitter imbalances occur. Additionally, non-neuronal cells in the brain--notably astrocytes--influence neuronal activity through both electrical and neurochemical modulation of nearby neurons. Precise monitoring/recording and modulating/stimulating (both electrical and neurochemical) can optimize therapy in specific disorders and specific patients. Carbon-fiber microelectrodes (5 microm diameter) in freely moving rodents have shown that dopamine release is heterogeneous within various regions in the nucleus accumbens, a region involved in many mood disorders. Because neurons are only several microns in diameter (axons, dendrites, and synaptic clefts smaller still), ultramicroelectrodes will be essential to selectively monitor/modulate the cell body, the axon, or at the intracellular level. Nanoelectrode arrays can monitor both electrical activity and dopamine in real time with submicron resolution, and stimulate neurons with equal precision. Computational models indicate that precise monitoring/modulating (electrically and neurochemically) at the subnucleus or neuron level will be necessary to restore normal firing patterns and neurotransmitter levels in many brain disorders. Endovascular techniques can introduce ultramicroelectrodes (0.5 micron or smaller) into the brain via capillaries; such electrodes can stimulate/record neuronal tissue with a response virtually identical to extra-vascular microelectrodes. Within the next decade, hundreds if not thousands of submicron-sized monitoring/modulating electrodes can be placed wherever needed to restore brain function to normal. The term "neuromodulation" will likely replace deep brain stimulation (DBS) as both neurochemistry and electrical activity are included in the therapeutic modalities.

Nanoparticle-mediated endothelial cell-selective delivery of pitavastatin induces functional collateral arteries (therapeutic arteriogenesis) in a rabbit model of chronic hind limb ischemia.

Oda S, Nagahama R, Nakano K, Matoba T, Kubo M, Sunagawa K, Tominaga R, Egashira K.

J Vasc Surg. 2010 Aug;52(2):412-20. Epub 2010 Jun 22.

OBJECTIVES: We recently demonstrated in a murine model that nanoparticle-mediated delivery of pitavastatin into vascular endothelial cells effectively increased therapeutic neovascularization. For the development of a clinically applicable approach, further investigations are necessary to assess whether this novel system can induce the development of collateral arteries (arteriogenesis) in a chronic ischemia setting in larger animals.

METHODS: Chronic hind limb ischemia was induced in rabbits. They were administered single injections of nanoparticles loaded with pitavastatin (0.05, 0.15, and 0.5 mg/kg) into ischemic muscle.

RESULTS: Treatment with pitavastatin nanoparticles (0.5 mg/kg), but not other nanoparticles, induced angiographically visible arteriogenesis. The effects of intramuscular injections of phosphate-buffered saline, fluorescein isothiocyanate (FITC)-loaded nanoparticles, pitavastatin (0.5 mg/kg), or pitavastatin (0.5 mg/kg) nanoparticles were examined. FITC nanoparticles were detected mainly in endothelial cells of the ischemic muscles for up to 4 weeks. Treatment with pitavastatin nanoparticles, but not other treatments, induced therapeutic arteriogenesis and ameliorated exercise-induced ischemia, suggesting the development of functional collateral arteries. Pretreatment with nanoparticles loaded with vatalanib, a vascular endothelial growth factor receptor (VEGF) tyrosine kinase inhibitor, abrogated the therapeutic effects of pitavastatin nanoparticles. Separate experiments with mice deficient for VEGF receptor tyrosine kinase demonstrated a crucial role of VEGF receptor signals in the therapeutic angiogenic effects.

CONCLUSIONS: The nanotechnology platform assessed in this study (nanoparticle-mediated endothelial cell-selective delivery of pitavastatin) may be developed as a clinically feasible and promising strategy for therapeutic arteriogenesis in patients.

Nanogel antigenic protein-delivery system for adjuvant-free intranasal vaccines.

Nochi T, Yuki Y, Takahashi H, Sawada S, Mejima M, Kohda T, Harada N, Kong IG, Sato A, Kataoka N, Tokuhara D, Kurokawa S, Takahashi Y, Tsukada H, Kozaki S, Akiyoshi K, Kiyono H. *Nat Mater.* 2010 Jul;9(7):572-8. Epub 2010 Jun 20.

Nanotechnology is an innovative method of freely controlling nanometre-sized materials. Recent outbreaks of mucosal infectious diseases have increased the demands for development of mucosal vaccines because they induce both systemic and mucosal antigen-specific immune responses. Here we developed an intranasal vaccine-delivery system with a nanometre-sized hydrogel ('nanogel') consisting of a cationic type of cholesteryl-group-bearing pullulan (cCHP). A non-toxic subunit fragment of Clostridium botulinum type-A neurotoxin BoHc/A administered intranasally with cCHP nanogel (cCHP-BoHc/A) continuously adhered to the nasal epithelium and was effectively taken up by mucosal dendritic cells after its release from the cCHP nanogel. Vigorous botulinum-neurotoxin-A-neutralizing serum IgG and secretory IgA antibody responses were induced without co-administration of mucosal adjuvant. Importantly, intranasally administered cCHP-BoHc/A did not accumulate in the olfactory bulbs or brain. Moreover, intranasally immunized tetanus toxoid with cCHP nanogel induced strong tetanus-toxoid-specific systemic and mucosal immune responses. These results indicate that cCHP nanogel can be used as a universal protein-based antigen-delivery vehicle for adjuvant-free intranasal vaccination.

Evaluation of the middle cerebral artery occlusion techniques in the rat by in-vitro 3-dimensional micro- and nano computed tomography .

Langheinrich AC, Yeniguen M, Ostendorf A, Marhoffer S, Kampschulte M, Bachmann G, Stolz E, Gerriets T. *BMC Neurol.* 2010 May 28;10:36.

BACKGROUND: Animal models of focal cerebral ischemia are widely used in stroke research. The purpose of our study was to evaluate and compare the cerebral macro- and microvascular architecture of rats in two different models of permanent middle cerebral artery occlusion using an innovative quantitative micro- and nano-CT imaging technique.

METHODS: 4h of middle cerebral artery occlusion was performed in rats using the macrosphere method or the suture technique. After contrast perfusion, brains were isolated and scanned en-bloc using micro-CT (8 μm)³ or nano-CT at 500 nm ³ voxel size to generate 3D images of the cerebral vasculature. The arterial vascular volume fraction and gray scale attenuation was determined and the significance of differences in measurements was tested with analysis of variance [ANOVA].

RESULTS: Micro-CT provided quantitative information on vascular morphology. Micro- and nano-CT proved to visualize and differentiate vascular occlusion territories performed in both models of cerebral ischemia. The suture technique leads to a remarkable decrease in the intravascular volume fraction of the middle cerebral artery perfusion territory. Blocking the medial cerebral artery with macrospheres, the vascular volume fraction of the involved hemisphere decreased significantly ($p < 0.001$), independently of the number of macrospheres, and was comparable to the suture method. We established gray scale measurements by which focal cerebral ischemia could be radiographically categorized ($p < 0.001$). Nano-CT imaging demonstrates collateral perfusion related to different occluded vessel territories after macrosphere perfusion.

CONCLUSION: Micro- and Nano-CT imaging is feasible for analysis and differentiation of different models of focal cerebral ischemia in rats

Near-isotropic 3D optical nanoscopy with photon-limited chromophores.

Tang J, Akerboom J, Vaziri A, Looger LL, Shank CV.
Proc Natl Acad Sci U S A. 2010 Jun 1;107(22):10068-73. Epub 2010 May 14.

Imaging approaches based on single molecule localization break the diffraction barrier of conventional fluorescence microscopy, allowing for bioimaging with nanometer resolution. It remains a challenge, however, to precisely localize photon-limited single molecules in 3D. We have developed a new localization-based imaging technique achieving almost isotropic subdiffraction resolution in 3D. A tilted mirror is used to generate a side view in addition to the front view of activated single emitters, allowing their 3D localization to be precisely determined for superresolution imaging. Because both front and side views are in focus, this method is able to efficiently collect emitted photons. The technique is simple to implement on a commercial fluorescence microscope, and especially suitable for biological samples with photon-limited chromophores such as endogenously expressed photoactivatable fluorescent proteins. Moreover, this method is relatively resistant to optical aberration, as it requires only centroid determination for localization analysis. Here we demonstrate the application of this method to 3D imaging of bacterial protein distribution and neuron dendritic morphology with subdiffraction resolution.

RNAi nanomedicines: challenges and opportunities within the immune system.

Weinstein S, Peer D.
Nanotechnology. 2010 Jun 11;21(23):232001. Epub 2010 May 13.

RNAi, as a novel therapeutic modality, has an enormous potential to bring the era of personalized medicine one step further from notion into reality. However, delivery of RNAi effector molecules into their target tissues and cells remain extremely challenging. Major attempts have been made in recent years to develop sophisticated nanocarriers that could overcome these hurdles. This review will present the recent progress with the challenges and opportunities in this emerging field, focusing mostly on the in vivo applications with special emphasis on the strategies for RNAi delivery into immune cells.

Diagnostic tools for animal diseases.

Schmitt B, Henderson L.
Rev Sci Tech. 2005 Apr;24(1):243-50.

While traditional testing methods are still widely used in veterinary diagnostic laboratories exciting new technologies, such as biosensors and microarray techniques, are being developed. Nucleic acid diagnostic techniques such as polymerase chain reaction (PCR) have become routine diagnostic tools in veterinary laboratories not only to make specific typing determinations but also to rapidly screen large numbers of samples during disease outbreaks. In addition, nanotechnologies, although not yet implemented in veterinary laboratories, hold the promise of screening for numerous pathogens in a single assay. Other biotechnologies are likely to be widely used in the future as they can improve diagnostic capabilities while reducing the time and perhaps, the costs, associated with conventional technologies. This paper describes some of these new technologies and concludes that although a lot of developmental work is still required, biotechnology and its applications hold great promise for improving the speed and accuracy of diagnostics for veterinary pathogens.

Directional neurite growth using carbon nanotube patterned substrates as a biomimetic cue.

Jang MJ, Namgung S, Hong S, Nam Y.
Nanotechnology. 2010 Jun 11;21(23):235102. Epub 2010 May 13.

Researchers have made extensive efforts to mimic or reverse-engineer in vivo neural circuits using micropatterning technology. Various surface chemical cues or topographical structures have been proposed to design neuronal networks in vitro. In this paper, we propose a carbon nanotube (CNT)-based network engineering method which naturally mimics the structure of extracellular matrix (ECM). On CNT patterned substrates, poly-L-lysine (PLL) was coated, and E18 rat hippocampal neurons were cultured. In the early developmental stage, soma adhesion and neurite extension occurred in disregard of the surface CNT patterns. However, later the majority of neurites selectively grew along CNT patterns and extended further than other neurites that originally did not follow the patterns. Long-term cultured neuronal networks had a strong resemblance to the in vivo neural circuit structures. The selective guidance is possibly attributed to higher PLL adsorption on CNT patterns and the nanomesh structure of the CNT patterns. The results showed that CNT patterned substrates can be used as novel neuronal patterning substrates for in vitro neural engineering.

Body distribution of inhaled fluorescent magnetic nanoparticles in the mice.

Kwon JT, Hwang SK, Jin H, Kim DS, Minai-Tehrani A, Yoon HJ, Choi M, Yoon TJ, Han DY, Kang YW, Yoon BI, Lee JK, Cho MH.
J Occup Health. 2008 Jan;50(1):1-6.

Reducing the particle size of materials is an efficient and reliable tool for improving the bioavailability of a gene or drug delivery system. In fact, nanotechnology helps in overcoming the limitations of size and can change the outlook of the world regarding science. However, a potential harmful effect of nanomaterial on workers manufacturing nanoparticles is expected in the workplace and the lack of information regarding body distribution of inhaled nanoparticles may pose serious problem. In this study, we addressed this question by studying the body distribution of inhaled nanoparticles in mice using approximately 50-nm fluorescent magnetic nanoparticles (FMNPs) as a model of nanoparticles through nose-only exposure chamber system developed by our group. Scanning mobility particle sizer (SMPS) analysis revealed that the mice were exposed to FMNPs with a total particle number of $4.89 \times 10^5 \pm 2.37 \times 10^4/\text{cm}^3$ (low concentration) and $9.34 \times 10^5 \pm 5.11 \times 10^4/\text{cm}^3$ (high concentration) for 4 wk (4 h/d, 5 d/wk). The body distribution of FMNPs was examined by magnetic resonance imaging (MRI) and Confocal Laser Scanning Microscope (CLSM) analysis. FMNPs were distributed in various organs, including the liver, testis, spleen, lung and brain. T2-weighted spin-echo MR images showed that FMNPs could penetrate the blood-brain-barrier (BBB). Application of nanotechnologies should not produce adverse effects on human health and the environment. To predict and prevent the potential toxicity of nanomaterials, therefore, extensive studies should be performed under different routes of exposure with different sizes and shapes of nanomaterials.

Beta-lapachone micellar nanotherapeutics for non-small cell lung cancer therapy.

Blanco E, Bey EA, Khemtong C, Yang SG, Setti-Guthi J, Chen H, Kessinger CW, Carnevale KA, Bornmann WG, Boothman DA, Gao J.
Cancer Res. 2010 May 15;70(10):3896-904. Epub 2010 May 11.

Lung cancer is the leading cause of cancer-related deaths with current chemotherapies lacking adequate specificity and efficacy. Beta-lapachone (beta-lap) is a novel anticancer drug that is bioactivated by NAD(P)H:quinone oxidoreductase 1, an enzyme found specifically overexpressed in non-small cell lung cancer (NSCLC). Herein, we report a nanotherapeutic strategy that targets NSCLC tumors in two ways: (a) pharmacodynamically through the use of a bioactivatable agent, beta-lap, and (b) pharmacokinetically by using a biocompatible nanocarrier, polymeric micelles, to achieve drug stability, bioavailability, and targeted delivery. Beta-lap micelles produced by a film sonication technique were small (approximately 30 nm), displayed core-shell architecture, and possessed favorable release kinetics. Pharmacokinetic analyses in mice bearing subcutaneous A549 lung tumors showed prolonged blood circulation ($t(1/2)$, approximately 28 h) and increased accumulation in tumors. Antitumor efficacy analyses in mice bearing subcutaneous A549 lung tumors and orthotopic Lewis lung carcinoma models showed significant tumor growth delay and increased survival. In summary, we have established a clinically viable beta-lap nanomedicine platform with enhanced safety, pharmacokinetics, and antitumor efficacy for the specific treatment of NSCLC tumors.

Nanotechnologies applied to veterinary diagnostics.

Bollo E.
Vet Res Commun. 2007 Aug;31 Suppl 1:145-7.

Improved, quality assured diagnostics are important for disease control in animals; they provide a basis for appropriate treatments of animal patients, for monitoring diseases and for the enhancement of disease-surveillance capacity. The past decade has brought about impressive advances in surface and materials science and engineering, as well as in the development of new microelectronic components. These tools hold the promise of miniaturizing diagnostic devices, which could dramatically reduce costs and increase throughput and sensitivity of a wide range of diagnostic tests for veterinary applications. Recent biotechnological developments, including micro- and nanotechnologies, have led to the proliferation of new, rapid diagnostic tests, based on microfluidic, microarray, electronic and photo-electronic, integrated on-chip and nanotechnology together with analytical systems, which enable the development of point-of-care analysers.