[Frontiers in Bioscience, Scholar, 9, 62-70, January 1, 2017]

Cancer treatment with nano-diamonds

Charu Gupta[1], Dhan Prakash[1], Sneh Gupta[2]

[1]Amity Institute for Herbal Research and Studies, Amity University UP, Sector-125, Noida-201313, India, [2]Department of Zoology, R.G.P.G. College, Chippi Tank, Meerut-250001, India

TABLE OF CONTENTS

1. ABSTRACT

Diamond nano-particles find new and far-reaching applications in modern biomedical science and biotechnologies. Due to its excellent biocompatibility, nano-diamonds serve as versatile platforms that can be embedded within polymer-based microfilm devices. Nano-diamonds are complexed with a chemotherapeutic that enables sustained/slow release of the drug for a minimum of one month, with a significant amount of drug in reserve. This opens up the potential for highly localized drug release as a complementary and potent form of treatment with systemic injection towards the reduction of continuous dosing, and as such, attenuation of the often powerful side effects of chemotherapy. Nano-diamonds are quite economical, enabling the broad impact of these devices towards a spectrum of physiological disorders e.g. serving as a local chemotherapeutic patch, or as a pericardial device to suppress inflammation after open heart surgery. Nano-diamond patch could be used to treat a localized region where residual cancer cells might remain after a tumor is removed. Nano-diamonds can be used to explore a broad range of therapeutic classes, including additional small molecules, proteins, therapeutic antibodies, RNAi.

2. INTRODUCTION

The current challenges facing the fields of biological agents and medical therapeutics, such as poor pharmacokinetics and chemo resistance, have necessitated the optimization of therapeutic delivery agents. Among the many platforms being explored, nanodiamonds (NDs) have emerged as promising carriers due to their biocompatibility, scalable synthetic methods, and unique surface-mediated binding of a wide variety of bioactive molecules. ND platforms have also been shown to enhance imaging efficiency, sustain drug release, boost therapeutic efficacy, and improve therapeutic safety profiles (1).

Nanodiamond application in biotechnological and medical fields is nowadays in continuous progress. In fact, biocompatibility, reduced dimensions and high surface chemical interaction are specific features that make nanodiamonds perfect intracellular carriers of bioactive compounds. Using confocal microscopy, it was confirmed that nanodiamonds were able to penetrate in cell cytoplasm but they remained embedded in nuclear membrane just exposing some little portions into nuclear area (2).

Nanoparticles, having found use in the treatment of cancers, the study of autoimmune diseases and cardiovascular affections are currently of interest as theranostic agents needed for the advent of personalized medicine (3-7). These nano-scale systems are expected

to integrate imaging, tracking and monitoring capabilities with targeted delivery of compounds to tumours, cellular functions and processes, or specific organs.

Nanodiamonds, range in size from 1 to 100 nm that can be artificially synthesized by detonation, chemical vapor deposition or high-temperature–high-pressure procedures (8). They are characterized by chemical stability, octahedral symmetry, rigid structure, large surface area and low costs of production (9, 10). The implementation of nano-medicine in cellular, preclinical, and clinical studies has led to exciting advances ranging from fundamental to translational, particularly in the field of cancer.

Many of the current barriers in cancer treatment are being successfully addressed using nanotechnology-modified compounds. These barriers include drug resistance leading to suboptimal intra-tumoral retention, poor circulation times resulting in decreased efficacy, and off-target toxicity, among others. The first clinical nano-medicine advances to overcome these issues were based on monotherapy, where small-molecule and nucleic acid delivery demonstrated substantial improvements over unmodified drug administration. Recent preclinical studies have shown that combination nano-therapies, composed of either multiple classes of nano-materials or a single nano-platform functionalized with several therapeutic agents can image and treat tumors with improved efficacy over single-compound delivery. Among the many promising nano-materials that are being developed, nanodiamonds have received increasing attention because of the unique chemical-mechanical properties on their faceted surfaces. More recently, nanodiamond-based drug delivery has been included in the rational and systematic design of optimal therapeutic combinations using an implicitly de-risked drug development platform technology, termed Phenotypic Personalized Medicine–Drug Development (PPM-DD). The application of PPM-DD to rapidly identify globally optimized drug combinations successfully addressed a pervasive challenge confronting all aspects of drug development, both nano and non-nano (11).

3. HISTORICAL BACKGROUND

The first records of nano-sized diamond particle production come from the Union of Soviet Socialist Republics in the 1960s (12). However, they remained unrecognized by the rest of the world until the mid-1980s, when they found use in wear-resistant coatings and as an anti-wear additive for motor oil (12). The first report of ND production in the United States did not arrive until 1988 (13) but today, there are a multitude of methods for commercially producing diamond nanoparticles ranging from the purification of detonation soot (14, 10) and laser ablation to milling down larger diamond micro-particles (15). However, it was not until the late 1990s that researchers began to take interest in NDs for biomedical applications. Since then, the field has expanded significantly, with NDs finding use in a multitude of applications from nano-scale magnetic resonance imaging to cancer therapy.

4. NANODIAMOND TYPES, APPLICATIONS AND MECHANISM

Among the different kinds of nanodiamonds, the most interesting ones are produced by detonation. The detonation nanodiamond (ND) can be easily modified and linked to different molecules and bio-compounds by electrostatic and/or hydrophobic interactions or covalent bonds (16). These complexes are stable for many months after their synthesis (17).

There are other novel technologies that are based on the use of self-assembled nano-diamonds in controlled structures (18), or decorated with nanoparticles (19) or embedded in polymers (20).

Nanodiamonds can be largely used for biotechnological and medical applications. They can also be employed as carriers of biomolecules (DNA, RNA, proteins) and drugs inside living cells and organisms (21-24). This phenomenon is because of the high compatibility between nanodiamond material and cell physiology and structure (25). In fact, nanodiamonds were identified as the less toxic among nano-carbons (i.e. carbon blacks, fullerenes, carbon nanotubes); they generally do not induce significant oxidative stress or apoptosis during cell treatments (26).

Clathrin-mediated endocytosis was identified as the cell mechanism for nanodiamond internalization (27). Scientific data proved that cell endocytic vesicles transport and arrange nanodiamonds everywhere in the cytoplasm, also in perinuclear area, but not inside the nucleus (8). On the other hand, Martìn (28) only proposed a controversial theory demonstrating that fenton-treated nanodiamonds were able to enter directly in cell nucleus. In literature, it was reported that nanodiamonds, yet absorbed in cells, could also be thrown out the cytoplasm by exocytosis. However, all these processes are not standard but depend on different factors, such as nanodiamond size, surface, concentration and treatment time but also temperature and employed cell line (29, 30).

Due to their auto-fluorescent structural defects, known as nitrogen-vacancy centers, nanodiamonds can also be detected by fluorescent microscopy. They also have a refractive index higher than cytoplasm therefore nanodiamonds show a strong light scattering signal that makes them clearly distinguishable in cell compartment, even by optical microscopy with good contrast (27).

5. NANO DIAMONDS FOR CANCER TREATMENT: APPROACHES

More recently, scientists have been looking into using nanodiamonds as more is learned about the electrostatic capabilities of their facet surfaces when they carry chemicals in a biological system, the ways their inert core can be useful in certain applications and as a means to capitalize on their tunable surfaces.

The nanodiamonds used in medical applications fall into two main categories, detonation nanodiamonds (DNDs) and fluorescent nanodiamonds (FNDs) as part of highlighting the major ways that nanodiamonds are currently being used.

Imaging both DNDs and FNDs, the researchers note are increasingly being eyed as a way to improve magnetic resonance imaging and more recently FNDs are also being seen as a way to track stem cells to learn more about their regenerative potential.

A lot of research is currently going on Drug Delivery to see about which types of drugs adhere well to nanodiamond facets, most specifically those used in chemotherapy applications.

Similarly, a lot of research is being conducted on bio-distribution and toxicity, to find the ways nanodiamonds can be placed into a living organism (injection, consumption, through the skin, etc.) and whether there is a danger of toxicity.

The researchers note that another area of study involves using nanodiamonds as part of drug testing if medications can be carried to specific sites, and then there might be less side-effect.

Another benefit of using nanodiamonds is that despite being associated with precious gems, nanodiamonds would be quite cheap to procure and use because they can be obtained from mining waste (11).

6. DETECTING CANCER WITH DIAMONDS IN EARLY STAGES

Researchers have recently developed tiny synthetic diamonds that can aid in the fight against cancer by lighting up areas of cancer in MRI scans. The innovative technique could help especially in detecting cancers that are difficult to find early on, like brain and pancreatic cancers. Brain and pancreatic cancers are two of the most deadly cancers so it potentially means that treatment can be more effective. This study was based on past research that examined how nanodiamonds are capable of acting as a delivery service for cancer drugs. In that study, researchers found that nanodiamonds could penetrate cell walls without damaging them, thus acting as potential drug delivery carriers during chemotherapy. Nano diamonds are of particular interest for delivering drugs during chemotherapy because they are largely non-toxic and non-reactive (31).

Since diamonds have magnetic characteristics enabling them to act as beacons in MRIs, they aligned atoms inside a diamond to give it a “signal” that would be detected by MRIs. When they attached the hyperpolarized diamonds to molecules targeting the cancers, the method allowed ‘tracking of the molecules’ movement in the body.

It is certainly quite innovative to employ quantum physics in the fight against cancer but researchers are finding other unique and interesting pathways to develop new cancer treatments as well. For example, there is a personalized cancer treatment which focuses on a tumor’s molecular makeup and a person’s genetics to decide which forms of medications or therapies will be best and most effective for that patient.

Researchers are also finding ways to harness the immune system to attack cancer cells, a field of interest known as immunotherapy, which has shown great promise in treating melanoma and other types of cancer (31).

7. NANODIAMONDS IN DELIVERING CANCER DRUG TO KILL CHEMO-RESISTANT CANCER STEM CELLS

Chemo resistance, which is the ability of cancer cells to escape chemotherapy treatment, is a primary cause of treatment failure in cancer. Cancer stem cells, a type of cancer cell which initiates the formation of tumours, are commonly found to be more resistant to chemotherapy than the rest of the bulk tumour, which can lead to cancer recurrence following chemotherapy treatment. As such, there is an intense interest in developing new drugs or treatment strategies that overcome chemo resistance, particularly in cancer stem cells.

A study found that attaching chemotherapy drug Epirubicin to nanodiamonds effectively eliminates chemo-resistant cancer stem cells. Research demonstrated the use of nanotechnology to repurpose existing chemotherapy drugs as effective agents against chemo resistant cancer stem cells. In this study, widely-used chemotherapy drug Epirubicin was attached to nanodiamonds, carbon structures with a diameter of about five nanometres, to develop a nanodiamond-Epirubicin drug delivery complex (EPND). The researchers found that while both standard Epirubicin as well as EPND were capable of killing normal cancer cells, only EPND was capable of killing chemo resistant cancer stem cells and preventing secondary tumour formation in xenograft models of liver cancer (32).

Compared to other approaches such as combinatorial therapy of chemotherapy drugs with inhibitors of chemo resistance pathways, delivery of existing chemotherapy drugs with nano-materials, in this case nano-diamonds provide a broader range of protection in a package that is both safer and more effective. The study showed that delivery of Epirubicin by nanodiamonds resulted in a normally lethal dosage of Epirubicin becoming a safe and effective dosage. As such, delivery of chemotherapy drugs by nanodiamonds not only enables enhanced killing of chemo resistant cancer stem cells, but may be a useful alternative for patients who cannot tolerate the toxic side effects of standard chemotherapy drugs (32).

Furthermore, the versatility of the nanodiamond-based drug delivery platform opens up the possibility of future applications of nanodiamonds such as the addition of other similar drugs as well as active targeting components such as antibodies or peptides against tumour cell surface proteins for targeted drug release. In addition, the application of a nanodiamond-drug delivery system is not limited to liver cancer. It offers a promising approach to treating a broad range of difficult cancers, particularly those driven by chemo resistant cancer stem cells (32).

8. CARBON NANOPARTICLES PROMISE MULTIFACETED BENEFITS IN TRANSPORTING DRUGS

Anticancer drugs tend to become ineffective because cancer cells quickly pump them out before they have had time to do their work. This kind of drug resistance accounts for 90% of treatment failure in malignant cancer. Attaching chemotherapy drugs to small particles called nanodiamonds can make the drugs more effective. Nanodiamonds are basically carbon-based particles 2–8 nm in diameter with a truncated octahedral structure that gives it multiple facets to overcome this problem because the cellular transport proteins that usually pump the drug out of the cell cannot carry them. The drug therefore stays inside the cell (8).

For a nanoparticle to have translational significance, it has to have as many benefits engineered into one system as simply as possible. The surface chemistry of nanodiamonds makes them special. The diamond's facet surfaces possess differing properties, such as electrical charge. So a drug could be attached to one neutral surface, for example, while another facet retains an electrostatic charge, allowing the nanodiamond to disperse in fluids. Theoretically, nanodiamonds could be loaded with both a drug and an agent to target cancer cells (11).

Other nanoparticles, such as synthetic polymers made from PLGA (poly(lactic-co-glycolic acid)), are already in clinical use for drug delivery, but they do not have this inbuilt surface versatility (24).

9. NANODIAMONDS BIO-COMPATIBILITY

Nanodiamonds (NDs) have been rapidly gaining popularity in biological imaging and drug delivery applications due to the nontoxic nature of the nanoparticles. The nanodiamonds, each being 4 to 6 nanometers in diameter, are minimally invasive to cells, and are biocompatible.

Nanodiamonds are non-toxic and do not cause inflammation. They are also cheap to produce in large quantities. They can be functionalized with nearly any type of therapeutic and can be suspended easily in water which is important for biomedical applications.

Concerns about the toxicity of other carbon-based nanoparticles, such as carbon nanotubes originally brought the safety of NDs into question (33). However, a wide variety of studies examining ND behavior in both cultured cells and complete organisms have found the particles to be highly biocompatible (34-37).

In a study, NDs were injected into the gonad of the worm *Caenorhabditis elegans* and tracked into healthy offspring without any deleterious effects from the NDs (37). Similarly, the NDs administered to mouse lungs through the trachea showed almost no pulmonary toxicity and were rapidly cleared by resident macrophages (36). An intravenous injection into mice with NDs failed to cause any indication of liver toxicity or systemic inflammation (34). Taken together, these results indicate that NDs are essentially nontoxic to both cells and live animals. However, given the abundance of possible surface modifications, it will be necessary to continue evaluating each subtype of ND as they are developed to further consider their potential for translation.

Furthermore, the process of generating nanodiamonds is cruder. It is like detonating TNT followed by a lot of purification. Further polishing of the nanodiamond production process might be necessary if they are to be used for human therapeutics.

10. APPLICATION OF NANODIAMONDS IN CANCER TREATMENT

10.1. Nanodiamonds for brain tumors

Researchers have developed an innovative drug-delivery system in which tiny particles called nanodiamonds are used to carry chemotherapy drugs directly into brain tumors. The new method was found to result in greater cancer-killing efficiency and fewer harmful side effects than existing treatments.

Glioblastoma is the most common and lethal type of brain tumor. Despite treatment with surgery, radiation and

chemotherapy, the median survival time for glioblastoma patients is less than one-and-a-half years. The tumors are notoriously difficult to treat, in part because chemotherapy drugs injected alone often are unable to penetrate the system of protective blood vessels that surround the brain, known as the blood–brain barrier. And those drugs that do cross the barrier do not stay concentrated in the tumor tissue long enough to be effective.

The drug doxorubicin, a common chemotherapy agent, has shown promise in a broad range of cancers, and it has served as model drug for the treatment brain tumors when injected directly into the tumor. Researcher's team originally developed a strategy for strongly attaching doxorubicin molecules to nanodiamond surfaces, creating a combined substance called ND–DOX.

Nanodiamonds are carbon-based particles roughly 4 to 5 nanometers in diameter that can carry a broad range of drug compounds. And while tumor-cell proteins are able to eject most anticancer drugs that are injected into the cell before those drugs have time to work, they cannot get rid of the nanodiamonds. Thus, drug–nanodiamond combinations remain in the cells much longer without affecting the tissue surrounding the tumor.

It was hypothesized that glioblastoma might be efficiently treated with a nanodiamond-modified drug by using a direct-injection technique known as convection-enhanced delivery (CED). They used this method to inject ND–DOX directly into brain tumors in rodent models.

The researchers found that ND–DOX levels in the tumors were retained for duration far beyond that of doxorubicin alone, showing that doxorubicin was taken into the tumor and remained their longer when attached to nanodiamonds. In addition, ND–DOX was also found to increase apoptosis programmed cancer-cell death and to decrease cell viability in glioma (brain cancer) cell lines.

The results also demonstrated for the first time that the ND–DOX delivery limited the amount of doxorubicin that was distributed outside the tumor. This reduced toxic side effects and kept more of the drug in the tumor for longer, increasing the drug's tumor-killing efficiency without affecting the surrounding tissue. Survival time increased significantly in the rats treated with ND–DOX, compared with those given only unmodified doxorubicin.

Nanodiamonds have many facets, almost like the surface of a soccer ball, and can bind to doxorubicin very strongly and quickly. Further research will expand the list of brain-cancer chemotherapy drugs that can be attached to the nanodiamond surfaces to improve treatment and reduce side effects.

This study showed that convection-enhanced delivery of ND–DOX offers a powerful treatment delivery system against these very difficult and deadly brain tumors (38).

10.2. Nanodiamonds for breast cancer

Scientists attached the anticancer drug doxorubicin to nanodiamonds. They treated mice with liver tumours with either this compound or with doxorubicin alone, and checked levels of the drug in the tumours two days later. They found that doxorubicin levels were ten times higher in mice treated with the nanodiamond compound compared with mice given doxorubicin alone, and remained high for seven days. The tumours of mice receiving nanodiamond-doxirubicin also shrank more and the mice survived longer.

Then the nanodiamonds were tested on a model of breast cancer which is highly resistant to doxorubicin. The nanodiamond-doxirubicin compound worked better there too. Strikingly, the nanodiamonds also reduced the toxicity of the drug by releasing it more slowly. Doses that would have killed mice if given as free drug did not even cause them to lose weight when the drug was carried on nanodiamonds (34).

But the concept of using nanodiamonds for drug delivery is still in its infancy stage. The concept needs more refining as synthetic polymers have reproducible properties and composition, and we structures can be fine-tuned.

11. NANODIAMOND THERAPEUTIC DELIVERY AGENTS MEDIATE ENHANCED CHEMO-RESISTANT TUMOR TREATMENT

In a study, it has been shown that chemotherapeutic efficiency can be enhanced through improved drug delivery that would facilitate the treatment of chemo-resistant cancers such as recurrent mammary tumors and liver cancer. In this study, the efficacy of nano- diamond conjugated chemotherapeutic was tested in mouse models of liver and mammary cancer. A complex (NDX) of ND and doxorubicin (Dox) overcame drug efflux and significantly increased apoptosis and tumour growth inhibition beyond conventional Dox treatment in both murine liver tumour and mammary carcinoma models. The unmodified Dox treatment represents the clinical standard for most cancer treatment regimens and NDX had significantly decreased toxicity *in vivo* compared to standard Dox treatment. Thus nano-diamond conjugated chemotherapy represents a promising and biocompatible strategy for overcoming chemo-resistance and enhancing chemotherapy efficacy and safety (34).

12. NANODIAMOND-EMBEDDED MICROFILM DEVICES FOR LOCALIZED CHEMOTHERAPEUTIC ELUTION

In this approach, nanodiamonds (2-8nm diameter) were physically bound with a chemotherapeutic

agent such as doxorubicin hydrochloride (DOX) that were embedded within a parylene C polymer microfilm through a facile and scalable process. The microfilm architecture consists of DOX-ND conjugates sandwiched between a base and thin variable layer of parylene C which allows for modulation of release. The successive layers of parylene and the DOX-ND conjugates were characterized through atomic force microscopy (AFM) images and drug release assays. The elution rates were tested separately over a period of 8 days to 1 month in order to illustrate the release characteristics of the microfilms. These microfilms displayed the stable and continuous slow-release of drug for atleast one month due to the powerful sequestration abilities of the DOX-ND complex and the release-modulating nature of the thin parylene layer. Since the fabrication process is devoid of any destructive steps, the DOX-ND conjugates are unaffected and unaltered. A DNA fragmentation assay was also performed to illustrate the retained activity of DOX under biological conditions (39).

In this study, the researchers conferred the ability to tangibly manipulate the NDs in a polymer-packaged microfilm format for directed placement over diseased areas. Thus by harnessing the innate ND benefits in a biostable patch platform and systemic drug release enabled by the microfilm devices; extended targeted and controlled release towards conditions such as cancer, viral infection and inflammation can allow for enhanced treatment efficacy (39).

To build the biomedical device, the researchers developed a streamlined approach whereby a double layer of parylene was fabricated, with the nanodiamond-drug complexes sandwiched in between. The bottom layer, approximately 20 to 30 microns thick, serves as the backbone of the device, allowing it to be easily handled. For the top layer, the research team created a thinner semi-porous film that allows the drug to slowly release from the device. One of the main advantages of this work is that the fabrication procedures are highly scalable, meaning that hundreds, or even thousands, of devices potentially could be manufactured in parallel and at low cost (40).

13. NANODIAMONDS COUPLED WITH PLANT BIOACTIVE METABOLITES

In a recent study, nanodiamonds were conjugated with plant secondary metabolites, ciproten and quercetin. Since drug-loading on nanoparticles was strongly conditioned by their chemical surface, different types of nanodiamonds (oxidized, wet chemical reduced and plasma reduced) were synthesized in this work and then functionalized with plant compounds. It was found that ciproten and quercetin antiproliferative effects, on human (HeLa) and murine (B16F10) tumor cells, were improved after nanodiamond conjugation. Moreover, plant molecules highly reduced their *in vitro* pro-oxidant, cytotoxic and pro-apoptotic activity when associated with nanodiamond. This research clearly depicts that natural drug-nanodiamond adducts would act at cellular level by different molecular mechanisms with respect to plant metabolite pure forms. Finally, the results showed that chemical and structural modifications of nanodiamond surfaces influenced the bioactivity of transported drugs. Thus bioactive plant molecules associated with nanodiamonds can be used for therapeutic purposes (2).

14. CONCLUSION

Thus from the above paragraphs it can be safely concluded that cancer treatment through the use of nanodiamonds seems promising and a potential approach due to their numerous benefits such as no side effects, target action, non-toxic nature, and do not cause inflammation. Nanodiamonds could penetrate cell walls without damaging them, thus acting as potential drug delivery carriers during chemotherapy Moreover they can be functionalized with nearly any type of therapeutic and can be suspended easily in water which is important for biomedical applications. Furthermore they are cheap and can be produced in large quantities. Besides their application in cancer treatment, nanoparticles also find applications in the study of autoimmune diseases and cardiovascular affections. They are currently of interest as theranostic agents needed for the advent of personalized medicine.

15. ACKNOWLEDGEMENTS

Authors are grateful to Dr. Ashok K. Chauhan, Founder President and Mr. Atul Chauhan, Chancellor, Amity University UP, Noida, India for the encouragement, research facilities and financial support.

16. REFERENCES

1. Moore, L.K., M. Gatica, E.K. Chow, and D. Ho: Diamond-Based Nanomedicine: Enhanced Drug Delivery and Imaging. *Disruptive Sc Techn 1(1), 54-61 (*2012) DOI: 10.1089/dst.2012.0007
2. Gismondi, A., G. Reina, S. Orlanducci, F. Mizzoni, S. Gay, M.L. Terranova, and A. Canini: Nanodiamonds coupled with plant bioactive metabolites: A nanotech approach for cancer therapy. *Biomater* 38, 22–35 (2015) DOI: 10.1016/j.biomaterials.2014.10.057
3. Wang, M., and M. Thanou: Targeting nanoparticles to cancer. *Pharmacol Res* 62, 90–99 (2010) DOI: 10.1016/j.phrs.2010.03.005

4. Li, C: A targeted approach to cancer imaging and therapy. *Nat Mater* 13(2), 110–115 (2014) DOI: 10.1038/nmat3877
5. Getts, D.R., R.L. Terry, M.T. Getts, C. Deffrasnes, M. Müller, C. van Vreden, T.M. Ashhurst, B. Chami, D. McCarthy, H. Wu, J. Ma, A. Martin, L.D. Shae, P. Witting, G.S. Kansas, J. Kühn, W. Hafezi, I.L. Campbell, D. Reilly, J. Say, L. Brown, M.Y. White, S.J. Cordwell, S.J. Chadban, E.B. Thorp, S. Bao, S.D. Miller, and N.J. King: Therapeutic inflammatory monocyte modulation using immune-modifying microparticles. *Sci Transl Med* 6(219), 219ra7 (2014) DOI: 10.1126/scitranslmed.3007563
6. Gupta, A.S.: Nanomedicine approaches in vascular disease: a review. *Nanomedicine* 7, 763–779 (2011) DOI: 10.1016/j.nano.2011.04.001
7. Mura, S. and P. Couvreur: Nanotheranostics for personalized medicine. *Adv Drug Deliv Rev* 64, 1394–1416 (2012) DOI: 10.1016/j.addr.2012.06.006
8. Kaur, R., and I. Badea: Nanodiamonds as novel nanomaterials for biomedical applications: drug delivery and imaging systems. *Int J Nanomedicine* 8, 203–220 (2013) No DOI Found
9. Puzyr, A.P., A.V. Baron, K.V. Purtov, E.V. Bortnikov, N.H. Skobelev, O.A. Mogilnaya, and V. S. Bondar: Nanodiamonds with novel properties: a biological study. *Diamond and Related Materials* 16(12), 2124–2128 (2007) DOI: 10.1016/j.diamond.2007.07.025
10. Mochalin, V.N., O. Shenderova, D. Ho, and Y. Gogotsi: The properties and applications of nanodiamonds. *Nat Nanotechnol* 7, 11–23 (2012) DOI: 10.1038/nnano.2011.209
11. Ho, D., C.-H.K. Wang, and E.K.-H. Chow: Nanodiamonds: The intersection of nanotechnology, drug development, and personalized medicine. *Science Advances* 1(7), e1500439 (2015) DOI: 10.1126/sciadv.1500439
12. Danilenko, V.: On the history of the discovery of nanodiamond synthesis. *Phys Solid State*; 46, 595–599 (2004) DOI: 10.1134/1.1711431
13. Greiner, N.R., D.S. Phillips, J.D. Johnson, and F. Volk: Diamonds in detonation soot. *Nature* 333, 440-442 (1988) DOI: 10.1038/333440a0
14. Osawa, E.: Single-nano buckydiamond particles: Synthesis strategies, characterization methodologies and emerging applications. In: Ho D, ed. Nanodiamonds: Applications in Biology and Medicine. New York City: Springer, pp. 1–33 (2010) DOI: 10.1007/978-1-4419-0531-4_1
15. Guo-Wei, Y., W. Jin-Bin, and L. Qui-Xiang: Preparation of nano-crystalline diamonds using pulsed laser induced reactive quenching. *Journal of Physics: Condensed Matter* 10(35), 7923 (1998) DOI: 10.1088/0953-8984/10/35/024
16. Osawaa, E., S. Sasakib, and R. Yamanoia: Ultananocrystalline diamond (2nd ed.) *Elsevier*, pp. 165–179 (2012) No DOI Found
17. Vial, S., C. Mansuy, S. Sagan, T. Irinopoulou, F. Burlina, J.P. Boudou, G. Chassaing, and S. Lavielle, Peptide-grafted nanodiamonds: preparation, cytotoxicity and uptake in cells. *Chem Bio Chem* 9, 2113–2119 (2008) DOI: 10.1002/cbic.200800247
18. Terranova, M.L., S. Orlanducci, E. Tamburri, V. Guglielmotti, F. Toschi, D. Hampai, and M. Rossi: Polycrystalline diamond on self-assembled detonation nanodiamond: a viable route for fabrication of all-diamond preformed micro-components. *Nanotechnology* 19, 415600–415605 (2008) DOI: 10.1088/0957-4484/19/41/415601
19. Orlanducci, S., I. Cianchetta, E. Tamburri, M.L. Terranova, M. Cassani, R. Matassa, and M. Rossi.: Gold nanoparticles on nanodiamond for nanophotonic applications. *MRS Proceedings* 1452, 13–19 (2012) DOI: 10.1557/opl.2012.1175
20. Tamburri, E., S. Orlanducci, V. Guglielmotti, M. Rossi, and M.L. Terranova: Engineering detonation nanodiamond-polyaniline nanocomposites by electrochemical routes: structural features and functional characterizations. *Polymer* 52, 5001–5008 (2011) DOI: 10.1016/j.polymer.2011.09.003
21. Vaijayanthimala, V., and H.C. Chang: Functionalized fluorescent nanodiamonds

for biomedical applications. *Future Med* 4, 47–55 (2009)
DOI: 10.2217/17435889.4.1.47

22. Purtov, K.V., A.I. Petunin, A.E. Burov, A.P. Puzyr, and V.S. Bondar: Nanodiamonds as carriers for address delivery of biologically active substances. *Nanoscale Res Lett* 5, 631–636 (2010)
DOI: 10.1007/s11671-010-9526-0

23. Alhaddad, A., M.P. Adam, J. Botsoa, G. Dantelle, S. Perruchas, T. Gacoin, C. Mansuy, S. Lavielle, C. Malvy, F. Treussart, and J-R. Bertrand: Nanodiamond as a vector for siRNA delivery to Ewing sarcoma cells. *Small* 7, 3087–3095 (2011)
DOI: 10.1002/smll.201101193

24. Zhu, Y., J. Li, W. Li, Y. Zhang, X. Yang, N. Chen, Y. Sun, Y. Zhao, C. Fan, and Q. Huang.: The biocompatibility of nanodiamonds and their application in drug delivery systems. *Theranostics* 2(3), 302–312 (2012)
DOI: 10.7150/thno.3627

25. Liu, K.K., C.L. Cheng, C.C. Chang, and J.I. Chao.: Biocompatible and detectable carboxylated nanodiamond on human cell. *Nanotechnol* 18, 325102 (2007)
DOI: 10.1088/0957-4484/18/32/325102

26. Horie, M., K.L. Komaba, H. Kato, A. Nakamura, K.Yamamoto, S. Endoh, K. Fujita, S. Kinugasa, K. Mizuno, Y. Hagihara, Y. Yoshida, and H. Iwahashi.: Evaluation of cellular influences induced by stable nanodiamond dispers: the cellular influences of nanodiamond are small. *Diam Relat Mat* 24, 15–24 (2012)
DOI: 10.1016/j.diamond.2012.01.037

27. Faklaris, O., V. Joshi, T. Irinopoulou, P. Tauc, M. Sennour, H. Girard, C. Gesset, J.-C. Arnault, A. Thorel, J.-P. Boudou, P.A. Curmi, and F. Treussart: Photo-luminescent diamond nanoparticles for cell labeling: study of the uptake mechanism in mammalian cells. *ACS Nano* 3(12), 3955–3962 (2009)
DOI: 10.1021/nn901014j

28. Martín, R., M. Alvaro, J.R. Herance, and H. García: Fenton-treated functionalized diamond nanoparticles as gene delivery system. *ACS Nano* 4, 65–74 (2010)
DOI: 10.1021/nn901616c

29. Fang, C.Y., V. Vaijayanthimala, C.A. Cheng, S.H. Yeh, C.F. Chang, C.L. Li, and H-C. Chang: The exocytosis of fluorescent nanodiamond and its use as a long-term cell tracker. *Small* 7 (23): 3363–3370 (2011)
DOI: 10.1002/smll.201101233

30. Schrand, A.M., J.B. Lin, S.C. Hens, an S.M. Hussain: Temporal and mechanistic tracking of cellular uptake dynamics with novel surface fluorophore-bound nanodiamonds. *Nanoscale* 3, 435–445 (2011)
DOI: 10.1039/C0NR00408A

31. Rej, E., T. Gaebel, T. Boele, D. Waddington, and D. Reilly: Hyperpolarized nanodiamond with long spin-relaxation times. *Nat Commun* 6, Article number 8459 (2015)
DOI: 10.1038/ncomms9459

32. Wang, X., X.C. Low, W. Hou, L.N. Abdullah, T.B. Toh, M. Mohd Abdul Rashid, D. Ho, and E.K. Chow: Epirubicin-Adsorbed Nanodiamonds Kill Chemoresistant Hepatic Cancer Stem Cells. *ACS Nano 8* (12), 12151–12166 (2014)
DOI: 10.1021/nn503491e

33. Poland, C.A., R. Duffin, I. Kinloch, A. Maynard, W.A. Wallace, A. Seaton, V. Stone, S. Brown, W. Macnee, and K. Donaldson: Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. *Nat Nanotechnol* 3(7), 423–428 (2008)
DOI: 10.1038/nnano.2008.111

34. Chow, E.K., X.-Q. Zhang, M. Chen, R. Lam, E. Robinson, H. Huang, D. Schaffer, E. Osawa, A. Goga, and D. Ho: Nanodiamond Therapeutic Delivery Agents Mediate Enhanced Chemoresistant Tumor Treatment. *Sci Transl Med* 3, 73ra21 (2011)
DOI: 10.1126/scitranslmed.3001713

35. Zhang, Q., V.N. Mochalin, I. Neitzel, I.Y. Knoke, J. Han, C.A. Klug, J.G. Zhou, P.I. Lelkes, and Y. Gogotsi. Fluorescent PLLA-nanodiamond composites for bone tissue engineering. *Biomaterials* 32(1): 87–94 (2011)
DOI: 10.1016/j.biomaterials.2010.08.090

36. Yuan, Y., X. Wang, G. Jia, J.-H. Liu, T. Wang, Y. Gu, S.-T. Yang, S. Zhen, H. Wang, and Y. Liu: Pulmonary toxicity and translocation of nanodiamonds in mice. *Diam Relat Mater* 19, 291–299 (2010)
DOI: 10.1016/j.diamond.2009.11.022

37. Mohan, N., C.-S. Chen, H.-H. Hsieh, Y.C. Wu, and H.C. Chang: *In vivo* Imaging and toxicity assessments of fluorescent nanodiamonds

in *Caenorhabditis elegans*. *Nano Lett* 10(9), 3692–3699 (2010)
DOI: 10.1021/nl1021909

38. Xi, G., E. Robinson, B. Mania-Farnell, E.F. Vanin, K.-W. Shim, T. Takao, E.V. Allender, C.S. Mayanil, M.B. Soares, D. Ho, and T. Tomita: Convection-enhanced delivery of nanodiamond drug delivery platforms for intracranial tumor treatment. *Nanomedicine: Nanotechnol Biol Med* 10(2), 381–391 (2014)
DOI: 10.1016/j.nano.2013.07.013

39. Lam, R., M. Chen, E. Pierstorff, H. Huang, E. Osawa, and D. Ho: Nanodiamond-Embedded Microfilm Devices for Localized Chemotherapeutic Elution. *ACS Nano 2* (10), 2095–2102 (2008)
DOI: 10.1021/nn800465x

40. Boudou, J.P., P.A. Curmi, F. Jelezko, J. Wrachtrup, P. Aubert, M. Sennour, G. Balasubramanian, R. Reuter, A. Thorel, and E. Gaffet: High yield fabrication of fluorescent nanodiamonds. *Nanotechnol* 20(23), 235602 (2009)
DOI: 10.1088/0957-4484/20/23/235602

Key Words: Cancer, Nanodiamonds, Drug delivery, Carbon nanoparticles, Brain tumors, Breast cancer, Chemo resistance, Review

Send correspondence to: Charu Gupta, Amity Institute for Herbal Research and Studies, Block J-1, Room LG-13, Amity University UP, Sector-125, Noida-201313, India, Tel: 0120-4392549, Fax: 0120-4392502, E-mail: charumicro@gmail.com