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EDITORIAL

Nanomedicine: An International Glimpse

1. Introduction to Nanomedicine

To understand nanomedicine, a definition of nanotechnology is helpful. Nanotechnology manipulates matter on an atomic and molecular scale as it deals with structures between 1 nm and 100 nm in at least one dimension and involves developing materials or devices that possess at least one dimension within that size. Nanotechnology is interdisciplinary because it includes applications in information science, material science, biology, engineering, and medicine. Nanomedicine is the medical application of nanotechnology and it ranges from medical applications of nanomaterials to nanoelectronic biosensors and future relevance of molecular nanotechnology.[1]

Current problems for nanomedicine involve understanding toxicity and environmental impact of nanoscale materials. Researchers in the speculative field of molecular nanotechnology believe that cell repair machines could revolutionize medicine, thus inspiring industry. Nanomedicine is enormous with sales reaching billions of dollars in 2004 and including an excess of 200 companies and 38 products worldwide; this suggests more than one billion dollars in nanotechnology Research and Development every year.[1] To focus on international examples, I will present highlights of activities devoted to nanomedicine at two familiar universities: University of California (UC), Los Angeles (UCLA) and Taipei Medical University (TMU).

2. Pioneering Nanomedicine: University of California and California Nanomedicine Institute

California seems far above many establishments and for that reason the thrust will be reviewed first followed by notable work at TMU. The California NanoSystems Institute (CNSI) is an integrated research center operating jointly at UCLA and UC Santa Barbara whose mission is to foster interdisciplinary collaborations for discoveries in nanosystems and nanotechnology; train the next generation of scientists, educators, and technology leaders; and facilitate partnerships with industry, fueling economic development and the social well-being of California, the United States and the world. In this fertile milieu, fortunate scientists benefit from an integrated laboratory culture that enables them to conduct dynamic research at the nanoscale, leading to significant breakthroughs in health, energy, environment, and information technology.

One important figure in this endeavor is Andre Nel, MD, PhD, member of the Department of Medicine and the newly formed CNSI. He was recruited as founder and chief of this new division. Now pooling efforts, the Division of Nanomedicine will play a prominent role in bringing high quality research opportunities in the CNSI for the convenience of physicians who wish to implement this novel enabling technology in their efforts to diagnose, image, and treat disease. The future envisions new paradigms for diagnosing and treating disease on a system wide scale; this is not possible using current technology.

3. Nanomedicine at UCLA

Relatively early and prudent work by Nel et al[2] revealed that nanomaterials of 100 nm or less can be used to perform exceptional feats of conductivity, reactivity, and optical sensitivity. However, possible undesirable effects may emerge on biological systems and the environment, with the potential to generate toxicity. Thus, as a cautionary note for beginners, it is crucial to develop test procedures and principles to ensure the safe manufacture and use of nanomaterials.

The following study demonstrates a possible solution to a particular type of nanoparticle toxicity. Xia et al[3] showed the dissolution of zinc (Zn) nanoparticles and Zn(2+) shedding contributes to several sublethal and lethal cellular toxicological responses that can be alleviated with iron doping. Doping is the general practice of adding impurities during the development of a product. They concluded this after conducting toxicity experiments in rodent and zebrafish models, confirming the utility of animal models as alternatives to human participants. They compared the effects of undoped to doped particles in rat lung, mouse lung, and zebrafish embryos. In mice, iron doping is associated with decreased polymorphonuclear cell (neutrophil) counts and interleukin-6 mRNA production. In mice, doped particles also caused decreased heme oxygenase 1 expression. Finally, iron doping may be a possible safe design strategy to prevent zinc oxide toxicity in animals and the environment.

Nel et al[4] found that nanoparticles interacting with proteins, membranes, cells, DNA, and organelles establish nanoparticle/biological interface, which leads to the formation of protein coronas, particle wrapping, and other biocatalytic processes. This interaction may have contrasting effects, that is, both biocompatible and bioadverse outcomes. Resulting biomolecules may induce phase transformations, free energy releases, restructuring, and dissolution at the nanomaterial surface. Thus, for the safe use of nanomaterials, it is necessary to probe these various interfaces to develop predictive relationships between structure and activity through nonmaterial properties in size, shape, surface chemistry, roughness, and surface coating.

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According to Meng et al,[5] multiple drug resistance in cancer cells is combated efficiently and in novel ways by using nanotechnology. Their work suggests that mesoporous silica nanoparticles (MSNP) can be used to deliver a chemotherapeutic agent doxorubicin as well as Pgp siRNA to a drug-resistant cancer cell line. With such results, it would therefore be possible to use MSNP to improve drug sensitivity to a chemotherapeutic agent via gene expression of a drug exporter. A key question regarding MSNP is whether they can be adapted for biological use through controlled nanovalve opening in cells. MSNP have proven to be an extremely effective solid support for controlled drug delivery because their surfaces can be easily functionalized to control the nanopore openings. Meng et al[6] described a series of mechanized silica nanoparticles that are capable of delivering cargo molecules using a series of nanovalves. Surpisingly, there is a novel MSNP delivery system capable of drug delivery based on the function of β-cyclodextrin nanovalves that are responsive to the endosomal acidification conditions in human differentiated myeloid (THP-1) and squamous carcinoma (KB-31) cells.

Another notable application of nanomedicine has been revealed with thin silica films and nanoparticles prepared using sol-gel chemistry that have been derivatized with active molecules and as a result generate new functional materials.[7] With the silica particles, donor-acceptor pairs can be doped into separate regions while photo-induced electron transgers between the molecules can be transgered. MSNP are promising materials for drug delivery and other biomedical applications because they are nontoxic and can be taken up by living cells. Recently, there have been novel results and findings with nanoparticles in treating cancer. Liong et al[8] suggested that drug delivery, magnetic resonance and fluorescence imaging, magnetic manipulation, and cell targeting are simultaneously possible using a multifunctional MSNP. These water insoluble drugs have been delivered into human cancer cells and increased the uptake into cancer cells when compared with other types, that is, cancerous fibroblasts. Such implications and findings suggest that these neoparticles can be used for simultaneous imaging and therapeutic applications.

4. Nanomedicine at TMU

Now, we move across the Pacific completing this international glimpse. Various studies have linked C60 fullerene-derived nanomaterials to their capacity of absorbing multiple free radicals. Huang at et al[9] investigated PEG-C(60)-3, a C(60) fullerene derivative incorporating poly(ethylene glycol), and its pentoxifylline-bearing hybrid (PTX-C(60)-2) against β-amyloid (Aβ)(25-35)-induced toxicity toward Neuro-2A cells. Pertinent findings include that PEG-C(60)-3 and PTX-C(60)-2 significantly reduced Aβ(25-35)-induced cytotoxicity, with comparable activities in decreasing reactive oxygen species (ROS) but maintaining the mitochondrial membrane potential. Such results offered new insights into therapeutic drug design using C(60) fullerene-PTX dyad nanoparticles against Aβ-associated diseases. With the presentation of a new property, C60 may enhance autophagy of β-amyloid peptide, which could minimize the damaging effects of the peptide. Huang et al[10] designed and prepared the new C60 fullerene hybrids bearing a xanthine moiety as potential double-action anti-inflammatory agents. These agents are capable of simultaneous inhibition of lipopolysaccharide (LPS)-induced nitric oxide (NO) and tumor mecrosis factor alpha (TNF-α) production. Throughout the study Huang et al[10] found that 10 mL of fulleropyrrolidine-xanthine dyad 2a and b were effective in suppressing LPS-induced NO production by $55.1 \pm 2.1\%$ and $58.6 \pm 2.6\%$, respectively, but only 2b was effective in suppressing LPS-induced TNF-α production by $34.0 \pm 2.7\%$. The agents synthesized here surely will hold promise for future development of a new generation of potent anti-inflammatory agents.

Expanding the field of C(60) fullerene derivatives has significantly increased because of the broad range of biological activities found for these compounds. Huang et al[11] designed and prepared a new C(60) fullerene hybrid bearing thalidomide as a potential double-action anti-inflammatory agent, capable of simultaneous inhibition of LPS-induced NO and TNF-α production. The C(60) fulleropyrrolidine-thalidomide dyad, CLT, was an effective agent suppressing the release of NO and TNF-α by the LPS-stimulated macrophages RAW 264.7. Ten micromolars of CLT effectively inhibited LPS-induced NO and TNF-α production by $47.3 \pm 4.2\%$ and $70.2 \pm 4\%$ when compared with the controls. In addition, preliminary biochemical investigations revealed that CLT was a potent agent that suppresses both LPS-induced intracellular ROS production and inducible nitric oxide synthase expression, and that CLT also inhibited the phosphorylation of extracellular signal-regulated kinase, which is an important protein kinase involved in the activation of TNF-α synthesis in LPS-activated macrophages. They concluded that their research holds promise for future development of a new generation of potent anti-inflammatory agents.

Lu et al[12] investigated PEG-C60-3, a C60 fullerene derivative against β-amyloid $(A\beta)_{25\text{-}35}$-induced toxicity toward Neuro-2A cells. Key results showed that PEG-C_{60}-3 reduced $A\beta_{25-35}$-induced cytotoxicity, revealing an increase in cell viability with C_{60} and $A\beta_{25-35}$ co-treated cells. Thus, the intracellular ROS that accumulated caused by Aβ-treated Neuro-2A cells was reduced by PEG-C_{60}-3 co-treatment. Those results suggest new understanding of the possible pathway of $A\beta_{25-35}$ gene expression and C_{60} protective mechanism. Thus, understanding the roles of Aβ and C_{60} will provide insight on the therapeutic effects using C C_{60} fullerene nanoparticles against Aβ-associated diseases, such as Alzheimer's disease. Clearly this and other pertinent work from TMU will be revealed in a future review that should do much to update and clarify the current editorial.

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Edwin L. Cooper, PhD, ScD
Chair Professor, Taipei Medical University (TMU);
Editor-in-Chief, Distinguished Professor,
Department of Neurobiology, Laboratory of Comparative Neuroimmunology, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA 90095-1763, USA.
E-mail: <cooper@mednet.ucla.edu>

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